

New anti HER2 drugs

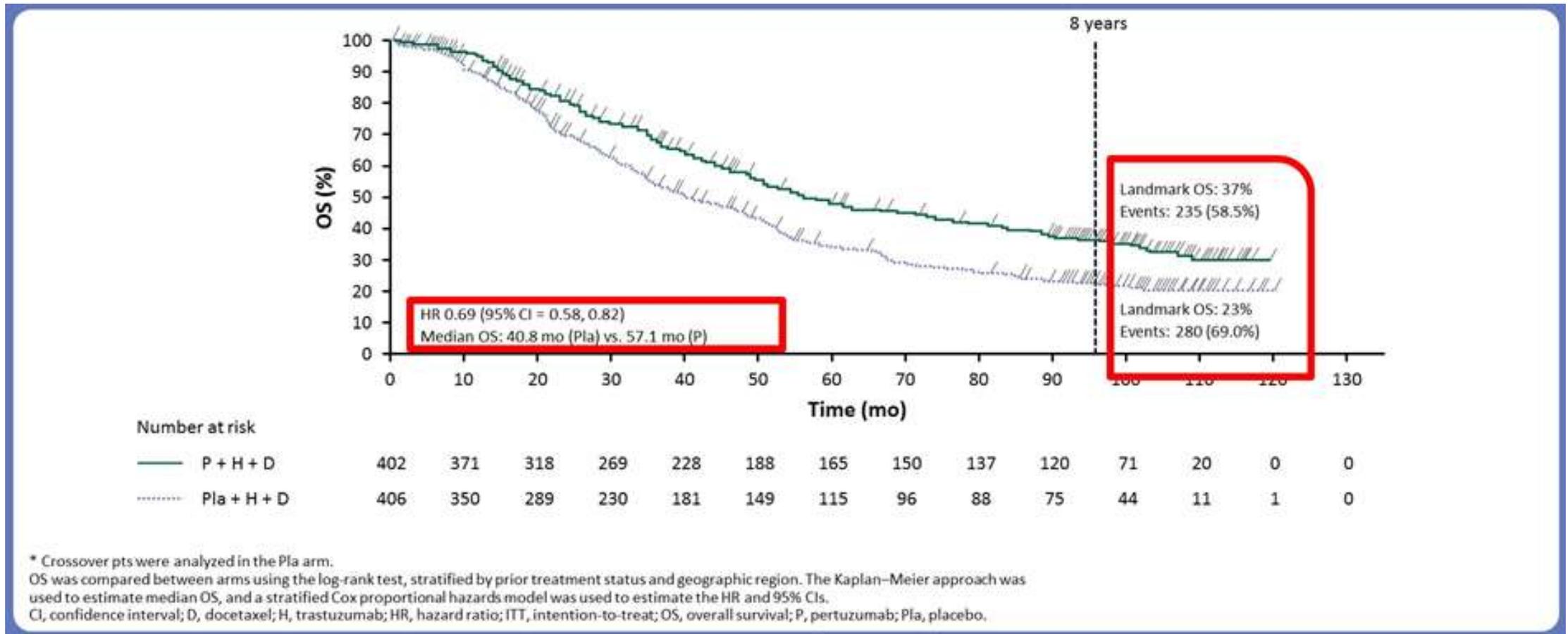
Filippo Montemurro

Direzione Day Hospital Oncologico Multidisciplinare
Istituto di Candiolo, FPO-IRCCS

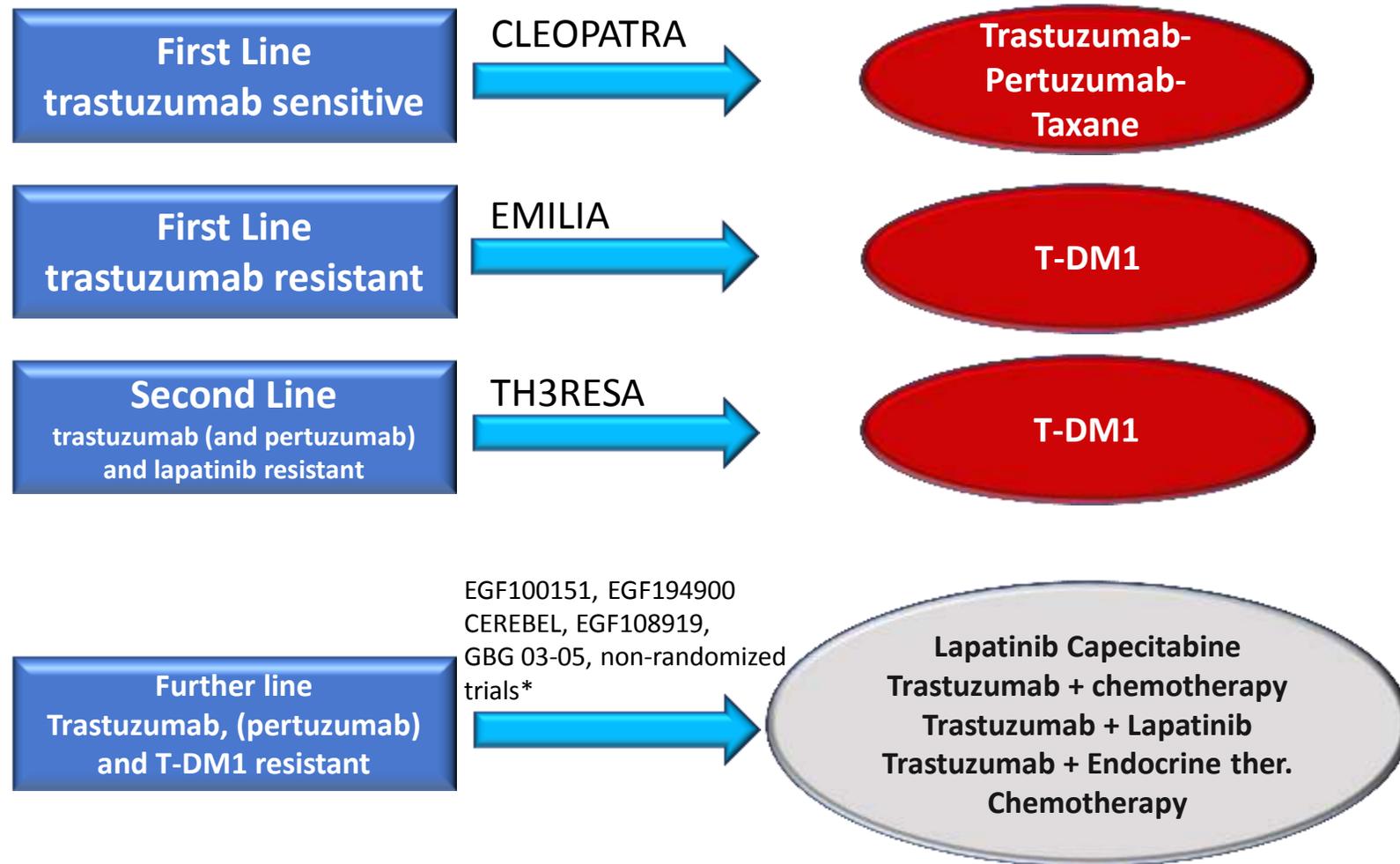
Disclosures

Relationship	Company/Organization
Advisory Role, Speaker's Bureau, Travel Grants	Roche
Speaker's Bureau, Compensation for editorial initiatives	Novartis
Speaker's Bureau	Pfizer
Advisory role	Lilly
Speaker's Bureau, Compensation for editorial initiatives	Astra Zeneca

8-year follow-up of the CLEOPATRA trial (OS)



Current treatment options for HER2-positive MBC



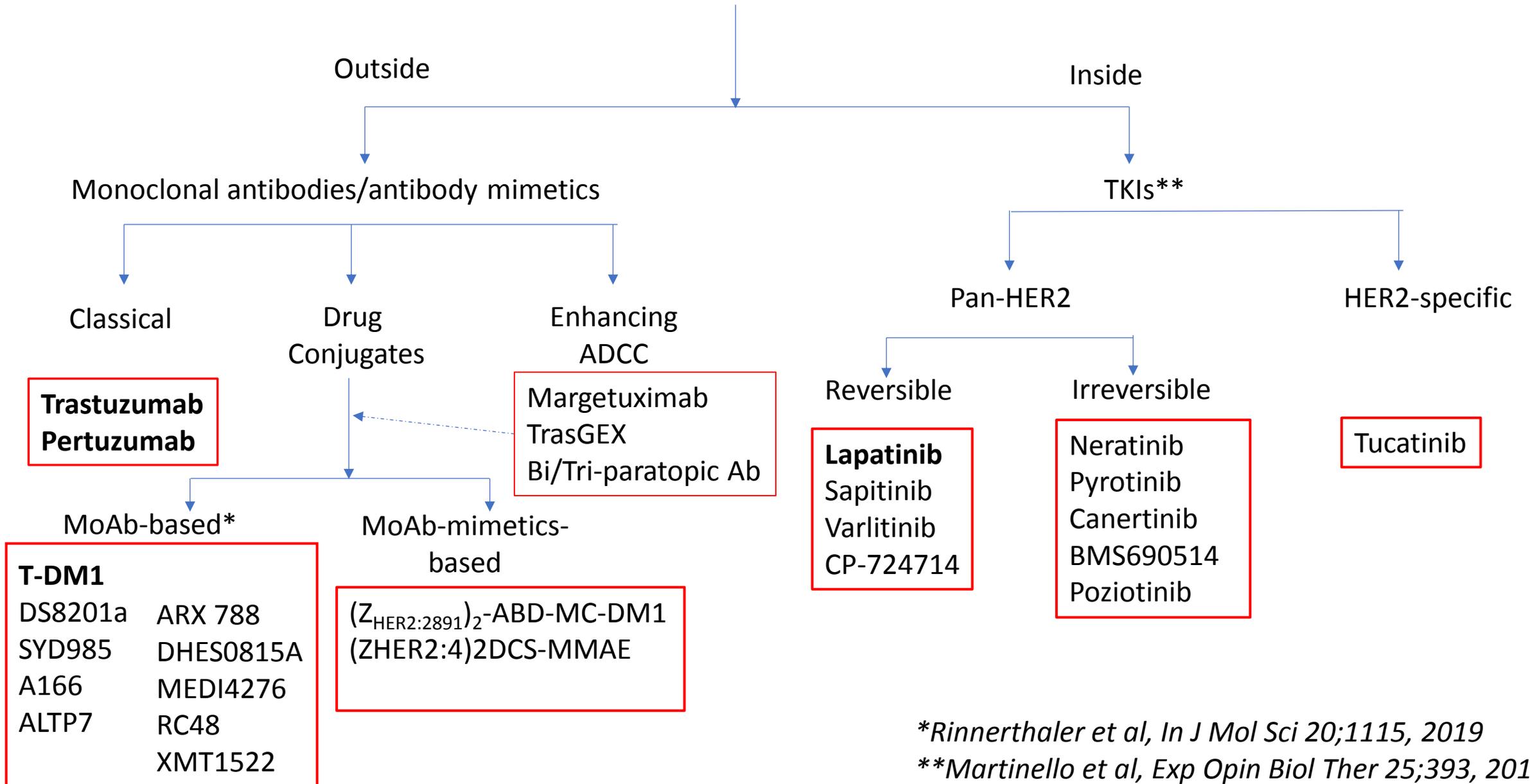
*Pertuzumab can not be used in Italy beyond first line

Based on *Giordano et al, J Clin Oncol 32; 2078, 2014*
Ramakrishna et al, J Clin Oncol 36;2804, 2018

Problems fueling further research in the field of HER2 targeting

- CNS involvement
- Primary resistance (i.e. PIK3CA mutations, p95 overexpression)
- Acquired resistance
- What to do beyond pertuzumab and T-DM1 progression
- Optimal management of HER2+/HR+ tumors
- De-escalation
- HER2-low tumors

Overview of HER2-targeting drugs

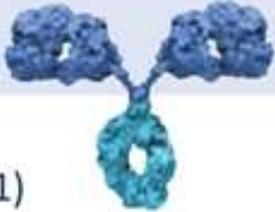


Margetuximab: FC-engineered to activate immune responses

Trastuzumab

Fab:

- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:

- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab^{1,2}

Fab:

- Same specificity and affinity
- Similarly disrupts signaling



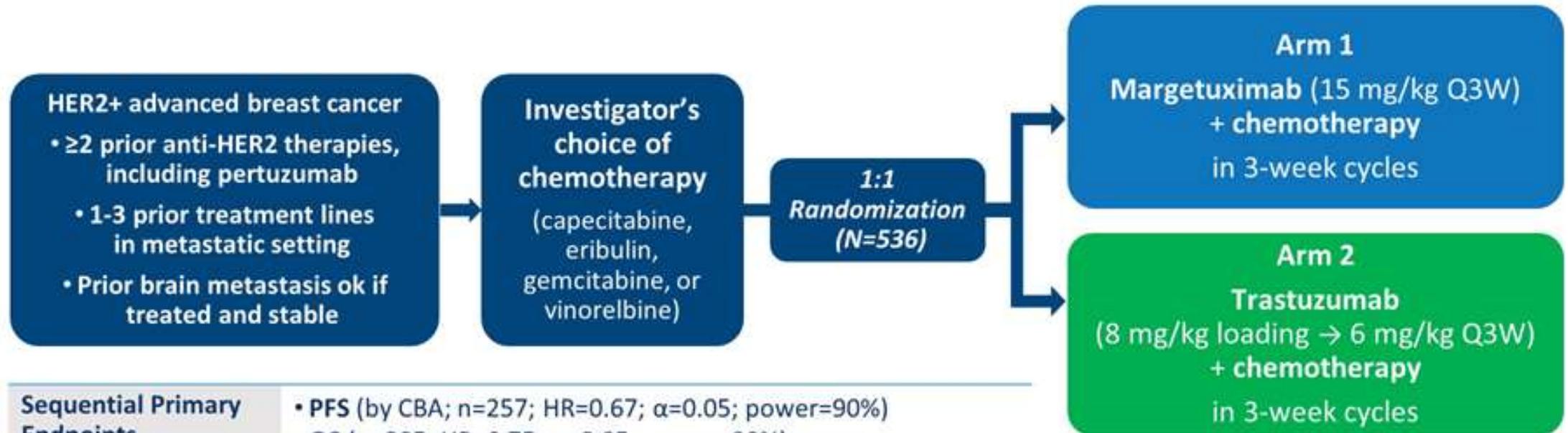
Fc engineering:

- ↑ Affinity for activating FcγRIIIA (CD16A)
- ↓ Affinity for inhibitory FcγRIIB (CD32B)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4x ↓

SOPHIA design



Sequential Primary Endpoints	<ul style="list-style-type: none"> • PFS (by CBA; n=257; HR=0.67; $\alpha=0.05$; power=90%) • OS (n=385; HR=0.75; $\alpha=0.05$; power=80%)
Secondary Endpoints	<ul style="list-style-type: none"> • PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	<ul style="list-style-type: none"> • Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

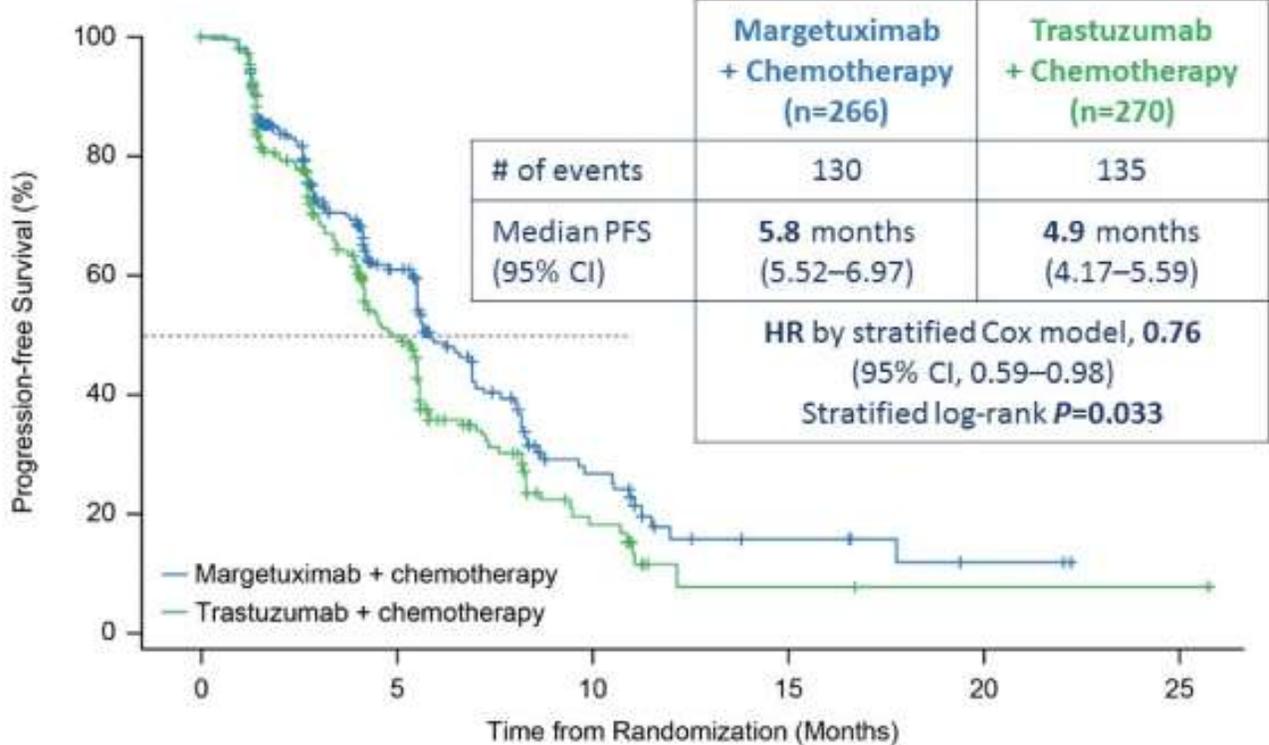
- Stratification:**
- Chemotherapy choice
 - Prior therapies (≤ 2 vs > 2)
 - Metastatic sites (≤ 2 vs > 2)

SOPHIA patient characteristics

	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Settings of prior therapy		
Adjuvant and/or neoadjuvant	158 (59%)	145 (54%)
Metastatic only	108 (41%)	125 (46%)
Prior metastatic lines of therapy		
≤2	175 (66%)	180 (67%)
>2	91 (34%)	90 (33%)
Prior anti-HER2 therapy		
Trastuzumab	266 (100%)	270 (100%)
Pertuzumab	266 (100%)	269 (100%)
T-DM1	242 (91%)	247 (92%)
Lapatinib	41 (15%)	39 (14%)
Other HER2	6 (2%)	6 (2%)
Prior chemotherapy		
Taxane	252 (95%)	249 (92%)
Anthracycline	118 (44%)	110 (41%)
Platinum	34 (13%)	40 (15%)
Prior endocrine therapy		
	126 (47%)	133 (49%)
Treatment arms overall balanced		

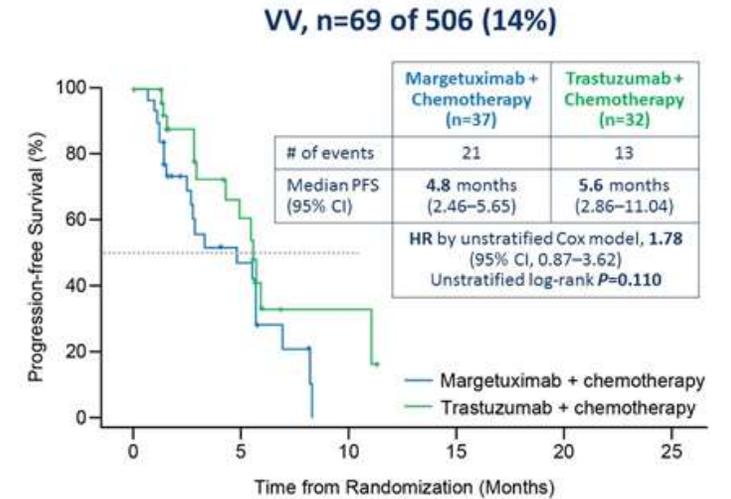
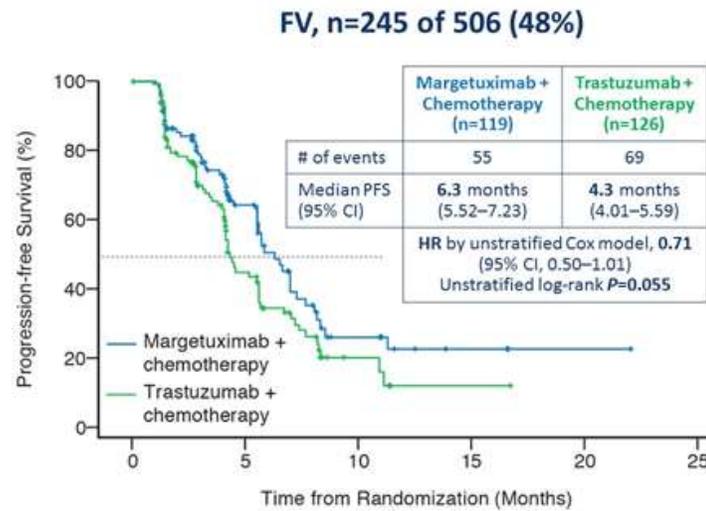
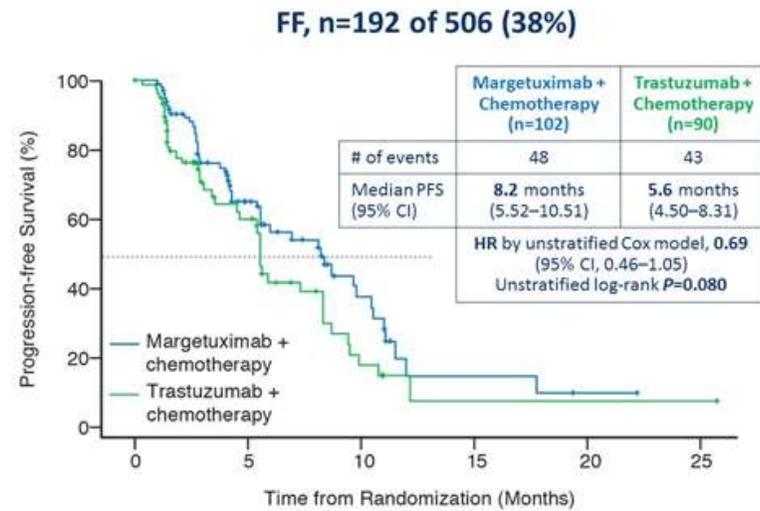
SOPHIA primary end-point: PFS

24% Risk Reduction of Disease Progression Central Blinded Analysis (Primary Endpoint)



Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

SOPHIA planned exploratory analyses based on *FCGRA3* 158 variants

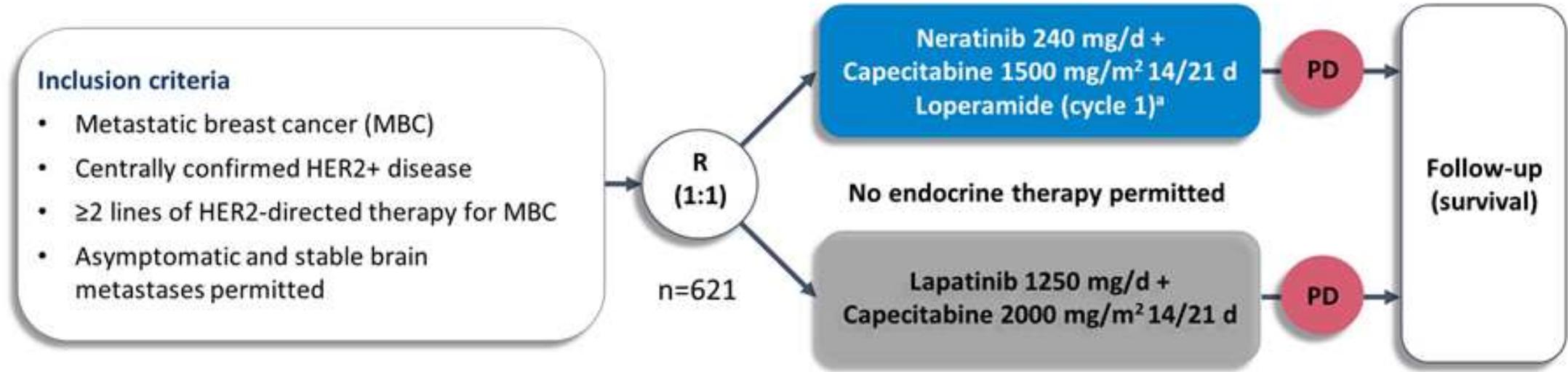


Margetuximab	102	75	41	23	12	3	3	3	1	0
Trastuzumab	90	49	29	14	6	1	1	1	1	1

Margetuximab	119	82	42	19	9	5	3	1	1	0
Trastuzumab	126	80	33	16	5	1	1	0		

Margetuximab	37	16	10	3	0
Trastuzumab	32	18	10	2	2

Neratinib: NALA study



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

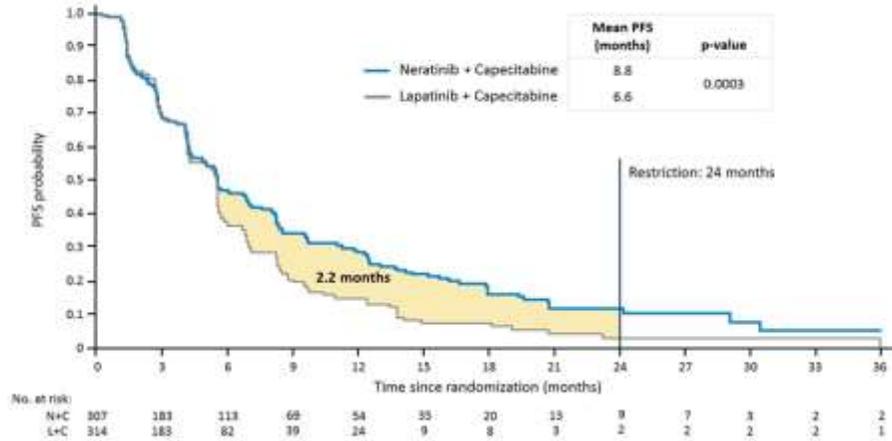
NALA patient characteristics

	Neratinib + Capecitabine (n=307)	Lapatinib + Capecitabine (n=314)
Age <65 years, n (%)	244 (79)	248 (79)
Female, n (%)	307 (100)	311 (99)
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)
Metastatic disease at initial diagnosis, n (%)	139 (45)	136 (43)
Median time from diagnosis to randomization, years [range] ^a	3.4 (0.5–20.0)	3.4 (0.5–25.1)
No. of prior HER2 targeted therapies for MBC, n (%)		
2	215 (70)	215 (68)
≥3	92 (30)	99 (32)
Prior therapies for MBC, n (%)		
Anthracyclines	46 (15)	45 (14)
Taxanes	255 (83)	269 (86)
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)

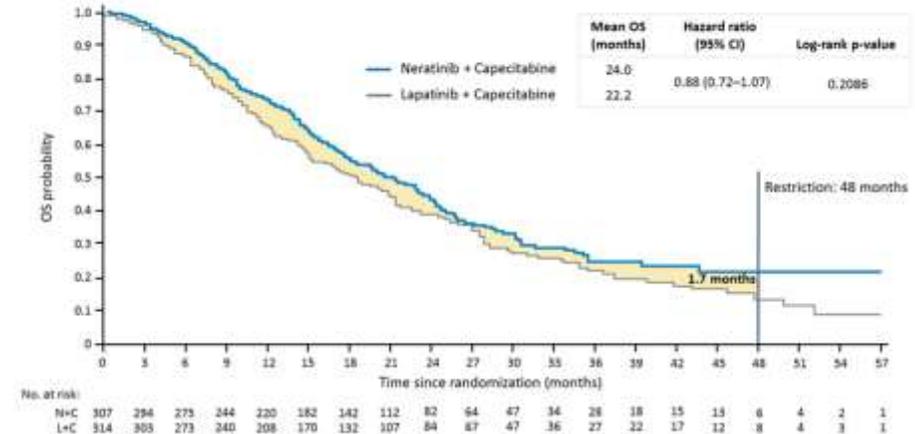
^aMedian time since first presentation with distant metastatic disease: Neratinib + Capecitabine 1.98 years (range 0.3–12.8); Lapatinib + Capecitabine 1.75 years (range 0.1–15.4)

NALA summary of results

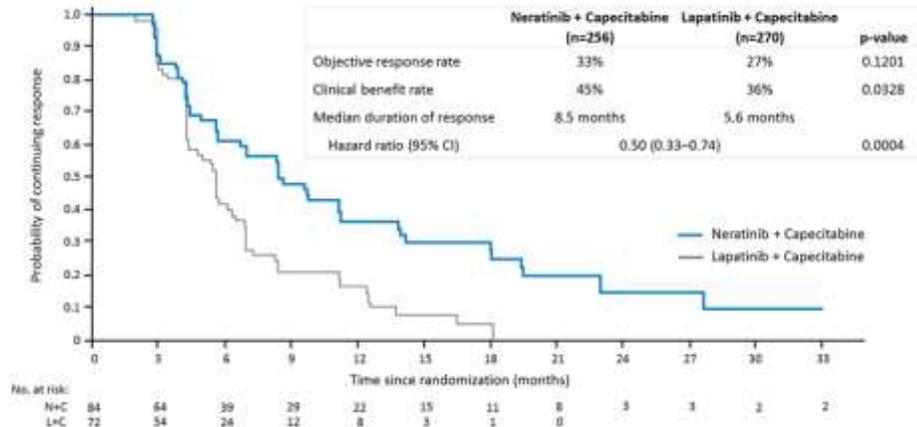
Prespecified restricted means analysis – PFS



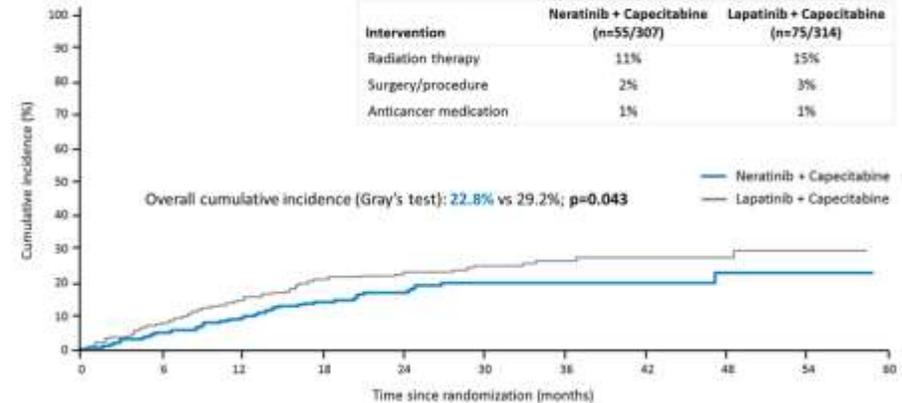
OS (co-primary endpoint)



Response rate and duration of response



Time to intervention for CNS metastases



NALA safety considerations

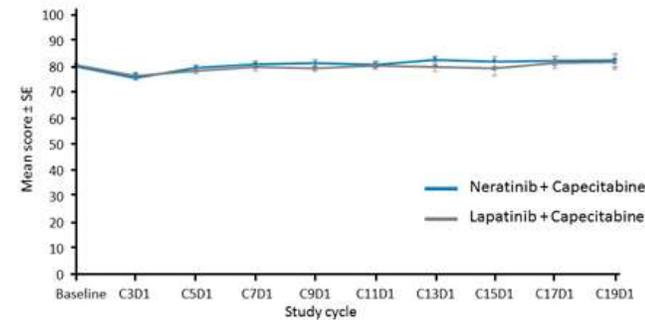
Incidence and duration of diarrhea

	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

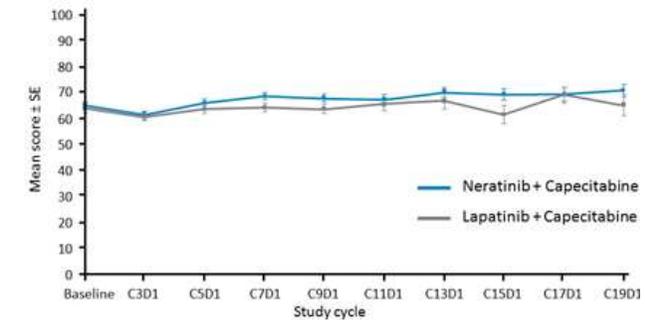
EORTC QLQ-C30 summary score
Mean score over time



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

PHENIX study design

Pyrotinib combined with capecitabine in women with HER2+ metastatic breast cancer previously treated with trastuzumab and taxanes: a randomized phase 3 study

- Double-blinded, multicenter, randomized phase 3 trial (NCT02973737)
- Primary objective: the efficacy of pyrotinib plus capecitabine after trastuzumab

Key eligibility criteria:

- Pathologically confirmed HER2-positive* metastatic breast cancer
- Disease progression during or after treatment with trastuzumab[#], and were not amenable or available for trastuzumab or lapatinib treatment
- Prior taxane-containing regimen
- No. of lines of prior chemotherapy in the metastatic setting ≤ 2
- At least one measurable lesion
- ECOG performance status of 0 or 1

Randomization 2:1

Pyrotinib (400 mg, orally, qd) +
Capecitabine (1000 mg/m², orally, bid
on days 1–14 of each 21-day cycle)

Stratification:

- Metastatic sites at screening (visceral versus non-visceral)
- Hormone receptor status (ER- and/or PR-positive versus ER- and PR-negative)

Placebo (400 mg, orally, qd) +
Capecitabine (1000 mg/m², orally, bid
on days 1–14 of each 21-day cycle)

At
progression

Investigator's choice of
pyrotinib
(400 mg, orally, qd)

Treatment until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision.

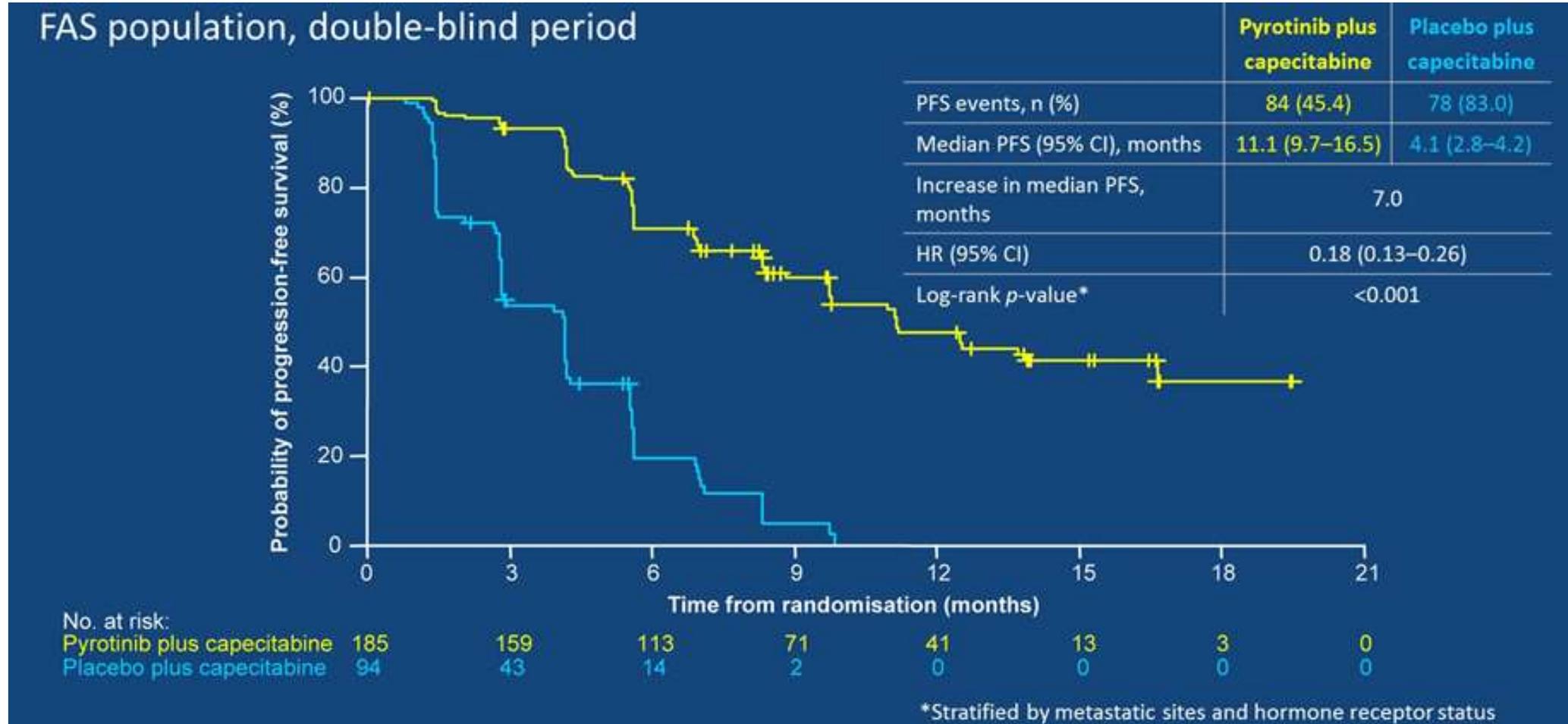
□ Primary endpoint: IRC-assessed PFS

□ Secondary endpoints: ORR, DoR, DCR, CBR, OS, and safety profile

*HER2-positive: immunohistochemistry 3+ and/or fluorescence in situ hybridization positive; [#]Progression with trastuzumab: ≥ 2 cycles in the metastatic setting, or ≥ 3 months in adjuvant setting)

Abbreviations: IRC, independent review committee; DoR, duration of response; DCR, disease control rate; CBR, clinical benefit rate; OS, overall survival.

Pyrotinib: PHENIX primary endpoint: PFS

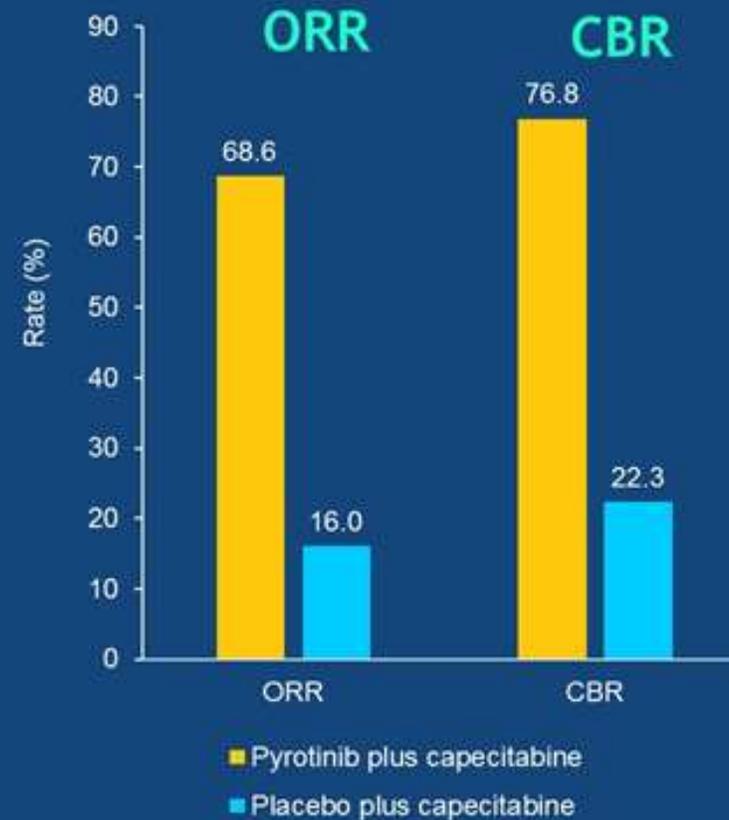


PHENIX ORR and CBR

FAS population, double-blind period

	IRC assessment		<i>p</i>
	Pyrotinib plus capecitabine (n=185)	Placebo plus capecitabine (n=94)	
Best of response, n (%)			
Complete response	12 (6.5)	0	
Partial response	115 (62.2)	15 (16.0)	
Stable disease	43 (23.2)	46 (48.9)	
Progressive disease	9 (4.9)	29 (30.9)	
Not evaluable	6 (3.2)	4 (4.3)	
ORR, n (%; 95% CI)	127 (68.6; 61.4–75.3)	15 (16.0; 9.2–25.0)	<0.001
DCR, n (%; 95% CI)	170 (91.9; 87.0–95.4)	61 (64.9; 54.4–74.5)	<0.001
CBR, n (%; 95% CI)	142 (76.8; 70.0–82.6)	21 (22.3; 14.4–32.1)	<0.001
Median DoR (95% CI), months	12.2 (9.5–NR)	4.2 (4.1–8.2)	<0.001*
Ongoing responses, n (%)	77 (60.6)	4 (26.7)	

* Calculated with the log-rank test; stratified by metastatic sites and hormone receptor status.



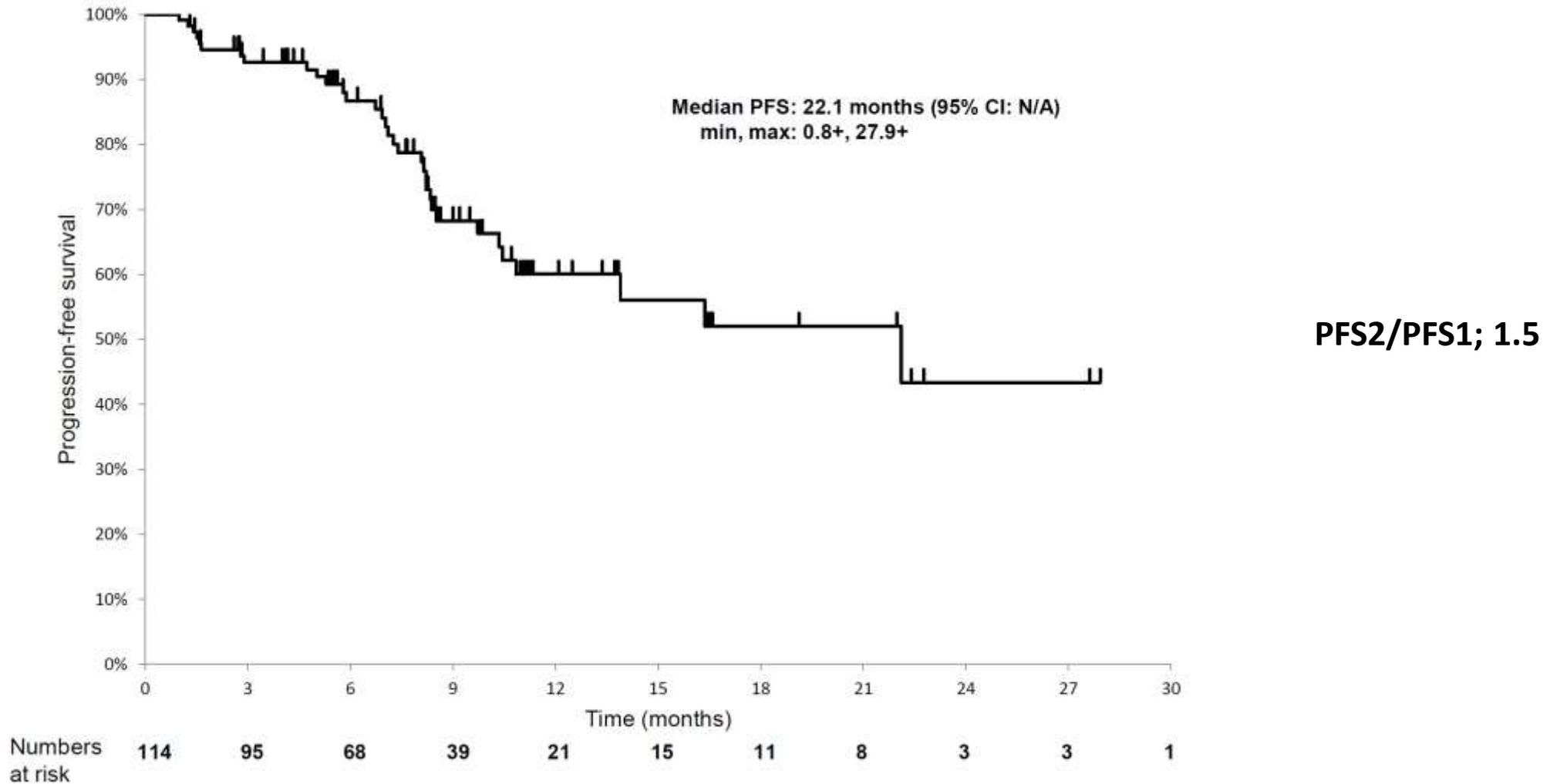
CNS Results

	Pyrotinib plus capecitabine (n=185)	Placebo plus capecitabine (n=94)
Proportion of progressive brain metastases, % (n/N)		
Patients without brain metastases at baseline	1.2 (2/164)	3.6 (3/84)
Patients with brain metastases at baseline	71.4 (15/21)	90.0 (9/10)
Received local therapy	66.7 (4/6)	100.0 (2/2)
Did not receive local therapy	73.3 (11/15)	87.5 (7/8)
Median time to progressive brain metastases (range), days		
Patients without brain metastases at baseline	397.5 (378–417)	132.0 (127–184)
Patients with brain metastases at baseline	176.0 (85–337)	131.0 (27–297)
Received local therapy	179.5 (94–212)	279.0 (261–297)
Did not receive local therapy	168.0 (85–337)	127.0 (27–215)

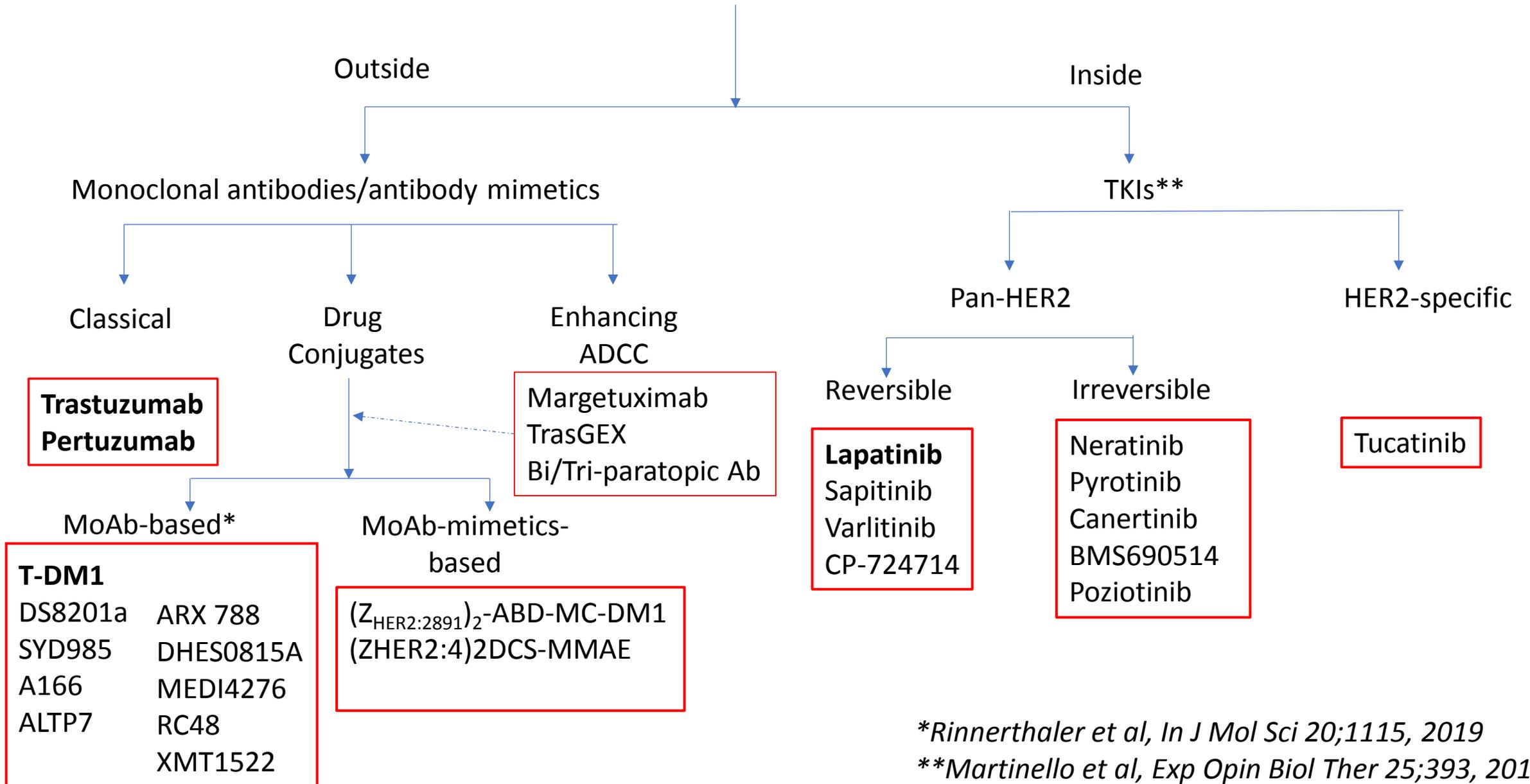
Two (among others) randomized trials are still to come

Strategia	Farmaco	Studio	Setting	Bracci
Irreversible PAN-HER TKI	Neratinib	PUMA-NALA	≥2 HER-2 directed metastatic lines	Lapatinib Capecitabine
				Neratinb Capecitabine
Selective HER2 TKI	Tucatinib	HER2-CLIMB	After T, P and TDM-1, with or without CNS metastases	Trastuzumab Capecitabine
				Trastuzumab Capecitabine Tucatinib
Fc optimized MoAb	Margetuximab	SOPHIA	1-3 prior HER2-directed lines fo MBC	Trastuzumab Chemo
				Margetuximab Chemo
Newer-ADO	DS 8201a	DESTINY-BREAST 3	Eligible for T-DM1	T-DM1
				DS 82001a

Trastuzumab Deruxtecan: PFS in heavily pre-treated patients



Overview of HER2-targeting drugs



What to expect

