New anti-HER2 molecules: monoclonal antibodies, antibody-drug conjugates, small molecule TKIs

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Disclosures

Advisor

Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceutical

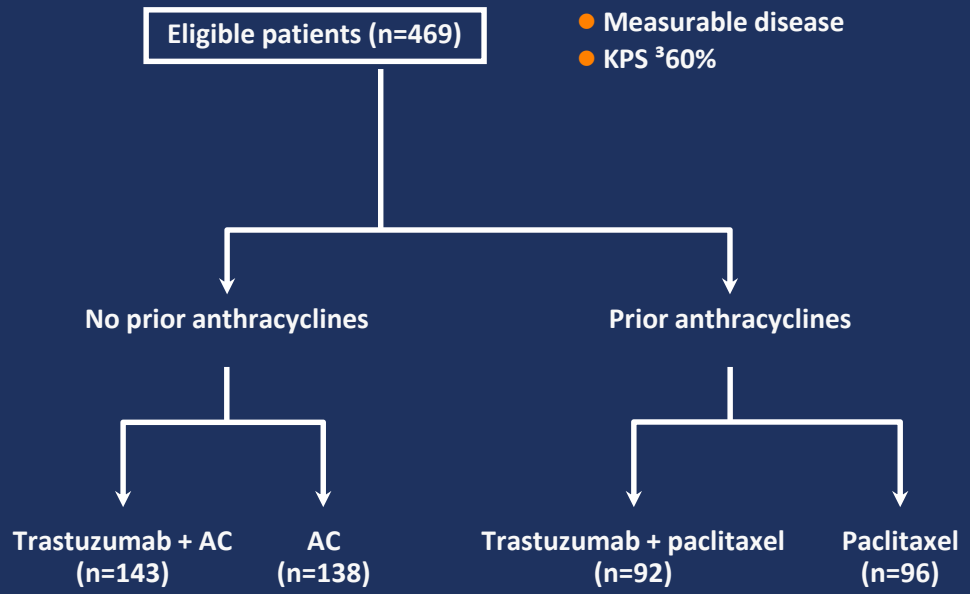
Honoraria

Roche, Novartis, Celgene, Eisai, Pfizer

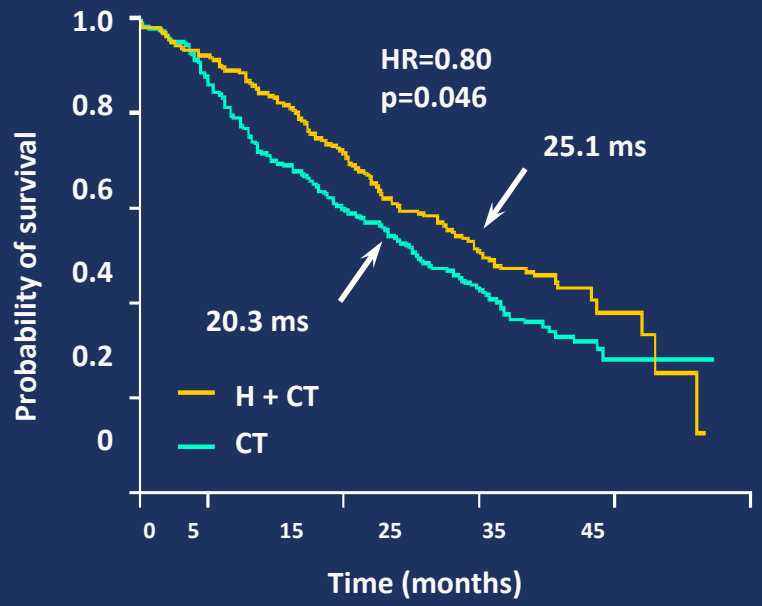
Going back… Trastuzumab in MBC: 1st Line

Study Design

- Metastatic breast cancer
- HER2 overexpression 2/3+
- No prior CT for MBC
- Measurable disease
- KPS ³60%



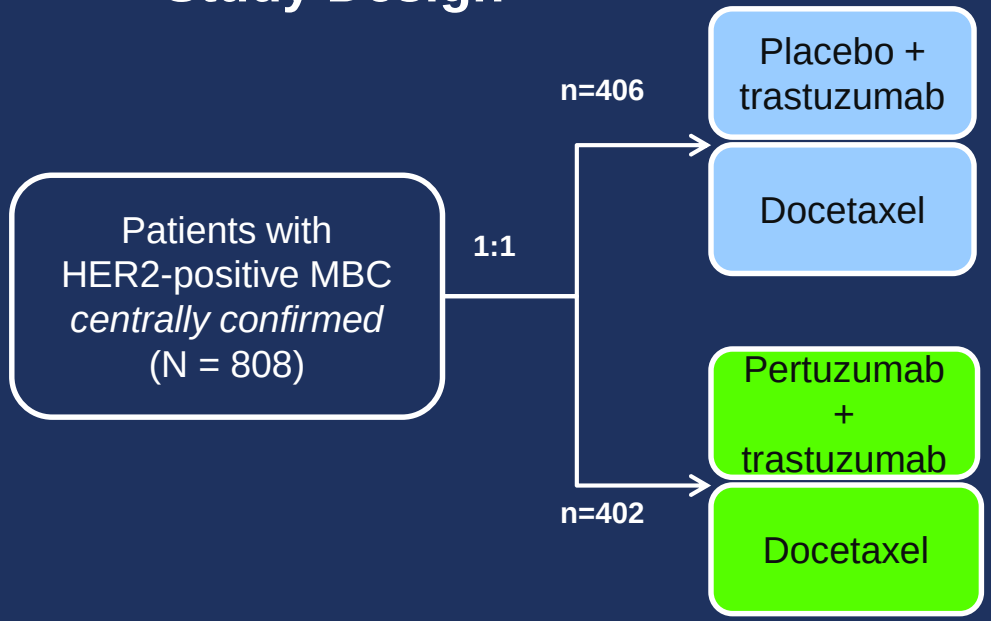
Overall survival



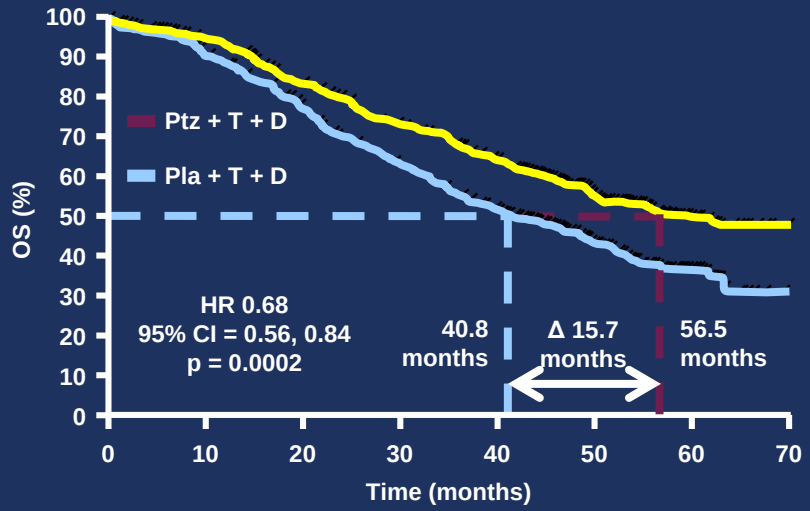
Slamon DJ et al. NEJM 2001

Pertuzumab in MBC: 1st Line

Study Design

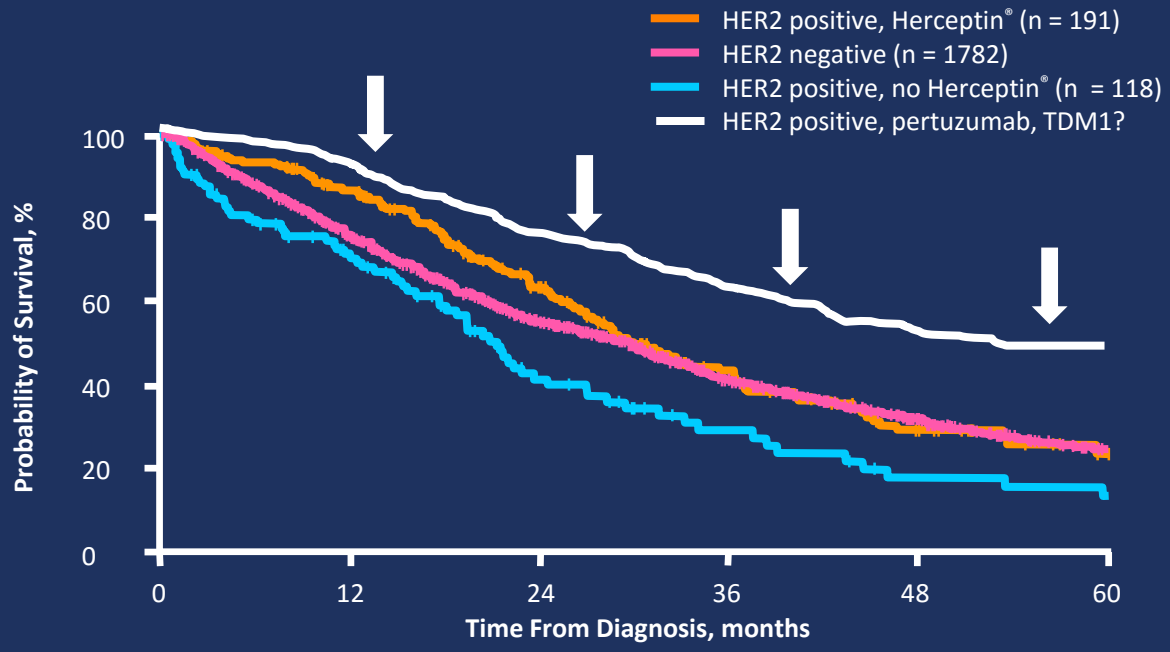


Overall survival

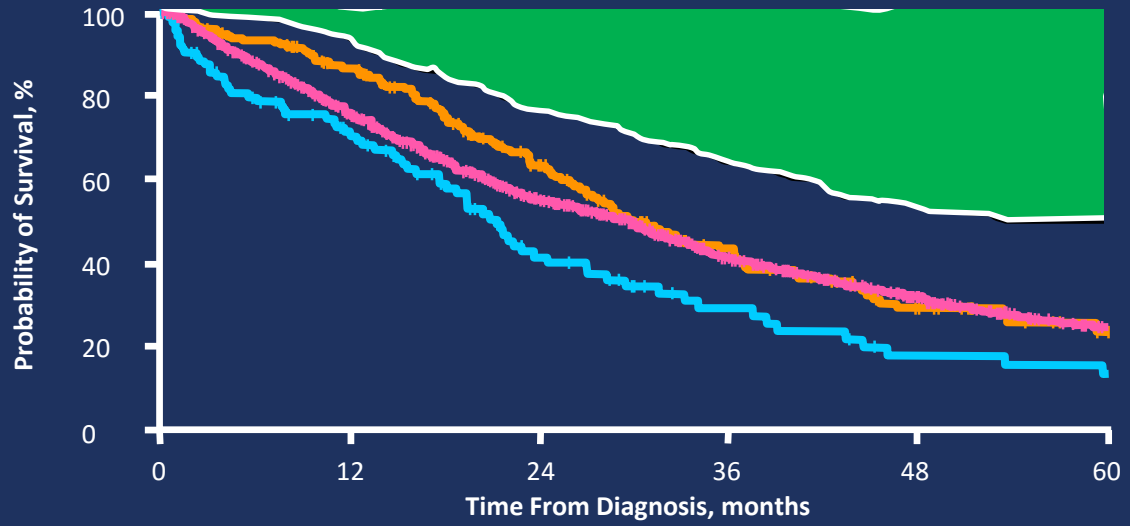


Baselga J, et al. NEJM 2012; Swain S, et al. NEJM 2015

HER2+ MBC: Current prognosis



HER2+ MBC: Still an unmet need...



Second Line and Salvage Therapy

Recent Achievements in HER2+ MBC

(with available therapies)

- **GBG 26 (Cap. + Trast.)** } **Trastuzumab-chemo**
- **EGF100151 (Cap. + Lapat.)** } **Lapatinib-chemo**
- **EGF104900 (Trast. + Lapat.)** } **Dual blockade**
- **PHEREXA (Trast+Cape +/- Pert.)** } **Dual blockade**
- **EMILIA**
- **TH3RESA** } **T-DM1**

Capecitabine ± Lapatinib

End point	Lapatinib plus capecitabine (N = 163)	Capecitabine alone (N = 161)	Hazard ratio (95% CI)	P value
Median time to progression - mo	8.4	4.4	0.49 (0.34 - 0.71)	<0.001
Median progression-free survival - mo	8.4	4.1	0.47 (0.33 - 0.67)	<0.001
Overall response % (95% CI)	22 (16 - 29)	14 (9 - 21)		0.09
Clinical benefit - no (%)	44 (27)	29 (18)		
Death - no (%)	36 (22)	35 (22)		

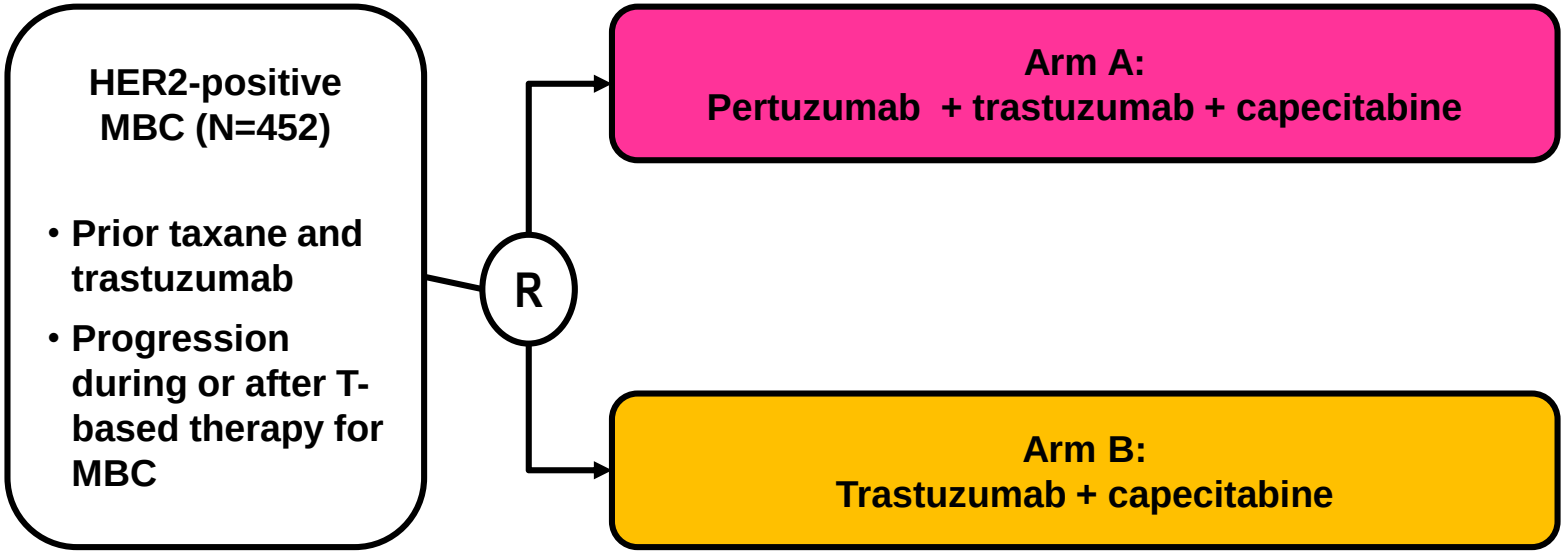
Geyer CE et al. NEJM 2006

Capecitabine ± Trastuzumab

End point	Lapatinib plus Trastuzumab (N = 78)	Capecitabine alone (N = 78)	Hazard ratio (95% CI)	P value
Median time to progression - mo	8.2	5.6	0.69 (0.48 - 0.97)	0.034
Median OS- mo	25.5	20.7	0.47 (0.33 - 0.67)	0.257
Overall response %	48	27		0.011
Median duration of response- mo	3.9	3.4		0.816
Death - no	33	38		

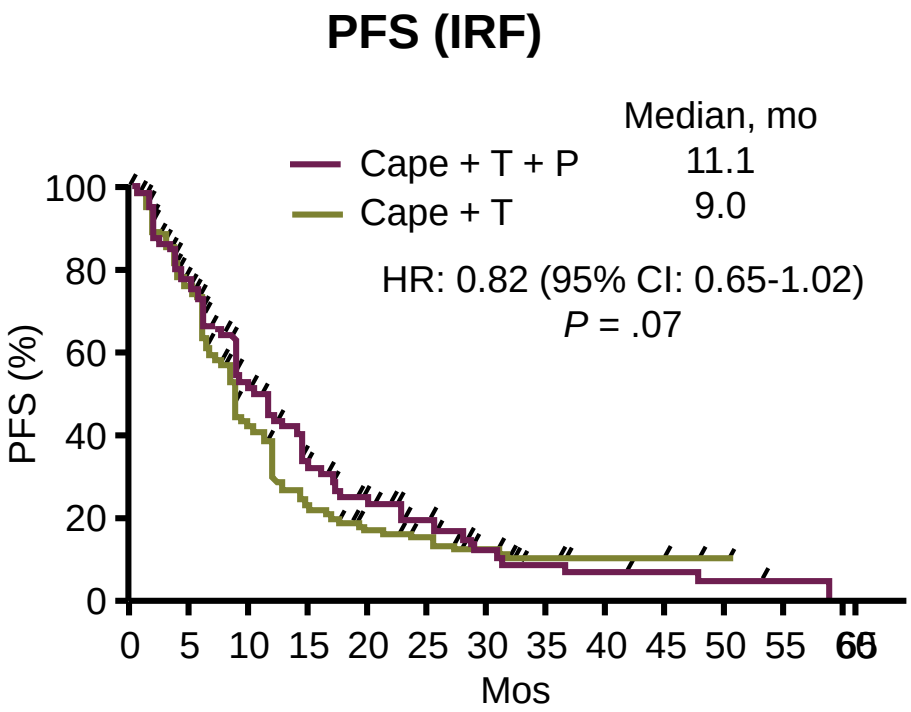
Von Minckwitz, et al. JCO 2009

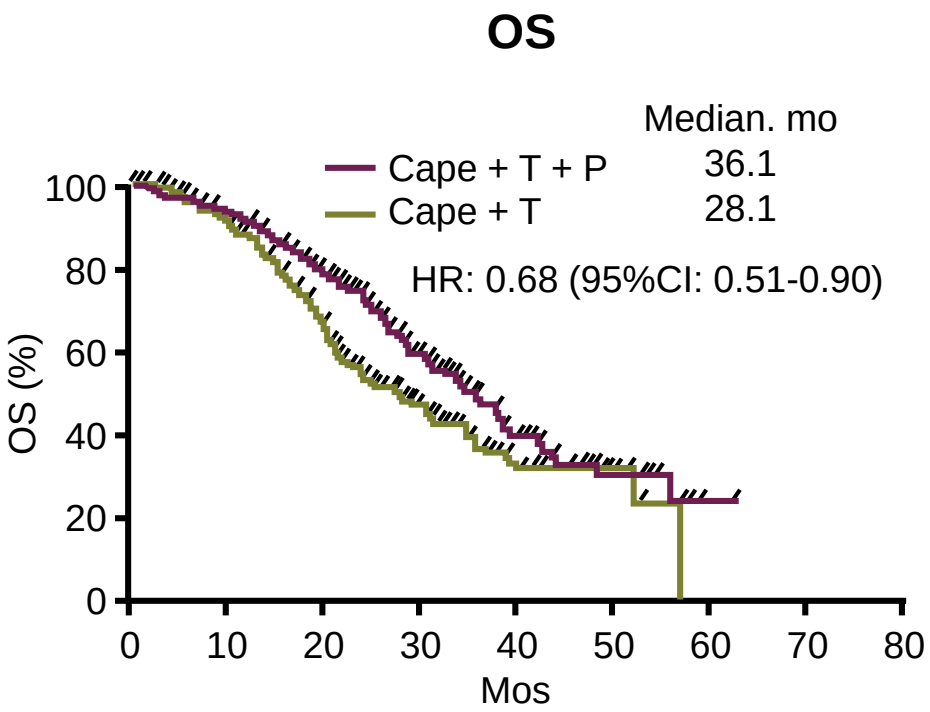
PHEREXA: Capecitabine + Trastuzumab ± Pertuzumab



Urruticoechea A, et al. ASCO 2016

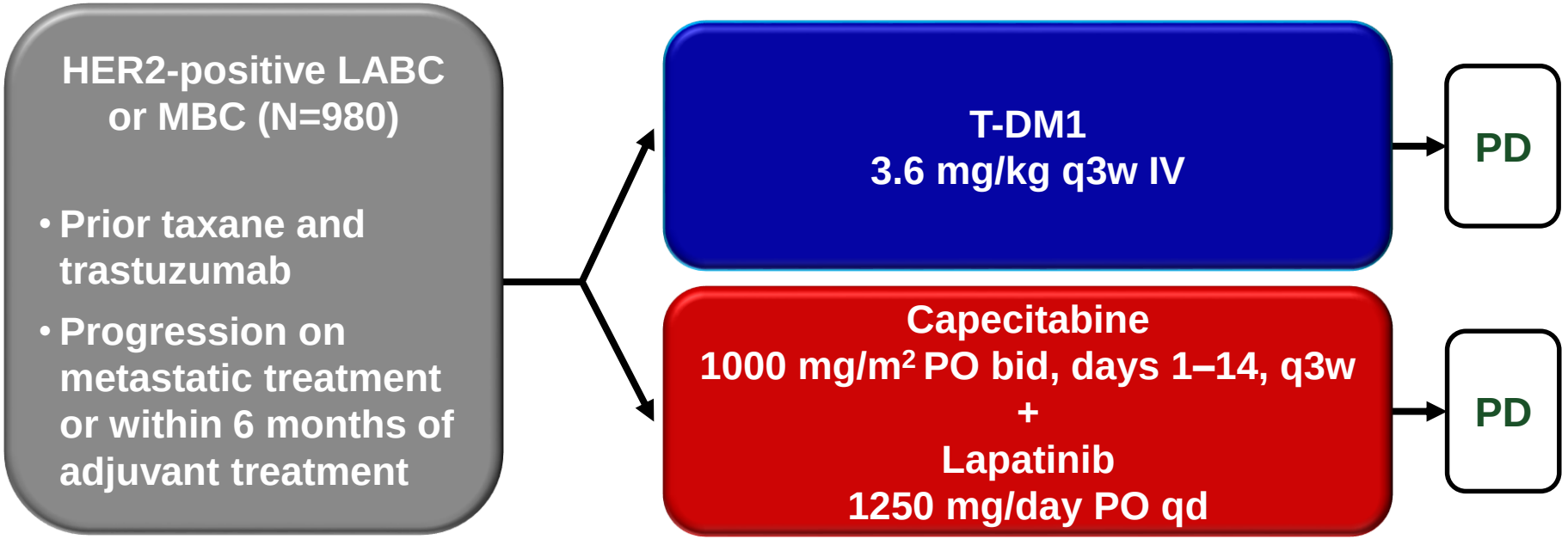
PHEREXA: PFS & OS





Urruticoechea A, et al. ASCO 2016

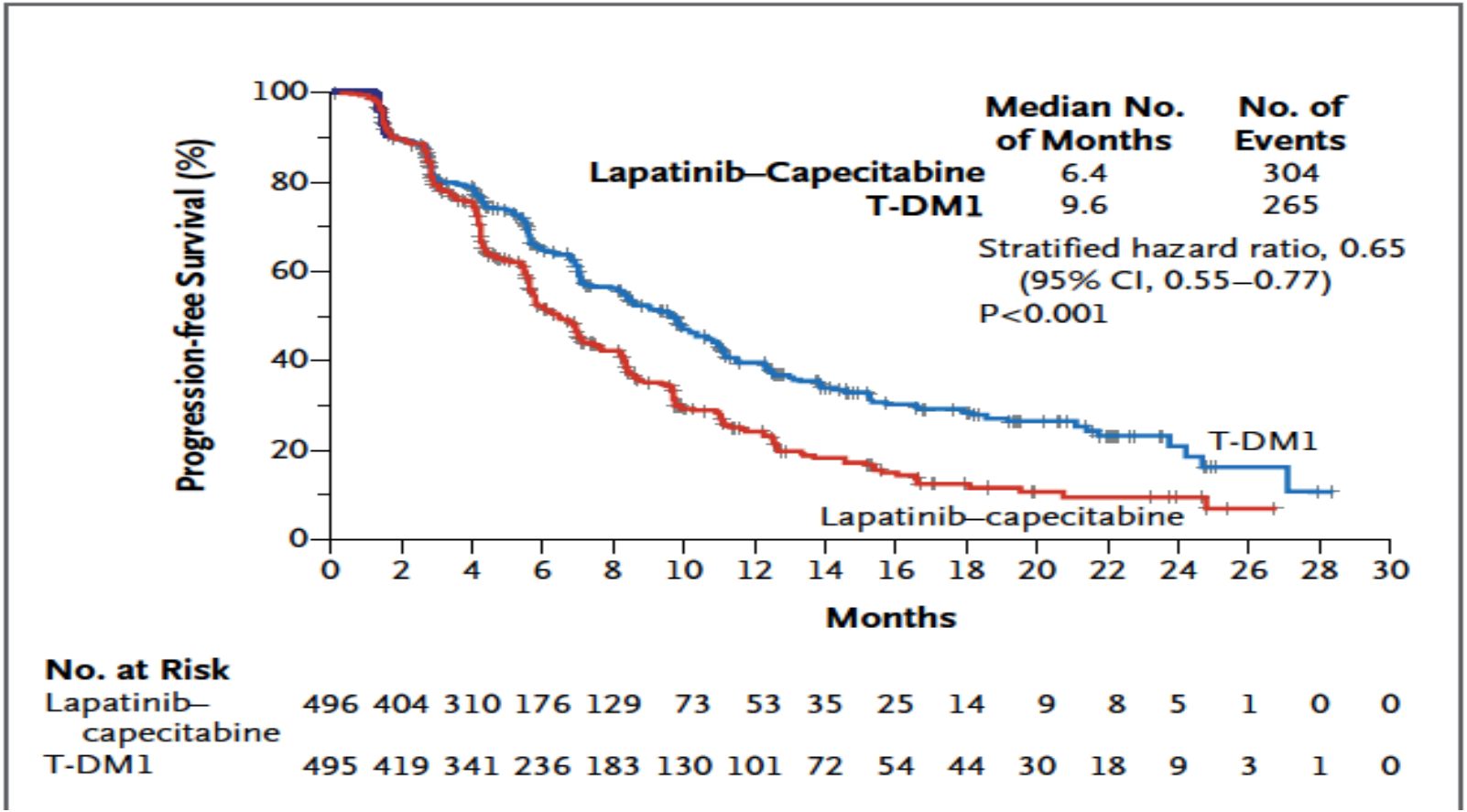
EMILIA: Lapatinib + Capecitabine vs T-DM1



- **Primary endpoints:** PFS by independent review, OS, and safety
- **Key secondary endpoints:** PFS by investigator, ORR, DOR
- **Statistical considerations:** Hierarchical statistical analysis: PFS by independent review → OS → secondary endpoints

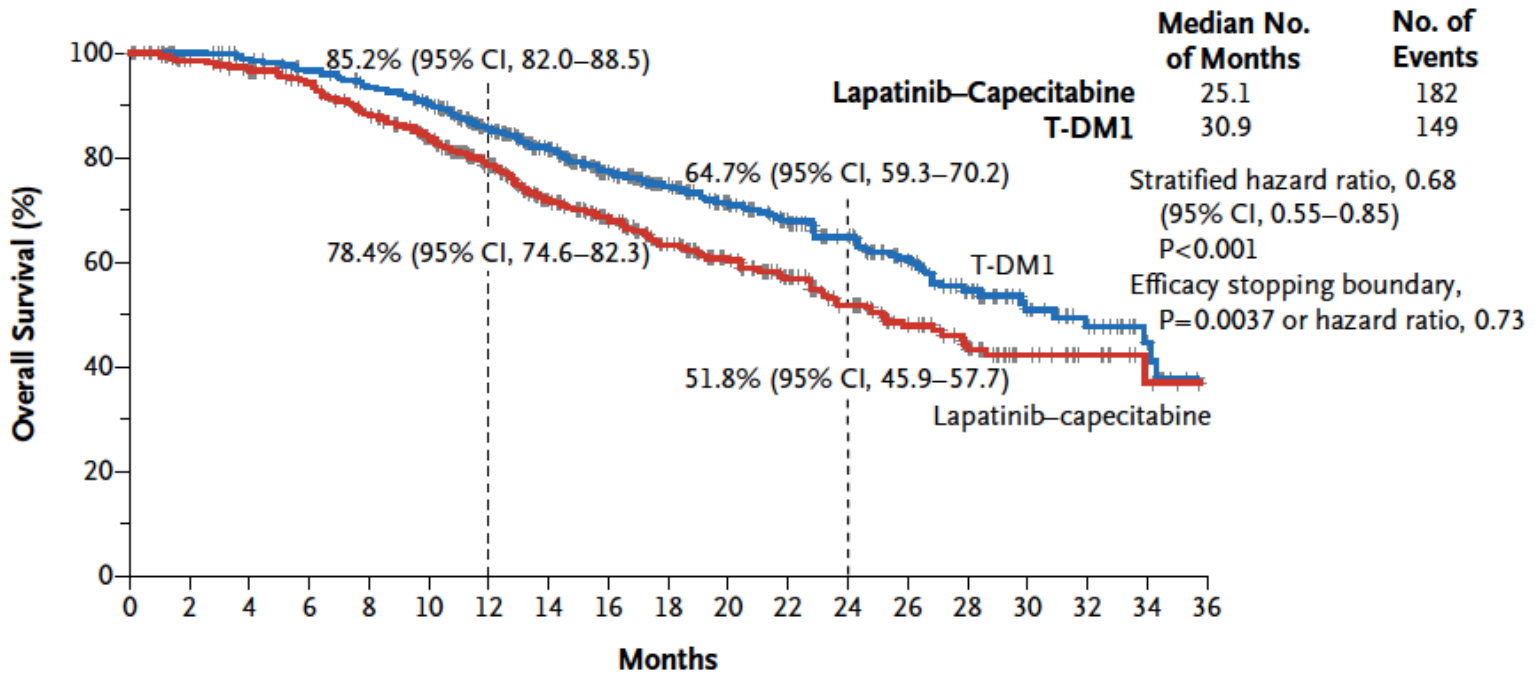
Verma S, et al. NEJM 2012

EMILIA: Progression-Free Survival



Verma S, et al. NEJM 2012

EMILIA: Overall Survival



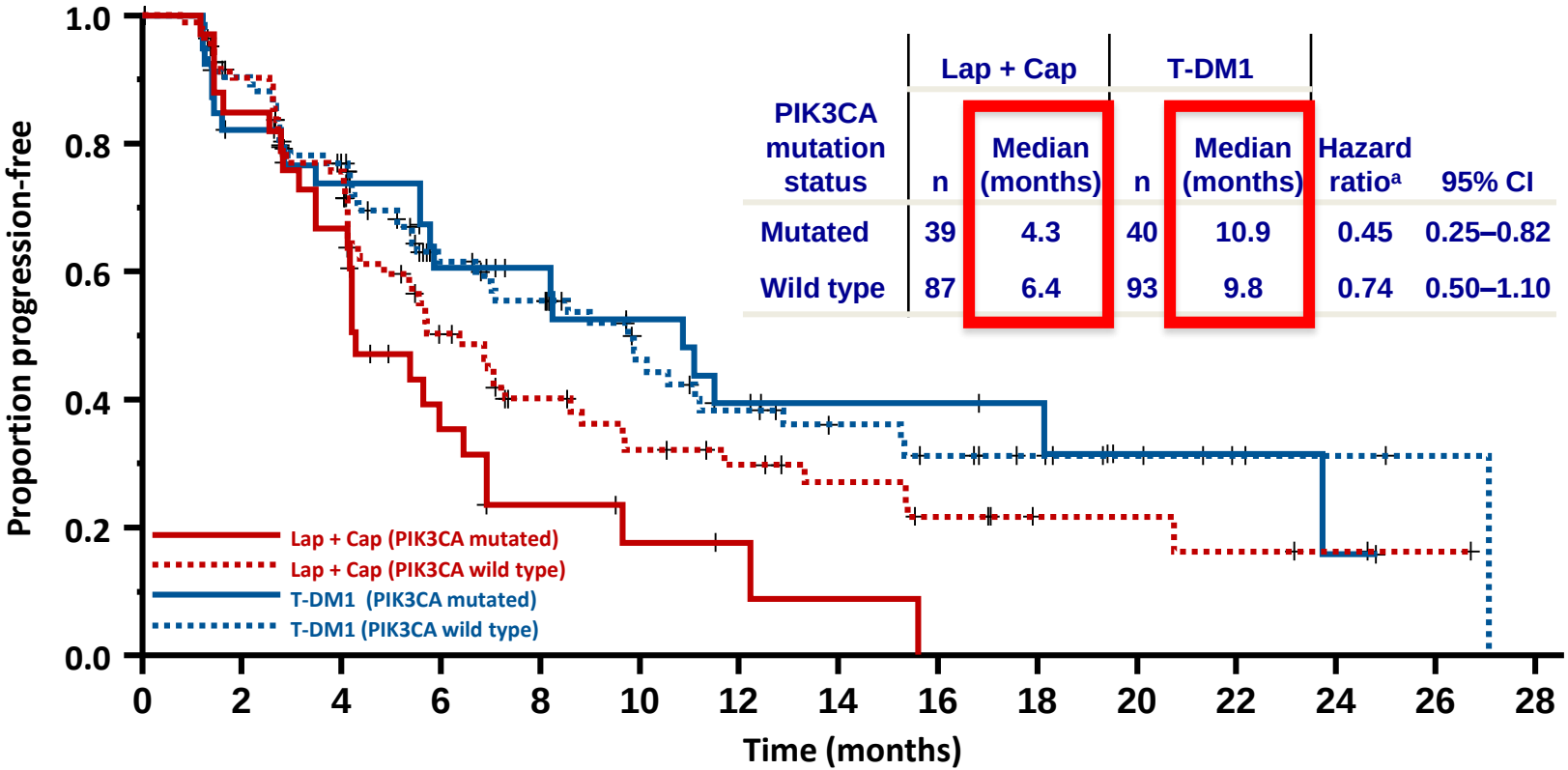
Verma S, et al. NEJM 2012

EMILIA: Toxicity

	Capecitabine + Lapatinib (N = 488)		T-DM1 (N = 490)	
AEs	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Nausea	**44.7**	**2.5**	39.2	0.8
Vomiting	**29.3**	**4.5**	19.0	0.8
Diarrhea	**79.7**	**20.7**	23.3	1.6
Hand-foot Syndrome	**58.0**	**16.4**	1.2	0
Neutropenia	**8.6**	**4.3**	**5.9**	**2.0**
Mucositis	**19.1**	**2.3**	**6.7**	**0.2**
Increased ALT	**8.8**	**1.4**	**16.9**	**2.9**
Increased AST	**9.4**	**0.8**	**22.4**	**4.3**
Thrombocytopenia	**2.5**	**0.2**	**28.0**	**12.9**
Alopecia	**4.1**	-	**2.9**	-

EMILIA: Biomarker Analysis

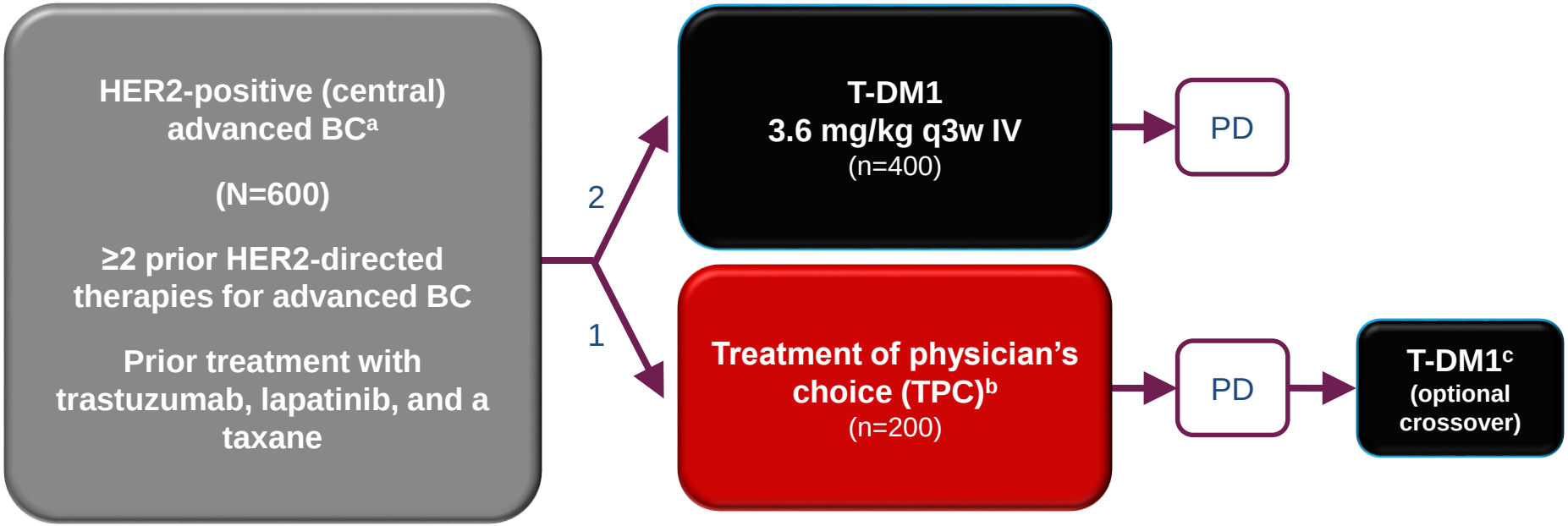
PFS by PI3K Mutation Status and Treatment Arm



PIK3CA mutation status	Lap + Cap n	Lap + Cap Median (months)	T-DM1 n	T-DM1 Median (months)	Hazard ratio[a]	95% CI
Mutated	39	4.3	40	10.9	0.45	0.25–0.82
Wild type	87	6.4	93	9.8	0.74	0.50–1.10

Baselga J, et al. CCR 2016

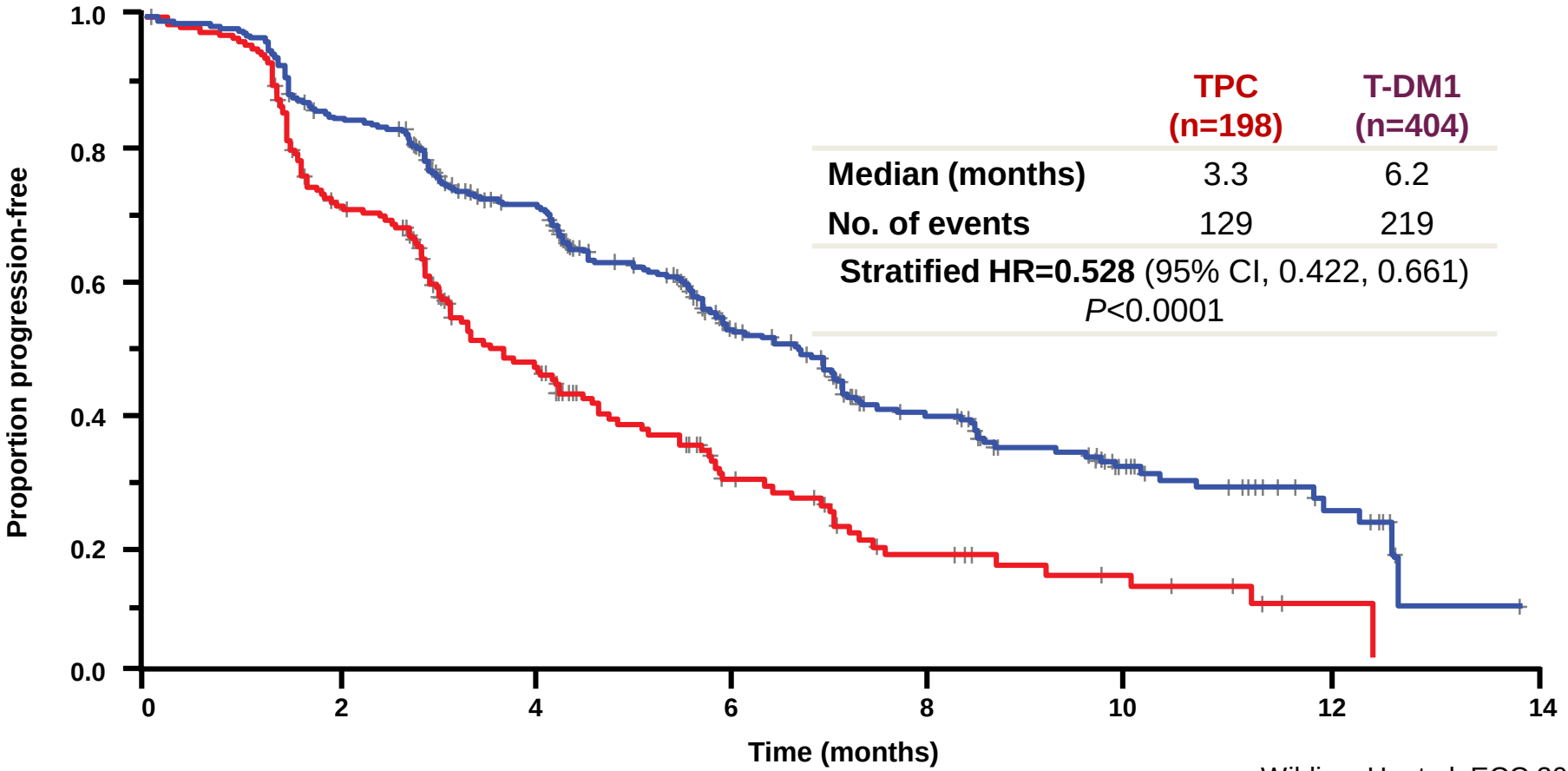
TH3RESA: T-DM1 vs TPC



- **Stratification factors:** World region, number of prior regimens for advanced BC,[d] presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safe

Krop I, et al. Lancet Oncol 2014; Wildiers H, et al. ECC 2013

TH3RESA: Progression-Free Survival

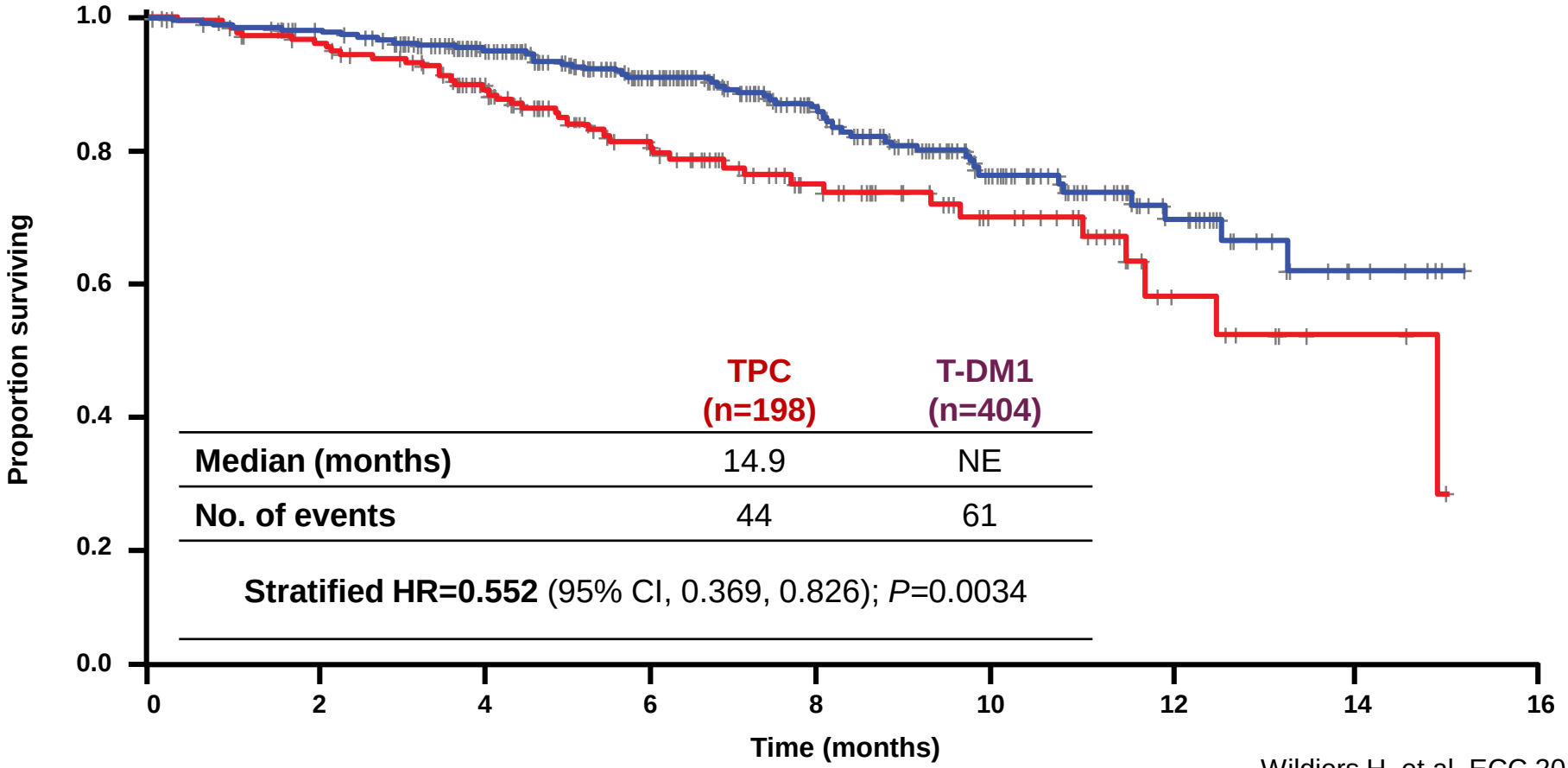


	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

Wildiers H, et al. ECC 2013

TH3RESA: Overall-Survival



	TPC (n=198)	T-DM1 (n=404)
Median (months)	14.9	NE
No. of events	44	61

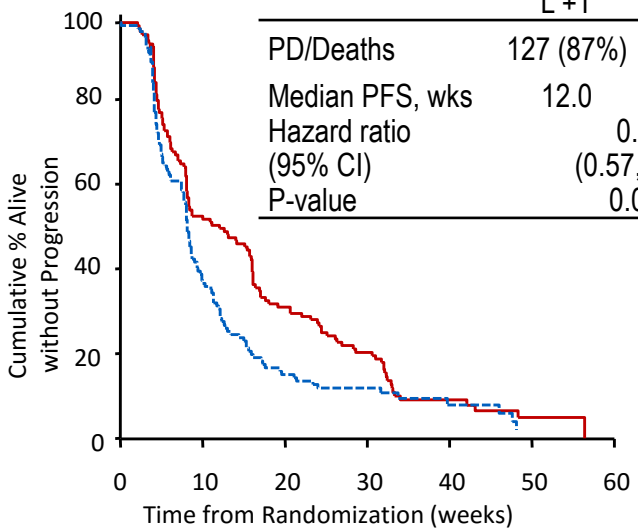
Stratified HR=0.552 (95% CI, 0.369, 0.826); *P*=0.0034

Wildiers H, et al. ECC 2013

EGF 104900
(Lapatinib + Trastuzumab vs Lapatinib)

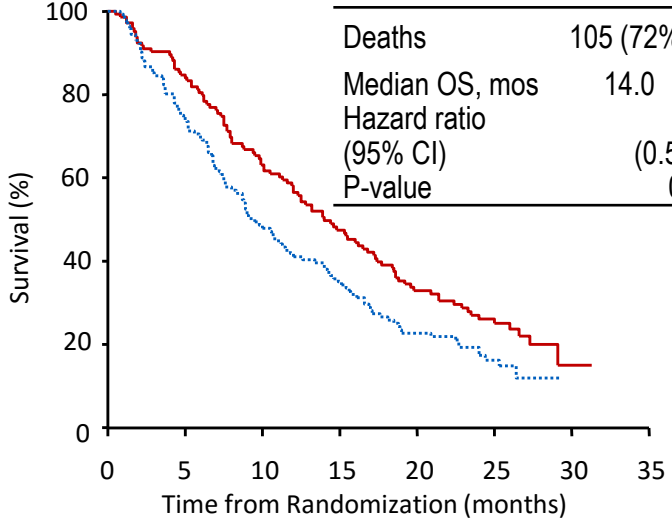
Primary Endpoint: PFS

	L +T	L
PD/Deaths	127 (87%)	128 (88%)
Median PFS, wks	12.0	8.1
Hazard ratio	0.73	
(95% CI)	(0.57, 0.93)	
P-value	0.008	



Secondary Endpoint: OS

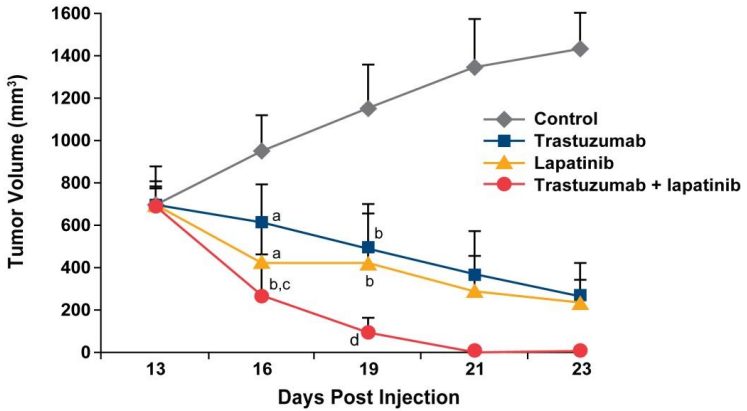
	L +T	L
Deaths	105 (72%)	113 (78%)
Median OS, mos	14.0	9.5
Hazard ratio	0.74	
(95% CI)	(0.57, 0.97)	
P-value	0.026	



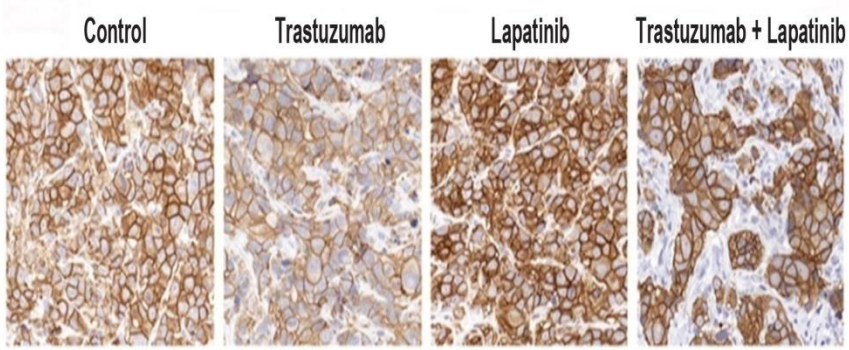
- **Unusual PFS/OS pattern (~CLEOPATRA)**
- **Is Dual Blockade able induce a post-treatment effect on subsequent therapies?**

Blackwell K, et al. JCO 2012

Dual HER2 blockade by Lapatinib and Trastuzumab



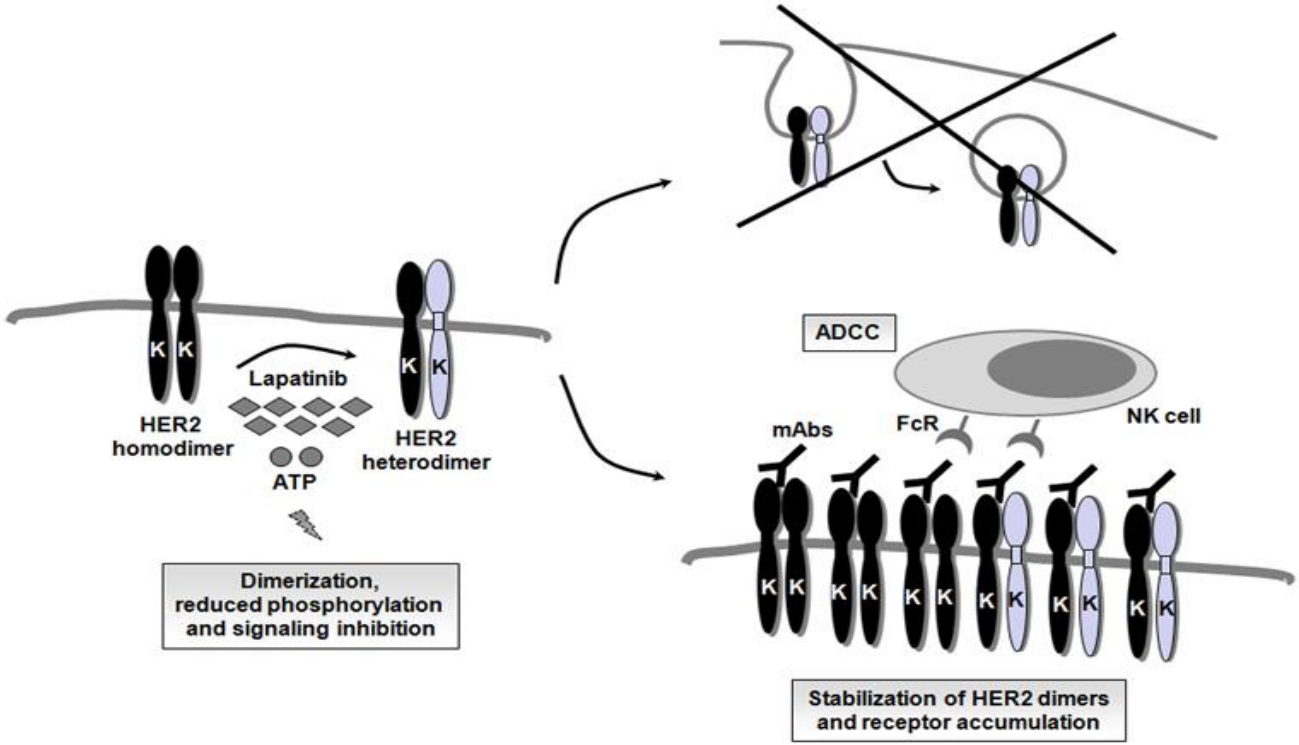
[a]*P*<.05; [b]*P*<.01 vs control; [c]*P*<.05 vs trastuzumab; [d]*P*<.01 vs both lapatinib and trastuzumab.



- Lapatinib induced accumulation of inactive HER2 at plasma membrane
  - Trastuzumab-mediated cytotoxicity was higher with the addition of lapatinib in MCF7/HER2 cells

Scaltriti M, et al. Oncogene 2009

Dual HER2 blockade by Lapatinib and Trastuzumab



ADCC: Antibody-dependent cell-mediated cytotoxicity

Scaltriti M, et al. Oncogene 2009

Pertuzumab + Trastuzumab + Taxane is best 1st line

T-DM1 is standard 2nd line in MBC

Lapatinib and/or Trastuzumab-based regimens remain as an option in 3rd line

New anti-HER2 drugs are needed

Future Questions

- Is there a benefit of Pertuzumab or T-DM1 (along with other partners) beyond progression?
- What is the effect on tumor biology once patients progress on Pertuzumab/T-DM1/Lapatinib?
  - What are potential targeted agents that may help overcome resistance?
- Who are the ideal patients for dual targeted treatment alone?
- The Next Generation of anti-Her 2 Drugs….

Future Questions

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- Who are the ideal patients for dual targeted treatment alone?
- The Next Generation of anti-Her 2 Drugs….

Novel HER2-directed agents in clinical development

Class	Example(s)
HER2-targeted TKI	Neratinib, afatinib, ONT-380
Antibody-drug conjugates	MM-302, SYD983, MEDI4276, ARX788, DS-8201a
Anti-HER3	AMG-888, MM-121, EZN-3920
Anti-HER2 monoclonal antibody with enhanced immune properties	Margetuximab
PI3K/AKT/mTOR inhibitors	Buparlisib, Pictilisib, Alpelisib, Taselisib, Everolimus
CDK 4/6 inhibitors	Palbociclib, Ribociclib, Abemaciclib
Peptide-based vaccines	E75, GP2
Immune checkpoints	Pembrolizumab, Atezolizumab, Nivolumab

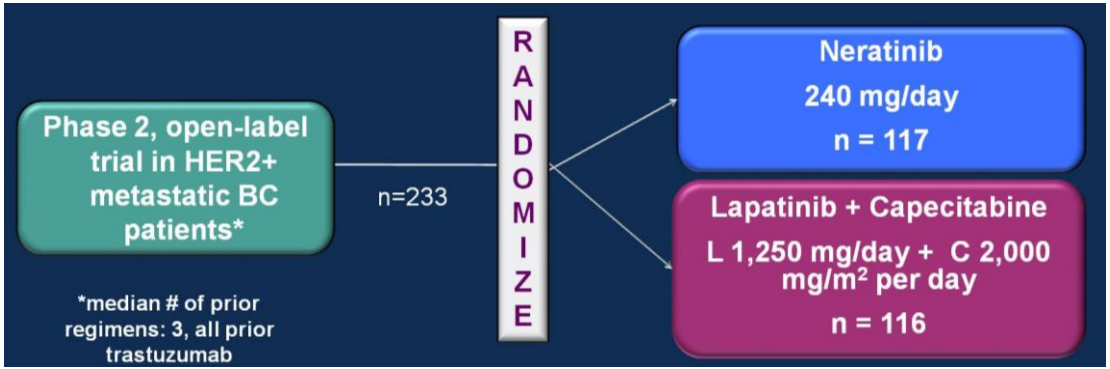
HER2-targeted TKI: Neratinib

	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**

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)

HER2-targeted TKI:

Neratinib Single Agent vs. Lapatinib + capecitabine



End point	Lapatinib plus capecitabine (N = 116)	Neratinib (N = 117)	P value
Median TTP- mo	6.8	4.4	0.231
Median OS - mo	23.6	19.7	
Overall response %	41	29	

Martin M, et al. EJC 2013

HER2-targeted TKI: Neratinib

Ongoing Clinical Trials

Study	Treatment	Inclusion
NALA	N+C vs. L+C	≥ 2 HER2 directed regimens in MBC setting
NCT01111825	Temsirolimus + N	MBC HER2+ or TN
NCT02236000	T-DM1 + N	Dose escalation HER2 +
NCT01494662	N ± C	HER2 + brain metastases

HER2-targeted TKI: ONT-380

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

- **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**

HER2-targeted TKI: ONT-380

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

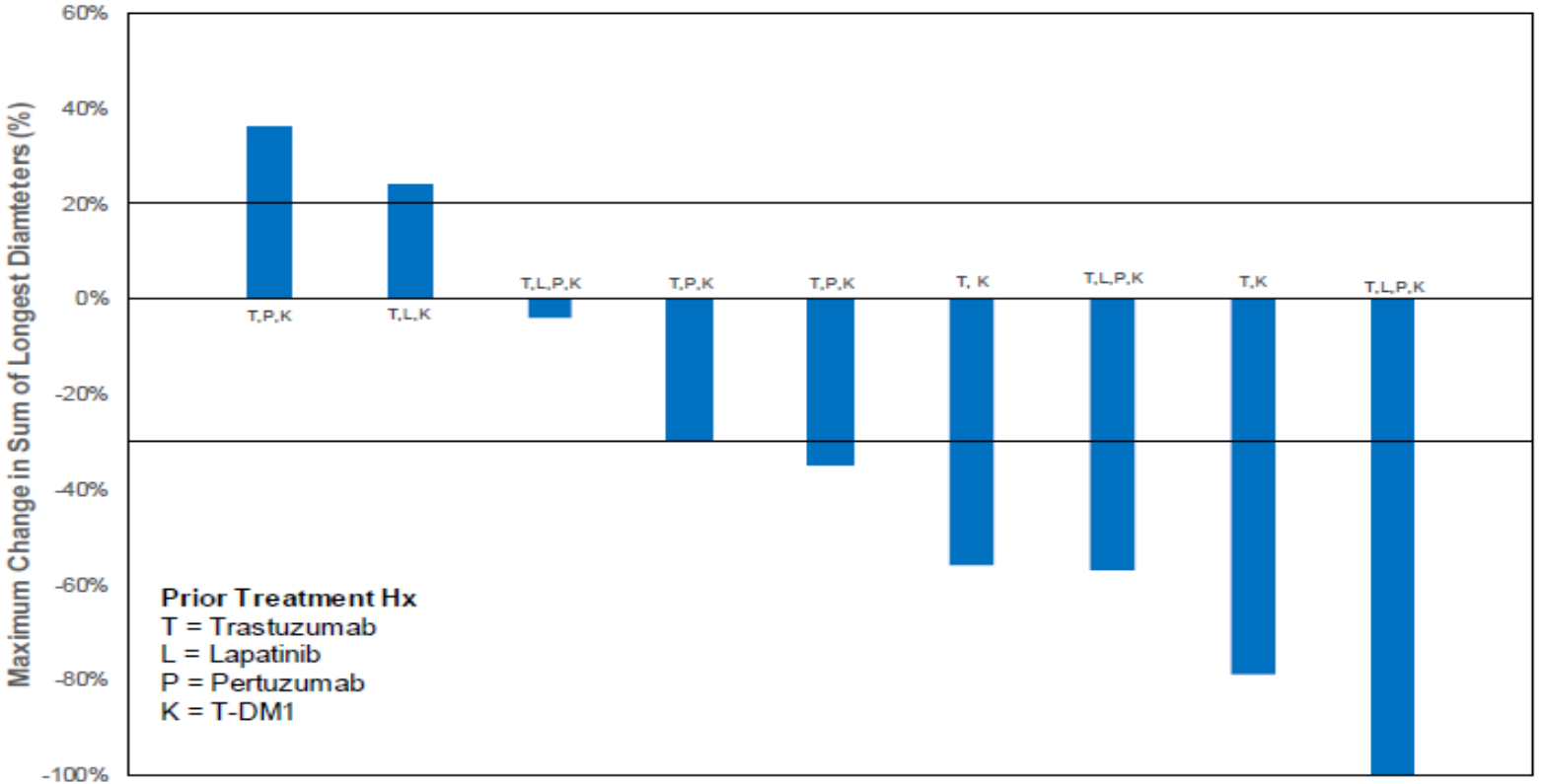
	ONT-380 +					
	C (n = 7)		T (n = 13)		C + T (n = 12)	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Diarrhea	5	0	8	0	8	0
Nausea	4	0	3	0	7	0
Constipation	4	0	5	0	2	0
Fatigue	5	0	1	0	4	0
PPE	4	1	0	0	6	0
Vomiting	2	0	2	0	4	0

No Grade 4 or 5 AEs among most common AEs

Hamilton et al, ASCO 2015

HER2-targeted TKI

(ONT-380 + Cape + TZB)

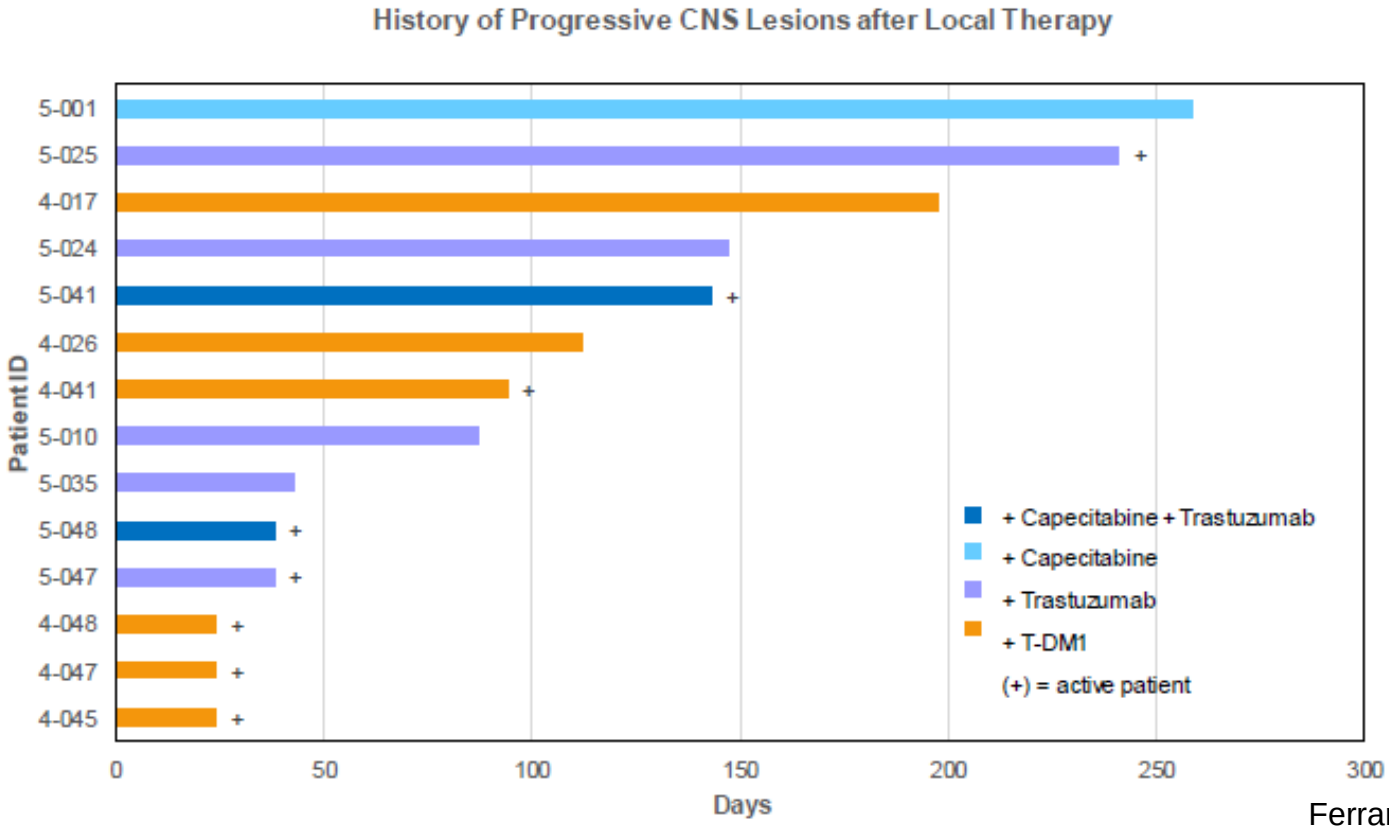


a. 3 pts active on study do not yet have a follow up scan

Hamilton et al, ASCO 2015

HER2-targeted TKI: ONT-380

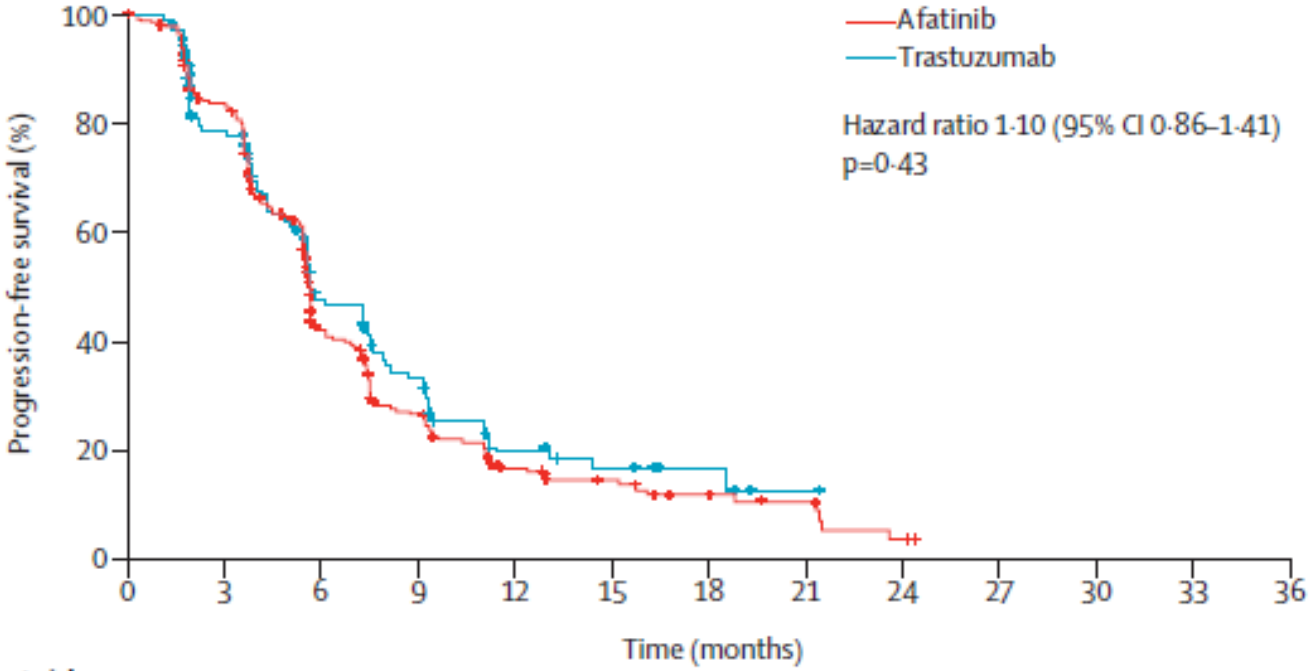
(+ cape + trast / + cape / + trastu / + TDM1)



Ferrario et al, ASCO 2015

HER2-targeted TKI: Afatinib

(Afatinib + VNB vs Trastuzumab + VNB): Trastuzumab Resistance



Harbeck N, et al. Lancet Oncol 2016

HER2-targeted TKI: Afatinib in CNS mets

- 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

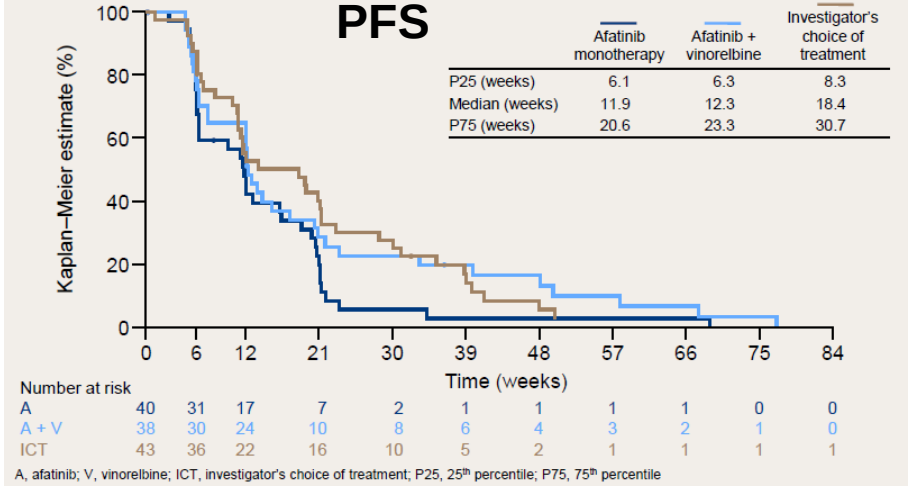
1 → Afatinib (40 mg oral once daily)*

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

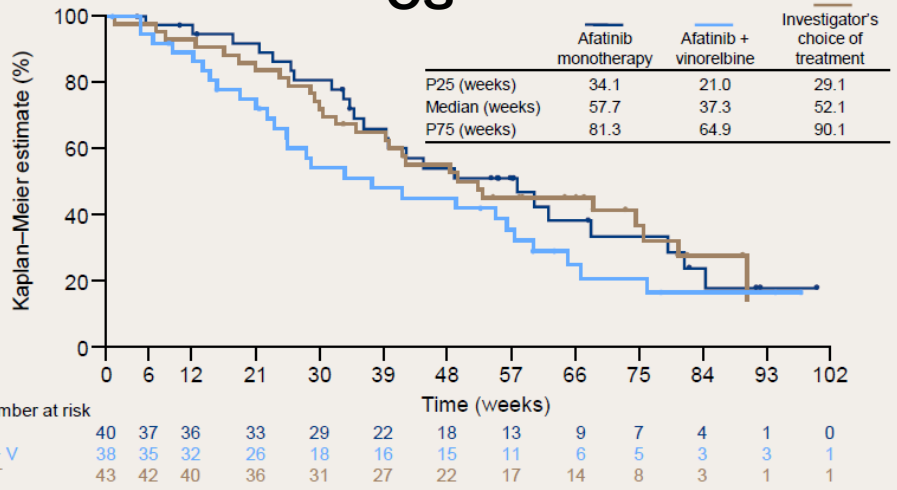
PFS



	Afatinib monotherapy	Afatinib + vinorelbine	Investigator's choice of treatment
P25 (weeks)	6.1	6.3	8.3
Median (weeks)	11.9	12.3	18.4
P75 (weeks)	20.6	23.3	30.7

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

OS

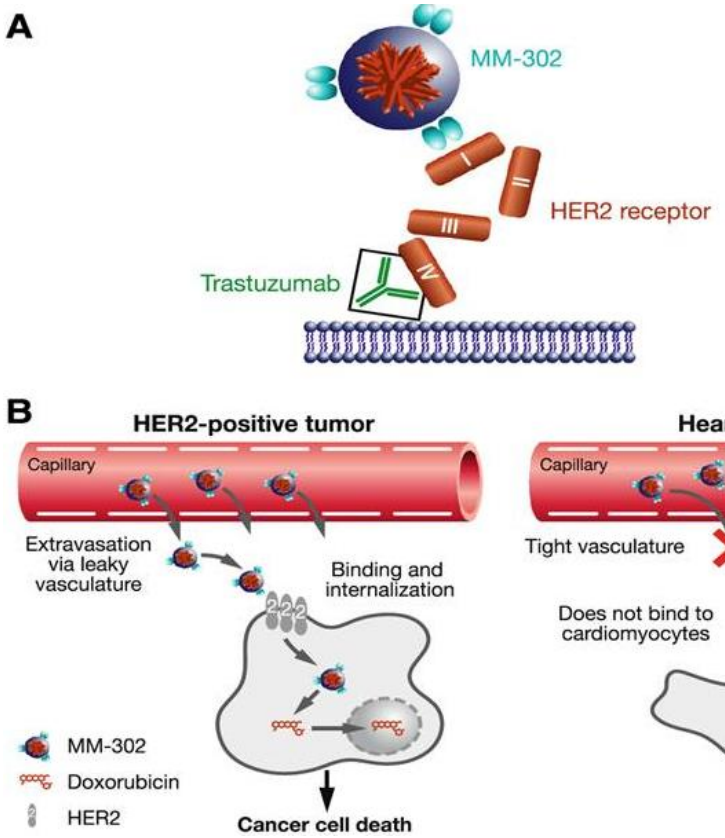


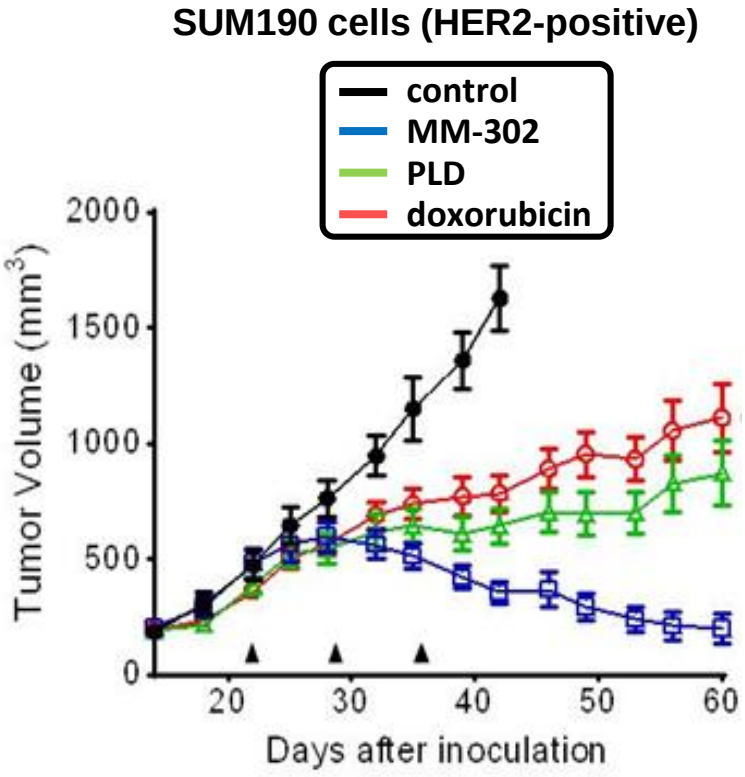
	Afatinib monotherapy	Afatinib + vinorelbine	Investigator's choice of treatment
P25 (weeks)	34.1	21.0	29.1
Median (weeks)	57.7	37.3	52.1
P75 (weeks)	81.3	64.9	90.1

Cortes J, et al. Lancet Oncol 2015

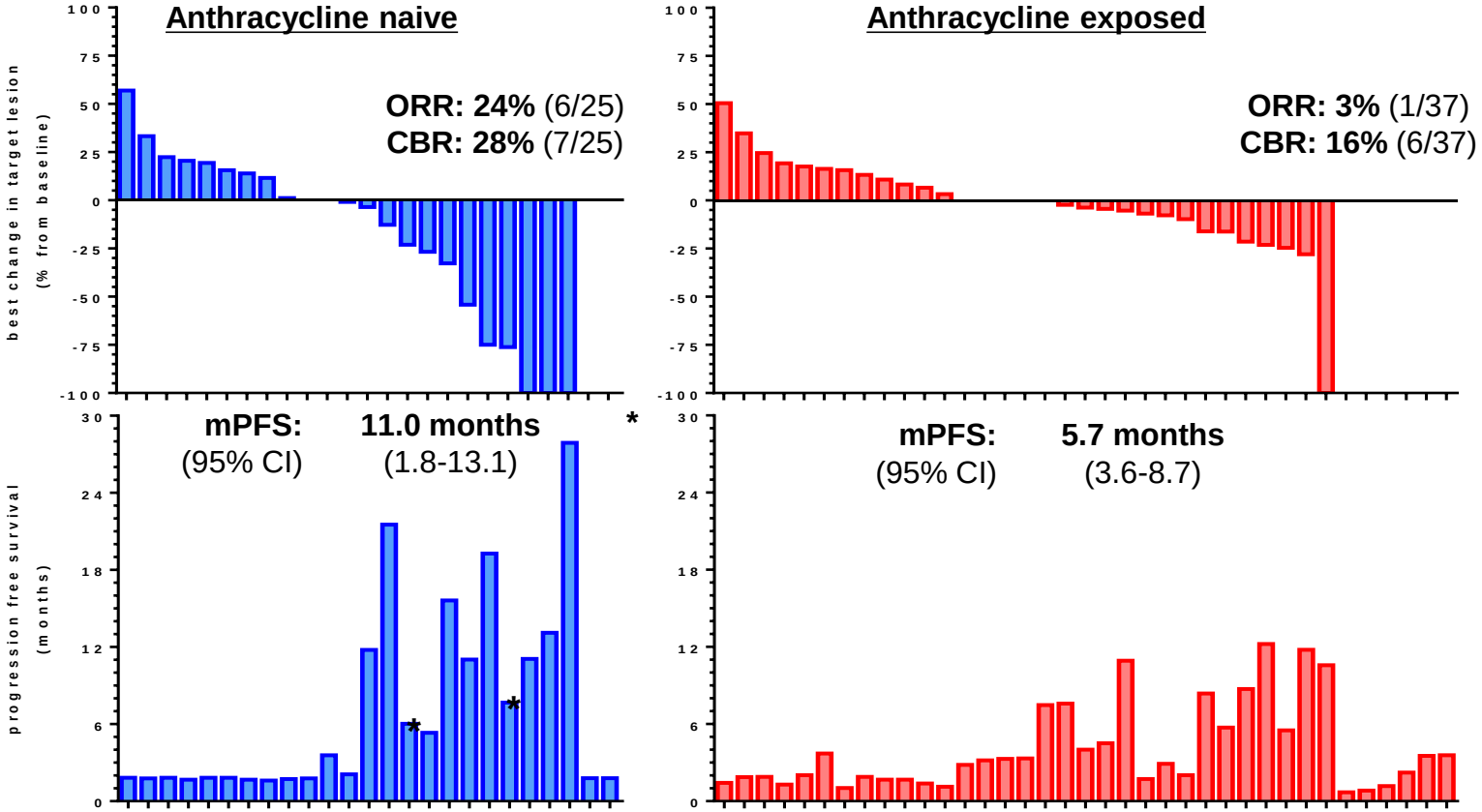
Antibody-Drug Conjugates: MM-302

(HER2-targeted PEGylated liposomal doxorubicin)





Antibody-Drug Conjugates: MM-302, Phase I



HERMIONE Study Schema (NCT02213744)

HER2-positive
locally advanced/metastatic BC
(N=250)

Anthracycline naive

Prior metastatic treatment with pertuzumab and T-DM1

Prior treatment with trastuzumab

1

1

MM-302
30 mg/m^2, Q3W
+ **trastuzumab**
6 mg/kg*, Q3W

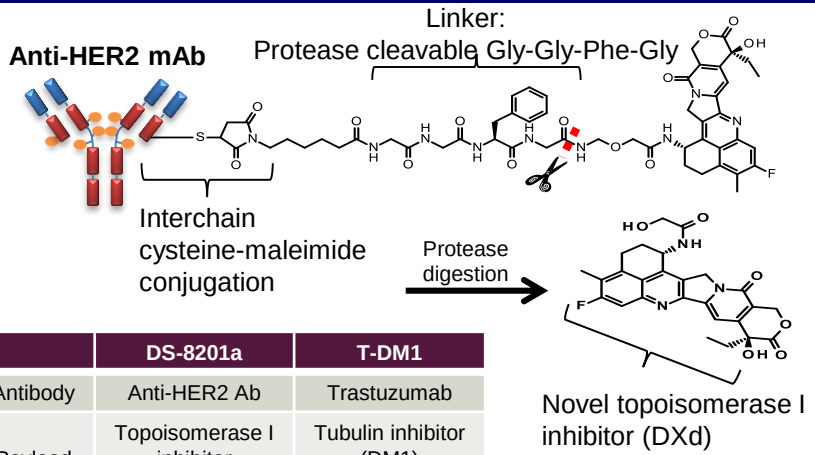
Chemotherapy of Physician's Choice
(*capecitabine, gemcitabine or vinorelbine*)
+ trastuzumab
6mg/kg*, Q3W

Enrollment expected to be completed late 2017

* 8 mg/kg trastuzumab loading dose

Antibody-Drug Conjugates: DS-8201a

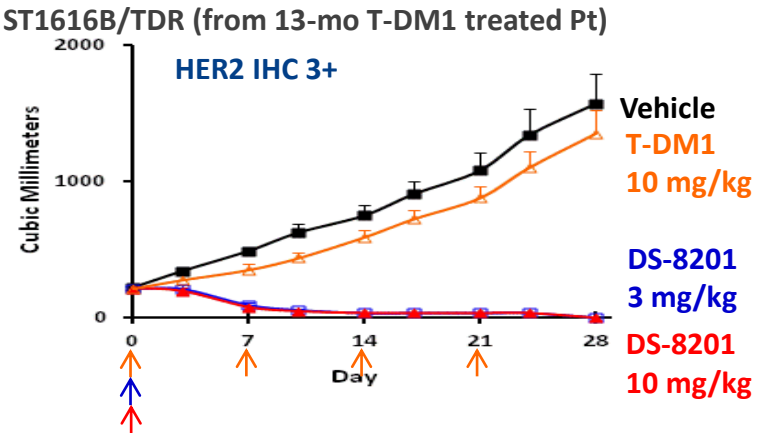
Structure of DS-8201a compared with T-DM1



	DS-8201a	T-DM1
Antibody	Anti-HER2 Ab	Trastuzumab
Payload	Topoisomerase I inhibitor (DXd)	Tubulin inhibitor (DM1)
DAR*	7-8	3.5

DAR *: Average drug-to-antibody ratio

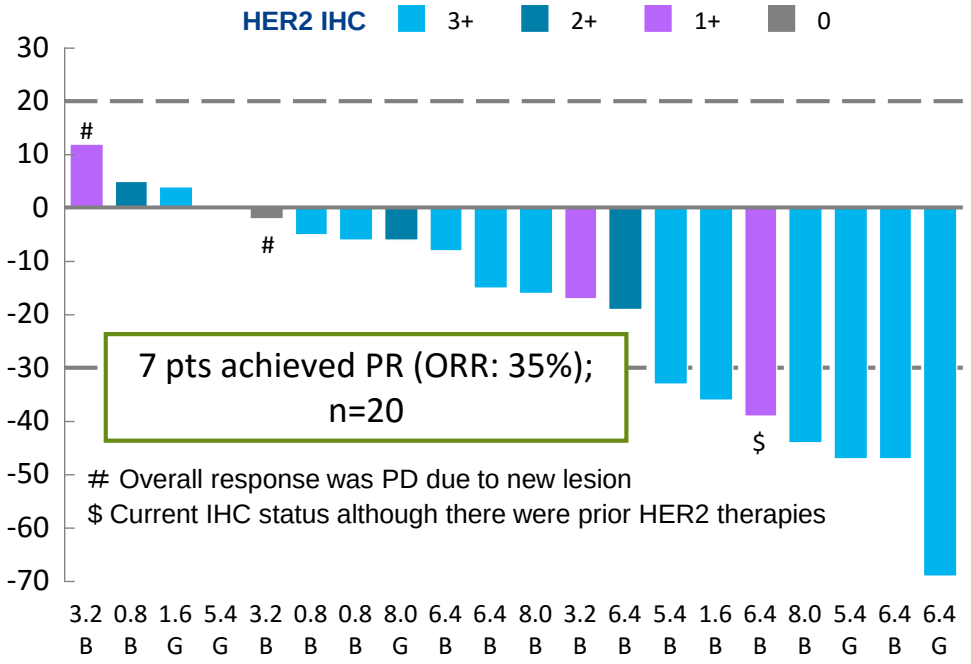
T-DM1 resistant breast cancer PDx mouse models



Tamura K, et al. ESMO 2016

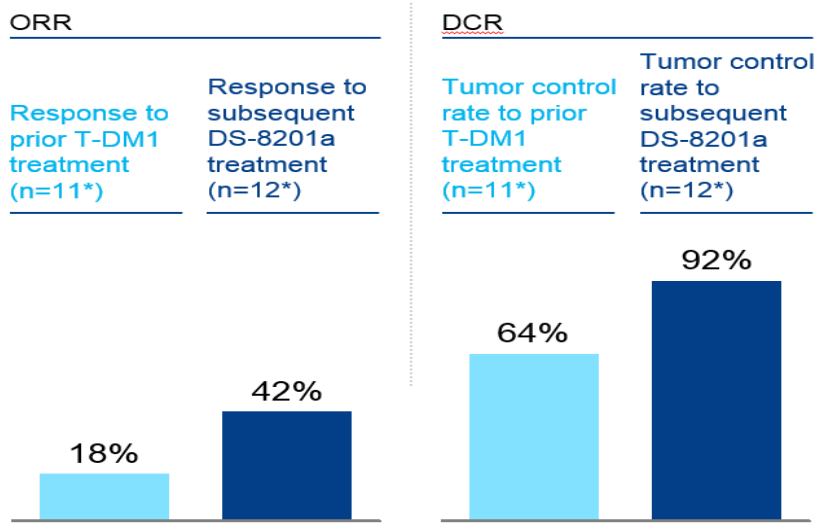
Antibody-Drug Conjugates: DS-8201a

Best percent change to date from baseline (all patients all doses)



Dose (mg/kg)
B: Breast Cancer. G: Gastric Cancer

Response to prior T-DM1 treatment compared to response to subsequent DS-8201a treatment (all doses)



Not only does DS-8201a treatment show benefit to patients, but **response is even better** than response to previous T-DM1 treatment

Prior T-DM1: Data by previous treatment of T-DM1
DS-8201a: Data by DS-8201a who already have been treated with T-DM1
* 1 of 12 patient data who had no information of the best response on prior T-DM1 treatment is excluded

Tamura K, et al. ESMO 2016

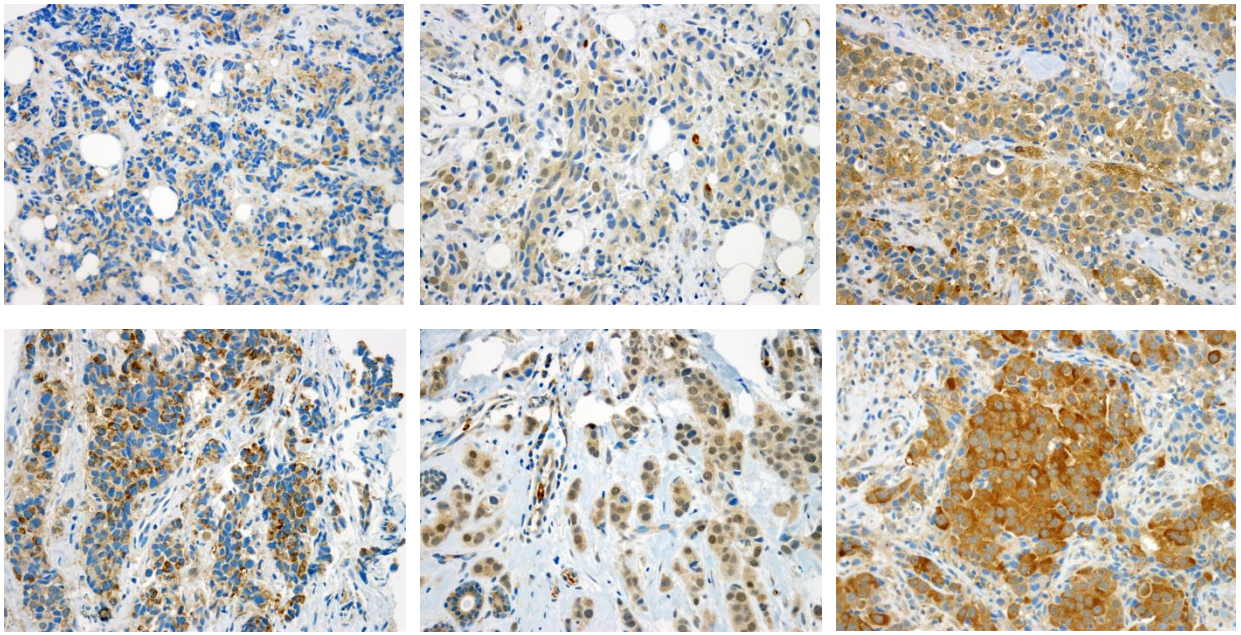
What about HER3? New opportunities

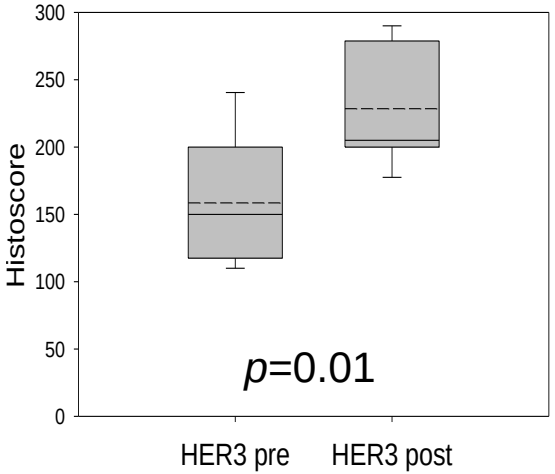
HER2 inhibition with lapatinib is followed by upregulation of HER3 in HER2+ tumors

HER3 IHC

Pre-therapy

Post-therapy (2 wks)



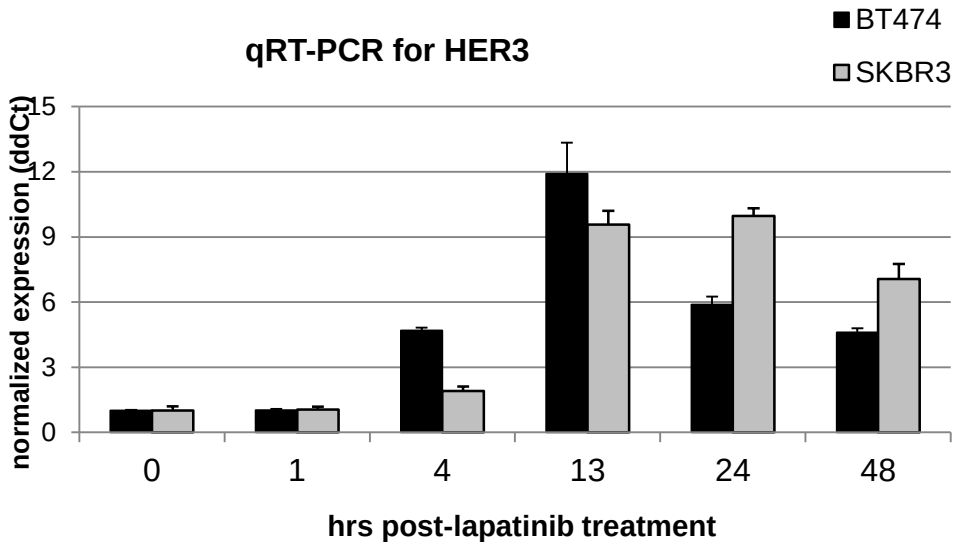


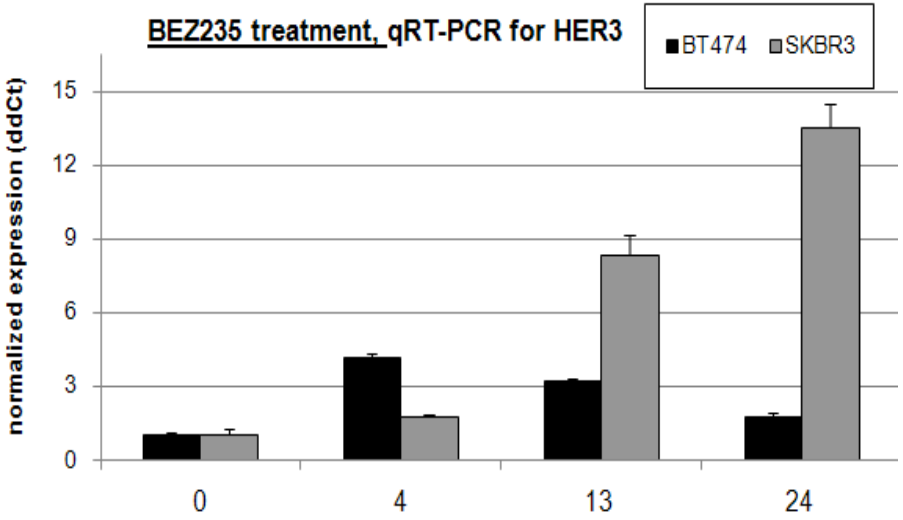
P-HER3 was also upregulated upon tx

Garrett, et al, Proc Natl Acad Sci USA 2011

What about HER3? New opportunities

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

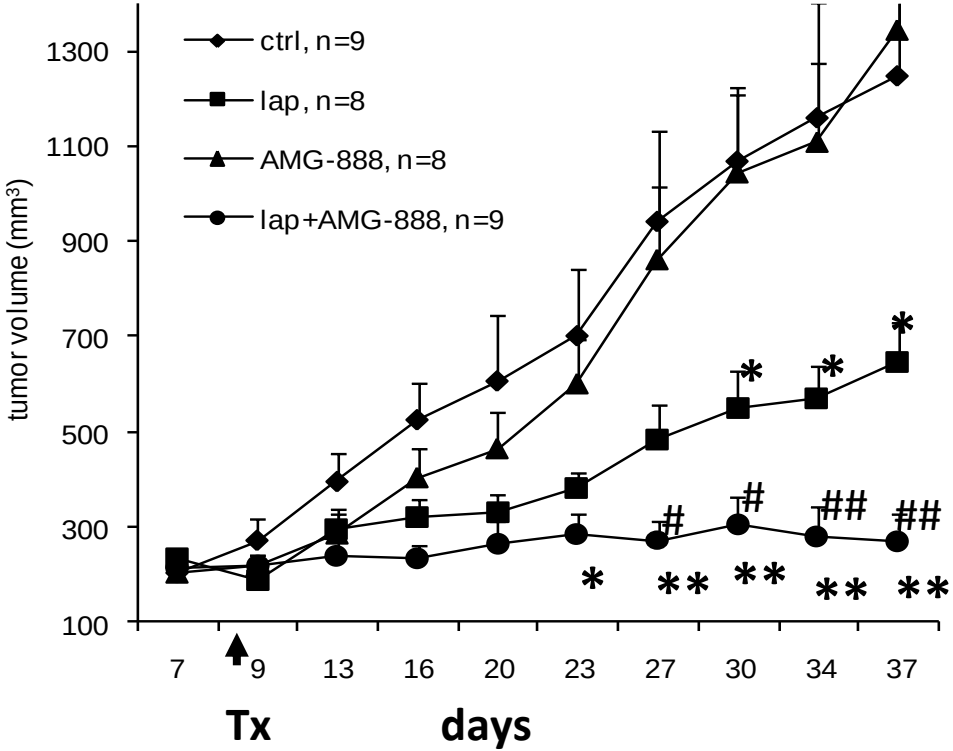




Garrett, et al, Proc Natl Acad Sci USA 2011

What about HER3? AMG-888

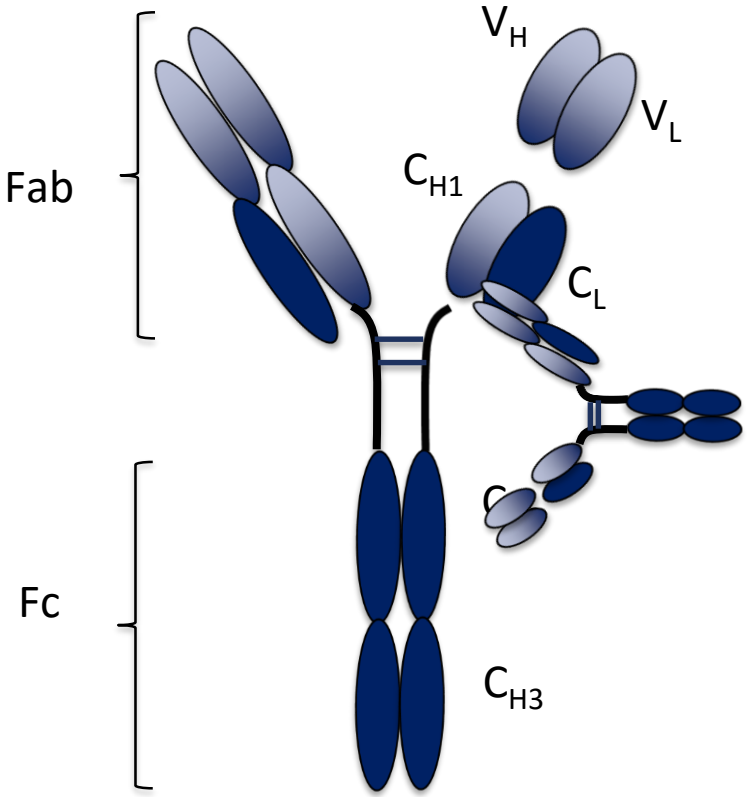
Neutralizing HER3 monoclonal antibody sensitizes BT-474 xenografts to lapatinib

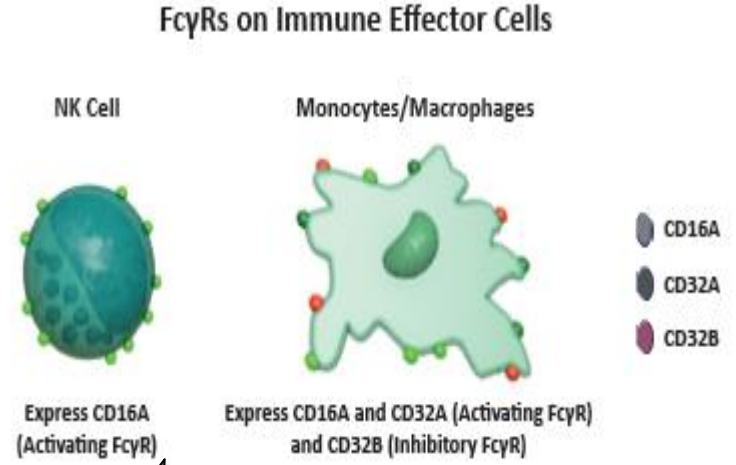


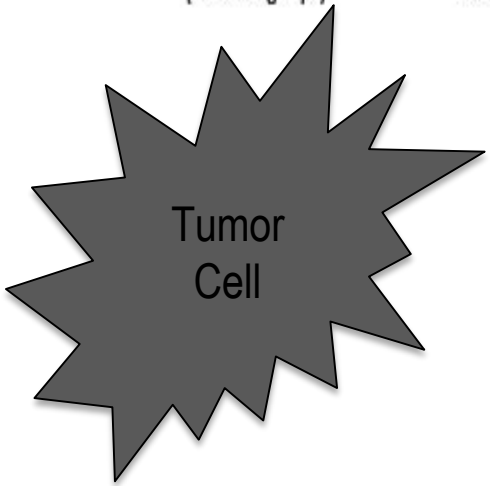
*** p<0.05, ** p<0.01 versus control**
 # p<0.05, ## p<0.01 versus lapatinib

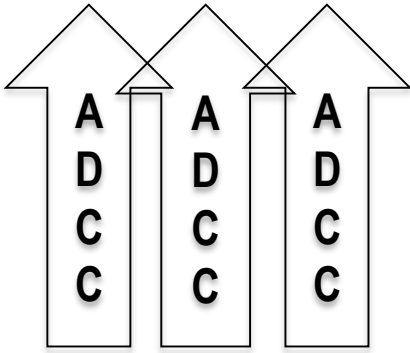
Garrett, et al, Proc Natl Acad Sci USA 2011

Margetuximab



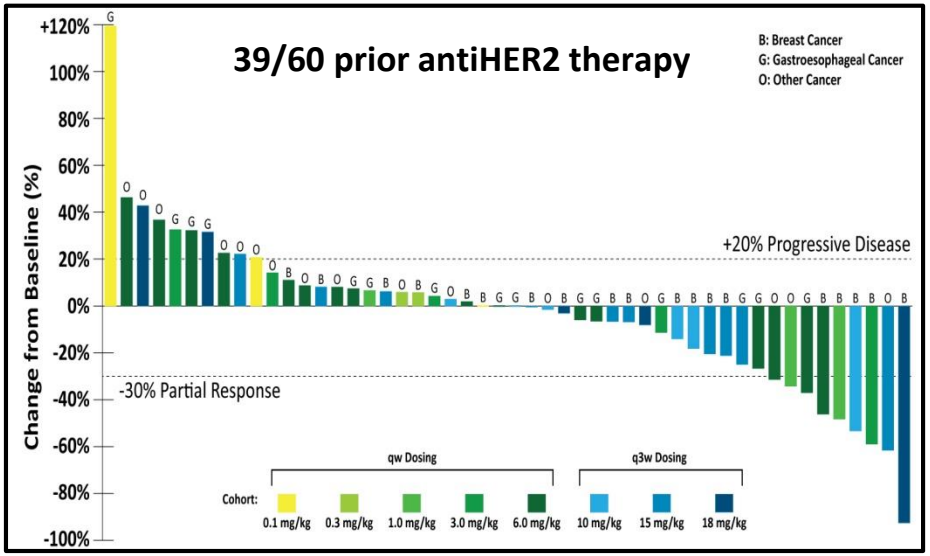




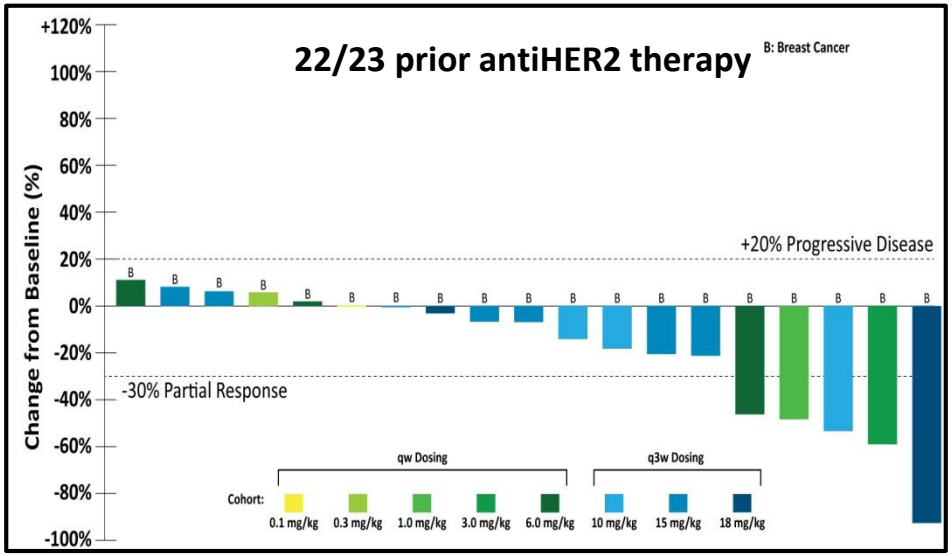


Margetuximab: FIH Phase 1 Study

All evaluable pts

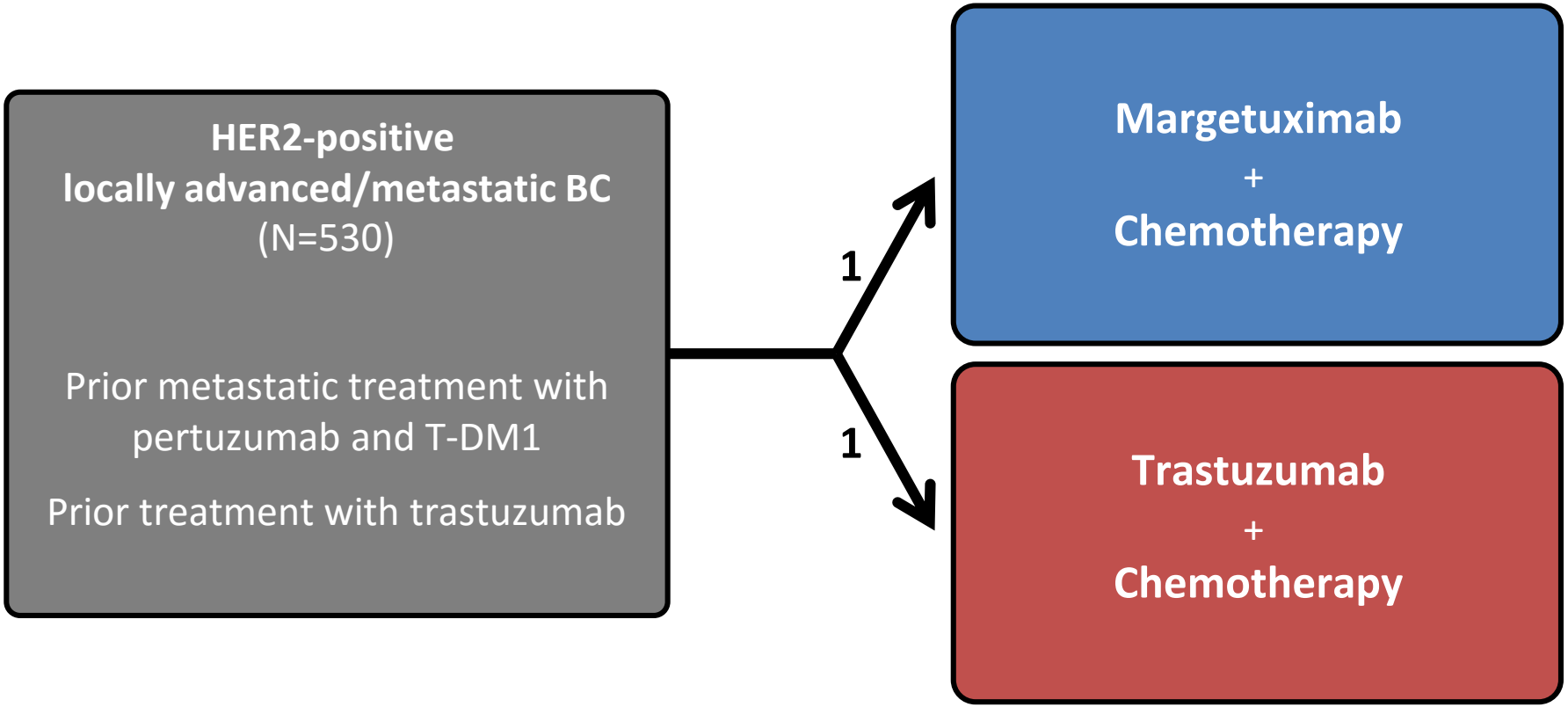


Evaluable MBC

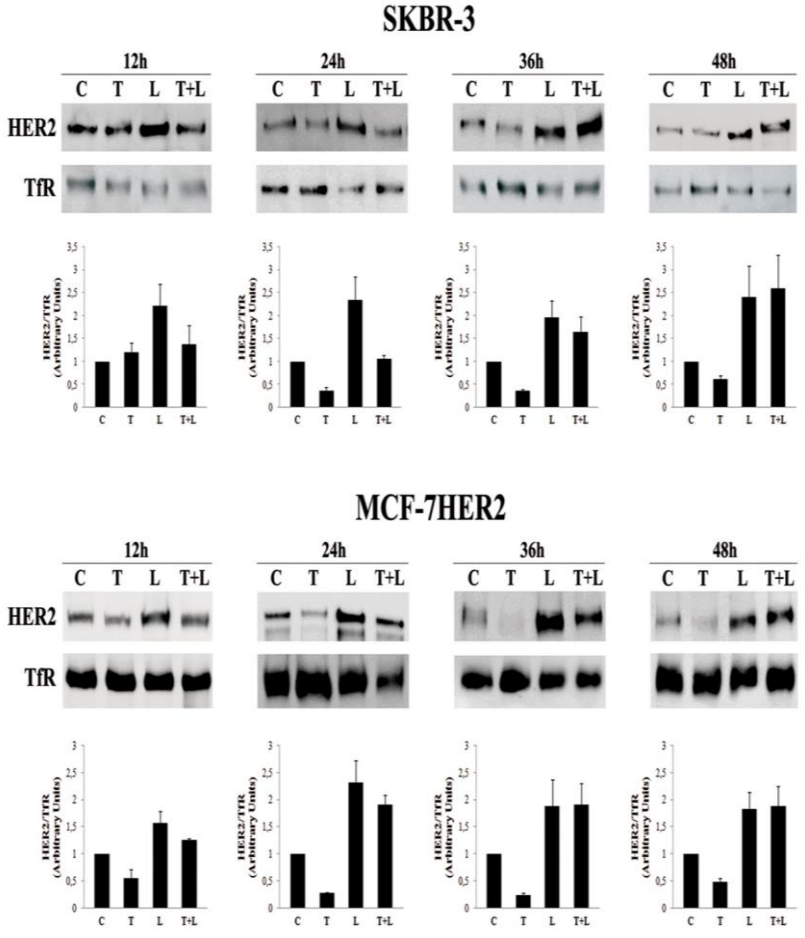


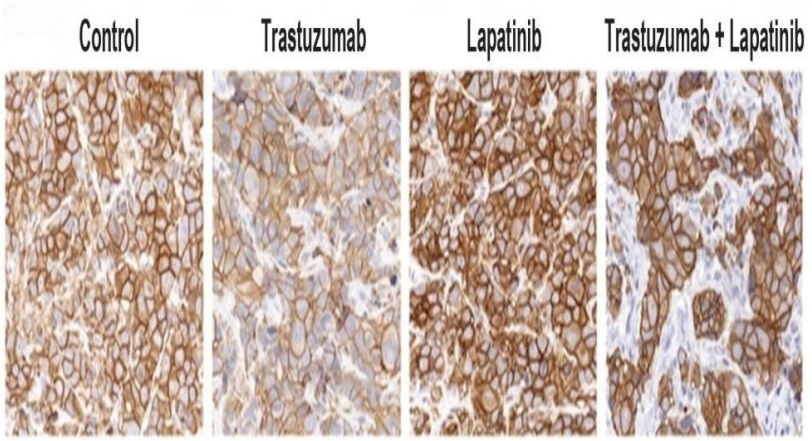
Burris HA, et al. ASCO 2015

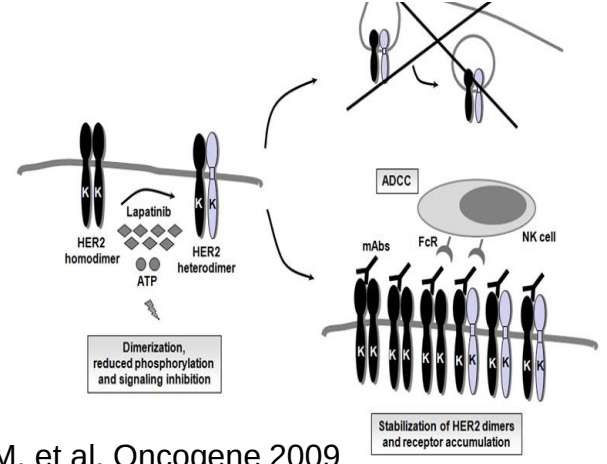
SOPHIA phase III Study Schema



New opportunities with margetuximab



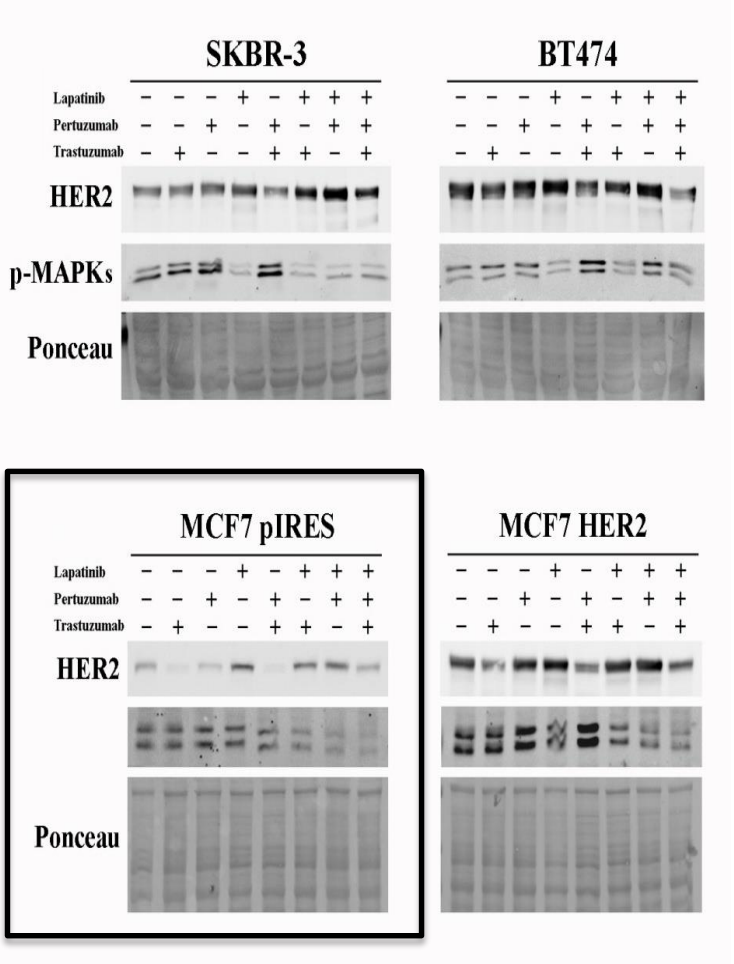




Scaltriti M, et al. Oncogene 2009

New opportunities with margetuximab

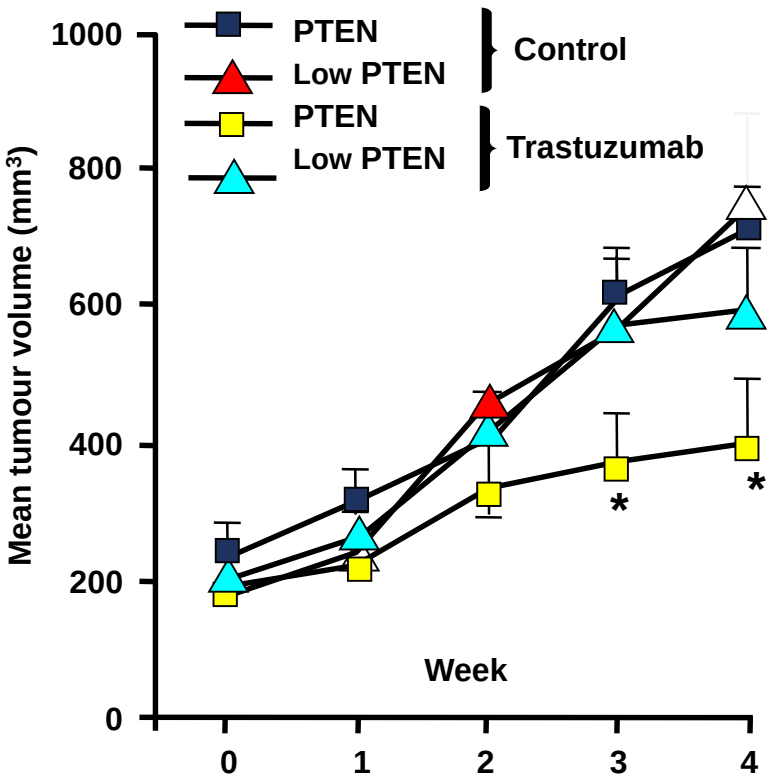
HER2 1+



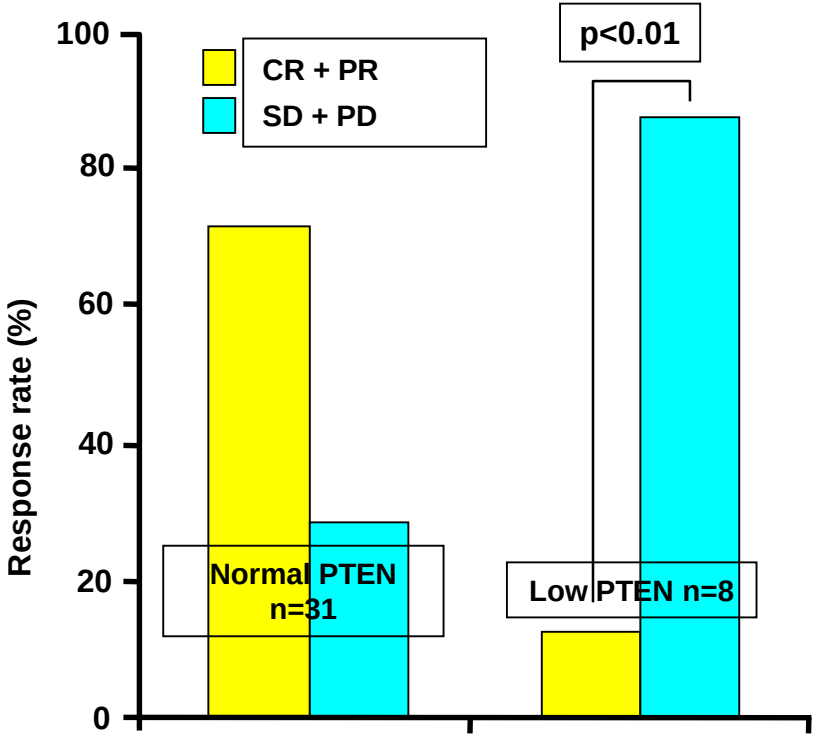
PI3K/AKT/mTOR inhibitors

Loss of PTEN results in reduced response to trastuzumab

Loss of PTEN† significantly reduced trastuzumab response in BT474 cell mouse xenografts



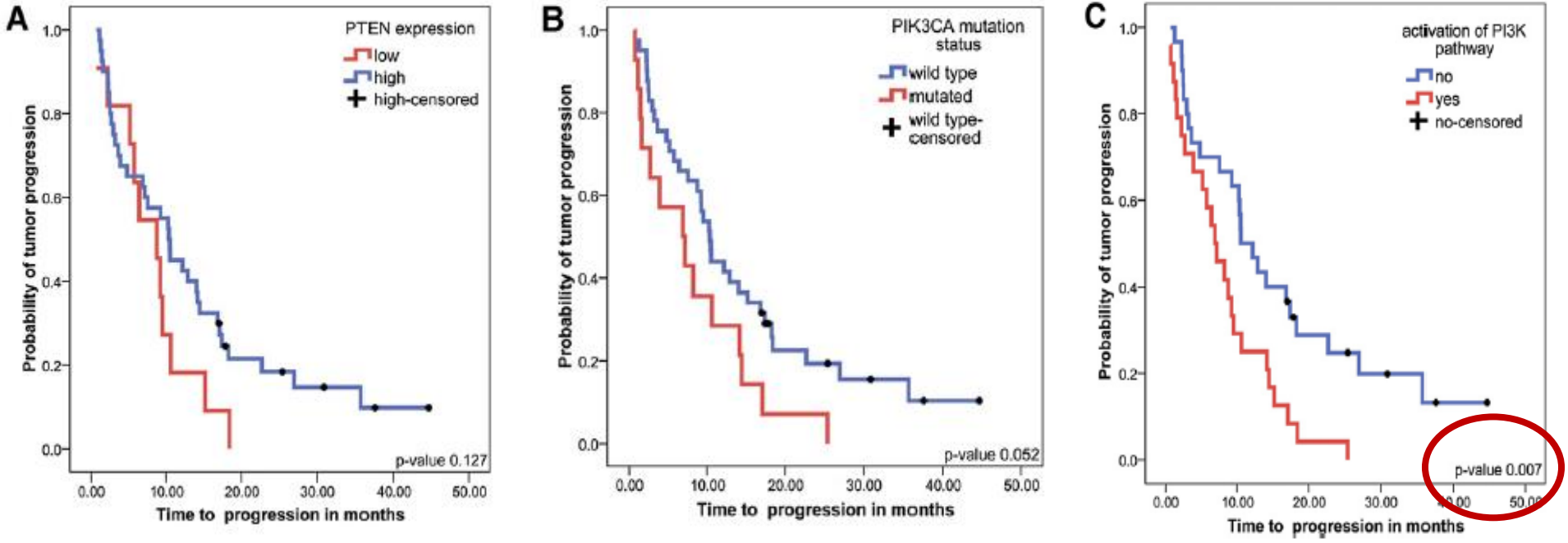
Low PTEN expression correlated with low response to trastuzumab in ErbB2-positive breast cancer patients



Nagata et al Cancer Cell 2004

PI3K/AKT/mTOR inhibitors

PI3K signaling pathway alteration results in reduced response to trastuzumab



Berns, et al. Cancer Cell 2007

Everolimus

BOLERO 3 randomized phase III study

Trastuzumab-resistant MBC
Prior taxane
≤3 Lines chemotherapy
HR status known

R

Trastuzumab weekly
Vinorelbine IV 25mg/m2 weekly
Placebo

N = 569

Trastuzumab weekly
Vinorelbine IV 25mg/m2 weekly
Everolimus 5mg/d

Prior treatment:

- Trastuzumab 100%, Pertuzumab 3%, T-DM1 4%

Andre F et al Lancet Oncology 2014

Everolimus

BOLERO 3 randomized phase III study: Primary endpoint

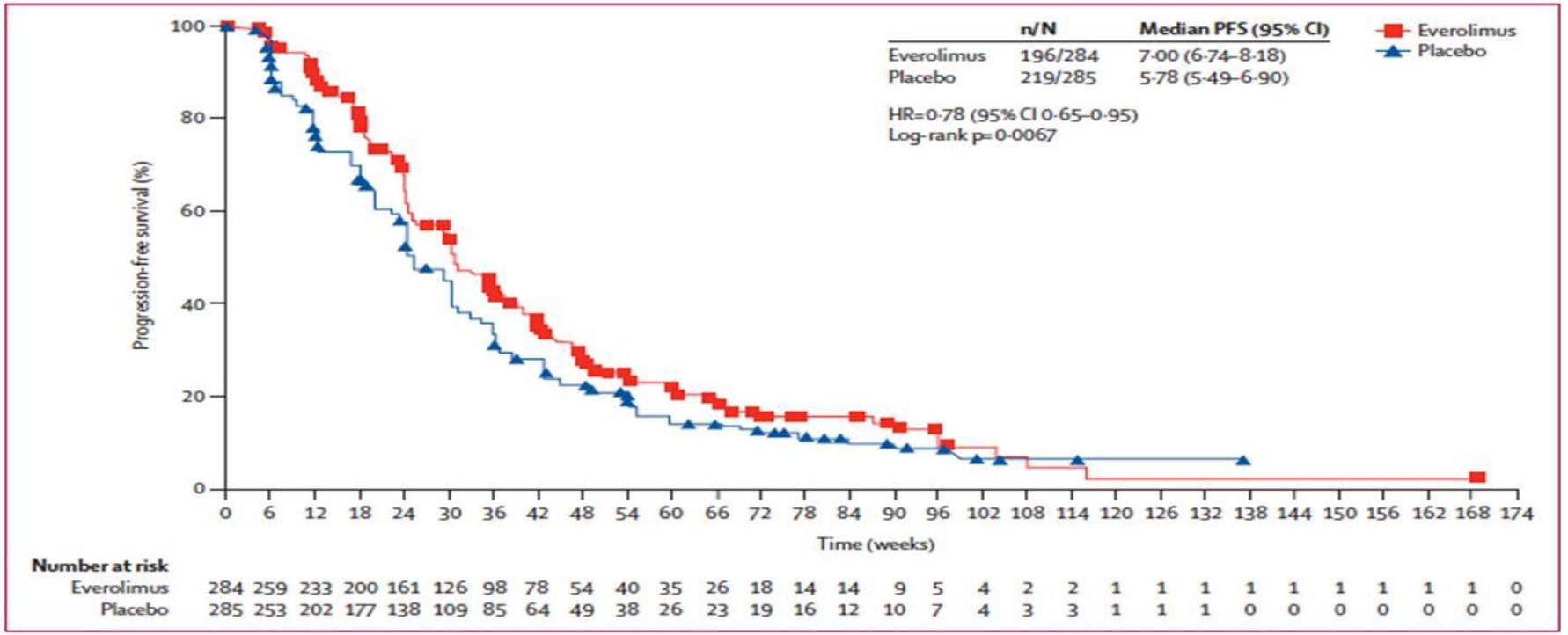
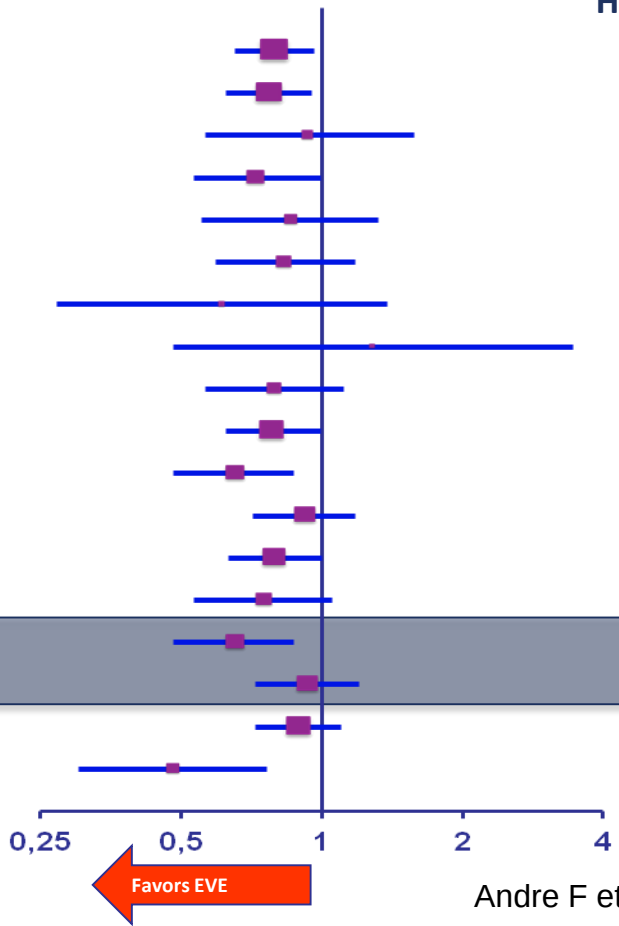


***Figure 2*: Kaplan-Meier estimates of locally assessed progression-free survival in the full analysis set**
Patients were stratified by previous lapatinib use. Symbols represent censoring events. PFS=progression-free survival.

Andre F et al Lancet Oncology 2014

Everolimus: BOLERO 3 Subgroup Analysis

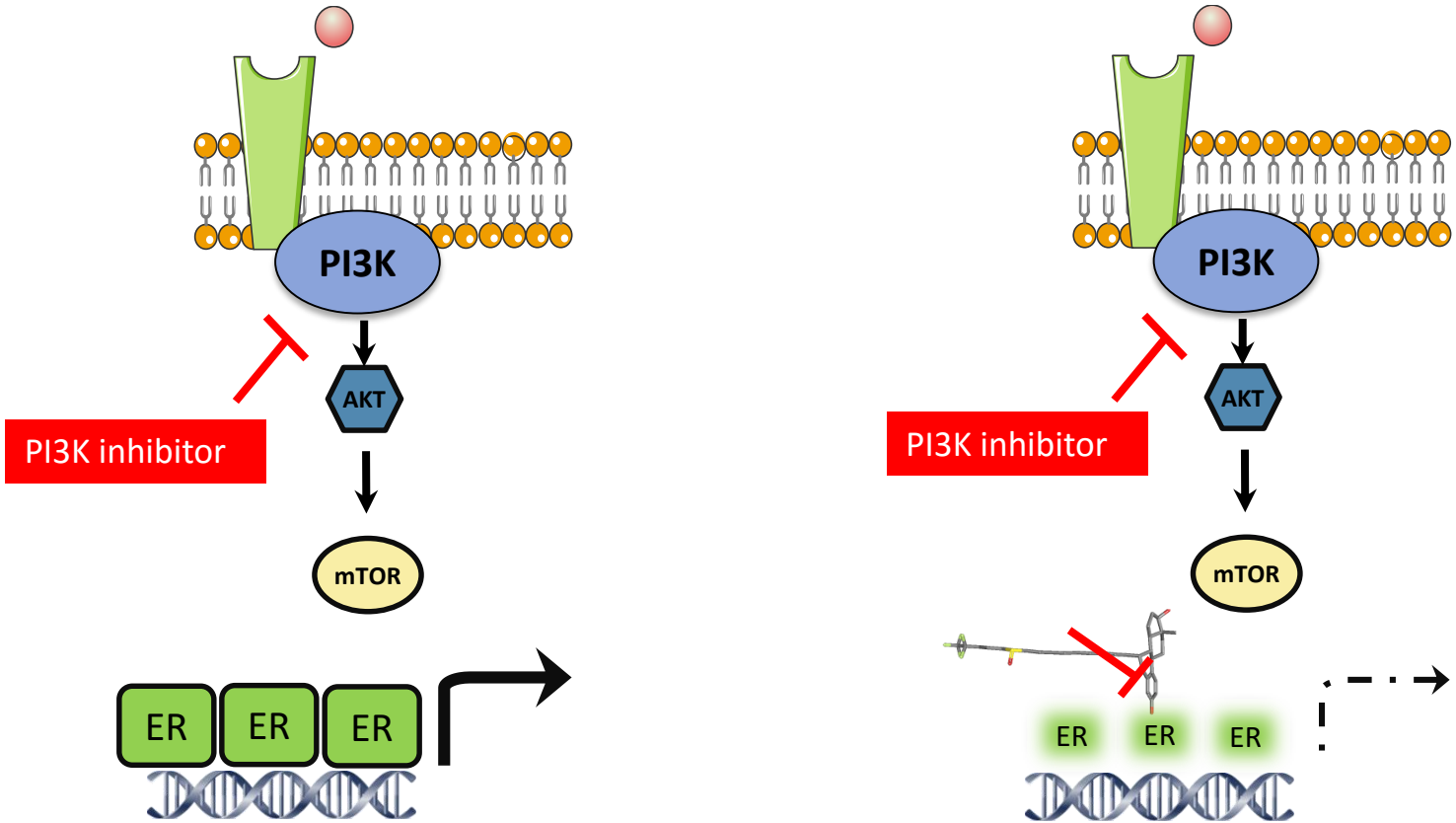
Subgroup		N	Hazard Ratio [95% CI]
All		569	0.78 [0.65-0.95]
Age	< 65 years	472	0.77 [0.62-0.95]
	≥ 65	97	0.93 [0.56-1.57]
Region	Europe	223	0.72 [0.53-0.99]
	North America	123	0.86 [0.55-1.32]
	Asia	166	0.83 [0.59-1.18]
	Latin America	36	0.61 [0.27-1.38]
	Other	21	1.28 [0.48-3.45]
Prior lapatinib*	Yes	161	0.79 [0.56-1.11]
	No	408	0.78 [0.62-0.99]
Prior adj/neo trastuzumab**	Yes	251	0.65 [0.48-0.87]
	No	318	0.92 [0.71-1.18]
Baseline ECOG PS	0	382	0.79 [0.63-1.00]
	1 or 2	186	0.75 [0.53-1.05]
Hormonal status	ER^-/PgR^-	250	0.65 [0.48-0.87]
	ER^+/PgR^+	317	0.93 [0.72-1.20]
Visceral involvement	Yes	439	0.89 [0.72-1.10]
	No	130	0.48 [0.30-0.76]



Andre F et al Lancet Oncology 2014

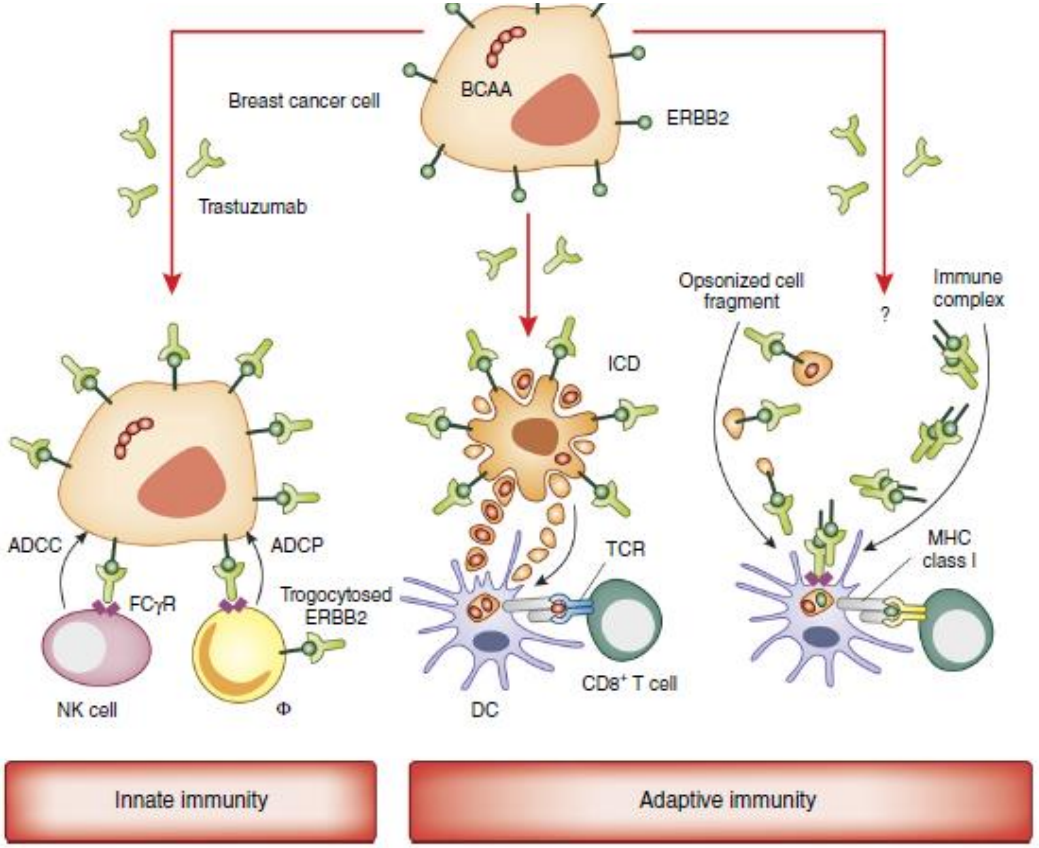
Rationale for combining taselisib and fulvestrant

PI3K inhibition augments ER function and dependence in ER+ BC



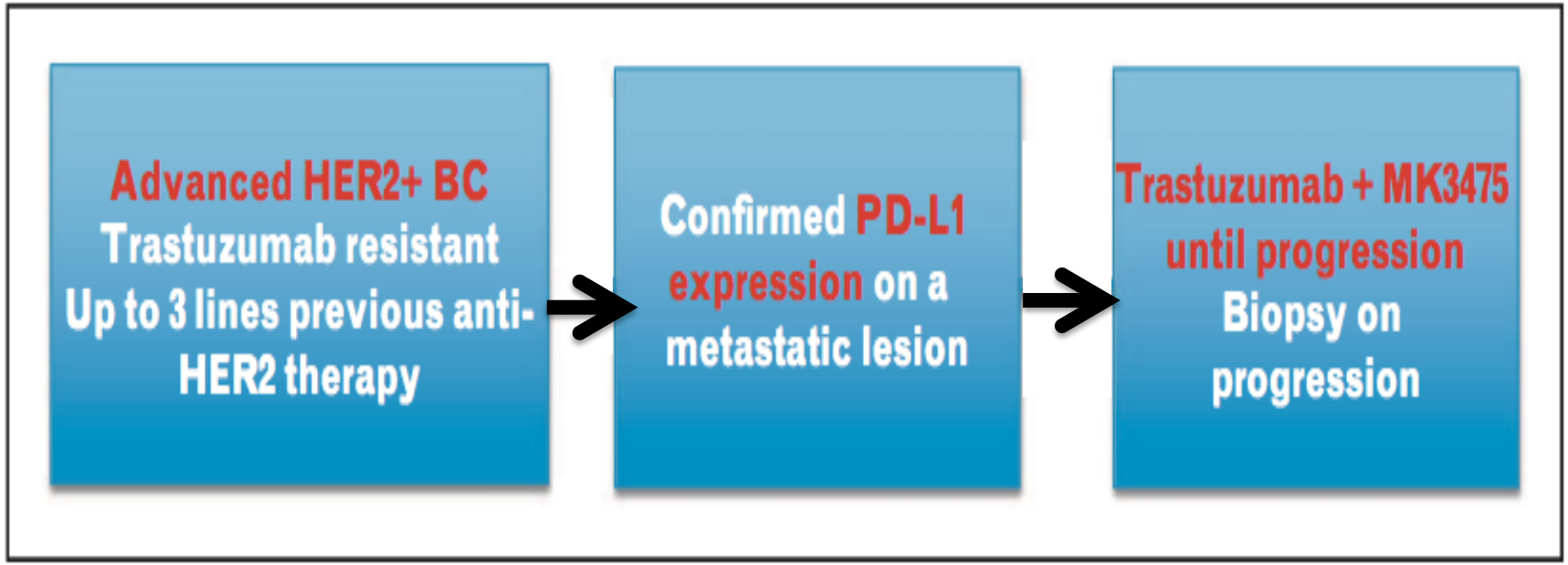
Bosch A, et al. Sci Transl med 2015

HER2 as a target in breast cancer therapy



Adapted from. G. Kroemer , et al. Nature Medicine 2015

BC HER2 POSITIVO: PANACEA

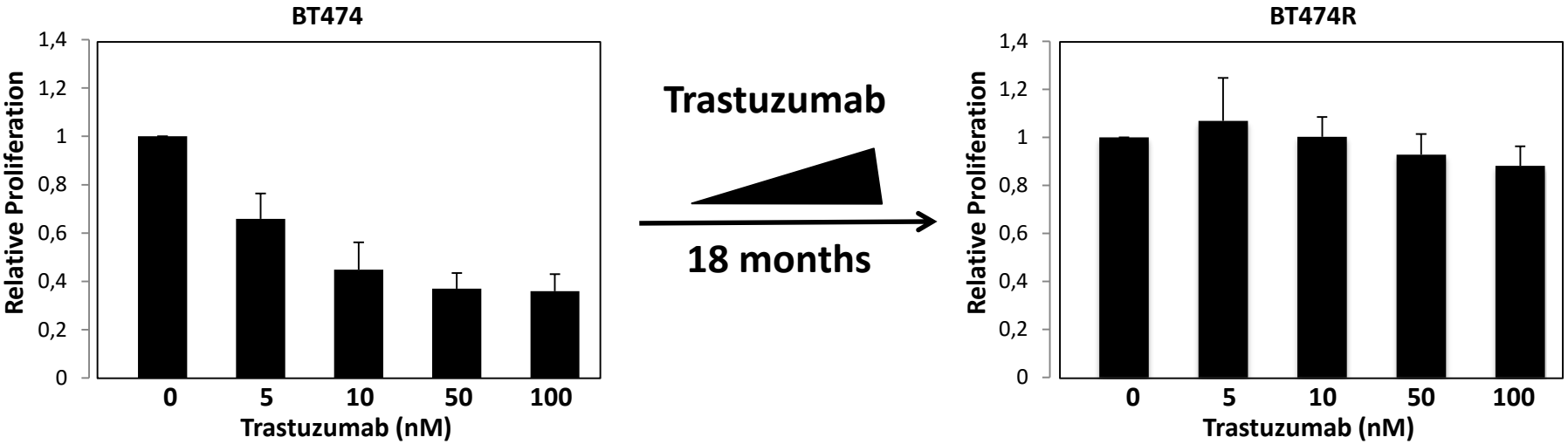


NCT02425891

CDK inhibitors

Selection of trastuzumab resistant BT474 (BT474R) cells

BT474R do not respond to the antiproliferative
effects of trastuzumab *in vitro*

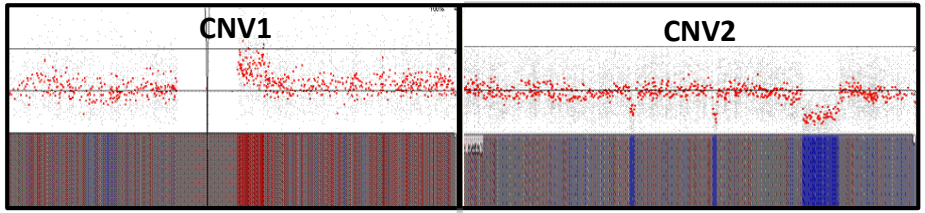


(IC50>1uM)

Scaltriti M, et al, PNAS 2011

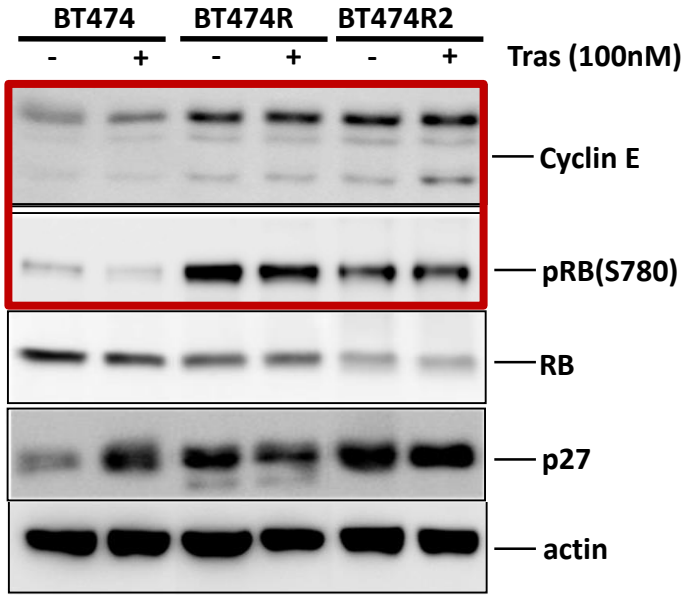
Characterization of BT474R cells

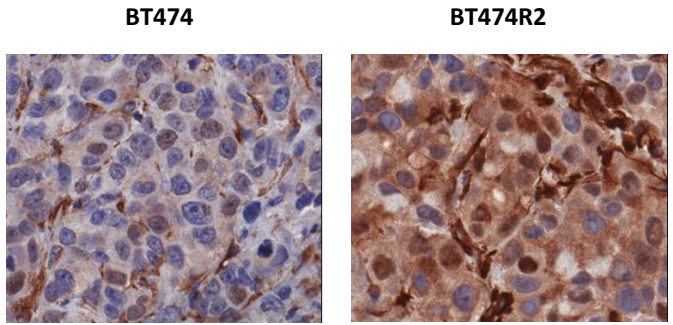
BT474R cells present cyclin E amplification and overexpression



CNV1 (Chr.19)
UQCRFS1
POP4
PLEKHF1
C19orf12
CCNE1
C19orf2
ZNF536

CNV2 (Chr.14)
GPR65
GALC



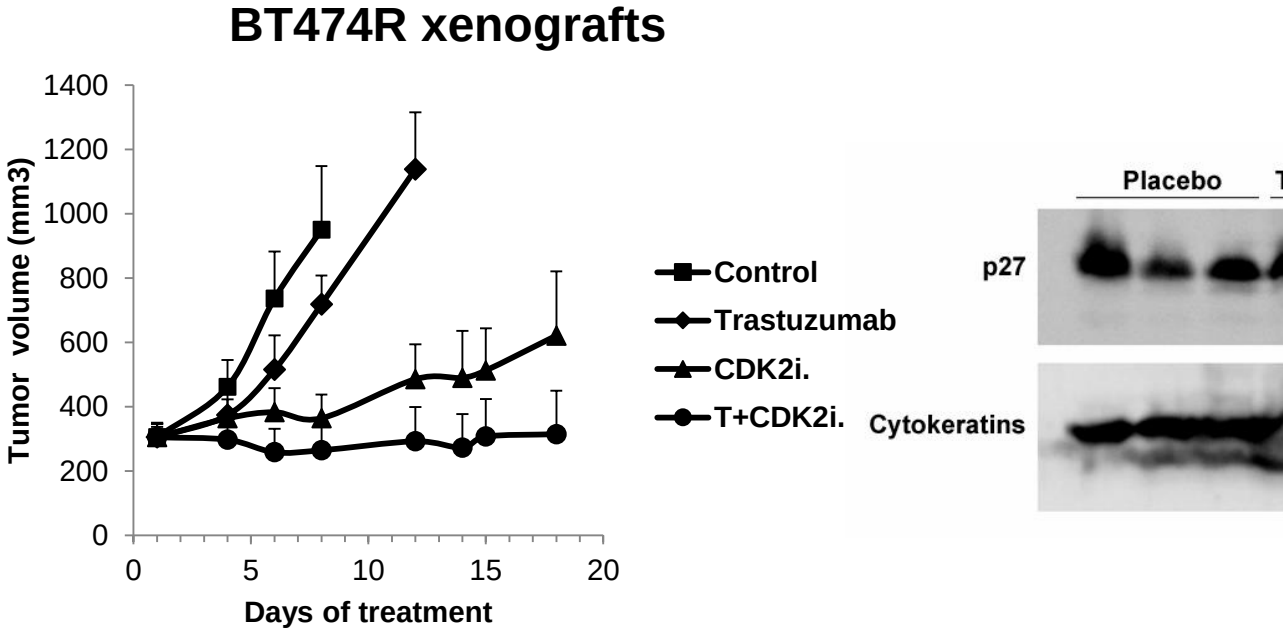


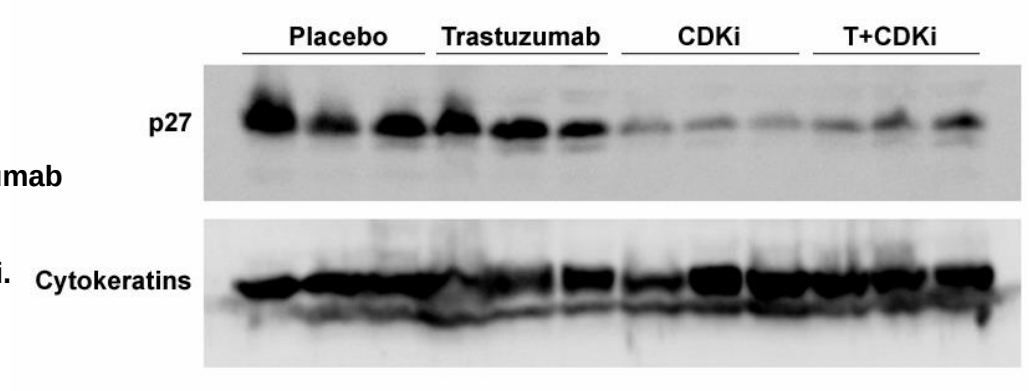
IHC: CYCLIN E

Scaltriti M, et al, PNAS 2011

Cyclin E/CDK2 addiction of BT474R cells

CDK2 inhibition reduces tumor growth of BT474R-derived xenografts

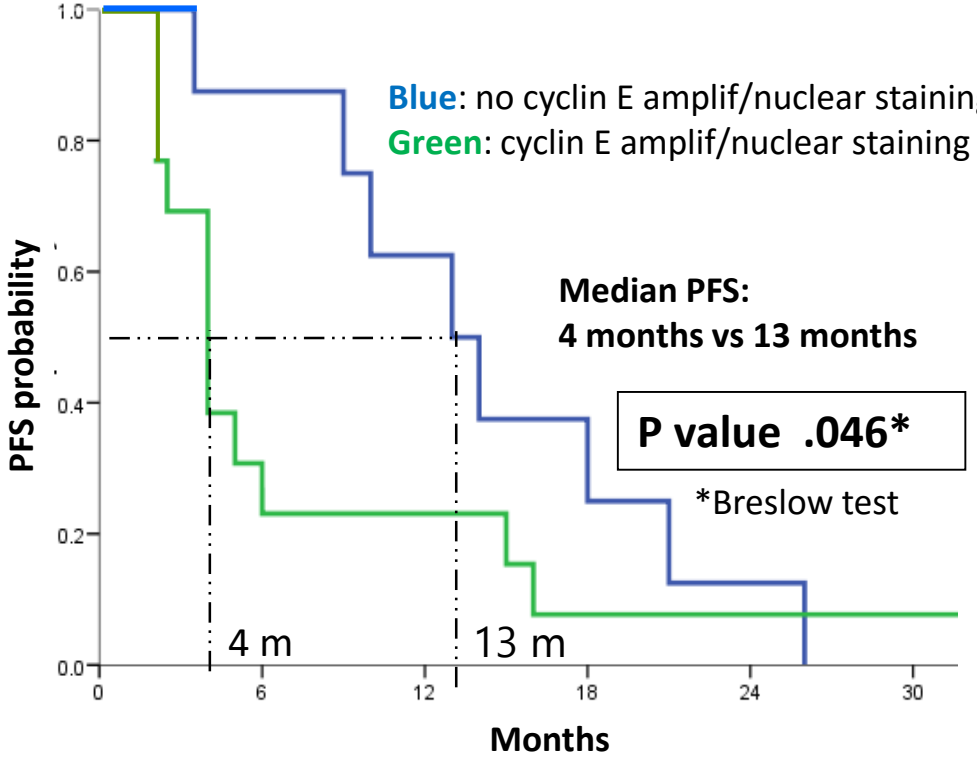




Scaltriti M, et al, PNAS 2011

Cyclin E amplification/overexpression in HER2+ patients and resistance to trastuzumab

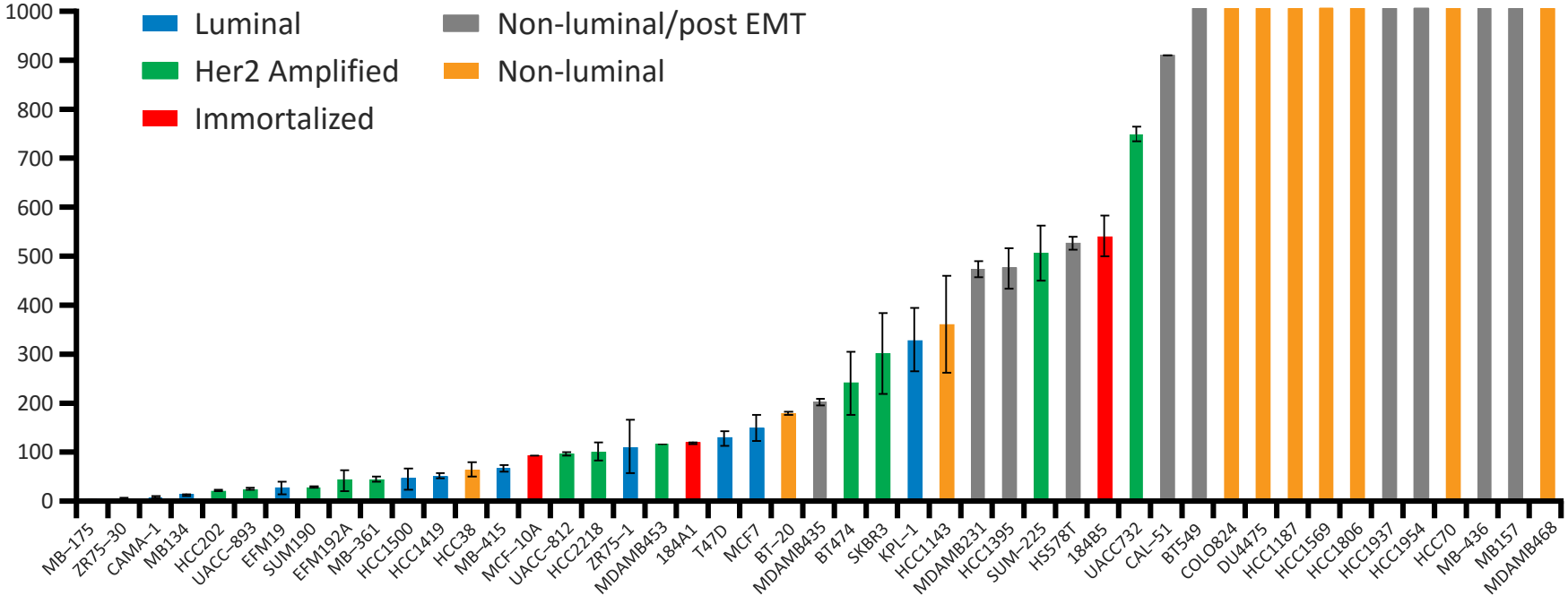
Cohort of patients with cyclin E + (n=16)



- HER+ MBC
- Cyclin E amplification/overexpression
- Treated with 1st-line trastuzumab-based
- Compared to similar cohort of patients cyclin E – (n=8)

Scaltriti M, et al, PNAS 2011

Sensitivity to Palbociclib in different human breast cancer cell lines



Luminal ER-positive and HER2-amplified breast cancer cell lines and HER2-amplified breast cancer cell lines are most sensitive to CDK4/6 inhibition of proliferation

Finn RS, et al. Breast Cancer Res 2009

CDK4/6 inhibitor: Palbociclib

Phase Ib trial: NCT01976169

- T-DM1 + palbociclib 3+3 trial design dose escalation cohorts

Inclusion:

- Previously received trastuzumab or other HER2 targeted therapies
- Tumor must be HER2-positive and RB-proficient.
  - RB-proficiency determined by tumor biopsy demonstrating RB normal and p16in4a low
- Primary outcome: MTD, DLT

CDK4/6 inhibitor: Palbociclib

PATRICIA: Palbociclib and Trastuzumab ± Letrozole in HER2-positive MBC

Inclusion:

- At least 2 (maximum 4) previous systemic anticancer treatment lines
- Must include trastuzumab or another anti-HER2 treatment in combination with a taxane or capecitabine.
- Previous treatment may include hormone therapy, other targeted anti-HER2 drugs (e.g., lapatinib, neratinib, pertuzumab, T-DM1) or other chemotherapy agents.

Arm A	Arm B1	Arm B2
ER negative, HER2 positive	ER positive, HER2 positive	ER positive, HER2 positive
Palbociclib + trastuzumab	Palbociclib + trastuzumab	Palbociclib + trastuzumab + letrozole

CDK4/6 inhibitor: Abemaciclib

NCT02057133

- Evaluate safety abemaciclib in combination with letrozole, anastrozole, tamoxifen, exemestane, exemestane plus everolimus, or trastuzumab

monarcHER NCT02675231

- Phase 2, randomized,, 3-arm, open-label study abemaciclib + trastuzumab + fulvestrant vs. abemaciclib + trastuzumab vs. single agent TPC + trastuzumab in women with HR+, HER2+ MBC
- Primary outcome: PFS. Goal 225 pts
- Inclusion: Postmenopausal, At least 2 anti-HER2 agents (T-DM1 mandatory)

I3Y-MC-JPBO(b)

- Phase 2 study in pts with brain metastatic secondary to BrC, NSCLC, Melanoma
- Breast cancer cohorts: HR+, HER2 +; or HR+, HER2 –
- Parenchymal or leptomeningeal disease

Conclusions

HER2+ MBC: Still an unmet need...