Bevacizumab plus erlotinib versus erlotinib alone in Japanese patients with advanced, metastatic, EGFR-mutantnon-small-cell lung cancer (NEJ026): overall survival analysis of an open-label, randomized, multicenter, phase 3 trial

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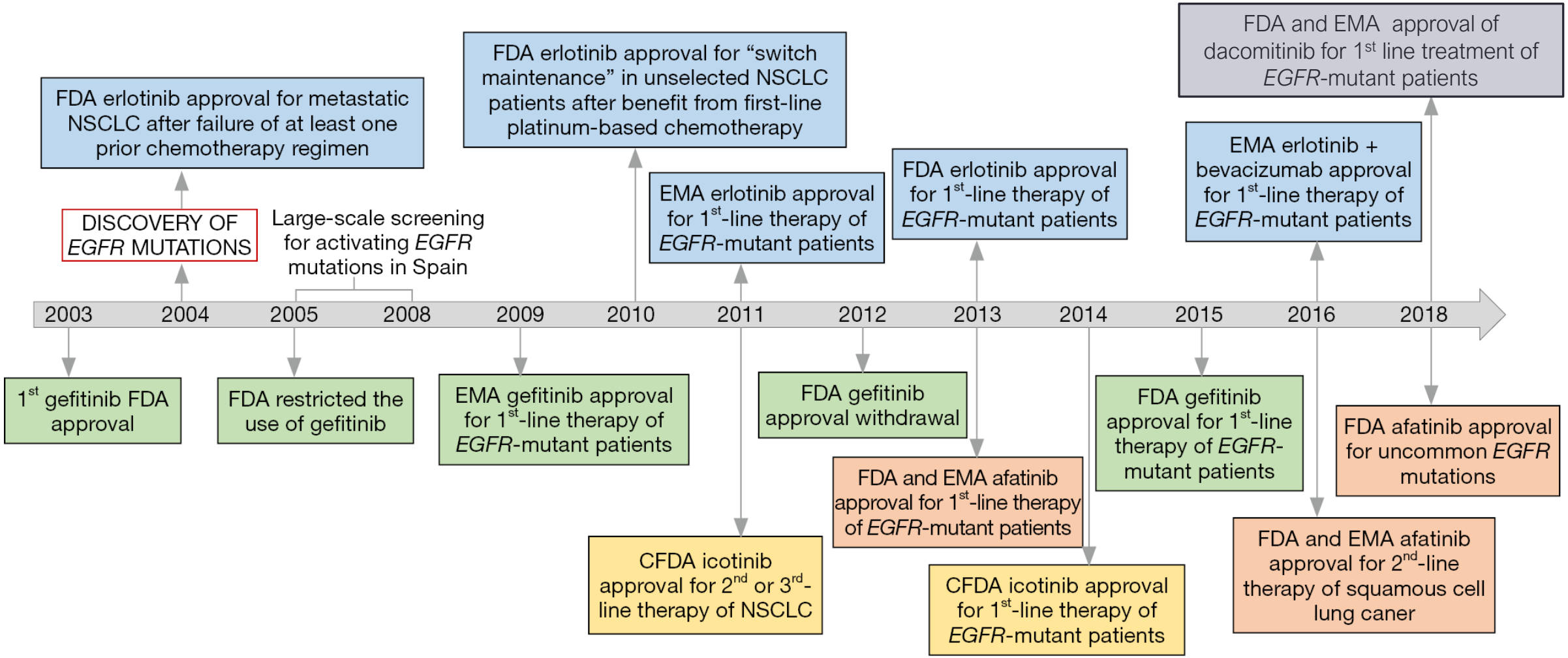
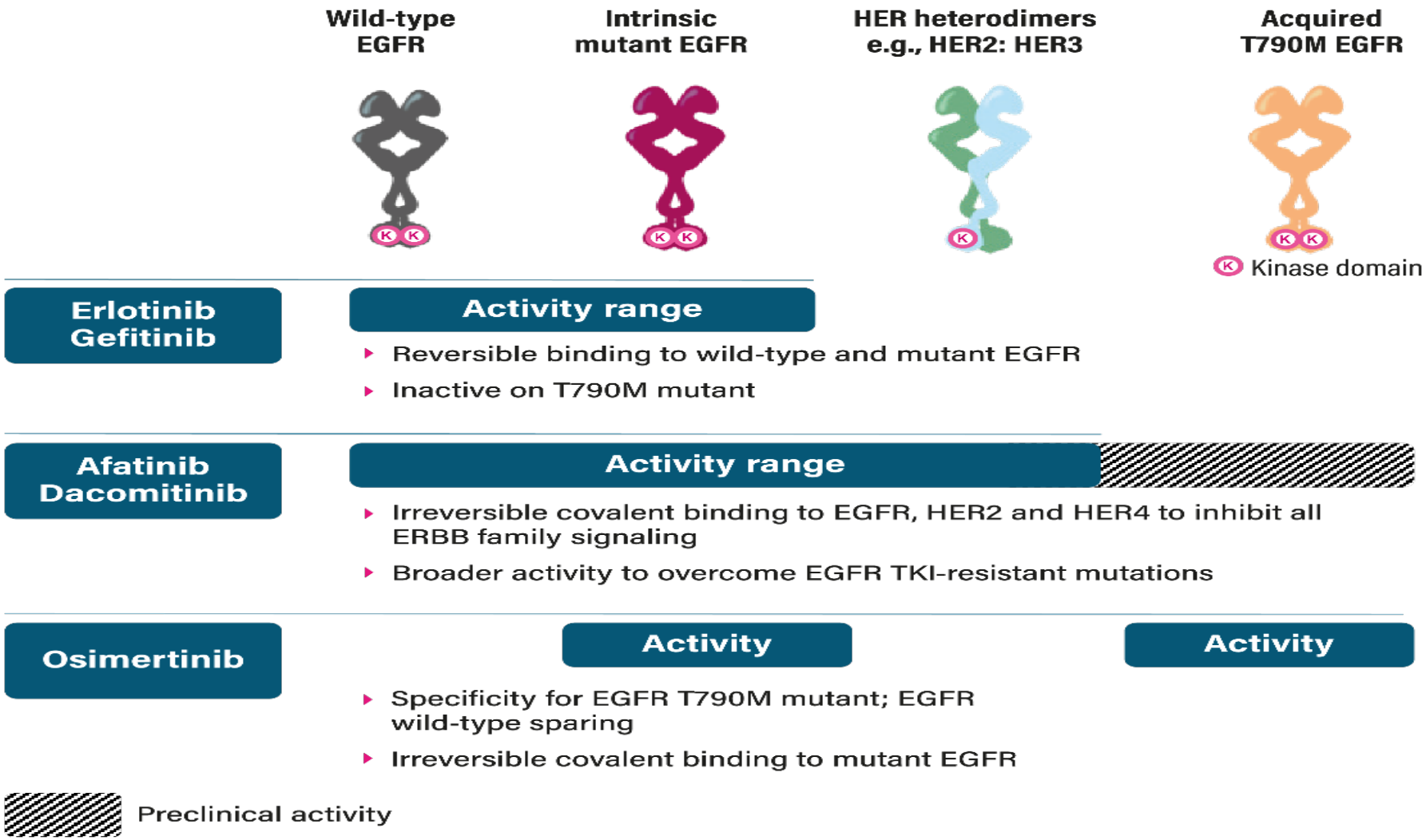
Personalized Therapy with EGFR TKIs: Timeline of Development



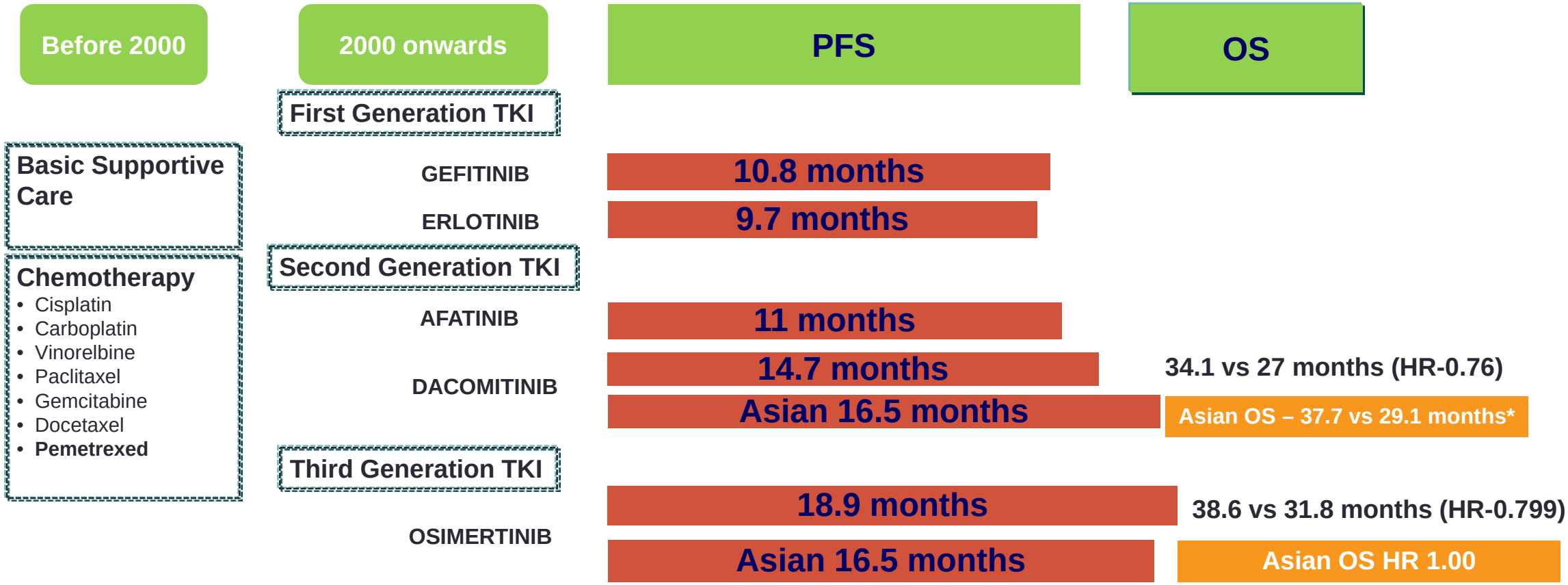
Karachaliou et al. Transl Cancer Res 2019;8(Suppl 1):S23-S47

Overview of activity range of first-, second- and third-generation EGFR tyrosine kinase inhibitors



Girard n. Future Oncol. (2018) 14(11), 1117–1132

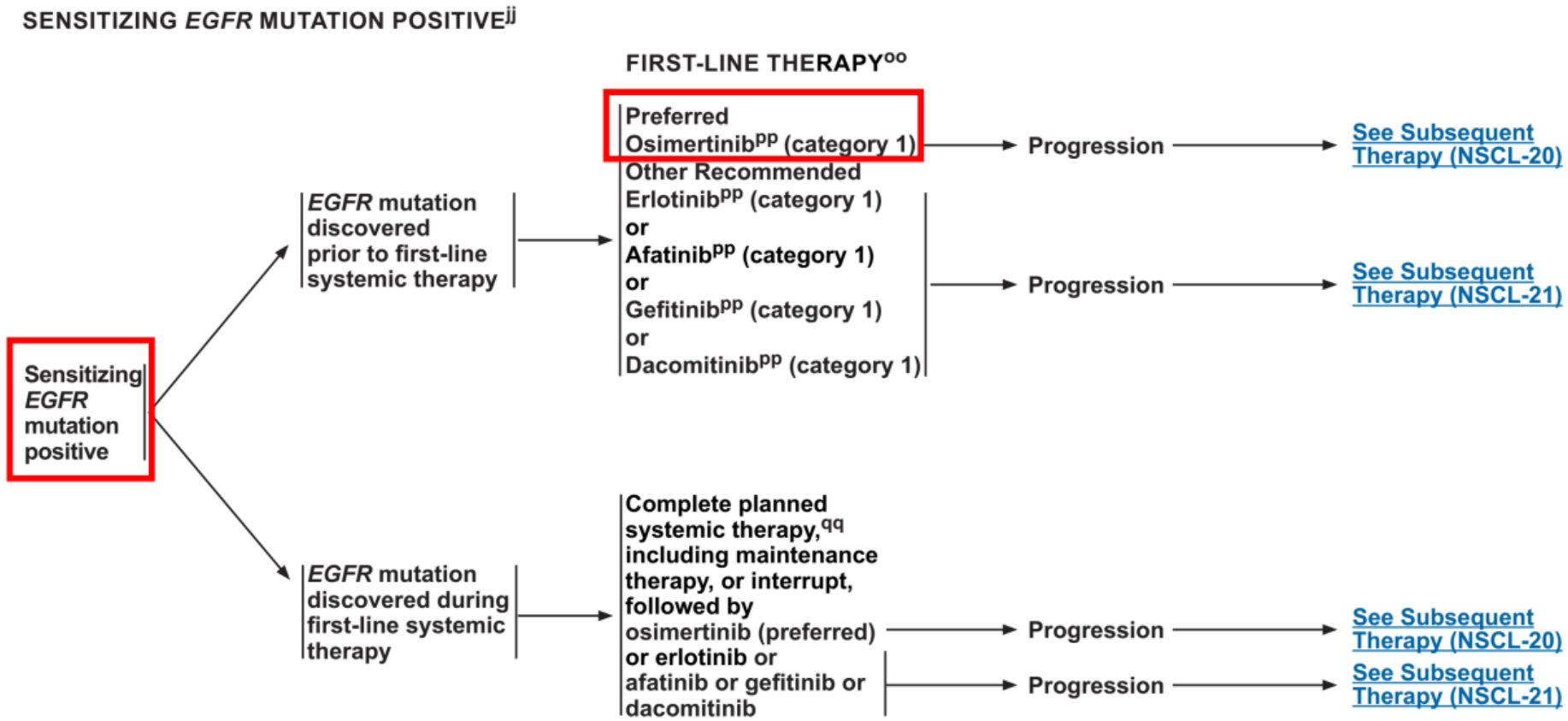
Treatment evolution in EGFR positive NSCLC



Data for understanding only, no cross-trial comparison

N. Engl. J. Med. 2010, 362, 2380–2388. Lancet Oncol. 2010, 11, 121–128. Lancet Oncol. 2011, 12, 735–742. Lancet Oncol. 2012, 13, 239–246. J. Clin. Oncol. 2013, 31, 3327–3334. Lancet Oncol.2014, 15, 213–222. Lancet Oncol. 2016, 17, 577–589. Lancet Oncol. 2017, 18, 1454–1466. NEJ026. ASCO Ann. Meet. Proc. 2018, 27, 9006. N. Engl. J. Med. 2017, 376, 629–640. N. Engl. J. Med. 2018, 378, 113–125.

NSCLC with EGFR mutation treatment



NCCN Guidelines Version 1.2020

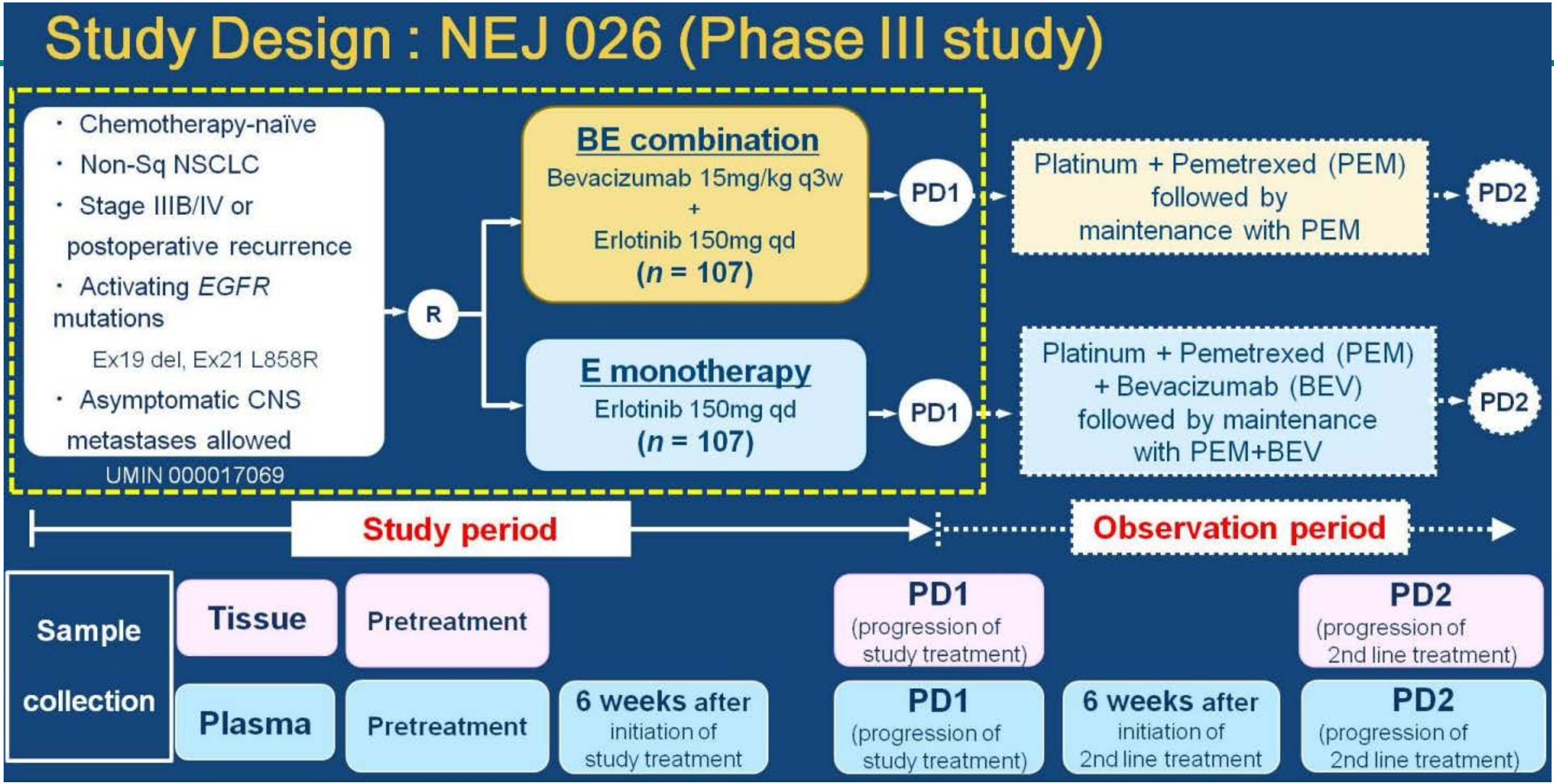
EGFR-TKI Plus anti-VEGF/VEGFR

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

Furuya N, Fukuhara T, Saito H, Watanabe K, Sugawara S, Iwasawa S, Tsunezuka Y, Yamaguchi O, Okada M, Yoshimori K, Nakachi I, Gemma A, Azuma K, Hagiwara K, Nukiwa T, Morita S, Kobayashi K, Maemondo M

Journal of clinical oncology, 2018, 36(15)

Study Design : NEJ 026 (Phase III study)



- Adapted from Naoki Furuya presentation during 2018 ASCO Annual Meeting

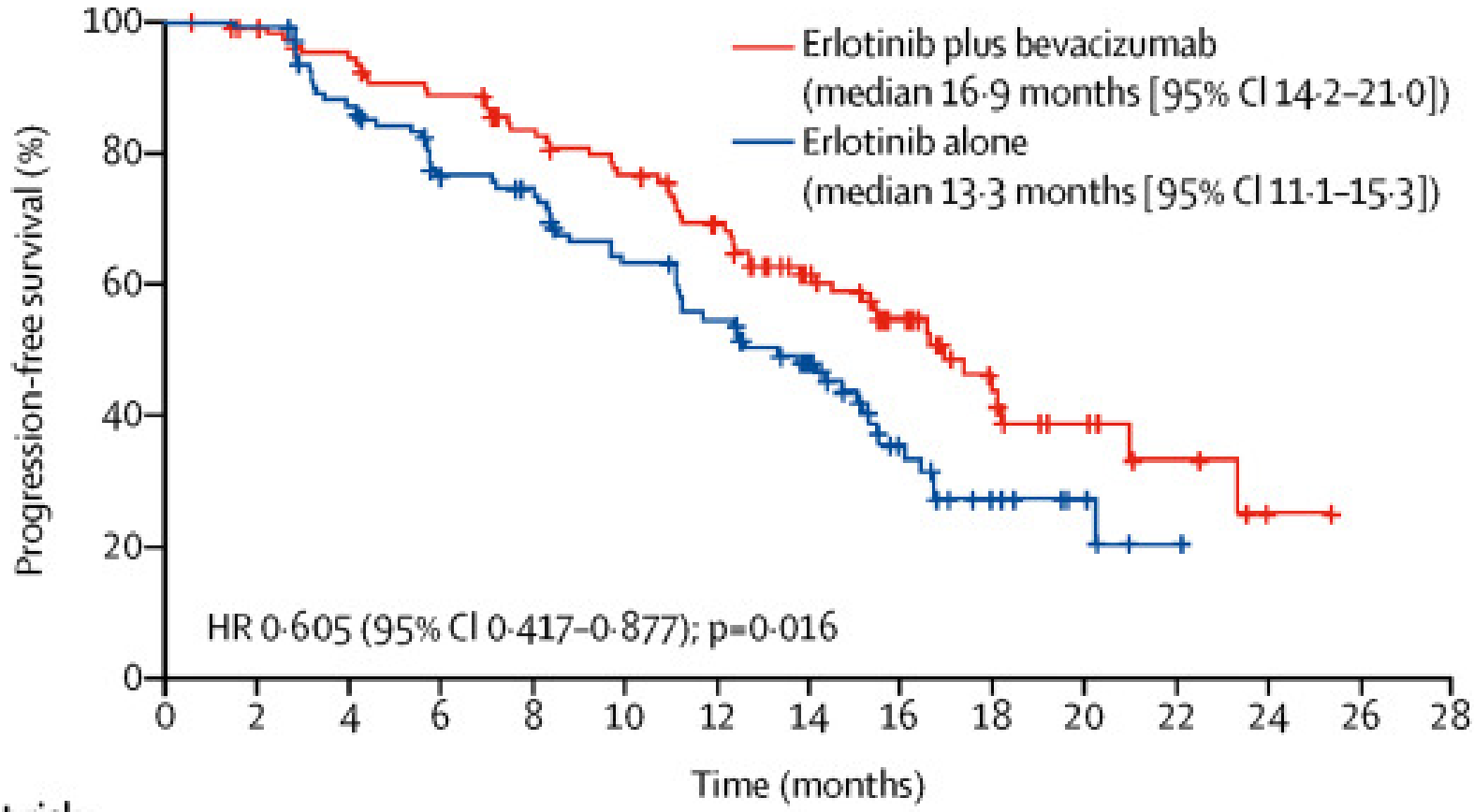
Baseline Characteristics

	Erlotinib plus bevacizumab (n=112)	Erlotinib (n=112)
Histopathological classification		
Adenocarcinoma	110 (98%)	112 (100%)
Large cell carcinoma	1 (1%)	0
Other	1 (1%)	0
EGFR genomic aberration		
Exon 19 deletion	56 (50%)	55 (49%)
Exon 21 Leu858Arg mutation	56 (50%)	57 (51%)
Clinical stage at screening		
IIIB	8 (7%)	8 (7%)
IV	82 (73%)	84 (75%)
Postoperative recurrence	22 (20%)	20 (18%)
CNS metastases		
Yes	36 (32%)	36 (32%)
No	76 (68%)	76 (68%)

Saito et al., Lancet Oncol 2019; 20: 625–35

Primary endpoint: PFS by independent review

The interim analysis: 117 events

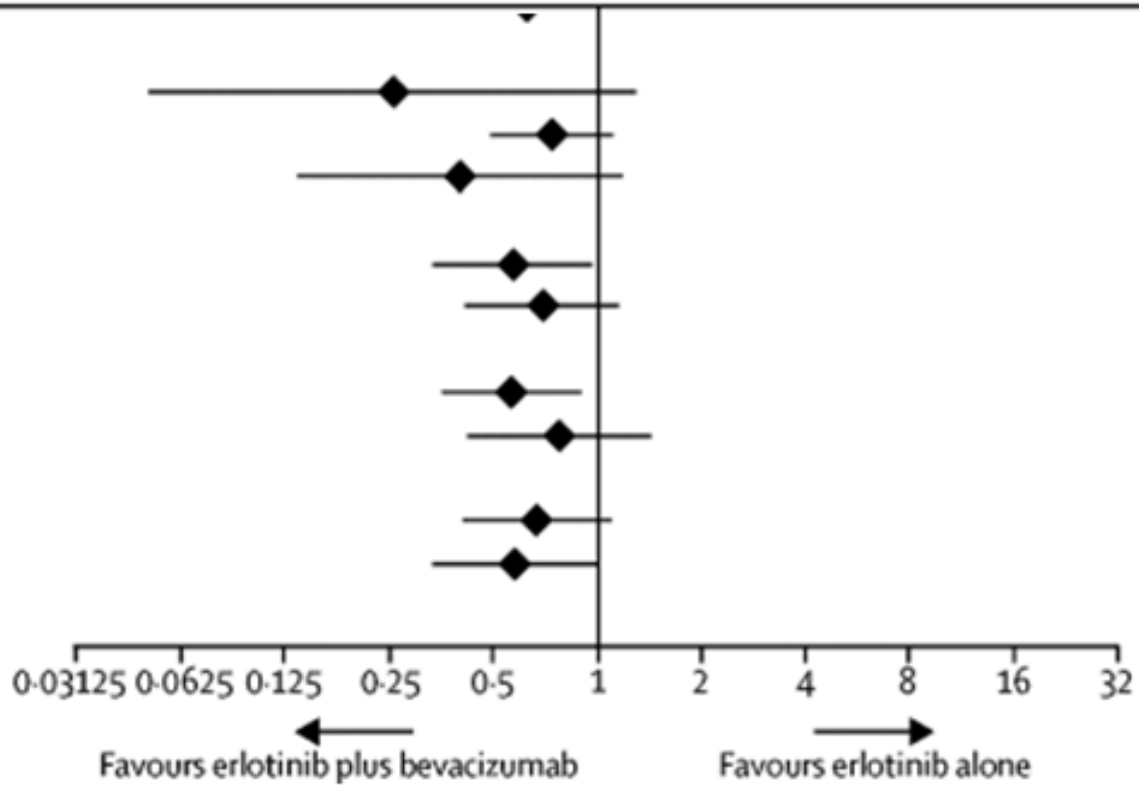


Number at risk (number censored)								
Erlotinib plus bevacizumab	112 (0)	100 (6)	83 (7)	64 (17)	34 (35)	10 (52)	1 (59)	0 (60)
Erlotinib alone	112 (0)	94 (4)	73 (12)	51 (15)	18 (34)	5 (43)	0 (47)	0 (47)

Saito et al., Lancet Oncol 2019; 20: 625–35

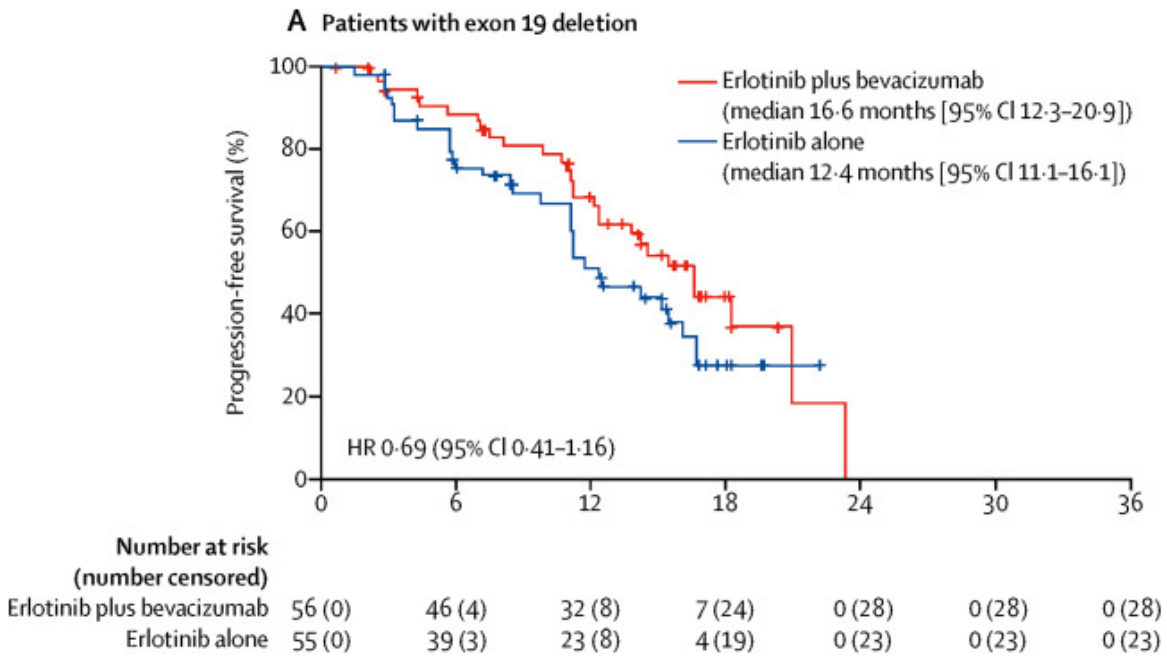
Subgroup analysis

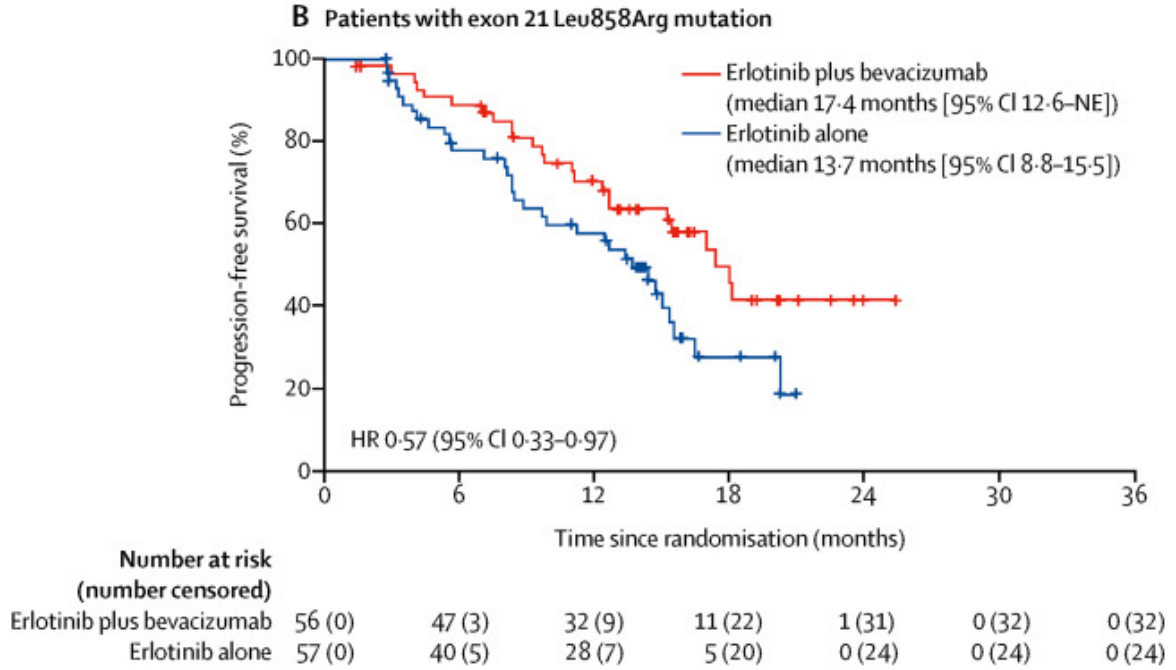
	Erlotinib plus bevacizumab (n/N)	Erlotinib alone (n/N)	HR (95% CI)
Clinical stage			
IIIB	2/8	6/8	0·26 (0·05–1·29)
IV	45/82	49/84	0·74 (0·49–1·11)
Postoperative recurrence	5/22	10/20	0·40 (0·14–1·18)
EGFR mutation			
Exon21 Leu858Arg mutation	24/56	33/57	0·57 (0·33–0·97)
Exon19 deletion	28/56	32/55	0·69 (0·41–1·16)
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., Lancet Oncol 2019; 20: 625–35

PFS by EGFR mutation subtype





Saito et al., Lancet Oncol 2019; 20: 625–35

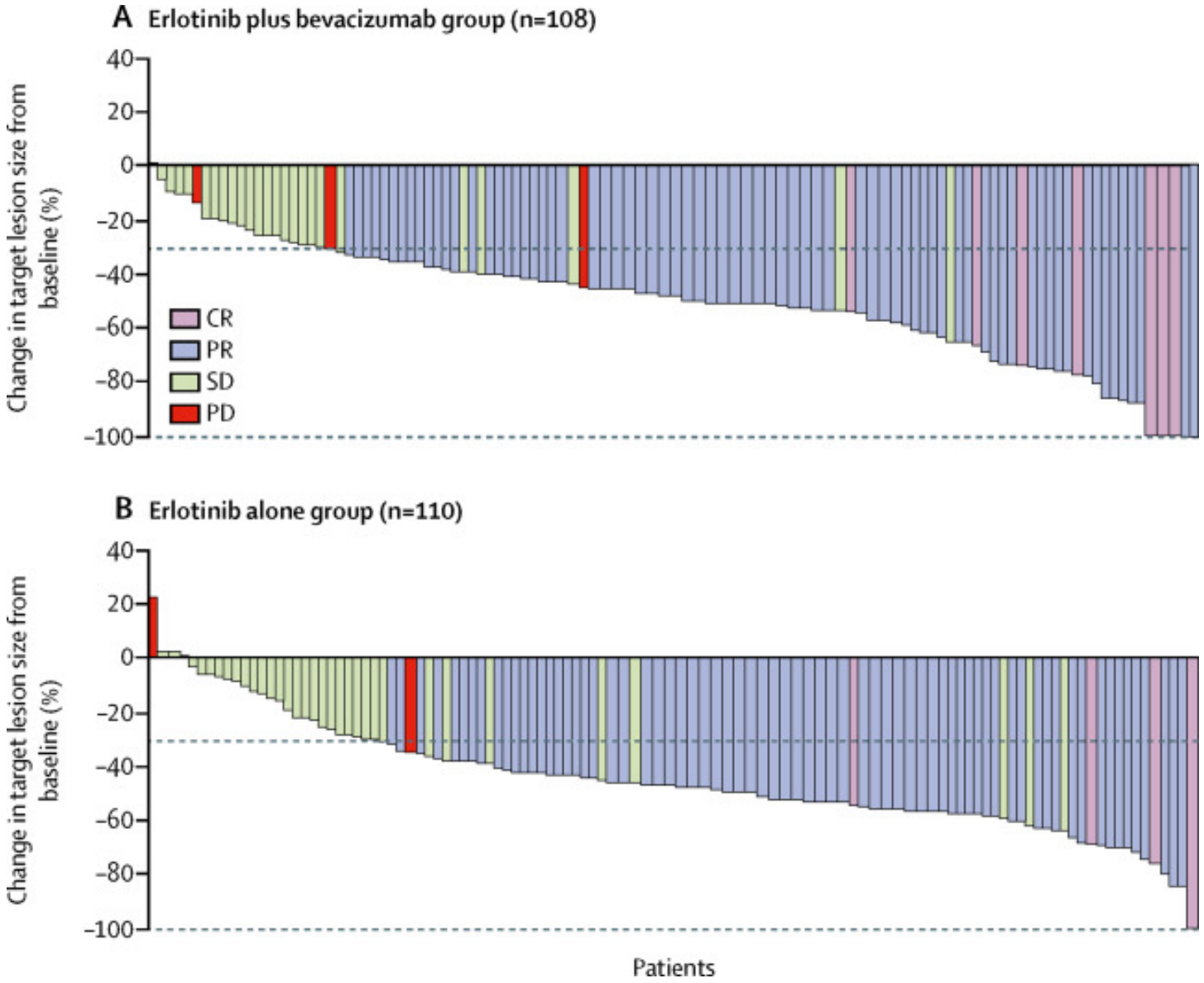
Response as per independent review committee's assessment

	Erlotinib plus bevacizumab group (n=112)	Erlotinib alone group (n=112)	p value*
Complete response	8 (7%)	4 (4%)	..
Partial response	73 (65%)	70 (63%)	..
Stable disease	25 (22%)	34 (30%)	..
Progressive disease	4 (4%)	2 (2%)	..
Not evaluable	2 (2%)	2 (2%)	..
Objective response	81 (72%; 63·1–80·4)	74 (66%; 56·5–74·7)	0·31
Disease control	106 (95%; 88·7–98·0)	108 (96%; (91·1–99·0)	0·52

Data are n (%). *p value for χ^2 test.

Saito et al., Lancet Oncol 2019; 20: 625–35

Best percentage change from baseline in target lesion size



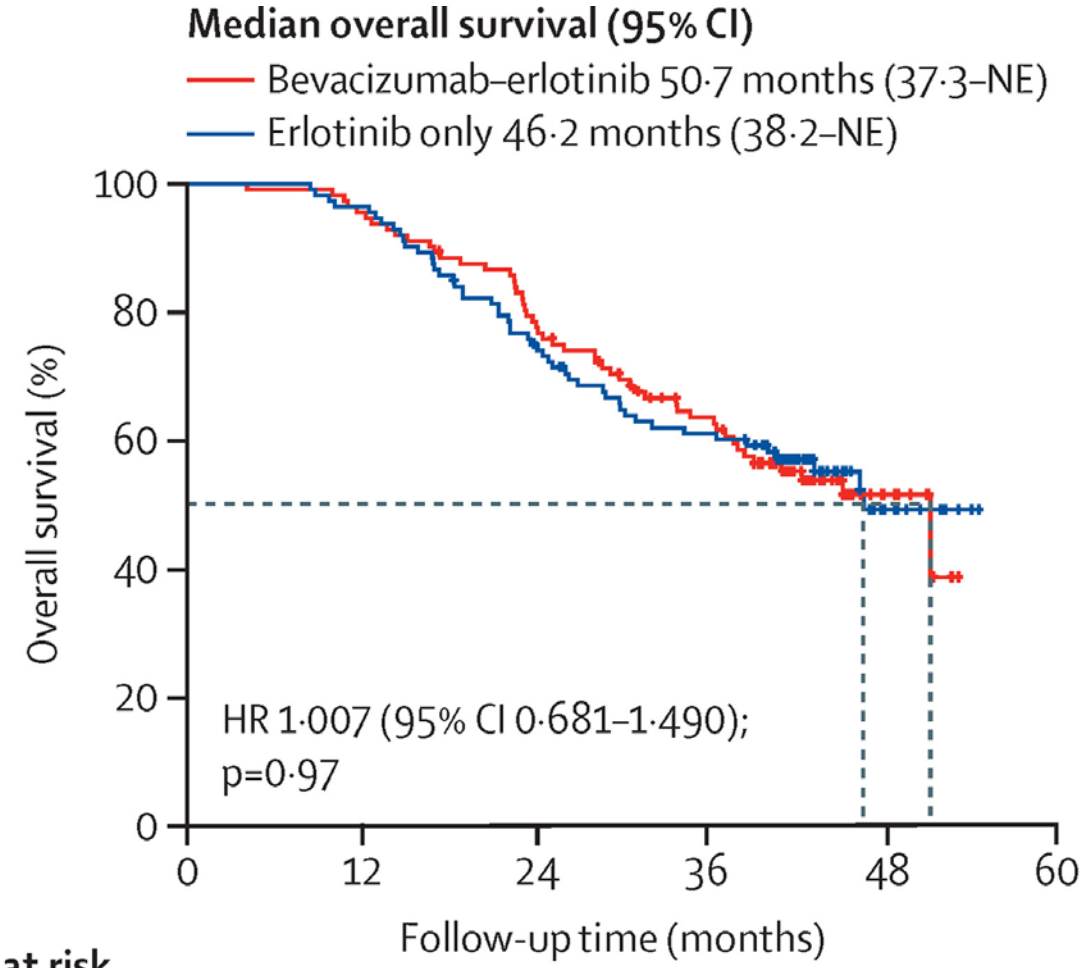
Saito et al., Lancet Oncol 2019; 20: 625–35

Adverse events in the safety population

	Erlotinib plus bevacizumab group (n=112)				Erlotinib alone group (n=114)			
	All	Grade 1–2	Grade 3	Grade 4	All	Grade 1–2	Grade 3	Grade 4
Rash	98 (88%)	75 (67%)	23 (21%)	0	99 (87%)	75 (66%)	24 (21%)	0
Diarrhoea	53 (47%)	47 (42%)	6 (5%)	0	47 (41%)	45 (39%)	2 (2%)	0
Proteinuria	36 (32%)	28 (25%)	8 (7%)	0	6 (5%)	5 (4%)	1 (1%)	0
Pulmonary haemorrhage	2 (2%)	2 (2%)	0	0	0	0	0	0
Non-pulmonary haemorrhage	29 (26%)	27 (24%)	2 (2%)	0	3 (3%)	2 (2%)	1 (1%)	0
Hypertension	52 (46%)	26 (23%)	26 (23%)	0	11 (10%)	10 (9%)	1 (1%)	0
Increased aminotransferase	30 (27%)	21 (20%)	6 (5%)	3 (3%)	34 (30%)	28 (25%)	5 (4%)	1 (1%)
Stomatitis	23 (21%)	22 (20%)	1 (1%)	0	12 (11%)	11 (10%)	1 (1%)	0
Paronychia	17 (15%)	15 (13%)	2 (2%)	0	18 (16%)	15 (13%)	3 (3%)	0

Saito et al., Lancet Oncol 2019; 20: 625–35

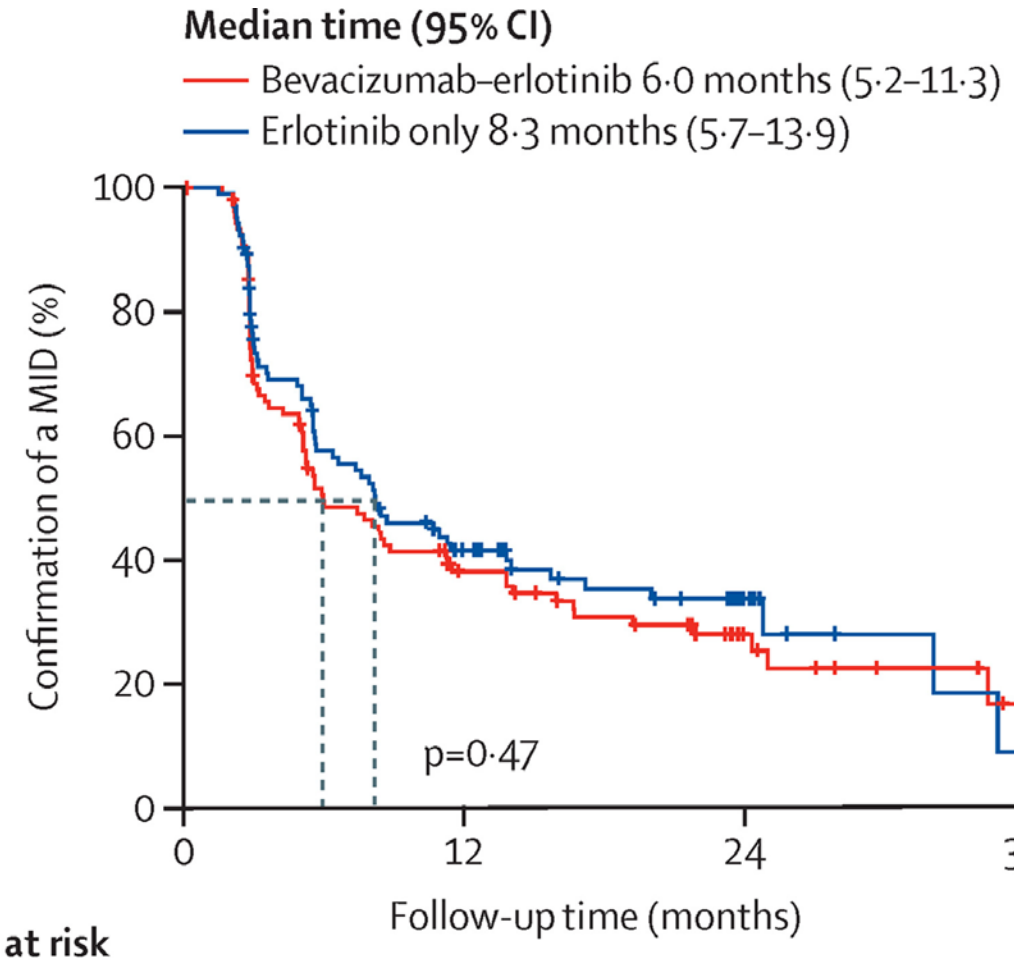
Overall survival



Number at risk (number censored)						
Bevacizumab–erlotinib	112 (0)	107 (0)	85 (1)	62 (9)	12 (50)	0 (61)
Erlotinib only	112 (0)	108 (0)	81 (2)	65 (4)	10 (52)	0 (62)

Kawashima Y, et al. Lancet Respir Med. 2022 Jan;10(1):72-82.

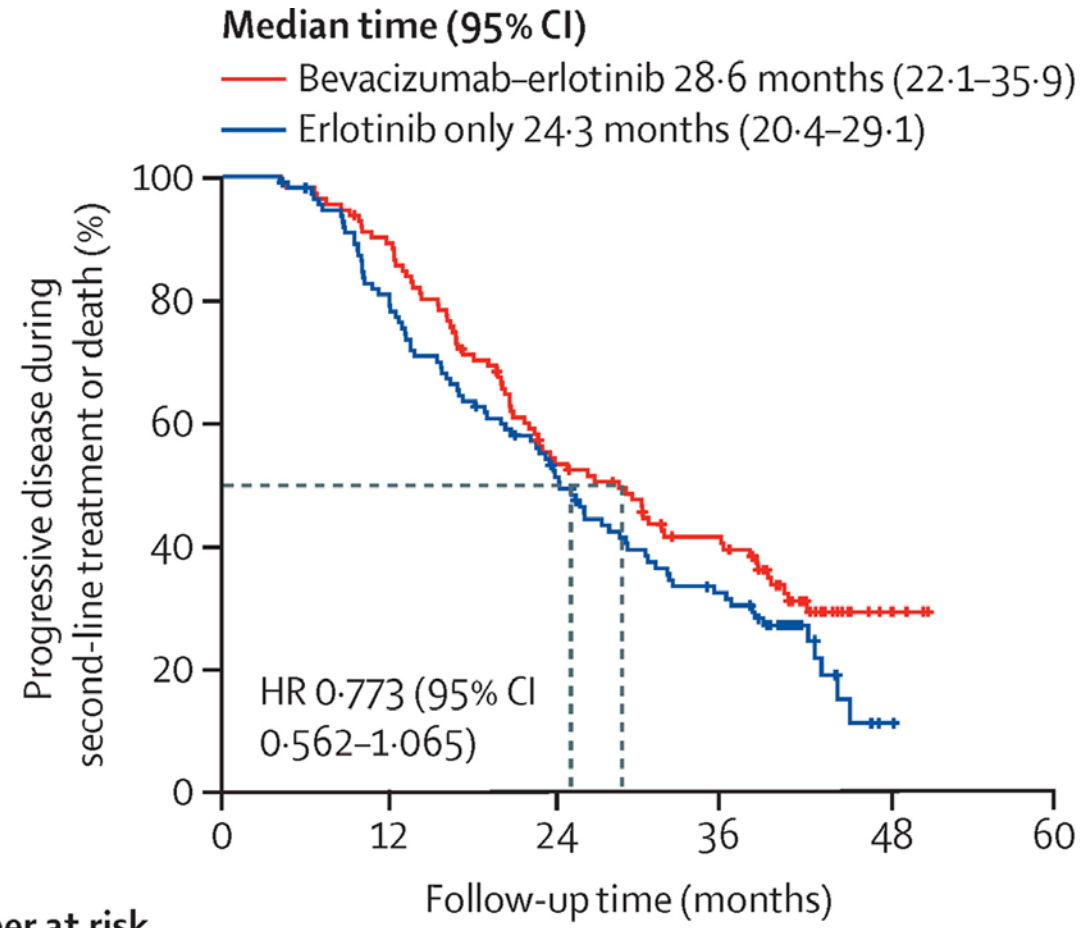
Quality of life with completed questionnaires



Number at risk (number censored)				
Bevacizumab–erlotinib	108 (0)	33 (12)	12 (25)	2 (32)
Erlotinib only	104 (0)	36 (11)	13 (29)	1 (38)

Kawashima Y, et al. Lancet Respir Med. 2022 Jan;10(1):72-82.

Time from enrolment to progressive disease during second-line treatment or death



Number at risk (number censored)						
Bevacizumab–erlotinib	112 (0)	99 (1)	57 (4)	39 (9)	6 (33)	0 (39)
Erlotinib only	112 (0)	88 (2)	54 (5)	32 (8)	1 (29)	0 (30)

Kawashima Y, et al. Lancet Respir Med. 2022 Jan;10(1):72-82.

Conclusion

- Unmet Need for EGFR mutation NSCLC patients
- Despite PFS benefit this trial didn’t show Significant OS benefit.
- The probable reasons for this might be second line treatment.
- Further Randomized trial like combination of first Generation TKI + CT+/- Bev may be planned in L858R subset only.

Thank You