# SABCS Highlights 2015
# Medical Oncology

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UCDAVIS COMPREHENSIVE CANCER CENTER

## Objectives

To present "clinically relevant" abstracts in:

1. Hormone receptor positive and HER2 negative breast cancer
2. HER-2 positive breast cancer
3. Triple negative breast cancer

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San Antonio Breast Cancer Symposium – December 8–12, 2015

# *PIK3CA* Status in Circulating Tumor DNA Predicts Efficacy of Buparlisib Plus Fulvestrant in Postmenopausal Women With Endocrine-resistant HR+/HER2– Advanced Breast Cancer: First Results From the Randomized, Phase III BELLE-2 Trial

José Baselga,[1] Seock-Ah Im,[2] Hiroji Iwata,[3] Mark Clemons,[4] Yoshinori Ito,[5] Ahmad Awada,[6] Stephen Chia,[7] Agnieszka Jagiello-Gruszfeld,[8] Barbara Pistilli,[9] Ling-Ming Tseng,[10] Sara Hurvitz,[11] Norikazu Masuda,[12] Javier Cortés,[13] Michele De Laurentiis,[14] Carlos L. Arteaga,[15] Zefei Jiang,[16] Walter Jonat,[17] Soulef Hachemi,[18] Sylvie Le Mouhaër,[18] Emmanuelle Di Tomaso,[19] Patrick Urban,[20] Cristian Massacesi,[18] Mario Campone[21]

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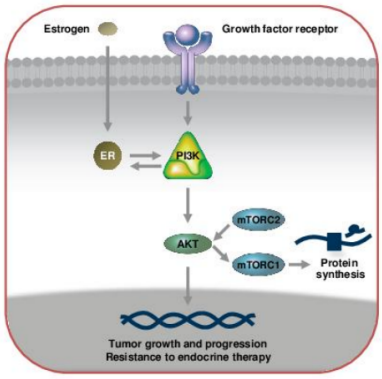
## Rationale for Combination of Fulvestrant With Buparlisib

- The PI3K/mTOR pathway is the most frequently altered oncogenic pathway in ER+ breast cancer. *PIK3CA* mutations are present in approximately 35% of ER+ breast cancer[1]
- PI3K/mTOR pathway activation is a hallmark of HR+/HER2– breast cancer cells that have developed resistance to endocrine therapy[2,3]
- PI3K inhibitors upregulate ER expression and transcriptional activity[2]
- Therefore, dual blockade of the PI3K/mTOR and ER pathways may act synergistically and help overcome resistance to endocrine therapies[2,4,5]




ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

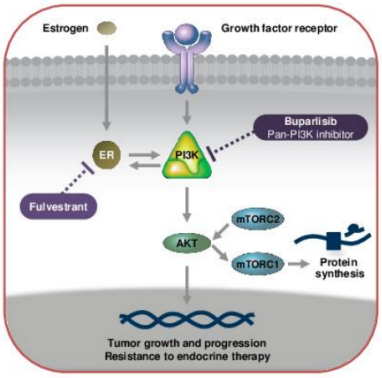
1. The Cancer Genome Atlas Network. *Nature.* 2012;490:61–70; 2. Bosch A, *et al. Sci Transl Med.* 2015;7:283ra51; 3. Miller TW, *et al. Cancer Discov.* 2011;1:338–351; 4. Fox EM, *et al. Front Oncol.* 2012;2:145; 5. Yardley D, *et al. Adv Ther.* 2013;30:870–884.

## Rationale for Combination of Fulvestrant With Buparlisib

- Buparlisib (BKM120) is an oral pan-class I PI3K inhibitor that targets all four isoforms of PI3K (α, β, γ, δ)[1]

| PI3K Isoform | α | β | γ | δ |
|---|---|---|---|---|
| $IC_{50}$, nM | 52 | 166 | 262 | 116 |

- Buparlisib has demonstrated preliminary clinical activity in combination with fulvestrant[2]
- **BELLE-2 is the first randomized Phase III study to assess the safety and efficacy of a pan-PI3K inhibitor combined with fulvestrant in HR+/HER2– advanced breast cancer**




ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

1. Maira SM, *et al. Mol Cancer Ther*. 2012;11:317–328; 2. Ma CX, *et al. Clin Cancer Res*. 2015;pii:1745 [ePub ahead of print].



## BELLE-2 Study Design and Endpoints

**Postmenopausal women with HR+/HER2– locally advanced or metastatic breast cancer that progressed on/after AI therapy**
**N=1147**

↓

**Randomization (1:1)**
*Stratification by PI3K pathway* and visceral disease status*

↓

**Buparlisib** (100 mg/day) **+ fulvestrant** (500 mg) n=576

**Placebo + fulvestrant** (500 mg) n=571

**Primary Endpoints**
- **PFS** in the full population
- **PFS** in the main population (PI3K activated and non-activated, excluding status unknown*)
- **PFS** in the PI3K activated group* (*PIK3CA* mutation and/or PTEN loss)

**Key Secondary Endpoint**
- **Overall survival**

**Other Secondary Endpoints**
- **Overall response rate**
- **Clinical benefit rate**
- **Safety, pharmacokinetics, quality of life**

**Exploratory Endpoint**
- **PFS** by ctDNA *PIK3CA* mutation status†

BELLE-2: ClinicalTrials.gov NCT01610284.

AI, aromatase inhibitor; BEAMing, beads, emulsification, amplification, and magnetics; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

*PI3K pathway activation (activated, non-activated, unknown) was assessed in archival tumor tissue provided at screening, defined as *PIK3CA* mutation by Sanger sequencing (any mutations in exons 1, 7, 9, or 20) and/or loss of PTEN expression by immunohistochemistry (1+ expression in <10% of cells); †ctDNA *PIK3CA* status was assessed by BEAMing technology.

## BELLE-2 Key Inclusion and Exclusion Criteria

### Key Inclusion Criteria

- Postmenopausal women with ER+ and/or PgR+ and HER2– inoperable locally advanced or metastatic breast cancer
- Disease progression on/after AI therapy:
  - Recurrence during or ≤12 months from end of adjuvant AI therapy
  - Progression on AI therapy for advanced/metastatic breast cancer
- Measurable disease or non-measurable lytic or mixed bone lesions (RECIST v1.1)
- Tumor tissue for analysis of PI3K-related biomarkers

### Key Exclusion Criteria

- Prior therapy with a PI3K, AKT, or mTOR inhibitor, or fulvestrant
- More than one prior chemotherapy line for metastatic disease
- History of, or active, anxiety, depression, or other major psychiatric disorders (measured using validated questionnaires)

AI, aromatase inhibitor; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2 negative; mTOR, mammalian target of rapamycin; PgR+, progesterone receptor-positive; PI3K, phosphatidylinositol 3-kinase; RECIST, Response Evaluation Criteria in Solid Tumors.







## Patient Demographics and Disease Characteristics

| Characteristic | Buparlisib + Fulvestrant (n=576) | Placebo + Fulvestrant (n=571) |
|---|---|---|
| **Median age, years (range)** | 62 (29–90) | 61 (31–90) |
| **ECOG performance status, %** | | |
| 0 | 57.8 | 60.2 |
| 1 | 40.1 | 37.0 |
| **Hormone receptor status, %** | | |
| ER+ | 99.1 | 98.6 |
| PgR+ | 74.8 | 74.1 |
| **PI3K pathway activation status, %** | | |
| Activated | 32.6 | 32.2 |
| Non-activated | 41.5 | 42.0 |
| Unknown | 25.9 | 25.7 |
| **Visceral disease present, %** | 59.2 | 59.0 |
| **Prior therapy in metastatic setting, %** | | |
| Any hormonal therapy | 72.6 | 75.1 |
| Any aromatase inhibitors | 69.4 | 71.5 |
| Any chemotherapy | 24.5 | 31.0 |
| **Prior lines of hormonal therapy in metastatic setting, %** | | |
| 0 | 27.4 | 24.9 |
| 1 | 53.1 | 52.7 |
| ≥2 | 19.4 | 22.4 |

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; PI3K, phosphatidylinositol 3-kinase.

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## BELLE-2 Safety Profile Was Characterized by Transaminitis, Hyperglycemia, Rash, and Mood Disorders

| | Buparlisib + Fulvestrant n=573 | | | Placebo + Fulvestrant n=570 | | |
|---|---|---|---|---|---|---|
| **Adverse event, %** | **All grades** | **Grade 3** | **Grade 4** | **All grades** | **Grade 3** | **Grade 4** |
| **Total** | **99.5** | **63.2** | **14.1** | **93.0** | **27.4** | **4.6** |
| Increased ALT | 40.1 | 18.7 | 6.8 | 6.8 | 1.1 | 0 |
| Increased AST | 37.3 | 15.0 | 3.0 | 9.3 | 2.8 | 0 |
| Hyperglycemia | 43.1 | 15.2 | 0.2 | 7.7 | 0.2 | 0 |
| Rash | 32.1 | 7.7 | 0.2 | 6.3 | 0 | 0 |
| Anxiety | 22.3 | 5.2 | 0.2 | 8.2 | 0.9 | 0 |
| Fatigue | 31.9 | 4.9 | 0 | 23.9 | 1.6 | 0 |
| Depression | 26.2 | 3.7 | 0.7 | 8.9 | 0.4 | 0 |
| Diarrhea | 34.2 | 3.7 | 0 | 14.6 | 1.1 | 0 |
| Asthenia | 20.1 | 2.8 | 0 | 10.5 | 1.1 | 0 |
| Stomatitis | 21.6 | 2.1 | 0 | 6.5 | 0.5 | 0 |
| Nausea | 38.7 | 1.7 | 0 | 23.2 | 1.4 | 0 |
| Decreased appetite | 29.8 | 1.6 | 0 | 11.1 | 0.2 | 0 |

- Serious adverse events occurred in 23.4% of patients in the buparlisib arm vs 15.8% in the placebo arm
- 12 on-treatment deaths (2.1%) were reported in each arm in the full population, the majority due to disease progression

ALT, alanine aminotransferase; AST, aspartate aminotransferase.



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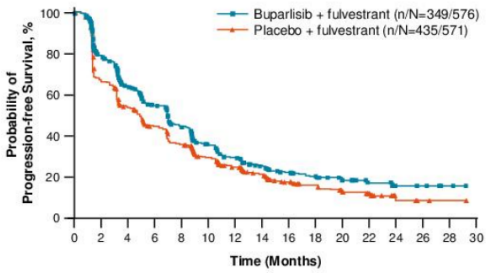
## BELLE-2 Met the Primary Endpoint for PFS Improvement in the Full Population




| Full Population (N=1147) | Buparlisib + Fulvestrant n=576 | Placebo + Fulvestrant n=571 |
|---|---|---|
| Median PFS, months (95% CI) | 6.9 (6.8–7.8) | 5.0 (4.0–5.2) |
| HR (95% CI) | 0.78 (0.67–0.89) | |
| One-sided *P* value | <0.001 | |

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided *P* value 0.003)
- Follow-up for OS analysis is ongoing, with a pre-specified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.



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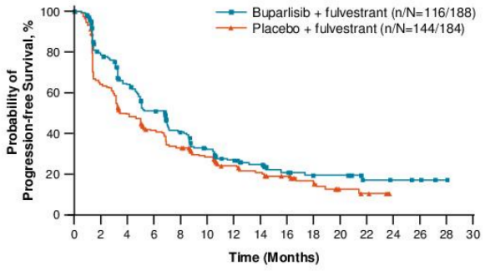
## PFS Improvement in the PI3K Activated Group Was Not Statistically Significant




| PI3K Activated Group (N=372) | Buparlisib + Fulvestrant n=188 | Placebo + Fulvestrant n=184 |
|---|---|---|
| Median PFS, months (95% CI) | 6.8 (4.9–7.1) | 4.0 (3.1–5.2) |
| HR (95% CI) | 0.76 (0.60–0.97) | |
| One-sided *P* value* | 0.014 | |

*PFS in the PI3K activated group was tested at a one-sided α=0.01 level of significance.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.





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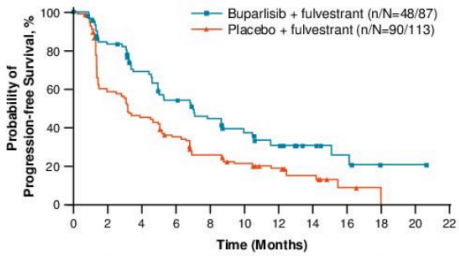
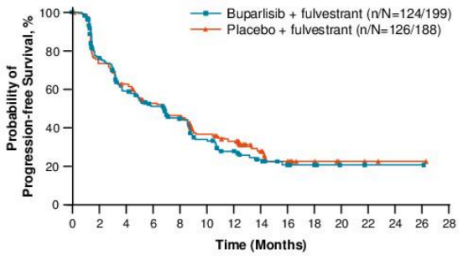
## Buparlisib Plus Fulvestrant Produced a Clinically Meaningful PFS Improvement in Patients With ctDNA *PIK3CA* Mutations

| ctDNA *PIK3CA* Mutant n=200 | Buparlisib + Fulvestrant n=87 | Placebo + Fulvestrant n=113 |
|---|---|---|
| Median PFS, months (95% CI) | 7.0 (5.0–10.0) | 3.2 (2.0–5.1) |
| HR (95% CI) | 0.56 (0.39–0.80) | |
| One-sided nominal *P* value | <0.001 | |

| ctDNA *PIK3CA* Non-mutant n=387 | Buparlisib + Fulvestrant n=199 | Placebo + Fulvestrant n=188 |
|---|---|---|
| Median PFS, months (95% CI) | 6.8 (4.7–8.5) | 6.8 (4.7–8.6) |
| HR (95% CI) | 1.05 (0.82–1.34) | |
| One-sided nominal *P* value | 0.642 | |




CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.

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## Conclusions

- The BELLE-2 study met its primary endpoint, demonstrating a modest PFS improvement for combined buparlisib and fulvestrant in postmenopausal women with HR+/HER2– advanced breast cancer that had progressed after prior AI therapy
- Frequent discontinuations due to adverse events reduced treatment duration in the buparlisib arm, potentially limiting the efficacy of combination therapy
- Patients with tumors harboring *PIK3CA* mutations detected in ctDNA performed poorly on fulvestrant monotherapy, achieving a clinically meaningful PFS improvement with the combination
  - 3.8 month PFS improvement was supported by higher response rates (18.4% vs 3.5%) in this patient population
- The BELLE-2 study suggests that assessment of *PIK3CA* mutations in ctDNA may help select patients who would benefit from adding a PI3K inhibitor to endocrine therapy
- Phase III studies with PI3Kα-selective inhibitors are underway to confirm the predictive value of *PIK3CA* mutations detected in ctDNA and tumor tissue





# How does this change clinical practice?

- The BELLE-2 trial is the first randomized trial to show a benefit to targeting the PI3K pathway in advanced cancer. However, the effect was modest in the entire population and not significant in the tumor PI3K activated group.
- PFS by ctDNA by *PIK3CA* mutation status was an exploratory endpoint and further confirmatory data is needed.

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# A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04)

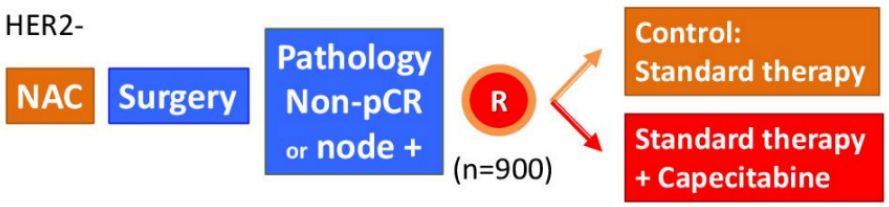
## Capecitabine for REsidual cancer as Adjuvant ThErapy

Lee S-J[1], Toi M[2], Lee E-S[3], Ohtani S[4], Im Y-H[5], Im S-A[6], Park B-W[7], Kim S-B[8], Yanagita Y[9], Takao S[10], Ohno S[11], Aogi K[12], Iwata H[13], Kim A[14], Sasano H[15], Yokota I[16], Ohashi Y[17] and Masuda N[18]

[1]Yeungnam University Hospital; [2]Kyoto University Hospital; [3]National Cancer Center; [4]Hiroshima City Hospital; [5]Samsung Medical Center; [6]Seoul National University Hospital; [7]Severance Hospital, Yonsei University College of Medicine; [8]Asan Medical Center; [9]Gunma Prefectural Cancer Center; [10]Hyogo Cancer Center; [11]National Kyusyu Cancer Center; [12]NHO Shikoku Cancer Center; [13]Aichi Cancer Center; [14]Korea University Guro Hospital; [15]Tohoku University; [16]Kyoto Prefectural University of Medicine; [17]Chuo University and [18]NHO Osaka National Hospital



# CREATE-X: Trial Design




Stratification factors:
ER, Age, NAC, ypN,
5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

## Capecitabine Therapy

Capecitabine (X): 2,500 mg/m$^2$/day, po, day 1-14
Repeat every 3 weeks for 8 cycles


According to the safety interim analysis of the first 50 pts treated with 6 cycles of X, the IDMC recommended extending X to 8 cycles.

## Key Inclusion Criteria

- Age: 20-74
- ECOG PS 0 or 1
- Stage I – IIIB
- HER2-negative (IHC 0 or 1 and/or FISH negative)
- Non-pCR and/or node-positive after NAC with anthracycline (A) and taxane (T), A-containing or TC (docetaxel, cyclophosphamide)
- No prior treatment with oral FU
- Adequate organ functions
- No toxicity reactions of grade 2 or higher carried over from NAC
- Written informed consent

## Patients & Tumor Characteristics (2)

| | | Capecitabine (N=440) | Control (N=445) |
|---|---|---|---|
| Neoadjuvant chemotherapy | A containing* | 18 (4.1) | 16 (3.6) |
| | A-T (sequential)* | 357 (81.1) | 371 (83.4) |
| | AT (concurrent)* | 60 (13.6) | 53 (11.9) |
| | TC* | 5 (1.1) | 3 (0.7) |
| 5FU containing regimen | Yes | 260 (59.1) | 269 (60.4) |
| | No | 180 (40.9) | 176 (39.6) |
| Adjuvant endocrine therapy | Yes for premenopausal | 187 (42.5) | 178 (40.0) |
| | Yes for postmenopausal | 108 (24.5) | 127 (28.5) |
| | No | 145 (33.0) | 140 (31.5) |
| Radiation therapy | Yes | 318 (72.3) | 327 (73.5) |
| | No | 122 (27.7) | 118 (26.5) |

*A: Anthracycline containing, T:Taxane (Docetaxel or Paclitaxel), TC: Docetaxel + Cyclophosphamide

## Compliance of capecitabine

| Total (N=439) | Cases planned for 6 cycles (N=159) | Cases planned for 8 cycles (N=280) |
|---|---|---|
| Completion | 92 (58.0) | 106 (37.9) |
| Reduction | 38 (23.9) | 104 (37.1) |
| Discontinued | 29 (18.2) | 70 (25.0) |
| RDI* (%) Mean (SD) | 87.9 (21.6) | 79.1 (29.0) |

* RDI: Relative dose intensity

# Safety

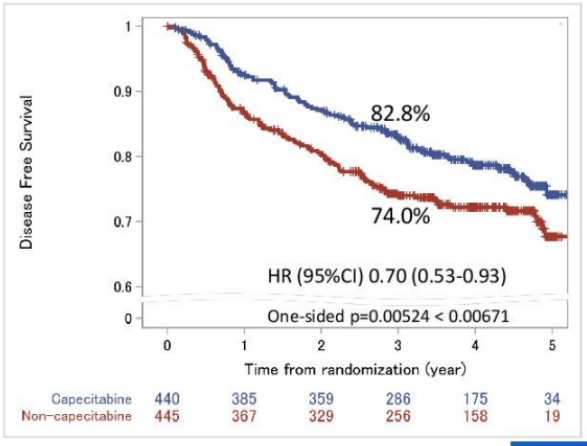
| ≥G3 (N, %) | Capecitabine arm (N=440) | Control arm (N=445) |
|---|---|---|
| Neutropenia * | 29 (6.6) | 7 (1.6) |
| Diarrhea * | 13 (3.0) | 2 (0.4) |

- significantly higher in the capecitabine arm
  (Neutropenia: p<0.001, Diarrhea: p=0.004)
- All grade incidence is significantly higher in the capecitabine arm as below,
  Leucopenia, Neutropenia, Anemia, Thrombocytopenia
  Elevated AST/ALT, Total bilirubin
  Appetite loss, Diarrhea, Stomatitis and Fatigue

| Capecitabine administrated Hand-Foot-Syndrome (N=440) | |
|---|---|
| Grade 0 | 122 (27.7) |
| Grade 1 | 160 (36.4) |
| Grade 2 | 110 (25.0) |
| Grade 3 | 48 (10.9) |
| Grade 1-3 | 318 (72.3) |

Ohtani S, et al. SABCS2013#P3-12-03

# Disease Free Survival

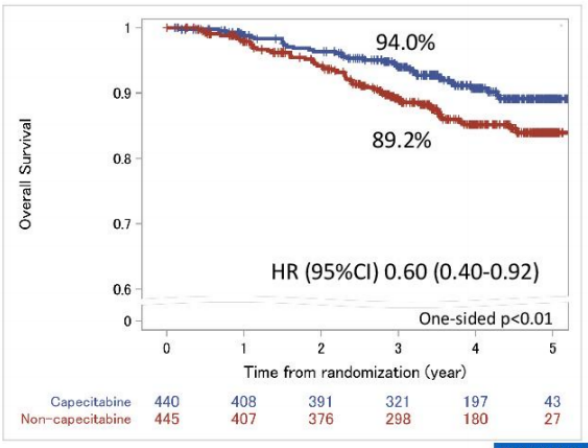



5yr DFS

74.1% Capecitabine

67.7% Control

# Overall Survival




5yr OS

89.2% Capecitabine

83.9% Control

# Conclusions

- After standard neoadjuvant chemotherapy containing A and/or T, postoperative adjuvant use of capecitabine improved DFS significantly in HER2-negative primary breast cancer patients with pathologically proven residual invasive disease.
- OS was significantly improved by capecitabine adjuvant therapy for non-pCR or node-positive patients after NAC.
- The balance of benefit and toxicity would favor the use of capecitabine in the post-NAC situation, but prediction for the therapeutic benefit needs to be investigated further.
- The cost-effectiveness analysis will be carried out.

## How does this change clinical practice?

- If the results hold up, it provides phase III data to consider "maintenance" chemotherapy in those who fail to achieve a pCR.
- Data stratified by hormone receptor status was not presented.
- The dose and schedule appeared better tolerated in this Asian population, perhaps due to differences in pharmacogenomics?

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## Objectives

To present "clinically relevant" abstracts in:

1. Hormone receptor positive and HER2 negative breast cancer
2. HER-2 positive breast cancer
3. Triple negative breast cancer

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# BCIRG 006
# Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients:

## 10-year Follow-up analysis

Slamon D, Eiermann W, Robert N, Giermerk J, Martin M, Jasiowka M, Mackey J, Chan A, Liu M, , Pinter T, Valero V, Falkson C, Fornander T, Shiftan T, Bensfia S, Hitier S, Xu N, Bee-Munteanu V, Drevot P, Press M, Crown J, on behalf of the BCIRG 006 Investigators.

Study sponsored by sanofi
Support from Genentech

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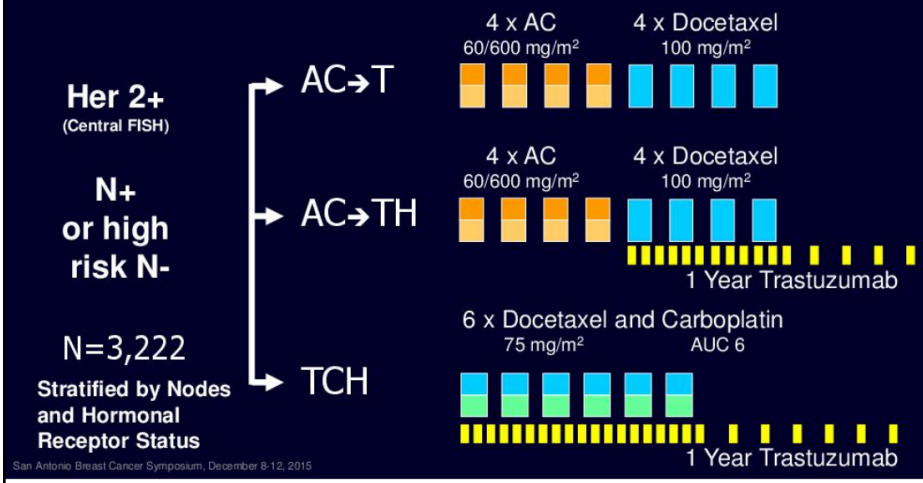
## BCIRG 006 Trial Design

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## BCIRG 006 Crossover

- 33 patients (3.1%) of the 1,073 randomized to the control arm (AC→T) crossed-over to receive trastuzumab
- 96.9 % of the control arm enrollment remained intact for long-term DFS, OS and safety comparisons

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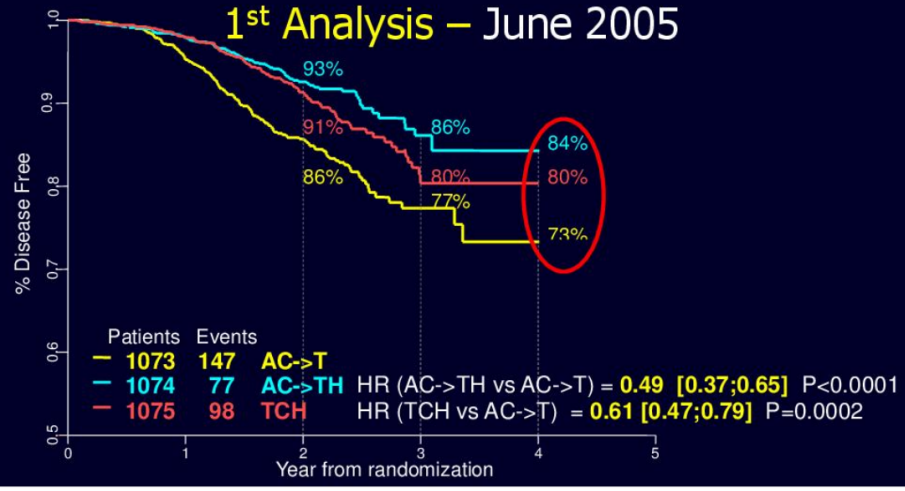
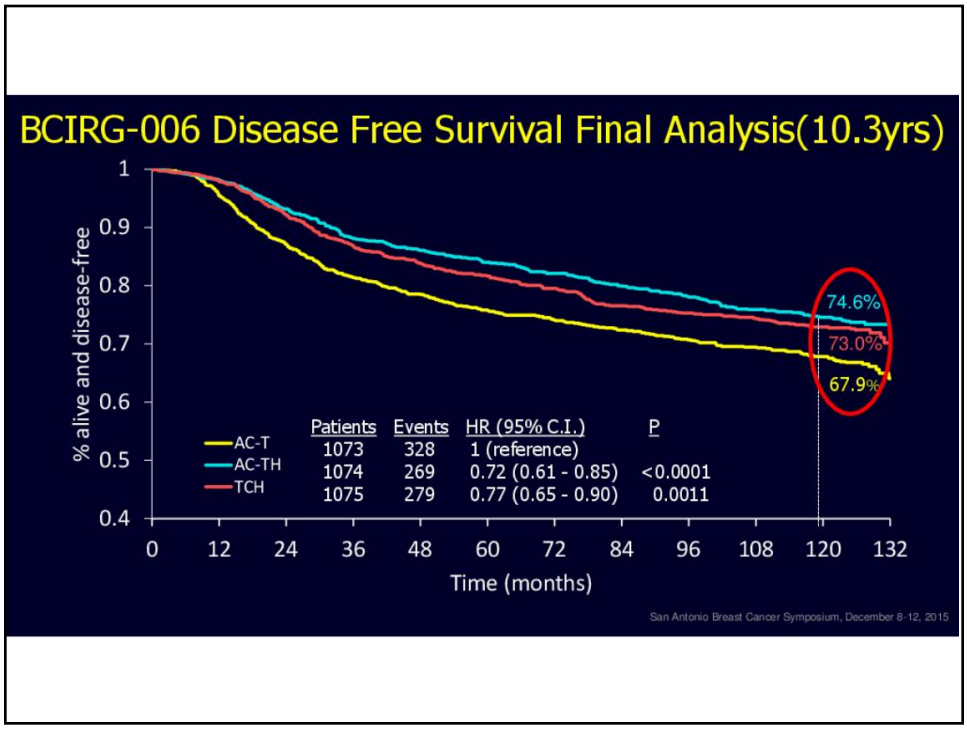
## Initial Disease Free Survival from 1st Analysis – June 2005




BCIRG-006 Disease Free Survival Final Analysis(10.3yrs)
% alive and disease-free
1
0.9
0.8
0.7
0.6
0.5
0.4
0
12
24
36
48
60
72
84
96
108
120
132
Time (months)
74.6%
73.0%
67.9%
Patients Events HR (95% C.I.) P
AC-T 1073 328 1 (reference)
AC-TH 1074 269 0.72 (0.61 - 0.85) <0.0001
TCH 1075 279 0.77 (0.65 - 0.90) 0.0011
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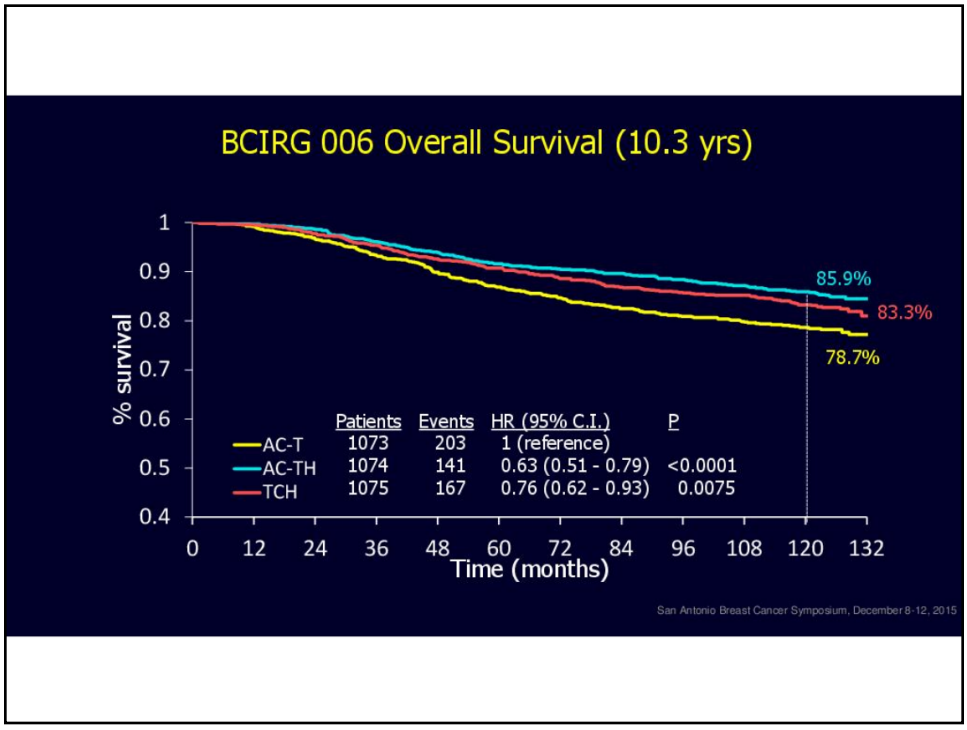
BCIRG 006 Overall Survival (10.3 yrs)
% survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0
12
24
36
48
60
72
84
96
108
120
132
Time (months)
85.9%
83.3%
78.7%
Patients Events HR (95% C.I.) P
AC-T 1073 203 1 (reference)
AC-TH 1074 141 0.63 (0.51 - 0.79) <0.0001
TCH 1075 167 0.76 (0.62 - 0.93) 0.0075
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## BCIRG 006 Grade 3/4 Hematological Toxicity

| | AC→T n=1,050 | AC→TH n=1,068 | TCH n=1,056 |
|---|---|---|---|
| | % | % | % |
| Neutropenia | 63.5 | 71.6 | 66.2* |
| Leucopenia | 51.9 | 60.4 | 48.4* |
| Febrile neutropenia | 9.3 | 11.0 | 9.6 |
| Neutropenic infection | 11.9 | 12.6 | 11.2 |
| Anemia | 2.3 | 3.0* | 5.4 |
| Thrombocytopenia | 1.6 | 2.1* | 6.1 |
| Acute Leukemias: #(%) | 6 (0.6) | 2 (0.1) | 1 (0.1**) |

Yellow=*Statistically significant less events

**B-cell lymphoma developed 24 months after TCH in this pt and represented her ITT DFS event.
The acute leukemia occurred 20 months after rx with CHOP for the B cell lymphoma.

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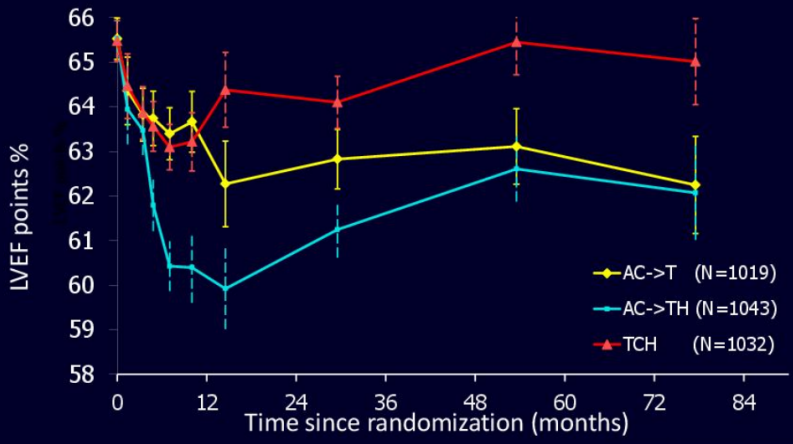
## BCIRG-006 Mean LVEF - All Observations (Final Analysis)

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# Trastuzumab emtansine (T-DM1) improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: final overall survival results from the phase 3 TH3RESA study

Hans Wildiers,[1] Sung-Bae Kim,[2] Antonio Gonzalez Martin,[3] Patricia M. LoRusso,[4] Jean-Marc Ferrero,[5] Tanja Badovinac-Crnjevic,[6] Ron Yu,[7] Melanie Smitt,[7] Ian E. Krop[8]

*[1]University Hospitals Leuven, Leuven, Belgium; [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [3]MD Anderson Cancer Center, Madrid, Spain; [4]Yale Cancer Center, Yale University Medical Center, New Haven, CT, USA; [5]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; [6]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [7]Genentech, Inc, South San Francisco, CA, USA; [8]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*



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## T-DM1: Background

- Antibody-drug conjugate composed of the HER2-targeted humanized monoclonal antibody trastuzumab stably linked to the cytotoxic microtubule inhibitor DM1
- Approved as a single-agent for treatment of patients with HER2-positive MBC who previously received trastuzumab and a taxane, separately or in combination
  - Patients should have received prior therapy for MBC, or
  - Developed disease recurrence during or within 6 months of completing adjuvant therapy
- Approval based on phase 3 EMILIA study of T-DM1 vs lapatinib + capecitabine[1]
  - Significantly longer PFS (median 9.6 vs 6.4 months; HR=0.65, $P<0.001$)
  - Significantly longer OS (median 30.9 vs 25.1 months; HR=0.68, $P<0.001$)

[1]Verma S, et al. *N Engl J Med* 2012.

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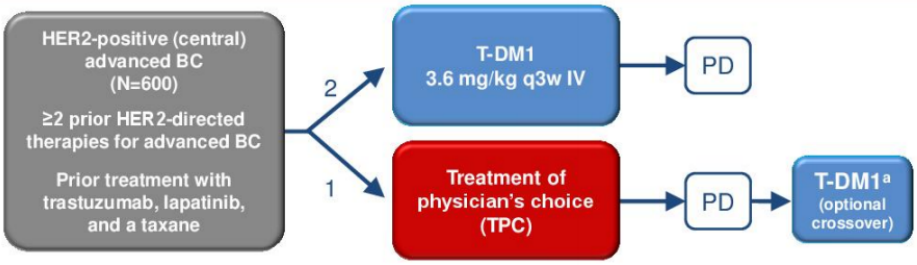
## TH3RESA Study Schema




**Stratification factors:** World region, number of prior regimens for advanced BC, presence of visceral disease

**Co-primary endpoints:** PFS by investigator and OS

**Key secondary endpoints:** ORR by investigator and safety

[a]First patient in: Sept, 2011. Study amended: Sept, 2012 following EMILIA 2nd interim OS results to allow patients in the TPC arm to receive T-DM1 after documented PD.



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## Statistical Considerations

### Statistical Analysis

- Overall type I error rate (5%) is split asymmetrically between the two co-primary endpoints:
  - 0.5% allocated to PFS
  - 4.5% allocated to OS

**Primary PFS Analysis[1]**
(cut-off date February 11, 2013)

- PFS (investigator-assessed)
  - HR=0.528, *P*<0.0001
  - Median PFS 3.3 months with TPC vs. 6.2 months with T-DM1
- First interim OS analysis
  - 105 (21%) of 492 targeted events
  - Trend for improved OS but stopping boundary not crossed

**Second Interim OS Analysis**
(cut-off date February 13, 2015)

- Planned: 330 (67%) of 492 targeted events
- Actual: 338 (69%) events; median follow-up 30.5 months
- Pre-specified stopping boundary HR<0.748 or *P*<0.012
- **If stopping boundary is crossed, this will be the final OS analysis**

[1]Krop IE, et al. *Lancet Oncol* 2014.

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## Treatment of Physician's Choice Regimen

| TPC treatment regimen | TPC (n=184[a]) | |
|---|---|---|
| **Combination with HER2-directed agent, %** | **83.2** | |
| Chemotherapy[b] + trastuzumab | 68.5 | **Trastuzumab-containing 80.4** |
| Lapatinib + trastuzumab | 10.3 | |
| Hormonal therapy + trastuzumab | 1.6 | |
| Chemotherapy[b] + lapatinib | 2.7 | |
| **Single-agent chemotherapy,[b] %** | **16.8** | |

[a]Includes patients who received study treatment. Excludes one patient who was randomized to the TPC arm but received two cycles of T-DM1 by mistake.
[b]The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.



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## Patient Disposition and Post-Progression Therapy

| | TPC (n=198) | T-DM1 (n=404) |
|---|---|---|
| **Discontinued study, %** | 79.3 | 67.1 |
| **Reasons for study discontinuation, %** | | |
| Death | 59.1 | 54.7 |
| Withdrawal by patient | 15.7 | 8.2 |
| Physician's decision | 2.0 | 0.7 |
| Other | 2.5 | 3.5 |
| **Post-progression therapy,[a] %** | | |
| Any | 62.6 | 46.8 |
| HER2-directed | 57.1 | 33.9 |
| **T-DM1 as crossover treatment** | 44.9 | n/a |
| T-DM1 as non-study treatment | 6.6 | 1.2 |
| Other | 26.3 | 33.7 |
| Chemotherapy | 34.3 | 42.1 |
| Hormonal | 7.6 | 10.1 |
| Other | 3.0 | 5.2 |

[a]Patients may have received post-progression therapy that was not recorded on the eCRF.

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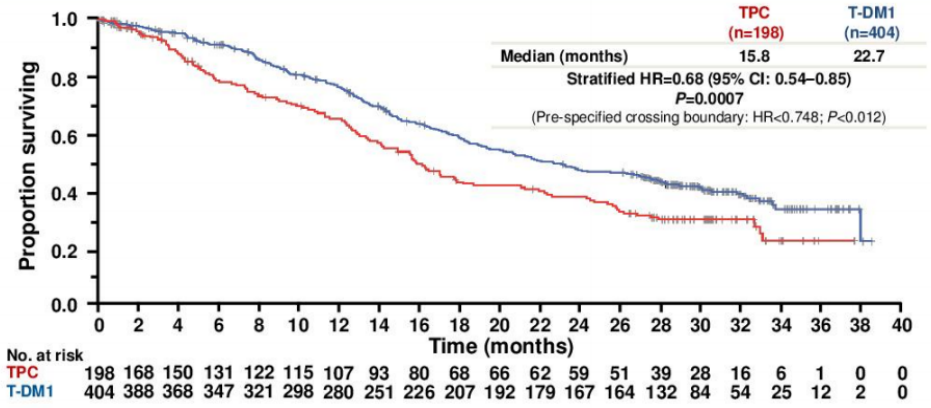
## Final OS Analysis



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## Conclusions

- T-DM1 demonstrated a clinically meaningful and statistically significant improvement in OS compared to TPC in patients with HER2-positive MBC previously treated with taxane, trastuzumab, and lapatinib
  - Median OS improved by **6.9 months** from 15.8 months (TPC) to 22.7 months (T-DM1)
  - Stratified HR=0.68, *P*=0.0007
  - Survival benefit despite substantial crossover
  - ~80% of patients in TPC arm received trastuzumab-containing regimens
- Despite longer treatment duration relative to control, T-DM1 had a favorable safety profile which was consistent with prior studies
- These data further solidify the role of T-DM1 in the treatment of previously treated HER2-positive advanced breast cancer

# MANTICORE 101:
# Multidisciplinary Approach to Novel Therapies In Cardio-Oncology REsearch

Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, Thompson R, Oudit G, Ezekowitz J, Paterson I.

University of Alberta, Edmonton, AB, Canada; Cross Cancer Institute, Edmonton, AB, Canada; Mazankowski Alberta Heart Institute, Edmonton, AB, Canada; University of Manitoba, Winnipeg, MB, Canada; University of Texas, Arlington, TX.

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## Background

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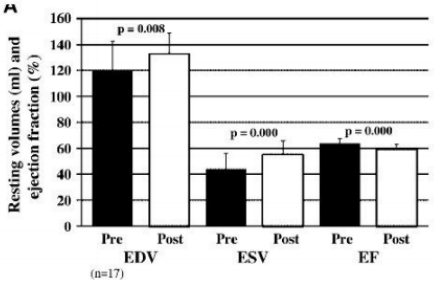
- Trastuzumab related cardiac toxicity is frequent and potentially lethal
  - Left ventricular (LV) dysfunction ~20%
  - Heart failure ~1-5%
- Cardiac function (LVEF) monitored Q3 months during trastuzumab Rx
  - 3-D imaging preferred (e.g. Cardiac MRI)
- No effective prevention strategies to date
  - ACE inhibitors and beta blockers recommended for established cardiac toxicity

Trastuzumab related LV remodeling and dysfunction on Cardiac MRI




Haykowsky et al. Clin Cancer Res 2009.

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## MANTICORE: Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research

Primary Aim:

- Determine if ACE inhibitors (ACEI) or beta blockers (BB) prevent LV remodeling in HER2+ EBC patients receiving trastuzumab-based chemotherapy

Design:

- Three arm, 1:1:1 randomization, placebo controlled, double blinded, multicentre trial

Pituskin et al. BMC Cancer 2011.



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## MANTICORE: Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research

Primary Outcome:

- Change in indexed left ventricular end-diastolic volume (ΔLVEDVi) on cardiac MRI following 17 cycles of trastuzumab

Secondary Outcomes:

- Change in left ventricular ejection fraction (ΔLVEF) on cardiac MRI following 17 cycles of trastuzumab
- Safety and tolerability of ACEI and BB in HER2+ EBC patients

Pituskin et al. BMC Cancer 2011.

## MANTICORE Design Overview

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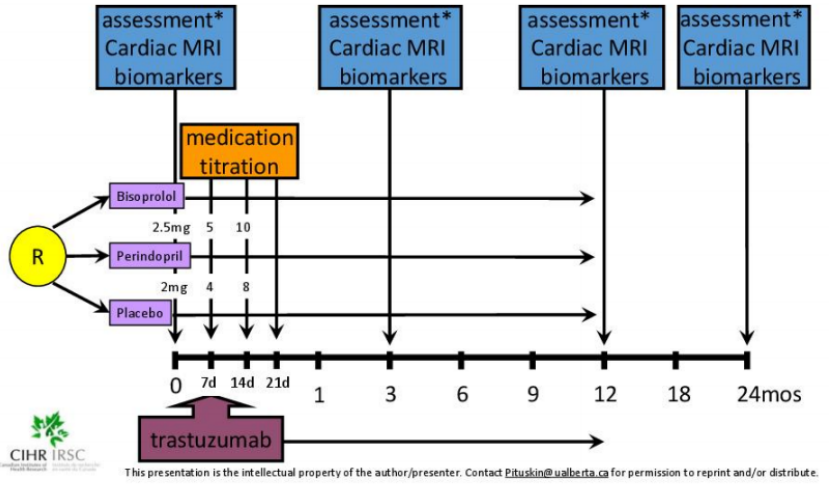




## CONSORT Flow Diagram

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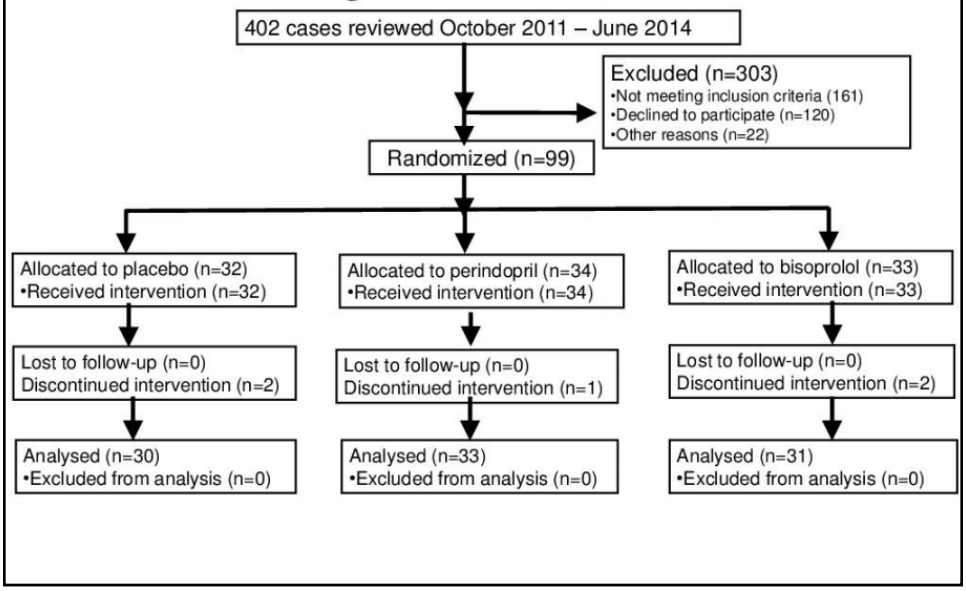

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## Safety

| | Placebo (N=30) | Perindopril (N=33) | Bisoprolol (N=31) |
|---|---|---|---|
| Premature study drug termination | 0 | 0 | 0 |
| Dose reductions explanations | | | |
| - hyperkalemia/renal | 1 (3%) | 6 (18%) | 6 (19%) |
| - bradycardia | 1 (3%) | 0 | 1 (3%) |
| - dizziness | 0 | 0 | 2 (6%) |
| - hypotension | 1 (3%) | 0 | 1 (3%) |
| - patient preference | 0 | 2 (6%) | 1 (3%) |



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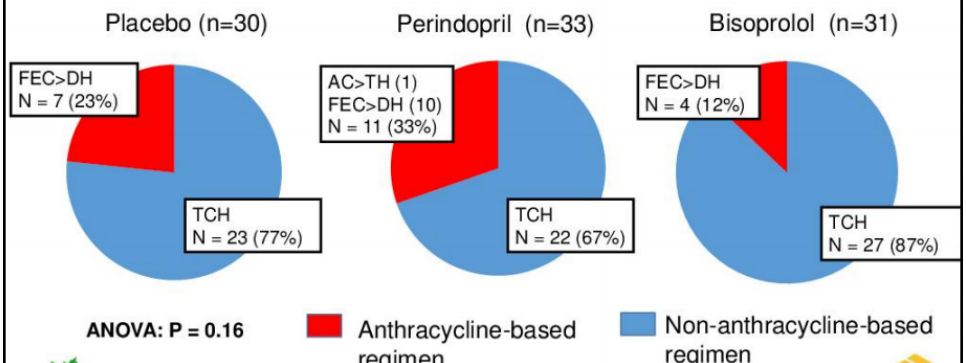
## Patient Characteristics – Anthracyclines



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## Results – Cardiac MRI

| | Placebo (N=30) | Perindopril (N=33) | Bisoprolol (N=31) | ANOVA P value |
|---|---|---|---|---|
| Pre LVEDVi (ml/m²) | 76 ± 13* | 67 ± 14 | 69 ± 10 | **< 0.01** |
| Post LVEDVi (ml/m²) | 79 ± 12 | 74 ± 16† | 76 ± 14† | **0.27** |
| Δ LVEDVi from baseline | +4 ± 11 | +7 ± 14 | +8 ± 9 | **0.36** |
| Pre LVEF (%) | 61 ± 5 | 62 ± 5 | 62 ± 4 | **0.55** |
| Post LVEF (%) | 56 ± 4*† | 59 ± 6† | 61 ± 4 | **0.0001** |
| Δ LVEF from baseline | -5 ± 5 | -3 ± 4 | -1 ± 5* | **0.001** |
| Trastuzumab interruptions due to drop in LVEF | 8* | 1 | 1 | **0.002** |

* P < 0.05 compared to other groups, † P < 0.05 from baseline



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## Multivariate analysis for prediction of Δ LVEF

| | Unstandardized Beta | Standard Error | 95% Confidence Interval of Beta | | Significance |
|---|---|---|---|---|---|
| Age | 0.098 | 0.050 | -0.002 | 0.199 | 0.199 |
| **Baseline LVEF** | **-0.494** | **0.096** | **-0.684** | **-0.303** | **<0.001** |
| Trastuzumab dose | 0.68 | 0.054 | -0.04 | 0.175 | 0.213 |
| Anthracyclines | 0.268 | 1.018 | -1.755 | 2.291 | 0.793 |
| Left Radiotx | 0.952 | 0.858 | -0.753 | 2.657 | 0.270 |
| **Perindopril** | **2.615** | **1.018** | **0.557** | **4.673** | **0.013** |
| **Bisoprolol** | **4.735** | **1.035** | **2.668** | **6.802** | **<0.001** |

ANOVA F-test = 7.986

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## Study Strengths and Limitations

- First effective intervention for trastuzumab-associated LV dysfunction
- RCT, placebo controlled, multicenter design
- Homogeneous patient population and uniform follow-up
- Ease and safety of intervention

- Underpowered for CHF events
- Negative for primary end-point of preventing LV remodeling
  - Importance of extended follow-up



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## Conclusions

- Prophylactic use of standard heart failure pharmacotherapy protects against trastuzumab associated declines in LVEF
  - reduces trastuzumab interruptions due to LV dysfunction

- Trastuzumab associated LV remodeling not prevented by ACE inhibitors or beta blockers

- Routine ACE inhibitors and beta blockers appear safe in HER2 over-expressing early breast cancer patients treated with trastuzumab

## How do these studies change clinical practice?

- Long-term follow up in BCIRG-006 confirms the DFS and OS benefit of trastuzumab in early stage HER2 positive breast cancer and provides data on 10-year risk of secondary leukemia and cardiac events.
- TH3RESA provides additional data for TDM-1 in patients with MBC previously treated with trastuzumab and lapatinib.
- It is too early to prophylactically treat all early stage patients with B-blockers or ACE inhibitors.

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## Objectives

To present "clinically relevant" abstracts in:

1. Hormone receptor positive and HER2 negative breast cancer
2. HER-2 positive breast cancer
3. Triple negative breast cancer

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GBG GERMAN BREAST GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

# Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)

Gunter von Minckwitz, Sibylle Loibl, Andreas Schneeweiss, Christoph Salat, Eric Hahnen, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens Uwe Blohmer, Hans Tesch, Fariba Khandan, Peter Fasching, Christian Jackisch, Rita Schmutzler, Valentina Nekljudova, Michael Untch
for the
GBG/AGO-B study groups

AGO-B BREAST STUDY GROUP



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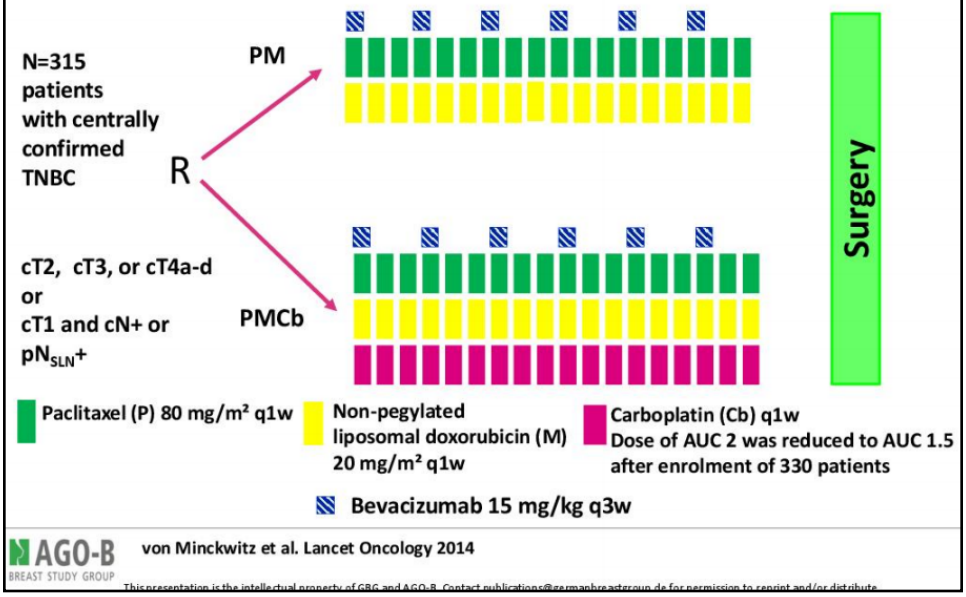
## Design for Patients with TNBC




AGO-B BREAST STUDY GROUP

von Minckwitz et al. Lancet Oncology 2014

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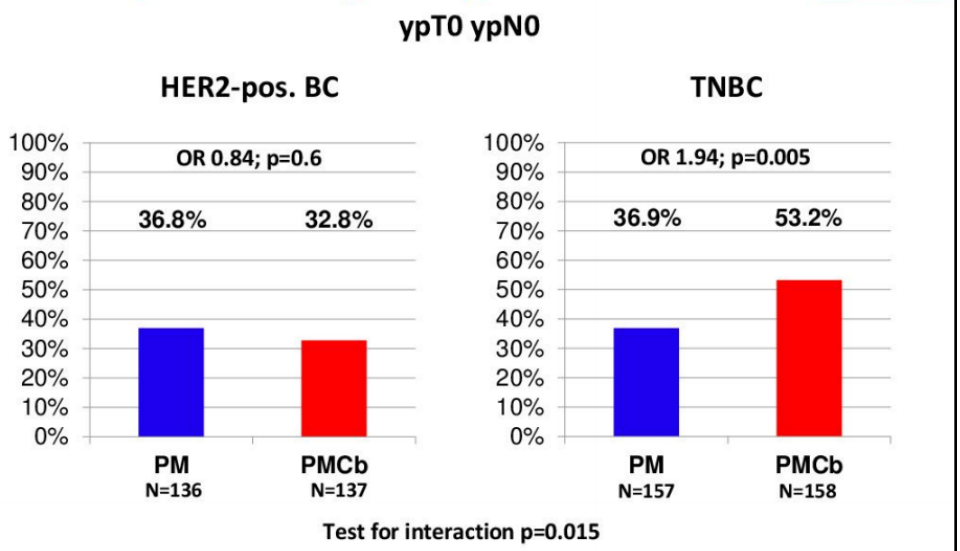
## pCR Rates by Subtype




AGO-B BREAST STUDY GROUP

von Minckwitz et al. Lancet Oncology 2014





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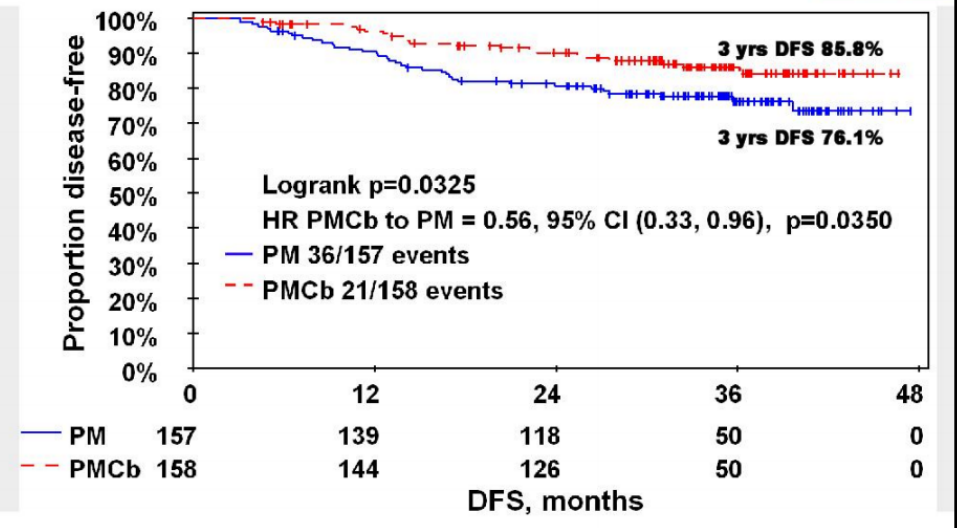
## DFS: Effect of Carboplatin in TNBC

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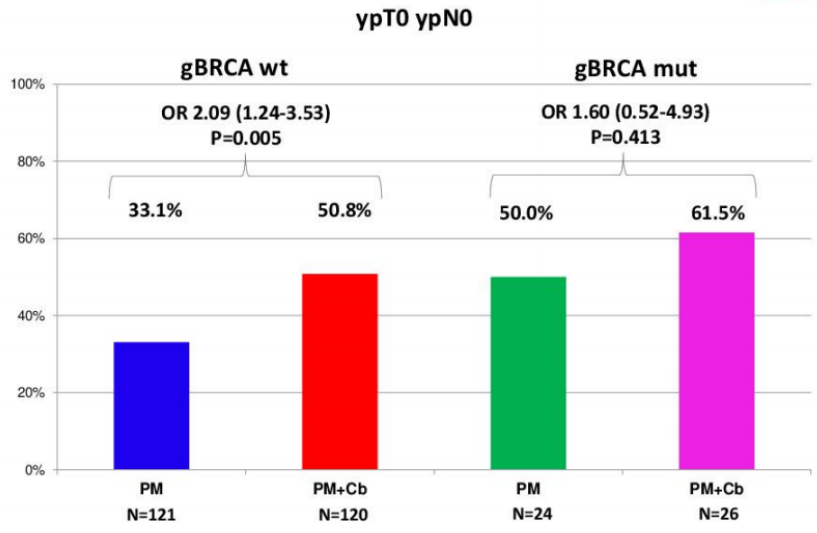
## pCR Rates by *gBRCA* Status and Carboplatin in TNBC

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von Minckwitz G et al., ASCO 2014, updated data; E. Hahnen in prep.



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## Conclusion

- Carboplatin improved DFS substantially (HR=0.56, p=0.035) in patients with TNBC; but showed no effect in patients with HER2-positive BC (HR 1.33, p=0.372; test for interaction p=0.046).
- DFS effect of carboplatin was correctly predicted by its extensive effect on pCR, supporting surrogacy of pCR (comparable to NOAH).
- Unexpectedly, a strong positive effect of carboplatin on pCR and DFS was observed in patients with wt *gBRCA*.
- Favorable prognosis after pCR was confirmed and is independent of *gBRCA* status.
- In summary, GeparSixto supports the use of carboplatin as part of neoadjuvant treatments in all patients with TNBC.

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# Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance)

William M Sikov, Donald A Berry, Charles M Perou, Baljit Singh, Constance T Cirrincione, Sara M Tolaney, George Somlo, Elisa R Port, Rubina Qamar, Keren Sturtz, Eleftherios Mamounas, Mehra Golshan, Jennifer R Bellon, Deborah Collyar, Olwen M Hahn, Lisa A Carey, Clifford A Hudis, Eric P Winer for the CALGB/Alliance



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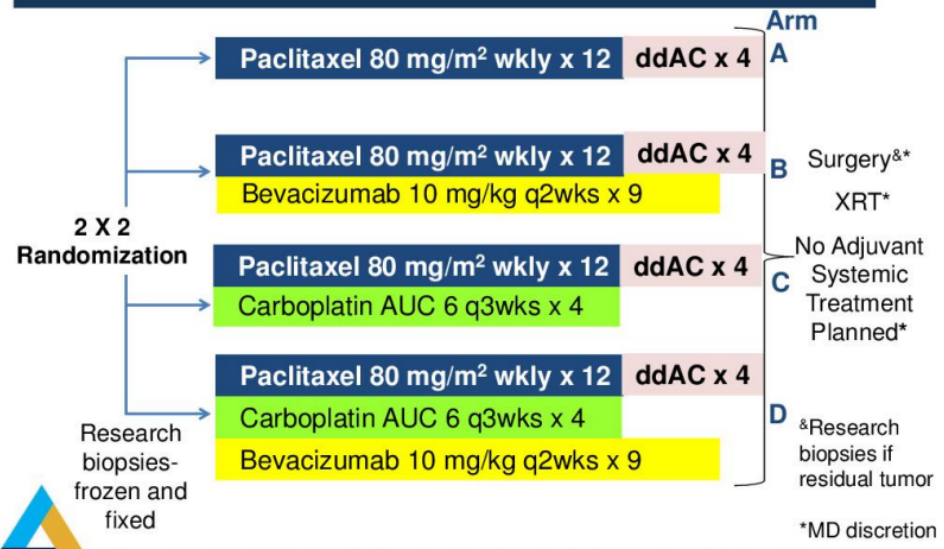
## CALGB 40603: Schema – Randomized Phase II

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## CALGB 40603 – pCR Results by factor

| pCR Breast ypT0/is (%, 95% CI) | | | | |
|---|---|---|---|---|
| Overall | Carbo | No Carbo | OR | p-value |
| 53 (49-58) | 60 (54-66) | 46 (40-53) | 1.76 | 0.0018 |
| | Bev | No Bev | OR | p-value |
| | 59 (52-65) | 48 (41-54) | 1.58 | 0.0089 |
| **pCR Breast/Axilla ypT0/is ypN0 (%, 95% CI)** | | | | |
| Overall | Carbo | No Carbo | OR | p-value |
| 48 (43-53) | 54 (48-61) | 41 (35-48) | 1.71 | 0.0029 |
| | Bev | No Bev | OR | p-value |
| | 52 (45-58) | 44 (38-51) | 1.29 | 0.0570 |

Sikov et al, J Clin Oncol 2015



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## CALGB 40603 - Endpoints

Presented SABCS 2013

Primary and secondary endpoints

- pCR Breast by factor (+/- carboplatin, bevacizumab)
- pCR Breast/Axilla by factor
- Treatment delivery, toxicities and adverse events

Presented SABCS 2014

- pCR rates in basal-like vs. non-basal-like
- Impact of select biomarkers on pCR

Being presented today

- EFS and OS by pathologic response, including RCB
- EFS and OS by factor - preplanned analyses, though study was underpowered to determine benefit

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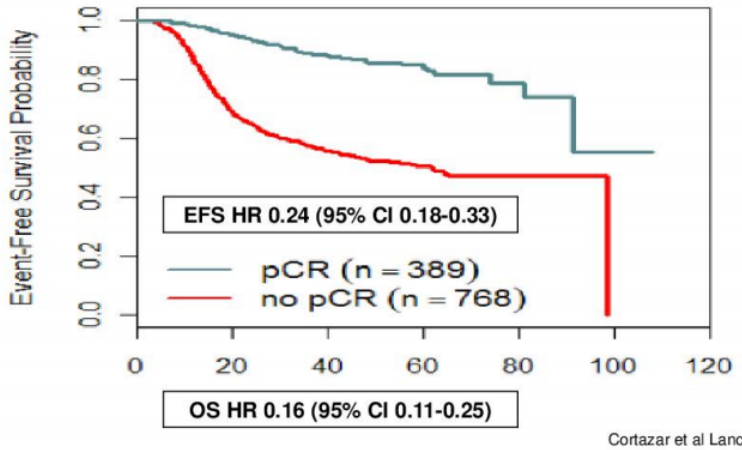
## Impact of pCR Breast/Axilla on EFS in TNBC

From FDA-requested meta-analysis




Cortazar et al Lancet 2014



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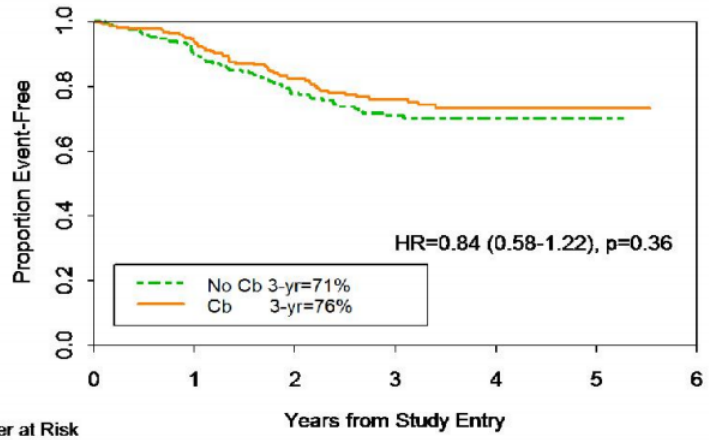
## CALGB 40603 – EFS for carboplatin vs. not




Number at Risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No Cb | 218 | 185 | 145 | 94 | 31 | 2 | 0 |
| Cb | 225 | 202 | 162 | 101 | 37 | 2 | 0 |

# How does this change clinical practice?

- Both of these trials were underpowered to determine DFS and OS.
- It remains unclear whether pCR is a reliable predictor of long-term DFS and OS.

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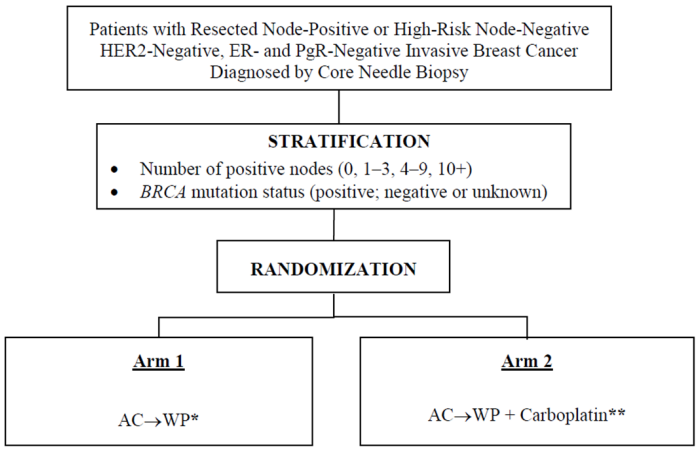
# NRG BR003

**Figure 1. NRG-BR003 SCHEMA**

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Thank you.
Questions?

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