Advances in the Diagnosis and Treatment of Breast Cancer

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Disclosures

• Genomic Health: Speaker and Consultant
• AstraZeneca: Advisory Board
• Off-label medication use will be discussed (sacituzumab govitecan, alpelisib, oxybutynin, and probably a few I’m forgetting to mention here...)}
COMBINATION CHEMOTHERAPY AS AN ADJUVANT TREATMENT IN OPERABLE BREAST CANCER

Gianni Bonadonna, M.D., Ercole Brusamolino, M.D., Pinuccia Valagussa, B.S., Anna Rossi, M.D., Luisa Brugnatelli, M.D., Cristina Brambilla, M.D., Mario De Lena, M.D., Gabriele Tancini, M.D., Emilio Bajetta, M.D., Renato Musumeci, M.D., and Umberto Veronesi, M.D.

Figure 1. Treatment-Failure Time Distribution in All Evaluable Patients.
Role of Adjuvant Chemotherapy in Early Breast Cancer

• Adjuvant chemotherapy reduces recurrence in ER-positive, node-negative breast cancer

• U.S. N.I.H consensus panel in 2000 concluded “…adjuvant chemotherapy … should be recommended to the majority of women with localized breast cancer regardless of lymph node, menopausal, or … receptor status.”
We all know the lasting effects of chemotherapy…

- neuropathy
- alopecia
- cognitive deficit
- early menopause
- infertility
- fatigue
- and so much more
Trial Assigning Individualized Options for Treatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score


on behalf of the TAILORx Investigators

References made to the Recurrence Score® or 21-Gene Assay Recurrence Score refer to the Oncotype DX Breast Recurrence Score® test, a test offered exclusively by Genomic Health, Inc.
Target Population: HR-positive, HER2-negative, Node-negative Breast Cancer

- **50% of all breast cancers in U.S.**

- Adjuvant chemotherapy recommended, but benefit small

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**Background: Rationale for Design of TAILORx Precision Medicine Trial**

**Biomarker Directed Chemotherapy**

**ALL PATIENTS (B-20)**

- TAM ± (±C)MF (N=668)
- 10-year DRFS
- 88% vs. 92%, p=0.02
**Assay Selected: 21-Gene Assay (Recurrence Score)**

- Two prospective validation studies in ER-positive, node-negative breast cancer
- Prognostic (B-14 study - tamoxifen): low recurrence with ET if RS low
- Predictive (B-20 study - tam ± CMF): large chemotherapy benefit if RS high
- Uncertain chemotherapy benefit for mid-range RS result

**HIGH RS (≥31)**

**PREDICTION**

10-year DRFS
61% vs. 88%, p<0.001


Used with permission from Dr. J Sparano and ASCO.
Background: Rationale for Adjusting RS Ranges in TAILORx

**NSABP B-20: Relationship Between Continuous RS Result and Distant Recurrence by Treatment**

- **RS range adjusted for mid-range**
  - Preserve prediction in high risk group
  - Minimize potential for undertreatment


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**Diagram Description**
- **Y-axis:** Distant Recurrence at 10 Years
- **X-axis:** Recurrence Score
- **Graph Lines:**
  - **Tam:** Continuous line at 0.1
  - **Tam + Chemo:** Continuous line at 0.0

**Legend:**
- **Tam**
- **Tam + Chemo**

**Benefit from chemo**

---

**Prepared by:**
Joseph A. Sparano, MD

**Used with permission from Dr. J Sparano and ASCO.**
Background: Rationale for Adjusting RS Ranges in TAILORx

Large Chemotherapy Benefit in NSABP B-20 With Recurrence Score® Result (RS) ≥26 Similar to RS Result ≥31

<table>
<thead>
<tr>
<th>RS</th>
<th>No.</th>
<th>%</th>
<th>Patients</th>
<th>10-year DRFS (%)</th>
<th>Recurrence by Addition of Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tam</td>
<td>Tam+Chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>0-10</td>
<td>177</td>
<td>27</td>
<td></td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>11-25</td>
<td>279</td>
<td>43</td>
<td></td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>26-100</td>
<td>195</td>
<td>30</td>
<td></td>
<td>63</td>
<td>88</td>
</tr>
</tbody>
</table>


DRFS: Distant recurrence-free survival
TAILORx Methods: Key Eligibility Criteria
(Met NCCN Guidelines for Recommending or Considering Adjuvant Chemotherapy)

- Women with invasive breast cancer
- Age 18-75 years
- Node-negative
- ER and/or PR-positive in local lab (before ASCO-CAP guidelines)
- HER2-negative in local lab
- Tumor size - 1.1-5.0 cm (or 0.6-1.0 cm and int-high grade)
- Willing to have chemotherapy treatment assigned or randomized based on RS assay results
**TAILORx Methods:**
Treatment Assignment & Randomization
Accrued April 2006 - Oct 2010

- **Preregister - Oncotype DX RS (N=11,232)**
- **Register (N=10,273)**

**ARM A:** Low RS 0-10
(N=1629 evaluable)
ASSIGN Endocrine Therapy (ET)

**ARM B:** Experimental Arm
(N=3399)
ET Alone

**Mid-Range RS 11-25**
(N=6711 evaluable)
RANDOMIZE

**ARM C:** Standard Arm
(N=3312)
ET + Chemo

**ARM D:** High RS 26-100
(N=1389 evaluable)
ASSIGN ET + Chemo

Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS

Joseph A. Sparano, MD
Used with permission from Dr. J Sparano and ECOG-ACRIN cancer research group.
### TAILORx Methods: Endpoints

**Primary endpoints:**
- RS 11-25: IDFS
- RS 0-10: DRFI

<table>
<thead>
<tr>
<th>endpoint</th>
<th>Distant Recurrence</th>
<th>Local-Regional Recurrence</th>
<th>Contralateral Breast Cancer</th>
<th>Other Second Primary Cancer</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive disease-free survival (IDFS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Distant recurrence-free interval (DRFI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Relapse-free interval (RFI)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

• **Patient characteristics**
  - Median age 55 years, and 33% were 50 or younger
  - 63% had tumor size 1-2 cm and 57% had intermediate grade histology
  - Clinical risk criteria: 74% low risk, 26% high risk

• **Systemic Treatment**
  - **Endocrine therapy**
    - Comparable adherence and duration in both arms
    - Postmenopausal - included AI in 90%
    - Premenopausal - included OS in 15%
  - **Chemotherapy**
    - Most common regimens were TC (56%) and anthracycline-containing (36%)
## Comparable Patient Populations Between TAILORx and SEER

### Patient Age

<table>
<thead>
<tr>
<th>Age</th>
<th>TAILORx&lt;sup&gt;1&lt;/sup&gt; 2006-2010</th>
<th>SEER&lt;sup&gt;2&lt;/sup&gt; 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RS 0-10</td>
<td>RS 11-25</td>
</tr>
<tr>
<td>Distribution – total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 years</td>
<td>58 (4%)</td>
<td>311 (5%)</td>
</tr>
<tr>
<td>41-50 years</td>
<td>371 (23%)</td>
<td>1905 (28%)</td>
</tr>
<tr>
<td>51-60 years</td>
<td>563 (35%)</td>
<td>2441 (36%)</td>
</tr>
<tr>
<td>61-70 years</td>
<td>518 (32%)</td>
<td>1763 (26%)</td>
</tr>
<tr>
<td>70-75 years</td>
<td>109 (7%)</td>
<td>291 (4%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Sparano et al. *N Engl J Med* 2018; <sup>2</sup>SEER Database N-, HR+, HER2-
## Comparable Patient Populations Between TAILORx and SEER

### Tumor Size

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>TAILORx&lt;sup&gt;1&lt;/sup&gt; 2006-2010</th>
<th>SEER&lt;sup&gt;2&lt;/sup&gt; 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution – total no. (%)</td>
<td>RS 0-10</td>
<td>RS 11-25</td>
</tr>
<tr>
<td>≤1 cm (grade 2/3)</td>
<td>202 (12%)</td>
<td>869 (13%)</td>
</tr>
<tr>
<td>1.1-2.0 cm</td>
<td>1018 (63%)</td>
<td>4253 (63%)</td>
</tr>
<tr>
<td>2.1-3.0 cm</td>
<td>297 (18%)</td>
<td>1265 (19%)</td>
</tr>
<tr>
<td>3.1-4.0 cm</td>
<td>83 (5%)</td>
<td>241 (4%)</td>
</tr>
<tr>
<td>≥4.1 cm</td>
<td>19 (1%)</td>
<td>81 (1%)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Sparano et al. *N Engl J Med* 2018; <sup>2</sup>SEER Database N-, HR+, HER2-

*Unknown tumor size - 3 patients
TAILORx Results: RS Distribution in TAILORx Compared with Concurrent Use in Clinical Practice

Genomic Health (data on file)
# TAILORx Patient Characteristics: Intention-to-Treat Population at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=9719)</th>
<th>Recurrence Score of 0-10 (n=1619)</th>
<th>Recurrence Score of 11-25 (n=3399)</th>
<th>Recurrence Score of 26-100 (n=1389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range) – years</td>
<td>56 (25-75)</td>
<td>58 (25-75)</td>
<td>55 (23-75)</td>
<td>56 (23-75)</td>
</tr>
<tr>
<td>Tumor Size – cm</td>
<td>1.5 (1.2-2.1)</td>
<td>1.5 (1.2-2.0)</td>
<td>1.5 (1.2-2.0)</td>
<td>1.7 (1.3-2.3)</td>
</tr>
<tr>
<td>Tumor Grade</td>
<td>L – 2512 (27%)</td>
<td>L – 34%</td>
<td>L – 29%</td>
<td>L – 7%</td>
</tr>
<tr>
<td></td>
<td>I – 5242 (56%)</td>
<td>I – 59%</td>
<td>I – 57%</td>
<td>I – 43%</td>
</tr>
<tr>
<td></td>
<td>H – 1676 (18%)</td>
<td>H – 7%</td>
<td>H – 13%</td>
<td>H – 50%</td>
</tr>
<tr>
<td>Clinical Risk</td>
<td>L – 6615 (70%)</td>
<td>L – 78%</td>
<td>L – 74%</td>
<td>L – 43%</td>
</tr>
<tr>
<td></td>
<td>H – 2812 (30%)</td>
<td>H – 22%</td>
<td>H – 26%</td>
<td>H – 57%</td>
</tr>
</tbody>
</table>

Clinical Risk Groups: HR-Positive, HER2-Negative, Node-negative Subgroup

Clinical risk in the TAILORx trial was defined as in the MINDACT trial via a modified Adjuvant! Online score.

**Low risk:**
- Tumor size ≤ 3 cm and Grade 1
- Tumor size ≤ 2 cm and Grade 2
- Tumor size ≤ 1 cm and Grade 3

**High risk:**
- All other cases with known values for grade and tumor size
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

Primary Endpoint
Invasive Disease-Free Survival

836 IDFS events after median of 7.5 years

- 338 of 836 (40.3%) with recurrence as first event
- 199 of 836 (23.8%) were distant recurrence

P = 0.26
Hazard Ratio Arm B vs. Arm C (95% CI)
1.08 (0.94, 1.24)

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Arm C</th>
<th>CHEMO + ET</th>
<th>Arm B</th>
<th>ET Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3312</td>
<td>3204</td>
<td>3104</td>
<td>2993</td>
</tr>
<tr>
<td>12</td>
<td>3399</td>
<td>3293</td>
<td>3194</td>
<td>3081</td>
</tr>
<tr>
<td>24</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>36</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>48</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>60</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>72</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>84</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>96</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
<tr>
<td>108</td>
<td>2849</td>
<td>2645</td>
<td>2335</td>
<td>2131</td>
</tr>
</tbody>
</table>

Used with permission from Dr. J Sparano and ASCO.
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

Other Secondary Endpoints

Relapse-Free Interval

- **CHEMO + ET**
- **ET Alone**

Overall Survival

- **CHEMO + ET**
- **ET Alone**

**TAILORx Results** - ITT Population: RS 11-25 (Arms B & C)

- **P = 0.33**
  - Hazard Ratio Arm B vs. Arm C (95% CI)
  - 1.11 (0.90, 1.37)

- **P = 0.89**
  - Hazard Ratio Arm B vs. Arm C (95% CI)
  - 0.99 (0.79, 1.22)

**Number at risk**

- **Arm C CHEMO + ET**
  - 3312, 3213, 3134, 3047, 2911, 2705, 2405, 1840, 1176, 543

- **Arm B ET Alone**
  - 3399, 3313, 3227, 3127, 3010, 2802, 2498, 1915, 1245, 568

**Number at risk**

- **Arm C CHEMO + ET**
  - 3312, 3252, 3201, 3144, 3084, 2962, 2783, 2292, 1565, 815

- **Arm B ET Alone**
  - 3399, 3355, 3315, 3260, 3204, 3082, 2903, 2400, 1614, 859

Used with permission from Dr. J Sparano and ASCO.
TAILORx Results - ITT Population: All Arms (A,B,C & D)

9-Year Event Rates

IDFS Decreases as RS Result Increases
P<0.001

Arm A: ET alone (RS 0-10) 3% Distant recurrence rate
Arms B & C: Randomized (RS 11-25) 5% Distant recurrence rate overall
Arm D: Chemoendocrine (RS 26-100) 13% Distant recurrence rate despite chemotherapy + endocrine therapy

Joseph A. Sparano, MD

Used with permission from Dr. J Sparano and ASCO.
TAILORx Results - ITT Population: Exploratory Analysis of Chemotherapy Treatment Interactions in RS 11-25 Arms

No Statistically Significant Chemotherapy Treatment Interactions in the Following Subgroups:

- Recurrence Score:
  - 11-15 vs. 16-20 vs. 21-25
  - 11-17 vs. 18-25

- Tumor size:
  - (≤2 cm vs. >2 cm)

- Grade:
  - (low vs. int. vs. high)

- Menopausal status:
  - (pre vs. post)

- Clinical risk category:
  - (high vs. low)

There was a significant chemotherapy treatment interaction with patient age and Recurrence Score (p=0.004) for IDFS.
TAILORx Results - ITT Population: Potential Chemotherapy Benefit in Women ≤50 Years (N=2,216) in RS 11-25 Arms

≤50 Years, RS 16-25 - some chemotherapy benefit

- RS 16-20: 9% fewer IDFS events, including ~2% fewer distant recurrences
- RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences

≤50 Years, RS 0-15 - good prognosis with endocrine therapy (ET)

- RS 0-15: 3% distant recurrence with ET alone
- RS 11-15: No evidence for chemotherapy benefit
Primary conclusions

- **RS 11-25**: Endocrine therapy (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 chemotherapy plus ET

Other observations

- **Age - RS - Chemotherapy treatment interaction**:
  - Some chemotherapy benefit in women 50 or younger with a RS 16-25
  - Greatest impact on distant recurrence with RS 21-25
Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age <50)

**Recurrence**
- 15 year gain 12.3% (SE 1.6)
- Logrank 2p<0.00001

**Breast Cancer Mortality**
- 15 year gain 10.0% (SE 1.6)
- Logrank 2p<0.00001

Polychemotherapy vs. Not, by Entry Age: 15-year Probabilities of Recurrence and Breast Cancer Mortality (Age 50-69)

**Recurrence**
- Control 57.6%
- Polychemotherapy 53.4%

**Breast Cancer Mortality**
- Control 50.4%
- Polychemotherapy 47.4%

15 year gain 4.1% (SE 1.2) Logrank 2p<0.00001

15 year gain 3.0% (SE 1.3) Logrank 2p<0.00001

<table>
<thead>
<tr>
<th>RS 0-10</th>
<th>RS 11-15</th>
<th>RS 16-20</th>
<th>RS 21-25</th>
<th>RS 26-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CT Benefit</td>
<td>No CT Benefit</td>
<td>No CT Benefit</td>
<td>No CT Benefit</td>
<td>Large CT Benefit¹</td>
</tr>
</tbody>
</table>

~85% of patients² | ~15% of patients²

¹Sparano and Paik, *J Clin Oncol* 2008; ²Genomic Health (data on file) RS distributions in tested US N-, HR+, HER2- patients in 2017
### TAILORx-Defined Cutoff for Definitively Determining Chemotherapy Benefit with Oncotype DX® Test
(Node-negative, HR-positive, HER2-negative)

#### Subgroup Age ≤50 years

<table>
<thead>
<tr>
<th>RS 0-10</th>
<th>RS 11-15</th>
<th>RS 16-20</th>
<th>RS 21-25</th>
<th>RS 26-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CT Benefit</td>
<td>No CT Benefit</td>
<td>~1.6% CT Benefit</td>
<td>~6.5% CT Benefit</td>
<td>Large CT Benefit</td>
</tr>
</tbody>
</table>

| ~50% of patients | ~23% of patients | ~12% of patients | ~15% of patients |

**SYSTEMIC ADJUVANT TREATMENT: NODE-NEGATIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE**

- **Tumor ≤0.5 cm**
  - pN0
  - Consider adjuvant endocrine therapy\(^{aa,bb}\) (category 2B)
  - Adjuvant endocrine therapy\(^{aa,bb}\)
  - or
  - Adjuvant chemotherapy\(^{cc,dd}\)
  - followed by endocrine therapy\(^{aa,bb}\) (category 1)

- **Not done**
  - Adjuvant endocrine therapy\(^{aa,bb,j}\)

- **Recurrence score <26\(^{ii}\)**
  - Adjuvant endocrine therapy\(^{aa,bb}\)
  - or
  - Adjuvant chemotherapy\(^{cc,dd}\)
  - followed by endocrine therapy\(^{aa,bb}\)

- **Recurrence score 26–30**
  - Adjuvant endocrine therapy\(^{aa,bb}\)
  - or
  - Adjuvant chemotherapy\(^{cc,dd}\)
  - followed by endocrine therapy\(^{aa,bb}\)

- **Recurrence score ≥31**
  - Adjuvant endocrine therapy\(^{aa,bb}\)
  - plus adjuvant chemotherapy\(^{cc,dd}\)

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\(^{aa}\) Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.

\(^{bb}\) Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

\(^{cc}\) Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).

\(^{dd}\) See NCCN Clinical Practice Guidelines for Older Adult Oncology.

\(^{ii}\) Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).

\(^{j}\) Patients with T1b tumors with low-grade histology should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

\(^{h}\) Consider the use of adjuvant chemotherapy in women 50 years of age or younger with a recurrence score of 16–25 based on an exploratory analysis from the TAILORx study demonstrating lower distant recurrences in women 50 years of age or younger randomized to chemotherapy.
# TAILORx: Significant Number Of Patients With RS 26-100 Had Low Clinical Risk

<table>
<thead>
<tr>
<th>Recurrence Score®</th>
<th>Clinical risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-25 (n=8068)</td>
<td>Low: 75% High: 25%</td>
</tr>
<tr>
<td>26-100 (n=1359)</td>
<td>Low: 43% High: 57%</td>
</tr>
</tbody>
</table>

*low clinical risk defined by low grade and tumor size <=3cm, intermediate grade and tumor size <=2cm, and high grade and tumor size <=1cm;
high clinical risk defined as all other cases with known values for grade and tumor size

Would have been overtreated

Would have been under-treated

Sparano et al. *N Engl J Med* 2018
Impassion 130
5 mg tamoxifen in prevention
Alpelisib+Fulvestrant
Oxybutynin for hot flashes
KATHERINE
Germline genetic testing
Extended AI therapy
Impassion 130 - Our first role for immunotherapy in breast cancer! Triple negative metastatic breast cancer...NOW FDA APPROVED ATEZOLIZUMAB.

- 5 mg tamoxifen in prevention
- Alpelisib+Fulvestrant
- Oxybutynin for hot flashes
- KATHERINE
- Germline genetic testing
- Extended AI therapy
FDA Accepts BLA, Grants Priority Review for Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

By The ASCO Post
Last Updated: 7/23/2018 10:32:07 AM

The U.S. Food and Drug Administration (FDA) accepted a Biologics license application (BLA) for filing and granted Priority Review to sacituzumab govitacan for the treatment of patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease. The prescription drug user fee application date is January 18, 2019.

Sacituzumab govitacan would be the first antibody–drug conjugate approved for the treatment of metastatic triple-negative breast cancer.

The filing is based on data from a phase I/II trial of sacituzumab govitacan in metastatic triple-negative breast cancer.

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Antonio Breast Cancer Symposium

- Impassion 130
- 5 mg tamoxifen in prevention
- Alpelisib+Fulvestrant
- Oxybutynin for hot flashes
- KATHERINE
- Germline genetic testing
- Extended AI therapy
Abs GS03-01. Randomized trial of low dose tamoxifen to prevent recurrence of breast intraepithelial neoplasia. Study TAM01


EudraCT Number
2007-007740-10
ClinicalTrials.gov
NCT01357772

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Study Design

Women aged <75yrs with IEN (ADH or LCIS or ER+ve or unk DCIS)

Tamoxifen 5 mg/day

Placebo

3 yr treatment + at least 2 yr FU

Primary endpoint: Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

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# Main subject and tumor characteristics (n = 500)

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen N=253</th>
<th>Placebo N=247</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>54 (9.6)</td>
<td>54 (9.1)</td>
</tr>
<tr>
<td>Pre-menopausal, %</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.7 (4.8)</td>
<td>25.3 (4.2)</td>
</tr>
<tr>
<td>ADH, %</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>LCIS, %</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>DCIS, %</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>ER/PR+ve/unknown, %</td>
<td>66 / 34</td>
<td>67 / 33</td>
</tr>
<tr>
<td>HER 2-neu 3+, %</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Quadrantectomy/Mastectomy %</td>
<td>84 / 16</td>
<td>82 / 18</td>
</tr>
<tr>
<td>Radiotherapy, %</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>

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San Antonio Breast Cancer Symposium®, December 4-8, 2018

Log-rank p=0.024

All breast events, 28 vs 14
HR=0.48, 95%CI: 0.26-0.92
Rate: 23.9 vs 11.6/1000 py

Log-rank p=0.018

Contralateral BrCa, 12 vs 3
HR=0.24, 95%CI: 0.07-0.87

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Slight difference in hot flash frequency. No difference in vaginal complaints or arthralgias.

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>DVT or PE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other neoplasms</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>

20 mg/d, expected Endometrial Cancer: 2.7; DVT+PE: 2.4

1INSABP-P1 trial (Fisher et al. JNCI 90:1371-86, 1998)
Tamoxifen 5 mg (prevention)

- In ADH, LCIS, DCIS patients, 5 mg is probably “OK”

- Less thrombosis, less uterine cancer, less menopausal complaints, and still decreases bilateral breast cancer risk

- TAKE HOME: No randomized data 20 mg vs 5 mg available, so start with 20 mg. If not tolerated, don’t lose sleep about discussing/using decreased dose. Can use 10 mg QOD (there is no 5 mg tablet, and half-life is 5-7 days).
Antonio Breast Cancer Symposium

- Impassion 130
- 5 mg tamoxifen in prevention
- Alpelisib+Fulvestrant
- Oxybutynin for hot flashes
- KATHERINE
- Germline genetic testing
- Extended AI therapy
Alpelisib (ALP) + Fulvestrant (FUL) for Advanced Breast Cancer (ABC): Phase 3 SOLAR-1 Trial Results

Dejan Juric,1* Eva Maria Ciruelos,2 Gabor Rubovszky,3 Mario Campone,4 Sibylle Loibl,5 Hope S. Rugo,6 Hiroji Iwata,7 Pierfranco Conte,6 Ingrid A. Mayer,9 Bella Kaufman,10 Toshinari Yamashita,11 Yen-Shen Lu,12 Kenichi Inoue,13 Masato Takahashi,14 Szuzsanna Pápai,15 Anne-Sophie Longin,16 David Mills,17 Celine Wilke,17 Michelle Miller,18 Naveen Babbar,18 Fabrice André19

1Massachusetts General Hospital, Boston, MA, USA; 2Hospital Universitario 12 de Octubre, Madrid, Spain; 3National Institute of Oncology, Budapest, Hungary; 4Institut de Cancérologie de l’Ouest, St Herblain, France; 5German Breast Group, Neu-Isenburg, Germany; 6UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; 7Aichi Cancer Center, Nagoya, Japan; 8Istituto Oncologico Veneto, and University of Padua, Padua, Italy; 9Vanderbilt University, Nashville, TN, USA; 10Chaim Sheba Medical Center, Tel HaShomer, Israel; 11Kanagawa Cancer Center, Yokohama, Japan; 12National Taiwan University Hospital, Taipei, Taiwan; 13Saitama Cancer Center, Saitama, Japan; 14NHO Hokkaido Cancer Center, Sapporo, Japan; 15Duna Medical Center, Budapest, Hungary; 16Novartis Pharma S.A.S., Paris, France; 17Novartis Pharma AG, Basel, Switzerland; 18Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 19Gustave Roussy, Université Paris-Saclay, Villejuif, France.

*Presenting authors.

alpelisib is a selective PI3K-alpha inhibitor
The Importance of the PI3K Pathway in HR+ Breast Cancer

- The PI3K pathway is frequently altered in HR+ breast cancer and has been implicated in resistance to endocrine therapies.1,2
- Approximately 40% of HR+ breast cancers harbor a PIK3CA mutation, leading to hyperactivation of the PI3K pathway.3-5
- PI3K signaling has been shown to promote estrogen-independent growth of ER+ breast cancer cells,6,7 and this growth is inhibited by the addition of PI3K inhibitors to antiestrogens.8


ER+, estrogen receptor-positive; HR+, hormone receptor-positive; PI3K, phosphatidylinositol 3-kinase.


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SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)¹

**Men or postmenopausal women with HR+, HER2- ABC**
- Recurrence/progression on/after prior AI
- Identified PIK3CA status (in archival or fresh tumor tissue⁴)
- Measurable disease or ≥ 1 predominantly lytic bone lesion
- ECOG performance status ≤ 1 (N = 572)

**PIK3CA-mutant cohort (n = 341)**
- ALP 300 mg PO QD + FUL 500 mg IM  
  n = 169
- PBO + FUL 500 mg IM  
  n = 172

**PIK3CA-non-mutant cohort (n = 231)**
- ALP 300 mg PO QD + FUL 500 mg IM  
  n = 115
- PBO + FUL 500 mg IM  
  n = 116

**Primary endpoint**
- PFS in PIK3CA-mutant cohort (locally assessed)

**Secondary endpoints include**
- OS (PIK3CA-mutant cohort)
- PFS (PIK3CA-non-mutant cohort)
- PFS (PIK3CA mutation in ctDNA)
- ORR/CBR (both cohorts)
- Safety

*The primary endpoint included all randomized patients in the PIK3CA-mutant cohort; PFS was analyzed in the PIK3CA-non-mutant cohort as a proof of concept.*

*Safety was analyzed for all patients who received ≥ 1 dose of study treatment, in both cohorts.*

ABB, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FUL, fulvestrant; HER2-, human epidermal growth factor receptor-2-negative; IM, intramuscular; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, oral; QD, once daily; R, randomization.

⁴ More than 90% of patients had mutational status identified from archival tissue.

⁵ Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.


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Primary Endpoint: Locally Assessed PFS in the PIK3CA-mutant Cohort

**Toxicity note:**
Hyperglycemia, which is manageable.

---

<table>
<thead>
<tr>
<th>Data cut-off: Jun 12, 2018</th>
<th>ALP + FUL (n = 169)</th>
<th>PBO + FUL (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PFS events, n (%)</td>
<td>103 (60.9)</td>
<td>129 (75.0)</td>
</tr>
<tr>
<td>Progression</td>
<td>99 (58.6)</td>
<td>120 (69.8)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (2.4)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Censored</td>
<td>66 (39.1)</td>
<td>43 (25.0)</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>11.0 (7.5-14.5)</td>
<td>5.7 (3.7-7.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.50-0.85)</td>
<td></td>
</tr>
<tr>
<td>One-sided P value</td>
<td>0.00065</td>
<td></td>
</tr>
</tbody>
</table>
Impassion 130
5 mg tamoxifen in prevention
Alpelisib+Fulvestrant
Oxybutynin for hot flashes
KATHERINE
Germline genetic testing
Extended AI therapy
A randomized, double-blind, placebo-controlled trial of oxybutynin for hot flashes: ACCRU study SC-1603

**Study design**

**Women with HF**
- ≥28 times/week
- >30 day duration
- Women taking tamoxifen or AIs eligible
- Concurrent antidepressants, gabapentin, pregabalin allowed
- Concurrent potent anticholinergics not allowed

**Treatment duration = 6 weeks**, after a baseline week without medication (questionnaires)

**Weekly questionnaires:**
- Hot Flash Diary
- HFRDIS
- Symptom experience questionnaire

**Endpoints:**
- **Primary**: Intra-patient change in weekly HF score\(^1\) and frequency
- **Secondary**: change in HFRDIS, change in self-reported symptoms

\(^1\)Sloan et al, JCO 2001
Results: Mean Hot Flash Score % Reduction from Baseline

HF Score = HF frequency x average severity
G1 = mild, G2 = moderate, G3 = severe, G4 = very severe

P < 0.01

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>37</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Oxybutynin 2.5 mg BID</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>36</td>
<td>35</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Oxybutynin 5mg BID</td>
<td>35</td>
<td>35</td>
<td>34</td>
<td>32</td>
<td>32</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>
Results: Mean Hot Flash Frequency % Reduction from Baseline

- Placebo
- Oxybutynin 2.5mg BID
- Oxybutynin 5mg BID

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>37</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Oxybutynin 2.5mg BID</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>36</td>
<td>35</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Oxybutynin 5mg BID</td>
<td>35</td>
<td>35</td>
<td>34</td>
<td>32</td>
<td>32</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>

P < 0.01
How does this compare with other HF trials?

Mean Hot Flash Score % Reduction Randomized Studies (positive trials)

- Placebo (n=420)
- Clonidine (n=75)
- Fluoxetine (n=36)
- Citalopram (n=57)
- Ven (vs MPA) (n=94)
- Venlafaxine (n=48)
- Pregabalin (n=63)
- Oxybutynin (n=35)

Not superior to placebo:
- Soy
- Flaxseed
- Black Cohosh
- Mg oxide
- Vitamin E
• Impassion 130
• 5 mg tamoxifen in prevention
• Alpelisib+Fulvestrant
• Oxybutynin for hot flashes
• KATHERINE
• Germline genetic testing
• Extended AI therapy
Phase III Study of Trastuzumab Emtansine (T-DM1) vs Trastuzumab as Adjuvant Therapy in Patients with HER2-Positive Early Breast Cancer with Residual Invasive Disease after Neoadjuvant Chemotherapy and HER2-Targeted Therapy Including Trastuzumab: Primary Results from KATHERINE (NSABP B-50-I, GBG 77 and Roche BO27938)


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Trastuzumab Emtansine

• First antibody drug conjugate approved in a solid tumor
• Trastuzumab connected via linker to small dose of emtansine (DM-1), a microtubule inhibitor 400-fold more potent than paclitaxel
• High affinity antibody and powerful payload
• Mechanism of action
  ▪ Targeted delivery of chemotherapy
  ▪ Anti-HER2 activity
• Limited toxicity
  ▪ Limited toxicity because of low systemic DM1 levels
  ▪ Rare liver toxicity
  ▪ Thrombocytopenia
  ▪ Mild fatigue
Influence of pCR on EFS in HER2+ Disease: I-SPY

HR-HER2+ (n=77)

- 3yr EFS: 93%
- 3yr EFS: 53%

Hazard Ratio: 0.10
(95% CI: 0.03-0.37)
Log rank p: 1.98e-5

non-pCR
pCR

HR+HER2+ (n=149)

- 3yr EFS: 96%
- 3yr EFS: 87%

Hazard Ratio: 0.26
(95% CI: 0.06-1.14)
Log rank p: 0.054

non-pCR
pCR

Difference between pCR vs. residual disease greater for ER- and ER+ consistent with meta-analysis from Cortazar et al, Lancet 2014

Yee et al, SABCS 2017
KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

T-DM1
- 3.6 mg/kg IV Q3W
- 14 cycles

Trastuzumab
- 6 mg/kg IV Q3W
- 14 cycles

Radiation and endocrine therapy per protocol and local guidelines

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4/2013 - 12/2015 enrollment
## Baseline Characteristics of ITT Population (3)

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab (n=743)</th>
<th>T-DM1 (n=743)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor stage (at definitive surgery)</strong>, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0, ypT1a, ypT1b, ypT1mic, ypTis</td>
<td>306 (41.2)</td>
<td>331 (44.5)</td>
</tr>
<tr>
<td>ypT1/ypT1c</td>
<td>184 (24.8)</td>
<td>175 (23.6)</td>
</tr>
<tr>
<td>ypT2</td>
<td>185 (24.9)</td>
<td>174 (23.4)</td>
</tr>
<tr>
<td>ypT3, ypT4</td>
<td>67 (9.0)</td>
<td>63 (8.5)</td>
</tr>
<tr>
<td><strong>Regional lymph node stage (at definitive surgery), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN0</td>
<td>335 (45.1)</td>
<td>344 (46.3)</td>
</tr>
<tr>
<td>ypN1</td>
<td>213 (28.7)</td>
<td>220 (29.6)</td>
</tr>
<tr>
<td>ypN2, ypN3</td>
<td>133 (17.9)</td>
<td>123 (16.6)</td>
</tr>
<tr>
<td>ypNX</td>
<td>62 (8.3)</td>
<td>56 (7.5)</td>
</tr>
<tr>
<td><strong>Residual invasive disease 1 cm or less AND negative axillary nodes (ypT1a, ypT1b or ypT1mic and ypN0)</strong></td>
<td>161 (21.7)</td>
<td>170 (22.9)</td>
</tr>
</tbody>
</table>

*One patient in the trastuzumab arm was reported as ypTX; Five patients had ypT1 disease without further subspecification.*
Invasive Disease-Free Survival

- Trastuzumab
- T-DM1

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Trastuzumab (n=743)</th>
<th>T-DM1 (n=743)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>~70</td>
<td>~70</td>
</tr>
<tr>
<td>24</td>
<td>~60</td>
<td>~60</td>
</tr>
<tr>
<td>36</td>
<td>~50</td>
<td>~50</td>
</tr>
<tr>
<td>48</td>
<td>~40</td>
<td>~40</td>
</tr>
<tr>
<td>60</td>
<td>~30</td>
<td>~30</td>
</tr>
</tbody>
</table>

IDFS Events, no. (%): 165 (22.2) vs. 91 (12.2)

Unstratified HR = 0.50 (95% CI, 0.39–0.64)

P < 0.0001

3-year IDFS: 77.0% vs. 88.3%

No. at Risk:
- Trastuzumab: 743 → 676 → 635 → 594 → 555 → 501 → 342 → 220 → 119 → 38 → 4
- T-DM1: 743 → 707 → 681 → 658 → 633 → 561 → 409 → 255 → 142 → 44 → 4

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### IDFS Subgroup Analysis (2)

<table>
<thead>
<tr>
<th>Group</th>
<th>Total N</th>
<th>Trastuzumab (n=743)</th>
<th>T-DM1 (n=743)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>1486</td>
<td>77.0</td>
<td>88.3</td>
<td>0.50</td>
<td>(0.39–0.64)</td>
</tr>
<tr>
<td>Primary tumor stage (at definitive surgery)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0, ypT1a, ypT1b, ypT1mic, ypTis</td>
<td>637</td>
<td>83.6</td>
<td>88.3</td>
<td>0.66</td>
<td>(0.44–1.00)</td>
</tr>
<tr>
<td>ypT1, ypT1c</td>
<td>359</td>
<td>75.9</td>
<td>91.9</td>
<td>0.34</td>
<td>(0.19–0.62)</td>
</tr>
<tr>
<td>ypT2</td>
<td>359</td>
<td>74.3</td>
<td>88.3</td>
<td>0.50</td>
<td>(0.31–0.82)</td>
</tr>
<tr>
<td>ypT3</td>
<td>108</td>
<td>61.1</td>
<td>79.8</td>
<td>0.40</td>
<td>(0.18–0.88)</td>
</tr>
<tr>
<td>ypT4+</td>
<td>23</td>
<td>30.0</td>
<td>70.0</td>
<td>0.29</td>
<td>(0.07–1.17)</td>
</tr>
<tr>
<td>Regional lymph node stage (at definitive surgery)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN0</td>
<td>679</td>
<td>83.9</td>
<td>91.9</td>
<td>0.46</td>
<td>(0.30–0.73)</td>
</tr>
<tr>
<td>ypN1</td>
<td>433</td>
<td>75.8</td>
<td>88.9</td>
<td>0.49</td>
<td>(0.31–0.78)</td>
</tr>
<tr>
<td>ypN2</td>
<td>189</td>
<td>58.2</td>
<td>81.1</td>
<td>0.43</td>
<td>(0.24–0.77)</td>
</tr>
<tr>
<td>ypN3</td>
<td>67</td>
<td>40.6</td>
<td>52.0</td>
<td>0.71</td>
<td>(0.35–1.42)</td>
</tr>
<tr>
<td>ypNX</td>
<td>118</td>
<td>88.7</td>
<td>98.1</td>
<td>0.17</td>
<td>(0.02–1.38)</td>
</tr>
<tr>
<td><strong>Residual disease ≤1 cm with negative axillary lymph nodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT1a, ypT1b or ypT1mic and ypN0</td>
<td>331</td>
<td>85.3</td>
<td>90.0</td>
<td>0.60</td>
<td>(0.33–1.12)</td>
</tr>
<tr>
<td><strong>Central HER2 status by IHC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/+</td>
<td>25</td>
<td>83.9</td>
<td>100.0</td>
<td>&lt;0.01</td>
<td>(0.00–NE)</td>
</tr>
<tr>
<td>2+</td>
<td>326</td>
<td>80.9</td>
<td>84.7</td>
<td>0.83</td>
<td>(0.50–1.38)</td>
</tr>
<tr>
<td>3+</td>
<td>1132</td>
<td>75.7</td>
<td>89.0</td>
<td>0.43</td>
<td>(0.32–0.58)</td>
</tr>
</tbody>
</table>

*Includes all ypT4 and 1 patient with ypTX; *Three patients had “unknown” HER2 IHC status.

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Some Additional Details and Caveats

- Most patients received anthracyclines and relatively few had pertuzumab

- The absolute benefit in patients with negative nodes and tumors 1 cm and less was modest, but still clinically significant

- The result was seen in spite of the fact that over 70% had ER+ disease
  - ER+ disease does not have as poor a prognosis in setting of residual disease
  - ER+ may be more heterogeneous and have lower level HER2 expression

- The result demonstrates that residual disease was often still HER2-driven

No impact on prevention of brain metastases — disappointing, as T-DM1 has known CNS efficacy. Overall survival analysis is immature at this time.
Majority of AE leading to treatment discontinuation in T-DM1 arm: LFT abnormalities or thrombocytopenia.
Majority of adverse events in either arm were grade 1 or 2. Fatigue and nausea were most frequent symptomatic side effects.
The Standard of Care Has Changed:

T-DM1 should be recommended to the vast majority of patients with residual disease after a taxane-based neoadjuvant regimen

- Eric Winer, MD
Antonio Breast Cancer Symposium

- Impassion 130
- 5 mg tamoxifen in prevention
- Alpelisib+Fulvestrant
- Oxybutynin for hot flashes
- KATHERINE
- Germline genetic testing
- Extended AI therapy
Germline Genetic Testing

• We are far beyond BRCA 1/2 as sole discussion in this space.

• There are frequent updates regarding which germline mutations are relevant to breast cancer risk, and to what extent.

• More and more information...testing is being performed broadly by many types of providers...direct to consumer. Ordering providers and consumers are often not fully aware of implications of results, limitations of the testing, which gene panel to order, and more. Genetic counselors are even more important than ever. [https://www.nsgc.org/page/find-a-genetic-counselor.](https://www.nsgc.org/page/find-a-genetic-counselor).  

• Face to face consult

• Phone consult

• Virtual consult
CARRIERS: CAncer RIsk Estimates Related to Susceptibility

• In discussing the CARRIERS study at SABCS 2018, Dr. Fergus Couch of the Mayo Clinic reviewed an update on CAncer RIsk Estimates Related to Susceptibility.

• This study was designed to define the population-based frequencies of pathogenic mutations in cancer predisposition genes.

• Participants included 60,000 women with breast cancer referred for hereditary testing by Ambry Genetics between 3/2012-6/2016.

• It also set out to estimate age-related and lifetime risks of breast cancer in the general population (to define the control rates).
<table>
<thead>
<tr>
<th>Consider/Recommend Breast MRI</th>
<th>Discuss Option of RRM/Consider based on family history</th>
<th>Unknown or insufficient evidence for BC risk</th>
<th>No increased BC Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>ATM</td>
<td>MLH1</td>
<td>BRIP1</td>
</tr>
<tr>
<td>BRCA1</td>
<td>BRCA1</td>
<td>MSH2</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>BRCA2</td>
<td>MRE11A</td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>CDH1</td>
<td>MSH6</td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>CHEK2</td>
<td>PMS2</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>NBN</td>
<td>RAD50</td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>NF1</td>
<td>RAD51C</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>PALB2</td>
<td>RAD51D</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>PTEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>TP53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BARD1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased risk of breast cancer</td>
<td>Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO</td>
<td>Unknown or insufficient evidence for pancreas or prostate cancer</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y±9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:** Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARD1</td>
<td>Potential increase in breast cancer risk, with insufficient evidence for management recommendations</td>
<td>Unknown or insufficient evidence for ovarian cancer risk</td>
<td>N/A</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Increased risk of breast cancer</td>
<td>Increased risk of ovarian cancer</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td></td>
<td>• See BRCA Pathogenic Variant-Positive Management</td>
<td></td>
<td>• See BRCA Pathogenic Variant-Positive Management</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Increased risk of breast cancer</td>
<td>Increased risk of ovarian cancer</td>
<td>Pancreas, Prostate, Melanoma</td>
</tr>
<tr>
<td></td>
<td>• See BRCA Pathogenic Variant-Positive Management</td>
<td></td>
<td>• See BRCA Pathogenic Variant-Positive Management</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Unknown or insufficient evidence</td>
<td>Increased risk of ovarian cancer</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• Consider RRSO at 45–50 y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:** Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in BRIP1 appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH1</td>
<td>Increased risk of lobular breast cancer</td>
<td>No increased risk of ovarian cancer</td>
<td>Diffuse gastric cancer</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y±9</td>
<td></td>
<td>• See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer</td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RRM:** Risk-reducing mastectomy  
**RRSO:** Risk-reducing salpingo-oophorectomy

**Footnotes on GENE-5**

**Continued**

---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>Increased risk of breast cancer • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y&lt;sup&gt;g&lt;/sup&gt; • RRM: Evidence insufficient, manage based on family history</td>
<td>No increased risk of ovarian cancer</td>
<td>Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td></td>
<td>Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2, MLH1, MSH6, PMS2, EPCAM</td>
<td>Unknown or insufficient evidence for breast cancer risk&lt;sup&gt;g&lt;/sup&gt; • Manage based on family history</td>
<td>Increased risk of ovarian cancer • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
<td>Colon, Uterine, Others • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td>NBN</td>
<td>Increased risk of breast cancer • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y&lt;sup&gt;g&lt;/sup&gt; • RRM: Evidence insufficient, manage based on family history</td>
<td>Unknown or insufficient evidence for ovarian cancer risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating pathogenic/likely pathogenic variant. Although risks for other pathogenic/likely pathogenic variants have not been established it is prudent to manage patients with other truncating pathogenic/likely pathogenic variants similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>Increased risk of breast cancer • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y&lt;sup&gt;g&lt;/sup&gt; • RRM: Evidence insufficient, manage based on family history</td>
<td>No increased risk of ovarian cancer</td>
<td>Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to NF1 specialist for evaluation and management</td>
</tr>
<tr>
<td></td>
<td>Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RRM:** Risk-reducing mastectomy

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**Footnotes on GENE-5**

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<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALB2</strong></td>
<td>Increased risk of breast cancer&lt;br&gt;• Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y&lt;sup&gt;1-9&lt;/sup&gt;&lt;br&gt;• RRM: Evidence insufficient, manage based on family history</td>
<td>Unknown or insufficient evidence for ovarian cancer risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Increased risk of breast cancer&lt;br&gt;• See Cowden Syndrome Management</td>
<td>No increased risk of ovarian cancer</td>
<td>See Cowden Syndrome Management</td>
</tr>
<tr>
<td><strong>RAD51C</strong></td>
<td>Unknown or insufficient evidence for breast cancer risk&lt;br&gt;• Consider RRSO at 45-50 y</td>
<td>Increased risk of ovarian cancer</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>RAD51D</strong></td>
<td>Unknown or insufficient evidence for breast cancer risk&lt;br&gt;• Consider RRSO at 45-50 y</td>
<td>Increased risk of ovarian cancer</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>Increased risk of breast cancer&lt;br&gt;• Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal&lt;br&gt;• RRM: Evidence insufficient, manage based on family history</td>
<td>Increased risk of non-epithelial ovarian cancer&lt;br&gt;• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Increased risk of breast cancer&lt;br&gt;• See Li-Fraumeni Syndrome Management</td>
<td>No increased risk of ovarian cancer</td>
<td>See Li-Fraumeni Syndrome Management</td>
</tr>
</tbody>
</table>

**RRM:** Risk-reducing mastectomy<br>**RRSO:** Risk-reducing salpingo-oophorectomy

---

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Evaluated ability for NCCN guidelines to identify which patients with breast cancer have pathogenic mutations in expanded panel testing.

Prospective registry. >1000 patients. 50% met NCCN criteria, 50% did not.

THIS PUBLICATION LENDS SUPPORT TO CONSIDERATION OF EXPANDED PANEL TESTING FOR ALL BREAST CANCER PATIENTS.

**TABLE 2.** Patient Genetic Test Positive Result Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>BRCA1/ Alone</th>
<th>HBOC Guidelines Panel (11 genes)</th>
<th>Large Cancer Panel (80 genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In guideline</td>
<td>2.51</td>
<td>6.26</td>
<td>9.39</td>
</tr>
<tr>
<td>Out of guideline</td>
<td>0.63</td>
<td>3.54</td>
<td>7.92</td>
</tr>
</tbody>
</table>
• Impassion 130
• 5 mg tamoxifen in prevention
• Alpelisib+Fulvestrant
• Oxybutynin for hot flashes
• KATHERINE
• Germline genetic testing
• Extended AI therapy
• Prospective randomized open-label phase III trial, conducted in Japan.

• Stage I-III ER+ postmenopausal breast cancer patients who were without disease after 5 years of anastrozole or tamoxifen —> anastrozole.

• Randomized to stop anastrozole or continue for another five years.

• N=1697, median f/u 5 years. 149 disease recurrence events: 51 continual group, 98 stop group. 7 deaths: 3 continual, 4 stop.
Primary endpoint: **5-year disease-free survival rate was 91.9% (95% confidence interval [CI], 89.4 to 93.8) in continual group and 84.4% (95% CI: 80.0 to 88.0) in stop group.**

- HR for DFS = 0.548, p=0.0004.

- **5-year OS was 99.5% in continual group and 99.6% in stop group.** (hazard ratio, 1.389 ;P=0.665).

- The rate of 5-year distant disease-free survival was 97.2% in continual group and 94.3% in stop group (hazard ratio, 0.514 ;P=0.0077).

- Bone-related adverse events were observed more frequently among patients in continual group than among patients in stop group, including a higher incidence of bone pain, stiff joints, bone fractures, and new-onset osteoporosis.
EBCTCG Meta-analysis: Extended Aromatase Inhibitor Therapy

• Analyzed individual patient (> 22,000 women) data for meta-analysis from 11 randomised trials that compared 3-5 years of aromatase inhibitor versus no further treatment after five or more years of endocrine therapy.

  • tamoxifen x 5 years —> AI —> EXTENDED AI

  • AI for 5 years —> EXTENDED AI

• 20% proportional reduction in recurrence if extended AI.

• **Absolute benefit of extended therapy far greater in patients with nodal involvement.**

  • 1% absolute reduction in recurrence risk in node-negative patients.

  • 7.7% absolute reduction in recurrence risk in women with >=4 nodes.
Extended Aromatase Inhibitor Therapy?

• Not associated with improvement in overall survival.

• Most of the small improvement seen in extended AI therapy trials is not metastatic risk improvement, but rather a reduction in second in-breast cancer events.

• Balance the very small improvement in recurrence risk with the side effects. Consider the patient’s personalized fracture risk prediction. Arthralgias/dyspareunia/hair loss…if these are not affecting quality of life in significant way, it is very reasonable to discuss extended therapy, particularly for higher risk (node positive) patients.

• “Endocrine therapy isn’t jail. If you don’t like it, you can get out.”
Thank you!