LUNG CANCER UPDATES

ASCO HIGHLIGHTS

1-5 JUNIO 2018, CHICAGO

Personalized approach in advanced NSCLC…EGFR mutated, what else could we do?

Rosario García Campelo

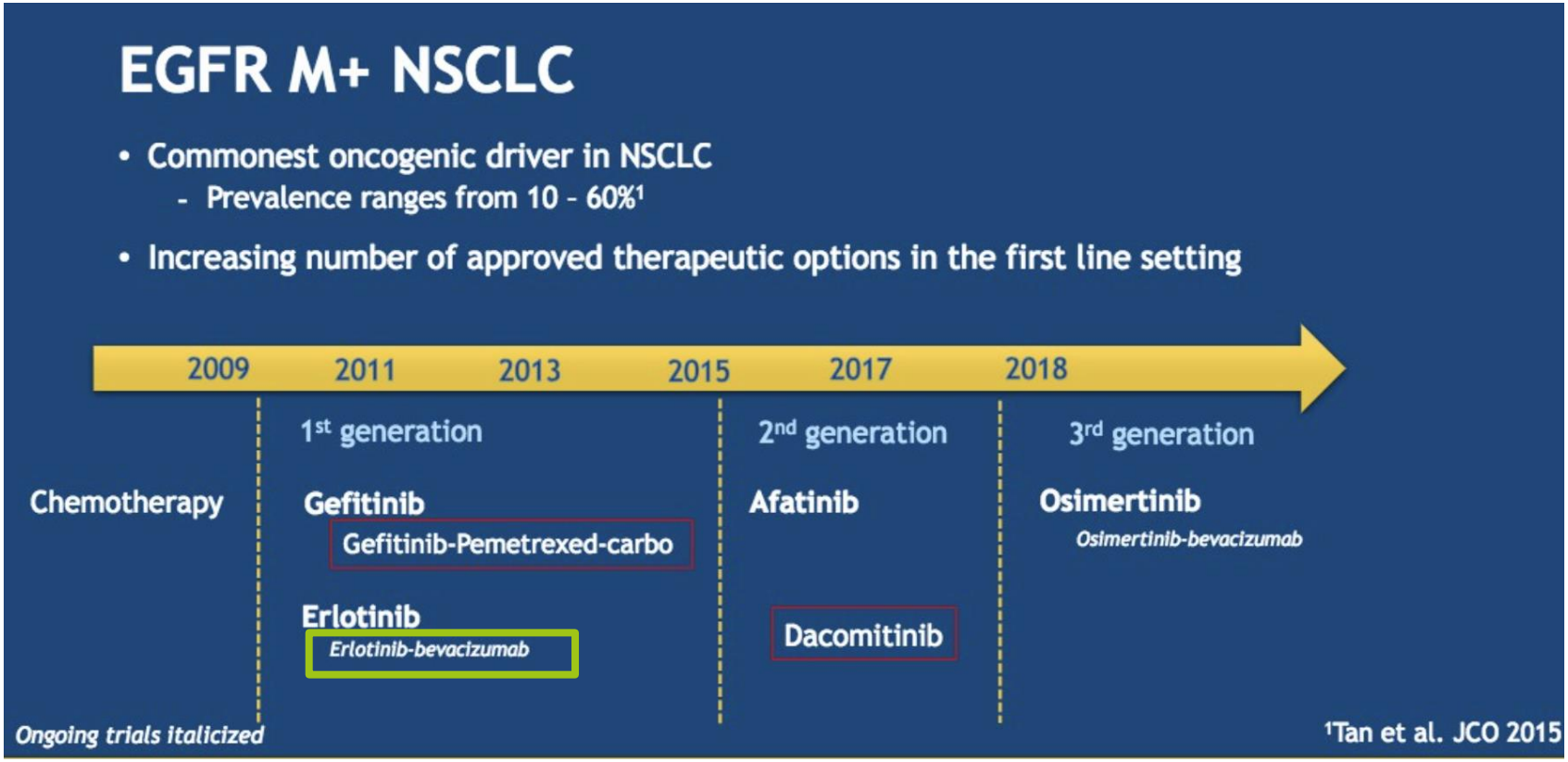
Medical Oncology Unit

University Hospital A Coruña

GECP

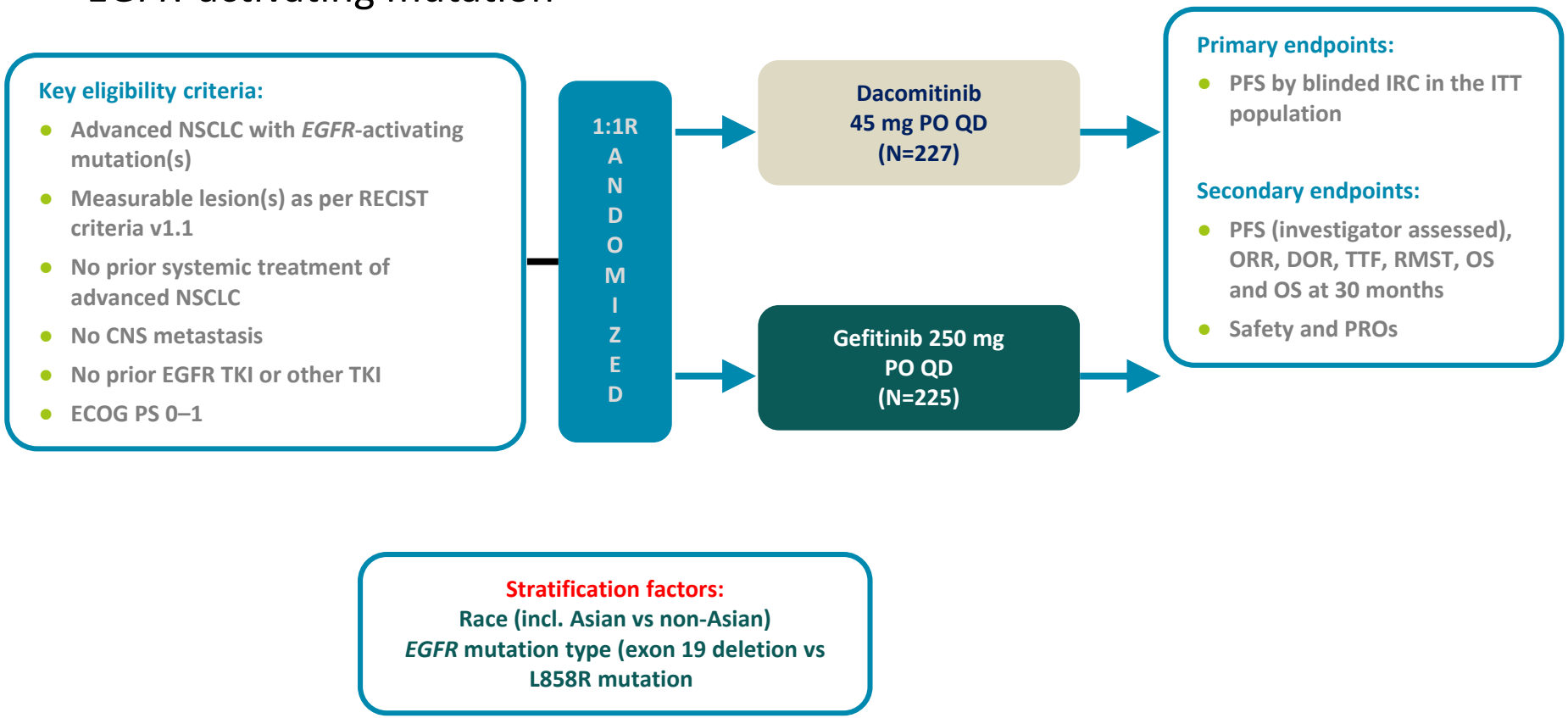
Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group


EGFR M+ NSCLC
• Commonest oncogenic driver in NSCLC
- Prevalence ranges from 10 - 60%[1]
• Increasing number of approved therapeutic options in the first line setting
2009
2011
2013
2015
2017
2018
1st generation
2nd generation
3rd generation
Chemotherapy
Gefitinib
Gefitinib-Pemetrexed-carbo
Erlotinib
Erlotinib-bevacizumab
Afatinib
Dacomitinib
Osimertinib
Osimertinib-bevacizumab
Ongoing trials italicized
[1]Tan et al. JCO 2015

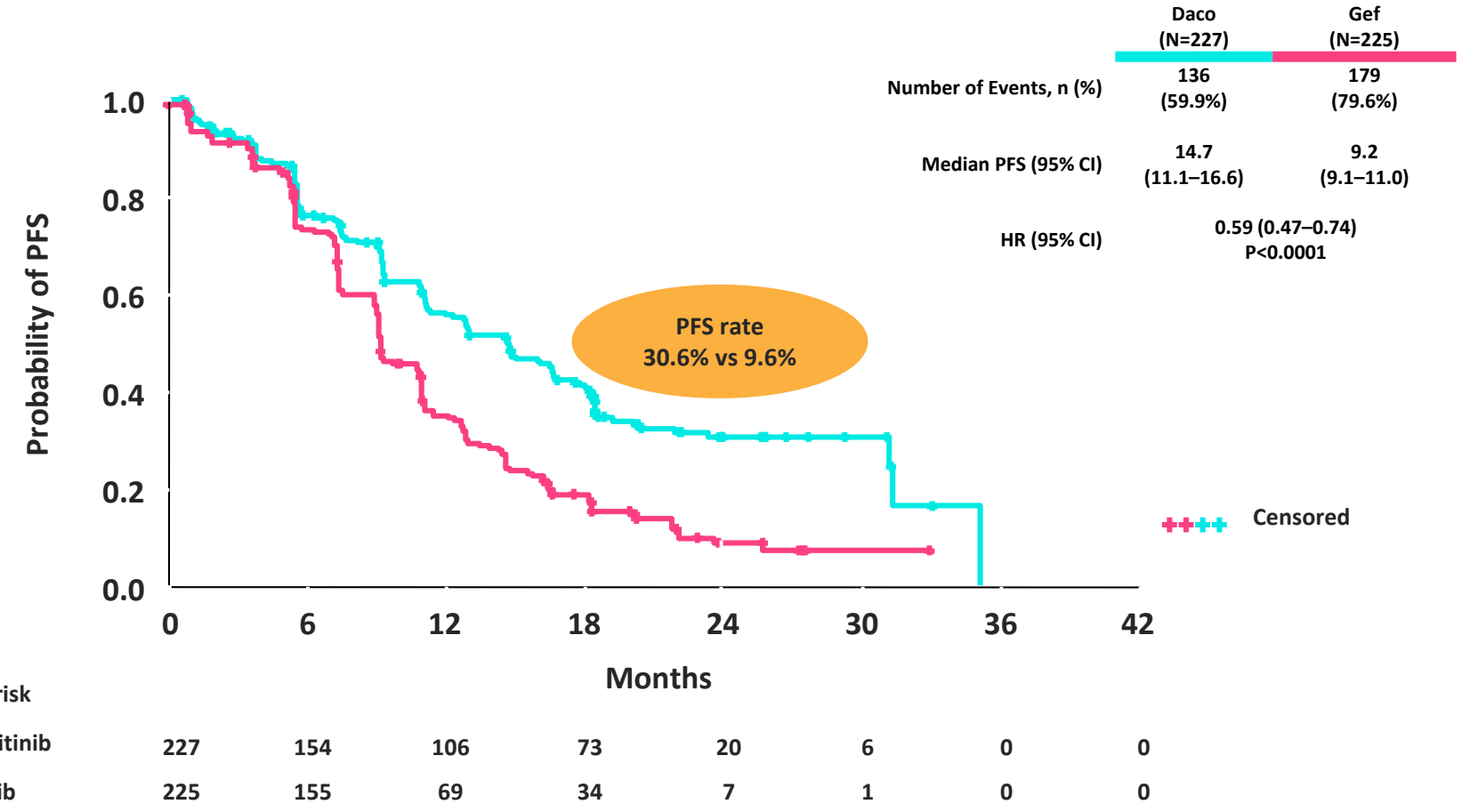
ARCHER 1050: Study Design

- Phase III randomized, open-label, study to evaluate dacomitinib as an alternative first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation



Mok et al. Abstr 9004

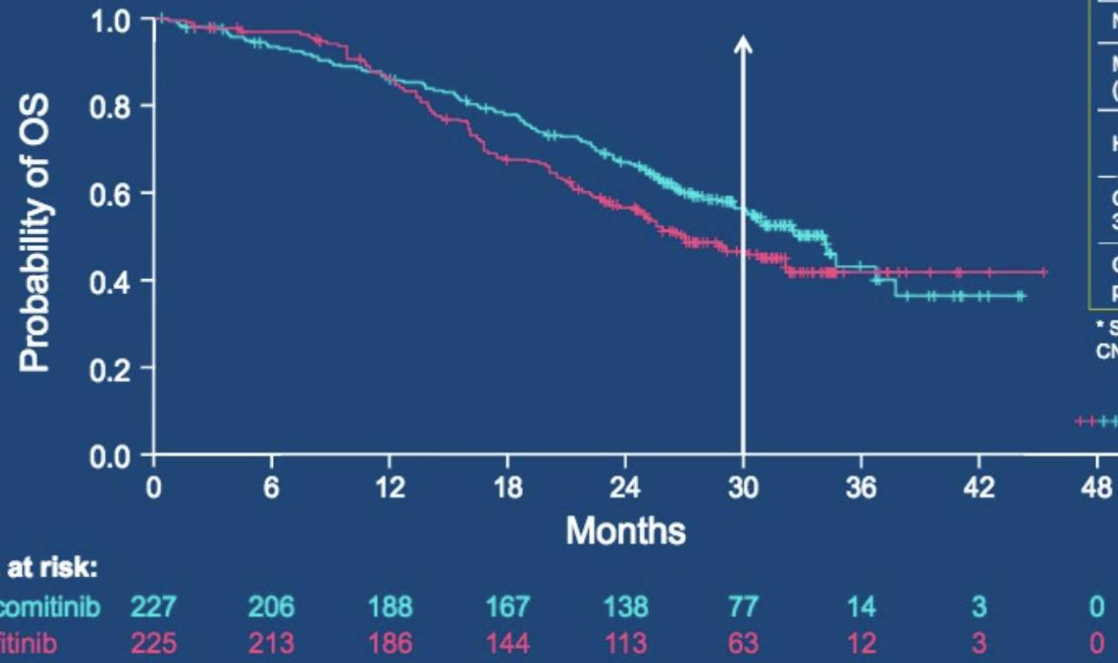
ARCHER 1050:
PFS by Independent Review – ITT Population



Wu Y-L, *et al. Lancet Oncol* 2017; doi:10.1016/S1470-2045(17)30608-3 (Epub ahead of print);
Dacomitinib (PF-00299804) is an investigational compound.

ARCHER 1050

Final OS (Primary Analysis)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Number of deaths, n (%)	103 (45.4)	117 (52.0)
Median OS, months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR* (95% CI)	0.760 (0.582, 0.993) 2-sided *P** = 0.0438	
OS probability at 30 months, %	56.2	46.3
CNS metastases at progression, n	1	11

* Stratified analysis.
CNS, central nervous system

ARCHER 1050

Updated Long-Term Adverse Events

Adverse Event,[a] n (%)	Dacomitinib (n = 227)			Gefitinib (n = 224)		
	Grade 1	Grade 2	≥ Grade 3[b]	Grade 1	Grade 2	≥ Grade 3[b]
Diarrhea[c]	113 (49.8)	65 (28.6)	20 (8.8)	103 (46.0)	20 (8.9)	2 (0.9)
Paronychia	46 (20.3)	77 (33.9)	17 (7.5)	30 (13.4)	12 (5.4)	3 (1.3)
Dermatitis acneiform	37 (16.3)	43 (18.9)	31 (13.7)	43 (19.2)	21 (9.4)	0
Stomatitis	51 (22.5)	40 (17.6)	8 (3.5)	33 (14.7)	6 (2.7)	1 (0.4)
Decreased appetite	40 (17.6)	23 (10.1)	7 (3.1)	48 (21.4)	6 (2.7)	1 (0.4)
Dry skin	42 (18.5)	18 (7.9)	3 (1.3)	35 (15.6)	3 (1.3)	0
Weight decreased	31 (13.7)	22 (9.7)	5 (2.2)	22 (9.8)	14 (6.3)	1 (0.4)
Alopecia	41 (18.1)	11 (4.8)	1 (0.4)	26 (11.6)	2 (0.9)	0
Cough	39 (17.2)	9 (4.0)	0	36 (16.1)	5 (2.2)	1 (0.4)
Pruritus	27 (11.9)	17 (7.5)	1 (0.4)	24 (10.7)	4 (1.8)	3 (1.3)
ALT increased	37 (16.3)	5 (2.2)	2 (0.9)	45 (20.1)	24 (10.7)	19 (8.5)
Conjunctivitis	27 (11.9)	16 (7.0)	0	6 (2.7)	3 (1.3)	0
Nausea	32 (14.1)	8 (3.5)	3 (1.3)	46 (20.5)	2 (0.9)	1 (0.4)
AST increased	41 (18.1)	1 (0.4)	0	56 (25.0)	16 (7.1)	9 (4.0)
Rash	19 (8.4)	11 (4.8)	10 (4.4)	22 (9.8)	2 (0.9)	0
Back pain	15 (6.6)	3 (1.3)	0	28 (12.5)	6 (2.7)	1 (0.4)

[a]Adverse events occurring in at least 15% of patients in either study group in the safety population. [b]There were no grade 4 events in either arm and one grade 5 event in the dacomitinib arm. [c]One patient (0.4%) in the dacomitinib arm had grade 5 diarrhea.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Dose Modification

Dacomitinib

- First dose reduction: 30 mg/day
- Second dose reduction: 15 mg/day

Gefitinib

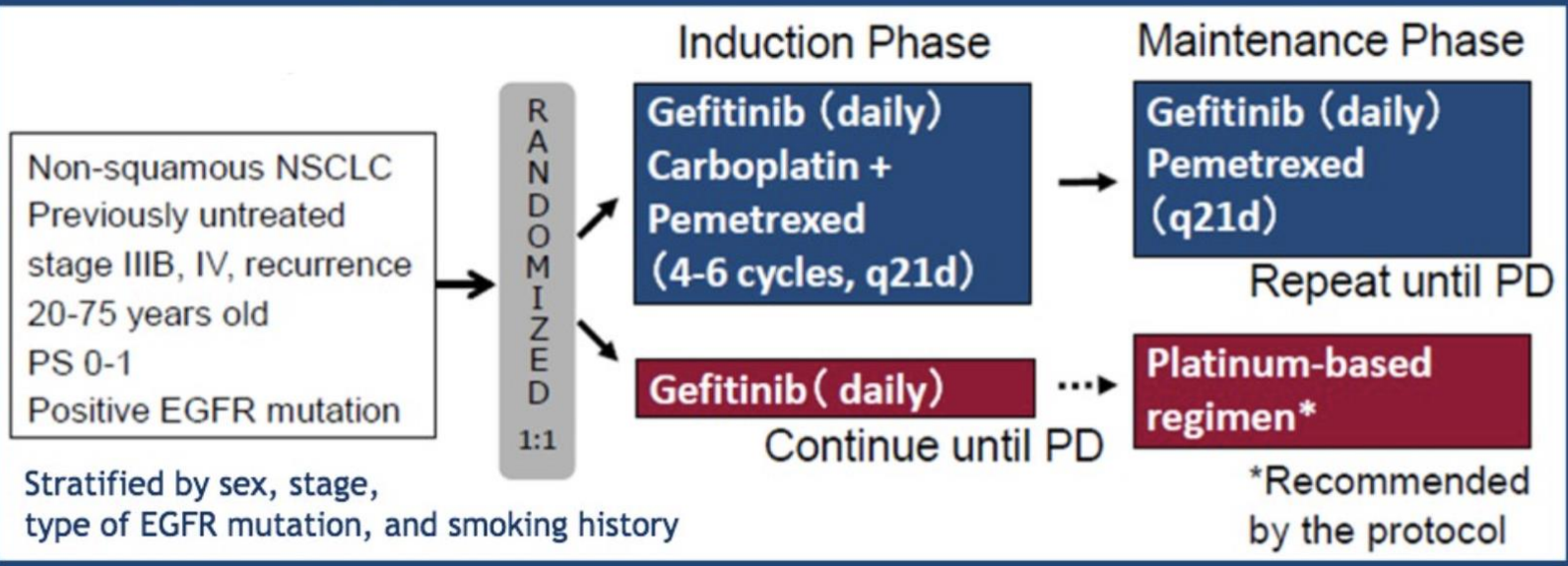
- 250 mg every 2 days

	Dacomitinib (n = 227)	Gefitinib (n = 224)
Median time to dose reduction, months (range)	2.8 (0.3–20.3)	3.3 (1.2–25.7)
Median duration of dose reduction, months (range)	11.3 (0.1–33.6)	5.2 (0.3–17.8)
Reduction to 30 mg daily, n (%)	88 (38.8)	NA
Reduction to 15 mg daily, n (%)	63 (27.8)	NA
Total number of patients with dose modification, n (%)	151 (66.5)	18 (8.0)

NA, not applicable.

NE J009: Phase III study comparing gefitinib to combination therapy with gefitinib, carboplatin, and pemetrexed for untreated patients with advanced NSCLC with EGFR mutations

Study Design of NEJ009

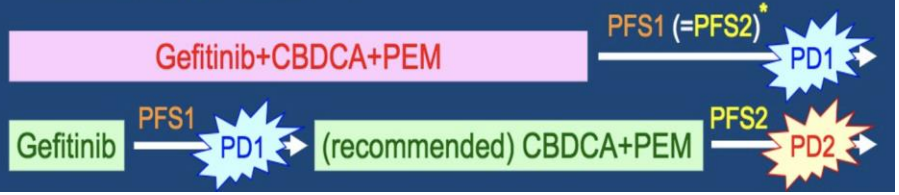


- From Oct. 2011 to Sep. 2014, 345 patients were enrolled from 47 institutions across Japan. In Oct.2017, a number of pre-planned events for primary endpoint analysis were observed.

Endpoints

- Initial protocol setting in Oct. 2011
  - Primary endpoint: OS
  - Secondary endpoints: PFS, PFS2*, ORR, Safety, QOL
- Protocol amendment in Feb. 2016 before the interim analysis
  - Multiple primary endpoints: PFS, PFS2*, and OS
  - Secondary endpoints: ORR, Safety, QOL

*PFS2 in this study indicates a comparison of PD2 in the reference arm and PD1 in the experimental arm.

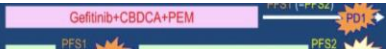


Statistical Considerations

- Planned patient enrollment: 340 patients (247 events required)
  - 80% power to show OS in HR=0.70 at two-sided α=0.05. (Study period 4 years with min follow-up 3.5 years)
- Multiple primary endpoints were sequentially (PFS → PFS2 → OS) analyzed.
  - Prespecified hierarchical sequential testing was used for multiplicity adjustment (two-sided α=0.05).
  - HR=0.70 was assumed (thus required number of events = 247) for PFS, PFS2, and OS, thus projected number of patients (= 340) was unchanged.

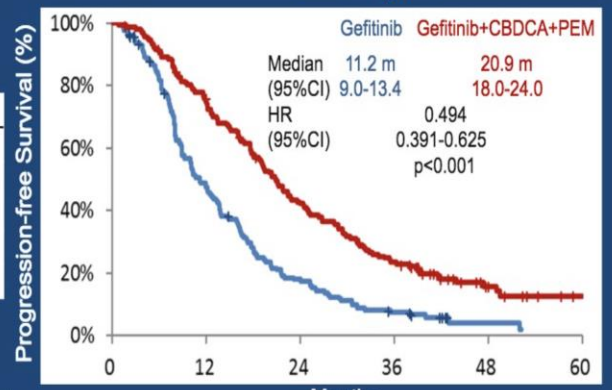
NEJ009

Progression-Free Survival 1



Response Rate (%)

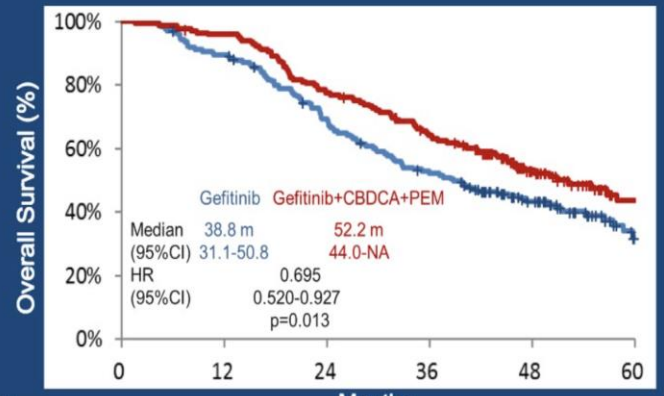
	Gefitinib	combo
CR	3.5	4.7
PR	64.0	79.3
SD	25.0	13.6
PD	4.7	1.2
ORR	67.4	84.0



No. at Risk

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

Overall Survival



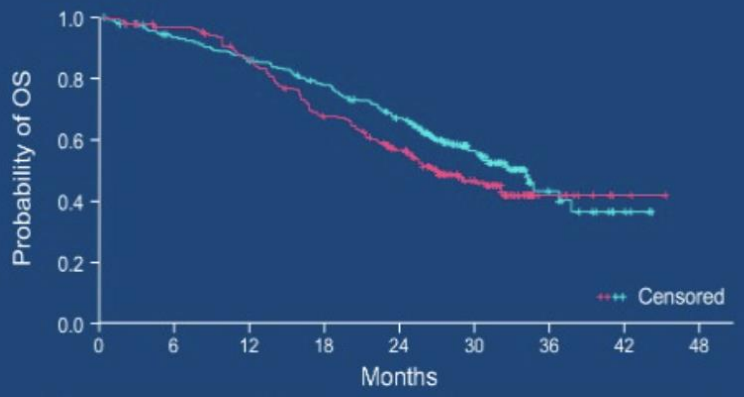
No. at Risk

Gefitinib	172	153	115	86	50	14
Gefitinib+CBDCA+PEM	170	162	131	105	57	20

First phase III trials demonstrating OS benefit in EGFR mutant NSCLC

ARCHER 1050 (n=452)

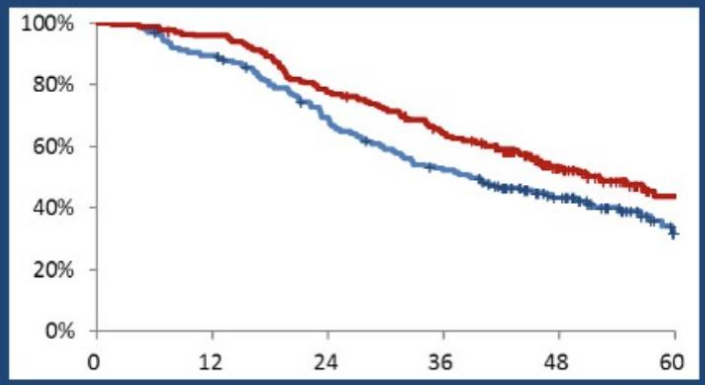
Median f/u 31.3 m



	Median OS	95% CI
Gefitinib	26.8 m	23.7 - 32.1
Dacomitinib	34.1 m	29.5 - 37.7
	HR 0.76 (95%CI 0.582 - 0.993) p=0.0219	

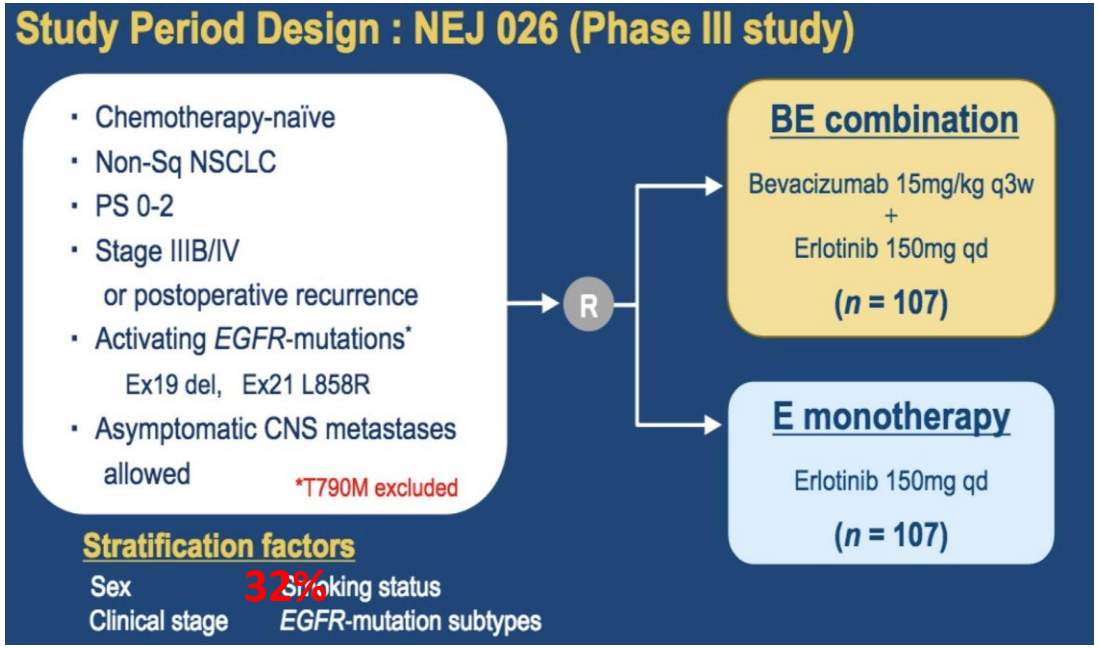
NEJ009 (n=345)

Median f/u minimum 42 m



	Median OS	95% CI
Gefitinib	38.8 m	31.1 - 50.8
Gefitinib + PemCb	52.2 m	44.0 - NR
	HR 0.695 (95%CI 0.520 - 0.927) p=0.013	

NEJ026: Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating EGFR mutations



Primary endpoint
PFS by independent review committee (IRC)

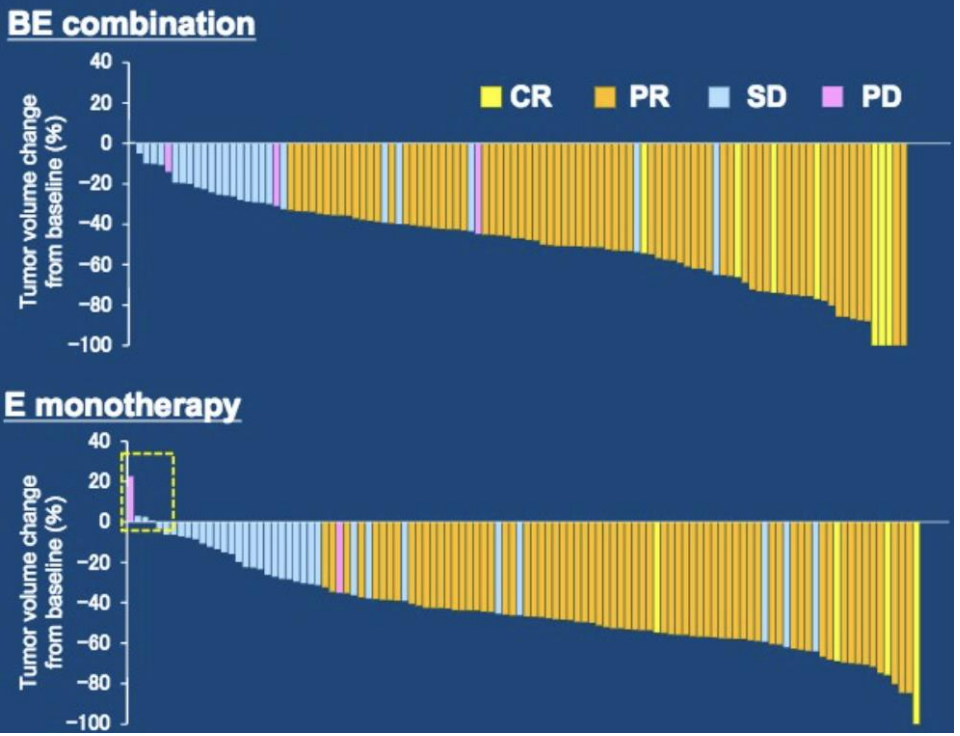
Secondary endpoints
- Overall survival
- Tumor response : RR, DCR, DR (Duration of response)
- Safety
- QOL : EORTC QLQ-C30 or QLQ-LC13

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

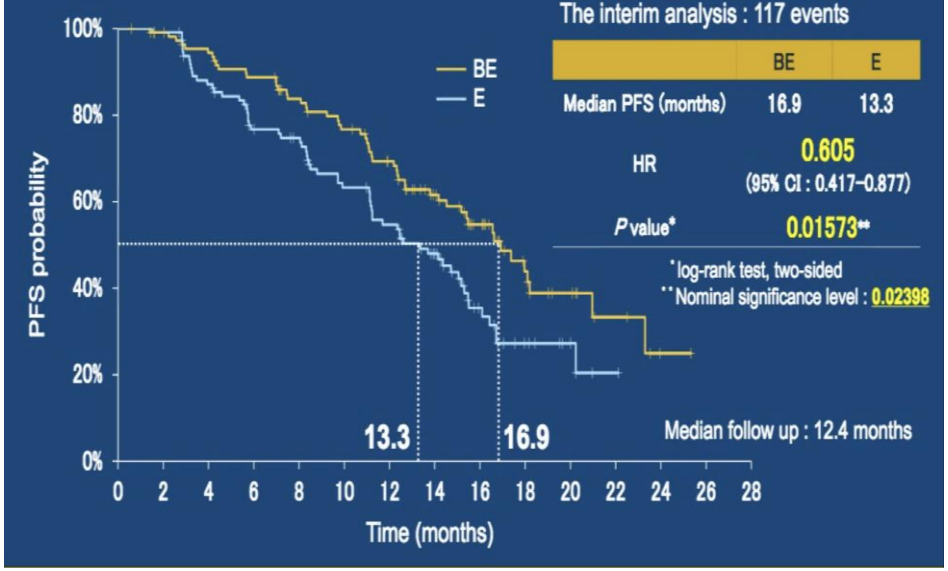
Objective tumor response by independent review

	BE (n=112)	E (n=112)	*P value
CR	8 (7.1%)	4 (3.6%)	
PR	73 (65.2%)	70 (62.5%)	
SD	25 (22.3%)	34 (30.4%)	
PD	4 (3.6%)	2 (1.8%)	
NE	2 (1.8%)	2 (1.8%)	
ORR	72.3%	66.1%	0.311
DCR	94.6%	96.4%	0.518

* χ^2 test



Primary endpoint : PFS by independent review



The interim analysis : 117 events

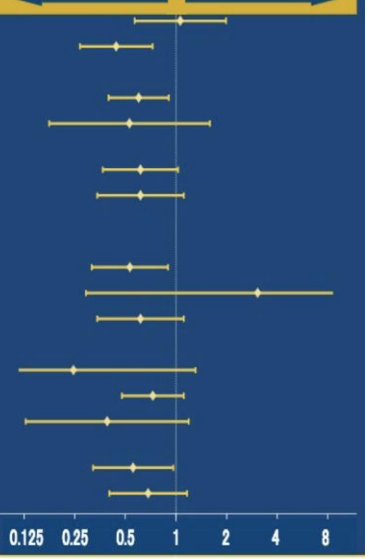
	BE	E
Median PFS (months)	16.9	13.3
HR	0.605 (95% CI : 0.417–0.877)	
P value*	0.01573**	

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

Median follow up : 12.4 months

Subgroup analysis of PFS

		n BE	n E	HR (95%CI)
Sex	Male	41	39	1.06 (0.58–1.94)
	Female	71	73	0.45 (0.28–0.73)
Age	< 75	92	89	0.61 (0.41–0.91)
	≥ 75	20	23	0.54 (0.19–1.57)
ECOG PS	0	64	68	0.63 (0.38–1.03)
	1	48	42	0.63 (0.35–1.11)
	2	0	2	-
Smoking status	Never smoker	65	64	0.54 (0.33–0.90)
	Former light smoker	6	7	2.94 (0.30–28.5)
	Other smoker	41	41	0.63 (0.35–1.11)
Stage	IIIB	8	8	0.26 (0.05–1.29)
	IV	82	84	0.74 (0.49–1.11)
	Postoperative recurrence	22	20	0.40 (0.14–1.18)
EGFR mutation	Exon 21 L858R	56	57	0.57 (0.33–0.97)
	Exon 19 deletion	56	55	0.69 (0.41–1.16)



Treatment exposure

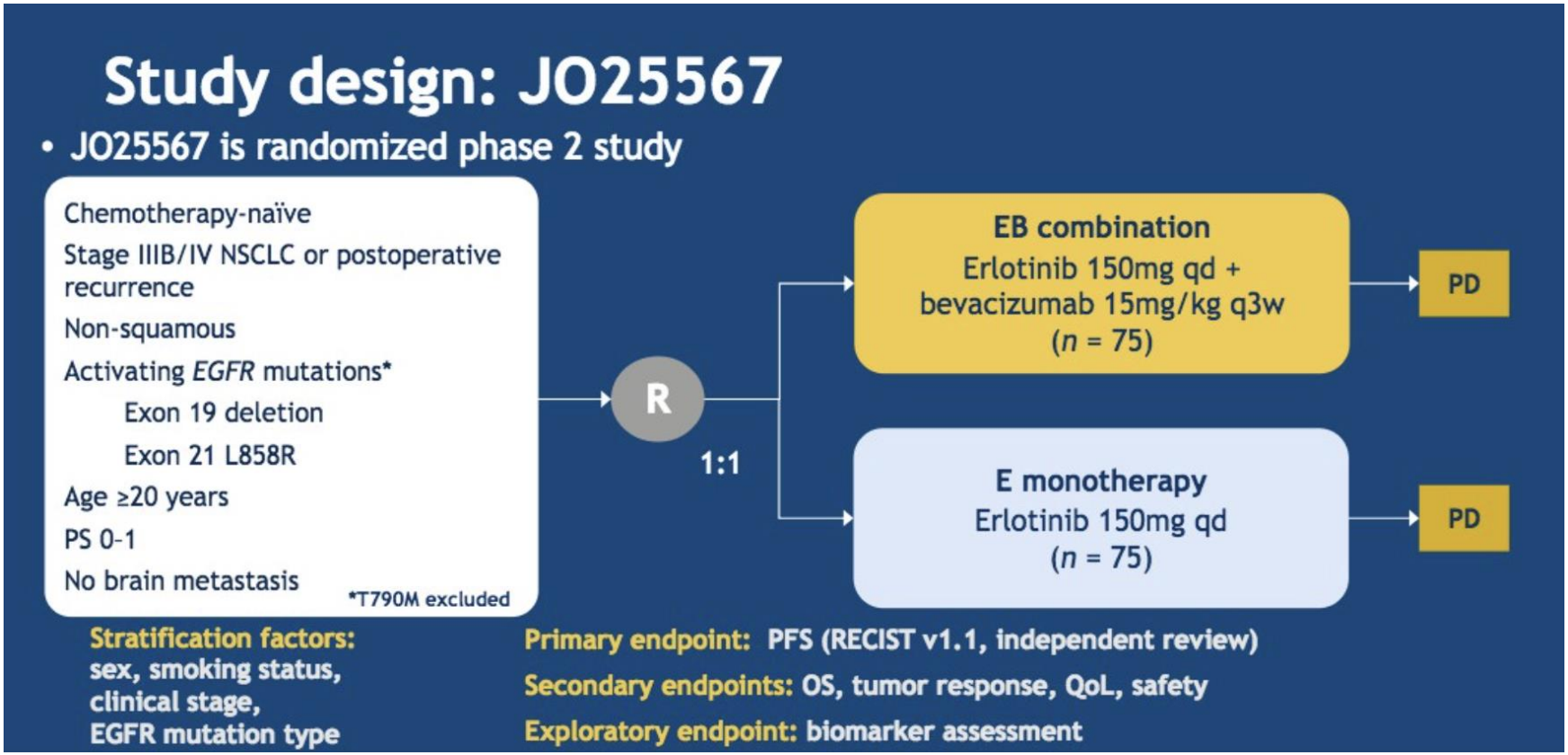
	BE (n=112)	E (n=112)
Erlotinib		
Treatment duration (median, days)	405 (5-807)	364 (43-736)
Dose intensity (mean, mg/day)	121.7	127.3
Discontinuation due to AE	21 (18.8%)	17 (15.2%)
Bevacizumab		
Treatment duration (median, days)	350 (21-736)	-
Discontinuation due to AE (%)	33 (29.5%)	-

Adverse events

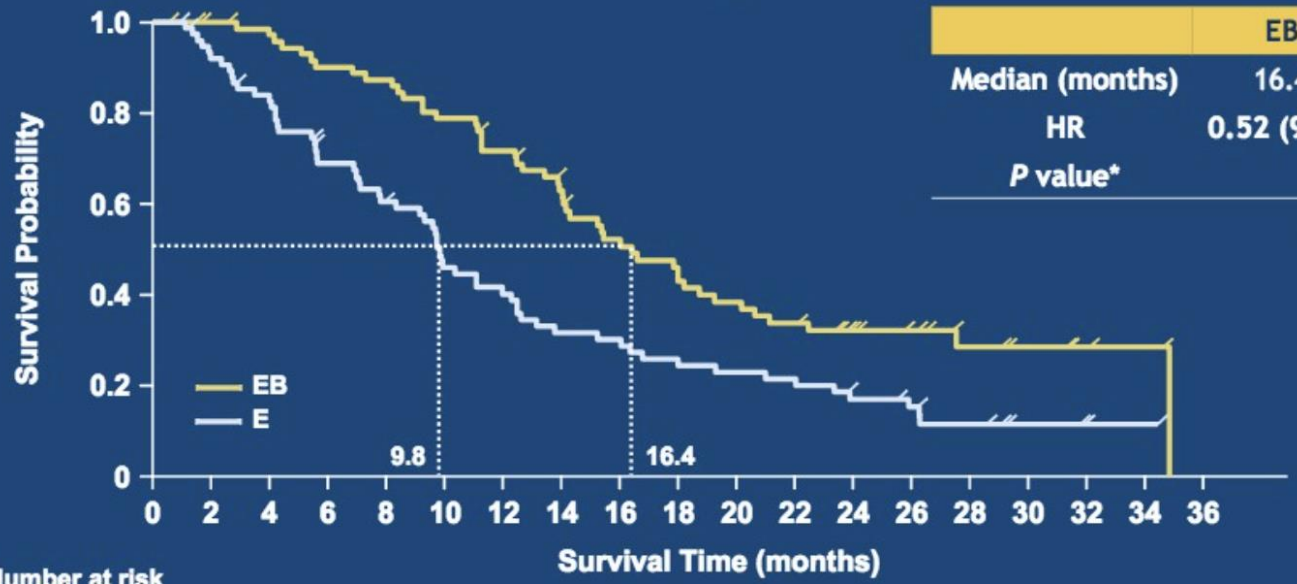
	All grades		Grade ≥3	
	BE (n=112)	E (n=114)	BE (n=112)	E (n=114)
Rash	99 (88.4%)	99 (86.8%)	23 (20.5%)	24 (21.1%)
Diarrhea	53 (47.3%)	47 (41.2%)	6 (5.4%)	2 (1.8%)
Hypertension	51 (45.5%)**	10 (8.8%)	25 (22.3%)**	0 (0%)
Proteinuria	36 (32.1%)**	3 (2.6%)	8 (7.1%)*	0 (0%)
Hepatic dysfunction	30 (26.8%)	34 (29.8%)	9 (8.0%)	6 (5.3%)
Pulmonary hemorrhage (PH)	3 (2.7%)	0 (0%)	0 (0%)	0 (0%)
Hemorrhage (PH excluded)	29 (25.9%)**	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%)

** $P < 0.001$ * $P < 0.01$

JO25567: Erlotinib plus bevacizumab vs erlotinib alone as firts line treatmetn for advanced EGFR mutation NSCLC: survival follow-up results of JO 25567



Updated PFS: investigator-assessed



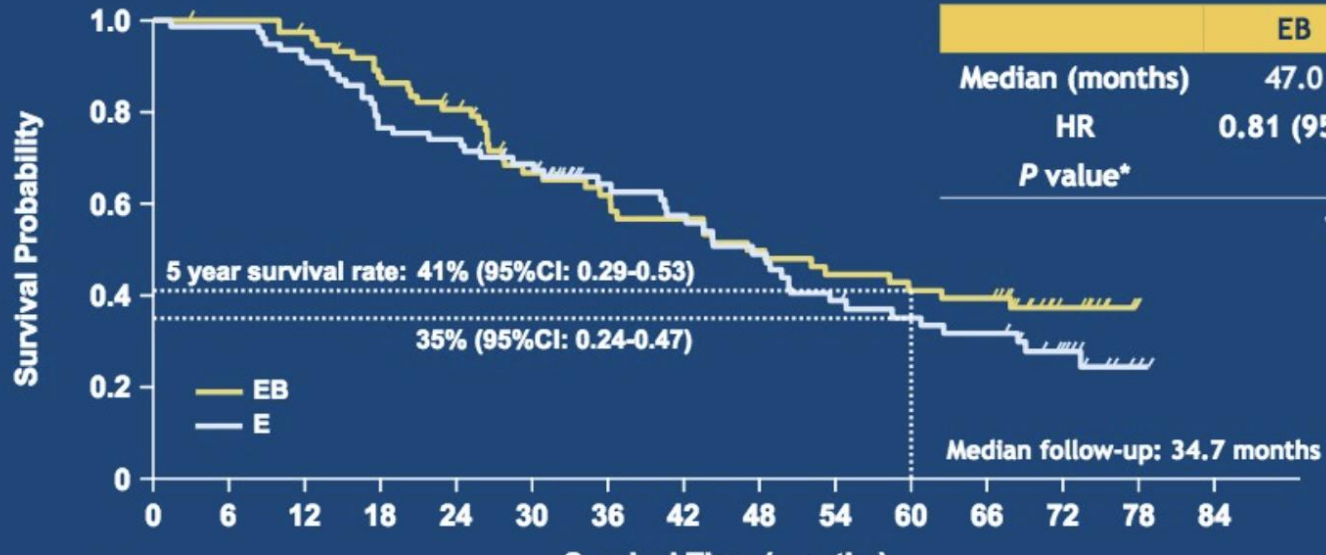
	EB	E
Median (months)	16.4	9.8
HR	0.52 (95% CI: 0.35-0.76)	
P value*	0.0005	

*log-rank test, two-sided

Number at risk																			
EB	75	72	69	64	62	56	50	42	33	28	25	22	16	14	8	6	4	3	0
E	77	69	61	49	42	32	28	22	21	17	16	15	11	9	6	3	1	1	0

Cut off date: March 31, 2014

Final Overall survival



	EB	E
Median (months)	47.0	47.4
HR	0.81 (95% CI: 0.53-1.23)	
P value*	0.3267	

*log-rank test, two-sided

Number at risk

EB	75	74	71	63	55	43	36	33	29	26	24	23	9	0	0
E	77	76	71	59	57	50	38	34	29	23	20	18	11	1	0

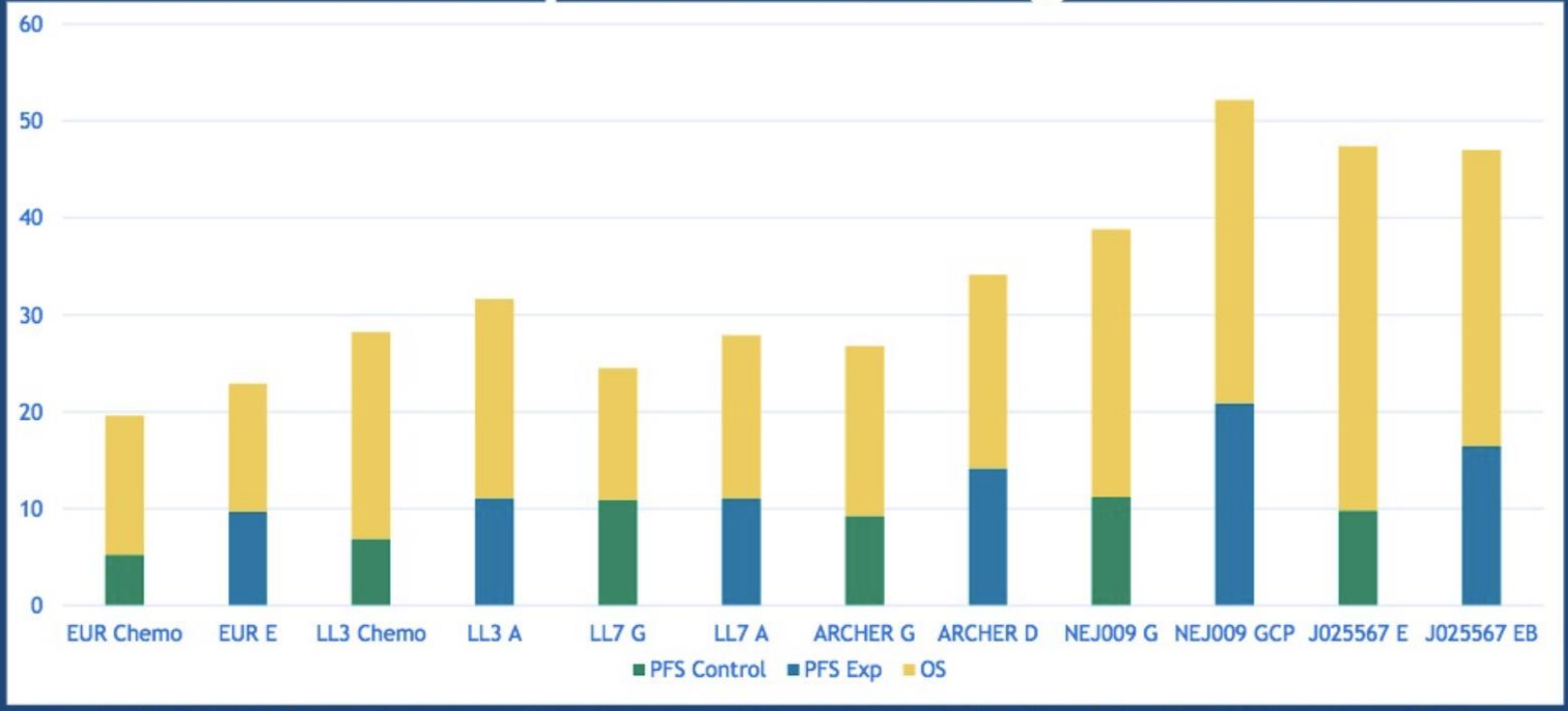
Cut off date: October 31, 2017

Study Results: Key highlights

- Both studies show statistically-significant and clinically-relevant improvements in PFS
- Update JO25567: no difference in OS
- Both studies have significantly higher rates of HTN in the bevacizumab arm, including 22-61% grade 3 HTN

Sequist L. ASCO 2018

What About PFS-positive/OS-negative result?



ell et al, *Lancet Oncol* 2012; Leon et al ESMO14; Sequist et al, *J Clin Oncol* 2013; Yang et al, *Lancet Oncol* 2015; Park et al, *Lancet Oncol* 2016; Paz-Ares et al, Ann Oncol 2017; Mok et ASCO18; Nakmura et al, ASCO18; Furuya et al, ASCO18

Sequist L. ASCO 2018