Therapeutic Strategies Targeting HER2neu

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Disclosures & Acknowledgements

- Serve on multiple pharma speaker bureaus
- No industry input in the development of this presentation
- Slides are original and obtained from downloadable content

Objectives

- Celebrate the HER Family Story
- Review therapeutic mechanisms of Action
- Analyze pertinent clinical trial data
- Offer observational conclusions

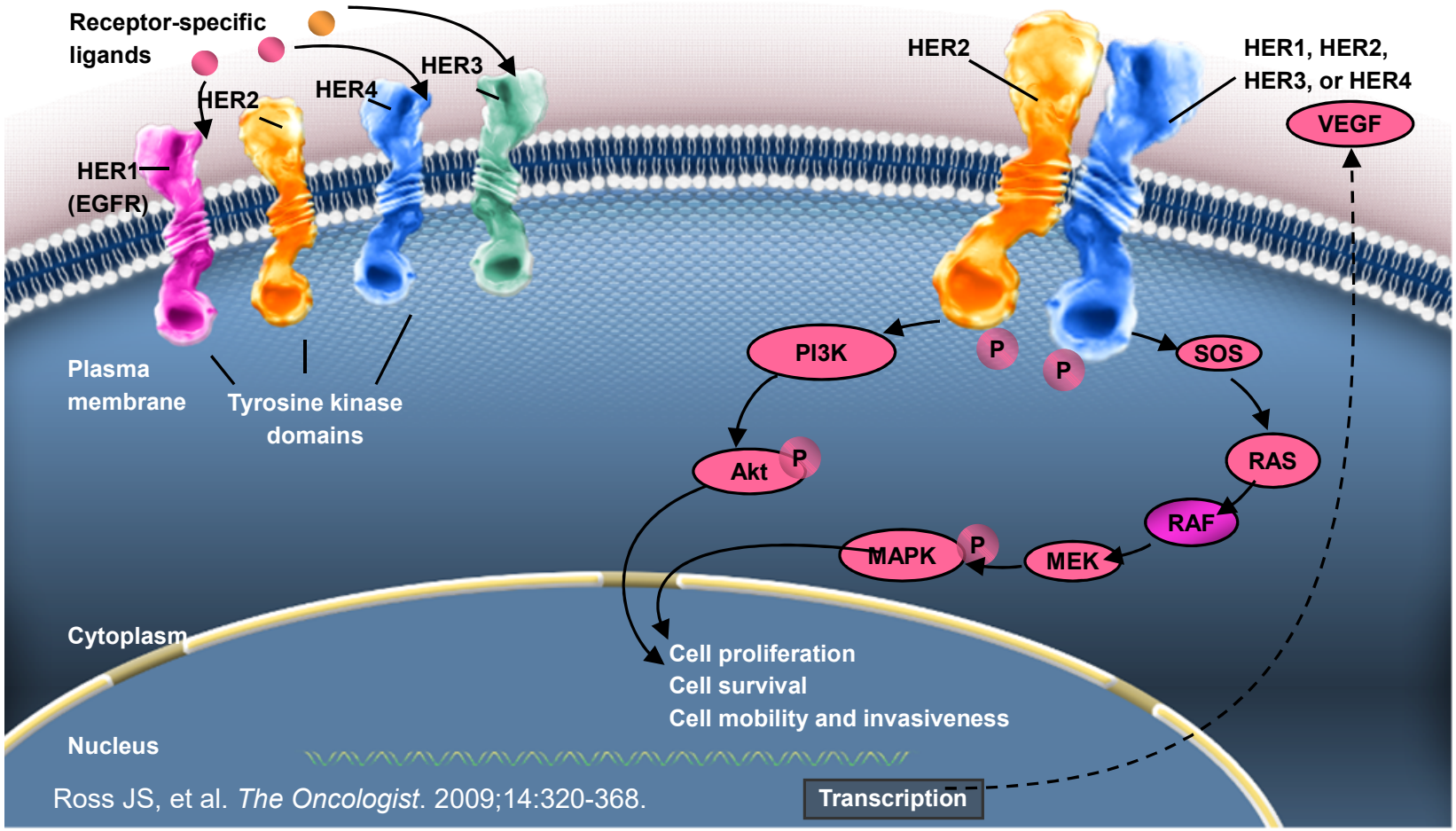
THE HER FAMILY STORY

HER2neu Positive Breast Cancer

- Accounts for 15-20% of breast cancer cases
- Short DFS and OS compared to other subtypes when treated with conventional therapy
- HER2 targeted therapy dramatically changed outcome
- Multiple agents available: questions about optimal (combinations and) sequencing

Gradishar W. *Curr Oncol Rep.* 2011;13:11-16.

HER Family Signal Transduction Promotes Proliferation, Survival, and Invasiveness



Ross JS, et al. *The Oncologist*. 2009;14:320-368.

THERAPEUTIC AGENT MECHANISMS

HER2neu Targeted Agents

Monoclonal Antibodies

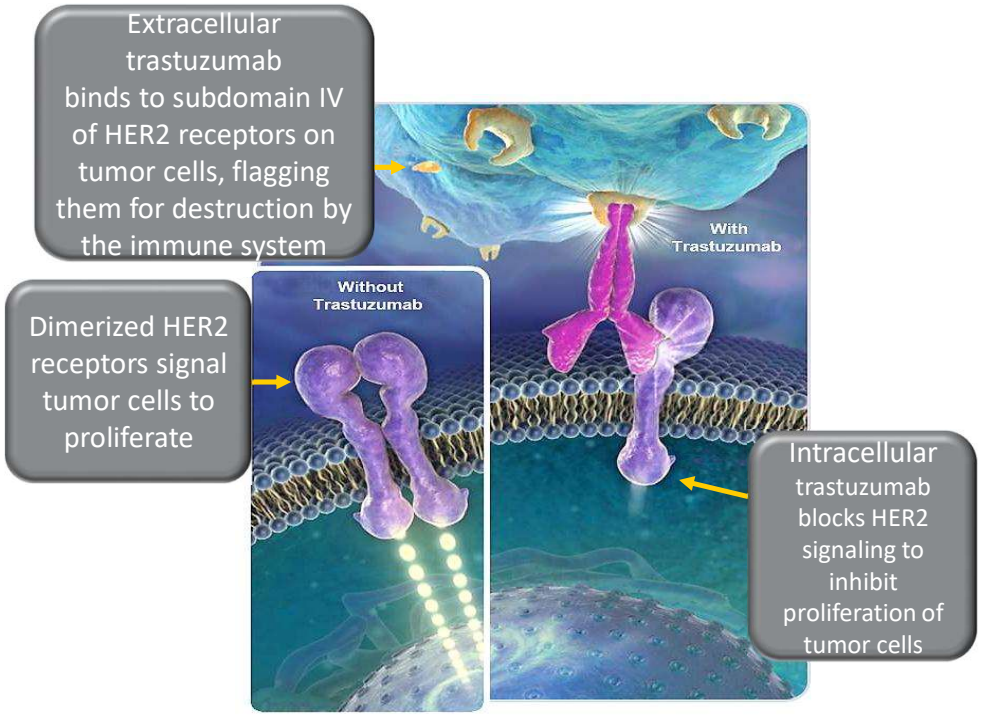
- Trastuzumab
- Pertuzumab
- ado-Trastuzumab Emtansine

Tyrosine Kinase Inhibitors

- Lapatinib
- Neratinib
- *Tucatinib*

Trastuzumab Mechanism Of Action

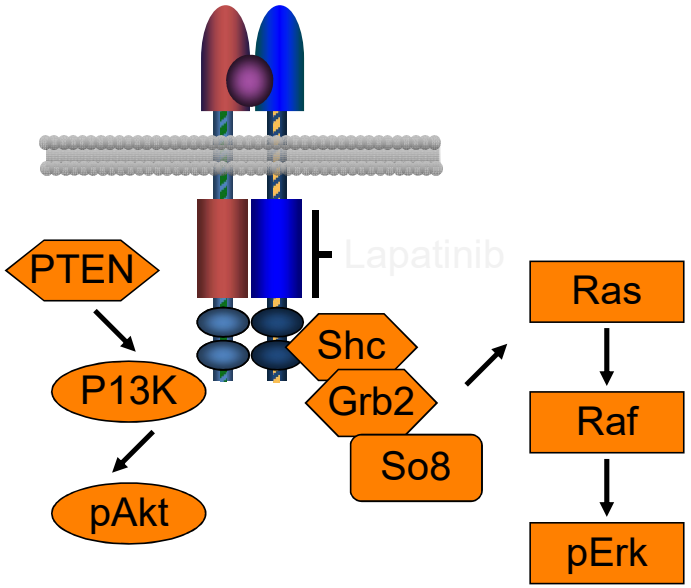
- Humanized monoclonal antibody specific for HER2
- Targets HER2 protein-overexpressing cells
- Proposed MOA based on preclinical studies
  - Extracellular
  - Intracellular



Arnould L, et al. Br J Cancer 2006;94:259-267. Bianco AR. J Chemother 2004;16(suppl 4):52-54. Harari D, Yarden Y. Oncogene 2000;19;6102-6114.
Lewis GD, et al. Cancer Immunol Immunother 1993;37:255-263.
Sliwkowski MX, et al. Semin Oncol 1999;26(suppl 12):60-70. Yakes FM, et al. Cancer Res 2002;62:4132-4141. Yarden Y. Oncology 2001;61(suppl 2):1-13.
Herceptin® (trastuzumab) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2010.

Lapatinib Mechanism Of Action

- **Lapatinib: oral tyrosine kinase inhibitor of HER1 and HER2**
  - **Blocks signaling through EGFR and HER2 homodimers and heterodimers**
  - **May also prevent signaling between HER1/HER2 and other HER family members**

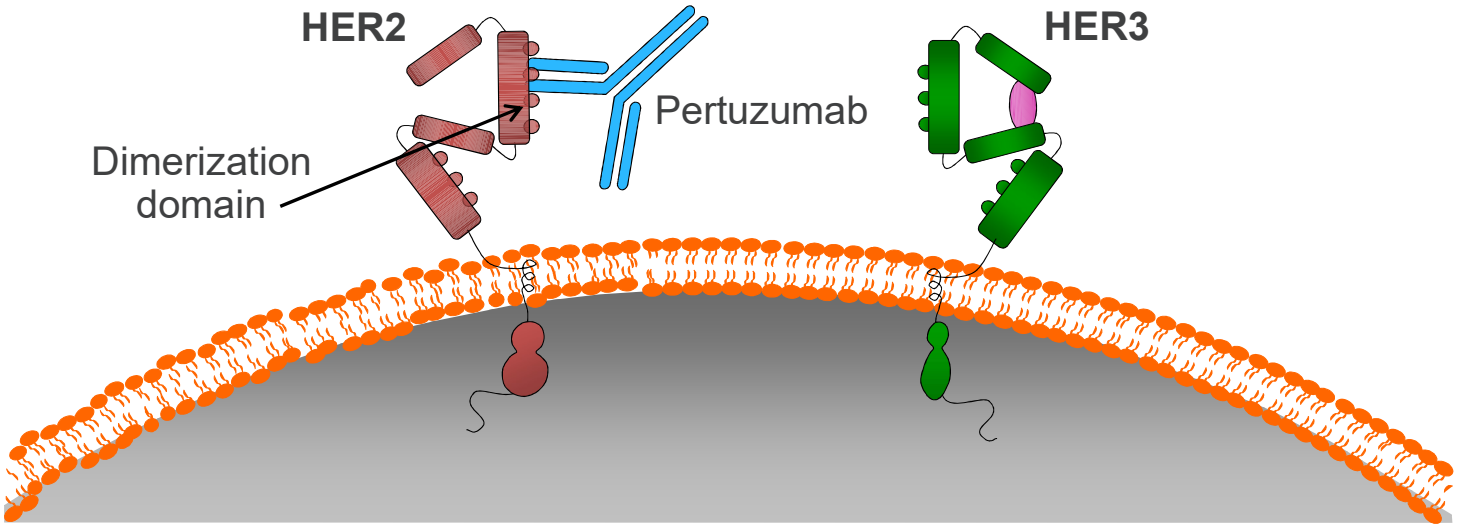


Rusnak DW, et al. *Mol Cancer Ther*. 2001;1:85-94; Xia W, et al. *Oncogene*. 2002;21:6255-6263.

Pertuzumab Mechanism Of Action

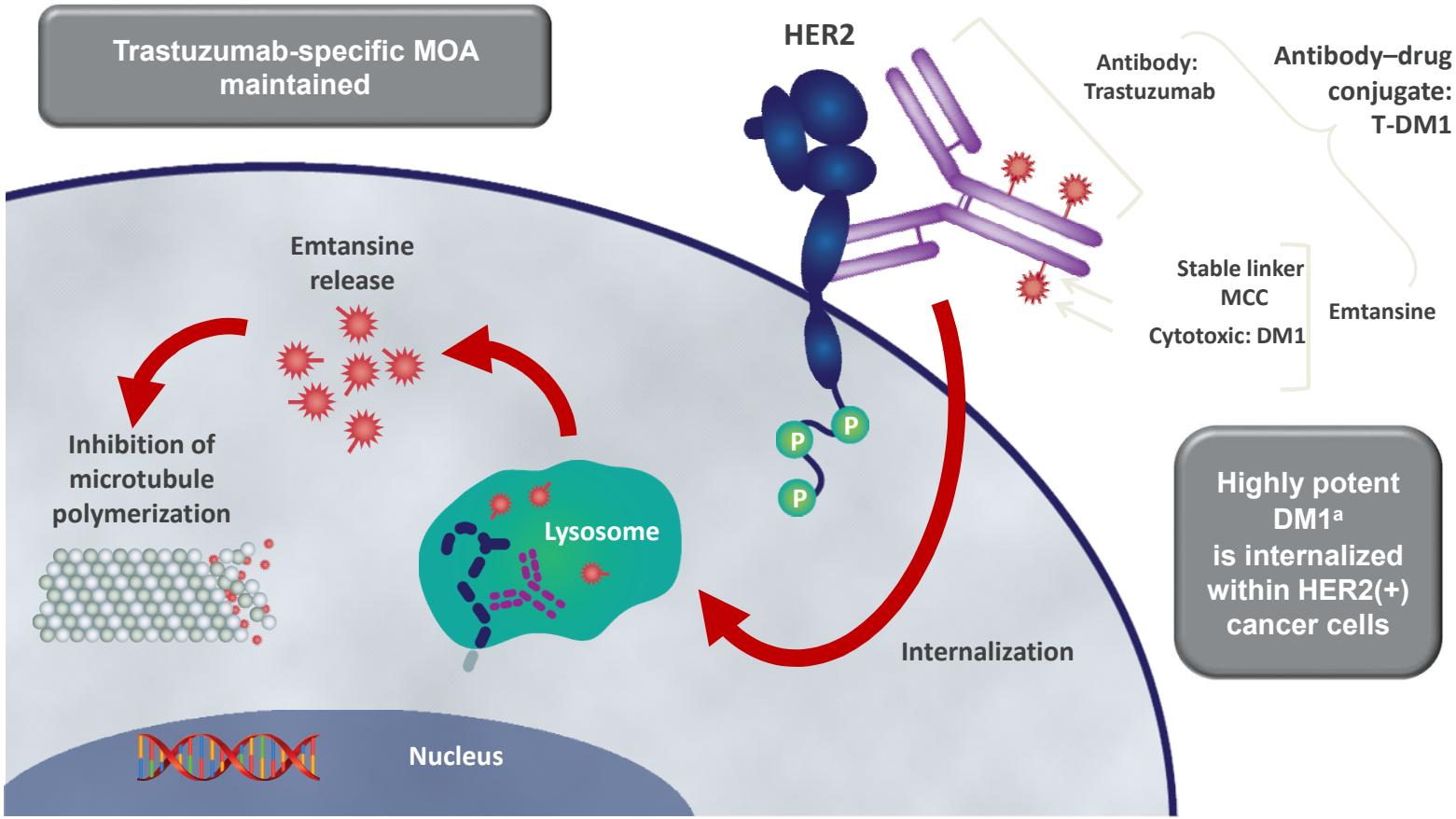
By blocking HER2 dimerization, pertuzumab inhibits key HER signaling pathways that mediate cancer cell proliferation and survival[1-4]

Pertuzumab prevents the formation of HER2:HER3 receptor pairs[1,5]



1. Agus, et al. Cancer Cell 2002;2:127-137. 2. Baselga. Cancer Cell 2002;2:93-95. 3. Citri, et al. Exp Cell Res 2003;284:54-65.
4. Franklin, et al. Cancer Cell 2004;5:317-328. 5. Hughes, et al. Mol Cancer Ther 2009;8:1885-1892.

ado-Trastuzumab Emtansine Mechanism Of Action

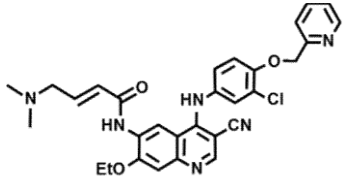


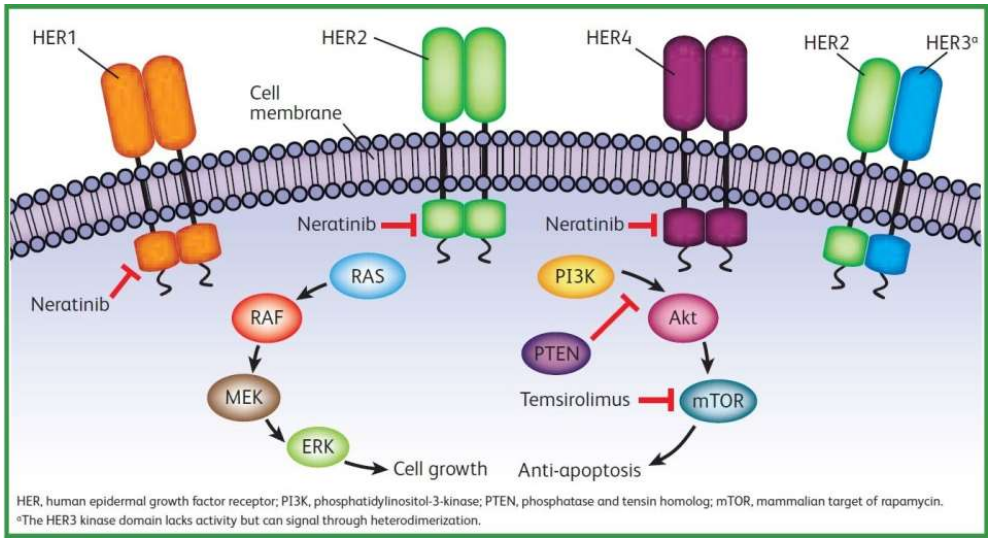
[a]DM1 is 24- to 270-fold more potent than taxane in cytotoxic assays

Junttila T, et al. Breast Cancer Res Treat 2011;128:347-356.

Neratinib Mechanism Of Action

- **Neratinib is an oral, irreversible tyrosine kinase inhibitor of HER1, 2, 4 receptors**



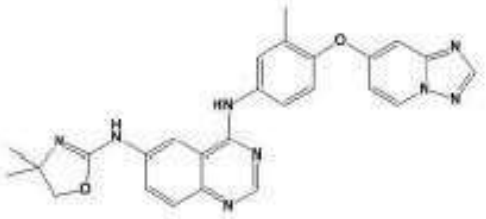


HER, human epidermal growth factor receptor; PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin.
[a]The HER3 kinase domain lacks activity but can signal through heterodimerization.

ONT-380 (Tucatinib)

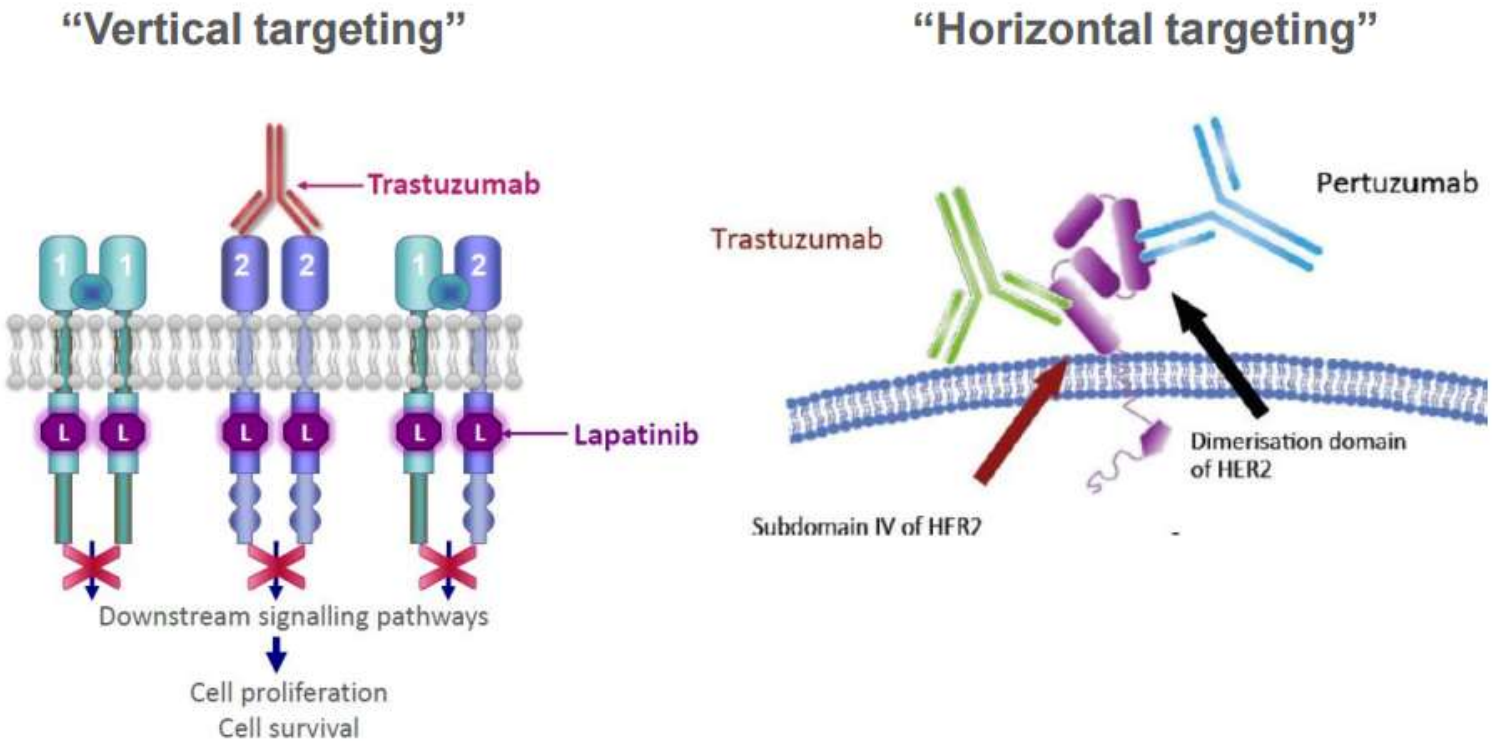
ONT-380 is the Only Selective HER2 Inhibitor in Clinical Development

ONT-380

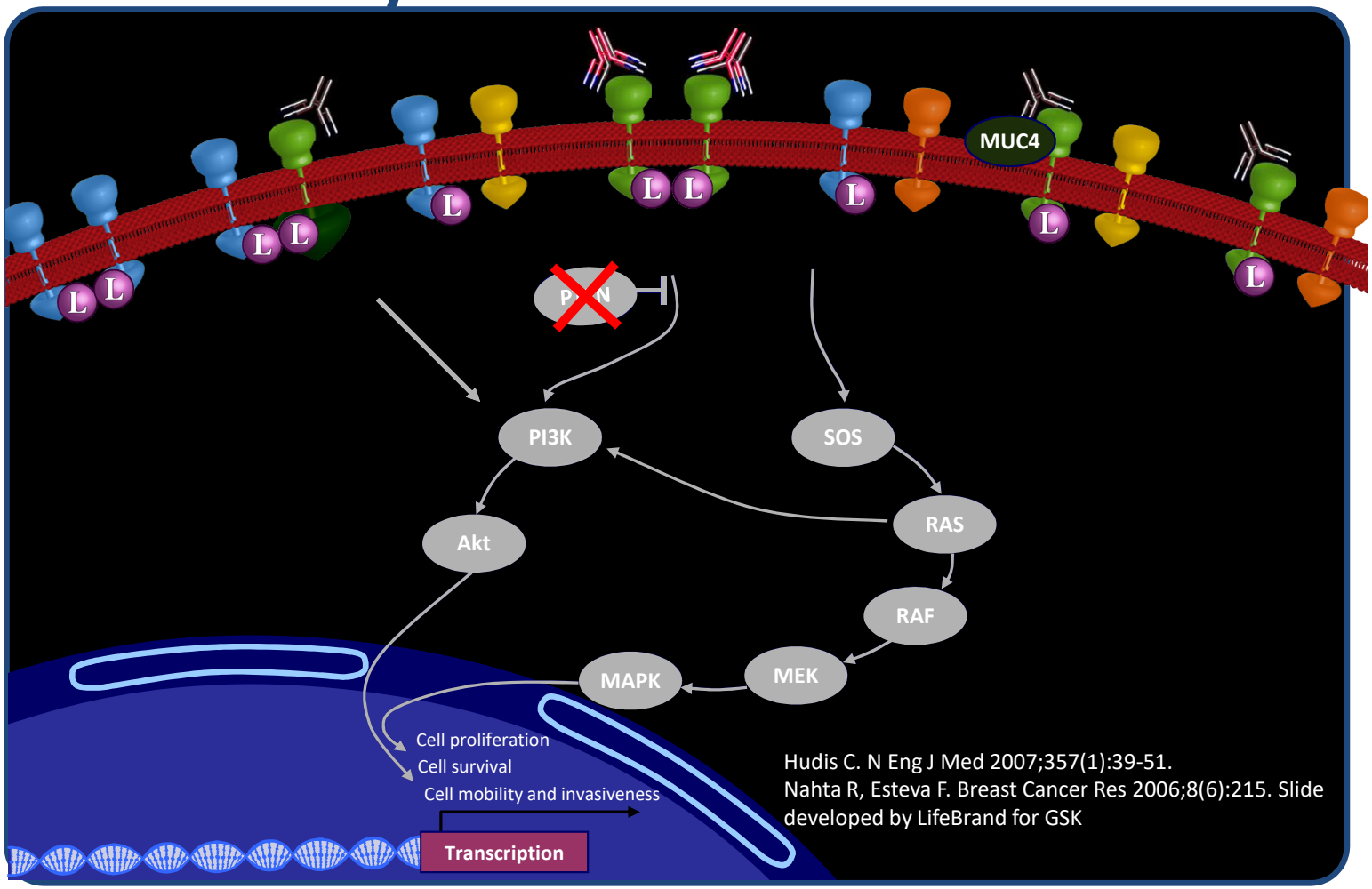


Compound	Cellular Selectivity Data		
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)	HER2 IC_{50} (nM) 50% Human
ONT-380	8	4000	67
Neratinib	7	8	39
Lapatinib	49	31	810

Dual HER2 Receptor Blockade



Total Blockade of HER2 May Provide Greater Anti-tumor Activity And Overcome Resistance



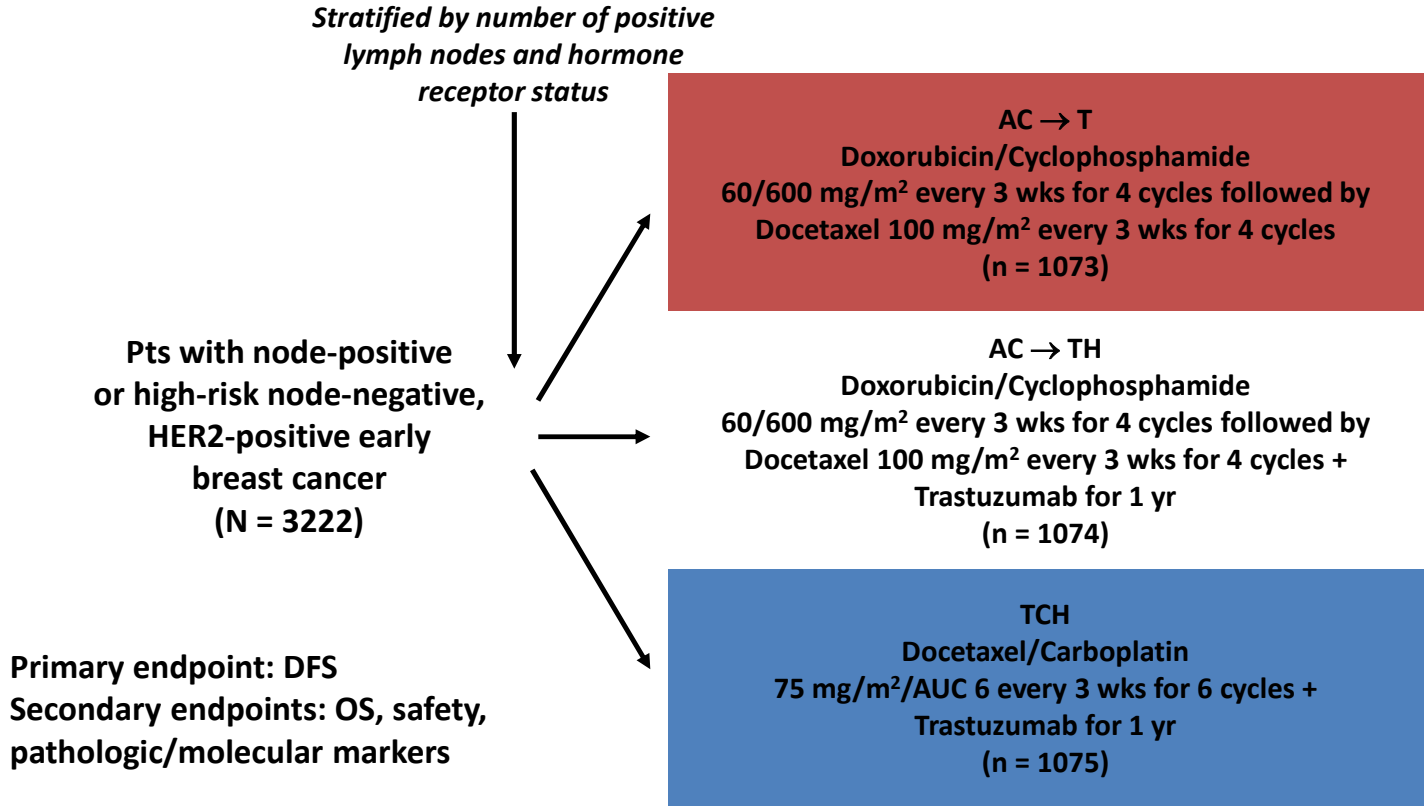
ADJUVANT TREATMENT STRATEGIES

Adjuvant Trastuzumab Improves DFS/OS For Patients With HER2neu+ EBC

Study	Follow-up, Yrs	N	DFS		OS	
			HR	*P* Value	HR	*P* Value
HERA[1-5] CT ± RT→H vs CT ± RT	1	3387	0.54	< .0001	0.76	.26
	2	3401	0.64	< .0001	0.66	.0115
	4	3401	0.76	< .0001	0.85	.1087
	8	3401	0.76	< .0001	0.76	.0005
	11	3401	0.76 Δ6.8%	.0001	0.74 Δ6.5%	< .0001
NCCTG N9831/ **NSABP B-31**[6-8] AC→TH→H vs AC→T	2	3351	0.48	< .0001	–	–
	4	4045	0.52	< .001	0.61	< .001
	8.4	4046	0.60 Δ11.0%	< .0001	0.63 Δ9.0%	< .0001
BCIRG 006[9,10] AC→TH→H vs AC→T TCH vs. AC→T	10	3222	0.72 Δ6.7%	< .0001	0.63 Δ7.2%	< .0001
			0.77 Δ5.1%	.0011	0.76 Δ4.6%	.075

1. Piccart-Gebhart. NEJM. 2005;353:1659. 2. Smith. Lancet. 2007;369:29. 3. Gianni. Lancet Oncol. 2011;12:236. 4. Goldhirsch. SABCS 2012. Abstr S5-2. 5. Cameron. Lancet. 2017;389:25. 6. Romond. NEJM. 2005;353:1673. 7. Perez. JCO. 2011;29:3366. 8. Romond. SABCS 2012. Abstr S5-5. 9. Slamon. NEJM. 2011;365:1273. 10. Slamon. SABCS 2015. Abstr S5-04.

BCIRG 006: Study Design



Slamon D, et al. N Engl J Med. 2011;365:1273-1283.
Slamon D, et al. SABCS 2015. Abstract S5-04.

BCIRG 006: Final Efficacy Analysis

- **Median follow-up: 10.3 yrs**
- **876 DFS events (33% more than 5-yr analysis)**
- **511 deaths (46% more than 5-yr analysis)**
- **33 pts (3.1%) randomized to control non-trastuzumab arm (AC → T) crossed over to receive trastuzumab**

Outcome	AC → T (n = 1073)	AC → TH (n = 1074)	TCH (n = 1075)
DFS, %	67.9	74.6	73.0
HR (95% CI)	1	0.72 (0.61-0.85)	0.77 (0.65-0.90)
P value vs AC → T		< .0001	.0011
OS, %	78.7	85.9	83.3
HR (95% CI)	1	0.63 (0.51-0.79)	0.76 (0.62-0.93)
P value vs AC → T		< .0001	.0075
DFS in Pts With Lymph Node Metastases, %	62.2	69.6	68.4
HR (95% CI)	1	0.72 (0.61-0.87)	0.75 (0.63-0.90)
P value vs AC → T		< .001	.0018

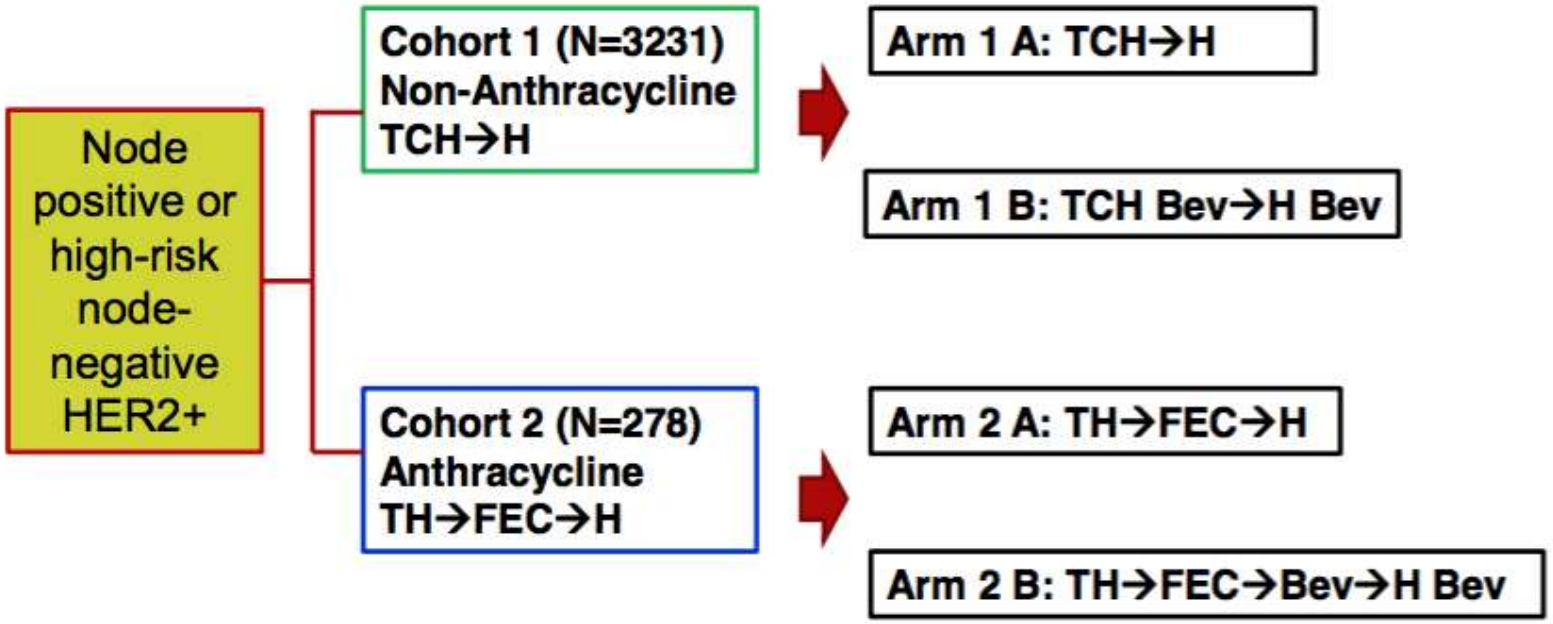
Slamon D, et al. SABCS 2015. Abstract S5-04.

BCIRG 006 10-Yr Follow-Up Conclusions

- This trial demonstrated a sustained advantage of adjuvant therapy with trastuzumab-containing regimens over the non-trastuzumab control in pts with HER2+ early breast cancer
- DFS and OS not statistically different between trastuzumab arms
  - Difference of only 10 DFS events between these arms at 10 yrs
- 5-fold increase in congestive heart failure, a higher rate of leukemia, and a higher rate of sustained left ventricular function loss with AC → TH compared with TCH

Slamon D, et al. SABCS 2015. Abstract S5-04.

BETH Study Design



Slamon D et al, SABCS 2013

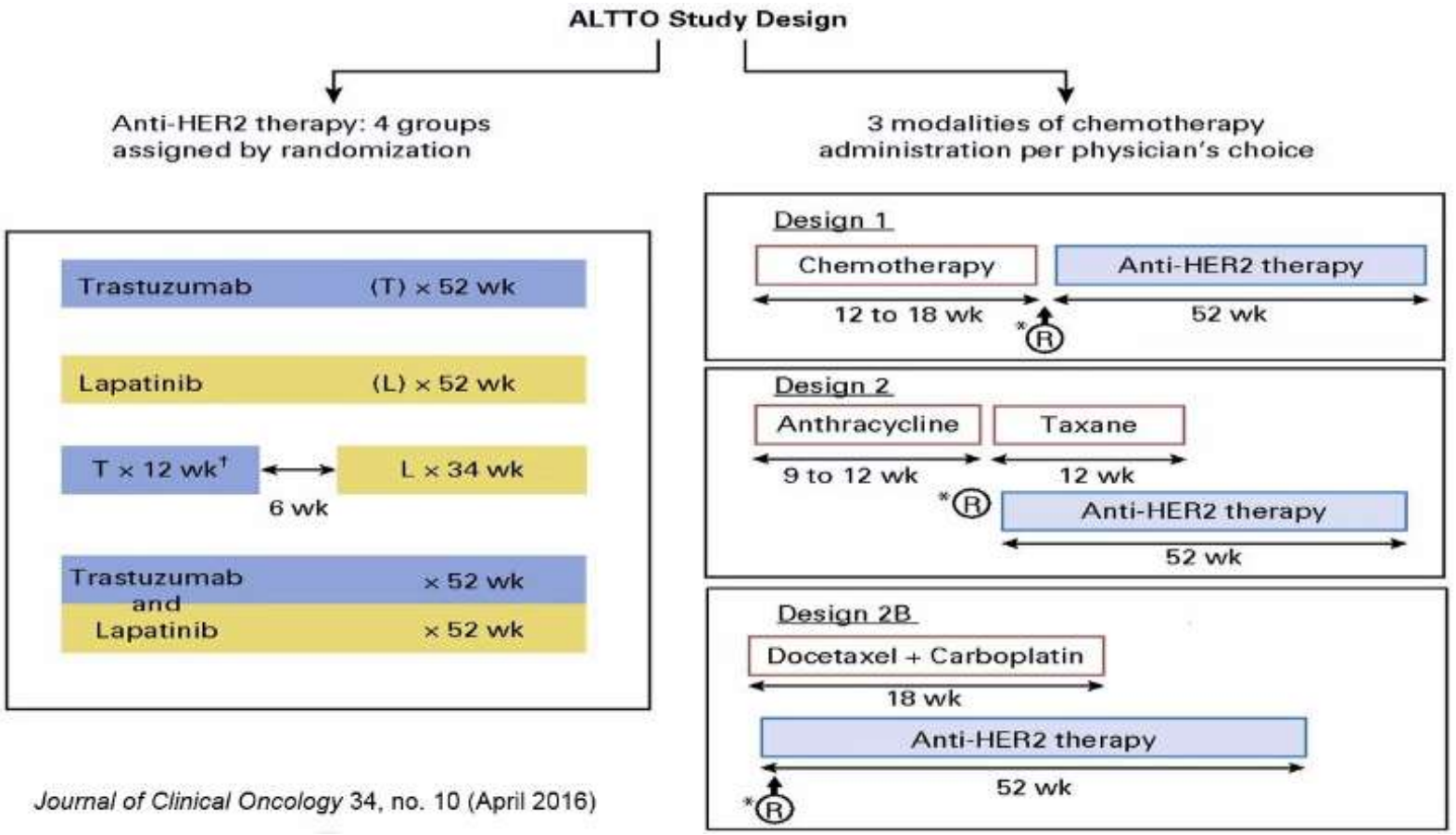
BETH Study Results

Median Follow up 38 months

	IDFS	OS
Without Bevacizumab	92%	96%
With Bevacizumab	92%	97%

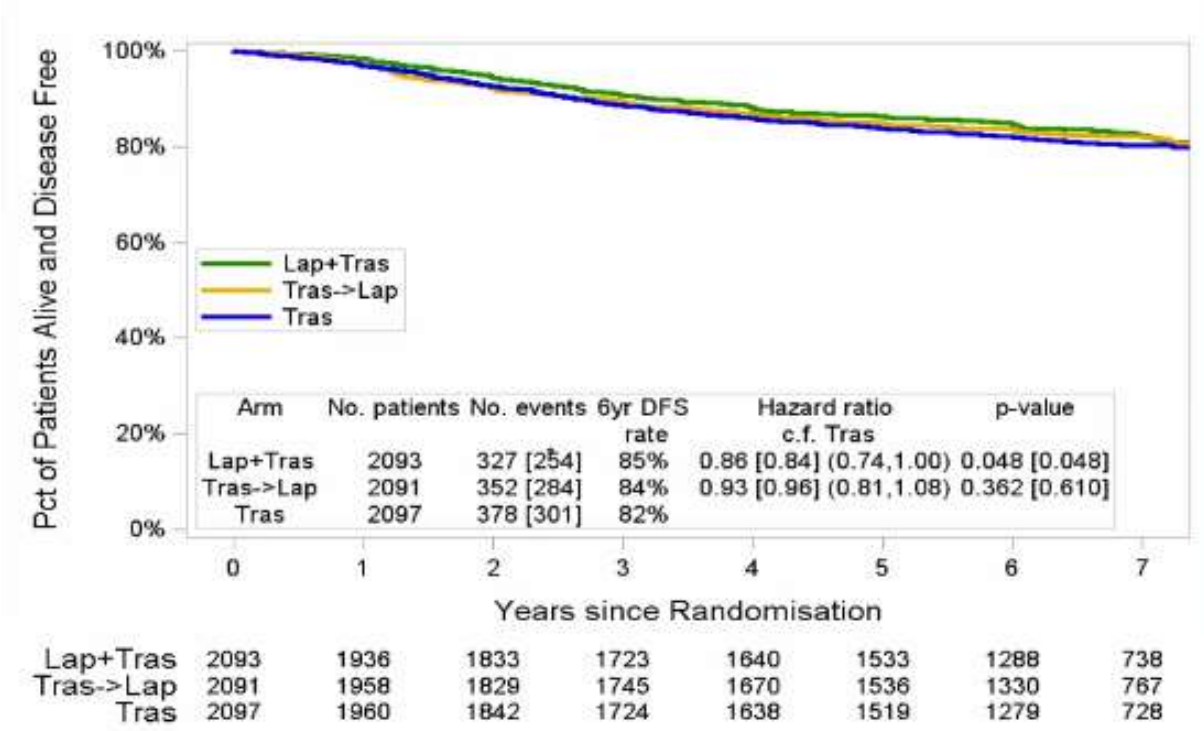
Slamon D et al, SABCS 2013

ALTTO Study Design



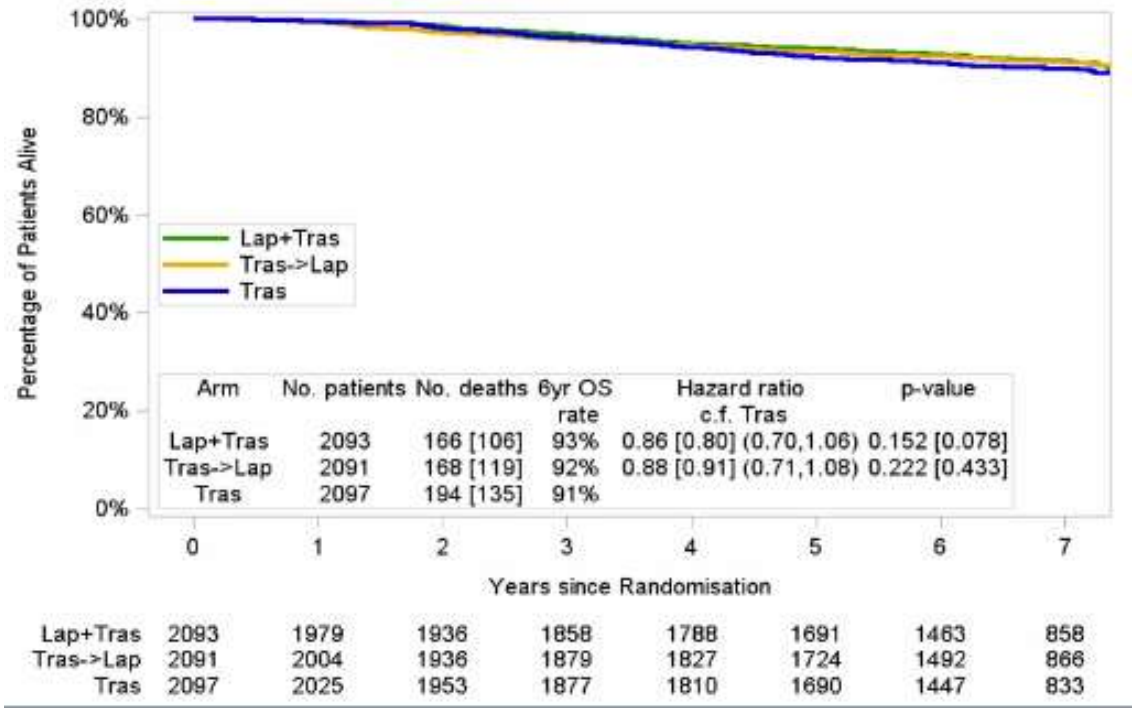
Journal of Clinical Oncology 34, no. 10 (April 2016)

ALTTO Study Update DFS



Aspitia AM et al. ASCO 2017

ALTTO Study Update OS



Aspitia AM et al. ASCO 2017

Clinical Trial Data on Shorter Duration of HER2neu-Targeted Therapy

Trial	Arms	DFS, %	Subset Analysis
PHARE[1] (N = 3384)	6 mos vs 12 mos of trastuzumab	2 yrs: 91.1 vs 93.8 (*P* = .29)	
Short-Her[2] (N = 1253)	9 wks vs 1 yr of trastuzumab	5 yrs: 85.4 vs 87.5	1 yr favored in high-risk: multiple positive nodes, stage III 9 wks may have similar benefit in lower-risk pts: stage I/II, limited nodal burden
FinHer[3] (N = 1010)	No trastuzumab vs 9 wks of trastuzumab	3 yrs: 77.6 vs 89.3 (*P* = .01)	
Persephone[4] (N = 4000)	6 mos vs 12 mos of trastuzumab	4 yrs: 89.4 vs 89.8 (*P* = .01)	12 mos favored in higher-risk, ER–, taxane chemotherapy without anthracycline, and neoadjuvant chemotherapy

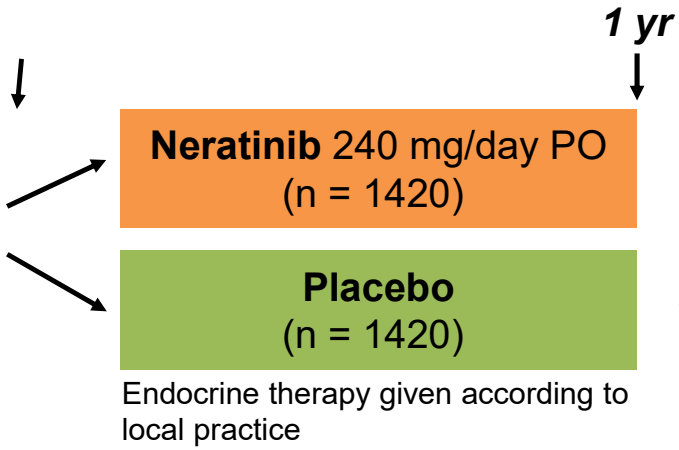
1 yr of trastuzumab remains standard of care, but shorter duration is better than nothing

1. Pivot X, et al. Lancet Oncol. 2013;14:741-748. 2. Conte PF, et al. ASCO 2017. Abstract 501. 3. Joensuu H, et al. N Engl J Med. 2006;354:809-820. 4. Earl HM, et al. ASCO 2018. Abstract 506.

ExteNET 5-Yr Update: Neratinib vs PBO After Adjuvant Trastuzumab in HER2neu+ EBC

Stratified by hormone receptor status (ER+ and/or PgR+ vs ER- and PgR-), nodal status (0 vs 1-3 vs ≥ 4), adjuvant trastuzumab regimen (sequential vs concurrent with CT)

Patients with HER2+ EBC (stage I-III); adjuvant trastuzumab completed ≤ 2 yrs before randomization*; **N+/- disease or residual disease after neoadjuvant therapy**; known ER and PgR status (N = 2840)

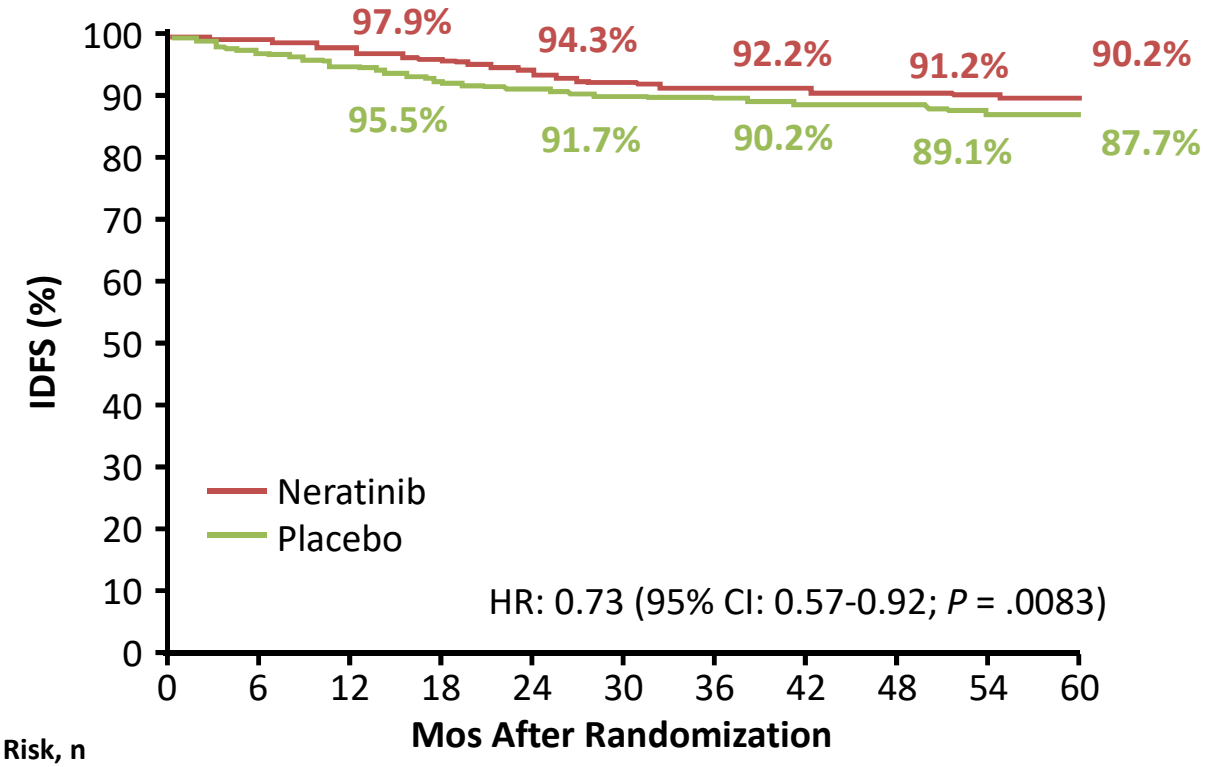


*Amendment in Feb 2010 **restricted enrollment to patients with N+ disease** who completed trastuzumab ≤ 1 yr before randomization.

- Primary endpoint: IDFS at 2 yrs
- Primary analysis of 2-yr IDFS rate: neratinib, 93.9%; placebo, 91.6% (HR: 0.67; 95% CI: 0.50-0.91; *P* = .0091)

Chan A, et al. Lancet Oncol. 2016;17:367-377. Martin M, et al. Lancet Oncol. 2017;18:1688-1700.

ExteNET 5-Yr IDFS Analysis



Patients at Risk, n											
Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

Martin M, et al. Lancet Oncol. 2017;18:1688-1700.

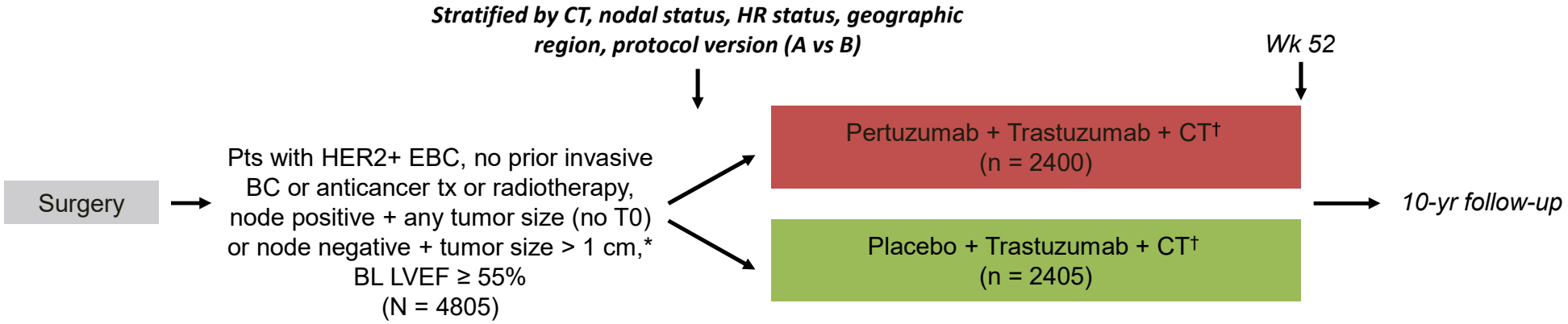
ExteNET Conclusions

- The 5-yr analysis of the ExteNET trial confirms sustained benefit with extended adjuvant neratinib:
  - 2.5% absolute benefit in ITT population (HR: 0.73; *P* = .008)
  - 4.4% absolute benefit in hormone receptor–positive cohort (HR: 0.60; *P* = .002)
- No evidence of long-term toxicity (ie, no increased symptomatic cardiac toxicity or second primary malignancies) with neratinib vs placebo or late-term consequences from neratinib-associated diarrhea

Martin M, et al. Lancet Oncol. 2017;18:1688-1700. Martin M, et al. ESMO 2017. Abstract 149O.

APHINITY Study Design

- **International, randomized, double-blind, placebo-controlled phase III trial[1,2]**

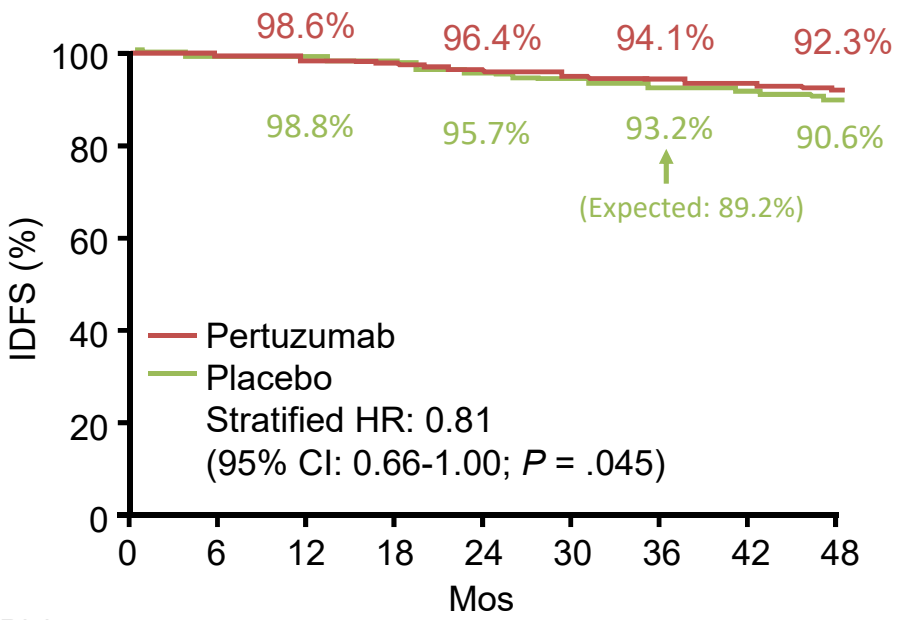


- **Primary endpoint: IDFS per modified STEEP definition[3] (excludes second primary non-BC as event)**
- **Secondary endpoints: IDFS per STEEP definition,[3] OS, distant recurrence-free survival, DFS, recurrence-free interval, safety, cardiac safety, health-related QoL**

*Or node negative + 1 of following: for tumors > 0.5, ≤ 1 cm, at least 1 histologic/nuclear grade 3; ER negative and PgR negative; aged < 35 yrs. †Tx initiated ≤ 8 wks post surgery. Permitted CT: standard anthracycline or nonanthracycline regimens. Endocrine and/or radiotherapy could be started at end of adjuvant CT.

1. von Minckwitz G, et al. ASCO 2017. Abstract LBA500. 2. ClinicalTrials.gov. NCT01358877. 3. Hudis CA, et al. J Clin Oncol. 2007;25:2127-2132.

APHINITY: Interim Analysis of IDFS



Pts at Risk, n

Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

ITT population.

- Data cutoff in December 2016 after 379 IDFS events (median f/u: 45.4 mos)
- Most first events were visceral, distant

IDFS Event, n (%)	Pertuzumab (n = 2400)	Placebo (n = 2404)
All pts with IDFS event	171 (7.1)	210 (8.7)
First event type		
▪ Distant recurrence	112 (4.7)	139 (5.8)
▪ Locoregional recurrence	26 (1.1)	34 (1.4)
▪ Contralateral BC	5 (0.2)	11 (0.5)
▪ Death	28 (1.2)	26 (1.1)
All pts with distant recurrence	119 (5.0)	145 (6.0)
First distant recurrence site		
▪ Lung/liver/pleural effusion	43 (1.8)	61 (2.5)
▪ CNS	46 (1.9)	45 (1.9)
▪ Other	9 (0.4)	9 (0.4)
▪ Bone	21 (0.9)	30 (1.2)

von Minckwitz G, et al. ASCO 2017. Abstract LBA500. Reproduced with permission.

APHINITY: Conclusions

- Adjuvant pertuzumab + trastuzumab + CT significantly reduced risk of recurrence events vs placebo + trastuzumab + CT in pts with HER2+ EBC
  - HR: 0.81 (95% CI: 0.66-1.00; *P* = .045)
  - Pts with node-positive or HR-negative disease had greatest IDFS benefit
  - Most recurrences to distant sites (pertuzumab: 4.7%; placebo: 5.8%)
- Investigators concluded:
  - No new safety signals identified with addition of pertuzumab to trastuzumab + CT
    - Low incidence of cardiac events
    - No difference in fatal AE rates between arms (0.8% for both)
    - Increased diarrhea incidence with pertuzumab (any-grade: 71.2% vs 45.2% with placebo)
  - Ongoing follow-up important to determine long-term IDFS, safety, and OS

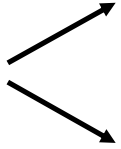
von Minckwitz G, et al. ASCO 2017. Abstract LBA500.

KATHERINE: Trastuzumab Emtansine vs Trastuzumab As Adjuvant Therapy For HER2+ EBC

- International, randomized, open-label phase III study

Stratified by clinical stage, HR status, single vs dual neoadjuvant HER2-targeted therapy, pathological nodal status after neoadjuvant therapy

Residual invasive disease in breast or axillary nodes after neoadjuvant chemotherapy plus HER2-targeted therapy* at surgery (N = 1486)



T-DM1† 3.6 mg/kg IV Q3W x 14 cycles (n = 743)

Trastuzumab 6 mg/kg IV Q3W x 14 cycles (n = 743)

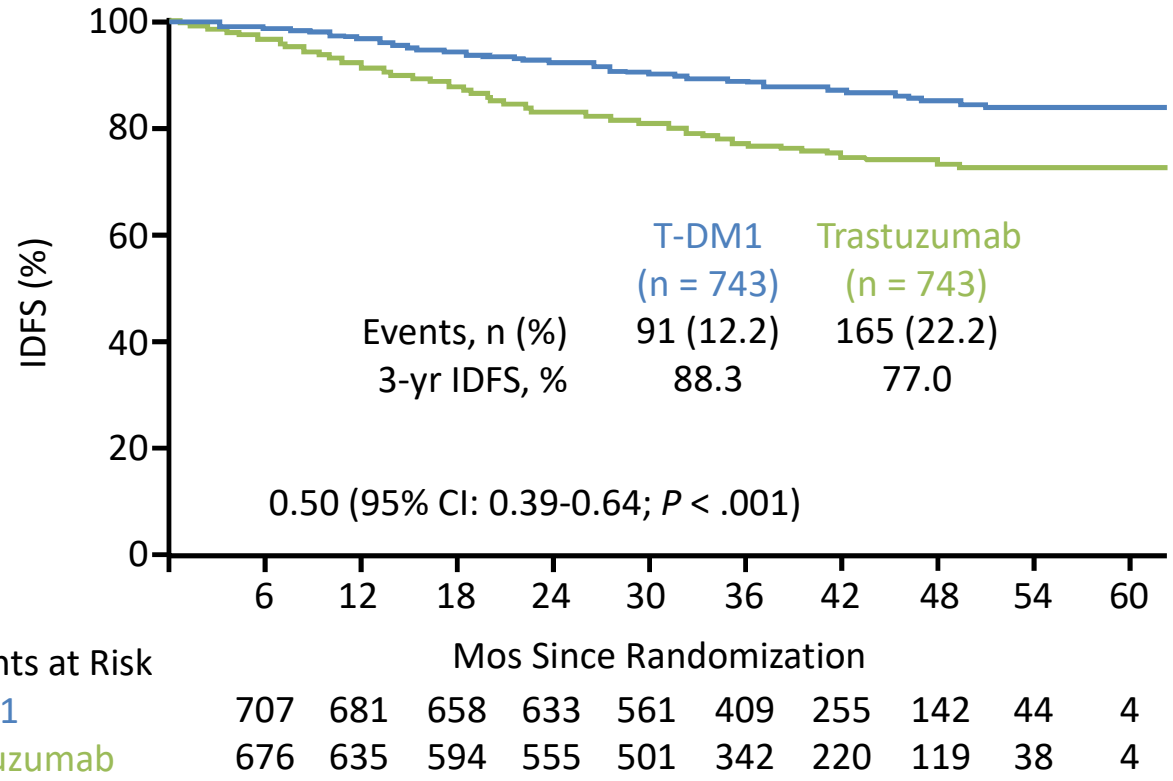
Randomization occurred within 12 wks of surgery; radiotherapy and/or endocrine therapy given per local standards. *Minimum of 9 wks taxane and trastuzumab. †Patients who d/c T-DM1 for toxicity allowed switch to trastuzumab to complete 14 cycles.

Primary endpoint: IDFS

Secondary endpoints including: distant recurrence-free survival, OS, safety

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz. NEJM. 2018;[Epub].

KATHERINE: IDFS



First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz. NEJM. 2018;[Epub].

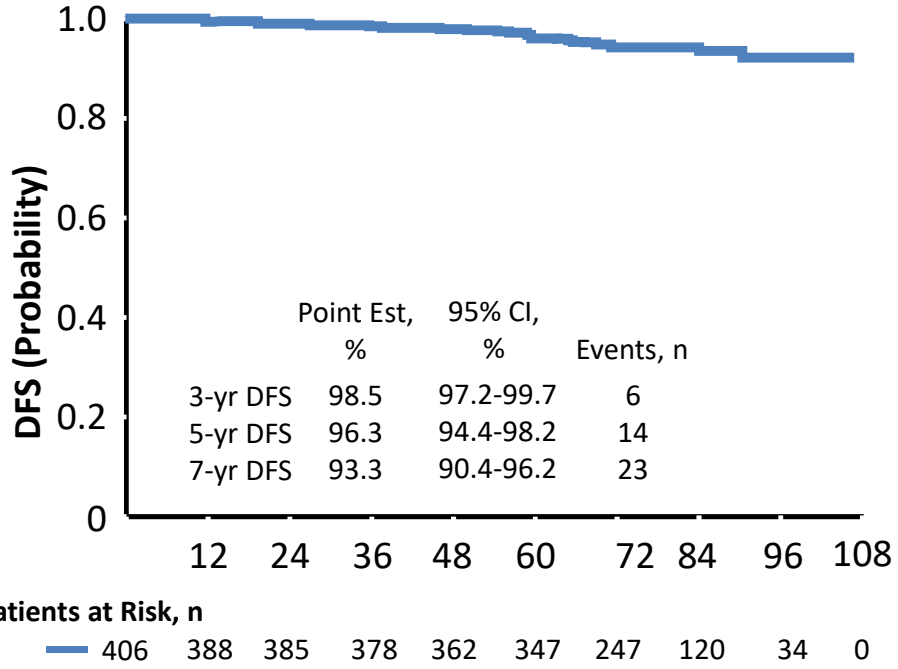
KATHERINE: Conclusions

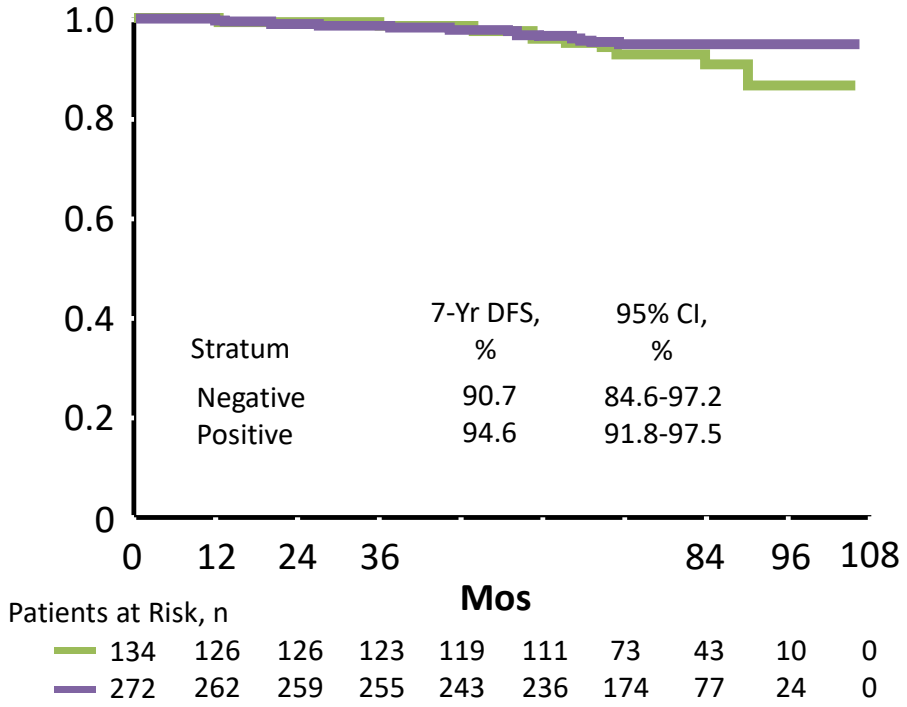
- In patients with HER2+ EBC who had residual invasive disease after neoadjuvant chemotherapy plus HER2-targeted therapy at surgery,
  T-DM1 significantly prolonged IDFS compared with trastuzumab
  - HR: 0.50 (95% CI: 0.39-0.64; *P* < .001)
  - Benefit with T-DM1 consistent across examined subgroups
- No unexpected safety signals
- Longer follow-up needed for OS
- Study investigators conclude that T-DM1 will likely represent a new standard of care in this population

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz. NEJM. 2018;[Epub].

APT Trial: Adjuvant Paclitaxel + Trastuzumab For Small (< 3 cm) Node-Negative HER2neu+ EBC

- Pts received paclitaxel + trastuzumab Q1W x 12 wks, followed by trastuzumab Q3W for 9 mos (N = 410)





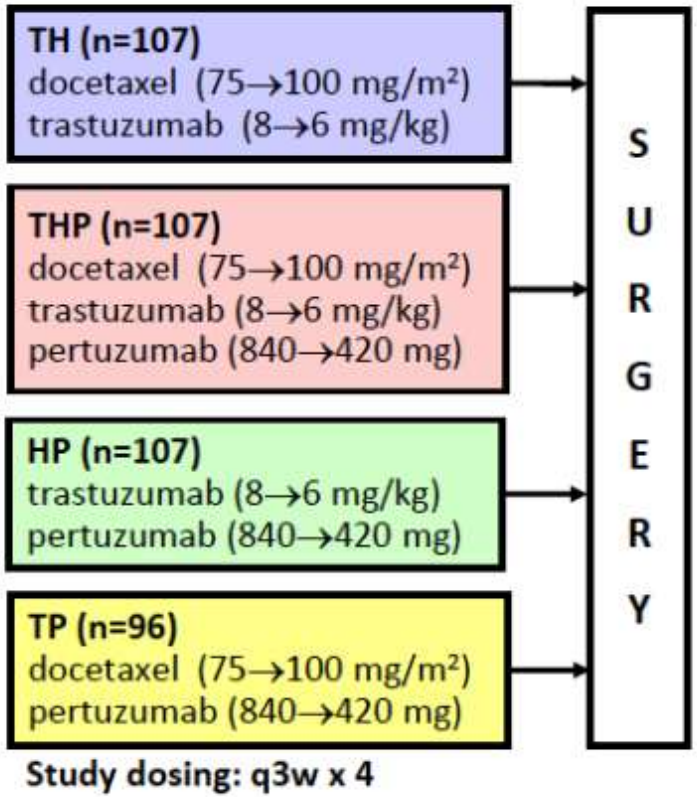
Tolaney. JCO. 2019;[Epub].

Adjuvant Strategy Conclusions

- Trastuzumab arguably represents the most important development in breast cancer in the modern era
- Additions to a trastuzumab-based backbone have resulted in incremental improvements
- Higher risk patients may benefit more from dual HER2neu targeted therapy (ER-, N+)
- De-escalation strategies may be appropriate for lower risk patients (ER+, small tumor, N-)
- Shorter duration of therapy may be better than none and reasonable in select patient populations

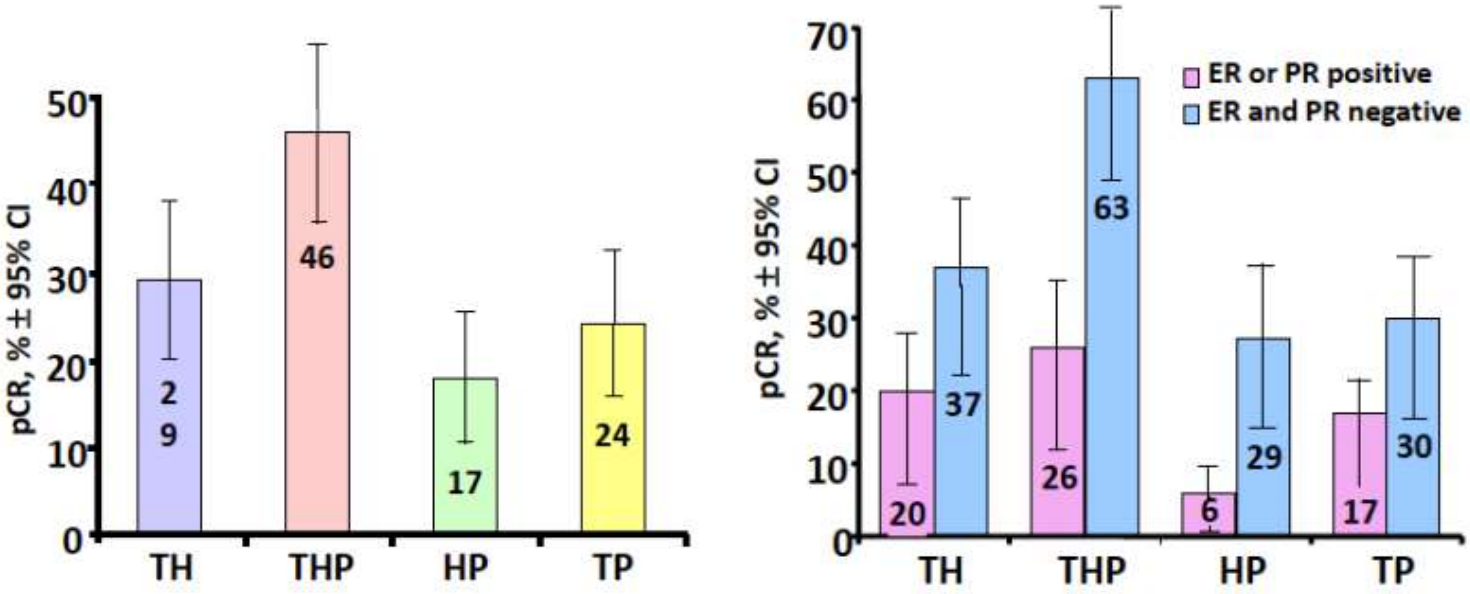
NEOADJUVANT TREATMENT STRATEGIES

NeoSphere Study Design



Gianni L et al. Lancet Oncol 2012

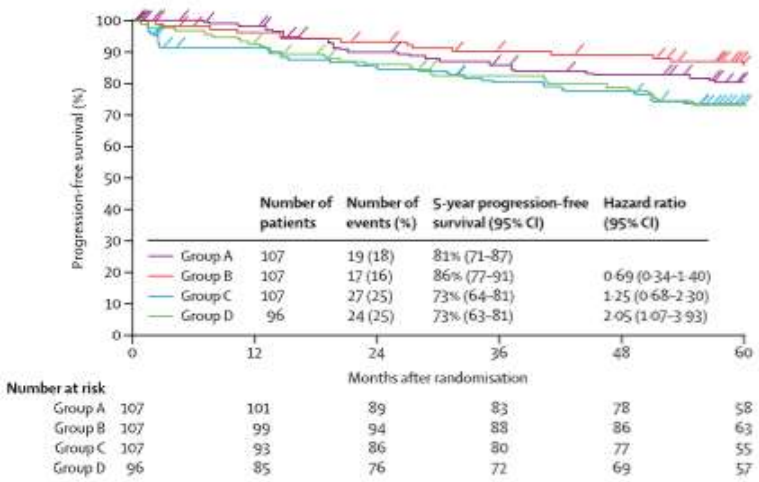
NeoSphere Study pCR



Gianni L et al. Lancet Oncol 2012

NeoSphere Study 5-Year Analysis

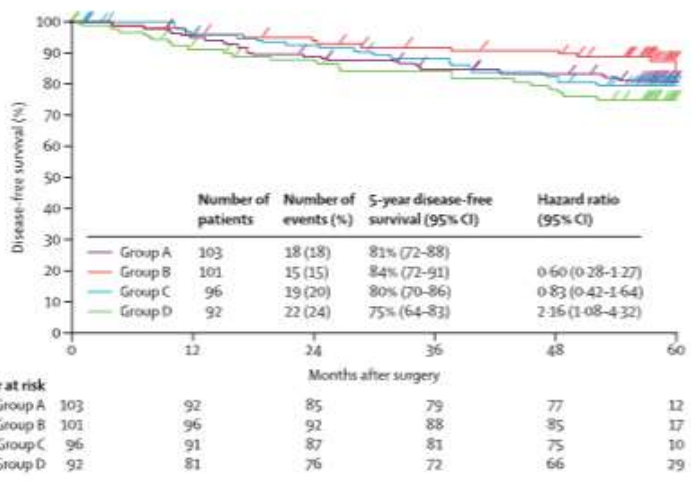
Progression-Free Survival



	Number of patients	Number of events (%)	5-year progression-free survival (95% CI)	Hazard ratio (95% CI)
Group A	107	19 (18)	81% (71–87)	
Group B	107	17 (16)	86% (77–91)	0·69 (0·34–1·40)
Group C	107	27 (25)	73% (64–81)	1·25 (0·68–2·30)
Group D	96	24 (25)	73% (63–81)	2·05 (1·07–3·93)

Number at risk						
Group A	107	101	89	83	78	58
Group B	107	99	94	88	86	63
Group C	107	93	86	80	77	55
Group D	96	85	76	72	69	57

Disease-Free Survival



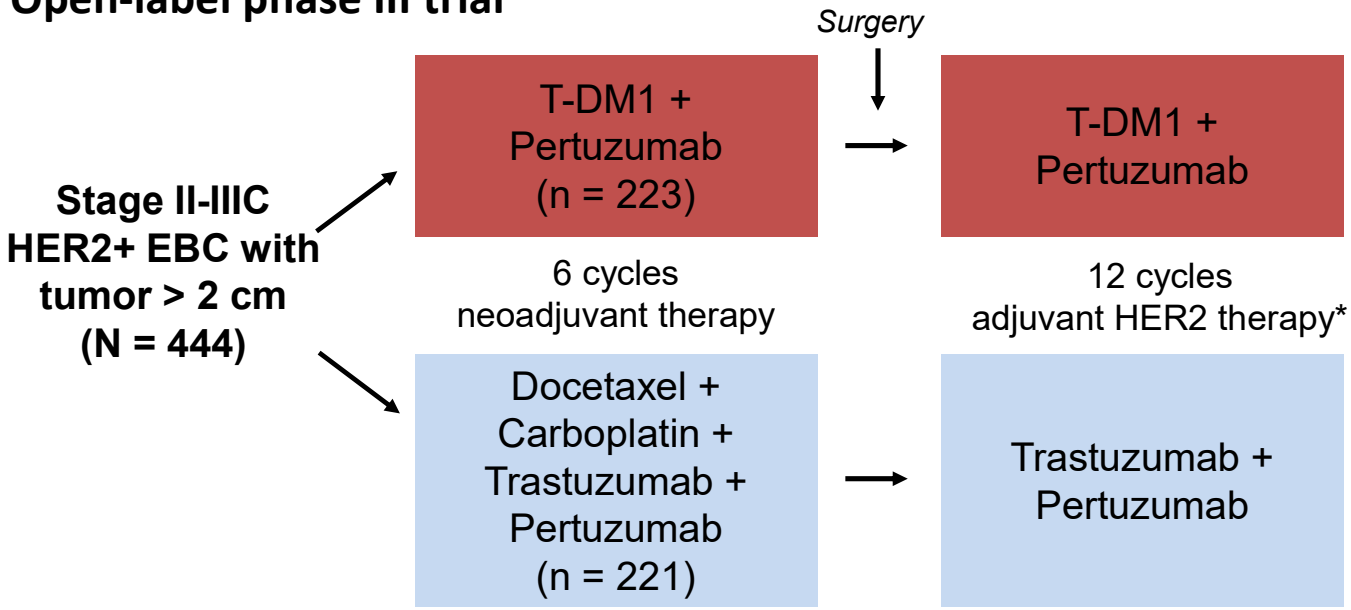
	Number of patients	Number of events (%)	5-year disease-free survival (95% CI)	Hazard ratio (95% CI)
Group A	103	18 (18)	81% (72–88)	
Group B	101	15 (15)	84% (72–91)	0·60 (0·28–1·27)
Group C	96	19 (20)	80% (70–86)	0·83 (0·42–1·64)
Group D	92	22 (24)	75% (64–83)	2·16 (1·08–4·32)

Number at risk						
Group A	103	92	85	79	77	12
Group B	101	96	92	88	85	17
Group C	96	91	87	81	75	10
Group D	92	81	76	72	66	29

Gianni L et al. Lancet Oncol 2016

KRISTINE Study Design

- **Open-label phase III trial**



*Adjuvant therapy recommended for pts in T-DM1/pertuzumab group with residual disease in lymph nodes or breast (> 1 cm).

- **Primary endpoint: pCR by local assessment in breast, lymph nodes (ypT0/is, ypN0)**
- **Secondary endpoints: safety, BCS rate, PROs, EFS, iDFS, OS**
- **Stratified by: local hormone receptor status, geographic location, stage**

Hurvitz SA, et al. ASCO 2016. Abstract 500.

KRISTINE Clinical Response

Outcome	TCHP (n = 221)	T-DM1 + P (n = 223)
pCR (ypT0/is, ypN0), %	56	44
	Difference: -11.3 (95% CI: -20.5 to -2.0; *P* = .0155)	
pCR by receptor status, %		
▪ ER- and PR-	73	54
▪ ER+ and/or PR+	44	35
BCS rate, %		
▪ Actual	53	42
▪ Conversion*	70	66

*Pts originally needing mastectomy who became eligible for BCS after neoadjuvant therapy.

- Longer maintenance of health-related QoL (HR: 0.60) and physical function (HR: 0.47) with T-DM1 + P vs TCHP

Hurvitz SA, et al. ASCO 2016. Abstract 500.

KRISTINE Conclusions

- Superior pCR rate with neoadjuvant TCHP compared with T-DM1 + P in early breast cancer
  - Same effect in hormone receptor status subgroup analysis
- Rate BCS lower in T-DM1 + P arm
- Favorable safety profile of T-DM1 + P with lower incidence of serious and grade ≥ 3 AEs
- Longer health-related QoL and physical functioning with
  T-DM1 + P compared with TCHP
- Investigators suggest chemotherapy with trastuzumab + pertuzumab remain neoadjuvant standard of care for HER2+ breast cancer

Hurvitz SA, et al. ASCO 2016. Abstract 500.

Disease-Free Survival And Response To Neoadjuvant HER2neu-Targeted Therapy

Trial Name	Therapy	pCR	Non-pCR
Techno (tpCR)[1] **3-yr DFS**	EC → T + H	**88%**	**73%**
GeparQuinto GBG-44 (tpCR)[2] **3-yr DFS**	EC → T + H EC → T + L	**90%**	**83%**
NeoALTTO (breast pCR only)[3] **3-yr EFS**	L → L + T → surgery → FEC + L H → H + T → surgery → FEC + H H/L → H/L + T → surgery → FEC + H/L	**86%**	**72%**
NSABP B-41 (breast pCR only)[4] **5-yr RFI**	AC → T + H AC → T + L AC → T + H/L	**90%**	**81%**
NeoSphere (tpCR)[5] **5-yr PFS**	H + T → surgery → FEC + H H/P + T → surgery → FEC + H H/P → surgery → T → FEC + H P + T → surgery → FEC + H	**85%**	**76%**

tpCR = total pathologic CR (pT0 ypN0).

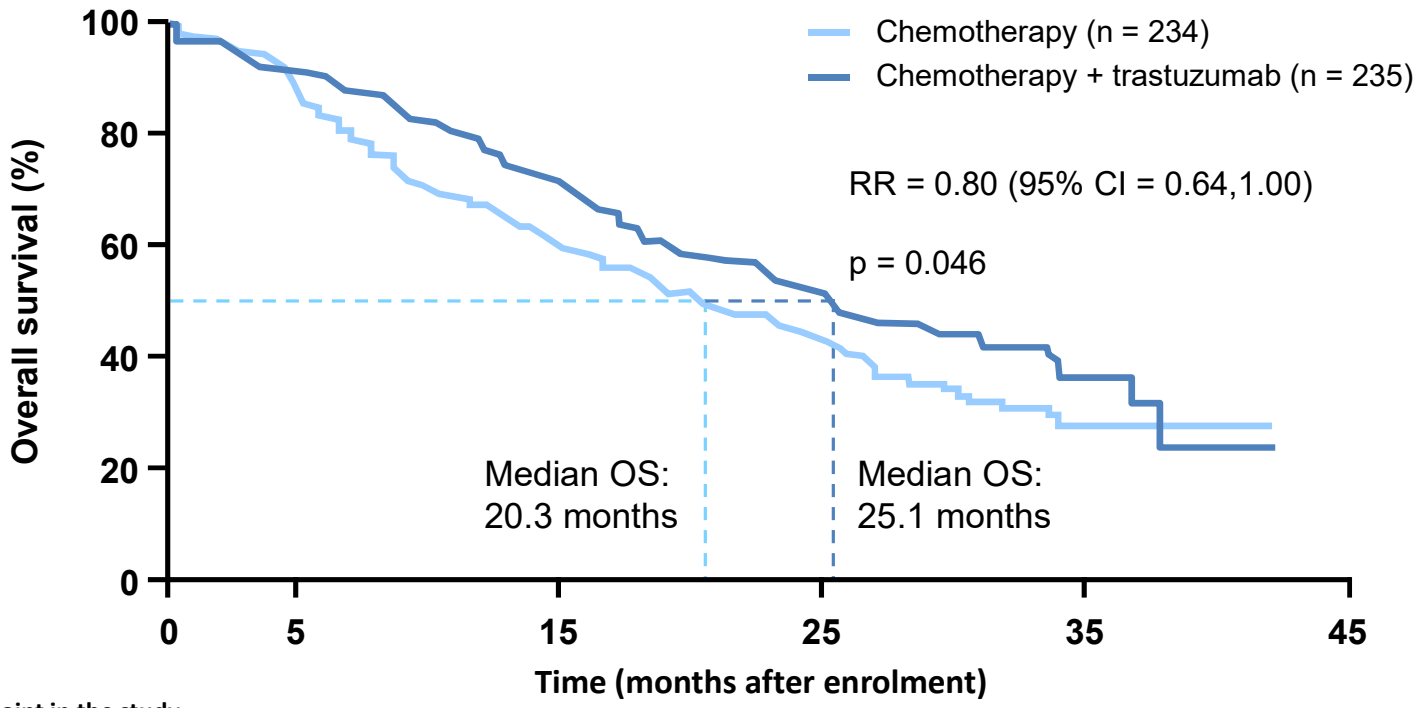
1. Untch. JCO. 2011;29:3351. 2. Untch. JCO. 2018; 36: 1308. 3. de Azambuja. Lancet Oncol. 2014;15:1137.
4. Robidoux. ASCO 2016. Abstr 501. 5. Gianni. Lancet Oncol. 2016;17:791.

Neoadjuvant Strategy Conclusions

- Neoadjuvant strategy results have been encouraging, but not entirely reliably predictive
- Those who respond well, respond well
- Caution should be exercised in interpreting neoadjuvant clinical trial results
- Additional research with novel combinations/strategies is needed

METASTATIC TREATMENT STRATEGIES

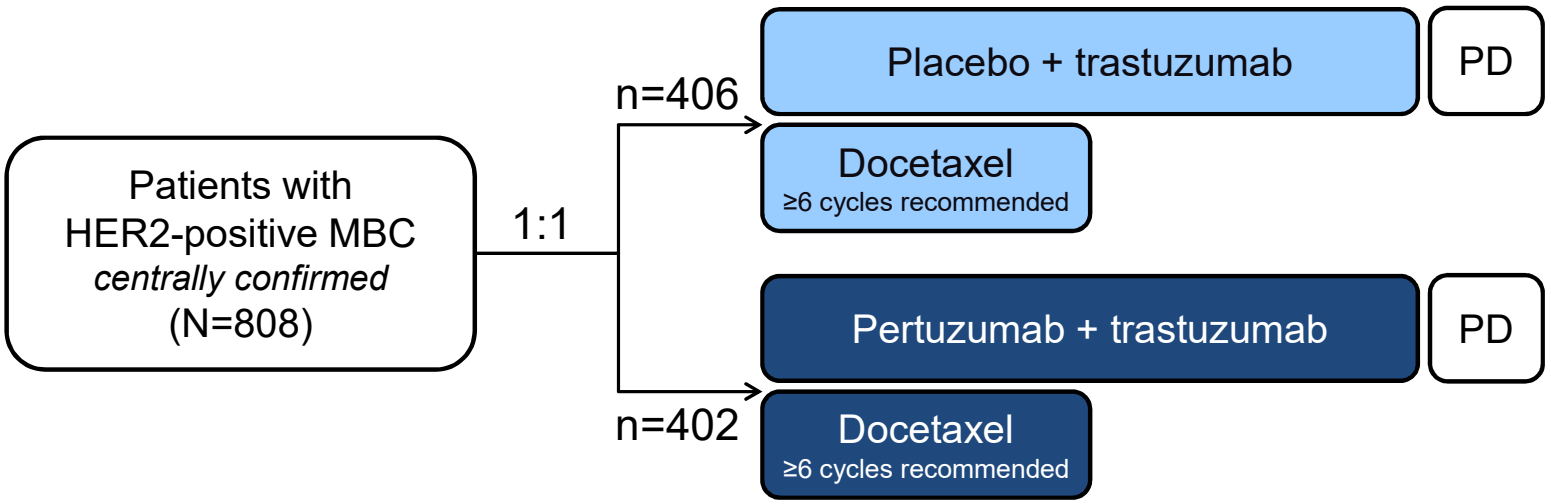
Trastuzumab Prolongs Overall Survival In HER2neu-positive MBC



OS was a secondary endpoint in the study
Chemotherapy = either doxorubicin or epirubicin + cyclophosphamide or paclitaxel
OS, overall survival; RR, relative risk of death

Slamon DJ, *et al. N Engl J Med* 2001; 344:783–792.

CLEOPATRA Study Design

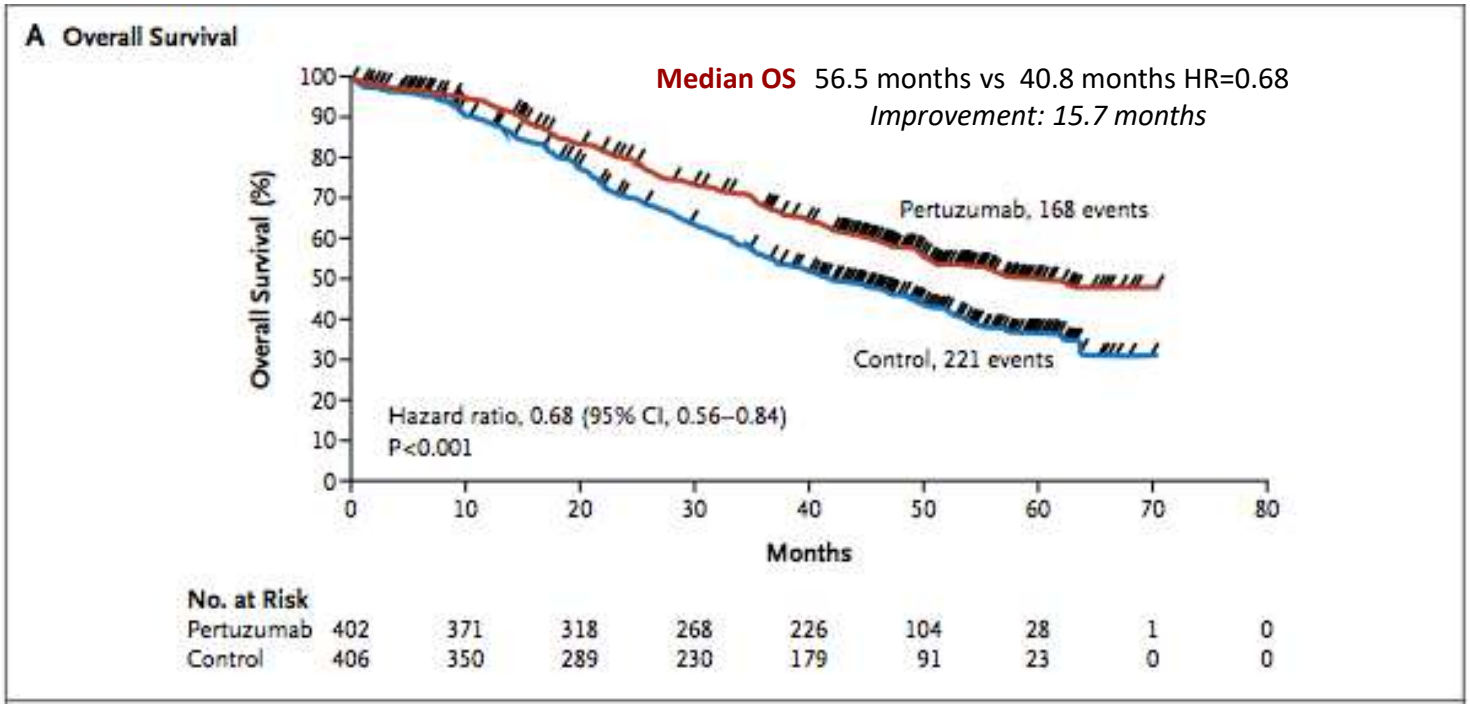


Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

Primary Endpoint: OS

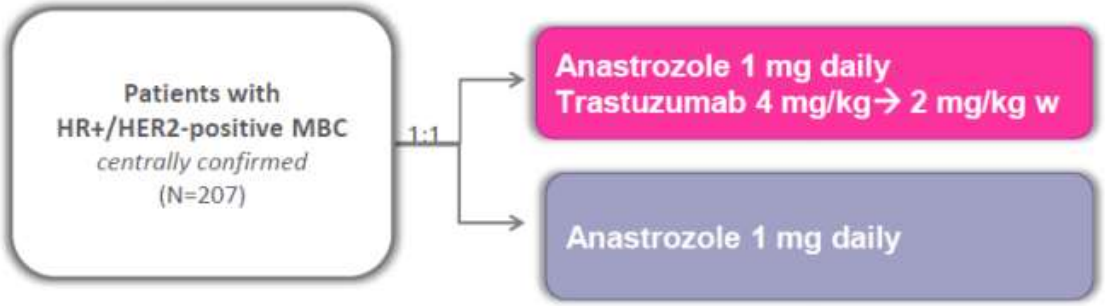
Swain SM, *et al. N Engl J Med* 2015.

CLEOPATRA Trial OS



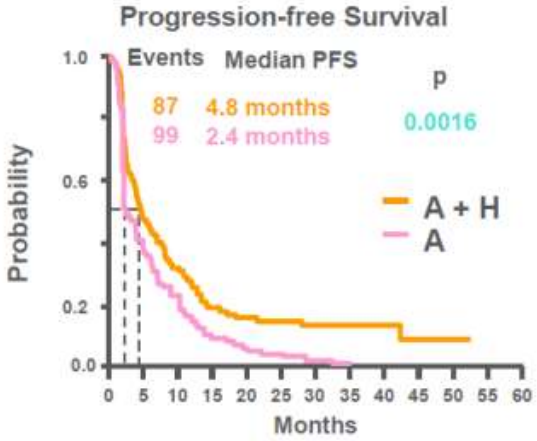
Swain SM, *et al. N Engl J Med* 2015.

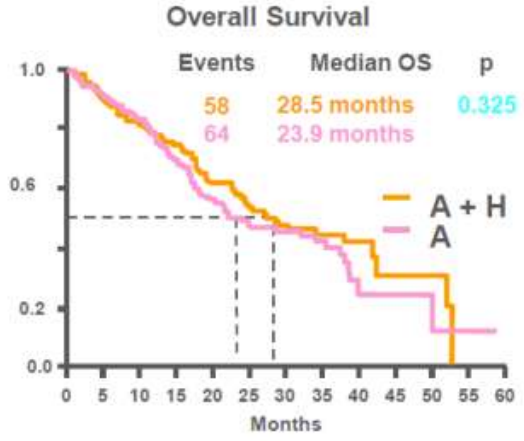
TAnDEM Study Design



Crossover to trastuzumab actively offered

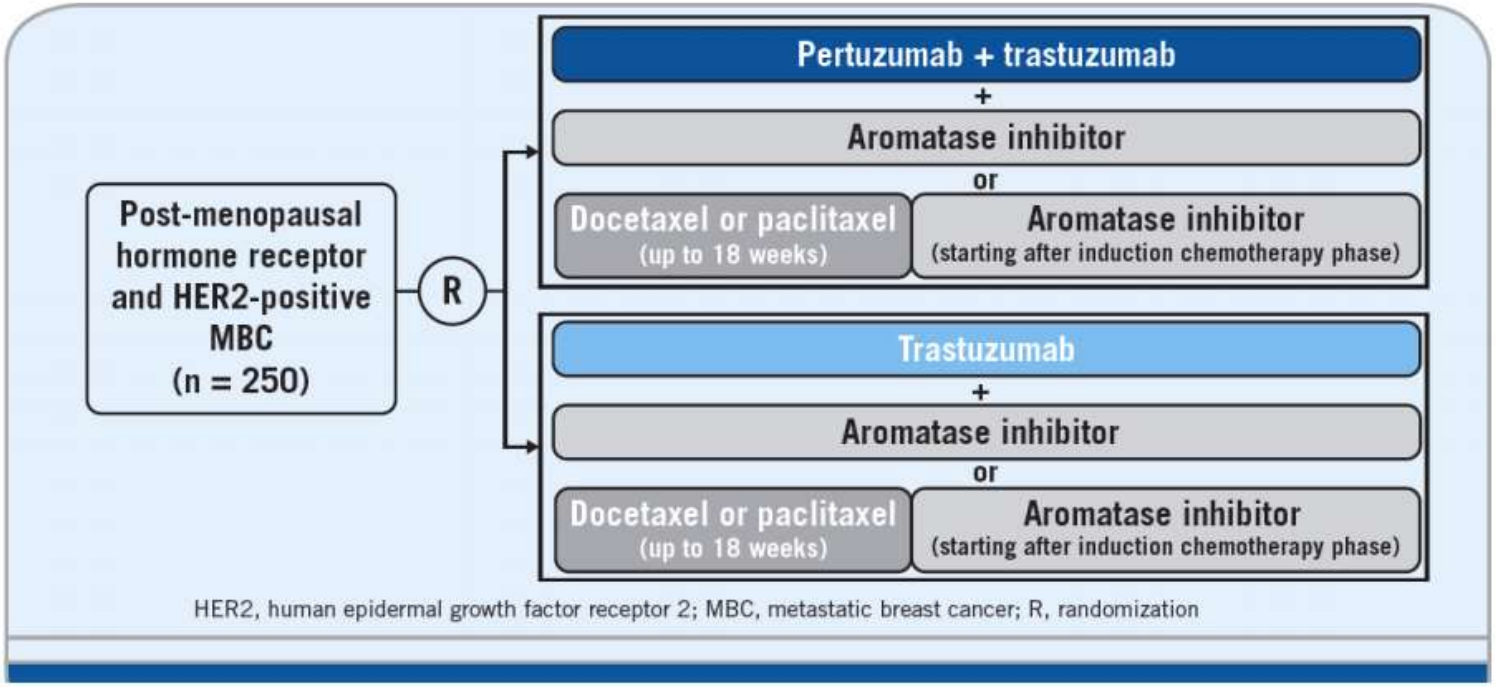
	Anastrozole	Anast.+Trastuzumab	
OR (%)	7	20	p=0.018
CBR (%)	28	43	p=0.026





Kaufman et al. J Clin Oncol 2009; 27:5529-37

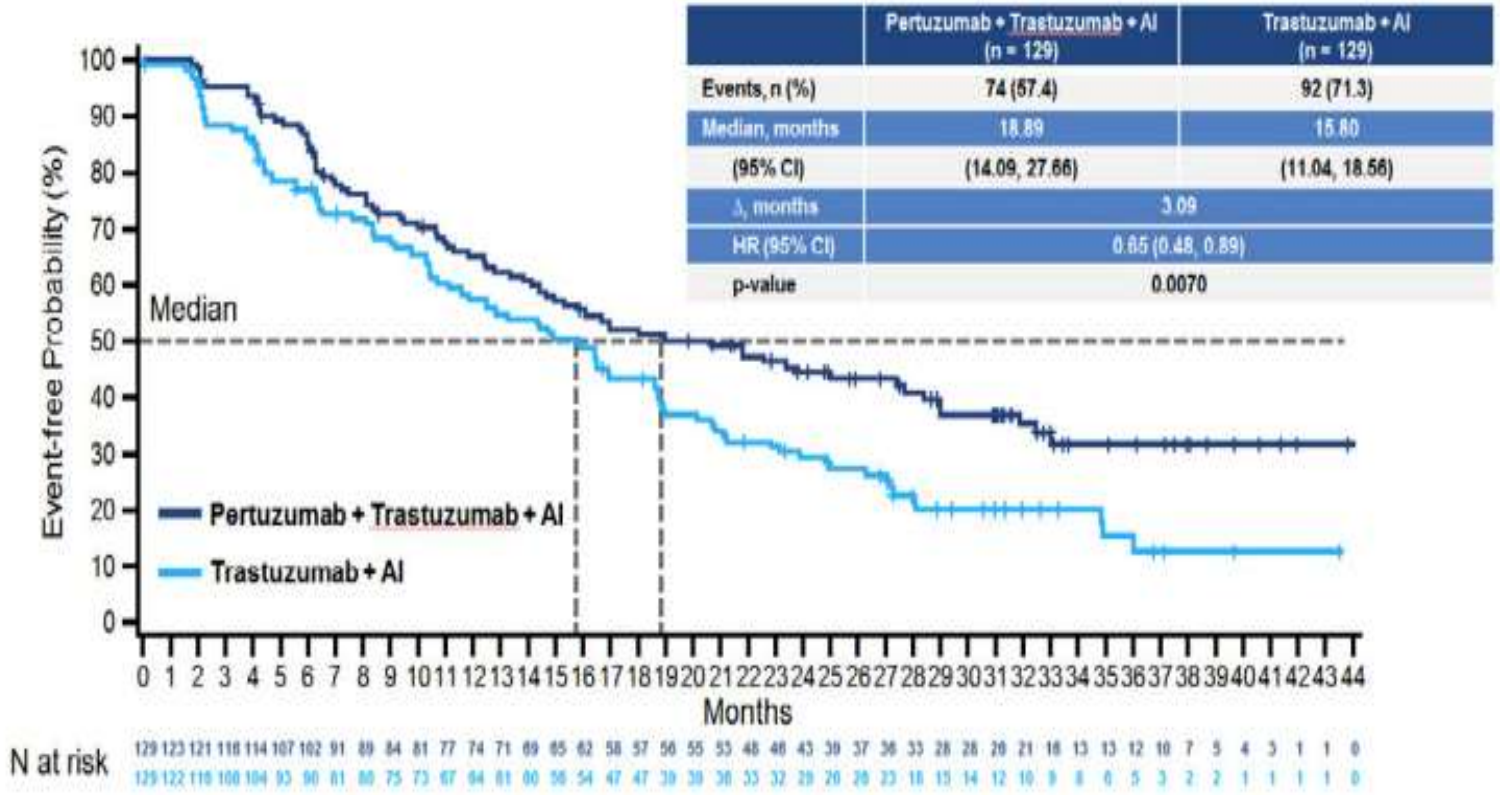
PERTAIN Study Design



Primary Endpoint: PFS

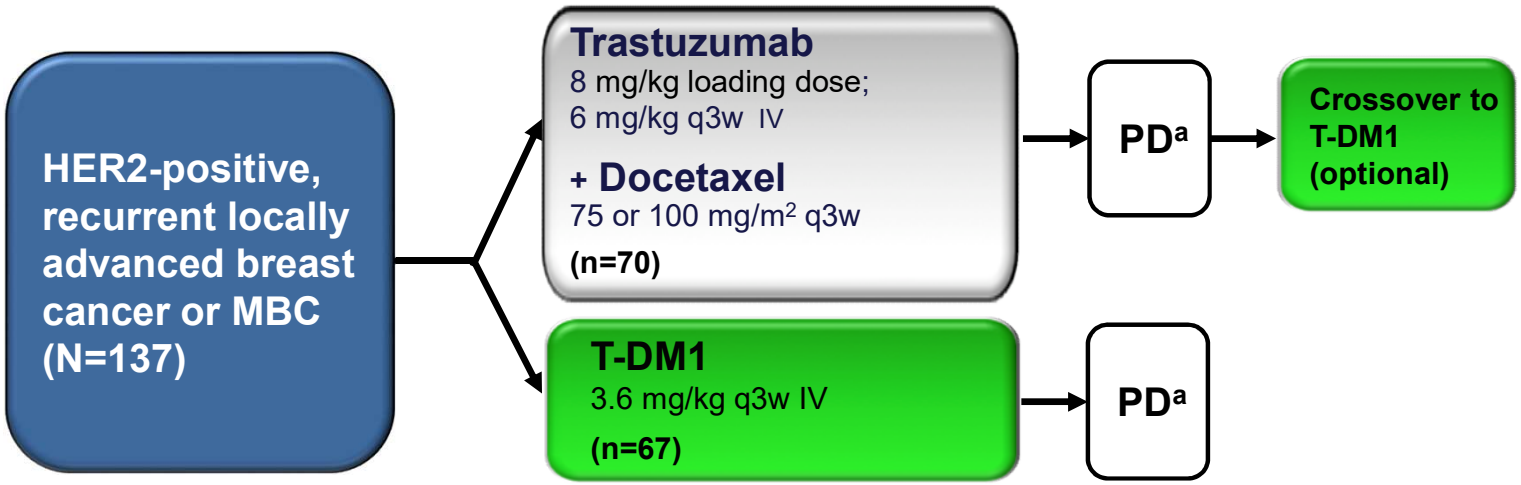
Arpino G *et al. SABCS* 2016.

PERTAIN PFS



Arpino G *et al. SABCS* 2016.

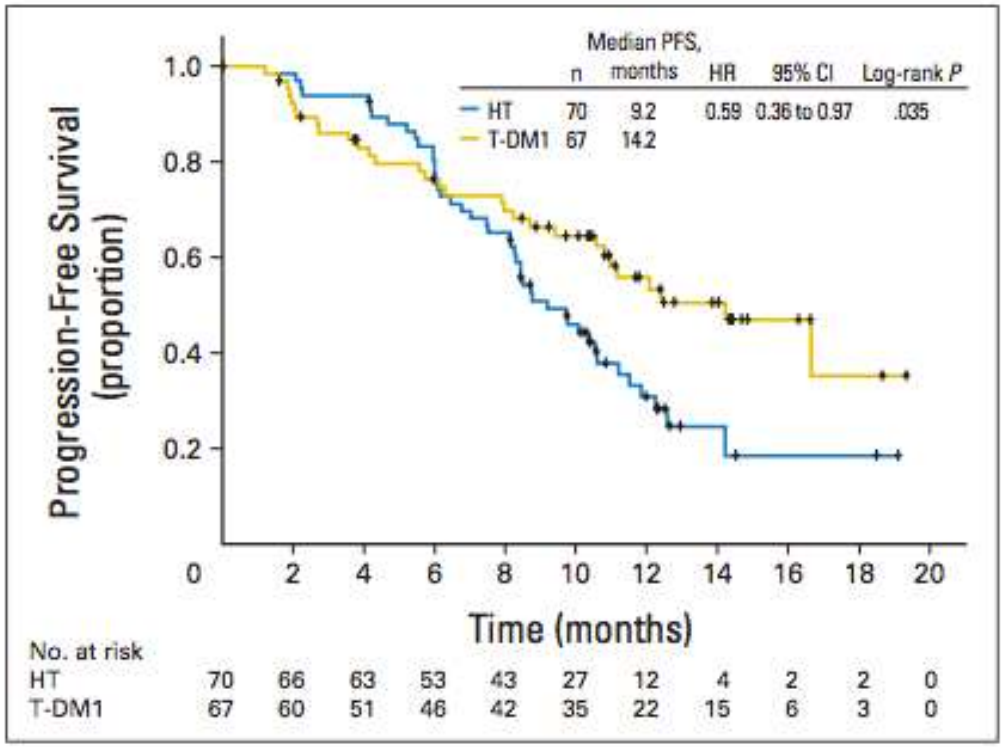
TDM4450g Phase II Study Design



Primary Endpoint: PFS

Hurvitz SA et al. JCO, 2013

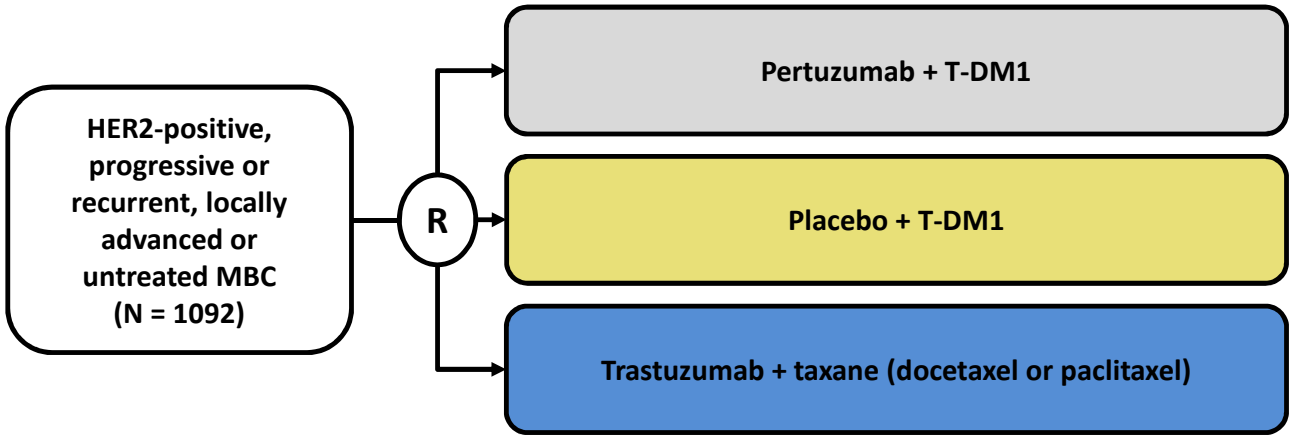
TDM4450g Phase II Study PFS



Hurvitz SA et al. JCO, 2013

MARIANNE Study Design

Pertuzumab and T-DM1 In First-line Metastatic Breast Cancer

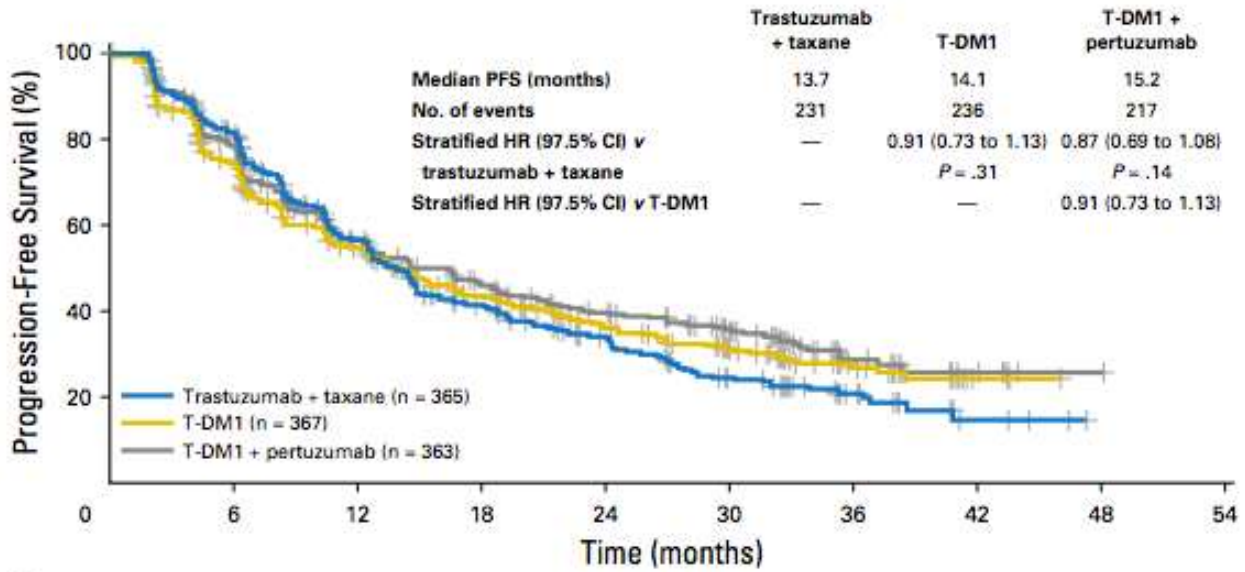


T-DM1 ± pertuzumab: blinded, placebo-controlled
Trastuzumab + taxane: open-label

Primary Endpoint: PFS

Perez EA et al. JCO 2017

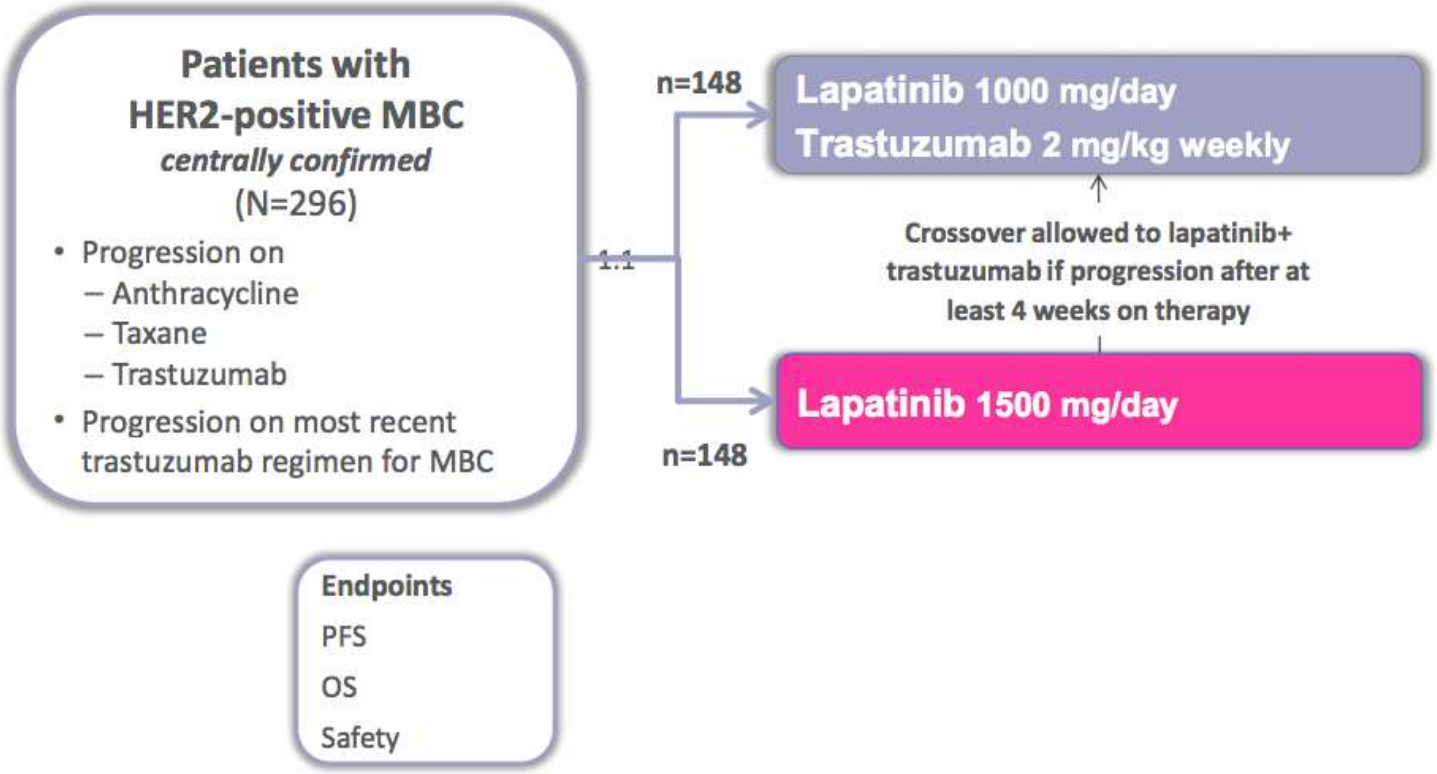
MARIANNE Study PFS



No. at risk:									
Trastuzumab + taxane	365	265	163	107	75	50	21	5	
T-DM1	367	257	176	133	104	67	28	3	
T-DM1 + pertuzumab	363	261	177	135	109	75	25	5	1

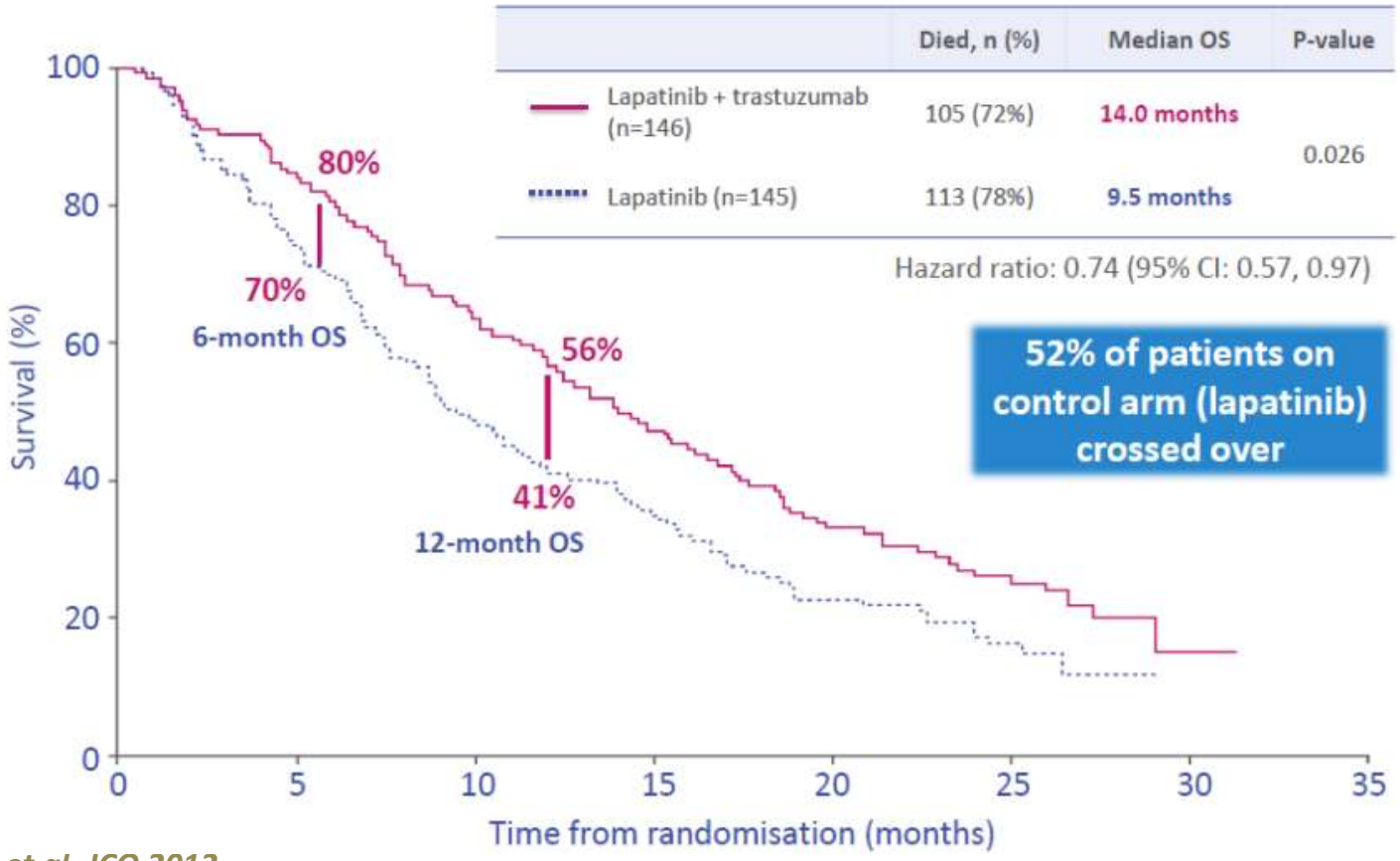
Perez EA et al. JCO 2017

EGF104900 Study Design



Blackwell KL et al. JCO 2012

EGF104900 Study OS



Blackwell KL et al. JCO 2012

Metastatic Strategy Conclusions

- Outcomes of HER2neu+ metastatic breast cancer treatment has significantly improved
- Standards of care are docetaxel/pertuzumab/trastuzumab and pertuzumab/trastuzumab/AI (ER+ disease)
- Lapatinib/trastuzumab is an option for heavily treated patients
- Increased toxicities with combinations

FUTURE STRATEGIES

Ongoing Clinical Trials In HER2neu+ EBC

Trial Name	Phase	Setting	Treatment Arms	Primary Endpoint
ATEMPT[1]	II	Stage I; Adjuvant	T-DM1 vs Paclitaxel/Tmab	DFS
KAITLIN[2]	III	Adjuvant; after surgery and anthracycline-based chemo	T-DM1 + Pmab vs Taxane + Tmab/Pmab	iDFS
IMpassion050[3]	III	Neoadjuvant; T2-4, N1-3, M0 with known HER2, HR, PD-L1 status	AC + Atezolizumab → THP + Atezolizumab vs AC + Pbo → THP + Pbo	pCR
APTneo[4]	III	Neoadjuvant; Early high-risk (T1c-2N1 or T3N0) or LA disease suitable for neoaj tx	TCHP vs TCHP + Atezolizumab vs AC + Atezolizumab → TCHP + Atezolizumab	EFS
PALTAN[5]	II	Neoadjuvant; Stage II-III ER+ HER2+ (tumor ≥ 2 cm)	Palbociclib + letrozole + Tmab +/- goserelin	pCR
NA-PHER2[6]	II	Neoadjuvant; early ER+ HER2+ (tumor > 1.5 cm)	Tmab + Pmab + Palbociclib +/- fulvestrant	Ki67

1. NCT01853748. 2. NCT01966471. 3. NCT03726879. 4. NCT03595592. 5. NCT02907918. 6. NCT02530424