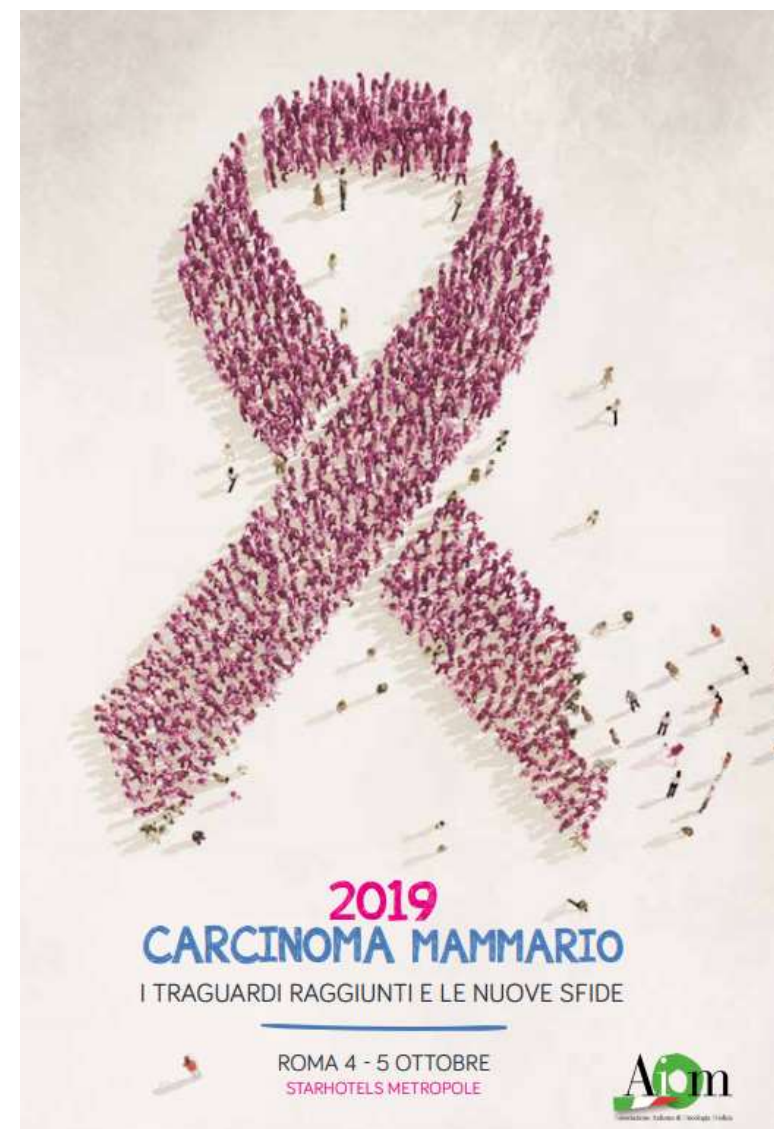


“DE-ESCALATION” NELLA TERAPIA SISTEMICA DEL CARCINOMA MAMMARIO: QUALI EVIDENZE?

Terapia del carcinoma mammario metastatico HER2-positivo

Carmen Criscitiello



Cleopatra trial: Study design

Abstract 1020

End-of-study analysis from the phase III, randomized, double-blind, placebo (Pla)-controlled CLEOPATRA study of first-line (1L) pertuzumab (P), trastuzumab (H), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC)

Santha M. Swain,¹ David Miles,² Sung-Bae Kim,³ Young-Hyuck Im,⁴ Seock-Ah Im,⁵ Vladimir Semiglazov,⁶ Eva Ciruelos,⁷ Andreas Schneeweiss,⁸ Estefania Montura,⁹ Emma Clark,¹⁰ Adam Knott,¹¹ Eleonora Rastorff,¹² Mark C. Bemyrnel,¹³ Javier Cortes¹⁴

¹Georgetown University Medical Center, Lombard Comprehensive Cancer Center, Washington, DC, USA; ²Mount Vernon Cancer Centre, Northwood, UK; ³Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; ⁴Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; ⁵Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; ⁶N.I.R. Petrov Research Institute of Oncology, St. Petersburg, Russia; ⁷12 de Octubre University Hospital, Medical Oncology Department, Madrid, Spain; ⁸National Cancer Institute, University Hospital, Heidelberg, Germany; ⁹H. H. Hoffmann-La Roche Ltd, Basel, Switzerland; ¹⁰Roche Products Limited, Welwyn Garden City, UK; ¹¹Genentech, Inc., South San Francisco, CA, USA; ¹²ICM Institute of Oncology, Quirónsalut Group, Madrid and Barcelona, and ¹³Valencia Institute of Oncology (VIO), Valencia, Spain

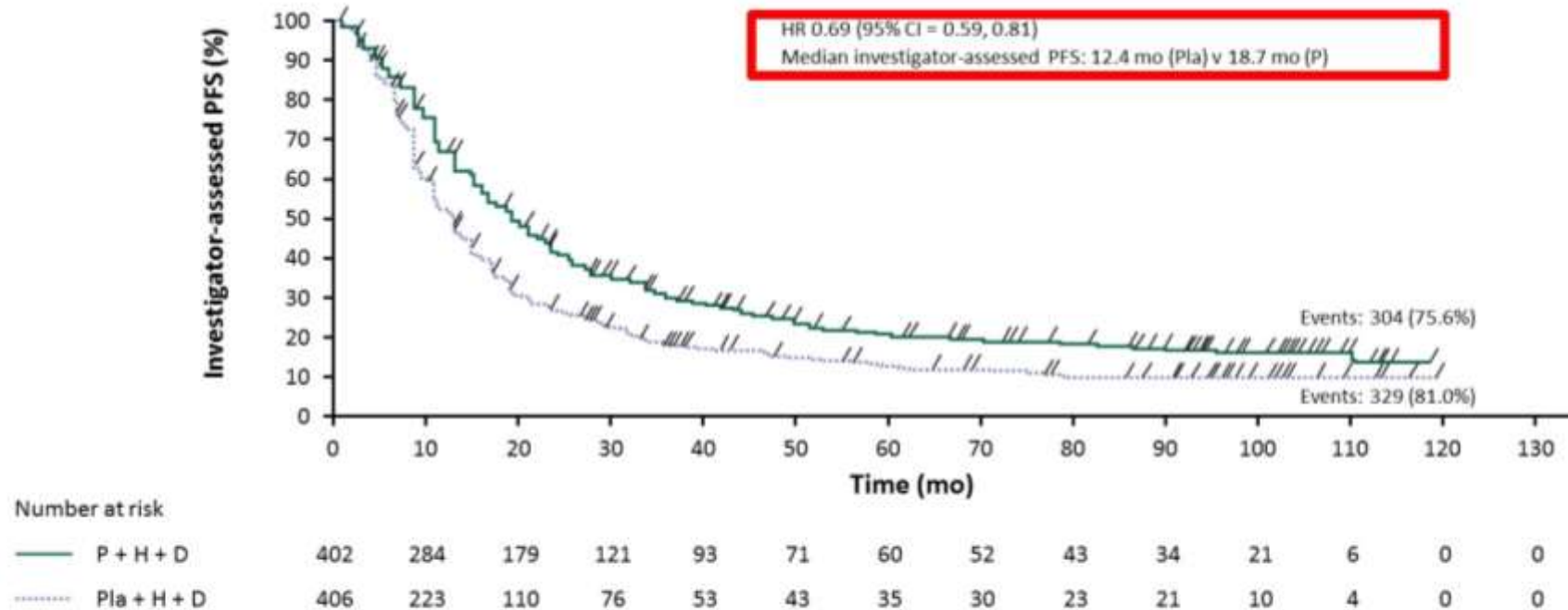
Presented at ASCO Annual Meeting, May 31 - June 4, 2019, Chicago, IL

N= 808
1:1 Randomization
MBC, Her2 +
No prior chemotherapy or
biological therapy for MBC

**Pertuzumab +
Trastuzumab/Docetaxel**

**Placebo +
Trastuzumab/Docetaxel**

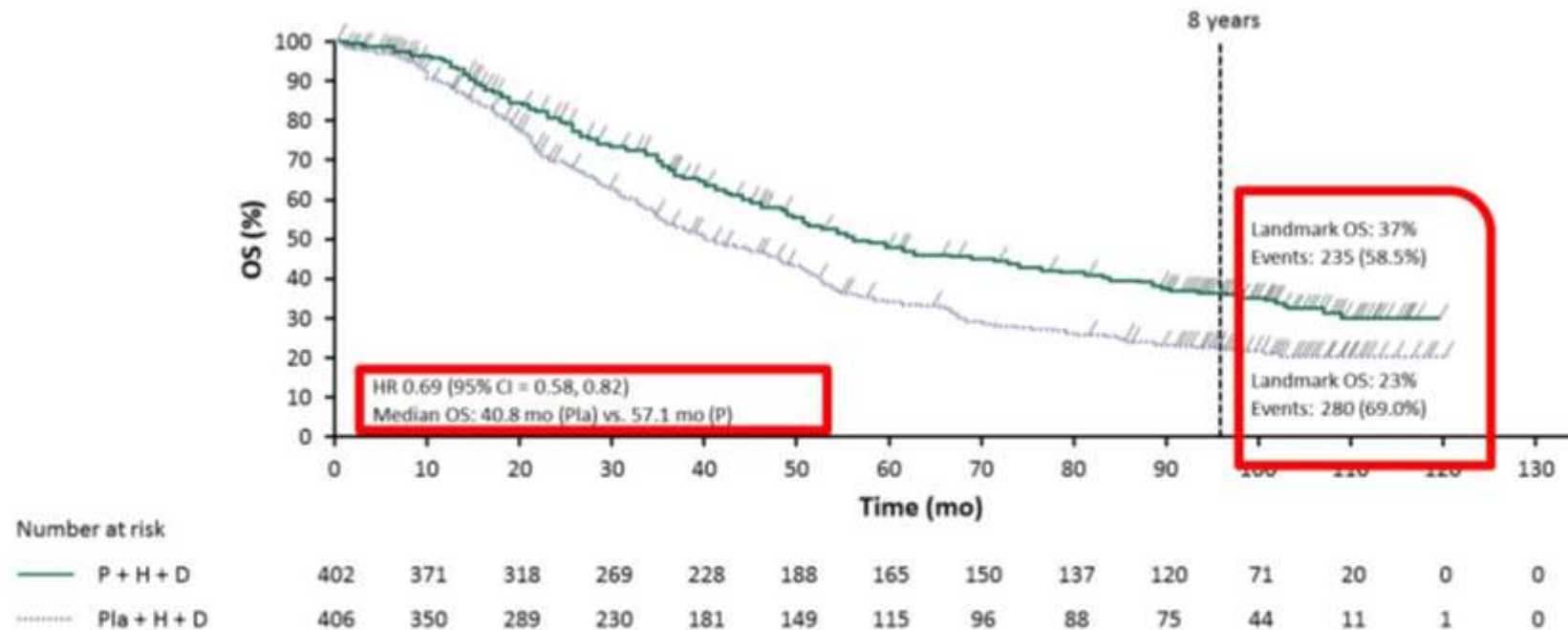
CLEOPATRA: End-of-study investigator-assessed PFS



* Crossover pts were analyzed in the Pla arm.

CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; P, pertuzumab; PFS, progression-free survival; Pla, placebo; pts, patients.

CLEOPATRA: End-of-study OS in the ITT population



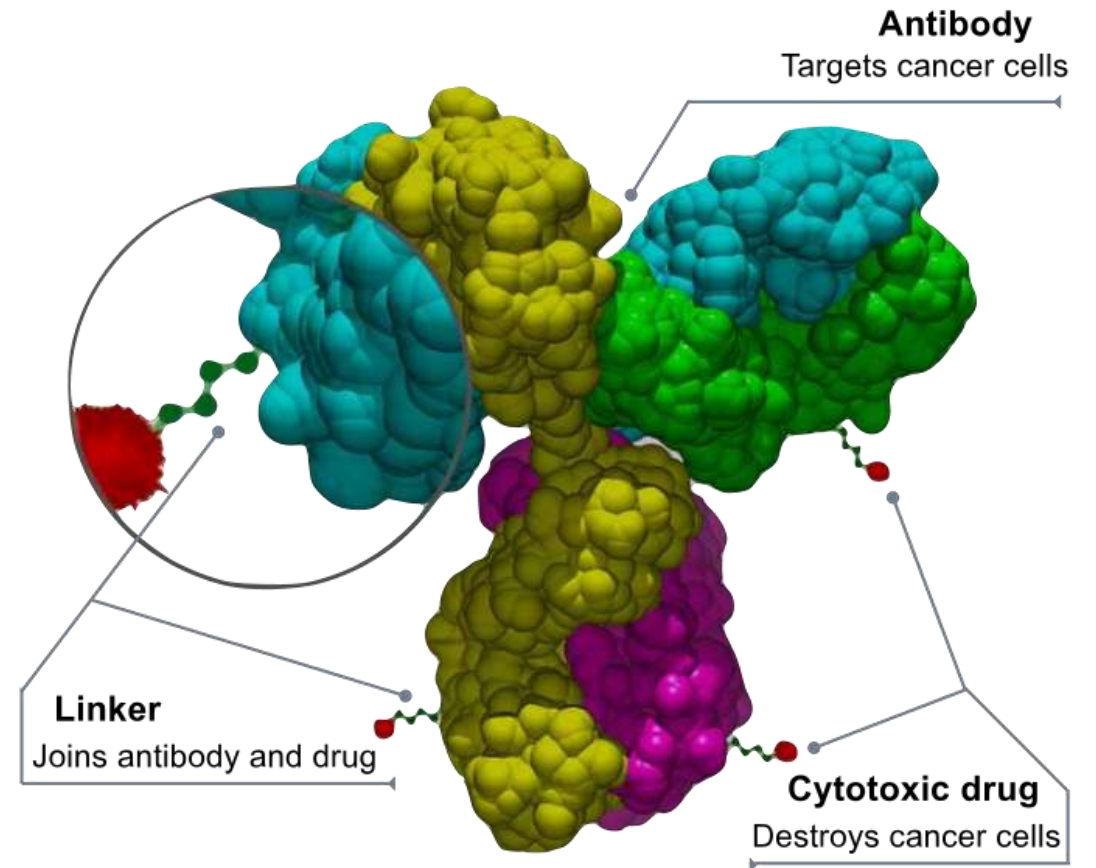
* Crossover pts were analyzed in the Pla arm.

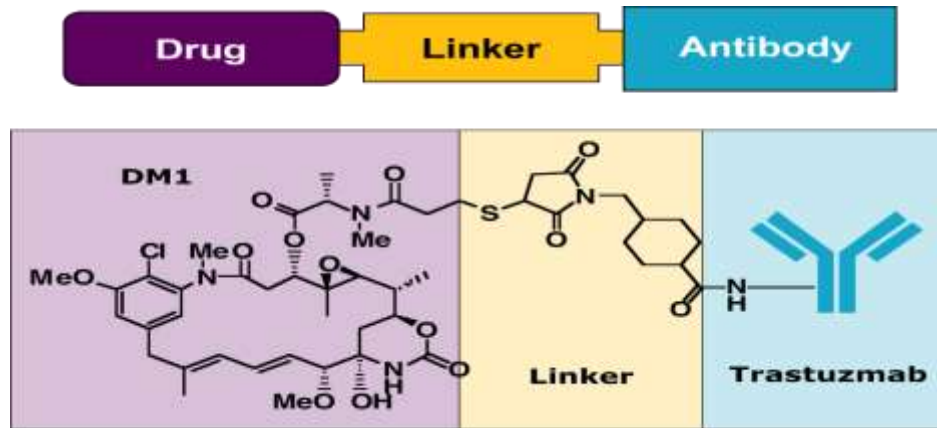
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan-Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.

CI, confidence interval; D, docetaxel; H, trastuzumab; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, pertuzumab; Pla, placebo.

Emerging Role of Antibody-Drug Conjugates (ADCs)

- New class of highly potent anti-cancer drugs
- Offer the hope of sensitive discrimination between cancer cells and healthy cells
- Key characteristics
 - Highly selective mAb for a tumor associated antigen with minimal expression on healthy cells
 - Potent cytotoxic agent with high systemic toxicity (too toxic to give alone)
 - Target cell death with internalization and release into the tumor cell
 - Stable linker in the circulation, but releases the cytotoxic agent in target cells.
- One ADC currently approved for breast cancer
 - Trastuzumab emtansine (T-DM1) for HER2+ disease





Target expression: HER2

Monoclonal antibody: Trastuzumab

Cytotoxic agent: DM1

Highly potent cytotoxic agent

Linker: MCC

Systemically stable

Trastuzumab Emtansine



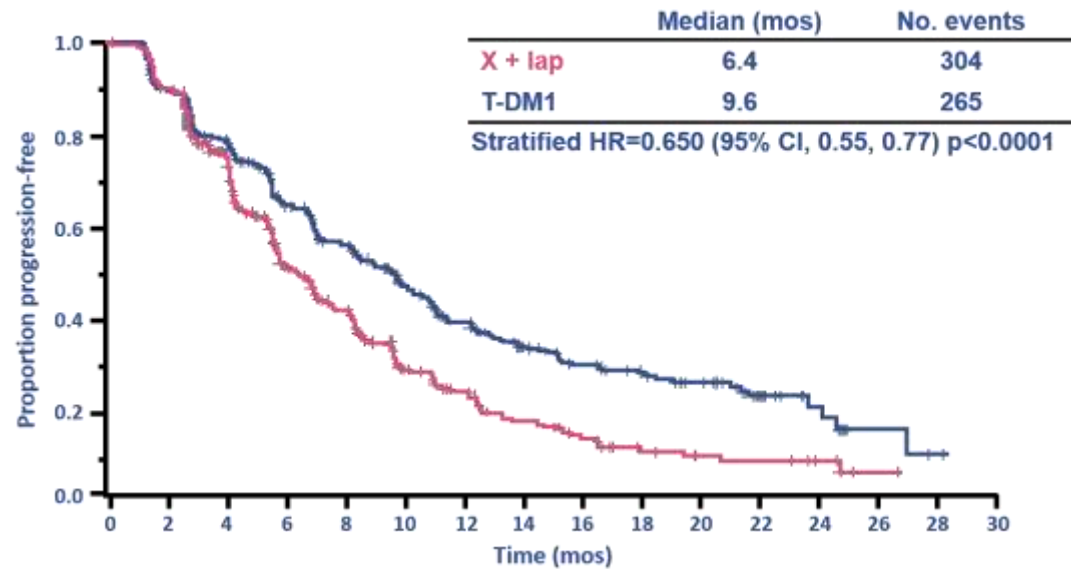
T-DM1

Average drug:
antibody ratio $\cong 3.5:1$

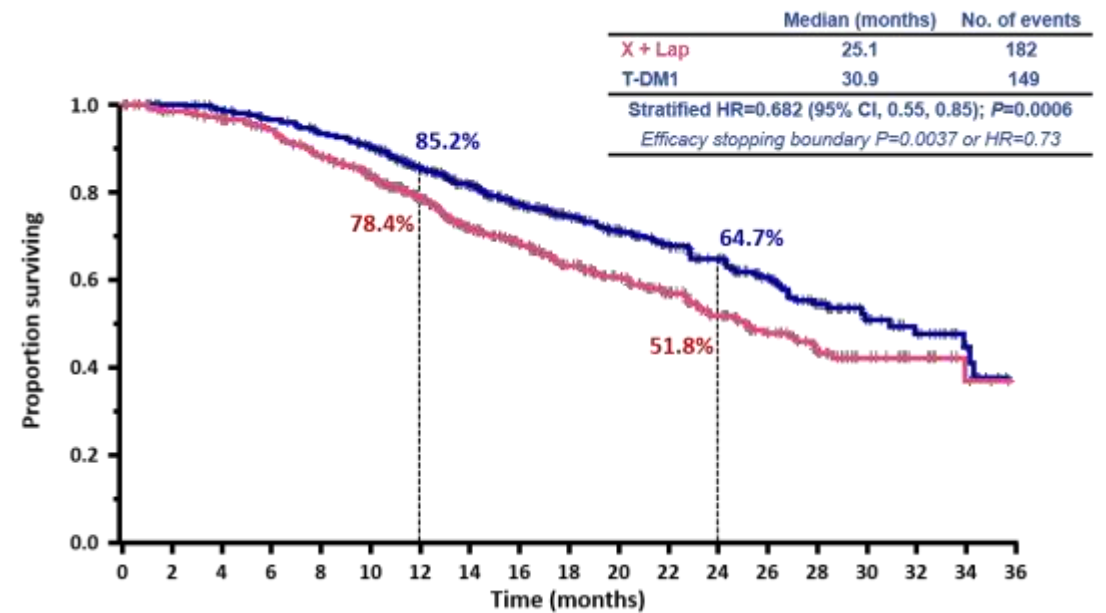
DM1: derivative of maytansine, a potent microtubule inhibitor

EMILIA study

PFS

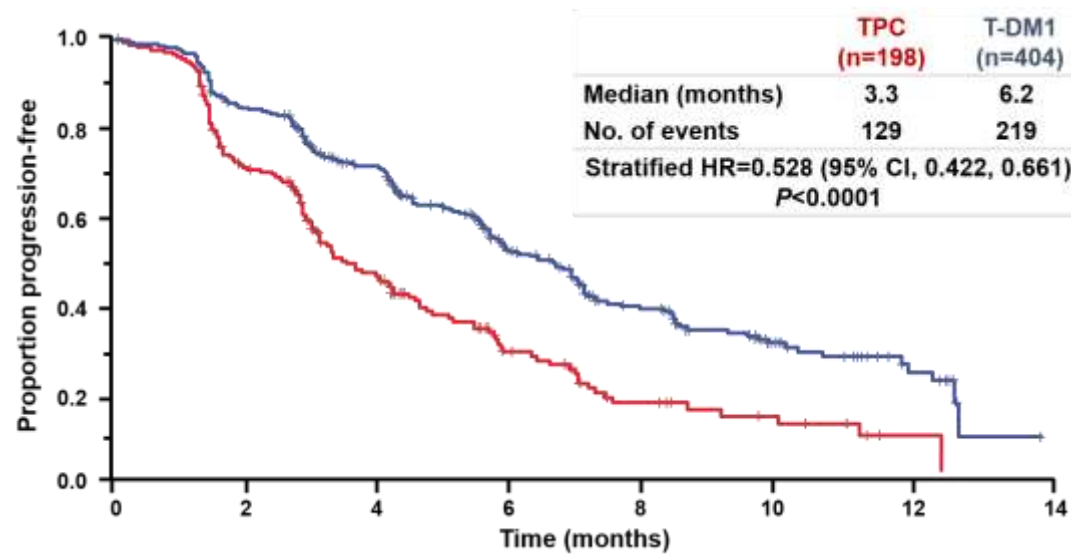


OS

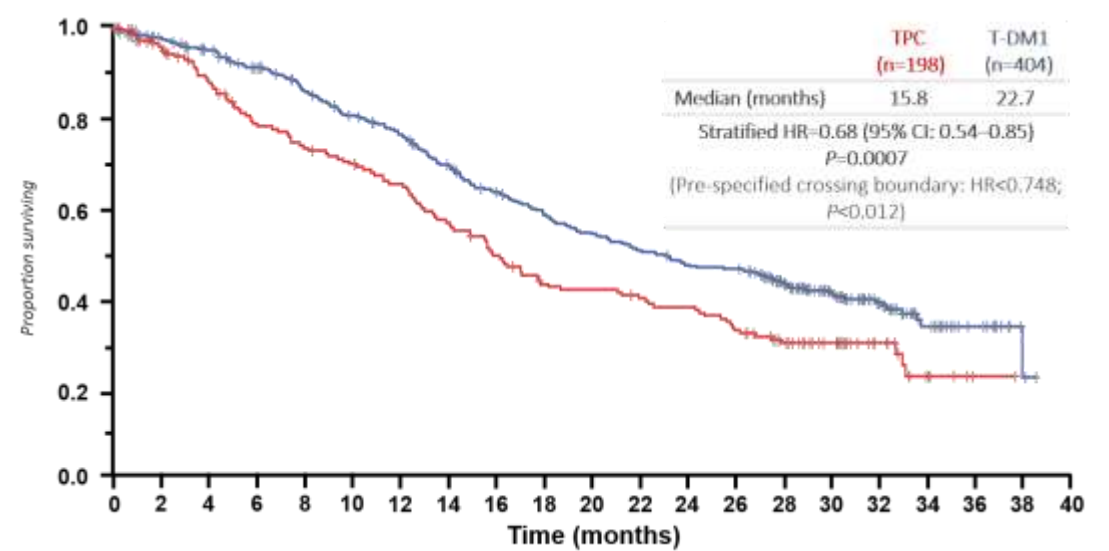


TH3RESA study

PFS



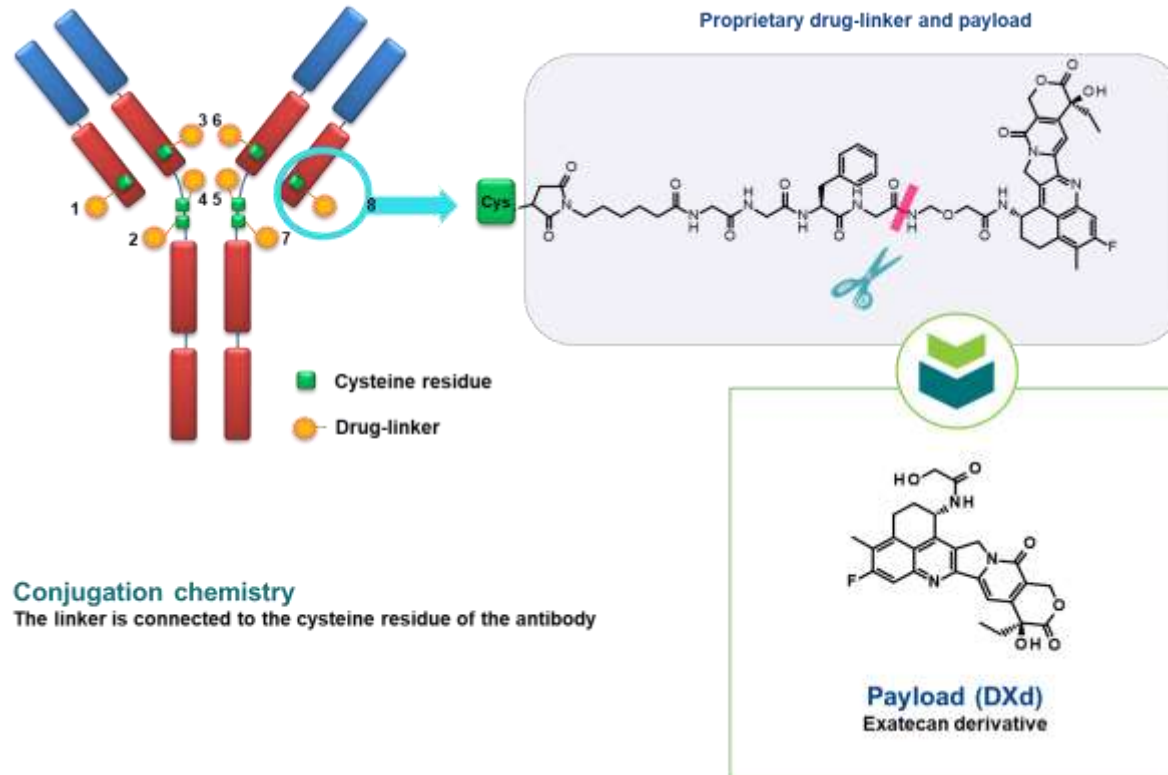
OS



Anti-HER2 ADC in clinical development for BC

Name	Anti-HER2 MAb	Isotype	Linker-drug	Drug class/target	Tumor indications ^a	Latest development stage ^a	Sponsor/Trial ID ^a
Kadcyla® T-DM1	Trastuzumab	Hu IgG1	SMCC-DM1 Non-cleavable	Maytansinoid/tubulin	HER2 + metastatic breast cancer prior trastuzumab & taxane	Approved	Genentech/Roche
MEDI-4276	MAb 39S with Trastuzumab scFv at N terminus	39S Hu IgG1	SC-Lys-AZ13599185 Cleavable	Tubulysin/tubulin	HER2 + advanced breast or gastric/stomach cancers	Phase 1/2	MedImmune/AZ NCT02576548
XMT-1522	XMT-1519	Hu IgG1	Fleximer® polymer ester-auristatin F-HPA Cleavable	Auristatin/tubulin	HER2 + (≥ IHC 1 +) breast, gastric and lung cancers	Phase 1	Mersana NCT02952729
ARX788	Anti-HER2 MAb incorporating non-natural amino acids for site-specific conjugation	Undisclosed IgG1	PEG4-AS-269 Non-cleavable	Auristatin/tubulin	Part 1: HER2 + breast or gastric cancers Part 2a: HER2 high (ISH + /IHC3 +) breast Part 2b: HER2 medium/low (ISH – / IHC2 –) breast	Phase 1/1b	Ambrx/Zhejiang Medicine Co NCT02512237
DS-8201a	Trastuzumab	Hu IgG1	Gly-Gly-Phe-Gly-Dxd Cleavable	Exatecan/ topoisomerase I	Part 1: advanced solid tumors Part 2: breast cancer: 2a: HER2 overexpressed, prior T-DM1 2c: HER2 low	Phase 1	Daiichi Sankyo NCT02564900
SYD985	Trastuzumab	Hu IgG1	Val-Cit-PABC-CM-seco-DUBA Cleavable	Duocarmycin/DNA	Part 1: Advanced solid tumors of any histology Part 2: Breast, gastric, urothelial and endometrial tumors	Phase 1	Synthon NCT02277717
ADCT-502	Trastuzumab	Hu IgG1	Val-Ala-PABC Cleavable	PBD dimer/DNA	HER2 + breast, NSCLC, gastroEsophageal, bladder cancer	Phase 1	ADC Therap. NCT03125200

Trastuzumab Deruxtecan (DS-8201a): Structure and Mechanism of Action



Payload with a different mechanism of action

High potency of payload

Payload with short systemic half-life

Bystander effect

Stable linker-payload

Tumor-selective cleavable linker

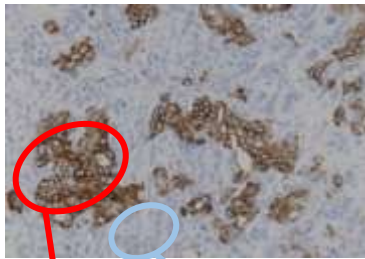
High drug-to-antibody ratio (~1:8)

DS-8201a: Bystander Effect

In Vivo Bystander Effect of DS-8201a vs T-DM1 After 14 days of treatment

Control

Co-culture of HER2+ and HER2- tumors in vivo

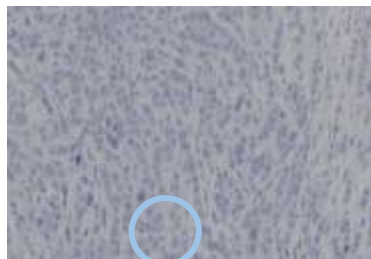


HER2+ cells
NCI-N87

HER2- cells
MDA-MB-468

TDM-1, 10 mg/kg

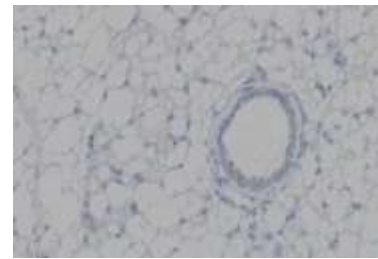
HER2- cells still persist



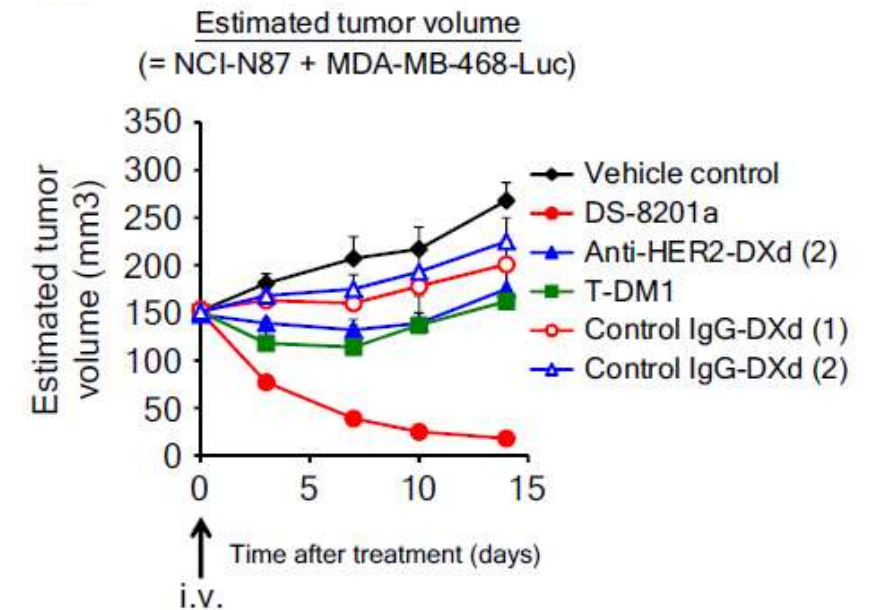
HER2- cells
MDA-MB-468

DS-8201a, 3.0 mg/kg

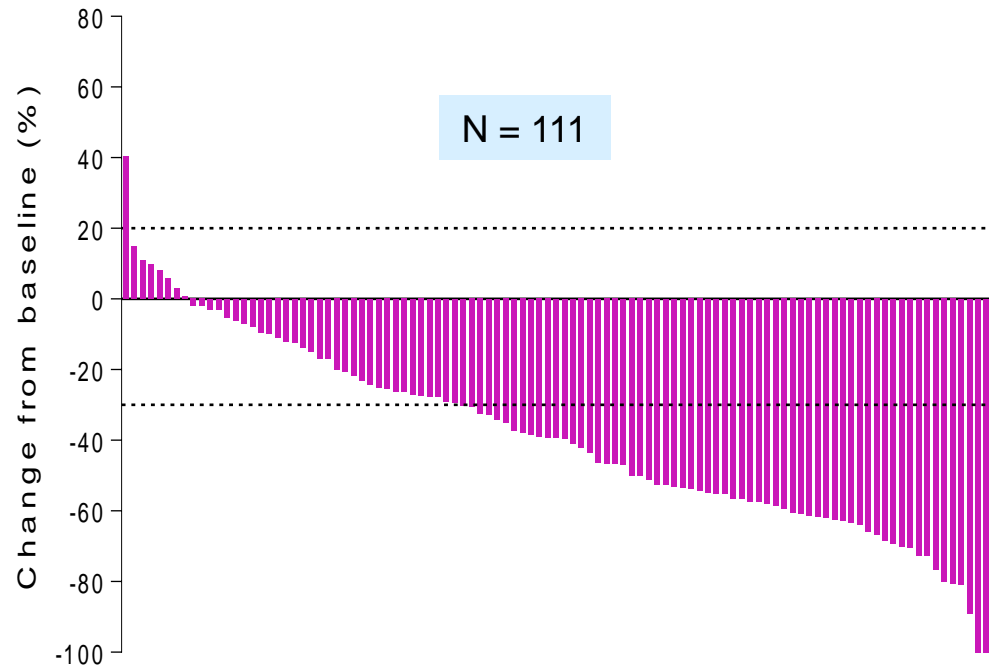
Both HER2+ and HER2- are impacted



Tumor regression



Efficacy of DS-8201a in HER2+ mBC: Phase I study



Previous anticancer regimens†	7.0 (5.0–11.0)
≥5 previous anticancer regimens	94 (82%)
Trastuzumab	114 (99%)
Pertuzumab	99 (86%)
Trastuzumab/emtansine	115 (100%)
Lapatinib	62 (54%)
Other HER2 therapy	6 (5%)

Confirmed ORR, n/N (%)	66/111 (60%)
Confirmed DCR, n/N (%)	104/111 (94%)
median TTR	n=73 1.6 mos
median DOR	n=73 20.7 mos
median PFS	n=114 22.1 mos
median OS	n=114 NR

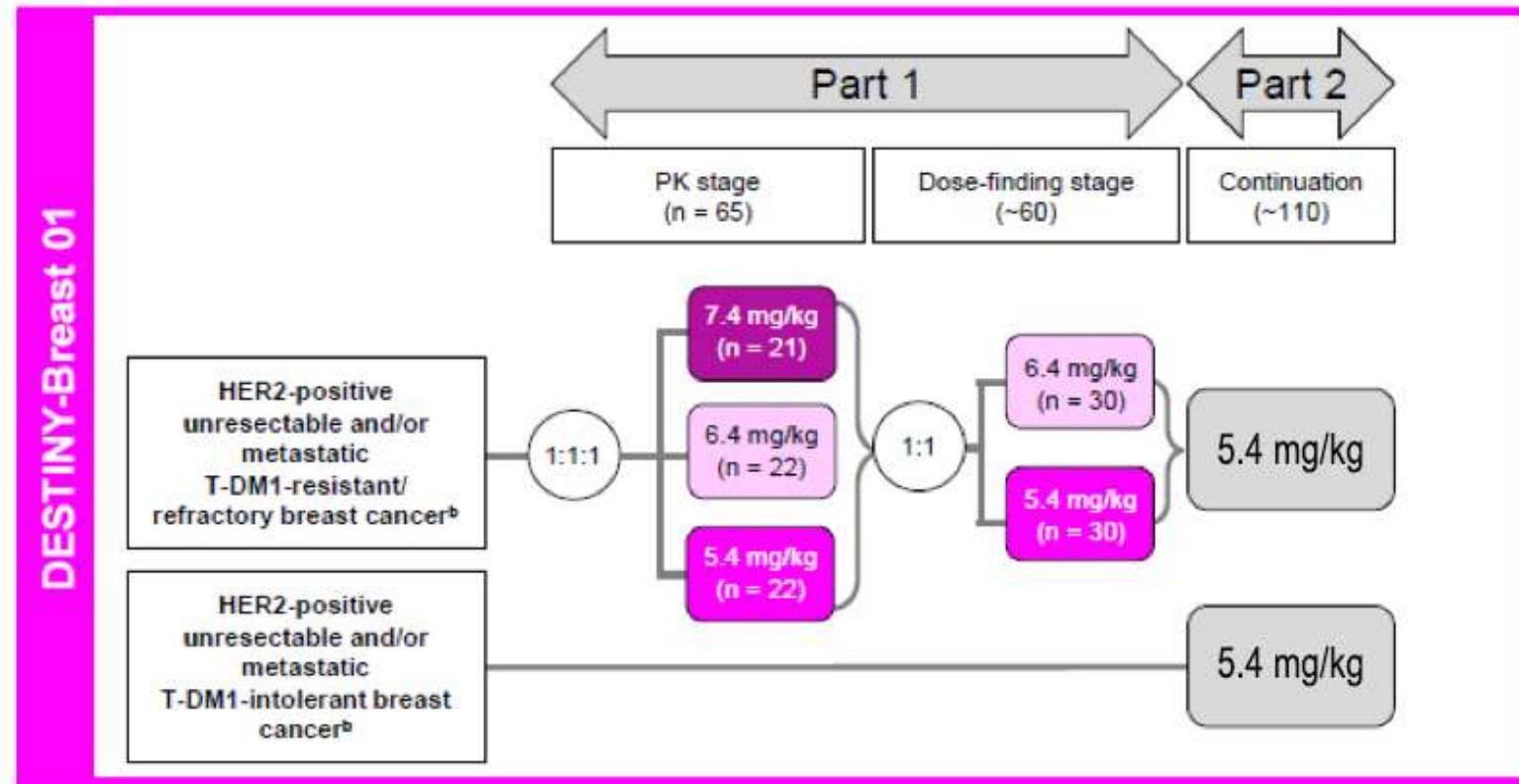
Hormone receptor status	
Positive	81 (70%)
Negative	33 (29%)
Missing	1 (1%)

DS-8201a Safety: Selected AEs

AEs	Overall (5.4 or 6.4 mg/kg), N = 259 ^a	
	All grades, n (%)	Grade ≥3, n (%)
AST increased	53 (20.5)	4 (1.5)
ALT increased	40 (15.4)	2 (0.8)
Blood bilirubin increased	6 (2.3)	1 (0.4)
Ejection fraction decreased	2 (0.8)	0
Electrocardiogram QT prolonged	13 (5.0)	1 (0.4)
ILD	10 (3.9)	2 (0.8)
Pneumonitis	22 (8.5)	6 (2.3)

- The most common TEAEs in breast cancer patients were nausea (79.4%), anorexia (54.1%) and alopecia (46.5%)
 - Generally mild, most grade ≤2
- ILD/pneumonitis including 5 fatal cases observed
 - One not due to drug; 3/4 dosed at 6.4 mg/kg
 - With detailed monitoring and early intervention, no further fatalities attributed to pneumonitis observed

DESTINY-Breast01 study: DS-8201a in HER2+ MBC with prior T-DM1



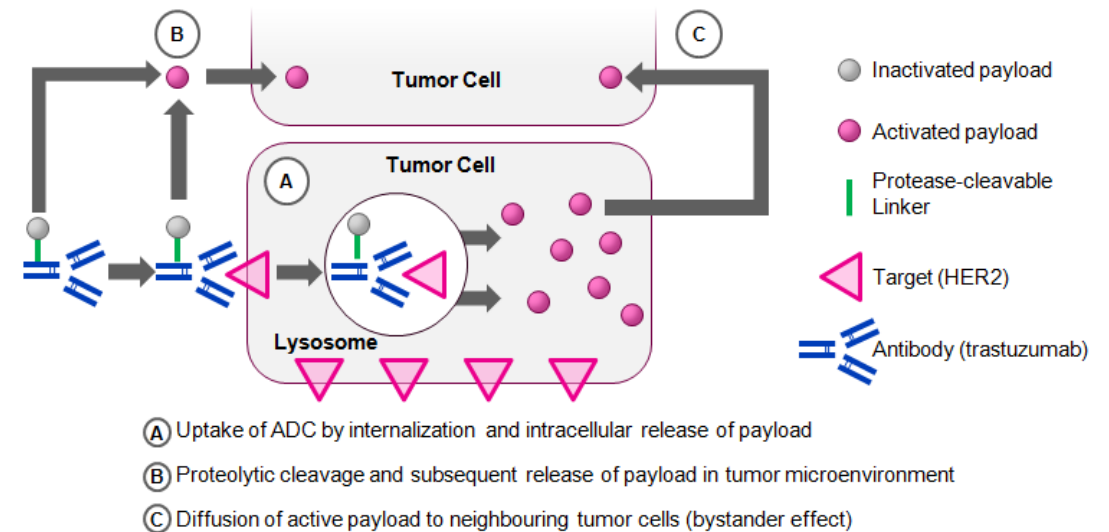
Accrual complete as of September 2018

Ongoing Phase III Trials: DS-8201a in MBC

Study Name	Description/Population	CT.gov Identifier and EUDRA CT Identifier	Recruitment Status
DESTINY-Breast02	DS-8201a vs investigator's choice in HER2-positive unresectable and/or MBC previously treated with standard of care anti-HER2 therapies including T-DM1	NCT03523585 * 2018-000221-31	Recruiting
DESTINY-Breast03	DS-8201a vs. T-DM1 in HER2-positive unresectable and/or MBC	NCT03529110 * 2018-000222-61	Recruiting
DESTINY-Breast04	DS-8201a vs. physician's choice in HER2-low, unresectable and/or MBC	NCT03734029 * 2018-003069-33	Recruiting
Phase I/II: Novel Combination			
U105	MBC (HER2 positive/HER2 low) Bladder cancer (HER2 high/low) DS_8201a plus nivolumab	NCT03523572	Recruiting

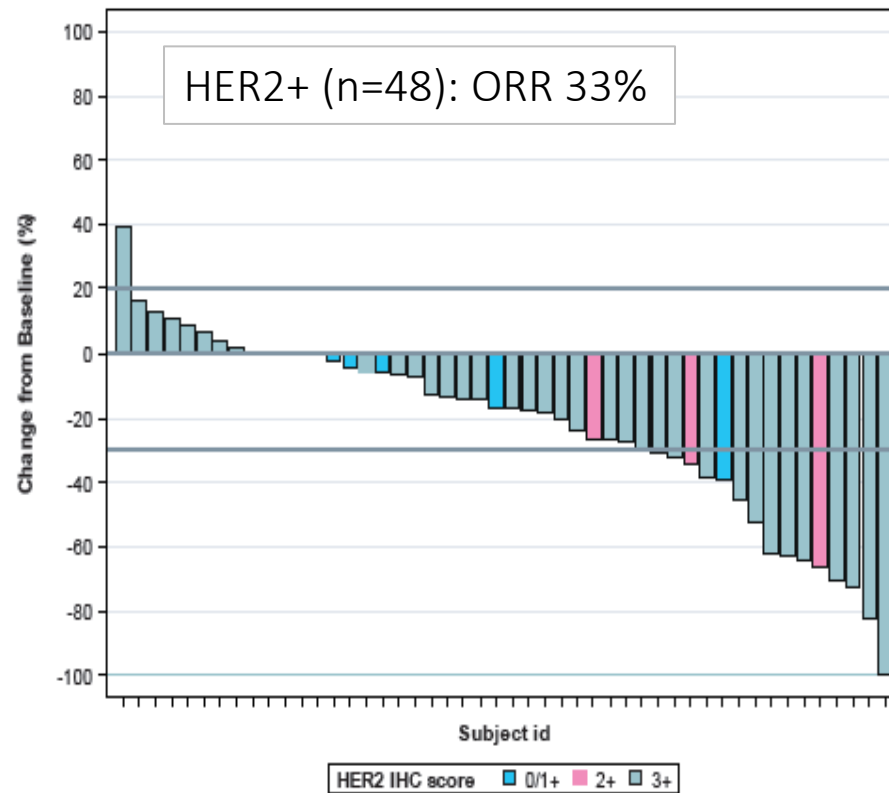
SYD-985: Trastuzumab Duocarmazine

- HER2-targeting ADC based on trastuzumab
- Protease cleavable linker with a DNA alkylating toxin duocarmycin
- Toxin incorporated into the linker as an inactive prodrug
- Proteolytic cleavage: release of the membrane permeable active toxin

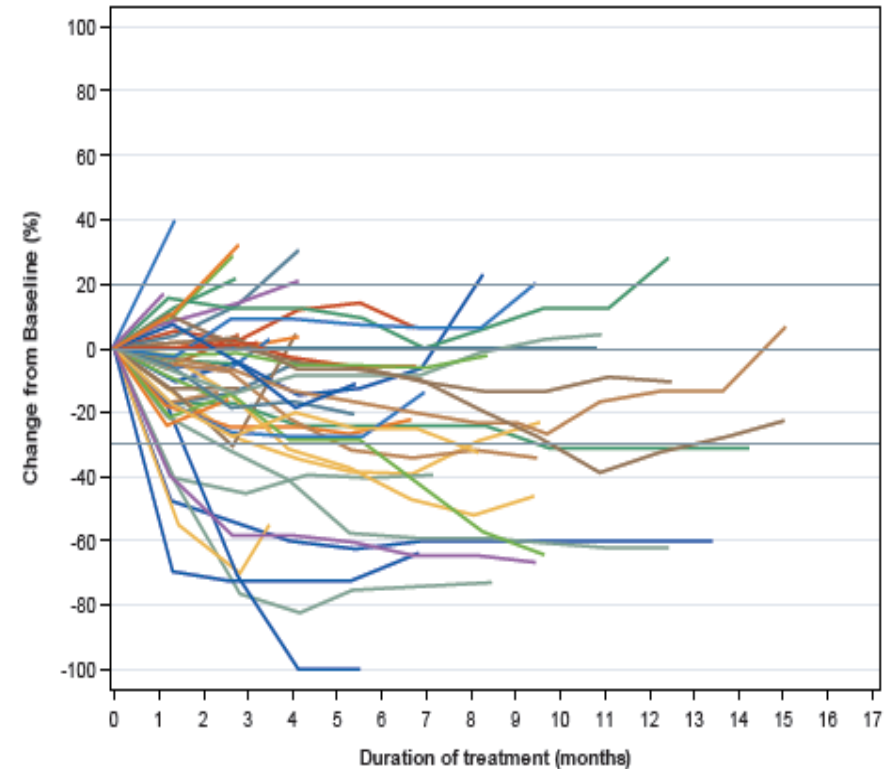


Efficacy of SYD-985 in MBC: Phase I study

Best percentage change from baseline in target lesions



Percentage change from baseline in target lesions over time

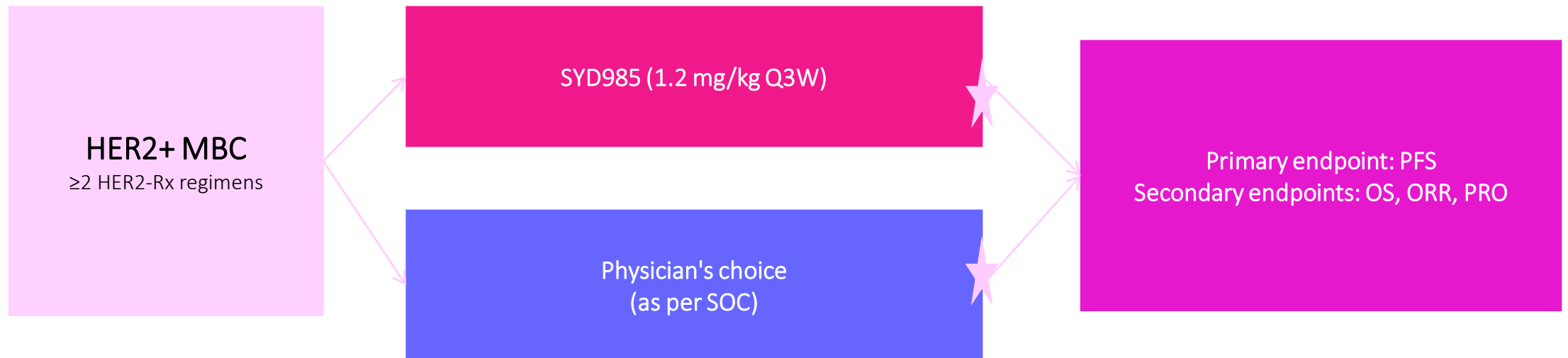


SYD-985: AEs in ≥10% of pts all cohorts (N=146)

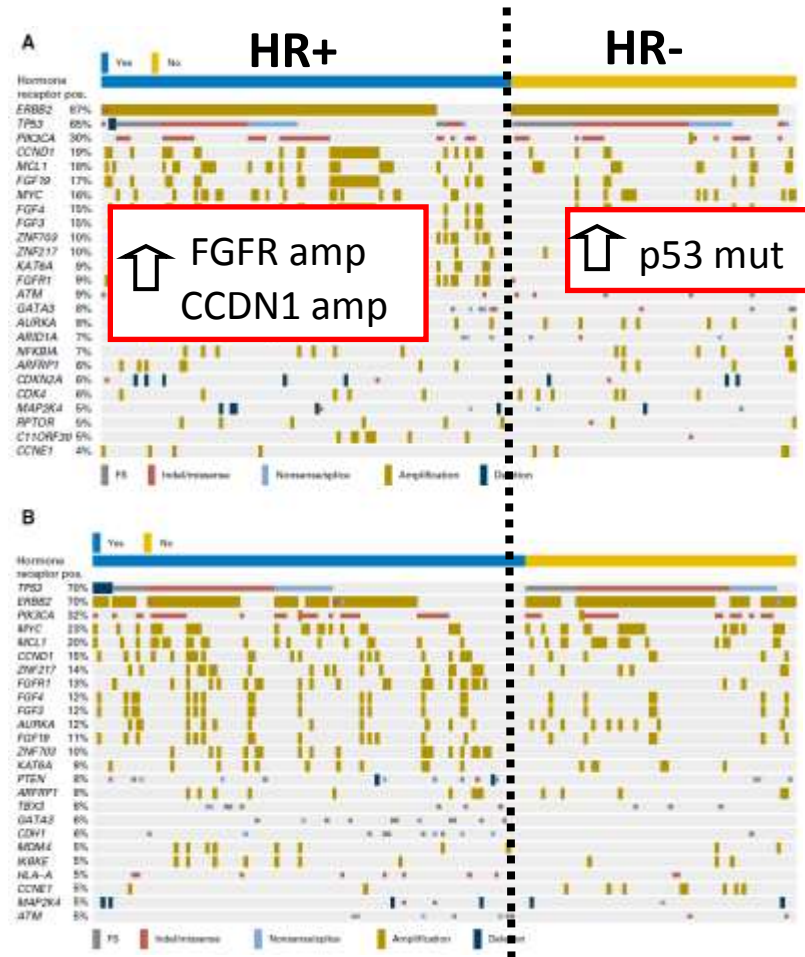
		All Patients (N=146)			
System Organ Class	Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	All Grades n (%)
Eye Disorders	◆ Dry eye	28 (19)	14 (10)	1 (1)	43 (29)
	◆ Conjunctivitis	11 (8)	22 (15)	4 (3)	37 (25)
	◆ Lacrimation increased	21 (14)	7 (5)	0 (0)	28 (19)
	◆ Keratitis	4 (3)	16 (11)	3 (2)	23 (16)
	◆ Vision blurred	12 (8)	3 (2)	1 (1)	16 (11)
General Disorders	◆ Fatigue	24 (16)	18 (12)	5 (3)	47 (32)
Gastrointestinal Disorders	◆ Nausea	22 (15)	7 (5)	0 (0)	29 (20)
	◆ Stomatitis	15 (10)	3 (2)	0 (0)	18 (12)
	◆ Vomiting	12 (8)	4 (3)	0 (0)	16 (11)
Skin and Subcutaneous Tissue Disorders	◆ Alopecia	22 (15)	4 (3)	0 (0)	26 (18)
	◆ Dry skin	25 (17)	0 (0)	0 (0)	25 (17)
	◆ Skin hyperpigmentation	13 (9)	6 (4)	0 (0)	19 (13)
Metabolism and Nutrition Disorders	◆ Decreased appetite	14 (10)	11 (8)	2 (1)	27 (18)
Blood and Lymphatic System Disorders	◆ Neutropenia	4 (3)	10 (7)	9 (6)	23 (16)
	◆ Anemia	8 (5)	6 (4)	2 (1)	16 (11)

- Ocular toxicity and fatigue most frequently reported
- 28 (19%) patients discontinued due to ADRs most commonly due to ocular toxicity
- Evaluation of prophylactic eye drops on ocular toxicity is ongoing

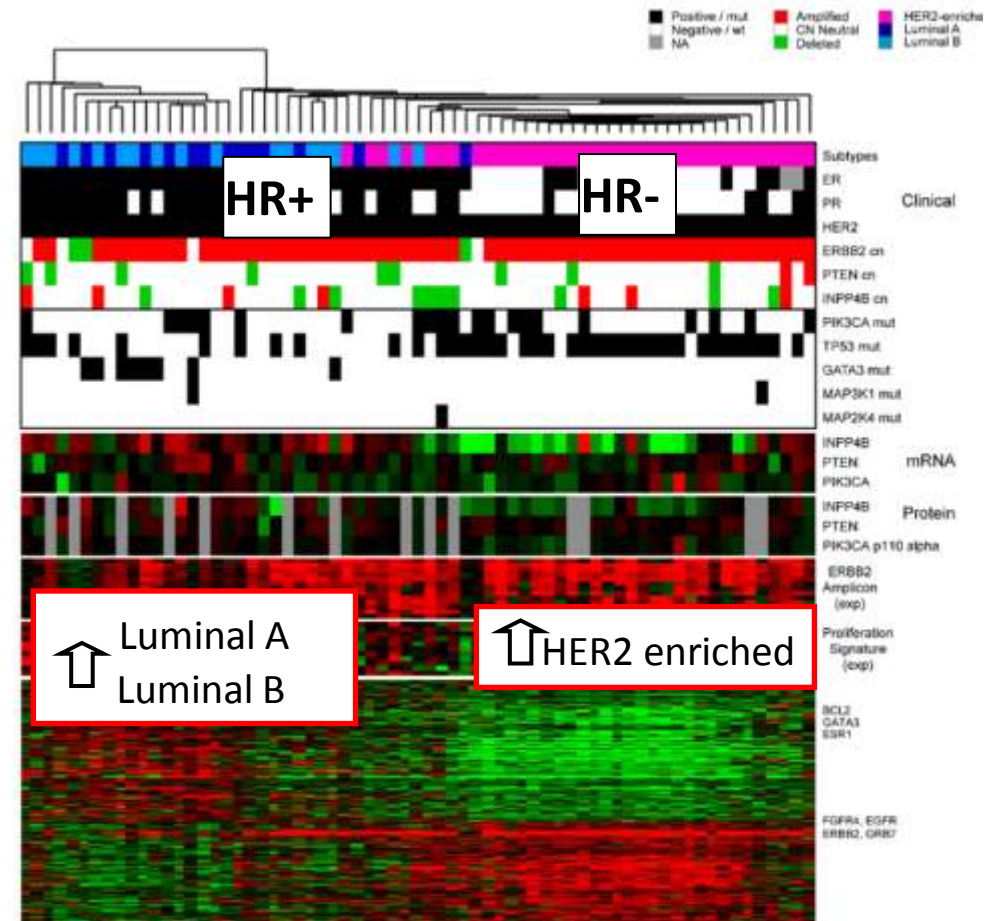
Phase III: Tulip Trial (n=345)



Molecular heterogeneity within HER2+ BC by HR status

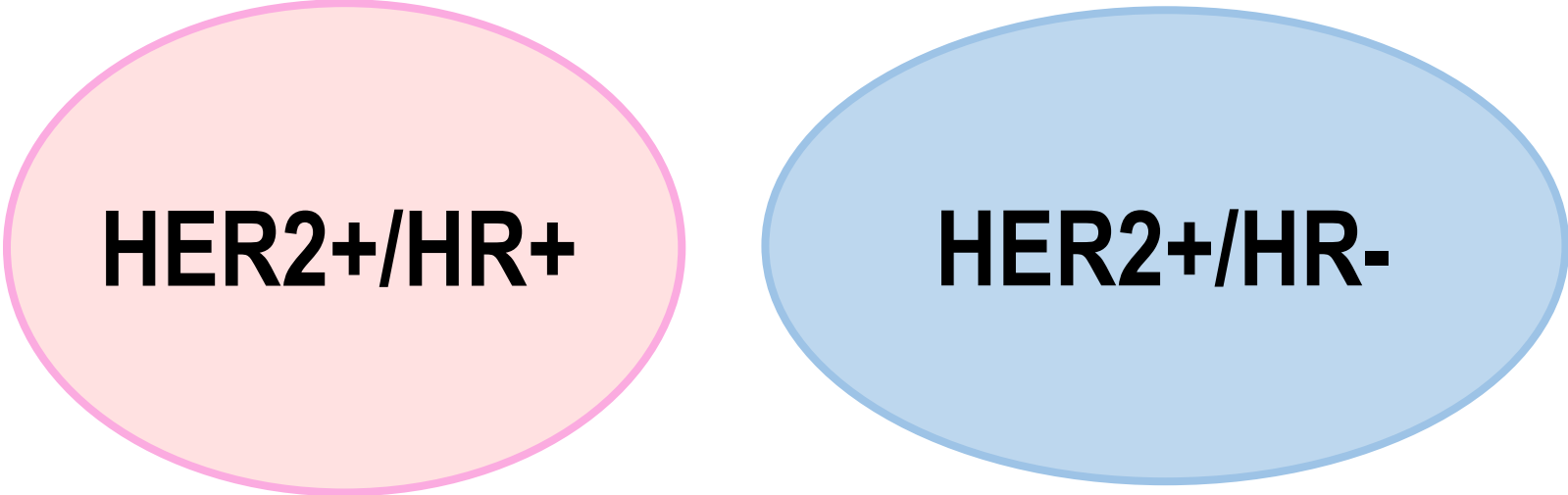


André F et al, JCO 2016



TCGA Nature 2012

HR+/HER2+ and HR-/HER2+: Two different diseases



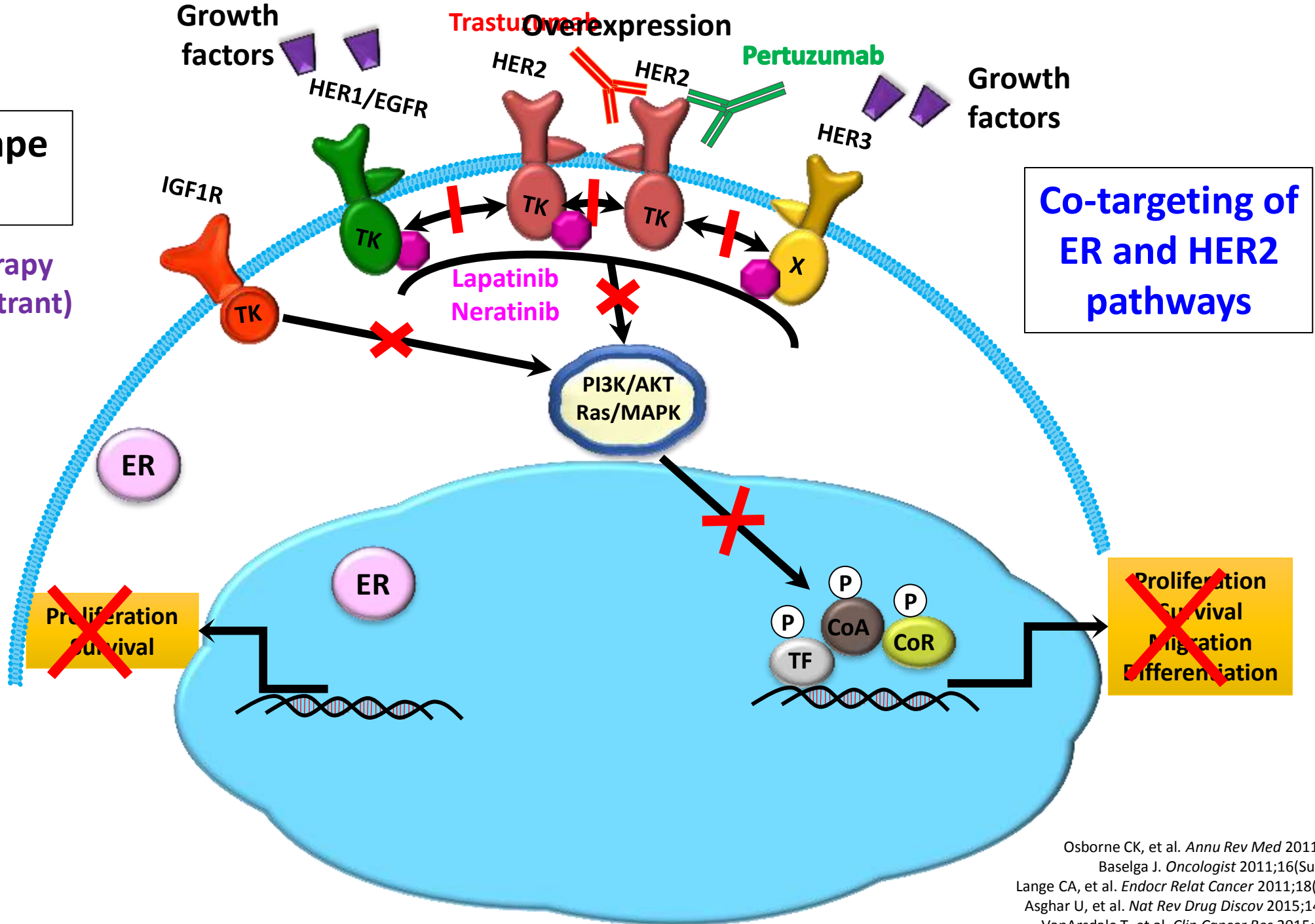
HER2+/HR+

HER2+/HR-

ER as an escape pathway

Endocrine therapy
(e.g. Als, Fulvestrant)

Estrogen



Co-targeting of
ER and HER2
pathways

Osborne CK, et al. *Annu Rev Med* 2011;62:233–47
Baselga J. *Oncologist* 2011;16(Suppl. 1):12–9
Lange CA, et al. *Endocr Relat Cancer* 2011;18(4):C19–C24
Asghar U, et al. *Nat Rev Drug Discov* 2015;14(2):130–46
VanArsdale T, et al. *Clin Cancer Res* 2015;21:2905–10

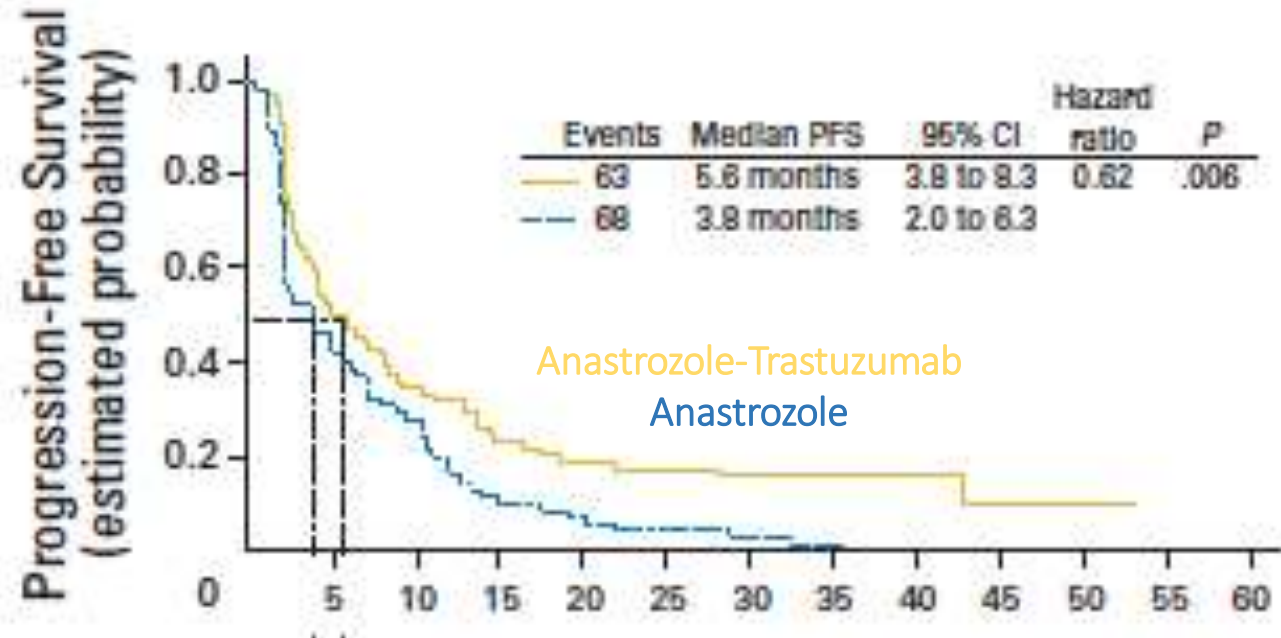
The cross-talk between ER and HER2
and the “chemo-less” goal

Anti-HER2 therapy + endocrine therapy (ET)

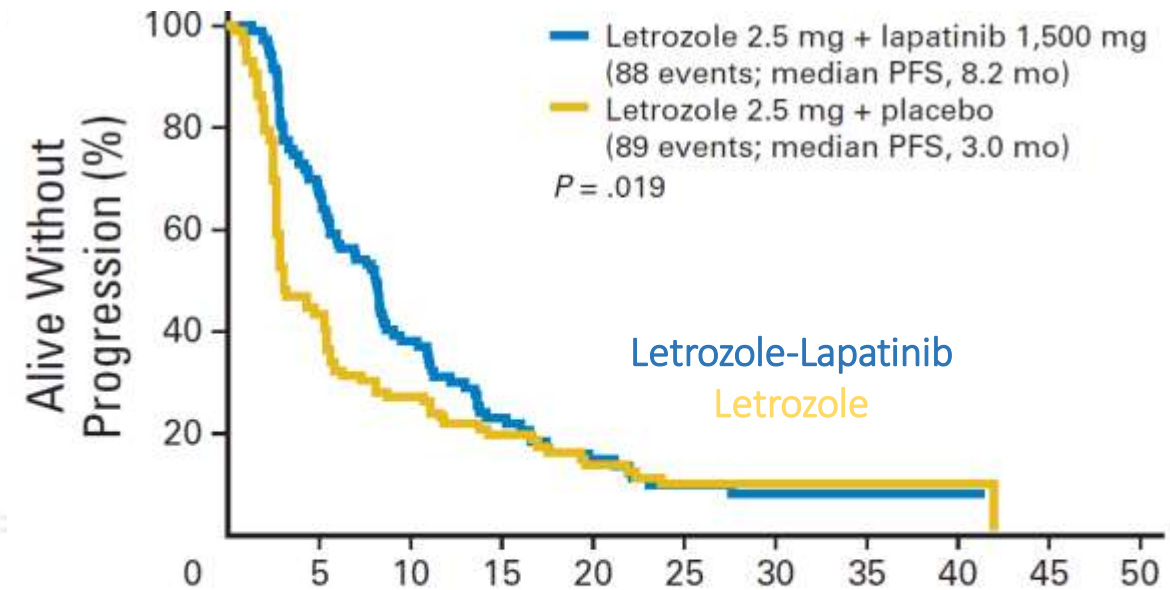
Author	No. of Patients	Trial Phase	Study Design	PFS
Johnston ¹	219	III	letrozole vs letrozole + lapatinib	3.0 vs 8.2 mo P = .019
Kaufman ²	207	III	anastrozole vs anastrozole + trastuzumab	3.8 vs 5.6 mo P = .0016

1. Johnston S, et al. J Clin Oncol. 2009
2. Kaufman B, et al. J Clin Oncol. 2009

Anti-HER2 therapy + ET in ER+/HER2+ MBC



Kaufman B et al, JCO 2009

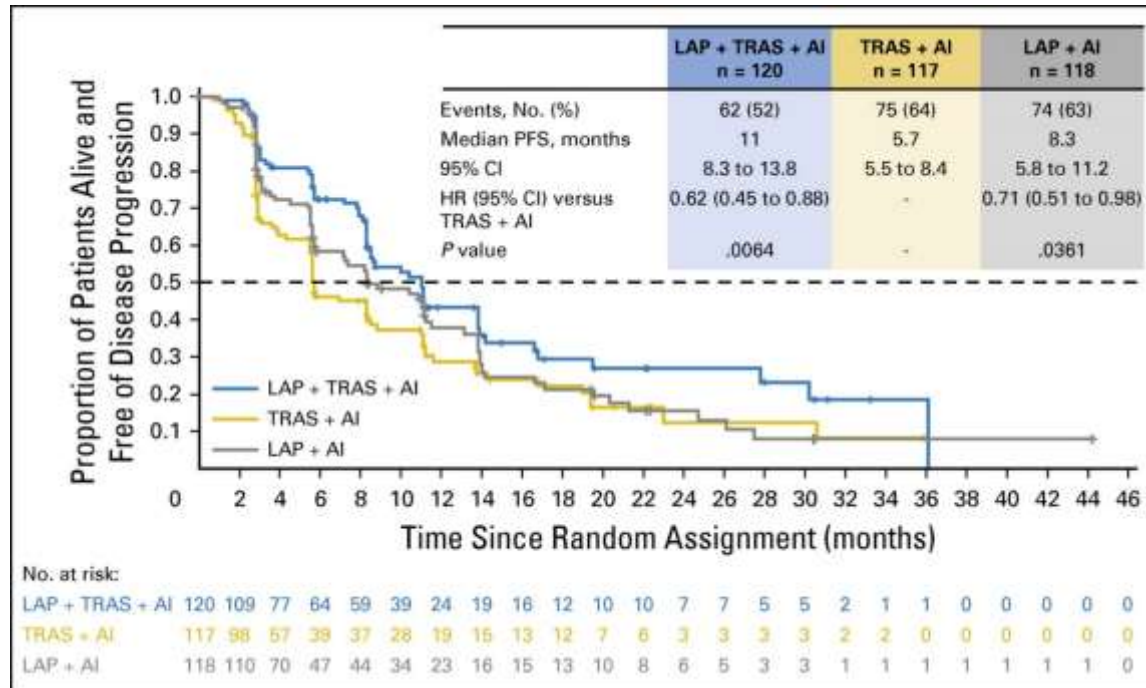


Johnston S et al, JCO 2009

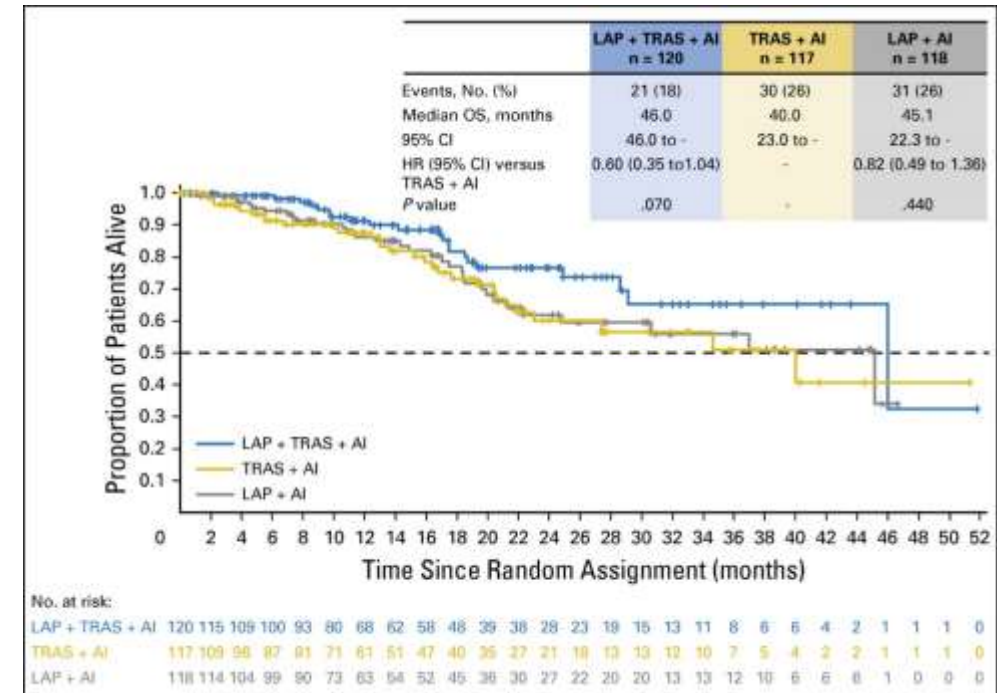
What about dual HER2 blockade +
endocrine therapy?

ALTERNATIVE study (Phase III)

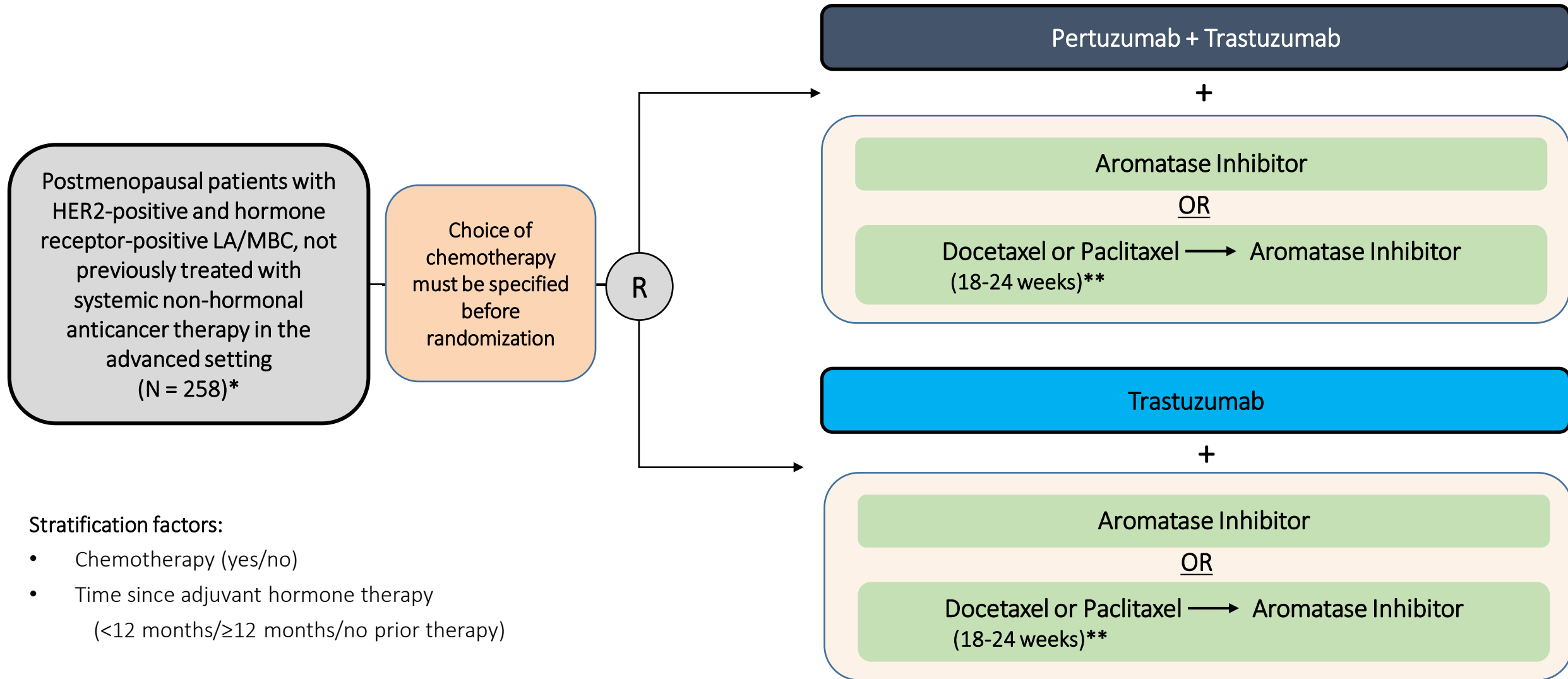
PFS



OS



PERTAIN Study Design (Phase II Trial)

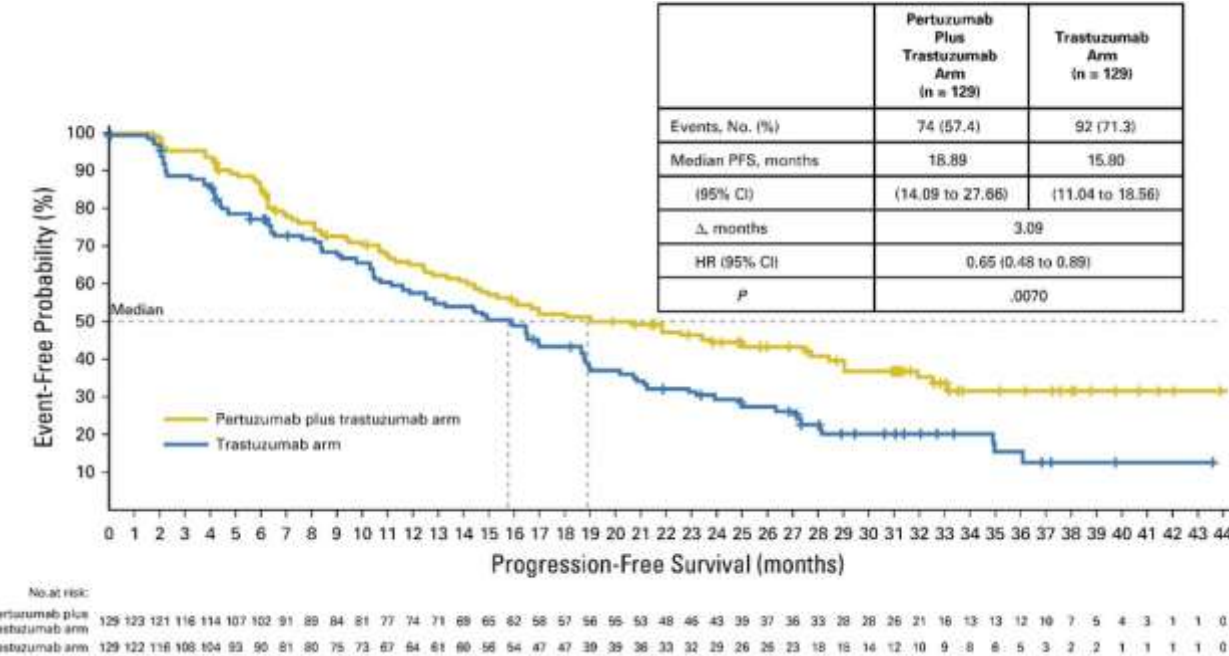


Stratification factors:

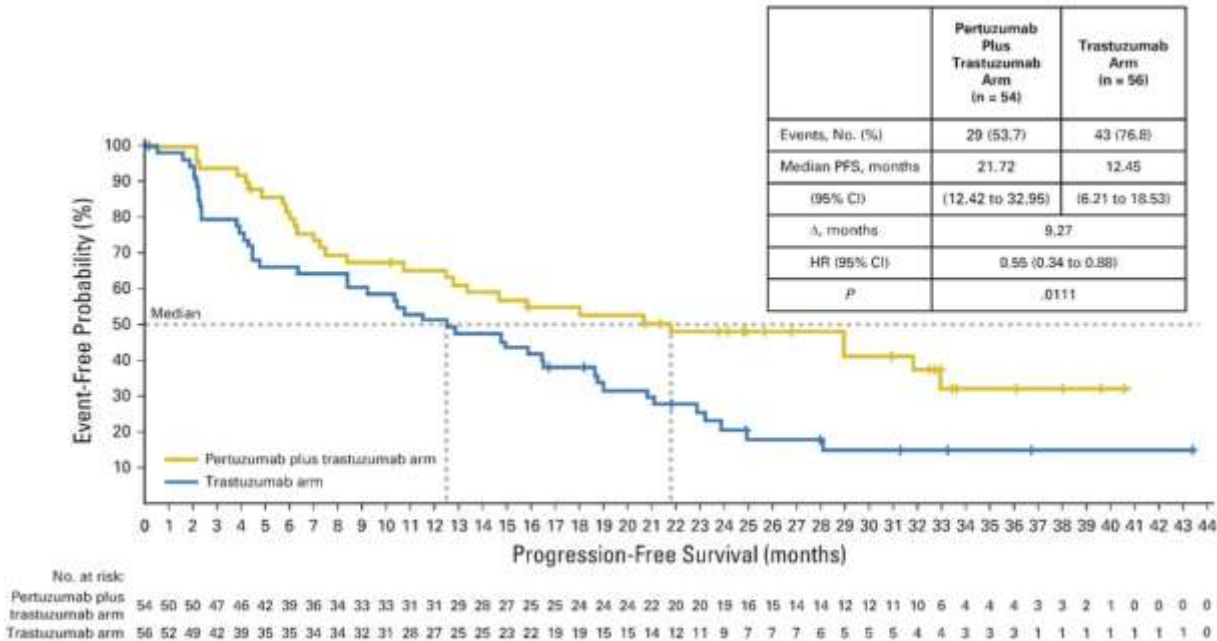
- Chemotherapy (yes/no)
- Time since adjuvant hormone therapy (<12 months/≥12 months/no prior therapy)

PERTAIN: PFS

ITT



Pts with no induction chemotherapy



ER and HER2 pathways require CDK4/6-mediated transcription for cell-cycle progression

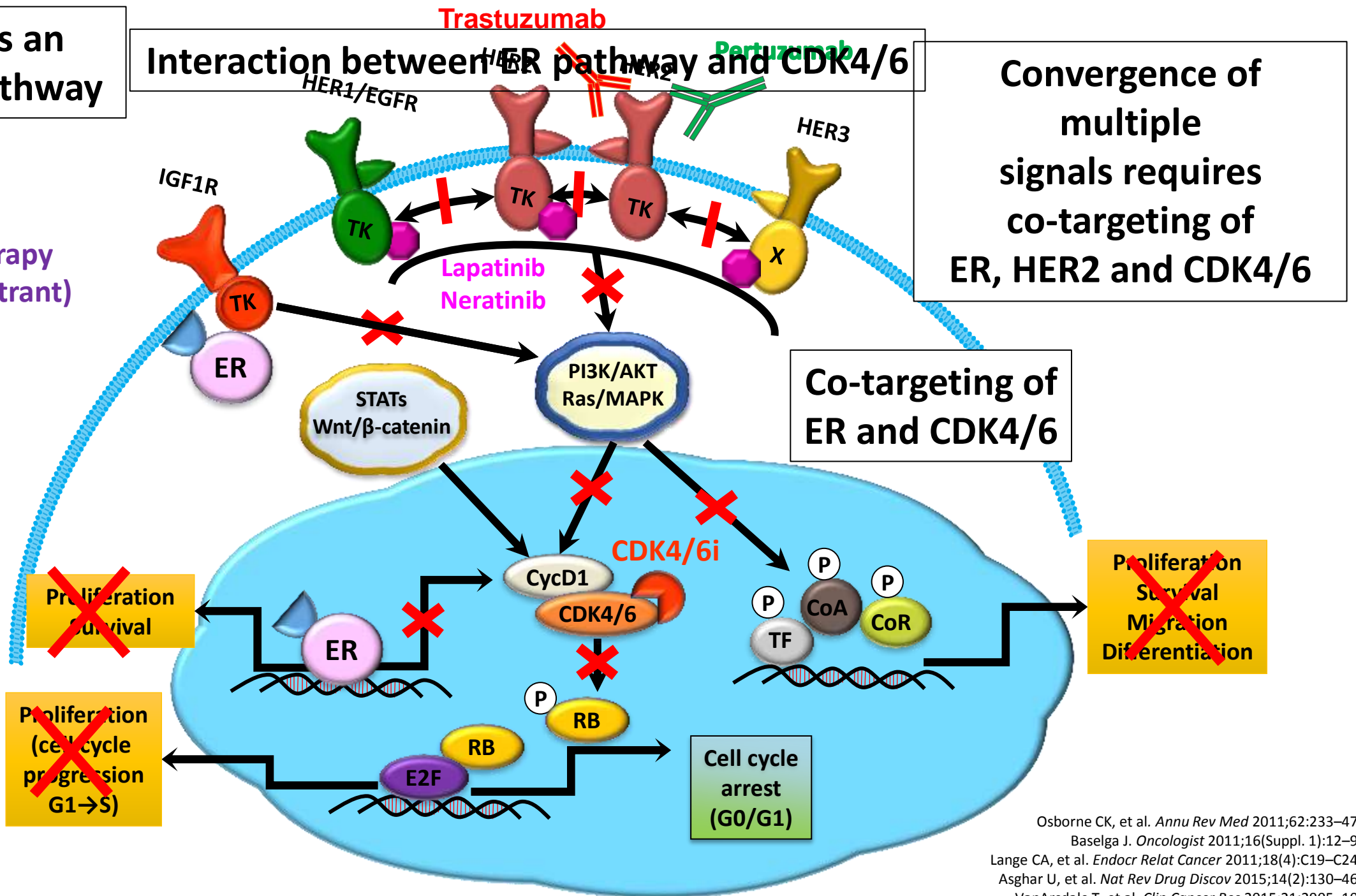
HER2 as an escape pathway

Interaction between ER pathway and CDK4/6

Convergence of multiple signals requires co-targeting of ER, HER2 and CDK4/6

Endocrine therapy
(e.g. AIs, Fulvestrant)

Estrogen

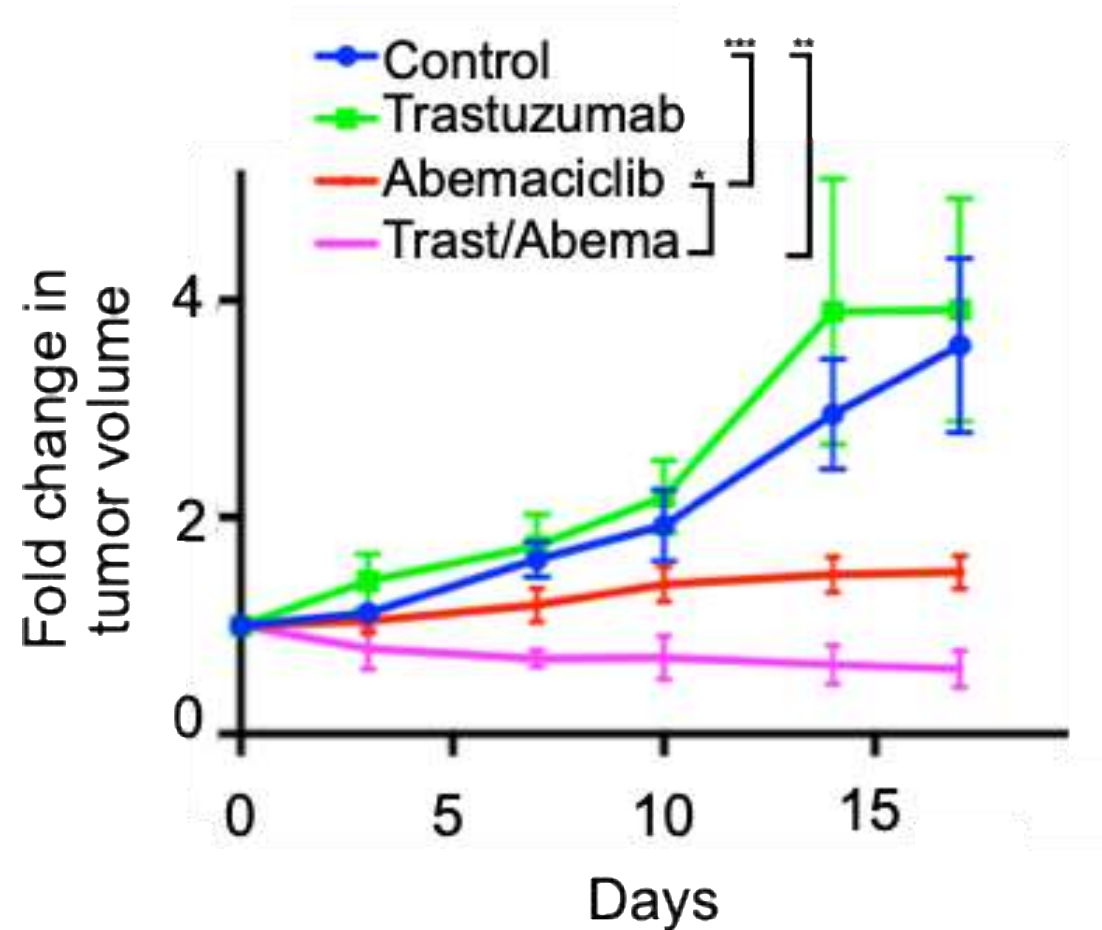


monarchHER: A RANDOMIZED PHASE 2 STUDY OF ABEMACICLIB PLUS TRASTUZUMAB WITH OR WITHOUT FULVESTRANT VERSUS TRASTUZUMAB PLUS STANDARD-OF-CARE CHEMOTHERAPY IN WOMEN WITH HR+, HER2+ ADVANCED BREAST CANCER (ABC)

Sara M Tolaney¹, Andrew M Wardley², Stefania Zambelli³, John F Hilton⁴, Tiffany A Troso-Sandoval⁵, Francesco Ricci⁶, Seock-Ah Im⁷, Sung-Bae Kim⁸, Stephen RD Johnston⁹, Arlene Chan¹⁰, Shom Goel^{1*}, Kristen Catron¹¹, Zhengyu Yang¹¹, M. Corona Gainford¹¹, Fabrice André¹²

¹Dana-Farber Cancer Institute, Boston, MA, USA, ²The Christie NHS Foundation Trust, Manchester Academic Health Science Centre and Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology Medicine & Health, University of Manchester, UK, ³IRCCS Ospedale San Raffaele, Milano, Italy, ⁴Department of Medicine, Division of Medical Oncology, The Ottawa Hospital and University of Ottawa, Ottawa, Canada, ⁵Memorial Sloan Kettering Cancer Center, New York, NY, USA, ⁶Institut Curie, PSL Research University, Department of Medical Oncology, Paris, France, ⁷Seoul National University College of Medicine, Seoul, Korea, ⁸Asan Medical Center, University of Ulsan College of Medicine, Songpa-gu, Seoul, Korea, ⁹Royal Marsden Hospital, London, UK, ¹⁰Breast Cancer Research Centre - WA and Curtin University, Nedlands, WA, Australia, ¹¹Eli Lilly and Company, Indianapolis, IN, USA, ¹²Gustave Roussy, Université Paris Sud, INSERM, Villejuif, France, *current affiliation: Peter MacCallum Cancer Centre, Cancer Research Division, Melbourne, Australia

Combined inhibition of CDK4/6 and HER2 is synergistic in PDX model resistant to HER2 directed therapies



monarcHER: Study design

Eligibility Criteria

- HR+/HER2+ ABC
- ≥2 prior anti-HER2 therapies for ABC
- prior T-DM1 and taxane required
- CDK4/6i/fulvestrant naive
- No untreated or symptomatic CNS metastases

Stratification Factors:

- number of previous systemic regimens (2–3 vs. >3)
- measurable vs. non-measurable

Randomization

N = 237
1:1:1

Sample Size Calculations:

- 165 PFS events give 80% power at 2-sided alpha of 0.20, assuming a HR of 0.667

Continue until PD

Arm A

abemaciclib 150 mg PO BID +
trastuzumab IV q21d +
fulvestrant IM q28d

Arm B

abemaciclib 150 mg PO BID +
trastuzumab IV q21d

Arm C

trastuzumab IV q21d +
investigator's choice chemotherapy

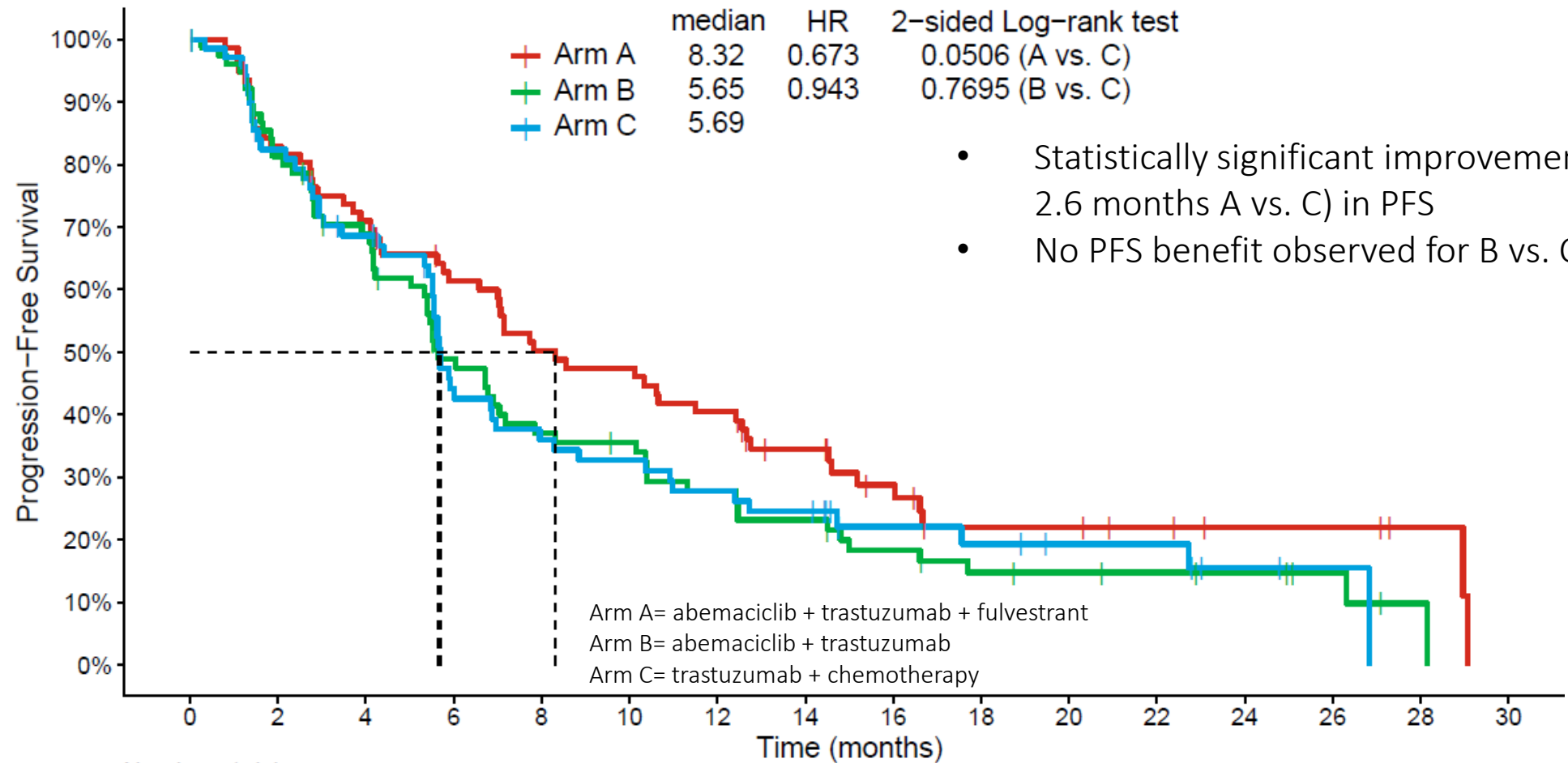
Primary Endpoint

- PFS (A vs. C, then B vs. C)

Secondary Endpoint

- ORR, safety, OS, PRO, PK

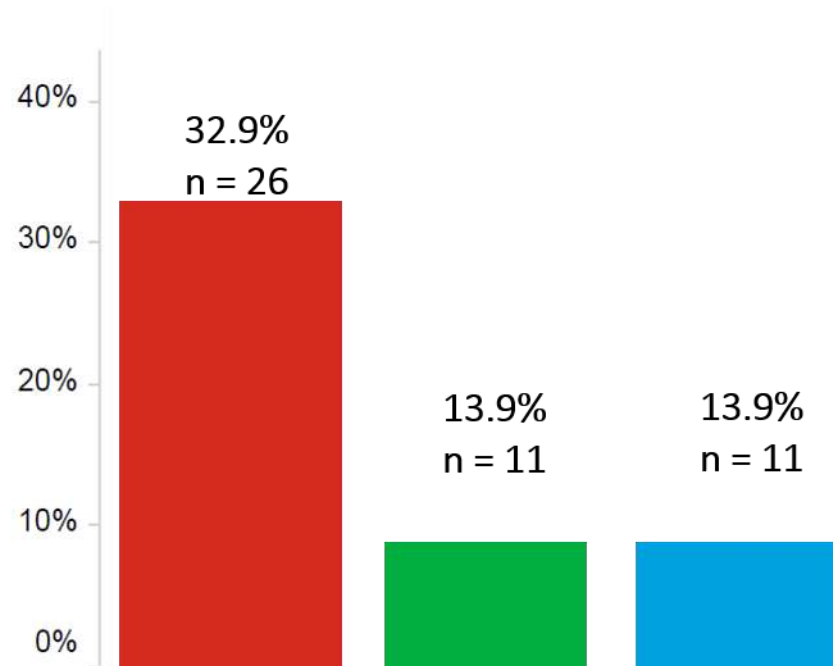
monarchHER: PFS



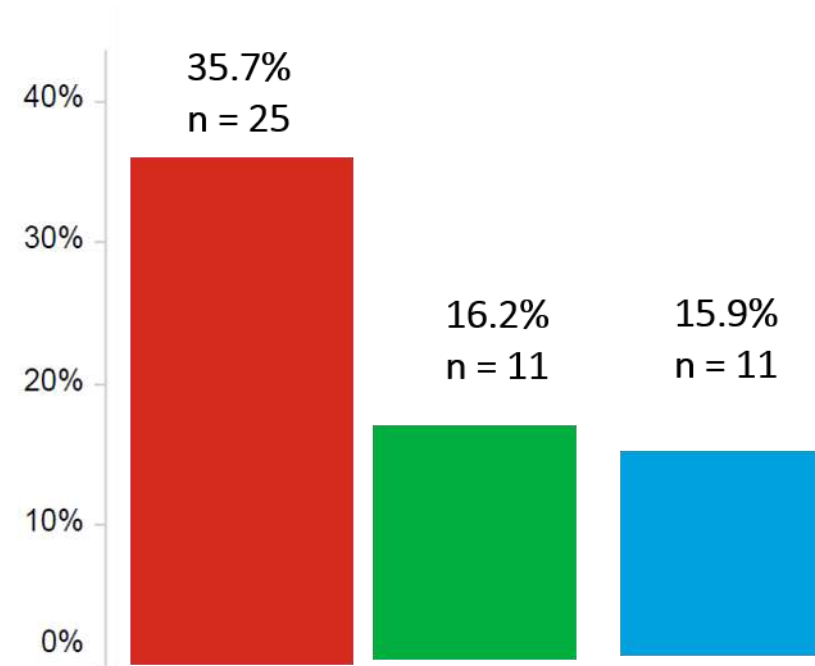
Number at risk																
Arm A	79	63	53	44	36	34	29	21	14	8	8	6	4	4	2	0
Arm B	79	60	49	33	25	23	18	15	11	8	7	6	5	3	1	0
Arm C	79	54	44	27	22	20	17	15	8	7	5	5	2	1	0	0

Confirmed Best Overall Response Rate

ITT (237 pts)



Measurable disease (207)



Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

Conclusions

- Excellent outcome has been achieved with standard treatments
- De-escalation in the metastatic setting is possible, but has to be done safely and cautiously without compromising outcome
- ADCs may improve outcome by ameliorating the toxicity profile
- Combinations of anti-HER2 agents and ET + CDK4/6 inhibitors are a valid and rational strategy for HR+/HER2+ disease