# 5 Minute JournalClub

**POST-SABCS** Issue 5, 2013

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# CME Information

**LEARNING OBJECTIVES**

- Determine the optimal duration of trastuzumab administration in the adjuvant setting using recent clinical trial evidence evaluating 1 year of adjuvant trastuzumab versus 6 months or 2 years.
- Assess the long-term survival outcomes of patients receiving 1 year of adjuvant trastuzumab combined with chemotherapy in comparison to those receiving only chemotherapy, and consider this information in the management of early HER2-positive breast cancer.
- Evaluate the association between immune biomarkers and clinical responses to trastuzumab and pertuzumab as support for the potential use of combined HER2-targeted and immunomodulatory agents.

# 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:

# CME Information (Continued)

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# CME Information (Continued)

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5 MinuteJournalClub

POST-SABCS Issue 5, 2013

# Key Papers on Adjuvant and Neoadjuvant Treatment of HER2-Positive Breast Cancer

It's now coming up on 8 years since that warm May day in Orlando when Dr George Sledge chaired the historic ASCO session during which the very first Phase III data sets confirming the benefit of adjuvant trastuzumab (T) with chemotherapy were unveiled. In San Antonio this past December we witnessed perhaps the final meaningful remnants of that generation of landmark studies while also getting a peek at the next set of relevant issues currently being addressed in ongoing trials. So to close out this year's SABCS highlights series we look at several of the most intriguing presentations focused on the management of early HER2-positive disease.

## 1. Duration of adjuvant trastuzumab: HERA and PHARE trials

During a CME symposium our group hosted on the first night of the conference, the ever-mirthful Dr Sledge was tasked with reviewing this pragmatic topic, and to get things started the first slide he showed was a beautiful photo of the earth orbiting the sun. Of course, Dr Sledge's visual metaphor related to the conclusion that he and most investigators had come to accept following the presentations of the HERA and PHARE data sets last October at the 2012

European Society for Medical Oncology Congress in Vienna — that 1 year of adjuvant T remains the optimal duration.

Both of these studies were updated in San Antonio. HERA, presented by Dr Martine Piccart-Gebhart, provided a definitive answer that 2 years of T is not better than 1. On the other hand, the French PHARE trial attempted to build on the signal observed in the underpowered but encouraging FinHer study of 9 weeks of T and compared 6 months to 12 months. During the presentation at San Antonio I got lost in terms like “failed to prove lack of inferiority,” but just looking at the numbers, 6 months didn’t look quite as efficacious as 12, and the collective sentiment appears to be that we’ve done the right thing all along by following Dr Sledge’s orbital concept.

## 2. Long-term impact of adjuvant trastuzumab

In a brilliant and detailed analysis presented to the FDA in early 2005, the late NSABP statistician Dr John Bryant proposed that combining the data from 2 ongoing simultaneous adjuvant T trials (NSABP-B-31 and NCCTG-N9831) not only was feasible but also would help to obtain a quicker answer for patients, particularly as clinicians in practice grew increasingly uncomfortable holding the line at not using this relatively nontoxic agent with such a great likelihood of success. The FDA agreed with this premise, and later that year I had the pleasure of interviewing the NSABP’s Dr Edward Romond just moments after his presentation to the ASCO multitudes of this combined data set. During this memorable conversation Dr Romond’s voice was tremulous with emotion as he recounted for our audio audience the amazing history leading to that moment.

Dr Romond was again center stage in San Antonio, presenting the 10-year survival data from that landmark combined effort. The data reveal that the effects of treatment were similar regardless of ER status (this was also seen in HERA) and the survival benefit was still maintained although somewhat attenuated due to crossover to T once the data were released (20% crossover in the NSABP/NCCTG data and an unprecedented 52% in HERA). However, the profound impact of this advance can be understood from a different perspective when we consider the final numbers from this analysis of 4,046 patients: 391 vs 227 patients with distant recurrence; 381 vs 234 deaths from breast cancer; 206 vs 137 deaths among patients with ER and/or PR-positive tumors; 212 vs 149 deaths among patients with ER and PR-negative tumors.

## 3. The way forward? Initial evidence suggesting a potential future role for immune checkpoint inhibitors combined with anti-HER2 agents

As this first adjuvant HER2 chapter closes, others on the horizon will soon open, and when one asks investigators which current study or concept seems most promising, the first response is quite frequently the classically straightforward but immensely interesting APHINITY trial comparing adjuvant chemotherapy/T with or without the HER2 dimerization inhibitor pertuzumab. The enthusiasm for this compelling concept is partially related to prior data from the Phase II NeoSphere trial presented by Dr Luca Gianni, which demonstrated a marked increase in pathologic CRs when pertuzumab was added to chemotherapy/T in the neoadjuvant setting.

As in many contemporary neoadjuvant trials, a critical component of NeoSphere was the collection and analysis of tumor tissue, and at San Antonio Dr Gianni presented thought-provoking findings that expression of immune-based biomarkers, including PD-1, PD-L1, CTLA-4 and others, may predict benefit from HER2-directed therapies. These hypothesis-generating data may open the door to a new frontier in which anti-HER2 therapy is combined with the immune modulators that are offering so much hope in melanoma, renal cell carcinoma, lung cancer and other challenging neoplasms. It will be fascinating to compare the NeoSphere translational findings to those about to be presented with the very first oral breast cancer paper at the upcoming ASCO meeting by Dr Lisa Carey from a major CALGB neoadjuvant HER2 study that also includes extensive tissue correlates.

This concludes our annual San Antonio wrap-up. Keep an eye out for our upcoming pre-ASCO email/video program with highlights from a recent breast cancer clinical investigator Think Tank with more on these and other new data sets and trial concepts.

**Neil Love, MD**
Research To Practice
Miami, Florida

# HERA TRIAL: 2 Years versus 1 Year of Trastuzumab After Adjuvant Chemotherapy in Women with HER2-Positive Early Breast Cancer at 8 Years of Median Follow-Up

**Goldhirsch A et al.**

*Proc SABCS* 2012;Abstract S5-2.

# Background

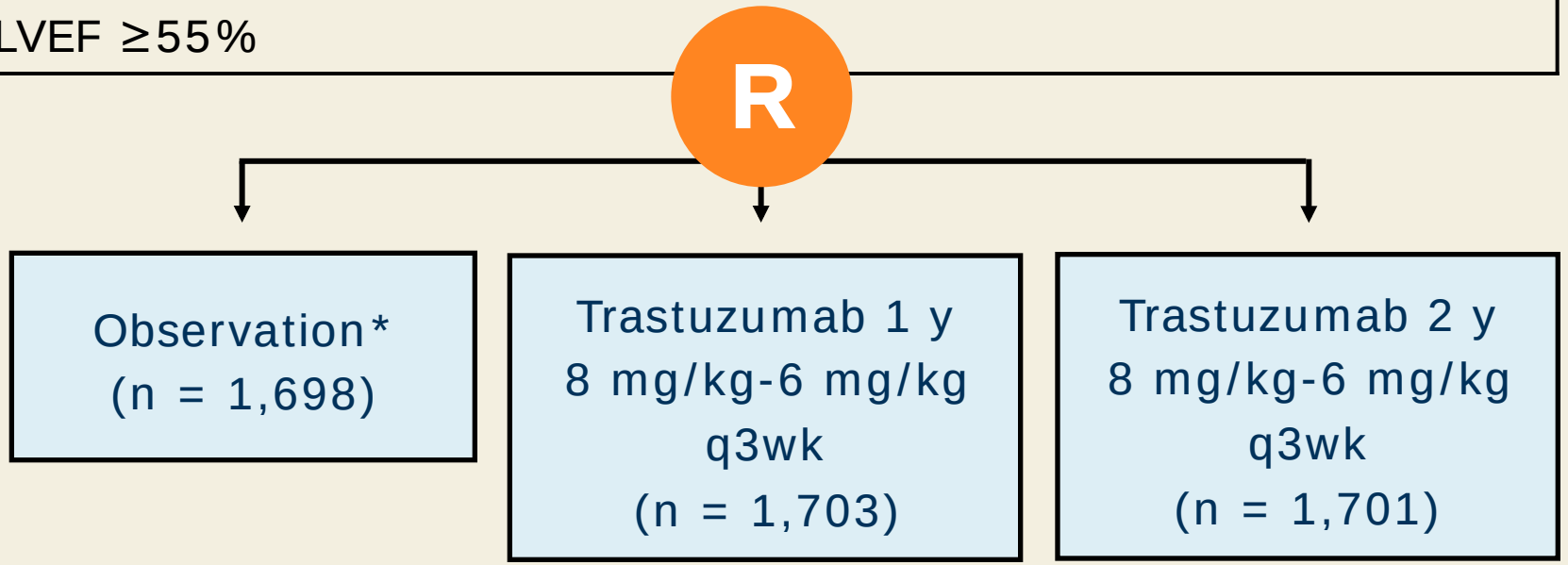
- The results of the Phase III HERA trial previously showed that 1 year of adjuvant trastuzumab (T) after chemotherapy is associated with a significant clinical benefit compared to observation in HER2-positive early BC after a median follow-up of 4 years (*Lancet Oncol* 2011;12:236-44).
- After 2005, the HERA protocol was revised to focus on the secondary objective of the trial, the assessment of whether 2 years of adjuvant T was superior to 1 year.
- **Objective:** Evaluate whether 2 years of T is superior to 1 year after adjuvant chemotherapy in women with HER2-positive early BC after a median follow-up of 8 years.

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# Phase III HERA Study Design

**Eligibility (N = 5,102)**

Locally determined HER2-positive invasive early BC
Treated with surgery + (neo)adjuvant chemotherapy +/- RT
Centrally confirmed IHC 3+ or FISH+
LVEF ≥55%




* 885 pts (52.1%) crossed over to trastuzumab after disclosure of first results in 2005

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# Landmark Analysis of 2 Years versus 1 Year of Trastuzumab

- Two interim analyses and 1 final analysis were planned for patients randomly assigned to T who remained disease free for at least 12 months from randomization.
  - n = 1,553 patients in 2-year arm
  - n = 1,552 patients in 1-year arm
- Final analysis was planned for 725 disease-free survival (DFS) events to obtain 80% power to detect a hazard ratio of 0.8.
- Current analysis was reported with 734 DFS events at a median follow-up of 8 years.

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# DFS with 2 Years versus 1 Year of T

| Patient subgroup | T (1 y) (n = 1,552) | T (2 y) (n = 1,553) | HR | *p*-value |
|---|---|---|---|---|
| **All patients** | | | | |
| 3 y | 86.7% | 89.1% | | |
| 5 y | 81.0% | 81.6% | 0.99 | 0.86 |
| 8 y | 76.0% | 75.8% | | |
| **HR-positive** | | | | |
| 3 y | 89.6% | 90.3% | | |
| 5 y | 82.9% | 83.1% | 1.05 | 0.67 |
| 8 y | 77.2% | 76.1% | | |
| **HR-negative** | | | | |
| 3 y | 83.8% | 87.8% | | |
| 5 y | 78.9% | 80.1% | 0.93 | 0.51 |
| 8 y | 74.7% | 75.4% | | |

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# Overall Survival with 2 Years versus 1 Year of T (All Patients)

| | T (1 y) (n = 1,552) | T (2 y) (n = 1,553) | HR | *p*-value |
|---|---|---|---|---|
| 3 y | 96.5% | 97.4% | | |
| 5 y | 91.4% | 92.6% | 1.05 | 0.63 |
| 8 y | 87.6% | 86.4% | | |

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# Adverse Events (AEs)

| AE | T (1 y) (n = 1,682) | T (2 y) (n = 1,673) |
|---|---|---|
| ≥1 Grade 3/4 | 16.3% | 20.4% |
| Primary cardiac* | 0.8% | 1.0% |
| Secondary cardiac† | 4.1% | 7.2% |
| Fatal AE | 1.1% | 1.2% |

* NYHA Class III or IV, confirmed by cardiologist, LVEF <50% and ≥10% below baseline or cardiac death

† LVEF <50% and ≥10% below baseline, confirmed by repeat assessment, excluding patients with a primary cardiac endpoint

- The majority of cardiac endpoints occurred during trastuzumab administration and were reversible.

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# Author Conclusions

- No evidence of long-term benefit was observed with 2 years versus 1 year of trastuzumab when administered as sequential treatment after chemotherapy.
- Secondary cardiac endpoints and other AEs are increased in the 2-year trastuzumab arm.
- The majority of cardiac endpoints occurred during trastuzumab administration and were reversible.
- A transient DFS advantage for the 2-year arm in the hormone receptor-negative cohort highlights the need for long-term follow-up in trials investigating different durations of adjuvant trastuzumab.

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

# Author Conclusions (Continued)

- Results of the HERA study at 8 years of median follow-up show sustained and statistically significant DFS and OS benefit for 1 year of trastuzumab versus observation in ITT analyses despite selective crossover (data not shown).
- 1 year of trastuzumab remains a standard part of adjuvant therapy for patients with HER2-positive early BC.
- Benefit for 1 year of trastuzumab, compared to observation, was shown across hormone receptor-positive and negative cohorts (data not shown).

Goldhirsch A et al. *Proc SABCS* 2012;Abstract S5-2.

## Investigator Commentary: HERA — 2 Years versus 1 Year of Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Early Breast Cancer at 8 Years of Median Follow-Up

The HERA trial compared 2 years versus 1 year of trastuzumab or observation for patients with HER2-positive early breast cancer. The results of the HERA trial, along with data from the PHARE trial that compared 6 versus 12 months of trastuzumab, suggest that 1 year of trastuzumab should be the standard treatment for patients with HER2-positive early breast cancer.

The next question for adjuvant trastuzumab remains whether we can add other agents to improve outcome. It remains to be determined whether we can use dual anti-HER2 blockade or anti-HER2 blockade with anti-HER2 vaccines.

***Interview with Edith A Perez, MD, January 17, 2013***

# PHARE Trial Results of Subset Analysis Comparing 6 to 12 Months of Trastuzumab in Adjuvant Early Breast Cancer

**Pivot X et al.**

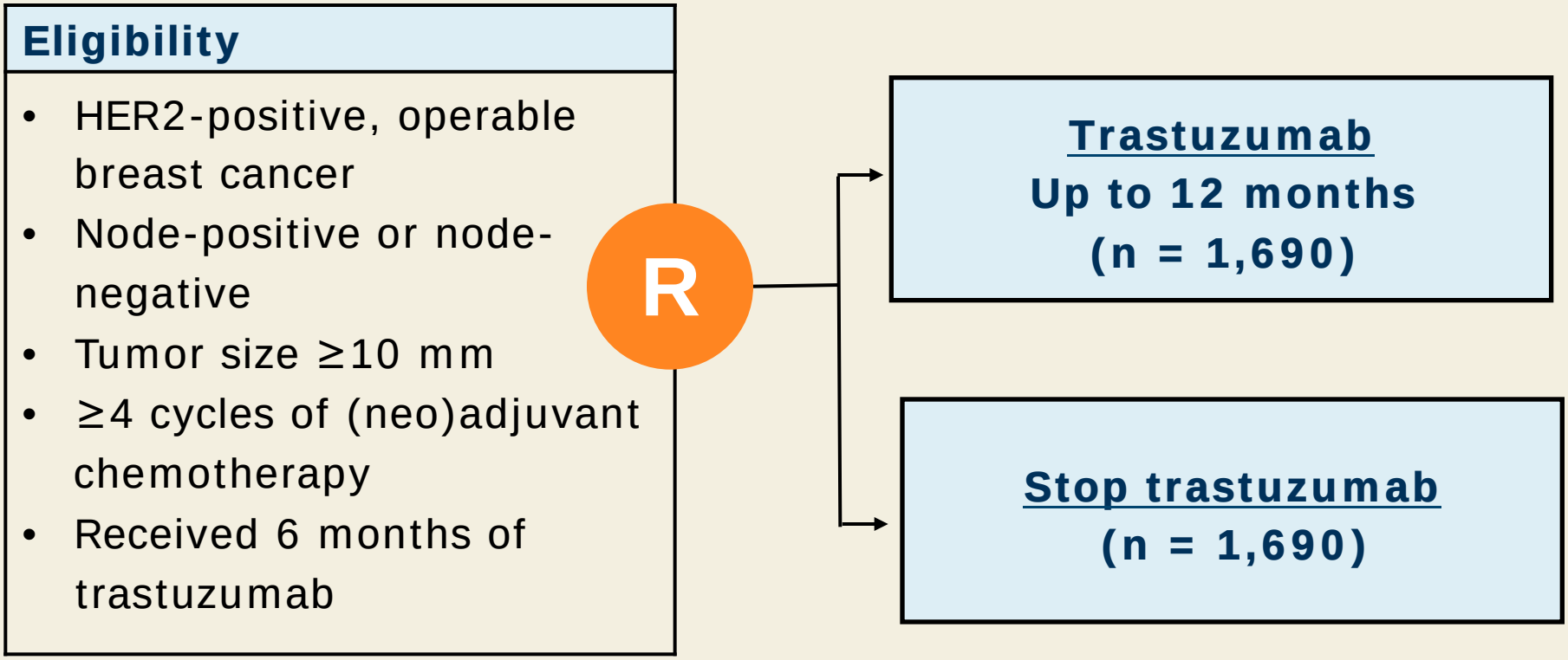
*Proc SABCS 2012*;Abstract S5-3.

# Background

- Since 2005, 4 large Phase III studies have demonstrated improvement in overall survival with the addition of 1 year of trastuzumab to adjuvant chemotherapy for patients with HER2-positive early breast cancer (*NEJM* 2005;353(16): 1673; *NEJM* 2005;353(16):1659; *Proc SABCS* 2006;Abstract 52).
- The FinHER study showed that 9 weeks of adjuvant trastuzumab was safe and effective for HER2-positive early breast cancer (*JCO* 2009;27(34):5685).
- The optimal duration of adjuvant trastuzumab remains uncertain, and concerns about cardiac toxicity persist.
- **Current study objective:** To evaluate 6 months and 12 months of adjuvant trastuzumab for patients with early breast cancer.

Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

# PHARE Noninferiority Trial Design

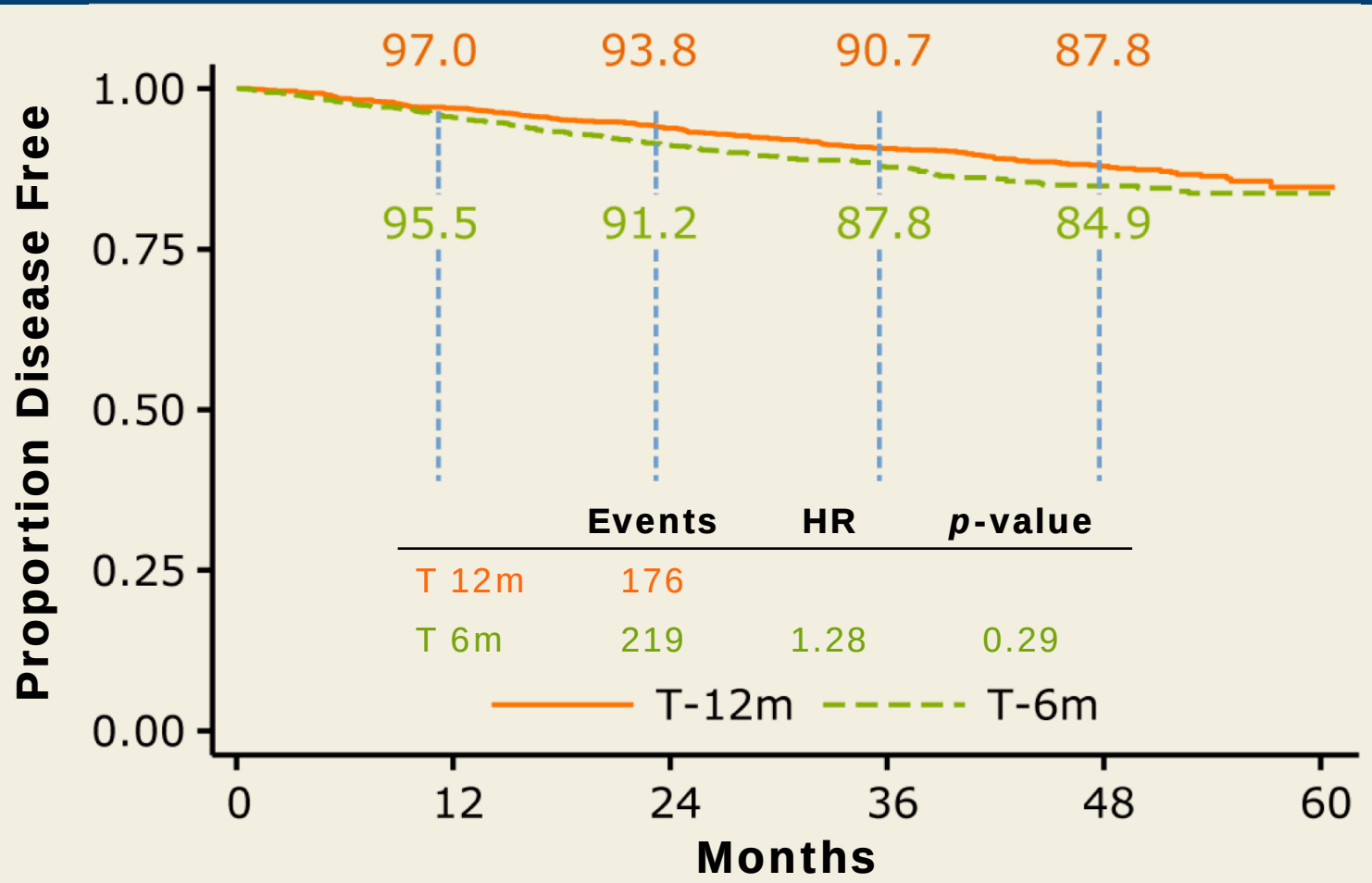



**Primary endpoint:** Disease-free survival

Noninferiority design: 2% variation in absolute difference in recurrence; 95% CI HR margins should not cross the 1.15 boundary

Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

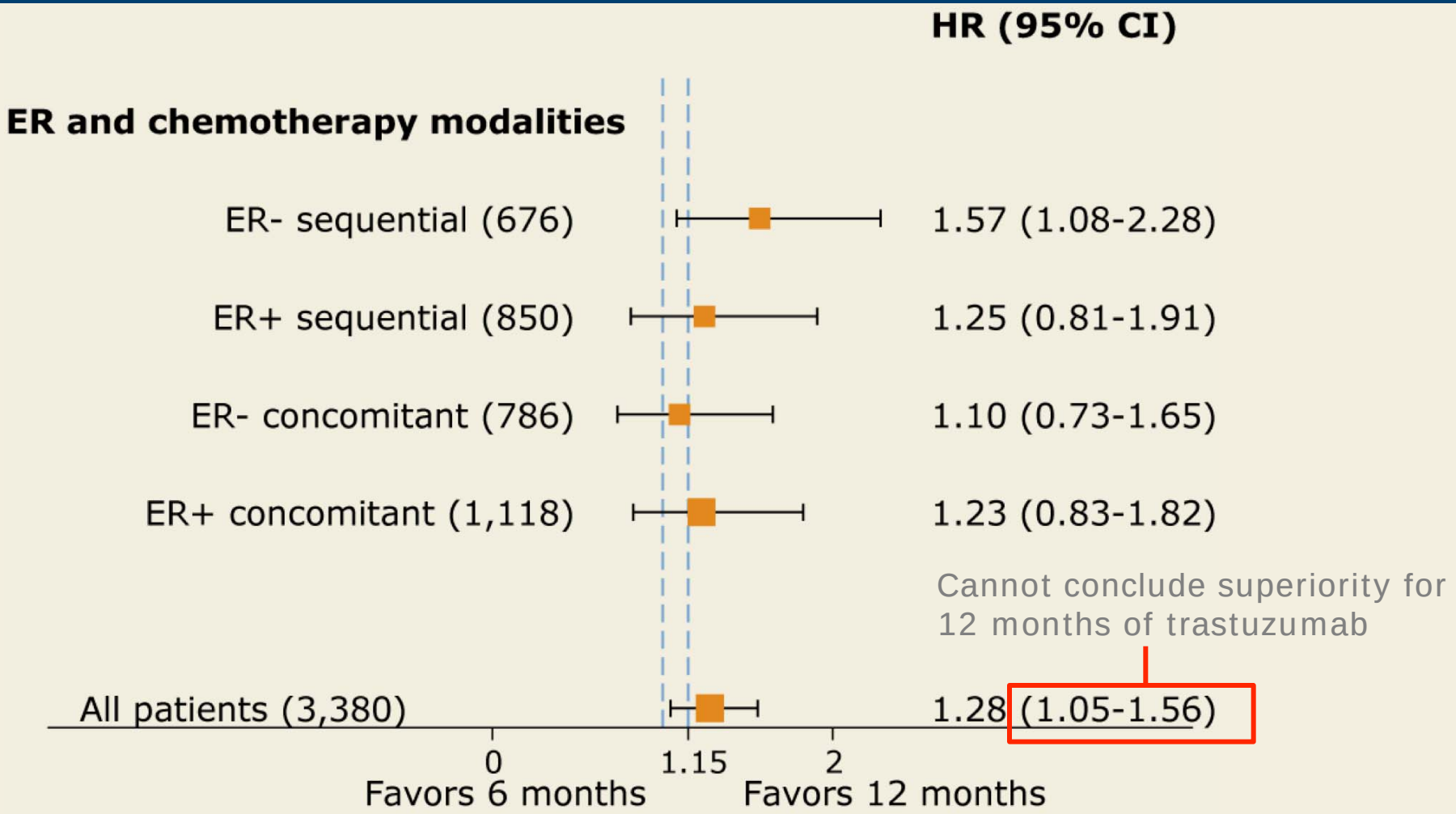
# Disease-Free Survival




Stratified by ER status and concomitant chemotherapy

With permission from Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

# Disease-Free Survival: Sub-Group Analysis




With permission from Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

# Author Conclusions

- PHARE failed to show that 6 months of trastuzumab is noninferior to 12 months.
- Subgroup analyses suggested:
  - Sequential modality for ER-negative tumors affected the overall results.
  - Results in other groups seemed compatible with the noninferiority hypothesis.
- PHARE longer follow-up and PERSEPHONE, SHORT-HER and SOLD trial results are expected.

Pivot X et al. *Proc SABCS* 2012;Abstract S5-3.

## Investigator Commentary: Six versus 12 Months of Adjuvant Trastuzumab in the PHARE Study

Several trials have evaluated the duration of adjuvant trastuzumab. Two of these studies — PHARE and HERA — were recently updated at the 2012 San Antonio Breast Cancer Symposium. Collectively, these studies involve more than 8,000 patients, and another 5,000+ patients will subsequently be analyzed in other trials.

What are these trials showing us? HERA compared 2 years to 1 year of adjuvant trastuzumab. Clearly no difference exists, so we have absolutely no reason to believe that continuing adjuvant trastuzumab past a year would benefit our patients.

How about 6 months versus 1 year? With about 4 years of follow-up, the PHARE study shows an approximately 2.9% absolute difference in disease-free survival favoring 1 year versus 6 months of adjuvant trastuzumab. This is not a statistically significant difference. Importantly, this was a noninferiority rather than a superiority trial, and the 95% confidence interval HR margins should not cross the 1.15 boundary. Strictly speaking, this study does not demonstrate the superiority of 1 year over 6 months of adjuvant trastuzumab. At least to date, 1 year of adjuvant trastuzumab appears to be scientifically supported, but of course we'll have other follow-up data that will emerge in the next few years.

***Presentation by George W Sledge Jr, MD, December 5, 2012***

# Trastuzumab plus Adjuvant Chemotherapy for HER2-Positive Breast Cancer: Final Planned Joint Analysis of Overall Survival from NSABP B-31 and NCCTG N9831

**Romond EH et al.**

*Proc SABCS* 2012;Abstract S5-5.

# Background

- NSABP-B-31 and NCCTG-N9831 are 2 parallel clinical trials investigating the use of paclitaxel and trastuzumab after anthracycline chemotherapy for the adjuvant treatment of high-risk HER2-positive breast cancer.
- The first interim analysis was presented with a median follow-up of 2 years (*NEJM* 2005;353:1673).
  - Reduction in disease-free survival: 52%
  - Reduction in mortality: 33%
- **Current study objective:** Report the survival results of the final planned joint analysis of NSABP-B-31 and NCCTG-N9831.

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# NSABP-B-31 and NCCTG-N9831 Study Arms


= doxorubicin/cyclophosphamide (AC) 60/600 mg/m$^2$ q3wk x 4

= paclitaxel (P) 175 mg/m$^2$ q3wk x 4

= paclitaxel (P) 80 mg/m$^2$ qwk x 12

= trastuzumab (H) 4 mg/kg LD + 2 mg/kg qwk x 51

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# Study Arms in the Combined Analysis of NSABP-B-31 and NCCTG-N9831

**Control: AC → P**

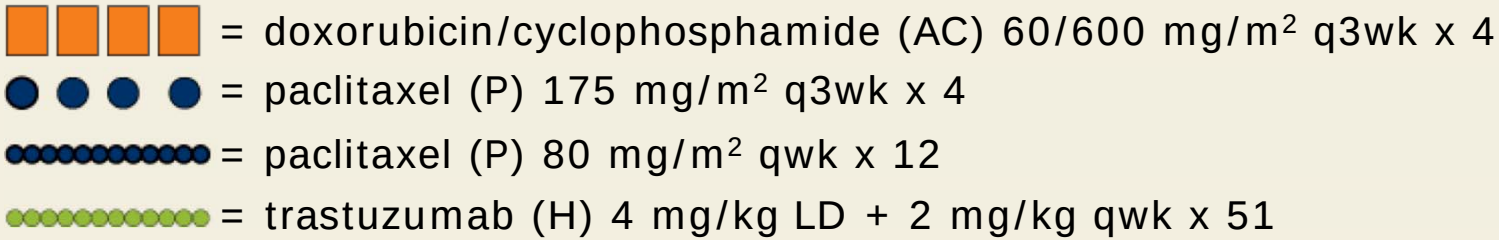
B-31 Arm 1

N9831 Arm A

**Investigational: AC → P + H**

B-31 Arm 2

N9831 Arm C



= doxorubicin/cyclophosphamide (AC) 60/600 mg/m$^2$ q3wk x 4

= paclitaxel (P) 175 mg/m$^2$ q3wk x 4

= paclitaxel (P) 80 mg/m$^2$ qwk x 12

= trastuzumab (H) 4 mg/kg LD + 2 mg/kg qwk x 51

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# N9831/B-31 Disease-Free Survival

| DFS | AC → P + H (n = 2,028) | AC → P (n = 2,018) |
|---|---|---|
| 10-year DFS* | 73.7% | 62.2% |
| First DFS events | | |
| Distant recurrence | 11.2% | 19.4% |
| Local/regional recurrence | 4.1% | 6.1% |
| Contralateral breast cancer | 2.3% | 2.0% |
| Other second primary cancer | 3.3% | 3.7% |
| Death without recurrence | 1.9% | 1.5% |

* Adjusted HR = 0.6, $p < 0.0001$

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# N9831/B-31 Cumulative Incidence of Distant Recurrence as a First Event

- ER- and/or PR-positive
  - AC → paclitaxel + trastuzumab: 12.7%
  - AC → paclitaxel: 22.3%
  - Absolute reduction with the addition of trastuzumab: 9.6% at 10 years
- ER- and PR-negative
  - AC → paclitaxel with trastuzumab: 11.9%
  - AC → paclitaxel: 21.5%
  - Absolute reduction with the addition of trastuzumab: 9.6% at 7 years

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# N9831/B-31 Overall Survival

| OS | AC → P+H (n = 2,028) | AC → P (n = 2,018) |
|---|---|---|
| 10-year OS* | 84.0% | 75.2% |
| OS events | | |
| Deaths | 14.1% | 20.7% |
| Due to this breast cancer | 10.3% | 16.8% |
| Due to second primary cancer | 1.2% | 2.0% |
| Due to other causes | 0.9% | 0.7% |
| Cause unknown | 1.6% | 1.1% |

* Adjusted HR = 0.63, $p < 0.0001$

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# Author Conclusions

- At a median follow-up of 8.4 years, the addition of trastuzumab to AC → P is associated with a significant and substantial improvement in OS, with a relative risk reduction of 37% (HR 0.63).
- For patients with high-risk HER2-positive breast cancer, treatment with this regimen reduces the risk of a DFS event at 10 years by 40% (HR 0.60).
- The relative risk reduction benefit for both DFS and OS was present and of similar magnitude in virtually all subsets of patients analyzed (data not shown).

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

# Author Conclusions (Continued)

- For patients with hormone receptor-positive disease, the absolute reduction in the rate of distant recurrence as a first event continues to improve over time with the addition of trastuzumab and reaches 9.6% at 10 years.
- For patients with hormone receptor-negative disease, the absolute risk of distant recurrence as a first event is reduced by 9.6% at 7 years, after which distant recurrence from breast cancer is unlikely.

Romond EH et al. *Proc SABCS* 2012;Abstract S5-5.

## Investigator Commentary: Trastuzumab with Adjuvant Chemotherapy for HER2-Positive Breast Cancer: Final Planned Joint Analysis of OS from NSABP-B-31 and NCCTG-N9831

The final joint analysis of the NCCTG-N9831 and NSABP-B-31 trials reported survival data after a long-term follow-up of 10 years. The data were fascinating in that they clearly demonstrated that adding trastuzumab to concurrent chemotherapy significantly improves DFS and OS for patients and that this improvement in survival is maintained for a long time. We believe that the data support the concept that many patients who present with HER2-positive breast cancer may be cured with combination strategies. Treatment included anthracycline-based therapy with a taxane and demonstrated no cause for major concern in terms of late toxicities. We are greatly encouraged by the results from this study.

The next question for adjuvant trastuzumab remains whether we can add other agents besides trastuzumab to improve outcomes, because we're still not curing every patient. We've made significant improvements in patient outcomes, but we can do better.

***Interview with Edith A Perez, MD, January 17, 2013***

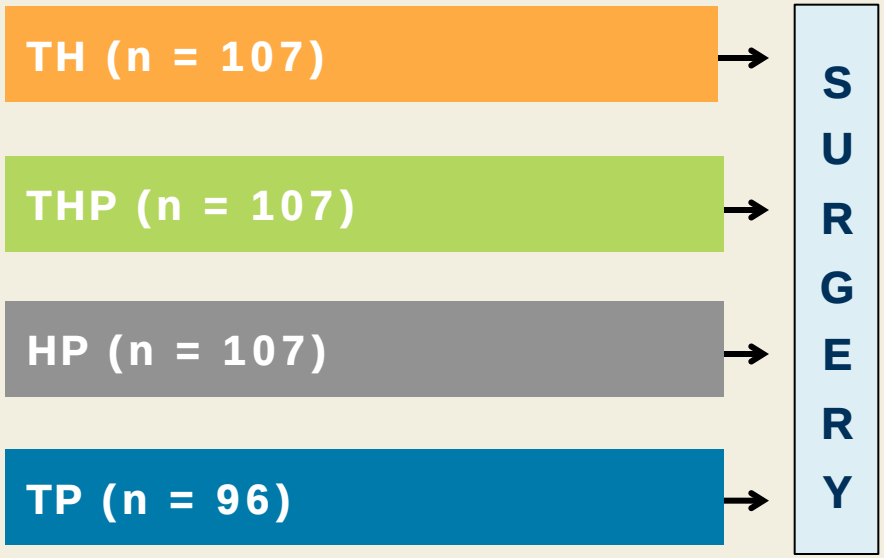
# Adaptive Immune System and Immune Checkpoints Are Associated with Response to Pertuzumab (P) and Trastuzumab (H) in the NeoSphere Study

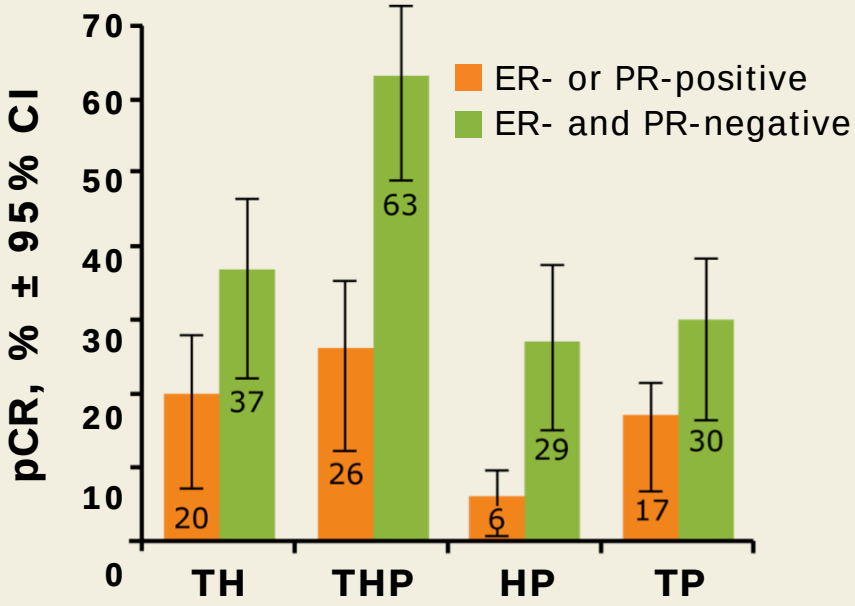
**Gianni L et al.**

*Proc SABCS 2012*;Abstract GS6-7.

# Background

**NEOSPHERE** Phase II study in HER2-positive operable, locally advanced or inflammatory breast cancer (N = 417)




T = docetaxel (75 → 100 mg/m$^2$)
H = trastuzumab (8 → 6 mg/kg)
P = pertuzumab (840 → 420 mg)

Study dosing: q3wk x 4

- Trastuzumab and pertuzumab work by inhibiting HER receptor activation and by cytotoxic immune mechanisms.
- This study assessed the association of preselected immune biomarkers with pathologic complete response (pCR).

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

# Methods

- Tumor samples collected in 98% of patients in NEOSPHERE:
  - mRNA extracted from 93% of patients
  - Gene expression profiles from 88% of patients

- Association of pCR in breast or residual disease with
  - Age, clinical nodal status, clinical stage, ER/PR status, treatment
  - Selected immune biomarkers (genes and metagenes expression) based on expected biologic relevance

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

# Selection of Immune Biomarkers Based on Expected Biologic Relevance

## Metagenes*

Specific immune cell subtypes
- **CD8A (CD8 / ~NK)**
- **IGG (immunoglobulins)**
- **MHC2 (dendritic cells)**

Genes under control of common transcription factors
- **STAT1** (GBP1, STAT1, CXCL10, CXCL11)
- **Interferon inducible** (ie, OAS1, IFI44L, MX1, IFIT1, IFIT2)
- **MHC1** (HLA Class I, ie, G, F, A, E)

## Individual Genes

**- IFNγ**
Key immune regulatory gene, also modulating PD-L1 expression by tumor cells

Genes associated with immune checkpoints **and target of therapies**
- PD-L1
- PD-L2
- PD-1
- CTLA4

*** Metagenes:** Average expression of highly correlated genes describing similar functions or under control of the same transcription factors

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

# Association of Select Gene Expression Patterns/Clinical Variables with pCR and Residual Disease

- Multivariate analysis demonstrated common immune biomarker patterns with pertuzumab in the HP and TP treatment arms:
  - High PD-1 expression was associated with high pCR.
- Analysis of the trastuzumab-containing arms, TH and HP, showed that
  - High expression levels of interferon-inducible gene (IF-I) were associated with residual disease.
  - High expression levels of dendritic cell metagene (MHC2) were associated with high pCR.
- Analysis of 3 arms (TH, HP and TP) demonstrated that
  - High PD-L1 expression was associated with residual disease.
  - High STAT1 expression was associated with pCR.
- Young age and ER-negative status were associated with pCR.

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

# Multivariate Analysis of Immune-Related Gene Expressions with THP Therapy

- A significant interaction was observed between ER status and the following genes:
  - Interferon-gamma (IFN-gamma) ($p$ = 0.0003)
  - PD-L1 ($p$ = 0.025)
  - CTLA4 ($p$ = 0.009)
- In ER-negative tumors
  - High gene expression levels of PD-L1 ($p$ = 0.016) and CTLA4 ($p$ = 0.007) were associated with residual disease.
  - High expression levels of IFN-gamma were associated with high pCR ($p$ = 0.002).
- In contrast, in ER-positive tumors high expression of the IFN-gamma gene was associated with residual disease ($p$ = 0.018).
- Overall, there was a clear indication that T-cell activation was associated with pCR.

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

# Author Conclusions

- Adaptive immune mechanisms seem to modulate benefit from HER2-directed therapies.
- High PD-L1 expression was strongly associated with residual disease consistently in all arms and with all treatments.
- In a treatment-dependent and ER status-dependent way,
  - High pCR was associated with high expression of 1 or more among IFNγ, STAT1, MHC2, CD8A and/or PD-1.
  - Probability of residual disease was associated with high expression of CTLA4, MHC1 and interferon-inducible genes.

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

# Author Conclusions (Continued)

- Confirmation of the involvement of adaptive immune mechanisms in the therapeutic effects of the HER2-directed therapies is ongoing in different case trials and with different assays.
- Available findings
  - Provide a rationale for combining HER2-targeted treatments with immune-modulating agents
  - May allow for the prediction of treatment benefit

Gianni L et al. *Proc SABCS* 2012;Abstract GS6-07.

## Investigator Commentary: Adaptive Immune System and Immune Checkpoints and Response to Pertuzumab and Trastuzumab

The NEOSPHERE trial addressed the dual HER2-targeting issue in the neoadjuvant setting. Patients with HER2-positive breast cancer all received neoadjuvant trastuzumab with or without pertuzumab, with or without docetaxel. The focus in this particular analysis was targeting the immune checkpoints.

Investigators evaluated a number of the immune-related genes, including PD-1, PD-L1 and others. A circle of activity that was observed has been described as the adaptive immune resistance mechanism of these cancer cells, producing factors that are inhibitory to the immune system. Some therapeutically relevant players were evaluated. The relationship of each of these immune-related genes and checkpoint genes to pCR was examined. The intriguing aspect of this study is that some of these biomarkers may be therapeutically targetable. I believe this may be the next frontier. These data add to the supposition that a therapeutic rationale might exist for combining cytotoxic drugs with anti-HER2 agents because ADCC induction is one mechanism of action for these monoclonal antibodies.

***Interview with Lisa A Carey, MD, January 17, 2013***