Advances in Neoadjuvant and Adjuvant Therapy

Kathy S. Albain, MD, FACP
Director, Breast Clinical Research Program
Co-Director, Breast Oncology Center
Director of the Thoracic Oncology Program
Professor of Medicine, Stritch School of Medicine
Loyola University Chicago

Dr. Albain has financial relationships with commercial interests that produce healthcare-related products or services relevant to the content I am planning, developing, presenting with Agendia, Novartis, PUMA, Genentech/Roche, Genomic Health and Nanostring.
Advances in Adjuvant and Neoadjuvant Therapy from the 2013 San Antonio Breast Cancer Symposium

Kathy S. Albain, MD, FACP
Professor of Medicine
Dean’s Senior Scholar
Loyola University Chicago Stritch School of Medicine
Cardinal Bernardin Cancer Center
kalbain@lumc.edu

Thanks to colleagues who shared slides, and to Susan Peck, PhD for assistance in program development/production
SYSTEMIC ADJUVANT THERAPY

Individualized Decision Making
(Educational session)
An old trial matures (GIM-2)
BETH first report (bevacizumab)
HER2+ Symposium (overview)
Small HER2+ tumors (metaanalysis, APT)
ATLAS: 10 years of Tamoxifen
A Definite Net Benefit? Yes, on Average!

- Continued tamoxifen to 10 years
- Skip tamoxifen at 5 years

2.8% BCM Improvement
Relative Risk Reduction ~ 20%

Uterine Cancer
Incidence Risk / Mortality Risk

- 3.1% / 0.4%
- 1.6% / 0.2%

Net Additional Risk?
1.5% / 0.2%

Risk Of BC Mortality In ATLAS (Years 5-15)
Improved by a relative risk of 0.80
Net Average Benefit 2.8%

But in this study
47% of the patients were node positive
53% of the patients had T2 or T3 disease
No patient is average

Depending on a number of variables
(Nodes, tumor size, molecular panel, the baseline risk might be at least 3 times higher or lower.)

Davies et al. Lancet 2013; 381: 805–16
Variance in Expected Endometrial Cancer Risk

Risk Of Endometrial Mortality In ATLAS (Years 5-15)
Worsened by a relative risk of 1.5
Net Average Worsening 0.2 %

No patient is average

There are several strong risk factors
Age, BMI, Parity, Genetic, Diabetes, etc

A validated predictive model\(^1\) gives estimates
Baseline estimates ranging over > 20 fold

(1) Pfeiffer et al. PLoS Med 10 (7) 2013

Benefit of Additional 5 Years of Tamoxifen in ATLAS

Average Outcome in Atlas

Risk of Death Due to Toxicity

Pfeiffer et al. PLoS Med 10 (7) 2013
### EBCTCG 2011 Chemotherapy Meta-analysis
#### Summary: Breast Cancer Mortality

<table>
<thead>
<tr>
<th>Trial Grouping*</th>
<th>ER+ and ER poor</th>
<th>RR</th>
<th>SE</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF vs no chemo</td>
<td>0.76 (0.05)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAF vs no chemo</td>
<td>0.64 (0.09)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4AC/EC vs no chemo</td>
<td>0.78 (0.09)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4AC vs CMF</td>
<td>0.98 (0.05)</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAF/CEF vs 4AC</td>
<td>0.78 (0.06)</td>
<td>0.0004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthra then T vs shorter anthra</td>
<td>0.86 (0.04)</td>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthra + taxane vs expanded anthracycline alone</td>
<td>0.94 (0.06)</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unselected for HER2 status

Lancet Dec 6, 2011

---

### GIM-2 Study 2X2 Factorial Design (n=2091)

<table>
<thead>
<tr>
<th>ARM A</th>
<th>ARM C</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC x 4 cycles -&gt; T x 4 cycles q3 wks</td>
<td>EC x 4 cycles -&gt; T x 4 cycles q2 + Pegfilgrastim</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARM B</th>
<th>ARM D</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC x 4 cycles -&gt; T x 4 cycles q3 wks</td>
<td>FEC x 4 cycles -&gt; T x 4 cycles q2 + Pegfilgrastim</td>
</tr>
</tbody>
</table>

**q3 wks vs q2 wks**

*EC-epirubicin 90 mg/m² IV, cyclophosphamide 600 mg/m² IV q 2 or 3 weeks
*T- paclitaxel 175 mg/m² IV 3-hour infusion, every 2 or 3 weeks
*FEC - 5-fluorouracil 600 mg/m² IV, epirubicin 90 mg/m² IV, cyclophosphamide 600 mg/m² IV, q 2 or 3 wks.

Cognetti et al. PSABCS 2013
**BEATRICE:**
Randomized open-label multicenter phase III trial

- Resected triple-negative breast cancer (centrally confirmed)
- Invasive early breast cancer (N=2591)

**Investigator’s choice of standard CT (4–8 cycles)**
- Observation

**Investigator’s choice of BEV monotherapy (total duration 1 year)**
- BEV (5 mg/kg/wk equivalent)

**Chemotherapy options:**
- Taxane based (24 cycles)
- Anthracycline based (24 cycles)
- Anthracycline + taxane (3–4 cycles each)

**Stratification factors:**
- Axillary nodal status (0 vs 1–3 vs ≥4)
- Adjuvant chemotherapy (antracycline vs taxane vs antracycline + taxane)
- Hormone receptor status (negative vs low)
- Surgery (breast-conserving vs mastectomy)

*HER2-negative and hormone receptor negative or low (total Allred score of 2 or 3; intensity score 1, proportion score 1 or 2)*

Cameron et al., Lancet Oncol 2013
Primary endpoint: IDFS

- Median duration of follow-up, months: CT (N=1290) 31.5, CT + BEV (N=1301) 32.0
- Events, n (%): CT 205 (15.9), CT + BEV 188 (14.5)
- 3-year IDFS rate, % (95% CI): CT 62.7 (60.5–65.0), CT + BEV 83.7 (81.4–85.0)
- Stratified HR (95% CI): 0.87 (0.72–1.07)
- Log-rank p-value: 0.1810

*Intention-to-treat, not corrected for non-protocol therapy.*

---

**BETH Trial Design**

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

**Cohort 1**
- Non-anthracycline regimen

- TCH⇒H
  - 6 (T 75 / C AUC 6)
  - 1 year H (load 8mg/kg ⇒ H 6 mg/kg q3w)

**Cohort 2**
- Anthracycline regimen

- TH⇒FEC⇒H
  - 3 T 100 ⇒ 3 5Fu 600 / E 90 / C 600
  - 1 year H (load 8mg/kg ⇒ H 6 mg/kg q3w - not during FEC)

**Stratification**

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

**Arm 1A**
- TCH⇒H
- N=1617

**Arm 1B**
- TCH⇒HB
- N=1614

**Arm 2A**
- TH⇒FEC⇒H
- N=140

**Arm 2B**
- TH⇒FEC⇒HB
- N=138
BEATRICE and BETH

- First reports of phase III adjuvant trials solely in TNBC and HER2+ breast cancer
- Neither trial showed a benefit
- BEATRICE: DFS at 3 years better than projected in both arms; no significant benefit, HR 0.87 (95% CI 0.72-1.07), but many lower risk N0 patients (subset with significant benefit)
- Await OS analysis when mature, as well as ECOG adjuvant bevacizumab trial
- BETH: no role for bevacizumab in HER2+ BC
- Still lack robust predictive biomarker(s) to select patients for bevacizumab-based therapy
HER2+ Disease: Major Clinical Advances Over The Past 15 Years

Incremental Improvement in Pathologic Complete Remission (pCR) Rates in HER2-Positive Breast Cancer

von Minckwitz et al. Oncology, January 2012
The Interaction of HER2 and ER/PR Status

Opposing Forces?

ER/PR → HER2

Or Potential Collaborators?

ER/PR ↔ HER2

Pathologic CR Rates By Tumor Subtype

Cotezar et al, AACR 2013
Small HER2+ (T<2.0 cm N0) Tumors Meta-analysis

- Identify a group of patients that could be excluded from trials evaluating additional therapy
- Analyze disease-free survival (DFS) & overall survival (OS) of patients with small HER2-positive BC treated with chemotherapy & trastuzumab in the seminal randomized controlled trials

O'Sullivan et al. PSABCS 2013
## Trials Included In Small HER2+ Meta-Analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. HER2+</th>
<th>Timing of trastuzumab</th>
<th>Duration of trastuzumab therapy</th>
<th>Chemo regimen</th>
<th>Median follow up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>5,102</td>
<td>Sequential</td>
<td>1 -2 years</td>
<td>Any – 94% A; 26% A and T</td>
<td>8.0</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>3,505</td>
<td>Concurrent or sequential</td>
<td>1 year</td>
<td>AC→T AC→ w TH AC→ w T→H</td>
<td>8.7</td>
</tr>
<tr>
<td>NSABP B31</td>
<td>3,222</td>
<td>Concurrent</td>
<td>1 year</td>
<td>AC→T AC→TH</td>
<td>9.4</td>
</tr>
<tr>
<td>PACS 04</td>
<td>528</td>
<td>Sequential</td>
<td>1 year</td>
<td>FEC→H DE→ H</td>
<td>5.0</td>
</tr>
<tr>
<td>FinHER</td>
<td>232</td>
<td>Concurrent</td>
<td>9 weeks</td>
<td>D+/H→FEC V+/H→FEC</td>
<td>5.6</td>
</tr>
</tbody>
</table>

O’Sullivan et al. PSABCS 2013

### Meta-analysis DFS (95% CI) for Cohort 0 or 1 N+ ≤ 2cm; All received Trastuzumab

- **HR positive**
- **HR negative**
Adjuvant Paclitaxel and Trastuzumab (APT)  
(Dana Farber Consortium Trial)

**HER2+**  
ER+ or ER-  
Node Negative ≤ 3 cm

Enroll

- PACLITAXEL 80 mg/m² + TRASTUZUMAB 2 mg/kg x 12
- FOLLOWED BY 13 EVERY 3 WEEK DOSES OF TRASTUZUMAB (6 mg/kg)*

*Planned N=400  
*Tolaney et al. PSABCS 2013

*Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks

**Adjuvant Paclitaxel/Trastuzumab for Stage I Disease: Disease-Free Survival**

- 3-year DFS 95% Conf. Interval
- 98.7%  
- 97.6% to 99.8%
- Poisson p-value: <0.0001

Similar DFS for HR+/HR- and for T1a/b vs T1c  
Tolaney et al, SABCS 2013
Adverse Events

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Maximum Grade</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>81 (20)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (12)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>39 (10)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26 (6)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>35 (9)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28 (7)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>28 (7)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>23 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>28 (7)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Cardiac Toxicity

![Cardiac event chart]

<table>
<thead>
<tr>
<th>Cardiac event</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Congestive Heart Failure*</td>
<td>2</td>
<td>0.5 (0.1-18)</td>
</tr>
<tr>
<td>Asymptomatic Declines in LVEF**</td>
<td>13</td>
<td>3.2 (1.7-5.4)</td>
</tr>
</tbody>
</table>

*Both patients had normalization of LVEF after discontinuation of trastuzumab
**11 of 13 were able to resume trastuzumab therapy after an interruption of trastuzumab
APT Trial Results
Chemotherapy Related Amenorrhea (CRA)

- CRA rates at least 50% in most adjuvant trials
- APT trial premenopausal substudy: CRA at 15 months

\[ n = 77 \text{ enrolled} \]

Menses data at month 15
\[ n = 65 (84\%) \]
- 29 (42%) no endocrine therapy
- 3 (7%) aromatase inhibitor
- 33 (51%) tamoxifen

Amenorrheic?

- 46 (79%)
- 19 (21%)

No\hspace{1cm}Yes

Ruddy K et al. PSABCS 2013

Node-Negative, HER2+ Cohorts
Tolaney et al. versus O’Sullivan et al.

**Treatment:** Tolaney = concurrent paclitaxel/trastuzumab
O’Sullivan = 87% seq (HERA), 13% seq or conc (N9831)

**Median follow up:** Tolaney = 3.6 years; O’Sullivan = 8.0 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hormone Receptor Positive</th>
<th>Hormone Receptor Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tolaney</td>
<td>O’Sullivan</td>
</tr>
<tr>
<td>No. of Pts.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>272</td>
<td>299</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T ≤ 0.5 cm</td>
<td>26%</td>
<td>1%</td>
</tr>
<tr>
<td>T &gt; 0.5 cm &amp; ≤ 1 cm</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>T &gt; 1 cm &amp; ≤ 2 cm</td>
<td>36%</td>
<td>87%</td>
</tr>
<tr>
<td>T &gt; 2 cm &amp; ≤ 3 cm</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>3-year DFS</td>
<td>98.5%</td>
<td>95.5%</td>
</tr>
</tbody>
</table>

O’Sullivan et al. PSABCS 2013
ATEMPT Trial Schema

Stage I HER2+*
ER+ or ER- PS 0-1
Adequate organ fx
N=500

3
Trastuzumab-DM1 q3weeks X17
N=375

1
Paclitaxel + Trastuzumab x12→
Trastuzumab q3weeks x13
N=125

*HER2-positive defined as IHC 3+ or FISH>2.0; will be confirmed by central HER2 testing prior to study enrollment
Adjuvant endocrine therapy can be initiated after completion of 12 weeks of therapy
Adjuvant radiation therapy can be administered concurrently with study treatment.

SABCS 2012 Chemotherapy Insights
Early Stage Breast Cancer

NEOADJUVANT CHEMOTHERAPY

NeoALTTO (survival)
TRIO US B07 (lapatinib)
CALGB 40603 (carboplatin)
I-SPY 2 (veliparib, neratinib)
AVAILABLE RESULTS OF DUAL HER2 BLOCKADE PRIOR TO SABCS 2013

**Advanced Disease**
- ↑ PFS and OS (2 trials)
  - EGF104900 (N=296)
  - Cleopatra (N=808)
  - NeoSPHERE (N=417)
  - NeoALTTO (N=455)
  - Cherlob (N=119)
  - LPT 109096 (N=78)

**Neoadjuvant setting**
- ↑ ↑ pCR (3 trials)
  - ALTTO (N=8381)
  - APHINITY (N=4805)

**Non significant ↑ pCR** (1 trial)
- NSABP B-41 (N=529)

**Adjuvant setting**
- 2014
- 2016 ?

**STRATEGY A**

**STRATEGY B**

NeoALTTO Primary Endpoint pCR in the Breast

Does the incremental gain in pCR observed with dual HER2 blockade translate into improved EFS and OS?

Baselga J et al; SABCS 2010; Lancet 2012
NeoALTTO SABCS 2013 Survival Analysis

• Pre-specified analysis at 3 years after the last breast cancer surgery
• Median clinical follow-up is 3.77 years (95% CI 3.72-3.98)
• Median survival follow-up is 3.84 years (95% CI 3.77-3.98)
• Analyses of EFS and OS by arm are underpowered and are intended to be descriptive. Assuming a HR of 0.78 for dual blockade, NeoALTTO has a power of approximately 20%
• ALTTO will robustly answer this question

EVENT-FREE SURVIVAL (EFS) ANALYSIS

Tests for interaction according to HR status
Lap + Tras vs. Tras p=0.48
Lap vs. Tras p=0.56
NeoALTTO Conclusions

- At approximately 4-year median follow-up and in line with previous observations, dual HER2 blockade appears to provide superior benefit (pCR, EFS, OS) in patients with HER2-positive / HR-negative tumors. A follow-up analysis is planned in 2.5 years.

- This trial provides further evidence that HER2+/HR- and HER2+/HR+ subgroups are 2 different disease

### pCR Rates (Breast and LN) with Trastuzumab (H) and/or Lapatinib (L) plus Weekly Paclitaxel

<table>
<thead>
<tr>
<th>Study/neoadjuvant regimen</th>
<th>Total pCR Trastuzumab</th>
<th>Total pCR Lapatinib</th>
<th>Total pCR H+L</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoALTTO(^1) (6 weeks H and/or L → (WP) x 12 plus H and/or L) N=455</td>
<td>27.6%</td>
<td>20.0%</td>
<td>46.8%</td>
</tr>
<tr>
<td>NSABP B-41(^2) (ACx4→ WPx12 plus H and/or L) N=519</td>
<td>49.4%</td>
<td>47.4%</td>
<td>60.2%</td>
</tr>
<tr>
<td>CALGB 40601(^3) (WPx16 plus H and/or L) N=299</td>
<td>43%</td>
<td>29%</td>
<td>52%</td>
</tr>
<tr>
<td>CHER-LOB(^4) (WP x 12→FEC x 4 plus H and/or L throughout) N=121</td>
<td>25%</td>
<td>26.3%</td>
<td>46.7%</td>
</tr>
</tbody>
</table>

WP=weekly paclitaxel; AC=doxorubicin/cyclophosphamide; FEC=5FU, epirubicin, cyclophosphamide

Hurvitz et al. PSABC 2013
Invasive HER2+ breast cancer 
N=140 
Stratification: baseline tumor size (< 3 cm or > 3 cm) and HR status

Arm 1 
Trastuzumab (H) x 1 
TCH 6 cycles

Arm 2 
Lapatinib (L) x 21d 
TCL 6 cycles

Arm 3 
H x 1 plus L x 21d 
TCHL 6 cycles

Surgery

Core biopsy (3 frozen, 1 FFPE) pre-H and/or Ty & 14-21d after H &/or L Biomarker Studies

Additional tissue taken from tumor location

Trastuzumab (H) 8 mg/kg loading dose IV followed by 6 mg/kg Lapatinib (L) 1000 mg po daily Docetaxel (T) 75 mg/m2 Carboplatin (C) AUC 6 IV q3 week
First 20 patients on TCHL; then randomize 1:1:1

TRIO-US B07 HER2+ Neoadjuvant

TRIO-US B07 pCR (breast and LN) by Arm

- TCH (n=34) 47%
- TCL (n=36) 25%
- TCHL (n=58) 52%

p = .07
p = .02

Hurvitz et al. PSABCS 2013
GeparSixto Subtype Specific Targeted Therapy

N=595 centrally confirmed TNBC or Her2-positive breast cancer

PM

PMCb

Surgery

Paclitaxel 80 mg/m² q1w
Non-pegylated liposomal doxorubicin 20 mg/m² q1w
Carboplatin AUC 1.5* q1w
Lapatinib 750 mg/d 18 wks

*reduced from AUC 2 at amendment 1 after enrolment of 330 patients
von Minckwitz et al. Proc ASCO 2013

GeparSixto pCR Rates by Subtype

TNBC
HER2-positive

ypT0 ypN0

P<0.05
n.s.

37.9% 58.7%
36.3% 33.1%

PM N=157 PMCb N=158
PM N=136 PMCb N=137

von Minckwitz et al. Proc ASCO 2013
CALGB 40603: Randomized Phase II in TNBC

2 X 2 Randomization

- Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
- Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
- Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
- Paclitaxel 80 mg/m² wkly x 12 ddAC x 4

Surgery※
XRT※
No Adjuvant Systemic Treatment Planned※

Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
Bevacizumab 10 mg/kg q2wks x 9
Carboplatin AUC 6 q3wks x 4
Bevacizumab 10 mg/kg q2wks x 9
Carboplatin AUC 6 q3wks x 4

Sikov et al. PSABCS 2013

CALGB 40603 pCR Breast/Axilla (ypT0/is N0) +/- Carboplatin

41% (35-48%) 54% (48-61%)

Odds ratio: 1.71
p = 0.0029

Sikov et al. PSABCS 2013

N=212  N=221
**CALGB 40603 pCR Breast/Axilla (ypT0/is N0) +/- Bevacizumab**

Odds ratio: 1.36  
$p = 0.0570$

N=218  
N=215

---

**pCR Breast/Axilla (ypT0/is N0)**

<table>
<thead>
<tr>
<th></th>
<th>No Carbo (n=212)</th>
<th>Carbo (n=221)</th>
<th>Bev effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bev (n=218)</td>
<td>39%</td>
<td>49%</td>
<td>44%</td>
</tr>
<tr>
<td>Bev (n=215)</td>
<td>43%</td>
<td>60%</td>
<td>52%</td>
</tr>
</tbody>
</table>
| Carbo effect   | 41%              | 54%           | Carbo/Bev Interaction  
$p=0.43$ |

Sikov et al. PSABCS 2013
Accelerated FDA Drug Approval through Neoadjuvant Trials using pCR as Surrogate with Biomarker Partner


Pertuzumab Accelerated FDA Approval
(from Product Information Brochure)

- **Approved Regimens:** Pertuzumab every 3 weeks for 3 to 6 cycles as part of one of the following regimens:
  - 4 preoperative cycles with trastuzumab and docetaxel followed by 3 postoperative cycles of FEC as in NeoSphere
  - 3 preoperative cycles of FEC alone followed by 3 preoperative cycles of pertuzumab in combination with docetaxel and trastuzumab as in Tryphaena.
  - 6 preoperative cycles with TCH as in Tryphaena

- Following surgery, continue trastuzumab to complete 1 year of treatment. ...insufficient evidence to recommend continued use of pertuzumab for greater than 6 cycles...

- **Limitations of Use:** The safety ... as part of a doxorubicin-containing regimen has not been well established....

Slide courtesy J Sparano SABCS Dec 14, 2013
Summary of I-SPY2 Study Plan for Patients with Tumor Size at least 2.5 cm

- MRI Biopsy for 70 gene Blood Draw MUGA/ECHO CT/PET
- Consent #1 Screening Consent
- Consent #2 Treatment Consent

- Paclitaxel * (12 weekly cycles) → AC (4 cycles)
  - Paclitaxel* + Investigational Agent A (12 weekly cycles)
  - Paclitaxel* + Investigational Agent B (12 weekly cycles)

* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.

I-SPY 2 Trial Current Status
National Investigators Meeting SABCS 2013

- 18 sites accruing
- >975 patients screened; >550 randomized
- 6 drug companies
- 3 device companies
- 2 drug/biomarkers “graduated”
- New pipeline drugs

Funding: Public/Private Partnerships
## I-SPY 2 Biomarker Profile Drives Randomization Assignment to Experimental Arms

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>HER2+ HR+</th>
<th>HER2+ HR-</th>
<th>HER2- HR+</th>
<th>HER2- HR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib (HKI-272)</td>
<td>Pan ErbB Inhibitor</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ABT-888**</td>
<td>PARP Inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 386</td>
<td>Angiogenesis Inhibitor</td>
<td>Yes***</td>
<td>Yes***</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 479</td>
<td>IGFR Inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MK-2206</td>
<td>AKT Inhibitor</td>
<td>Yes***</td>
<td>Yes***</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pertuzumab + trastuzumab</td>
<td>Anti-HER2 doublet</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TDM-1 + pertuzumab****</td>
<td>Anti HER2 doublet</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Neratinib delivered in place of trastuzumab in HER2+  
**ABT-888 delivered in combination with both paclitaxel and carboplatin in HER2-negative  
***AMG 386 and MK-2206 delivered in combination with trastuzumab in HER2+  
****Taxol deleted during TDM-2, optional postoperatively

---

## The I-SPY 2 Trial Design is Novel

- **Adaptive randomization**
  - Uses a pre-specified and automated algorithm  
  - Randomization probabilities update as study proceeds  
    - By signature, and based on MRI and pCR results  
- Algorithm triggers the decision to graduate when 60-120 patients are enrolled
Randomization based on Performance of Regimens within Biomarker Subtypes/Signatures

- 8 biomarker subtypes based on HR, Her2, and MP Hi-1 and Hi-2
- Agent eligible for graduation in 10 marketable signatures

<table>
<thead>
<tr>
<th></th>
<th>MP Hi-1</th>
<th>MP Hi-2 (ultra Hi)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR+</td>
<td>HR-</td>
</tr>
<tr>
<td>HER2+</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>HER2-</td>
<td>27%</td>
<td>8%</td>
</tr>
</tbody>
</table>

MammaPrint (MP) Hi-1 and Hi-2 (ultra Hi) is based on the median cut point of MammaPrint for I-SPY 2 eligible patients.

This presentation is the intellectual property of I-SPY. Contact hrqo@medicine.ucsf.edu for permission to reprint and/or distribute.

I-SPY 2 Eligibility

Tumor size \( \geq \) 2.5 cm

Is Patient Eligible?
(based on stratifying biomarkers)

<table>
<thead>
<tr>
<th></th>
<th>MammaPrint Low</th>
<th>MammaPrint High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR+</td>
<td>HR-</td>
</tr>
<tr>
<td>HER2+</td>
<td>Eligible</td>
<td>Eligible</td>
</tr>
<tr>
<td>HER2-</td>
<td>Not Eligible*</td>
<td>Eligible</td>
</tr>
</tbody>
</table>

*May be eligible to participate in Low-Risk Registry Trial (supplement 1)

This presentation is the intellectual property of I-SPY. Contact hrqo@medicine.ucsf.edu for permission to reprint and/or distribute.
Threshold for Graduation

- 85% predicted likelihood of success in a randomized phase 3 neoadjuvant trial
  - N=300 patients
  - pCR is the endpoint

- A drug graduates; accrual to that arm stops
  - When the 85% success threshold is reached
    - Based on MRI response over time
    - pCR for patients who have had definitive surgery

- Results are recalculated when pathology is complete
  - pCR
  - For all patients in that arm and concurrent controls

---

I-SPY 2 First Two Drugs Graduate Late 2013

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>HER2+ HR+</th>
<th>HER2+ HR-</th>
<th>HER2- HR+</th>
<th>HER2- HR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib (HKI-272)</td>
<td>Pan ErbB Inhibitor</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ABT-888**</td>
<td>PARP Inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 386</td>
<td>Angiogenesis Inhibitor</td>
<td>Yes***</td>
<td>Yes***</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AMG 479</td>
<td>IGFR Inhibitor</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MK-2206</td>
<td>AKT Inhibitor</td>
<td>Yes***</td>
<td>Yes***</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pertuzumab + trastuzumab</td>
<td>Anti-HER2 doublet</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TDM-1 + pertuzumab****</td>
<td>Anti HER2 doublet</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Neratinib delivered in place of trastuzumab in HER2+
** ABT-888 delivered in combination with both paclitaxel and carboplatin in HER2-negative
*** AMG 386 and MK-2206 delivered in combination with trastuzumab in HER2+
**** Taxol deleted during TDM-2, optional postoperatively

This presentation is the intellectual property of I-SPY. Contact hmg@medicine.ucsf.edu for permission to reprint and/or distribute.

Albain KS. 11th Annual Best of San Antonio – Bench to Bedside 2014
Experimental Arm 1: Veliparib/Carboplatin

- Veliparib (ABT888) is a potent PARP inhibitor.
- For this analysis, patients were ADAPTIVELY randomized to receive:
  - Veliparib 50 mg po BID x 12 weeks/carboplatin AUC 6 q 3 weeks x 4
  - Weekly paclitaxel followed by AC
- Weekly paclitaxel followed by AC

- Enrollment open only to patients with HER2 negative disease
- Eligible to graduate in 3 signatures: all HER2-, HR+/HER2-, TN

---

Veliparib/Carboplatin GRADUATES in the Triple Negative Signature

<table>
<thead>
<tr>
<th>SIGNATURE</th>
<th>Estimated pCR Rate (95% probability interval)</th>
<th>Probability Veliparib + Carbo is Superior to Control</th>
<th>Predictive Probability of Success in Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HER2-</td>
<td>33% (22-43%) 22% (10-35%)</td>
<td>92%</td>
<td>55%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>14% (4-27%) 19% (6-35%)</td>
<td>28%</td>
<td>9%</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>52% (35-69%) 26% (11-40%)</td>
<td>99%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Carboplatin in Neoadjuvant Therapy of TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemo</th>
<th>Chemo + Carbo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 40603 (N=443)</td>
<td>41%</td>
<td>54%</td>
<td>P=0.003</td>
</tr>
<tr>
<td>GeparSixto (TNBC N=315)*</td>
<td>38%</td>
<td>59%</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>I-SPY 2</td>
<td>26%</td>
<td>52%</td>
<td>90% probability for superiority</td>
</tr>
</tbody>
</table>

* Paclitaxel 80 mg/m² + Liposomal Dox 20 mg/m² qw + Bev 15 mg/kg q3w +/- carboplatin AUC 1.5-2 qw x 18
48% of patients on carboplatin arms unable to complete planned treatment (G von Minckwitz ASCO 2013)

Improved pCR
Greater toxicity

Should Carboplatin Now be Standard for TNBC?

- Three trials show improved pCR in TNBC with addition of carboplatin: GeparSixto (with bevacizumab), CALGB 40603 (in part with bev) and I-SPY2 (with veliparib)
- Improvements in pCR could simply be the result of conversion of low volume residual disease to pCR and not ultimately impact on survival (low volume residual disease = RCB1, same outcome as pCR in Symmans et al)
- Follow-up insufficient for IDFS and OS outcomes in GeparSixto and C40603
- Biomarkers to predict platin-sensitive disease needed (eg, basal subtype)
- What about cisplatin?
### Neratinib (HER 1/2/4 irreversible TKI) Graduates in I-SPY 2*

- 115 patient cohort, of which 65 patients with HER2+ tumors randomized to paclitaxel + neratinib (no trastuzumab)
- Control paclitaxel + trastuzumab
- Each arm followed by AC x 4
- Higher pCR in neratinib arm for HER2+ER- and HER2+ER(any) subsets

* Puma Biotechnology News Release December 2014; abstract submitted

---

### I-SPY 2 Trial Neratinib Arm HER2(+) Subset (n = 65)*

<table>
<thead>
<tr>
<th>Biomarker Subset</th>
<th>Probability of neratinib superiority</th>
<th>Probability of success in 300-pt phase III trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2(+) ER(-)</td>
<td>94.7% (p = 0.053)</td>
<td>78.1%</td>
</tr>
<tr>
<td>HER2(+) ER(any)</td>
<td>95.3% (p = 0.047)</td>
<td>72.5%</td>
</tr>
</tbody>
</table>

* Puma Biotechnology News Release December 2014; abstract submitted
I-SPY 2: After Drug Graduates, What’s Next?

I-SPY 3

• FDA will accept results of a 300-patient validation study of drug/biomarker pair for accelerated approval (will NOT accept “pCRs live longer than non-pCRs” from general trial results)
• NOAH results could have been confirmed more rapidly in a trial like I-SPY 3
• I-SPY 3 an option for both veliparib and neratinib; another study will also open to dissect roles of carboplatin and veliparib
• Trials like these will be critical to bring novel pipeline agents to our patients more efficiently and effectively!