Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Findings from the multinational, randomized, phase 3 NALA trial

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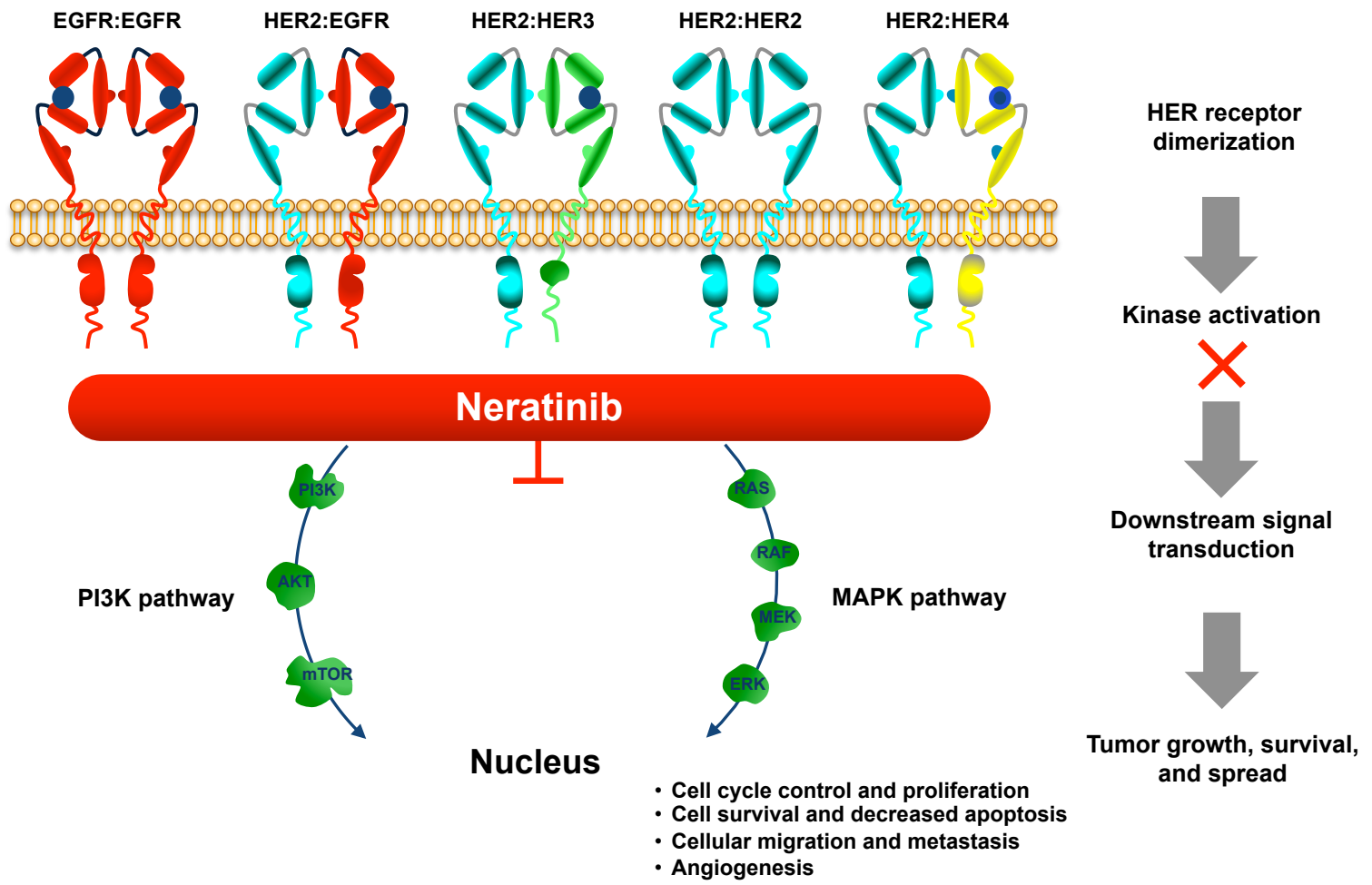
Disclosure information – Adam Brufsky

Consulting or Advisory Role

Eisai, Myriad Pharmaceuticals, Merck, Bioarray Therapeutics, Puma Biotechnology, Genomic Health, NanoString Technologies, BioTheranostics, Lilly, Bayer, Novartis, Celgene, Agendia, Genentech/Roche, Pfizer

Neratinib: An irreversible pan-HER TKI

- Neratinib: pan-HER (HER1, 2, and 4) TKI
- Breadth of targets for neratinib in HER family of receptors (HER1, 2, and 4 for neratinib; HER1 and 2 for lapatinib)
- Neratinib binds irreversibly to HER1, 2, and 4; lapatinib binds reversibly



TKI, tyrosine kinase inhibitor

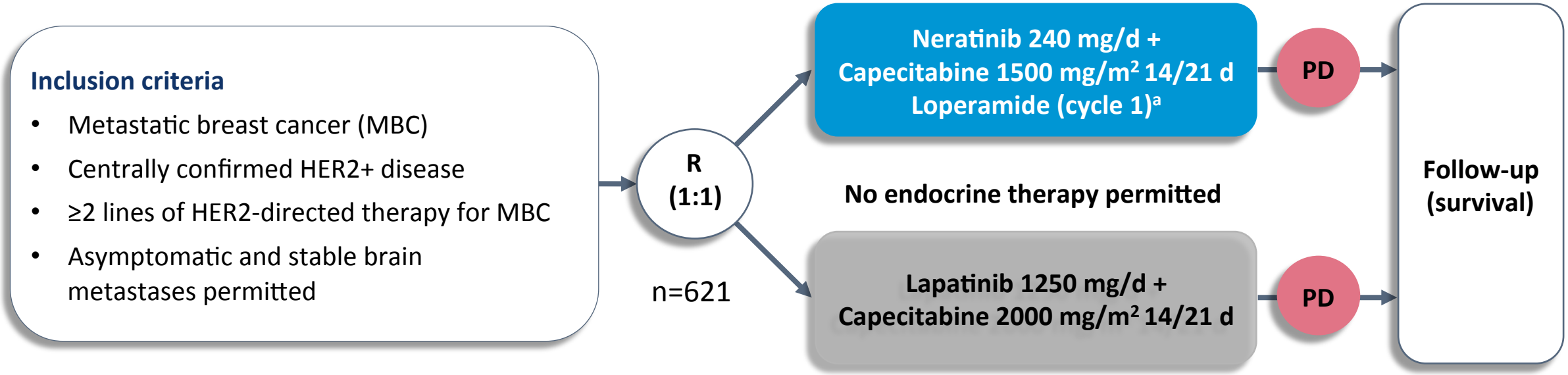
Rabindran et al. Cancer Res 2004
Neratinib US PI 2018

Clinical experience with neratinib

- **Extended adjuvant:** Approved by FDA and EMA based on reduced risk of recurrence of iDFS event with neratinib vs placebo in ExteNET[1]
- **Neoadjuvant:** Higher pCR rates with chemotherapy + neratinib vs chemotherapy + trastuzumab in patients with HER2+ breast cancer in I-SPY2[2]
- **Metastatic HER2+ disease:**
  - Study 2206: Promising efficacy with neratinib + capecitabine in trastuzumab-pretreated patients (recommended doses: neratinib 240 mg/d + capecitabine 1500 mg/m^2)[3]
  - NSABP FB-10: Evidence of efficacy with neratinib + T-DM1 in patients previously treated with trastuzumab + pertuzumab[4]
  - NEfERT-T: Delayed CNS progression with neratinib + paclitaxel in patients with HER2+ brain metastases[5]
  - TBCRC 022: Neratinib + capecitabine active against refractory brain metastases in patients with HER2+ brain metastases[6]

1. Martin et al. Lancet Oncol 2017; 2. Park et al. N Engl J Med 2016; 3. Saura et al. J Clin Oncol 2014
4. Abraham et al. J Clin Oncol 2018; 5. Awada et al. JAMA Oncol 2016; 6. Freedman et al. J Clin Oncol 2019

NALA study design



Stratification variables

- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

Statistical methods

Co-primary endpoints of PFS and OS

- Conducted under an FDA Special Protocol Assessment
- Study positive if either co-primary endpoint met:
  - $p<0.01$ for PFS (419 target events required for 85% power)
  - $p<0.04$ for OS (378 target events required for 85% power)

Planned analyses

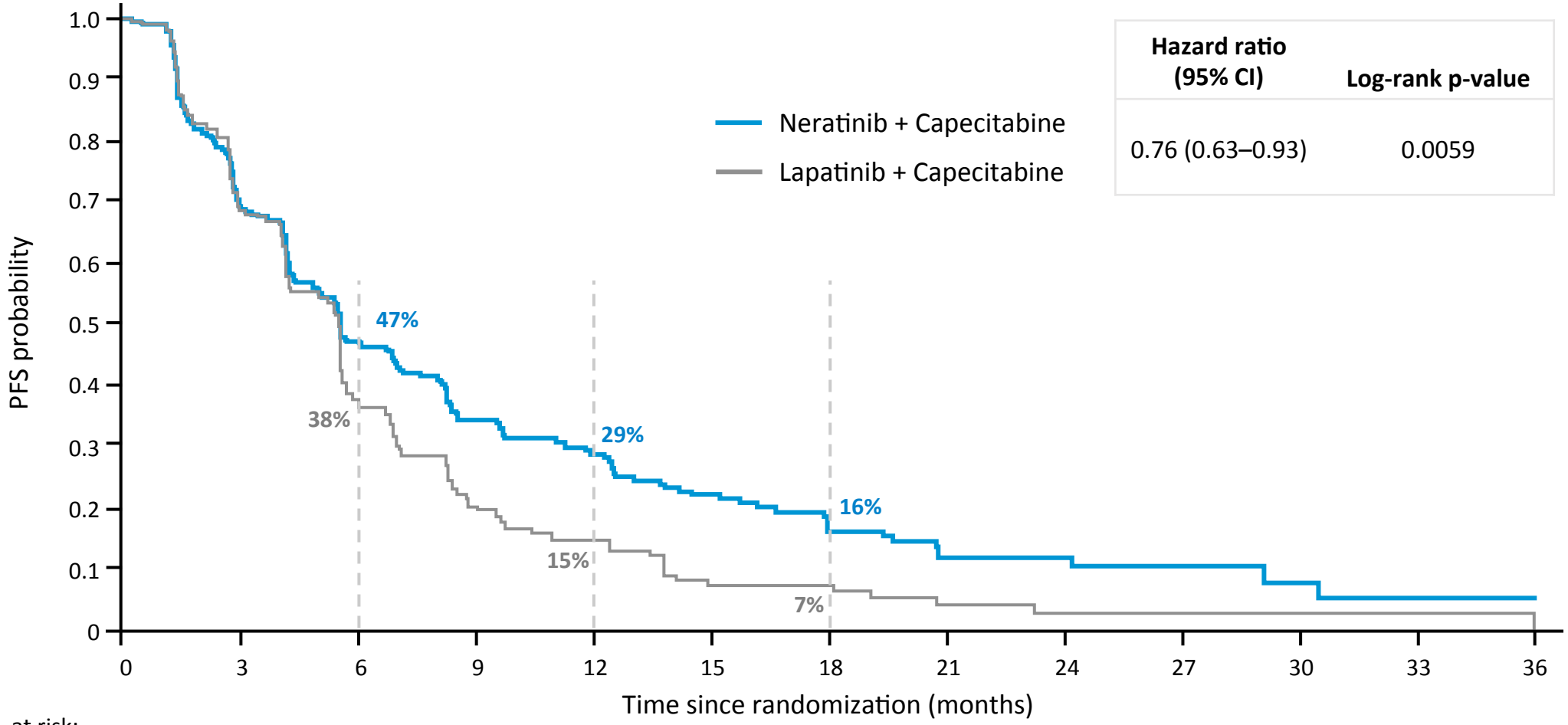
- Stratified log-rank test; Kaplan–Meier curves for PFS and OS
- Stratified Cox proportional hazards model for hazard ratios
  - Prespecified restricted means analysis, if proportional hazards assumption did not hold[1]
- Gray's test of cumulative incidence for CNS endpoints

1. Uno et al. J Clin Oncol 2014

Baseline characteristics

	Neratinib + Capecitabine (n=307)	Lapatinib + Capecitabine (n=314)
Age <65 years, n (%)	244 (79)	248 (79)
Geographic region, n (%)		
Europe	121 (39)	123 (39)
North America	59 (19)	65 (21)
Rest of world	127 (41)	126 (40)
HR+ (ER+ and/or PR+), n (%)	181 (59)	186 (59)
Disease location at enrollment, n (%)		
Non-visceral only	60 (20)	61 (19)
Visceral	247 (80)	253 (81)
De novo metastatic disease, n (%)	139 (45)	136 (43)
No. of prior HER2 targeted therapies for MBC, n (%)		
2	215 (70)	215 (68)
≥3	92 (30)	99 (32)
Prior HER2 therapies for MBC, n (%)		
Trastuzumab only	124 (40)	113 (36)
Trastuzumab + pertuzumab	24 (8)	23 (7)
Trastuzumab + T-DM1	58 (19)	64 (20)
Trastuzumab + pertuzumab + T-DM1	101 (33)	114 (36)

Centrally confirmed PFS (co-primary endpoint)

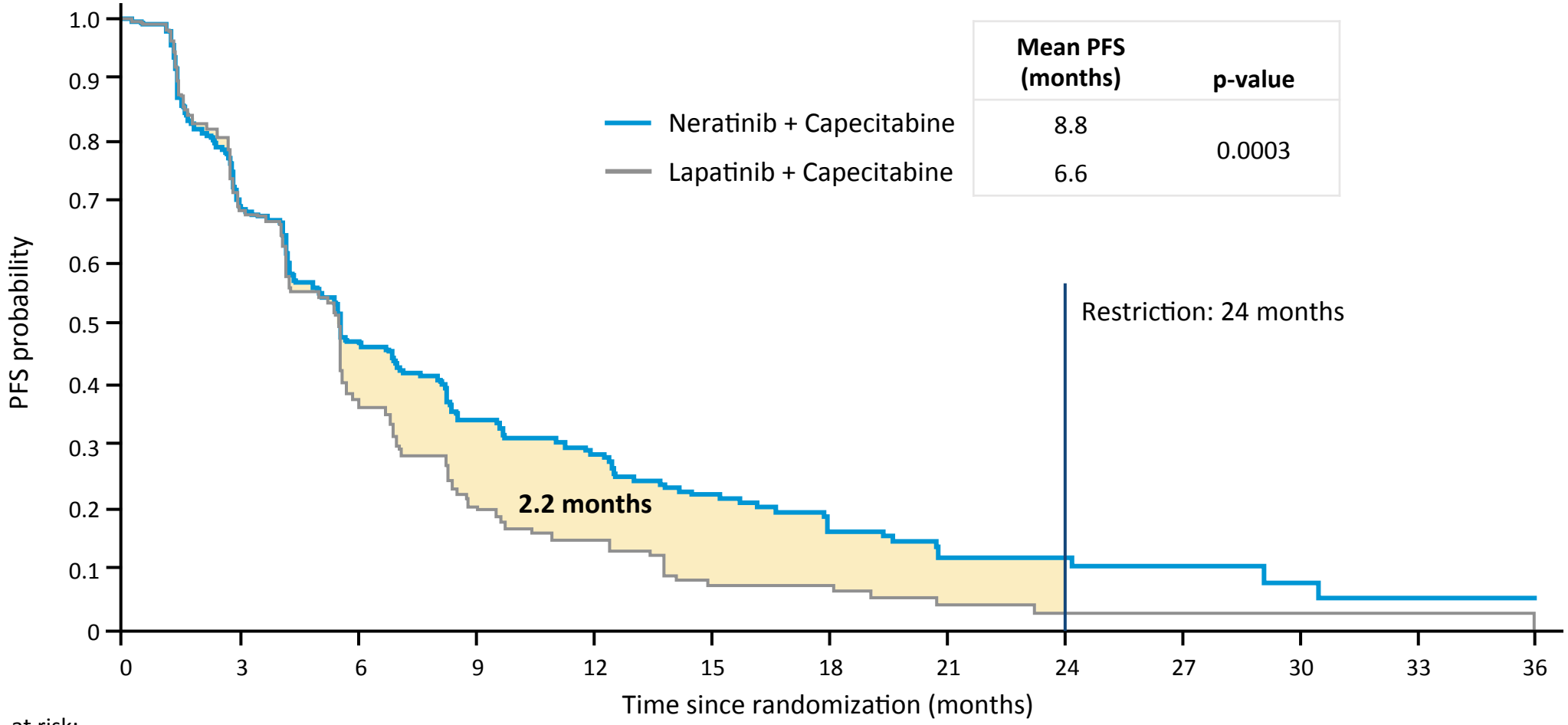


Hazard ratio (95% CI)	Log-rank p-value
0.76 (0.63–0.93)	0.0059

No. at risk:

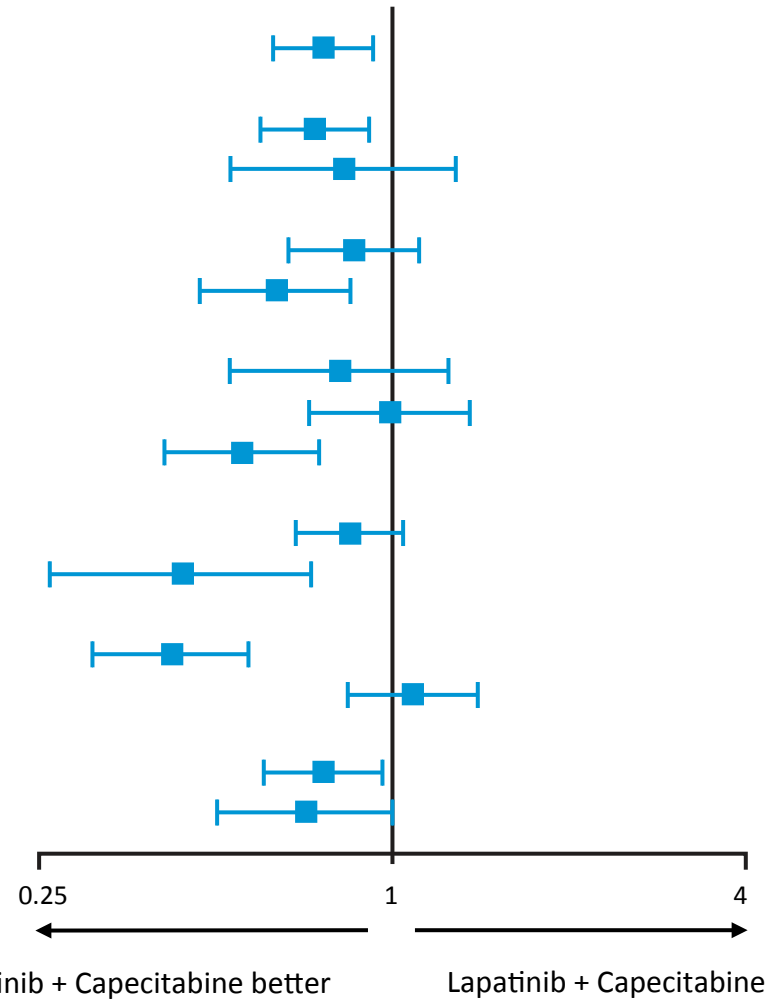
N+C	307	183	113	69	54	35	20	13	9	7	3	2	2
L+C	314	183	82	39	24	9	8	3	2	2	2	2	1

Prespecified restricted means analysis – PFS



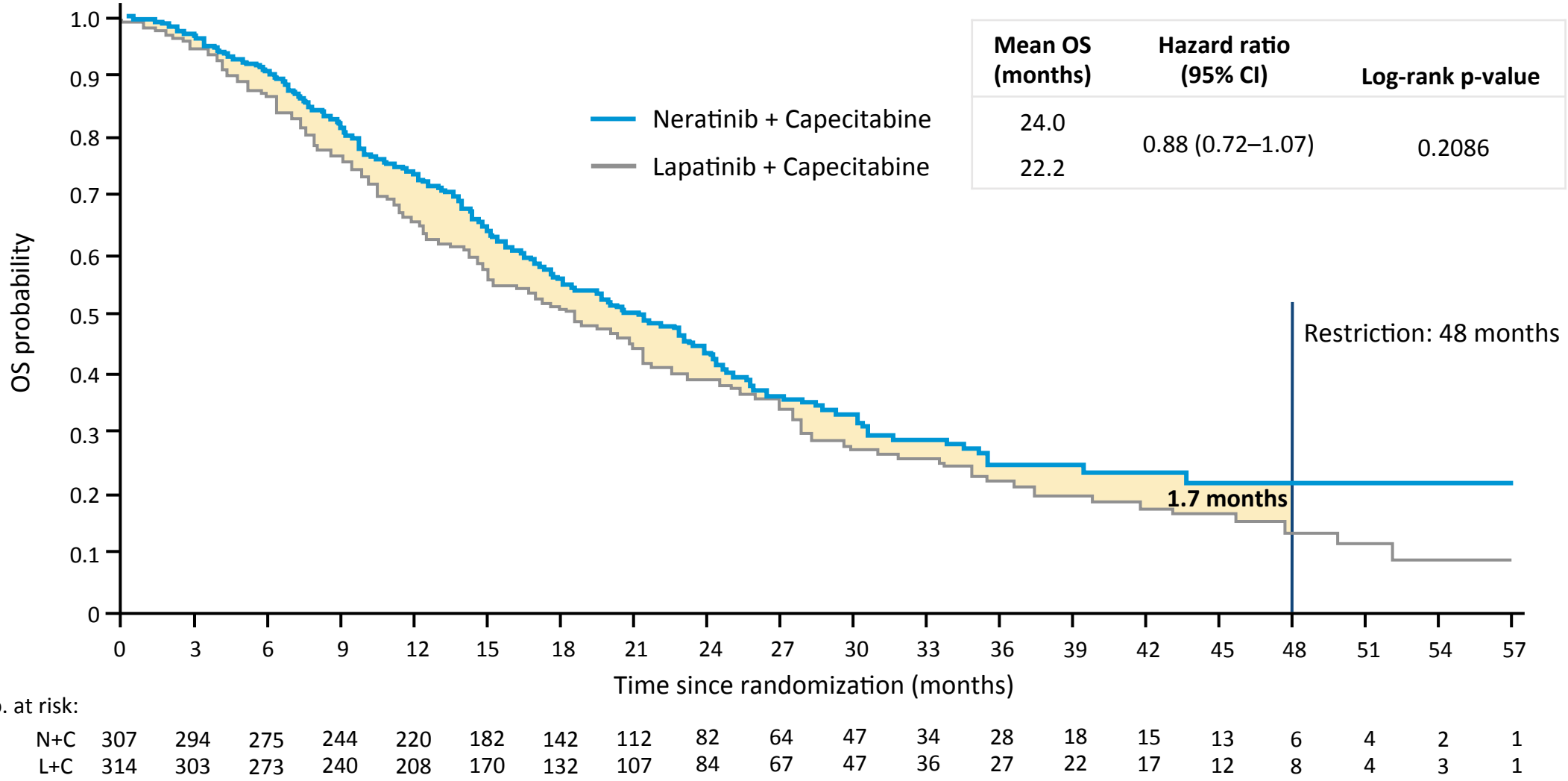
PFS: Forest plot

Subgroup	N	Events N+C vs L+C	Hazard ratio (95% CI)	Interaction test p-value
Overall	**621**	**210 vs 223**	**0.76 (0.63–0.93)**	
Age group				
<65 years	492	169 vs 181	0.74 (0.60–0.91)	**0.463**
≥65 years	129	41 vs 42	0.83 (0.53–1.28)	
Race				
White	355	125 vs 117	0.86 (0.67–1.11)	**0.166**
Asian, black, or other	266	85 vs 106	0.63 (0.47–0.85)	
Geographic region				
North America	124	41 vs 46	0.81 (0.53–1.25)	**0.051**
Europe	244	83 vs 78	0.99 (0.72–1.35)	
Rest of world	253	86 vs 99	0.55 (0.41–0.75)	
Disease location				
Visceral	500	181 vs 185	0.85 (0.69–1.04)	**0.007**
Non-visceral only	121	29 vs 38	0.44 (0.26–0.73)	
HR status				
HR–	254	82 vs 108	0.42 (0.31–0.57)	**<0.001**
HR+	367	128 vs 115	1.08 (0.84–1.40)	
No. of prior HER2 regimens				
2	430	148 vs 151	0.76 (0.60–0.96)	**0.614**
≥3	191	62 vs 72	0.71 (0.50–1.00)	



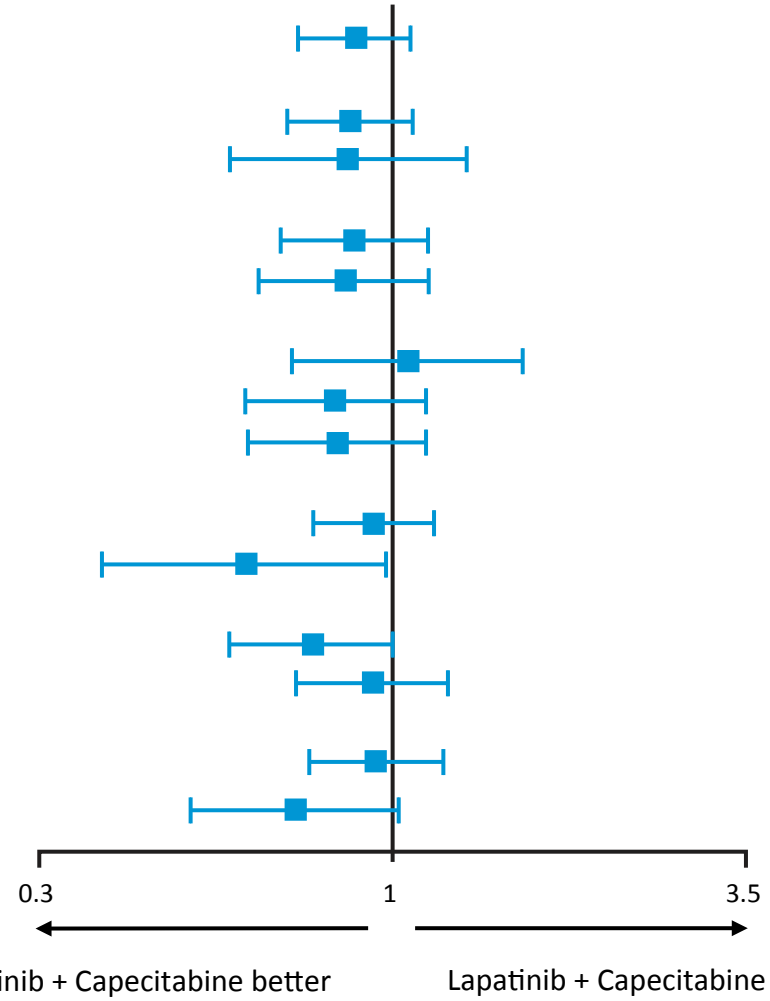
OS (co-primary endpoint)

Mean OS (months)	Hazard ratio (95% CI)	Log-rank p-value
24.0 22.2	0.88 (0.72–1.07)	0.2086



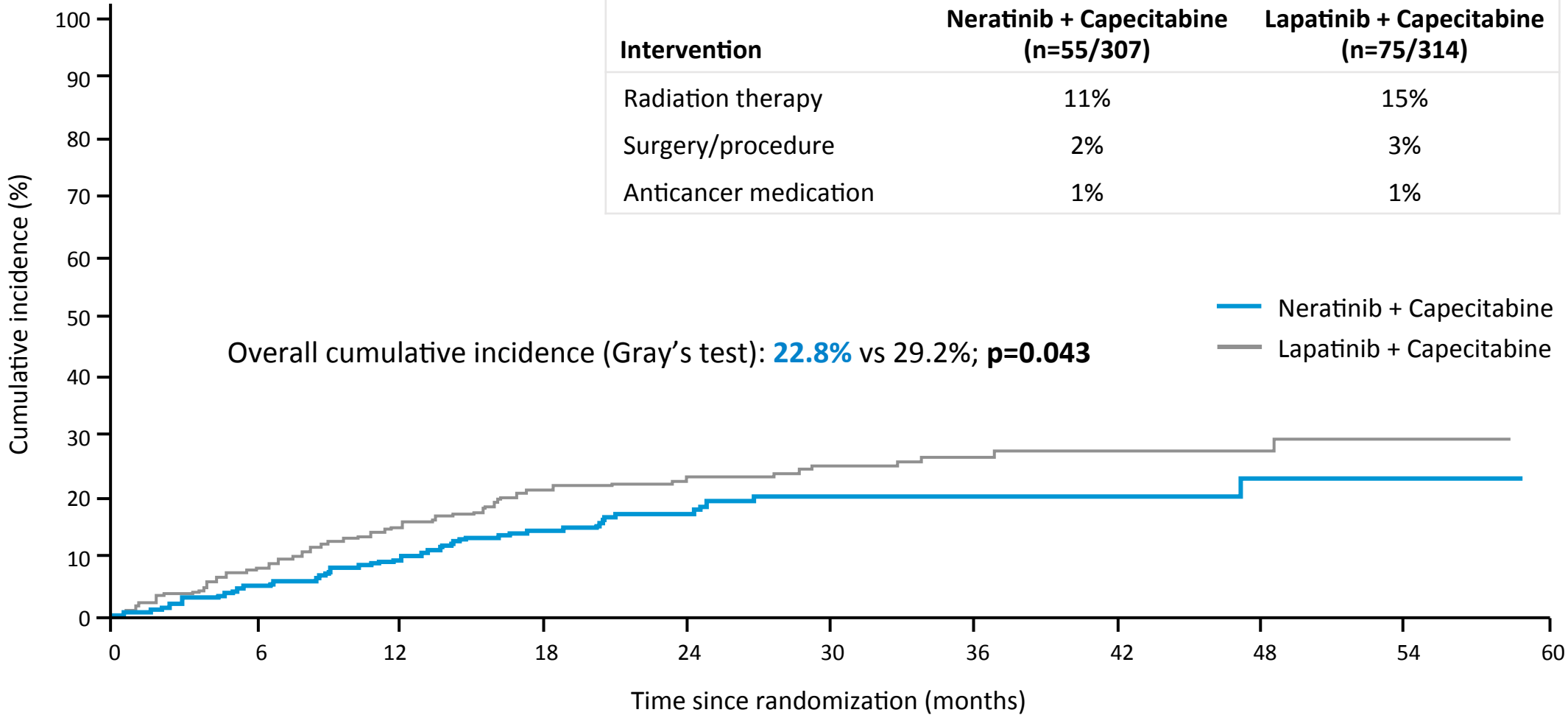
OS: Forest plot

Subgroup	N	Events N+C vs L+C	Hazard ratio (95% CI)	Interaction test p-value
Overall	**621**	**192 vs 218**	**0.88 (0.72–1.07)**	
Age group				
<65 years	492	149 vs 171	0.86 (0.69–1.08)	**0.941**
≥65 years	129	43 vs 47	0.86 (0.57–1.30)	
Race				
White	355	113 vs 122	0.88 (0.68–1.13)	**0.939**
Asian, black, or other	266	79 vs 96	0.85 (0.63–1.14)	
Geographic region				
North America	124	46 vs 51	1.06 (0.71–1.58)	**0.313**
Europe	244	70 vs 85	0.82 (0.60–1.13)	
Rest of world	253	76 vs 82	0.83 (0.60–1.13)	
Disease location				
Visceral	500	165 vs 180	0.94 (0.76–1.16)	**0.067**
Non-visceral only	121	27 vs 38	0.60 (0.36–0.98)	
HR status				
HR–	254	87 vs 101	0.76 (0.57–1.01)	**0.252**
HR+	367	105 vs 117	0.94 (0.72–1.22)	
No. of prior HER2 regimens				
2	430	139 vs 149	0.95 (0.75–1.19)	**0.146**
≥3	191	53 vs 69	0.71 (0.50–1.02)	



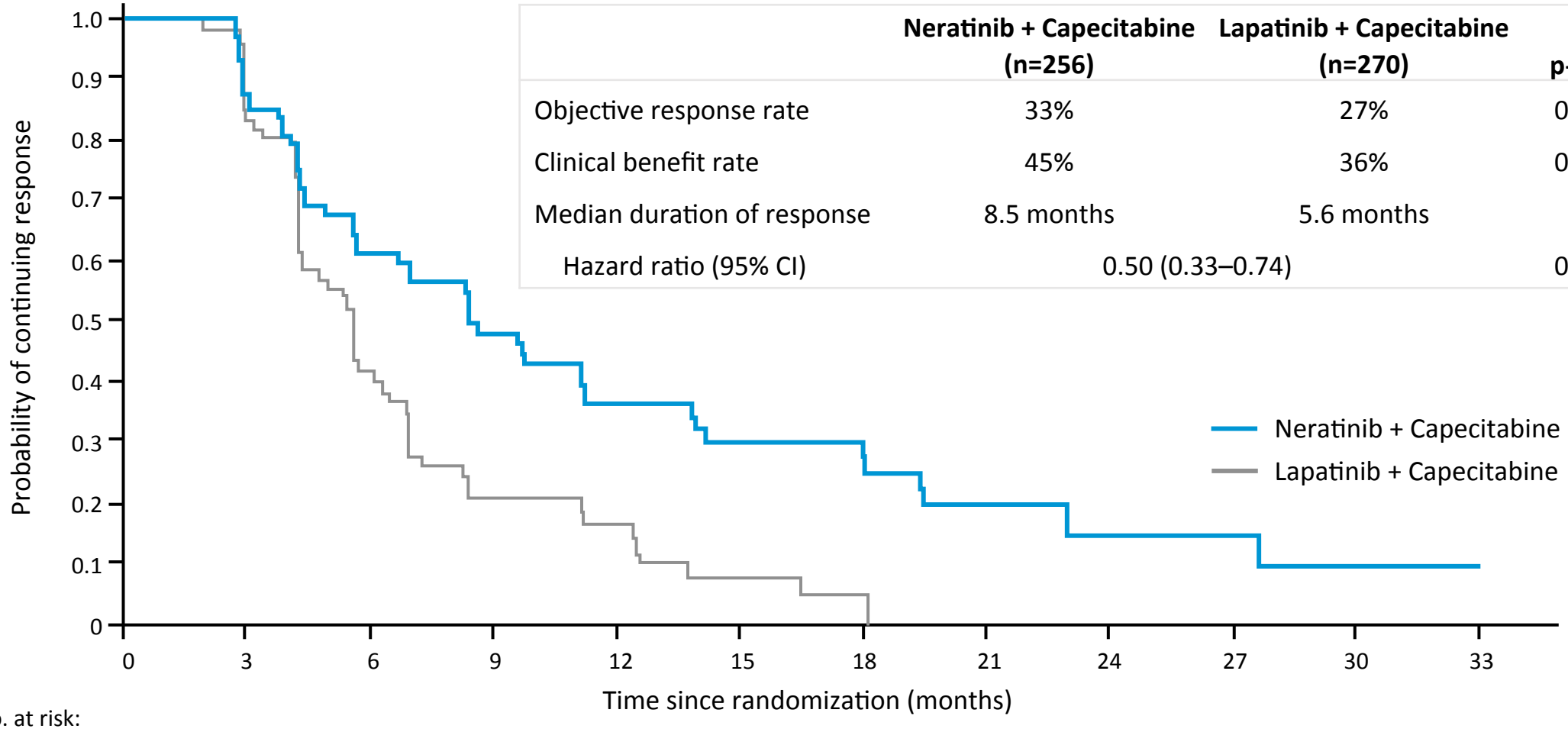
Time to intervention for CNS metastases

Intervention	Neratinib + Capecitabine (n=55/307)	Lapatinib + Capecitabine (n=75/314)
Radiation therapy	11%	15%
Surgery/procedure	2%	3%
Anticancer medication	1%	1%



Response rate and duration of response

	Neratinib + Capecitabine (n=256)	Lapatinib + Capecitabine (n=270)	p-value
Objective response rate	33%	27%	0.1201
Clinical benefit rate	45%	36%	0.0328
Median duration of response	8.5 months	5.6 months	
Hazard ratio (95% CI)	0.50 (0.33–0.74)		0.0004



Treatment exposure

	Neratinib + Capecitabine (n=303)	Lapatinib + Capecitabine (n=311)
Lapatinib/Neratinib		
Median duration of treatment, months	5.7	4.4
Dose reduction, n (%)	73 (24)	61 (20)
Dose hold, n (%)	145 (48)	134 (43)
Capecitabine		
Median duration of treatment, months	5.5	4.8
Dose reduction, n (%)	117 (39)	152 (49)
Dose hold, n (%)	178 (59)	184 (59)

Most frequent grade 3/4 adverse events

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (n=311)	
	All grade	Grade 3/4	All grade	Grade 3/4
Treatment-emergent AE, %	100	61	99	60
Diarrhea	83	24*	66	13*
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment discontinuation due to treatment-emergent AEs: N+C: 10.9%; L+C: 14.5%

*No Grade 4 diarrhea

Incidence and duration of diarrhea

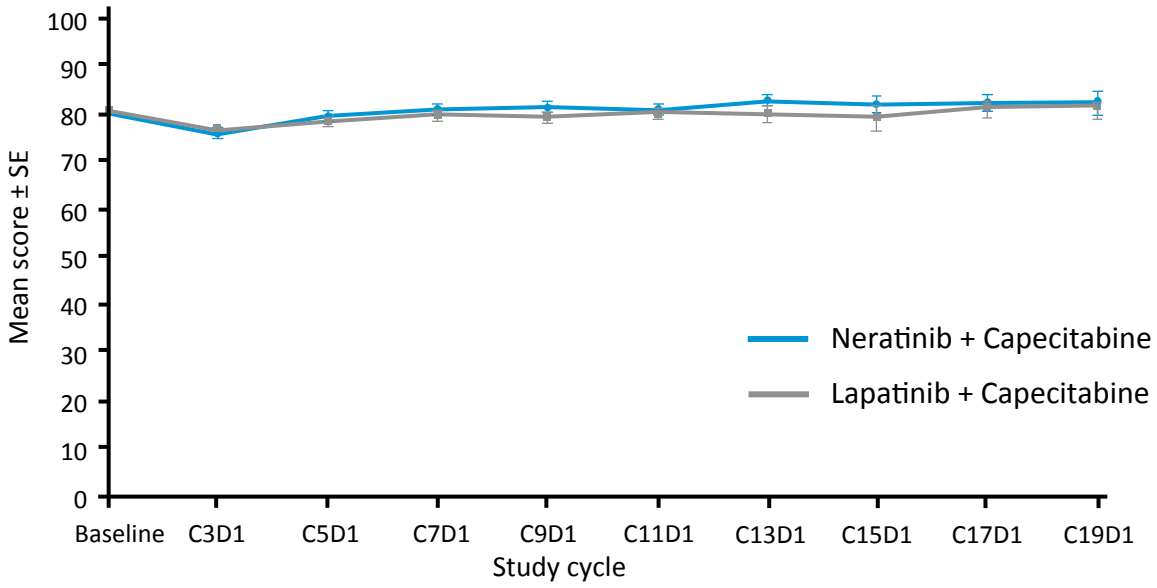
	Neratinib + Capecitabine (n=303)	Lapatinib + Capecitabine (n=311)
Maximum toxicity, n (%)		
Grade 1	91 (30)	111 (36)
Grade 2	87 (29)	56 (18)
Grade 3	74 (24)	39 (13)
Time to first onset of diarrhea, days		
Grade 2 or 3	9	18
Grade 3	11	38
Median cumulative duration per patient, days		
Grade 2 or 3	7	9
Grade 3	4	4

Treatment discontinuation due to diarrhea: N+C: 2.6% L+C: 2.3%

Patient reported outcomes

EORTC QLQ-C30 summary score

Mean score over time

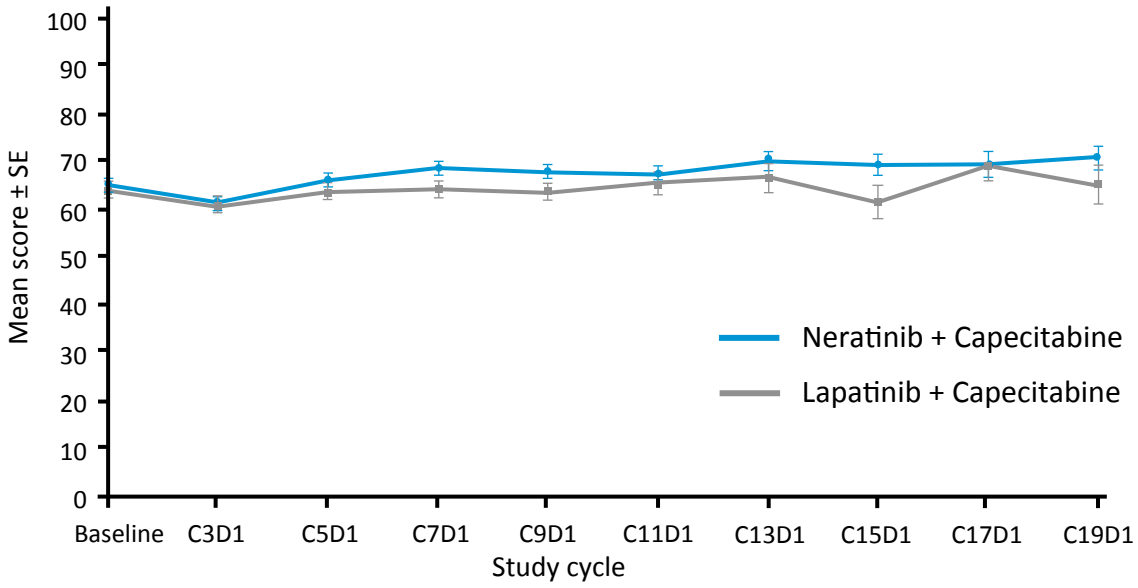


No. of patients:

N+C	275	265	210	181	147	112	99	80	70	55
L+C	281	270	215	178	132	90	64	44	32	27

EORTC QLQ-C30 Global health status

Mean score over time



No. of patients:

N+C	277	267	212	182	150	115	99	81	71	55
L+C	283	273	219	179	133	93	64	44	32	27

Conclusions

- NALA met its primary objective: N+C superior to L+C in ≥3L HER2+ MBC
  - Significant PFS benefit favoring N+C: HR=0.76; p=0.0059
  - Numerical improvement in OS favoring N+C: HR=0.88; p=0.2086
- Fewer patients required intervention for symptomatic CNS metastases with N+C (p=0.043), suggestive of a delay in CNS progression
  - Consistent with results from previous neratinib studies[1,2]
- Duration of response significantly improved with N+C: HR=0.50; p=0.0004
- No new safety signals seen. Discontinuations due to diarrhea 2.3% with N+C and a median cumulative duration of grade 3 diarrhea of 4 days
- Trial results suggest N+C is an effective option for treating progressive HER2+ MBC

1. Awada et al. JAMA Oncol 2016; 2. Martin et al. Lancet Oncol 2017

Thank you

The authors would like to thank patients and their families, and the investigators and site staff for participating in this trial

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