# Breast Cancer Update

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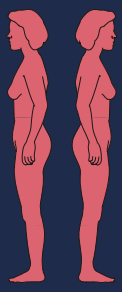
January 2019

## Treating and Diagnosing Breast Cancer

- Objectives
  - Risk Factors
  - Screening and Imaging
  - Treatment

## Cancer Statistics 2017: Female

| Estimated incidence | | Estimated deaths | |
|---|---|---|---|
| Melanoma of skin | 4% | 3% | Brain |
| Thyroid | 5% | 25% | Lung and Bronchus |
| **Breast** | **30%** | **14%** | **Breast** |
| Lung | 12% | 7% | Pancreas |
| Leukemia | 3% | 8% | Colon & Rectum |
| Colon & Rectum | 8% | 3% | Liver and bile duct |
| Pancreas | 3% | 5% | Ovary |
| Uterine Corpus | 7% | 4% | Uterine Corpus |
| Kidney & Renal pelvis | 3% | 4% | Leukemia |
| Non-Hodgkin's Lymphoma | 4% | 3% | Non-Hodgkin's Lymphoma |
| All others | 21% | 24% | All others |



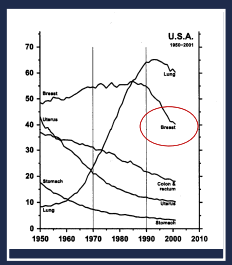
**New cases: 231,840** **Deaths: 40,290**

Cancer Facts & Figures 2017 American Cancer Society

## Breast Cancer

- Estimated statistics for 2017
  - New cases in WI 4,850
  - Deaths in WI 740
- Most common malignancy in women in the U.S.
  - 30% of all new cancer cases in women
- Second-leading cause of cancer deaths
- Increasing incidence
- Decreasing mortality

## Mortality Trends




EBCTG, Lancet 2005


## RISK FACTORS

## Risk of Breast Cancer

| Age | 10 year risk | |
|---|---|---|
| Birth-49 | 1.9% | 1 in 52 |
| 50-59 | 2.3% | 1 in 44 |
| 60-69 | 3.5% | 1 in 29 |
| ≥ 70 | 6.8% | 1 in 15 |
| Lifetime | 12.4% | 1 in 8 |

## Non-modifiable risk factors

| Other factors | Reproductive Factors |
|---|---|
| Age | Age of menses |
| Sex | Number of full term pregnancies |
| Family history | Age at first full-term pregnancy |
| Previous breast pathology | Breast feeding |
| Radiation exposure | Age at menopause |

## Postmenopausal Hormone Replacement

- Hot flashes, bone and cardiac health
- Increased risk found in 2 subgroups:
  - >5 yr duration of use increases risk by 30-45%
  - Current users
- Increased risk associated with combination pills vs. estrogen alone
- Since 2002, numbers of breast cancers have declined (parallel to reduction in HRT use)

## Bioidentical Hormones

- Marketed as "natural"
- Act in a similar fashion as estrogen and progestin to treat menopausal symptoms
- No data confirming safety
- Should be treated similar to standard HRT in terms of risk

## Coffee and Breast Cancer Risk


- Update from the Women's Health Initiative study
- No increase in risk in women who drank 4 or more cups of coffee per day
- Possible link of coffee and risk of benign breast disease
- No correlation with caffeine and other cancers

## Alcohol and Breast Cancer

- Alcohol increases circulating levels of estrogen, reduces folate
- Studies have consistently shown increase in risk of breast cancer with each drink
- Highest change in post-menopausal women

## Food Choices

- No definitive studies establish benefit or harm with consumption of certain foods
  - Antioxidants
  - Mineral supplements
  - Fat containing foods
  - Meat
  - Organic foods
  - Soy foods
  - Sugar containing foods

## Obesity

- Obesity is an independent risk factor for certain types of breast cancer
- Fat produces estrogen, relationship with insulin-like growth factors
- Weight gain in adult life increases risk

## Unlikely Causes of Cancer

- Hair dyes
- Cellular phone towers/use
- Use of antiperspirant
- Aspartame
- Fluoride within drinking water
- Use of water bottles
- Soy

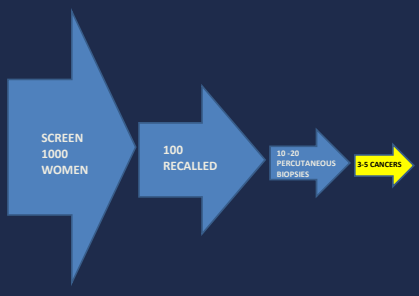
## SCREENING AND IMAGING

## Mammography

GOAL OF SCREENING:

- Detect as many cancers as possible, without undue harms.
  - ➢ Choose modalities and populations based on evidence
- Detect breast cancers before they can be felt (earlier stage) and more likely to be curable
  - ➢ Only screening test shown to decrease mortality

## Recall Rates and Yield



## Screening vs. Diagnostic

- Screen
  - Women with no complaints
  - Typically doctor order NOT needed
  - Performed and interpreted in batch read
- Diagnostic
  - Clinical concern
    - Lump, thickening, skin changes, nipple retraction, clear or bloody nipple discharge, FOCAL pain
  - Short-term follow-up (BIRADS 3)
  - Must have a doctor order
  - Radiologist on site will work-up abnormality and give results

## Diagnostic Mammogram vs. Ultrasound

- ACR appropriateness criteria:
  - Women 30 and older always get a mammogram first then focused ultrasound if indicated
  - Women < 30 get a **FOCUSED** ultrasound first

## Screening

- Annual screening mammography is recommended starting at
  - Age 40 for general population
  - Age 25-30 for BRCA carriers and untested relatives of BRCA carriers
  - Age 25-30 or 10 years earlier than age of first-degree relative at diagnosis (whichever is later) or lifetime risk of breast cancer ≥20%
  - 8 years after radiation therapy but not before age 25 for women who received mantle radiation between the ages of 10-30

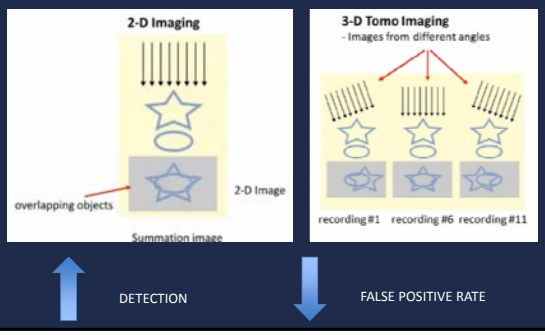
## Screening For High Risk Women

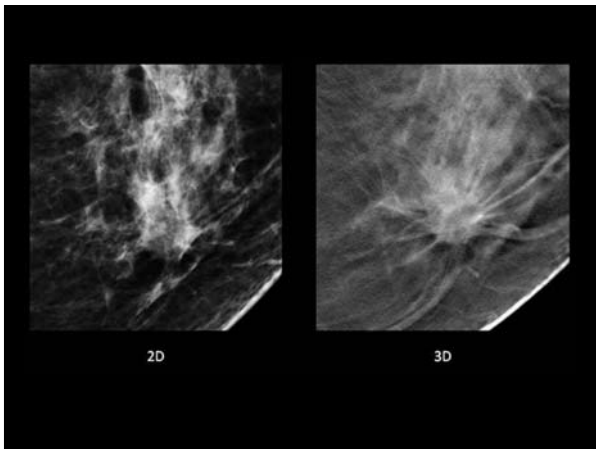
- MRI and a mammogram every year starting at age thirty. Includes:
  - Known BRCA1 or BRCA2 mutation carrier
    - 60-80% risk of breast cancer
    - Average age at diagnosis 42
  - Untested first-degree relative of known mutation carrier
  - Radiation to chest, especially ages 10-30
    - 12-25% develop breast cancer by age 45
    - Initiate screening age 25 or 8 years post-XRT
  - Other genetic abnormality (Li-Fraumeni, Cowden's, etc.)
  - Lifetime risk >20% by models based on family history

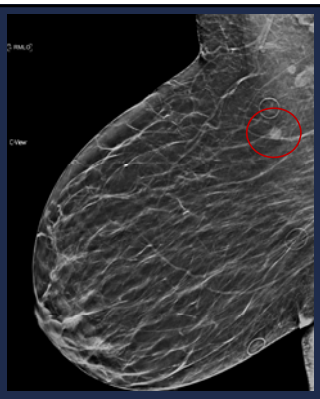
## Tomosynthesis (3D Mammography)

- FDA approval 2011
- Screening and diagnostic
- Same breast positioning and standard compression
- Acquires images at several angles in a short amount of time and reconstructs the images into thin, high-resolution slices
- Removes challenges from overlapping tissue
- Increases margin visibility and improves localization of masses

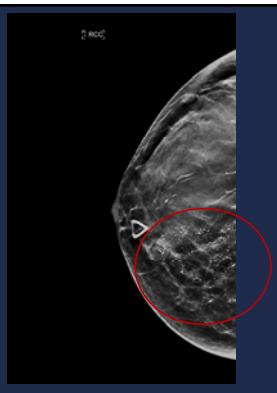
## How does it work?



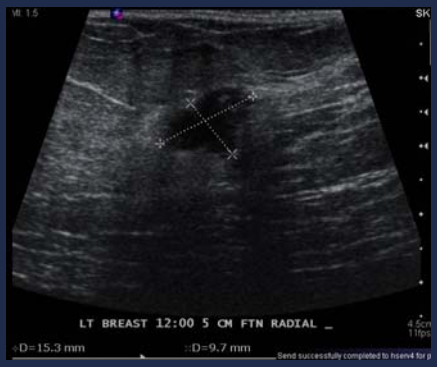


MASS



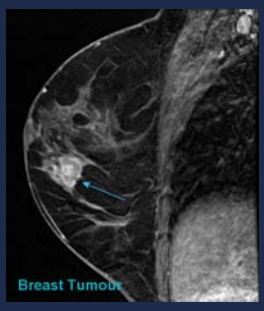
CALCIFICATIONS




## MRI

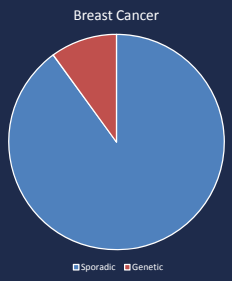
- Sensitivity 93%, Specificity 76%
- Looks at morphology and enhancement with gadolinium
  - Not indicated in pregnant or lactating women
- Screening in certain populations by ACS guidelines
- Diagnostic uses
  - Discordant imaging findings
  - Axillary cancer with no obvious breast primary
  - Extent of disease workup in pt with new diagnosis of breast cancer
  - Integrity of silicone implants (without contrast)

## MRI

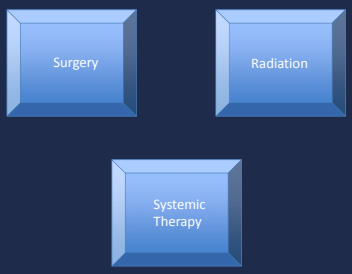


## Genetics

- BRCA-1 & -2
  - Tumor suppressor genes
  - Breast and ovarian cancer (BRCA-1)
  - Female and male breast cancer (BRCA-2)
  - Ashkenazi Jewish population
- P53
  - Tumor suppressor gene
  - 50% breast cancers have mutation
- NCCN guidelines for referral
- Multi-gene panels




## Breast Cancer Treatment




## The Team Approach

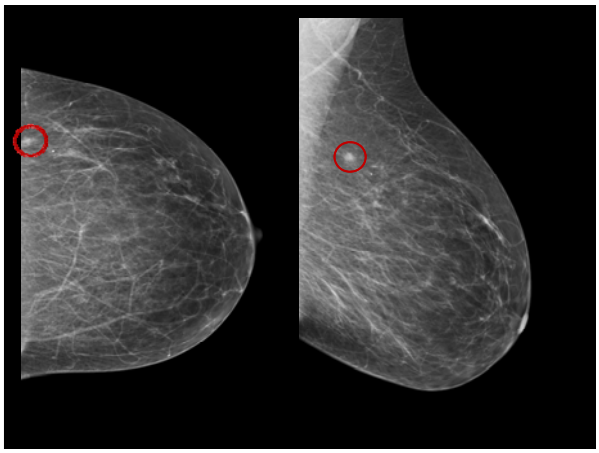

## CASE #1

## Tumor genetics shaping treatment

- 59 year old female found to have abnormality in her left breast on routine screening mammogram
- Menarche at 12. Menopause at 42. OCPs x 3 years. G2P2.
- FamilyHx
  - Brother- esophageal cancer at 64
  - Great niece- leukemia
  - Aunt- breast cancer in her 60s

## Early Stage Disease

- Exam: well-healed biopsy site at 1 o'clock posterior location.
  - No adenopathy
- Diagnosis
  - Invasive ductal carcinoma, grade I
  - ER+/PR+/HER2 non-amplified



## Treatment

- Multidisciplinary tumor board
  - Surgery upfront
  - T1N0Mx (ER+/PR+/Her2 non-amp) left breast ca
- OR
  - Left needle localized segmental mastectomy and sentinel lymph node biopsy
- Pathology
  - 7mm grade I IDC
  - 4 sentinel nodes: one with a macromet, one with a micromet
  - Margins negative: no tumor on ink

## Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

- Multicenter, randomized phase III trial
- Women with invasive breast cancer <5cm, clinically node negative, with a positive sentinel node → randomized to ALND or SLND alone
- >95% received systemic therapy in both groups
- 88-89% received whole breast irradiation in both groups

JAMA. 2011;305(6):569-575

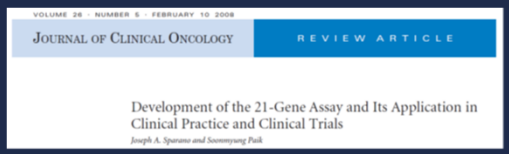
## Z1011 Findings

| | 10 yr Overall Survival | 10 yr Disease Free Survival | 10 yr Locoregional recurrence rate |
|---|---|---|---|
| ALND | 83.6% | 78.2% | 6.2% |
| SLND | 86.3% | 80.2% | 5.3% |

## Tailored Therapy

- Oncotype Dx score 13
- whole breast irradiation with boost
- Initiated Arimidex

## OncotypeDx

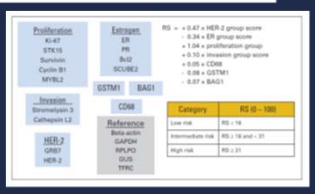

VOLUME 26 · NUMBER 5 · FEBRUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

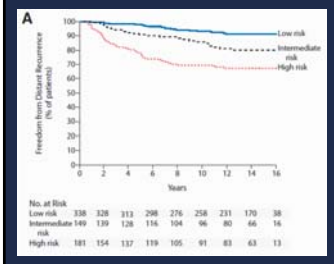
Development of the 21-Gene Assay and Its Application in Clinical Practice and Clinical Trials

Joseph A. Sparano and Soonmyung Paik

- 21 Gene Assay developed for ER+ tumors
  - 16 tumor associated genes
  - 5 reference genes



J Clin Oncol 2008; 26:721-728



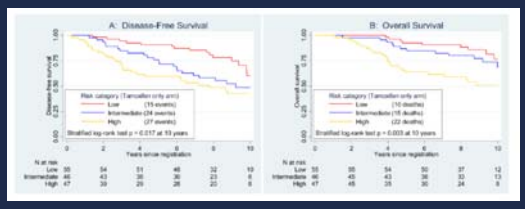

- NSABP- B14: validation study
- Shown to predict distant recurrence in node negative patients better than classic clinicopathologic features
- Multivariate model
  - RS predicted distant recurrence independent of age and tumor size (0<.001 and predictive of OS (p<0.001)

| Recurrence Score | Risk Group | No. of Patients | % | 10-Year Distant Recurrence (%) Rate | 95% CI |
|---|---|---|---|---|---|
| < 18 | Low | 338 | 51 | 6.8 | 4 to 9.6 |
| 18-30 | Intermediate | 149 | 22 | 14.3 | 8.3 to 20.3 |
| ≥ 31 | High | 181 | 27 | 30.5 | 23.6 to 37.4 |

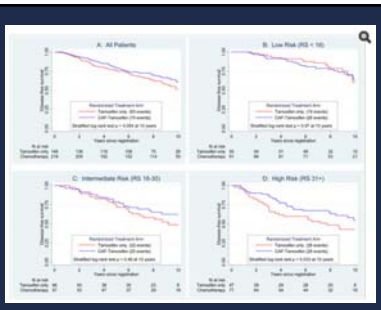
**Prognostic and Predictive Value of the 21-Gene Recurrence Score Assay in a Randomized Trial of Chemotherapy for Postmenopausal, Node-Positive, Estrogen Receptor-Positive Breast Cancer**

- SWOG 8814 trial
  - Postmenopausal women with node positive ER/PR+ breast cancer
    - Randomized to tamoxifen x 5y, 6 cycles of CAF followed by tamoxifen (CAF-T) or CAF with concurrent tamoxifen
  - Retrospective study using banked tissue looking at tamoxifen v. CAF-T group since concurrent group inferior
    - Oncotype Dx performed on 148 tam only and 219 CAF-T groups

Lancet Oncol . 2010 January ; 11(1): 55–65




- Recurrence score (RS) highly predictive for DFS stratified for number of nodes (p=0.017) as well as overall survival (p=0.003)



- RS strong predictive factor of CAF benefit for DFS
  - Larger benefit for high risk RS patients for CAF over tamoxifen alone (p=0.033)

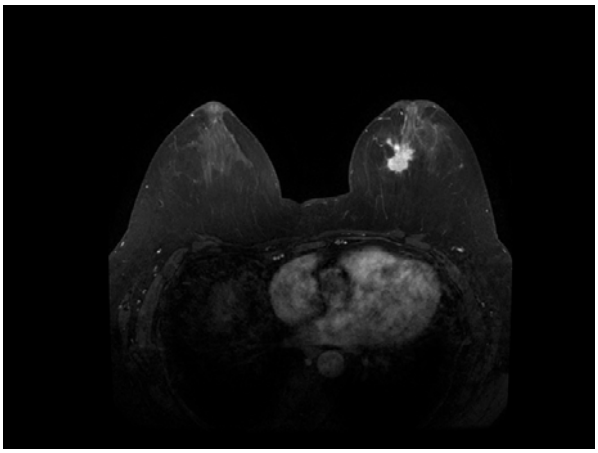
## CASE #2

## Moving Beyond Chemotherapy

- 56 year old found to have a left breast abnormality on screening mammogram
- Menarche at age 13, Surgical menopause at 48, estrogen patch for 5 years after TAH/BSO, G2P2
- FamilyHx
  - Maternal aunt- bilateral breast cancer 40s
  - Maternal cousin- breast cancer, unknown age
  - Maternal aunt- ovarian cancer at 82 (daughter is first cousin with breast cancer)

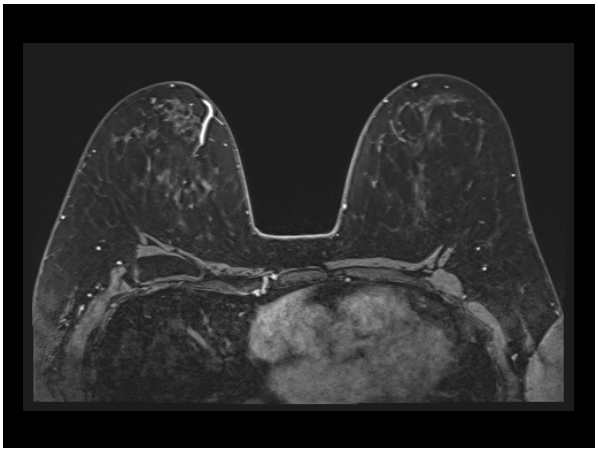
## Diagnosis

- Exam: vaguely palpable non-discrete mass-like 2-3 cm area at 9 o'clock
  - No lymphadenopathy
- Diagnosis
  - invasive ductal carcinoma grade III
  - ER+/PR+/HER2 amplified



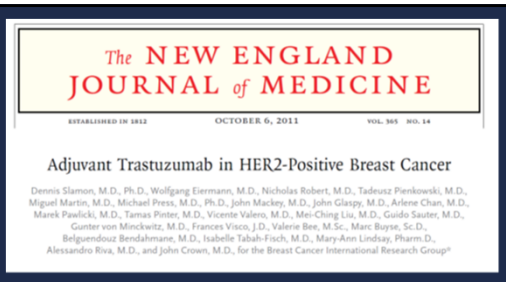
## Targeted Therapy

- Multidiscipinary conference
  - Neoadjuvant chemotherapy with THP followed by AC
  - Genetic testing
  - T2N0Mx (ER+/PR+/ HER2 amplified) left breast cancer
- MyRisk panel negative



## Treatment

- Left total mastectomy and sentinel node biopsy
- Pathology
  - Complete pathologic response
- Continue herceptin for one year & tamoxifen



The NEW ENGLAND JOURNAL of MEDICINE

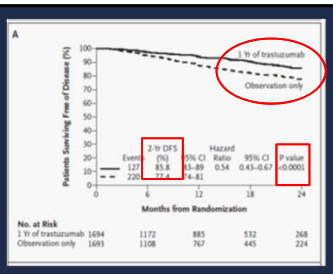
ESTABLISHED IN 1812 OCTOBER 6, 2011 VOL. 365 NO. 14

Adjunct Trastuzumab in HER2-Positive Breast Cancer

Dennis Slamon, M.D., Ph.D., Wolfgang Eiermann, M.D., Nicholas Robert, M.D., Tadeusz Pienkowski, M.D., Miguel Martin, M.D., Michael Press, M.D., Ph.D., John Mackey, M.D., John Glaspy, M.D., Arlene Chan, M.D., Marek Pawlicki, M.D., Tamas Pinter, M.D., Vicente Valero, M.D., Mei-Ching Liu, M.D., Guido Sauter, M.D., Gunter von Minckwitz, M.D., Frances Visco, J.D., Valerie Bee, M.Sc., Marc Buyse, Sc.D., Belguendouz Bendahmane, M.D., Isabelle Tabah-Fisch, M.D., Mary-Ann Lindsay, Pharm.D., Alessandro Riva, M.D., and John Crown, M.D., for the Breast Cancer International Research Group*

- Trastuzumab → recombinant monoclonal antibody against HER2
- HERA trial
  - International, multicenter, randomized trial comparing one or two years of trastuzumab every three weeks who have completed locoregional therapy and at least 4 cycle s of chemotherapy (adjuvant or neoadjuvant)
  - Comparison of observation v. one year trastuzumab

N Engl J Med 2005; 353: 1659-72



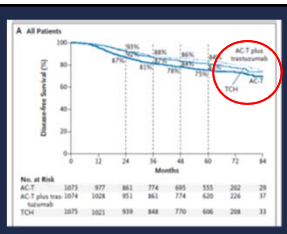

- 1694 in trastuzumab group, 1693 in observation group
  - 127 events in trastuzumab group, 220 in obs group
- Absolute benefit in DFS of 8.4% at 2 years
- HR for event in trastuzumab group compared to obs was 0.54 (95% CI 0.43-0.67; p<0.0001)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 6, 2011 VOL. 365 NO. 14

Adjuvant Trastuzumab in HER2-Positive Breast Cancer

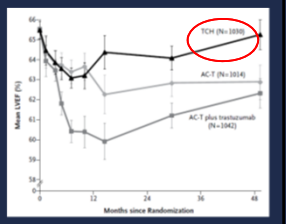
- 3,222 women with HER2 positive early stage breast cancer
  - Randomized to AC-T, AC-TH, TCH
- Addition of 1 year of trastuzumab significantly improves DFS and OS
  - Favor TCH over AC-T + H given similar efficacy, fewer, toxic effects and lower risks of cardiotoxicity and leukemia

N Engl J Med 2011; 365: 1273-83.




Disease Free Survival

LVEF at 48 months




Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

- Multicenter open-label phase II study of treatment-naïve women with HER-2 positive breast cancer (operable, locally advanced or inflammatory) N = 417
- Randomized to receive neoadjuvant:
  - Trastuzumab + docetaxel (A)
  - Pertuzumab and trastuzumab + docetaxel (B)
  - Pertuzumab + trastuzumab (C)
  - Pertuzumab + docetaxel (D)
- Primary endpoint → pathologic complete response

Lancet Oncol 2012; 13: 25-32.


Table 2: Pathological complete responses in the ITT population, by hormone-receptor status, and by axillary lymph node status at surgery

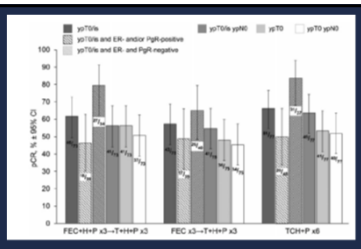
- Pertuzumab + trastuzumab + docetaxel (B) had a significantly improved pathological complete response rate compared to trastuzumab + docetaxel

**Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)**

A. Schneeweiss[1*], S. Chia[2], T. Hickish[3], V. Harvey[4], A. Eniu[5], R. Hegg[6], C. Tausch[7], J. H. Seo[8], Y.-F. Tsai[9], J. Ratnayake[10], V. McNally[10], G. Ross[10] & J. Cortés[11]

- Multicenter open-label phase II study of HER2 positive breast cancer patients (operable, locally advanced or inflammatory) N= 225
- Randomized to receive neoadjuvant:
  - FEC x 3 + H + P → docetaxel + H + P x3
  - FEC x3 → THP x 3
  - TCHP x 6
- Primary objective: evaluate safety and tolerability
- Secondary objective: PCR

Annals of Oncology 2013; 24: 2278-2284




- Combination of trastuzumab and pertuzumab generally well-tolerated
  - No additional cardiac dysfunction
- pCR rates of 57-66%

## Summary

- Risk factors→ some are modifiable (weight, alcohol, HRT), some are not (age, genetics)
- Screening is still the best method of detection
  - Movement towards 3D mammography for all
- Surgery
  - Less is more without change in survival
- Breast cancer is a systemic disease
  - Treatments are improving pathologic complete response rate

Thank you