Systemic Therapy Progress 2007-2009

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National Cancer Institute
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Breast cancer subtypes

A

B

C

D

Luminal A
Normal-like
Luminal B
ErbB2
Basal
Wound Signature
70 gene "Poor"
Metastasis
Death

70 gene Good prognosis signature correlation

Fraction Metastasis-Free

Years after Surgery

P=6.94 x 10^{-6}
BIG 1-98: Letrozole and Tamoxifen for the Adjuvant Treatment of Breast Cancer

- Tamoxifen: n = 2459
- Letrozole: n = 2463
- Tamoxifen, Then Letrozole: n = 1548
- Letrozole, Then Tamoxifen: n = 1540

619 tamoxifen patents crossed over to letrozole after unblinding (mostly years 3-5)

**BIG 1-98: Letrozole monotherapy improves DFS compared with tamoxifen monotherapy**

Tamoxifen vs. letrozole (intent-to-treat) median follow-up 76 months

<table>
<thead>
<tr>
<th></th>
<th>Tam (n = 2459)</th>
<th>Let (n = 2463)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>565 events</td>
<td>509 events</td>
<td>0.88</td>
<td>.03</td>
</tr>
<tr>
<td>OS</td>
<td>343 events</td>
<td>303 events</td>
<td>0.87</td>
<td>.08</td>
</tr>
</tbody>
</table>

BIG 1-98: Sequential Treatment Letrozole and Tamoxifen

Sequential treatment: Median follow-up 71 months*

<table>
<thead>
<tr>
<th></th>
<th>Let (n=1546)</th>
<th>Let→Tam (n = 1540)</th>
<th>Tam→Let (n = 1548)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DFS</strong></td>
<td>88%</td>
<td>88%; HR 0.96</td>
<td>86%; HR 1.05</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>–</td>
<td>HR 0.90</td>
<td>HR 1.13</td>
</tr>
</tbody>
</table>

- Hazard ratios numerically lower with starting with Letrozole
- Differences have not reached significance for any endpoint.

**BIG 1-98: Breast Cancer Events for Letrozole Versus Sequential Strategies**

Breast Cancer Recurrence Events at 5 Years (%)

<table>
<thead>
<tr>
<th></th>
<th>Let</th>
<th>Let→Tam</th>
<th>Tam→Let</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>7.3%</td>
<td>7.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td><strong>Node Negative</strong></td>
<td>3.5%</td>
<td>3.9%</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>Node Positive</strong></td>
<td>12.4%</td>
<td>12.5%</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

BIG-1-98 Summary

- Initial letrozole indicated, especially in high-risk patients
- Patients can be switched to tamoxifen after 2 years, if needed
Trial ABCSG-12: Endocrine Therapy With or Without Zoledronic Acid

ABCSG-12: 1801 patients, stage I/II < 10 nodes, ER and/or PgR+
No adjuvant chemo

Bone substudy (N = 404)

Surgery + RT

Goserelin 3.6 mg q28d

− Tamoxifen 20 mg/d
− Tamoxifen 20 mg/d + Zoledronic acid 4 mg q6m
− Anastrozole 1 mg/d
− Anastrozole 1 mg/d + Zoledronic acid 4 mg q6m

1533 centrally reviewed BMD measurements, both trochanter and spine

Gnant, SABCS 2007, Abstract 26
ABCSPG -12 Disease Free Survival
Tamoxifen versus OFS anastrazole

Cancer and the Bone Microenvironment

- **PTHrP**, prostaglandins, interleukins, RANK-L
- IGF, PDGF, TGF-B

Cancer cells → osteoblasts, macrophages → osteoclasts

Bisphosphonates prevent bone resorption
Primary Endpoint: Disease-Free Survival
Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone

HR = 0.643 (0.46-0.91)
35% reduction in recurrences from adding zoledronic acid
S0307 Intergroup/NSABP: Phase III Comparison of 3 Bisphosphonates as Adjuvant Therapy for Breast Cancer
PIs: J Gralow, A Paterson

- **Patients**: 5,400 stage I, II, III breast cancer patients receiving “standard” systemic therapy
- **Treatment**: (3 years)
  - Clodronate 1,600 mg po qd
  - Ibandronate 50 mg po qd
  - Zoledronic acid 4 mg IV q month x 6, followed by q3 month
SOFT and TEXT in pre-menopausal breast cancer

Accrual 31 Jan 09: 2173 / 3000

Original target reached (n=2039) extension for 600 patients approved
Endocrine therapy 2009

- Aromatase inhibitors demonstrate a modest improvement in DFS
  - Start with an AI in postmenopausal women unless contraindications
- Not yet clear
  - Duration of endocrine treatment
  - Which AI?
  - Role of OFS
  - Tailored endocrine therapy
- Promising early data with zoledronate in improving DFS
NSABP B-30: Combinations of doxorubicin, cyclophosphamide and docetaxel for early-stage node-positive breast cancer

Stage I, II or IIIA BC
N0-1, M0
HR+ or HR-
No metastatic disease

Stratification:
# Nodes
Radiotherapy
Surgery
Tamoxifen

Randomize

N=5351

Primary aims:
- Concurrent vs. sequential: effect on DFS, OS
- Utility of cyclophosphamide

Swain, SABCS 2008, Abstract 75
NSABP B-30 Disease-Free Survival

<table>
<thead>
<tr>
<th>Years After Randomization</th>
<th>% Disease-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

% Disease-Free for AC→T and AT

- **AC→T**: 1,753 events, HR 0.83 vs. TAC, p-value 0.006
- **AT**: 1,753 events, HR 0.80 vs. AT, p-value 0.001
- **TAC**: 1,758 events, HR 0.96 vs. AT, p-value 0.58
% Surviving

<table>
<thead>
<tr>
<th>Years After Randomization</th>
<th>% Surviving</th>
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<tbody>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>90</td>
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<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>70</td>
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<tr>
<td></td>
<td>60</td>
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<td>50</td>
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<td>30</td>
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<td>10</td>
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<tr>
<td></td>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th># Events</th>
<th>HR vs. TAC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>1,753</td>
<td>240</td>
<td>0.86</td>
<td>0.086</td>
</tr>
<tr>
<td>AT</td>
<td>1,753</td>
<td>285</td>
<td>0.83</td>
<td>0.034</td>
</tr>
<tr>
<td>TAC</td>
<td>1,758</td>
<td>278</td>
<td>0.96</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**NSABP B-30 Overall Survival**
NSABP B-30
Amenorrhea Data (DFS) by Subgroups
(Adjusted by ER, LN, Tumor Size)
HR with 95% CI

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>0.60</td>
</tr>
<tr>
<td>AT</td>
<td>0.69</td>
</tr>
<tr>
<td>TAC</td>
<td>0.69</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>0.61</td>
</tr>
<tr>
<td>40-44</td>
<td>0.81</td>
</tr>
<tr>
<td>&gt;44 years</td>
<td>0.57</td>
</tr>
<tr>
<td>Hormonal Tx</td>
<td>0.64</td>
</tr>
<tr>
<td>No Hormonal Tx</td>
<td>0.70</td>
</tr>
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</table>
NSABP B-30: Summary

• AC→T superior to TAC and AT for DFS

• AC→T superior to AT, and marginally better than TAC for OS

• No treatment interactions between outcome and nodal, ER or menopausal status

• Significantly improved OS and DFS across all arms in patients with amenorrhea ≥ 6 months

Swain, SABCS 2008, Abstract 75
FinXX trial: Capecitabine added to a taxane-anthracycline

Capecitabine/docetaxel improves survival in MBC

Screen → Randomize

T (80 mg/m², d1 q3wx3) → CEF (600/75/600 mg/m², d1 q3w x3)

T (60 mg/m², d1 q3wx3) + X (900 mg/m² bid d1-14 q3wx3) → CE (600/75 mg/m², d1 q3w x3) + X (900 mg/m² bid d1-14 q3wx3)

Primary:
- RFS
Secondary:
- OS, safety

T: Docetaxel; X: Capecitabine

Joensuu et al. SABCS 2008, Abstract 82
FinXX Recurrence-free survival

$HR = 0.66 \ (95\% \ CI: \ 0.47 - 0.94)$

$P = 0.020$

Patients at risk:
- T + CEF: 745, 727, 563, 336, 94, 0
- TX + CEX: 751, 739, 577, 337, 98, 0
FinXX Overall survival

HR = 0.66 (95% CI: 0.40 – 1.07)

$P = 0.089$

Patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>T + CEF</td>
<td>745</td>
<td>738</td>
<td>589</td>
<td>362</td>
<td>105</td>
<td>0</td>
</tr>
<tr>
<td>TX + CEX</td>
<td>751</td>
<td>745</td>
<td>595</td>
<td>352</td>
<td>103</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary FinXX: Capecitabine added to a taxane-anthracycline

- TX/CEX improves RFS over T/CEF
  - Despite lower docetaxel dose
  - 34% risk reduction

- TX/CEX: higher rate of treatment discontinuation
  (25% over 6 cycles vs. 4% for T/CEF)

Joensuu et al. SABCS 2008, Abstract 82
Efficacy of BSI-201, a PARP Inhibitor, in Combination with Gemcitabine/Carboplatin in Triple Negative Metastatic Breast Cancer: Results of a Phase II Study

Joyce O’Shaughnessy,1,2,4 Cynthia Osborne,1,2,4 John Pippen,1,2,4, Debra Patt,3,4
Christine Rocha,5 Valeria Ossovskaya,5 Barry M. Sherman,5 Charles Bradley 5

1Baylor Sammons Cancer Center, 2Texas Oncology, Dallas, TX;
3Texas Oncology Cancer Center, Austin, Texas; 4US Oncology, Dallas, TX;
5BiPar Sciences, Inc., Brisbane, CA
DNA damage and repair

**Cause of damage:**
- Radio- and chemotherapy
- UV light
- Replication errors
- Alkylating agents
- X-rays

**Type of damage:**
- Double-strand breaks
- Bulky adducts
- Insertions
- Deletions
- O6-alkylguanine
- Single-strand breaks

**Repair Enzymes:**
- DNA-PK, ATM
- XP, polymerases
- MSH2, MLH1
- AGT
- PARP
- Recombinational repair (HR, NHEJ)
- Nucleotide-excision repair
- Mismatch repair
- Direct reversal (AGT)
- Base excision repair (BER)
PARP Inhibitor Mechanism of Action

1. PLATINUM CHEMOTHERAPY
   Inflicts DNA damage via adducts and DNA crosslinking

2. PARP1 UPREGULATION
   Base-excision repair of DNA damage

3. INHIBITION OF PARP1
   Disables DNA base-excision repair

4. REPLICATION FORK COLLAPSE
   Double strand DNA break

CELL SURVIVAL

CELL DEATH
Phase II TNBC Study: Treatment Schema

Metastatic TNBC
N = 120

RANDOMIZE

21-Day Cycle

bsi-201 (5.6 mg/kg, IV, d 1, 4, 8, 11)

Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

RESTAGING
Every 2 Cycles

* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression
Progression-Free Survival

BSI-201 + Gem/Carbo (n = 57)
Median PFS = 6.9 months

Gem/Carbo (n = 59)
Median PFS = 3.3 months

P < 0.0001
HR = 0.342 (95% CI, 0.200-0.584)
Conclusions

- PARP1 was upregulated in most evaluated TNBC patients
- BSI-201 + gemcitabine/carboplatin was well tolerated and did not potentiate chemotherapy-related toxicities
- BSI-201 improved patients’ clinical outcomes
  - Clinical Benefit Rate (62% vs. 21%; \( P = 0.0002 \))
  - ORR (48% vs. 16%; \( P = 0.002 \))
  - Median PFS (6.9 months vs. 3.3 months; \( P < 0.0001 \))
  - Median OS (9.2 months vs. 5.7 months; \( P = 0.0005 \))

Promising safety and efficacy data from this Phase II study justify further investigation of BSI-201 in a Phase III study
The EGFR/HER Family

ALTTO Study Design

HER2+ invasive breast cancer
Centrally-determined HER2+
Surgery, complete (neo) adjuvant anthracycline-based chemotherapy (approved list)
LVEF ≥ 50
1:1 RANDOMIZATION (N=8000)

* Trastuzumab for 1 yr
Lapatinib for 1 yr
Trastuzumab for 3 mo
Trastuzumab 3-weekly + lapatinib for 1 yr

6 wk break Lapatinib x 7.5 mo

* = weekly paclitaxel x 12w; as per investigator’s discretion

Pls. M Piccart, EA Perez
BETH Trial

Node-Positive or High Risk Node-Negative Breast Cancer HER2 Positive by Central Testing

STRATIFICATION
- Number of positive Nodes (0, 1-3 4+)
- Hormone Receptor Status (+/-)

Chemotherapy* q3wks x 6 + Trastuzumab x 1 yr

Chemotherapy* q3wks x 6 + Trastuzumab x 1 yr + Bevacizumab x 1 yr

*CIRG/NSABP/Investigators - Docetaxel/Carbo q3wk x 6
*Independent Investigators - Docetaxel q3wk x 3 -> FEC-90 x 3
(Targeted therapy held during FEC-90)
Thank you!!