Neoadjuvant therapy for HER2-overexpressing and triple negative breast cancers

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OS RATES IN RELATION TO pCR RATES

MD Anderson experience (Kuerer et al, JCO 1999)

- 272 LABC pts treated by anthracycline-based NAC
- pCR= 12%

Relationship between OS and differential pCR irates in breast and axilla
pCR% depends on cellular type and on molecular type

N=22
10 pCR (45%)
61 genes signature

N=20
9 pCR (45%)
no signature identified

N=28
2 pCR

Sorlie et al. PNAS 2001
Rouzier et al. Clin Cancer Res 2005
I-SPY: Neoadjuvant Chemotherapy for Breast Cancer and Biomarker Analysis

I-SPY: study to identify biomarkers of response to neoadjuvant CT

<table>
<thead>
<tr>
<th>ER</th>
<th>PgR</th>
<th>HER2</th>
<th>Ki67 Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>P</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>.02</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>(n = 115)</td>
<td>(n = 95)</td>
<td>(n = 28)</td>
<td>(n = 50)</td>
</tr>
<tr>
<td>16%</td>
<td>12%</td>
<td>39%</td>
<td>10%</td>
</tr>
<tr>
<td>44%</td>
<td>43%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Int</td>
</tr>
<tr>
<td>(n = 88)</td>
<td>(n = 107)</td>
<td>(n = 137)</td>
<td>(n = 62)</td>
</tr>
<tr>
<td>12%</td>
<td>43%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>43%</td>
<td>10%</td>
<td>43%</td>
<td>43%</td>
</tr>
</tbody>
</table>

- Tumor basal (ER<sup>-</sup>/PgR<sup>-</sup>/HER2<sup>-</sup>), luminal B (ER<sup>+</sup>/PgR<sup>+</sup>/HER2<sup>+</sup>), and HER2 (ER<sup>-</sup>/PgR<sup>-</sup>/HER2<sup>+</sup>) associated with higher pCR rates

- Luminal A (ER<sup>+</sup>/PgR<sup>+</sup>/HER2<sup>-</sup>) showed low pCR (9%)

- ER<sup>-</sup>/HER2<sup>+</sup> tumors showed higher pCR (88%) compared to ER<sup>+</sup>/HER2<sup>+</sup> tumors (25%)

Neoadjuvant therapy for HER-2+ breast cancer

• The role of neoadjuvant trastuzumab
• Anti-HER-2 agent in neoadjuvant or adjuvant setting?
  • Other anti-HER-2 agents
    • Dual blockade
  • Which chemotherapy?
    • Biomarkers
Meta-analysis: Neoadjuvant anthracyclines/taxanes with or without trastuzumab

All cooperative neoadjuvant trials in Germany between 1998 and 2006 using anthra/taxanes (N=4913) plus GeparQuattro and TECHNO trials (N=1721) using trastuzumab for HER2+ tumors

Goals:

• Overall pCR rate
• Effects according to treatment:
  - Trastuzumab
  - Dose-Density
  - Duration
  - Concurrent versus sequential

Total 6634 pts

Von Minckwitz et al, SABCS 2008, Abstract 79
Meta-analysis: pCR rate based on treatment

In patients with HER2+ tumors:

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab (N=671)</th>
<th>No Trastuzumab (N=736)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate</td>
<td>41%</td>
<td>23%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Other characteristics associated with high rate of pCR (multivariate analysis):

- Younger age (P<.001)
- Ductal (P<.001)
- Histological grade 3 (p<.001)
- Positive HER2 (P<.001)
- Negative HR (P<.001)
- Tumor size (P<.001)
- Conventional dosage (vs. dd) (P<.001)

No significant difference between concurrent vs. sequential therapy (P=.329)

Von Minckwitz, SABCS 2008, Abstract 79
MD Anderson Neoadjuvant Trastuzumab randomised study: pathological complete response rate

Final results

<table>
<thead>
<tr>
<th>Pathological complete response (final results) (%)</th>
<th>P+FEC alone</th>
<th>P+FEC + T</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI (9–51%)</td>
<td>26.3%</td>
<td>65.2%</td>
</tr>
<tr>
<td>95% CI (43–84%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=19</td>
<td></td>
<td>n=23</td>
</tr>
<tr>
<td>p=0.016</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P, paclitaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; T, trastuzumab
NOAH: Phase III, Open-Label Trial of Neoadjuvant Trastuzumab

HER2-positive LABC (IHC 3+ or FISH+)
- n = 115
  - Trastuzumab + chemotherapy
  - Surgery followed by radiotherapy
  - Trastuzumab continued to week 52
  - 19 patients crossed over to trastuzumab

HER2-negative LABC (IHC 0/1+)
- n = 99
  - Chemotherapy

CT: AP x 3 followed by P x 4, followed by CMF x 3

HR+ pts received adjuvant tamoxifen

NOAH Trial: Trastuzumab Improves pCR Rates in HER2-Positive LABC

NOAH: Event-Free Survival (EFS) and OS in HER2-Positive Population (ITT)

EFS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Unadjusted HR</th>
<th>p value</th>
<th>Adjusted HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With trastuzumab</td>
<td>117</td>
<td>118</td>
<td>0.59</td>
<td>0.58</td>
<td>0.0126</td>
</tr>
</tbody>
</table>

| With trastuzumab | 36     | 51            | 0.013   |

<table>
<thead>
<tr>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>With trastuzumab</td>
</tr>
<tr>
<td>Without trastuzumab</td>
</tr>
</tbody>
</table>

OS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With trastuzumab</td>
<td>117</td>
<td>113</td>
<td>113</td>
</tr>
</tbody>
</table>

| Without trastuzumab | 118     | 113 | 110     | 104     | 93      | 81      | 57      | 34   |

GeparQuattro study design

- **EC**: Epirubicin 90 mg/m², Cyclophosphamide 600 mg/m², Radiotherapy
- **R**: n=445 ErbB2+
- **D**: Docetaxel (D) 100 mg/m² (Arm 1), 75 mg/m² (Arms 2 and 3)
- **DX**: n=144
- **D→X**: n=136
- **Op**: Capecitabine (X) 1800 mg/m², If ErbBr2+ trastuzumab 6 mg/kg q3wk 1 year, If endocrine responsive Tam/AIs

AI, aromatase inhibitor; C, cyclophosphamide; E, epirubicin; D, docetaxel; Op, surgery; R, randomisation; Tam, tamoxifen; X, capecitabine
When trastuzumab was added in patients with HER-2+ disease (n=445), the pCR rate rose significantly to 31.8% (p<0.001).

pCR, pathological complete response. Defined as grades 4 and 5 on a modified regression scale (grade 5, no microscopic evidence of residual viable tumour cells (invasive or non-invasive) in breast and nodes; grade 4, no residual tumour in breast tissue, but involved nodes)

Neoadjuvant therapy for HER-2+ breast cancer

• Anti-HER-2 agent in neoadjuvant or adjuvant setting?

NO DIRECT COMPARISON ADJUVANT VS. NEOADJUVANT

INDIRECT EVIDENCE (Higher pCR rates!!)
Neoadjuvant therapy for HER-2+ breast cancer

• The role of neoadjuvant trastuzumab

• Anti-HER-2 agent in neoadjuvant or adjuvant setting?
  • Other anti-HER-2 agents
    • Dual blockade
    • Which chemotherapy?
    • Biomarkers
GeparQUINTO
HER2-Positive Study Design

**Core Biopsy**

- **E:** Epirubicin 90 mg/m²
- **C:** Cyclophosphamide 600 mg/m²
- **Doc:** Docetaxel 100 mg/m²* + G-CSF

**Trastuzumab (T)**

- T: Trastuzumab 6 (8) mg/kg
- L: Lapatinib 1250-1000 mg/day orally

**Lapatinib (L)**

- Doc: Docetaxel 100 mg/m²* + G-CSF

**Surgery**

- T for 6 months
- T for 12 months

(Day 21-Day 35 after last infusion)

*G-CSF = granulocyte colony-stimulating factor; R = randomized

Pathologic Complete Response

Doc = docetaxel; EC = epirubicin + cyclophosphamide; L = lapatinib; pCR = pathologic complete response; T= trastuzumab

Pathologic Complete Response
Trastuzumab/Chemo vs Lapatinib/ Chemo

Inability to give planned doses of lapatinib ~35% in both studies

Courtesy E. Winer
Neoadjuvant therapy for HER-2+ breast cancer

• The role of neoadjuvant trastuzumab
• Anti-HER-2 agent in neoadjuvant or adjuvant setting?
  • Other anti-HER-2 agents
    • Dual blockade
  • Which chemotherapy?
    • Biomarkers
NeoALTTO Study Design

- Invasive operable HER2+ BC
- T >2 cm (inflammatory BC excluded)
- LVEF ≥50%

N = 450

Stratification
• T≤5 cm vs T>5 cm
• ER or PgR+ vs ER & PgR-
• N0-1 vs N≥2
• Conservative surgery or not

52 weeks of anti-HER2 therapy

IBC exclusion criteria

NeoALTTO: Overall Clinical Response
at 6 weeks (w/o chemo) and at surgery

At Week 6 (w/o chemo)

- L (lapatinib) N = 154
- T (trastuzumab) N = 149
- L+T N = 152

- L = 52.6%
- T = 30.2%
- L+T = 67.1%

P < .001

At surgery

- L (lapatinib) N = 154
- T (trastuzumab) N = 149
- L+T N = 152

- L = 74%
- T = 70.5%
- L+T = 80.3%

P = .49
P = .049


L = lapatinib; T = trastuzumab
NeoALTTO: pCR by HR Status

HR positive

- N = 80
- L: 16.2%
- T: 22.7%
- L+T: 41.6%
- P = .24

HR negative

- N = 75
- L: 33.8%
- T: 36.5%
- L+T: 61.3%
- P = .005

P = .03

P = .75

HR = hormone receptor; L = lapatinib; pCR = pathologic complete response; T = trastuzumab

NSABP B-41: Lapatinib in Neoadjuvant Treatment of HER2+ Breast Cancer

- **Primary endpoint:** pCR
- **Secondary endpoints:** pCR in N0, toxicity, cCR, RFS, OS

**Lapatinib in Neoadjuvant Treatment of HER2+ Breast Cancer (NSABP B-41): pCR**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>pCR*, %</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC → WP + T</td>
<td>176</td>
<td>49.4</td>
<td></td>
</tr>
<tr>
<td>AC → WP + L</td>
<td>171</td>
<td>47.4</td>
<td>.78</td>
</tr>
<tr>
<td>AC → WP + T + L</td>
<td>171</td>
<td>60.2</td>
<td>.056</td>
</tr>
</tbody>
</table>

*Absence of invasive tumor in resected breast specimen and histologically negative axillary nodes.
†Relative to AC → WP + T regimen.

- Similar results for dual blockade
- No significant difference between T and L

CherLob study plan

Guarneri, V et al. ASCO 2011 Abst 507
Breast & axillary pCR rate by HR

- Similar results for dual blockade
- Different results for T vs. L depending on HR status

T, trastuzumab; L, lapatinib; T+L, trastuzumab plus lapatinib

Guarneri, V et al. ASCO 2011 Abst 507
Neoadjuvant lapatinib and trastuzumab prior to and during chemotherapy: study design

Eligible patients had biopsy-proven ErbB2+ Stage II or III invasive breast cancer and were healthy.

- Lapatinib 1250 mg qd (arm1), 750 mg qd (1000 mg after FEC) (arm 3)
- Trastuzumab 2 mg/kg qwk (4 mg/kg loading dose)

2 weeks

12 weeks

12 weeks

C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; q, every; qd, once daily
Neoadjuvant lapatinib and trastuzumab prior to and during chemotherapy: pCR

- Similar results for dual blockade & T vs. L, with the “more commonly used” sequence A followed by Taxanes

CI, confidence interval; pCR, pathological complete response: defined as absence of all invasive cancer in breast and lymph nodes
Holmes et al. J Clin Oncol 2011;29(Suppl.):506
Patients with operable or locally advanced/inflammatory* HER2-positive breast cancer

Chemo-naïve and primary tumors >2 cm (N = 417)

TH (n = 107)

THP (n = 107)

HP (n = 107)

TP (n = 96)

docetaxel + trastuzumab

docetaxel + trastuzumab + pertuzumab

trastuzumab + pertuzumab
docetaxel + pertuzumab

BC, breast cancer; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel

*Locally advanced = T2-3, N2-3, M0 or T4a-c, any N, M0; operable = T2-3, N0-1, M0; inflammatory = T4d, any N, M0

NeoSphere: pCR Rates (ITT Population)

*Ci, confidence interval; H, trastuzumab; P, pertuzumab; pCR, pathologic complete response; T, docetaxel*

NeoSphere: pCR and HR Status

CI = confidence interval; H = trastuzumab; HR = hormone receptor; P = pertuzumab; pCR = pathologic complete response; T = docetaxel

TRYPHAENA Ph 2 STUDY

Primary endpoint: cardiac safety
2ary endpoints: Toxicity, pCR, RR, BCS rate, DFS, OS

Concomitant w/ anthracycline

HER2-positive EBC centrally confirmed (n = 225)

Cycles 1–3
A

B

C

FEC
Pertuzumab + trastuzumab
Docetaxel

Docetaxel

Docetaxel

FEC

Pertuzumab + trastuzumab

Pertuzumab + trastuzumab

Carboplatin

Surgery

Trastuzumab to complete 1 year

No anthracycline

• All 3 arms were experimental

• Study dosing q3w:
  − Pertuzumab: 840 mg loading dose, 420 mg maintenance
  − Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  − FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  − Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)
  − Carboplatin: AUC 6
## Cardiac events in the treatment period

<table>
<thead>
<tr>
<th></th>
<th>FEC+H+P x3 → T+H+P x3 n = 72</th>
<th>FEC x3 → T+H+P x3 n = 75</th>
<th>TCH+P x6 n = 76</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic LVSD (grade ≥3), n (%)</strong></td>
<td>-</td>
<td>2 (2.7)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td><strong>LVSD (all grades), n (%)</strong></td>
<td>5 (6.9)</td>
<td>3 (4.0)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td><strong>LVEF decline ≥10% points from baseline to &lt;50%, n (%)</strong></td>
<td>5 (6.9)</td>
<td>5 (6.7)</td>
<td>5 (6.6)</td>
</tr>
</tbody>
</table>

**Primary endpoint: cardiac safety**

NO SIGNIFICANT DIFFERENCES (safe to combine with A)

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab
Pathological complete response

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Lower pCR
BUT also
Shorter duration of TP

ypT0/is

FEC+H+P x3
→ T+H+P x3
(n = 73)

ypT0 ypN0

FEC x3
→ T+H+P x3
(n = 75)

TCH+P x6
(n = 77)

61.6 [49.5‒72.8]
50.7

57.3 [45.4‒68.7]
45.3

66.2 [54.6‒76.6]
51.9

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Pathological complete response by hormone receptor status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ER and PR negative</th>
<th>ER and/or PR positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC+H+P x3 → T+H+P x3</td>
<td>79.4 [62.1–91.3]</td>
<td>83.8 [68.0–93.8]</td>
</tr>
<tr>
<td>(n = 73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC x3 → T+H+P x3</td>
<td>65.0 [48.3–79.4]</td>
<td>50.0 [33.8–66.2]</td>
</tr>
<tr>
<td>(n = 75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCH+P x6</td>
<td>46.2 [30.1–62.8]</td>
<td>48.6 [31.4–66.0]</td>
</tr>
<tr>
<td>(n = 77)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; PR, progesterone receptor; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab
Neoadjuvant therapy for HER-2+ breast cancer

• The role of neoadjuvant trastuzumab
• Anti-HER-2 agent in neoadjuvant or adjuvant setting?
  • Other anti-HER-2 agents
    • Dual blockade
    • **Which chemotherapy?**
  • Biomarkers (example: p95)
If indicated, the majority of the Panel considered that the neoadjuvant chemotherapy regimen should include both a taxane and an anthracycline and (for HER2-positive disease) an anti-HER2 drug. Thus, the choice of a regimen for adjuvant or neoadjuvant chemotherapy might be made using similar criteria.

# Neoadjuvant trials in HER2-positive B.C. Comparison of pCR-rates

<table>
<thead>
<tr>
<th></th>
<th>Neo-Sphere</th>
<th>Neo-Altto</th>
<th>NOAH</th>
<th>GeparQuinto</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>417</td>
<td>455</td>
<td>235</td>
<td>640</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Neo-Sphere</th>
<th>Neo-Altto</th>
<th>NOAH</th>
<th>GeparQuinto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-H</td>
<td>Doc+H</td>
<td>Pw+H</td>
<td>APH-PH-CMFH</td>
<td>ECH-DocH</td>
</tr>
<tr>
<td>Duration</td>
<td>12</td>
<td>12+6</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>ypT₀/is ypN₀</td>
<td>21.5</td>
<td>27.6</td>
<td>38.0</td>
<td>45.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Neo-Sphere</th>
<th>Neo-Altto</th>
<th>NOAH</th>
<th>GeparQuinto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combo-H</td>
<td>Doc+HP</td>
<td>Pw+HL</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>ypT₀/is ypN₀</td>
<td>39.3</td>
<td>46.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

→ **Duration or use of anthracyclines add efficacy!**

Courtesy G. von Minckwitz, ASCO 2011
TBCRC 006: Neoadjuvant Lapatinib & Trastuzumab **Without CT**: Study Schema

- **Lapatinib (1000 mg/day)**
- **Trastuzumab (4 mg/kg load, 2 mg/kg q-weekly)**

_Weeks_

0 | 2 | 8 | 12
---|---|---|---
Lap (L) + Tras (T) + Endocrine Rx if ER+

- **pCR rates: 18/61 (30%)**
  - ER pos: 8/39 (21%)
  - ER neg: 10/22 (46%)
Neoadjuvant therapy for TNBC

• Which chemotherapy? Different than non-TNBC?
  • Platinum compounds
Heterogeneity of TNBC: Data from the UNC337, NKI1295, MDACC133 databases

Basal-like (39-54%)

Claudin-Low (25-39%)

HER2 enriched (7-14%)

Luminal B (4-7%)

Luminal A (4-5%)

Basal-like
- Up to 19% are ER+

Claudin-low
- Up to 33% are ER+

Pratt et al, Breast Cancer Res, 2010

Courtesy H. Rugo, ASCO 2011
# Pathologic Response to Anthracycline/Taxane by Subtype

## Overall pCR rate = 22% (82/369)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Residual disease</th>
<th>Pathologic complete response (pCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>47 (58%)</td>
<td>34 (42%)</td>
</tr>
<tr>
<td>Claudin-low</td>
<td>29 (67%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>31 (63%)</td>
<td>18 (37%)</td>
</tr>
<tr>
<td>LumA</td>
<td>110 (98%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>LumB</td>
<td>56 (85%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Normal-like</td>
<td>13 (76%)</td>
<td>4 (24%)</td>
</tr>
</tbody>
</table>

*Courtesy C. Perou*
German neoadjuvant meta-analysis: Association of pCR with treatment characteristics stratified by HR & HER2 status*

**Number of cycles (per 2 additional cycles)**

- HER2 - / HR +: 1.30 (1.02 to 1.65)
- HER2 + / HR +: 1.42 (1.04 to 1.94)
- HER2 + / HR -: 1.00 (0.71 to 1.41)
- HER2 - / HR -: 1.09 (0.88 to 1.35)

**Antracycline (high vs low dose)**

- HER2 - / HR +: 1.92 (1.14 to 3.21)
- HER2 + / HR +: 0.94 (0.31 to 2.85)
- HER2 + / HR -: 0.72 (0.20 to 2.58)
- HER2 - / HR -: 1.49 (0.98 to 2.27)

**Taxane (high vs low dose)**

- HER2 - / HR +: 1.52 (0.84 to 2.76)
- HER2 + / HR +: 2.23 (0.75 to 6.61)
- HER2 + / HR -: 1.87 (0.51 to 6.92)
- HER2 - / HR -: 1.73 (1.02 to 2.94)

*P = 0.28

**P = 0.55

# Platinum Sensitivity in BRCA1+/TNBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Regimen</th>
<th>N</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrski</td>
<td>BRCA1+</td>
<td>Nonplatinum</td>
<td>90</td>
<td>14 (16%)</td>
</tr>
<tr>
<td></td>
<td>BRCA1+</td>
<td>CDDP 75mg/m² x4</td>
<td>12</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Silver</td>
<td>Sporadic TNBC</td>
<td>CDDP 75mg/m² x4</td>
<td>26</td>
<td>4 (15%)</td>
</tr>
<tr>
<td></td>
<td>BRCA1+</td>
<td>“ “</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Ryan</td>
<td>Sporadic TNBC</td>
<td>CDDP 75mg/m2 x4 + bevacizumab 15 mg/kg q3wk x3</td>
<td>51</td>
<td>8 (16%)</td>
</tr>
</tbody>
</table>

- Neoadjuvant trials:
  - Retrospective trial suggests exquisite sensitivity in BRCA1+
  - Prospective trial in TNBC less clear

- Metastatic TNBC:
  - BALI-1 control arm cisplatin only – 10% RR

Neoadjuvant & Adjuvant Platinum CT regimens for TNBC

- Very small number of patients
- Response to Platinum is mostly in BRCA+ TNBC

Currently, there is no preferred standard form of chemotherapy for triple-negative breast cancer, and treatment should be selected as it is for other cancer subtypes.
Overall survival as a function of response to neoadjuvant PCT

Liedtke C et al, J Clin Oncol, 2008, 26:1275
I-SPY 2 TRIAL
Learn, Drop, Graduate, and Replace Agents Over Time

Randomize

HER 2 (+)
Paclitaxel + Trastuzumab
Paclitaxel + Trastuzumab* + New Agent A
Paclitaxel + Trastuzumab* + New Agent B
Paclitaxel + Trastuzumab* + New Agent C
Paclitaxel + New Agent F
Paclitaxel + New Agent GH
Paclitaxel + New Agent E

HER 2 (-)

Patient is on Study

AC → Surgery
Learn and adapt from each patient as we go along

Key
MRI
Residual Disease (Pathology)

AC → Surgery

*Investigational agent may be used in place

Courtesy H. Rugo, ASCO 2011
BACK-UP
RECENT GUIDANCE DOCUMENT FROM FDA

• Preoperative trials with pathologic complete response can, in selected circumstances, can be used for accelerated approval

• Trials evaluating clinically significant endpoints (DFS, OS) must be planning/pending

• Expectation is that triple negative breast cancer will be first area explored

• Guidance was well received by academic, advocate, and pharma communities

• Potentially major implications for drug development
pCR IS NOT YET AN ENDPOINT
FOR DRUG APPROVAL OR PRACTICE CHANGE

- Path CR is consistently associated with excellent outcome
- Improvements in path CR have not always associated with better DFS/OS
- Failure to achieve path CR is associated with variable outcome
- Will more effective anti-HER-2 therapy in neoadjuvant setting lead to long term benefit?

Courtesy E. Winer