Breast Cancer Genetics and Management of ER+ Breast Cancer

Harold J. Burstein, MD, PhD

hburstein@partners.org

@drhburstein
Disclosure
I have no commercial interest relationships to disclose.

Off Label/Investigational Discussion
In accordance with Annenberg Center policy, faculty have been asked to disclose any discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Question 1.

A 48 year old woman with newly diagnosed, ER positive, HER2 negative breast cancer has undergone genetic testing with a panel for hereditary cancer syndromes. It reveals a CHEK21100delC mutation. She is perimenopausal and not planning additional childbearing. In addition to bilateral mastectomy or breast MRI screening, which testing, surveillance or prophylaxis is appropriate?

A. Nothing further is required
B. Nothing further is required because 1100delC is not a pathological mutation (it is a VUS)
C. Testing for ATM because of interactions between non-pathological ATM mutations and CHEK2
D. Bilateral Oophorectomy
E. Colonoscopy
A 62 year old woman returns to discuss treatment options. Five years ago, she was diagnosed with a 2.1 cm, grade III, ER positive, HER2 negative breast cancer affecting 1 of 3 axillary lymph nodes. OncotypeDX score was 21. She received TC chemotherapy and 5 years of an AI. In discussing extended adjuvant endocrine therapy beyond 5 years, you would note that:

- A. Benefits were only observed in subsets of women who did not receive chemotherapy
- B. After 5 years of an AI, extended duration with an AI improves DFS
- C. She warrants additional genomic signature testing to see if her risk is sufficient for extended endocrine therapy
- D. Extended endocrine therapy will improve her overall survival
- E. If her BMD is “normal” after 5 years of an AI, she is not at jeopardy for osteoporosis with another 5 years of treatment
Breast Cancer Genetics and Management of ER+ breast cancer

- Genetic testing: who and what
- The diversity of ER+ breast cancer
- Role of ovarian suppression
- Adjuvant choices: years 0-5
- The Long Run: choices beyond year 5
- Adjuvant Chemotherapy, or not?
- Impact on local recurrence
- Innovations in metastatic disease
CRITERIA FOR FURTHER GENETIC RISK EVALUATION

- An individual with an ovarian cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries in a single individual
  - Breast cancer at any age, and
    - ≥1 close blood relative with breast cancer ≤50 y, or
    - ≥1 close blood relative with invasive ovarian cancer at any age, or
    - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
    - Pancreatic cancer at any age, or
    - From a population at increased risk
  - Male breast cancer

- An individual with no personal history of cancer but with
  - A close relative with any of the following:
    - A known mutation in a cancer susceptibility gene within the family
    - ≥2 breast cancer primaries in a single individual
    - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - Ovarian cancer
    - Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract
Lifetime Cancer Risk in BRCA1/2 Carriers

- **Female Breast**:
  - BRCA1: 54-84%
  - BRCA2: 4-20%

- **Male Breast**:
  - BRCA1: 4%
  - BRCA2: 7%

- **Ovary**:
  - BRCA1: 40-60%
  - BRCA2: 15%

- **Pancreas**:
  - BRCA1: 3%
  - BRCA2: 7%

- **Prostate**:
  - BRCA1: 20-34%
  - BRCA2: 4-20%
## Management Guidelines *BRCA1/2* Carriers

<table>
<thead>
<tr>
<th>Management Option</th>
<th>Screening Interval/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCREENING</strong></td>
<td></td>
</tr>
<tr>
<td>• Clinical Breast Exam</td>
<td>• Q6-12 mos beginning age 25</td>
</tr>
<tr>
<td>• Breast MRI</td>
<td>• Yearly age 25-75 (then individualize)</td>
</tr>
<tr>
<td>• Mammogram</td>
<td>• Yearly age 30-75 (then individualize)</td>
</tr>
<tr>
<td>• Transvaginal ultrasound*</td>
<td>• Q6 mos beginning age 30</td>
</tr>
<tr>
<td>• CA-125*</td>
<td>• Q6 mos beginning age 30</td>
</tr>
<tr>
<td><strong>PREVENTION</strong></td>
<td></td>
</tr>
<tr>
<td>• Bilateral mastectomy</td>
<td>• Discuss option with patient</td>
</tr>
<tr>
<td>• Bilateral salpingo-oophorectomy</td>
<td>• Recommend by age 35-40 and when childbearing complete</td>
</tr>
<tr>
<td>• Consider oral contraceptive</td>
<td></td>
</tr>
<tr>
<td>• Consider tamoxifen</td>
<td></td>
</tr>
</tbody>
</table>

Modified from NCCN guidelines – v1.2014
## Sensitivity and Specificity of Mammography and MRI in Women with BRCA1/2 Mutations

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ages</td>
<td>39.6</td>
<td>93.6</td>
<td>85.3</td>
<td>84.7</td>
<td>93.4</td>
<td>80.3</td>
</tr>
<tr>
<td>&lt;50 (n=1514)</td>
<td>40</td>
<td>93</td>
<td>85.7</td>
<td>83.5</td>
<td>93.2</td>
<td>78.7</td>
</tr>
<tr>
<td>&gt;50 (n=437)</td>
<td>39.1</td>
<td>95.9</td>
<td>84.4</td>
<td>88.5</td>
<td>94.1</td>
<td>85.3</td>
</tr>
</tbody>
</table>

- All values significantly different from mammography
- Specificity of mammography and MRI significantly better in age >50 vs. <50 years

Xi PA et al. J Clin Oncol. 2015;33:349-56
Phenotypic Effect Size and Frequency of Occurrence of Cancer Susceptibility Genes

Genes typically included in the larger multi-gene panels

Rare, high risk breast cancer syndromes:

- **TP53***: Li-Fraumeni syndrome
- **PTEN***: Cowden syndrome
- **CDH1***: Hereditary diffuse gastric cancer
- **STK11***: Peutz-Jeghers syndrome
- **BRCA1/2***: BRCA-associated breast cancer

Intermediate Risk for Breast Cancer (Fanconi Anemia)

- **ATM***, **BARD1**, **BRIP1**, **CHEK2***, **NBN**, **PALB2**

Ovarian Cancer

- **RAD51C**, **RAD51D**

Polyposis and colon cancer (FAP, MAP):

- **APC**, **MutYH**

Juvenile Polyposis

- **SMAD4**, **BMPR1A**

Lynch Syndrome

- **MLH1**, **MSH2**, **MSH6**, **PMS2**, **EPCAM**

Melanoma

- **CDKN2A**, **CDK4**

*Genes on limited breast panels*
Other Moderate Penetrance Breast Cancer Syndromes

**Cowden Syndrome (PTEN)**
Breast cancer risk **25-50%**

**Peutz Jegher’s (STK11)**
Breast cancer risk **45%**

**Hereditary Diffuse Gastric Cancer (CDH1)**
Invasive Lobular Breast Cancer **39%**
Gastric Cancer **~75%**

Eng C for ASCO
Pharoah P. et al. Gastroenterology 2001;121:1348-1353
Loss-of-Function *PALB2* Germline Mutations in Relation to Functional Domains and Structural Motifs of the *PALB2* Protein, and Cumulative Breast-Cancer Risk for Female Mutation Carriers.
Estimated avg 5-yr and lifetime Br Ca risks for women with moderate penetrance mutations in selected genes

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>ATM / NBN (RR2.7-2.8)</th>
<th>CHEK2 1100delC (RR 3.0)</th>
<th>CHEK2 I157T (RR 1.58)</th>
<th>PALB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-39</td>
<td>1.4</td>
<td>1.5</td>
<td>0.8</td>
<td>4</td>
</tr>
<tr>
<td>45-49</td>
<td>5.6</td>
<td>5.9</td>
<td>3.2</td>
<td>14</td>
</tr>
<tr>
<td>55-59</td>
<td>11.8</td>
<td>12.6</td>
<td>6.8</td>
<td>26</td>
</tr>
<tr>
<td>65-69</td>
<td>20.8</td>
<td>22.1</td>
<td>12.3</td>
<td>35</td>
</tr>
<tr>
<td>Cumulative Lifetime Risk</td>
<td>30.0</td>
<td>31.8</td>
<td>18.3</td>
<td>44</td>
</tr>
</tbody>
</table>

Genetics: Key Take-aways

• Panel testing is becoming the “norm”

• Remember to revisit family history in light of shifting guidelines on which patients should be tested
# Relationship of Grade, ER Expression, and Clinical Factors

<table>
<thead>
<tr>
<th>Histologic Grade</th>
<th>ER expression</th>
<th>PR expression</th>
<th>Proliferation</th>
<th>HER2 Overexpression</th>
<th>Genetic / Genomic / multipanel markers</th>
<th>Intrinsic subtype</th>
<th>Genomic Grade</th>
<th>IHC4</th>
<th>MammaPrint</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (I of III)</td>
<td>+++</td>
<td>++ to +++</td>
<td>Low (&lt;10%)</td>
<td>Never</td>
<td>Low (&lt;18)</td>
<td>Luminal A</td>
<td>Lower risk</td>
<td>Lower risk</td>
<td>Low</td>
<td>Endocrine therapy</td>
</tr>
<tr>
<td>Intermediate (II of III)</td>
<td>++ to +++</td>
<td>0 to +++</td>
<td>Intermediate (10-20%)</td>
<td>Occasional</td>
<td>Intermediate (18-25)</td>
<td>Luminal A</td>
<td>Lower risk</td>
<td>Lower risk</td>
<td>Intermediate (18-25)</td>
<td>+ to ++</td>
</tr>
<tr>
<td>High (III of III)</td>
<td>+ to ++</td>
<td>0 to ++</td>
<td>High (&gt;20%)</td>
<td>Occasional</td>
<td>High (&gt;25)</td>
<td>Luminal B</td>
<td>Higher risk</td>
<td>Higher risk</td>
<td>High ( &gt;25)</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

### Nearly all decision making in ER+ breast cancer requires considering the risk by stage, the risk by biology / biomarker, and the effectiveness of endocrine or chemo treatments
PREMENOPAUSAL ER+ BREAST CANCER:
The Role of Ovarian Suppression
The Paradox of Tamoxifen and OFS


E3193  Tamoxifen ± OFS (no chemo)

IBCSG 13-93

IBCSG, JCO 2006; 24:1332-1341

Tevaarwerk A J et al. JCO 2014;32:3948-3958

Premeno.

ER $\geq 10\%$ and/or
PgR $\geq 10\%$

Patients with estradiol (E$_2$) in the premenopausal range either after CT or without CT

Strata

Any CT

No CT
Primary Analysis Comparisons of Tamoxifen plus Ovarian Suppression (OS) with Tamoxifen Alone.

A Disease-free Survival

- **Graph and Data**: Comparison of Tamoxifen-OS and Tamoxifen on disease-free survival over time.

B End Points, Overall and According to Chemotherapy Cohort

- **Table**: Detailed analysis of end points such as disease-free survival, freedom from breast cancer, and overall survival.

Resolving the Paradox: SOFT / TEXT – a Tale of Two Populations
The role of ovarian suppression in premenopausal ER+ breast cancer

Clinical Assessment
Low Risk
Chemotherapy No
Benefit from OFS No

Higher Risk
Chemotherapy Yes
Benefit from OFS Yes

DFS: women < 35 years old
Tam 68%
Tam + OFS 79%
Exe + OFS 83%
SOFT DFS
8 years median follow-up

<table>
<thead>
<tr>
<th>Group</th>
<th>Pts</th>
<th>Events</th>
<th>8-yr %</th>
<th>HR (95% CI) vs. T</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>1018</td>
<td>208</td>
<td>78.9</td>
<td></td>
</tr>
<tr>
<td>T+OFS</td>
<td>1015</td>
<td>167</td>
<td>83.2</td>
<td>0.76 (0.62-0.93) P=0.009</td>
</tr>
<tr>
<td>E+OFS</td>
<td>1014</td>
<td>143</td>
<td>85.9</td>
<td>0.65 (0.53-0.81)</td>
</tr>
</tbody>
</table>

Absolute Benefit at 8 years vs. T:
- T+OFS 4.2%
- E+OFS 7.0%
SOFT: No chemotherapy

SOFT: chemotherapy
Treatment Effect: Symptoms

- Hot flushes
- Sweats
- Vaginal discharge
- Vaginal dryness
- Vaginal itching/irritation
- Loss of sexual interest
- Arousal difficulties

## Advising Patients on Ovarian Suppression: risk stratification

<table>
<thead>
<tr>
<th>Risk</th>
<th>Higher: typically stage II or III, intermediate-high grade</th>
<th>Intermediate: Higher anatomic stage, lower risk biology; lower stage, higher risk biology</th>
<th>Lower: typically stage I, lower-grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 35</td>
<td>Variable</td>
<td>40+</td>
</tr>
<tr>
<td>Chemo?</td>
<td>Yes</td>
<td>Yes*</td>
<td>±</td>
</tr>
<tr>
<td>OFS</td>
<td>Yes</td>
<td>Discuss</td>
<td>?</td>
</tr>
<tr>
<td>Tablet</td>
<td>Tamoxifen or AI</td>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
</tr>
</tbody>
</table>

*more likely to experience chemotherapy-induced amenorrhea*
POSTMENOPAUSAL ER+ BREAST CANCER: TAMOXIFEN, AIS, AND DURATION
### BIG 1-98: Long-term outcomes

#### Monotherapy

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Evts</th>
<th>Yearly BCFI %</th>
<th>HR (95% Robust CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>2463</td>
<td>263</td>
<td>91 82 79</td>
<td>0.91 (.80-1.04)</td>
</tr>
<tr>
<td>T</td>
<td>2459</td>
<td>264</td>
<td>88 80 78</td>
<td>Ref</td>
</tr>
</tbody>
</table>

- **Letrozole**
- **Tamoxifen**

- $P_{interaction} = .02$
- $P = .16$

---

BIG 1-98: Long-term outcomes

**4-Arm Option**

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Evts</th>
<th>5</th>
<th>10</th>
<th>14</th>
<th>HR (95% Robust CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>1546</td>
<td>198</td>
<td>93</td>
<td>84</td>
<td>82</td>
<td>0.94 (.79-1.13)</td>
</tr>
<tr>
<td>T-L</td>
<td>1548</td>
<td>227</td>
<td>90</td>
<td>83</td>
<td>80</td>
<td>1.06 (.90-1.27)</td>
</tr>
<tr>
<td>L-T</td>
<td>1540</td>
<td>223</td>
<td>92</td>
<td>83</td>
<td>80</td>
<td>1.05 (.88-1.25)</td>
</tr>
<tr>
<td>T</td>
<td>1548</td>
<td>204</td>
<td>90</td>
<td>84</td>
<td>82</td>
<td>Ref</td>
</tr>
</tbody>
</table>

*P*<sub>interaction</sub> = .08

*P* = .53

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

**TAM**<sub>5</sub> vs **AI**<sub>5</sub>

**TAM**<sub>2-3</sub> → **AI**<sub>2-3</sub> vs **AI**<sub>5</sub>

AIs are equally effective*

MA 27: ANA vs EXE

FACE: LET vs ANA

Goss PE, et al
JCO 2012;31:1398-1404

Smith I, et al.
JCO 2017; DOI: 10.1200/JCO.2016.69.2871

*anecdotally and idiosyncratically, patients occasionally tolerate one AI better than another
# Common Side Effects of Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Tamoxifen</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal Symptoms</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Genitourinary Symptoms</td>
<td>+/- (vaginal discharge)</td>
<td>++ (vaginal dryness)</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Osteoporosis / osteopenia</td>
<td>0 to +</td>
<td>++</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Hair thinning</td>
<td>0 to +</td>
<td>++</td>
</tr>
<tr>
<td>VTE</td>
<td>(rare)</td>
<td>0</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>(rare)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>↓ chol</td>
<td>? HTN</td>
</tr>
</tbody>
</table>
WHAT ARE THE PROGNOSTIC FACTORS OR PREDICTIVE FACTOR FOR AI VS TAMOXIFEN THERAPY?
Risk of recurrence among postmenopausal women with ER-positive early breast cancer treated with adjuvant tamoxifen
British Columbia 1986-1999, age ≥ 50

Risk of distant recurrence with endocrine therapy: genomic profiles by nodal stage: ATAC

21-gene recurrence score

PAM50 Risk of Recurrence


Dowsett M, et al. JCO 2013;31:2783-2790
Distant metastatic recurrence following endocrine therapy

**ABCSG 8**

**Luminal A vs Luminal B**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>10 year DRFS (95% CI)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LumA</td>
<td>1004</td>
<td>65</td>
<td>93.9 (92.0 – 95.3)</td>
<td>2.85</td>
</tr>
<tr>
<td>LumB</td>
<td>418</td>
<td>70</td>
<td>82.2 (77.8 – 85.8)</td>
<td></td>
</tr>
</tbody>
</table>

Cox P-value <0.0001

**PAM50 ROR score**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>10 year DRFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>502</td>
<td>17</td>
<td>96.7 (94.6 – 98.0)</td>
</tr>
<tr>
<td>Int</td>
<td>478</td>
<td>41</td>
<td>91.3 (88.1 – 93.8)</td>
</tr>
<tr>
<td>High</td>
<td>498</td>
<td>97</td>
<td>79.9 (75.7 – 83.4)</td>
</tr>
</tbody>
</table>

No. at risk:
- LumA: 1004, 983, 962, 933, 909, 886, 857, 835, 789, 633, 481
- LumB: 418, 410, 400, 375, 349, 331, 309, 294, 271, 207, 171
- Low: 502, 497, 488, 479, 469, 460, 447, 439, 412, 331, 250
- Int: 478, 466, 454, 437, 423, 416, 400, 387, 370, 289, 220
- High: 498, 484, 465, 428, 399, 370, 347, 330, 301, 238, 198

BIG 1-98: tamoxifen vs AI
Outcomes by Intrinsic Subtype and Histology

Luminal A

Luminal B

Proportional benefit of AI vs tam seems greater among tumors with higher risk biologies

Initial Adjuvant Endocrine Therapy

- Familiar prognostic factors
- AI during 1st 5 years offers some advantage over non-AI, tamoxifen-only regimen
  - Sequential therapy narrows any differences
  - All aromatase inhibitors have comparable results
- As risk increases by stage, biomarker, subtype (Ki-67, “luminal B,” lobular), the incremental benefits of AIs are more apparent
- At low risk end of spectrum, outcomes likely similar for either tamoxifen or AI
- AIs and tamoxifen have different side effect profiles
- The “best” treatment is the one the patient will take
PROGNOSTIC FACTORS: LATE
Effects of hormonal therapy for early breast cancer on recurrence: an overview of the randomised trials

BIG 1-98: Long-term outcomes

4-Arm Option

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Evts</th>
<th>5</th>
<th>10</th>
<th>14</th>
<th>HR (95% Robust CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>1546</td>
<td>198</td>
<td>93</td>
<td>84</td>
<td>82</td>
<td>0.94 (.79-1.13)</td>
</tr>
<tr>
<td>T-L</td>
<td>1548</td>
<td>227</td>
<td>90</td>
<td>83</td>
<td>80</td>
<td>1.06 (.90-1.27)</td>
</tr>
<tr>
<td>L-T</td>
<td>1540</td>
<td>223</td>
<td>92</td>
<td>83</td>
<td>80</td>
<td>1.05 (.88-1.25)</td>
</tr>
<tr>
<td>T</td>
<td>1548</td>
<td>204</td>
<td>90</td>
<td>84</td>
<td>82</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Risk factors for recurrence after 5 years of tamoxifen: British Columbia data registry

Nodal status

10-Year Risk

N0 10%
N1 16%
N2 32%

Grade (I vs II vs III)

ER (low vs high)

### Distant Recurrence in Oxford Overview after 5 years of endocrine therapy

<table>
<thead>
<tr>
<th></th>
<th>No. of women</th>
<th>Annual, Years 5-9</th>
<th>Rate (%), Years 10-14</th>
<th>Cum risk (%), Years 5-14</th>
<th>Trend P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>23,870</td>
<td>1.0</td>
<td>1.1</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>16,630</td>
<td>2.0</td>
<td>1.5</td>
<td><strong>15.6</strong></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>4-9</td>
<td>5,638</td>
<td>4.1</td>
<td>2.6</td>
<td><strong>27.7</strong></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>N0 by T</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>16,286</td>
<td>0.7</td>
<td>0.9</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>7,584</td>
<td>1.6</td>
<td>1.3</td>
<td><strong>13.6</strong></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>T1N0 by Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2,996</td>
<td>0.4</td>
<td>0.7</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>6,120</td>
<td>0.8</td>
<td>0.9</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2,135</td>
<td>1.0</td>
<td>1.2</td>
<td><strong>10.0</strong></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*If HR for extended therapy is < 0.9, then there is a > 1% benefit in N+, T2N0, and T1 gr3*

Pan, et al. J Clin Oncol 34, 2016 (suppl; abstr 505)
Risk of late recurrence after 5 years of tamoxifen: British Columbia data registry

10-Yr Risk by N
N0 10%
N1 16%
N2 32%

Recurrence score and prediction of late distant recurrence after 5 years of tamoxifen: NSABP B-14

<table>
<thead>
<tr>
<th>RS Group</th>
<th>N (%) of pts</th>
<th>% distant recurrence 5 to 10 years</th>
<th>% distant recurrence 5 to 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>289 (58%)</td>
<td>4.7%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>111 (22%)</td>
<td>4.1%</td>
<td>11.2%</td>
</tr>
<tr>
<td>High</td>
<td>97 (20%)</td>
<td>12.6%</td>
<td>16.4%</td>
</tr>
</tbody>
</table>

Wolmark N, et al.
J Clin Oncol 32:5s, 2014 (suppl; abstr 11024)
Kaplan-Meier curves and estimates for distant recurrence risk in B-28 and B-14 by recurrence score risk groups and time period.

Kaplan–Meier plots of late DRFS according to Luminal A/B molecular subtypes in all patients with breast cancer (A) and in the node-negative subgroup (B). ABCSG8

Distant recurrence according to immunohistochemical markers (IHC4), recurrence score (RS), and risk of recurrence (ROR) score group split at the median value.
Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population

EndoPredict Score: prognosis for distant recurrence

WOULD LONGER DURATION OF ADJUVANT ENDOCRINE THERAPY REDUCE LATE RECURRENCE?
<table>
<thead>
<tr>
<th>Year after Diagnosis</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies of tamoxifen after 5 years of tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTOM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies of AI after 5 years of tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAPB B-33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG 6a#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies of extended after 5 years of that included AI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA17R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studies of Optimal Duration or Dosing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOOG 2006-05 IDEAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**De Facto Comparisons**

- **HR for DFS**
- **% exposed to AI yrs 0-5**

- **ATLAS**: 5 v 10, 0.75-0.99##, 0%
- **ATTOM**: 5 v 10, 0.75-0.99##, 0%
- **MA17**: 5 v 10, 0.57, 0%
- **NSAPB B-33**: 5 v 10, 0.68, 0%
- **ABCΣG 6a#**: 5 v 8, 0.62, 0%
- **DATA**: 6 vs 9, 0.79, 100%
- **NSABP B-42**: 5 v 10, 0.85, 100%
- **MA17R**: 10 vs 15, 0.66, 100%
- **BOOG 2006-05 IDEAL**: 7.5 vs 10, 0.92, 88%
- **ABCΣG 16**: 7 vs 10, 1.007, 49%
- **SOLE**: Cont vs Intermitt, 1.08, 81%
MA 17: Letrozole or Placebo after 5 years of Tamoxifen

DFS and OS

A Disease-free Survival

Women Surviving Free of Breast Cancer (%)

Letrozole group

Placebo group

P<0.001

Months after Randomization

No. at Risk

Letrozole 2575 2308 1327 624 183 9 0

Placebo 2582 2298 1295 610 180 11 0

B Overall Survival

Women Surviving (%)

Letrozole group

Placebo group

P=0.25

Months after Randomization

No. at Risk

Letrozole 2575 2329 1349 641 188 9 0

Placebo 2582 2328 1335 645 196 14 0

Contralateral BC

Cumulative rate/1,000

Time from randomization (years)

Placebo

Letrozole


Events in trials of extended adjuvant endocrine therapy: NSABP B-33

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial


Summary

Background For women with oestrogen receptor (ER)-positive early breast cancer, treatment with tamoxifen for 5 years substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis. We aimed to assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years.
ATTOM Trial:
10 vs 5 years of Tamoxifen: Breast Cancer Death by Treatment Allocation

Gray R, et al. ASCO 2013
MA17R: extended AI therapy

DFS and OS

A Disease-free Survival

![Graph showing DFS and OS for Letrozole and Placebo over 10 years.]

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Letrozole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>0-1</td>
<td>959</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>942</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>925</td>
</tr>
<tr>
<td></td>
<td>6-7</td>
<td>899</td>
</tr>
<tr>
<td></td>
<td>8-9</td>
<td>879</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>850</td>
</tr>
<tr>
<td></td>
<td>11-12</td>
<td>652</td>
</tr>
<tr>
<td></td>
<td>13-14</td>
<td>324</td>
</tr>
<tr>
<td></td>
<td>15-16</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>17-18</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>19-20</td>
<td>14</td>
</tr>
</tbody>
</table>

B Overall Survival

![Graph showing overall survival for Letrozole and Placebo over 10 years.]

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Letrozole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>0-1</td>
<td>959</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>952</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>941</td>
</tr>
<tr>
<td></td>
<td>6-7</td>
<td>921</td>
</tr>
<tr>
<td></td>
<td>8-9</td>
<td>903</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>880</td>
</tr>
<tr>
<td></td>
<td>11-12</td>
<td>680</td>
</tr>
<tr>
<td></td>
<td>13-14</td>
<td>343</td>
</tr>
<tr>
<td></td>
<td>15-16</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td>17-18</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>19-20</td>
<td>14</td>
</tr>
</tbody>
</table>

Contralateral BC

![Graph showing cumulative incidence of contralateral BC for Placebo and Letrozole over 10 years.]

Placebo, observed events: 31 (3%)

Letrozole, observed events: 13 (1%)

NSABP B-42

- Postmenopausal Pts with ER+ or PR+ Breast Cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free After 5 Years of Endocrine Therapy

Stratification:
Pathological nodal status (Negative, Positive)
Prior adjuvant TAM (Yes, No)
Lowest BMD T score: spine, hip, femur (>−2.0, ≤−2.0 SD)

Letrozole X 5 yrs  Placebo X 5 yrs

Mamounas T et al. SABCS2016; St Gallen / Vienna 2017
NSABP B-42: Disease-Free Survival

**Letrozole vs Placebo**

- **Years After Randomization**
  - 0
  - 2
  - 4
  - 6
  - 8

- **Disease-Free Survival**
  - Letrozole
    - 1959: 292 events
    - 1813 patients
    - HR=0.85 (0.73-0.999)
    - P = 0.048
  - Placebo
    - 1964: 339 events
    - 1814 patients
    - 81.3%

- **# Events**
  - Letrozole: 292
  - Placebo: 339

- **P-value**
  - *P-value did not reach statistical significance level of 0.0418*
NSABP B-42:
Cumulative Incidence of Distant Recurrence

Letrozole
Placebo

# Pts # Events
1959 73
1964 102

HR=0.72 (0.53-0.97)  P=0.03

5.8%
DATA Study Design

- 80% power to detect an increase in 3-year adapted Disease-Free Survival (aDFS) from 90% to 94%, i.e., a hazard ratio (HR) of 0.60 and a significance level of 0.05
- Accounting for 10% drop-out: 950 patients per group to be included (n=1912 patients actually included)
- Minimum follow-up: ≥6 years after randomization, i.e., ≥ 3 years of adapted follow-up (last patient included in August 2009)

**Stratification**
- Nodal status
- ER/PR status
- HER2 status
- Tamoxifen duration

**6 years anastrozole**
- 1 mg daily

**3 years anastrozole**
- 1 mg daily

- Postmenopausal at randomization
- ER+ and/or PR+
- No sign of disease recurrence
- M0 breast cancer
- After 2-3 years adjuvant tamoxifen

Tjan et al. SABCS 2016
From: Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05)
J Natl Cancer Inst | © The Author 2017. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
From: Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05)
J Natl Cancer Inst | © The Author 2017. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
ABCSDG-16 Trial Design

4-6 years endocrine treatment

Local Therapy: Surgery ± Radiotherapy

Tam

AI

Tam->AI

R 1:1

Anastrozole 2 years

Anastrozole 5 years

N=3,484
Postmenopausal, HR+, T1-3, N0/N+, M0
Recruitment in 75 centers in Austria, 2004-2010
Median Follow-Up: 106.2 months (102.7-107.7)
ABCMSG-16 Disease-Free Survival

Time from randomization to first DFS event

Disease-free survival, %

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|       | 71.1% | 70.3% |

<table>
<thead>
<tr>
<th>Number of Events/Patients</th>
<th>Hazard ratio vs 2 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years 378/1,731</td>
<td>1.007 (0.87, 1.16)</td>
<td>0.925</td>
</tr>
<tr>
<td>5 years 384/1,738</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>2 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1731</td>
<td>1738</td>
</tr>
<tr>
<td>2 years</td>
<td>1651</td>
<td>1667</td>
</tr>
<tr>
<td>1538</td>
<td>1605</td>
<td>1551</td>
</tr>
<tr>
<td>1477</td>
<td>1485</td>
<td>1399</td>
</tr>
<tr>
<td>1368</td>
<td>1233</td>
<td>1028</td>
</tr>
<tr>
<td>1206</td>
<td>779</td>
<td>741</td>
</tr>
<tr>
<td>990</td>
<td>554</td>
<td>540</td>
</tr>
<tr>
<td>741</td>
<td>214</td>
<td>209</td>
</tr>
</tbody>
</table>
Forest plots showing odds ratio (OR) for recurrence associated with clinico-pathological factors and treatment effect for each of the HOXB13/IL17BR (H/I) groups.

Menopausal status
T stage
Tumor grade
ER
PR
HER2
Node status

Treatment (letrozole vs placebo)
H/I-low
H/I-high

Odds ratio (95% CI)

Dennis C. Sgroi et al. JNCI J Natl Cancer Inst 2013;jnci.djt146
© The Author 2013. Published by Oxford University Press.
Extended Adjuvant Endocrine Therapy

- Late recurrences are real
  - Baseline stage / grade / biomarkers are persistent prognostic factors and can be used to frame risk of late recurrence

- Treatment pros / cons
  - Benefits include lower distant recurrence and secondary prophylaxis
  - Side effects include ongoing, familiar symptoms and bone health risks

- Consider extended adjuvant endocrine therapy in:
  - Women with stage 3 cancers
  - Women with stage 2 cancers at higher risk, especially node-positive
  - Women with stage 1 cancers on individualized basis and with additional goal of secondary prevention
  - Especially patients who have tolerated treatment
  - Especially patients who started with tamoxifen
  - For most “ordinary risk” patients, probably not to exceed 10 years, total
DECISION MAKING:
ADJUVANT CHEMOTHERAPY FOR
ER+ BREAST CANCER
NSABP B-20
Outcome by Recurrence Score

Overall

Int risk 18-30

Low risk < 18

High risk > 30

Benefit of adjuvant chemotherapy as a function of stage and OncotypeDX recurrence score: node negative and node-positive patients.
Example of recurrence score (RS) and RS-pathology-clinical (RSPC) risk assessments with 95% CIs for patients of age 50 years with specific tumor grades and sizes.

Tang G et al. JCO 2011;29:4365-4372

Low grade: RS overestimates risk

High grade: RS underestimates risk
TAILORx

Preregister

Oncotype DX assay

Register
Specimen banking

Secondary study group 1
RS < 11

ARM A
Hormonal therapy alone

Primary study group
RS 11-25

Randomly Assigned
Stratification factors:
Tumor size, menopausal status,
planned chemo, planned radiation

Secondary study group 2
RS > 25

ARM D
Chemotherapy +
hormonal therapy

ARM B
Hormonal therapy alone

ARM C
Chemotherapy +
hormonal therapy

TAILORx: Outcomes for node-negative, ER positive, HER2 negative cancers with low recurrence score (< 10)

Stage 1: 70%
Stage 2: 30%
Grade 1: 29%
Grade 2: 57%
Grade 3: 14%
Grade = only significant predictor of recurrence

West German Study Group PlanB Trial: Outcomes for N0 or N1 (1 to 3 positive nodes) tumors

3-year DFS in RS < 12 with ET, only

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>DFS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>98.6%</td>
</tr>
<tr>
<td>N1</td>
<td>97.9%</td>
</tr>
</tbody>
</table>

Oleg Gluz et al. JCO 2016;34: epub ahead of print
Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen

A. Prat¹,², J. S. Parker¹, C. Fan¹, M. C. U. Cheang¹, L. D. Miller³, J. Bergh⁴,⁵, S. K. L. Chia⁶, P. S. Bernard⁷, T. O. Nielsen⁶,⁸, M. J. Ellis⁹, L. A. Carey¹,¹⁰ & C. M. Perou¹,¹¹,¹²*

Table 2. Low-risk group comparison among signatures

<table>
<thead>
<tr>
<th>Node-negative</th>
<th>Node-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group</td>
<td>DRFS at 8.5 years</td>
</tr>
<tr>
<td>% of luminal A</td>
<td>N</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>RORP (PAM50)</td>
<td>82 (24%)</td>
</tr>
<tr>
<td>RORS (PAM50)</td>
<td>140 (41%)</td>
</tr>
<tr>
<td>PROLIF² (PAM50)</td>
<td>72 (22%)</td>
</tr>
<tr>
<td>GHI</td>
<td>47 (14%)</td>
</tr>
<tr>
<td>ROT76b</td>
<td>164 (48%)</td>
</tr>
<tr>
<td>IE-IIEb</td>
<td>235 (69%)</td>
</tr>
<tr>
<td>NKI70b</td>
<td>136 (40%)</td>
</tr>
<tr>
<td>SET</td>
<td>26 (8%)</td>
</tr>
<tr>
<td>RORP (PAM50)c</td>
<td>116 (21%)</td>
</tr>
<tr>
<td>RORS (PAM50)c</td>
<td>197 (36%)</td>
</tr>
<tr>
<td>PROLIF (PAM50)c</td>
<td>142 (26%)</td>
</tr>
</tbody>
</table>

Unlikely that chemotherapy will **meaningfully** improve prognosis. At the extremes, a prognostic marker becomes predictive.
<table>
<thead>
<tr>
<th>Clinical Genomic</th>
<th>Low Low</th>
<th>Low High</th>
<th>High Low</th>
<th>High High</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>2745</td>
<td>592</td>
<td>1550</td>
<td>1806</td>
</tr>
<tr>
<td>N+</td>
<td>6%</td>
<td>3%</td>
<td>48%</td>
<td>26%</td>
</tr>
<tr>
<td>T &lt; 2 cm</td>
<td>96%</td>
<td>98%</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2%</td>
<td>15%</td>
<td>29%</td>
<td>76%</td>
</tr>
<tr>
<td>ER+ Luminal</td>
<td>96%</td>
<td>79%</td>
<td>90%</td>
<td>50%</td>
</tr>
<tr>
<td>TNBC</td>
<td>0%</td>
<td>9%</td>
<td>1%</td>
<td>31%</td>
</tr>
<tr>
<td>HER2+</td>
<td>4%</td>
<td>12%</td>
<td>8%</td>
<td>19%</td>
</tr>
<tr>
<td>5 year DDFS</td>
<td>97.6%</td>
<td>94.8%</td>
<td>95.1%</td>
<td>90.6%</td>
</tr>
<tr>
<td>Δ DFS with chemo</td>
<td></td>
<td>2.2%</td>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR .74, p NS</td>
<td>HR .64, p 0.026</td>
<td></td>
</tr>
</tbody>
</table>
MINDACT: Survival without Distant Metastasis, Disease-free Survival, and Overall Survival in the Two Discordant-Risk Groups, According to Randomized Treatment.
ABC Trials Schema (nee TC/TAC, B-46I, B-49)

**Node+ or High Risk Node-Negative**

Stratification Variables

- Number of + Nodes (0, 1-3, 4-9, 10+)
- Hormone Receptor (ER or PgR+, Both Negative)

<table>
<thead>
<tr>
<th>Arm 1 Options Per Study</th>
<th>Arm 2 (TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC q 3 wk</td>
<td>TC q 3 wk</td>
</tr>
<tr>
<td>AC q 3 wk</td>
<td></td>
</tr>
<tr>
<td>AC q 2 wk</td>
<td></td>
</tr>
<tr>
<td>AC q 2 wk</td>
<td></td>
</tr>
</tbody>
</table>

**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 a minimum of 5 years

Designed to prove noninferiority of nonanthracycline arm
Anthracyclines in Early Breast Cancer
The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49

Adjuvant Chemotherapy for ER+ breast cancer

- Key question is “whether?” not “which”

- For node-negative tumors with low-intermediate clinical and genomic risk, there is very little evidence that chemotherapy adds meaningful benefit

- Challenges: discordance between anatomic stage and biomarker profile

- Preferred regimens:
  - Higher risk: AC → paclitaxel
  - Lower risk: TC (or AC)

- Tricks in the bag:
  - Single-agent sequential therapy (CALGB 9741)
  - No more than 4 cycles of any agent (CALGB 40101)
IMPACT OF ENDOCRINE THERAPY ON LOCAL-REGIONAL RECURRENCE
### TAMOXIFEN CHEMOTHERAPY

**EBCTCG Overview. Lancet 2005;365:1687**

#### (i) Site of first recurrence ($\chi^2 = 0.2; p > 0.1; $NS)

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Tamoxifen events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Variances of O-E</td>
</tr>
<tr>
<td></td>
<td>polychemo.</td>
<td>control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polychemo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O-E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated local</td>
<td>206/15684</td>
<td>268/12271</td>
<td>-48.6</td>
</tr>
<tr>
<td></td>
<td>(1.3%/y)</td>
<td>(2.2%/y)</td>
<td></td>
</tr>
<tr>
<td>Contralateral*</td>
<td>55/15684</td>
<td>60/12271</td>
<td>-9.6</td>
</tr>
<tr>
<td></td>
<td>(0.4%/y)</td>
<td>(0.5%/y)</td>
<td></td>
</tr>
<tr>
<td>Distant/multi.</td>
<td>528/15684</td>
<td>613/12271</td>
<td>-104.2</td>
</tr>
<tr>
<td></td>
<td>(3.4%/y)</td>
<td>(5.0%/y)</td>
<td></td>
</tr>
</tbody>
</table>

- 99% or $\leftarrow\rightarrow$ 95% confidence intervals

#### (j) Site of first recurrence ($\chi^2 = 5.4; p = 0.07; $NS)

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Tamoxifen events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Variances of O-E</td>
</tr>
<tr>
<td></td>
<td>polychemo.</td>
<td>control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O-E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated local</td>
<td>114/22257</td>
<td>208/18819</td>
<td>-57.8</td>
</tr>
<tr>
<td></td>
<td>(0.5%/y)</td>
<td>(1.1%/y)</td>
<td></td>
</tr>
<tr>
<td>Contralateral*</td>
<td>79/22257</td>
<td>120/18819</td>
<td>-26.9</td>
</tr>
<tr>
<td></td>
<td>(0.4%/y)</td>
<td>(0.6%/y)</td>
<td></td>
</tr>
<tr>
<td>Distant/multi.</td>
<td>507/22257</td>
<td>631/18819</td>
<td>-116.0</td>
</tr>
<tr>
<td></td>
<td>(2.3%/y)</td>
<td>(3.4%/y)</td>
<td></td>
</tr>
</tbody>
</table>

- 99% or $\leftarrow\rightarrow$ 95% confidence intervals

---

Treatment effect $2p < 0.000001$
Lumpectomy and tamoxifen ± XRT in women 70+
CALGB 9343

INNOVATIONS IN ER+ BREAST CANCER
Emergence of constitutively active ER-α mutations in breast cancers

ER-α Mutations are Acquired: Genetic alteration in primary versus metastatic breast cancer.

Progression-free survival (PFS) in SoFEA by ESR1 mutation status.

**ESR mutation**

- Exemestane
  - Median PFS: 2.6 months (95% CI: 2.4 to 6.2)
- Fulvestrant-containing regimen
  - Median PFS: 5.7 months (95% CI: 3.0 to 8.5)

**ESR wildtype**

- Exemestane
  - Median PFS: 8.0 months (95% CI: 3.0 to 11.5)
- Fulvestrant-containing regimen
  - Median PFS: 5.4 months (95% CI: 3.7 to 8.1)

---

Charlotte Fribbens et al. JCO 2016;34:2961-2968

©2016 by American Society of Clinical Oncology
FIRST study: 1\textsuperscript{st} line Fulvestrant 500 mg vs ANA

HR = 0.63; 95% CI, 0.39 to 1.00; \( P = .0496 \)

Robertson J F et al. JCO 2009;27:4530-4535
FIRST: overall survival analysis

HR = 0.70
95% CI (0.50, 0.98)
p = 0.041

Roberston, et al. SABCS 2014
FALCON: PHASE III STUDY DESIGN
ELLIS, ET AL. ESMO 2016

- Postmenopausal women
- Locally advanced or metastatic breast cancer
- ER+ and / or PgR+
- HER2-
- Endocrine therapy-naïve

Randomised, double-blind, parallel-group, international, multicentre study

Follow-up for disease progression and survival

Randomisation of 450 patients was planned to achieve 306 progression events; if the true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test)

Stratification factors: prior chemotherapy for advanced disease (yes / no); measurable vs. non-measurable disease (at baseline); locally advanced vs. metastatic disease

Subgroup analysis of PFS for pre-defined baseline covariates

Fulvestrant 500 mg
(500 mg IM on Days 0, 14 and 28, then every 28 days)
+ placebo to anastrozole

Anastrozole 1 mg
(daily PO)
+ placebo to fulvestrant

Primary endpoint: PFS\(^a\)

Secondary endpoints
- OS\(^b\)
- ORR
- CBR
- DoR, EDoR
- DoCB, EDoCB
- HRQoL (FACT-B total and TOI)
- Safety

\(^a\)Assessed via RECIST 1.1, surgery / radiotherapy for disease worsening, or death; \(^b\)Interim analysis at the time of PFS analysis
EDoCB, expected duration of clinical benefit; EDoR, expected duration of response; FACT-B, Functional Assessment of Cancer Therapy – Breast; TOI, Trial Outcome Index
FALCON: PRIMARY ENDPOINT, PFS

HR 0.797 (95% CI 0.637, 0.999); p=0.0486

Median PFS
- Fulvestrant: 16.6 months
- Anastrozole: 13.8 months

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant</th>
<th>Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>230</td>
<td>232</td>
</tr>
<tr>
<td>3</td>
<td>187</td>
<td>194</td>
</tr>
<tr>
<td>6</td>
<td>171</td>
<td>162</td>
</tr>
<tr>
<td>9</td>
<td>150</td>
<td>139</td>
</tr>
<tr>
<td>12</td>
<td>124</td>
<td>120</td>
</tr>
<tr>
<td>15</td>
<td>110</td>
<td>102</td>
</tr>
<tr>
<td>18</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>21</td>
<td>81</td>
<td>60</td>
</tr>
<tr>
<td>24</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>27</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>30</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>33</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>36</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Proportion of patients alive and progression free
FACT Trial
AI +/- fulvestrant after tamoxifen

Bergh J et al. JCO 2012;30:1919-1925

©2012 by American Society of Clinical Oncology
SWOG 0226:
Anastrozole +/- fulvestrant for MBC

Progression-free Survival, According to Subgroups.

PD-0332991 arrests the cell cycle at G1 by selective inhibition of CDK 4/6

Fry DW et al. Mol Cancer Ther 2004;3:1427
Carnero A. Br J Cancer 2002;87:129
PD 0332991 Preferentially Inhibits Proliferation of Luminal Estrogen Receptor-Positive Human Breast Cancer Cell Lines in Vitro

Subtype
- Luminal
- HER2 amplified
- Non-luminal/post EMT
- Non-luminal
- Immortalized

• CDK4/6 I
• First-line trials
PFS results Paloma-2 and Monaleesa 2

**PALOMA-2**

- Median PFS: 24.8 m
- Hazard ratio: 0.58 (95% CI: 0.46-0.82)
- Two-sided P < 0.001


**Monaleesa 2 - Updated results**

- Median PFS: 25.3 m
- Median PFS: 16 m

Hortobagyi G, et al. ASCO 2017
MONARCH3 Primary Endpoint: PFS (ITT)

Median PFS
- abemaciclib + NSAI: not reached
- placebo + NSAI: 14.7 months

HR (95% CI): 0.543 (0.409, 0.723)
p = 0.000021

PFS benefit confirmed by blinded independent central review: HR (95% CI): 0.508 (0.359, 0.723); p = 0.000102
• CDK4/6 I
• Second-line trials
Monarch 2 and Paloma 3 - PFS


<table>
<thead>
<tr>
<th>Line</th>
<th>Study Name</th>
<th>Endocrine Agent</th>
<th>CDK4/6i</th>
<th>PFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>PALOMA1</td>
<td>Letrozole</td>
<td>Palbociclib</td>
<td>10.2m → 20.2m</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Lancet 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PALOMA2</td>
<td>Letrozole</td>
<td>Palbociclib</td>
<td>14.5m → 24.8m</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>NEJM 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MONALEESA2</td>
<td>Letrozole</td>
<td>Ribociclib</td>
<td>14.5 → ~26m</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>NEJM 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MONALEESA7*</td>
<td>Letrozole + OFS</td>
<td>Ribociclib</td>
<td>13.0m → 23.8m</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>SABCS 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MONARCH3</td>
<td>NSAI</td>
<td>Abemaciclib</td>
<td>14.7m → NR</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>JCO 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>PALOMA3</td>
<td>Fulvestrant</td>
<td>Palbociclib</td>
<td>3.8m → 9.2m</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>NEJM 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MONARCH2</td>
<td>Fulvestrant</td>
<td>Abemaciclib</td>
<td>9.3m → 16.4m</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>JCO 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*premenopausal women*
Side effects of CDK4/6 inhibitors

Table 2. Dosing and Toxicity for Cyclin-Dependent Kinase 4/6 Inhibitors

<table>
<thead>
<tr>
<th>Common Adverse Event*</th>
<th>Palbociclib (125 mg per day [3 weeks on, 1 week off])</th>
<th>Ribociclib (600 mg per day [3 weeks on, 1 week off])</th>
<th>Abemaciclib (200 mg twice per day [continuous])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 and 4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74-81</td>
<td>54-67</td>
<td>74</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16-22</td>
<td>2-3</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57-60</td>
<td>2-4</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21-26</td>
<td>1-4</td>
<td>35</td>
</tr>
<tr>
<td>Nausea</td>
<td>25-35</td>
<td>0-2</td>
<td>92</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. Data are given as percent.
Abbreviation: NR, not reported; QTc, corrected QT interval.
*Common adverse events in phase III trials in the metastatic setting.
Progression-free survival (PFS) in PALOMA3 by ESR1 mutation status.

ESR mutation  
ESR wildtype

Charlotte Fribbens et al. JCO 2016;34:2961-2968
ADD PALBO

LET + FULV
PALLAS: Phase III Randomized Trial of Adjuvant Endocrine Therapy +/- Palbociclib

**Patient Population**
- N = 4600
- HR+ and HER2-
- Stage II or III

**Arm A**
Palbociclib (2 yrs) + Endocrine Treatment (5+ yrs)

**Arm B**
Endocrine treatment (5+ yrs)

1:1 Survival/Disease Follow-up

**Arm A**: palbociclib at a dose of 125 mg once daily, Day 1-21 in a 28-day cycle for total duration of 2 years, in addition to standard adjuvant endocrine therapy

**Arm B**: standard adjuvant endocrine therapy (AI, tamoxifen)

Opened 9/2015....
**BOLERO-2. PFS**

**EXE +/- everolimus after prior AI**

**RR:**
- EXE 1%
- EXE + EVO 13%

BOLERO-2. Cumulative risks for grade ≥ 2 adverse events

**Stomatitis**

- **A**
  - Probability of event (%)
  - Number of patients still at risk:
    - EVE + EXE: 482, 417, 317, 242, 184, 136, 94, 59, 38, 21, 15, 9, 3, 1, 0, 0
    - PBO + EXE: 238, 173, 119, 72, 48, 34, 21, 11, 7, 3, 1, 0, 0, 0

**Pneumonitis**

- **B**
  - Probability of event (%)
  - Number of patients still at risk:
    - EVE + EXE: 482, 394, 306, 242, 189, 145, 96, 64, 43, 22, 15, 10, 4, 1, 0
    - PBO + EXE: 238, 171, 117, 72, 48, 34, 21, 11, 7, 3, 1, 0, 0, 0

**Hyperglycemia / diabetes**

- **C**
  - Probability of event (%)
  - Number of patients still at risk:
    - EVE + EXE: 482, 417, 317, 242, 184, 136, 94, 59, 38, 21, 15, 9, 3, 1, 0, 0
    - PBO + EXE: 238, 173, 119, 72, 48, 34, 21, 11, 7, 3, 1, 0, 0, 0

**Fatigue**

- **D**
  - Probability of event (%)
  - Number of patients still at risk:
    - EVE + EXE: 482, 384, 284, 216, 141, 87, 49, 33, 13, 8, 2, 1, 0
    - PBO + EXE: 238, 164, 110, 64, 34, 18, 7, 5, 4, 1, 0, 0, 0
Typical Sequence of Endocrine Therapy

circa 2018

No prior Rx / Endocrine naïve
- Post: AI ± fulvestrant
- Post: AI ± CDK4/6i
- Pre: OFS + tam/AI +/- CDK4/6i

Prior Tam/AI
- Fulvestrant ± palbociclib
- AI ± CDK4/6i

Prior Tam/AI/F
- AI + mTORi
- Progestins
- Estrogens
- CDK4/6i
- Chemotherapy
Don’t forget to remember ...

- Re-introduction of anti-estrogen therapy