NSABP Pivotal Breast Cancer Clinical Trials: Historical Perspective, Recent Results and Future Directions

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NSABP Breast Cancer Trials
Six Broad Research Themes

1. Optimizing local-regional management

2. Optimizing adjuvant hormonal therapy in early-stage BC

3. Identifying prognostic and predictive factors for outcome and response to therapy
NSABP Breast Cancer Trials
Six Broad Research Themes

4. Optimizing adjuvant chemotherapy in early-stage BC

5. Evaluating novel targeted therapies alone or in combination with standard adjuvant therapy

6. Evaluating neoadjuvant chemotherapy in order to individualize L-R therapy, outcome, and identify predictive markers of response
Optimizing Loco-Regional Management
Operable Breast Cancer

Clinically Node-Negative

Radical Mast.
Total Mast.
Total Mast. + XRT

Overall Survival

Patients
Deaths
RM 362 259
TMR 352 274
TM 365 259

Global p=0.68

Fisher B: NEJM, 2002
NSABP B-06

Operable Breast Cancer

Clinical Tumor Size ≤ 4 cm

Total Mast. + Ax. Diss.  
Lump. + Ax. Diss.  
Lump. + Ax. Diss. + XRT

Overall Survival

Global p=0.57

Patients  Deaths

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAST</td>
<td>589</td>
<td>299</td>
</tr>
<tr>
<td>LUMP</td>
<td>634</td>
<td>338</td>
</tr>
<tr>
<td>LUMP/XRT</td>
<td>628</td>
<td>317</td>
</tr>
</tbody>
</table>

Fisher B: NEJM, 2002
### NSABP B-06

**Effect of XRT on IBTR (20-Years)**

<table>
<thead>
<tr>
<th></th>
<th>IBTR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lump.</td>
</tr>
<tr>
<td>All Patients</td>
<td>39%</td>
</tr>
<tr>
<td>Node-Negative</td>
<td>36%</td>
</tr>
<tr>
<td>Node-Positive*</td>
<td>44%</td>
</tr>
</tbody>
</table>

*Received adjuvant chemotherapy*

Fisher B: NEJM, 2002
Effect of Systemic Therapy on IBTR
Ten-Year Cumulative Incidence
NSABP Node-Negative Trials

Mamounas, SSO 2003
Tamoxifen and XRT for Occult Breast Cancer

NSABP B-21
Tumors \( \leq 1 \text{ cm} \)
Treated with Lumpectomy

Breast XRT
Placebo

Breast XRT
Tamoxifen

Tamoxifen

8-Yr IBTR
9.3%
2.8%
16.5%

NSABP Trials in Patients with DCIS

**B-17:**
Lumpectomy $\pm$ XRT

**B-24:**
Lumpectomy + XRT
Placebo vs. TAM

**B-35:**
Lumpectomy + XRT
TAM vs. Anastrozole

**B-43:**
Lumpectomy + XRT $\pm$ Trastuzumab
NSABP B-17 and B-24
12-Yr Cumulative Incidence of IBTR

NSABP B-17 and B-24
12-Yr Cumulative Incidence of IBTR

Invasive IBTR

Non-Invasive IBTR

NSABP B-24
Effect of Tamoxifen by ER-Status

ER-Positive

ER-Negative

B

Breast Cancer–Free Survival (%)

10-year $P < .001$
Overall $P = .003$

Time Since Surgery (years)

Placebo group (n = 274): 84 events
Tamoxifen group (n = 284): 58 events

A

Breast Cancer–Free Survival (%)

10-year $P = .59$
Overall $P = .68$

Time Since Surgery (years)

Placebo group (n = 94): 25 events
Tamoxifen group (n = 80): 20 events

No. at risk
Placebo 274 262 237 208 180 156 144 51
Tamoxifen 284 270 254 236 218 198 169 69

Allred et al: J Clin Oncol, 2012
NSABP B-35
Anastrozole vs. Tamoxifen for DCIS

- Postmenopausal Patients
- ER or PR Positive DCIS
- Lumpectomy with free margins

Randomization

XRT

- Tamoxifen
- Anastrozole

Activated: 1/03
Completed: 3106 pts

Primary endpoint: BC event
Secondary endpoints: DFS, OS, IBTR, CBC, fractures, QOL
NSABP B-43: Trastuzumab + XRT for HER-2 + DCIS

Radiation Therapy

Hormonal Rx PRN

Activated: 11/08
Accrual: 1960/2000 pts

HER2+ DCIS Lx

Radiation Therapy + Trastuzumab

q3-week Trastuzumab cycles x 2

- Trastuzumab 8 mg/kg loading dose
- Trastuzumab 6 mg/kg final dose
NSABP B-32: Lymphatic Mapping and Sentinel Node Biopsy
Clinically Negative Axillary Nodes

**Stratification**
- Age
- Clinical Tumor Size
- Type of Surgery

**Randomization**

**GROUP 1**
Sentinel Node Biopsy

**GROUP 2**
Sentinel Node Biopsy*

*Axillary node dissection only if the SN is positive

**Accrual: 5611 (5/99-2/04)**
NSABP B-32

Disease-Free Survival for SLN Negative Pts

% Disease-Free

Years after Randomization

Trt  N  Events
SNR+AD  1975  455
SNR  2011  475  HR=1.02  p=0.72

Data as of Dec 31, 2012

Julian T et al: ASCO 2013
Overall Survival for SLN Negative Patients

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Deaths</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR+AD</td>
<td>1975</td>
<td>228</td>
<td>1.09</td>
<td>0.35</td>
</tr>
<tr>
<td>SNR</td>
<td>2011</td>
<td>252</td>
<td></td>
<td></td>
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</tbody>
</table>

Data as of Dec 31, 2012

Julian T et al: ASCO 2013
NSABP B-32: Local and Regional Recurrences as First Events

<table>
<thead>
<tr>
<th>Recurrence Type</th>
<th>SNR + ALND (n = 1975)</th>
<th>SNR (n = 2011)</th>
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</thead>
<tbody>
<tr>
<td>Local</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Axillary</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Extra-axillary</td>
<td>0.25</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Krag D et al: Lancet Oncol 2010
NSABP B-32: Significantly Lower Morbidity Without vs. With ALND

- Shoulder Abduction Deficit: SNR + ALND (n = 1975) had 19% and SNR (n = 2011) had 13%
- Arm Volume Difference > 5%: SNR + ALND (n = 1975) had 28% and SNR (n = 2011) had 17%
- Arm Numbness: SNR + ALND (n = 1975) had 31% and SNR (n = 2011) had 8%
- Arm Tingling: SNR + ALND (n = 1975) had 13% and SNR (n = 2011) had 7%

Significance: $P < 0.001$ for all comparisons

Ashikaga T. J Surg Oncol 2010
NSABP B-32: Occult Metastases

Clinically Negative Axillary Nodes

Randomization

GROUP 1
Sentinel Node Biopsy
Axillary Dissection

GROUP 2
Sentinel Node Biopsy*

*I Axillary node dissection only if the SN is positive

IHC and detailed pathologic examination of the SNs performed centrally and results were not disclosed

NSABP B-32: Effect of Occult Metastases on Survival in Node-Negative Breast Cancer

- 1608 were negative for occult metastases
  - 316 were positive for occult metastases

- 1660 were negative for occult metastases
  - 300 were positive for occult metastases

- 3268 were negative for occult metastases
  - 616 were positive for occult metastases
  - 430 had isolated tumor-cell clusters
  - 172 had micrometastases
  - 14 had macrometastases

15.9%
NSABP B-32: Disease-Free Survival by Status of Occult Metastases

Data as of Dec 31, 2012

Occult Mets Absent 3268 pts., 738 events
Occult Mets Present 616 pts., 170 events

HR=1.25  Adjusted p=0.01

Data as of Dec 31, 2012

Julian T et al: ASCO 2013
NSABP B-32: Overall Survival by Status of Occult Metastases

Data as of Dec 31, 2012

HR=1.26     Adjusted p=0.06

Occult Mets Absent  3268 pts., 378 deaths
Occult Mets Present 616 pts., 90 deaths

Data as of Dec 31, 2012

Julian T et al: ASCO 2013
NSABP B-32: Effect of Occult Metastases on the FNR of SNB

- Including the information from the additional pathologic assessment, the FNR of SLNB in B-32 was reduced to from 9.7% to **6.4%** (49 of 763 cases)
- This 35% reduction in FNR was statistically significant (**p< 0.001**)
- This approach would have resulted in an additional **16%** of patients undergoing completion axillary dissection
Operable Breast Cancer Treated with Lumpectomy

External Beam Whole Breast XRT

Partial Breast XRT

Accrual: 4211 (3/04-3/13)

Primary endpoint: IBTR rates between whole breast XRT and PBI
Optimizing Adjuvant Hormonal Therapy in Early-Stage BC
NSABP ER-Positive Trials

B-14:
Plac. vs TAM

B-20:
TAM vs MFT/CMFT

B-33:
TAM --> AI vs PLAC

B-42:
AI --> LET vs PLAC
NSABP Node (-), ER (+) Studies

**Results**

**B-14**
- **RFS**: 78% (HR: 0.58, 95% CI: 0.50-0.67)
- **OS**: 71% (HR: 0.80, 95% CI: 0.71-0.91)

**B-20**
- **RFS**: 89% (HR: 0.52, 95% CI: 0.39-0.68)
- **OS**: 87% (HR: 0.78, 95% CI: 0.60-1.01)
More Than Half of Breast Cancer Recurrences and Deaths Occur Post-Tamoxifen

NSABP B-33 Trial

- Stage I-II Breast Cancer
- Postmenopausal, ER or PgR-Positive
- Tamoxifen for 5 Years
- Disease-Free
- Randomization

- Exemestane
  - X 5 years
- Placebo
  - X 5 years

Opened: May 1, 2001
Target Accrual: 3000 pts
Accrual in 10/03: 1598 pts

Accrual stopped in 10/03 after disclosure of results from the NCIC MA.17 trial and the study was unblinded.

B-33: Relapse-Free Survival*

% Event-Free

RR = 0.44  p = 0.004

Group       N   Events
             Placebo  779  37
             Exemestane 783  17

*Eligible pts with follow-up

NSABP B-42: Trial Evaluating Adjuvant AI Duration

Postmenopausal, Disease-free, Stage I, II, or III invasive BC at diagnosis ER-positive and/or PgR-positive

- **Primary Endpoint**
  - Disease-free survival
- **Secondary Endpoints**
  - Overall survival
  - Time to treatment failure
  - Osteoporosis-related fractures

Accrual: 3966 pts
Identifying Prognostic and Predictive Factors for Outcome and Response to Therapy
21-Gene Recurrence Score Validation Study

16 Cancer and 5 Reference Genes

ESTROGEN
- ER
- PR
- Bcl2
- SCUBE2

PROLIFERATION
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

INVASION
- Stromolysin 3
- Cathepsin L2

BAG1

HER2
- GRB7
- HER2

CD68

5 REFERENCE GENES

NSABP B-14
668 Node (-), ER (+) Pts

P<0.00001

NSABP B-20: Chemotherapy Benefit By Recurrence Score Category

Low Risk (RS < 18)
- Tam + Chemo
- Tam
- $p = 0.76$

Interm. Risk (RS 18–30)
- Tam + Chemo
- Tam
- $p = 0.71$

High Risk (RS ≥ 31)
- Tam + Chemo
- Tam
- $p = 0.001$

Low Risk Patients (RS < 18)
- 96% vs 95%

Int Risk (RS 18–30)
- 89% vs 90%

High Risk (RS ≥ 31)
- 88% vs 60%

RS and Loco-Regional Failure

TAM-Treated Patients (B-14/B-20, n=895)

P<0.0001

Optimizing Adjuvant Chemotherapy in Early-Stage BC
NSABP: Node-Negative, ER-Negative Protocols

B-13: Surg. vs MF

B-19: MF vs CMF

B-23: CMF vs AC+/- TAM

B-36*: AC vs FEC+/- CEL

*ER-/ER+
NSABP Node (-), ER (-) Studies

Results

NSABP Node-Positive Trials Evaluating Adjuvant Taxanes

**B-28:**
AC vs. AC → T

**B-30:**
AC → T vs. AT X 4 vs. TAC X 4

**B-38:**
TAC X 6 vs. dd AC → T vs. dd AC → TG

n=3059
n=5351
n=4800
NSABP B-28: Effect of RS on Outcomes

**DFS**
- RS Low: 386 events, 109
- RS Intermediate: 364 events, 105
- RS High: 315 events, 121

**OS**
- RS Low: 386 events, 48
- RS Intermediate: 364 events, 105
- RS High: 315 events, 121

**DRFI**
- RS Low: 386 events, 85
- RS Intermediate: 364 events, 134
- RS High: 315 events, 140

**BCSS**
- RS Low: 386 events, 28
- RS Intermediate: 364 events, 87
- RS High: 315 events, 102
RS in B-28: Effect of RS on LRR

\[ \text{Cumulative Incidence Rate} \]

- RS Low: 12.3%
- RS Intermediate: 7.2%
- RS High: 3.3%

\[ \text{N} \]
- RS Low: 386
- RS Intermediate: 364
- RS High: 315

\[ \text{LRR Events} \]
- RS Low: 16
- RS Intermediate: 25
- RS High: 39

\[ P\text{-value} < .001 \]
NSABP B-37/IBCSG : CALOR Trial
Evaluation of Adjuvant Chemotherapy for LRR

Strata
- Prior Chemo-Tx
- ER+ and/or PR+
- Location ILRR

Randomize

Chemotherapy

No chemotherapy

Chemotherapy chosen by investigators
Recommendation: ≥ 2 drugs, 3 to 6 mos of therapy

Primary Endpoint: DFS
2° Endpoint: OS
All analyses: ITT

+ Endocrine therapy for ER+ and/or PR+
+ HER2-directed therapy (optional)

Aebi S. et al: SABCS 2012
CALOR Trial – DFS and OS

Number at Risk
Chemotherapy 85 72 66 57 45 23 12
No Chemotherapy 77 58 53 46 34 21 10

Number at Risk
Chemotherapy 85 80 76 65 51 29 14
No Chemotherapy 77 72 68 61 47 30 15
CALOR Trial: DFS and OS by ER Status

ER+

Univariate Interaction term: Treatment x ER: P = 0.044

DFS

OS

Aebi S. et al: SABCS 2012
Evaluating Novel Targeted Therapies Alone or in Combination with Standard Adjuvant Therapy
**U.S. Adjuvant Trastuzumab Trials**

**NSABP B-31**
- Operable Breast Cancer
  - HER-2 neu Positive
  - Path Node-Positive
- Randomization
  - AC x 4
  - Paclitaxel x 4
- Paclitaxel x 4 + Trastuzumab X 1 year
- TAM X 5 years for ER+ or PgR+, Optional for ≥ 50 yrs. With ER– and PgR–

**NCCTG 9831**
- HER 2/Neu Positive
  - NP/High-Risk NN
- AC x 4
- Paclitaxel weekly X 12
- Trastuzumab weekly X 52

Opened: 2/00

Opened: 5/00
B-31/N9831: Disease-Free Survival

% Event-Free Years from Randomization

AC → P
2018 680

AC → P+H
2028 473

AC → P
73.7%

AC → P+H
11.5%

HR_{adj}=0.60 (95% CI: 0.53-0.68)
P<0.0001

Romond et al: SABCS 2012
B-31/N9831 Overall Survival

AC → P

AC → P+H

\[ \text{HR}_{\text{adj}} = 0.63 \ (95\% \ CI \ 0.54-0.73) \]

\[ P < 0.0001 \]

Romond et al: SABCS 2012
Effect of Trastuzumab According to HER-2 Status by Central IHC and FISH

NSABP B-47

Node-Positive or High-Risk Node-Negative IBC HER2-Normal (n=3260)

Stratification
Age, # nodes, ER/PR Status, Adj. Chemo

Randomize

TC(6) or AC(4) → T(4)

TC(6) + H or AC(4) → T(4) + H

+ Hormonal Therapy for ER or PR positive

Accrual: 2976/3260
Evaluating Neoadjuvant Chemotherapy in Order to Individualize L-R Therapy, Outcome, and Identify Predictive Markers of Response
NSABP Neoadjuvant Trials

B-18: Adj. vs. Neoadj. AC

B-27: Neoadj. AC vs. AC → T

B-40/B-41: Neoadj. Chemo +/- Biologics
B-18: 16-Year Update

DFS

OS

Surviving (%)

Disease-Free (%)

Time After Random Assignment (years)

HR = 0.99  P = .90

HR = 0.93  P = .27

Trt  N  Deaths
Post-Op AC  751  315
Pre-Op AC  742  310

Post-Op AC  751  434
Pre-Op AC  742  410

B-18: Overall Survival by Age

<50yrs

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Ev</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post</td>
<td>388</td>
<td>167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>381</td>
<td>139</td>
<td>.81</td>
<td>0.06</td>
</tr>
</tbody>
</table>

≥50yrs

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Ev</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post</td>
<td>363</td>
<td>148</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>361</td>
<td>171</td>
<td>1.23</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Qualitative Treatment by Age Interaction

p=0.01

NSABP B-27 Schema

Operable Breast Cancer (2411 pts)

Randomization

AC x 4 Tam X 5 Yrs

Surgery

pCR: 13.7%

AC x 4 Tam X 5 Yrs

Docetaxel x 4

Surgery

pCR: 25.6%

AC x 4 Tam X 5 Yrs

Surgery

Docetaxel x 4
B-27: 8-Year Update

**DFS**

Disease-Free (%)

- Trt
  - Pre-Op AC: 784, 304
  - Pre-Op ACT: 783, 292
  - Pre-Op AC + Post Op T: 777, 286

HR = 0.93, 0.92  P = .29, .29

**RFS**

Relapse-Free (%)

- Trt
  - Pre-Op AC: 784, 254
  - Pre-Op ACT: 783, 220
  - Pre-Op AC + Post Op T: 777, 227

HR = 0.83, 0.87  P = .04, .14

**OS**

Surviving (%)

- Trt
  - Pre-Op AC: 784, 192
  - Pre-Op ACT: 783, 182
  - Pre-Op AC + Post Op T: 777, 189

HR = 0.93, 0.97  P = .46, .76

Effect of pCR on Overall Survival

NSABP B-18

NSABP B-27

SNB After NC
Multi-Center Studies: NSABP B-27 (n=428)

- Identification Rate: 85%
  - With blue dye: 78%
  - With isotope + blue dye: 88-89%
- False Negative Rate: 11%
  - With blue dye: 14%
  - With isotope + blue dye: 8.4%

Clinically Node (-): 12.4%
Clinically Node (+): 7.0%
P=0.51

Mamounas EP: J Clin Oncol, 2005
### Combined Analysis of B-18/B-27

**Independent Predictors of LRF**

<table>
<thead>
<tr>
<th>Lumpectomy + XRT (1890 Pts, 190 Events)</th>
<th>Mastectomy (1070 Pts, 128 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>Clinical Tumor Size</strong></td>
</tr>
<tr>
<td>(≥50 years vs. &lt;50 years)</td>
<td>(&gt;5 cm vs. ≤5 cm)</td>
</tr>
<tr>
<td><strong>Clinical Nodal Status</strong></td>
<td><strong>Clinical Nodal Status</strong></td>
</tr>
<tr>
<td>(+) vs. (-)</td>
<td>(+) vs. (-)</td>
</tr>
<tr>
<td><strong>Breast/Nodal Path Status</strong></td>
<td><strong>Breast/Nodal Path Status</strong></td>
</tr>
</tbody>
</table>

NRG 9353: Schema

Clinical T1-3N1M0 BC

Axillary Node (+) (FNA or Core Needle Biopsy)

Neoadjuvant Chemo (+ Anti-HER-2 Therapy for HER-2 neu + Pts)

Path Negative Axillary Nodes at Surgery (Axillary Dissection or SNB ± Axillary Dissection)

Randomization

No Regional Nodal XRT with Breast XRT if BCS and No Chest Wall XRT if Mastectomy

Regional Nodal XRT with Breast XRT if BCS and Chest Wall XRT if Mastectomy
NSABP
New Directions with Neoadjuvant Chemotherapy

• Use pCR as a correlate of chemotherapy efficacy to test new drugs and regimens (FDA approval pathway)

• Utilize NC based on BC subtypes with higher likelihood to achieve pCR such as triple-negative and HER-2 positive

• Utilize micro-array technology to identify genomic profiles associated with pCR to specific drugs or combinations
NSABP B-40

Operable Breast Cancer

Endpoints: pCR, cCR, DFS, OS, gene expression patterns

Accrual: 1205 pts
NSABP B-40: Effect of Bevacizumab on pCR

N=592

N=588

NSABP B-40: Effect of Bevacizumab on pCR by Hormone-Receptor Status

% pCR (Breast) OR = 1.70 p=0.008 OR = 1.17 p=0.44

N=349 N=352 N=243 N=236

Interaction p value = 0.166

NSABP B-41: Neoadjuvant Study with Lapatinib vs. Trastuzumab vs. Combo

Operable Breast Cancer HER-2 neu Positive

Endpoints: pCR, cardiac events, DFS, OS

Trastuzumab for a total of 1 year

Accrual: 529 pts
NSABP B-41: pCR Breast and Negative Nodes

- AC→WP+T (N=176): 49.4%
- AC→WP+L (N=171): 47.4%
- AC→WP+T+L (N=171): 60.2%

P-values:
- AC→WP+T vs AC→WP+L: P=0.056
- AC→WP+T vs AC→WP+L+L: P=0.78
Several of the pivotal NSABP breast cancer clinical trials have been instrumental in establishing/changing the standard of care for patients with early stage breast cancer:

- Loco-regional management
- Adjuvant hormonal therapy
- Adjuvant chemotherapy
- Adjuvant targeted therapy with biologics
- Neoadjuvant chemotherapy