蔡 俊明 教授
Chun-Ming Tsai

顧問
臺北 榮民總醫院 腫瘤醫學部
臺北 國泰醫學中心
台中 中山醫學大學 附設醫院
臺北 振興醫學中心

Advancement in first-line therapeutics for EGFRm NSCLC

— *Navigation of current treatment options for stage IV NSCLC*

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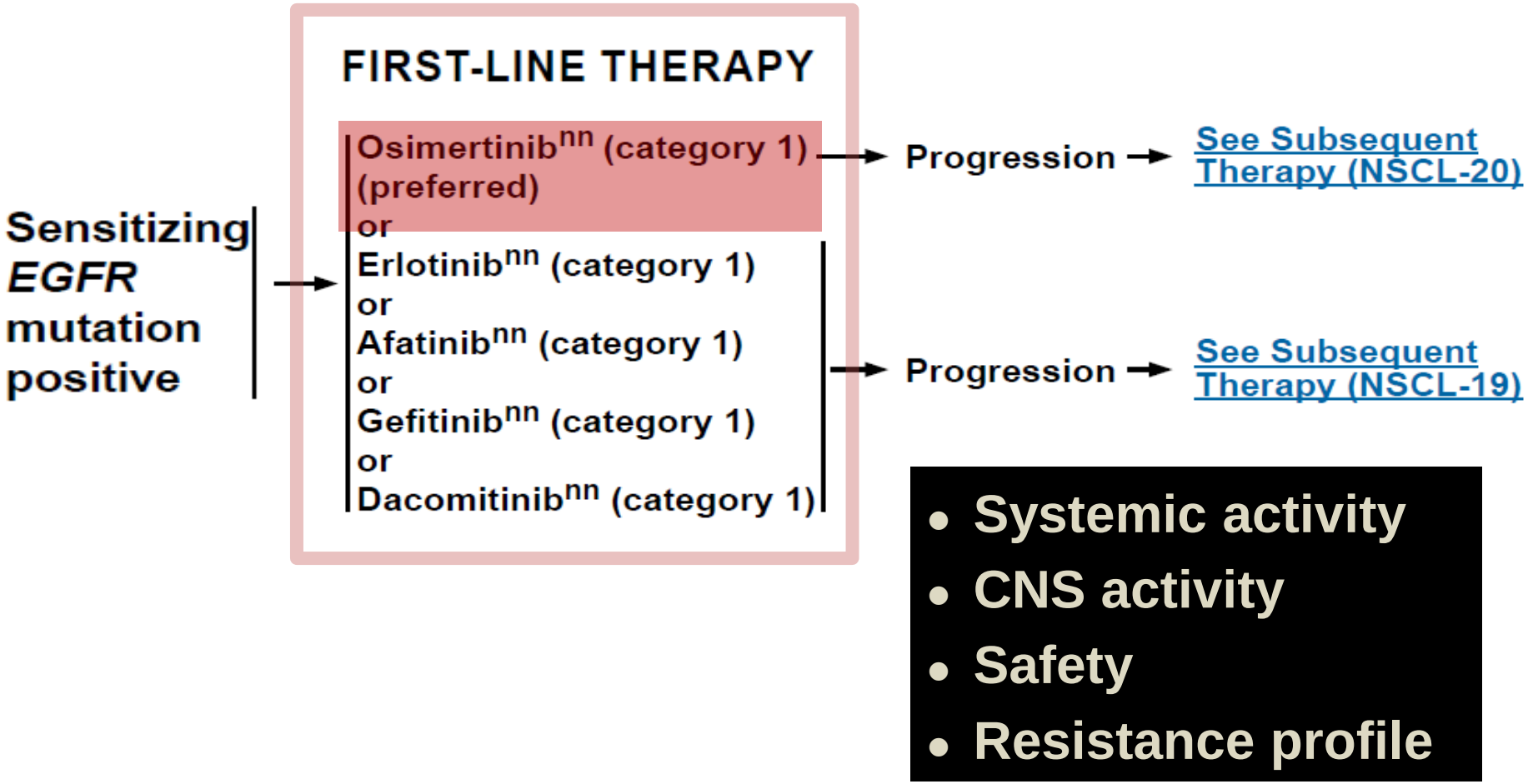
Maximizing the benefit of each line of management
— aim for the best PFS rather than OS
(except immunotherapy)

SENSITIZING EGFR MUTATION POSITIVE



LUX-lung 7 Ph II

Patients (N=319)

- Stage IIIB/IV adenocarcinoma of the lung
- *EGFR* mutation (Del19 and/or L858R) in the tumour tissue*
- No prior treatment for advanced/metastatic disease
- ECOG PS 0/1

1:1

Stratified by
- Mutation type (Del19/L858R)
- Brain metastases (present/absent)

Afatinib 40 mg QD†

Gefitinib 250 mg QD

16% *(51/319)*

Co-primary endpoints:
- PFS (independent review)
- TTF
- OS

Secondary endpoints:
- ORR
- Time to response
- Duration of response
- Tumour shrinkage
- HRQoL

ARCHER 1050 Ph III

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systemic treatment of advanced NSCLC
- No CNS metastasis
- No prior EGFR TKI or other TKI
- ECOG PS 0,1

N=452

R 1:1

Dacomitinib 45 mg PO QD (N=227)

Gefitinib 250 mg PO QD (N=225)

Stratification factors

Race (inc. Asian vs non-Asian)

EGFR mutation type (exon 19 vs 21)

Primary endpoint

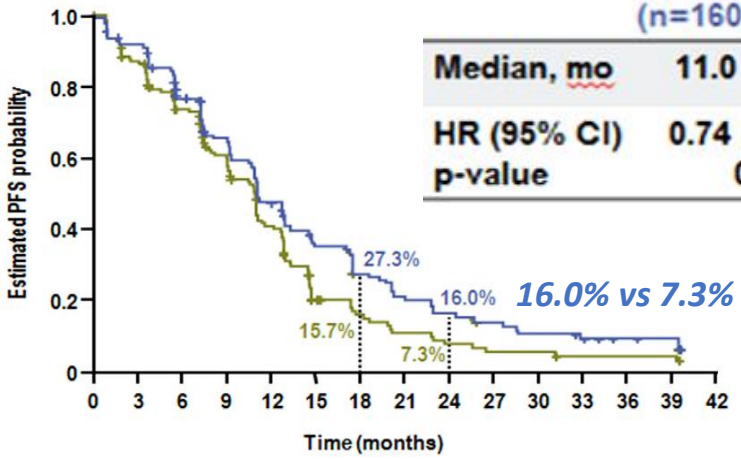
PFS by blinded independent review (IR)
- ≥256 PFS events
- PFS HR≤0.667 (50%↑)
- 90% power
- 1-sided α =0.025
- mPFS: 14.3 vs 9.5 months

Secondary endpoints

PFS (investigator assessed), ORR, DOR,

TTF, OS, Safety, PROs

LUX-lung 7 Ph II

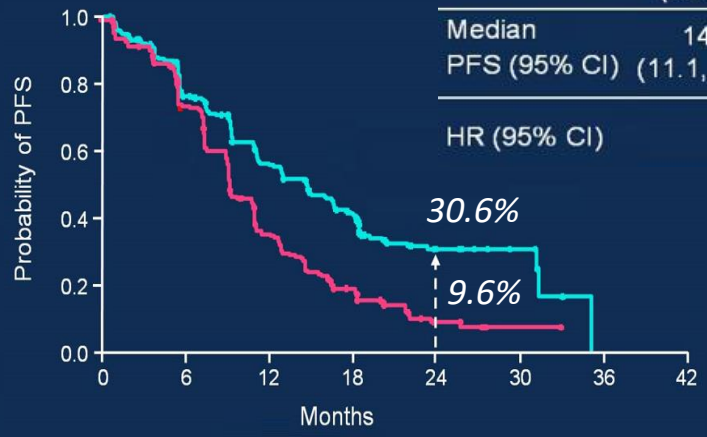


	Afatinib (n=160)	Gefitinib (n=159)
Median, mo	11.0	10.9
HR (95% CI)	0.74 (0.57–0.95)	
p-value	0.0178*	

LL-7 vs ARCHER 1050: Efficacy & Dosing

Trial	LUX7	1050	LUX7	1050
Drug	gefitinib	gefitinib	afatinib	dacomitinib
n	159	225	160	227
	Efficacy			
Median PFS	10.9	9.2	11.0	14.7
PFS HR (95%CI)	-	-	0.73 (0.57-0.95)	0.59 (0.47-0.74)
24 month PFS	8%	10%	18%	31%
	Dosing			
Dose modificatior	2%	8%	42%	66%

ARCHER 1050 Ph III



	Daco (N=227)	Gef (N=225)
Number of Events, n (%)	136 (59.9%)	179 (79.6%)
Median PFS (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)	0.59 (0.47–0.74) P<0.0001	

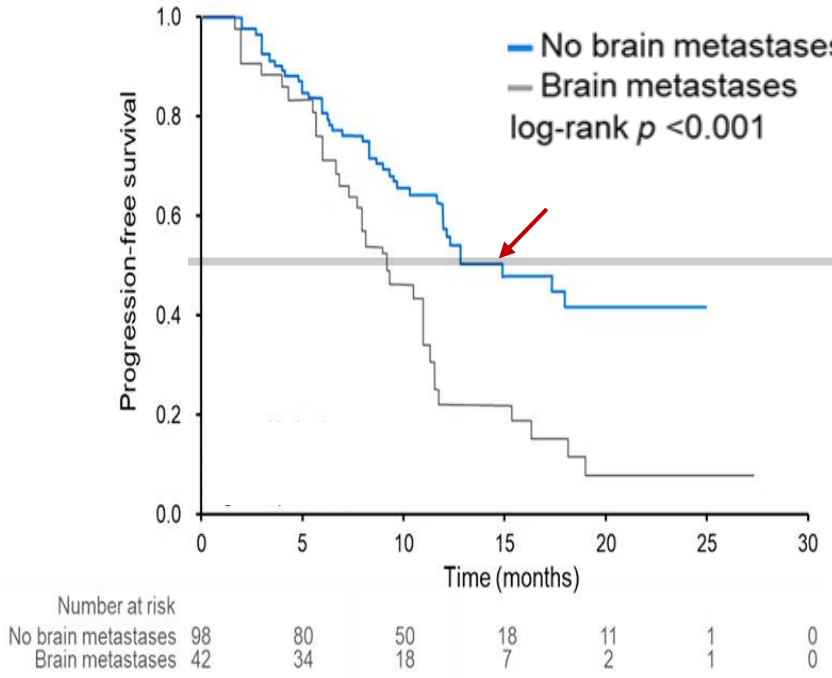
LL-7 vs ARCHER 1050: Safety

Trial	LUX7	1050	LUX7	1050
Drug	gefitinib	gefitinib	afatinib	dacomitinib
Term	Grade ≥3%			
Diarrhoea	1	1	13	9
Rash/Acne/Dermatitis	3	0	9	14
Stomatitis	0	1	4	4
Nail effect/ Paronychia	1	1	2	8
ALT/AST rise	9	9	0	1

Mok, LBA9007 ASCO 2017

Afatinib PFS for presence or absence of brain metastasis at diagnosis- Taiwan real world

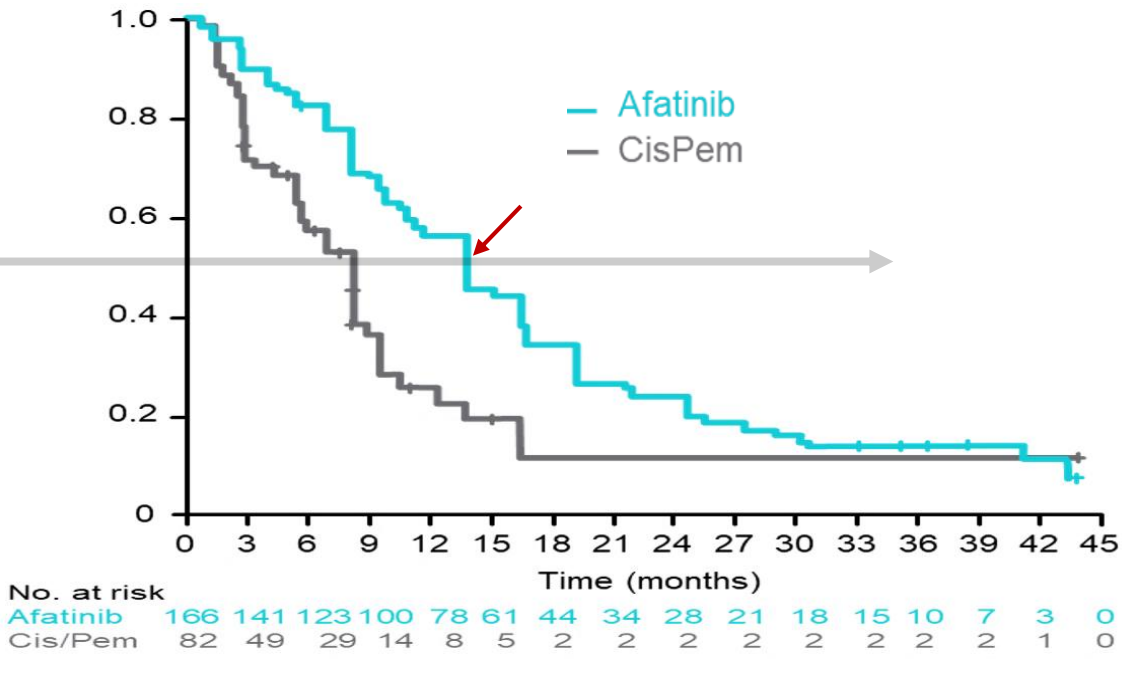
	Brain meta	No brain meta
Median PFS	9.2 months	14.9 months
HR (95% CI)	2.29 (1.46–3.60) P < 0.001	



Liang et al. Oncotarget. 2017 Jul 26

LL3: PFS in patients without brain metastases (common mutations, independent review)

	Afatinib	CisPem
Median, mo	13.8	8.1
HR (95% CI)	0.48 (0.34-0.69)	
P-value	*P*<0.0001	



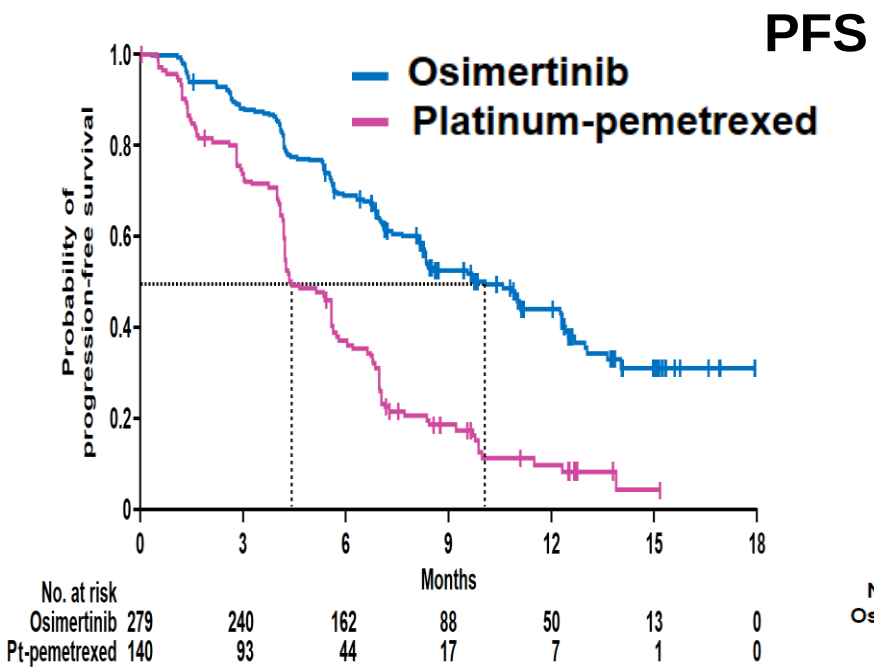
Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

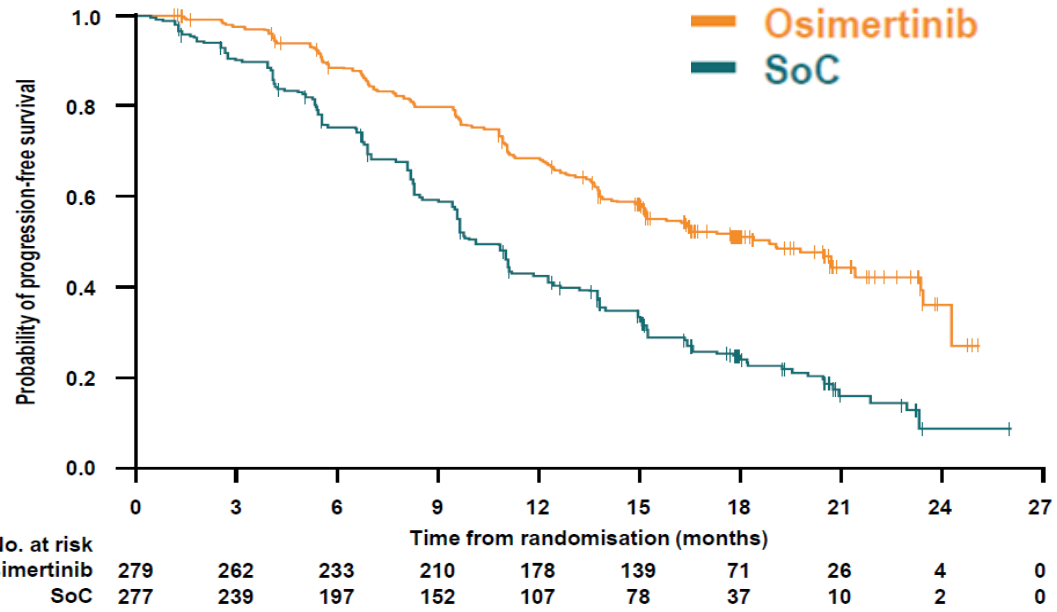
AURA3 *post-1st line TKI*

	Median PFS Mo (95%CI)	HR (95% CI)
Osimertinib	**10.1** (8.3,12.3)	**0.30** (0.23,0.41)
Pt-Pem	**4.4** (4.2,5.6)	***P <0.001***

FLAURA *frontline TKI*

	Median PFS Mo (95%CI)	HR (95% CI)
Osimertinib	**18.9** (15.2,21.4)	**0.46** (0.37,0.57)
SoC Gefitinib /erlotinib	**10.2** (9.6,11.1)	***P <0.0001***

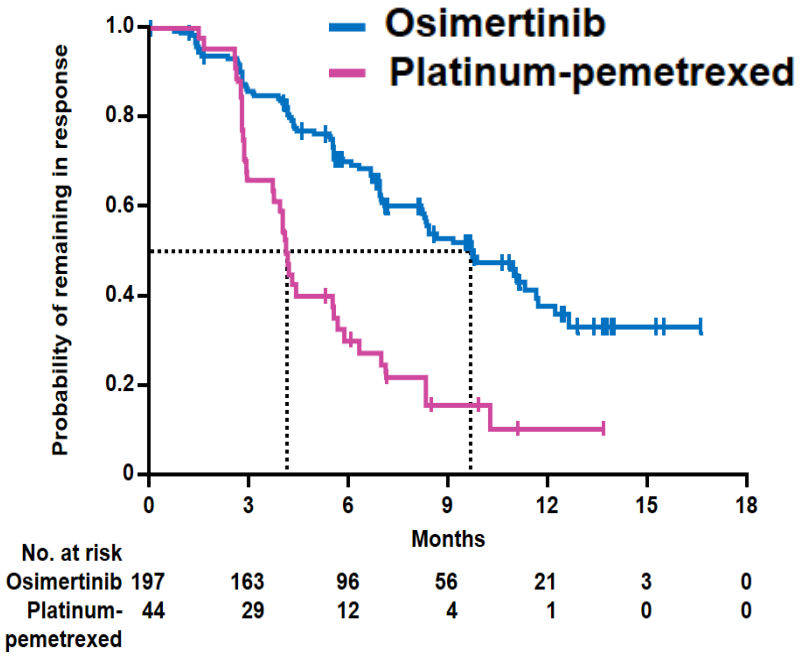


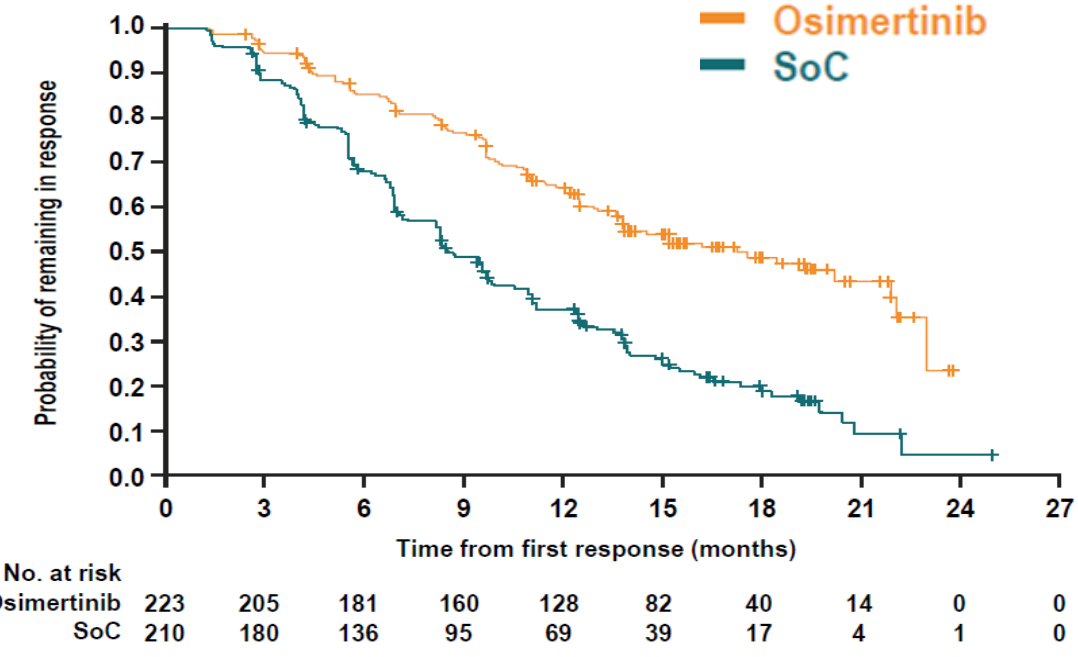


Durable response to osimertinib in AURA3 and FLAURA

AURA 3	Osimertinib (n=279)	Platinum-pemetrexed (n=140)
ORR (95% CI)	**71% (65, 76)**	**31% (24, 40)**
Odds ratio* (95% CI)	5.39 (3.47, 8.48); p<0.001	
Complete response, n (%)	4 (1)	2 (1)
Partial response, n (%)	193 (69)	42 (30)
Stable disease ≥6 weeks, n (%)	63 (23)	60 (43)
Progression, n (%)	18 (6)	26 (19)
Not evaluable, n (%)	1 (<1)	10 (7)
Median DoR#, months (95% CI)	**9.7 (8.3, 11.6)**	**4.1 (3.0, 5.6)**

FLAURA	Osimertinib (n=279)	SoC (n=277)
ORR (95% CI)	80% (75, 85)	76% (70, 81)
Odds ratio# (95% CI)	1.28 (0.85, 1.93); p=0.2335	
Complete response‡, n (%)	7 (3)	4 (1)
Partial response‡, n (%)	216 (77)	206 (74)
Stable disease ≥6 weeks, n (%)	47 (17)	46 (17)
Progression, n (%)	3 (1)	14 (5)
Not evaluable, n (%)	6 (2)	7 (3)
Duration of response	17.2 (13.8, 22.0)	8.5 (7.3, 9.8)

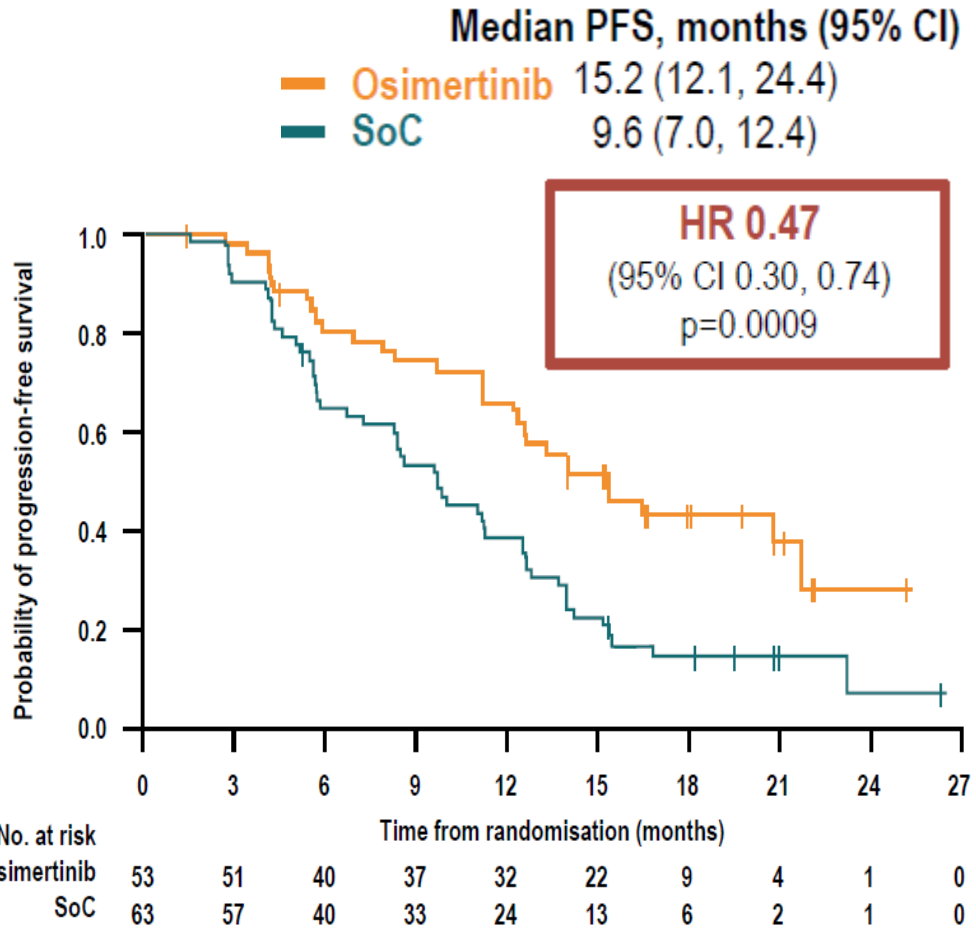




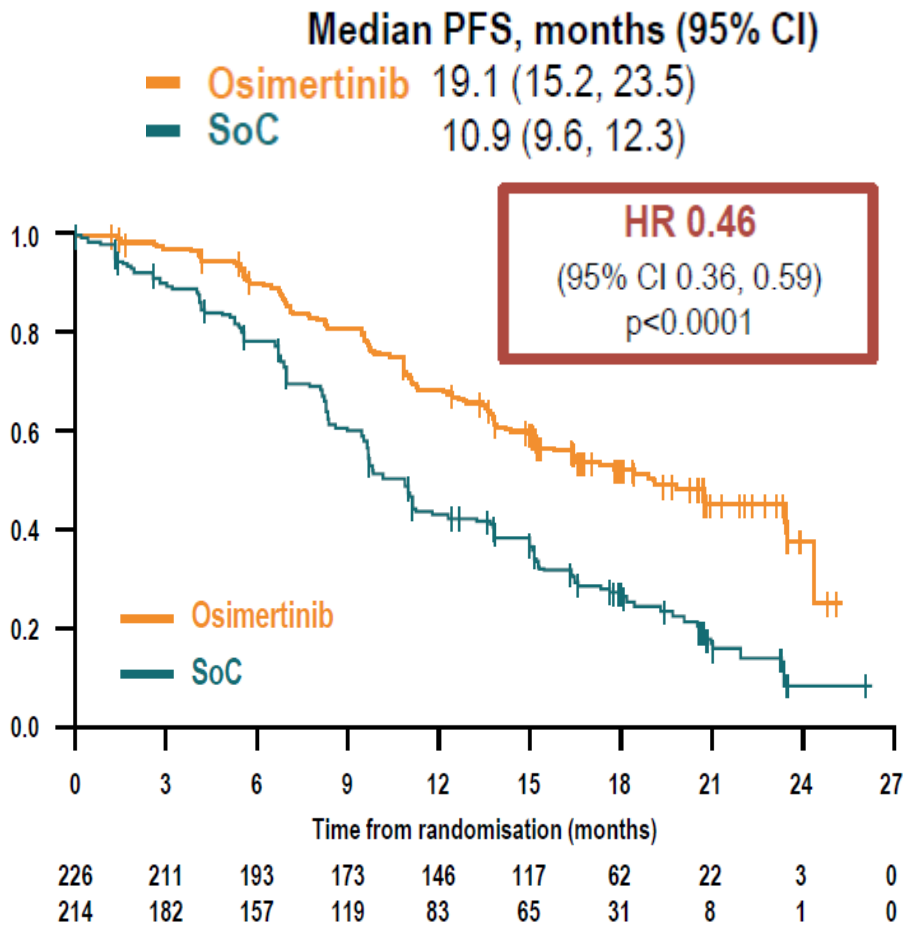
PFS benefit in FLAURA patients with & without CNS metastases at baseline

Frontline TKI

With CNS metastases (n=116)

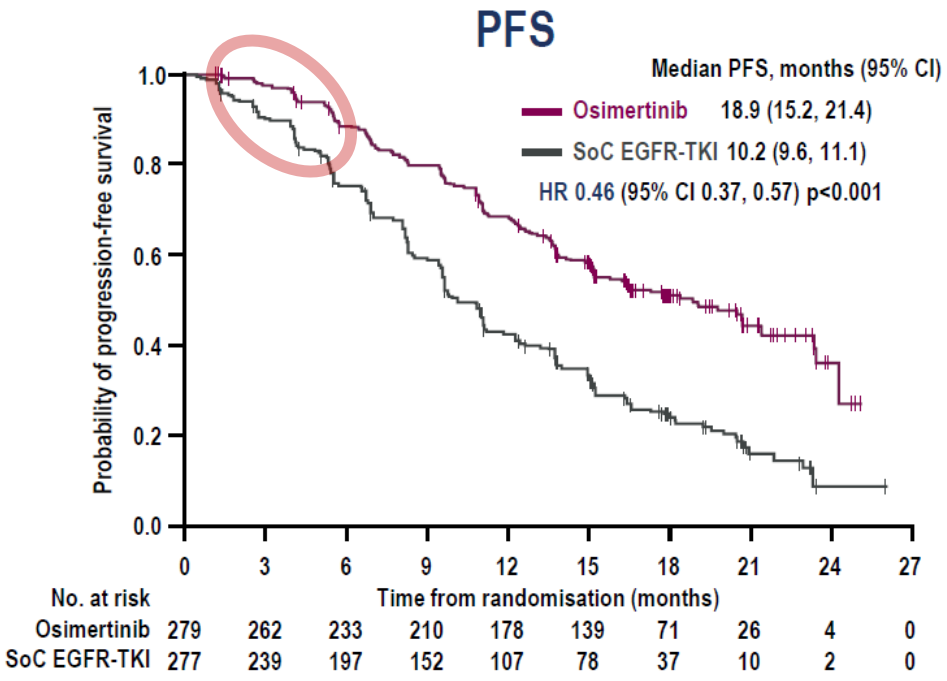


Without CNS metastases (n=440)



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

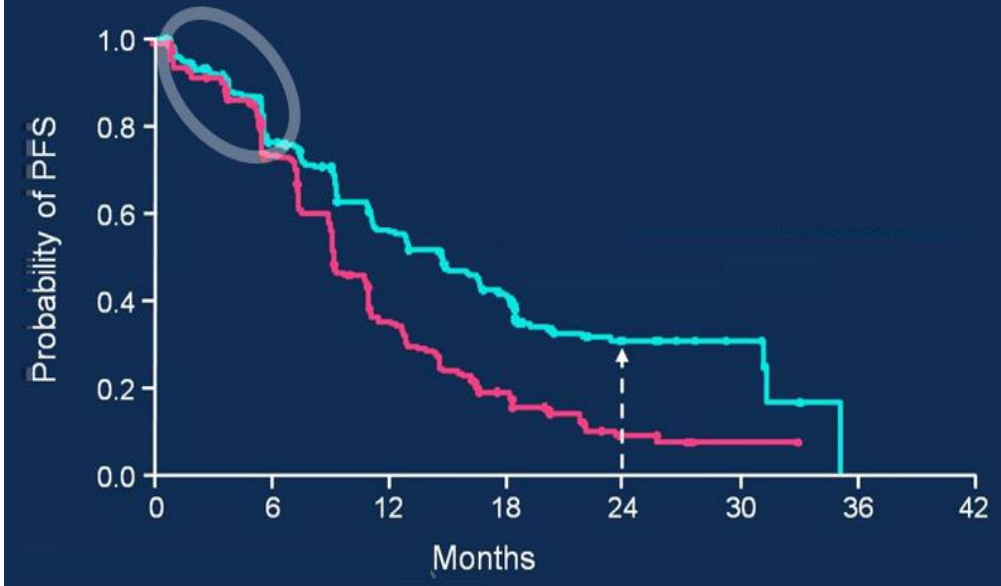
PFS of ARCHER 1050 and FLAURA



	Osimertinib	SoC
ORR (95% CI)	80% (75, 85)	76% (70, 81)
Odds ratio# (95% CI)	1.28 (0.85, 1.93); p=0.2335	

	mPFS Mo (95%CI)	HR (95% CI)
Osimertinib	**18.9** (15.2,21.4)	**0.46** (0.37,0.57)
SoC Gefitinib/erlotinib	**10.2** (9.6,11.1)	***P <0.0001***

Soria J-C, et al. N EngJ Med 2018;378:113



	Daco	Gef
Median PFS (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)	0.59 (0.47–0.74) P<0.0001	

EGFR-TKI + anti-angiogenetic agent

RELAY: Study Design

Key inclusion criteria
- Stage IV NSCLC
- *EGFR* mutation-positive (Ex19del or Ex 21 L858R)
- ECOG PS 0-1

Key exclusion criteria
- Known *EGFR* T790M mutation
- Prior treatment with EGFR TKI or chemotherapy
- Brain metastases

RANDOMIZE 1:1

- Ramucirumab 10 mg/kg Q2W + Erlotinib 150 mg/day
- Placebo Q2W + Erlotinib 150 mg/day

Treatment until progression or unacceptable toxicity

Primary end point: Progression-Free Survival

Phase 3[a]
N=449

Stratification factors
- *EGFR* status (exon 19 deletion vs. exon 21 L858R)
- Sex
- Region (East Asia vs. other)
- EGFR testing method (therascreen®/cobas® vs. other)

[a]Phase 3 enrollment began after confirmation of dose and schedule in Phase 1b[2]

NEJ 026 (Phase III study)

- Chemotherapy-naïve
- Non-Sq NSCLC
- PS 0-2
- Stage IIIB/IV or postoperative recurrence
- Activating *EGFR*-mutations*
  Ex19 del, Ex21 L858R
- Asymptomatic CNS metastases allowed

*T790M excluded

R

BE combination
Bevacizumab 15mg/kg q3w
+
Erlotinib 150mg qd
(*n* = 107)

E monotherapy
Erlotinib 150mg qd
(*n* = 107)

Stratification factors
Sex
Clinical stage
Smoking status
EGFR-mutation subtypes

Target PFS HR : **0.63**

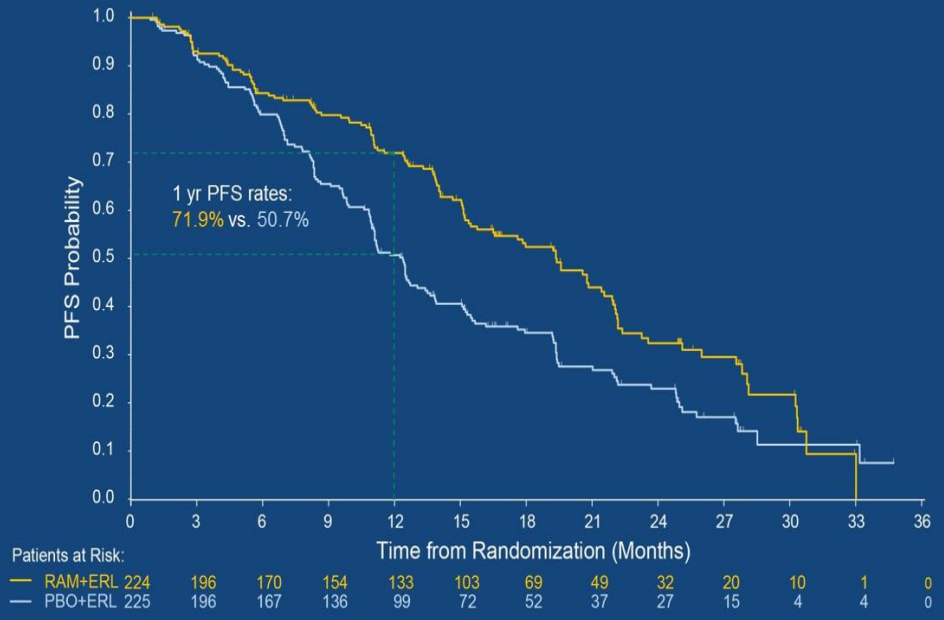
Primary endpoint
PFS by independent review committee (IRC)

Secondary endpoints
- Overall survival
- Tumor response : RR, DCR, DR
- Safety
- QOL : EORTC QLQ-C30 or QLQ-LC13

Exploratory endpoints
- Biomarker analyses : tissue and plasma samples (PNA-LNA PCR clamp method)
- Combined OS analysis : NEJ026 plus JO25567 study

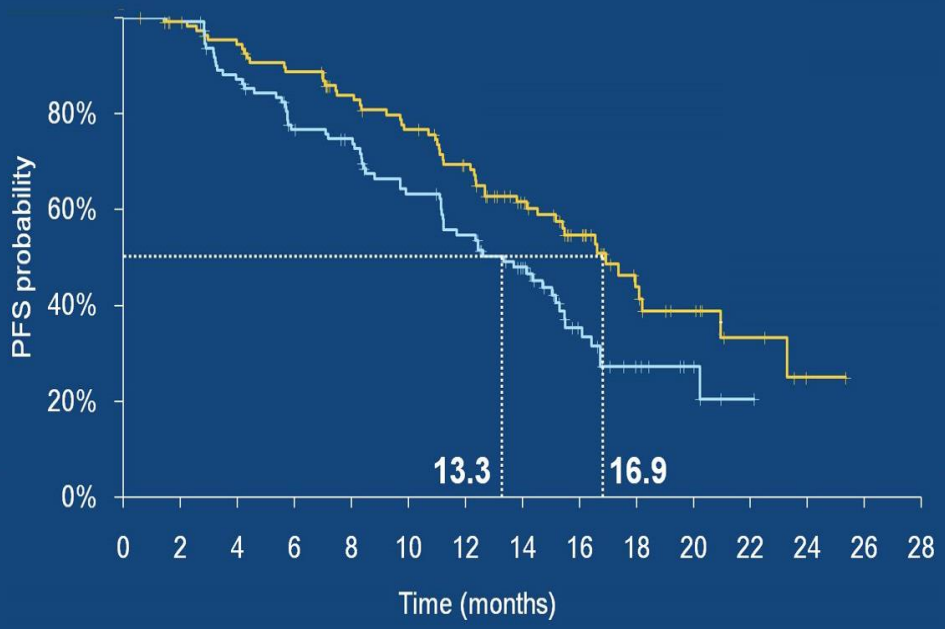
EGFR-TKI + anti-angiogenetic agent

RELAY



PFS	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	

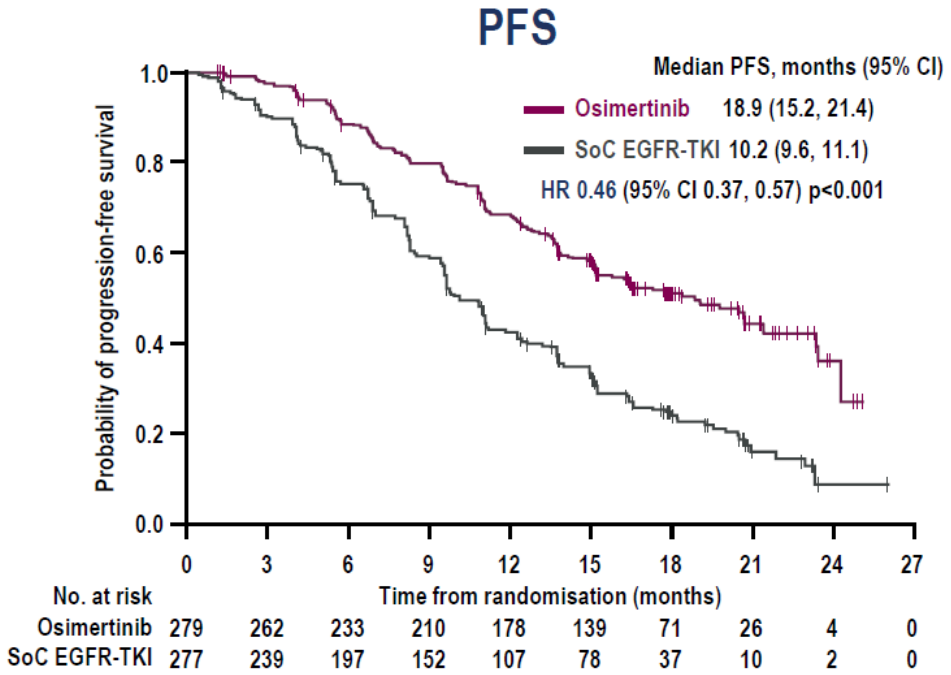
NEJ026



The interim analysis 117 events		
	BE	E
mPFS (mo)	16.9	13.3
HR	**0.605** (95% CI: 0.417 – 0.877)	
P value	0.01573	

Median follow up : 12.4 months

FLAURA



	Osimertinib	SoC
ORR (95% CI)	80% (75, 85)	76% (70, 81)
Odds ratio# (95% CI)	1.28 (0.85, 1.93); p=0.2335	

	mPFS Mo (95%CI)	HR (95% CI)
Osimertinib	**18.9** (15.2,21.4)	**0.46** (0.37,0.57)
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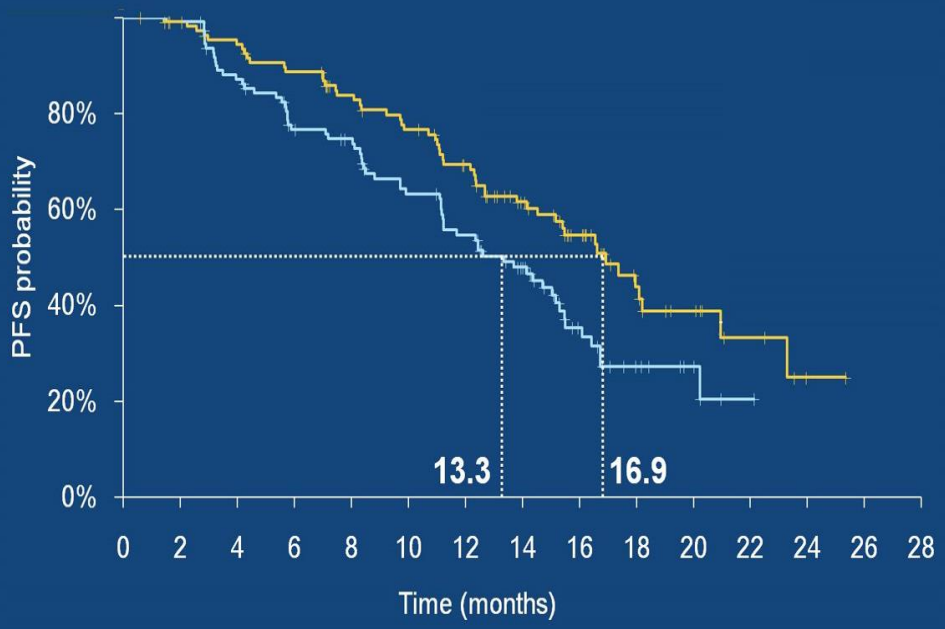
Soria J-C, et al. N EngJ Med 2018;378:113

NEJ026



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P value		0.01573

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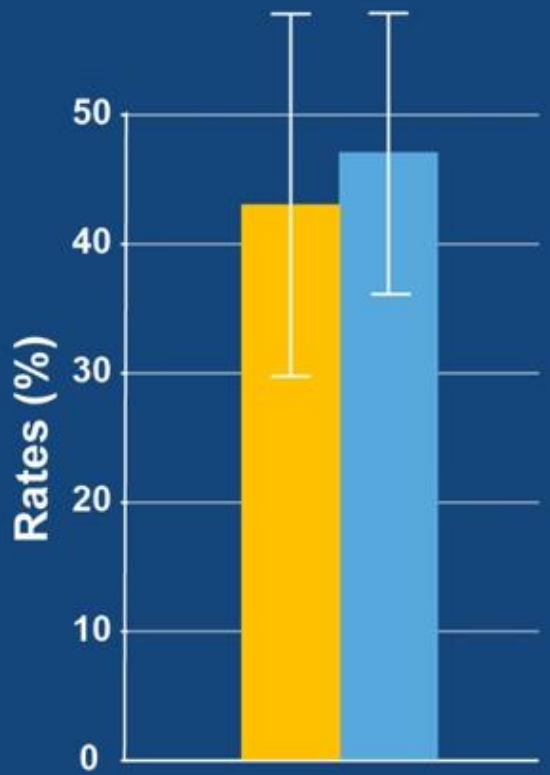
RELAY: EGFR T790M Rates Post-Progression

30-Day FU Post-progression



- Assessed in liquid biopsies by Guardant360 NGS at baseline and 30-Day follow up
- No T790M detected at baseline
- Rates shown for patients (n=119) with progression and EGFR activating mutation (Ex19del or L858R) detected at 30-Day follow-up
- Sensitivity analyses (e.g. not requiring EGFR activating mutation at 30-Day follow-up) also found no difference between arms following progression

	RAM+ ERL	PBO+ERL
T790M (+)/patients with results	19/44	35/75
T790M rates (95% CI)	**43** (30, 58)	**47** (36, 58)
P-value	0.849	

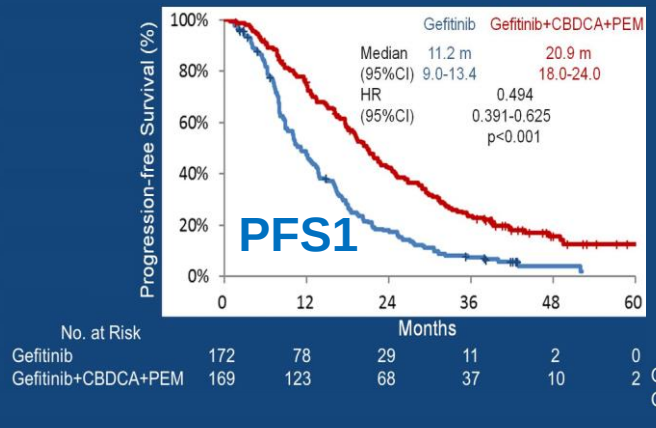
PRESENTED BY: Prof. Kazuhiko Nakagawa, MD, PhD
Kindai University Faculty of Medicine, Osaka, Japan

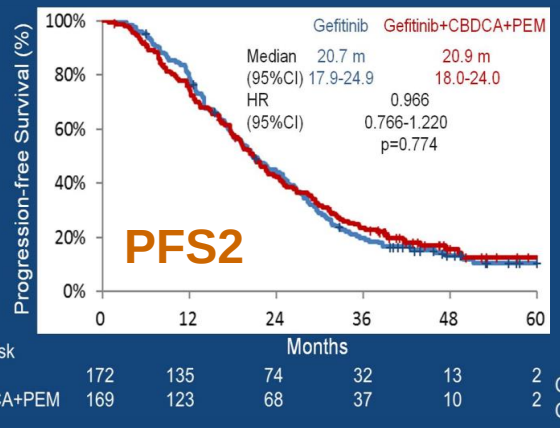
NEJ 009

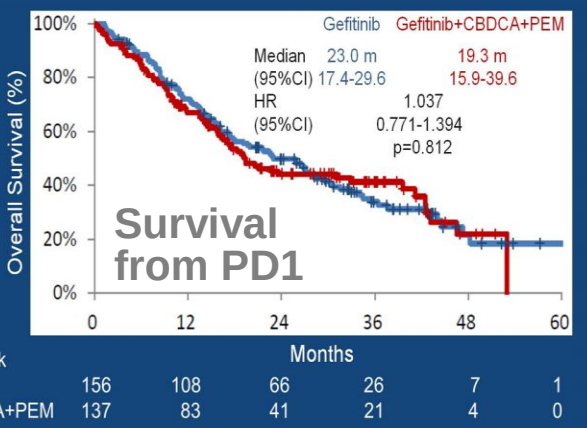
Gefitinib+CBDCA+PEM

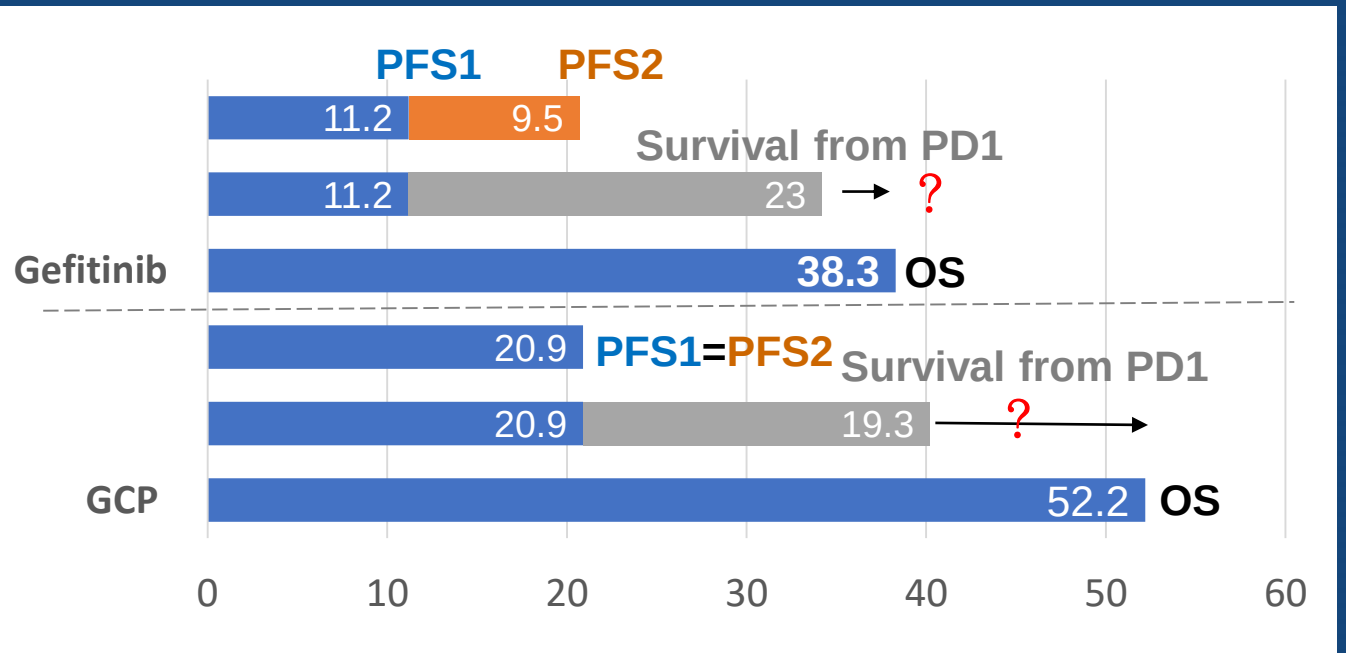
PFS1 (=PFS2)* → PD1

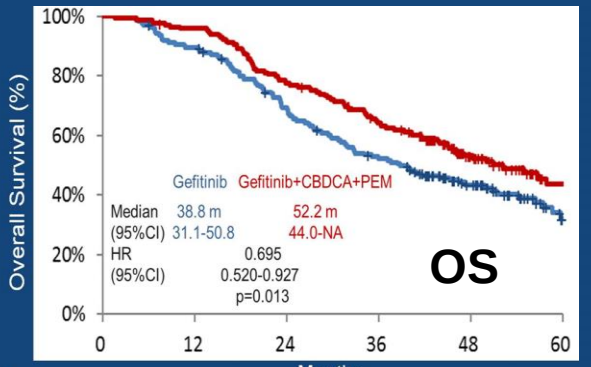
Gefitinib → PFS1 → PD1 → (recommended) CBDCA+PEM → PFS2 → PD2









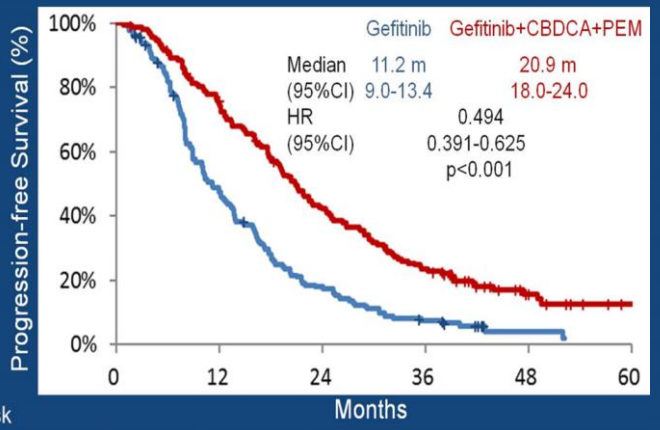


NEJ 009

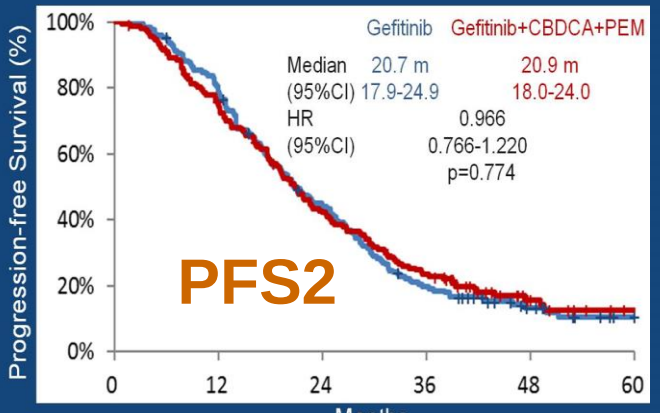
Gefitinib+CBDCA+PEM → PFS1 (=PFS2)* → PD1

Gefitinib → PFS1 → PD1 → (recommended) CBDCA+PEM → PFS2 → PD2

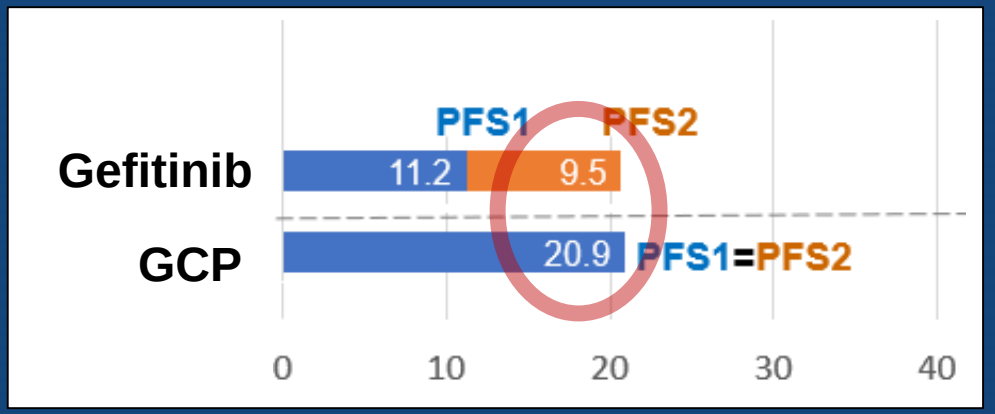
% pt



No. at Risk						
Gefitinib	172	78	29	11	2	0
Gefitinib+CBDCA+PEM	169	123	68	37	10	2



No. at Risk						
Gefitinib	172	135	74	32	13	2
Gefitinib+CBDCA+PEM	169	123	68	37	10	2



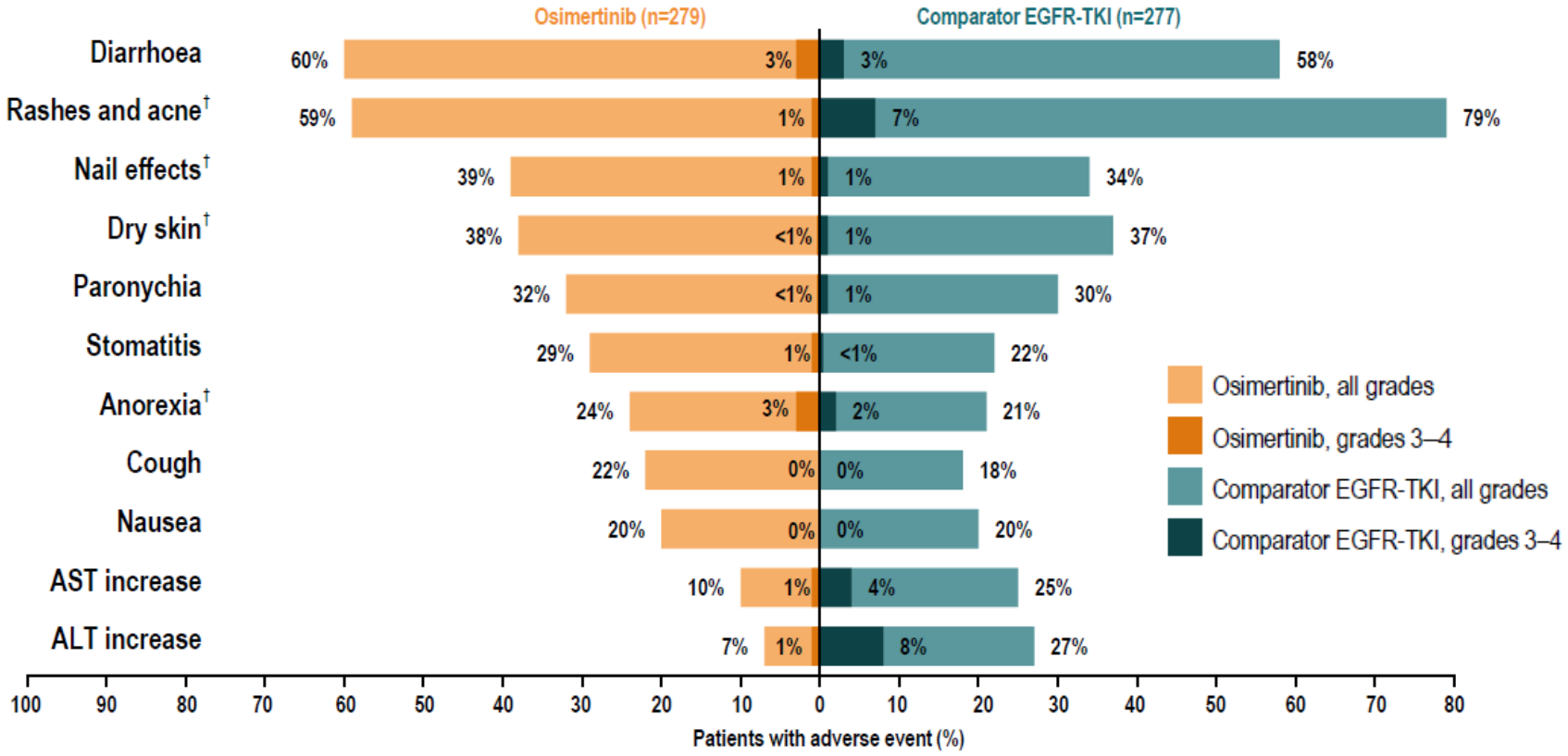
Safety data of first-line treatment for EGFR mutation-positive NSCLC

Trial	Drug	N	Rash (%)		Paronychia (%)		Diarrhoea (%)		Liver dys-function (%)		ILD (%)	
			All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
WJTOG3405	Gefitinib	87	85	2	32	1	54	1	70	28	2	1
NEJ002	Gefitinib	114	71	5	-	-	34	1	55	26	5	3
LUX-Lung 7	Gefitinib	159	81	3	17	0.6	61	1	21/24	3/8	2.5	2.5
FLAURA	Gef / Erl	277	48	5	29	1	57	2	25/27	4/9	-	-
EURTAC	Erlotinib	84	80	13	-	-	57	5	6	2	1	1
OPTIMAL	Erlotinib	83	43	2	4	0	25	1	37	4	-	-
Japan PII	Erlotinib	103	83	14	66	1	81	1	33	8	5	2
LUX-Lung 3	Afatinib	230	89	16	57	11	95	14	10	2	1	1
All pts Asian pts		165	91	17	65	14	96	16	9	1	1	1
LUX-Lung 6	Afatinib	239	81	15	33	0	88	5	20	2	0.4	0.4
LUX-Lung 7	Afatinib	160	89	9	56	2	90	12	6/9	0	-	-
AURA 3	Osimertinib	279	34	1	22	0	41	1	-	-	4	< 1
FLAURA	Osimertinib	279	25	0	29	< 1	58	2	9/6	1 / <1	-	-

SAFETY SUMMARY

- Median duration of exposure: osimertinib, 20.7 months; comparator EGFR-TKI, 11.5 months
- Grade ≥3 possibly causally related AEs: osimertinib, 51 patients (**18%**); comparator EGFR-TKI, 79 patients (**29%**)

Any adverse event* (in ≥20% of patients)



BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

*As assessed by the investigator; Patients with multiple events in the same category counted only once in that category; Patients with events in more than one category counted once in each of those categories; †Grouped term

Outcomes and Toxicities: Single Agent EGFR TKIs versus 1st Gen EGFR TKI plus VEGF(R)i

Drug(s)	Trial	mPFS (mos)	ORR	Diarrhea (Any Grade/ G≥3)	Rash (Any Grade/ G≥3)	Hypertension (Any Grade/ G≥3)	Proteinuria (Any Grade/ G≥3)	Hemorrhage (Any Grade/ G≥3)
Osimertinib	FLAURA	18.9	80%	58%/2%	32%/<1%	NR	NR	NR
Erlotinib/ Placebo	RELAY	12.4	75%	71%/1%	68%/9%	12%/5%	8%/0%	26%/2%
Erlotinib/ Ramucirumab	RELAY	19.4	76%	70%/7%	67%/15%	45%/24%	34%/3%	55%/2%
Erlotinib	NEJ026	13.3	66.1%	41%/1.8%	87%/21%	9%/0%	2.6%/0%	2.6%/0.9%
Erlotinib/ Bevacizumab	NEJ026	16.9	72.3%	47%/5.4%	88%/21%	46%/22%	32%/7%	25%/1.8%
Erlotinib	J025567	9.8		79%/1%	99%/20%	14%/12%	4%/0%	30%/0%
Erlotinib/ Bevacizumab	J025567	16.4		81%/3%	99%/25%	79%/61%	55%/8%	75%/3%

NEJ026 Adverse events

30% discontinued Bev for AE's 15% Erlotinib*

	All grades		Grade ≧3	
	BE (n=112)	E (n=114)	BE (n=112)	E (n=114)
Rash	98 (87.5%)	99 (86.8%)	23 (20.5%)	24 (21.1%)
Diarrhea	53 (47.3%)	47 (41.2%)	6 (5.4%)	2 (1.8%)
Hypertension	51 (45.5%)**	10 (8.8%)	25 (22.3%)**	0 (0%)
Proteinuria	36 (32.1%)**	3 (2.6%)	8 (7.1%)*	0 (0%)
Hepatic dysfunction	30 (26.8%)	34 (29.8%)	9 (8.0%)	6 (5.3%)
Pulmonary hemorrhage (PH)	2 (1.8%)	0 (0%)	0 (0%)	0 (0%)
Hemorrhage (PH excluded)	28 (25.0%)**	3 (2.6%)	2 (1.8%)	1 (0.9%)
Thrombosis	2 (1.8%)	6 (5.3%)	1 (0.9%)	1 (0.9%)
Interstitial lung disease (ILD)	0 (0%)	5 (4.4%)	0 (0%)	0 (0%)

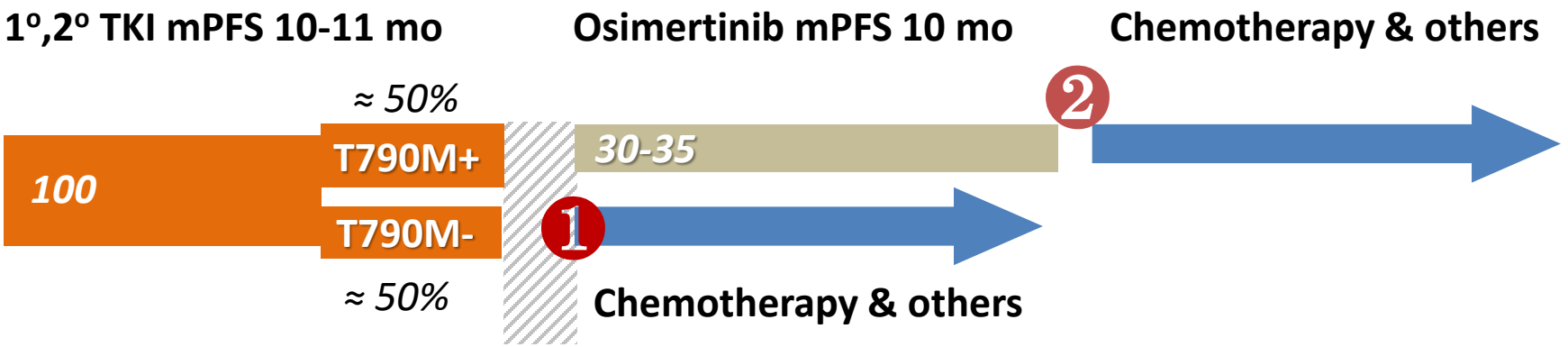
. Median treatment duration: Bev 350 (21-736) days; Erlotinib 405 (5 – 807) days

. ≥ Grade 3 AES: BE 56.3%; E 37.7%.

* FLAURA Osimertinib 13% ARCHER Dacomitinib 10%
FLAURA Erlo/Gef 18% ARCHER Gefitinib 7%

Sequencing of EGFR-TKIs: What Strategy Is Best?

FLAURA	N:277	**19.8%**
REMEDY	N:243 [49]	**23.7%**



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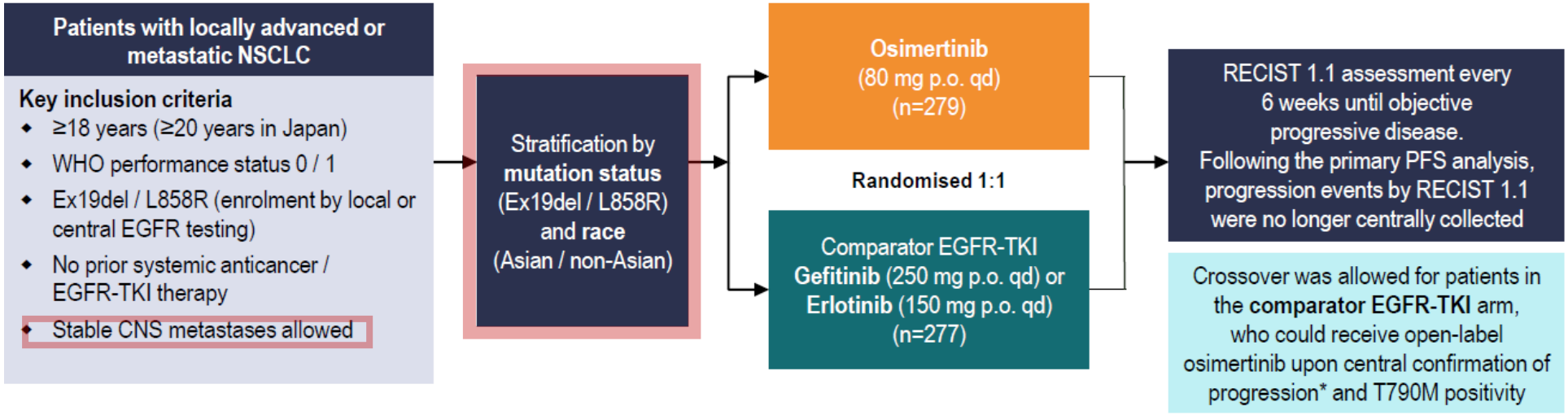
OSIMERTINIB VS COMPARATOR EGFR-TKI AS FIRST-LINE TREATMENT FOR EGFRm ADVANCED NSCLC (FLAURA): FINAL OVERALL SURVIVAL ANALYSIS

Suresh S Ramalingam[1], Jhanelle E Gray[2], Yuichiro Ohe[3], Byoung Chul Cho[4], Johan Vansteenkiste[5], Caicun Zhou[6], Thanyanan Reungwetwattana[7], Ying Cheng[8], Busayamas Chewaskulyong[9], Riyaz Shah[10], Ki Hyeong Lee[11], Parneet Cheema[12], Marcello Tiseo[13], Thomas John[14], Meng-Chih Lin[15], Fumio Imamura[16], Rachel Hodge[17], Yuri Rukazenkov[17], Jean-Charles Soria[18,19], David Planchard[19]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [3]Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; [4]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]University Hospital KU Leuven, Leuven, Belgium; [6]Pulmonary Hospital of Tongji University, Shanghai, China; [7]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [8]Jilin Provincial Cancer Hospital, Changchun, China; [9]Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; [10]Kent Oncology Centre, Maidstone Hospital, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK; [11]Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, Korea; [12]William Osler Health System, University of Toronto, Toronto, ON, Canada; [13]Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [14]Department of Medical Oncology, Austin Health, Melbourne, Australia; [15]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [16]Department of Thoracic Oncology, Osaka International Cancer Institute, Chuo-ku, Osaka, Japan; [17]Global Medicines Development, AstraZeneca, Cambridge, UK; [18]Early Oncology Research & Development, AstraZeneca, Gaithersburg, Maryland / Université Paris-Sud, Orsay, France; [19]Department of Medical Oncology, Gustave Roussy, Villejuif, France

FLAURA DOUBLE-BLIND STUDY DESIGN



OS was a key secondary endpoint

- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment

Data cut-off: 25 June 2019

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

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

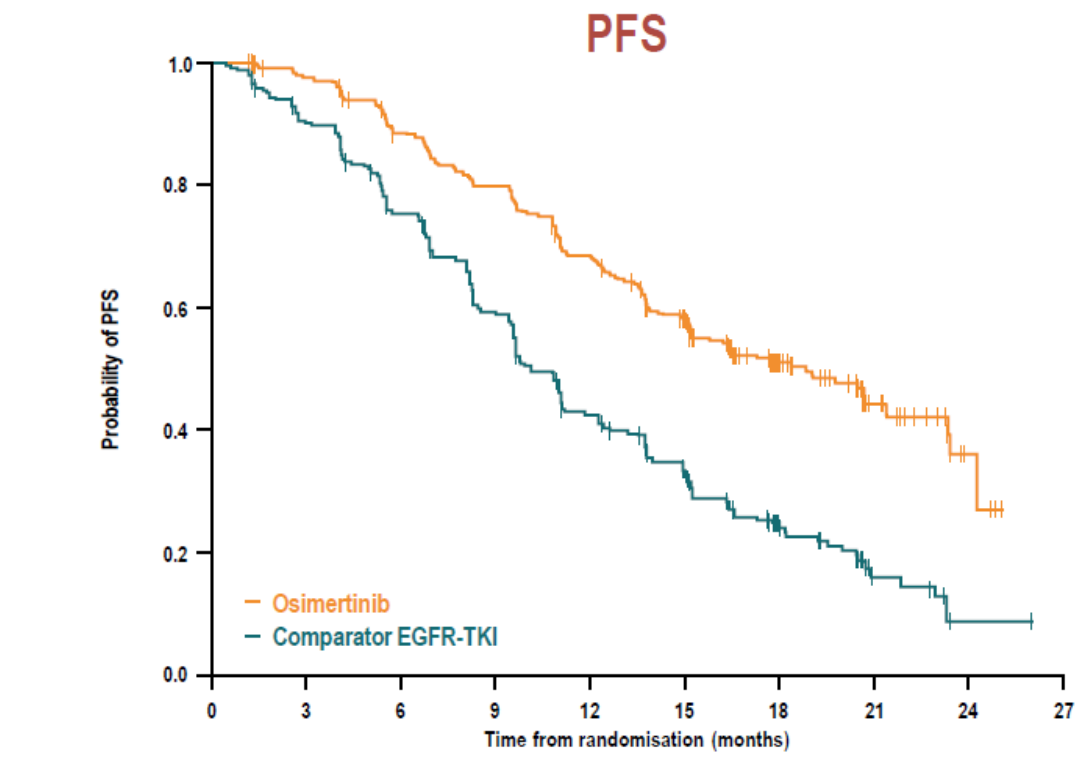
p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

BASELINE CHARACTERISTICS

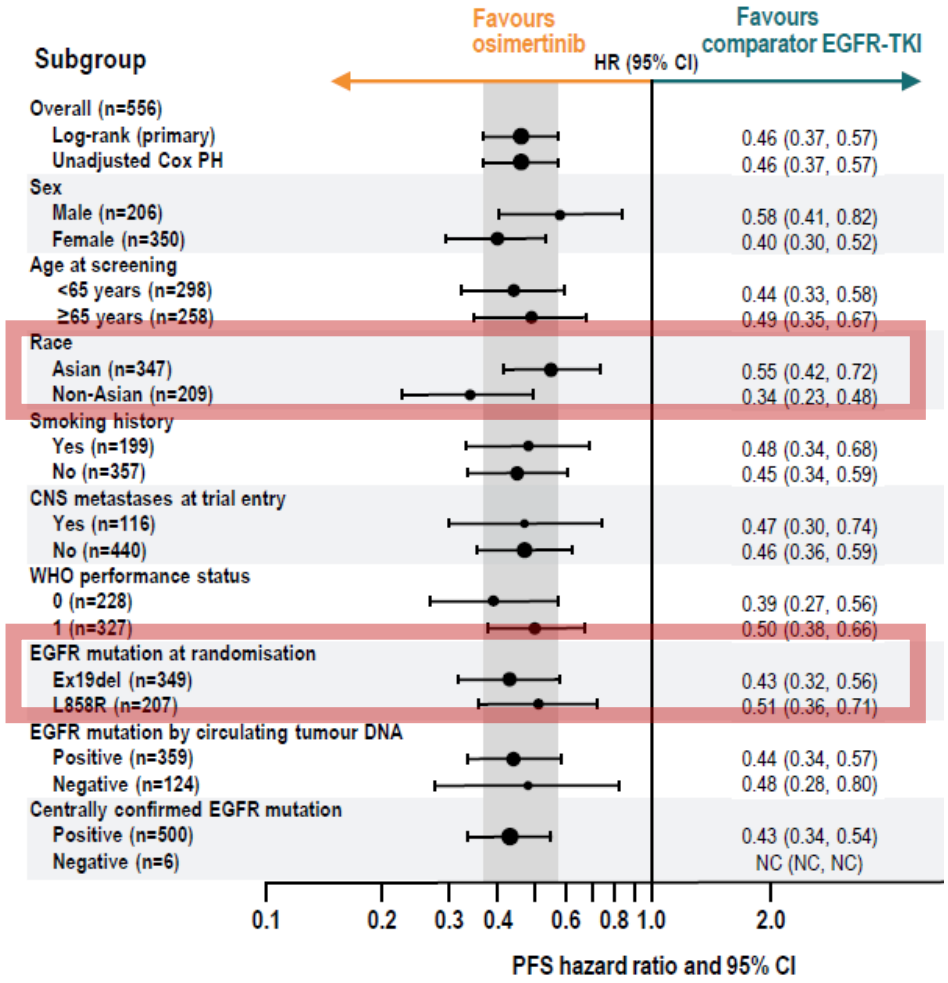
Characteristic, %	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Sex: male / female	36 / 64	38 / 62
Age, median (range), years	64 (26–85)	64 (35–93)
Race: Asian / non-Asian	62 / 38	62 / 38
Smoking status: never / ever	65 / 35	63 / 37
CNS metastases at study entry	19	23
WHO performance status: 0 / 1	40 / 60	42 / 58
Overall disease classification: metastatic / advanced	95 / 5	95 / 5
Histology: adenocarcinoma / other	99 / 1	98 / 2
EGFR mutation at randomisation: Ex19del / L858R	63 / 37	63 / 37

Data cut-off: 12 June 2017
Soria et al. N Engl J Med 2018;378:113-25

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



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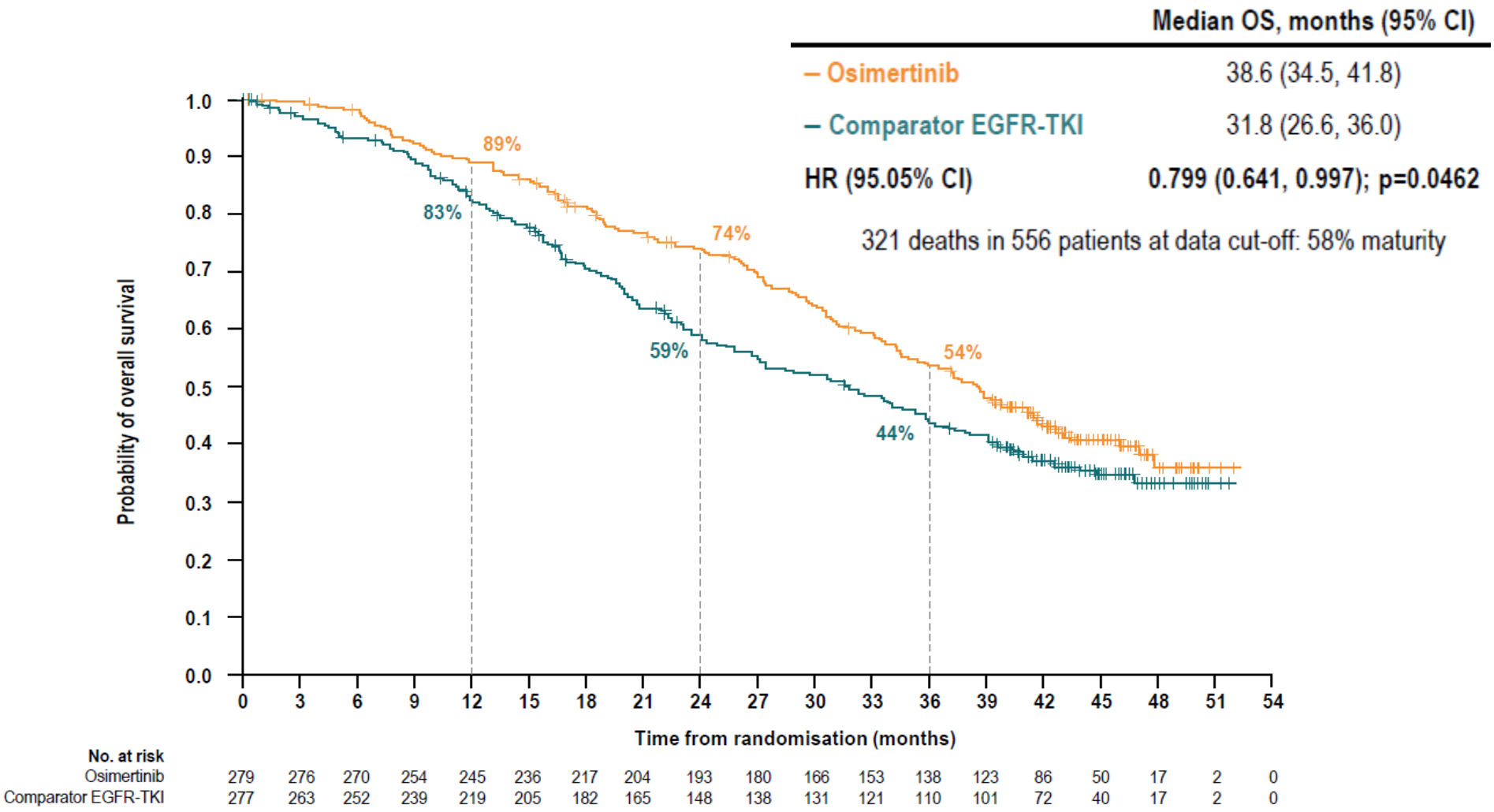
Data cut-off: 12 June 2017

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

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

FINAL ANALYSIS: OVERALL SURVIVAL



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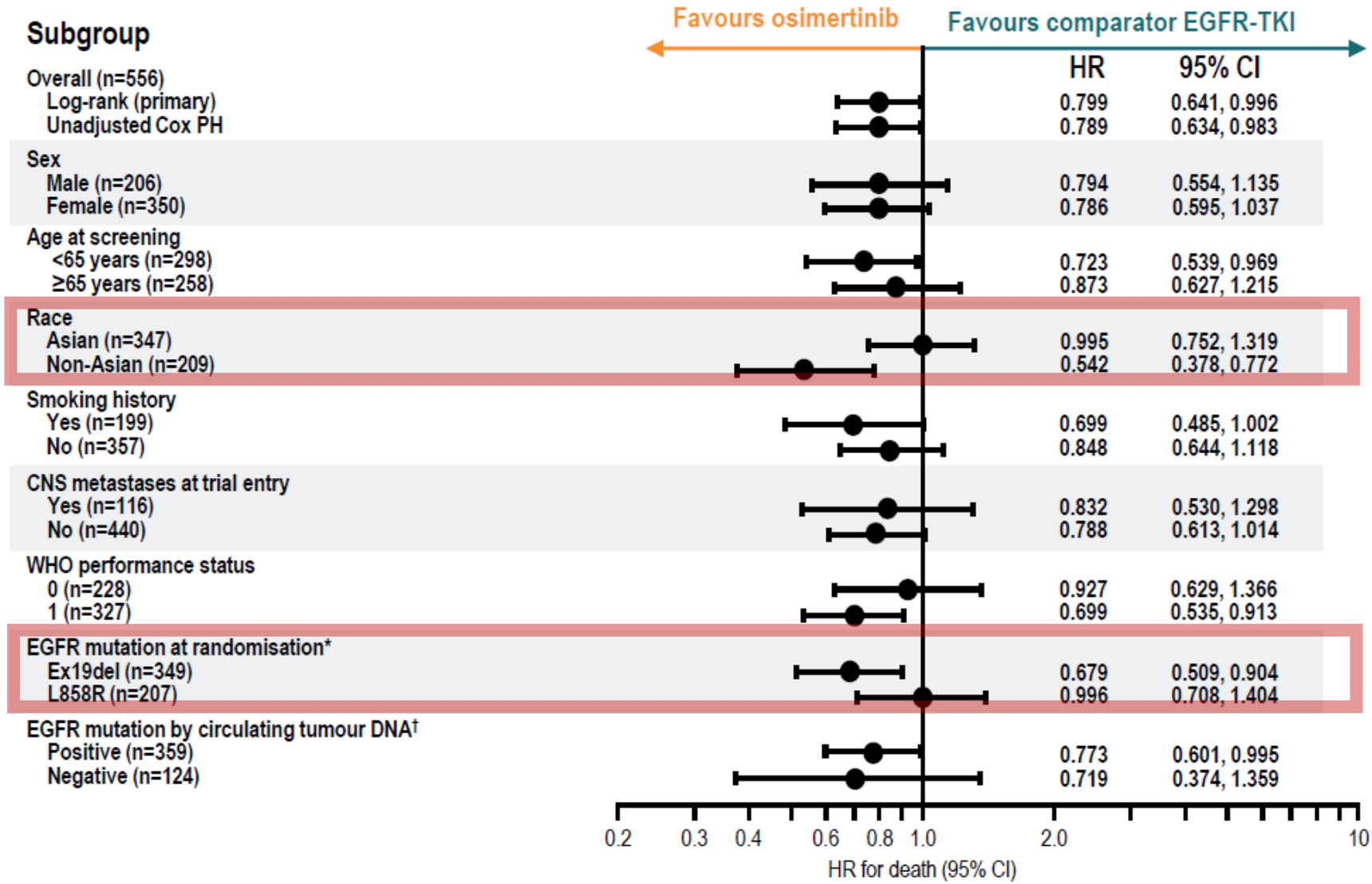
Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

OVERALL SURVIVAL ACROSS SUBGROUPS



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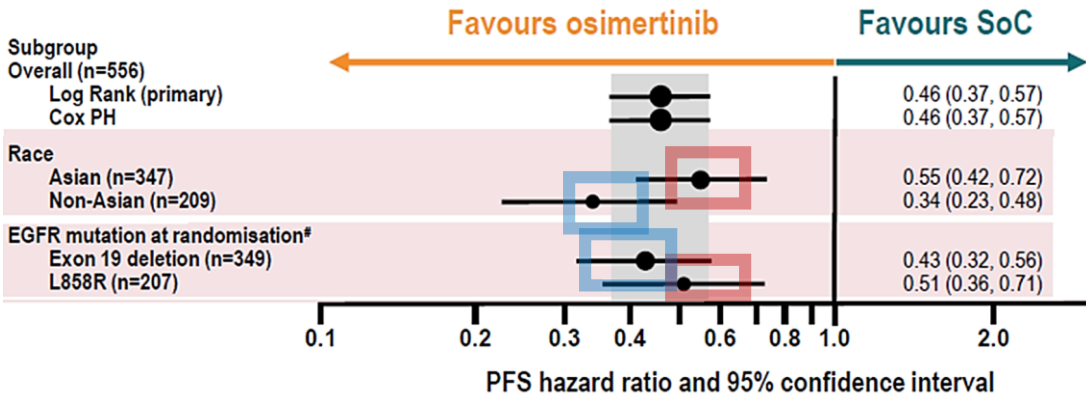
Data cut-off: 25 June 2019

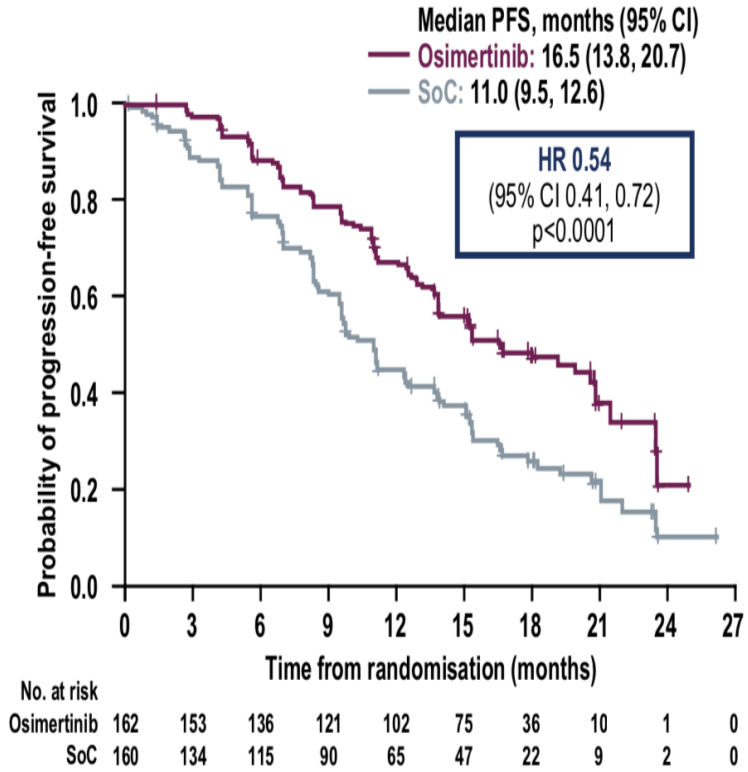
Hazard ratio <1 implies a lower risk of death on osimertinib

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

PFS by race

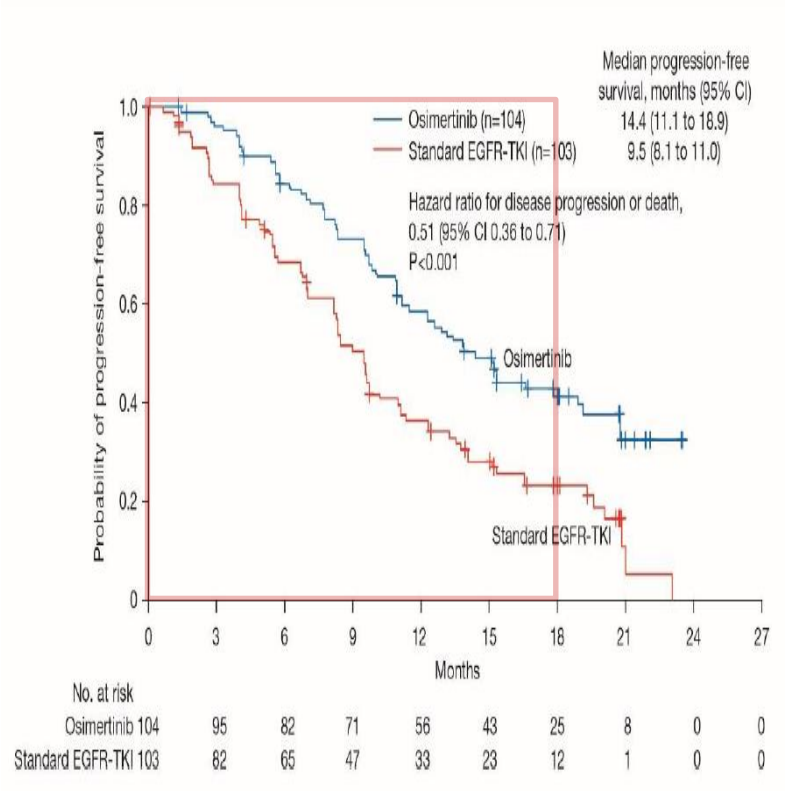


Asian patients

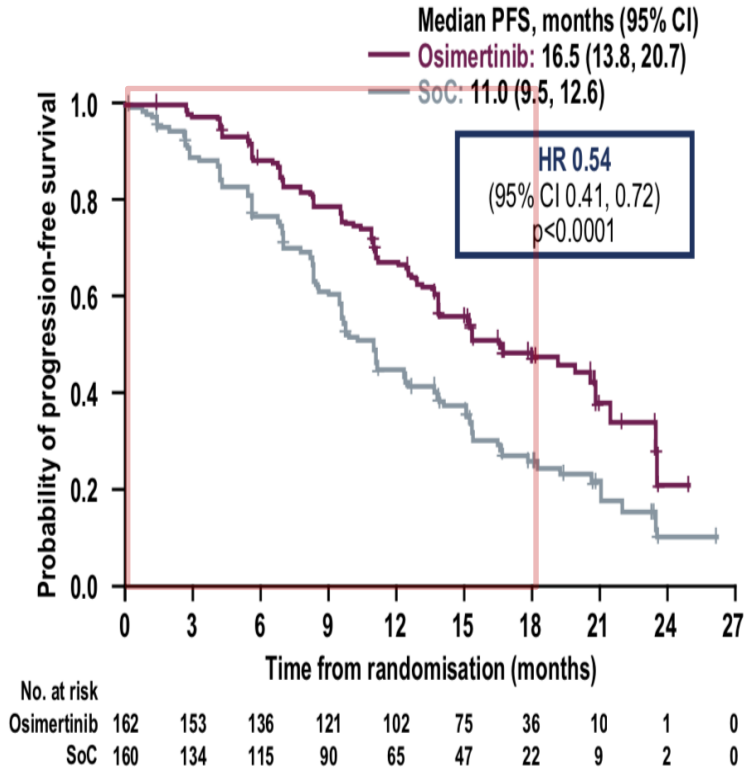


PFS: L858R vs. Asian subgroup

L858R

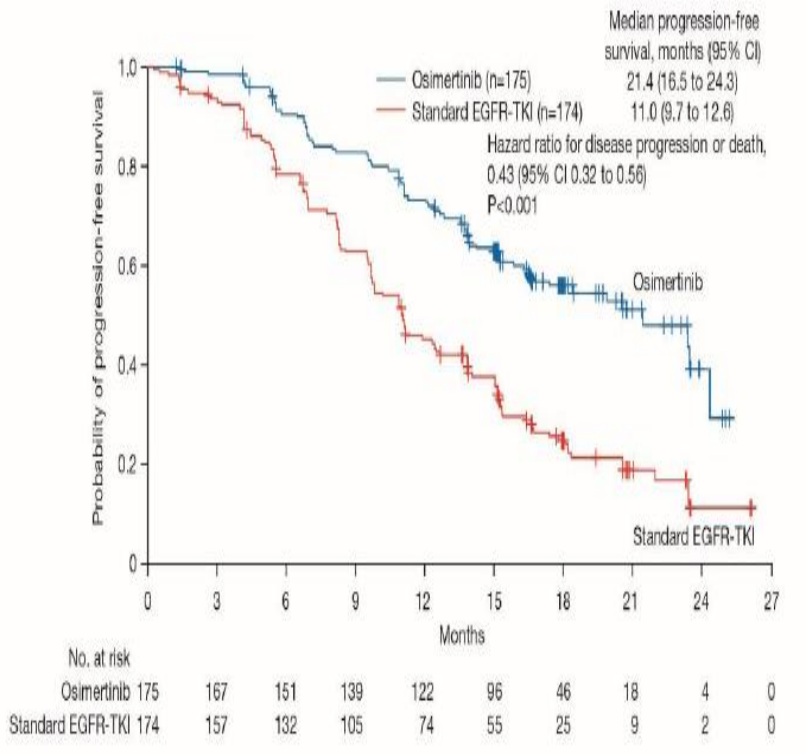


Asian patients

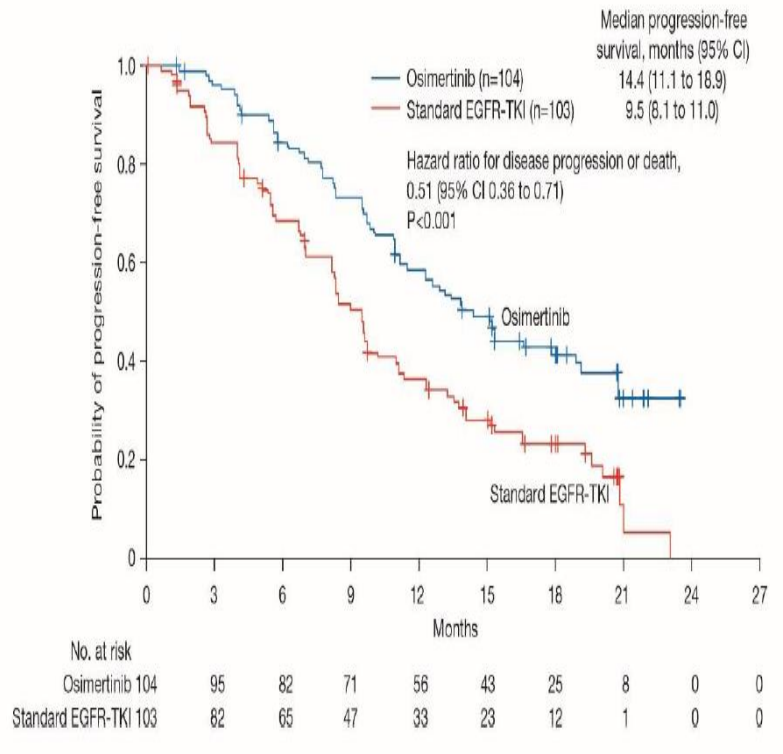


PFS by EGFR mutation

Exon 19 deletion

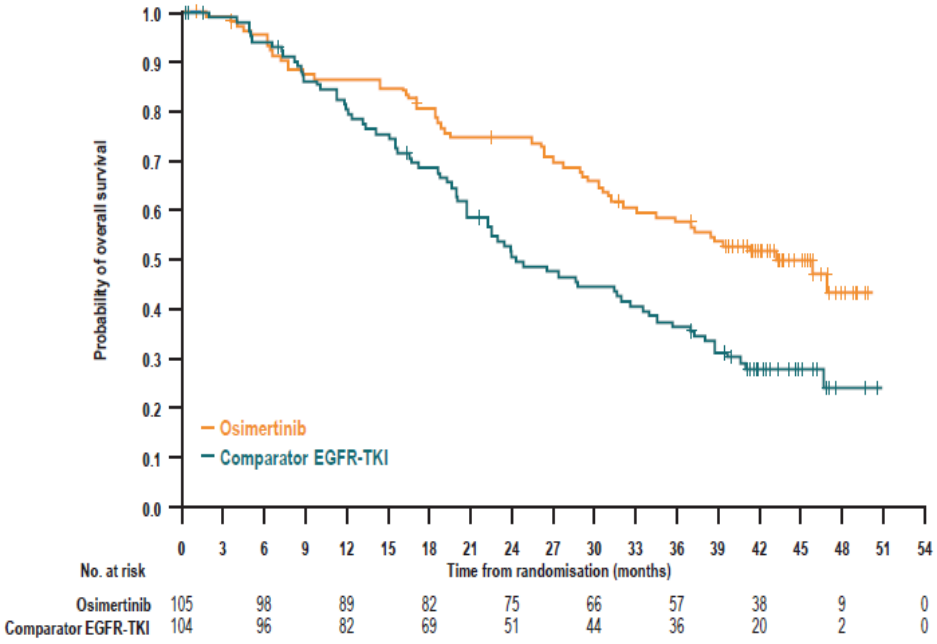


L858R

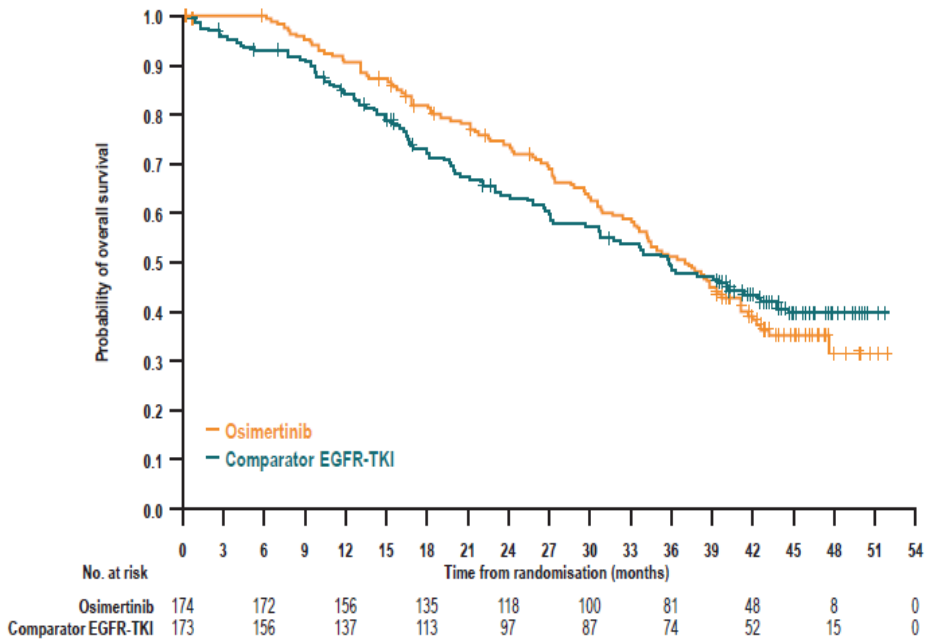


OS by race

Non-Asian patients



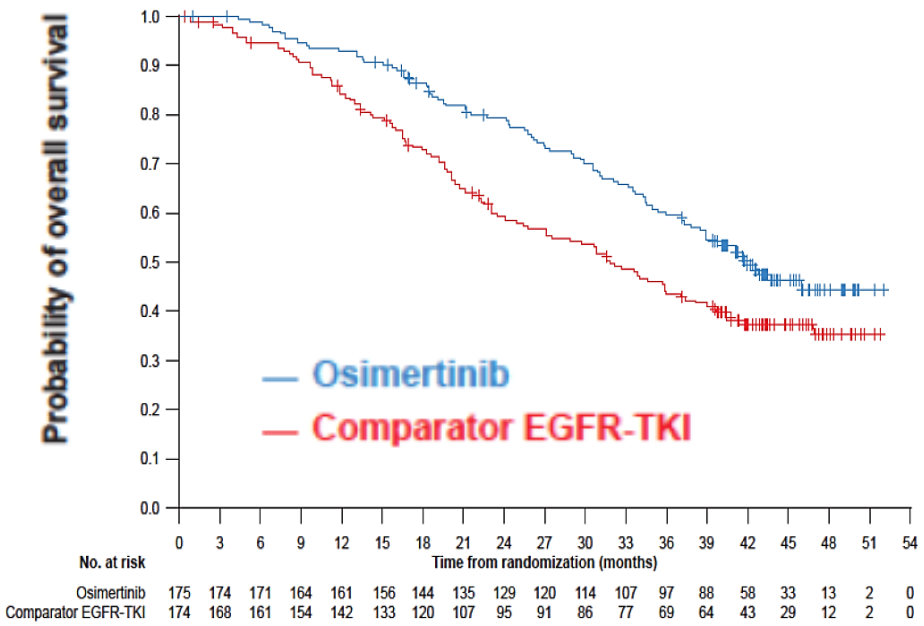
Asian patients



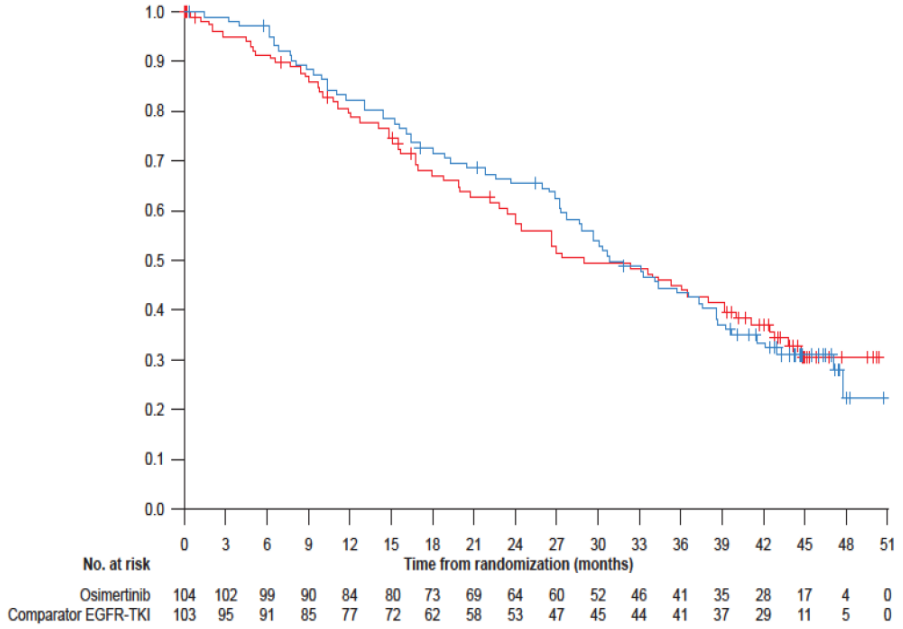
Data cut-off: 25 June 2019

OS by EGFR mutation

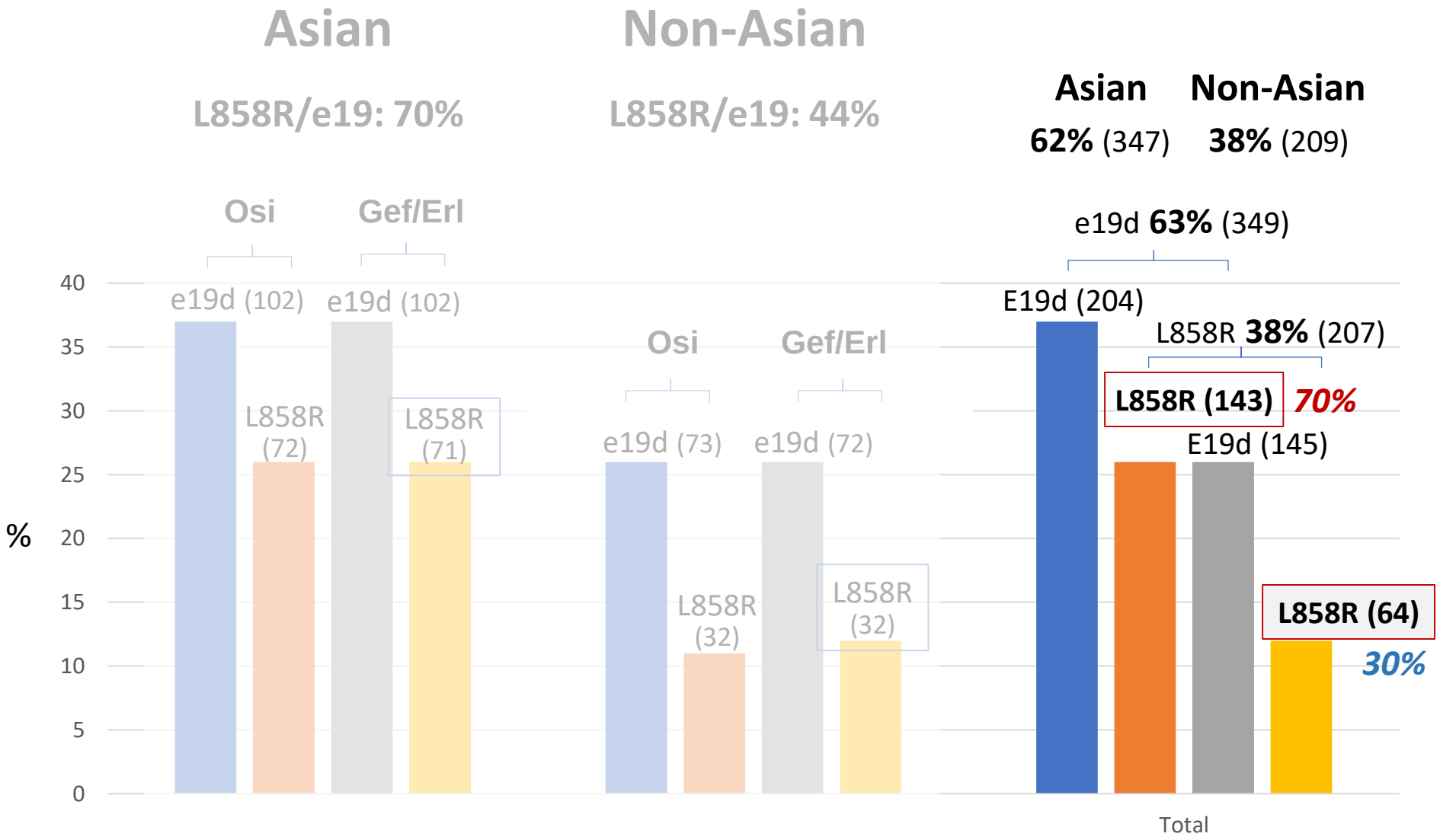
Exon 19 deletion



L858R



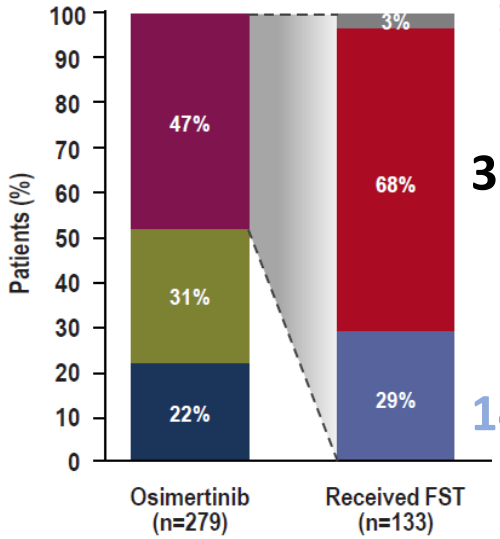
EGFR mutation subtype by race



SECOND-LINE TREATMENT FOLLOWING PROGRESSION

- Of the 180 patients in the comparator EGFR-TKI arm who received a first subsequent treatment, **85 patients (47%) crossed over to osimertinib** (31% of all patients randomised from the comparator EGFR-TKI arm)

Osimertinib



1%

32% [90/**84**]

14%

Patient disposition

Received first subsequent (second-line) anticancer treatment

No subsequent anti-cancer treatment

Still on study treatment

First subsequent (second-line) anticancer therapies

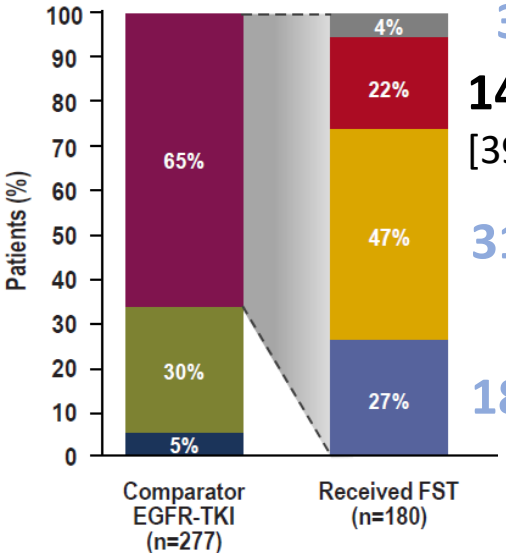
Other*

Cytotoxic chemotherapy†

Osimertinib

EGFR-TKI containing regimen, other than osimertinib

Gef/erlo



3%

14% [39/**36**]

31% [85] [T790M]

18%

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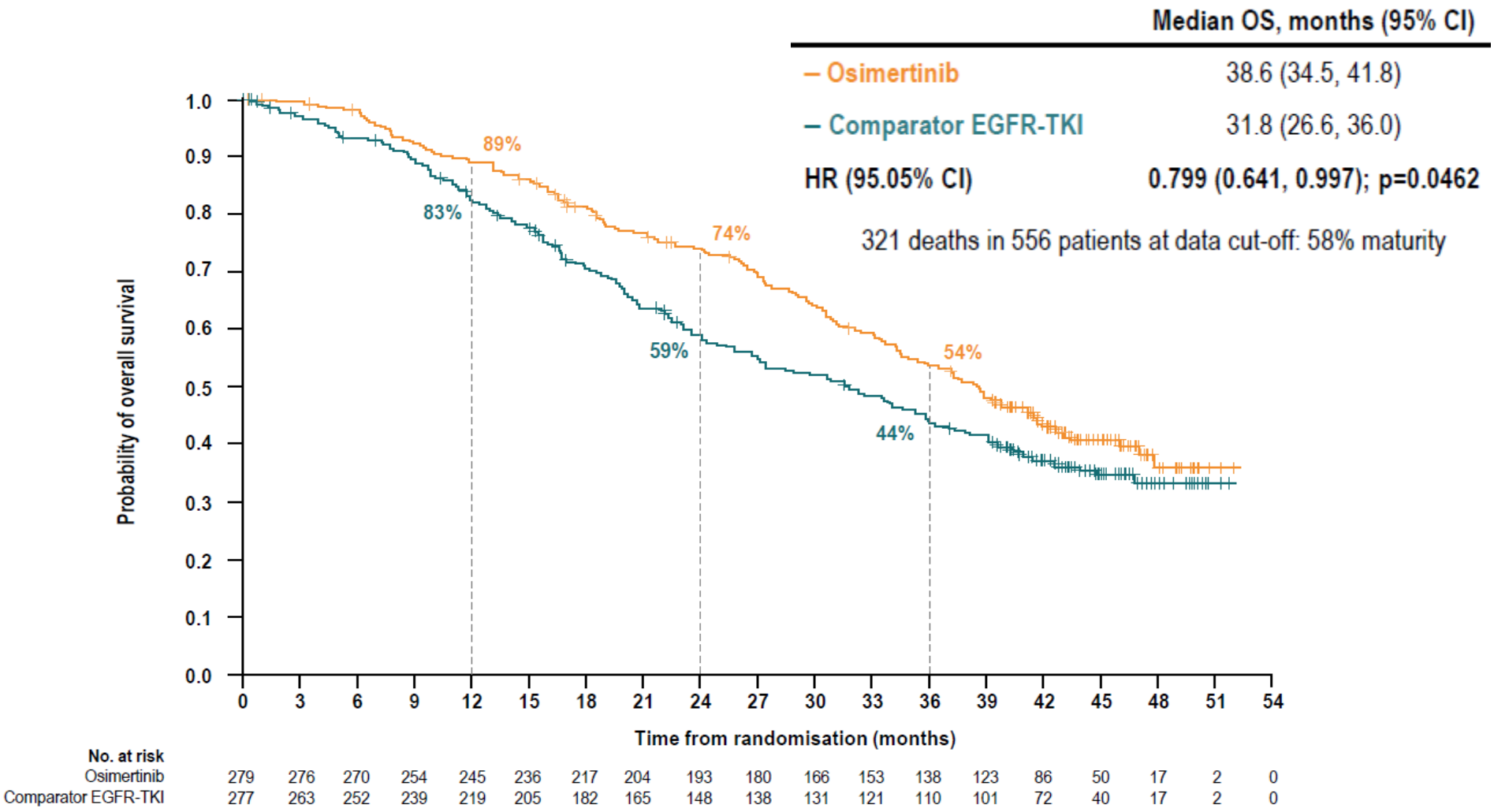
Data cut-off: 25 June 2019

*Refers to those patients who did not receive either chemotherapy or an EGFR-TKI; †The majority of patients who received cytotoxic chemotherapy received a platinum-based chemotherapy regimen
FST, first subsequent treatment

First and second subsequent therapies

Subsequent therapy	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Number of patients		
First subsequent therapies		
Received a first subsequent therapy	133	180
Cytotoxic chemotherapy	90 (32%)	39 (14%)
Platinum-containing chemotherapy	84 (30%)	36 (13%)
EGFR-TKI†	38	49
Other TKI‡	2	3
Osimertinib	1	85 (31%)
Immunotherapy	4	4
VEGF inhibitor§	10	4
Other¶	2	2
Second subsequent therapies		
Received a second subsequent therapy	72	92
Cytotoxic chemotherapy	38 (14%)	56 (20%)
Platinum-containing chemotherapy	15 (5%)	42 (15%)
EGFR-TKI‖	25	25
Immunotherapy	6	5
VEGF inhibitor**	11	11
Other	2	6

FINAL ANALYSIS: OVERALL SURVIVAL



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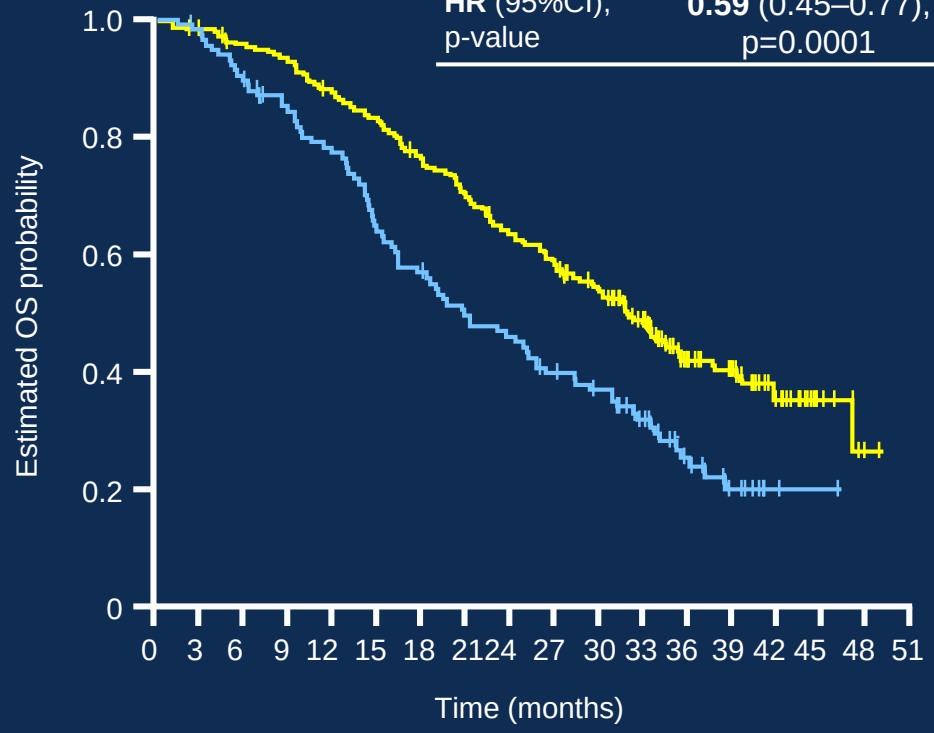
Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

Combined OS analysis: mutation categories

Del19

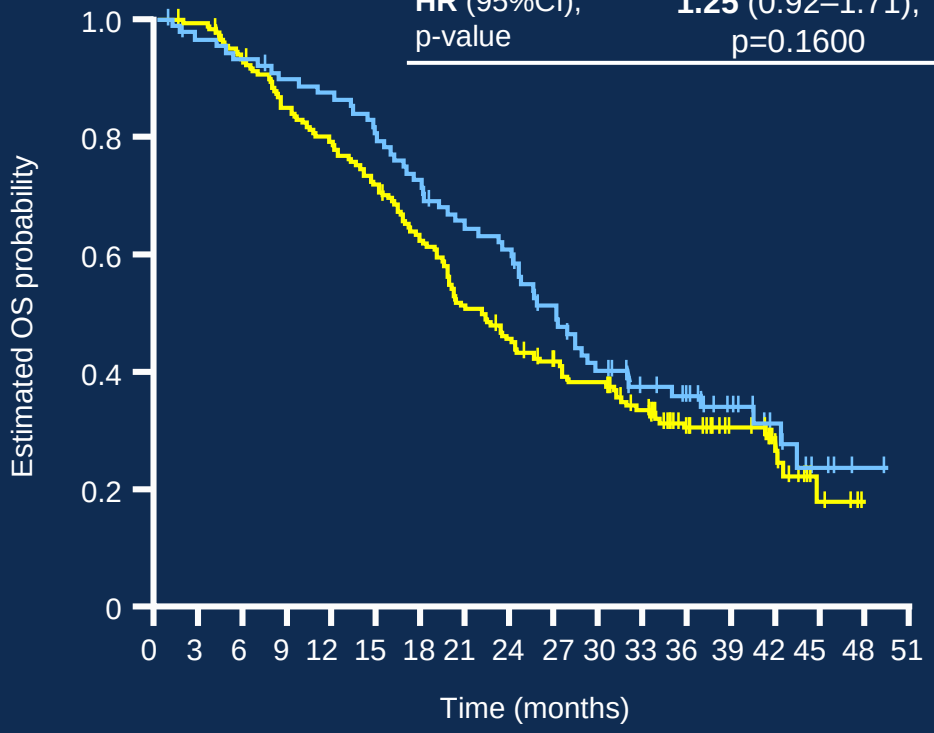
	Afatinib n=236	Chemo n=119
Median, mo	**31.7**	**20.7**
HR (95%CI), p-value	**0.59** (0.45–0.77), p=0.0001	



No of patients																		
Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0

L858R

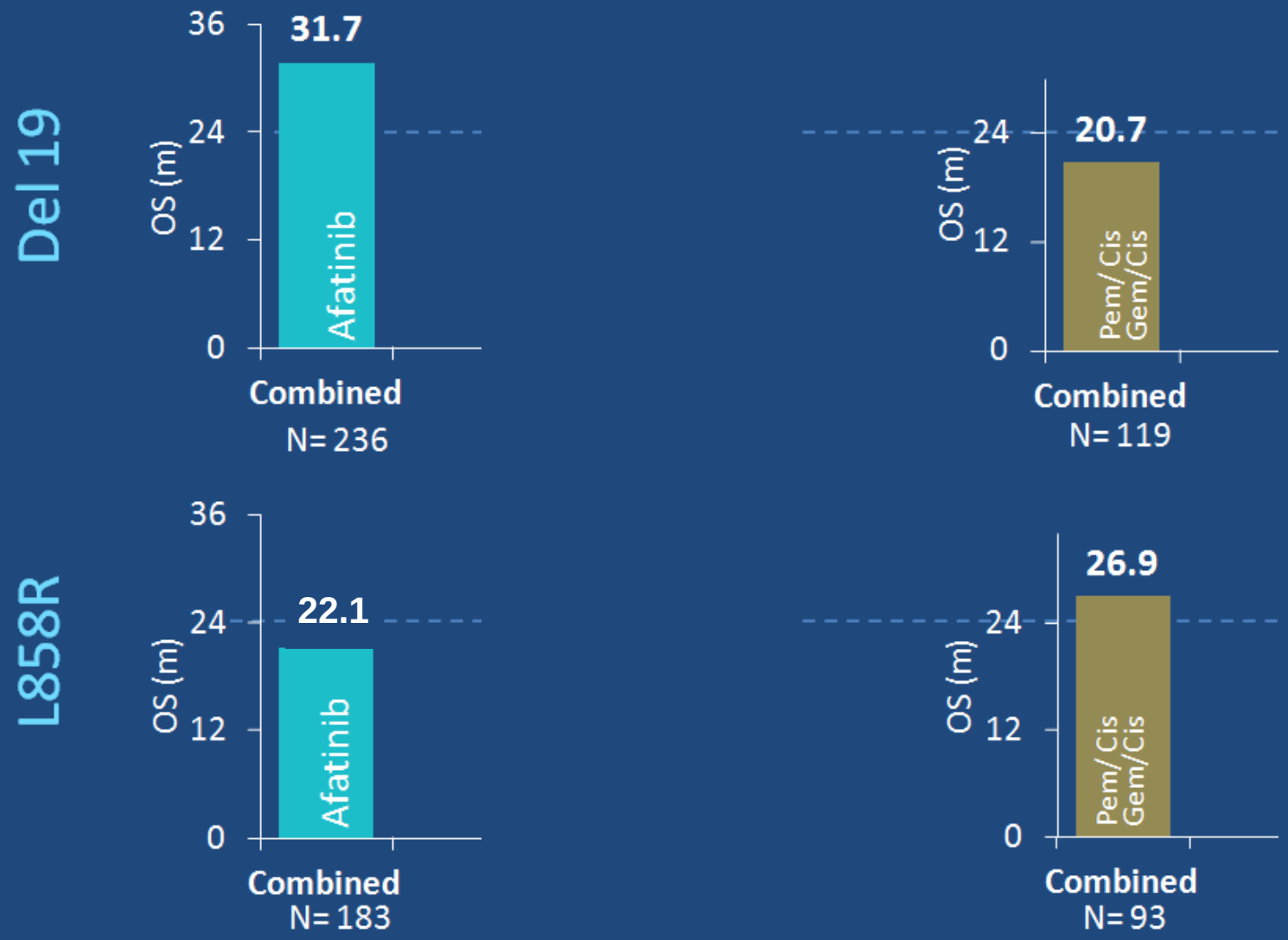
	Afatinib n=183	Chemo n=93
Median, mo	**22.1**	**26.9**
HR (95%CI), p-value	**1.25** (0.92–1.71), p=0.1600	



No of patients																		
Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

OS of Afatinib and Chemotherapies by Site of Mutation

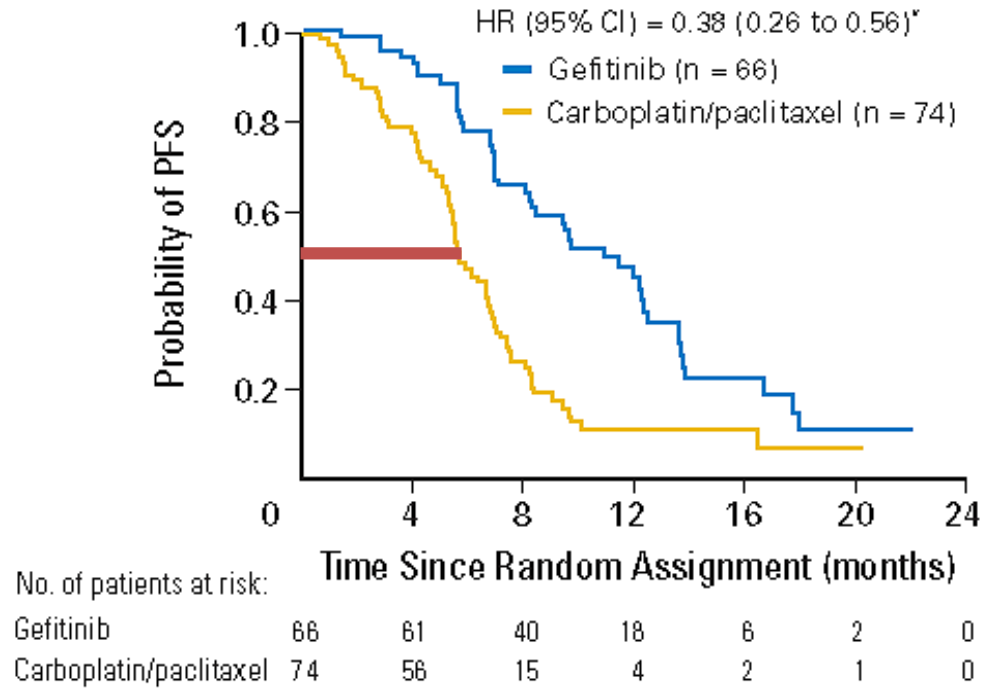
Lux-lung 3+6



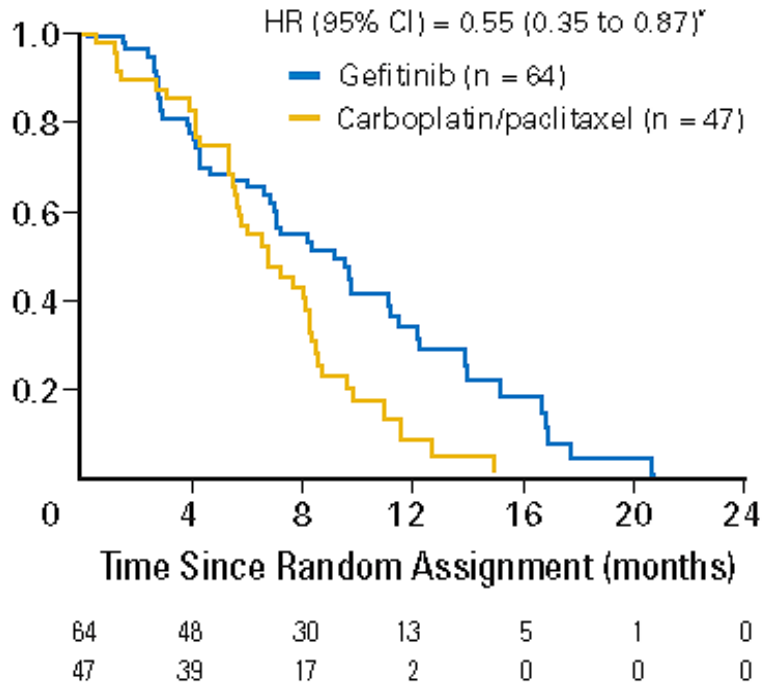
IPASS: PFS by *EGFR* mutation type

Fukuoka M. et al. JCO 2011

Exon 19 deletion



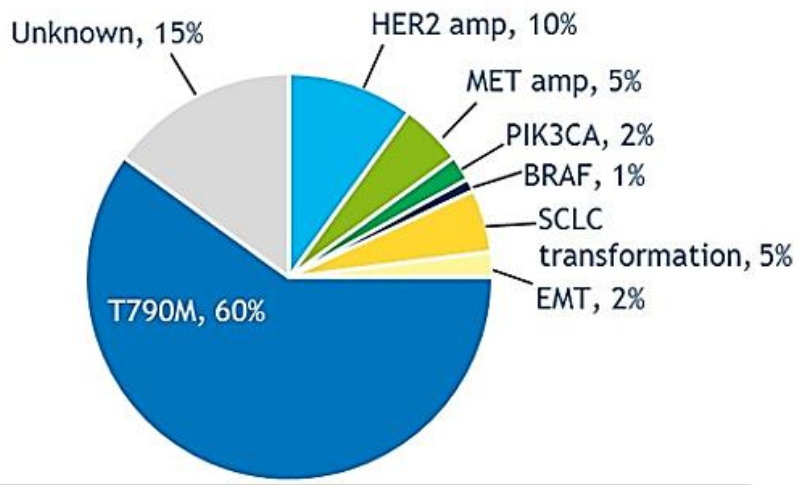
L858R



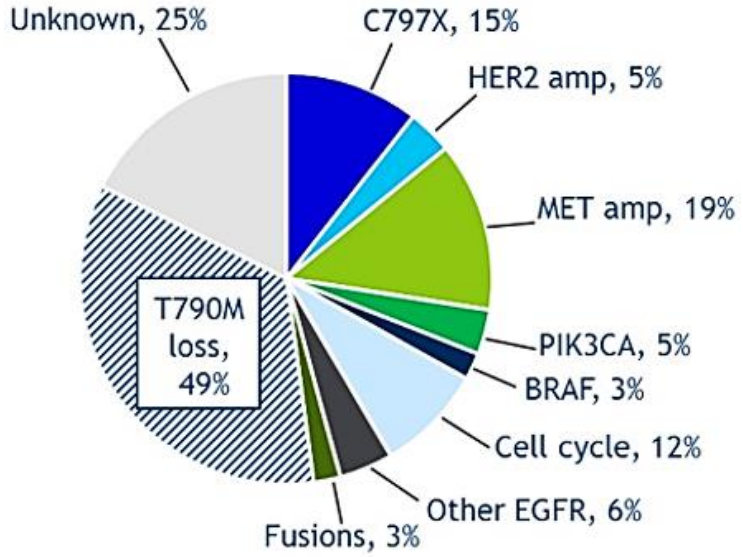
	Exon 19				L858R			
	ORR	OR	95% CI	P	ORR	OR	95% CI	P
Pac/Carbo	43.2%	7.23	3.19-16.37	< .05	53.2%	1.41	0.65-3.05	NS
Gefitinib	84.8%				60.9%			

Mechanisms of resistance to EGFR TKIs in EGFR-mutant NSCLC

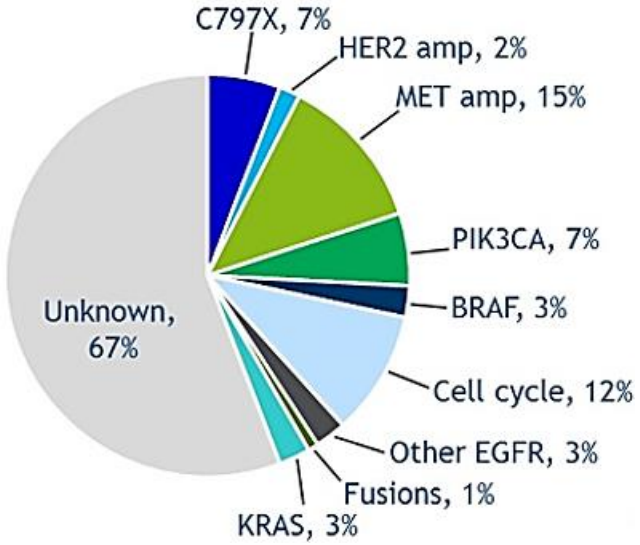
1st line gefitinib, erlotinib, afatinib

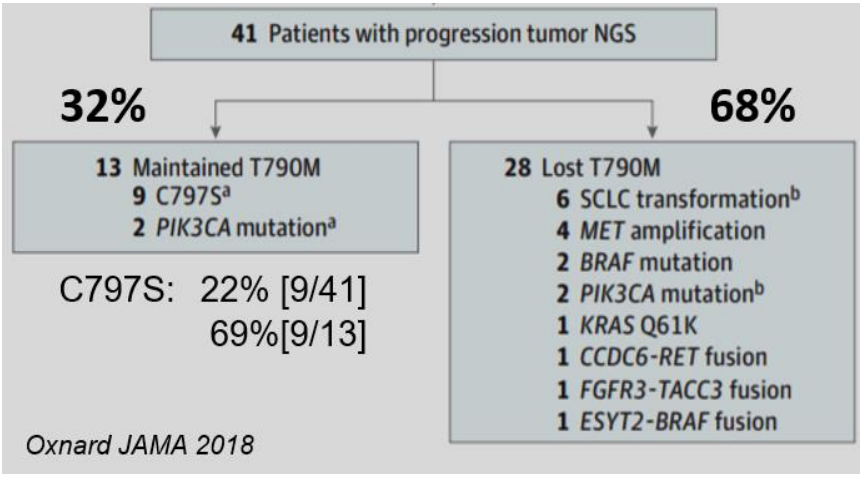


2nd line osimertinib



1st line osimertinib





Comparing osimertinib resistance:
after 1st line vs after subsequent lines

	FLAURA	AURA3	Le *et al.* *CCR 2018*	Piotrowska *et al.* Cancer disc 2018
N	91	83	42	41
T790M loss (%)	NA	49	50	63
Acquired changes (%)				
EGFR mut	9	21	26	24
C797X	7	15 *all in cis with T790M		20
MET amp	15	19	15	19
HER2 amp	2	5	2	5
PIK3CA mut	7	1	5	12
BRAF mut	3	3		
KRAS mut	3		2	
Fusions	1	3	5	10
SCLC/SqCC			5	7
Other	60	52	40	23

Adapted from Charles Rudin, ESMO 2018

1. N Engl J Med 2018; 378:113-125 **2.** N Engl J Med 2017; 376:629-640.**3.** Clin Cancer Res. 2018 Dec 15;24(24):6195-6203.
4. Cancer Discov. 2018 Dec;8(12):1529-1539

② Treatment options for acquired osimertinib resistance

Local therapy for oligometastatic disease

Double dose with 160mg QD [limited data]

Add bevacizumab to osimertinib [limited data]

Target possible targetable Pathway

tissue and/or liquid biopsy for NGS

Clinical trial

Chemotherapy and continuation maintenance

Platinum/pemetrexed

Carboplatin/paclitaxel/bevacizumab

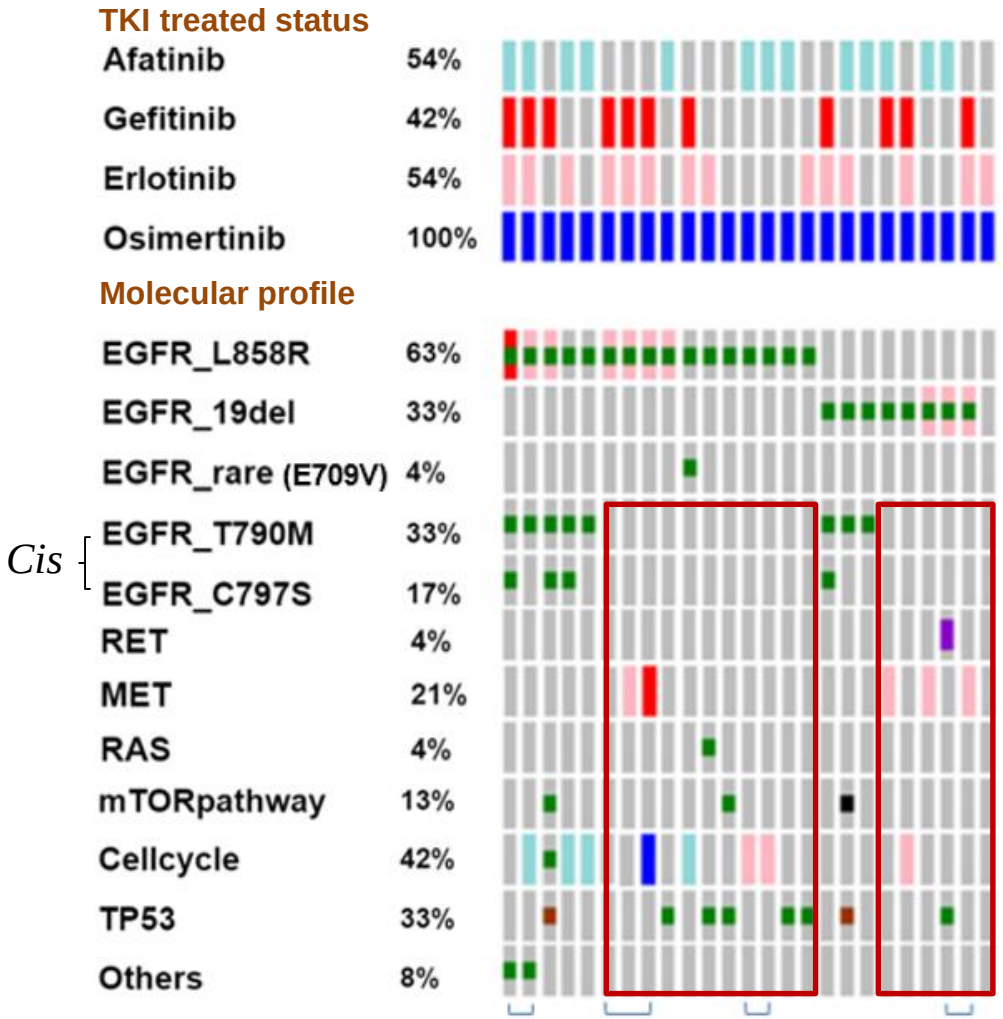
(+/-) Immunotherapy

Second line chemotherapy +/- bevacizumab or ramucizumab

TKI (1-3^{o}) retreatment ⇒ add chemo [single agent, no pt]

Tissue with osimertinib treatment

Total cases: 25 (20)



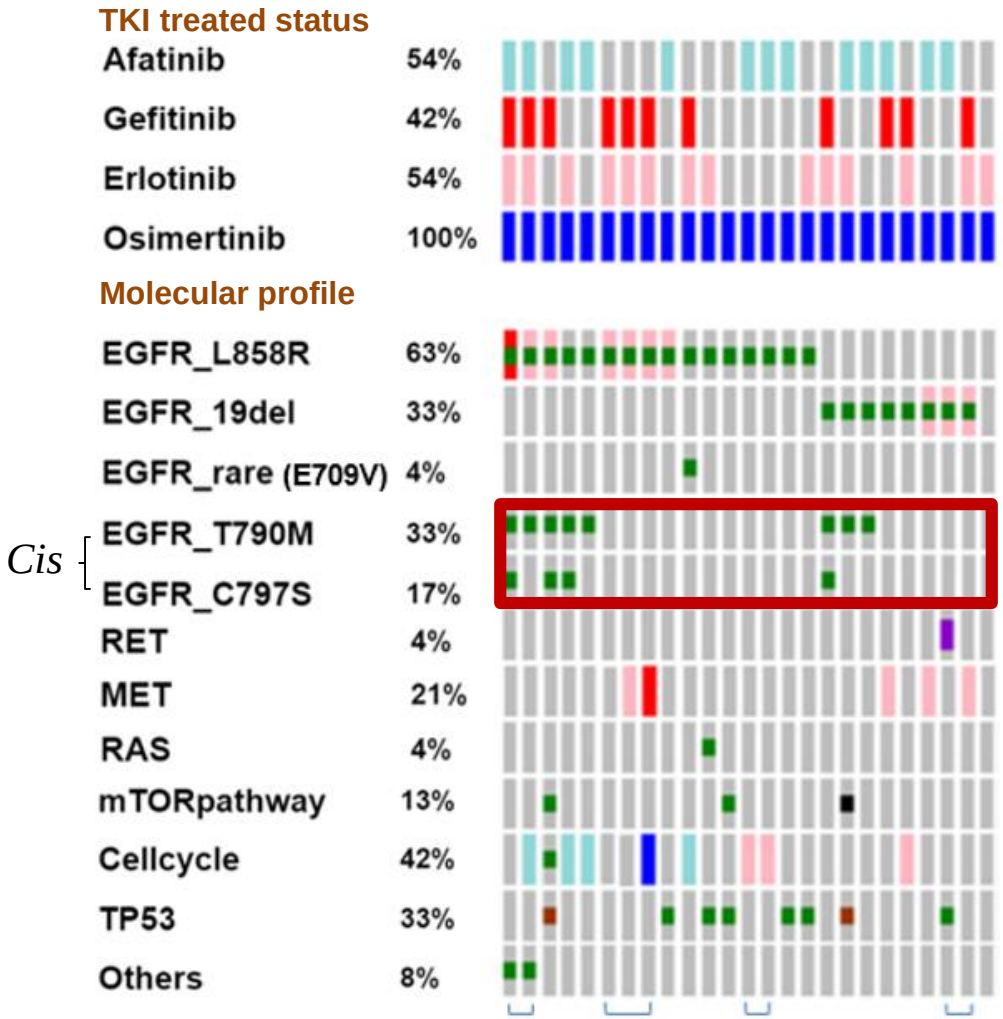
Potential treatment strategy:

1. EGFR C797S, n=4 (**brigartinib+cetucimab**)
2. MET amp, n=5 (4):
   combine with MET inhibitor
   (**crizotinib, savolitinib, cabozantinib,** capmatinib,, etc.)
3. RET fusion, n=1 (0):
   combine with RET inhibitor
   (BLU-667, LOXO-292, RXDX-105, etc.)
4. mTOR pathway, n=3 (0):
   combine with mTOR inhibitor
   (everolimus, temsirolimus, vistusertib, etc.)
5. Cell cycle, n=10 (0):
   combine with CDK4/6 inhibitor
   (palbociclib, ribociclib, abemaciclib, etc.)

mTOR pathway: PIK3CA, PTEN
Cell cycle: CDK4, CCND1, CDKN2A, CDKN2B
Others: CTNNB1, POLE

Tissue with osimertinib treatment

Total cases: 25 (20)



Potential treatment strategy:

1. EGFR C797S, n=4 (**brigartinib+cetucimab**)
2. MET amp, n=5 (4):
   combine with MET inhibitor
   (**crizotinib, savolitinib, cabozantinib,** capmatinib,, etc.)
3. RET fusion, n=1 (0):
   combine with RET inhibitor
   (BLU-667, LOXO-292, RXDX-105, etc.)
4. mTOR pathway, n=3 (0):
   combine with mTOR inhibitor
   (everolimus, temsirolimus, vistusertib, etc.)
5. Cell cycle, n=10 (0):
   combine with CDK4/6 inhibitor
   (palbociclib, ribociclib, abemaciclib, etc.)

mTOR pathway: PIK3CA, PTEN
Cell cycle: CDK4, CCND1, CDKN2A, CDKN2B
Others: CTNNB1, POLE

F/1956 Adenocarcinoma, with brain and multiple bone metastases. **EGFR e19d**

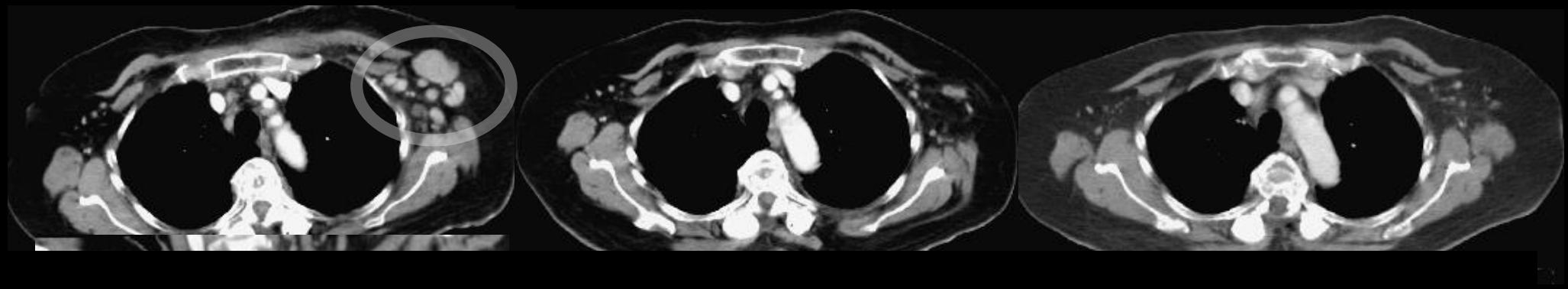
2013/09 – 2015/06 Gefitinib **[T790M +]**
2015/07 – 08 Afatinib PD
2015/08 – 2017/06 Osimertinib
2017/06/13 Osimertinib/Savolitinib (AZD6094)

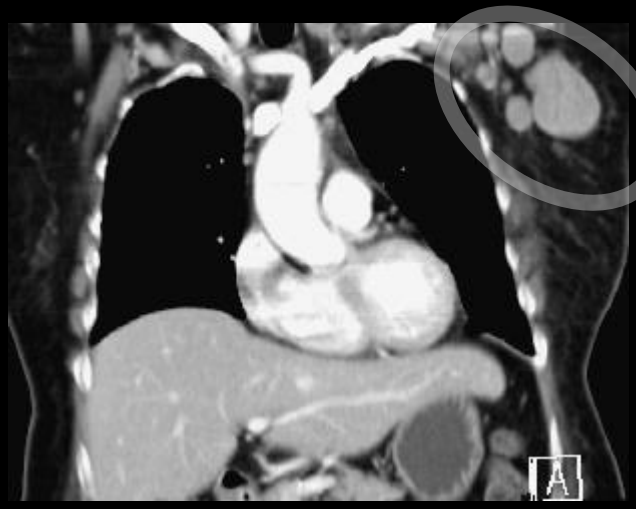
Single Nucleotide and Small Indel Variants

Gene	Amino acid change	Mutation frequency	Coverage	COSMIC ID
EGFR	p.E746_A750del	12.50%	3721	COSM6225

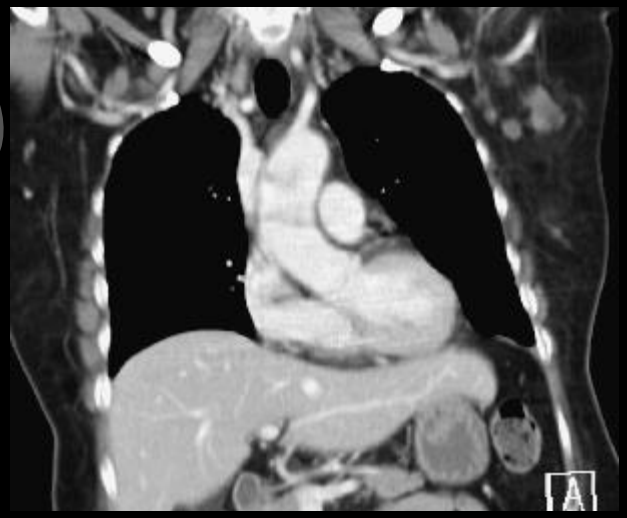
Amplification / Gain

Chr	Cytoband	Gene	Observed copy number
chr7	7q31.2	*MET*	3.5

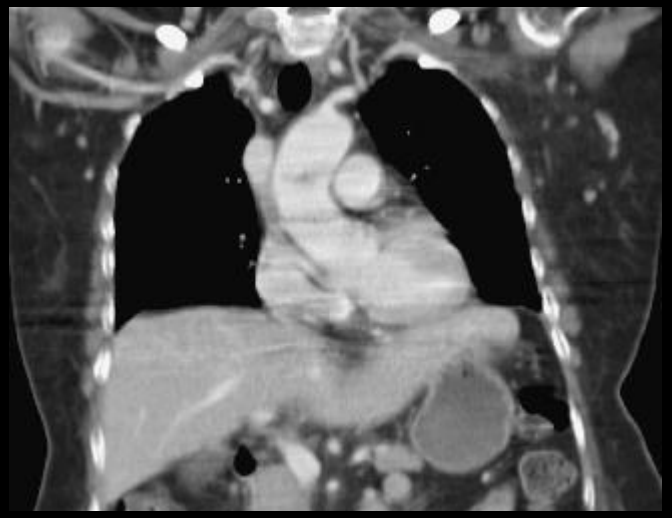




2017/06/06



2017/07/25



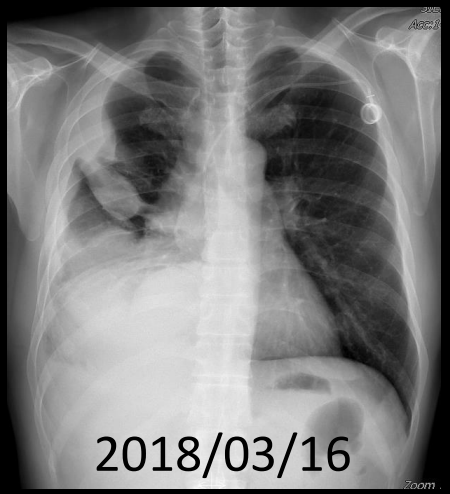
2017/10/16

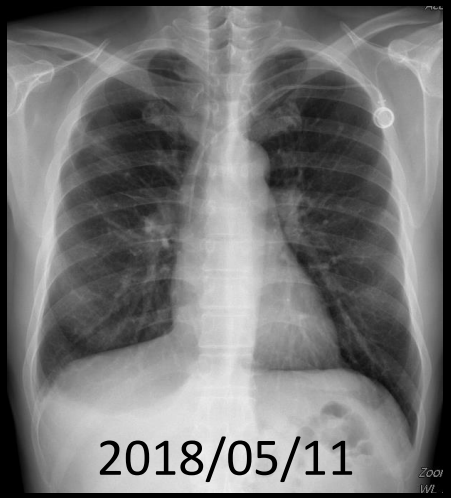
M/1966 Adenoca. Rt. Stage IV. EGFR e19d; PD-L1 0%

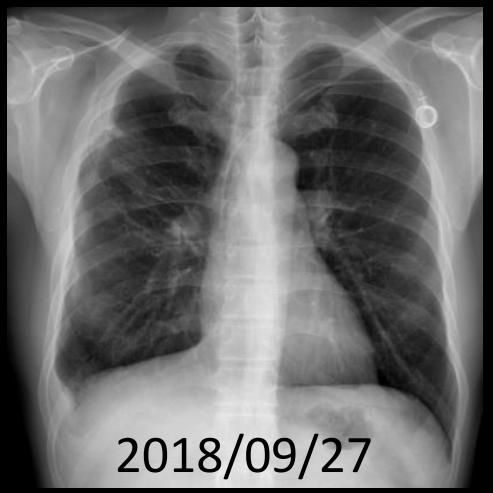
2018/03 – 11 Afatinib [8 mo]

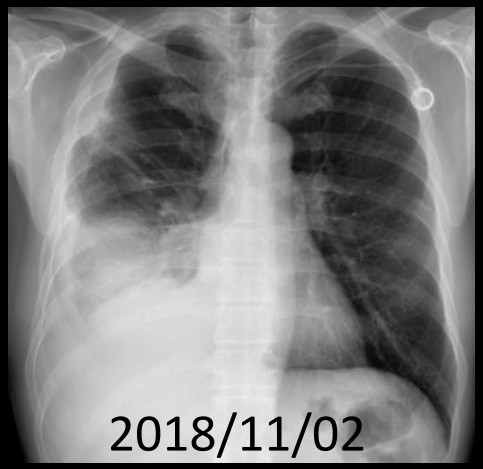
2018/11 – 12 Afatinib/bev [3] [2 mo]

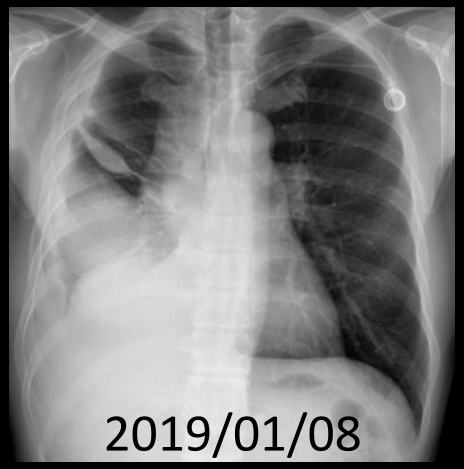
2019/01/04 C1: Pembro 100mg/pem 50mg/m2/cis 60mg/m2/bev 400mg [C5 2019/4/03]











Patient and Sample Information

Gender: Male	**Ordering Facility:** 中山醫學大學附設醫院
Date of Birth: May 01, 1966	**Ordering Physician:** 蔡俊明醫師
Diagnosis: Lung cancer	**Date Received:** Oct 09, 2018
Sample Type: FFPE	**Date Reported:** Oct 23, 2018
Collection Site: Lung	**Test:** ACTDrug® +

Variant(s) With Clinical Relevance

Single Nucleotide and Small Indel Variants

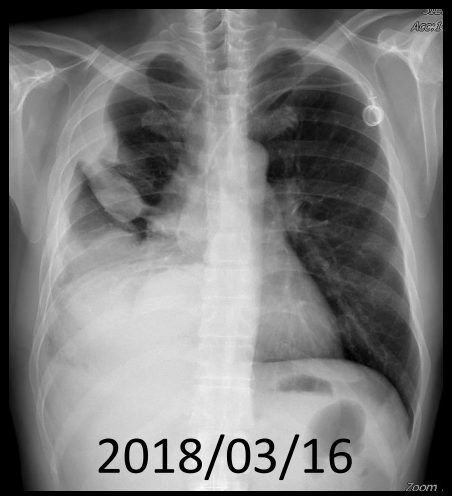
Gene	Amino Acid Change	Coverage	Allele Frequency
EGFR	E746_A750del (Exon 19 deletion)	2569	23.1%
TP53	R273H	994	15.2%

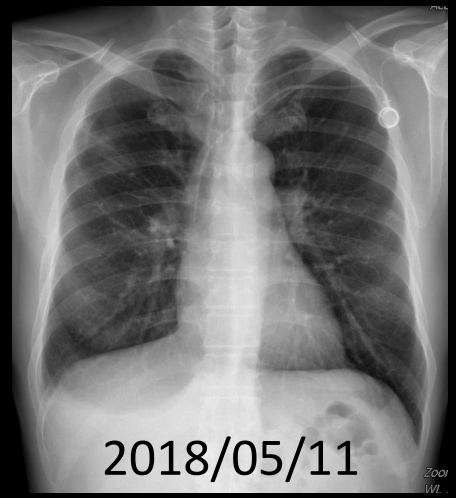
M/1966 Adenoca. Rt. Stage IV. EGFR e19d; PD-L1 0%

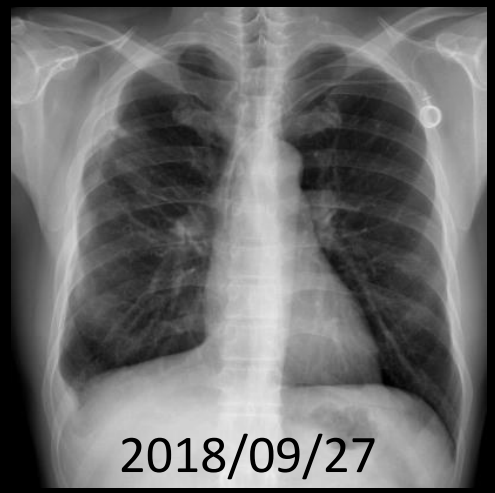
2018/03 – 11 Afatinib

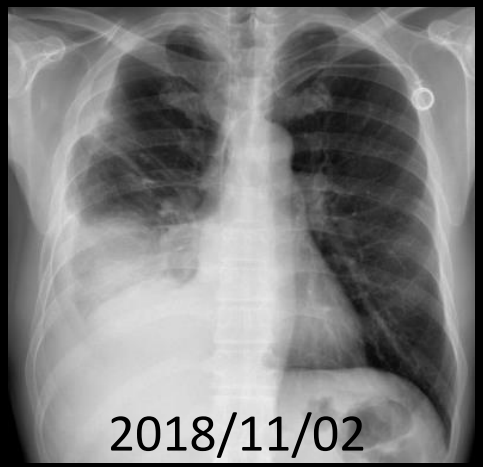
2018/11 – 12 Afatinib/bev [3]

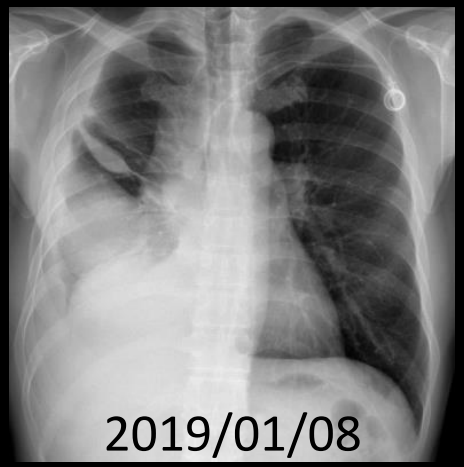
2019/01/04 C1: Pembro 100mg/pem 50mg/m2/cis 60mg/m2/bev 400mg
[C5 2019/4/03]

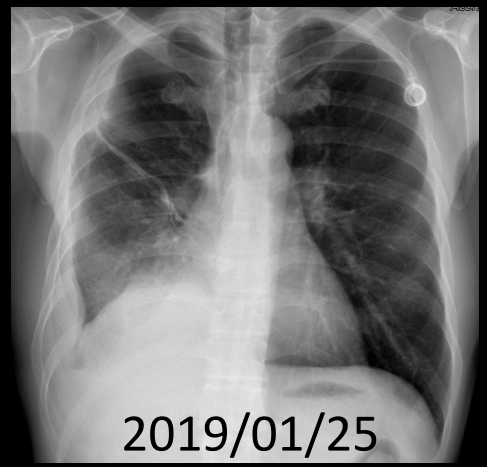


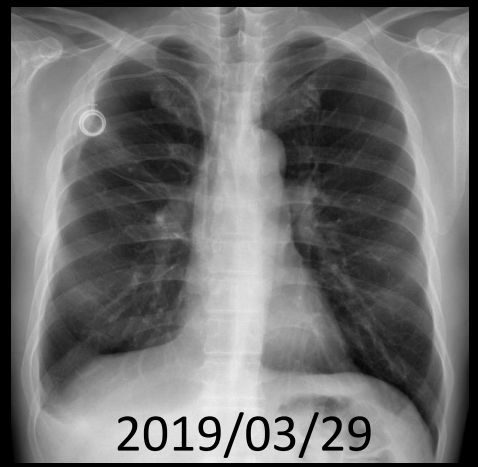










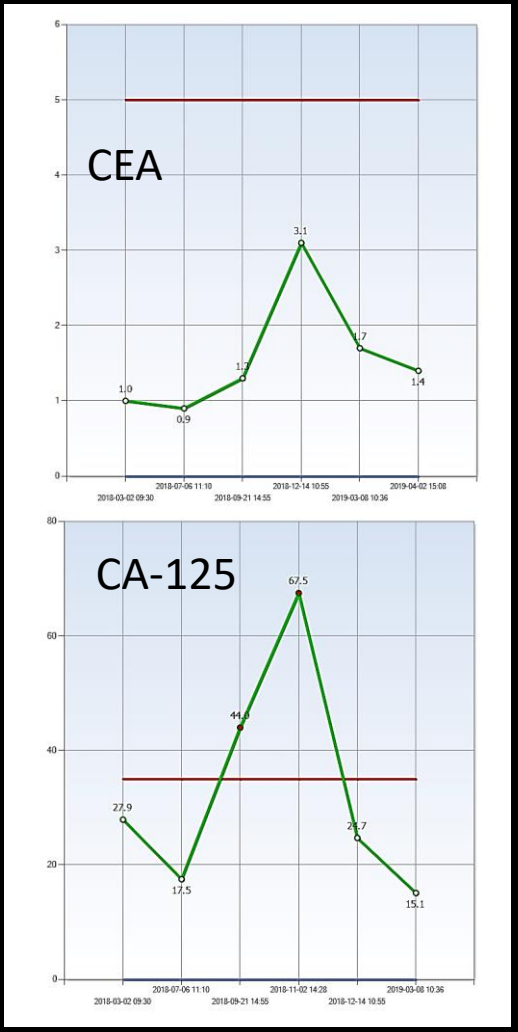


M/1966 Adenoca. Rt. Stage IV. EGFR e19d; PD-L1 0%

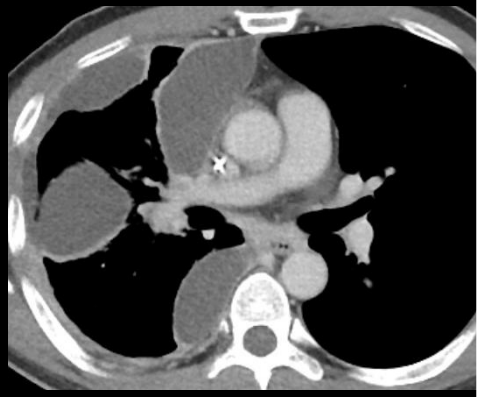
2018/03 – 11 Afatinib

2018/11 – 12 Afatinib/bev [3]

2019/01/04 C1: Pembro 100mg/pem 50mg/m2/cis 60mg/m2/bev 400mg
[C5 2019/4/03]



2019/01/02



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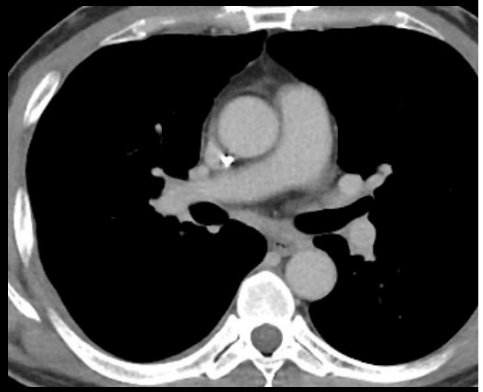
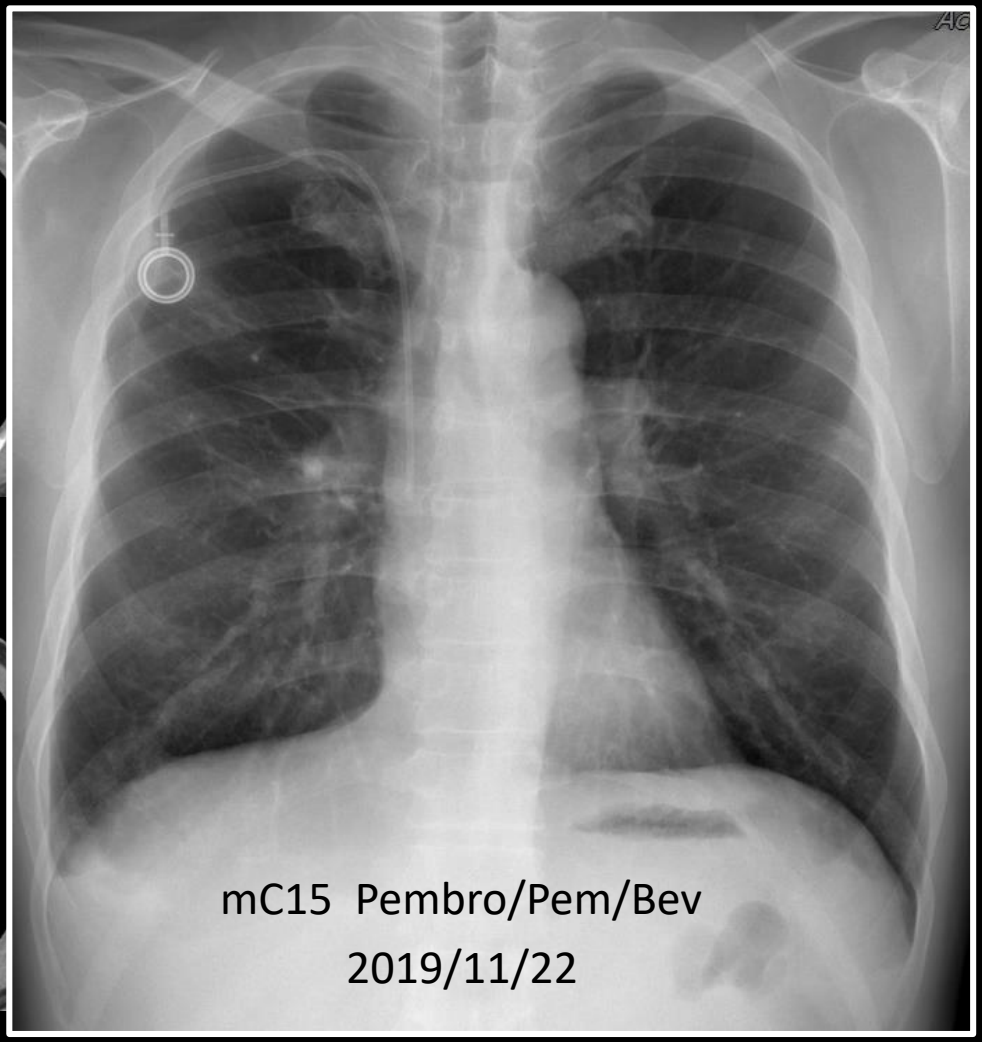
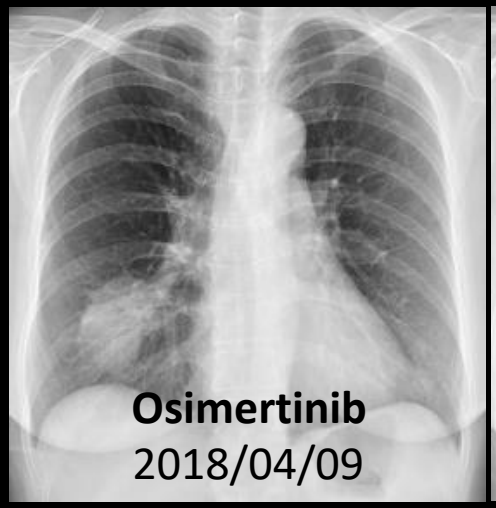


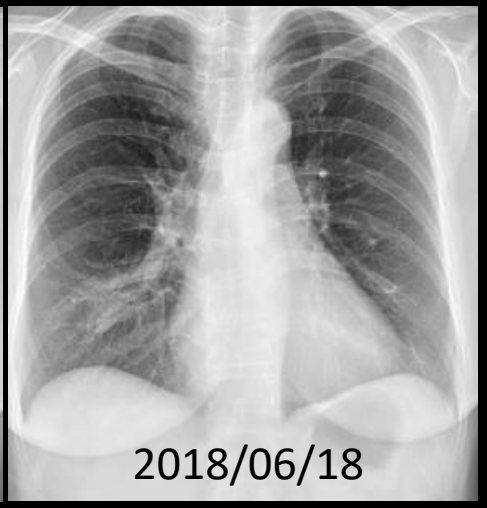


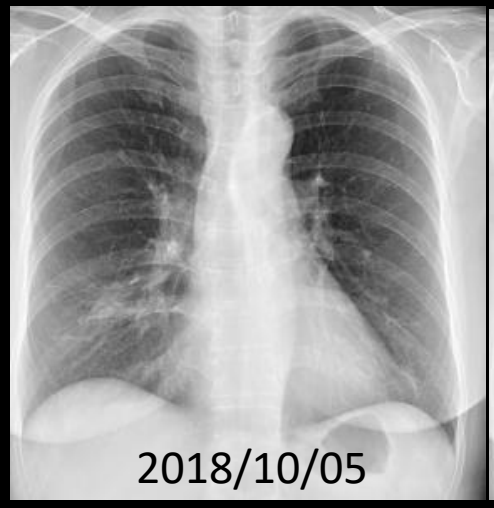
F/1958 Adenoca. RML with lung-to-lung & bone metastases
EGFR L858R

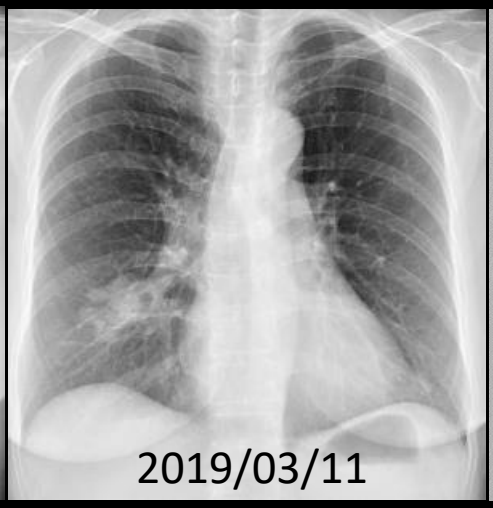
2016/05 – 11	Pem/pt, mPem
2016/12 – 2017/05	Erlotinib [6 mo]
2017/06 – 08	oNVB [2 mo]
2017/08 – 12	Doc [4 mo]
2018/03	Gefitinib [2 wk]
2018/04 – 2019/05	Osimertinib [13 mo]
2019/05 – 07	Gem [2 mo]

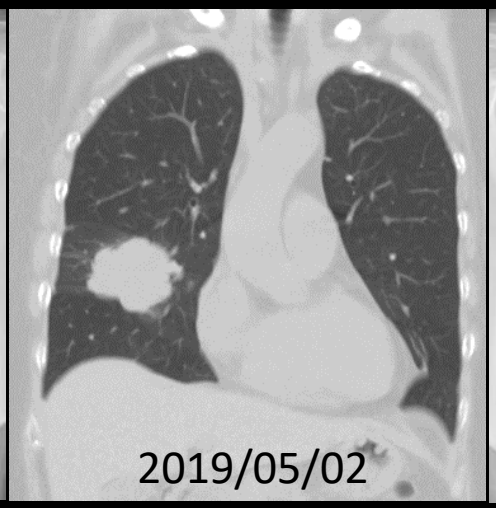
2019/08/20 Cathay H.

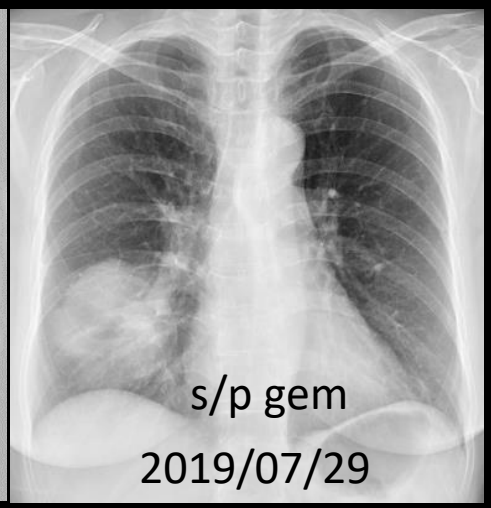






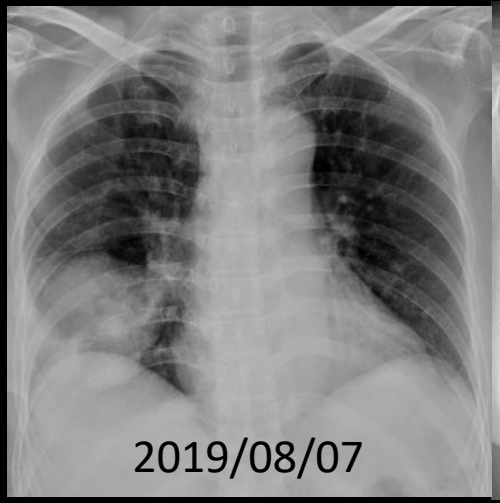


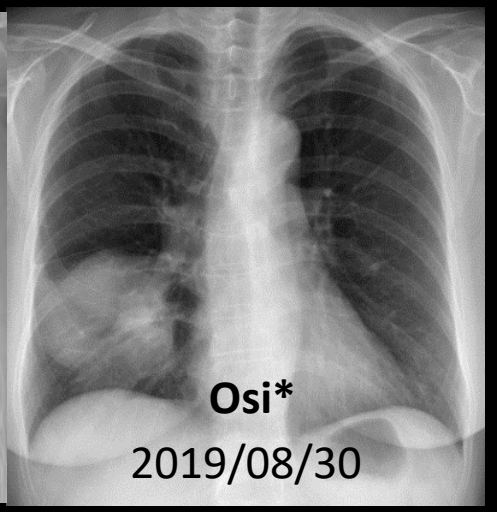


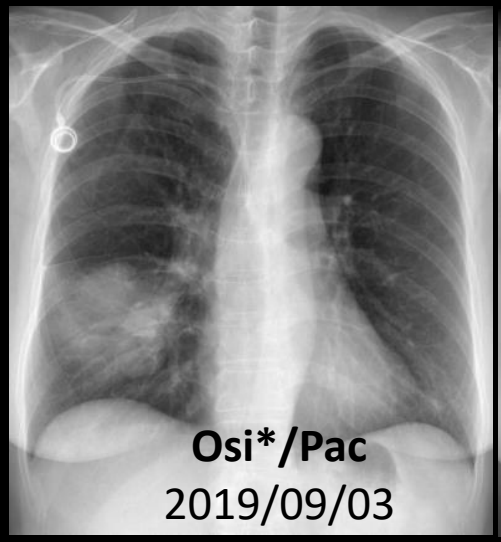


F/1958 Adenoca. RML with lung-to-lung & bone metastases
EGFR L858R

2016/05 – 11	Pem/pt, mPem
2016/12 – 2017/05	Erlotinib [6 mo]
2017/06 – 08	oNVB [2 mo]
2017/08 – 12	Doc [4 mo]
2018/03	Gefitinib [2 wk]
2018/04 – 2019/05	Osimertinib [13 mo]
2019/05 – 07	Gem [2 mo]
2019/08/20	Cathay H.
2019/08/30	Osimertinib*/Pac


2019/08/07


Osi*
2019/08/30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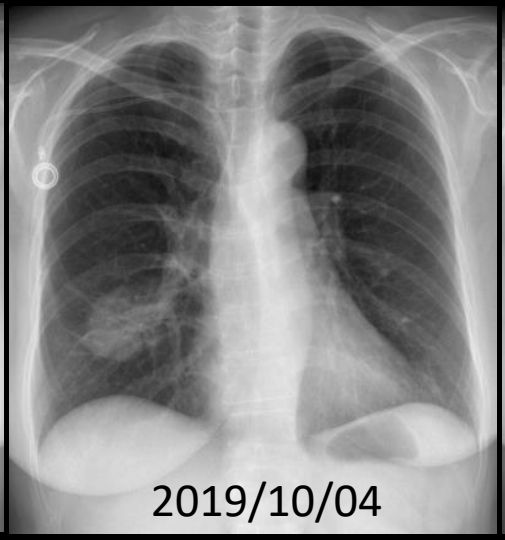
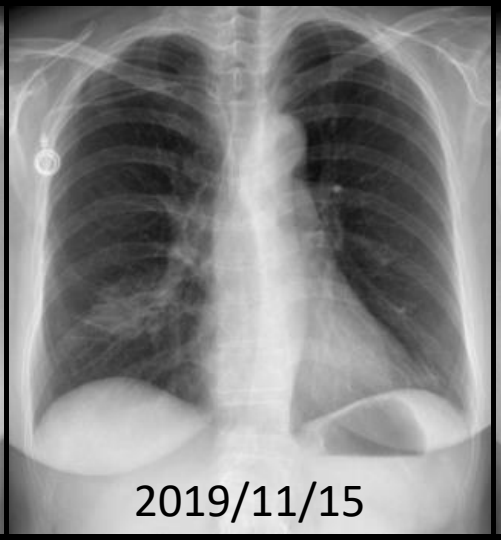
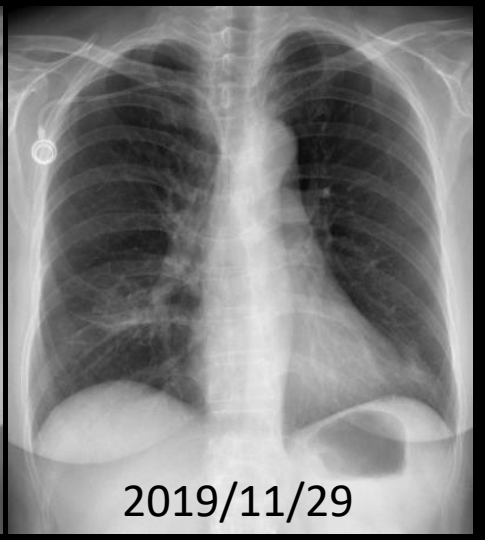
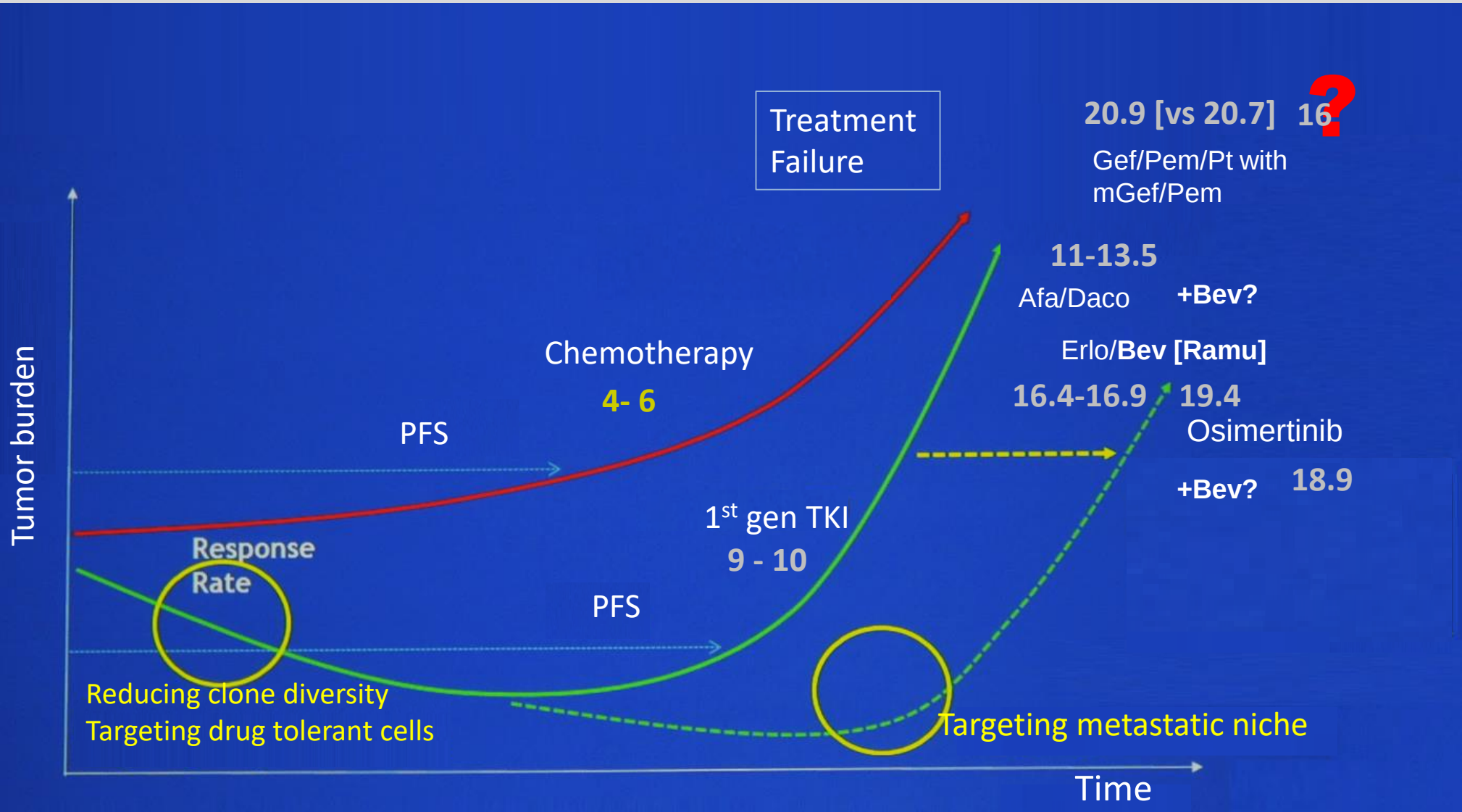
2019/09/03


2019/10/04


2019/11/15


2019/11/29

Impact of initial therapy in EGFR M+ NSCLC



Maximizing the benefit of each line of management — aim for the best PFS rather than OS

(except immunotherapy)

Thank you for your attention!

Overall Survival – Intention-to-Treat Population

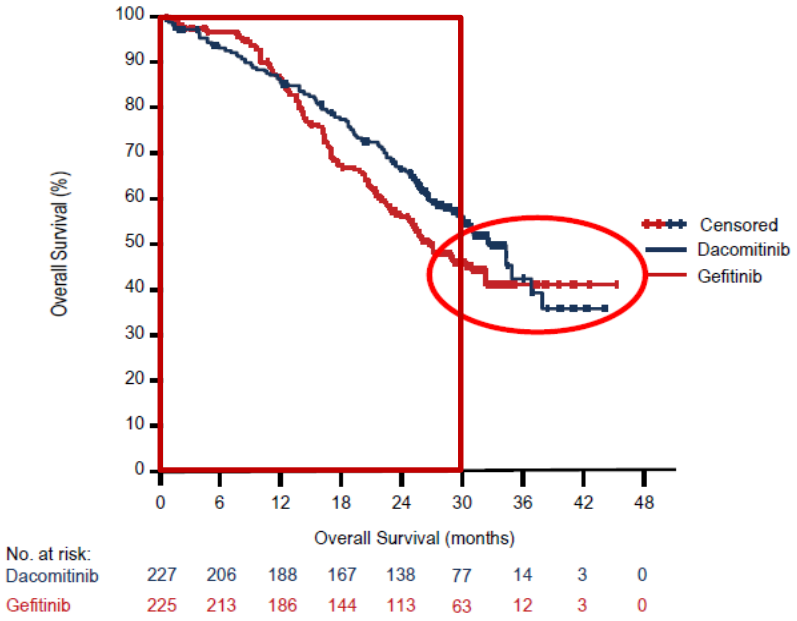
Overall Survival (Feb. 17, 2017)

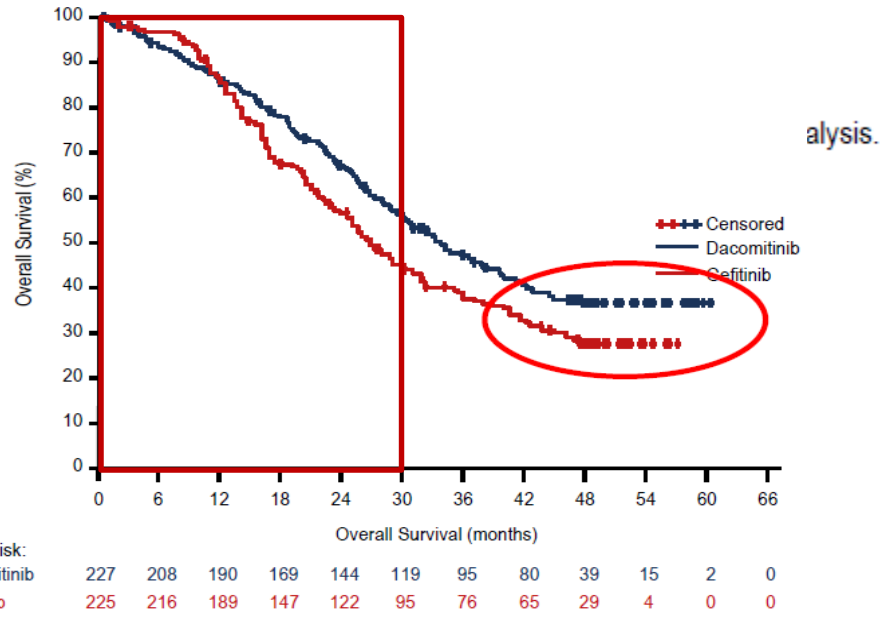
	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	103	117
Median OS (95% CI), months	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)	0.760* (0.582, 0.993); P* = 0.0438 (2-sided)	

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)	
OS_{42} (95% CI), %	41.0 (34.3, 47.6)	33.6 (27.2, 40.0)

ARCHER 1050 Ph III





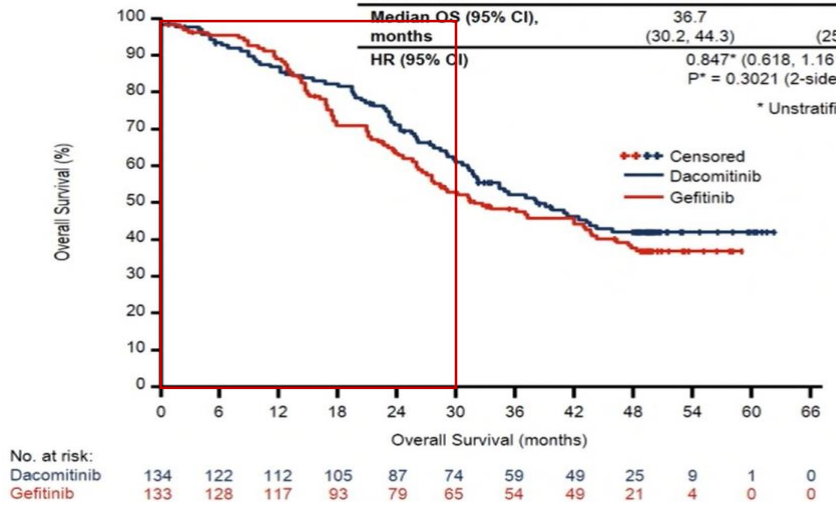
alysis.

Mok TS et al. *J Clin Oncol*. 2018;36(22):2244–2250.

EGFR exon 19 deletion

	Dacomitinib (n = 134)	Gefitinib (n = 133)
Events, No.	73	82
Median OS (95% CI), months	36.7 (30.2, 44.3)	30.8 (25.2, 42.2)
HR (95% CI)	0.847* (0.618, 1.161); P* = 0.3021 (2-sided)	

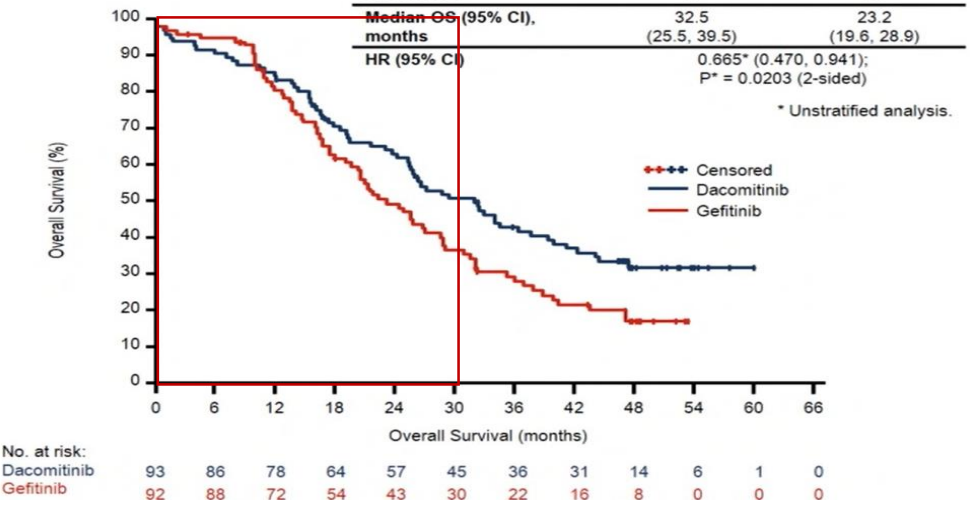
* Unstratified analysis.



EGFR exon 21 L858R

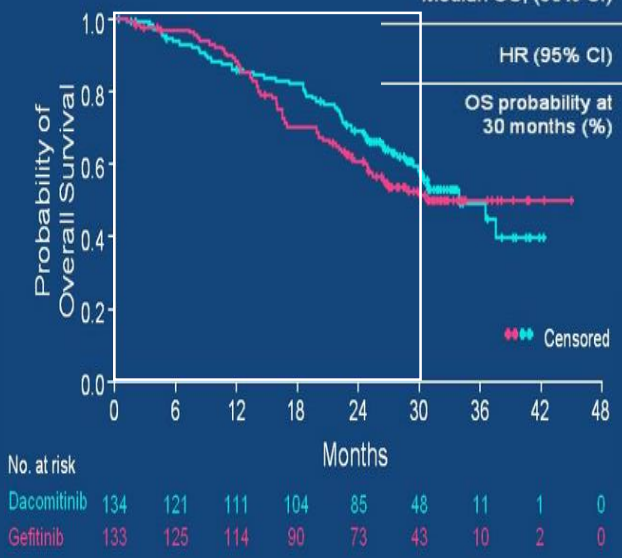
	Dacomitinib (n = 93)	Gefitinib (n = 92)
Events, No.	60	70
Median OS (95% CI), months	32.5 (25.5, 39.5)	23.2 (19.6, 28.9)
HR (95% CI)	0.665* (0.470, 0.941); P* = 0.0203 (2-sided)	

* Unstratified analysis.



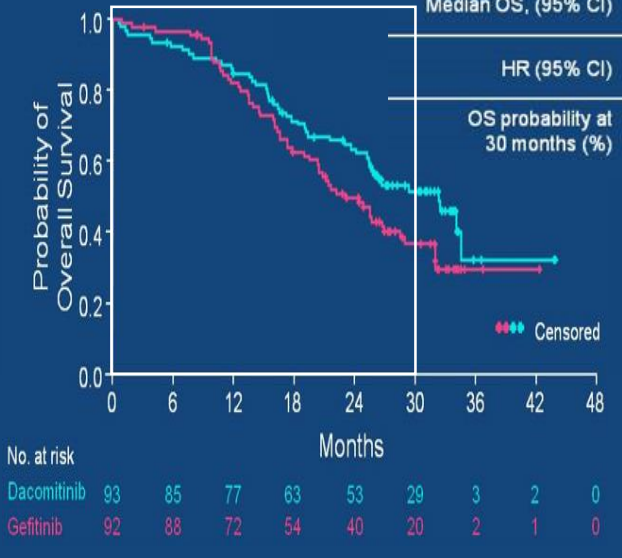
e19d

	Daco (N=134)	Gef (N=133)
Number of deaths, n (%)	57	61
Median OS, (95% CI)	34.1 (30.1, NR)	NR (25.0, NR)
HR (95% CI)	0.880 (0.613, 1.262) *P*=0.4862	
OS probability at 30 months (%)	59.7	52.7

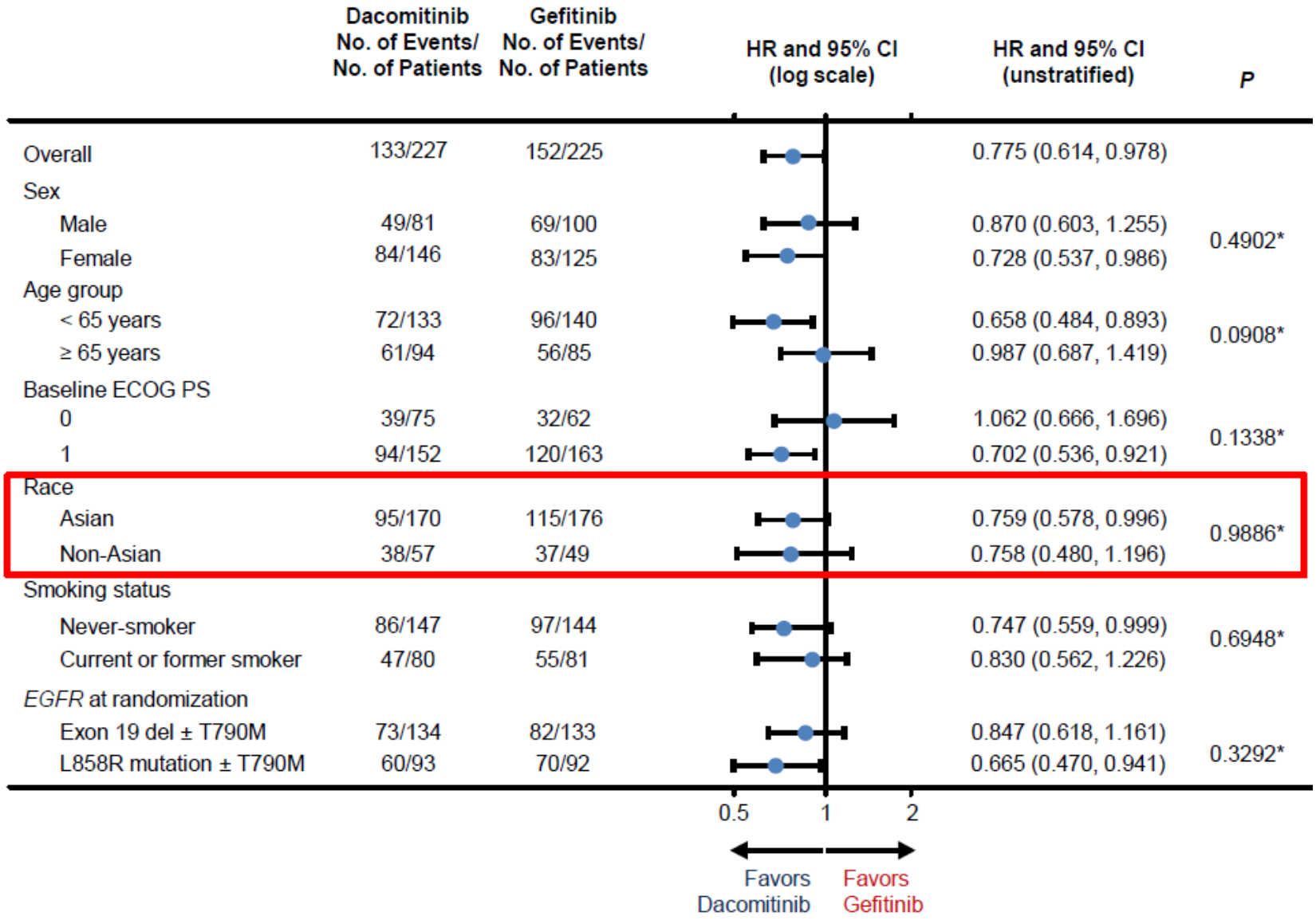


L858R

	Daco (n=93)	Gef (n=92)
Number of deaths, n (%)	46	56
Median OS, (95% CI)	32.5 (25.5, NR)	23.2 (19.6, 28.6)
HR (95% CI)	0.707 (0.478, 1.045) *P*=0.0805	
OS probability at 30 months (%)	51.6	36.7



Overall Survival – Forest Plot

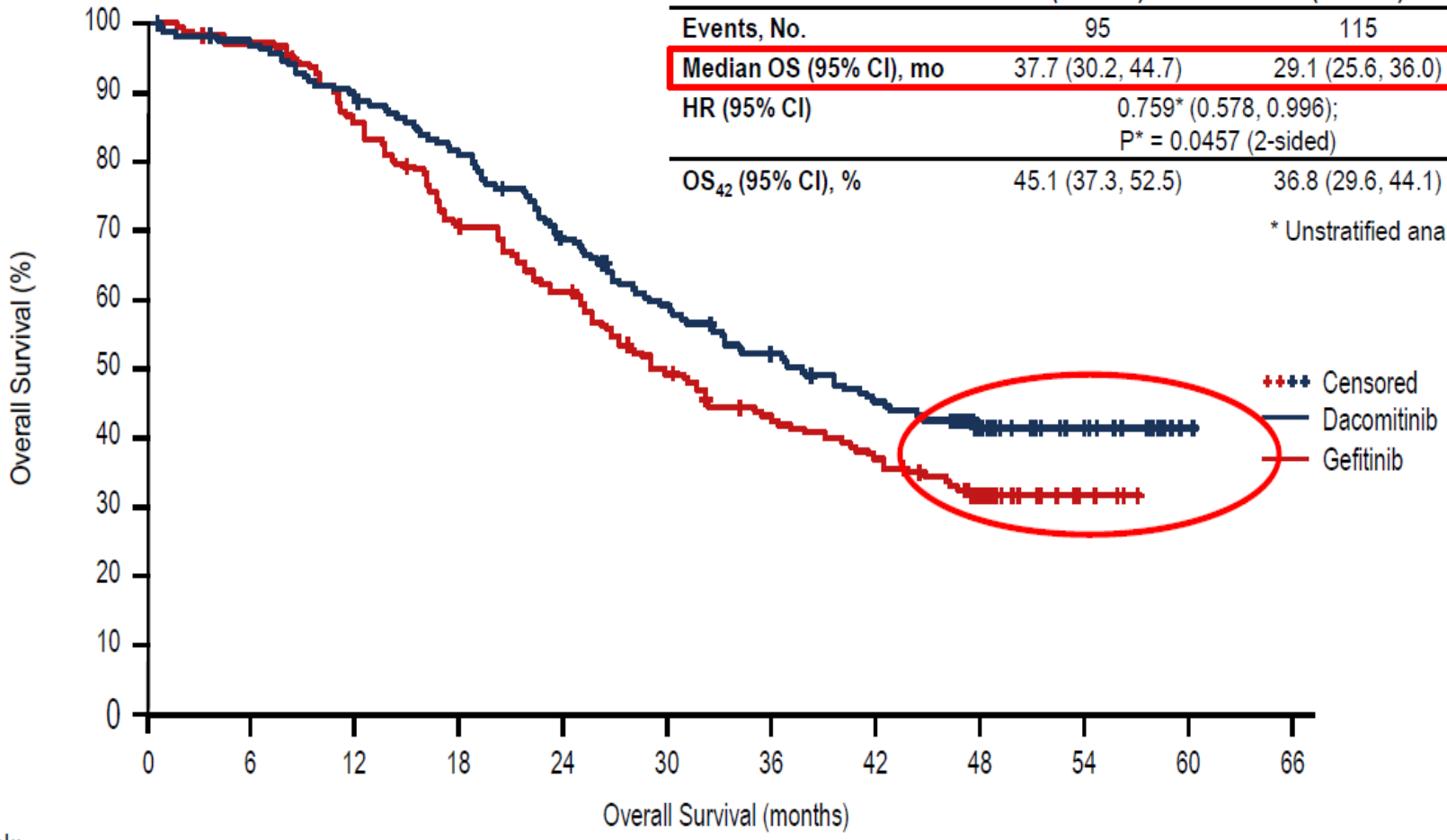


Subgroup analyses for overall survival. *, *P* interaction. HR, hazard ratio; PS, performance status.

Overall Survival – Asian

	Dacomitinib (n = 170)	Gefitinib (n = 176)
Events, No.	95	115
Median OS (95% CI), mo	37.7 (30.2, 44.7)	29.1 (25.6, 36.0)
HR (95% CI)	0.759* (0.578, 0.996); P* = 0.0457 (2-sided)	
OS_{42} (95% CI), %	45.1 (37.3, 52.5)	36.8 (29.6, 44.1)

* Unstratified analysis.



No. at risk:												
Dacomitinib	170	163	149	135	113	95	82	70	33	15	2	0
Gefitinib	176	170	148	120	104	83	69	59	25	4	0	0

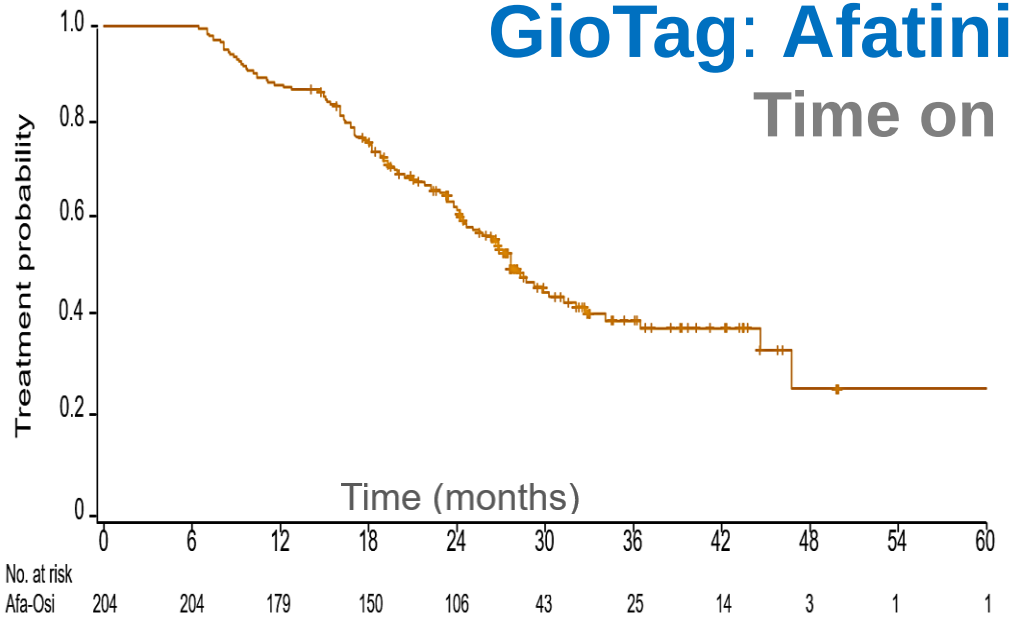
SUBSEQUENT THERAPIES LUX lung 7

Characteristic, n (%)	Afatinib	Gefitinib	Total
Patients discontinued	146 (100.0)	151 (100.0)	297 (100)
Systemic anticancer therapy	106 (72.6)	116 (76.8)	222 (74.7)
Chemotherapy*	84 (57.5)	91 (60.3)	175 (58.9)
Platinum−based therapy	70 (47.9)	71 (47.0)	141 (47.5)
EGFR TKI	67 (45.9)	84 (55.6)	151 (50.8)
EGFR TKI monotherapy	63 (43.2)	74 (49.0)	137 (46.1)
Gefitinib/Erlotinib (1st-generation)	45 (30.8)	58 (38.4)	103 (34.7)
Afatinib/Poziotinib (2nd-generation)	6 (4.1)	16 (10.6)	22 (7.4)
Osimertinib/Olmutinib (3rd-generation)	20 (13.7)	22 (14.6)	43 (14.1)
EGFR TKI−containing combination†	7 (4.8)	15 (9.9)	22 (7.4)
Immune checkpoint inhibitor	3 (2.1)	4 (2.6)	7 (2.4)
Radiotherapy	26 (17.8)	34 (22.5)	60 (20.2)

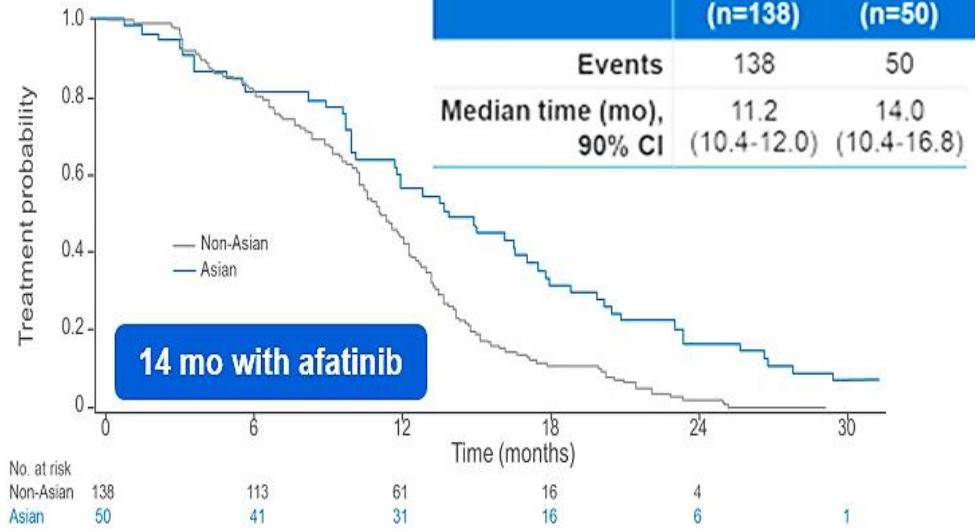
*Including chemotherapy-based combination; †including gefitinib (afatinib, n=7; gefitinib, n=11), erlotinib (gefitinib, n=5), or osimertinib (gefitinib, n=1)

GioTag: Afatinib ⇒ Osimertinib

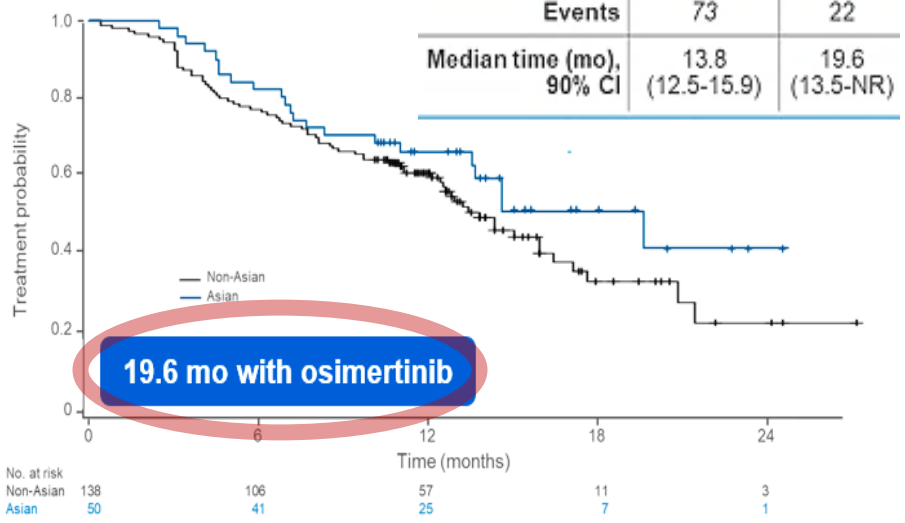
Time on treatment



Afatinib followed by osimertinib	N=204
Events	106
Median time (mo), 90% CI	27.6 (25.9-31.3)



	Non-Asian (n=138)	Asian (n=50)
Events	138	50
Median time (mo), 90% CI	11.2 (10.4-12.0)	14.0 (10.4-16.8)



	Non-Asian (n=138)	Asian (n=50)
Events	73	22
Median time (mo), 90% CI	13.8 (12.5-15.9)	19.6 (13.5-NR)

Hochmair M et al. Future Oncol. 2018 Oct. 19; doi:10.2217/fon-2018-0711

Thank you for your attention!