Recent Advances and Unmet Need of NSCLC with EGFR mutation

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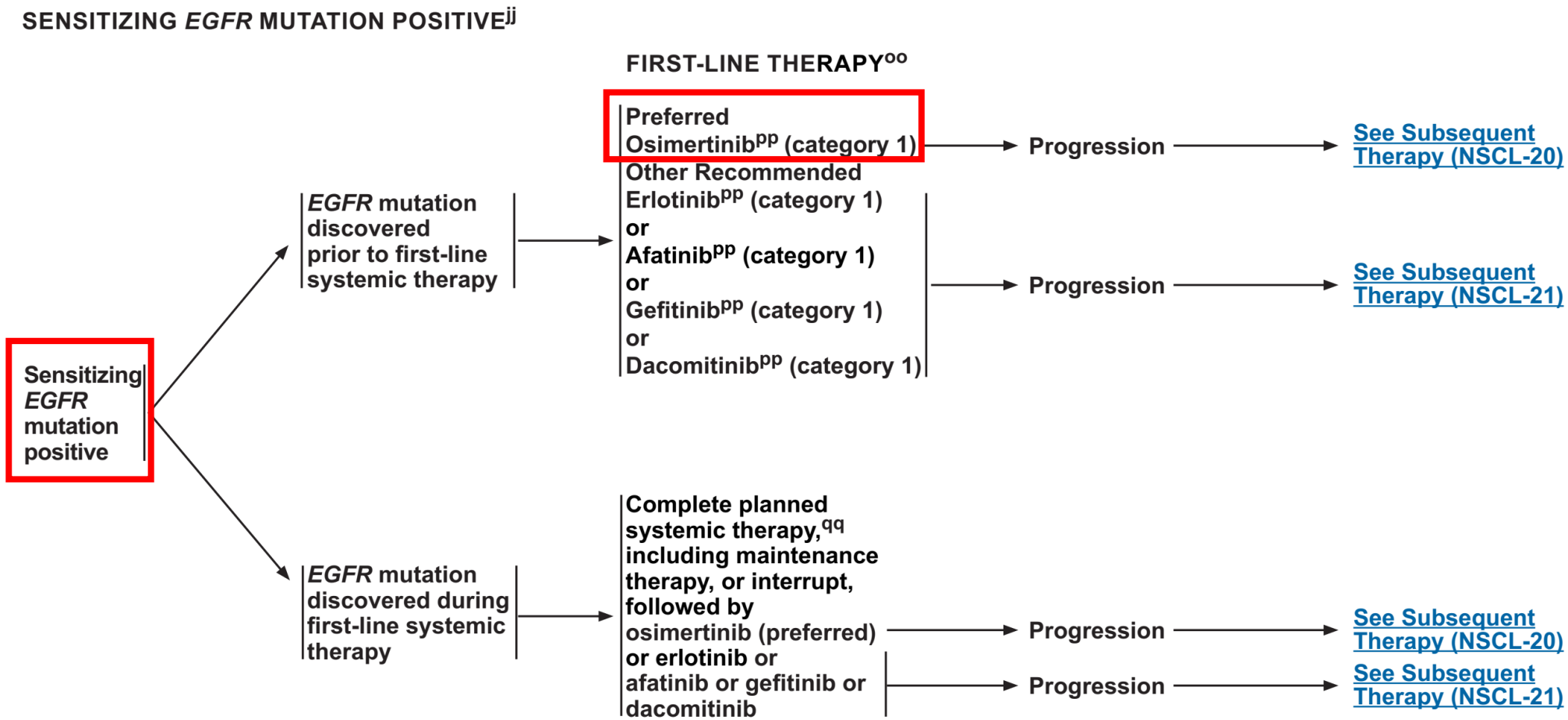
There are currently no published head-to-head studies between therapeutics such as checkpoint inhibitors or TKIs, and slides summarising studies together are provided only for scientific discussion purposes.

NSCLC with EGFR mutation treatment



NCCN Guidelines Version 1.2020

EGFR TKI Monotherapy

BARCELONA 2019 ESMO congress

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]

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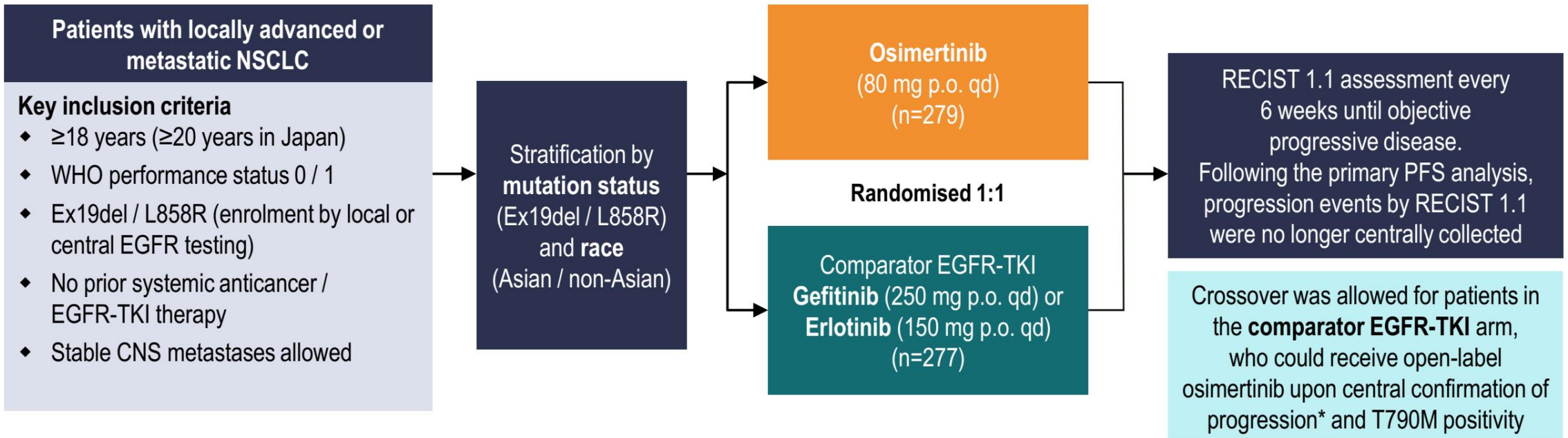
esmo.org

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

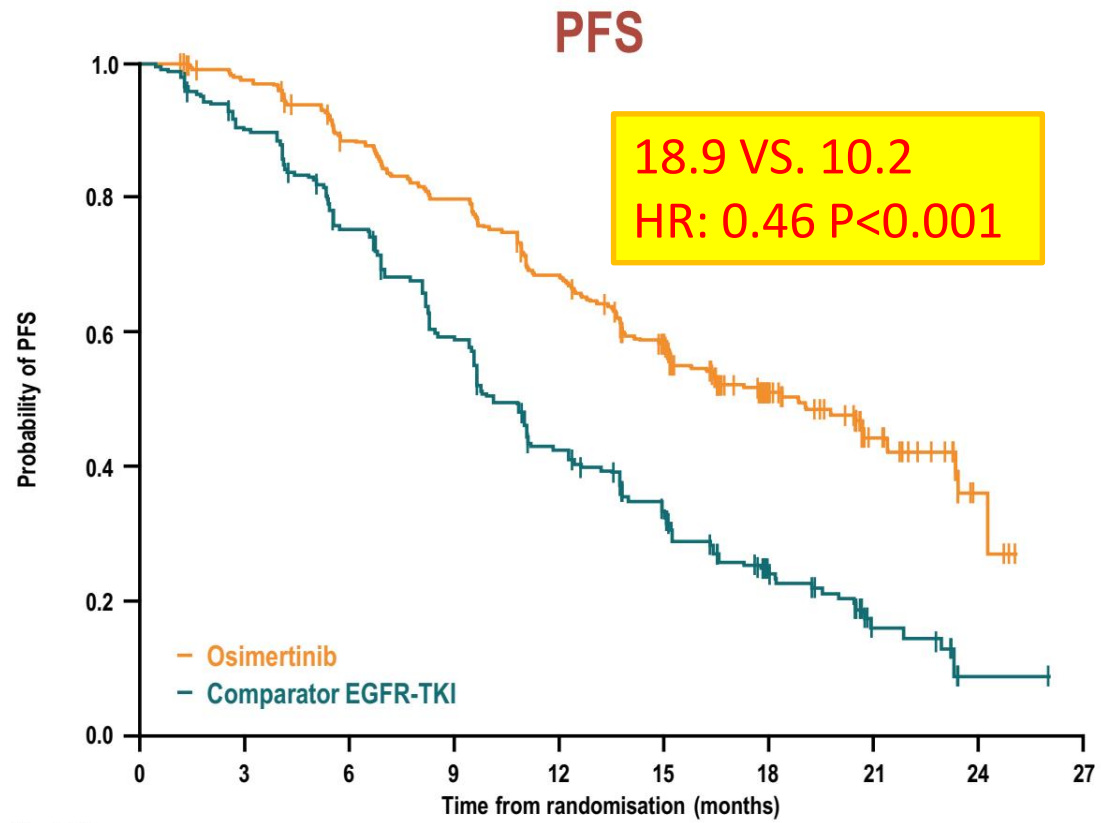
Data cut-off: 25 June 2019

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

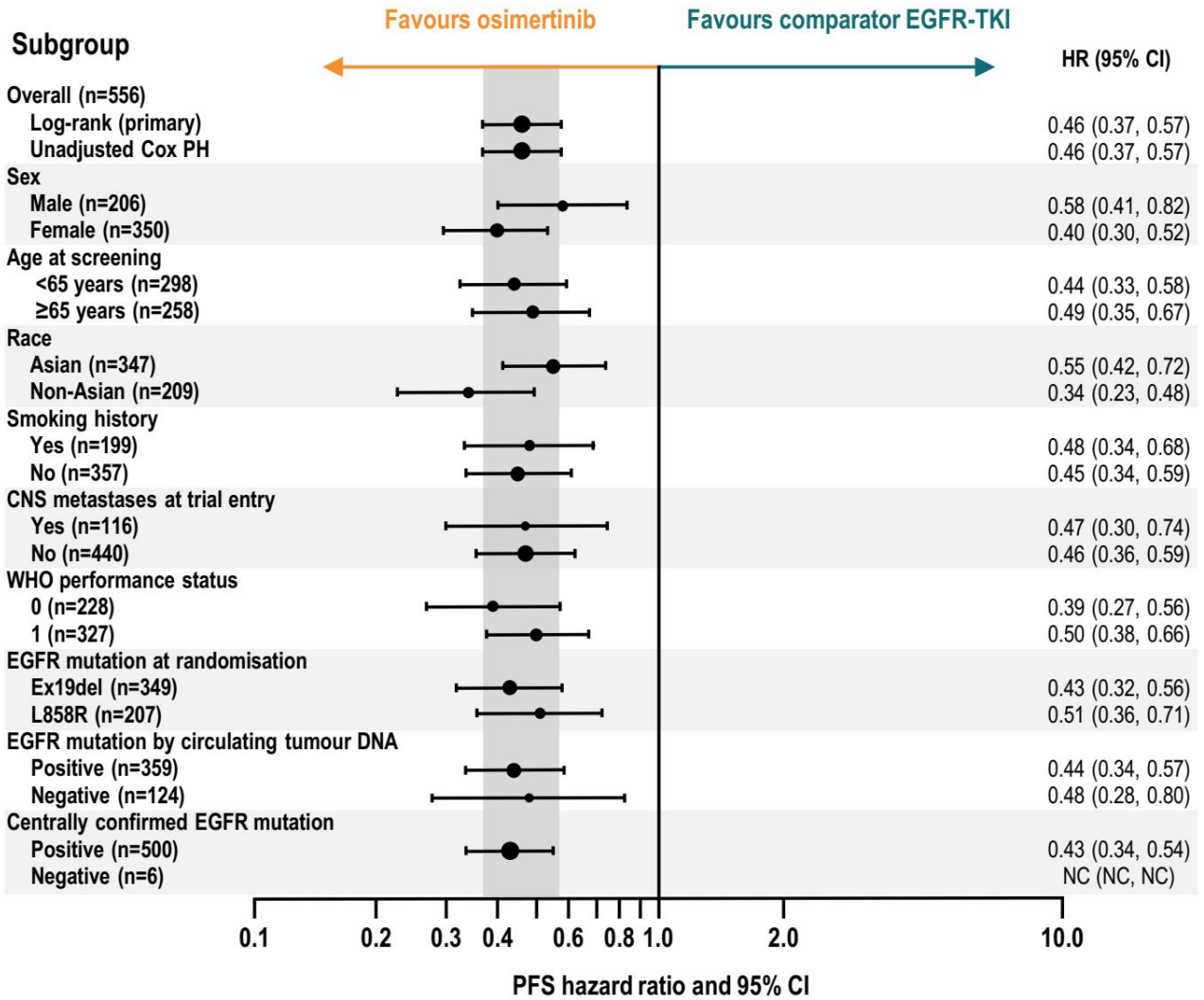
*By investigator assessment if disease progression occurred after the primary analysis data cut-off

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

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)	

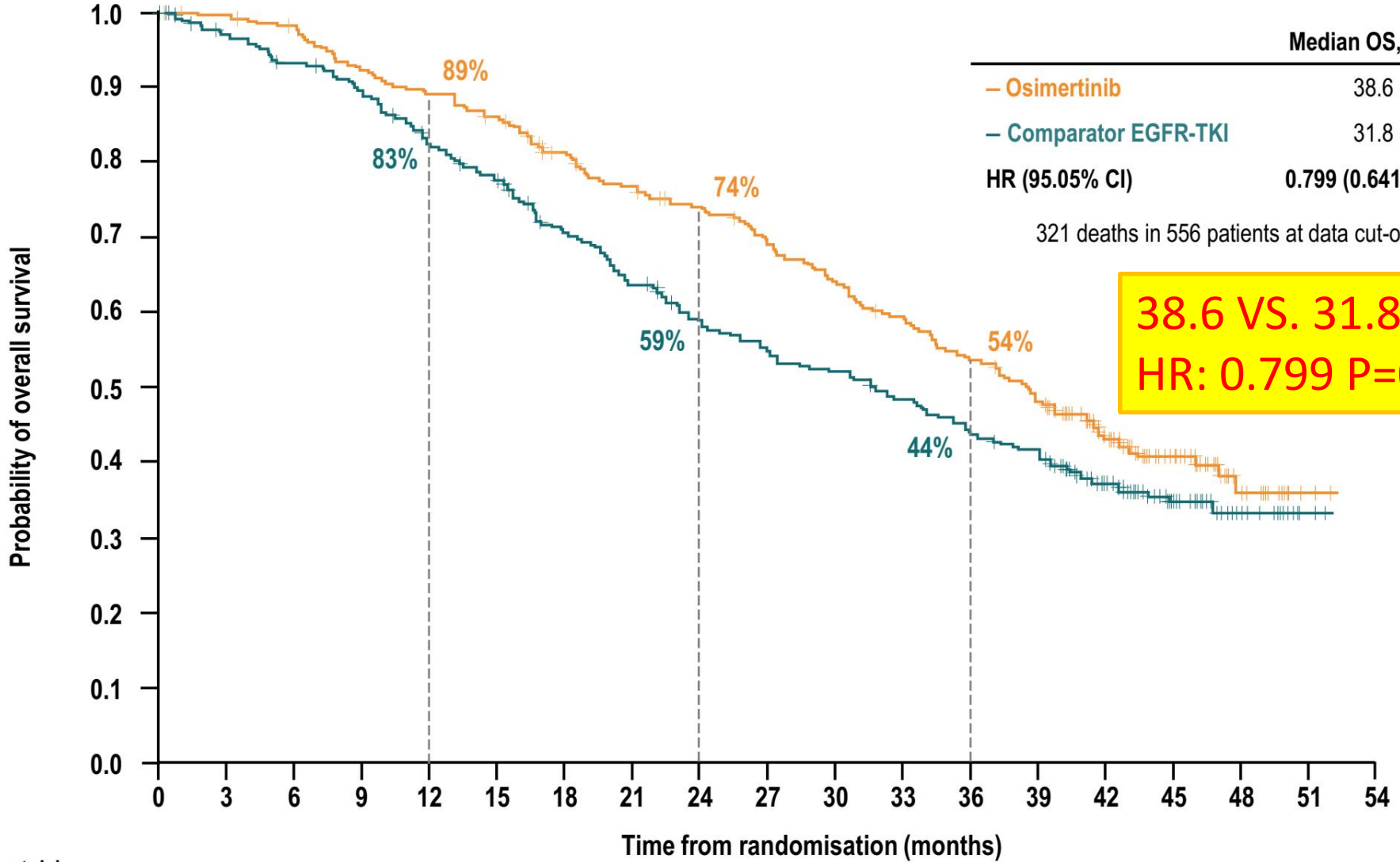


Data cut-off: 12 June 2017

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



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

321 deaths in 556 patients at data cut-off: 58% maturity

38.6 VS. 31.8
HR: 0.799 P=0.0462

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

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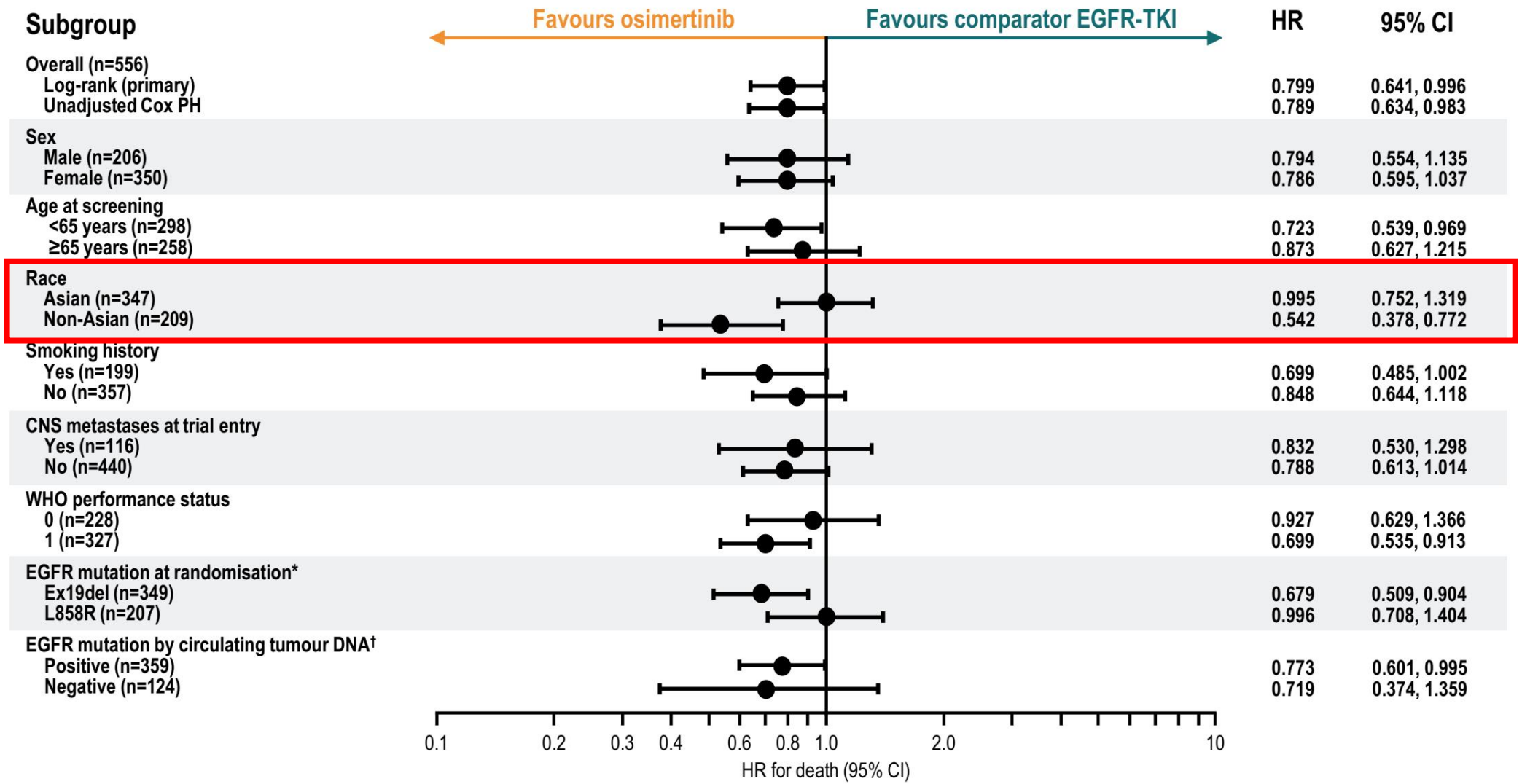
Data cut-off: 25 June 2019
For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

OVERALL SURVIVAL ACROSS SUBGROUPS



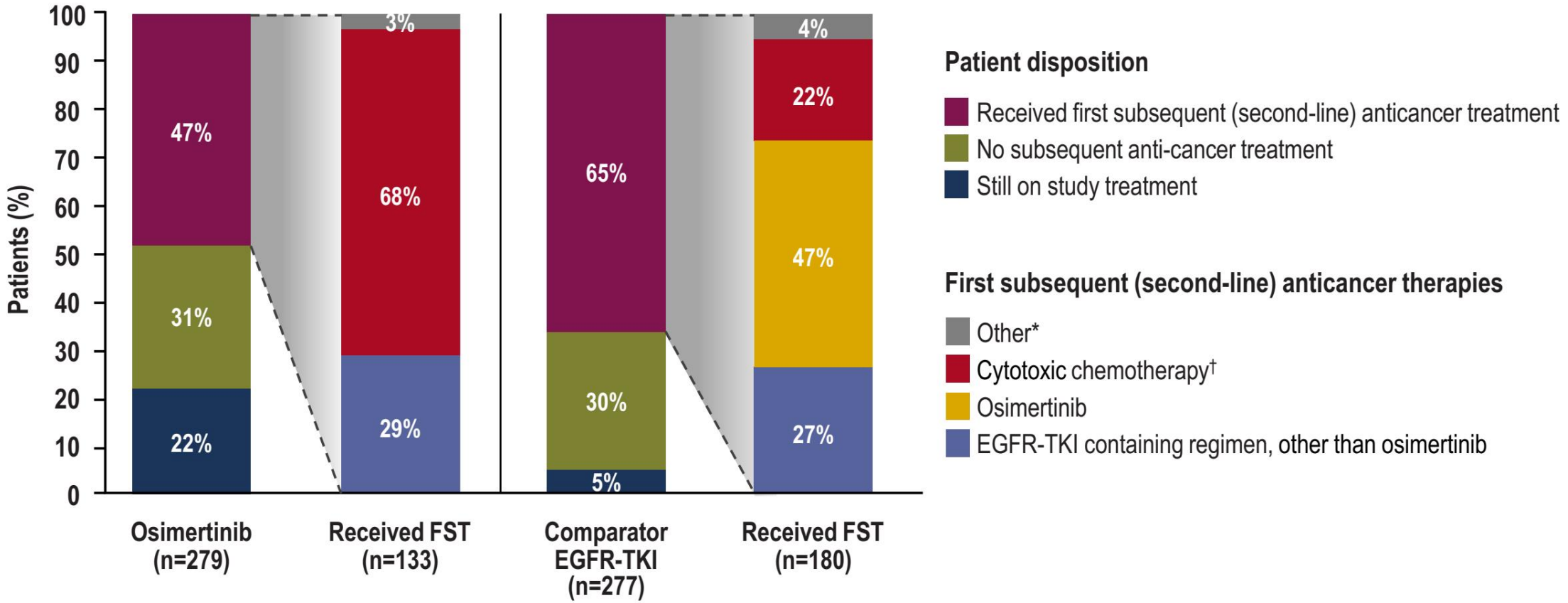
Data cut-off: 25 June 2019

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

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)



*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

Data cut-off: 25 June 2019

EGFR-TKI Plus anti-VEGF/VEGFR

North East Japan Study Group

Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating *EGFR*-mutations: NEJ 026

Naoki Furuya[1], Tatsuro Fukuhara[2], Haruhiro Saito[3], Kana Watanabe[2], Shunichi Sugawara[4], Shunichiro Iwasawa[5], Yoshio Tsunezuka[6], Ou Yamaguchi[7], Morihito Okada[8], Kouzou Yoshimori[9], Ichiro Nakachi[10], Akihiko Gemma[11], Koichi Azuma[12], Koichi Hagiwara[13], Toshihiro Nukiwa[14], Satoshi Morita[15], Kunihiko Kobayashi[7], and Makoto Maemondo[16],

North East Japan Study Group

[1]St. Marianna University School of Medicine, [2]Miyagi Cancer Center, [3]Kanagawa Cancer Center, [4]Sendai Kousei Hospital, [5]Chiba University Hospital, [6]Ishikawa Prefectural Central Hospital, [7]Saitama Medical University International Medical Center, [8]Hiroshima University, [9]Fukujuji Hospital, JATA, [10]Saiseikai Utsunomiya Hospital, [11]Nippon Medical School, [12]Kurume University School of Medicine, [13]Jichi Medical University, [14]Tohoku University, [15]Kyoto University Graduate School of Medicine, [16]Iwate Medical University.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Naoki Furuya

Presented By Naoki Furuya at 2018 ASCO Annual Meeting

Study Design : NEJ 026 (Phase III study)

- Chemotherapy-naïve
- Non-Sq NSCLC
- Stage IIIB/IV or postoperative recurrence
- Activating *EGFR* mutations

  Ex19 del, Ex21 L858R
- Asymptomatic CNS metastases allowed

UMIN 000017069

R

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

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

PD1

Platinum + Pemetrexed (PEM) followed by maintenance with PEM

PD2

PD1

Platinum + Pemetrexed (PEM) + Bevacizumab (BEV) followed by maintenance with PEM+BEV

PD2

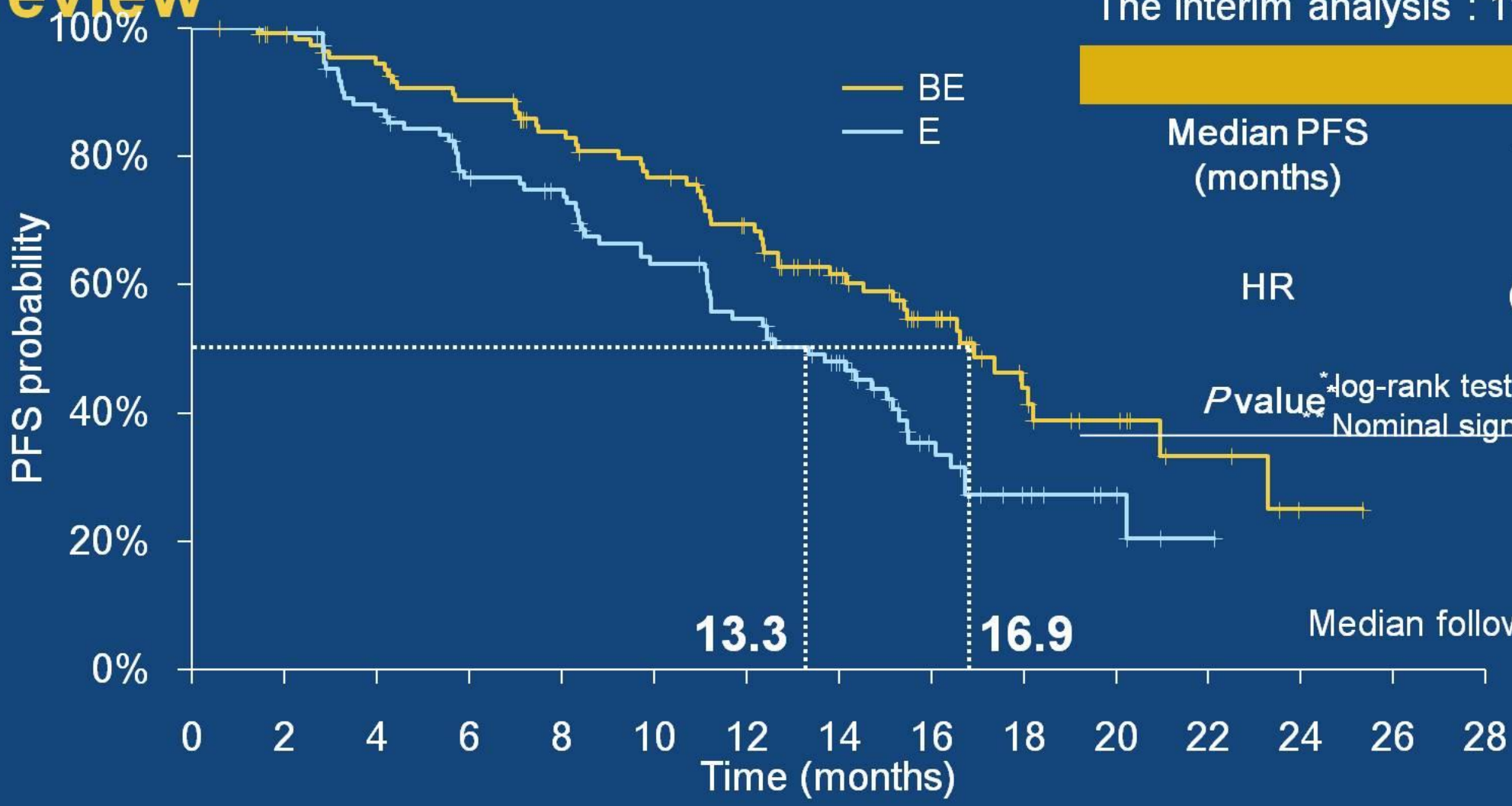
Study period → **Observation period**

Sample collection						
Tissue	Pretreatment		PD1 (progression of study treatment)		PD2 (progression of 2nd line treatment)	
Plasma	Pretreatment	6 weeks after initiation of study treatment	PD1 (progression of study treatment)	6 weeks after initiation of 2nd line treatment	PD2 (progression of 2nd line treatment)	

Baseline characteristics

		BE (n=112)	E (n=112)
Pathology	Adenocarcinoma	110 (98.2%)	112 (100.0%)
	Large cell carcinoma	1 (0.9%)	0 (0%)
	Other	1 (0.9%)	0 (0%)
EGFR-mutation type	Ex19 deletion	56 (50.0%)	55 (49.1%)
	Ex21 L858R	56 (50.0%)	57 (50.9%)
Stage at screening	IIIB	8 (7.1%)	8 (7.1%)
	IV	82 (73.2%)	84 (75.0%)
	Postoperative recurrence	22 (19.6%)	20 (17.9%)
CNS metastases	(+)	**36 (32.1%)**	**36 (32.1%)**
	(-)	76 (67.9%)	76 (67.9%)

Primary endpoint : PFS by independent review



The interim analysis : 117 events

	BE	E
Median PFS (months)	16.9	13.3
HR	0.605 (95% CI : 0.417-0.877)	
*P*value**	0.01573**	

*log-rank test, two-sided
** Nominal significance level : 0.02398

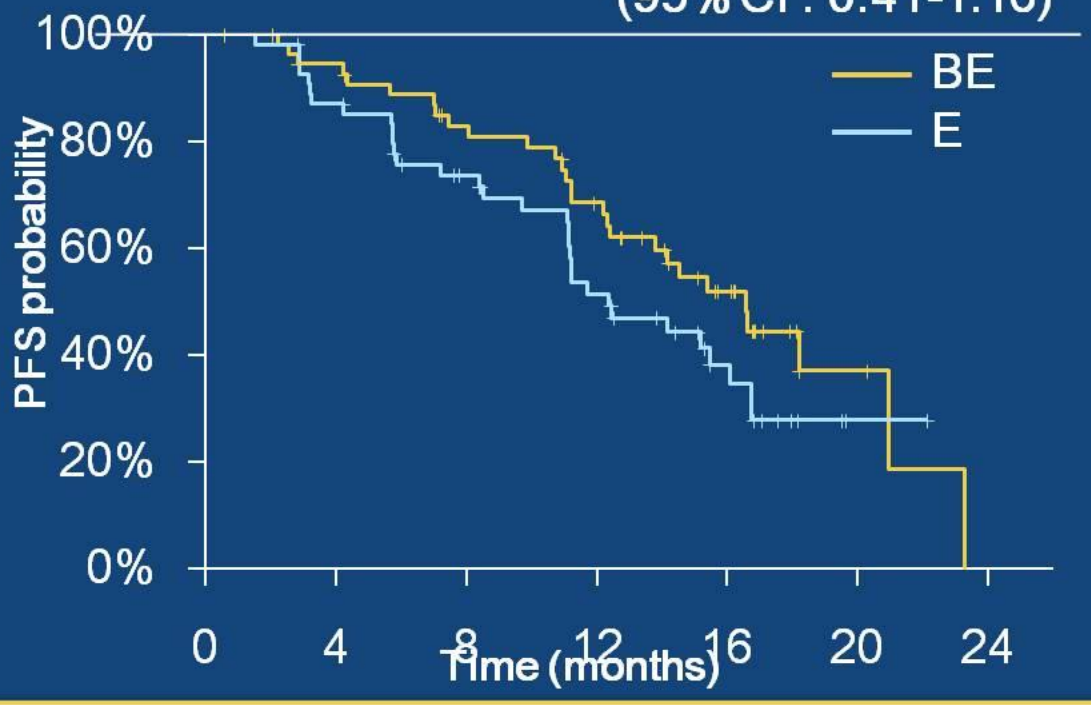
Median follow up : 12.4 months

PFS by *EGFR*-mutation subtypes

Exon19 deletion

	BE	E
Median PFS (months)	16.6	12.4

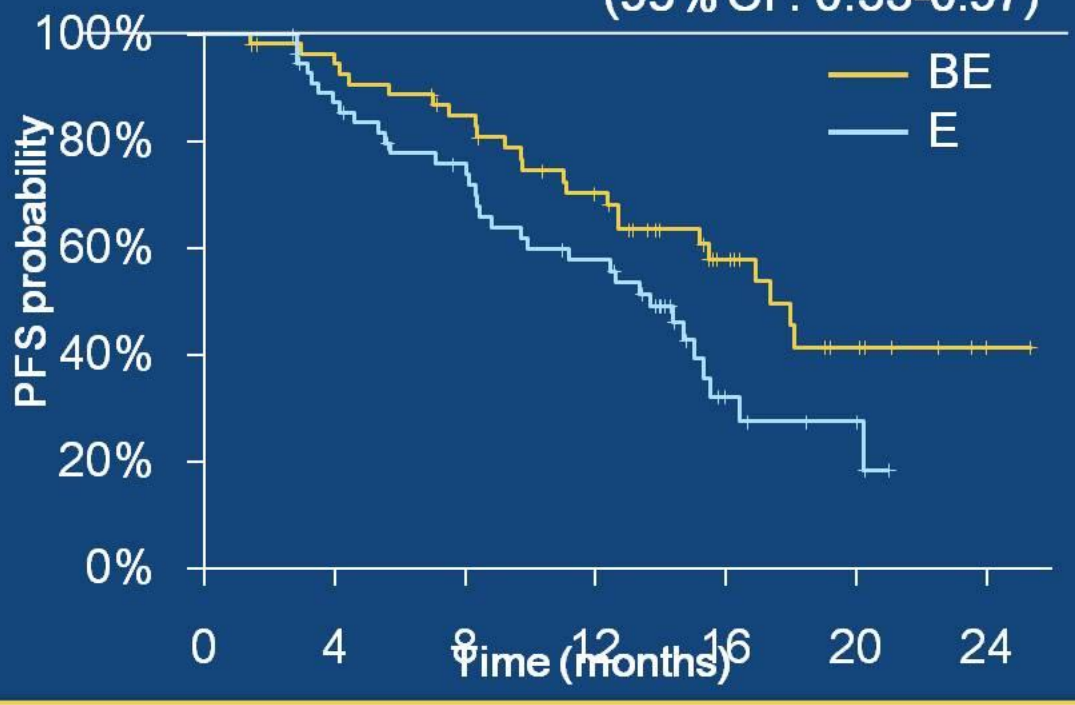
HR 0.69 (95% CI : 0.41-1.16)



Exon21 L858R

	BE	E
Median PFS (months)	17.4	13.7

HR 0.57 (95% CI : 0.33-0.97)



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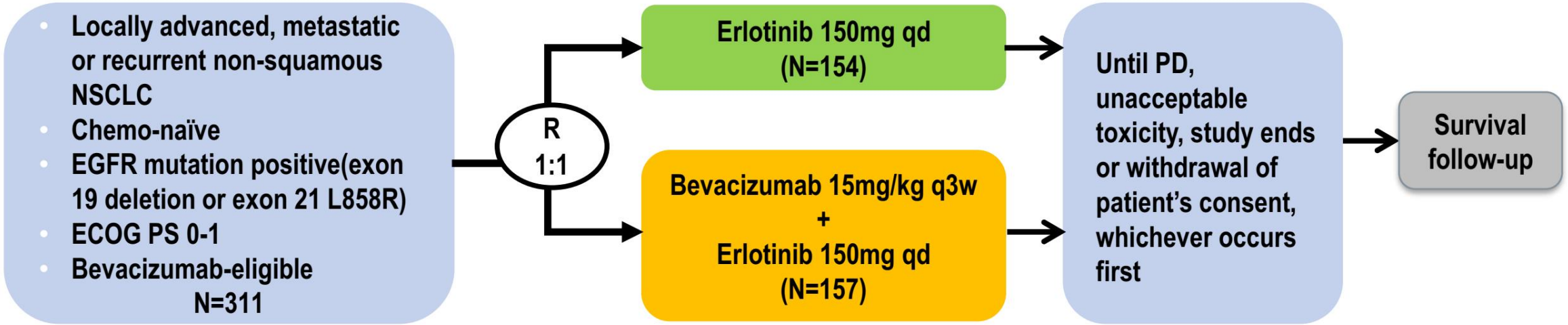
ARTEMIS(CTONG 1509) : PHASE 3 STUDY OF BEVACIZUMAB WITH OR WITHOUT ERLOTINIB IN UNTREATED CHINESE PATIENTS WITH ADVANCED EGFR-MUTATED NSCLC

Q. Zhou[1], Y.-L. Wu[1], Y. Cheng[2], Y. Liu[3], G. Chen[4], J. Cui[5], N. Yang[6], Y. Song[7], X.-L. Li[8], S. Lu[9], J.Zhou[10], Z. Ma[11], S.-Y. Yu[12], C.Huang[13], Y. Shu[14];

[1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China, [2]Department of Thoracic Oncology, Jilin Cancer Hospital, Changchun, China, [3]Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China, [4]Medical Oncology, Affiliated Cancer Hospital of Harbin Medical University, Harbin, China, [5]Cancer Center, The First Hospital of Jilin University, Changchun, China, [6]Department of Medical Oncology, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, China, [7]Respiratory Medicine, Jinling Hospital, Nanjing, China, [8]Medical Oncology, Cancer Hospital of China Medical University Liaoning Cancer Hospital & Institute, Shenyang, China, [9]Medical Oncology, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China, [10]Respiratory Medicine, The First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, China, [11]Respiratory Medicine, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China, [12]Medical Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [13]Medical Oncology, Fujian Cancer Hospital, The Affiliated Cancer Hospital of Fujian Medical University, Fuzhou, China, [14]Medical Oncology, Jiangsu Province Hospital,The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Presented by Q. Zhou

STUDY DESIGN

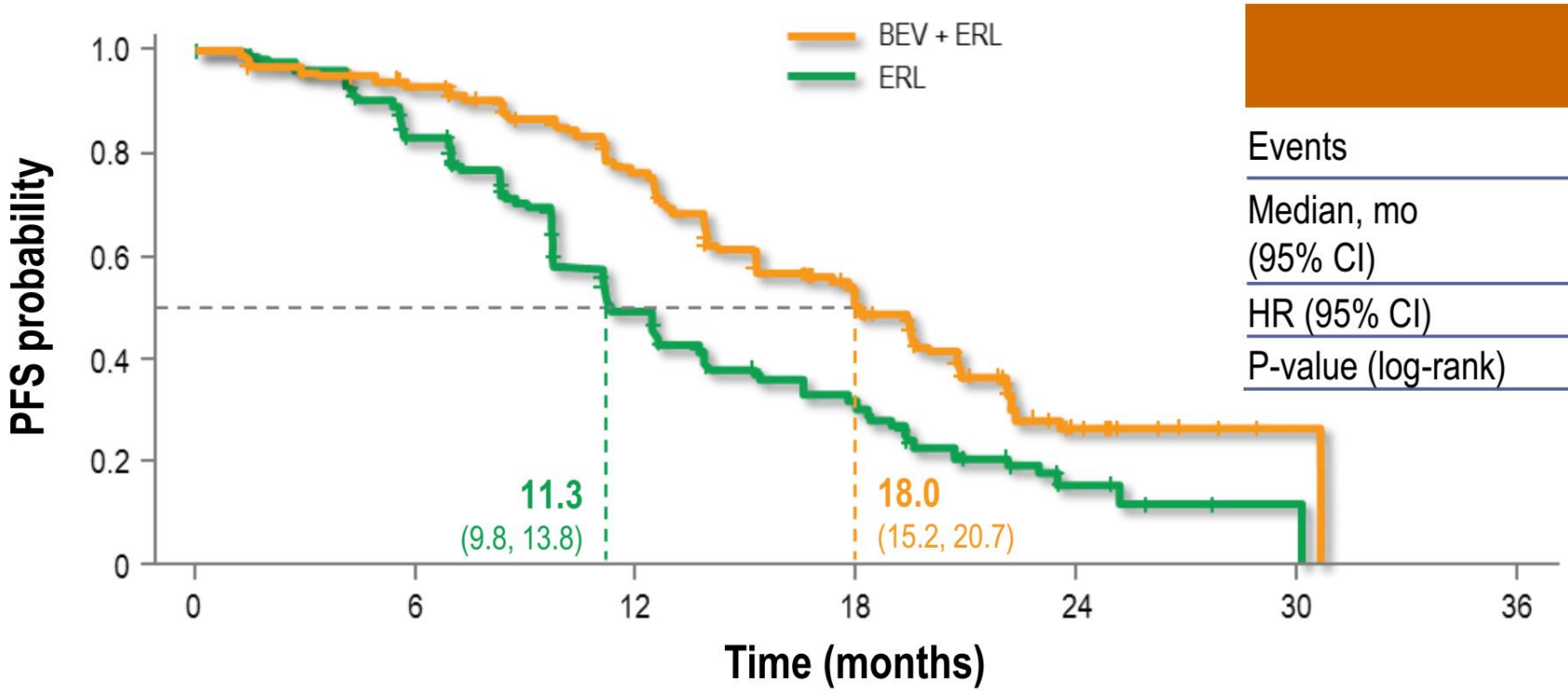


- **Primary endpoint: PFS (Independent Review Committee,IRC)**
- **Secondary endpoints:**
  - ✓ PFS(Investigator, INV), ORR, DCR, DOR, OS, TTF, safety
- **Exploratory endpoints:**
  - ✓ To identify biomarkers in tissue and plasma that are associated with acquired resistance to bevacizumab combined with erlotinib or erlotinib alone in NSCLC

- **Stratified by**
  - ✓ Sex (female vs. male)
  - ✓ Disease stage(stage IIIb vs. stage IV vs. recurrence)
  - ✓ EGFR gene mutation (exon 19 del vs. exon 21 L858R)

PFS: Progression-free Survival; ORR: Objective Response Rate; DCR: Disease Control Rate; DOR: Duration of Response; OS: Overall Survival; TTF: Time to Treatment Failure

PRIMARY ENDPOINT : PFS BY IRC (ITT POPULATION)

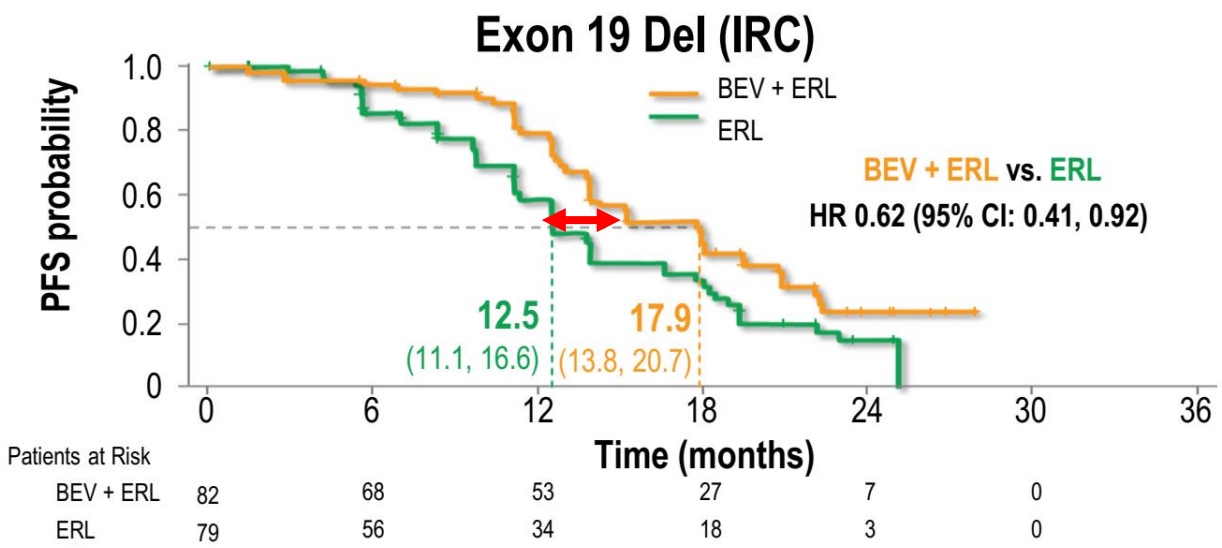


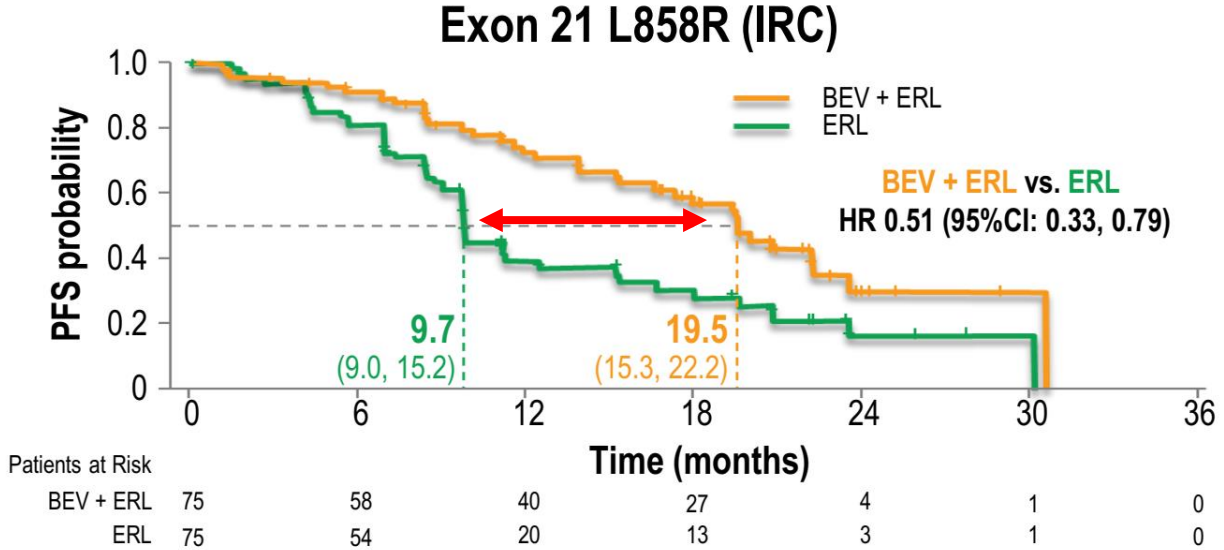
	BEV+ERL (n=157)	ERL (n=154)
Events	81 (51.6%)	97 (63.0%)
Median, mo	18.0	11.3
(95% CI)	(15.2, 20.7)	(9.8, 13.8)
HR (95% CI)	0.55 (0.41, 0.75)	
P-value (log-rank)	<0.001	

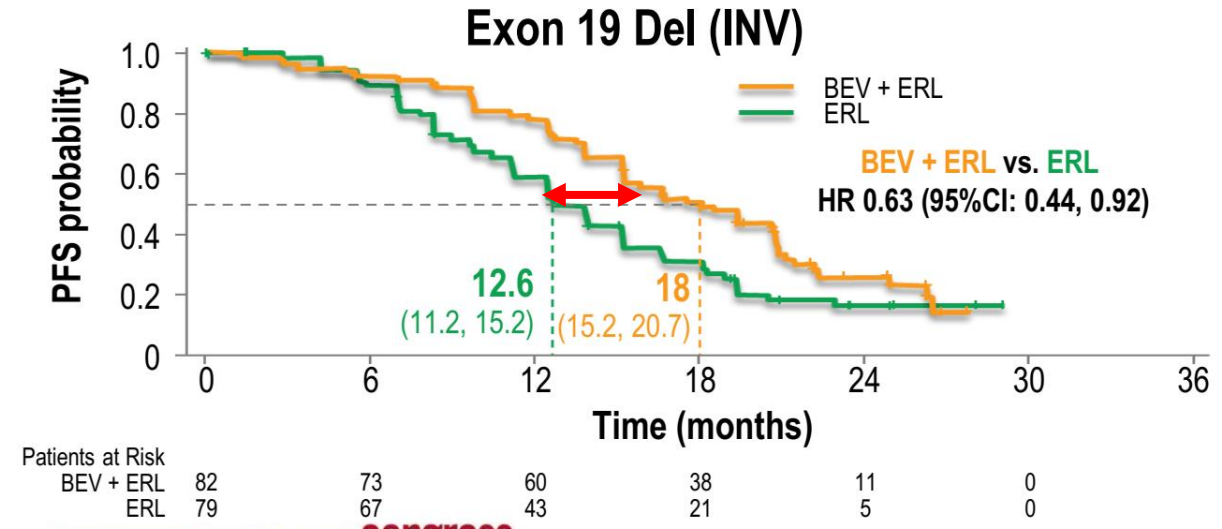
Patients at Risk

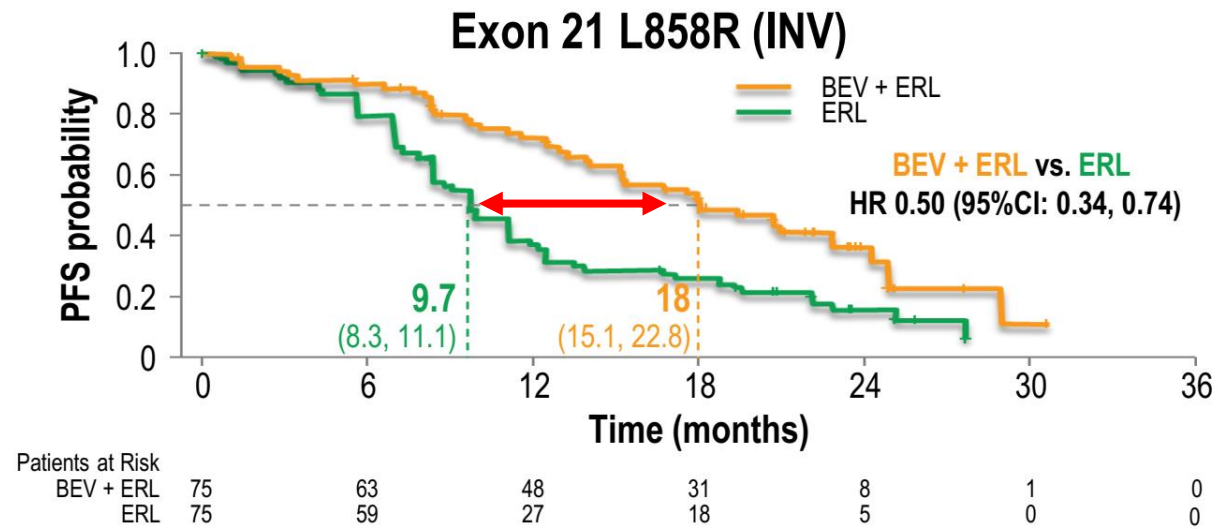
BEV + ERL	157	126	93	54	11	1	0
ERL	154	110	54	31	6	1	0

PFS BY EGFR MUTATUION TYPE（ITT POPULATION）









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TUMOR RESPONSE (RESPONSE EVALUABLE POPULATION)

RR (IRC)

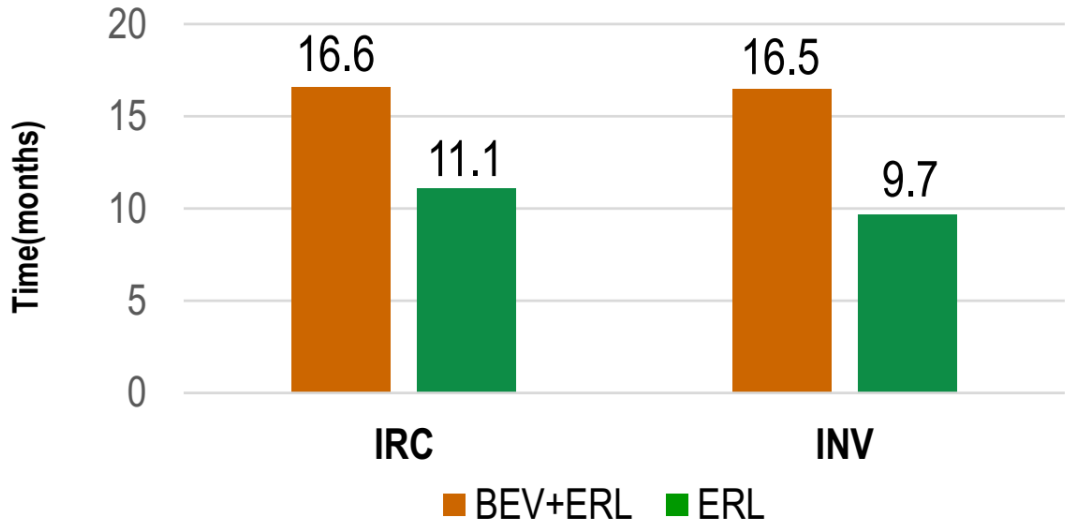
	BEV+ERL (n=146)	ERL (n=144)	*P -value
ORR	86.3%	84.7%	0.741
DCR	95.9%	96.5%	>0.999

RR (INV)

	BEV+ERL (n=156)	ERL (n=152)	*P -value
ORR	80.1%	77.6%	0.676
DCR	94.9%	95.4%	>0.999

*Based on Fisher's exact test.

DOR

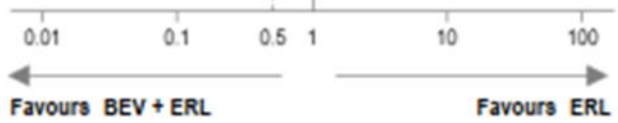


DOR(IRC)	BEV+ERL (n=126)	ERL (n=122)
Median, mo (95% CI)	16.6 (13.8, 18.1)	11.1 (8.6, 12.5)
HR (95% CI)	0.59 (95%CI: 0.42, 0.82)	
DOR(INV)	**BEV+ERL (n=125)**	**ERL (n=118)**
Median, mo (95% CI)	16.5 (13.8, 19.3)	9.7 (8.4, 11.2)
HR (95% CI)	0.57 (95%CI: 0.43, 0.77)	

Subgroup analyses: EGFR+ patients with brain metastases

CTONG 1509

Subgroup	Total number of patients/events (n/N)	BEV + ERL (n/N)	ERL (n/N)	Hazard Ratio and 95% CI	HR with its 95%CI
All	311/178	157/81	154/97		0.55 (0.41, 0.75)
Baseline brain metastasis: Yes	91/53	44/23	47/30		0.50 (0.28, 0.88)
Baseline brain metastasis: No	220/125	113/58	107/67		0.59 (0.42, 0.85)



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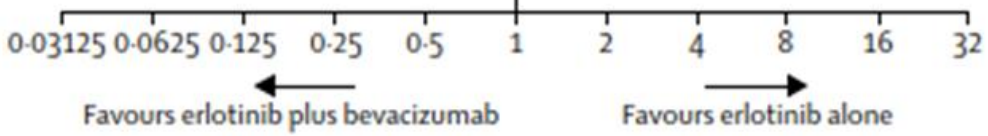
NEJ 026

	Erlotinib plus bevacizumab (n/N)	Erlotinib alone (n/N)	HR (95% CI)
CNS metastases			
No	30/76	44/76	0·56 (0·35–0·90)
Yes	22/36	21/36	0·78 (0·42–1·43)
Pleural effusion			
No	29/67	36/66	0·67 (0·41–1·10)
Yes	23/45	29/46	0·58 (0·34–1·02)
Overall	**52/112**	**65/112**	**0·63 (0·43–0·91)**



Saito et al., 2019 *the lancet*
Wu et al., 2019 ESMO

RELAY: A multicenter, double-blind, randomized Phase 3 study of erlotinib in combination with ramucirumab or placebo in previously untreated patients with epidermal growth factor receptor mutation-positive metastatic non-small cell lung cancer

Kazuhiko Nakagawa[1], Edward B. Garon[2], Takashi Seto[3], Makoto Nishio[4], Santiago Ponce Aix[5], Chao-Hua Chiu[6], Keunchil Park[7], Silvia Novello[8], Ernest Nadal[9], Fumio Imamura[10], Kiyotaka Yoh[11], Jin-Yuan Shih[12], Kwok Hung Au[13], Denis Moro-Sibilot[14], Sotaro Enatsu[15], Annamaria Zimmermann[16], Bente Frimodt-Moller[17], Carla Visseren-Grul[18], Martin Reck[19], for the RELAY study investigators

[1]Kindai University Faculty of Medicine, Osaka, Japan; [2]David Geffen School of Medicine at UCLA/TRIO-US Network, Los Angeles, CA, USA; [3]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [4]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [5]Universidad Complutense & Ciberonc, Madrid, Spain; [6]Taipei Veterans General Hospital, Taipei, Taiwan; [7]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [8]University of Turin, AOU San Luigi, Orbassano, Italy; [9]Catalan Institute of Oncology, Barcelona, Spain; [10]Osaka International Cancer Institute, Osaka, Japan; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]National Taiwan University Hospital, Taipei, Taiwan; [13]Queen Elizabeth Hospital, Kowloon, Hong Kong; [14]Grenoble University Hospital, Grenoble, France; [15]Eli Lilly Japan K.K. Kobe, Japan; [16]Eli Lilly and Company, Indianapolis, IN; [17]Eli Lilly and Company, Copenhagen, Denmark; [18]Lilly Oncology, Utrecht, Netherlands; [19]German Center for Lung Research (DZL), Grosshansdorf, Germany

PRESENTED AT: 2019 ASCO ANNUAL MEETING

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

RELAY: Study Design[1,2]

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

Phase 3[a]
N=449

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

Stratification factors

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

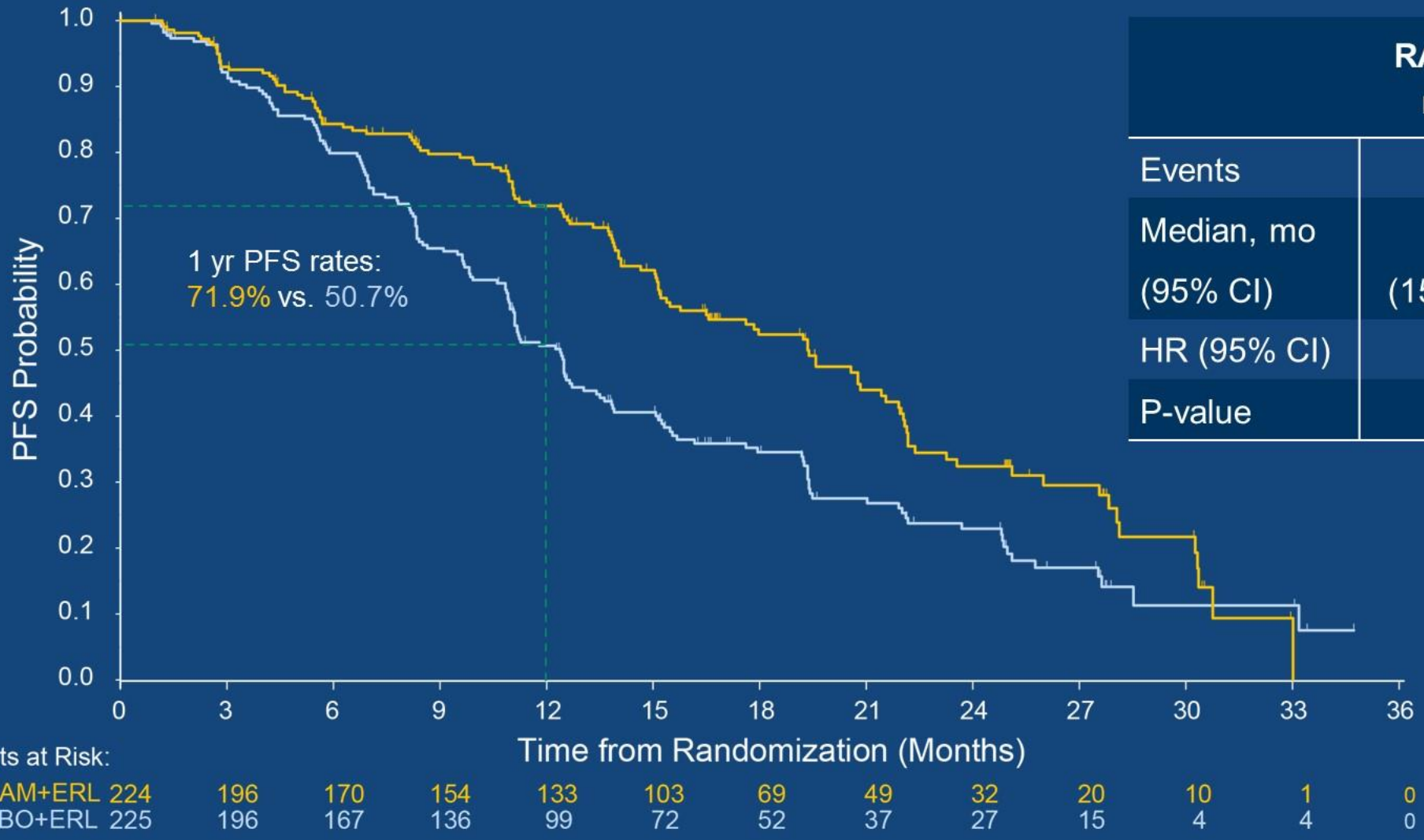
[a]Phase 3 enrollment began after confirmation of dose and schedule in Phase 1b[2]

1. Garon EB et al. *Clin Lung Cancer* 2017; 2. Reck M et al. *Clin Lung Cancer* 2018

Clinicaltrials.gov NCT02411448

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

RELAY Primary Endpoint: PFS (Investigator-Assessed)



	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	

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

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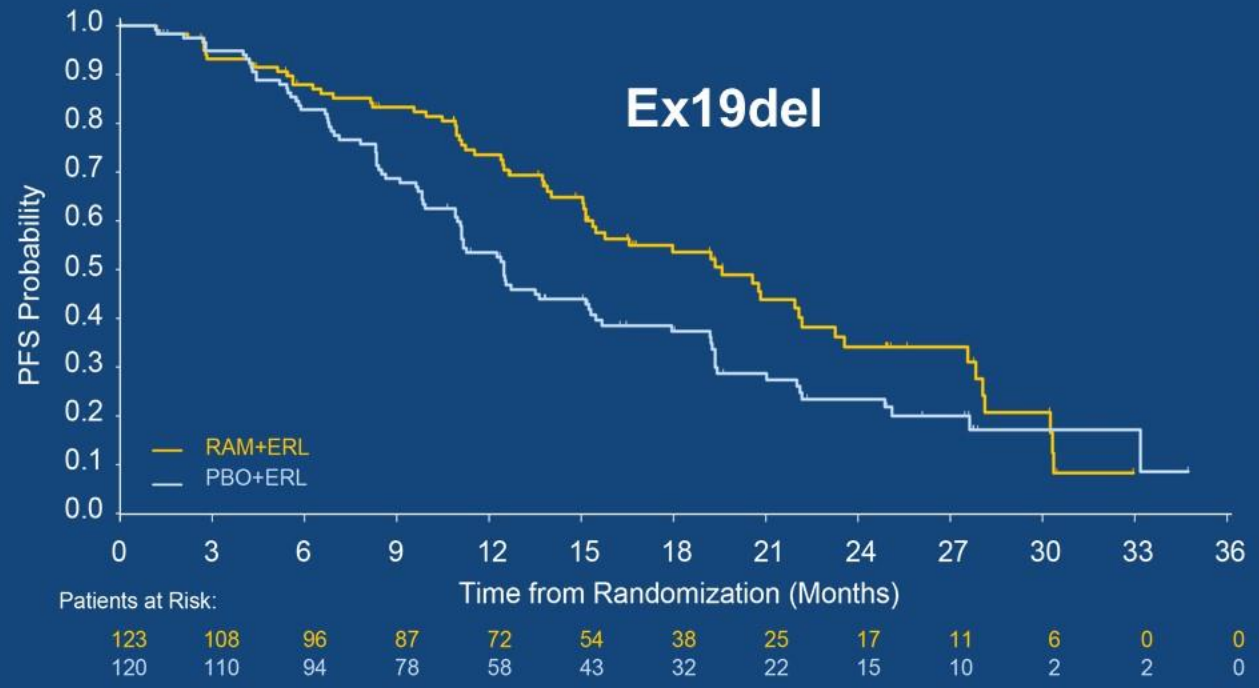
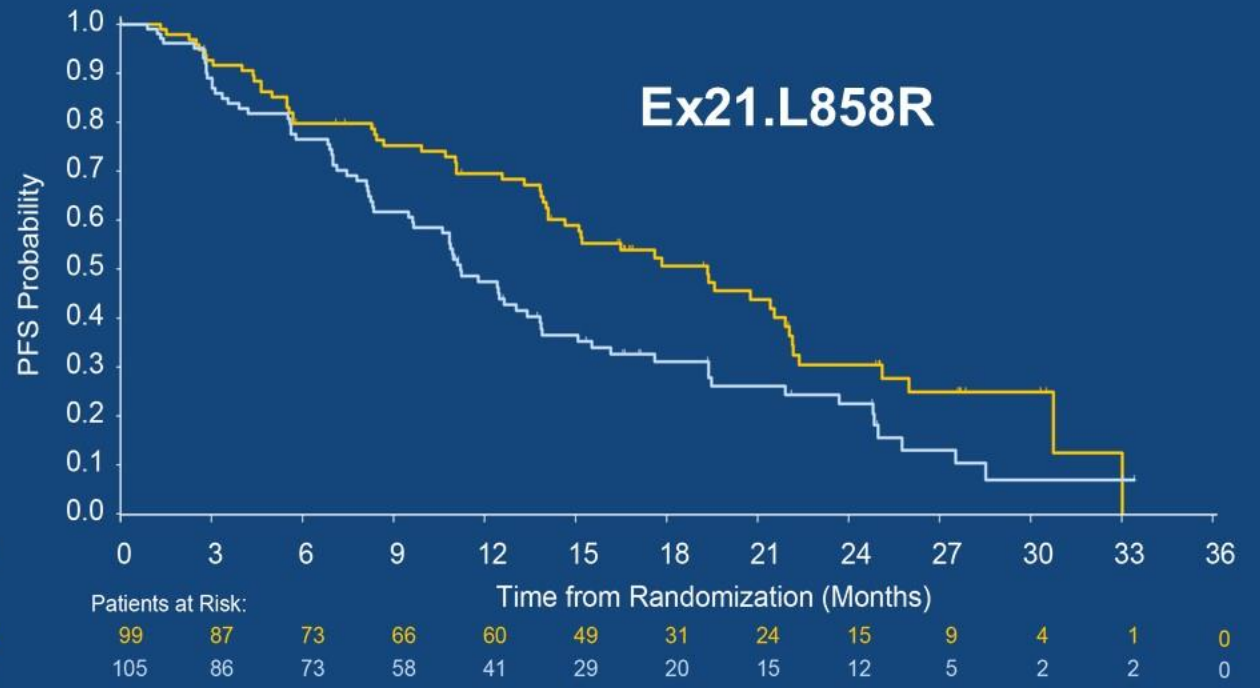
RELAY: PFS by EGFR Mutation Type





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

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

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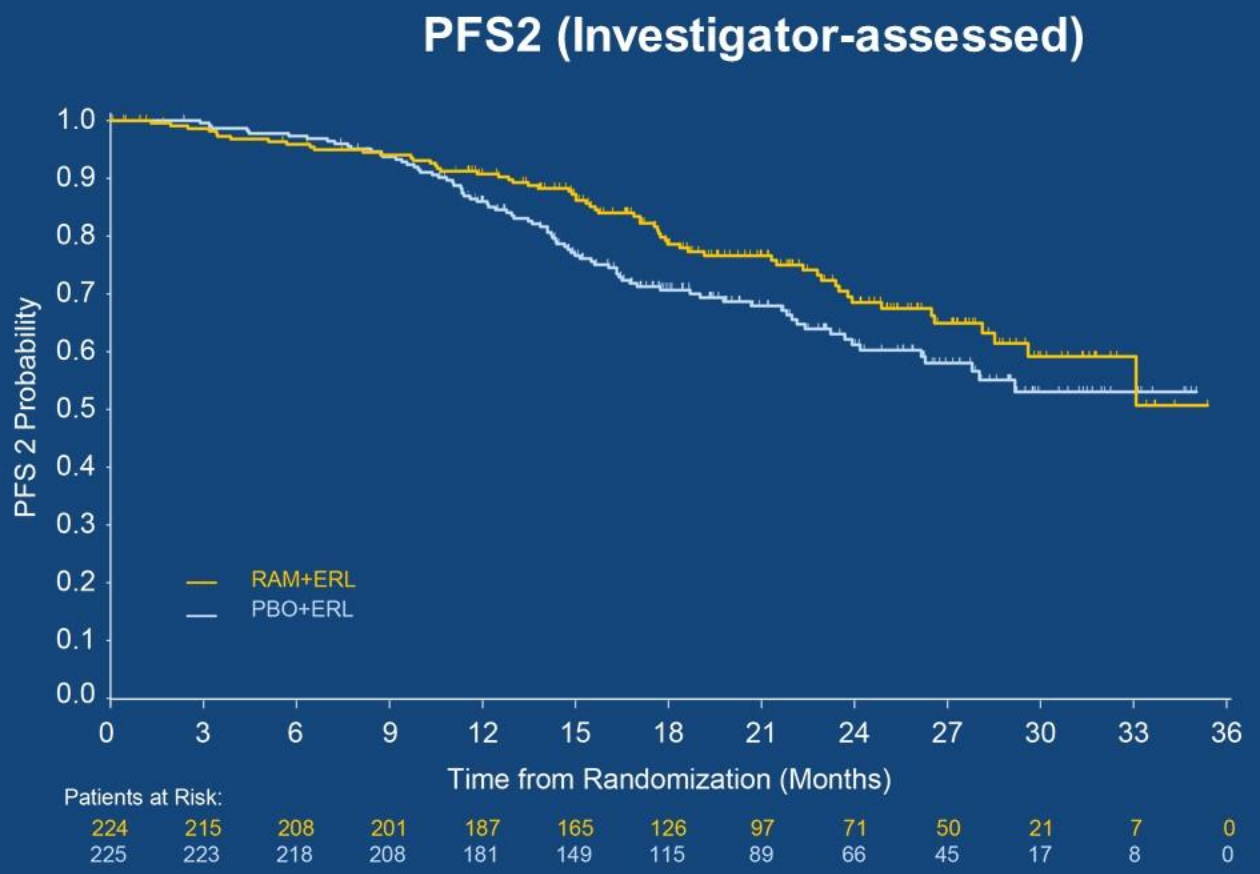
RELAY: PFS2 and Interim OS

		RAM+ERL N=224	PBO+ERL N=225
PFS2	Events,	61	79
	Censoring rate	73%	65%
	Median, mo	NR	NR
	HR (95% CI)	0.690 (0.490, 0.972)	
Interim OS	Events	37	42
	Censoring rate	83%	81%
	Median, mo	NR	NR
	HR (95% CI)	0.832 (0.532, 1.303)	



PFS2 defined as the time from randomization to 2nd disease progression (defined as objective radiological or symptomatic progression after start of additional systematic anticancer treatment), or death from any cause, whichever comes first.

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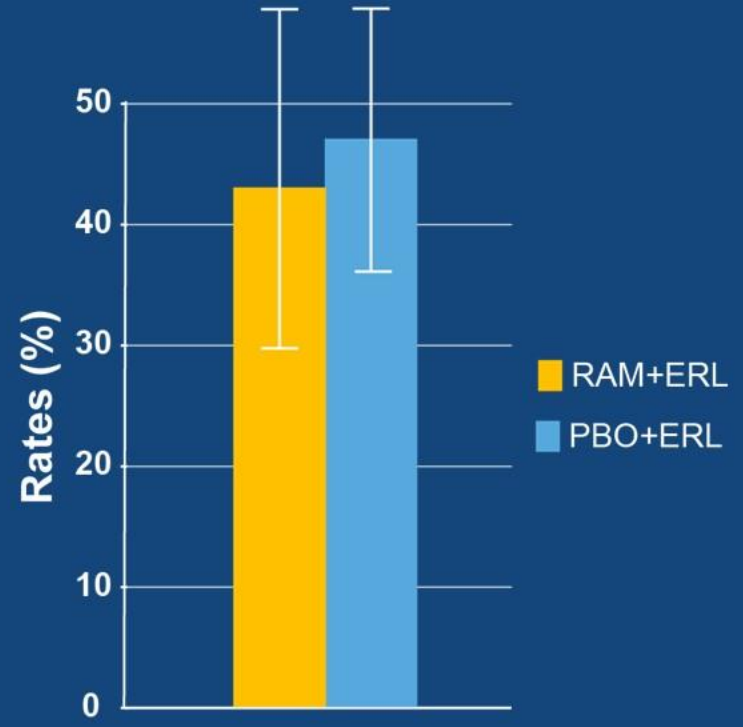
RELAY: EGFR T790M Rates Post-Progression

- 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

NGS = Next Generation Sequencing



30-Day FU Post-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	

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Summary of NEJ-026, CTONG 1509, and RELAY

	NEJ-026 (ph III)	CTONG 1509 (ph III)	RELAY (ph III)
Regimen	Erlotinib + Bevacizumab	Erlotinib + Bevacizumab	Erlotinib + Ramucirumab
Patient number	114+114 (Japanese)	157+154 (Chinese)	224+225 (Global)
Recruit criteria	CNS meta allowed	**CNS meta allowed**	no CNS meta
PFS HR	ITT **0.605**(0.42-0.88) No CNS **0.56**(0.35-0.90) CNS **0.78**(0.42-1.43)	ITT **0.55**(0.41-0.75) No CNS **0.59**(0.42-0.85) CNS **0.50**(0.28-0.88)	**0.59**(0.46-0.76)
median PFS	ITT **16.9** vs **13.3** no CNS **18.0** vs **15.1** CNS **12.7** vs **11.2**	ITT **18** vs **11.3**	19.4 vs 12.4
ORR	**72%** vs **66%**	**86.3%** vs **84.7%**	**76%** vs **75%**

Saito et al., 2019 *the lancet*
Nakagawa et al., 2019 ASCO
Wu et al., 2019 ESMO

Ongoing trials with TKI + Bevacizumab

ongoing

ELSEVIER

Clinical Lung Cancer

Volume 20, Issue 2, March 2019, Pages 134-138

Current Trial Report

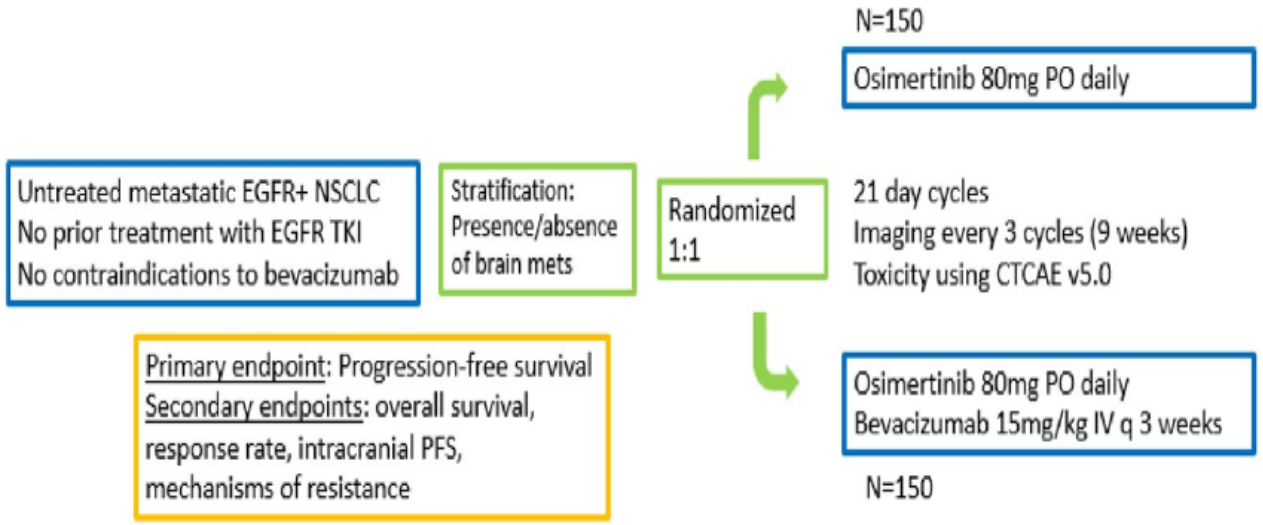
Phase 2 Study of Afatinib Alone or Combined With Bevacizumab in Chemonaive Patients With Advanced Non–Small-Cell Lung Cancer Harboring *EGFR* Mutations: AfaBev-CS Study Protocol

Takashi Ninomiya [1, 2], Nobuhisa Ishikawa [3], Koji Inoue [4], Toshio Kubo [5], Masayuki Yasugi [6], Takuo Shibayama [7], Tadashi Maeda [8], Kazunori Fujitaka [9], Masahiro Kodani [10], Toshihide Yokoyama [11], Shoichi Kuyama [12], Nobuaki Ochi [13], Yutaka Ueda [14], Seigo Miyoshi [15], Toshiyuki Kozuki [16], Yoshihiro Amano [17], Tetsuya Kubota [18], Keisuke Sugimoto [19] ... Katsuyuki Kiura [2]

Show more

https://doi.org/10.1016/j.cllc.2018.10.008

planning



Yu et al., 2019 ASCO

Tyrosine Kinase Inhibitor Plus Metformin

JAMA Oncology | Original Investigation

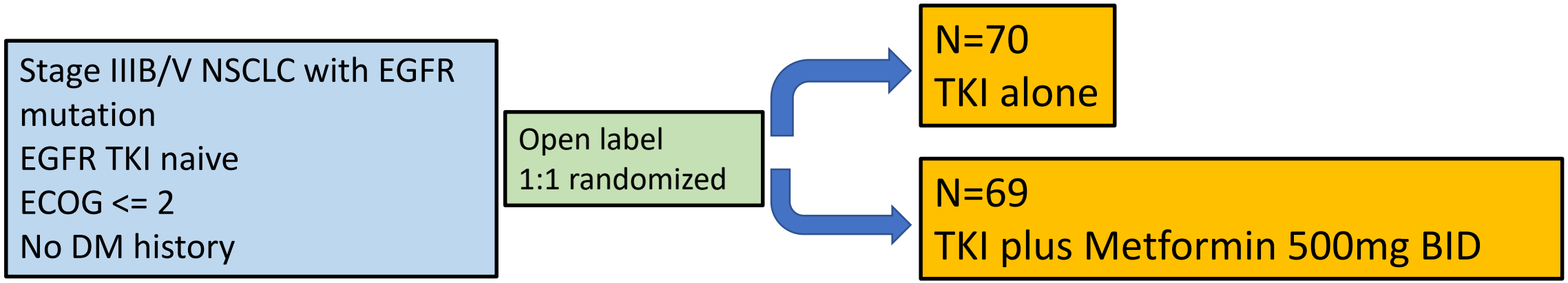
Effect of Metformin Plus Tyrosine Kinase Inhibitors Compared With Tyrosine Kinase Inhibitors Alone in Patients With Epidermal Growth Factor Receptor–Mutated Lung Adenocarcinoma

A Phase 2 Randomized Clinical Trial

Oscar Arrieta, MD, MSc; Feliciano Barrón, MD; Miguel-Ángel Salinas Padilla, MD; Alejandro Avilés-Salas, MD; Laura Alejandra Ramírez-Tirado, MD, MSc; Manuel Jesús Arguelles Jiménez, MD; Edgar Vergara, MD, PhD; Zyanya Lucia Zatarain-Barrón, MD, MSc; Norma Hernández-Pedro, PhD; Andrés F. Cardona, MD, PhD; Graciela Cruz-Rico, PhD; Pedro Barrios-Bernal, BBs; Masao Yamamoto Ramos, MD; Rafael Rosell, MD, PhD

JAMA Oncol. Published online September 5, 2019

Study Design: TKI plus Metformin



Primary endpoint:

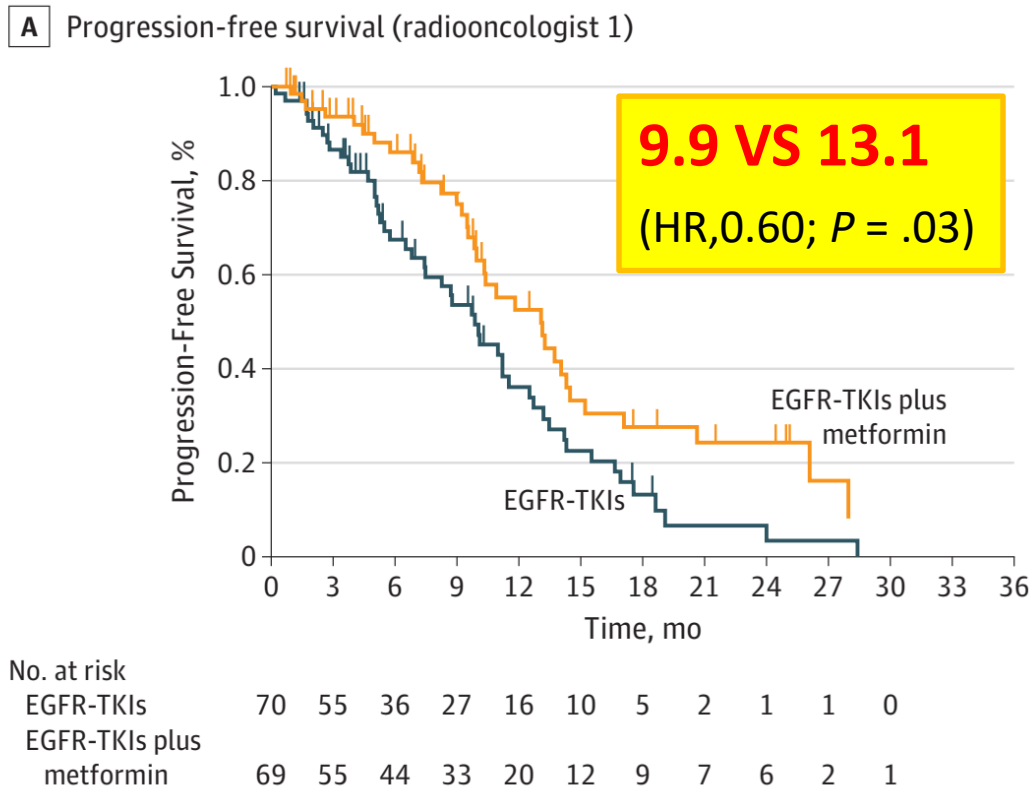
- PFS in the intent-to-treat population.

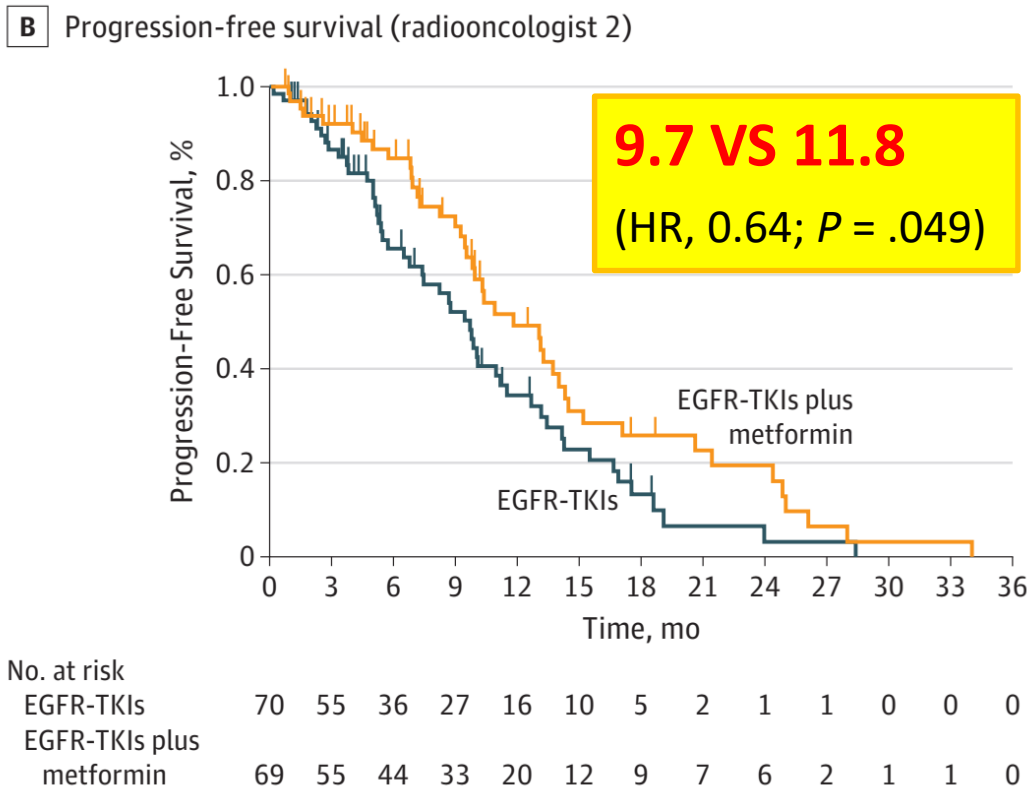
Secondary endpoin:

- objective response rate(ORR), disease control rate (DCR), overall survival (OS), and safety.

JAMA Oncol. Published online September 5, 2019

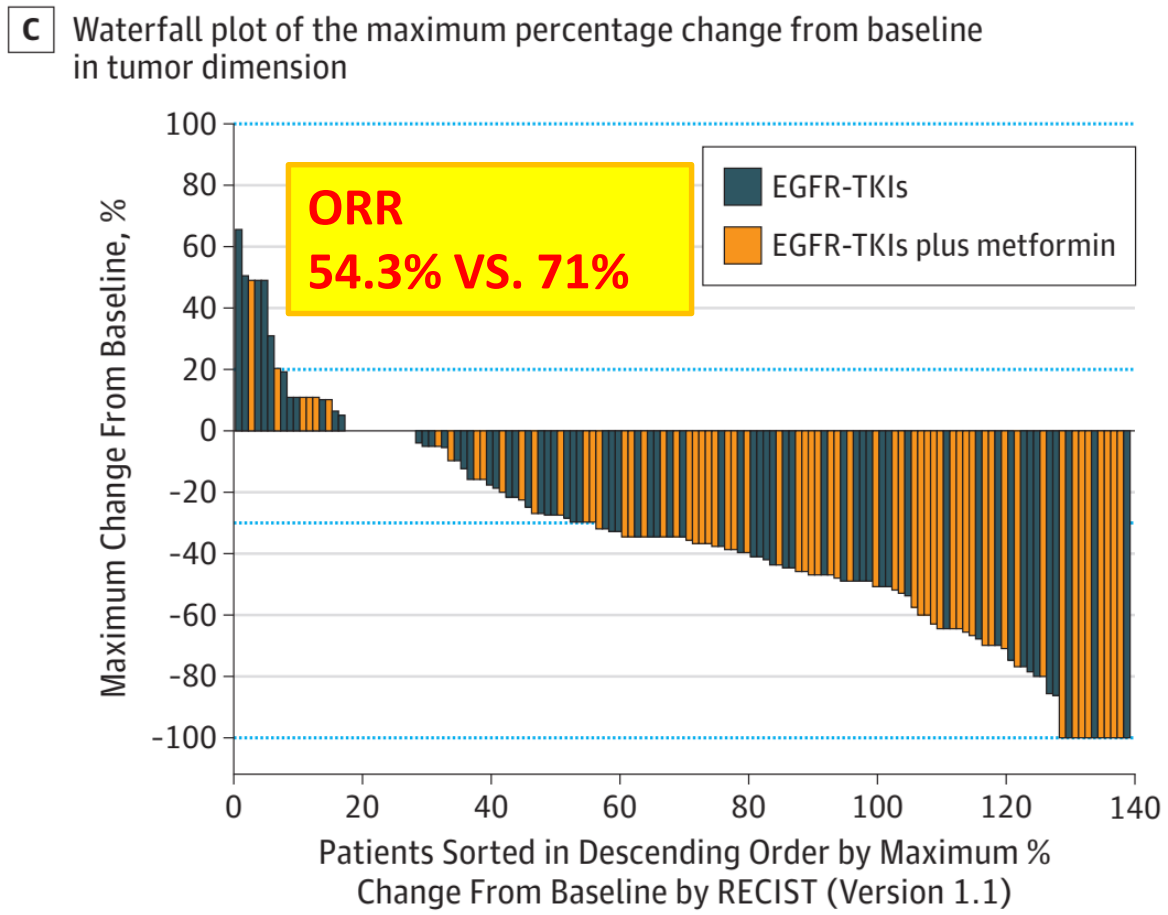
Primary endpoint: PFS

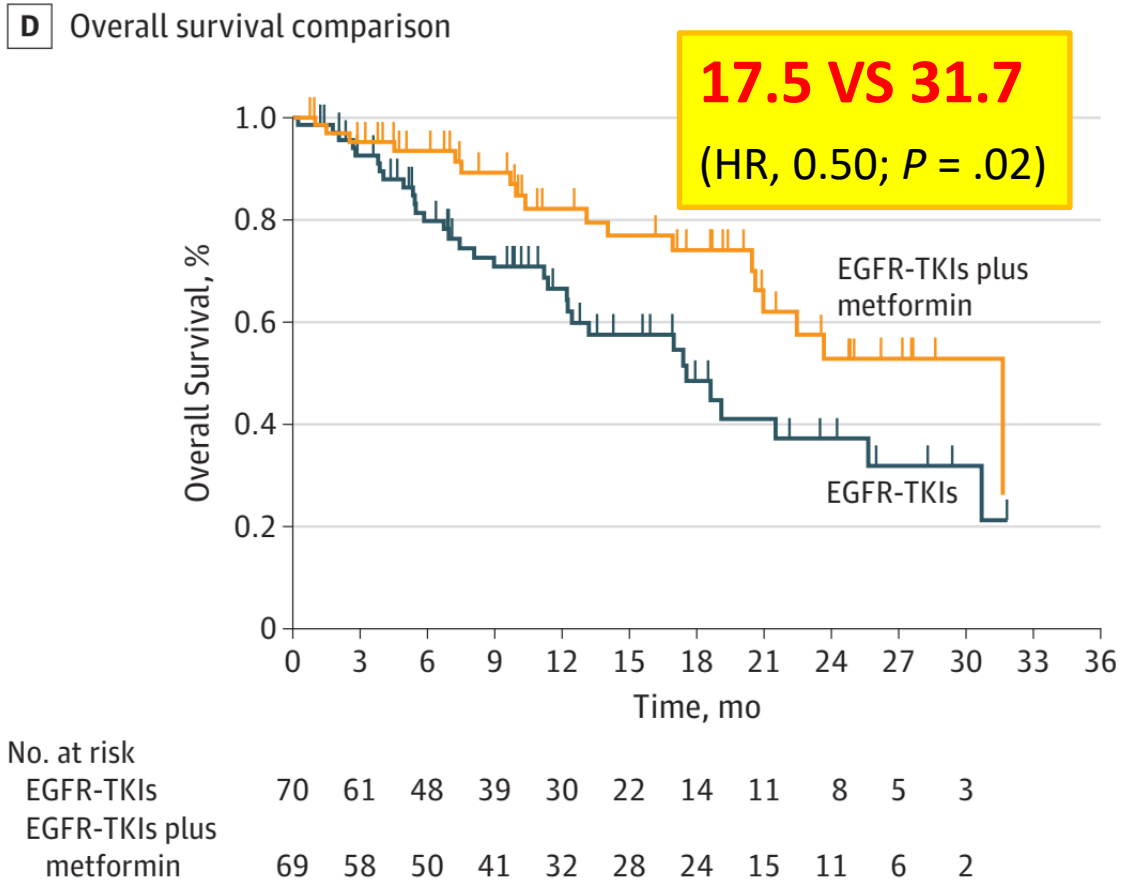




JAMA Oncol. Published online September 5, 2019

ORR and OS





JAMA Oncol. Published online September 5, 2019

Controversial result from China gefitinib + metformin study

Combination of metformin and gefitinib as first-line therapy for nondiabetic advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations: A multicenter, randomized, double-blind, placebo-controlled phase II trial.

Yong He, Li Li, Liyan Jiang, Yubo Wang, Yizhuo Zhao, Xiaoju Zhang, Guoming Wu, Xiangdong Zhou, Jianguo Sun, Jun Bai, Biyong Ren, Kun Tian, Zhi Xu, Hualiang Xiao, Qi Zhou, Rui Han, Hengyi Chen, Haidong Wang, Zhenzhou Yang, Chan Gao

We hereby examined metformin's first-line use alongside gefitinib in EGFR mutation positive (EGFRm) patients without diabetes. **Methods:** In this trial (NCT01864681), 224 non-diabetic patients with treatment naïve stage IIIB-IV EGFRm NSCLC were randomly assigned at 1:1 to receive gefitinib plus metformin or placebo. Gefitinib was administered at 250 mg once daily, while metformin/placebo was initiated at 500 mg once daily and then escalated to 1000 mg twice daily over 2 weeks. Dose reduction was permitted for metformin/placebo in case of intolerable toxicity. The primary endpoint was progression-free survival (PFS) rate at 1 year. Secondary endpoints were overall survival (OS), PFS, objective response rate (ORR), and safety. Serum levels of interleukin-6 were also subjected to exploratory analysis. **Results:** Baseline characteristics were well balanced between treatment groups. The median duration of follow-up was 19.15 (IQR 12.99-28.44) months. The estimated 1-year PFS rate was 41.2% (95% confidence interval [CI] 30.0-52.2) in the metformin group versus 42.9% (95% CI 32.6-52.7) in the placebo group (p = 0.6268). Metformin did not increase median PFS (10.3 months vs. 11.4 months), median OS (22.0 months vs. 27.5 months), or ORR (66.0% vs. 66.7%) over placebo. No significant treatment group differences in terms of PFS were detected across subgroups either, including those with elevated levels of interleukin-6. Metformin plus gefitinib shared a similar safety profile with the control group, except for a remarkably higher incidence of diarrhea (78.38% vs. 43.24%). **Conclusions:** Our study did not show enhanced gefitinib efficacy upon addition of metformin and hence does not support its concurrent use with first-line EGFR-TKI therapy in non-diabetic EGFRm NSCLC patients. Clinical trial information: NCT01864681.

He et al ., ASCO 2019

EGFR TKI Plus Chemotherapy

Phase III Study Comparing Gefitinib Monotherapy to Combination Therapy with Gefitinib, Carboplatin, and Pemetrexed for Untreated Patients with Advanced Non-Small Cell Lung Cancer with EGFR Mutations (NEJ009)

Atsushi Nakamura[1], Akira Inoue[2], Satoshi Morita[3], Yukio Hosomi[4], Terufumi Kato[5]
Tatsuro Fukuhara[6], Akihiko Gemma[7], Kazuhisa Takahashi[8], Yuka Fujita[9], Toshiyuki Harada[10]
Koichi Minato[11], Kei Takamura[12], Kunihiko Kobayashi[13], Toshihiro Nukiwa[14]

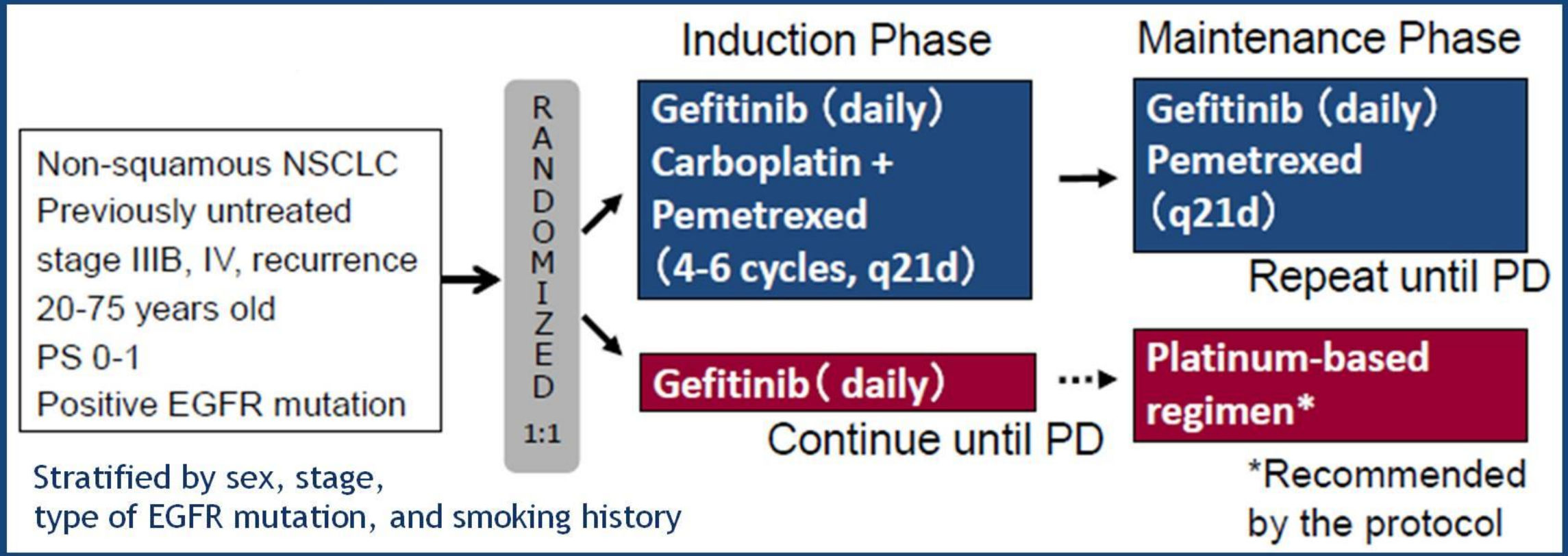
[1]Sendai Kousei Hospital, [2]Tohoku University School of Medicine, [3]Kyoto University Graduate School of Medicine
[4]Tokyo Metropolitan Komagome Hospital, [5]Kanagawa Cardiovascular & Respiratory Center, [6]Miyagi Cancer Center
[7]Nippon Medical School, [8]Juntendo University Graduate School of Medicine, [9]Asahikawa Medical Center
[10]JCHO Hokkaido Hospital, [11]Gunma Prefectural Cancer Center, [12]Obihiro Kosei General Hospital
[13]Saitama Medical University, [14]Tohoku University, Professor Emeritus

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Atsushi Nakamura

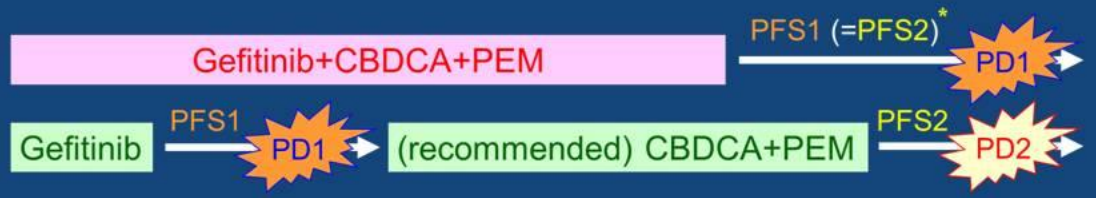
http://clicktoeditURL.com

Study Design of NEJ009



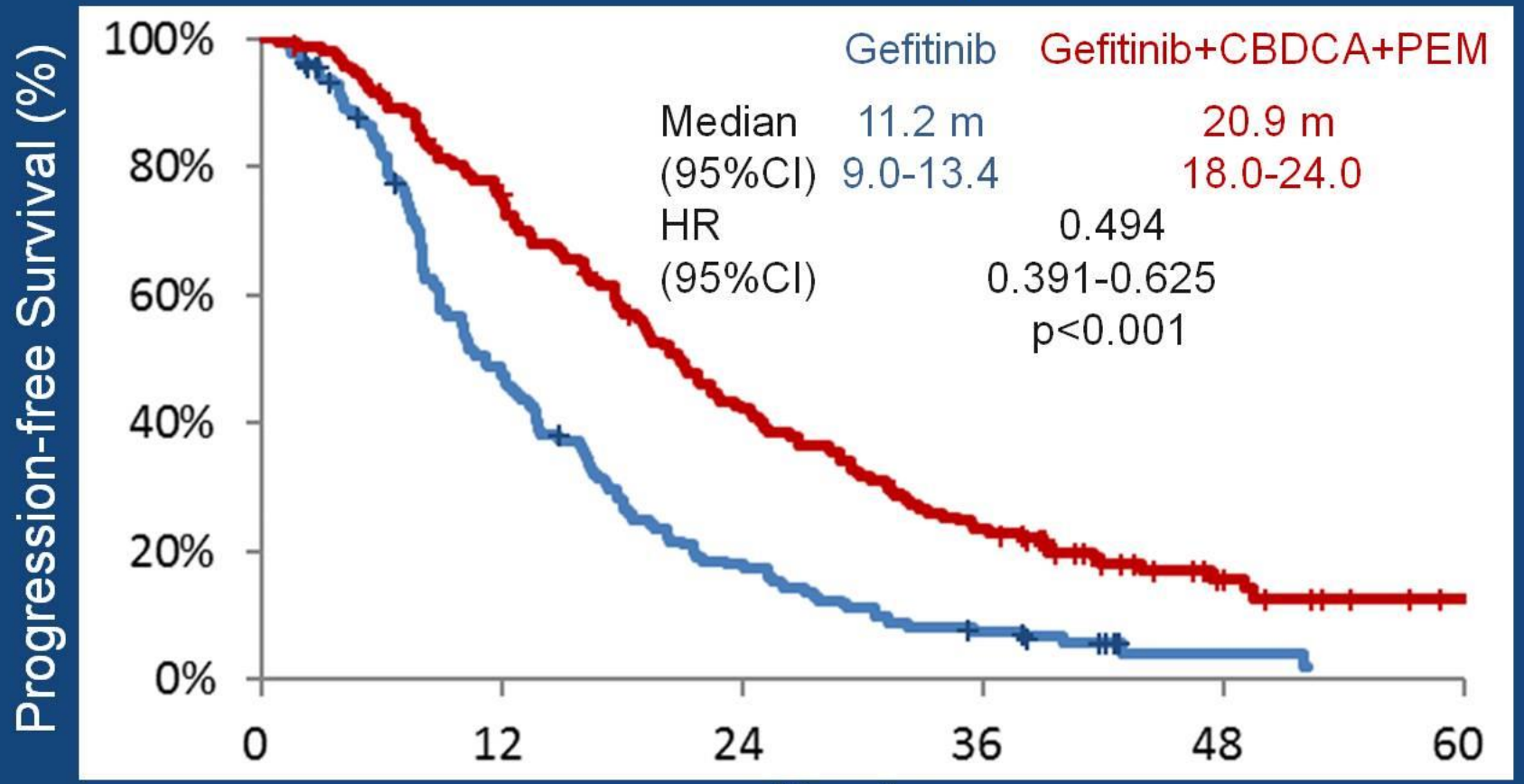
- From Oct. 2011 to Sep. 2014, 345 patients were enrolled from 47 institutions across Japan. In Oct.2017, a number of pre-planned events for primary endpoint analysis were observed.

Progression-Free Survival 1



Response Rate (%)

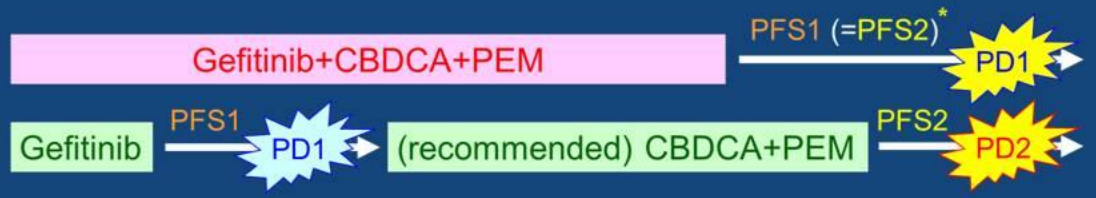
	Gefitinib	combo
CR	3.5	4.7
PR	64.0	79.3
SD	25.0	13.6
PD	4.7	1.2
ORR	67.4	84.0

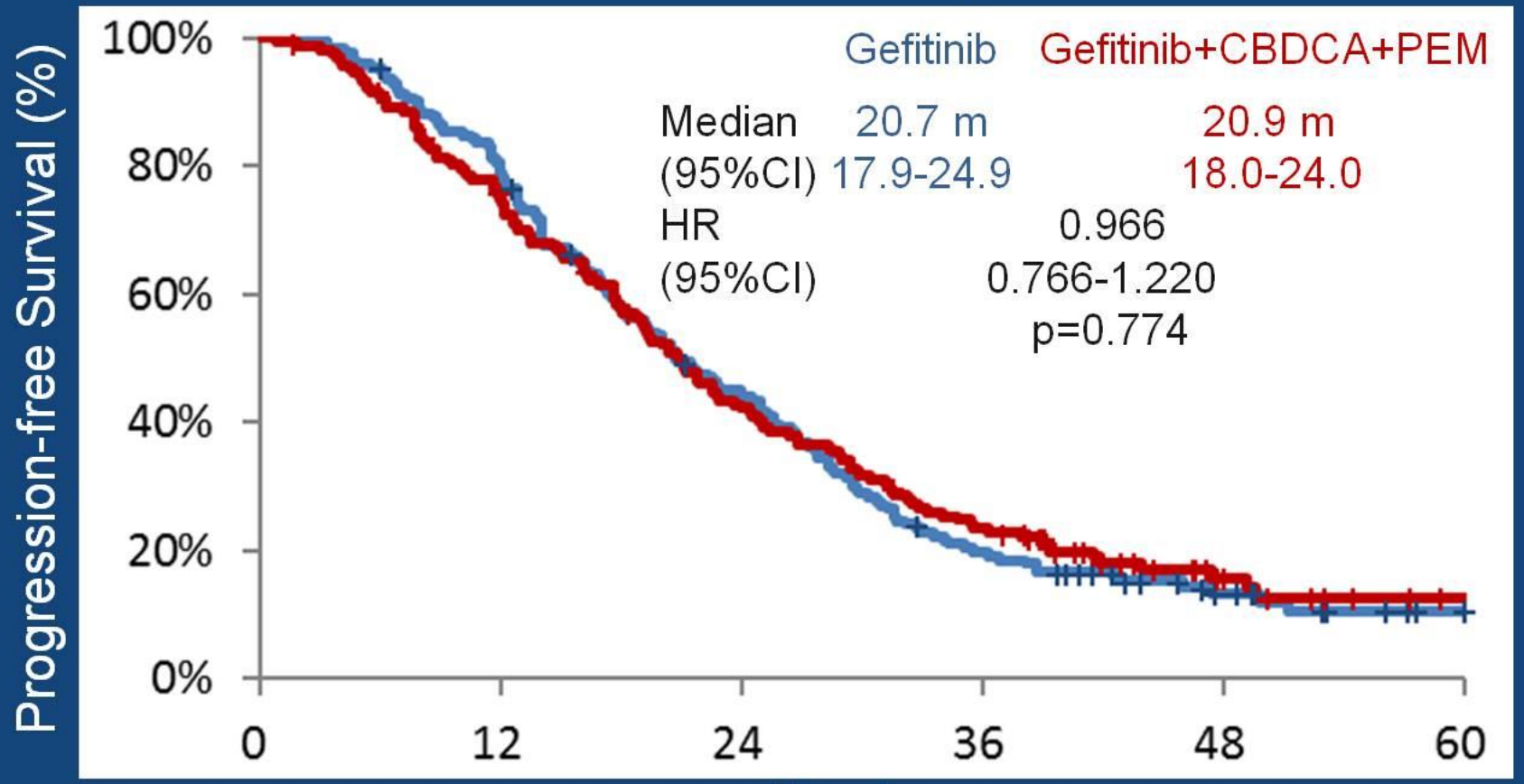


No. at Risk

Gefitinib	172	78	29	11	2	0
Gefitinib+CBDCA+PEM	169	123	68	37	10	2

Progression-Free Survival 2

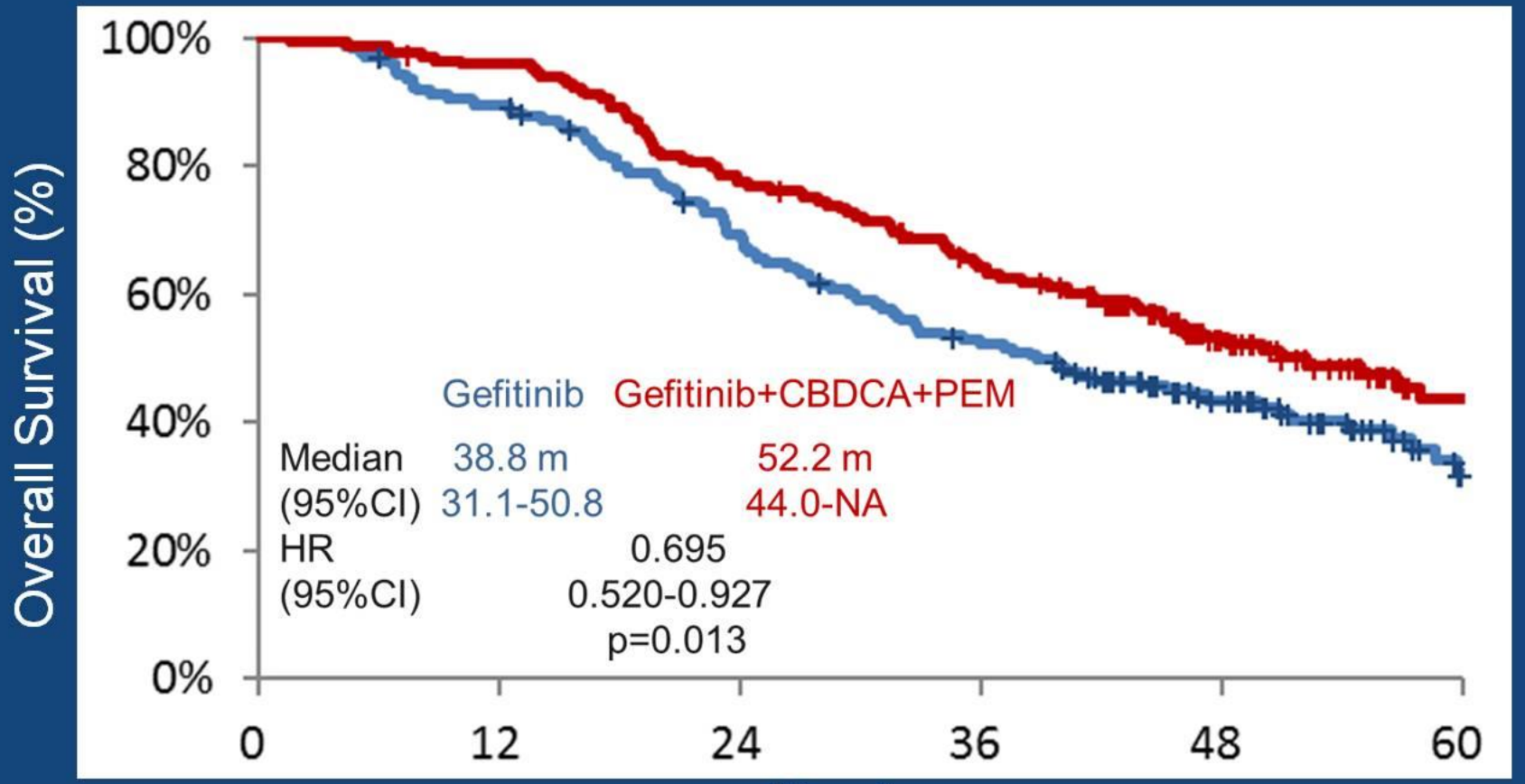




No. at Risk

Gefitinib	172	135	74	32	13	2
Gefitinib+CBDCA+PEM	169	123	68	37	10	2

Overall Survival



No. at Risk						
Gefitinib	172	153	115	86	50	14
Gefitinib+CBDCA+PEM	170	162	131	105	57	20

Adverse Events (>20%)

	Gefitinib (n=172)		Gefitinib+CBDCA+PEM (n=169)	
	Any Grade	≥ Grade3	Any Grade	≥ Grade3
Neutropenia	7 (4.1%)	1 (0.6%)	101 (59.8%)	53 (31.4%)
Anemia	35 (20.3%)	4 (2.3%)	113 (66.9%)	36 (21.3%)
Thrombocytopenia	9 (5.2%)	0 (0%)	91 (53.8%)	29 (17.2%)
Liver Dysfunction	99 (57.6%)	37 (21.5%)	100 (59.2%)	20 (11.8%)
Creatinine Elevation	10 (5.8%)	0 (0%)	43 (25.4%)	0 (0%)
Hyponatremia	6 (3.5%)	1 (0.6%)	34 (20.1%)	5 (3%)
Diarrhea	63 (36.6%)	2 (1.2%)	60 (35.5%)	7 (4.1%)
Stomatitis	29 (16.9%)	0 (0%)	52 (30.8%)	1 (0.6%)
Rash	136 (79.1%)	5 (2.9%)	109 (64.5%)	7 (4.1%)
Nail Changes	53 (30.8%)	2 (1.2%)	41 (24.3%)	4 (2.4%)
Constipation	16 (9.3%)	0 (0%)	52 (30.8%)	0 (0%)
Anorexia	29 (16.9%)	2 (1.2%)	99 (58.6%)	12 (7.1%)
Fatigue	20 (11.6%)	0 (0%)	58 (34.3%)	6 (3.6%)

Conclusion:

Unmet Need for EGFR mutation NSCLC patients

- Better PFS and OS despite current 1st and 2nd generation TKI use
  - 1st line Osimertinib
  - Combination therapy (TKI plus anti-VEGF/VEGFR, TKI plus Metformin??)
  - Combination with Immunotherapy / Chemotherapy / Anti-VEGF
- Less TKI related side effects
  - Can we predict who will developed severe side effects and give early treatment?
- Early prediction of treatment failure/acquired resistance
  - Quantitative plasma EGFR mutation monitor?
  - Add on treatment before major recurrence developed.