The TAILORx Trial: A review of the data and implications for practice

Angela DeMichele, MD, MSCE
Jill & Alan Miller Endowed Chair in Breast Cancer Excellence
Professor of Medicine and Epidemiology
University of Pennsylvania
Philadelphia, PA
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
The Problem of Overtreatment

Early 2000s:

Most ER+ node-negative breast cancer patients received chemo

Most did not benefit

NSABP B-20 tamoxifen + CMF

88% only needed ET
8% relapsed in spite of chemotherapy

Absolute benefit = 4%

Oncotype Dx® Recurrence Score

- Available beginning 2006
- Wide adoption in U.S.
- Impact primarily in ↓ chemotherapy use
- Cost ~ $4500 per assay
- Recommended by ASCO, NCCN, Cancer Care Ontario (based on “prospective / retrospective” data)

Prospective trials: TailoRx, RxPonder (node +)

Retrospective data on the benefits of chemotherapy based upon OncotypeDx RS: Unclear in the Intermediate Group

NSABP- B20 Trial: TAM +/- (+C)MF (N=668)

ALL PATIENTS

10 yr DRFS
88% vs. 92%, p=0.02

HIGH RS (>= 31)

10 year DRFS
61% vs. 88%, p=0.001
Rationale for TAILORx

- **Target Population:** HR+, HER2-neg, node-neg BCA
  - 50% of all breast cancers in U.S.
  - Adjuvant chemo recommended, but benefit small
  - Most are overtreated

- **Assay Selected:** 21-Gene Assay (Recurrence Score)
  - Two prospective validation studies in ER+, node-neg BCA
    - Prognostic (B14 study - tamoxifen): low recurrence with ET if RS low
    - Predictive (B20 study – tam +/- CMF): large chemo benefit if RS high
  - Uncertain chemo benefit for mid-range RS

TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 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)

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

RANDOMIZE

Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

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

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

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

Joseph A. Sparano, MD
TAILORx Randomized Trial

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

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

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

**TailoRx randomized population**

Non-inferiority, 5-yr IDFS threshold HR 1.32

Sparano J et al, ASCO 2018
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: 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>
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<tr>
<td>Distant recurrence-free interval (DRFI)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse-free interval (RFI)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Overall survival (OS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

TAILORx Methods: Statistical Analysis Plan for RS 11-25

- Non-inferiority design for randomized arms

- Intention-to-treat for primary analysis, as-treated analysis also planned

- Hazard ratio margin 1.322 for IDFS (5 year IDFS rate 90% vs. 87%)
  - Null hypothesis of no difference, type I error rate 10% (1-sided), type II 5%
  - \( P \) values shown are stratified log-rank test, and hazard ratios shown are from stratified proportional hazards models
  - Sample size adjusted for non-adherence rate (12%) - Lachin-Foulkes correction
  - Full information - 835 IDFS events

- Exploratory interaction tests for subgroups that may derive chemo benefit (ITT)
TAILORx Results - ITT Population: Demographics & Treatment in RS 11-25 Arms (N=6,711)

• 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 (57%)
  • 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%)
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant.

**Primary Endpoint**
Invasive Disease-Free Survival

- CHEMO + ET
- ET Alone

**Secondary Endpoint**
Distant Relapse-Free Interval

- CHEMO + ET
- ET Alone

Hazard Ratio Arm B vs. Arm C (95% CI):
- Primary Endpoint: 1.08 (0.94, 1.24)
- Secondary Endpoint: 1.10 (0.85, 1.41)

Number at risk:
- Primary Endpoint: CHEMO + ET - 3312, 3204, 3104, 2993, 2849, 2645, 2335, 1781, 1130, 523
- Secondary Endpoint: CHEMO + ET - 3312, 3215, 3142, 3059, 2935, 2734, 2432, 1866, 1197, 554

Joseph A. Sparano, MD
TAILORx Results – ITT Population: RS 11-25 (Arms B & C)

Other Secondary Endpoints

Relapse-Free Interval

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

Overall Survival

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

Interaction with age

iDFS Δ with chemo ~ 6%

DFS Hazard Ratios for Subsets
Arm B vs. Arm C

<table>
<thead>
<tr>
<th>Group</th>
<th>Ratio</th>
<th>95% Conf Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premeno</td>
<td>1.36</td>
<td>(1.06, 1.75)</td>
</tr>
<tr>
<td>Postmeno</td>
<td>0.99</td>
<td>(0.84, 1.17)</td>
</tr>
</tbody>
</table>

iDFS Δ with chemo ~ ≤1%
TAILORx Results: 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
How Does This Affect Practice Tomorrow? (for node-negative patients appropriate for chemo)

<table>
<thead>
<tr>
<th>Recurrence Score: Postmenopausal</th>
<th>11</th>
<th>18</th>
<th>25</th>
<th>31</th>
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<tbody>
<tr>
<td>ET alone</td>
<td>ET alone</td>
<td>ET alone</td>
<td>ET + chemo (who knows?)</td>
<td>Chemotherapy + ET</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence Score: Premenopausal</th>
<th>11</th>
<th>16/18</th>
<th>25</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET alone</td>
<td>ET alone</td>
<td>ET + chemo (esp &gt; 20)</td>
<td>Chemotherapy + ET (omitting chemo not tested but consistent)</td>
<td>Chemotherapy + ET</td>
</tr>
</tbody>
</table>
RxPONDER Trial will address patients with positive lymph nodes
Thank you!