5 Minute JournalClub

Key SABCS Presentations

Issue 1, 2011

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CME Information

LEARNING OBJECTIVES

- Apply the results of new research when recommending neoadjuvant chemotherapy with anti-HER2 treatment to patients with untreated HER2-positive primary breast cancer.
- Recognize the contribution of agent-specific toxicities to the rate of overall compliance with neoadjuvant anti-HER2 therapy.
- Compare and contrast response rate and tolerability of trastuzumab- and lapatinib-based neoadjuvant therapy versus the combination approach in the treatment of HER2-positive primary breast cancer.
- Recall new data to support the adjuvant investigation of pertuzumab in combination with trastuzumab without chemotherapy in HER2-positive early breast cancer.
- Describe the efficacy and safety of the neoadjuvant docetaxel/trastuzumab/pertuzumab combination for patients with HER2-positive early, locally advanced or inflammatory breast cancer.
- Counsel patients receiving neoadjuvant trastuzumab-based therapy about the impact of pathologic complete response on longer-term clinical outcome.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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No real or apparent conflicts of interest to disclose.

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Advisory Committee: Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Eisai Inc, Genentech BioOncology, Genomic Health Inc, GlaxoSmithKline, Millennium — The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Aventis; *Consulting Agreements:* Biogen Idec, GlaxoSmithKline, Millennium — The Takeda Oncology Company.

CME Information (Continued)

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No real or apparent conflicts of interest to disclose.

Eric P Winer, MD
Thompson Investigator in Breast Cancer Research
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No real or apparent conflicts of interest to disclose.

Lapatinib versus Trastuzumab in Combination with Neoadjuvant Anthracycline-Taxane-Based Chemotherapy: Primary Efficacy Endpoint Analysis of the GEPARQUINTO Study (GBG 44)

Untch M et al.

Proc SABCS 2010;Abstract S3-1.

Objectives

- Primary: Pathological CR rates
- Secondary:
  - Pathological CR rates with alternate definitions of pathological CR
  - Breast conservation rate
  - Compliance and toxicity
  - Efficacy in stratified risk groups
  - Disease-free and overall survival

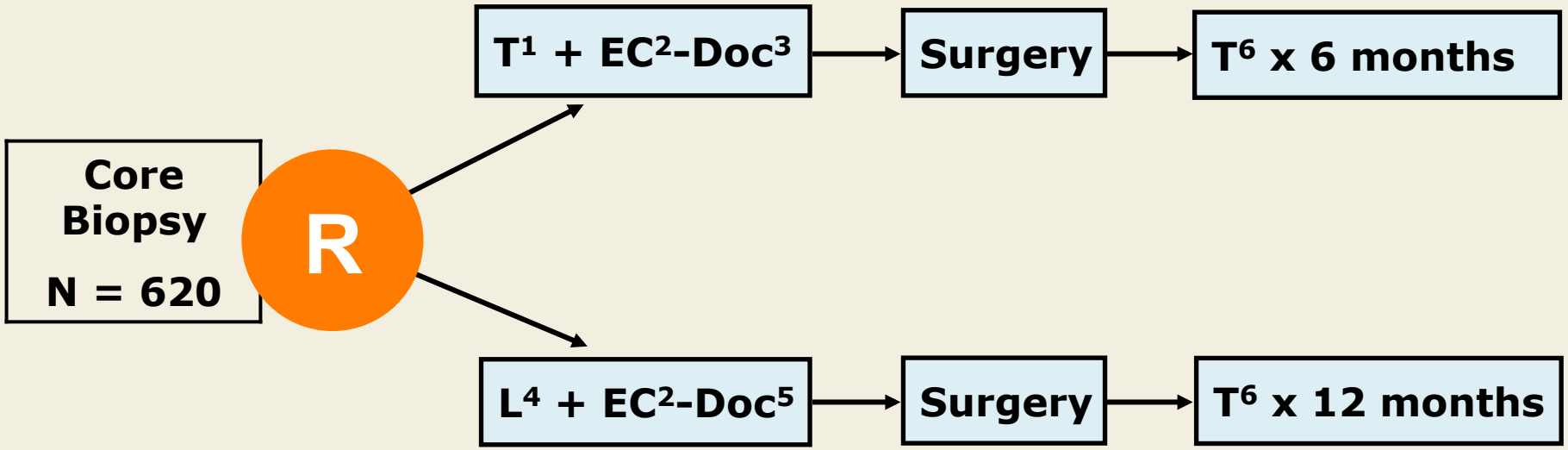
Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

Eligibility

- Untreated primary breast carcinoma
- HER2-positive by local pathology (IHC score 3+ or FISH+)
- Tumor stages:
  - cT4 or cT3
  - cT2 if HR- or cN+
  - cT1 if HR- or if SLN+
- Breast lesion ≥ 2 cm by palpation or ≥ 1 cm by ultrasound
- No metastasis
- Normal organ function
- Left ventricular ejection fraction ≥ 55%

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

Study Schema



[1] Trastuzumab (T) 6 mg/kg q3wk x 8 (initial loading dose 8 mg/kg)
[2] Epirubicin (E) 90 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 q3wk x 4
[3] Docetaxel (Doc) 100 mg/m^2 q3wk x 4
[4] Lapatinib (L) 1,000-1,250 mg PO QD
[5] Doc 100 mg/m^2 q3wk (with G-CSF support) x 4
[6] T 6 mg/kg q3wk

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

Efficacy Results

	T + EC-Doc	L + EC-Doc	*p*-value
Pathological CR (no invasive or noninvasive residual in breast and nodes based on central pathology report review)	31.3%	21.7%	< 0.05
Pathological CR (no invasive residual in breast and nodes according to other definitions)	45.0%	29.9%	< 0.05
Pathological CR (no invasive residual in breast only according to other definitions)	50.4%	35.2%	< 0.05
Breast conservation rate	65.6%	56.0%	—

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

Efficacy Results by Stratification

	Odds Ratio
Overall	0.61
ER/PR-negative	0.63
ER/PR-positive	0.56
T1-3 and N0-2	0.54
T4 or N3	0.97

A lower odds ratio suggests results favorable to T + EC-Doc vs L + EC-Doc.

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

Safety and Compliance Results

	T + EC-Doc	L + EC-Doc
Discontinued chemotherapy + anti-HER2 agent	10%	16%
Discontinued anti-HER2 agent only	3.1%	7.0%
Serious adverse events	13.5% (T + EC) 14.5% (T + Doc)	17.7% (L + EC) 15.2% (L + Doc)

Untch M et al. *Proc SABCS* 2010;Abstract S3-1.

Conclusions

- Trastuzumab + EC-docetaxel achieved a significantly higher pathological CR rate in unselected HER2-positive primary breast cancer when compared to the lapatinib combination with the same chemotherapy.
- Efficacy results were consistent in most prespecified subsets, including ER/PR-negative and ER/PR-positive subtypes.
- Compliance of lapatinib with EC-docetaxel was lower than trastuzumab plus EC-docetaxel.
- Results should be seen in the context of other studies like Neo-ALTTO, which uses a higher dose of lapatinib (1,500 mg/d), but a shorter treatment duration.

Untch M et al. *Proc SABCS* 2010;Abstract S3-1; Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Investigator Commentary: GEPARQUINTO Neoadjuvant Study (GBG 44)

GEPARQUINTO is the first clinical trial to compare chemotherapy/trastuzumab with chemotherapy/lapatinib. According to NSABP criteria, the pCR was 50 percent with chemotherapy/trastuzumab and 35 percent with chemotherapy/lapatinib, which was unexpectedly lower than was hypothesized at the beginning of this study.

In the intention-to-treat analysis 23 percent of patients in the chemotherapy/lapatinib arm had treatment discontinued due to Grade III and higher diarrhea compared to a 13 percent rate of discontinuation in patients who received chemotherapy/trastuzumab. This was the first time that lapatinib has been administered with anthracyclines and docetaxel, and we had to learn how to cope with the side effects of this combination. We learned that it was necessary to reduce the dose of lapatinib from 1,250 mg to 1,000 mg to avoid the diarrhea, and we also learned to add G-CSF to avoid febrile neutropenia from lapatinib and docetaxel. These are important lessons learned from this trial, and we now discuss with patients which side effects to expect and how to deal with them.

Interview with Michael Untch, MD, PhD, December 11, 2010

First Results of the NeoALTTO Trial (BIG 01-06/EGF 106903): A Phase III, Randomized, Open-Label, Neoadjuvant Study of Lapatinib, Trastuzumab, and Their Combination Plus Paclitaxel in Women with HER2-Positive Primary Breast Cancer

Baselga J et al.

Proc SABCS 2010;Abstract S3-3.

Neo ALTTO (BIG 01-06/EGF 106903) Study Design

Eligibility (N = 450)

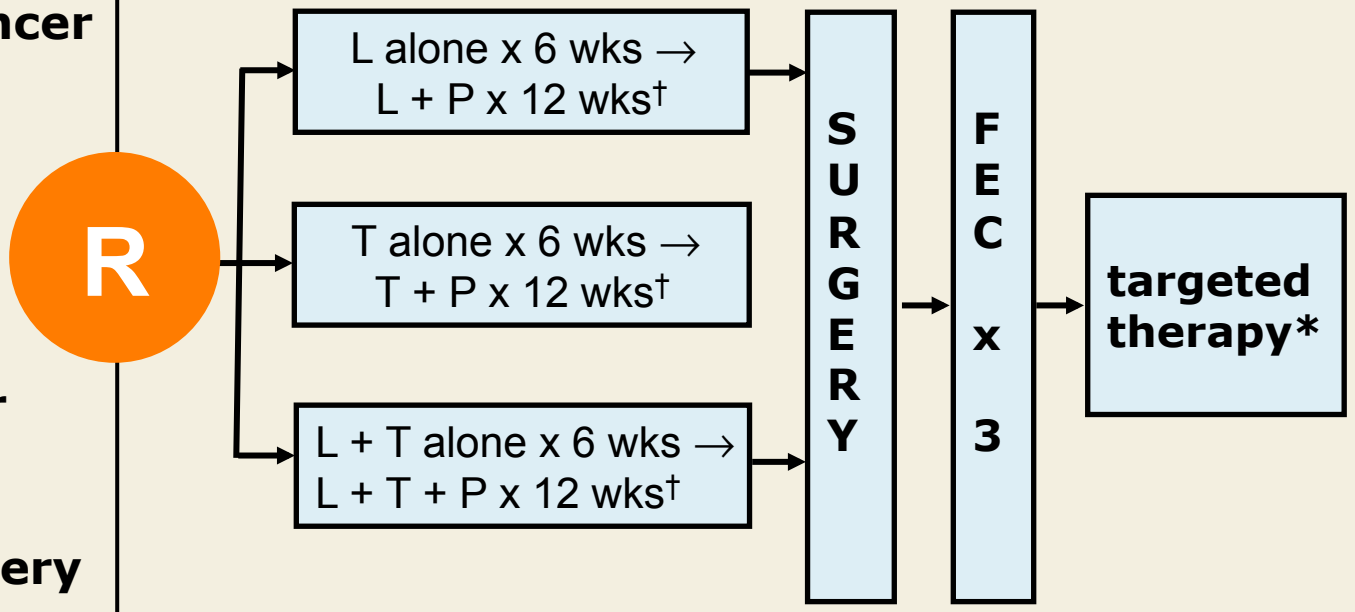
Invasive operable HER 2+ breast cancer

T > 2 cm

LVEF ≥ 50%

<u>Stratification</u>

T ≤5 cm vs >5cm;
ER/PR positive or negative;
N 0-1 vs N ≥ 2;
Conservative surgery vs not



L = lapatinib, T = trastuzumab, P = paclitaxel

† Neoadjuvant therapy consisted of 6 wks of anti-HER2 therapy alone (biologic window) followed by 12 wks of the same anti-HER2 therapy with weekly paclitaxel; total neoadjuvant therapy duration of 18 wks

* Same anti-HER2 therapy as in the neoadjuvant phase for an additional 34 wks

Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Study Endpoints

- Primary endpoint:
  - Pathologic complete response in the breast (pCR)
- Secondary endpoints:
  - pCR rate in breast AND lymph nodes [total pCR (tpCR)]
  - Safety and tolerability
  - Objective response rate at week 6 (end of biological window)
  - % of patients with node-negative disease at surgery
  - Rate of conversion to breast conserving surgery
  - Rate of conversion to breast surgery in those with non-operable disease at presentation
  - Disease free survival (DFS) and overall survival (OS)

Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Efficacy: pCR and tpCR

Response	L (N = 154)	T (N = 149)	L + T (N = 152)
pCR (no invasive cancer in the breast)	24.7%	29.5%	51.3%
	***p*-value: 0.34 (L vs T); 0.0001 (L +T vs T)**		
Response	**L (N = 150)**	**T (N = 145)**	**L + T (N = 145)**
tpCR (no invasive cancer in the breast or LNs)*	20.0%	27.6%	46.9%
	***p* - value: 0.13 (L vs T); 0.001 (L+T vs T)**		

* Excludes 15 patients with non-evaluable nodal status

Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Efficacy: Overall Clinical Response at 6 Weeks and at Surgery

Response	L (N = 154)	T (N = 149)	L + T (N = 152)
Week 6	52.6%	30.2%	67.1%
	***p*-value: <0.001 (L vs T); <0.001 (L +T vs T)**		
Surgery	74.0%	70.5%	80.3%
	***p*-value: 0.49 (L vs T); 0.049 (L+T vs T)**		

Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Efficacy: % with Conservative Surgery and % Node Negative

Response	L (N = 154)	T (N = 149)	L + T (N = 152)
Conservative Surgery	42.9%	38.9%	41.4%
	***p*-value: >0.5 (L vs T); >0.5 (L +T vs T)**		
Response	**L (N = 150)**	**T (N = 143)**	**L + T (N = 147)**
Node-Negative*	48%	56.6%	69.0%
	***p*-value: 0.14 (L vs T); 0.03(L+T vs T)**		

* Excludes 15 patients with non-evaluable nodal status

Baselga J et al. *Proc SABCS* 2010;Abstract S3-3.

Conclusions

- pCR rate with L + T was significantly higher than with T (51.3% vs 29.5%).
- The overall response rate at 6 weeks was higher for both arms containing lapatinib vs the trastuzumab arm.
- Increased but manageable toxicity (diarrhea and liver enzyme alterations) was observed in the arms containing lapatinib (data not shown).
- Dual blockage of HER2 is a valid concept.
- Correlation between pCR and DFS and OS is pending events and follow-up.
- Accrual is continuing to the ALTTO trial, which includes T $\rightarrow$ L, L, T, and L + T in the adjuvant setting (NCT00490139).

Baselga J et al. *Proc SABCS* 2010;Abstract S3-3;www.clinicaltrials.gov.

Investigator Commentary: NEO-ALTTO Neoadjuvant Study in HER2-Positive Breast Cancer

This study was meant to complement the ALTTO adjuvant study, for which we will likely have results in a few years. In NEO-ALTTO the pCR rates in the breast for trastuzumab versus lapatinib were not statistically different, although a trend appeared to favor trastuzumab. However, lapatinib could not be administered as planned in approximately one third of patients, which necessitated dose reductions.

The remarkable observation from this study was the substantial improvement in pCR with the combination of trastuzumab/lapatinib compared to either lapatinib or trastuzumab. These findings are consistent with both preclinical data and data from the study published by Dr Blackwell in the *Journal of Clinical Oncology* earlier in 2010, which demonstrated that in a HER2-positive, refractory setting, the combination of trastuzumab and lapatinib compared to lapatinib alone resulted in an improvement in progression-free and overall survival. I hope the results of NEO-ALTTO will correlate with an improvement outcome for the combination regimen in the ALTTO trial.

Comments from Eric P Winer, MD, December 11, 2010

Neoadjuvant Pertuzumab (P) and Trastuzumab (H): Antitumor and Safety Analysis of a Randomized Phase II Study ('NeoSphere')

Gianni L et al.

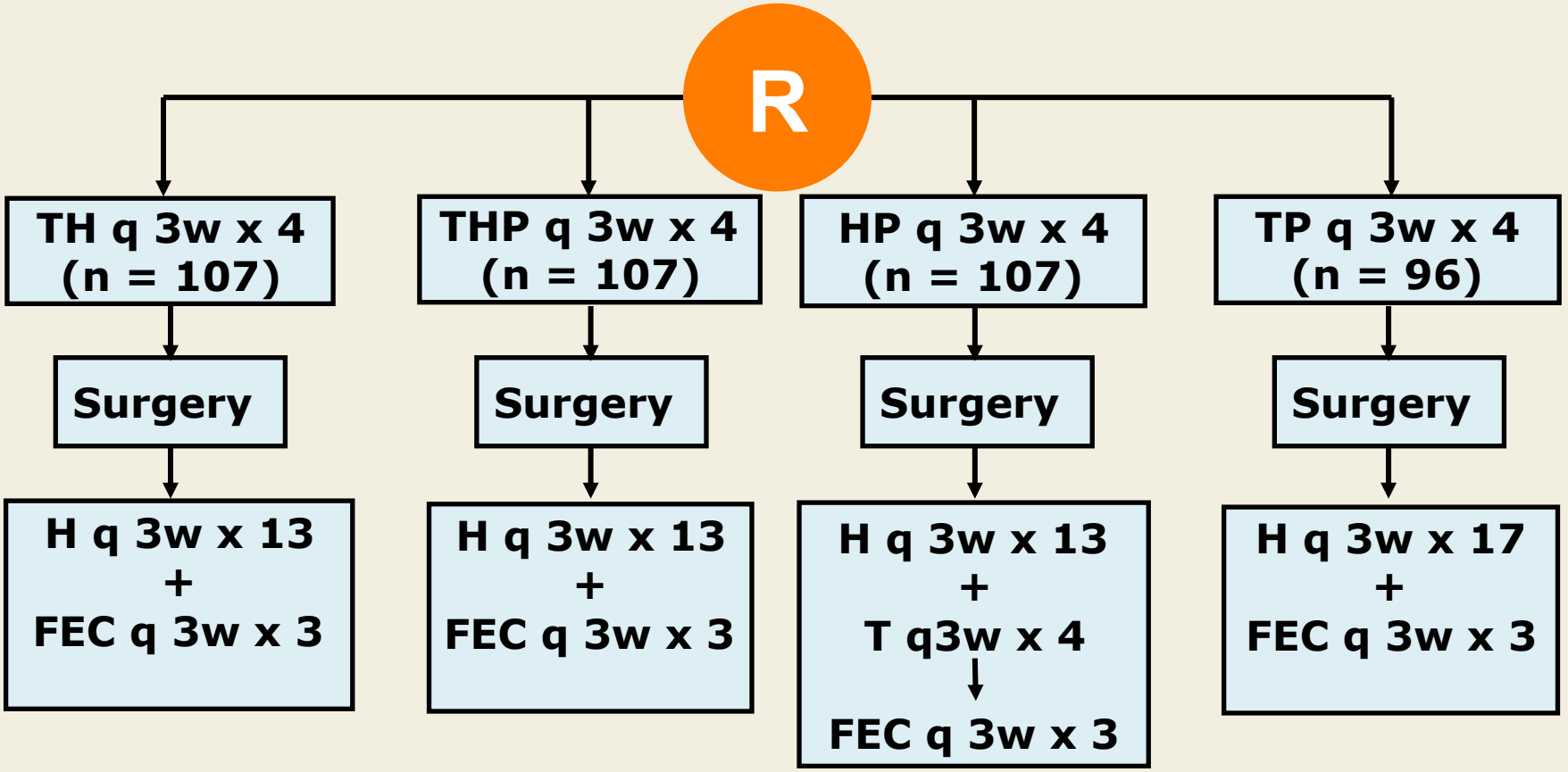
Proc SABCS 2010;Abstract S3-2.

Study Eligibility and Objectives

- Eligibility:
  - Operable or locally advanced/inflammatory breast cancer
  - Centrally confirmed HER2-positive (IHC 3+ or FISH positive)
  - Chemotherapy naïve
  - Primary breast tumor >2 cm
  - No metastasis
- Objectives:
  - Primary: pathological CR (pCR) rates
  - Secondary: clinical response, disease-free survival, breast conservation rate, biomarker evaluation

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Study Schema



T = Docetaxel, H = Trastuzumab, P = Pertuzumab
F = 5-fluorouracil, E = Epirubicin, C = Cyclophosphamide

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Efficacy Results by Breast and Lymph Nodal Status

	TH (n = 107)	THP (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node positive at surgery	7.5%	6.5%	5.6%	6.3%

The differences between the THP arm and other arms for pCR were statistically significant, with all the *p*-values being <0.05.

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Efficacy Results by ER/PR Status

	TH	THP	HP	TP
pCR (ER- or PR-positive)	22.0%	26.0%	5.9%	17.4%
pCR (ER- and PR-negative)	36.8%	63.2%	29.1%	30.0%

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Safety Results

	TH (n = 107)	THP (n = 107)	HP (n = 108)	TP (n = 94)
Grade 3-4 neutropenia	57.0%	44.9%	0.9%	55.3%
Febrile neutropenia	7.5%	8.4%	0.0%	7.4%
Grade 3-4 diarrhea	3.7%	5.6%	0.0%	4.3%
Grade 3-4 rash	1.9%	1.9%	0.0%	1.1%
Grade 3-4 increased ALT	2.8%	0.0%	0.0%	1.1%
Serious adverse events	16.8%	10.3%	3.7%	17.0%

Any changes in left ventricular ejection fraction did not appear clinically meaningful and were similar among all the four arms.

Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Conclusions

- Combination of docetaxel, trastuzumab and pertuzumab (THP) achieved a significantly higher pCR rate when compared to docetaxel-trastuzumab (TH), trastuzumab-pertuzumab (HP) or docetaxel-pertuzumab (TP) combinations.
- Efficacy results are most pronounced in ER- and PR-negative tumors.
- Excellent tolerability of the combination regimen of THP.
- There is no appreciable increase in cardiac risk with the addition of pertuzumab to TH combination over a short course of neoadjuvant therapy.

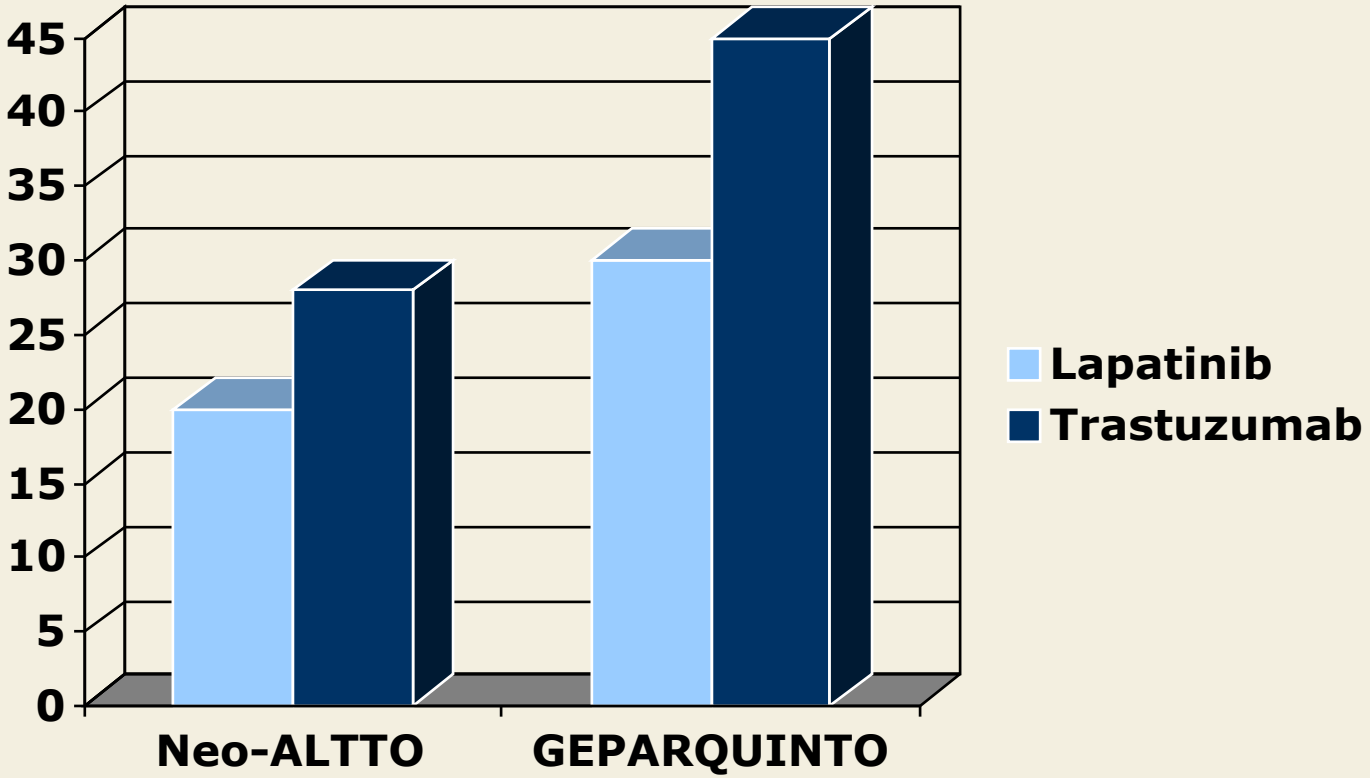
Gianni L et al. *Proc SABCS* 2010;Abstract S3-2.

Neoadjuvant Therapy for HER2+ Breast Cancer

Winer E.

Proc SABCS 2010;Discussant.

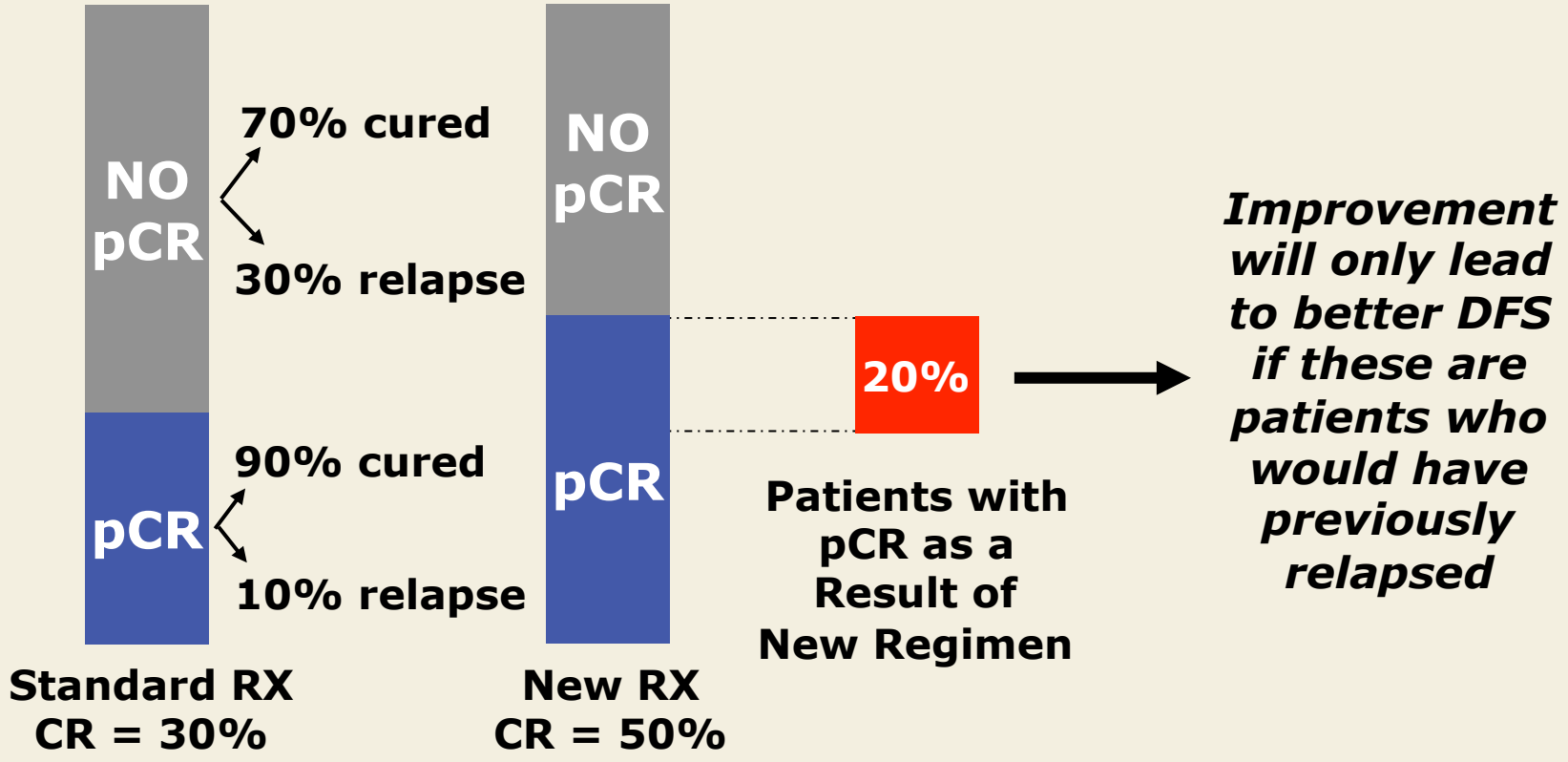
Pathologic CR Trastuzumab/Chemo vs Lapatinib/Chemo



Inability to give planned doses of lapatinib ~35% in both studies.

Winer E. Discussant. *Proc SABCS* 2010.

Will Pathologic Response Predict Long-Term Outcome?



Winer E. Discussant. *Proc SABCS* 2010.

What Can Be Accomplished in the Neoadjuvant Setting?

- Identification of promising treatment strategies for patients at high risk of recurrence
- Identification of patients who may fare well with less toxic treatment
  - Single-agent chemotherapy + biologic therapy
  - Biologic therapy alone
- Interrogation of tissue for molecular predictors of outcome
- Discovery of new targets

Winer E. Discussant. *Proc SABCS* 2010.

The Score Card: What's Up and What's Down?

Trastuzumab + lapatinib with paclitaxel

Not ready for adjuvant or neoadjuvant use yet, but eagerly await ALTTO

Trastuzumab + pertuzumab with docetaxel

Ready for adjuvant trial (Non-chemo containing doublet should move forward)

Lapatinib alone + chemo

Appears a little less active and more toxic. Jury out until ALTTO results in.

Pertuzumab alone + chemo

Hard to get excited

Winer E. Discussant. *Proc SABCS* 2010.

Investigator Commentary: NeoSphere Neoadjuvant Trial

The triplet combination of docetaxel/trastuzumab and pertuzumab is associated with a very high pathological complete response (pCR) rate of 46 percent in the breast, which is significantly higher than the pCR rate of 29 percent with conventional treatment of docetaxel and trastuzumab achieved in our trial. The pCR rate for pertuzumab and chemotherapy was 24 percent, and interestingly we observed a pCR rate of about 17 percent with the pertuzumab/trastuzumab combination alone.

NeoSphere establishes that the addition of pertuzumab to a conventional regimen of chemotherapy/trastuzumab provides additional benefit for women with HER2-positive breast cancer, which justifies the conduct of an adjuvant trial evaluating this combination. Additionally, the activity observed with the combination of trastuzumab/pertuzumab without chemotherapy justifies continuing the doublet monoclonal antibodies together for 12 months after completion of chemotherapy without risk of incurring an increase in toxicity. As a result of NeoSphere, the Breast International Group will launch such an adjuvant trial by the end of 2011.

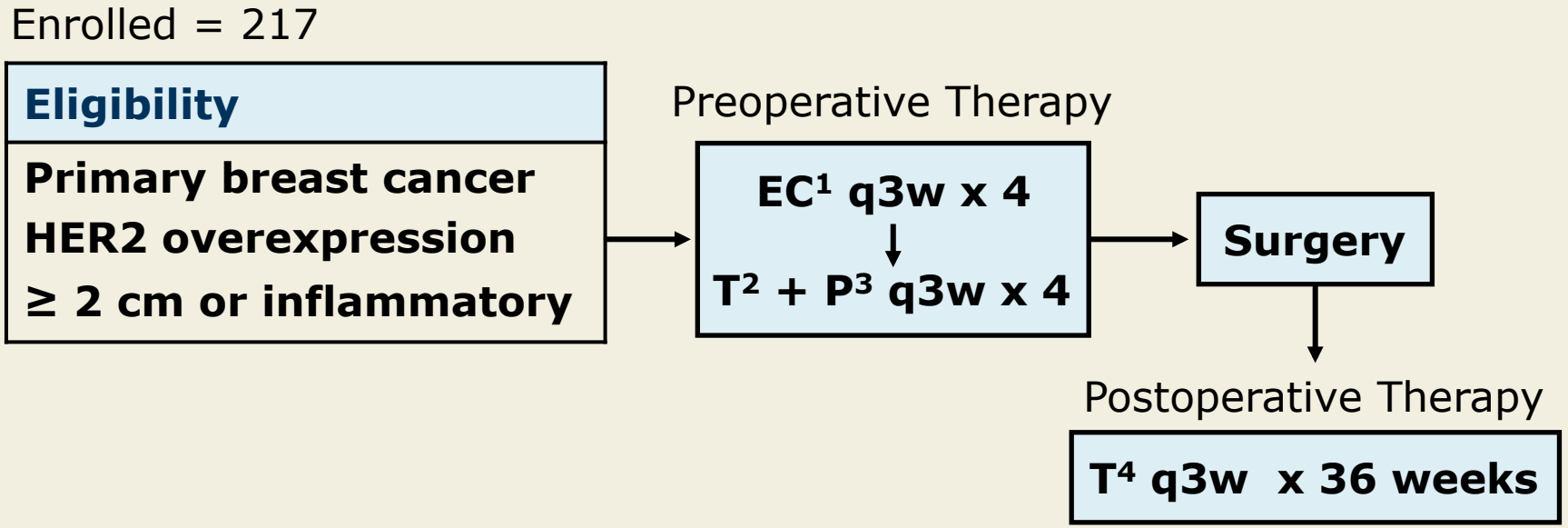
Interview with Luca Gianni, MD, December 10, 2010

Pathological Complete Response After Neoadjuvant Chemotherapy + Trastuzumab Treatment Predicts Survival and Detects a Patient Subgroup at High Need for Improvement of Anti-HER2 Therapy. Three Year Median Follow-Up Data of the TECHNO Trial (An AGO GBG Cooperative Multicenter Study)

Untch M et al.

Proc SABCS 2010;Abstract P1-11-03.

Study Schema



[1] Epirubicin 90 mg/m^2 + Cyclophosphamide 600 mg/m^2 (C 1-4)
[2] Trastuzumab 8 mg/kg loading dose (C 5) followed by 6 mg/kg q3wks (C 6-8)
[3] Paclitaxel 175 mg/m^2 (C 5-8)
[4] Trastuzumab 8 mg/kg loading dose (C 9) followed by 6 mg/kg q3wks (C 10-21)

Untch M et al. *Proc SABCS* 2010;Abstract P1-11-03.

Efficacy Results

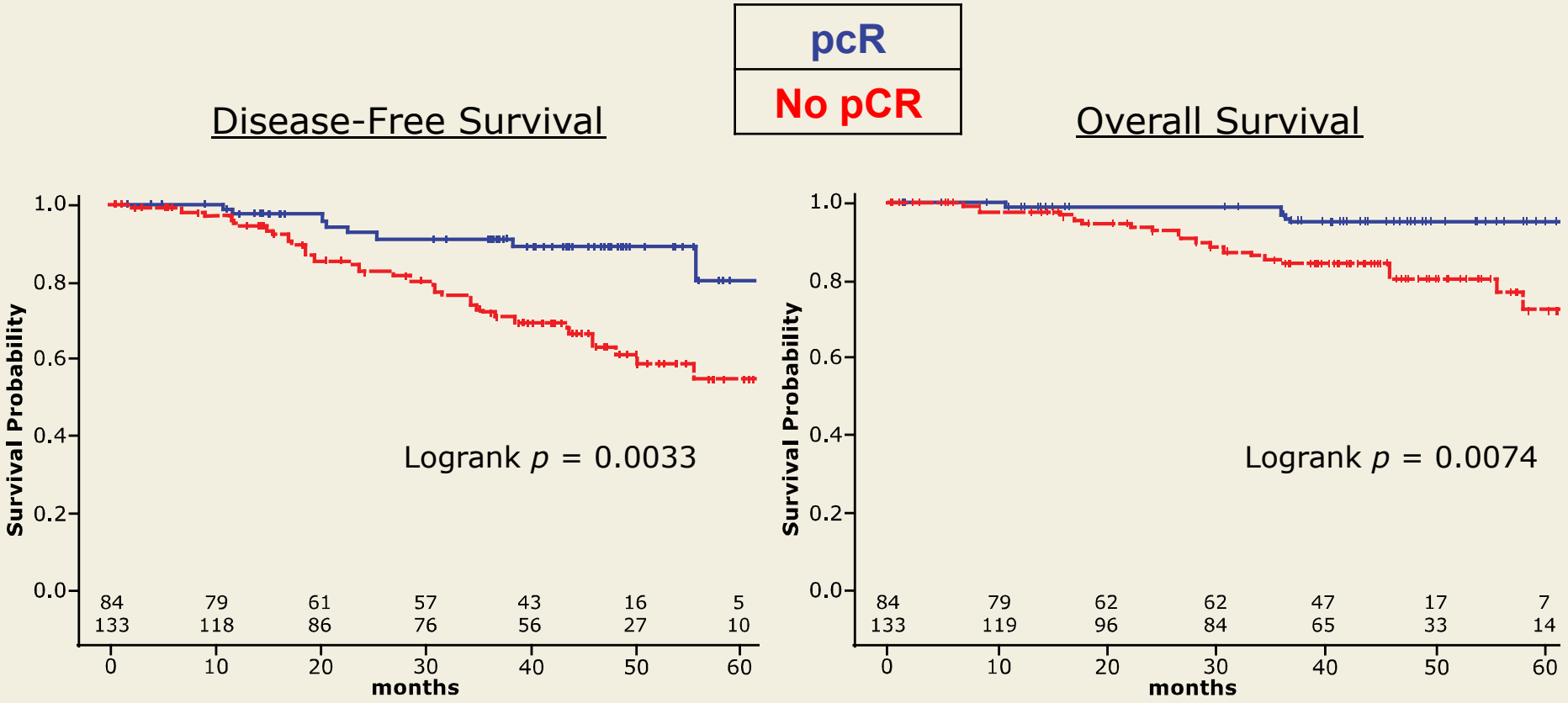
Enrolled = 217

pCR (no invasive tumor in breast and axillary nodes)	39%
Breast conservation rate	64%

	Patients with pCR	Patients without pCR	*p*-value
3-year overall survival	96%	86%	0.025
3-year disease-free survival	88%	73%	0.01

Untch M et al. *Proc SABCS* 2010;Abstract P1-11-03.

pCR is Prognostic for Disease-Free and Overall Survival



With permission from Untch M et al. *Proc SABCS 2010*; Abstract P1-11-03.

Multivariate Analysis of Efficacy Results by Baseline Factors and pCR

	Disease-Free Survival (DFS)		Overall Survival (OS)	
	Hazard Ratio	*p*-value	Hazard Ratio	*p*-value
Age (< 40 vs ≥ 40)	1.03	0.925	6.94	0.059
Initial T stage (T 1-3 vs T4)	1.90	0.084	1.83	0.205
ER/PR status (negative vs positive)	1.14	0.672	2.67	0.034
pCR (yes vs no)	2.49	0.013	4.91	0.012

In multivariate analysis, pCR remained a significant prognostic factor for DFS and OS.

Untch M et al. *Proc SABCS* 2010;Abstract P1-11-03.

Cardiac Safety Results

Cardiac events	8/217 (3.7%)
Decrease in left ventricular ejection fraction	6/217 (2.8%)
Clinical congestive heart failure (CHF)	2/217 (0.9%)

Untch M et al. *Proc SABCS* 2010;Abstract P1-11-03.

Conclusions

- Neoadjuvant combination of trastuzumab and chemotherapy results in a high pathologic CR rate in the breast and lymph nodes of 39% and breast conservation rate of 64%.
- Symptomatic CHF rate <1%.
- Patients without a pCR have an increased risk for relapse and death and are therefore candidates for further improvement of anti-HER2 directed adjuvant therapy.

Untch M et al. *Proc SABCS* 2010;Abstract P1-11-03.

Investigator Commentary: Pathologic Complete Response with Trastuzumab-Based Neoadjuvant Therapy Predicts Survival in the TECHNO Study

TECHNO was another European neoadjuvant study for patients with HER2-positive breast cancer, of which several were presented at San Antonio 2010. Notably, this study has longer-term follow-up, which is important because in addition to evaluating short-term endpoints, such as pathologic complete response (pCR) in the breast, the investigators were also able to evaluate longer-term endpoints, such as disease-free and overall survival.

In this study, women who received trastuzumab-based neoadjuvant therapy and achieved a pCR fared better in the long term than those who did not achieve a pCR. That's not a big surprise in the sense that many other studies have demonstrated that women who experience a pCR to other types of therapy fare better in the long run, but it is a nice confirmation that the same trends will be observed in women who receive trastuzumab-based therapy.

Interview with Harold J Burstein, MD, PhD, December 22, 2010