Available Therapeutic Options for the Management of HER2-Positive Metastatic Breast Cancer

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Disclosures

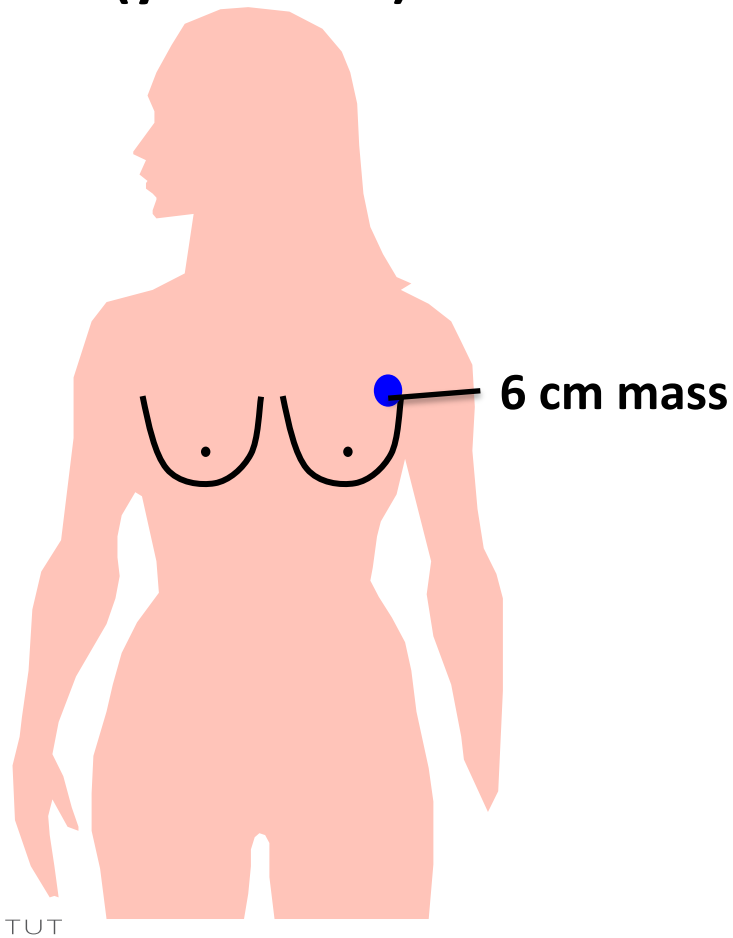
Consulting Agreements	Agendia Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, bioTheranostics Inc, Celgene Corporation, Daiichi Sankyo Inc, Eisai Inc, Genentech, Lilly, Novartis, Pfizer Inc, Puma Biotechnology Inc, Sandoz Inc, a Novartis Division

Case Presentation: Dr Hurvitz

- 62 yo woman diagnosed 9 years ago with stage II ER/PR negative, HER2+ breast cancer, s/p adjuvant AC-TH; diagnosed with metasatatic breast cancer to liver (same biomarkers) 3 years ago, treated with THP→HP with CR in liver. 8 months ago develops headaches, scans show 7 lesions in CNS. No extracranial disease.
  - Question: In addition to local (RT/SRS) therapy, what systemic treatment do you recommend?
    - Continue HP
    - Continue HP, add neratinib
    - Neratinib/capecitabine
    - Lapatinib/capecitabine
    - Trastuzumab/capecitabine/tucatinib

Case Presentation: Prof Piccart-Gebhart

37 y old premenopausal pt (year 2013)



- **Unremarkable past and familial medical Hx/ 2 months after the delivery of a baby boy**
- **Physical exam: no hypertension, BMI<25, LVEF>65%**
- **Pathology: ductal invasive carcinoma grade 2 RO+ RPg+ HER2 3+ FISH+**
- **PET-CT scan: « de novo » metastatic disease with liver, lung, bone involvement**

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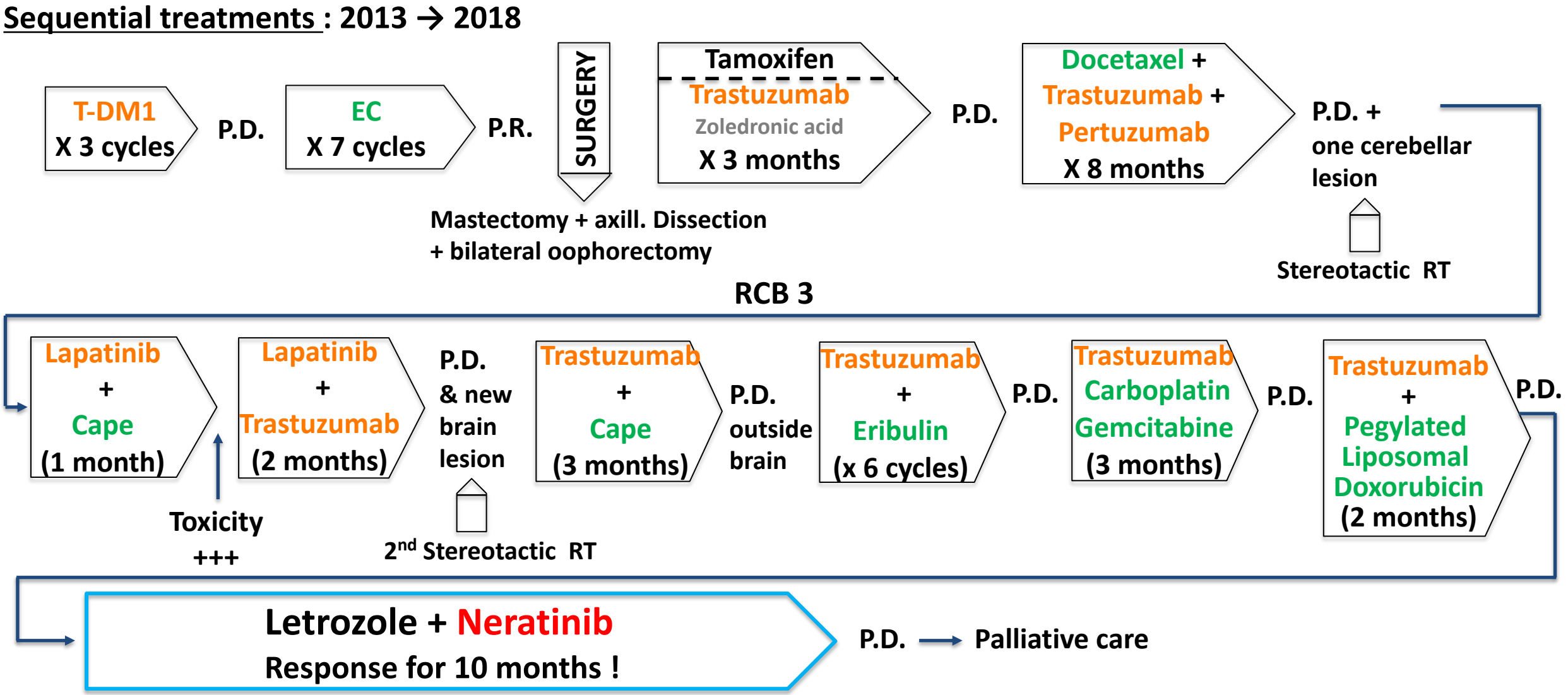
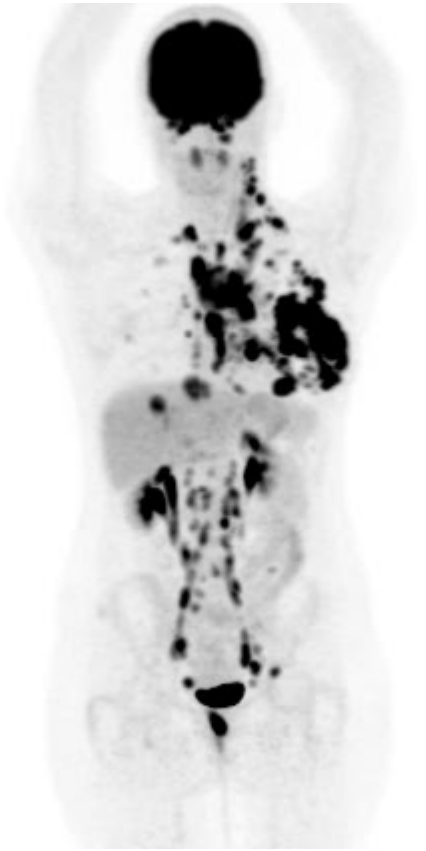
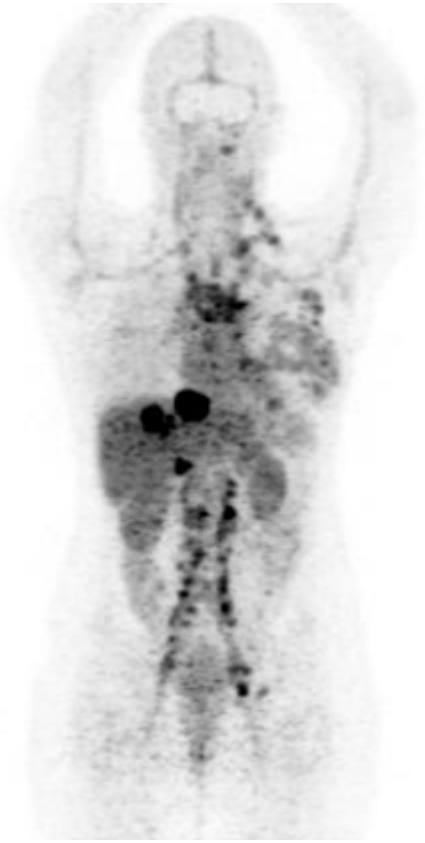
Case Presentation: Prof Piccart-Gebhart

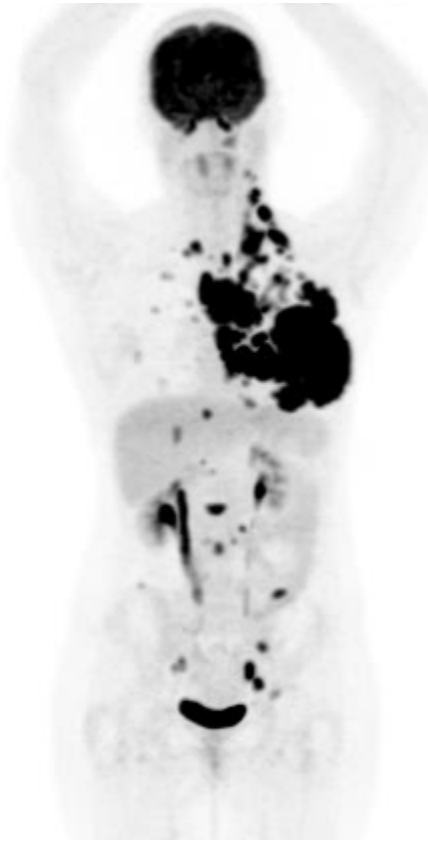




Baseline FDG PET



HER2 PET



FDG PET post 3 T-DM1 cycles

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SystHERs: Characteristics of De Novo vs Recurrent HER2-Positive mBC

Characteristic	De Novo (n = 487)	Recurrent (n = 490)	P-Value
Median Age at Diagnosis, years	55	58	<0.001
Hormone Receptor Status			<0.001
ER- and/or PR-positive	65.1%	75.1%	
ER- and/or PR-negative	34.9%	24.9%	
Selected Metastatic Sites			
Bone	57.1%	45.9%	<0.001
Liver	41.9%	33.1%	0.005
Lung	29.6%	33.9%	0.15
CNS	4.3%	13.5%	<0.001

Tripathy D et al. The Oncologist 2019;24:1-9.

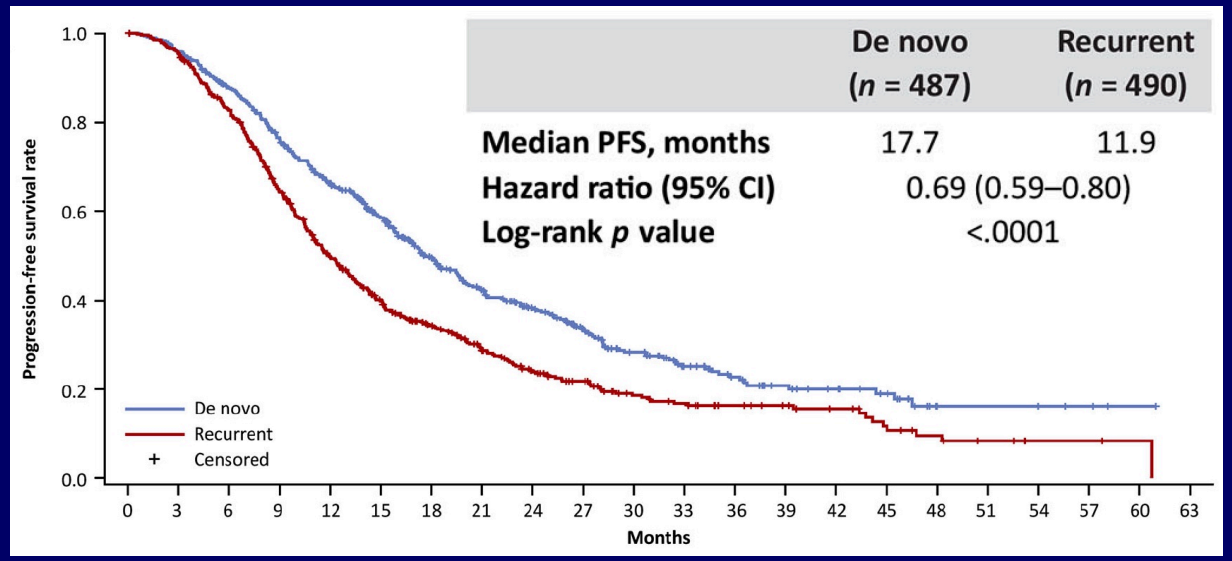
SystHERs: First-Line Systemic Treatment

Treatment	De Novo (n = 487)	Recurrent (n = 490)
Pts treated with 1st-line therapy for mBC	97.9%	96.1%
Pts treated with 1st-line HER2-targeted therapy for mBC	96.7%	92.2%
Trastuzumab use	95.7%	85.9%
Pertuzumab use	77.8%	68.6%
Pts treated with any 1st-line chemotherapy for mBC	89.7%	80.0%
Most common regimen: Pertuzumab/trastuzumab/taxane ± ET	73.3%	59.8%

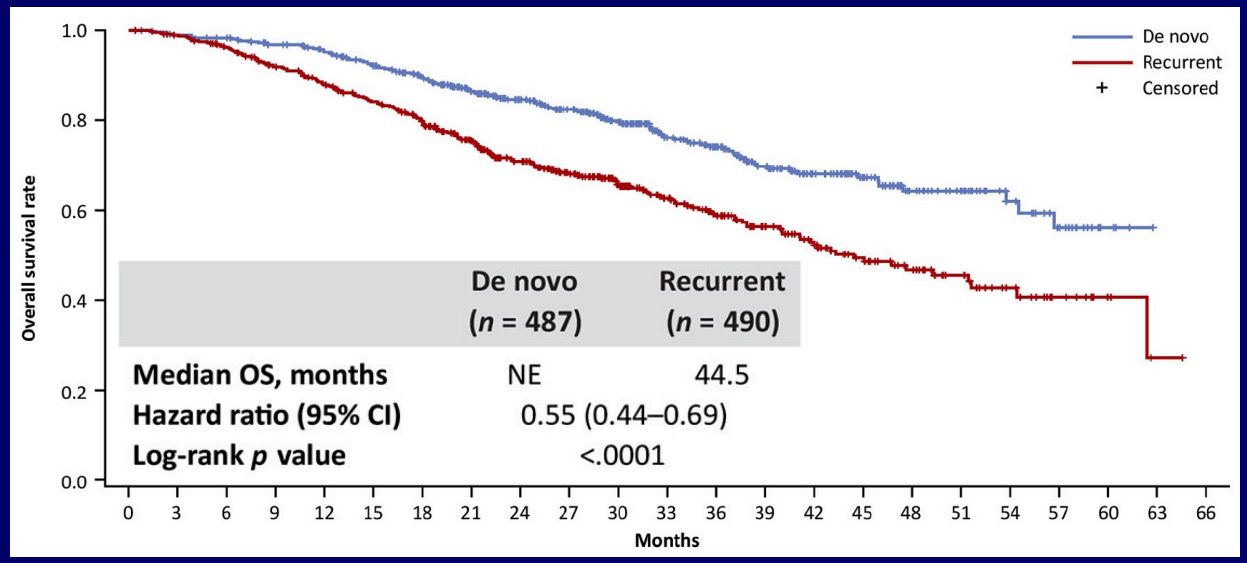
Tripathy D et al. The Oncologist 2019;24:1-9.

SystHERs: Survival Analyses in De Novo and Recurrent HER2-Positive mBC

Progression-Free Survival



Overall Survival

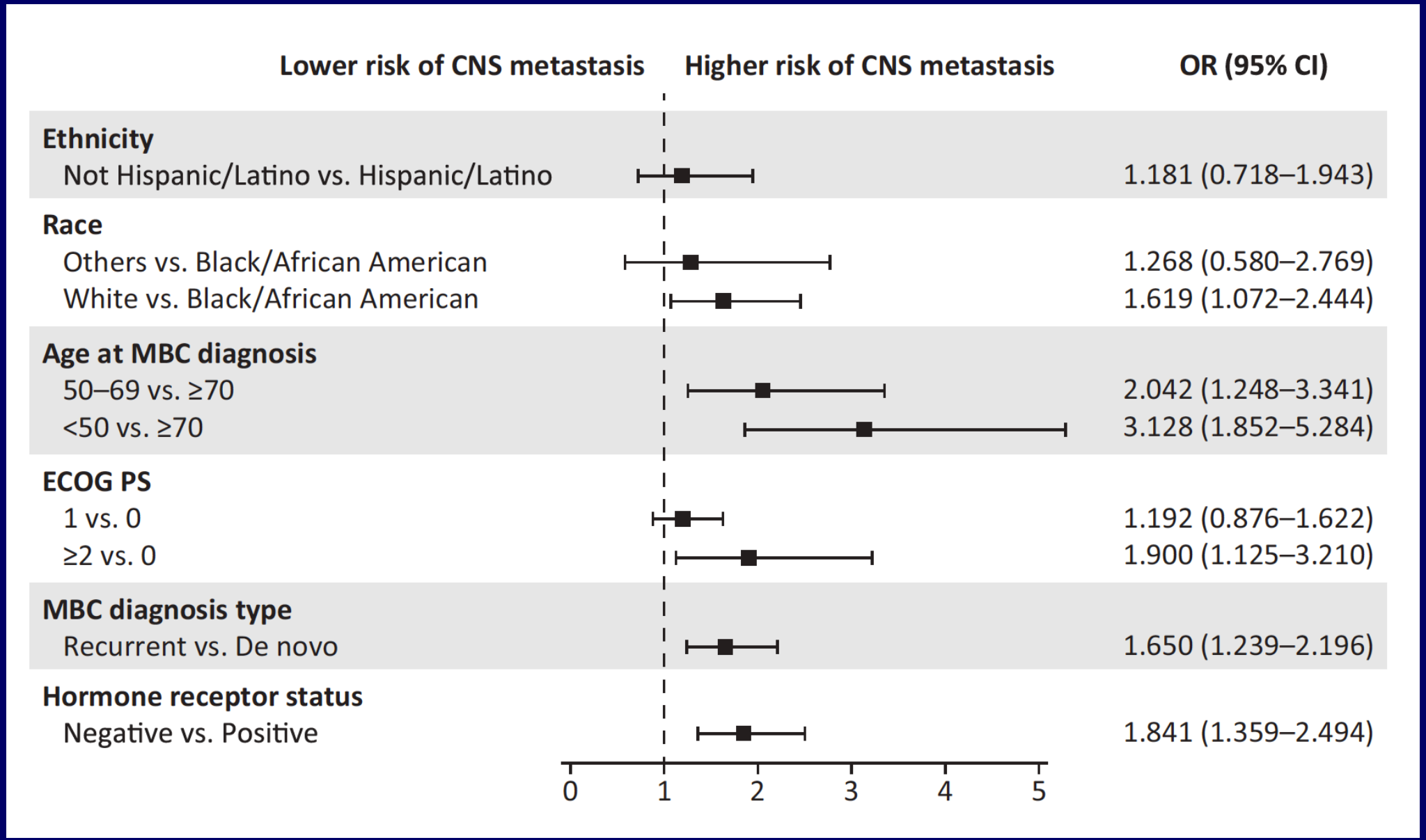


Tripathy D et al. The Oncologist 2019;24:1-9.

Metastatic CNS Disease Remains Incurable, Despite Current Treatment Options

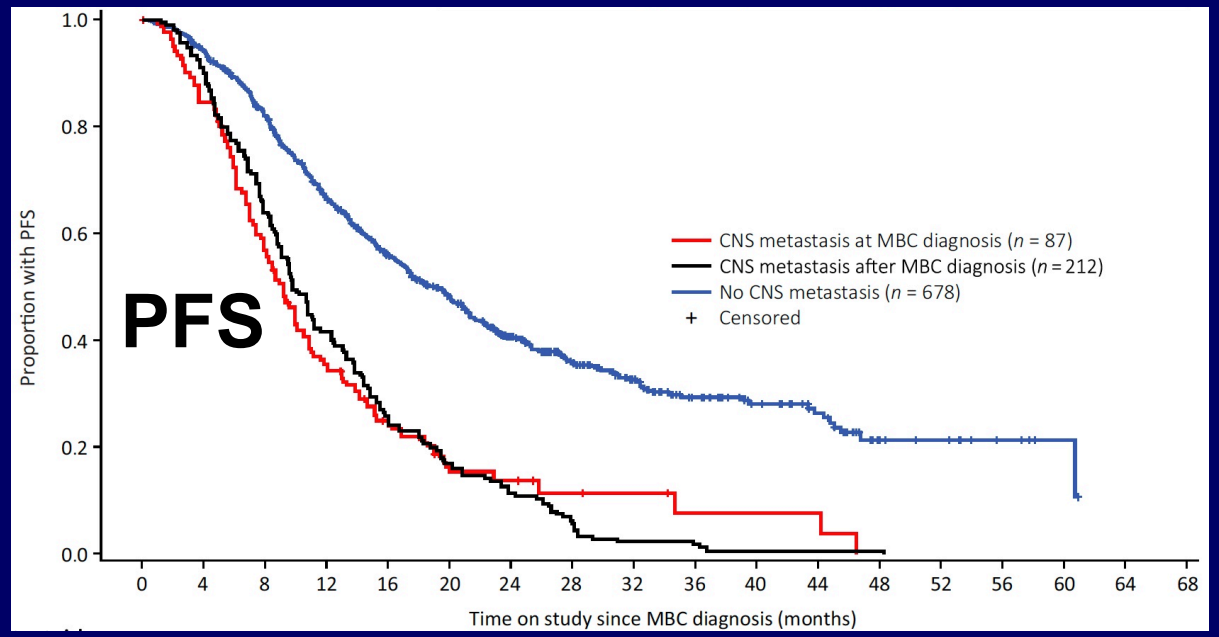
- Up to 50% of patients with HER2+ MBC will develop brain metastases
- Lapatinib plus capecitabine is a treatment option for patients with disease that has metastasized to the brain; however, only a fraction of patients respond to therapy
  - Overall response rate of brain metastases was 21.4%, median PFS/time to progression was 4.1 months, and median OS was 11.2 months
  - There is still significant unmet need for patients with CNS metastases
- T-DM1, trastuzumab, and pertuzumab do not penetrate the CNS under normal conditions

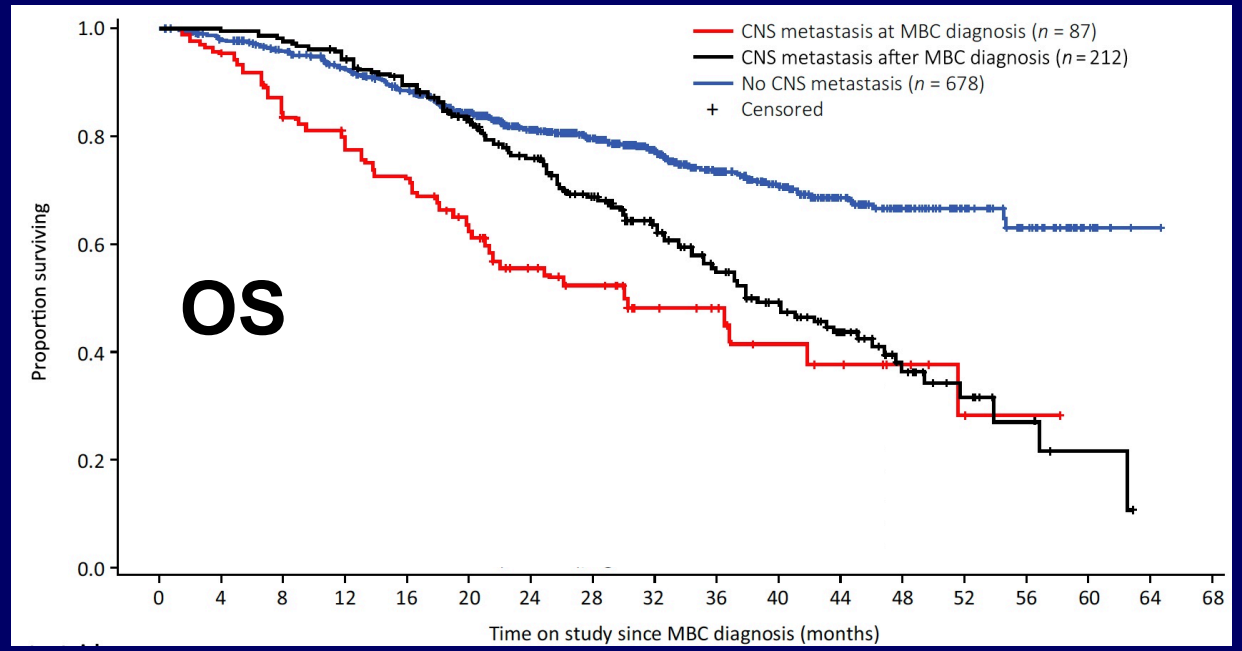
Petrelli et al. *Eur J Cancer*. 2017;84:141-148.



Hurvitz et al *Clin Cancer Res* 2019;25:2433-2441

SystHERs: Survival Analyses for CNS Mets in HER2-Positive mBC





	CNS metastasis at MBC diagnosis *n* = 87	CNS metastasis after MBC diagnosis *n* = 212	No CNS metastasis *n* = 678
Median PFS, months	9.2	9.9	19.1
	CNS metastasis at MBC diagnosis vs. no CNS metastasis at any time		
HR (95% CI)	2.49 (1.93–3.20), log-rank *P* < 0.0001		
	CNS metastasis after MBC diagnosis vs. no CNS metastasis at any time		
HR (95% CI)	2.52 (2.13–2.99), log-rank *P* < 0.0001		

	CNS metastasis at MBC diagnosis *n* = 87	CNS metastasis after MBC diagnosis *n* = 212	No CNS metastasis *n* = 678
Median OS, months	30.2	38.3	NE
	CNS metastasis at MBC diagnosis vs. no CNS metastasis at any time		
HR (95% CI)	2.86 (2.05–4.00), log-rank *P* < 0.0001		
	CNS metastasis after MBC diagnosis vs. no CNS metastasis at any time		
HR (95% CI)	1.94 (1.52–2.49), log-rank *P* < 0.0001		

Hurvitz et al *Clin Cancer Res* 2019;25:2433-2441

Phase III CEREBEL: Study Design

Planned N = 650

Key eligibility
- HER2+ MBC*
- Prior anthracyclines or taxanes
- Any-line therapy
- **No CNS metastases†**

Evaluable systemic dx

Stratification
- Prior trastuzumab
- Prior MBC tx
- 0 vs ≥ 1

RANDOMIZE

→ **Lapatinib 1250 mg/day + Capecitabine 2000 mg/m²/day, days 1-14 q21d**

→ **Trastuzumab 6 mg/kg IV q21 days + Capecitabine 2500 mg/m²/day, days 1-14 q21d**

Primary Endpoint: CNS metastasis as the site of first relapse

Independent Data Monitoring Committee recommended termination of the study: June 2012

*FISH+/IHC 3+.

†Confirmed by independently reviewed MRI scan.

Pivot X, et al. *ESMO 2012*. LBA 11.

CEREBEL: Endpoints

Study Endpoints	L + C (n = 251)	T + C (n = 250)	*P* Value
CNS as first site of progression	8 (3%)	12 (5%)	0.360
Incidence of CNS progression at any time	17 (7%)	15 (6%)	0.865
Median time to first CNS progression	5.7 mo (2-17)	4.4 mo (2-27)	
Media PFS (ITT) **Trastuzumab Naïve**	6.6 mo 6.3 mo	8.0 mo 10.9 mo	0.021 NR
Median OS	22.7 mo	37.3 mo	0.095
ORR	27%	32%	NR

Pivot X, et al. *ESMO 2012*. LBA 11.

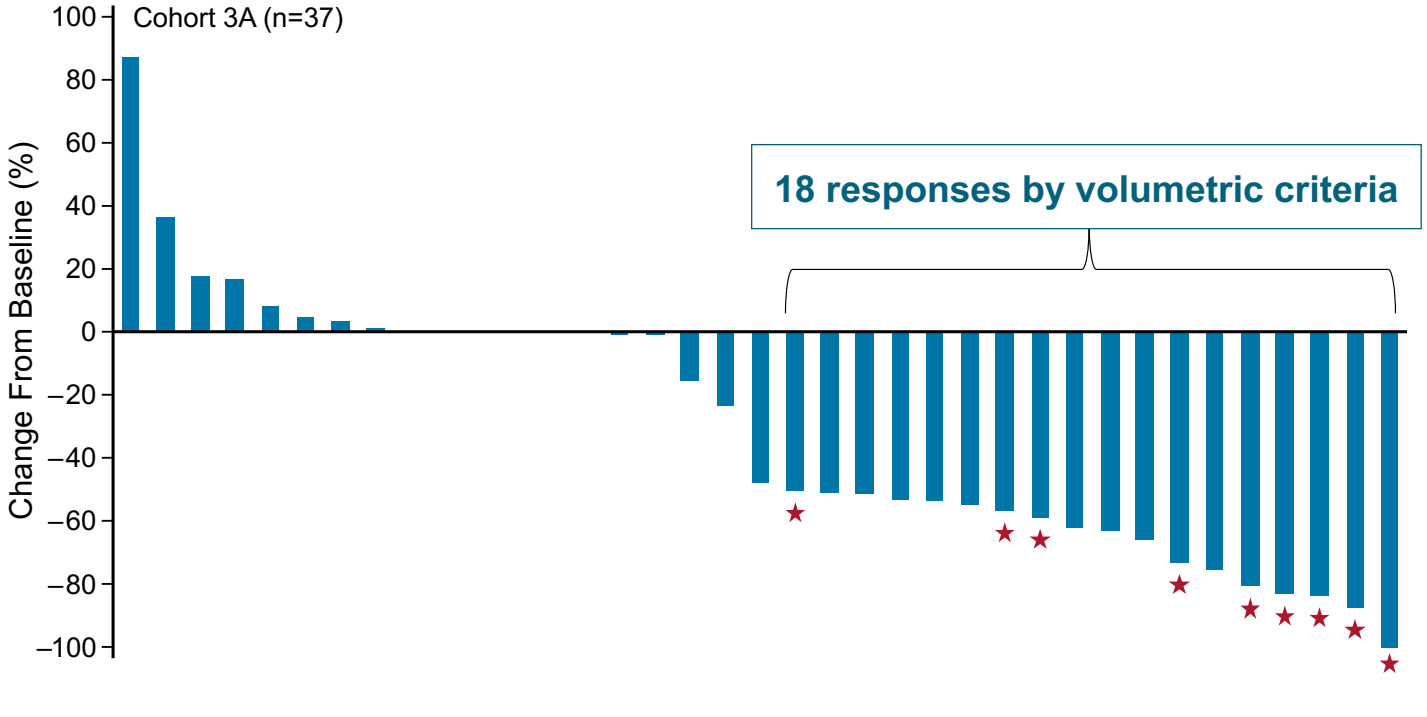
TBCRC 022 Cohort 3A

Primary endpoint – CNS volumetric response

Cohort 3A: no prior lapatinib

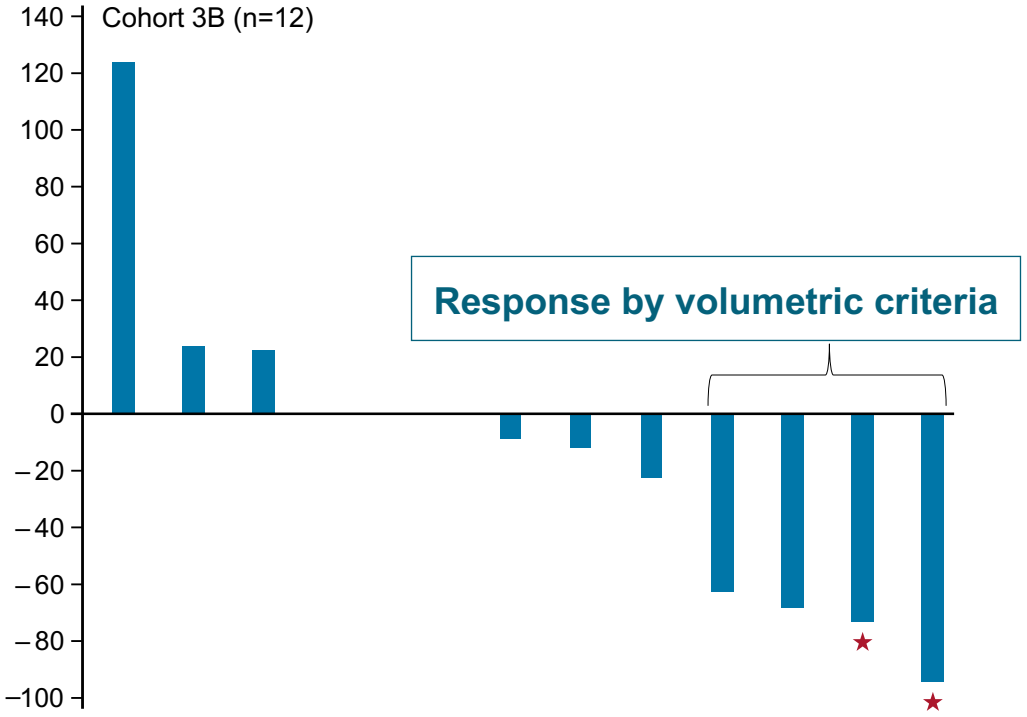
Best CNS volumetric response (n=31)*

CNS ORR=49% (95% CI 32–66%)



Cohort 3B: prior lapatinib

CNS ORR=33% (95% CI 10–65%)



6 patients did not reach first reimaging and were categorized as '0' [3 for toxicity].

★Patients who also had a CNS response by RANO-BM criteria.

CNS, central nervous system; ORR, objective response rate.

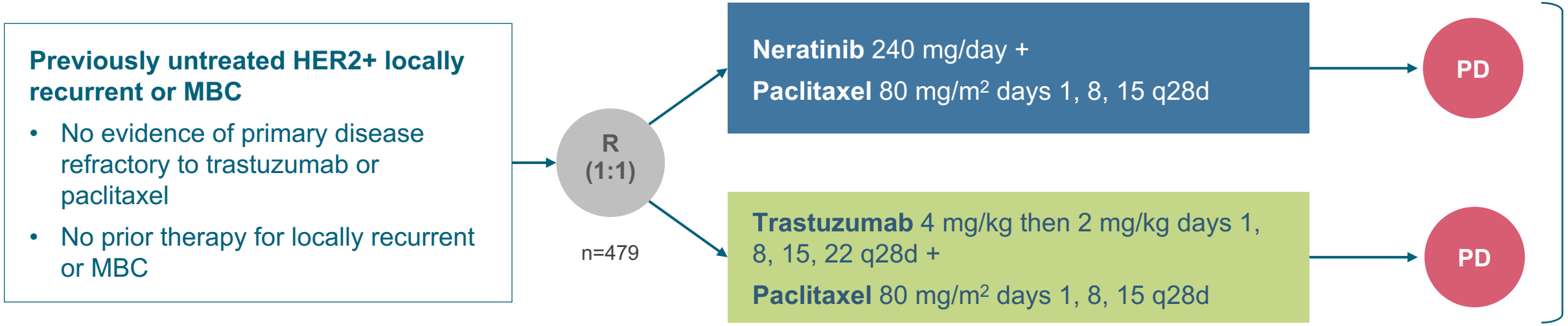
Freedman RA et al. *J Clin Oncol*. 2019 Mar 12.

Phase II NEfERT-T Trial

Randomized study of HER2-directed therapy in 1st-line MBC

STUDY OBJECTIVES:

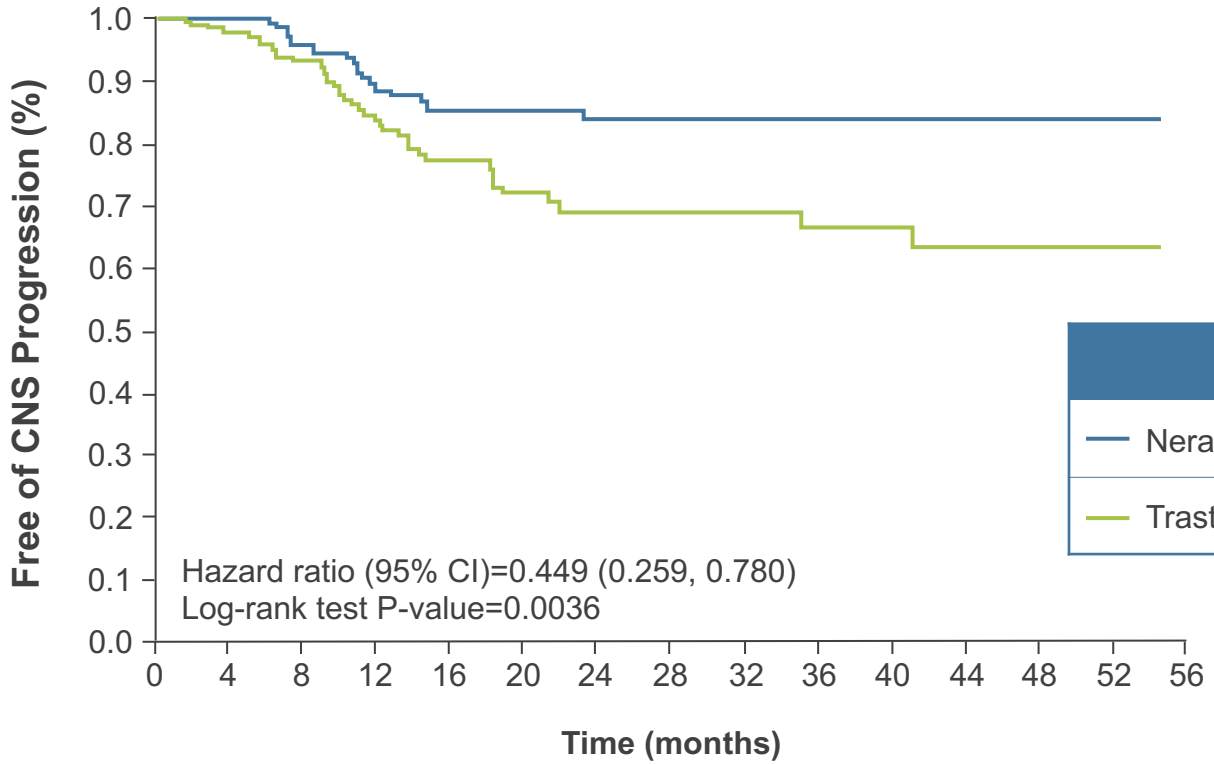
- **Primary:** PFS
- **Secondary:** ORR, DoR, CBR, frequency and time to symptomatic/progressive CNS metastases, safety



Awada A et al. *JAMA Oncol*. 2016 Dec 1;2(12).

NEfERT-T Efficacy

CNS progression is limited with neratinib + paclitaxel



	N	Event	Median (95% CI), mo
Neratinib + paclitaxel	242	20	Not estimable
Trastuzumab + paclitaxel	237	41	Not estimable

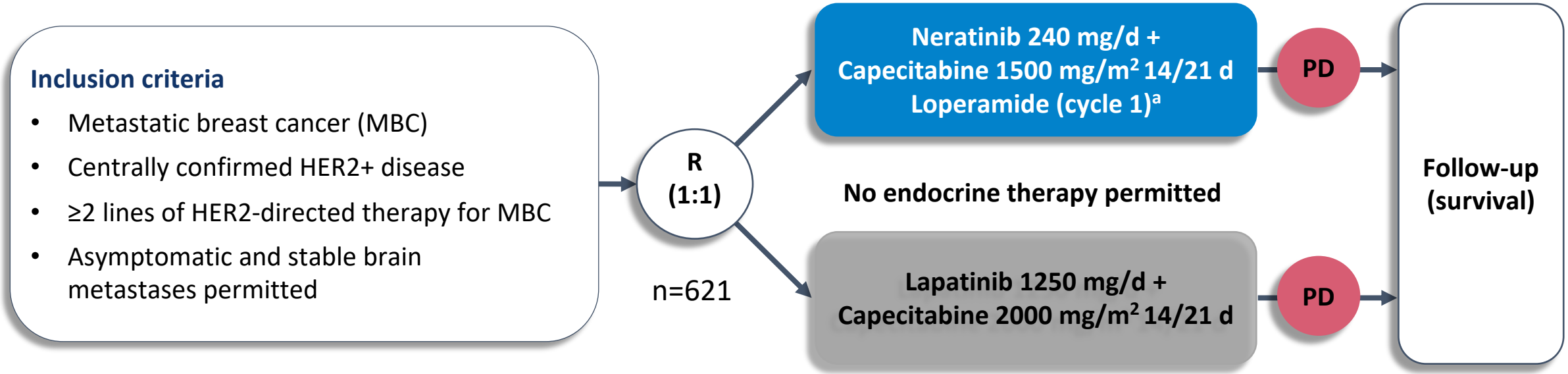
No. at risk

Neratinib + paclitaxel	242	191	141	102	73	57	45	38	35	32	22	14	10	3	0
Trastuzumab + paclitaxel	237	196	144	96	70	53	44	35	33	27	23	14	6	3	0

Neratinib treatment effect on both CNS endpoints remained statistically significant after adjusting for the imbalance of baseline CNS metastases (Cox model hazard ratio 0.56, p=0.045; Cochran Mantel-Haenszel p=0.015).

Awada A et al. *JAMA Oncol*. 2016 Dec 1;2(12).

Phase III NALA study design



Stratification variables

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

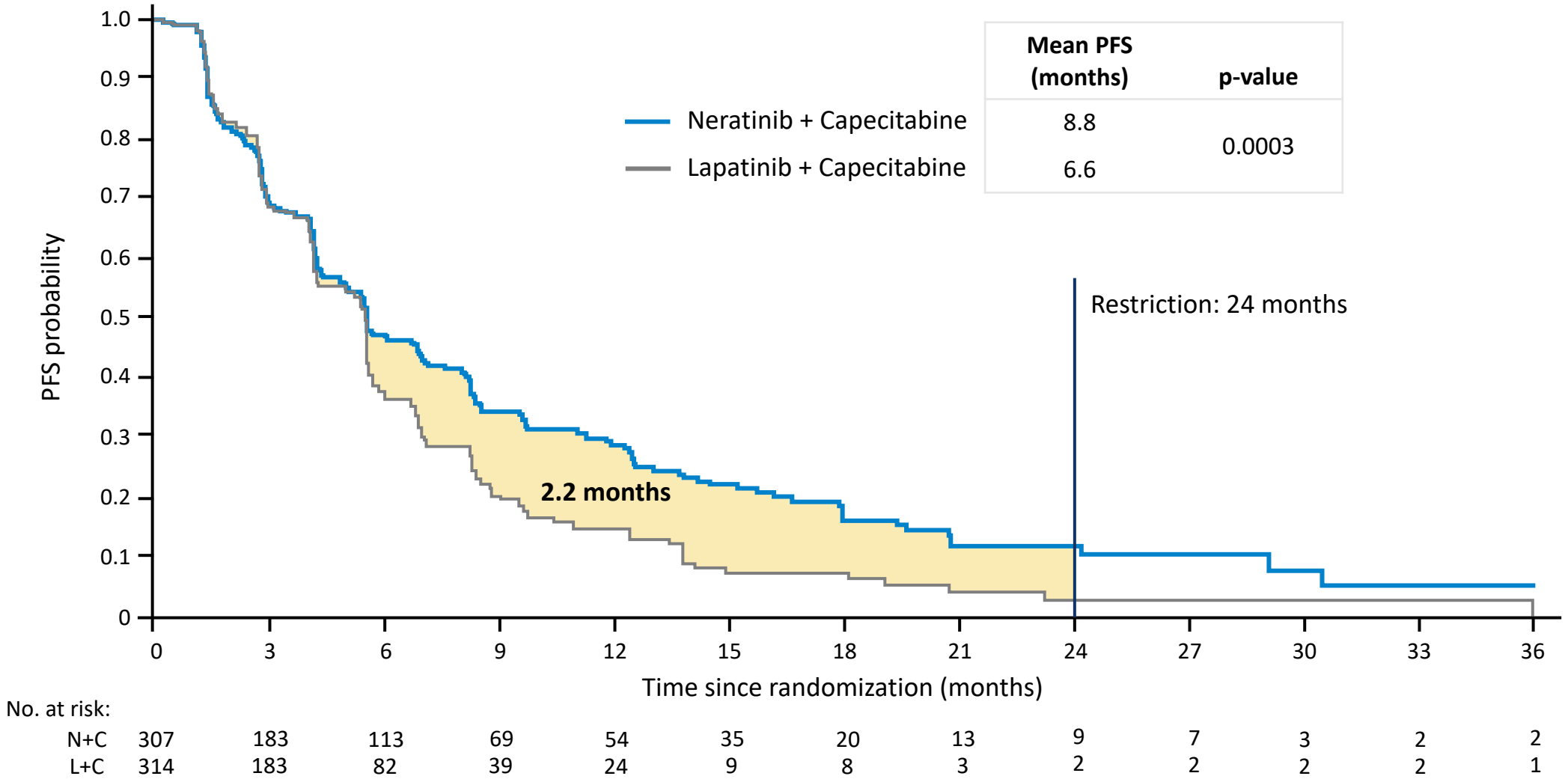
Endpoints

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

[a] 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

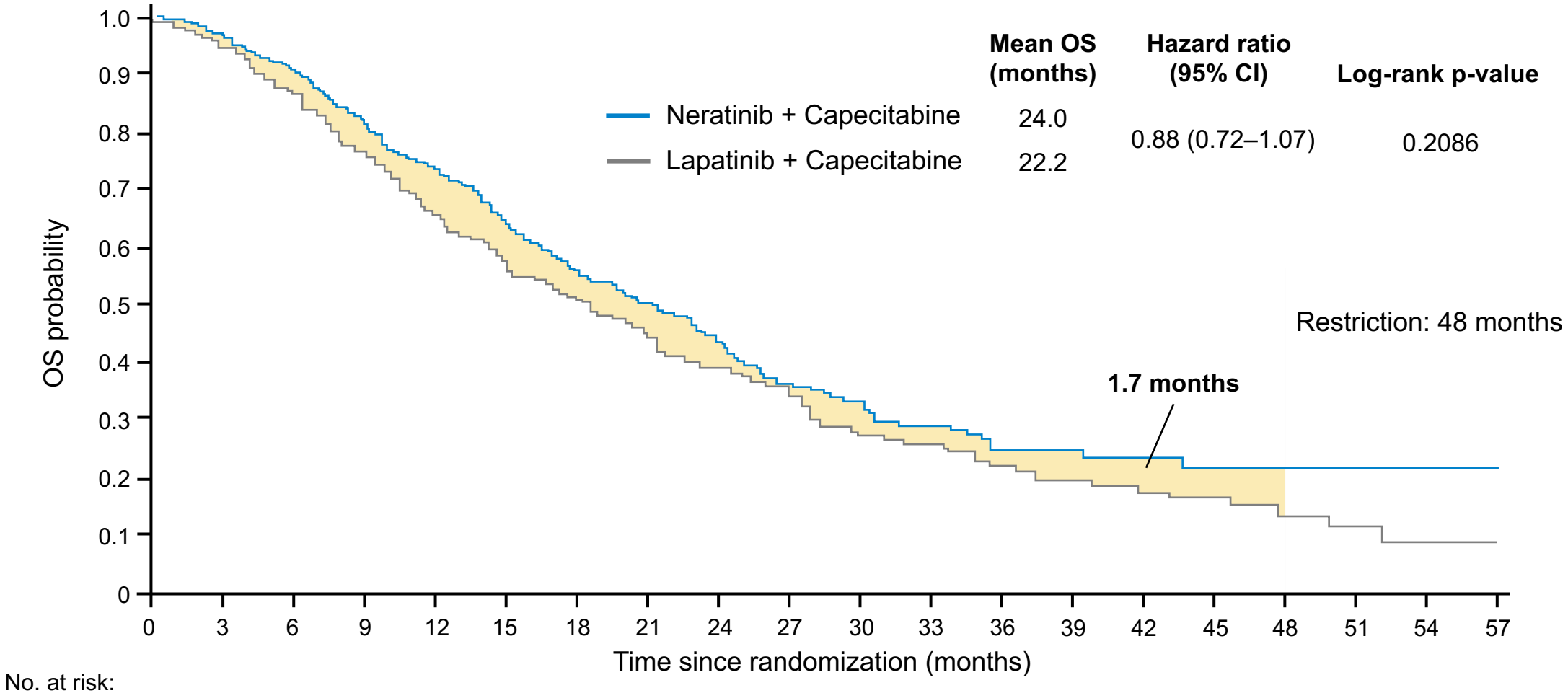
Saura C et al. ASCO 2019;Abstract 1002.

NALA: Prespecified restricted means analysis – PFS



Saura C et al. ASCO 2019;Abstract 1002.

OS (co-primary endpoint)



Saura et al. ASCO 2019 presentation. Abstract 1002.

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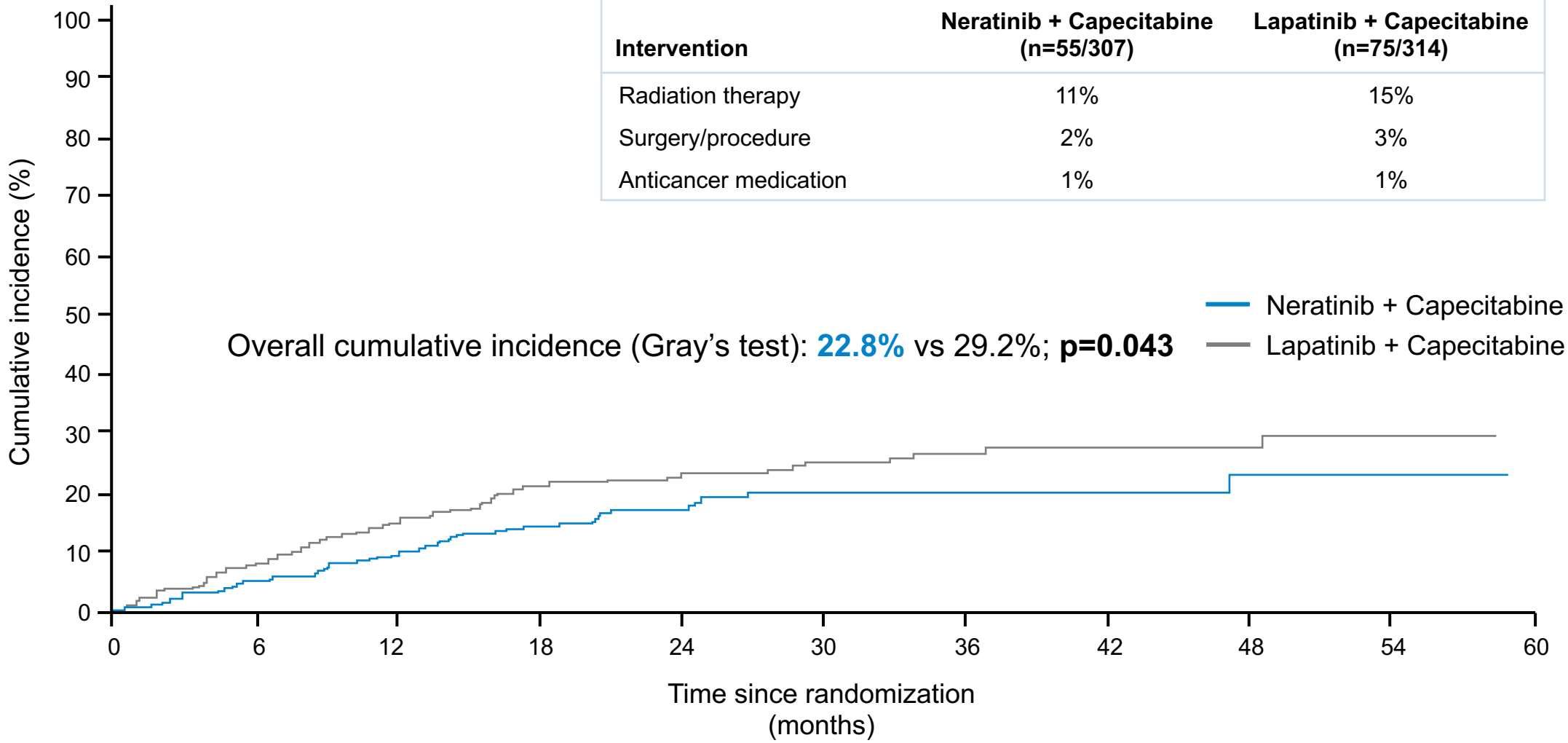
Time to intervention for CNS metastases

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



Saura et al. ASCO 2019 presentation. Abstract 1002.

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Implications for Practice

- Neratinib is likely new SOC for third line HER2 MBC therapy
- Prevents CNS progression as major benefit?
- Await data from tucatinib (SABCS 2019)
- Pyrotinib studies can add to these data