More potent HER-2 inhibition: New EGFR/HER family-directed strategies

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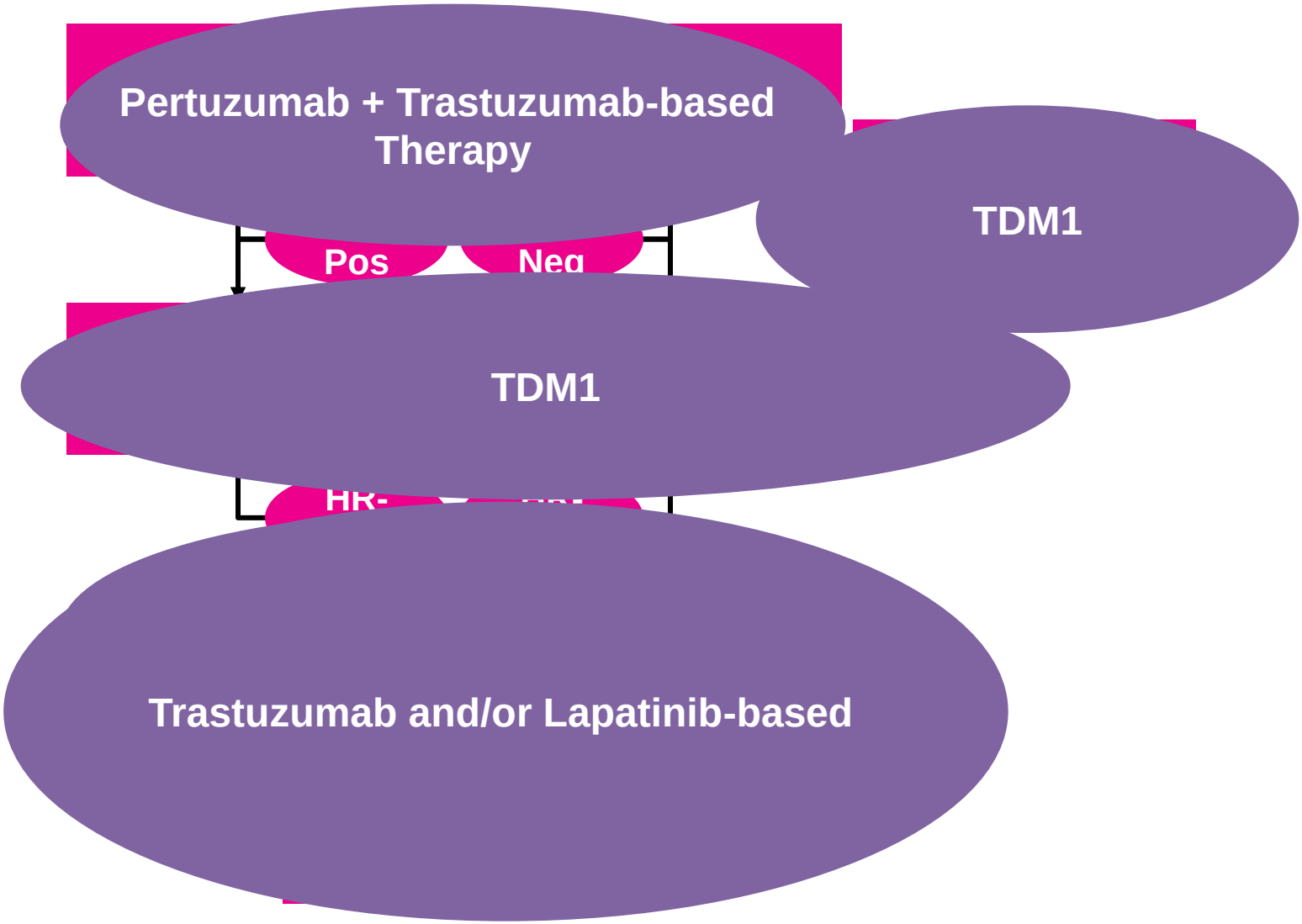
Disclosures

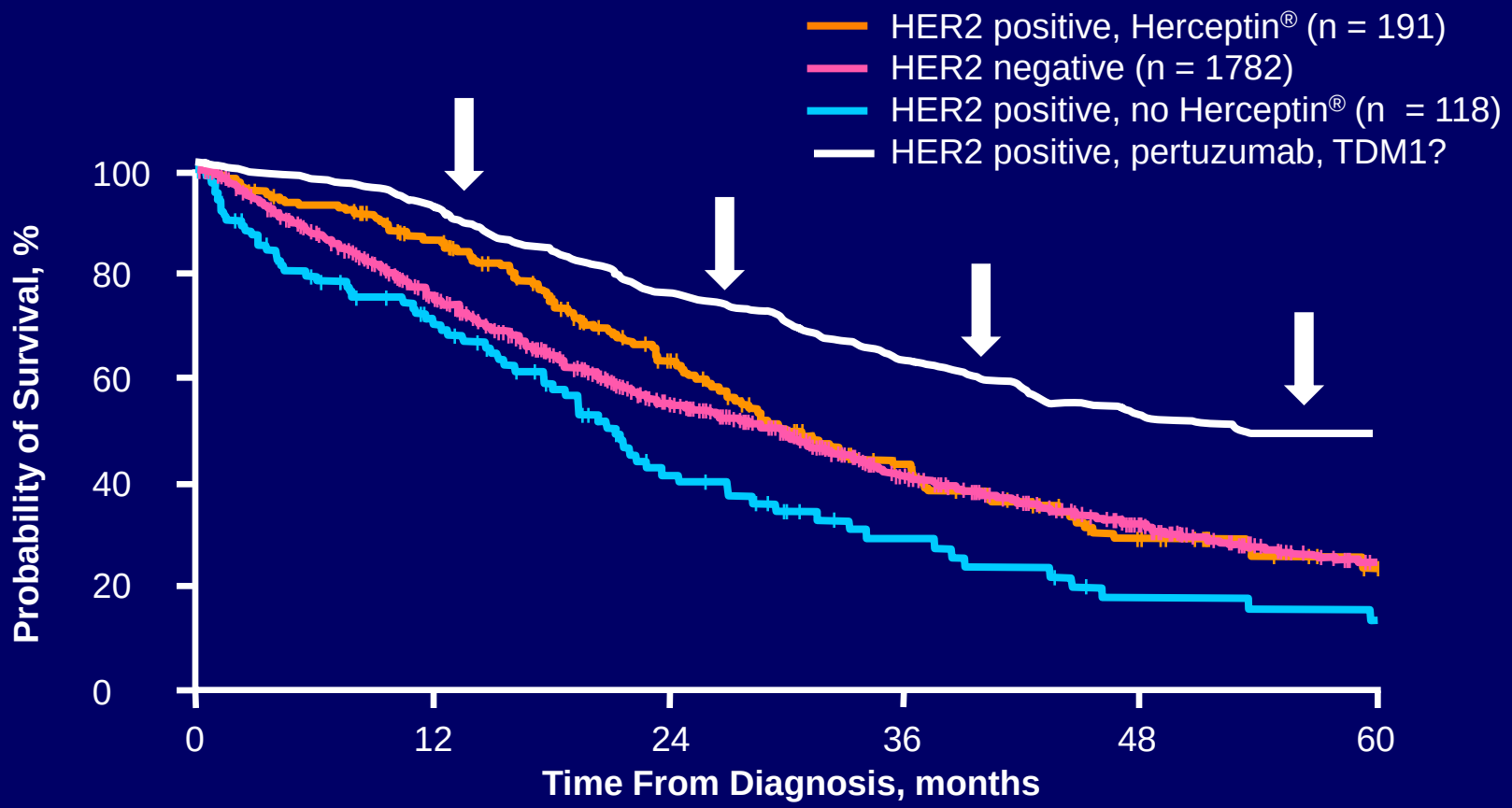
- Advisor
  - Roche, Novartis, Celgene
- Honoraria
  - Roche, Novartis, Celgene, Eisai

- Partner
  - MedSIR ARO

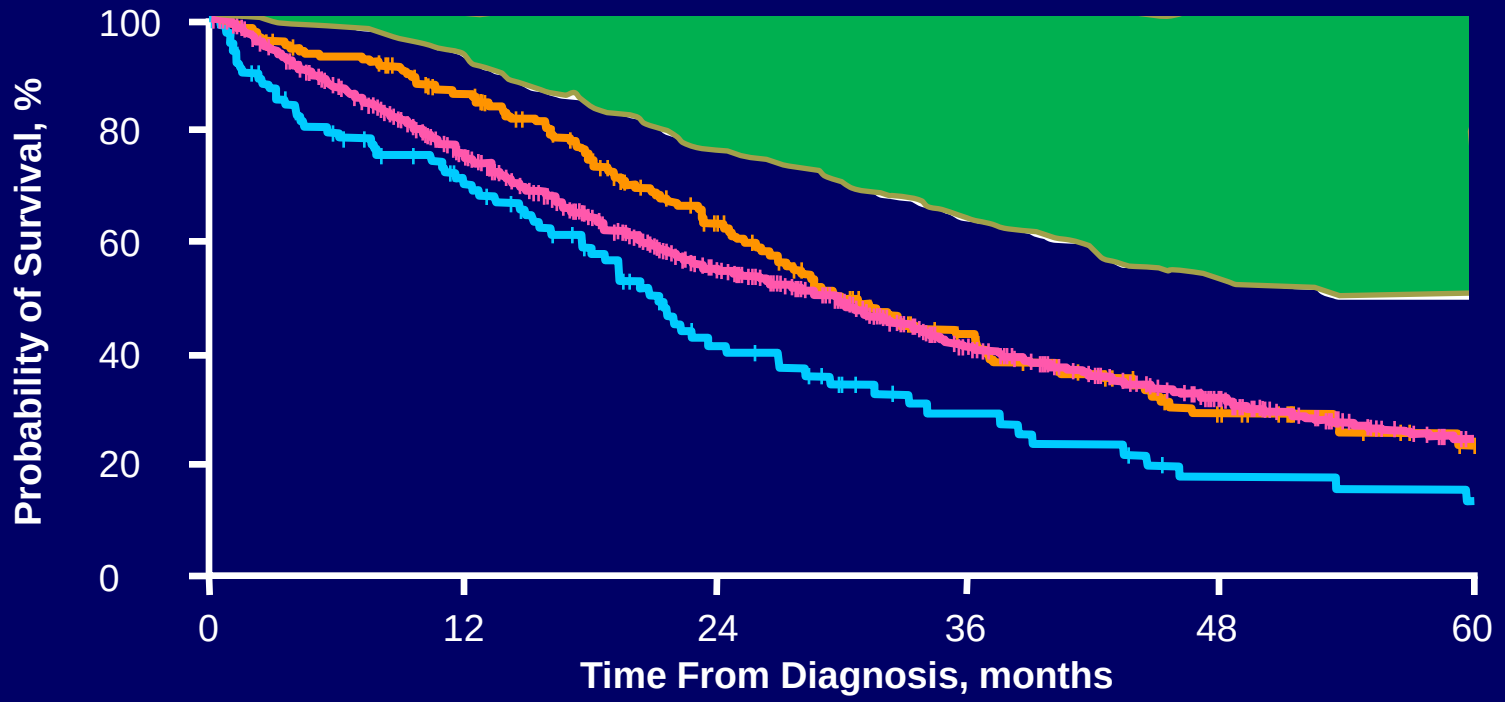
HER2+MBC: Current approach



HER2+MBC: Current prognosis



HER2+MBC: Still an unmet need...



Novel HER2-directed agents in clinical development

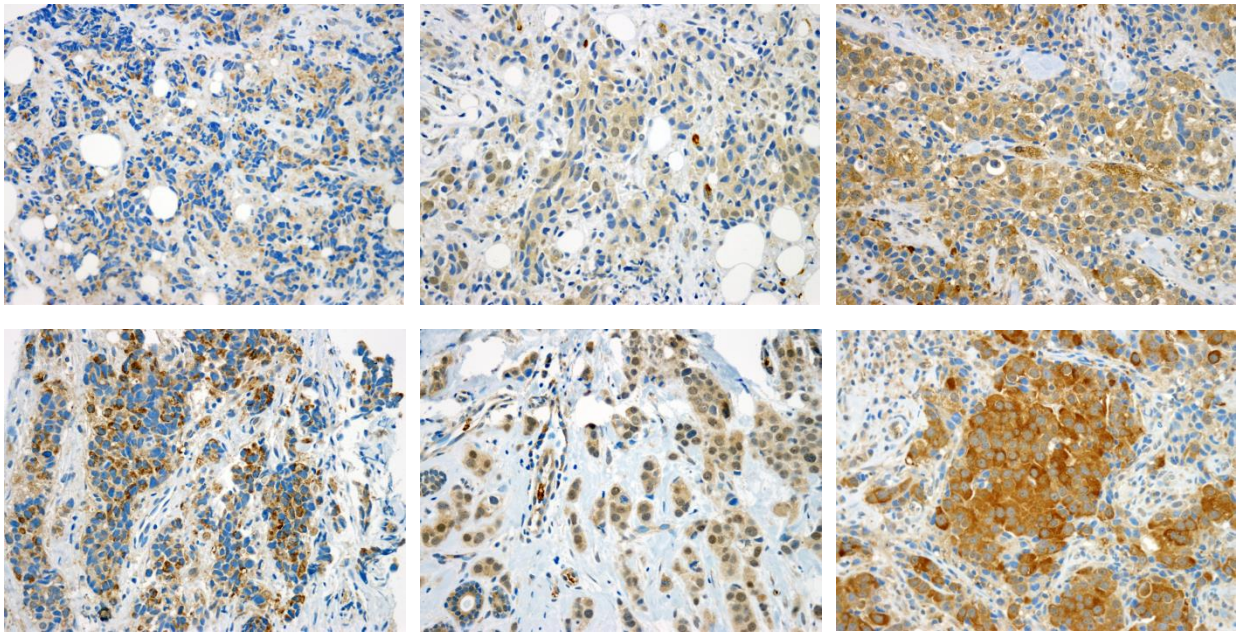
Class	Example(s)
HER2-targeted TKI	Neratinib, afatinib, ARRY-380
HER2-targeted liposome	MM-302
Anti-HER3	AMG-888, MM-121, EZN-3920
Anti-HER2 monoclonal antibody with enhanced immune properties	Margetuximab

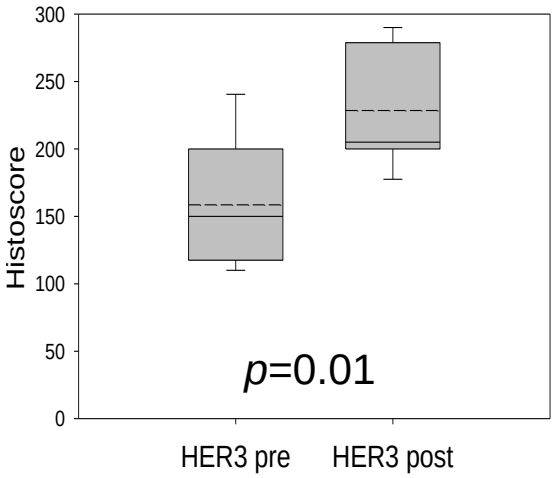
HER2 inhibition with lapatinib is followed by upregulation of HER3 in HER2+ tumors

HER3 IHC

Pre-therapy

Post-therapy (2 wks)

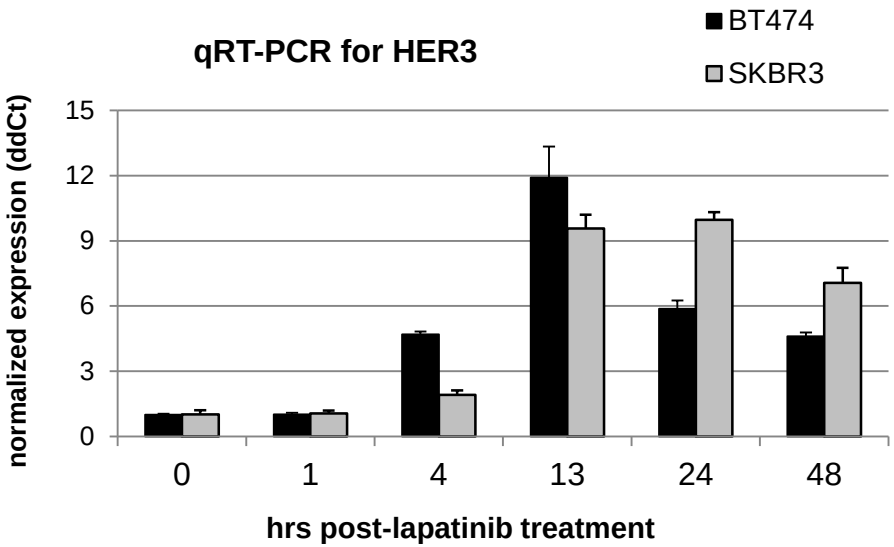


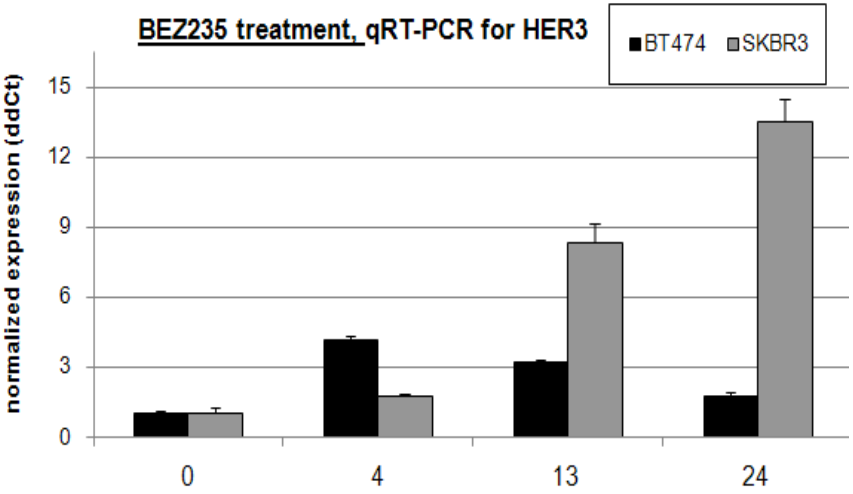


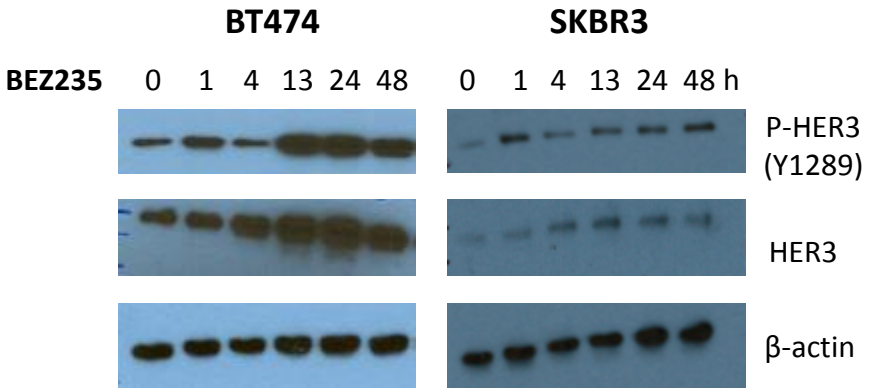
P-HER3 was also upregulated upon tx

Garrett, et al, Proc Natl Acad Sci USA 2011

Inhibition of either HER2 or PI3K/Akt results in upregulation of HER3 RNA and protein and P-HER3

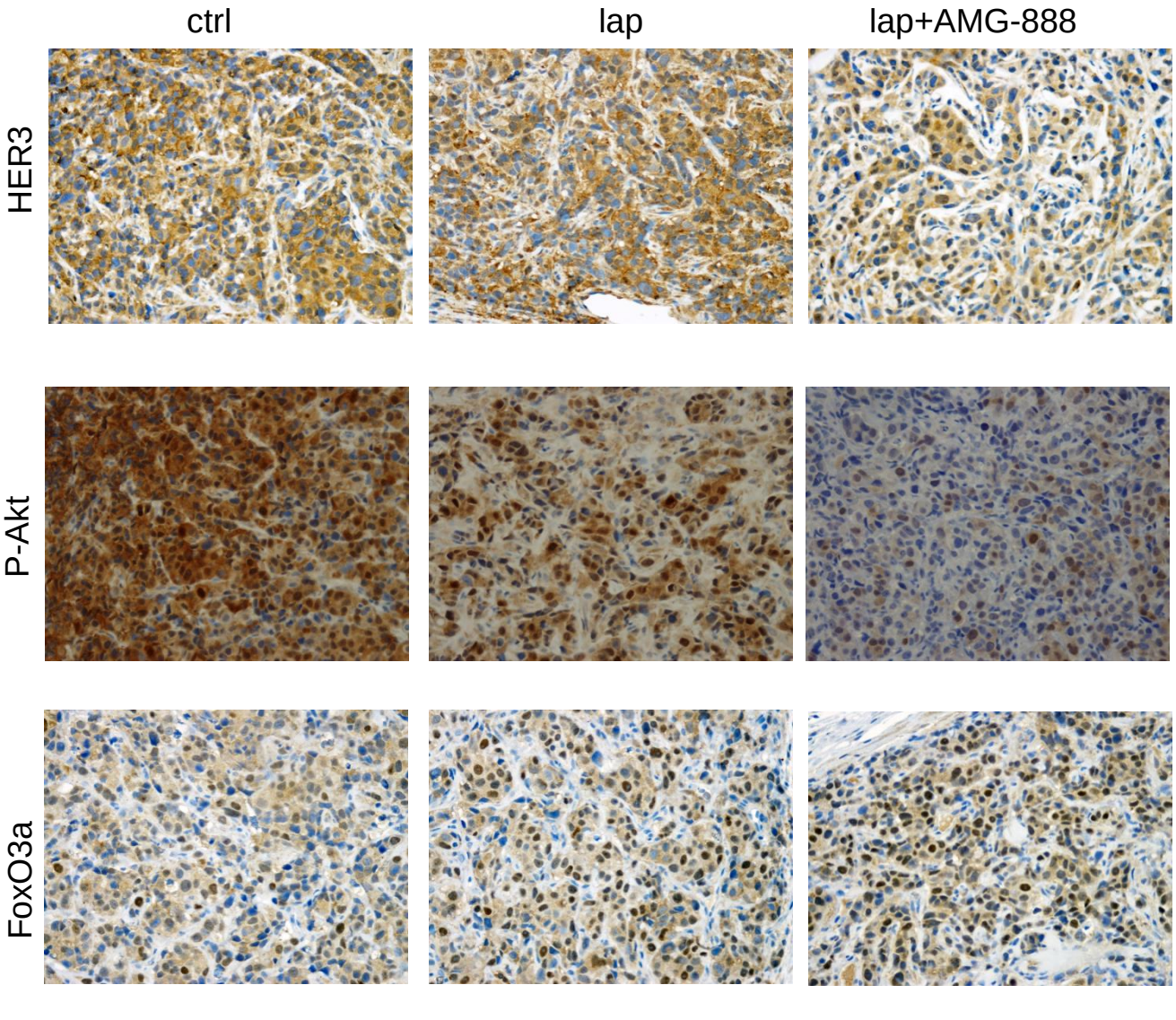






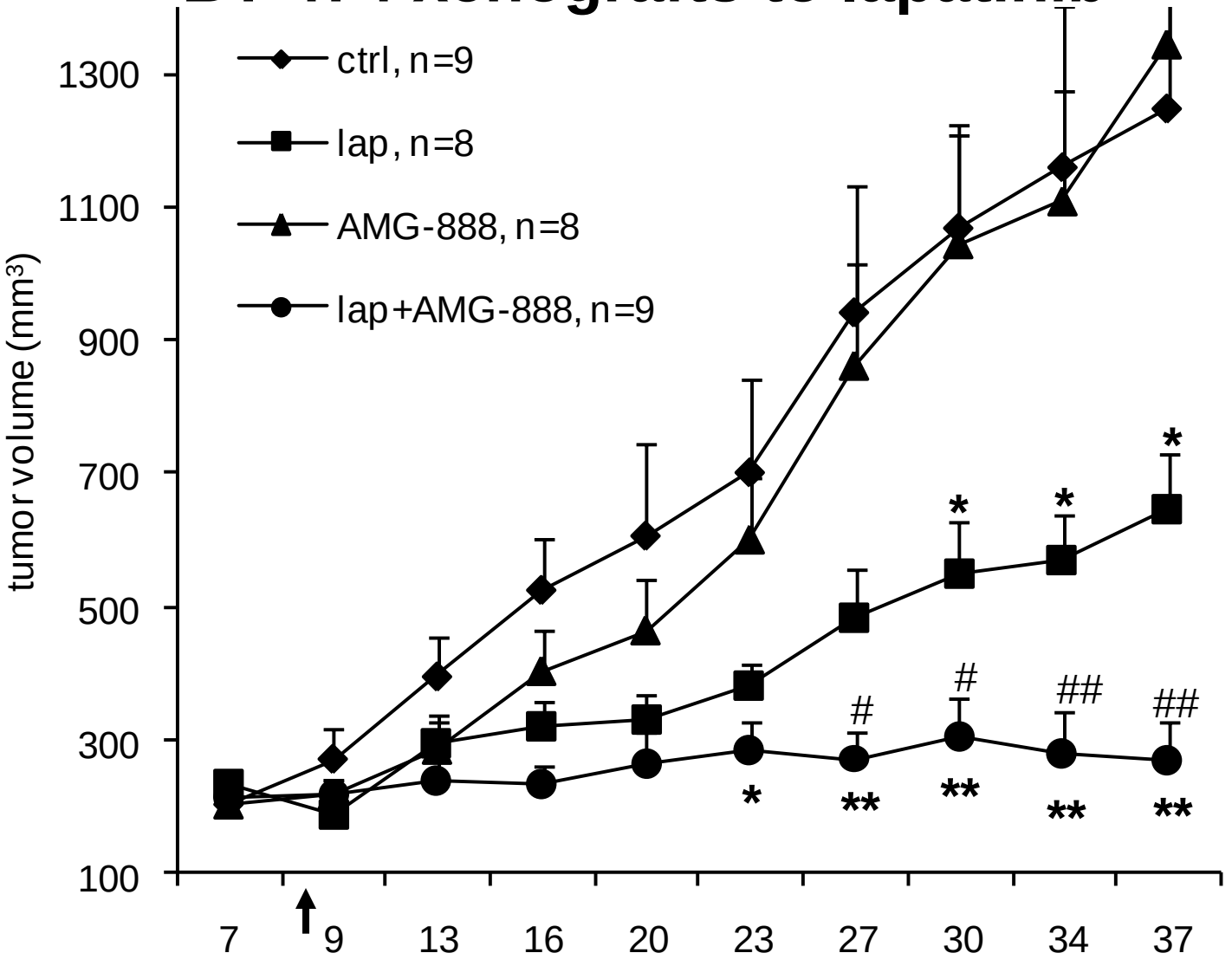
Garrett, et al, Proc Natl Acad Sci USA 2011

Biomarkers of combined HER2 and HER3 inhibition

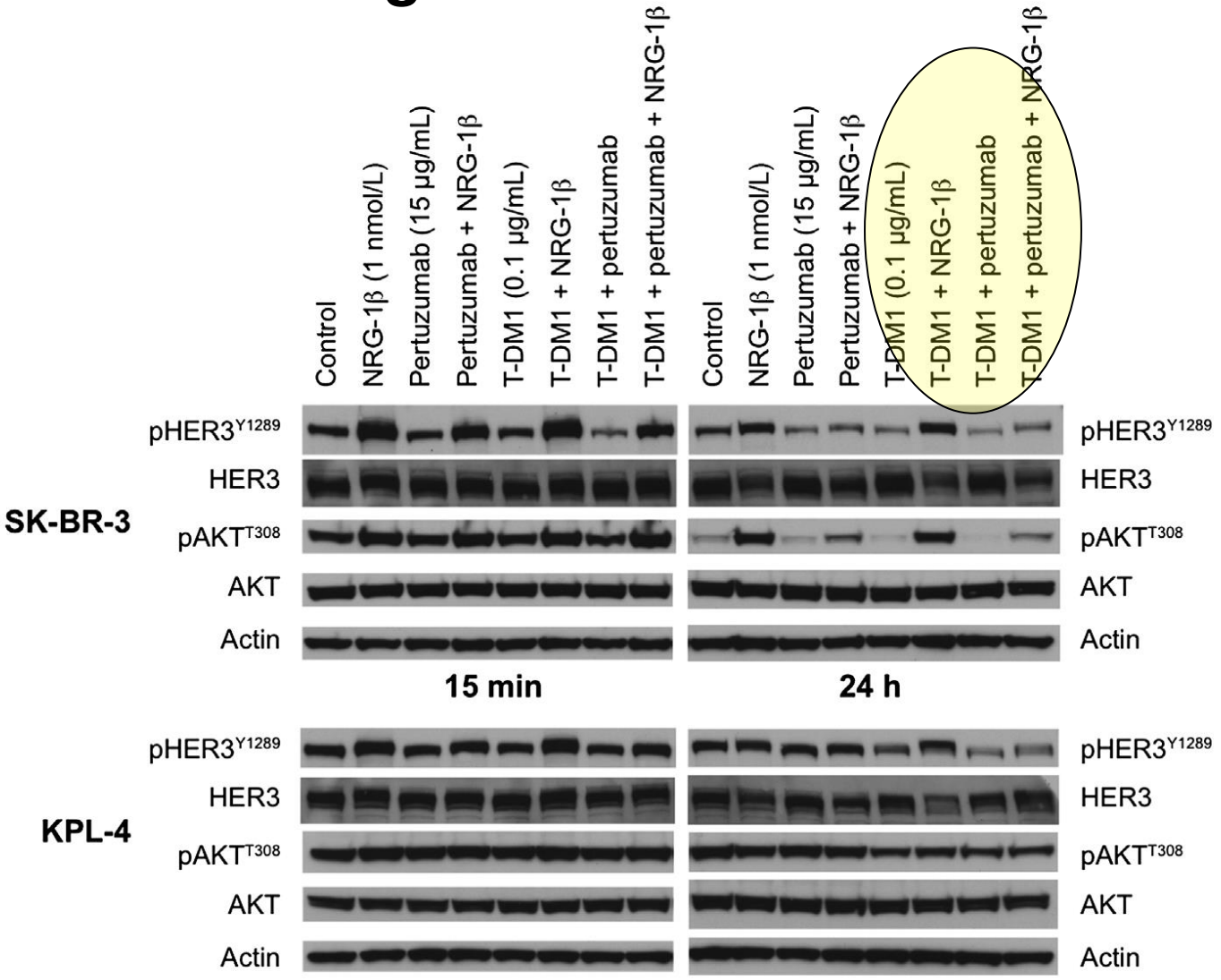


Garrett, et al, Proc Natl Acad Sci USA 2011

Neutralizing HER3 monoclonal antibody sensitizes BT-474 xenografts to lapatinib



TDM1 and pertuzumab on HER2-HER3 mediated signal transduction



Lewis Philips G, et al. Clin Cancer Res 2013

pan-HER-2 – Targeting TKIs for HER2/neu +++BC

Neratinib: Orally Available, Irreversible Inhibitor of the EGFR- and Her-2 Receptor Tyrosine Kinases and Inhibitor of Proliferation of EGFR-Dependent Cells

Phase II[1]

Phase II, Randomised[2,3]

Phase III[4]

Afatinib: Orally Available, Irreversible pan-ErbB Family Blocker and Blocker of Homo- and Heterodimerisation

Phase II[5]

Phase II, Randomised, (LUX-Breast 3)[6]

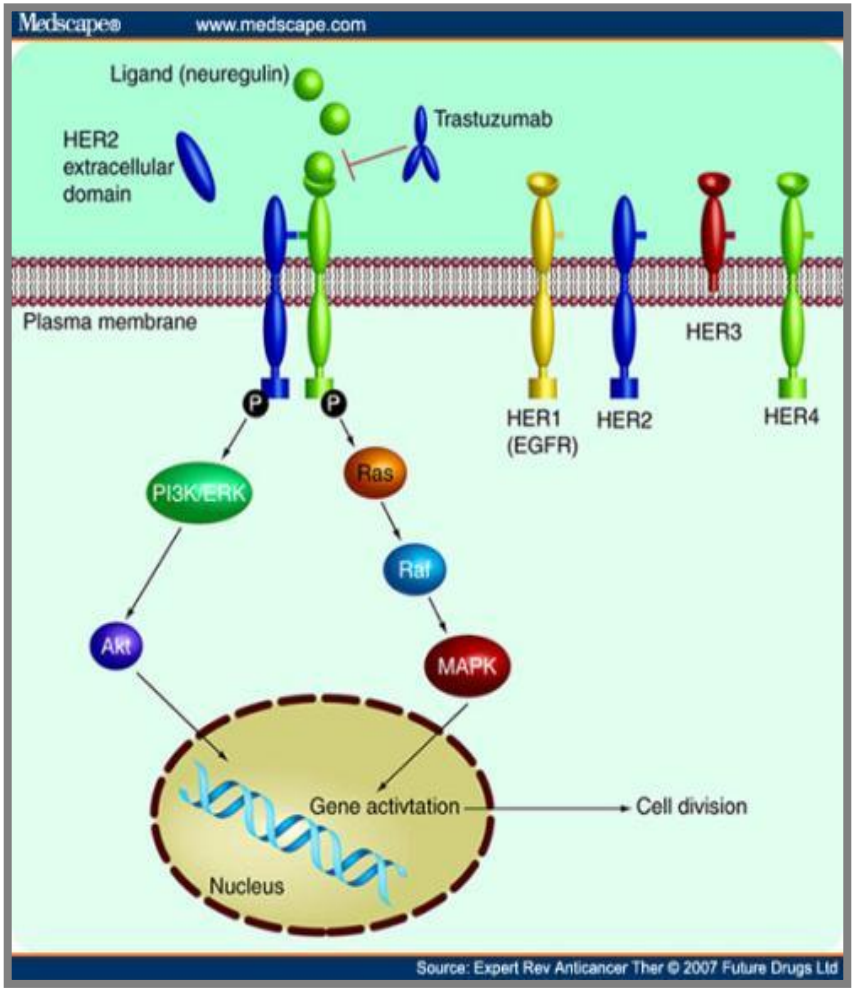
Phase III (LUX-Breast 1 and 3)[7]

[1] Burstein et al., J Clin Oncol 2010; [2] M. Martin et al., Europ J Cancer, 2013; [3] Awada A et al., Proc Am Soc Clin Oncol 2015, Abstract #610; [4] Chan et al., ASCO 2015 & Lancet Oncol 2016

[5] Lin et al., Breast Cancer Res Treat 2012; [6] Cortes et al., Lancet Oncol. 2015; [7] Harbeck et al., SABCC 2014, closed for recruitment (IDMC)

Neratinib Overview

Neratinib Inhibits Receptor Tyrosine Kinases and Signal Transduction



Inhibition of erbB Receptor Kinases

Kinase	IC_{50} (nM)
erbB1	92
erbB2	59
erbB4	19

Inhibition of erbB Signaling Pathways

Kinase	IC_{50} (nM)
Phospho-erbB1	3
Phospho-erbB2	5
Phospho-MAP Kinase	2
Phospho-AKT	2

Neratinib: a pan-HER Inhibitor

	IC_{50} (nM)		
Compound	**erbB1**	**erbB2**	**erbB4**
erbB1-specific inhibitor			
Erlotinib	2	350	-
erbB2-specific inhibitor			
CP-724,414	4300	8	-
Dual ErbB inhibitor			
Lapatinib	11	9	367
Pan ErbB inhibitor			
Neratinib	92	59	19

Neratinib Breast Cancer Program

Study	Design	Indication / Population		n	Response Rate (%)	Clinical Benefit Rate (%)	PFS (months) (95% CI)
102	Neratinib FIH	Advanced tumor (ErbB1+ or ErbB2+)		25	32 (15-54)	36 (18-58)	3.6 (1.7-5.6)
2205	Neratinib + Temsirolimus	Breast Cancer		12	17 (2-48)	25 (5-57)	
201	Neratinib	HER2+ mBC	Prior Trastuzumab	63	24 (14-36)	33 (22-46)	5.1 (3.7-7.3)
			No Prior Trastuz.	64	56 (43-69)	69 (56-80)	9.1 (7.1-12.7)
202	Neratinib + Trastuzumab	HER2+ LABC or mBC		28	29 (13-49)	36 (19-56)	3.7 (3.5-7.2)
203	Neratinib + Paclitaxel	HER2+ mBC	≤ 1 cytotoxic reg.	68	71 (58-81)		
			≥2 cytotoxic regs	31	77 (59-90)		
2204	Neratinib + Vinorelbine	HER2+ mBC	Prior Lapatinib	12	8 (0-38)	42 (15-72)	5.2 (2.8-9.4)
			No Prior Lapatinib	56	41 (28-55)	70 (56-81)	11.0 (7.1-15.0)
2206	Neratinib + Capecitabine	HER2+ mBC	Prior Lapatinib	7	57 (18-90)	71 (29-96)	8.3 (4.4-13.8)
			No Prior Lapatinib	61	64 (51-76)	72 (59-83)	9.3 (7.0-15.2)
3003	Neratinib	HER2+ LRBC / mBC		117	29 (21-38)	44 (35-54)	4.5 (3.1-5.7)
	Lapatinib + Capecitabine			116	41 (32-50)	64 (54-73)	6.8 (5.9-8.2)

Neratinib-induced diarrhea

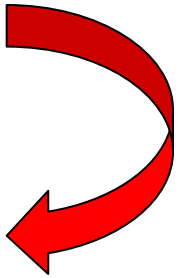
Primary Diarrhea prophylaxis initiated with start of Neratinib therapy significantly reduces the frequency & severity of AEs

Study	Therapy / Indication	Prophylaxis	≥ Grade 3 Diarrhea Rate (%)
202	Trastuzumab-refractory	None	30
2206	Neratinib + Capecitabine	None	26
2205	Neratinib + Temsirolimus	None	23
10-005	Neratinib + Temsirolimus	Imodium 4 mg/day	22
TBCRC 022	Neratinib in CNS+ disease	Imodium 8 mg/day	7.5
NSABP FB-8	Neratinib + Paclitaxel + Trastuzumab	Imodium 16 mg/day	< 5

Neratinib vs. Lapatinib + Capecitabine in Her-2/neu+++ Trastuzumab-Resistant MBC

Randomized Phase II Study (117 vs. 116 patients)

PFS: 4.5 vs. 6.8 months **OS: 19.7 vs. 23.6 months**



Inconclusive Result: **Neither Inferiority nor Non-Inferiority (HR: 1.19)**

BUT: Single-agent clinical activity of Neratinib confirmed

M. Martin et al. Eur J Cancer 2013

Randomized Phase II Trial of Paclitaxel plus Ner or Trastuzumab as First-Line Treatment for HER2+ MBC (NEfERTT)

479 pts, MBC, Her2-positive, First-Line

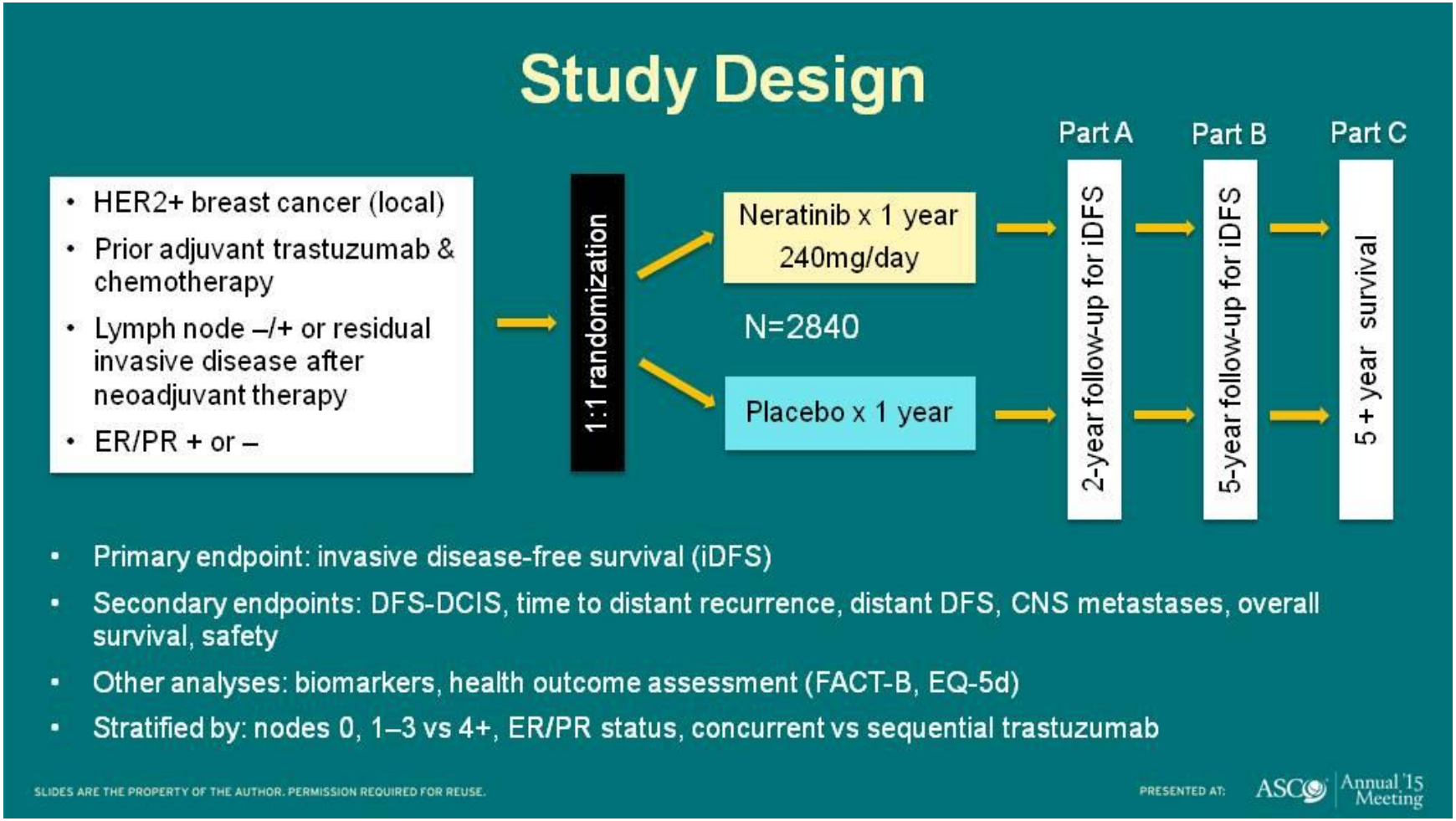
PFS (median) 12.9 Mos. (11.0-4.8) *vs* 12.9Mos. (11.1-14.7)

CNS Progression 8% *versus* 16%; *p*=0.0037

Diarrhoea Grade 3: 30% *vs* 4%

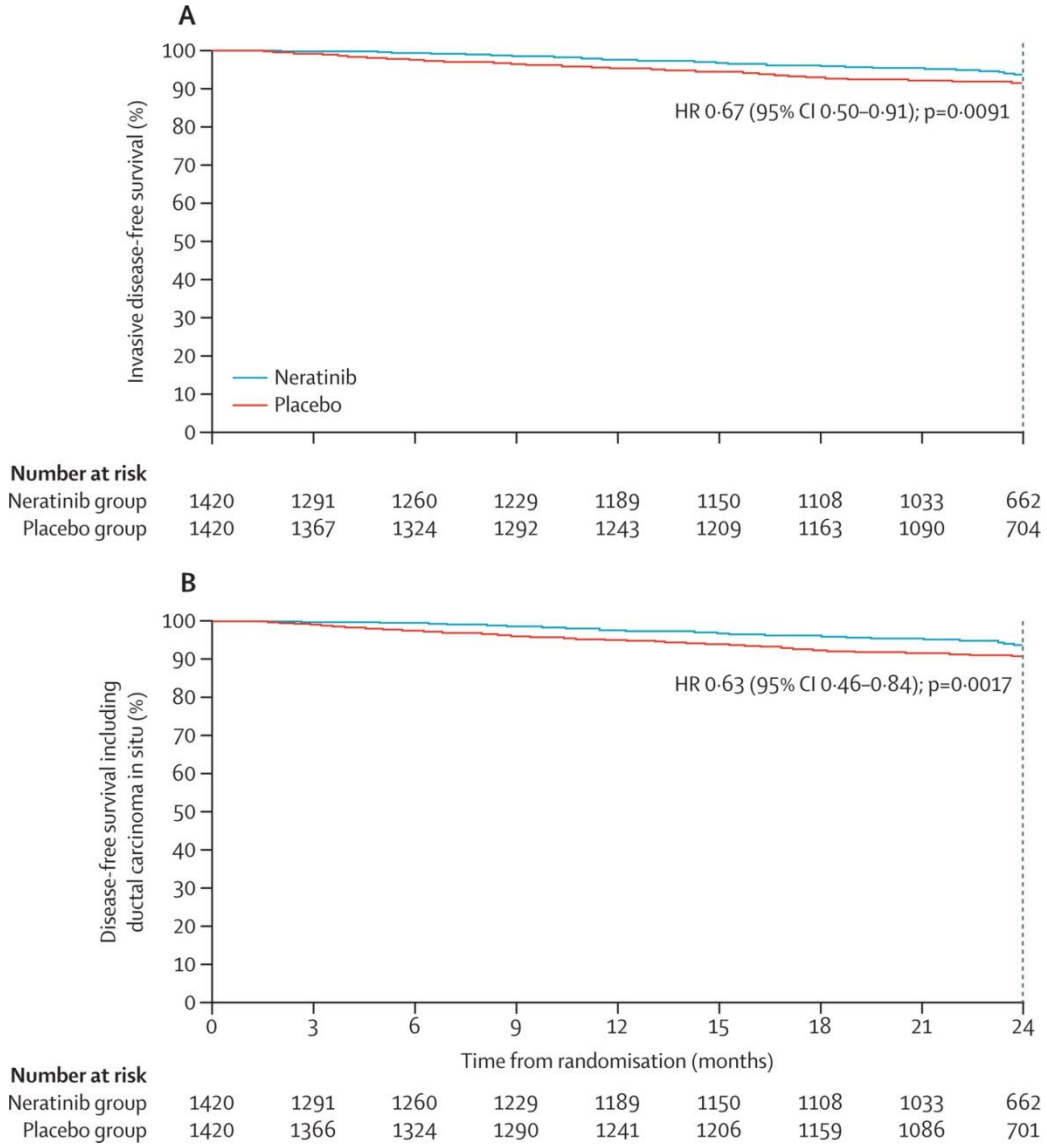
Awada A et al., Proc Am Soc Clin Oncol 2015

One Year Neratinib Extends Invasive DFS in HER2-Positive EBC following Chemo + Trastuzumab: The ExteNET Trial



Chan A et al.
Lancet Oncol 2016

One Year Neratinib Extends Invasive DFS in HER2-Positive EBC following Chemo + Trastuzumab: The ExteNET Trial



Chan A et al.
Lancet Oncol 2016

Neratinib Clinical Development Plan

HER2 AMPLIFICATION / OVEREXPRESSION

3rd line MBC:
- NC vs LC

4th line MBC:
- NT vs N vs PI's choice

Neoadjuvant - breast cancer:
- NSABP FB-7:

[P+T] vs [P+N] vs [P+N+T] > [AC4] > Sx > T for 1yr
- I-SPY2:

[P+N+T] > AC

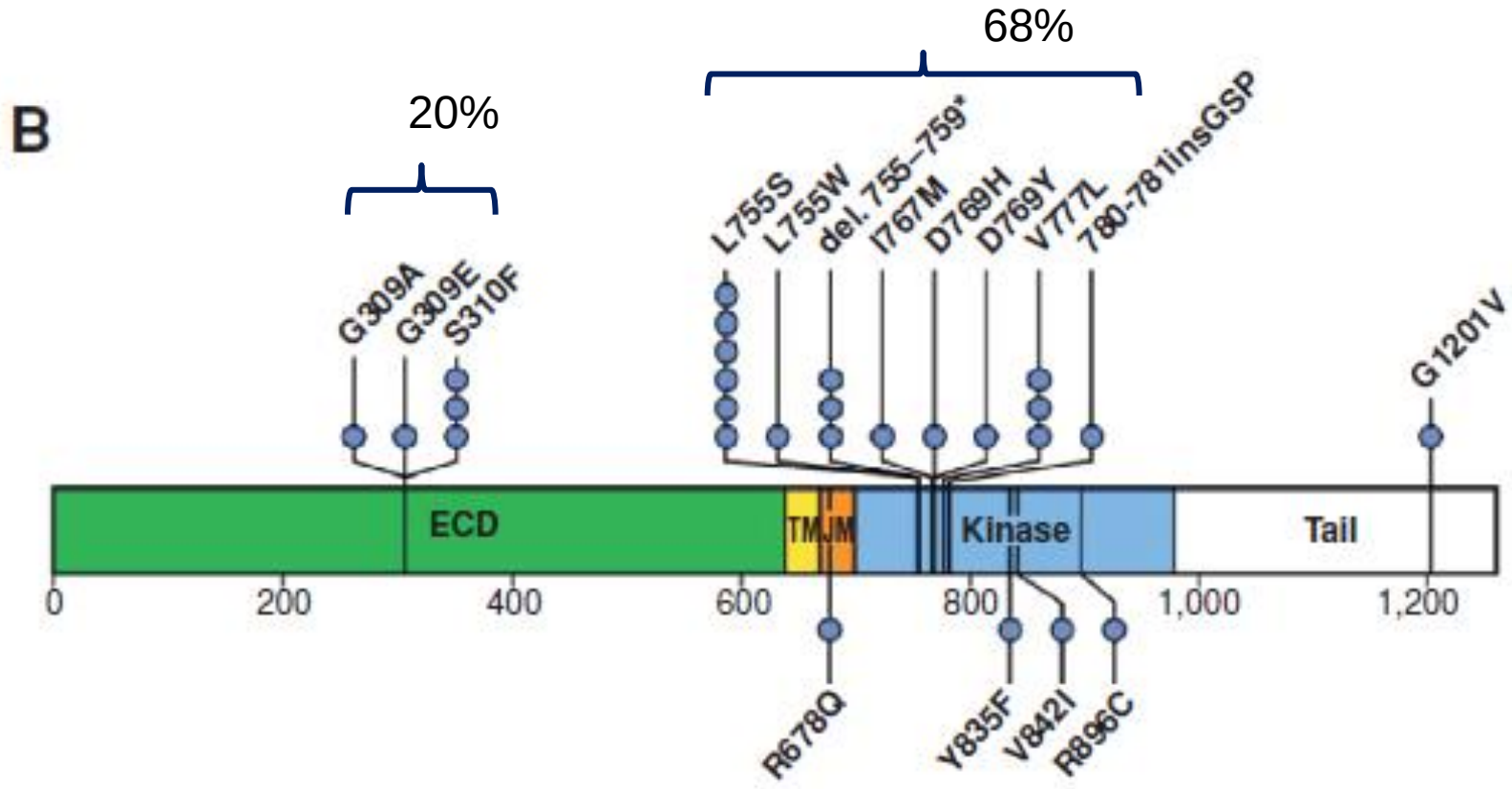
HER2 DRIVER MUTATIONS

N monotherapy:
- "basket" study
- advanced breast cancer
  - WashU
  - Europe

N + temsirolimus:
- NSCLC

HER2 Mutations in HER2 Neg. MBC

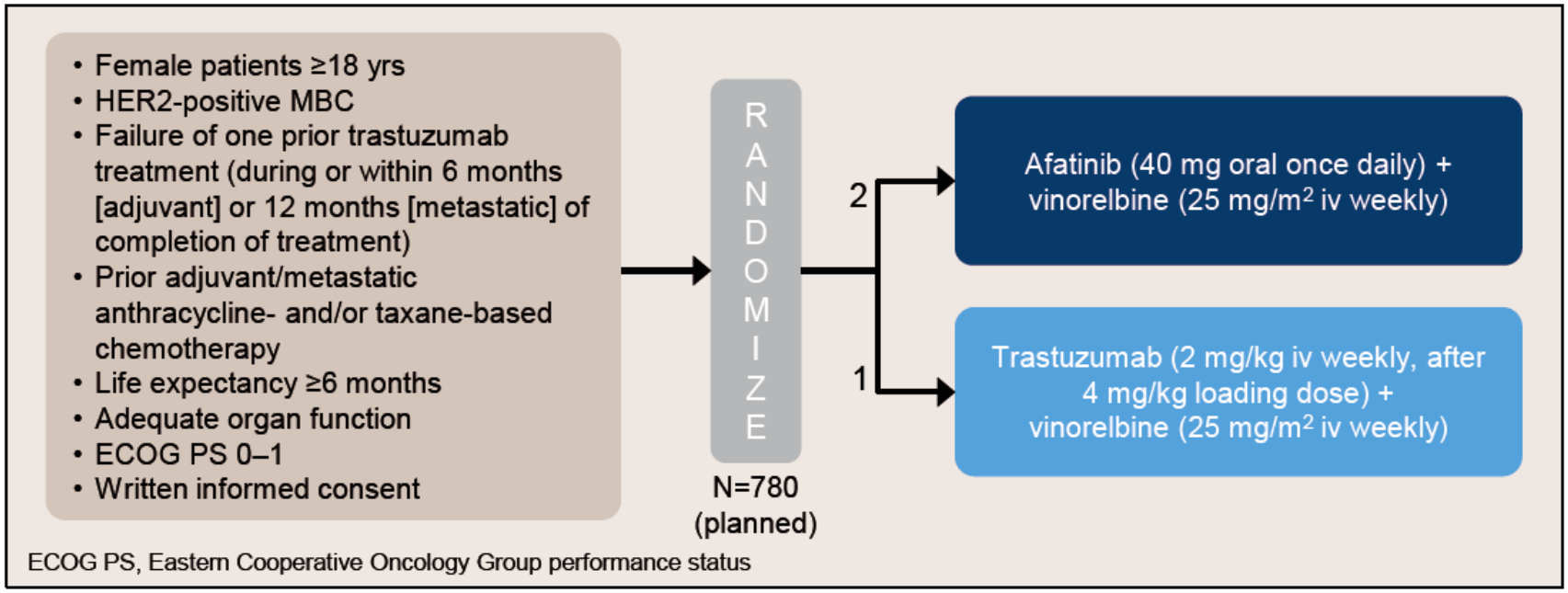
HER2 mutant BC = 1.6% of 220,000 US cases/year = 4000 cases



Afatinib Breast Cancer Program

Randomized Phase III trial of afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing MBC who had progressed on one prior trastuzumab treatment (LUX-Breast 1)

Figure 1. LUX-Breast 1 study design



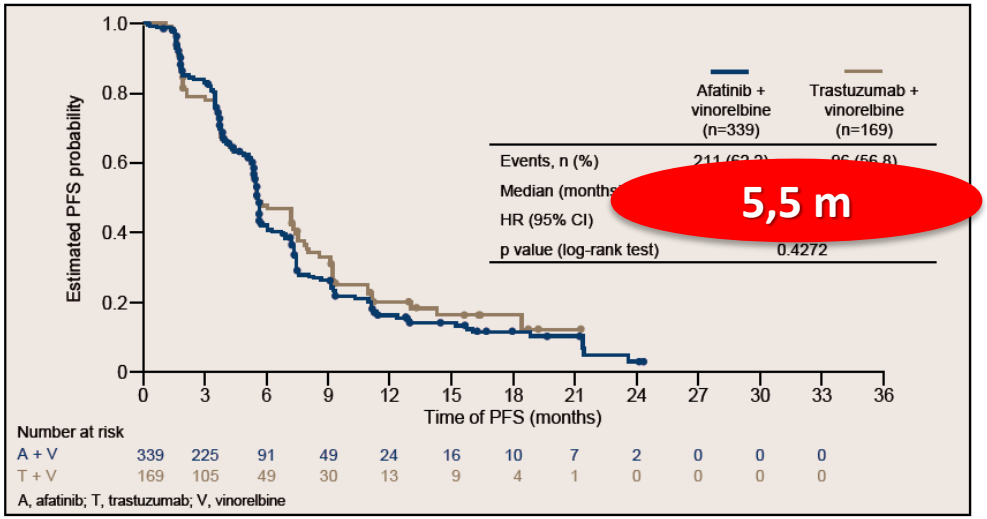
Harbeck N, et al. Lancet Oncol 2016

Afatinib Breast Cancer Program

Randomized Phase III trial of afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing MBC who had progressed on one prior trastuzumab treatment (LUX-Breast 1)

	Afatinib + VNB	Trastu + VNB
Dose reduction	55.2%	3.0%
Discontinuation	15.4%	7.1%
Fatal AE	5.3%	3.0%
G ≥ 3 diarea	17.8%	0%
G ≥ 3 acne	4.7%	0%

Figure 2. PFS for all randomized patients (data cut-off June 2013)



Harbeck N, et al. Lancet Oncol 2016

Afatinib vs Afatinib + VNB vs TPC

- Female patients ≥18 years
- HER2-overexpressing MBC
- CNS recurrence/progression during or after trastuzumab and/or lapatinib therapy
- ≥1 measurable and progressive CNS lesion (≥10 mm on MRI) after prior systemic and/or radiation therapy
- Adequate organ function
- ECOG PS 0–2

RANDOMIZE

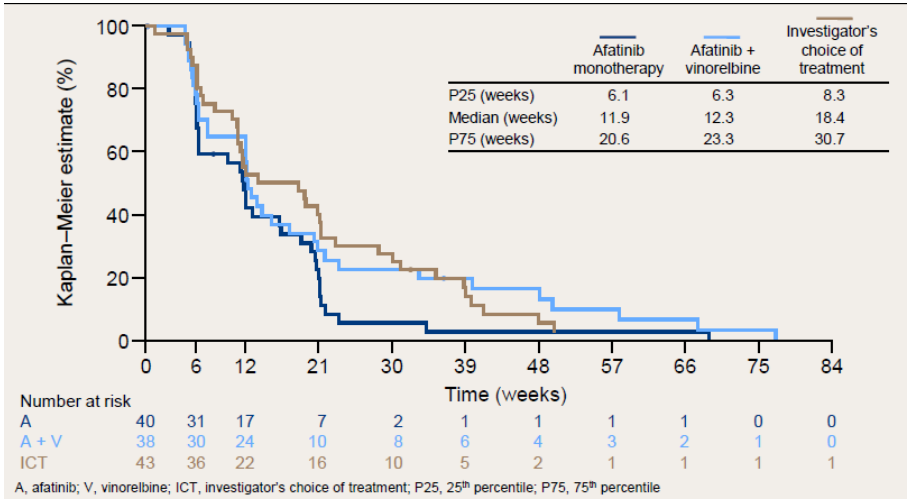
1 → Afatinib (40 mg oral once daily)*

1 → Afatinib (40 mg oral once daily) + vinorelbine (25 mg/m² iv weekly)

1 → Investigator's choice of treatment (any chemotherapy and/or other medical treatment approved for MBC)

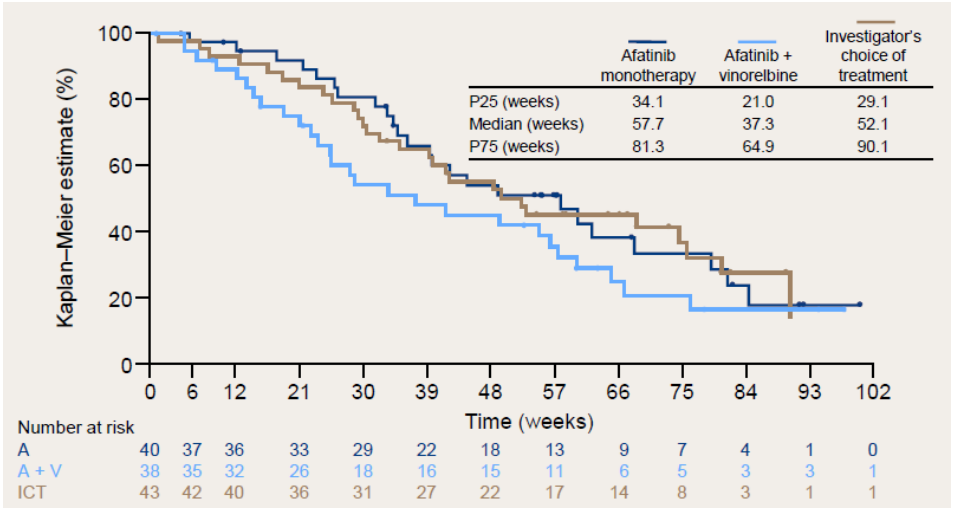
*If well tolerated in cycle 1, dose could be increased to 50 mg
iv, intravenous

PFS



A, afatinib; V, vinorelbine; ICT, investigator's choice of treatment; P25, 25th percentile; P75, 75th percentile

OS

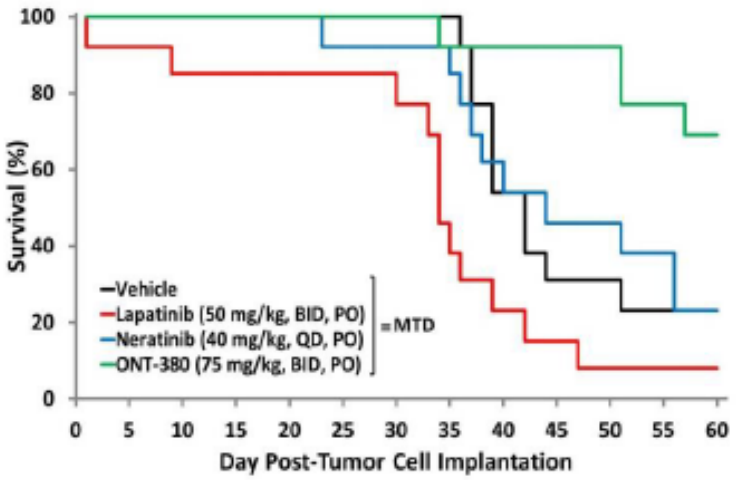


Cortes et al, Lancet Oncol 2015

ONT-380: an Oral HER2-Specific Inhibitor

- ONT-380 is a HER2 selective small molecule tyrosine kinase inhibitor with nanomolar potency
  - 500-fold more selective for HER2 compared to EGFR
  - HER2 IC_{50}: 8 nM; EGFR IC_{50}: 4000 nM
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
- In a model of HER2+ CNS metastases, ONT-380 was associated with improved survival compared to either lapatinib or neratinib (Figure 1)
- ONT-380 is currently being evaluated in two ongoing Phase 1b combination studies [+ T-DM1 and ± capecitabine [C] ± trastuzumab [T])

Figure 1 BT-474 CNS Metastases Model



Dinkel et al, AACR 2012

Dinkel et al, AACR 2012

ONT-380 Breast Cancer Program

- **ONT-380-004: Phase 1b, open-label study of ONT-380 + ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1)**
  - **Population: Patients with HER2+ breast cancer with progression after prior therapy with both T and a taxane**

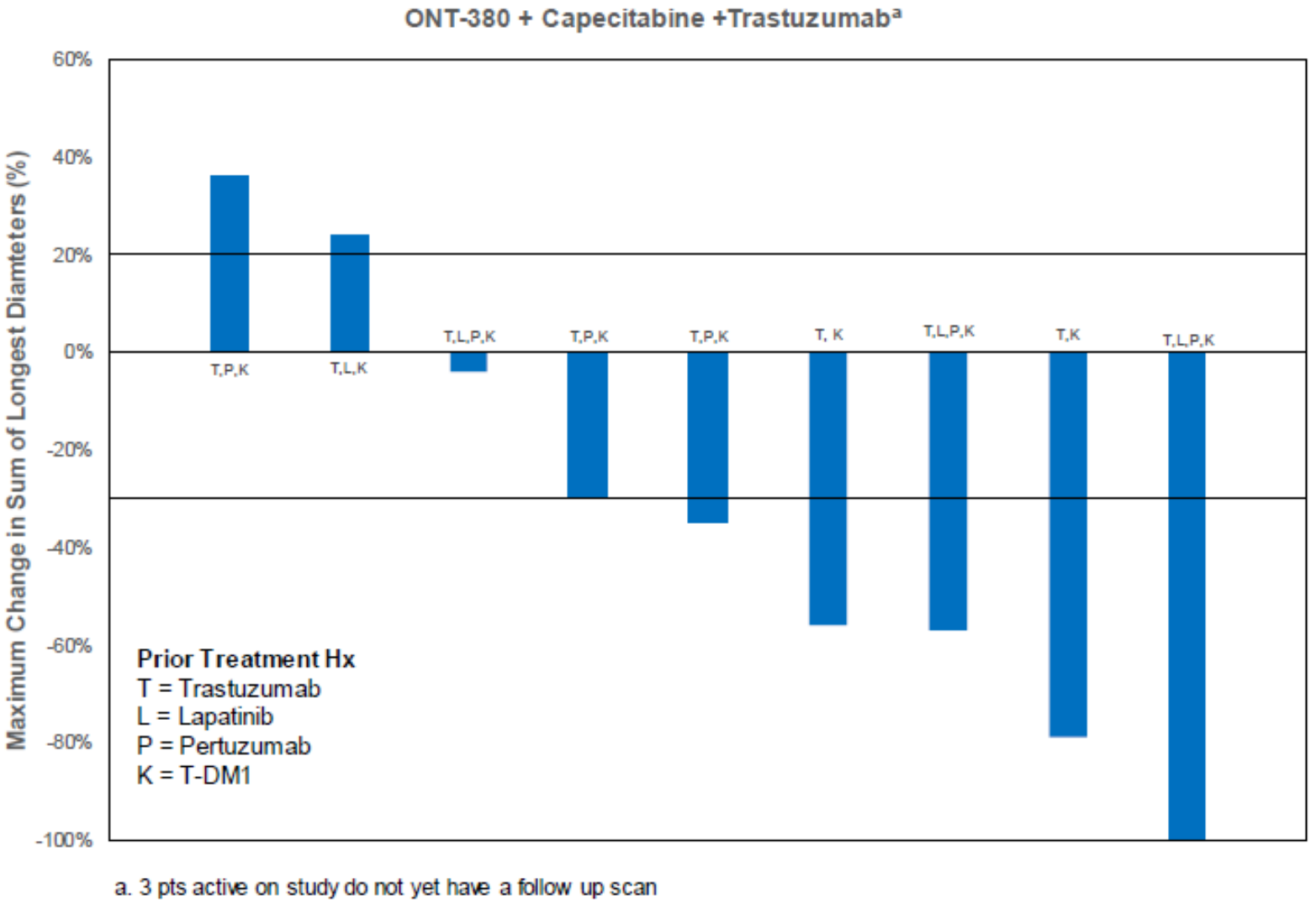
- **ONT-380-005: Phase 1b, open-label study of ONT-380 +/- C and +/- T**
  - **Population: Patients with HER2+ breast cancer with progression after prior therapy with both T and T-DM1**

	ONT-380 +					
	C (n = 7)		T (n = 13)		C + T (n = 12)	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Diarrhea	5	0	8	0	8	0
Nausea	4	0	3	0	7	0
Constipation	4	0	5	0	2	0
Fatigue	5	0	1	0	4	0
PPE	4	1	0	0	6	0
Vomiting	2	0	2	0	4	0

No Grade 4 or 5 AEs among most common AEs

Hamilton et al, ASCO 2015

ONT-380 + Capecitabine + Trastuzumab

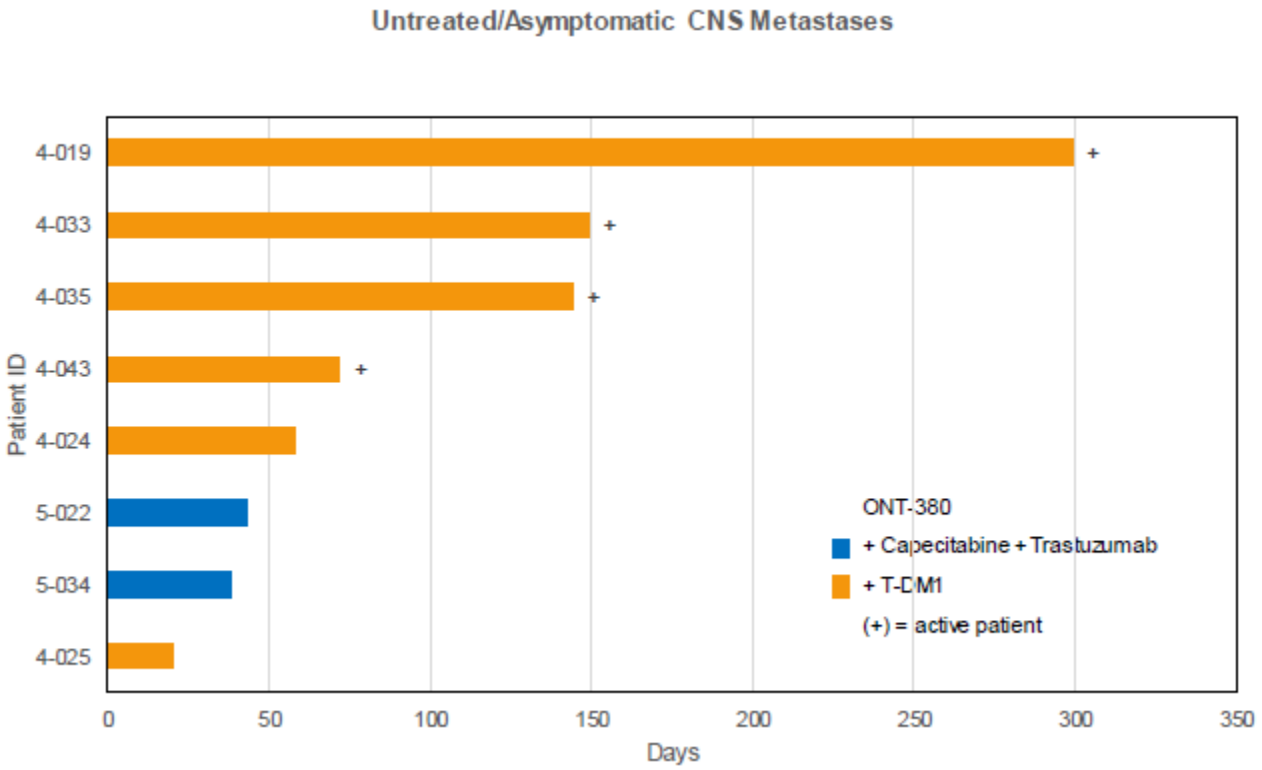


a. 3 pts active on study do not yet have a follow up scan

Hamilton et al, ASCO 2015

ONT-380 + Capecitabine + Trastuzumab
ONT-380 + TDM1

- Untreated, asymptomatic lesions in patients who had never received radiotherapy or surgery to the CNS
- Progressive or new lesions in patients who had received previous radiotherapy and/or surgery to the CNS



Ferrario et al, ASCO 2015

ONT-380 + Capecitabine + Trastuzumab
ONT-380 + TDM1

- Untreated, asymptomatic lesions in patients who had never received radiotherapy or surgery to the CNS
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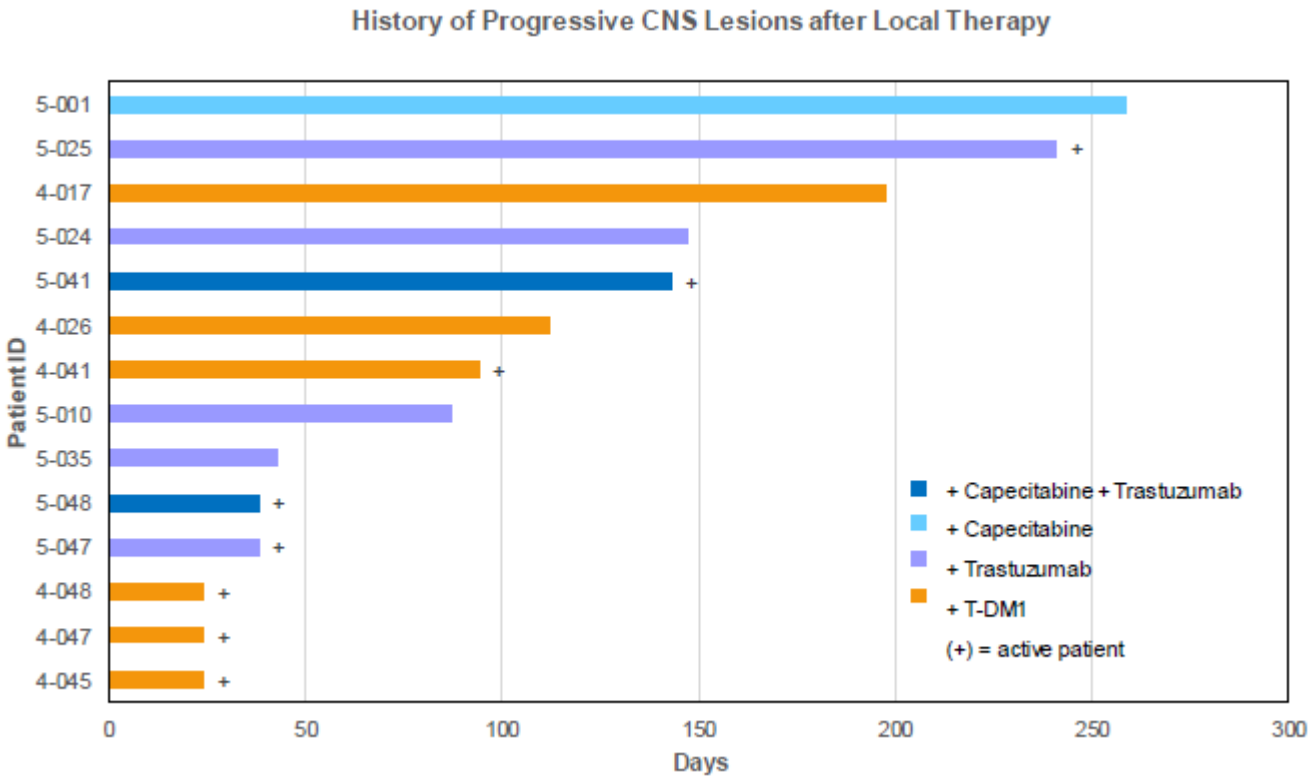
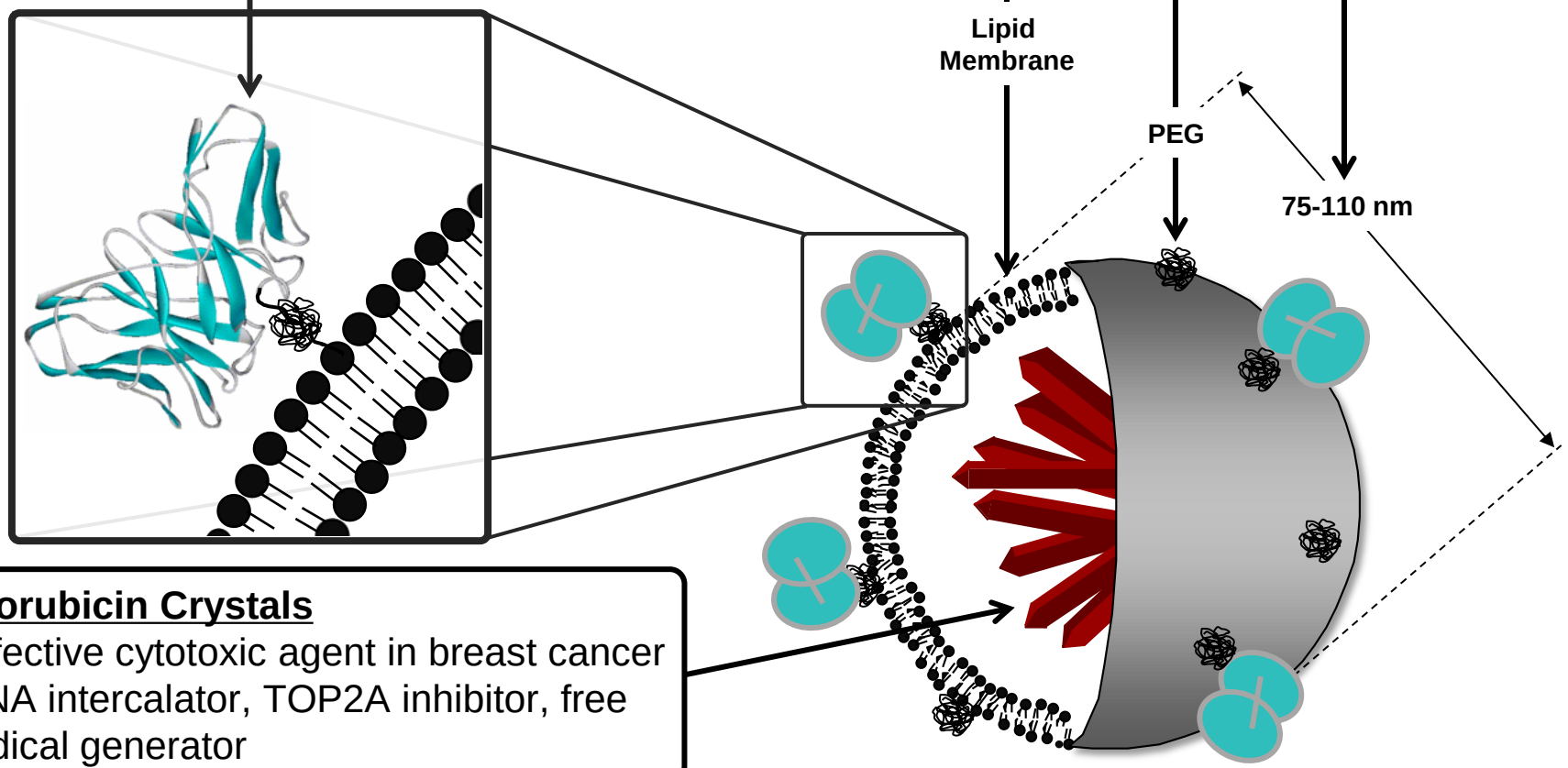


Ferrario et al, ASCO 2015

MM-302: HER2-targeted PEGylated liposomal doxorubicin

anti-HER2 scFv
- Targets liposome to HER2-overexpressing cells
- Promotes internalization
- Binds to a different epitope than trastuzumab
- Does not bind to cardiomyocytes

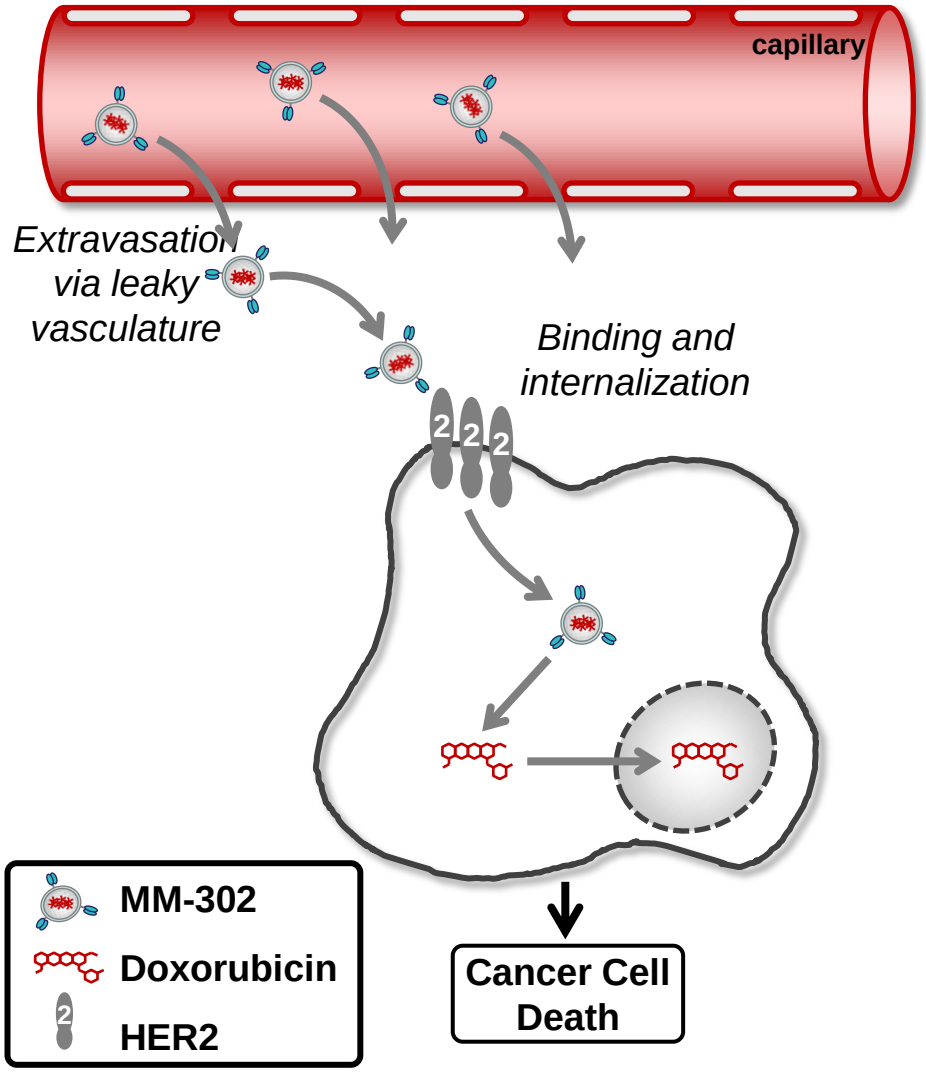
Liposome
- Extended half-life
- Stably encapsulates doxorubicin
- Passive accumulation in tumors
- Size precludes delivery to cardiac tissue



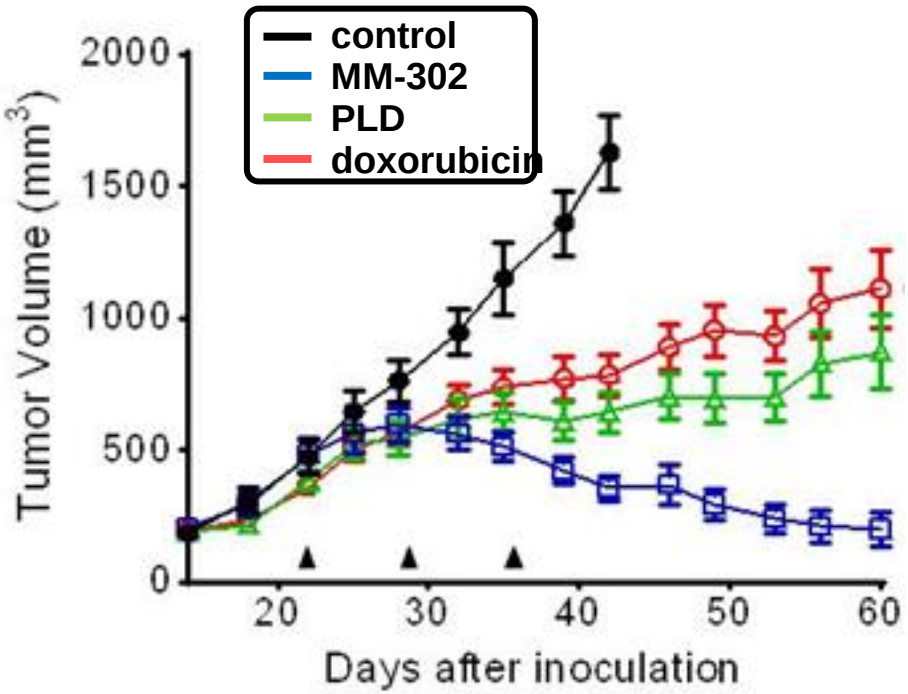
Doxorubicin Crystals
- Effective cytotoxic agent in breast cancer
- DNA intercalator, TOP2A inhibitor, free radical generator

MM-302: Proposed mechanism of action

HER2-positive tumor

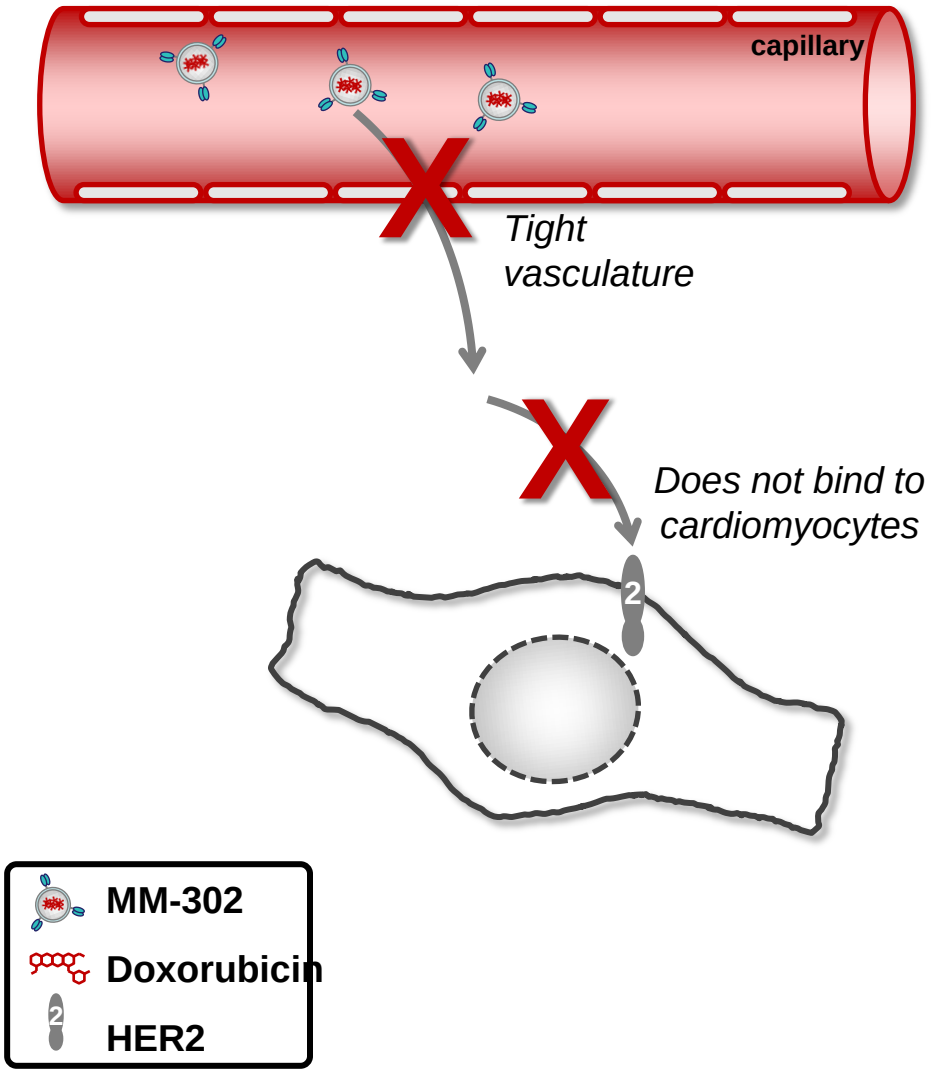


SUM190 cells (HER2-positive)

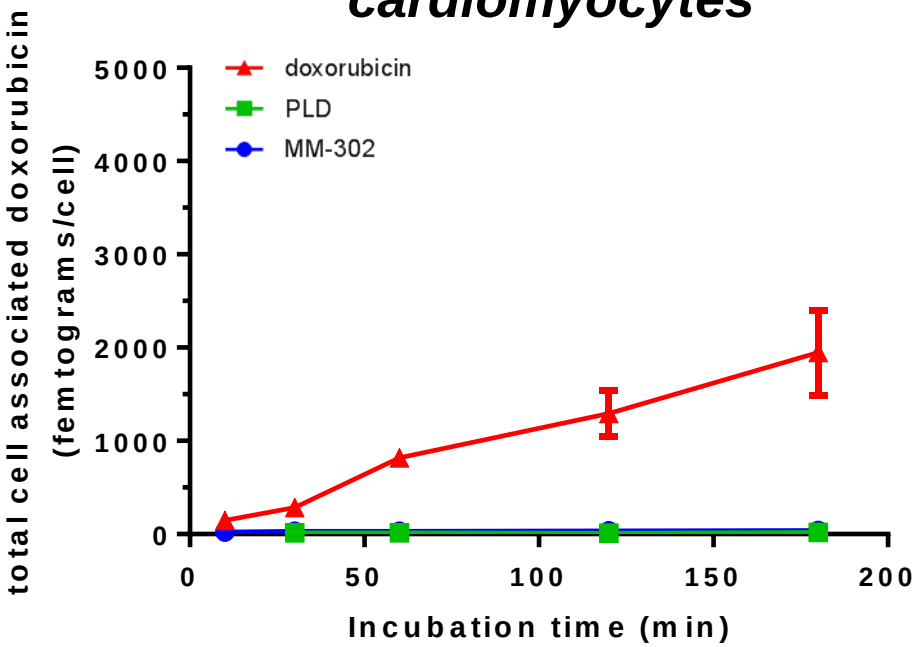


MM-302: Proposed mechanism of action

Cardiac tissue



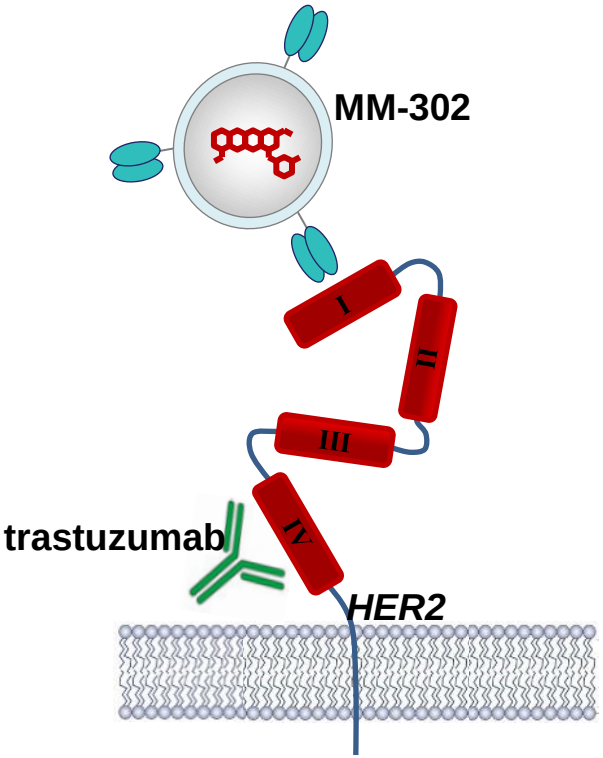
Human stem cell-derived cardiomyocytes

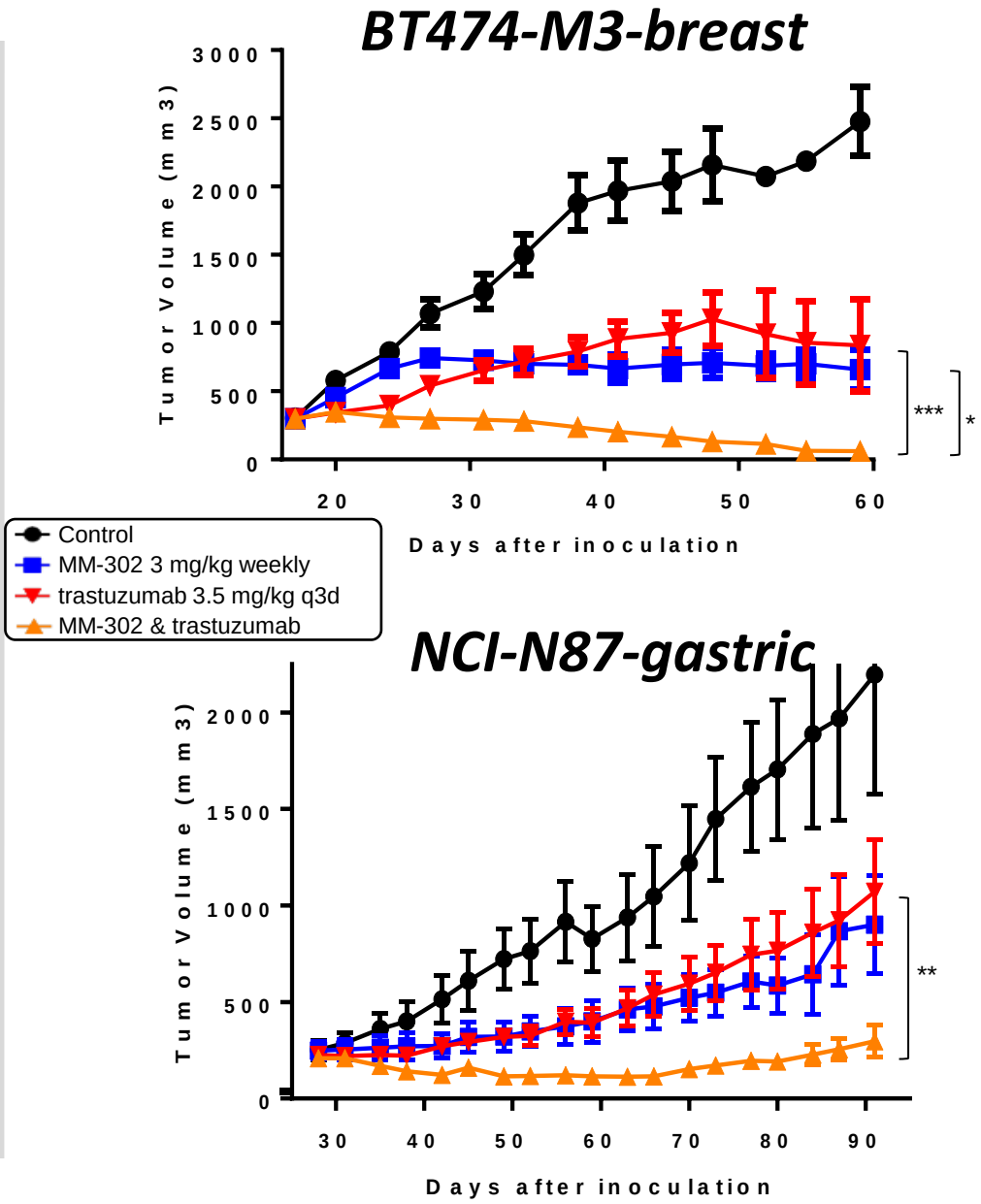


Reynolds et al., Toxicol Appl Pharmacol 2012

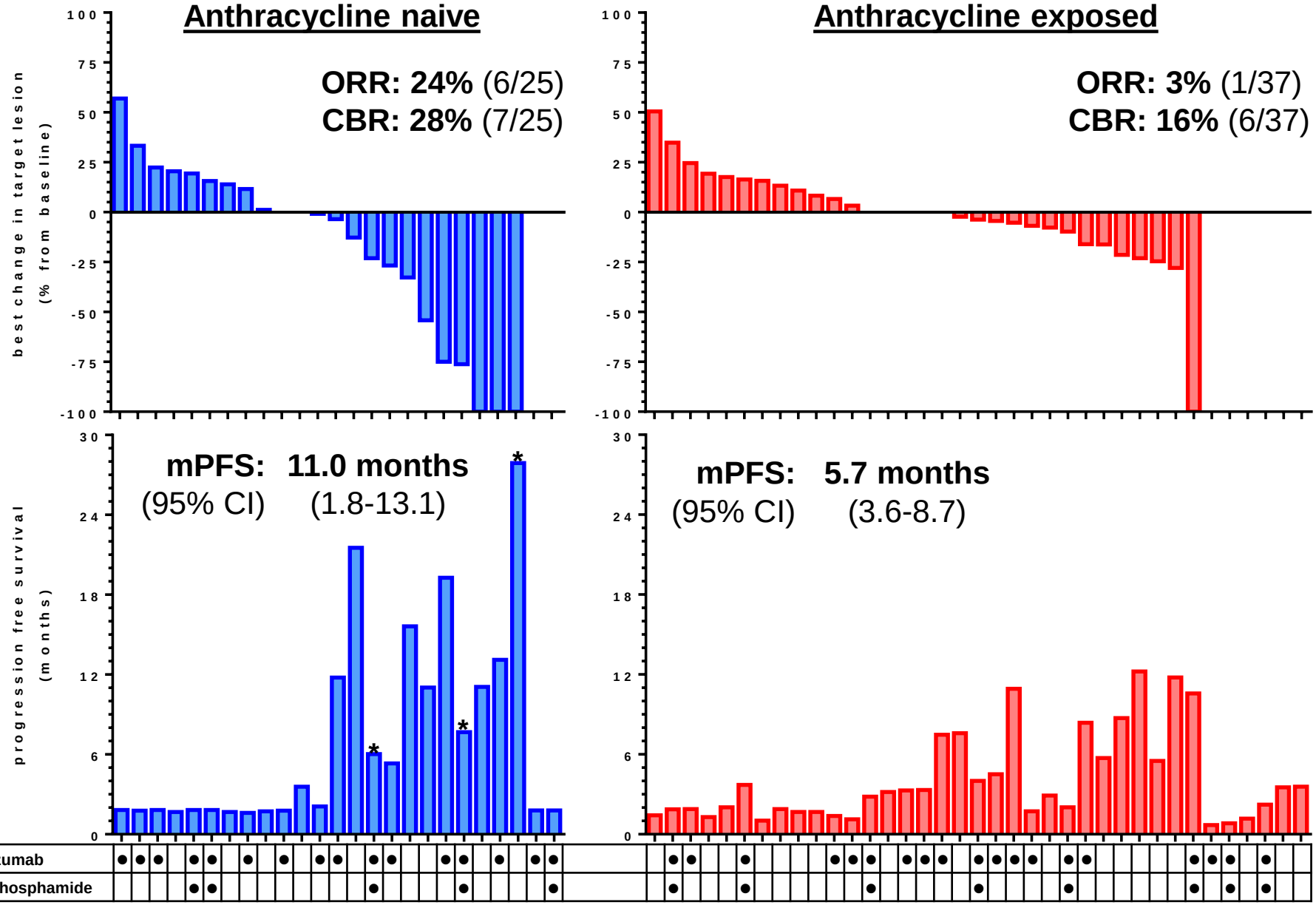
MM-302: Proposed mechanism of action

MM-302 binds to a different epitope than trastuzumab



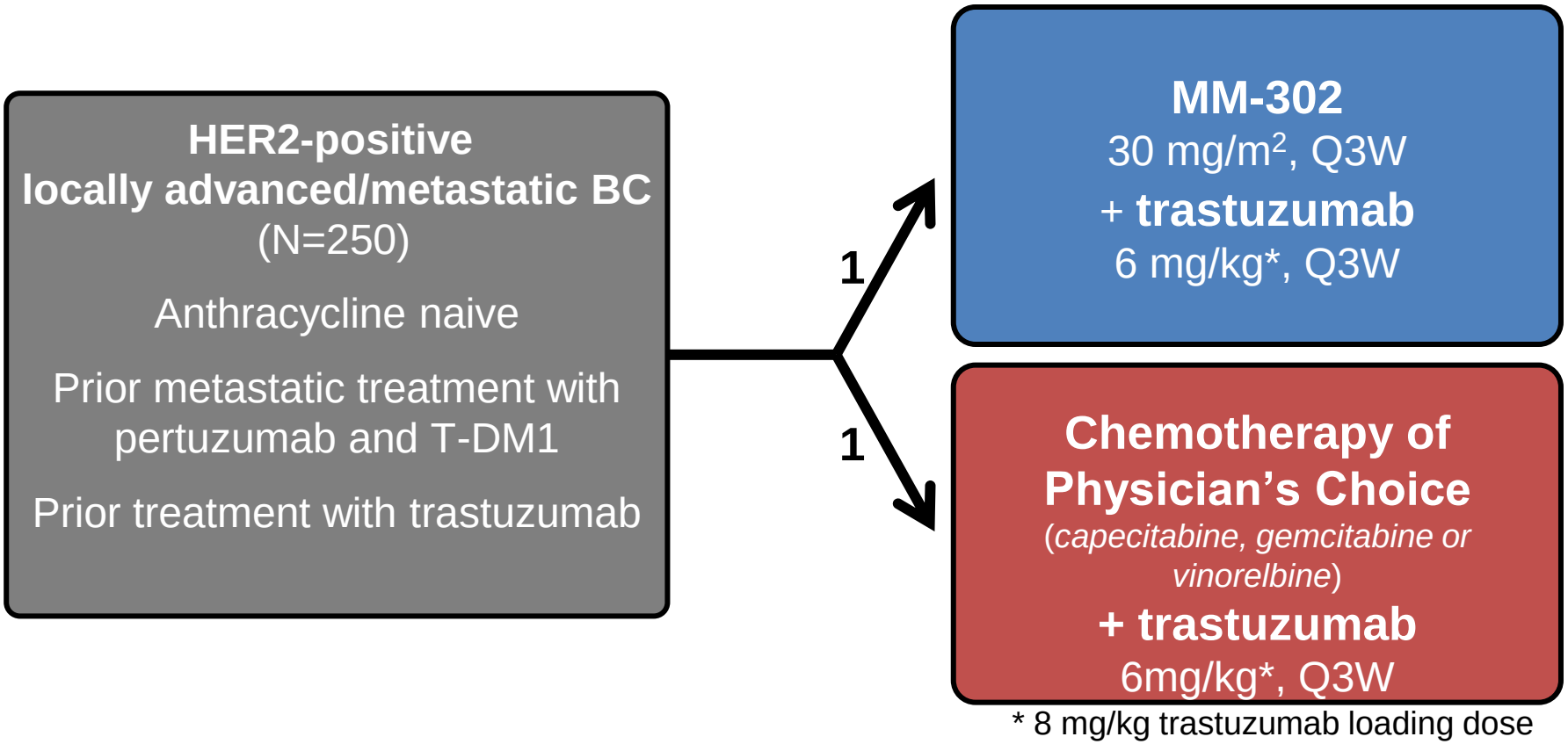


MM-302: Data from phase I study



*: patients still on study, ORR: Overall Response Rate, CBR: Clinical Benefit Rate (CR, PR and Stable Disease (SD) at 24 weeks)

HERMIONE Study Schema (NCT02213744)



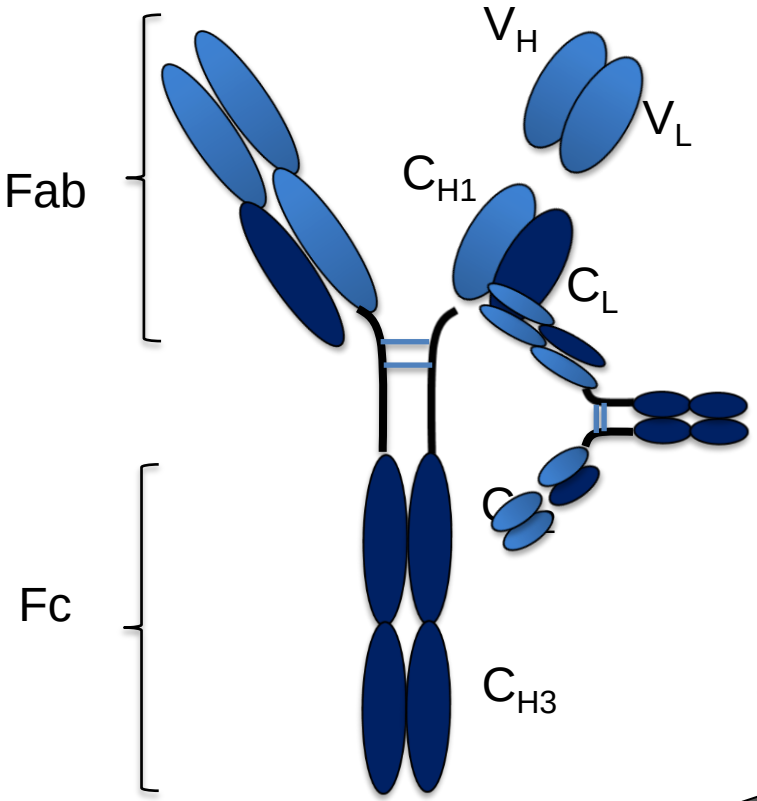
* 8 mg/kg trastuzumab loading dose

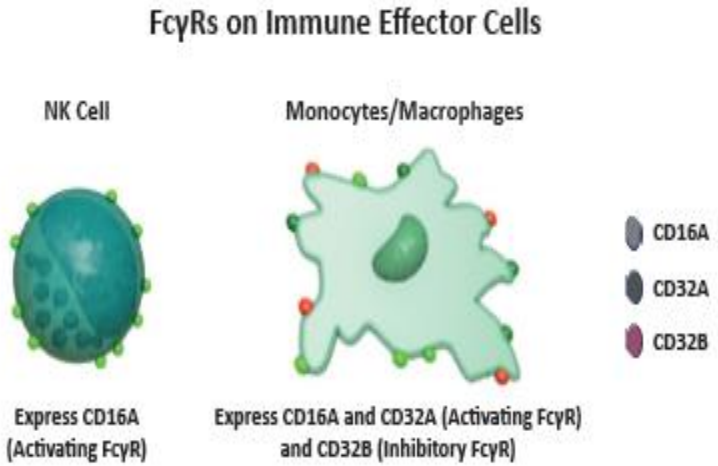
- 70 participating sites (46 in the US, 4 in Canada and 20 in Europe)
- Study currently open and enrolling patients
- Enrollment expected to be completed late 2017

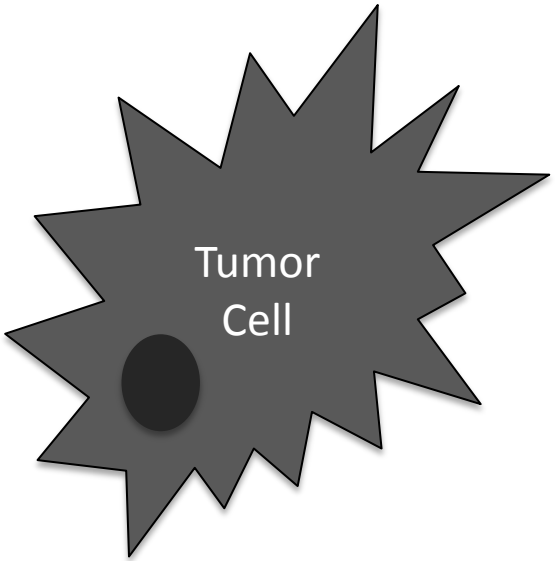
Margetuximab

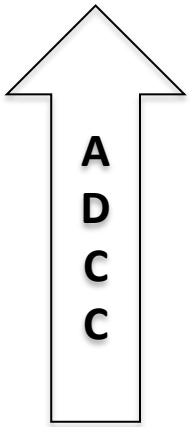
To evaluate the safety of margetuximab using two dosing regimens

Trastuzumab





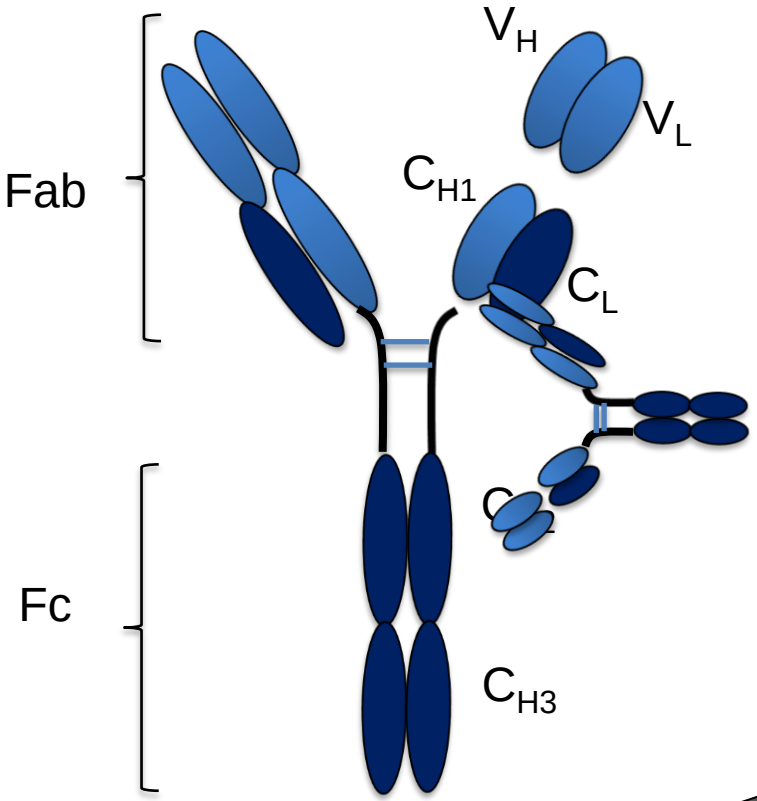


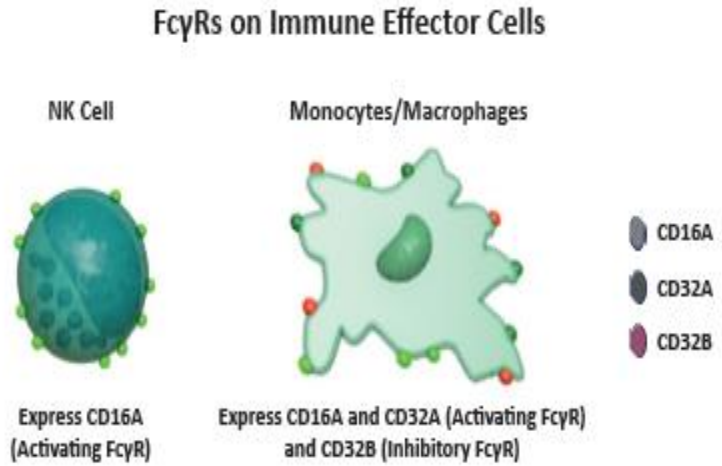


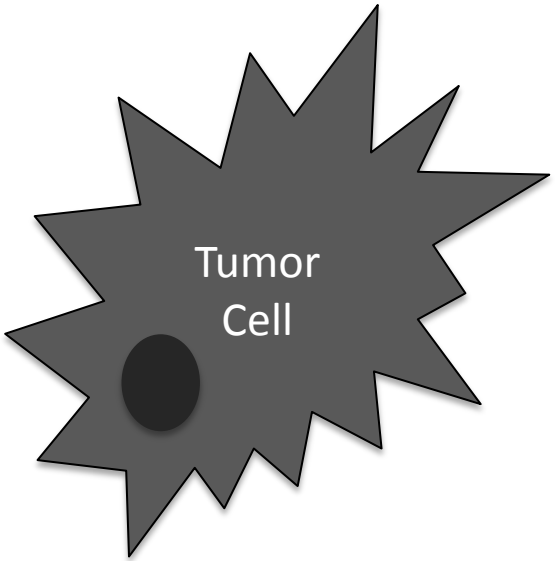
Margetuximab

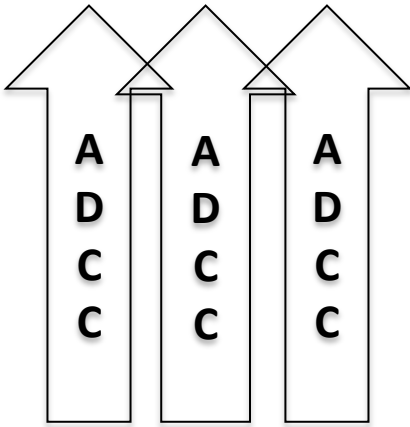
To evaluate the safety of margetuximab using two dosing regimens

Margetuximab



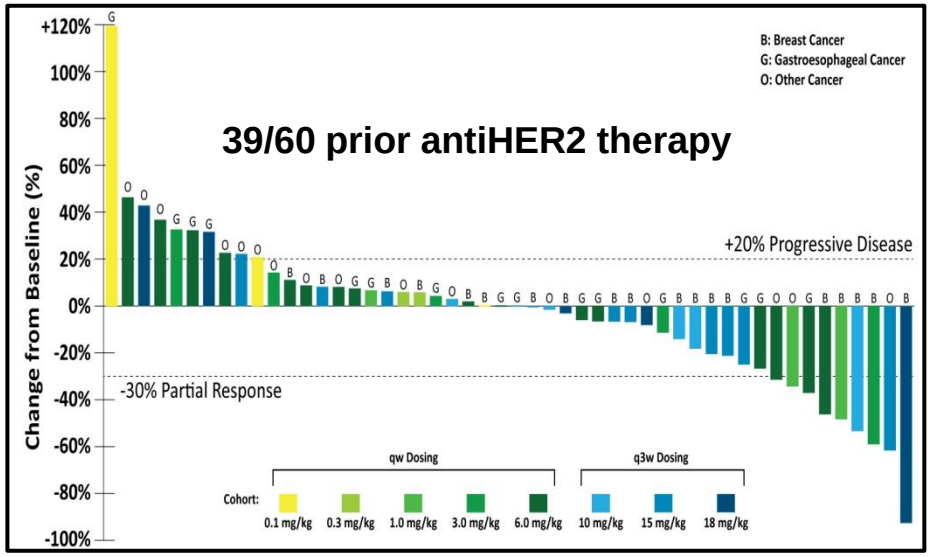




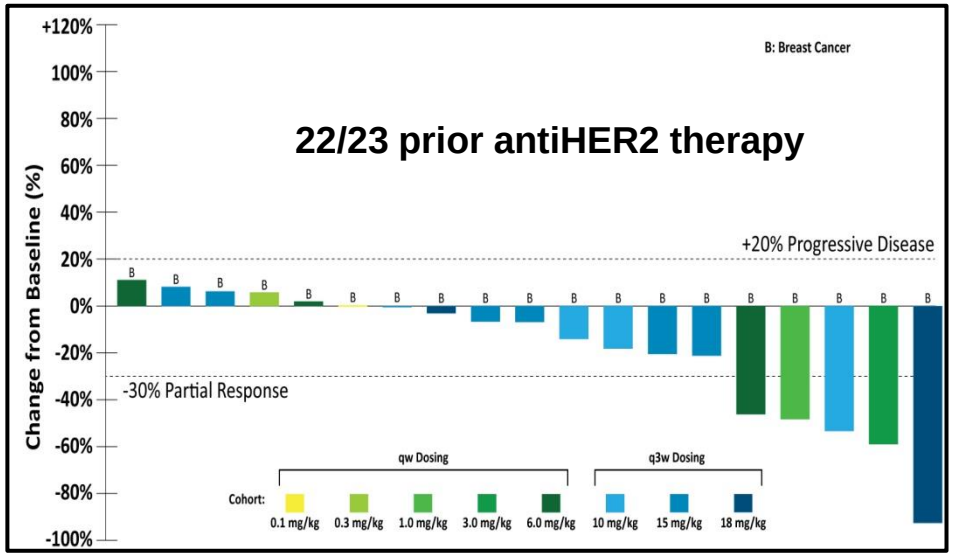


FIH phase 1 Study with Margetuximab

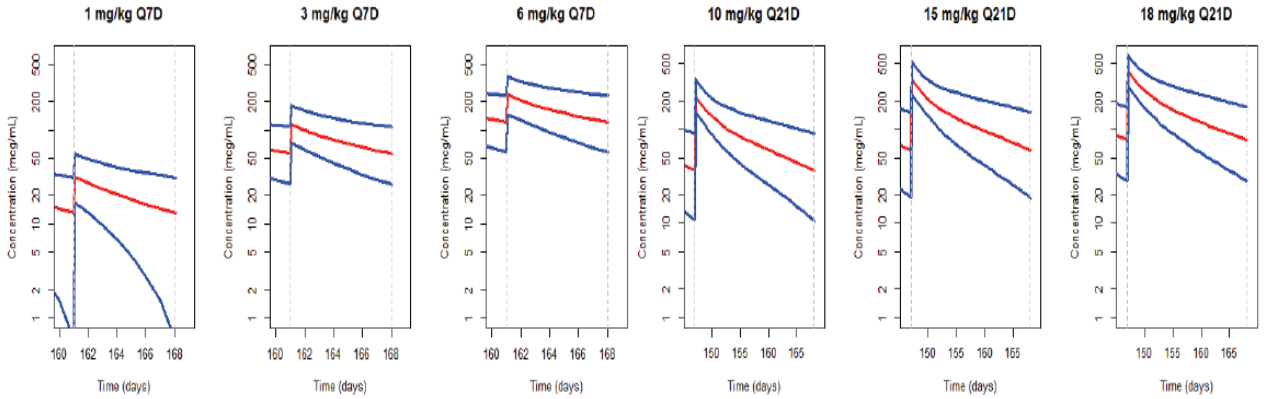
All evaluable pts



Evaluable MBC

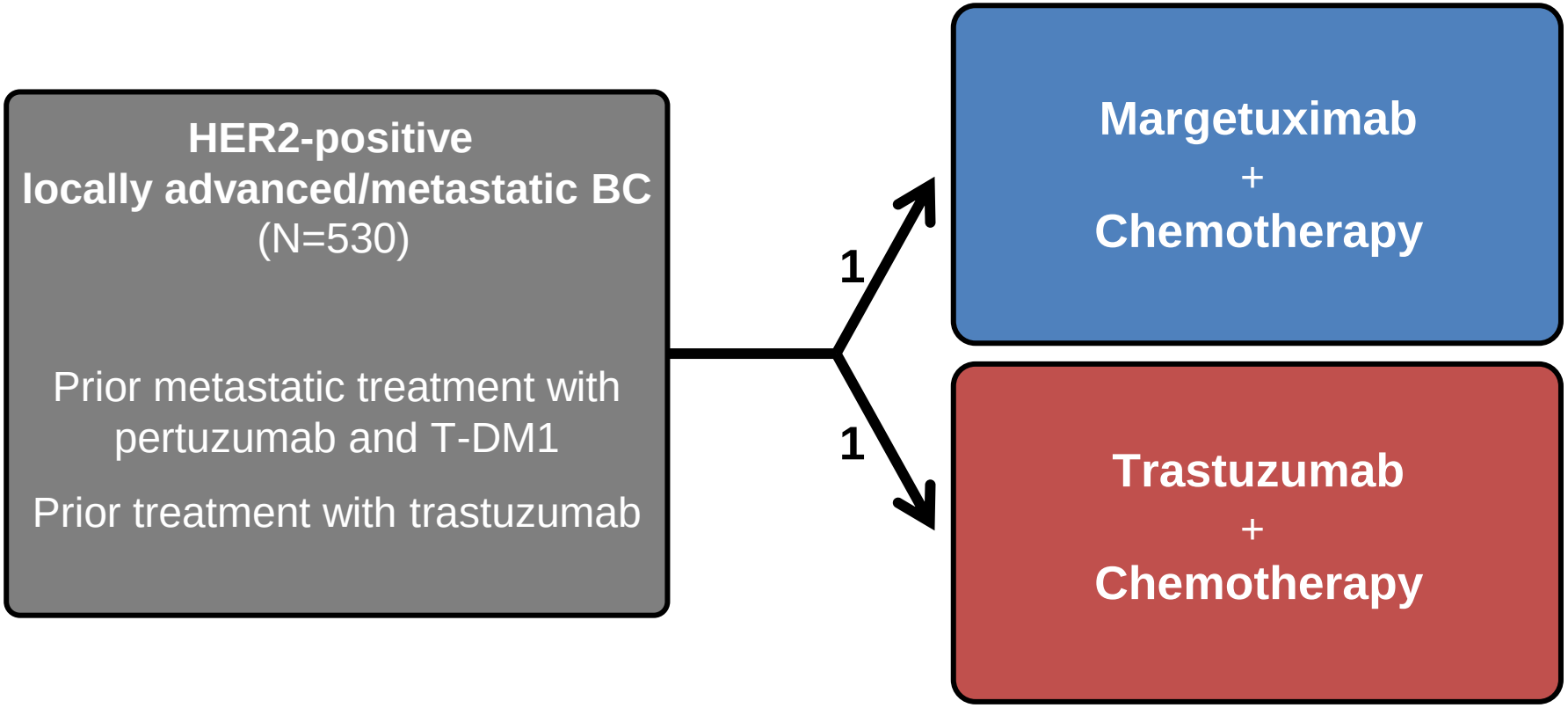


Pharmacokinetics

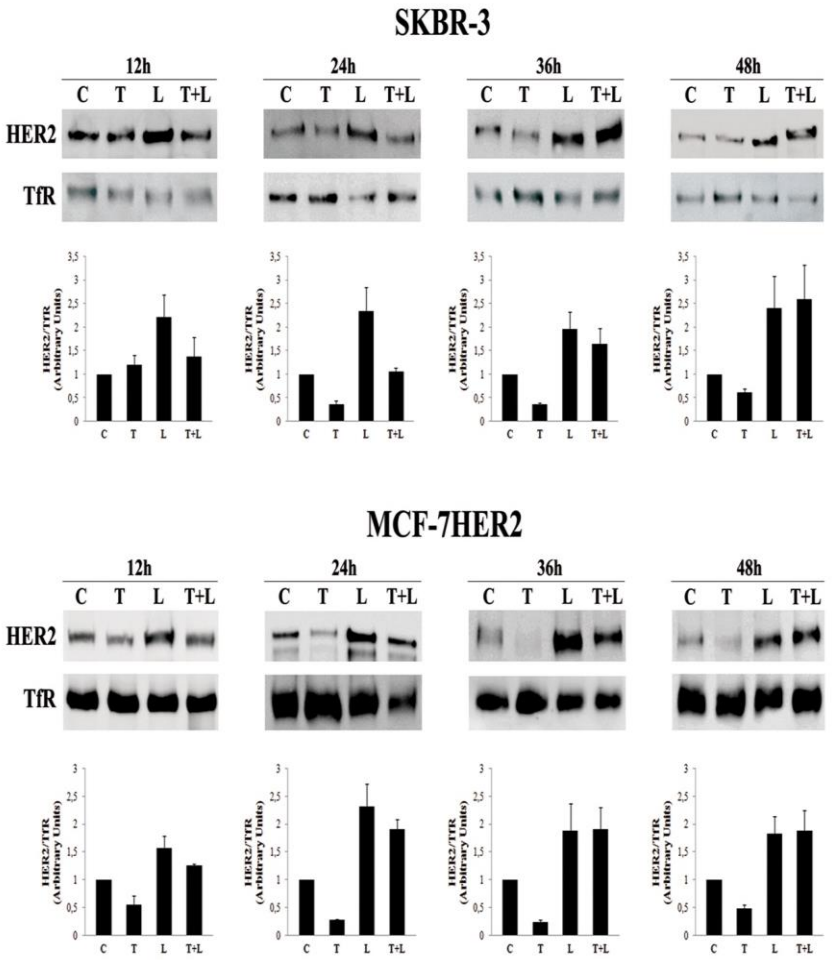


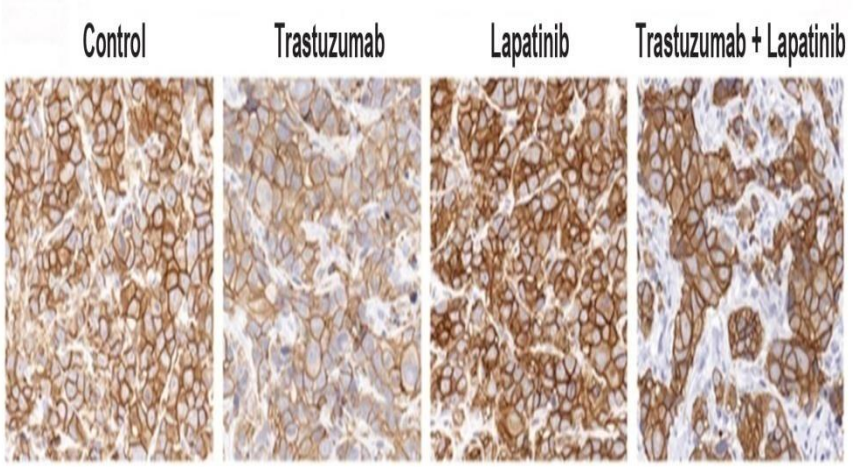
Burris HA, et al. ASCO 2015

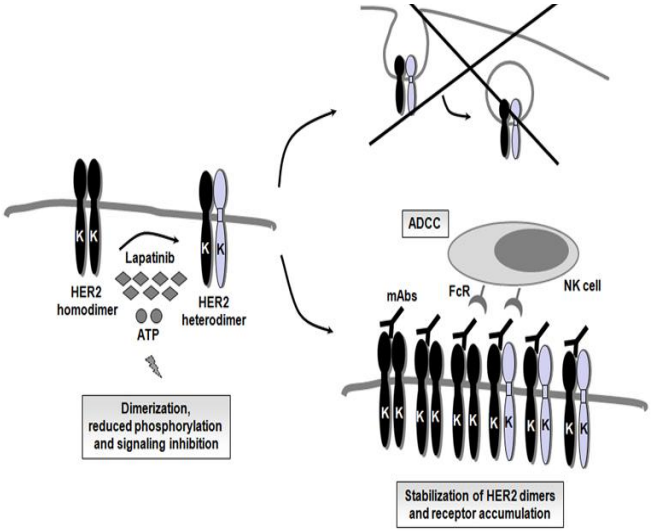
SOPHIA phase III Study Schema



New opportunities with Margetuximab

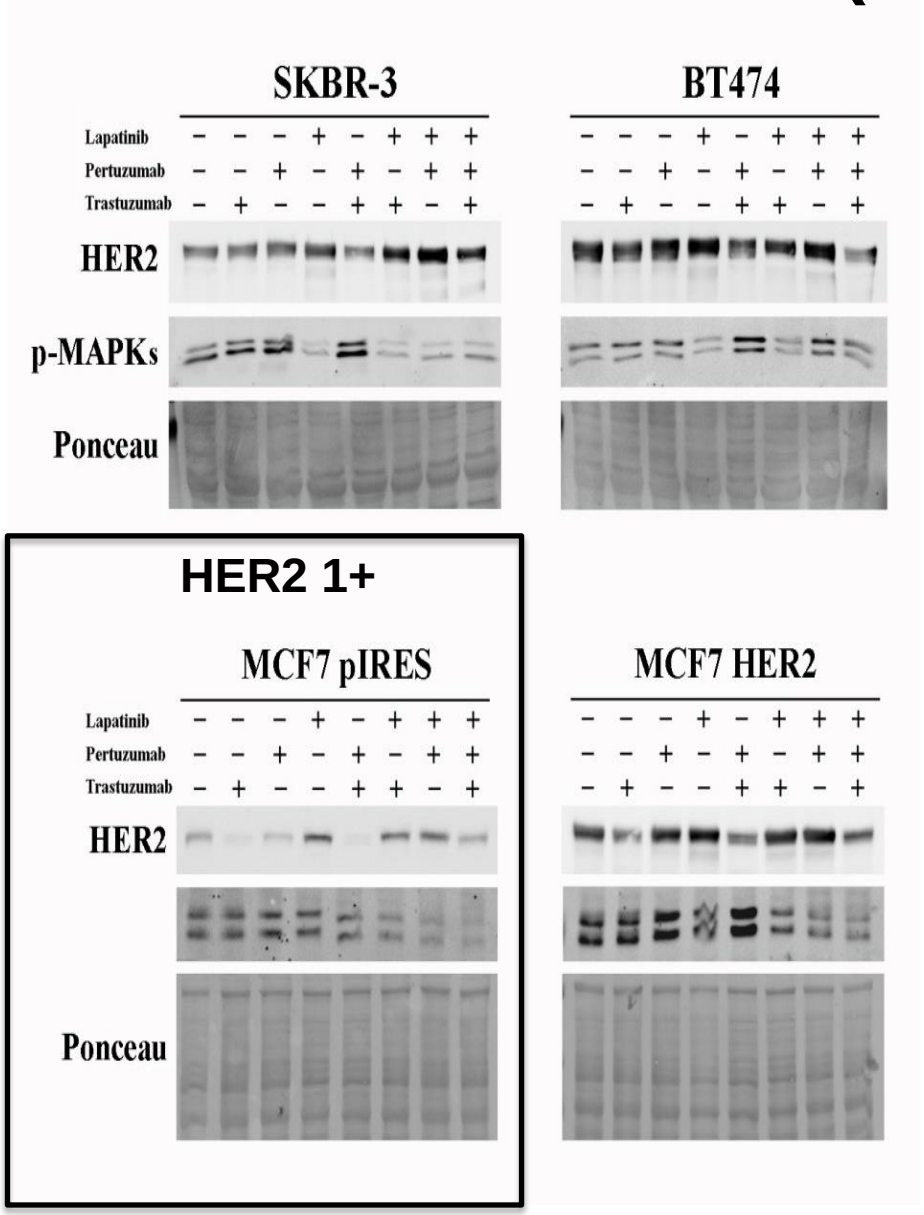






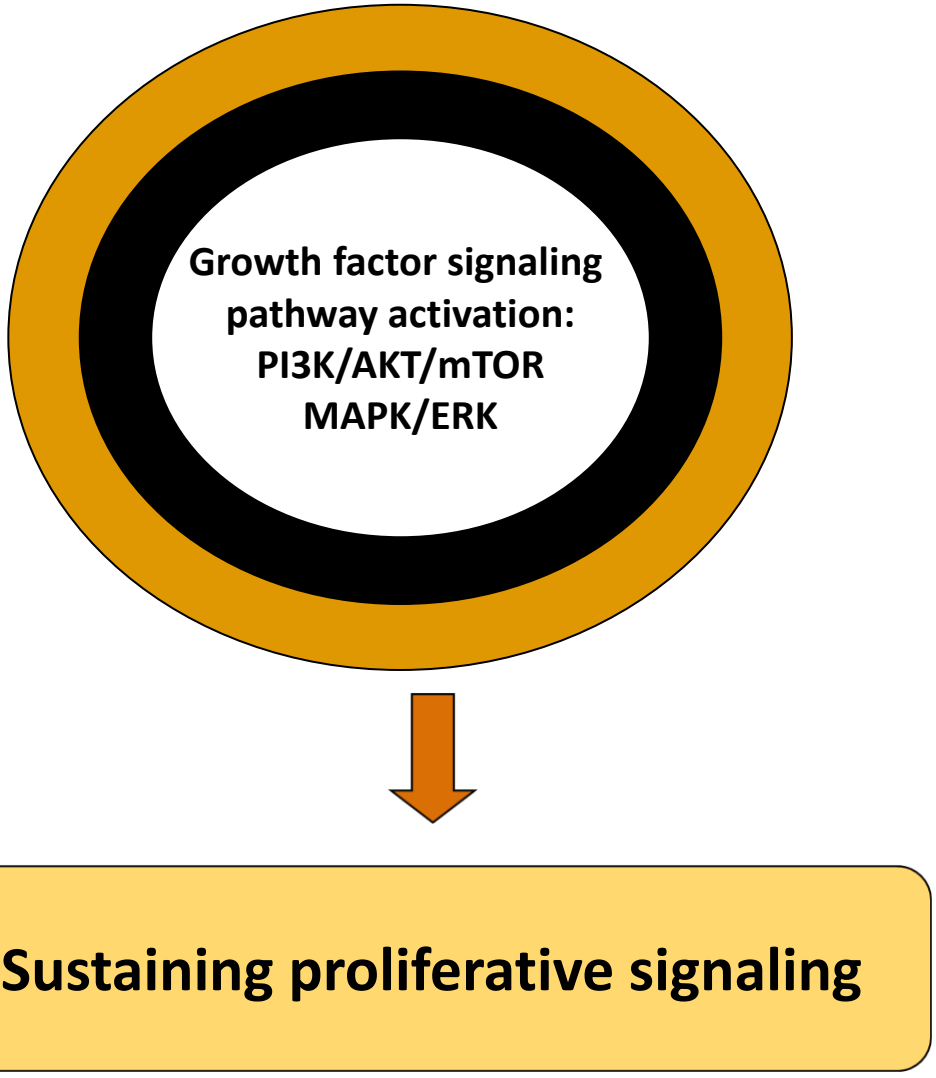
Scaltriti M, et al. Oncogene 2009; 28:803

Margetuximab in HER2 1+/2+ (FISH neg)?

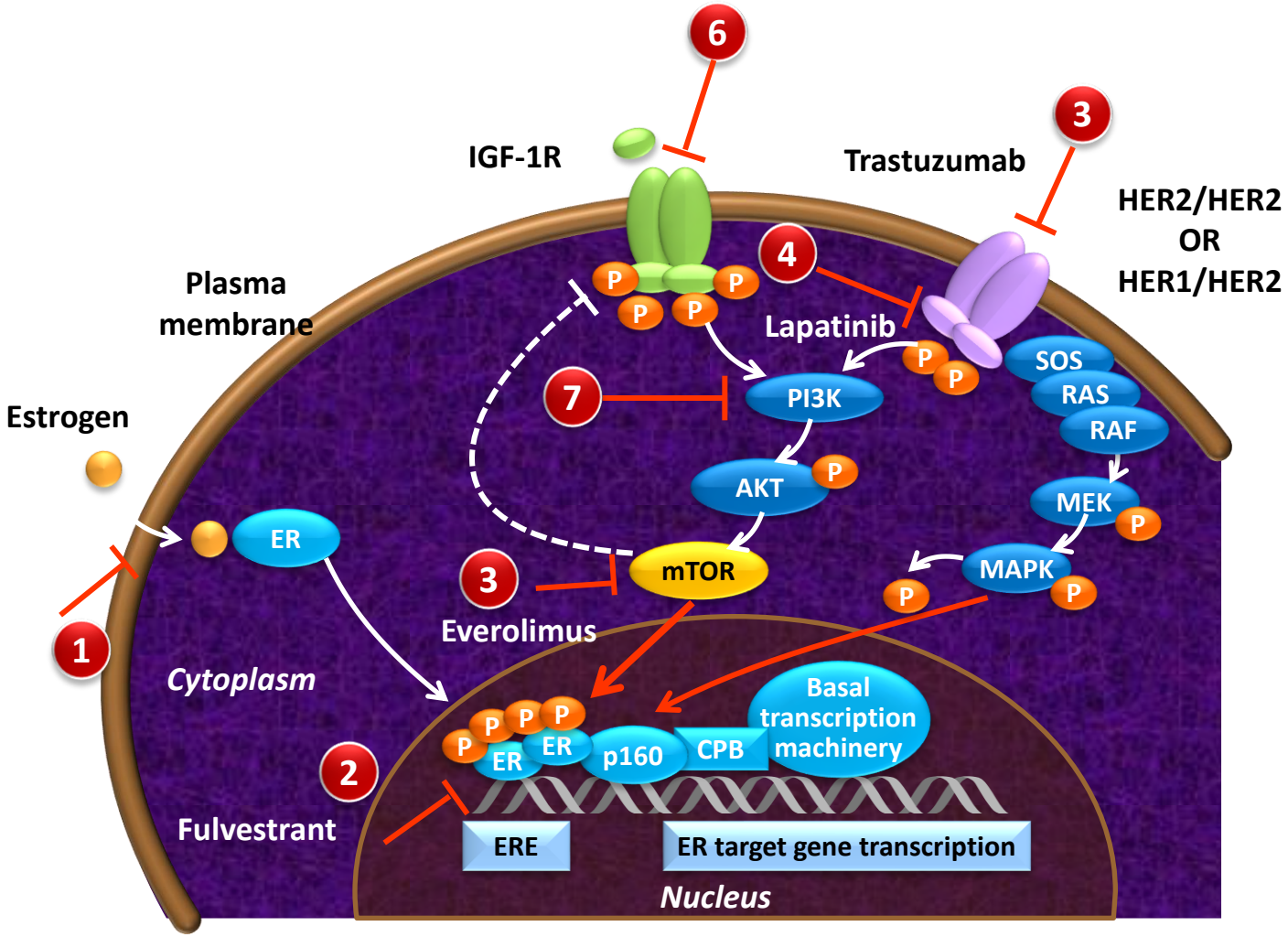


Unpublished data

Is there a role for EGFR/HER2 inhibitors in HER2-neg BC?

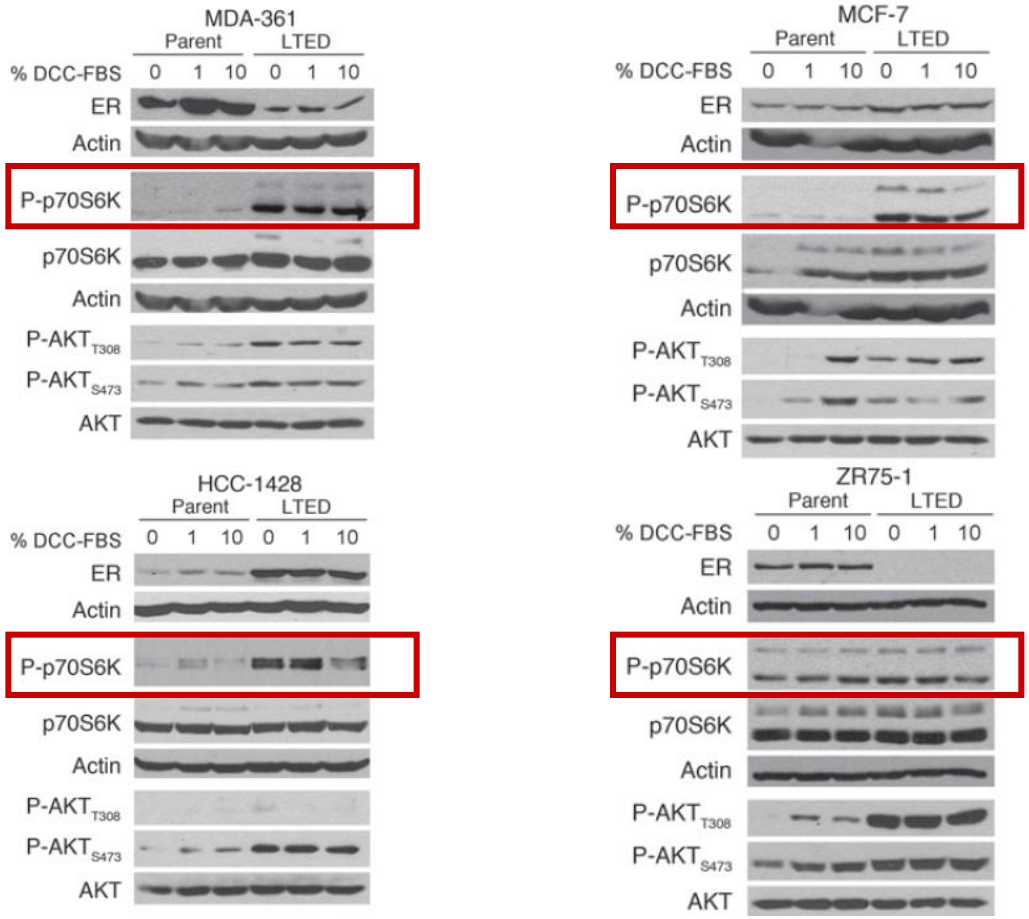


PI3K/AKT/mTOR pathway



Di Cosimo. Nat Rev Clin Oncol. 2009.

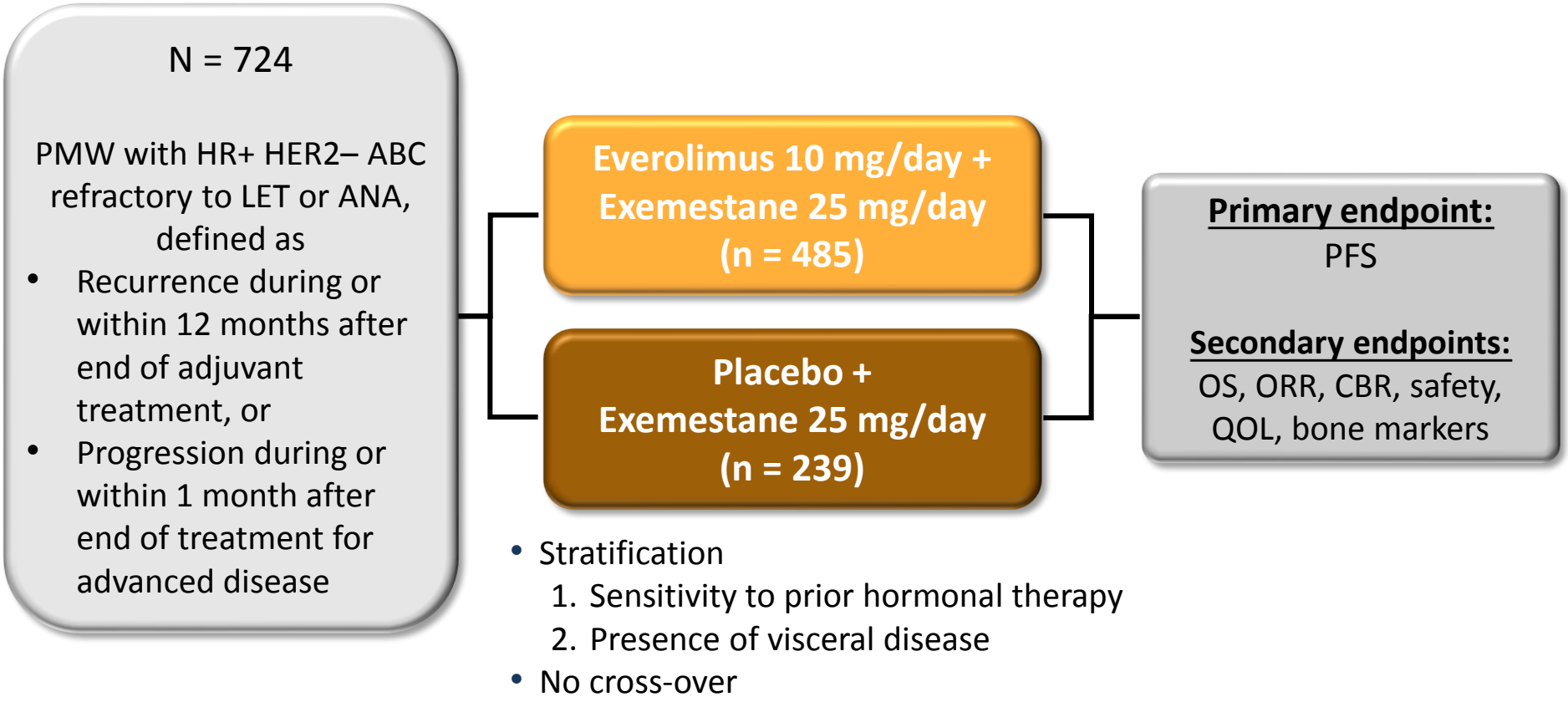
LTED is associated with acquired endocrine resistance



Cell lines resistant after long-term estrogen deprivation present ⬆ activation of the PI3K/AKT/mTOR pathway[1]

Sanchez CG, et al. Breast Cancer Res. 2011

Pivotal BOLERO-2 study: exemestane ± everolimus in ABC progressing after NSAIs

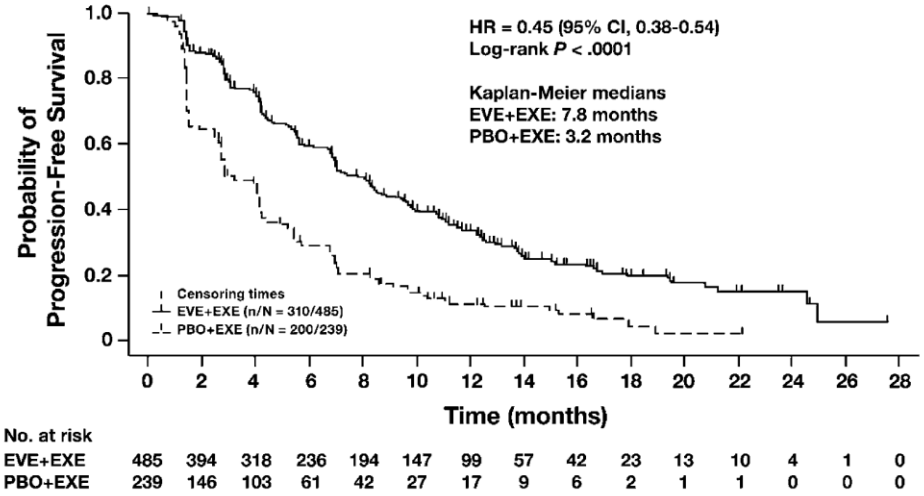


ANA, anastrozole; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor; HR+, hormone receptor-positive; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR; overall response rate; OS, overall survival; PFS, progression-free survival; PMW, postmenopausal women; QOL, quality of life.

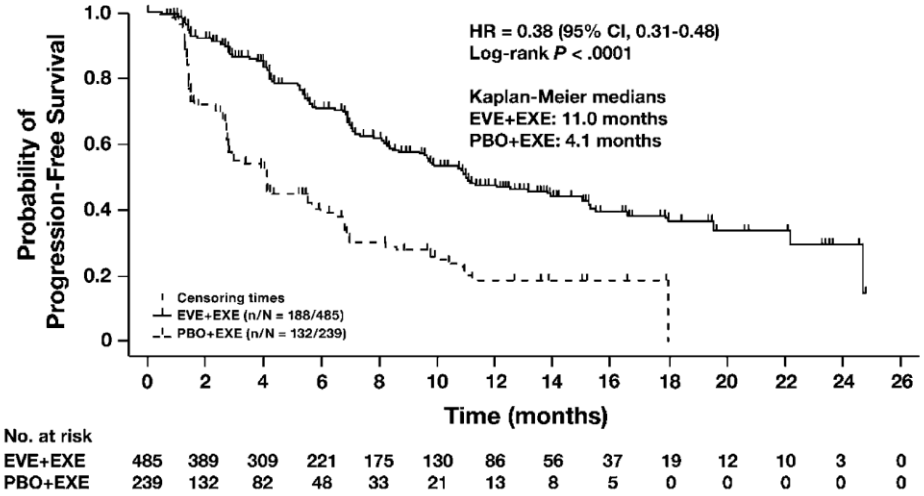
Baselga J, et al. N Engl J Med 2012

BOLERO-2: progression-free survival by (A) local and (B) central assessment

A.



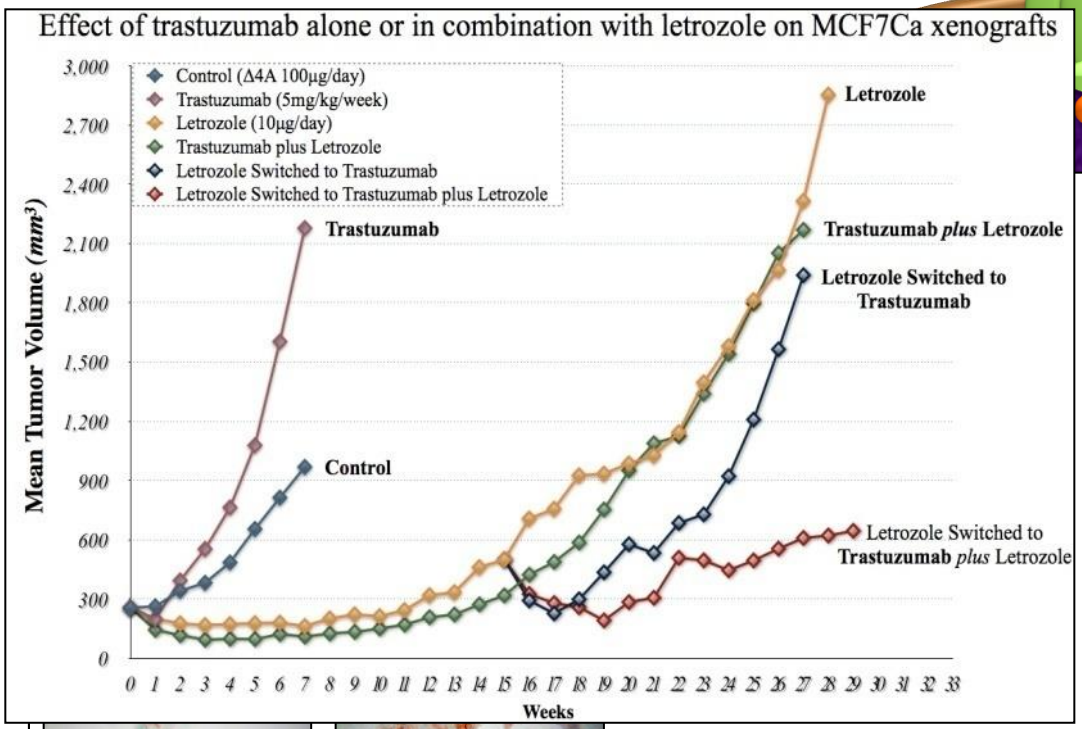
B.



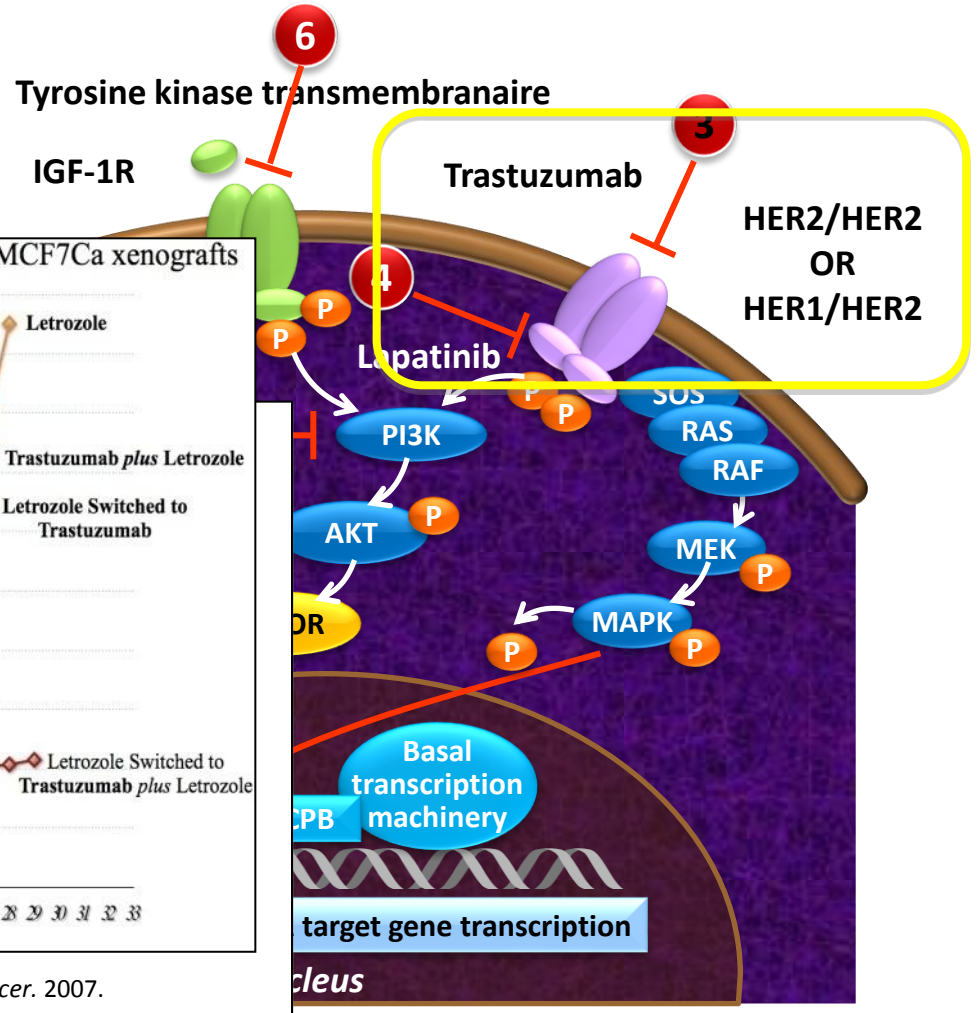
HR, hazard ratio; CI, confidence interval; EVE, everolimus; EXE, exemestane; PBO, placebo; mo, months.

Baselga J, et al. N Engl J Med 2012

EGFR/HER2 in HER2- tumors



Brodie et al. *Cancer.* 2007.

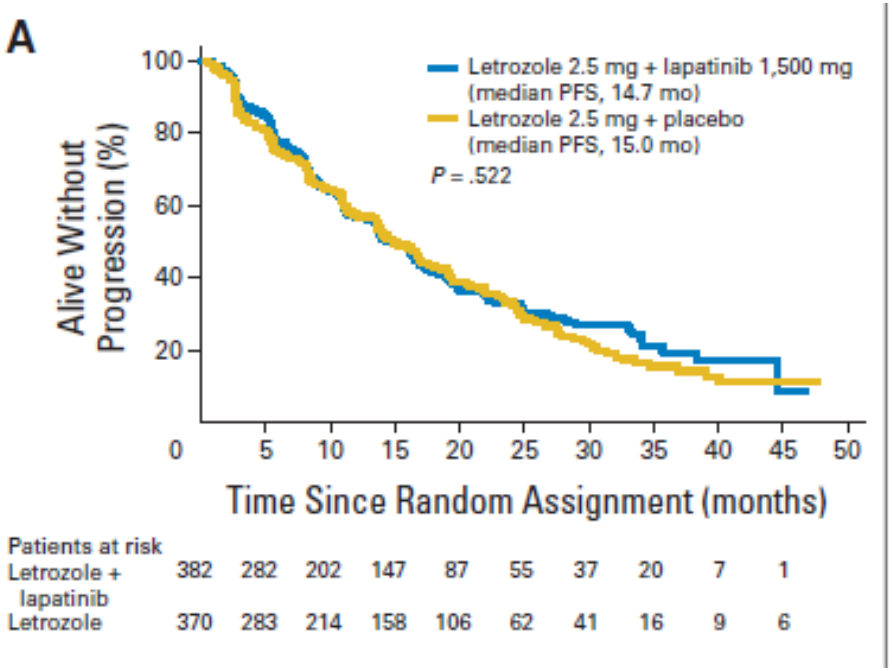


Knowlden JM, et al. *Endocrinology.* 2003

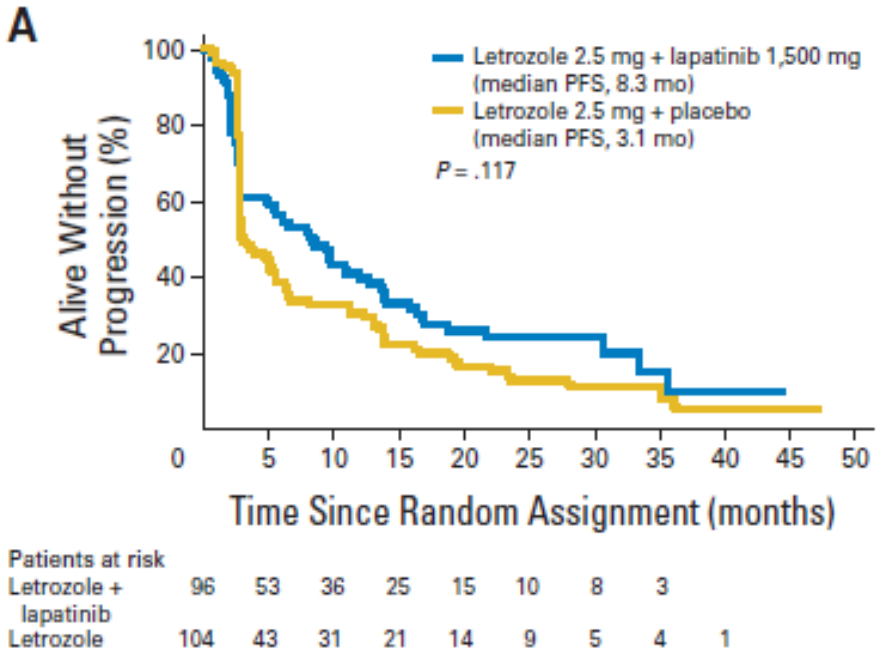
Di Cosimo. Nat Rev Clin Oncol. 2009.

Growth factor signaling pathway activation
Letrozole ± lapatinib

HR+, HER2-
DFI > 6 m

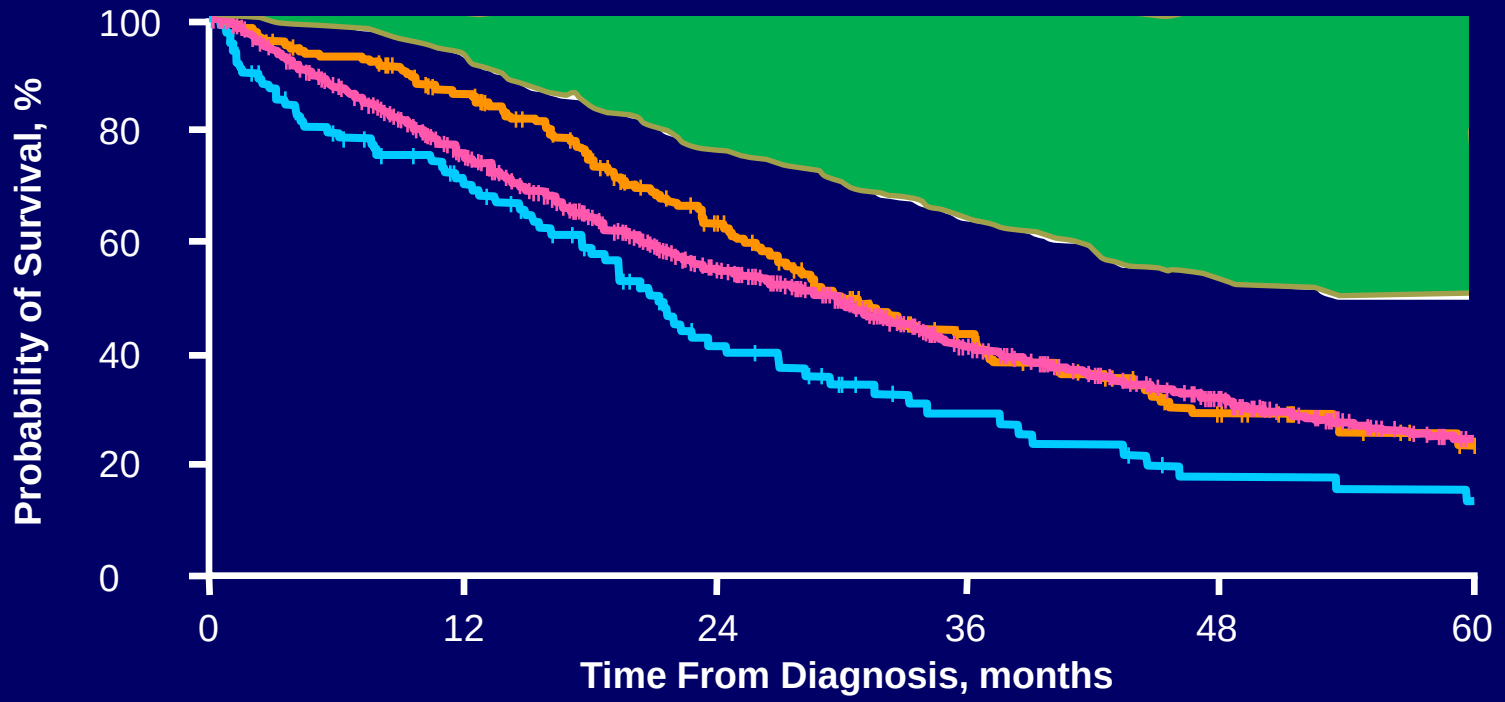


HR+, HER2-
DFI < 6 m

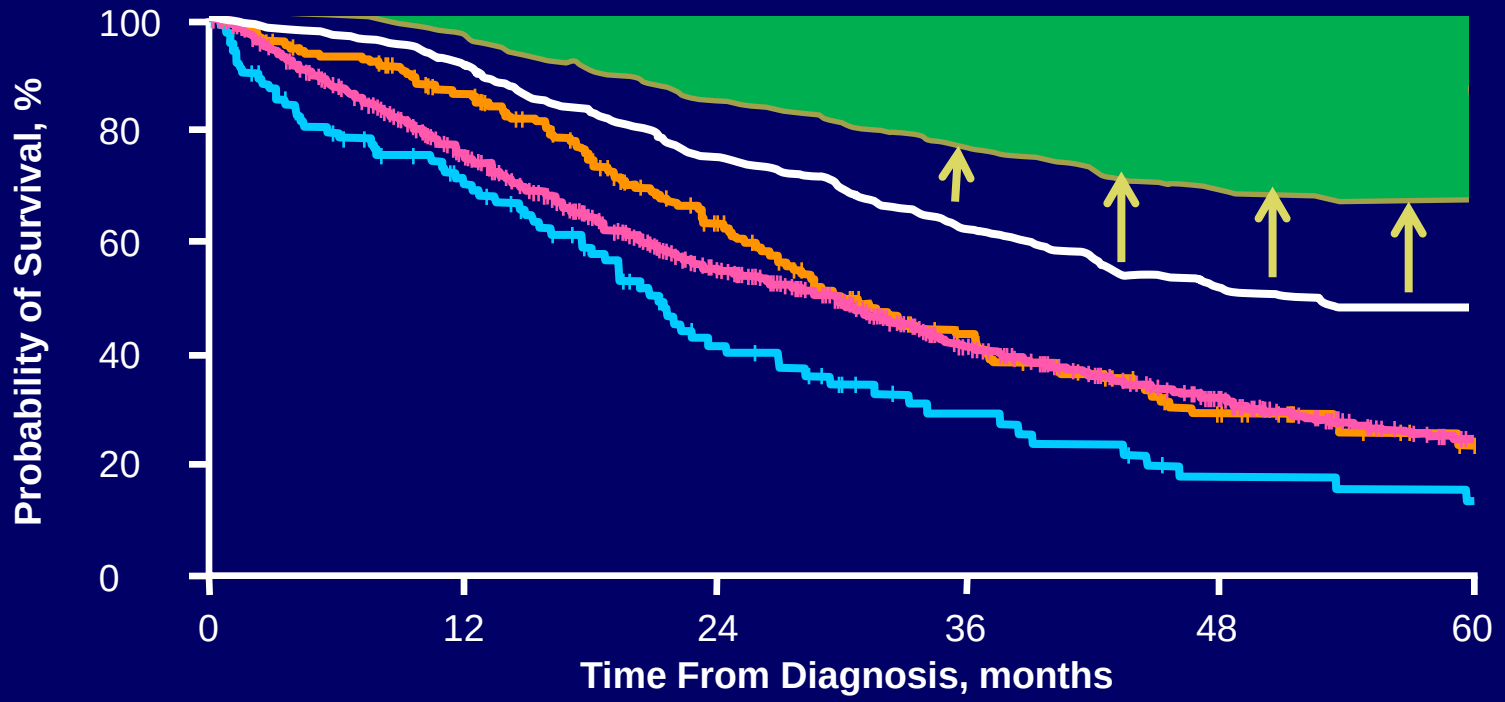


Johnston S, et al. J Clin Oncol 2009

Conclusion


Probability of Survival, %
100
80
60
40
20
0
0
12
24
36
48
60
Time From Diagnosis, months

Conclusion


Probability of Survival, %
100
80
60
40
20
0
0
12
24
36
48
60
Time From Diagnosis, months

Conclusion: BCSS~100%