Emerging Therapies for Triple Negative Breast Cancer

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Barriers to Improved Therapy

• Selection
• Tumor heterogeneity
• Resistance
Search of Clinical Trials.Gov Using Search Term “Triple Negative Breast Cancer” (accessed 10/25/12)

- Number of trials
  - 105 active trials (51 specific for TNBC), 15 phase III trials
- Selected adjuvant phase III trials
  - BEATRICE (N=2581) - adjuvant chemotherapy +/- bevacizumab
  - TITAN (N=1800) - AC → weekly paclitaxel x 12 vs. ixabepilone x 4
  - PACS08 (N=2500) - FEC100 x 3 → docetaxel x 3 vs. ixabepilone x 3
  - Spanish Breast Cancer Group (N=876) – AC-T +/- capecitabine
  - China (N=520) – FEC → docetaxel vs. doc/capecitabine → capecitabine + EC
  - China (N=600) – AC-T +/- capecitabine
  - China (N=500) – Docetaxel/carbo vs. EC → docetaxel
- Neoadjuvant trials
  - C40603 (400): Paclitaxel (+/- carbopatin) → AC (+/- bevacizumab)
  - Neo-TN (N=270) – AC→docetaxel/capecitabine vs. high-dose alkylators
  - GeparSixto (N=600) – AC-taxane +/- carboplatin
  - China (N=600) – TAC vs. TC
- Metastatic trials
  - China (N=232) – Gemcitabine/cisplatin vs. gem/paclitaxel
  - UK (N=400) – Carboplatin vs. docetaxel

- Met inhibitor: ARQ197, Onartuzumab (Metmab), foretinib
- PI3K and/or inhibitor: BKM 120, temsirolimus (+neratinib)
- HDAC inhibitors: entinostat, vorinosat
- Demethylating agents: azacitidine (+entinostat)
- PARP inhibitors: ABT-888, E7449
- Angiogenesis inhibitor: cediranib (+olaparib), ramicurumab, IMC18F1, foretenib, sorefenib
- Hsp90 Inhibitors: ganetespib
- Aurora kinase inhibitors: ENMD 2076
- EGF inhibitorsR: erlotinib (+metformin,), apatanib
- MEK inhibitors: GSK1120212
- Wnt inhibitor: LGK974
- CDK inhibitor: Dnacliclib, P276-00
- FMS-Kit inhibitor: PLX3397
- Apoptosis inducer: LCL161 (deactivating inhibitor of apoptosis proteins (IAPs),
- Immunotherapy: MUC1 vaccine, adoptive cellular therapy (DC-CIK)
- Cytotoxics: SN38 -NK012, AEZS-108 (LHRH-dox)
Epidemiology and Clinical Presentation
Triple-Negative Disease Compared with Other Phenotypes in the California Cancer Registry Study

*Bauer et al. Cancer 2007: 109; 721*

- Population-based study
  - 6370 with “triple-negative” disease compared with 44,704 “other” cases (12% of all cases)
- Findings – more likely to be associated with
  - Younger age (<40): OR 1.53
  - Non-Hispanic black (OR 1.77) or Hispanic (OR 1.23)
  - Higher grade (72% grade 3)
  - Poorer 5 year RFI irrespective of stage
    - TNBC: 76% (similar to 76% for HER2-Pos)
    - HR-Pos, HER2-Neg: 94%
Characteristics of Triple Negative Breast Cancer

- Usually poor histologic grade
- Presents with larger tumor size but less commonly associated with nodal metastases
- Commonly associated with BRCA mutations
- Early relapse (< 5 years of diagnosis)
- Relapse in visceral sites and CNS
- Usually basal genotype in gene expression profiling
Clinicopathologic Features, Patterns of Recurrence, and Survival Among Women With Triple-Negative Breast Cancer in the National Comprehensive Cancer Network

Nancy U. Lin, MD\(^1\); Ann Vanderplas, MS\(^2\); Melissa E. Hughes, MSc\(^3\); Richard L. Theriault, DO, MBA\(^4\); Stephen B. Edge, MD, FACS\(^5\); Yu-Ning Wong, MD, MSCE\(^6\); Douglas W. Blayney, MD\(^7\); Joyce C. Niland, PhD\(^2\); Eric P. Winer, MD\(^1\); and Jane C. Weeks, MD, MSc\(^1,3\)

<table>
<thead>
<tr>
<th>Site(^b)</th>
<th>Triple Negative vs HR+/HER2−</th>
<th>OR (95% CI)</th>
<th>(P)</th>
<th>HER2+ vs HR+/HER2−</th>
<th>OR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional vs other</td>
<td>1.32 (1.01-1.74)</td>
<td>.045</td>
<td></td>
<td>1.12 (0.83-1.51)</td>
<td>.45</td>
<td></td>
</tr>
<tr>
<td>Lung vs other</td>
<td>2.17 (1.47-3.21)</td>
<td>&lt;.001</td>
<td></td>
<td>1.73 (1.13-2.66)</td>
<td>.012</td>
<td></td>
</tr>
<tr>
<td>Brain vs other</td>
<td>3.50 (2.10-5.85)</td>
<td>&lt;.001</td>
<td></td>
<td>3.97 (2.35-6.72)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Bone vs other</td>
<td>0.26 (0.19-0.36)</td>
<td>&lt;.001</td>
<td></td>
<td>0.39 (0.29-0.54)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Liver vs other</td>
<td>1.09 (0.74-1.61)</td>
<td>.67</td>
<td></td>
<td>1.58 (1.07-2.33)</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

Lin et al. Cancer 2012
E1199: Hazard Rates for Recurrence for TNBC and Other Subtypes and Influence of Obesity

Recurrence hazard rate by cancer subtype and obesity

- TN, non-obese
- ER+/PR+, non-obese
- HER2+, non-obese
- TN, obese
- ER+/PR+, obese
- HER2+, obese
Genomics
Breast cancer intrinsic subtypes by gene expression profiling

Sorlie et al. PNAS 2003
Perou et al. Nature 2000
Intrinsic Subtype Frequencies by ER/PgR Cut-offs within TNBC Across 3 Adjuvant Trials: GIECAM 9906, MA5, MA12

ER/PR <1% (n=283)

- Basal: 73%
- HER2-enriched: 17%
- LumB: 5%
- LumA: 2%
- Normal: 3%

ER/PR <10% (n=331)

- Basal: 65%
- HER2-enriched: 19%
- LumB: 8%
- LumA: 5%
- Normal: 3%

Cheang et al. ASCO 2012, abstract 1008
The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Whole-genome analysis informs breast cancer response to aromatase inhibition

The clonal and mutational evolution spectrum of primary triple-negative breast cancers

Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*
# Summary of Genomics Studies

Nature, 2012

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Clinical Outcomes</th>
<th>Population</th>
<th>Profiling Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtis et al</td>
<td>1992</td>
<td>Yes</td>
<td>All types</td>
<td>Inherited variants (copy number [CNV] &amp; sequence changes [SNPs]), acquired somatic copy number aberrations (CNA), and gene transcription</td>
</tr>
<tr>
<td>Ellis et al</td>
<td>77</td>
<td>Yes</td>
<td>ER-pos</td>
<td>Whole genome sequencing (N=46) or exome sequencing (N=31)</td>
</tr>
<tr>
<td>Shah et al</td>
<td>104</td>
<td>No</td>
<td>TNBC</td>
<td>RNA-seq; mutations, copy number, and gene expression</td>
</tr>
<tr>
<td>Stephens et al</td>
<td>100</td>
<td>No</td>
<td>All types</td>
<td>Somatic mutations and copy number variants</td>
</tr>
<tr>
<td>Banerji et al</td>
<td>103</td>
<td>No</td>
<td>All types</td>
<td>Whole exome sequencing</td>
</tr>
<tr>
<td>TCGA</td>
<td>825</td>
<td>No</td>
<td>All types</td>
<td>DNA copy number, DNA methylation, exome sequencing, messenger RNA arrays, microRNA arrays, reverse-phase protein arrays</td>
</tr>
</tbody>
</table>
### Summary of Genomics Studies

**Nature, 2012**

<table>
<thead>
<tr>
<th>Author</th>
<th>Key Findings</th>
</tr>
</thead>
</table>
| Curtis et al    | • 10 subtypes identified—correlate with clinical outcomes  
|                 | • deletions in *PPR2A, MTAP, MAP2K4*                                                                                                                                                                      |
| Ellis et al     | • 18 significantly mutated genes  
|                 | • MAP3K1 (luminal A), GATA3 (response to AI)                                                                                                                                                            |
| Shah et al      | • Wide and continuous spectrum of genomic evolution  
|                 | • p53, PIK3CA, PTEN mutations clonally dominant                                                                                                                                                           |
| Stephens et al  | • Driver mutations found in at least 40 cancer genes and 73 different combinations                                                                                                                                                           |
| Banerji et al   | • PIK3CA, TP53, AKT1, GATA3, MAPK3K1, RUNX1 mutations  
|                 | • MAGI3-AKT3 fusion in TNBC with activation of AKT-kinase                                                                                                                                               |
| TCGA            | • P53, PIK3CA, GATA3 mutations in > 10%  
|                 | • specific mutations in luminal A (GATA3, PIK3CA, MAP3K1)  
|                 | • basal like tumor similar to serous ovarian cancer                                                                                                                                                     |
The Genomic and Transcriptomic Architecture of 2000 Breast Tumors Reveals Novel Subgroups

Breast Cancer: Subtypes Reflect Intertumor Genomic Complexity

Genome-wide Circos plots of somatic rearrangements

Vanderbilt TNBC Subtypes

- Analyzed gene expression profiles from 21 breast cancer data sets (587 cases of TNBC filtered by ER, PR, HER2 mRNA expression)
- Identified 6 TNBC subtypes by cluster analysis displaying unique gene expression and ontologies
- Identified breast cancer cell lines representative of each subtype

Vanderbilt TNBC Subtypes

**Basal-like 1 (BL1):** Cell-cycle, proliferation and DNA damage response genes

**Basal-like 2 (BL2):** Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)

**Immunomodulatory (IM):** Immune cell & cytokine signaling (overlap with medullary signature)

**Mesenchymal (M):** Cell motility and differentiation (Wnt, ALK, TGF-β)

**Mesenchymal stem-like (MSL):** Similar to M, but increased growth factors signaling, low proliferation, enrichment of stem cell genes

**Luminal androgen receptor (LAR):** Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)

Intrinsic subtype distribution among Vanderbilt TNBC subtypes

“Intrinsic” Subtypes

- Luminal B
- Luminal A
- Normal Breast-like
- HER2
- Basal-like
- Unclassified
Are the Subtypes Clinically Relevant? Maybe

- Basal → Cisplatin
- LAR → Bicalutamide
- Mesenchymal-like → Src inhibition
Targeting the androgen receptor (AR) in women with AR+ ER-/PR- MBC

ER/PR(-) (IHC ≤10%) LABC/MBC

Measurable/ non-measurable
No limit to prior therapy

AR testing
Central testing at MSKCC*

12% AR+

AR(+) IHC >10%

Bicalutamide 150mg daily

5/24 (21%) patients with clinical benefit

Response evaluation by RECIST
every 12 weeks (± 2 weeks)

*AR tested using primary antibody AR 441 (Dako; dilution: 1:300)

Gucalp et al. ASCO 2012, abstract 1000
Homologous Recombination Deficiency (HRD) Score

• Count of the number of LOH regions of specified size (>15 Mb and < whole chromosome) observed in a tumor genome.

• Elevated HRD score is associated with defects in HR pathway genes.

• Elevated HRD score may therefore predict response to therapeutics targeting this pathway, or DNA damage in general.
HRD Score Identifies BRCA Deficiency

Samples with BRCA1 or BRCA2 deficiency

Samples with intact BRCA1 and BRCA2

\( p = 9 \times 10^{-11} \)
HRD Score > 10 in Other Cancers

- Colon cell lines (n=42)
- Prostate tumors (n=23)
- Brain cell lines (n=19)
- Lung cell lines (n=93)
- Lung tumors (n=226)
- Esophagus cell lines (n=44)
- Esophagus tumors (n=51)
- Ovarian cell lines (n=41)
- Ovarian tumors (n=747)
- Breast cell lines (n=45)
- Breast tumors (n=138)

% Samples with HRD Score >10
BRCA1-Deficient Cells are Hypersensitive to Cisplatin

- BRCA1 deficient cells have defect in DNA DS repair
- BRCA1 deficient cells were more sensitive to cisplatin compared to other cell lines
- BRCA1 loss increases sensitivity to DNA damaging agents like cisplatin

HCC1937, BRCA-deficient cell line
MCF-7, hormone-sensitive
MDA-MB230, hormone-insensitive

pCR in BRCA1-Associated Breast Cancer Receiving Neoadjuvant Chemotherapy

- Registry of 6,903 patients
- 102 BRCA1 founder mutation and received neoadjuvant chemotherapy
- 24 (24%) has a pCR
  - CMF: 1 of 14 (7%)
  - AT (docetaxel): 2 of 25 (8%)
  - AC of FAC: 11 of 51 (22%)
  - Cisplatin: 10 of 12 (83%)

## Breast pCR Rates after Single Agent Cytotoxic Neoadjuvant Therapy in Triple Negative Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>No.</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garber et al. JCO 2009</td>
<td>Cisplatin 75 mg/m2 q 3 wks x 4</td>
<td>22</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Baselga JCO 2009</td>
<td>Ixabepilone 100 mg/m2 q3 wks x 4</td>
<td>42</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>Martin ASCO 2010</td>
<td>Doxorubicin 75 mg/m2 q 3wks x 4</td>
<td>20</td>
<td>2 (10%)</td>
</tr>
<tr>
<td></td>
<td>Docetaxel 100 mg/m2 q 3 wks x 4</td>
<td>28</td>
<td>8 (27%)</td>
</tr>
</tbody>
</table>
Proposed Phase II-III ECOG Neoadjuvant Trial in TNBC

Study Chair: Melinda Telli, MD

Candidate of Neoadjuvant Chemotherapy

Randomize/Stratify
- HRD Assay
- BRCA Mutation Status

Sequential AC-weekly paclitaxel
Carboplatin plus gemcitabine
Chemotherapy for Metastatic Disease
Has Survival Improved for Metastatic Breast Cancer?

<table>
<thead>
<tr>
<th>Study</th>
<th>No. With MBC(^a) (and % With De Novo Stage IV)</th>
<th>Time Period Examined</th>
<th>Source</th>
<th>Median Survival, Months</th>
<th>DFI or DRFI in Model</th>
<th>Survival Over Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chia 2007(^5)</td>
<td>2150 (21.4%)</td>
<td>1991-2001</td>
<td>Population-based registry</td>
<td>15-22(^b)</td>
<td>No</td>
<td>Improved</td>
</tr>
<tr>
<td>Dabakuyo 2008(^2)</td>
<td>1459 (12%)</td>
<td>1982-2005</td>
<td>Population-based registry</td>
<td>Relative survival reported</td>
<td>No</td>
<td>Improved</td>
</tr>
<tr>
<td>Dawood 2010(^2)</td>
<td>2091 (22.4%)</td>
<td>1991-2007</td>
<td>Single-institution database</td>
<td>28.6</td>
<td>No</td>
<td>Improved(^c)</td>
</tr>
<tr>
<td>Dawood 2008(^6)</td>
<td>15,438 (100%)</td>
<td>1988-2003</td>
<td>Population-based registry</td>
<td>23</td>
<td>No</td>
<td>Improved</td>
</tr>
<tr>
<td>Giordano 2004(^4)</td>
<td>834 (0%)</td>
<td>1974-1994</td>
<td>Single-institution database</td>
<td>21</td>
<td>Yes</td>
<td>Improved</td>
</tr>
<tr>
<td>Largillier 2008(^2)</td>
<td>1038 (0%)</td>
<td>1975-2005</td>
<td>Single-institution database</td>
<td>23.1</td>
<td>Yes</td>
<td>Not improved(^d)</td>
</tr>
<tr>
<td>Current study</td>
<td>3477 (0%)</td>
<td>1978-2010</td>
<td>Multiinstitution database</td>
<td>20</td>
<td>Yes</td>
<td>Not improved overall</td>
</tr>
</tbody>
</table>

Tevaarwerk et al. Cancer 2012
Survival in Patients With Metastatic Recurrent Breast Cancer After Adjuvant Chemotherapy

Little Evidence of Improvement Over the Past 30 Years

Amye J. Tevaarwerk, MD; Robert J. Gray, PhD; Bryan P. Schneider, MD; Mary Lou Smith, JD, MBA; Lynne L. Wagner, PhD; John H. Fetting, MD; Nancy Davidson, MD; Lori J. Goldstein, MD; Kathy D. Miller, MD; and Joseph A. Sparano, MD

- 11 ECOG adjuvant trials in operable breast cancer
- Accrued over 34 year period (1988-2002)
- All patients received adjuvant chemotherapy
- 13,785 patients, of whom 3447 (25%) had distant recurrence
- Median OS after recurrence was 20 months

DRFI improved over time

P<0.0001

Tevaarwerk et al. Cancer 2012
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DRFI $\leq$ 3 years
p=0.04

DRFI > 3 years
p=0.47

Tevaarwerk et al. Cancer 2012
Duration of Chemotherapy for Metastatic Breast Cancer: A Systemic Review & Metaanalysis of Randomized Clinical Trials

J Clin Oncol 2011: 29; 2144

<table>
<thead>
<tr>
<th>Study</th>
<th>HR + 95% CI</th>
<th>% Weight</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coates 1987</td>
<td>0.79</td>
<td>13</td>
<td>0.62 to 1.01</td>
<td></td>
</tr>
<tr>
<td>Harris 1990</td>
<td>1.06</td>
<td>2</td>
<td>0.57 to 1.97</td>
<td></td>
</tr>
<tr>
<td>Muss 1991</td>
<td>1.11</td>
<td>5</td>
<td>0.74 to 1.67</td>
<td></td>
</tr>
<tr>
<td>Ejlertsen 1993</td>
<td>0.78</td>
<td>17</td>
<td>0.63 to 0.97</td>
<td></td>
</tr>
<tr>
<td>Gregory 1997</td>
<td>0.81</td>
<td>5</td>
<td>0.54 to 1.21</td>
<td></td>
</tr>
<tr>
<td>Falkson 1998</td>
<td>0.94</td>
<td>8</td>
<td>0.69 to 1.28</td>
<td></td>
</tr>
<tr>
<td>Bastit 2000</td>
<td>0.96</td>
<td>18</td>
<td>0.78 to 1.18</td>
<td></td>
</tr>
<tr>
<td>Nooij 2003</td>
<td>1.03</td>
<td>17</td>
<td>0.83 to 1.27</td>
<td></td>
</tr>
<tr>
<td>Gennari 2006</td>
<td>1.12</td>
<td>4</td>
<td>0.73 to 1.72</td>
<td></td>
</tr>
<tr>
<td>Majordomo 2009</td>
<td>0.94</td>
<td>7</td>
<td>0.67 to 1.32</td>
<td></td>
</tr>
<tr>
<td>Alba 2010</td>
<td>0.86</td>
<td>5</td>
<td>0.58 to 1.27</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.91</td>
<td>100</td>
<td>0.84 to 0.99</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity, P = .69
Test for treatment effect, P = .046
Ixabepilone plus Capecitabine Associated with Improved Survival in Patients with Impaired Performance Status (KPS 70-80)

- Pooled analysis of 2 trials of ixabepilone/capecitabine vs. capecitabine
- Anthracycline and taxane pretreated disease
- 1955 patients, including 606 with KPS 70-80 and 1349 with KPS 90-100
- Combination therapy associated with improved outcomes if KPS 70-80
  - Overall survival: median 12.3 vs. 9.5 months (HR 0.75, p=0.0015)
  - PFS: median 4.6 vs. 3.1 months (HR 0.76, p=0.0021)
  - Objective response: 35% vs. 19%
- Safety profile similar comparable for combination in patients with impaired and intact performance status

Roche et al. BCRT 2011; 125: 755-765
## Ixabepilone/capecitabine vs. Capecitabine: Pooled Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>Ixa + Cape, %</th>
<th>Cape, %</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triple negative tumors</strong></td>
<td>31</td>
<td>15</td>
<td>.0005</td>
</tr>
<tr>
<td><strong>Taxane resistant tumors</strong></td>
<td>39</td>
<td>22</td>
<td>.0003</td>
</tr>
<tr>
<td><strong>Poor KPS (70-80)</strong></td>
<td>35</td>
<td>19</td>
<td>.0007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ixa + Cape, months</th>
<th>Cape, months</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triple negative tumors</strong></td>
<td>4.2</td>
<td>1.7</td>
<td>.0005</td>
</tr>
<tr>
<td><strong>Taxane resistant tumors</strong></td>
<td>5.1</td>
<td>3.7</td>
<td>.0003</td>
</tr>
<tr>
<td><strong>Poor KPS (70-80)</strong></td>
<td>4.6</td>
<td>3.1</td>
<td>.0007</td>
</tr>
</tbody>
</table>

Hortobagyi et al. BCRT 2010; 122; 409-418
Study Population:
- Stage IV TNBC
- ECOG PS 0–1
- Stable CNS metastases allowed
- 0-2 prior chemotherapies for mTNBC

Randomization stratified by prior chemo in the metastatic setting:
- 1\textsuperscript{st}-line (no prior therapy)
- 2\textsuperscript{nd}/3\textsuperscript{rd}-line (1-2 prior therapies)

Study Design: Multi-center, randomized open-label Phase III Trial

N = 519

Gem/Carbo (GC) (N= 258)
- Gemcitabine 1000 mg/m\textsuperscript{2} IV d 1, 8
- Carboplatin AUC2 IV d 1, 8
- 21-day cycles

Gem/Carbo + Iniparib (GCI) (N= 261)
- Gemcitabine 1000 mg/m\textsuperscript{2} IV d 1, 8
- Carboplatin AUC2 IV d 1, 8
- Iniparib - 5.6 mg/kg IV d 1,4,8,11
- 21-day cycles

Crossover allowed to GCI following Disease Progression* (central review)

96% (n=152) of progressing patients crossed over to GCI at time of primary analysis

*Prospective central radiology review of progression required prior to crossover

NCT00938652
### Efficacy Endpoints – ITT population

#### PFS

<table>
<thead>
<tr>
<th></th>
<th>GC (N=258)</th>
<th>GCI (N=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>4.1 (3.1, 4.6)</td>
<td>5.1 (4.2, 5.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.79 (0.65, 0.98)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.027</td>
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</tr>
</tbody>
</table>

Pre-specified alpha = 0.01

#### OS

<table>
<thead>
<tr>
<th></th>
<th>GC (N=258)</th>
<th>GCI (N=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>11.1 (9.2, 12.1)</td>
<td>11.8 (10.6, 12.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.88 (0.69, 1.12)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

Pre-specified alpha = 0.04

---

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>GC</th>
<th>GCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td>258</td>
<td>261</td>
</tr>
<tr>
<td>GCI</td>
<td>239</td>
<td>248</td>
</tr>
<tr>
<td>GC</td>
<td>214</td>
<td>230</td>
</tr>
<tr>
<td>GCI</td>
<td>181</td>
<td>204</td>
</tr>
<tr>
<td>GC</td>
<td>151</td>
<td>169</td>
</tr>
<tr>
<td>GCI</td>
<td>99</td>
<td>111</td>
</tr>
<tr>
<td>GC</td>
<td>38</td>
<td>52</td>
</tr>
<tr>
<td>GCI</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>GC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GCI</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**Months Since Study Entry**

**Probability of Progression Free Survival**

**Probability of Survival**

Pre-specified alpha = 0.04
## Overall Response Rate* – ITT Population

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>GC (N = 258)</th>
<th>GCI (N = 261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>4 (1.6)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>74 (29)</td>
<td>83 (32)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>89 (35)</td>
<td>99 (38)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>62 (24)</td>
<td>62 (24)</td>
</tr>
<tr>
<td>Inevaluable</td>
<td>29 (11)</td>
<td>12 (4.6)</td>
</tr>
<tr>
<td>SD &gt; 6 months</td>
<td>14 (5.4)</td>
<td>19 (7.3)</td>
</tr>
<tr>
<td>ORR, n (%) (95% CI)</td>
<td>78 (30) (25–36%)</td>
<td>88 (34) (28–40%)</td>
</tr>
<tr>
<td>Clinical Benefit Rate, n (%) [CR + PR + SD(&gt; 6 mos)]</td>
<td>92 (36)</td>
<td>107 (41)</td>
</tr>
</tbody>
</table>

* Independent central review, RECIST 1.1 + confirmation of response
Exploratory Analysis 1st-line ITT Population

1st-line = 57% of patients (297/519)

**PFS**
- GC: 4.6 mos (3.9, 5.7)
- GCI: 5.6 mos (4.2, 6.9)
- HR=0.88 (0.66, 1.13); 197 events

**OS**
- GC: 12.6 mos (11.9, NE)
- GCI: 12.4 mos (10.6, NE)
- HR=1.1 (0.78, 1.56); 129 events

No. at risk
- GC: 149 110 74 44 29 13 5 1 0
- GCI: 148 106 79 51 35 7 2 0 0
Exploratory Analysis 2\textsuperscript{nd} /3\textsuperscript{rd}-line ITT Population

2\textsuperscript{nd} / 3\textsuperscript{rd} -line = 43\% patients (222/519)

**PFS**

- GCI: 4.2 mos (3.8, 5.7)
- GC: 2.9 mos (1.9, 4.1)
- HR=0.67 (0.5, 0.92); 169 events

**OS**

- GCI: 10.8 mos (9.7, 13.1)
- GC: 8.1 mos (6.6, 10)
- HR=0.65 (0.46, 0.91); 132 events

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>GC</th>
<th>GCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>109</td>
<td>113</td>
</tr>
<tr>
<td>61</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>GC</th>
<th>GCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>109</td>
<td>113</td>
</tr>
<tr>
<td>96</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>70</td>
<td></td>
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<tr>
<td>29</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>
Neoadjuvant and Adjuvant Cytotoxic Therapy
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Non-TNBC</th>
<th>Single agent</th>
<th>FAC/FAC/AC</th>
<th>T-FAC/T-FEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent taxane</td>
<td>166</td>
<td>12%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>FAC/FAC/AC</td>
<td>308</td>
<td>20%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>T-FAC/T-FEC</td>
<td>588</td>
<td>28%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>5 year DFS</td>
<td>5 year OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-Pos, HER2-Neg</td>
<td>83%</td>
<td>91%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple Negative</td>
<td>69%</td>
<td>77%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-Positive *</td>
<td>78%</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No adjuvant trastuzumab
Increased Intensification and Total Dose of Cyclophosphamide in a Doxorubicin-Cyclophosphamide Regimen for the Treatment of Primary Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-22

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Courses*</th>
<th>Drug Dose (mg/m²)</th>
<th>Total Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Standard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>4</td>
<td>60</td>
<td>240</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4</td>
<td>600</td>
<td>2,400</td>
</tr>
<tr>
<td>2. Intensified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>4</td>
<td>60</td>
<td>240</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2</td>
<td>1,200</td>
<td>2,400</td>
</tr>
<tr>
<td>3. Intensified and increased total dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>4</td>
<td>60</td>
<td>240</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4</td>
<td>1,200</td>
<td>4,800</td>
</tr>
</tbody>
</table>

*Every 21 days.

J Clin Oncol 1997; 15: 1858-1869
Increased Intensification and Total Dose of Cyclophosphamide in a Doxorubicin-Cyclophosphamide Regimen for the Treatment of Primary Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-22
Further Evaluation of Intensified and Increased Total Dose of Cyclophosphamide for the Treatment of Primary Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-25

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Group* (cyclophosphamide dose)</th>
<th>No. of Courses †</th>
<th>Dose (mg/m²/wk)</th>
<th>Total Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-22</td>
<td>1. Standard</td>
<td>4</td>
<td>600</td>
<td>2,400</td>
</tr>
<tr>
<td></td>
<td>2. Intensified</td>
<td>2</td>
<td>1,200</td>
<td>2,400</td>
</tr>
<tr>
<td></td>
<td>3. Intensified and increased</td>
<td>4</td>
<td>1,200</td>
<td>4,800</td>
</tr>
<tr>
<td>B-25†</td>
<td>1. Standard or control (as group 3 of B-22)</td>
<td>4</td>
<td>1,200</td>
<td>4,800</td>
</tr>
<tr>
<td></td>
<td>2. Intensified</td>
<td>2</td>
<td>2,400</td>
<td>4,800</td>
</tr>
<tr>
<td></td>
<td>3. Intensified and increased</td>
<td>4</td>
<td>2,400</td>
<td>9,600</td>
</tr>
</tbody>
</table>
Further Evaluation of Intensified and Increased Total Dose of Cyclophosphamide for the Treatment of Primary Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-25

![Graphs showing disease-free survival and event rates](image)

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,506</td>
<td>Age* ≤ 49 years</td>
<td>11.1</td>
<td>10.0</td>
<td>8.4</td>
<td>.02</td>
</tr>
<tr>
<td>1,039</td>
<td>Age* ≥ 50 years</td>
<td>8.1</td>
<td>7.9</td>
<td>8.8</td>
<td>.67</td>
</tr>
<tr>
<td>910</td>
<td>Tumor ER 0-9 fmol</td>
<td>11.2</td>
<td>10.1</td>
<td>11.1</td>
<td>.66</td>
</tr>
<tr>
<td>561</td>
<td>Tumor ER 10-49 fmol</td>
<td>10.3</td>
<td>11.8</td>
<td>6.8</td>
<td>.004</td>
</tr>
<tr>
<td>272</td>
<td>Tumor ER 50-99 fmol</td>
<td>10.1</td>
<td>7.2</td>
<td>7.2</td>
<td>.29</td>
</tr>
<tr>
<td>385</td>
<td>Tumor ER ≥ 100 fmol</td>
<td>8.9</td>
<td>7.0</td>
<td>8.1</td>
<td>.55</td>
</tr>
<tr>
<td>417</td>
<td>Unknown</td>
<td>7.5</td>
<td>6.7</td>
<td>7.6</td>
<td>.84</td>
</tr>
</tbody>
</table>

J Clin Oncol 1999; 17: 3374-3388
Neo-tAnGo Treatment Schema

2 x 2 factorial design

Epirubicin 90mg/m²
Cyclophosphamide 600mg/m²
Q 21 days

Paclitaxel 175mg/m²
Gemcitabine 2000mg/m²
Q 14 days

ASCO 2009, abstract 522
Primary endpoint: pCR rates

- A 2-reader review of pathology reports, blinded to treatment, was undertaken (812 pts)
- pCR defined as
  - pCR in all breast tumours AND
  - absence of disease in AxLN in all breast tumours

<table>
<thead>
<tr>
<th>Component qn</th>
<th>EC &amp; T (n=404)</th>
<th>EC &amp; TG (n=408)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate (95% CI)</td>
<td>17% (14-21)</td>
<td>17% (14-21)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sequencing qn</th>
<th>EC→T±G (n=406)</th>
<th>T±G→EC (n=406)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate (95% CI)</td>
<td>15% (11-18)</td>
<td>20% (16-24)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adjustment for stratification variables does not alter results
(Age, ER status, Tumour size, Nodal status, Inflammatory / Locally advanced disease)
## pCR rate (95%CI), split by HER2 & ER

<table>
<thead>
<tr>
<th>Component qn</th>
<th>EC &amp; T</th>
<th>EC &amp; TG</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 neg (n=506)</td>
<td>14% (10-19)</td>
<td>16% (12-21)</td>
<td>0.44</td>
</tr>
<tr>
<td>HER2 pos (n=186)</td>
<td>21% (13-30)</td>
<td>22% (14-32)</td>
<td></td>
</tr>
<tr>
<td>ER neg (n=270)</td>
<td>32% (24-40)</td>
<td>31% (23-40)</td>
<td>0.96</td>
</tr>
<tr>
<td>ER pos (n=542)</td>
<td>10% (7-14)</td>
<td>11% (7-15)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sequencing qn</th>
<th>EC→T±G</th>
<th>T±G→EC</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 neg (n=506)</td>
<td>12% (9-17)</td>
<td>18% (13-23)</td>
<td>0.03</td>
</tr>
<tr>
<td>HER2 pos (n=186)</td>
<td>17% (10-26)</td>
<td>26% (17-36)</td>
<td></td>
</tr>
<tr>
<td>ER neg (n=270)</td>
<td>30% (22-38)</td>
<td>33% (25-42)</td>
<td>0.02</td>
</tr>
<tr>
<td>ER pos (n=542)</td>
<td>7% (4-10)</td>
<td>14% (10-19)</td>
<td></td>
</tr>
</tbody>
</table>

*p-value for pCR rates across randomised groups, adjusted for characteristic
tAnGo Treatment Schema

Epirubicin 90mg/m²
Cyclophosphamide 600mg/m²
Q 21/7

Paclitaxel 175mg/m² d1
Gemcitabine 1250mg/m² d1&8
Q 21/7, P-then-G seq admin d1
Disease-Free Survival (DFS)

No significant difference between treatments

HR = 1.0 (95% CI 0.8-1.2)

No.s at Risk:

ECT  1571  1545  1479  1392  1156  834  533  162  86
ECGT 1570  1550  1488  1385  1158  813  531  154  88
Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer

C  Patients with Hormone-Receptor–Positive Tumors

- Relapse-free Survival (%)
  - CMF or AC
  - Capecitabine

- Years
  - No. of Patients at Risk
    - CMF or AC: 218
    - Capecitabine: 209
  - No. of Events
    - CMF or AC: 21
    - Capecitabine: 26

D  Patients with Hormone-Receptor–Negative Tumors

- Relapse-free Survival (%)
  - CMF or AC
  - Capecitabine

- Years
  - No. of Patients at Risk
    - CMF or AC: 106
    - Capecitabine: 97
  - No. of Events
    - CMF or AC: 14
    - Capecitabine: 34

E  Patients with Hormone-Receptor–Positive Tumors

- Overall Survival (%)
  - CMF or AC
  - Capecitabine

- Years
  - No. of Patients at Risk
    - CMF or AC: 218
    - Capecitabine: 209
  - No. of Events
    - CMF or AC: 15
    - Capecitabine: 16

F  Patients with Hormone-Receptor–Negative Tumors

- Overall Survival (%)
  - CMF or AC
  - Capecitabine

- Years
  - No. of Patients at Risk
    - CMF or AC: 106
    - Capecitabine: 97
  - No. of Events
    - CMF or AC: 9
    - Capecitabine: 22
FinXX Study Design

Study Endpoints
Primary: RFS
Secondary: OS, safety

Eligibility:
- Invasive BC
- High risk of recurrence
  - pN+ or pN0 if T>2cm and PR-
- Center
- No. of +ve nodes
- HER2 status

D80n = 1500
D80
D80
D80

C600
E75
F600

X900
X900
X900
X900
X900
X900

Capecitabine dose: 900 mg/m² twice daily, days 1-14, every 21 days
Protocol amendment allowed adjuvant trastuzumab for HER2+ BC

FinXX: Recurrence-Free Survival

CEF = cyclophosphamide+epirubicin+5FU; HR = hazard ratio; T = docetaxel; X = capecitabine

Exploratory: Biological Subtype and RFS

CEF = cyclophosphamide+epirubicin+5FU; HR = hazard ratio; RFS = recurrence-free survival; T = docetaxel; X = capecitabine

CEF = cyclophosphamide+epirubicin+5FU; HR = hazard ratio; RFS = recurrence-free survival; T = docetaxel; X = capecitabine

Exploratory: Biological Subtype and RFS

CEF = cyclophosphamide + epirubicin + 5FU; HR = hazard ratio; RFS = recurrence-free survival; T = docetaxel; X = capecitabine

ER+ and/or PR+, HER2-

\[ P = 0.591 \]
\[ HR = 0.91 \]
\[ n = 1009 \]

ER- and PR-, HER2+

\[ P = 0.786 \]
\[ HR = 0.91 \]
\[ n = 122 \]

ER+ and/or PR+, HER2+

\[ P = 0.845 \]
\[ HR = 1.11 \]
\[ n = 163 \]

ER- and PR-, HER2-

\[ P = 0.0177 \]
\[ HR = 0.48 \]
\[ n = 202 \]

Biological Agents

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + chemo (n = 363)</th>
<th>Chemo alone (n = 258)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo)</td>
<td>8.1</td>
<td>5.4</td>
<td>0.649 (0.538-0.783)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>42</td>
<td>23</td>
<td>NR</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>18.9</td>
<td>17.5</td>
<td>0.959 (0.790-1.164)</td>
<td>.6732</td>
</tr>
<tr>
<td>1-yr OS rate</td>
<td>71</td>
<td>65</td>
<td>NR</td>
<td>.1140</td>
</tr>
</tbody>
</table>

- This meta-analysis represents the largest reported population of patients randomized to treatment for metastatic TNBC

O’Shaughnessy et al. SABCS 2010; abstract P6-12-03
E2100: Weekly paclitaxel alone or plus bevacizumab as first-line therapy for metastatic breast cancer – outcomes by ER/PR expression

### ER/PR Negative

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>P+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>17%</td>
<td>34%</td>
</tr>
<tr>
<td>Measurable (79%)</td>
<td>17%</td>
<td>41%</td>
</tr>
</tbody>
</table>

### ER and/or PR Positive

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>P+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>23%</td>
<td>37%</td>
</tr>
<tr>
<td>Measurable (46%)</td>
<td>30%</td>
<td>51%</td>
</tr>
</tbody>
</table>
## Randomized Trials of Cetuximab in Triple Negative Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Treatment Arms</th>
<th>ORR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey et al TBCRC001</td>
<td>102</td>
<td>Cetuximab ➔ Cet/carbo Carboplatin + cetuximab</td>
<td>6%</td>
<td>1.4 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin + cetuximab</td>
<td>17%</td>
<td>2.1 mo.</td>
</tr>
<tr>
<td>Baselga et al BALI-1</td>
<td>173</td>
<td>Cisplatin Cisplatin + cetuximab</td>
<td>10%</td>
<td>1.5 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20%</td>
<td>3.7 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p=0.03)</td>
</tr>
<tr>
<td>O’Shaughnessy et al</td>
<td>154</td>
<td>Irinotecan + carbo ➔ cetuximab Irinotecan + carbo + cetuximab</td>
<td>28%</td>
<td>4.5 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33%</td>
<td>4.7 mo.</td>
</tr>
</tbody>
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Baselga et al. *Proc SABCS* 2010; Abstract PD01-01  
O’Shaughnessy et al. Proc SABCS 2008; Abstract 308.
Conclusions: Presentation and Management of TNBC and Emerging Therapies

- **Presentation and course**
  - Young, black or Hispanic, larger tumors but node negative
  - Higher risk of early relapse, visceral sites

- **Biology**
  - Frequently associated with BRCA mutations, defective DNA repair
  - About 80% basal subtypes, other subtypes identified

- **Treatment**
  - Anthracyclines, alkylators, taxanes play important role
  - Alkylators – dose escalation not effective
  - Gemcitabine – no role as adjuvant therapy (with paclitaxel), but role in metastatic disease combined with carboplatin
  - Capecitabine – no role for adjuvant monotherapy, low single agent activity in metastatic disease
  - Platinums – role remains to be defined in adjuvant/neoadjuvant therapy
  - Biological agents – bevacizumab enhances response to chemotherapy a
  - Many candidate agents being tested