Principles of HER2-Positive Breast Cancer Management

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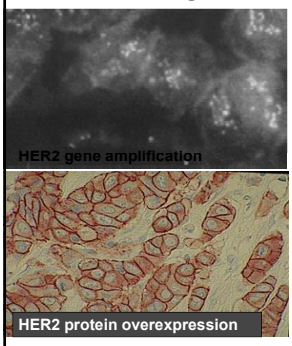
Financial Disclosure

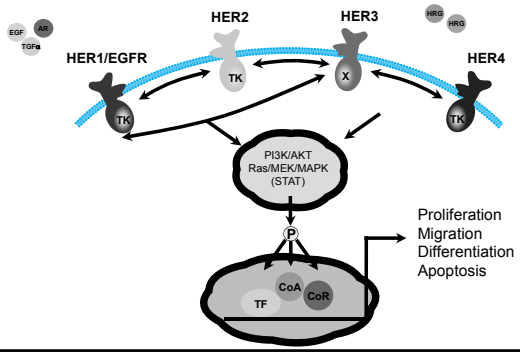
- I have no significant relationships to disclose

HER2 Oncogene: A Biological Target

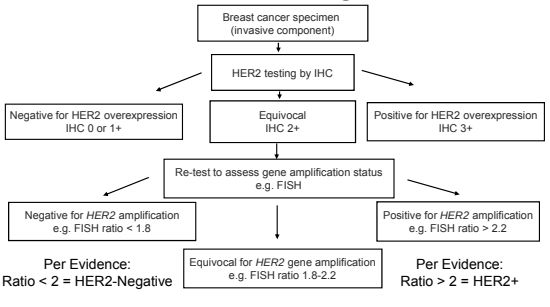


- Increased Aggressiveness
- Shortened Survival
- Hormonal Resistance

HER Family Ligands and Signaling

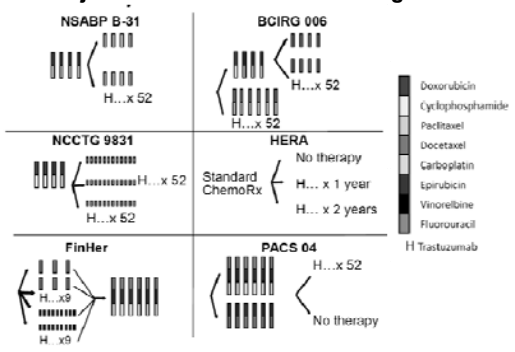


HER2 Testing in Clinical Practice: 2007 ASCO/CAP Algorithm



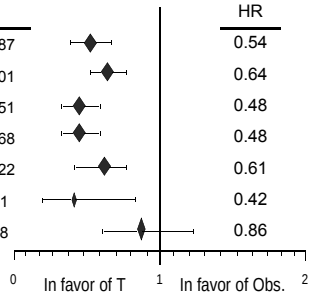
Wolff A, et al. J Clin Oncol. 2007

Adjuvant Trastuzumab Trial Designs

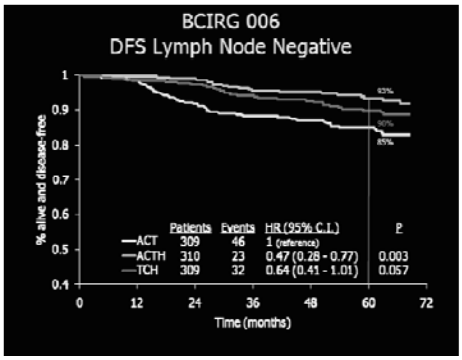


Summary of Trastuzumab Adjuvant Trial DFS Benefits

Study	FU, yrs	N	HR
HERA	1	3,387	0.54
	2	3,401	0.64
NSABP B-31/ NCCTG 9891	2	3,351	0.48
	4	3,968	0.48
BCIRG 006	3	3,222	0.61
FinHer	3	231	0.42
PACS 04	4	528	0.86



BCIRG 006 DFS Lymph Node Negative



Slamon D et al. SABCS 2009

Clinical Cardiomyopathy from Trastuzumab Adjuvant Trials

Trial	Arm	Baseline LVEF, %	CHF, %	Cardiac death, n
HERA	Control	≥55	0	1
	H 1 year		0.6 / 2.1	0
B31	AC→P	≥50	0.8	1
	AC→PH		3.8	0
N9831	AC→P	>50	0.3	1
	AC→P→H		2.8	1
	AC→PH		3.3	0
BCIRG 006	AC→D	≥50	0.4	0
	AC→DH		1.9	0
	DCarboH		0.4	0
FinHer	Any Chemo → No H		1	0
	Any Chemo → H		0	0

H = Trastuzumab; A = Doxorubicin; C = Cyclophosphamide; P = Paclitaxel; D = Docetaxel

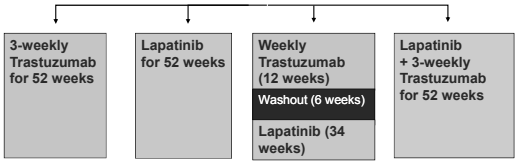
Smith et al 2007; Perez et al 2008; Slamon et al 2006; Rastogi et al 2007

Ongoing Controversies Regarding Adjuvant Therapy for HER2+ Breast Cancer

- Are anthracylines more effective for higher risk disease?
- Can shorter duration be as effective?
- Is longer duration optimal
- Should trastuzumab be used for T1a or T1b N0 disease?
- Can trastuzumab be given with single agent paclitaxel or hormonal therapy for low risk disease?
- Are there predictors for cardiac toxicity other than age, hypertension, use of anthracyclines?
- How to handle borderline subnormal and subclinical drops in cardiac ejection fraction

ALLTO Adjuvant Trial

Chemotherapy is flexible (eg. AC-Taxane, TCH)

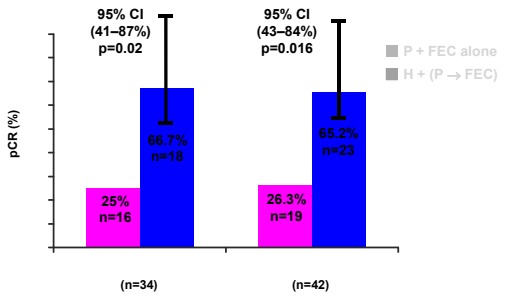


Anti-HER2 therapy can overlap chemotherapy

Key Findings to Date in the Neoadjuvant Therapy of HER2+ Breast Cancer

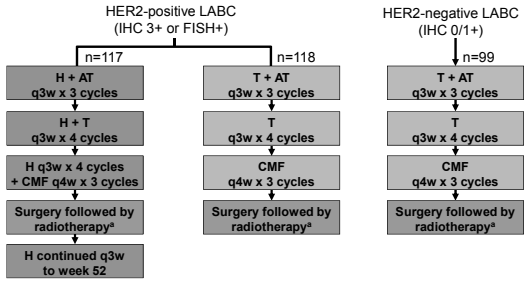
- Addition of trastuzumab significantly improves pCR rate and DFS when added to chemotherapy
- Pathological complete response (pCR) rate predicts long-term outcome, possibly to a greater extent than HER2- (esp HR+) cases
- HER2+ cases exhibit greater pCR rate than HER2- cases with chemotherapy alone
- pCR rates are greater in HR-negative vs HR+ cases for HER2+ and the difference in outcome based on pCR is greater in HR- (as is the case with HER2-negative)

Effect of Trastuzumab on Neo-Adjuvant Therapy for HER2-Positive Disease



Buzdar A, et al. JCO 2004

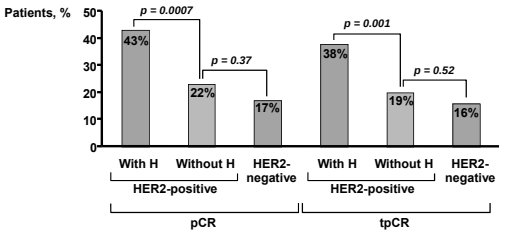
NOAH Study Design



AT, doxorubicin (60 mg/m²), paclitaxel (150 mg/m²);
H, trastuzumab (8 mg/kg loading dose then 6 mg/kg); T, paclitaxel (175 mg/m²);
[a]Hormone receptor-positive patients received adjuvant tamoxifen

Gianni L, et al., Lancet 2010

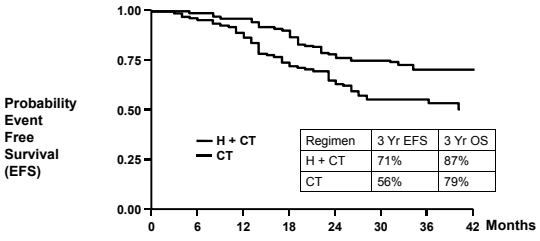
NOAH: pCR: Intent-to-Treat Population



pCR: pathologic complete response in breast
tpCR: total pathologic complete response in breast and nodes

Gianni L, et al., Lancet 2010

NOAH: EFS in HER2+ Population Median F/U 3.2 yr



Regimen	3 Yr EFS	3 Yr OS
H + CT	71%	87%
CT	56%	79%

	H + CT (n =115)	CT (n = 112)	HR (95% CI)	*P* value
EFS (events)	36	51	0.59 (0.38–0.90)	.013
OS (events)	18	26	0.62	.114

Symptomatic CHF = 2%

Gianni L, et al., Lancet 2010

Critical Questions and Hypotheses about HER2-Directed Neoadjuvant Therapy

- Are anthracylines more effective in combination with trastuzumab and is the combination safe?
- Are HER2+ tumors addicted to HER2?
- Can bypass pathways be overcome by dual targeting?
- Is dual targeting safe?
- Can dual targeting replace chemotherapy?

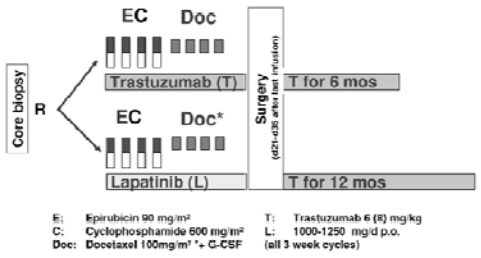
Concurrent Neoadjuvant Trastuzumab and Anthracyline compared to TCH: MDACC Experience 2001-2009

	PH → FECH	TCH	
N	235	65	
pCR	60.6%	43.3%	p = 0.016
cCR	80.8%	58.9%	p = 0.006
3 Yr RFS	93%	71%	p < 0.001
3 Yr OS	96%	86%	p = 0.008
Decline in LVEF from baseline	0.08%	0.08%	p = 0.52

Note: PH → FECH Group was significantly younger and had lower tumor stage and less pre-existing cardiac disease

Bayraktar S, et al., ASCO 2011; abstract 532

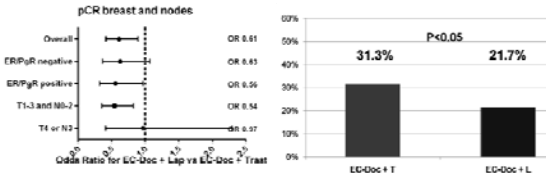
Lapatinib or Trastuzumab Combined With Neoadjuvant Chemotherapy: The GeparQuinto Study (GBG 44)



Untch et al. SABCS 2010; abstract S3-1

Neoadjuvant Chemotherapy Plus Lapatinib or Trastuzumab: Efficacy

pCR Rate	EC→D/ Lapatinib	EC→D/ Trastuzumab	*P* Value
ypT0, ypN0	22%	31%	< .05
ypT0/is, ypN0	30%	45%	< .05
ypT0/is, ypNX	35%	50%	< .05
Breast Conservation Rate	56%	66%	NR

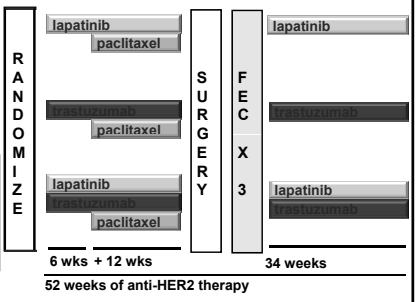


Untch et al. SABCS 2010; abstract S3-1

Neo ALTTO Study Design

Invasive operable HER2+ BC
T > 2 cm (inflammatory BC excluded)
LVEF ≥ 50%
N=450

Stratification:
- **T ≤ 5 cm vs. T > 5 cm**
- **ER or PgR + vs. ER & PgR –**
- **N 0-1 vs. N ≥ 2**
- **Conservative surgery or not**



Baselga J et al. SABCS 2010; abstract S3-3

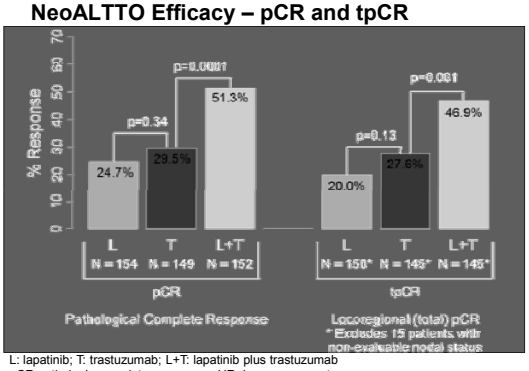
NeoALTTO: Safety

	Lapatinib/ Trastuzumab (n = 152)	Lapatinib (n = 154)	Trastuzumab (n = 149)
Grade ≥ 3 Adverse Events			
Diarrhea	32 (21%)	36 (23%)	3 (2%)
Liver	13 (9%)	20 (13%)	2 (1%)
Neutropenia	13 (9%)	24 (16%)	4 (3%)
Skin	10 (7%)	10 (7%)	4 (3%)
Treatment Discontinuation Due to Adverse Event	33 (22%)	29 (19%)	2 (1%)

- No major cardiac events
- 1 death on lapatinib/trastuzumab arm immediately after treatment ended

Baselga J et al. SABCS 2010; abstract S3-3

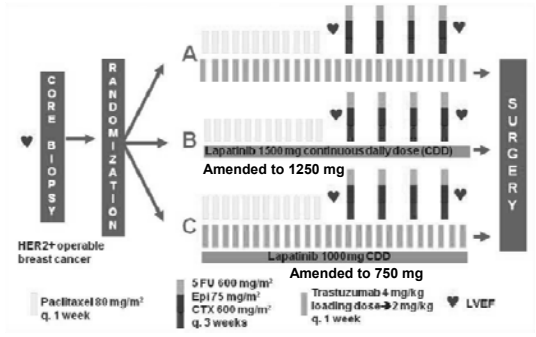
NeoALTTO Efficacy – pCR and tpCR



L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response HR: hormone receptors

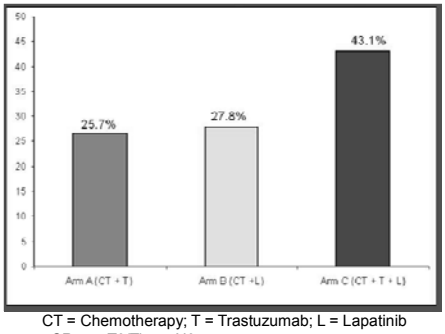
Baselga J et al. SABCS 2010; abstract S3-3

CHER-LOB Trial



Guarneri V, et al. ASCO 2011 Abstr # 507

CHER-LOB Trial: Efficacy



CT = Chemotherapy; T = Trastuzumab; L = Lapatinib
pCR = ypT0/Tis, ypN0

Guarneri V, et al. ASCO 2011 Abstr # 507

Randomized Phase II Study of Neoadjuvant Pertuzumab Plus Trastuzumab: NeoSphere

Eligibility criteria:
- Operable or locally advanced/ inflammatory HER2+ breast cancer
- Chemonaive
- Primary tumors > 2 cm

RANDOMIZE

- **Docetaxel (T) Trastuzumab (H)** (n = 107) → **FEC** q 3 weeks × 3 **H** q 3 weeks, cycles 5-17
- **Docetaxel (T) Trastuzumab (H) Pertuzumab (P)** (n = 107) → **FEC** q 3 weeks × 3 **H** q 3 weeks, cycles 5-17
- **Trastuzumab (H) Pertuzumab (P)** (n = 107) → **T** q 3 weeks × 4 → **FEC** q 3 weeks × 3 **H** q 3 weeks, cycles 5-17
- **Docetaxel (T) Pertuzumab (P)** (n = 96) → **FEC** q 3 weeks × 3 **H** q 3 weeks, cycles 5-21

SURGERY

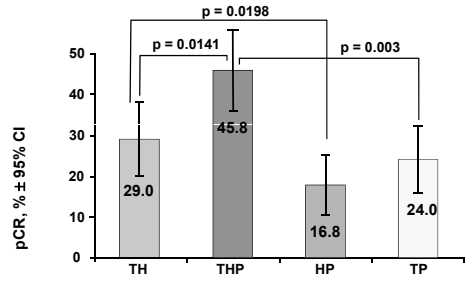
Primary endpoint: pCR rates
Secondary endpoints including: clinical response

All q 3 weeks × 4

FEC: 5-fluorouracil/epirubicin/ cyclophosphamide

Gianni et al. SABCS 2010; abstract S3-2

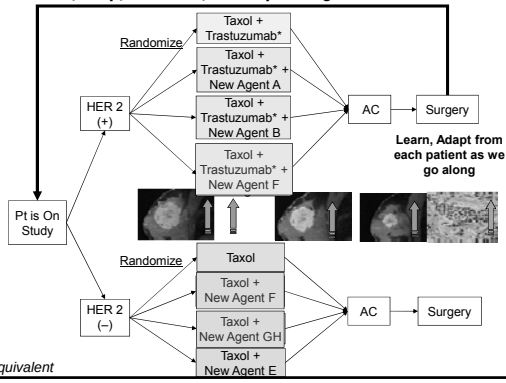
NeoSphere pCR rates: ITT Population Summary



H, trastuzumab; P, pertuzumab; T, docetaxel

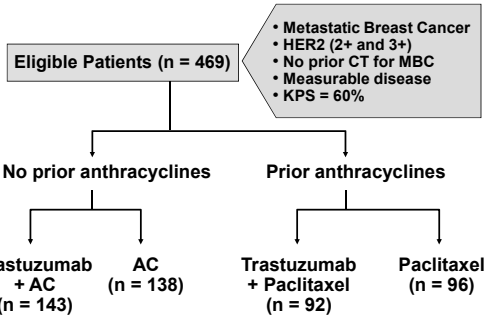
Gianni et al. SABCS 2010; abstract S3-2

I-SPY 2 Adaptive Trial: Learn, Drop, Graduate, and Replace Agents Over Time

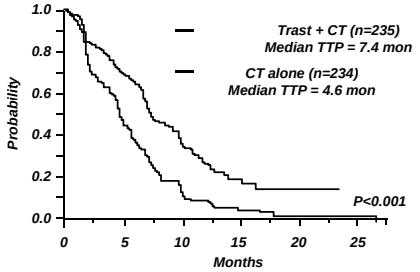


*Or Equivalent

Pivotal Trastuzumab Randomized Trial for HER2+ Advanced Breast Cancer

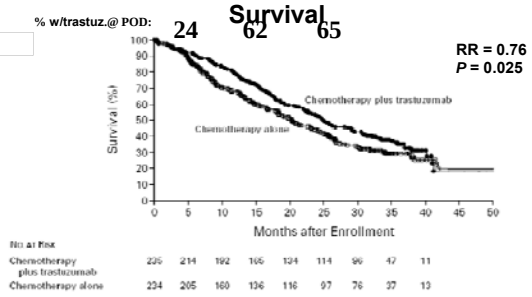


Trastuzumab Added to Chemotherapy for Advanced HER2+ Breast Cancer: Time to Progression



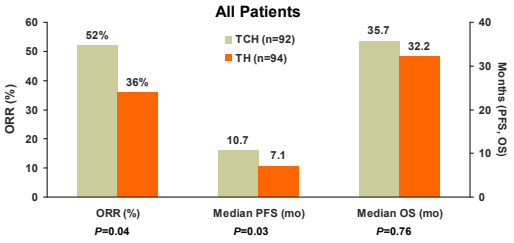
Slamon DJ et al. NEJM 2001

Trastuzumab Added to Chemotherapy for Advanced HER2+ Breast Cancer: Survival



Slamon DJ et al. NEJM 2001

Phase III Trial of First-Line Trastuzumab and Paclitaxel ± Carboplatin (TCH) in MBC: Efficacy



Robert N et al JCO 2006

Commonly Used Trastuzumab Regimens for HER2+ MBC

Regimens Tested in Phase II trials	Response Rate Range
Trastuzumab + vinorelbine	52-86%
Trastuzumab + capecitabine	60-77%
Trastuzumab + gemcitabine	33-38%
Trastuzumab + liposomal doxorubicin	52-58%

Triplet Combinations of Trastuzumab With Chemotherapy

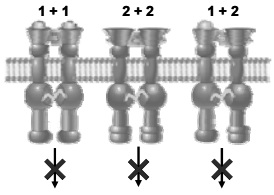
Phase II Trial in MBC (First-Line)	N	ORR, % (95% CI)
Trastuzumab, docetaxel, carboplatin[1]	62*	58 (44-70)
Trastuzumab, docetaxel, cisplatin[1]	62	79 (66-89)
Trastuzumab, paclitaxel, gemcitabine[2]	27	78 (58-91)
Trastuzumab, docetaxel, vinorelbine[3]	34	70 (NR)
Trastuzumab, docetaxel, gemcitabine[4]	34	56 (39-73)
Trastuzumab, liposomal doxorubicin, paclitaxel[5]	24	91.7 (NR)
Trastuzumab, liposomal doxorubicin, docetaxel[6]	43	46 (31-62)

*59/62 first-line.

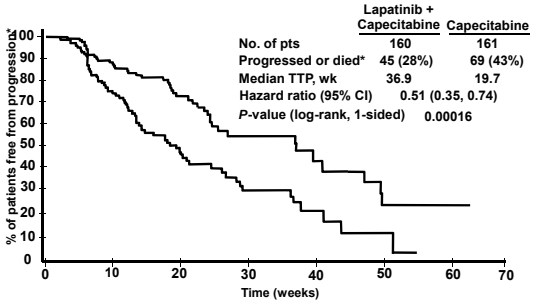
1. Pegram et al. *J Natl Cancer Inst.* 2004;96:759.
2. Update of Colomer et al. *Breast Cancer Res Treat.* 2004;88(suppl 1):S127. Abstract 3046.
3. Update of Yardley et al. *Proc Am Soc Clin Oncol.* 2004;23(suppl 1):37. Abstract 643.
4. Polyzos et al. *Proc Am Soc Clin Oncol.* 2004;23(suppl 1):58. Abstract 728.
5. Update of Cortes et al. *Breast Cancer Res Treat.* 2004;88(suppl 1):S125. Abstract 3041.
6. Update of Wolff et al. *Breast Cancer Res Treat.* 2004;88(suppl 1):S125. Abstract 3040.

Lapatinib Blocks Signaling Through Multiple Receptor Combinations

- Blocks signaling through ErbB1 and ErbB2 homodimers and heterodimers
- Might also prevent signaling through heterodimers between these receptors and other ErbB family members
- Potentially blocks multiple ErbB signaling pathways



Capecitabine +/- Lapatinib in HER2+ MBC Time to Progression

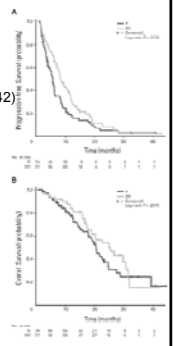


Geyer C et al. NEJM 2006

Capecitabine +/- Trastuzumab in Patients who Have Previously Received Trastuzumab

Administered pre-treatments (N=156)

- 1st-line taxane + trastuzumab (N=111)
- Trastuzumab alone or with other 1st-line chemotherapy (N=42)
- Taxane + trastuzumab as adjuvant therapy (N=3)

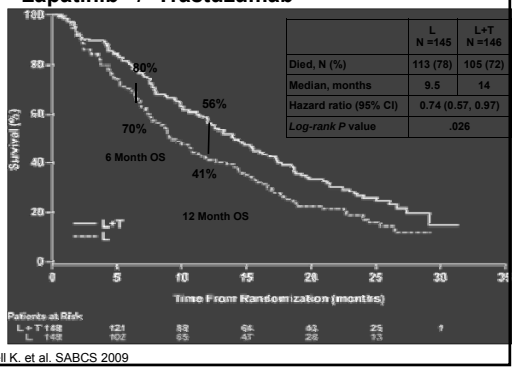


	Capecitabine	Capecitabine + Trastuzumab	HR	P-value
Median TTP	5.6 months	8.2 months	0.69	.034
Median OS	20.4 months	25.5 months	0.76	.26
ORR	27%	48%	-	.011
CBR	54%	75%	-	.0068

TTP=Time to Progression; OS=Overall Survival
ORR: Overall Response Rate (CR+PR)
CBR: Clinical Benefit Rate (CR+PR+SD >24 weeks)

Von Minckwitz G et al. JCO 2009

Combined Vertical Blockade: Lapatinib +/- Trastuzumab



	L N =145	L+T N =146
Died, N (%)	113 (78)	105 (72)
Median, months	9.5	14
Hazard ratio (95% CI)	0.74 (0.57, 0.97)	
Log-rank P value	.026	

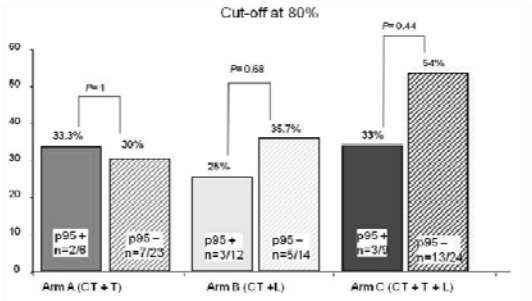
Blackwell K. et al. SABCS 2009

Ongoing Clinical Strategies to Overcome Resistance to HER2+ BC

- Combination with signal transduction pathway inhibitors
  - HER1
  - HER2
  - IGFR-1
  - MET
  - Akt
  - mTOR
- Combinations with anti-angiogenic therapies
- Combinations with interacting pathway modulators
  - ER
  - NFκB

Markers of Resistance to Trastuzumab	
p95 (truncated HER2	C-Met Receptor
PI3K (PI3KCA) mutations	HER3
PTEN Loss	CXCR4
IGF-1 Receptor	MUC4

CHER-LOB Trial: pCR Rate by p95 Status

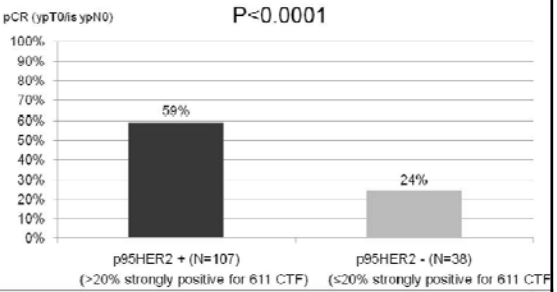


CT = Chemotherapy; T = Trastuzumab; L = Lapatinib

Guarneri V, et al. ASCO 2011 Abstr # 507

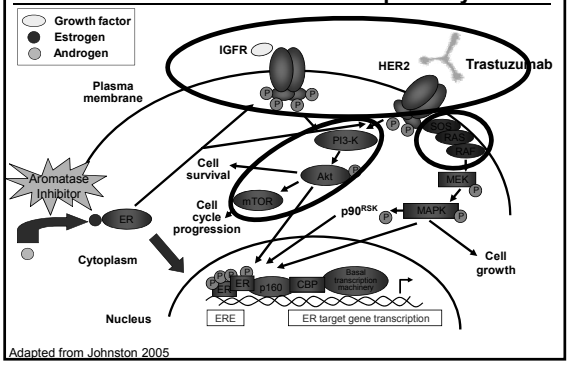
GeparQuattro: p95HER2 and response to trastuzumab

(N=145 patients treated with EC+T → Doc+T)



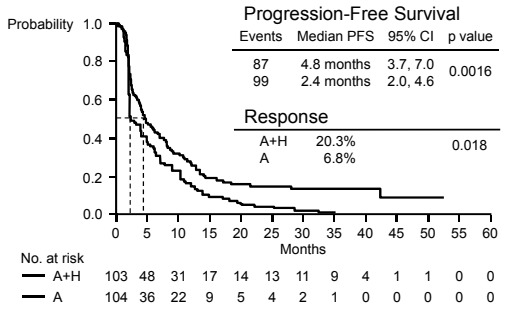
Loibl S et al, ASCO 2011 Abstr #530

Cross-talk between signal transduction and endocrine pathways



Adapted from Johnston 2005

Anastrozole +/- Trastuzumab: TAnDEM Trial



Progression-Free Survival

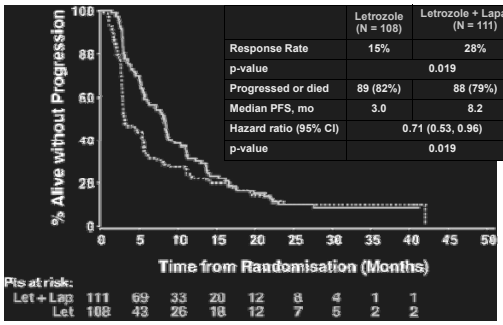
Events	Median PFS	95% CI	p value
87	4.8 months	3.7, 7.0	0.0016
99	2.4 months	2.0, 4.6	

Response

A+H	20.3%	0.018
A	6.8%	

Kaufman B et al. JCO 2009

Letrozole +/- Lapatinib: PFS and Response in HER2+ Population



	Letrozole (N = 108)	Letrozole + Lapatinib (N = 111)
Response Rate	15%	28%
p-value	0.019	
Progressed or died	89 (82%)	88 (79%)
Median PFS, mo	3.0	8.2
Hazard ratio (95% CI)	0.71 (0.53, 0.96)	
p-value	0.019	

Johnston S et al. JCO 2009

Newer HER2-Targeting Agents

HER1/2 TKI	*Lapatinib, Neratinib, BIBW 2992, PKI-166, EKB-569*
Pan HER TKI	*Canertinib, BMS-599626*
HER1/2/VEGFR TKI	*XL647, AEE788*
HER2 dimerization inhibitor	*Pertuzumab*
Bi/Tri-specific antibodies	*MM-111, Ertumaxomab*
Conjugated antibodies	*Trastuzumab-MCC-DM1, trastuzumab-A-Z-CINN 310-paclitaxel*
HSP90 inhibitors	*Tanespimycin, alvespimycin, CNF2024, IPI-504, AUY922, SNX5422*
IGF-1R inhibitors (mAb, TKI)	*CP-751871, EM164, IMC-A12, NVP-ADW742, OSI-906*
HDAC inhibitors	*Vorinostat, LBH589, PXD101, NVP-LAQ824, depsipeptide, CI-994, MS-275*
PI3K inhibitors	*SF1126, BEZ235, XL147, XL765*
Akt inhibitors	*Perifosine, XL418. MK-2206*
mTOR inhibitors	*Rapamycin (sirolimus), temsirolimus, everolimus, deforolimus*
HER2 vaccines	*Peptides (E75), engineered cells, dendritic cells*

Trastuzumab and Pertuzumab: Distinct Epitopes on HER2 Extracellular Domain

Trastuzumab

- Potent inhibitor of HER2-mediated signaling pathways
- Activates antibody-dependent cellular cytotoxicity
- Inhibits shedding and, thus, formation of p95

Pertuzumab

Prevents receptor dimerization
Potent inhibitor of HER-mediated signaling pathways

Dual Antibody Targeting with Pertuzumab + Trastuzumab in Patients with HER2+ MBC Previously Treated with Trastuzumab

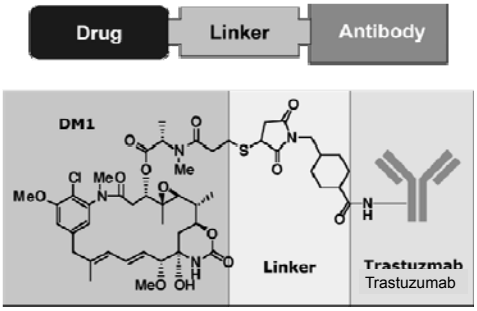
	N	ORR	CBR	Common adverse events
Baselga	66	24% (CR rate: 8%)	50%*	Diarrhea, fatigue, nausea, rash
Portera	11	18% (all PRs)	45%†	Diarrhea, allergic reaction, rash, left ventricular systolic dysfunction

Efficacy Endpoint	Pertuzumab (n = 29)	Pertuzumab/ Trastuzumab (n = 14 of 29 who progressed)
Overall Response Rate	1 (3%)	3 (21%)
Clinical Benefit Rate (ORR + SD ≥ 8 Cycles)	3 (10%)	6 (43%)

* CR + PR + SD ≥ 6 months
† CR + PR + SD ≥ 18 weeks

Baselga J, et al., J Clin Oncol 2010
Portera et al., Clinical Cancer Res 2008
Baselga et al., SABCS 2009, abstract 5114

Structure of Trastuzumab-DM1



Phase II Study of Trastuzumab-DM1 in Heavily Pretreated HER2-Positive MBC

Efficacy N=112	Indep Rev Assessed	Investigator Assessed
ORR	25.9%	37.5%
Median PFS	4.6 months	4.6 months
HER+ (n = 74) ORR	33.8%	47.3%
HER2 Normal (n = 21) ORR	4.8%	9.5%

Grade 3/4 AEs	
Thrombocytopenia	8.0%
Required transfusion	3.6%
Hypokalemia	8.9%
Fatigue	4.5%
Hemorrhagic AE (all Gr3)	5.2%
Discontinued therapy due to AE	3.6%

- **No dose-limiting cardiotoxicity, 2 patients had LVEF declines to 40% and 45%**
- **3 deaths occurred on treatment, 2 associated with progression, 1 due to underlying MBC**

Burris HA III, et al. J Clin Oncol 2011

Neratinib: Response and Clinical Benefit Rates: Independent Radiology Assessment

	Prior T (n = 61)	No prior T (n = 66)	Total (n = 127)
Objective Response Rate (95% CI)	26% (16, 39)	56% (43, 68)	42% (33, 51)
Clinical Benefit Rate (95% CI)	36% (24, 49)	68% (56, 79)	53% (44, 62)
Partial Response	26%	56%	42%
Stable Disease <24 wks ≥24 wks	44% 34% 10%	32% 20% 12%	38% 27% 11%
Progressive Disease	26%	8%	17%
Unknown	3%	5%	4%

Objective response rate = (CR + PR/evaluable pts); Clinical benefit rate = (CR + PR + SD ≥ 24 weeks /evaluable pts)

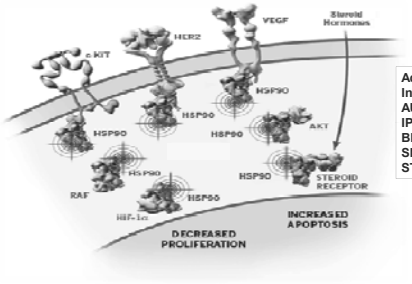
Burstein H et al, J Clin Oncol 2010

Phase II trial of BIBW 2992 in HER2+ MBC after trastuzumab progression

- **BIBW 2992: Irreversible dual tyrosine kinase inhibitor of EGFR/HER1 and HER2**
  - Demonstrated preclinical activity in trastuzumab-resistant cell lines
- **Study design: Patients with Stage IIIB or IV HER2+ MBC with progression on prior trastuzumab (n = 41)**
  - Dose: 50 mg qd
- **Efficacy (n = 34): PR = 12%; SD = 41%**
- **Adverse events:**
  - Grade 3 diarrhea (22%), rash (10%), nausea (5%), vomiting (5%), stomatitis (5%)
  - No grade 4 adverse events
  - 18 patients required dose reductions

Hickish et al ASCO 2009

Tanespimycin (KOS-953): Heat Shock Protein 90 (HSP90) Inhibitor



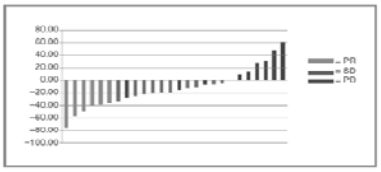
Additional HSP90 Inhibitors
AUY922
IPI-504 (retaspimycin)
BIIB021 (CNF2024)
SNX-5422
STA-9090

Tanespimycin Phase 2 Results

Efficacy (n=27)

- 22% ORR (all PRs)
- 63% clinical benefit (ORR+SD ≥6 weeks)

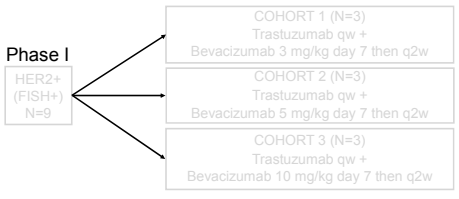
Event Type (n=31)	All Grades	Grade 3
Diarrhea	81%	3%
Fatigue	77%	7%
Nausea	52%	3%
Transaminasemia	48%	10%



- No Grade 4 toxicities seen
- 1 episode of asymptomatic drop in cardiac EF from 60 to 42%

Modi S. et al. J Clin Oncol 2011

Trastuzumab + Bevacizumab in Relapsed/MBC: Phase I/II Trial



- Phase II, N = 37
- Response 54.1% (1 Patient with CR)
- Stable Disease 29.7%
- Cardiac Event in 13 Patients (Most Grade 1, 2)
- Grade 4 Cardiac Event in 1 Patients

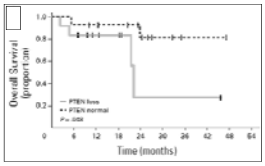
Recently completed BETH Trial
TCH +/- Bevacizumab (+/- extended Bev x 1 y

Pegram M et al, SABCS 2006 Abstract 301

Everolimus Added to Trastuzumab after Progression on Trastuzumab

- 47 patient pooled for 2 trials at 3 institutions, received everolimus 10 mg/daily
- Most patients had received 2 or more trastuzumab-based regimens

Efficacy Measure			
ORR (all PRs	7 (19%)		
ORR + SD > 6 mo	16 (34%)		
Median PFS	4.1 mo		
Toxicity (%)	**Grade 2/3/4**		
Mucositis	25	9	0
Hyperglycemia	9	11	2
Fatigue	23	9	0
Thromboembolism	2	0	2



Morrow PK, et al. J Clin Oncol 2011

HER2 Peptide Vaccine (E75) In Early Stage Breast Cancer

- E75 is a immunogenic peptide (aa 369-377) of the HER2 protein
- Combined analysis of 2 trials (Trial 1: dose-escalation trial of node+ pts with BC, Trial 2: dose-optimization trial of node-pts with BC), median F/U = 20 mo.
- N = 186 pts; E75 vaccine: 101 pts, Controls (non randomized): 85 pts
- 6 cycles of monthly intradermal administrations of E75 with GM-CSF (250 mcg

Results:

- Toxicity - Local reactions (Gr2: 18%)
  - Systemic toxicity (Gr2: 16%,Gr3: 3%)
  - Delayed hypersensitivity reaction (14.6mm vs. 2.1 mm, P<.0001)

	Vaccinated (n=101)	**"Control" (n=85)**	**P value**
Recurrence Rate	**5.6%**	**14.2%**	**0.04**
DFS	**92.5%**	**77%**	
Deaths	**1**	**4**	**0.1**

Updated recurrence at 26 mo f/u = 8.3 vs 14.8% (p=0.15)

Peoples GE et al. Clinical Cancer Res 2008

Personalizing Combinatorial Therapy for HER+ Breast Cancer