Fifth Annual Wisconsin Review of the San Antonio Breast Cancer Summit:

Hormone Receptor-Positive Breast Cancer

AMANDA PARKES
ASSISTANT PROFESSOR, UW CARBONE CANCER CENTER

JANUARY 25, 2020
Agenda

<table>
<thead>
<tr>
<th>Theme</th>
<th>Presentations</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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| **Metastatic Disease**       | • PEARL study: Phase III trial of Palbociclib + Endocrine Therapy versus Capecitabine                                                          |
Adjuvant Endocrine Therapy

CURRENT NCCN GUIDELINES
Current NCCN Guidelines: Adjuvant Endocrine Therapy

Adjuvant endocrine therapy is considered for all patients with hormone receptor positive breast cancer.
Optimal duration of adjuvant endocrine therapy beyond 5 years continues to evolve.
Ten-year results from NRG Oncology/NSABP B-42

EXTENDED ADJUVANT ENDOCRINE THERAPY WITH LETROZOLE IN POSTMENOPAUSAL WOMEN WITH HORMONE-RECEPTOR+ BREAST CANCER WHO HAVE COMPLETED PREVIOUS ADJUVANT THERAPY WITH AN AROMATASE INHIBITOR

NSABP B-42: Background/Rational

• NSABP B-42 aimed to determine whether 5 years of letrozole vs. placebo improves DFS in patients who have completed 5 years of hormonal therapy with either an AI or TAM → AI.
NSABP B-42: 7 Year Results

Presented at SABCS 2016 (published at Lancet Oncology 2019)
7 year analysis (median follow-up 6.9 years)

- The beneficial effect of extended L therapy on DFS did not reach statistical significance (HR=0.85, p=0.048)
  - To adjust for interim analyses, statistical significance level of 0.0418 was used
- No significant difference in Overall Survival with L vs. P
- Extended L provided:
  - 29% significant reduction in rate of Breast Cancer Free Interval (BCFI) events (HR=0.71, p=0.003)
  - 28% significant reduction in rate of Distant Recurrence (DR) events (HR=0.72, p=0.03)
- L did not significantly increase risk of osteoporotic fractures
- Risk of arterial thrombotic events was elevated for L after 2.5 years
Ten-year results demonstrate a statistically significant improvement in DFS with extended L therapy:
- 16% reduction in DFS event
- 4% absolute improvement at 10 years in favor of L

Patients excluded: 43 (no follow-up, or not at risk for DFS), 20 (no clinical follow-up assessment)
## NSABP B-42: Updated Results

**10 year follow up (9.3 years median follow up)**

**DFS First Events by Treatment**

<table>
<thead>
<tr>
<th>First Event</th>
<th>Placebo (n=1953)</th>
<th>Letrozole (n=1950)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>Distant Recurrence</td>
<td>111</td>
<td>5.7</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td>43</td>
<td>2.2</td>
</tr>
<tr>
<td>Second Primary Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>230</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>4.1</td>
</tr>
<tr>
<td>Non-Breast</td>
<td>149</td>
<td>7.6</td>
</tr>
<tr>
<td>Death</td>
<td>95</td>
<td>4.9</td>
</tr>
<tr>
<td>Total First Event</td>
<td>479</td>
<td>24.5</td>
</tr>
</tbody>
</table>

DFS first events by treatment difference was primarily from differences in distant recurrence (1.5% difference favoring L) and second primary breast cancers (2.4% difference favoring L).
NSABP B-42: Updated Results
10 year follow up (9.3 years median follow up)

### Overall Survival

- No significant difference in overall survival with L vs. P

**Table:**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>P</th>
<th>L</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-yr</td>
<td>146</td>
<td>164</td>
<td>1.15 (0.92-1.44)</td>
<td>0.15</td>
</tr>
<tr>
<td>10-yr</td>
<td>252</td>
<td>243</td>
<td>0.97 (0.82-1.16)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**Graph:**

- Overall Survival over Years after Random Assignment
- 86.1% at 10 years
- 85.5% at 7 years

**Note:** Patients excluded: 43 (no follow-up, or not at risk for DFS)
NSABP B-42: Updated Results
10 year follow up (9.3 years median follow up)

Breast Cancer-Free Interval

- **Extended L provided:**
  - Statistically significant improvement in BCFI
  - 26% reduction in BCFI event; 3% absolute improvement with L

Patients excluded: 43 (no follow-up, or not at risk for DFS), 20 (no clinical follow-up assessment)
NSABP B-42: Updated Results
10 year follow up (9.3 years median follow up)

### Distant Recurrence

<table>
<thead>
<tr>
<th># Events</th>
<th>Analysis</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-yr</td>
<td>102</td>
<td>73</td>
<td>0.72 (0.53-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>10-yr</td>
<td>133</td>
<td>96</td>
<td>0.71 (0.55-0.93)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- **Extended L provided:**
  - Statistically significant reduction in DR
  - 29% reduction in DR; 1.8% absolute improvement with L

Patients excluded: 43 (no follow-up, or not at risk for DFS), 20 (no clinical follow-up assessment)
NSABP B-42: Updated Results

10 year follow up (9.3 years median follow up)

Osteoporotic Fractures and Arterial Thrombotic Events

- L did not significantly increase risk of osteoporotic fractures or arterial thrombotic events.

Patients excluded: 43 (no follow-up, or not at risk for DFS), 20 (no clinical follow-up assessment)
NSABP B-42: Summary

Ten-year results demonstrate a statistically significant improvement in DFS with extended L therapy
No significant difference in overall survival with L vs. P

Extended L provided:
- Statistically significant improvement in Breast Cancer-Free Interval (BCFI)
- Statistically significant reduction in Distant Recurrence (DR)

L did not significantly increase risk of osteoporotic fractures or arterial thrombotic events
Need for further validation of tools to identify late recurrence, which may be used to select patients at risk who could benefit from extended endocrine therapy.
CTS5 validation from TAILORX study

VALIDATION OF THE CLINICAL TREATMENT SCORE POST 5 YEARS (CTS5) IN WOMEN WITH HORMONE RECEPTOR POSITIVE, HER2-NEGATIVE, NODE-NEGATIVE DISEASE FROM THE TAILORX STUDY

Sestak I, Crager M, Cuzick J, Dowsett M, Shak S, Tang G, Gray RJ, Sparano JA
CTS5: Background

• Continued risk of late recurrence in ER-positive disease

• Extended endocrine therapy can reduce risk of recurrence (ATLAS, aTTom, MA.17, MA.17R, NSABP B-14/B-33/B-42, ABCSG-6a/16, DATA, IDEAL, SOLE)

• Identification of patients who are at high risk of late recurrence is crucial

• Clinical Treatment Score (CTS5) developed to predict late distant recurrence (Dowsett et al., 2018, JCO; 36: 1941-1948)

• CTS5: nodal status, tumor size, tumor grade, and age

www.cts5-calculator.com
CTS5: Background

• Continued risk of late recurrence in ER-positive disease

• Extended endocrine therapy can reduce risk of recurrence (ATLAS, aTTom, MA.17, MA.17R, NSABP B-14/B-33/B-42, ABCSG-6a/16, DATA, IDEAL, SOLE)

• Identification of patients who are at high risk of late recurrence is crucial

• Clinical Treatment Score (CTS5) developed to predict late distant recurrence (Dowsett et al., 2018, JCO; 36: 1941-1948)

• CTS5: nodal status, tumor size, tumor grade, and age

**Primary Objectives:**

• To evaluate CTS5 for prediction of late distant recurrence in TAILORx

• To evaluate cut-off points and risk stratification

**Secondary objectives:**

• To evaluate CTS5 separately
  • for patients aged ≤50 years versus >50 years
  • in the 4 study arms of TAILORx
Conclusions

• Low rates of late distant recurrence were observed in the TAILORx cohort (note: short median FU time)
  ◦ RS 0-25 (ET only): 3.1% (2.4-4.0); RS 11-100 (CET): 3.8% (2.9-4.8)

• CTS5 highly prognostic for prediction of late distance recurrence
  • Specifically for patients older than 50 years
  • Much less prognostic in women aged ≤ 50 years

• Most prognostic value of CTS5 in intermediate or high risk group (RS 11-100)

• CTS5 not significantly prognostic in low risk women by Oncotype Dx (RS 0-10)

• Further evaluation in premenopausal cohorts is needed before CTS5 can be applied to younger patients
Outcome data for patients with early stage hormone receptor positive breast cancer treated with adjuvant endocrine therapy is maturing.
EBCTCG: Improvements since 2000 in the outcome of ER+ disease after 5 years of adjuvant endocrine therapy: Analyses of 86,000 women in 110 trials

IMPROVEMENTS IN LONG-TERM OUTCOME FOR WOMEN WITH ESTROGEN RECEPTOR POSITIVE (ER+) EARLY STAGE BREAST CANCER TREATED WITH 5 YEARS OF ENDOCRINE THERAPY: ANALYSES OF 82,598 WOMEN IN THE EARLY BREAST CANCER TRIALISTS’ COLLABORATIVE GROUP (EBCTCG) DATABASE

Adjuvant endocrine therapy (ET) in ER+ disease

- In women given 5 years adjuvant ET, appreciable risks of distant recurrence continue during years 5-20, even for T1N0 (NEJM 2017; 377: 1836)

- After 5 years of ET for N0 disease, the risks of distant recurrence during years 5-20 were reported to be T1N0: 13% & T2N0: 19%
  - This is primarily from data from patients diagnosed prior to 2000

- In disease diagnosed since 2000 and given 5 years adjuvant ET, it is not yet known how much lower the 10- & 20-year risks will be
Material and methods

- Analyzed 86,000 women in 110 trials in EBCTCG database with T1/T2 ER+ disease who were scheduled to stop adjuvant ET at year 5
  - Median age at diagnosis 55 (31% pre-menopausal)

- Analyzed **FIRST DISTANT** recurrence (ignoring any other recurrences)
  - By period of diagnosis: < 2000, 2000-4, ≥ 2005

Analyses: Kaplan-Meier risks (with 95% CIs) & Cox regressions (adjusted for TN & mm diameter) for M0, T1 or T2 tumours (≤ 20 or 21-50 mm) with < 10 nodes and age < 80 at year 5 of ET
All analyses of RRs by period of diagnosis are fully adjusted for type of systemic therapy, TN status, mm diameter, grade & 5-year age group
**ER+ N+ disease: Distant recurrence during years 5-9, * by period of diagnosis**

<table>
<thead>
<tr>
<th>Period of diagnosis</th>
<th>No. of women</th>
<th>No. of events</th>
<th>Fully adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2000</td>
<td>17,874</td>
<td>1,968</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>2000-04</td>
<td>18,446</td>
<td>1,048</td>
<td>0.75 (0.69-0.82)</td>
</tr>
<tr>
<td>≥ 2005</td>
<td>8,683</td>
<td>394</td>
<td>0.76 (0.67-0.86)</td>
</tr>
</tbody>
</table>

* Note: Women diagnosed since 2000 have limited follow-up beyond year 10.

Women diagnosed after 2000 had 25% fewer distant recurrences.
ER+ N0 disease: Distant recurrence during years 5-9,* by period of diagnosis

<table>
<thead>
<tr>
<th>Period of diagnosis</th>
<th>No. of women</th>
<th>No. of events</th>
<th>Fully adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2000</td>
<td>19,924</td>
<td>898</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>2000-04</td>
<td>11,691</td>
<td>220</td>
<td>0.81 (0.69-0.96)</td>
</tr>
<tr>
<td>≥ 2005</td>
<td>9,646</td>
<td>131</td>
<td>0.62 (0.50-0.76)</td>
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* Note: Women diagnosed since 2000 have limited follow-up beyond year 10

Heterogeneity tests indicate that the difference in the risk ratios is not significant – combined risk ratio of 0.73
**ER+ N0 disease: Distant recurrence during years 5-9,* by period of diagnosis**

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<td>131</td>
<td>0.62 (0.50-0.76)</td>
</tr>
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Therefore in both node positive and node negative disease, the proportional reduction in risk of distant recurrence is about 25% in patients diagnosed ≥ 2000.

* Note: Women diagnosed since 2000 have limited follow-up beyond year 10.

Heterogeneity tests indicate that the difference in the risk ratios is not significant – combined risk ratio of 0.73.

Heterogeneity NS

RR = 0.73
(0.63-0.85)
ER+ T1N0 disease: Distant recurrence during years 5-20 after diagnosis, by period of diagnosis (before or after 2000)

<table>
<thead>
<tr>
<th></th>
<th>Diagnosed &lt; 2000</th>
<th>Diagnosed ≥ 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. initially at risk</td>
<td>13,367</td>
<td>15,199</td>
</tr>
<tr>
<td>No. of distant recurrences</td>
<td>466, 0.8%</td>
<td>197, 0.5%</td>
</tr>
<tr>
<td>Annual rate</td>
<td>8,540, 1.0%</td>
<td>2,046, 15.0%</td>
</tr>
<tr>
<td>No. of distant recurrences</td>
<td>249, 1.0%</td>
<td>15, 0.5%</td>
</tr>
<tr>
<td>Annual rate</td>
<td>3,204, 1.1%</td>
<td>86, 11.1%</td>
</tr>
<tr>
<td></td>
<td>878, 5.5%</td>
<td></td>
</tr>
</tbody>
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ET for 5 years

- ~13% if diagnosed < 2000 (as in NEJM 377:1836)
- 3% if diagnosed ≥ 2000 (but, median FU only 3 years)
ER+ T1N0 disease: Distant recurrence during years 5-20 after diagnosis, by period of diagnosis (before or after 2000)

- **ET for 5 years**
- **Observed 25% proportional reduction in DR risk during years 5-10** – this was then applied to 20 year risk to estimate risk of DR at 20 years in patients diagnosed ≥ 2000
- **~13% if diagnosed < 2000** (as in NEJM 377:1836)
- **3% if diagnosed ≥ 2000** (but, median FU only 3 years)

**Observed risk of distant recurrence**

- **Diagnosed < 2000**
  - Years 5-9: 13,367, 466, 0.8%
  - Years 10-14: 8,540, 249, 1.0%
  - Years 15-20: 3,204, 99, 1.1%
  - 878

- **Diagnosed ≥ 2000**
  - Years 5-9: 15,199, 197, 0.5%
  - Years 10-14: 2,046, 15, 0.5%
  - 86
ER+ T1N0 disease: Distant recurrence during years 5-20 after diagnosis, by period of diagnosis (before or after 2000)

% distant recurrence

ET for 5 years

~13% if diagnosed < 2000

~10%? if diagnosed ≥ 2000
ER+ T2N0 disease: Distant recurrence during years 5-20 after diagnosis, by period of diagnosis (before or after 2000)

- ~5% if diagnosed < 2000
- ~13% if diagnosed ≥ 2000

% distant recurrence

ET for 5 years

~19%
if diagnosed < 2000

~14%
if diagnosed ≥ 2000
Possible reasons for the improvement

- Treatment: **Real** improvements (in surgery, radiotherapy, chemotherapy, endocrine therapy & HER2-directed therapy)

- Treatment guidelines: More patients get optimal therapies

- Stage migration: **Apparent** improvements in all TN categories

- Screening: Earlier detection, and lower-risk lesions
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| Metastatic Disease            | • PEARL study: Phase III trial of Palbociclib + Endocrine Therapy versus Capecitabine |
Adjuvant Therapy/Gene Expression Assays

CURRENT NCCN GUIDELINES
Current NCCN Guidelines: Adjuvant Therapy/Gene Expression Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Predictive</th>
<th>Prognostic</th>
<th>NCCN Category of Preference</th>
<th>NCCN Category of Evidence and Consensus</th>
<th>Recurrence Risk and Treatment Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-gene (OncoType Dx) (for pN0 or node negative)</td>
<td>Yes</td>
<td>Yes</td>
<td>Preferred</td>
<td>1</td>
<td>BINV-N (2 of 4)</td>
</tr>
<tr>
<td>21-gene (OncoType Dx) (for pN+ or node positive)</td>
<td>N/A*</td>
<td>Yes</td>
<td>Other</td>
<td>2A</td>
<td>BINV-N (2 of 4)</td>
</tr>
<tr>
<td>*awaiting results of RxPONDER study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-gene (MammaPrint) (for node negative and 1–3 positive nodes)</td>
<td>Not determined</td>
<td>Yes</td>
<td>Other</td>
<td>1</td>
<td>BINV-N (3 of 4)</td>
</tr>
<tr>
<td>50-gene (PAM 50) (for node negative and 1–3 positive nodes)</td>
<td>Not determined</td>
<td>Yes</td>
<td>Other</td>
<td>2A</td>
<td>BINV-N (3 of 4)</td>
</tr>
<tr>
<td>12-gene (EndoPredict) (node negative and 1–3 nodes)</td>
<td>Not determined</td>
<td>Yes</td>
<td>Other</td>
<td>2A</td>
<td>BINV-N (3 of 4)</td>
</tr>
<tr>
<td>Breast Cancer Index (BCI)</td>
<td>Not determined</td>
<td>Yes</td>
<td>Other</td>
<td>2A</td>
<td>BINV-N (3 of 4)</td>
</tr>
</tbody>
</table>
Current NCCN Guidelines: Adjuvant Therapy/Gene Expression Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Recurrence Risk</th>
<th>Treatment Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-gene (Oncotype Dx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(for pN0 or node negative)</td>
<td>26</td>
<td>Patients with T1b/c and T2, hormone receptor-positive, HER2-negative, and lymph node-negative tumors, with risk scores (RS) between 0–10 have a risk of distant recurrence of &lt;4% and those with RS 11–25, derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study. In women ≤50 years of age with RS 16–25, addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy. Consideration should be given for the addition of chemotherapy to endocrine therapy in this group.</td>
</tr>
<tr>
<td></td>
<td>26–30</td>
<td>In patients with T1 and T2, hormone receptor-positive, HER2-negative, and lymph node-negative tumors and an RS of 26–30, the omission of chemotherapy has not been studied prospectively. Clinicians should consider additional clinical and pathologic factors with regard to the addition of chemotherapy to endocrine therapy in decision-making.</td>
</tr>
<tr>
<td></td>
<td>≥31</td>
<td>For patients with T1b/c and T2, hormone receptor-positive, HER2-negative, and lymph node-negative tumors and an RS ≥31, the addition of chemotherapy to endocrine therapy is recommended.</td>
</tr>
<tr>
<td>21-gene (Oncotype Dx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(for pN+ or node positive)</td>
<td>Low (&lt;18)</td>
<td>The RS is prognostic in women with hormone receptor-positive, lymph node-positive tumors receiving endocrine monotherapy. A secondary analysis of the Oncotype DX trial showed that patients with an RS of 18-25 had a disease-free survival of 94.4% with hormone receptor-positive, HER2-negative, lymph node-positive tumors. The optimal RS cut-off (&lt;11 vs. ≥18) showed a 5-year disease-free survival of 87% with hormone receptor-positive, HER2-negative, lymph node-positive tumors. It is not yet known if this cut-off is generalizable.</td>
</tr>
<tr>
<td></td>
<td>Intermediate (18–30) or High (≥31)</td>
<td>In a secondary analysis of the SWOG 8814 trial of women with hormone receptor-positive, lymph node-positive tumors, high RS (≥31) was predictive of chemotherapy benefit. Because of a higher risk of distant recurrence, patients with hormone receptor-positive, 1–3 positive lymph nodes and RS of ≥18 should be considered for adjuvant chemotherapy in addition to endocrine therapy.</td>
</tr>
</tbody>
</table>
Current NCCN Guidelines: Adjuvant Therapy/Gene Expression Assays

Thus far, no age specific consideration for MammaPrint

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### Gene Expression Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Assay</th>
<th>Recurrence Risk</th>
<th>Treatment Implications</th>
</tr>
</thead>
</table>
| **70-gene** (MammaPrint)  
(for node negative and 1–3 positive nodes) | Low            | With a median follow-up of 5 years, among patients at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% CI, 92.5%–96.2%) among those who did not receive adjuvant chemotherapy. Among patients with 1–3 positive nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1–98.1) in those who received adjuvant chemotherapy vs. 95.6 (95% CI, 92.7–97.4) in those who did not receive adjuvant chemotherapy. Therefore, the additional benefit of adjuvant chemotherapy may be small in this group. |
| 50-gene (PAM 50)  
(for node negative and 1–3 positive nodes) | Low (0–40)      | For patients with T1 and T2 hormone receptor-positive, HER2-negative, lymph node-negative tumors, a risk of recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0,M0. |
|                    | Intermediate (41–60) |                                           |
|                    | High (61–100)     |                                           |
| Node positive:     | Low (0–40)       | In patients with hormone receptor-positive, HER2-negative, lymph node-negative tumors with low risk of recurrence score, treated with endocrine therapy, the risk was less than 3.5% at 10 years and no distant recurrence was observed in a similar group. |
| Node positive:     | High (41–100)    |                                           |
| 12-gene (EndoPredict)  
(none negative and 1–3 nodes) | Low (<3.33)     | For patients with T1 and T2 hormone receptor-positive, HER2-negative, lymph node-negative tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0,M0. In ABCSG 6/8, patients in the low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1–3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years. The risk score is predictive of chemo-benefit based on a prospective analysis of 3,746 archived, HR-positive, HER2-negative, T1–T3 tumors from chemo-endocrine and endocrine-only cohorts, that included women with lymph node-negative and lymph node-positive disease. |
|                    | High (>3.33)     |                                           |
| Breast Cancer Index (BCI) | Low risk of late occurrence (0–5) | For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0,M0. Results of a secondary analysis of the aTTom trial demonstrated that in patients with hormone-receptor positive, node-positive breast cancer, patients with a high BCI (HOXB13/IL17BR (H/I)) derived significant benefit from extending tamoxifen therapy to 10 years vs. 5 years. In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy. |
|                    | High risk of late occurrence (5.1–10) |                                           |
Consideration for Age Integration with Clinical and Genomic Risk

SHOULD AGE BE INTEGRATED TOGETHER WITH CLINICAL AND GENOMIC RISK FOR ADJUVANT CHEMOTHERAPY DECISION IN EARLY LUMINAL BREAST CANCER? MINDACT RESULTS COMPARED TO THOSE OF TAILOR-X

Background

- Unplanned subgroup analysis of MINDACT that was initiated after the observation of heterogeneous clinical outcomes according to age in TAILORx.
Sought to provide prospective evidence of the clinical utility of the addition of the 70-gene signature test (MammaPrint) to standard clinical-pathological criteria in selecting patients for adjuvant chemotherapy.
MINDACT IS A POSITIVE STUDY

The primary statistical test (DMFS at 5Y)

MINDACT was a de-escalation study with primary endpoint of distant metastasis free survival at 5 years for C-high/G-low without chemotherapy

Null Hypothesis 5 Year DMFS: set at 92%

Observed 5 Year DMFS = 94.7%
95% CI ≈ 92.5 – 96.2% exceeds 92% !!!

Primary test significant

Primary test 5-year DMFS rate significant if 95% 2-sided Confidence interval exceeds 92%

F. Cardoso, NEJM 2016
Efficacy Secondary Endpoint: 
CT vs no CT in discordant risk group c-High/g-Low in ITT analysis

No statistical difference at 5 years for CT vs no CT for C-high/G-low patients (95.9 vs. 94.4%) (Δ 1.5%, non-significant)

Among the c-High risk patients, the trial shows that 46% who are genomic low risk (MammaPrint) can safely forego chemotherapy.
TAILORx Results AT MEDIAN FU OF 9 YEARS: Summary

• Primary conclusions
  • **RS 11-25**: ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  
  • **RS 0-10**: Distant recurrence rates very low (2-3%) with ET alone at 9 years
  
  • **RS 26-100**: Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET

• Other observations
  • **Age – RS – Chemo treatment interaction:**
    • Some chemo benefit in women 50 or younger with a RS 15-25
    • Greatest impact on distant recurrence with RS 21-25
MINDACT-Age
CONSORT DIAGRAM

Analysis ITT population (1317 pts):
- HR+/HER2 neg
- ≤ 50 vs >50
- C-High/G-Low (452 and 865 pts)
- Randomized to G vs. C (and consequent CT/no CT)
DMFS at 5 years

AGE ≤ 50 years-old

### Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Event/Total</th>
<th>Hazard Ratio</th>
<th>5-year Survival Estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ACT</td>
<td>17/225</td>
<td>Reference</td>
<td>93.1 (88.6-95.8%)</td>
</tr>
<tr>
<td>ACT</td>
<td>9/227</td>
<td>0.54 (0.24-1.22)</td>
<td>96.1 (91.9-98.2%)</td>
</tr>
</tbody>
</table>

Kaplan-Meier method: Cox model

3% difference

DMFS events (26): distant recurrences (24) and death any cause (2)

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DMFS at 5 years

AGE >50 years-old

DMFS events (46) : distant recurrences (31) and death any cause (15)

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<table>
<thead>
<tr>
<th>ITT1 population</th>
<th>Patients ≤50y old</th>
<th>Patients &gt; 50y old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events / total</td>
<td>Kaplan Meier</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>SY DMFS (95% CI)</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.54 (0.24-1.22)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
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</tbody>
</table>

Absolute difference

DMFS

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<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

Absolute difference

DMFI

- C-High/G-low patients, ≤50y have a small numeric benefit of CT (DMFS 3%, DMFI 2.5%) (stats descriptive only)
- Observed absolute difference is smaller than seen in TailorX
- Median FU in the 2 trials is different (MINDACT: 5 years; TailorX: 7.5 years)
CONCLUSIONS

1. This **unplanned and underpowered** subgroup analysis of MINDACT was initiated following the observation in TailorX of heterogenous clinical outcomes according to age in women at “high clinical risk” using MINDACT’s definition.

2. Although **cautious interpretation is needed** (see large confidence intervals), the present analysis suggests that in women younger than 50, in the ch/gL group, tamoxifen alone might not be the optimal treatment, though the difference seen between CT and no-CT groups is small (<3%).

3. It is possible that this age-dependent effect is due to chemotherapy-induced ovarian function suppression. Neither MINDACT nor TailorX are able to answer this question.
## Agenda

<table>
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| **Adjuvant Endocrine Therapy** | • Ten-year results from NRG Oncology/NSABP B-42  
• Validation of the clinical treatment score post 5 years (CTS5) from the TAILORx study  
• Analyses of 82,598 women in the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) database |
| **Adjuvant Therapy/Gene Expression Assays** | • Should age be integrated together with clinical and genomic risk for adjuvant chemotherapy decision in early luminal breast cancer? MINDACT results compared to those of TAILOR-X |
| **Neoadjuvant Therapy**      | • **SOLTI-1402/CORALLEEN** phase 2 trial of neoadjuvant ribociclib + letrozole vs chemotherapy in PAM50 Luminal B early breast cancer |
| **Metastatic Disease**       | • PEARL study: Phase III trial of Palbociclib + Endocrine Therapy versus Capecitabine                                                     |
SOLTI-1402/CORALLEEN

PHASE 2 TRIAL OF NEOADJUVANT RIBOCICLIB PLUS LETROZOLE VERSUS CHEMOTHERAPY IN PAM50 LUMINAL B EARLY BREAST CANCER: AN OPEN-LABEL, MULTICENTER, TWO-ARM, RANDOMIZED STUDY

Background

- Hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer is clinically and biologically heterogeneous.
- The PAM50 Luminal B subtype represents ~30-40% of all HR+/HER2- breast tumors.
- Patients with Luminal B disease have >10% risk of distant recurrence at 10 years.
- Today, most patients with Luminal B disease receive (neo)adjuvant chemotherapy.

Luminal B breast cancers is defined by aggressive clinical behavior and a prognosis similar to that of non-luminal cancers

**CORALLEEN trial Design**

Phase II randomized study of neoadjuvant ribociclib + letrozole versus chemotherapy in patients with PAM50 luminal B early stage breast cancer

Postmenopausal HR+/HER2-, Stage I-IIIA
Tumor size ≥ 2 cm
PAM50 Luminal B (Prosigna®)

1:1

Stratification factors:
- Tumor size: T1/2 vs T3
- Nodal involvement

Evaluate PAM50 risk of recurrence (ROR) score following neoadjuvant therapy

**Treatment**

- AC (60/600) every 3 weeks x 4
- Weekly paclitaxel 80mg/m² x 12
- Letrozole 2.5 mg/day + Ribociclib 600 mg/day, 3/4w

6 months

PAM50 + RNA/DNA seq & plasma samples

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Primary objective

To evaluate the proportion of PAM50/Prosigna® ROR-low disease at surgery in each treatment arm

Distant Metastasis-Free Survival

ROR score (0-100) = subtype + proliferation + tumor size

Definition of ROR-low/med/high disease

<table>
<thead>
<tr>
<th>Node-negative</th>
<th>Node+ 1-3</th>
<th>Node+ &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROR-low</td>
<td>0-40</td>
<td>0-15</td>
</tr>
<tr>
<td>ROR-intermediate</td>
<td>&gt;40-60</td>
<td>&gt;15-40</td>
</tr>
<tr>
<td>ROR-high</td>
<td>&gt;60-100</td>
<td>&gt;40-100</td>
</tr>
</tbody>
</table>

Question if neoadjuvant ribociclib + letrozole can switch patients with luminal B disease to luminal A disease at time of surgery

Follow-Up Time (Years)

Percent Without Distance Recurrence

Intrinsic subtypes at surgery

Intrinsic subtype conversion to luminal A, which is a less aggressive subtype, occurred in 87.8% of patients in the ribociclib + letrozole arm and in 82.7% of the chemotherapy arm.
Absolute changes in ROR score

$\Delta$ ROR change = ROR score at surgery − ROR at baseline

Chemotherapy

Ribociclib + letrozole

ROR low = 46.1%

ROR low = 46.9%
## Safety

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Ribociclib + letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>n=52</strong></td>
<td><strong>n=51</strong></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 1-2 AEs</strong></td>
<td>52 (100%)</td>
<td>50 (98.0%)</td>
</tr>
<tr>
<td><strong>Grade ≥3 AEs</strong></td>
<td>36 (69.2%)</td>
<td>29 (56.9%)</td>
</tr>
<tr>
<td><strong>Grade ≥3 AEs &gt;10%</strong></td>
<td>Neutropenia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Febrile</td>
<td>Increased Transaminases</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td><strong>AEs leading to</strong></td>
<td>10 (19.2%)</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td><strong>discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AEs leading to dose</strong></td>
<td>43 (82.7%)</td>
<td>30 (58.8%)</td>
</tr>
<tr>
<td><strong>reduction/temporary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>interruption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious AEs All</strong></td>
<td>8 (15.4%)</td>
<td>2 (3.9%)</td>
</tr>
</tbody>
</table>
Conclusions

• CORALLEEN is the first trial testing the activity of ribociclib and endocrine therapy versus multi-agent chemotherapy using a combined biomarker that integrates pathological, biological and prognostic data.

• Neoadjuvant ribociclib and letrozole in high-risk Luminal B breast cancer achieves high rates of ROR-low disease at surgery.

• Multi-agent chemotherapy also achieves high rates of ROR-low disease at surgery but with higher toxicity.

• This suggests that, in clinically high-risk Luminal B disease, a chemo-free treatment strategy based on CDK4/6 inhibition is worth exploring in future neo(adjuvant) trials.
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• Multi-agent chemotherapy also achieves high rates of ROR-low disease at surgery but with higher toxicity.

• This suggests that, in clinically high-risk Luminal B disease, a chemo-free treatment strategy based on CDK4/6 inhibition is worth exploring in future neo(adjuvant) trials.

Supports the hypothesis that we could possibly substitute this combination for chemotherapy, however remember that ROR-low disease is a surrogate and it is unknown what is the best surrogate endpoint to test targeted treatments in the neoadjuvant setting.
In a biomarker analysis of the CORALLEEN trial, an increase in stromal tumor infiltrating lymphocytes (sTILs) is noted in ~30% of patients following treatment with ribociclib + letrozole and was associated with poor ROR response.

- Suggests that immune checkpoint blockade may be worth exploring in this setting.
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<td>• <strong>PEARL study: Phase III trial of Palbociclib + Endocrine Therapy versus Capecitabine</strong></td>
</tr>
</tbody>
</table>
Metastatic Disease

NCCN GUIDELINES
Current NCCN Guidelines: Metastatic Disease

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE

<table>
<thead>
<tr>
<th>HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression</th>
<th>HER2-Positive and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimens: First-Line Therapy</strong></td>
<td><strong>Preferred Regimens: Second- and Subsequent-Line Therapy</strong></td>
</tr>
<tr>
<td>• Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)(^a)</td>
<td>• Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)(^a)</td>
</tr>
<tr>
<td>• Selective ER down-regulator (fulvestrant, category 1)(^b)</td>
<td>• For PIK3CA-mutated tumors, see additional targeted therapy options (see BINV-R)(^c)</td>
</tr>
<tr>
<td>• Non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)(^b)</td>
<td>• Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)(^a)^(^b)</td>
</tr>
<tr>
<td>• Selective estrogen receptors modulator (tamoxifen or toremifene)</td>
<td>• Non-steroidal aromatase inhibitor (anastrozole, letrozole)</td>
</tr>
<tr>
<td>• Steroidal aromatase inactivator (exemestane)</td>
<td>• Steroidal aromatase inactivator (exemestane)</td>
</tr>
<tr>
<td><strong>Useful in Certain Circumstances:</strong></td>
<td></td>
</tr>
<tr>
<td>• Megestrol acetate</td>
<td>• Aromatase inhibitor ± trastuzumab</td>
</tr>
<tr>
<td>• Fluoxymesterone</td>
<td>• Aromatase inhibitor ± lapatinib</td>
</tr>
<tr>
<td>• Ethynyl estradiol</td>
<td>• Aromatase inhibitor ± lapatinib + trastuzumab</td>
</tr>
<tr>
<td>• Abemaciclib(^a)^(^d)</td>
<td>• Fulvestrant ± trastuzumab</td>
</tr>
<tr>
<td></td>
<td>• Tamoxifen ± trastuzumab</td>
</tr>
</tbody>
</table>
### Current NCCN Guidelines: Metastatic Disease

**HER2-Negative**

**Preferred Regimens**
- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- For germline BRCA1/2 mutations<sup>d</sup> see additional targeted therapy options (<sup>BINV-R</sup>)<sup>e</sup>
- Platinum (option for patients with triple-negative tumors and germline BRCA1/2 mutation)<sup>d</sup>
  - Carboplatin
  - Cisplatin
- For PD-L1–positive TNBC see additional targeted therapy options (<sup>BINV-R</sup>)<sup>e</sup>

**Other Recommended Regimens<sup>f</sup>**
- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

**Useful in Certain Circumstances<sup>f</sup>**
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab<sup>g</sup>
- Carboplatin + paclitaxel or albumin-bound paclitaxel
Results from PEARL study (GEICAM/2013-02_CECOG/BC.1.3.006)

A PHASE 3 TRIAL OF PALBOCICLIB IN COMBINATION WITH ENDOCRINE THERAPY VERSUS CAPECITABINE IN HORMONAL RECEPTOR-POSITIVE/HER2-NEGATIVE METASTATIC BREAST CANCER PATIENTS WHOSE DISEASE PROGRESSED ON AROMATASE INHIBITORS

Study Design (Cohort 1, initial design)

**HR+/HER2- MBC**
- recurrence on or within 12m of completed adjuvant NSAI
- or progression while on or within 1m of completing NSAI for advanced disease
- one line of chemo for MBC allowed
- no prior capecitabine or exemestane for MBC

**N=300**

**Stratification:**
- visceral vs non visceral metastases
- prior sensitivity to hormonal treatment (yes vs no)
- prior chemotherapy for MBC (yes vs no)
- country

**Randomization 1:1**

- Exemestane 25 mg daily + Palbociclib 125 mg 3 weeks on/1 week off, q 28-days
- Capecitabine 1250 mg/m² (1000 mg/m² in patients >70 years old) twice daily 2 weeks on/1 week off, q 21-days

*Treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent*

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PEARL: Study Design

Addition of cohort 2 after report of high frequency of ESR1 mutations in patients previously treated with AIs and studies suggesting fulvestrant may be active in ESR1 mutant tumors
The main aims of the trial were testing if:

- PAL + FUL is superior to CAP, or/and
- PAL + ET (EXE or FUL) is superior to CAP in patients with presumed hormonal sensitivity (ESR1 wild type tumors)
The combination of PAL+FUL was not superior to CAP in terms of PFS in MBC patients resistant to aromatase inhibitors.
The combination of PAL+ET was not superior to CAP in terms of PFS in patients with ESR1 wild type tumors.

The adjusted hazard ratio was obtained using a stratified Cox proportional hazard model with treatment arm and the stratification factors as covariates.
Treatment with palbociclib plus endocrine therapy was generally better tolerated than capecitabine.
The PEARL study did not meet its two co-primary endpoints:

- The combination of PAL+FUL was not superior to CAP in terms of PFS in MBC patients resistant to aromatase inhibitors.
- The combination of PAL+ET was not superior to CAP in terms of PFS in patients with ESR1 wild type tumors.

Similar results were observed in:

- All patients (cohort 1 + cohort 2)
- The luminal population

Treatment with palbociclib plus endocrine therapy was generally better tolerated than capecitabine:

- Lower treatment discontinuations (ET + PAL 3.7% vs CAP 12.8%)
- Smaller proportion of patients with treatment-related Serious Adverse Events (ET + PAL 3.7% vs CAP 10.4%)
The PEARL study did not meet its two co-primary endpoints:

- The combination of PAL+FUL was not superior to CAP in terms of PFS in MBC patients resistant to aromatase inhibitors.
- The combination of PAL+ET was not superior to CAP in terms of PFS in patients with ESR1 wild type tumors.

Similar results were observed in:

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Treatment with palbociclib plus endocrine therapy was generally better tolerated than capecitabine:

- Lower treatment discontinuations (ET + PAL 3.7% vs CAP 12.8%)
- Smaller proportion of patients with treatment-related Serious Adverse Events (ET + PAL 3.7% vs CAP 10.4%)

PEARL: Summary/Conclusions

Take Home Considerations:

1. Stresses the importance of giving CDK4/6 inhibitors as first or early line therapy in patients with hormone receptor positive metastatic breast cancer before they become resistant to endocrine therapy
   a. Data shows decreased PFS when given after resistance to endocrine therapy
2. Capecitabine is an effective drug
SABCS 2019 Hormone Receptor Positive Breast Cancer

TAKE HOME POINTS
Take Home Points

**Adjuvant Endocrine Therapy:**
- Extended letrozole therapy demonstrated a statistically significant improvement in DFS without OS benefit.
- CTS5 was highly prognostic for prediction of late distant recurrence in TAILORx for patients older than 50 years, particularly in intermediate or high risk group patients (RS 11-100).
- Improved outcomes were seen in patients diagnosed after 2000, with 25% fewer distant recurrences ≥ 2000 vs < 2000 in years 5-9.
Take Home Points

• Adjuvant Endocrine Therapy:
  • Extended letrozole therapy demonstrated a statistically significant improvement in DFS without OS benefit
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• Adjuvant Therapy/Gene Expression Assays:
  • The unplanned MINDACT subgroup analysis showed that women younger than 50 in the cH/gL group may be insufficiently treated with tamoxifen alone, although the difference seen between chemotherapy and no chemotherapy groups was small (<3%)
Take Home Points

• Adjuvant Endocrine Therapy:
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• Adjuvant Therapy/Gene Expression Assays:
  • The unplanned MINDACT subgroup analysis showed that women younger than 50 in the cH/gL group may be insufficiently treated with tamoxifen alone, although the difference seen between chemotherapy and no chemotherapy groups was small (<3%)

• Neoadjuvant Therapy:
  • In the phase II CORALLEEN trial, both neoadjuvant ribociclib + letrozole and neoadjuvant chemotherapy achieved high rates of ROR-low disease at surgery in patients with high-risk luminal B breast cancer
Take Home Points

- **Metastatic Disease**
  - In the phase III PEARL study, the combination of palbociclib + endocrine therapy had similar outcomes to capecitabine in terms of PFS in hormone receptor positive metastatic breast cancer whose disease progressed on aromatase inhibitors
Questions?
Thank You!

QUESTIONS: AMPARKESTMEDICINE.WISC.EDU