Any News in EBC?

Ann H. Partridge, MD, MPH
Dana-Farber Cancer Institute
November 11, 2016
Yes!

- Age disparities vary by tumor subtype
- Genomic risk prediction data in young women
- Adjuvant systemic therapy considerations for young women
Young Women Are More Likely to Die in NCCN

‡Adjusted for race/ethnicity, insurance, employment, center, education, treatment, stage at diagnosis, grade, year of diagnosis, and detection method (symptomatic or Screen)

Partridge et al, JCO 2016
Breast Cancer Subtypes by Increasing Age

Keegan et al, BCR, 2012
Young Women Are More Likely to Die from Luminal A Tumors

Hazard Ratio

HER2 type
N = 1243
Luminal A
N = 7738
Luminal B
N = 5149
Triple Negative
N = 2886

‡Adjusted for race/ethnicity, insurance, employment, center, education, treatment, stage at diagnosis, grade, year of diagnosis, and detection method (symptomatic or screen)

Partridge et al, JCO 2016
# TAILORx RS ≤ 10

## Table 1. Characteristics of the Patients at Baseline, According to Recurrence-Score Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrence Score, 0–10 (N = 1620)</th>
<th>Recurrence Score, 11–25 (N = 6897)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of all enrolled patients</td>
<td>15.9</td>
<td>67.3</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)—yr</td>
<td>58 (50–64)</td>
<td>55 (48–62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean — yr</td>
<td>57±9</td>
<td>55±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤40 yr</td>
<td>58 (4)</td>
<td>319 (5)</td>
<td></td>
</tr>
<tr>
<td>41–50 yr</td>
<td>372 (23)</td>
<td>1964 (28)</td>
<td></td>
</tr>
<tr>
<td>51–60 yr</td>
<td>566 (35)</td>
<td>2503 (36)</td>
<td></td>
</tr>
<tr>
<td>61–70 yr</td>
<td>519 (32)</td>
<td>1811 (26)</td>
<td></td>
</tr>
<tr>
<td>&gt;70 yr</td>
<td>111 (7)</td>
<td>300 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Menopausal status — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1143/1623 (70)</td>
<td>4396/6873 (64)</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>480/1623 (30)</td>
<td>2477/6873 (36)</td>
<td></td>
</tr>
</tbody>
</table>

Sparano et al, NEJM, 2015
**Table 1. Characteristics of the Patients and Tumors at Baseline, According to Risk Group.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Clinical Risk</th>
<th>High Clinical Risk</th>
<th>All Patients (N=6693)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Genomic Risk</td>
<td>High Genomic Risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=2745)</td>
<td>(N=592)</td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>24 (0.9)</td>
<td>13 (2.2)</td>
<td>20 (1.3)</td>
</tr>
<tr>
<td>35 to &lt;50</td>
<td>774 (28.2)</td>
<td>165 (27.9)</td>
<td>514 (33.2)</td>
</tr>
<tr>
<td>50 to 70</td>
<td>1928 (70.2)</td>
<td>403 (68.1)</td>
<td>1000 (64.5)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>19 (0.7)</td>
<td>11 (1.9)</td>
<td>16 (1.0)</td>
</tr>
</tbody>
</table>

Cardoso et al, NEJM, 2016
HER2+: BCIRG-006 Disease Free Survival Final Analysis (10.3yrs)

- Trastuzumab-containing regimens remain superior at 10y follow-up
- No formal comparison of anthracycline containing vs not
  - G3/4 CHF: 21 vs 4
- Despite benefits of trastuzumab, 25% of patients still recur by 10 years – still room for improvement!

Slamon et al, SABCS 2015
ALTTO Trial: DFS Analysis
No added benefit from Lapatinib

MFU = 4.5 yrs

<table>
<thead>
<tr>
<th>Arm</th>
<th>No. patients</th>
<th>No. events</th>
<th>4yr DFS rate</th>
<th>Hazard ratio c.f. Tras*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap+Tras</td>
<td>2093</td>
<td>254</td>
<td>88%</td>
<td>0.84 (0.70, 1.02)</td>
<td>0.048 **</td>
</tr>
<tr>
<td>Tras-&gt;Lap</td>
<td>2091</td>
<td>284</td>
<td>87%</td>
<td>0.96 (0.80, 1.15)</td>
<td>0.610</td>
</tr>
<tr>
<td>Tras</td>
<td>2097</td>
<td>301</td>
<td>86%</td>
<td>*97.5% CI</td>
<td></td>
</tr>
</tbody>
</table>

**p-value ≤ 0.025 required for statistical significance

Piccart et al, NEJM 2016
Can We Improve in the Adjuvant HER2+ Setting? ExteNet: Study Design

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab & chemotherapy
- Lymph node −/+ or residual invasive disease after neoadjuvant therapy
- ER/PR + or −

25% of patients may still recur despite HER2 therapy. HERA did not support longer duration Trastuzumab.

Primary endpoint: invasive disease-free survival (iDFS) at 2 years (4 years after treatment completion)

Complicated study with many amendments
ExteNet Primary Endpoint: Invasive DFS (ITT)

- Disease-free survival (%)
- Months after randomization

P-value = 0.009
HR (95% CI) = 0.67 (0.50–0.91)

2.5% absolute difference
40% grade 3 diarrhea

Chan et al, ASCO 2015
APHINITY Schema

Central confirmation of HER2 status

N=4800

Population: Node + or high risk node negative

ACT or TCH

trastuzumab + pertuzumab* x 1 year

ACT or TCH

trastuzumab + placebo* x 1 year

*antibody therapy starts with taxane
HER2+: Standard Regimens for Moderate to High Risk Disease

- AC-TH
- TCH

Role of adjuvant pertuzumab?
  - Based on results in preoperative setting without any DFS or OS data
  - Included in NCCN guidelines as a footnote
  - Not ready for routine use outside of selected patients as neoadjuvant therapy

I don’t think regimen choice here should vary by age
Preoperative Use of Pertuzumab

• FDA accelerated approval to pertuzumab in neoadjuvant setting 11/2013 as THP -> FEC or AC, or TCHP

• Approval based on NEOSPERE data, metastatic survival advantage, and completion of adjuvant trial

• NEOSPERE underpowered to determine if PFS predicts DFS/OS; await APHINITY

• Preoperative THP best reserved for patients at high risk of recurrence who need downstaging (e.g. stage IIB and III disease)
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)*

Accrual N=406

Less than 20% had T1a
50% had T1c or T2

* Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks
** Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney et al, NEJM 2015
APT Disease-Free Survival

3-year DFS 95% Conf. Interval
98.7% 97.6% to 99.8%

Poisson p-value: <0.0001

10 events; only 2 distant and 4 local-regional recurrences
Majority had stable LVEF during treatment

3.2%: asymptomatic drop in LVEF requiring trastuzumab hold

0.5%: grade 3 LV dysfunction, all had risk factors for cardiac dysfunction

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### Table 3. Summary of LVEF at Protocol-Specified Time Points and Changes From Baseline Values

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>6 mo</th>
<th>1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF reduction from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>343 (84)</td>
<td>325 (80)</td>
<td>302 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%-15%</td>
<td>29 (7)</td>
<td>36 (9)</td>
<td>35 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥16%</td>
<td>2 (&lt;1)</td>
<td>5 (1)</td>
<td>7 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required, not evaluated(^a)</td>
<td>7 (1)</td>
<td>9 (2)</td>
<td>22 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not required(^b)</td>
<td>25 (6)</td>
<td>31 (8)</td>
<td>40 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF level, %</td>
<td></td>
<td>65 (50-81)</td>
<td>64 (45-81)</td>
<td>64 (45-83)</td>
<td>64 (41-90)</td>
</tr>
</tbody>
</table>

Abbreviation: LVEF, left ventricular ejection fraction.

\(^a\) Patients for whom cardiac evaluation was required but reported as not completed were counted as **required but not evaluated**.

\(^b\) Cardiac evaluations were not required for patients who went off protocol therapy due to noncardiac toxic effects. Assessments after the off-treatment visit for patients who went off treatment before completing 1-year protocol-specified therapy due to noncardiac toxic effects were counted as **not required**.
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.

PI: Sara Tolaney, MD, MPH
A Sequential Antracycline-Taxane Combination is the Standard of Care for Moderate-Risk TNBC

**NSABP-B30**

AC-T x 8 vs AT x 4 vs TAC x 6

**POSSIBLE REGIMENS**

- AC-paclitaxel (dose dense)
- AC-weekly paclitaxel
- AC-docetaxel (every 3 weeks)
- FEC-docetaxel

Is Anthracycline Necessary for TNBC?
ABC Trials (TC/TAC, B-46I, B-49)

Node+ or High Risk Node-Negative

ARM 1 (TaxAC Options)
A TAC q 3 wk
B AC q 3 wk
C AC q 2 wk
D AC q 2 wk

Arm 1 Options Per Study
• USOR 06-090 - 1A only
• NSABP B-46I/USOR 07132 - 1A only
• NSABP B-49 - investigator choice 1A-1D

Endocrine therapy for ER+ or PgR+ patients for minimum of 5 years

Designed to prove non-inferiority of non-anthracycline arm

Blum et al, ASCO 2016
ABC Trials: Invasive Disease Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>IDFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>2094</td>
<td>220</td>
<td>88.2%</td>
</tr>
<tr>
<td>TaxAC</td>
<td>2062</td>
<td>179</td>
<td>90.7%</td>
</tr>
</tbody>
</table>

Δ=2.5%

HR=1.23, 95% CI (1.01-1.50) P=0.04

Observe HR on initial 334 events - 1.202

Exceeded pre-specified threshold for futility (> 1.18) → not non-inferior

Blum et al, ASCO 2016
### ABC Trials: IDFS by Hormone and Nodal Status
#### Exploratory Analysis

<table>
<thead>
<tr>
<th></th>
<th>Pts TaxAC</th>
<th>Events TaxAC</th>
<th>4 yr IDFS 4 yr IDFS Delta</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>TC</td>
<td>TaxAC TC</td>
<td></td>
</tr>
<tr>
<td>ER/PgR (-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-</td>
<td>459</td>
<td>488</td>
<td>37 52</td>
<td>89.5 87.0</td>
</tr>
<tr>
<td>1-3 N+</td>
<td>153</td>
<td>119</td>
<td>21 28</td>
<td>85.5 74.6</td>
</tr>
<tr>
<td>4+ N+</td>
<td>42</td>
<td>40</td>
<td>11 16</td>
<td>71.8 60.8</td>
</tr>
<tr>
<td>ER or PgR (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-</td>
<td>358</td>
<td>378</td>
<td>29 22</td>
<td>91.5 94.2</td>
</tr>
<tr>
<td>1-3 N+</td>
<td>771</td>
<td>789</td>
<td>46 53</td>
<td>94.3 92.3</td>
</tr>
<tr>
<td>4+ N+</td>
<td>279</td>
<td>280</td>
<td>35 49</td>
<td>87.2 81.4</td>
</tr>
</tbody>
</table>

Suggests all groups aside from ER+ N0 benefit from A-containing regimens, especially ER- N+.

Blum et al, ASCO 2016
Adjuvant Capecitabine?

CREATE-X: Trial Design

Eligibility: HER2- with residual disease after A- and T-containing NAC

Pathology Non-pCR node + (n=900)

Control: Standard therapy

Standard therapy + Capecitabine

Dose: 2,500 mg/m²/day, D1-14, x 8 cycles (24 wks)

Stratification factors:
ER, Age, NAC, ypN, 5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

DFS

OS

DFS

OS

HR (95%CI) 0.70 (0.53-0.93)
One-sided p=0.00524 < 0.00671

82.8%
74.0%

94.0%
89.2%

HR (95%CI) 0.60 (0.40-0.92)
One-sided p<0.01

Toi et al, SABCS 2015
Randomized Trials of Preoperative Platinum Chemotherapy for TNBC

**GeparSixto Schema**

- N=315 centrally confirmed TNBC
- PM
- PMCb
- Paclitaxel 80 mg/m² q1w
- Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w
- Carboplatin AUC 1.5-2
- Bevacizumab 15 mg/kg

**GerparSixto pCR: platinum vs not**

- N=157
- N=158
- OR 1.94 [1.24 – 3.04]
- P=0.005

**CALGB 40603 Schema**

- 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 q3wks x 4 ddAC x 4
- Carboplatin AUC 6 q3wks x 4 ddAC x 4

**CALGB pCR: platinum vs not**

- 46% (40-53%) vs 60% (54-66%)
- Odds Ratio: 1.76
- p = 0.0018

Does Addition of Preoperative Platinum Improve Survival Outcomes for TNBC?

- Mixed results on survival benefits from preop platinum in TNBC
- Achieving pCR is a good surrogate for long-term outcomes on a patient level
- No evidence that pCR rates can be used as a surrogate for survival on a trial level to compare regimens in TNBC

Sikov et al. SABCS 2015; von Minckwitz et al. SABCS 2015
Is Carboplatin Ready for Primetime in Unselected TNBC in the Adjuvant or Neoadjuvant Setting?

**NO**

- Need definitive study showing improvement in DFS and/or OS
- If platinum is ultimately used, should it be added to standard therapy or substituted for one or more drugs?
- Are there triple negative subtypes that are particularly sensitive to platinum, ie biomarker driven?
Preoperative Cisplatin As Preoperative Therapy in Patients With BRCA1 Mutations

- 107 patients with *BRCA1* mutations
- Stage I-III disease
- Treatment:
  - Preoperative Cisplatin 75 mg/m$^2$ q 3 weeks x 4
  - Mastectomy
- Path CR defined as no invasive tumor in breast/nodes

Pathologic complete response = 61%

**12-258 INFORM: preop cisplatin vs AC for BRCA 1/2 carriers**

**Schema: Randomized Phase 2: 166 patients**

- **Stage II/III BC with BRCA1 or 2 mutation**
- **N = 170; approximately 60 enrolled**

- Multicenter study
- Designed to show 20% improvement in pCR with cisplatin over AC

**Principal Investigators:**
Nadine Tung and Judy Garber
Do We Have Sufficient Data To Incorporate Platinum in Early Treatment of BRCA Associated TNBC?

• May never have large, definitive trial
• Mounting evidence in neoadjuvant and metastatic settings
• Biology is consistent with clinical observations
• Probably ready or close to it – ideally would like to see results of neoadjuvant INFORM trial
• How do we do it? Add to standard? Substitute for one or more agents?
Ovarian Suppression through chemotherapy: POEMS/S0230

Premenopausal Stage I, II, IIIA ER-/PR- Breast Cancer Under Age 50

Stratified by age and chemotherapy regimen

Randomization

Standard cyclophosphamide containing (neo)adjuvant chemotherapy

Standard cyclophosphamide containing (neo)adjuvant chemotherapy + goserelin

Moore et al, ASCO 2014, NEJM 2015
POEMS/S0203

257 Patients Randomized

131 Standard Chemotherapy

120 Eligible

113 Evaluable for Pregnancy, DFS & OS

9 withdrew consent; 6 hysterectomy/oophorectomy

14 deaths prior to 2 year f/u; 69 with missing FSH

69 Evaluable for Ovarian Failure

126 Chemotherapy plus goserelin

24 ineligible

113 Eligible

105 Evaluable for Pregnancy, DFS & OS

66 Evaluable for Ovarian Failure

Moore et al, ASCO 2014, NEJM 2015
POEMS Ovarian Failure

<table>
<thead>
<tr>
<th>Ovarian failure at 2 years</th>
<th>Standard Chemotherapy</th>
<th>Chemotherapy + Goserelin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15/69 = 22%</td>
<td>5/66 = 8%</td>
</tr>
</tbody>
</table>

Logistic Regression Results:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>One-sided</td>
<td>Two-sided</td>
</tr>
<tr>
<td>Univariate</td>
<td>0.30</td>
<td>0.10 – 0.87</td>
<td>p=.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=.03</td>
</tr>
<tr>
<td>Stratified*</td>
<td>0.30</td>
<td>0.09 – 0.97</td>
<td>p=.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=.04</td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.36</td>
<td>0.11 – 1.14</td>
<td>p=.04</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td></td>
<td>p=.08</td>
</tr>
</tbody>
</table>

*Accounting for age and regimen through stratification (“Stratified”) or covariate (“Multivariate”) adjustment, respectively.
## POEMS Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Standard Chemotherapy n=113</th>
<th>Chemotherapy + Goserelin n=105</th>
<th>Adjusted OR</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attempted pregnancy</td>
<td>18 (16%)</td>
<td>25 (24%)</td>
<td></td>
<td>p=.12</td>
</tr>
<tr>
<td>Achieved pregnancy</td>
<td>12 (11%)</td>
<td>22 (21%)</td>
<td>2.45</td>
<td>p=.03</td>
</tr>
<tr>
<td>Patients with ≥ 1 delivery</td>
<td>8 (7%)</td>
<td>16 (15%)</td>
<td>2.51</td>
<td>p=.05</td>
</tr>
<tr>
<td>Delivery or ongoing pregnancy</td>
<td>10 (9%)</td>
<td>19 (18%)</td>
<td>2.45</td>
<td>p=.04</td>
</tr>
<tr>
<td>Total number of babies</td>
<td>12</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing pregnancies</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total adverse events</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscarriages</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective termination</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery complication</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of H. Moore
## Ovarian Suppression Through Treatment: RCTs

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Bawady</th>
<th>Sverrisdottir</th>
<th>Del Mastro</th>
<th>Leonard</th>
<th>Gerber</th>
<th>Munster</th>
<th>Elgindy</th>
<th>SWOG 0230</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>80</td>
<td>285</td>
<td>281</td>
<td>227</td>
<td>60</td>
<td>49</td>
<td>100</td>
<td>257</td>
</tr>
<tr>
<td>Study type</td>
<td>Phase II RCT</td>
<td>Substudy from combined analysis of 4 RCTs using core protocol</td>
<td>Phase III RCT</td>
<td>Phase III RCT (abstract only)</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>CT + goserelin vs CT</td>
<td>TAM^+/-CT Goserelin +/- CT Goserelin/TAM +/- CT TAM +/- CT</td>
<td>CT + triptorelin vs. CT</td>
<td>CT + goserelin vs. CT</td>
<td>CT + triptorelin vs. CT</td>
<td>CT + triptorelin vs. CT</td>
<td>CT + goserelin vs. CT</td>
<td></td>
</tr>
<tr>
<td>Premenopausal definition</td>
<td>Regular menstruation FSH &lt;10 IU/L</td>
<td>LMP &lt;6 months prior to study entry, including irregular cycles</td>
<td>Actively menstruation during 6 weeks pre-CT</td>
<td>Regular menses in 12 months preceding surgery</td>
<td>Regular menstruation FSH &lt;15 in follicular phase</td>
<td>Regular menstruation (≥3 periods in 6 months, lasting ≥2 days, 21-35 days apart FSH &lt;40 IU/L)</td>
<td>Regular menstruation (≥3 consecutive periods within 21-35 days)</td>
<td>LMP &lt; 6 weeks pre-randomisation or FSH &amp; E2 in premenopausal range</td>
</tr>
<tr>
<td>%ER+</td>
<td>NR</td>
<td>45%</td>
<td>81%</td>
<td>NR*</td>
<td>0%</td>
<td>73%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>Marker of 'fertility preservation'</td>
<td>Resumption of menstruation or spontaneous ovulation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation</td>
<td>Resumption of menstruation, postmenopausal FSH, pregnancy</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Rate of POF (no menstruation/spontaneous ovulation) 3 months post-CT</td>
<td>Recovery of menstruation</td>
<td>Rate of CIA (no menstruation and post-menopausal FSH/E2 levels) for 12 months post-CT</td>
<td>Rate of amenorrhea 12 months after start of CT</td>
<td>Rate of normal ovarian function at 6 months post-CT</td>
<td>Uninterrupted or restored menstruation during f/u of at least 2 years post CT</td>
<td>Rate of regular menstruation at 12 months after completion of CT</td>
<td>Rate of ovarian failure (amenorrhea) at 2 years, FSH</td>
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<tr>
<td>Median f/u [range]</td>
<td>NR [3-8 months]</td>
<td>NR</td>
<td>12 months post-CT</td>
<td>NR</td>
<td>6, 12, 24, 48 months post-CT</td>
<td>18 months [5-43 months] after CT</td>
<td>NR</td>
<td>All patients followed for at least 12 months</td>
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<tr>
<td>Rate of recovery of menstruation:</td>
<td>90% (goserelin) vs. 33% (control), p&lt;0.001</td>
<td>At 6 months post ET cessation: 36% (goserelin) vs. 10% (control), 13% (TAM), 7% (goserelin + TAM), p=0.006</td>
<td>91.1% (triptorelin) vs. 74.1% (control), p&lt;0.001</td>
<td>NR</td>
<td>No statistically significant difference between treatment arms (further details not published)</td>
<td>70% (goserelin) vs. 56.7% (control)</td>
<td>88.5% (triptorelin) vs. 90.5% (control)</td>
<td>Trial stopped early for futility</td>
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<tr>
<td></td>
<td>8% (goserelin) vs. 22% (control)</td>
<td>Trial stopped prior to full accrual due to funding issues</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td>No data on pregnancies</td>
<td>No data on pregnancies</td>
<td>3 pregnancies in triptorelin arm, 1 in control arm</td>
<td>No data on pregnancies</td>
<td>1 pregnancy in each group</td>
<td>2 pregnancies in control arm</td>
<td>3 pregnancies, one in early CT + triptorelin + cetorelix arm, 1 in early CT control arm</td>
<td>21% vs. 11% pregnancy favouring goserelin</td>
</tr>
</tbody>
</table>

Adapted from N. Turner et al., Ann Oncol 2013
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Bawady</th>
<th>Sverrisdottir</th>
<th>Del Mastro</th>
<th>Leonard</th>
<th>Gerber</th>
<th>Munster</th>
<th>Elgindy</th>
<th>SWOG 0230</th>
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<tbody>
<tr>
<td>Patients(n)</td>
<td>80</td>
<td>285</td>
<td>281</td>
<td>227</td>
<td>60</td>
<td>49</td>
<td>100</td>
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<td>Study type</td>
<td>Phase II RCT</td>
<td>Substudy from combined analysis of 4 RCTs using core protocol</td>
<td>Phase III RCT</td>
<td>Phase III RCT (abstract only)</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
<td>Phase II RCT</td>
<td>Phase III RCT</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>CT + goserelin vs CT</td>
<td>TAM^ +/− CT Goserelin +/-CT Goserelin/TAM +/- CT TAM +/- CT</td>
<td>CT + triptorelin vs. CT</td>
<td>CT + goserelin vs. CT</td>
<td>CT + goserelin vs. CT</td>
<td>CT + triptorelin vs. CT</td>
<td>'Delayed CT': CT + triptorelin vs. CT 'Early CT': CT + triptorelin + cetrorelix^3 vs. CT</td>
<td>CT + goserelin vs. CT</td>
</tr>
</tbody>
</table>

- Meta-analysis ongoing
- No hint of a safety problem
- Reasonable to consider as an additional option for preservation of menstrual functioning and fertility

Adapted from N. Turner et al., Ann Oncol 2013
THANK YOU!