Treatment Strategies for Early Stage Breast Cancer: Past, Present, and Future

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Boston, USA
The Plan

• A brief look back

• The progress we have made, and state of the science today

• A look into the future
Breast Cancer: circa 1990 in the U.S.

• 150,000 cases and 44,300 deaths
• Seen as single monolithic disease
• Most cancers presented as lump/mass
• Extensive surgery often performed and resulted in psychological and physical distress
• Adjuvant chemotherapy and hormonal therapy were recent additions to treatment approach
Progress Over the Past 25 Years
A Few Comments About Local Therapy

• Less extensive surgery to breast
  – Widespread acceptance of conservative surgery and radiation, though still underutilized
  – Less extensive axillary surgery – in patients with and without axillary involvement

• Reduction in late radiation toxicity and more convenient fractionation schedules

• More rational use of radiation – with appropriate increase and reduction in use in selected patients

• Improvement in reconstructive surgery

• Greater individualization based on stage, subtype, and patient preferences
NCI Consensus Conference: 2001
Little Variation in Treatment Among Patients

- All women with tumors > 1 cm with or without nodal involvement should receive adjuvant chemotherapy
- As a result, vast majority of patients were treated with chemotherapy, often with considerable toxicity
- Only endocrine treatment was tamoxifen which was added to all patients with ER+ tumors
- There was no adjuvant anti-HER2 therapy
Three Major Changes That Have Changed The Approach to Systemic Therapy

• Understanding of heterogeneity across breast cancer – prognosis varies by subtype

• Recognition that benefits of treatment track with subtype

• Development of targeted therapeutics, particularly for HER2+ disease
HETEROGENEITY
Overall and Relapse Free Survival by Tumor Types Defined with Gene Expression Patterns

Sorlie, et al. PNAS 2001
Breast Cancer is a Family of Diseases

- Convergence of clinical and genomic data
- Still uncertain how many members of the family
- At a minimum:
  - HER-2 +
    - HER-2 enriched
    - Luminal
  - Basal-like or (ER/PR-negative, HER2-negative)
  - Low Grade
  - HER2-positive
    - ER-positive Luminal B (High Grade)
    - ER-positive Luminal A (Low Grade)
  - Several subtypes
    - Low-intermediate grade ER+ (luminal A)
    - High grade ER+ (luminal B)

WE WILL RETURN TO THE CONCEPT OF HETEROGENEITY LATER IN THE TALK, THAT IS HETEROGENEITY WITHIN SUBTYPES
## Reduction in Breast Cancer Recurrence from Chemotherapy by Age and Receptor Status

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>#</th>
<th>% Node Positive</th>
<th>Absolute Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50, ER-poor</td>
<td>1757</td>
<td>20%</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>&lt; 50, ER+ tamoxifen</td>
<td>2254</td>
<td>34%</td>
<td>7.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>50-69 ER- poor</td>
<td>4071</td>
<td>67%</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
<tr>
<td>50-69, ER+ tamoxifen</td>
<td>11,333</td>
<td>73%</td>
<td>4.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.00001</td>
</tr>
</tbody>
</table>

EBCTCG, Lancet 2005
Impact of ER Status and on Benefits of More Effective Chemotherapy

CALGB 8541
1985-1991
1550 pts

CA(30)F x 4
CA(40)F x 6
CA(60)F x 4

CALGB 9344
Int 0148
1994-1996
3121 pts

CA(60) x 4
CA(75) x 4
CA(90) x 4

No tax
Tax x 4
No tax
Tax x 4
No tax
Tax x 4

CALGB 9741
Int C9741
1997-1995
2005 pts

AC → T
A → T → C

Berry et al, JAMA 2015
Reduction in Hazards
(Lower Dose CAF → Dose Dense AC-T)

Adjusted for:
- # pos nodes
- tumor size
- menopausal status

<table>
<thead>
<tr>
<th>Event</th>
<th>ER neg</th>
<th>ER pos</th>
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</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>63%</td>
<td>32%</td>
</tr>
<tr>
<td>(43-76)</td>
<td>[7-56]</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>59%</td>
<td>18%</td>
</tr>
<tr>
<td>(34-74)</td>
<td>[-41-25]</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for:
- # pos nodes
- tumor size
- menopausal status

Berry....Winer; JAMA 2005
Prevention of Recurrence is Now Subtype Dependent

- Triple Negative
- ER+/HER-
  - Low grade (Luminal A)
  - High grade. (Luminal B)
- HER2+

Why get it right?
Still over 40,000 deaths per year from breast cancer in U.S. and >500,000 worldwide
Timing of TNBC Recurrence is Early

Rates of distant recurrence following surgery in triple-negative vs other breast ca

Dent et al, Clin Cancer Res 2007
What is Optimal Therapy for Early TNBC?

Immunohistochemistry

- ER and PR <1% nuclear with positive normal breast internal control
- HER2 “negative” is 0 or 1+ staining or 2+ staining with negative FISH – usually HER2 is 0
- Rarely lobular

High grade ductal

slide courtesy of Andrea Richardson, MD, PhD
Adjuvant = Neoadjuvant

Purpose of Neoadjuvant Therapy is Given to Minimize Extent of Surgery and to Decrease Risk of Disease Recurrence

Neoadjuvant Therapy Should Never Be Given If There Is a Question About the Need for Adjuvant Treatment
A Sequential Antracycline-Taxane Combination is the Standard of Care for Moderate-Risk TNBC

NSABP-B30
AC-T x 8 vs AT x 4 vs TAC x 6

POSSIBLE REGIMENS

1. AC-paclitaxel (dose dense)
2. AC- paclitaxel (weekly)
3. AC-docetaxel (every 3 weeks)
4. FEC-docetaxel

Pooled Analysis of Dose Dense vs Not Fewer Recurrences with Dose Dense Approach

**ER Negative**
- 9209 women
- RR 0.82 (0.76–0.88)
- Logrank 2p < 0.00001
- 10–y gain 4.7% (CI 2.3 – 7.1)
- Stnd 38.3%
- Dose dense 33.6%

**ER Positive**
- 23495 women
- RR 0.86 (0.81–0.91)
- Logrank 2p < 0.00001
- 10–y gain 3.1% (CI 1.5 – 4.7)
- Stnd 29.4%
- Dose dense 26.3%

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Grey et al, SABCS 2017
For EBCTCG
## AC-T vs TC: Results

<table>
<thead>
<tr>
<th></th>
<th>Pts TaxAC</th>
<th>Events TaxAC</th>
<th>4 yr IDFS TaxAC</th>
<th>4 yr IDFS TC</th>
<th>Delta</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>ER/PgR (-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-</td>
<td>459</td>
<td>37</td>
<td>89.5</td>
<td>87.0</td>
<td>2.5%</td>
<td>1.31 (0.86-1.99)</td>
</tr>
<tr>
<td>1-3 N+</td>
<td>153</td>
<td>21</td>
<td>85.5</td>
<td>74.6</td>
<td>10.9%</td>
<td>1.58 (0.90-2.79)</td>
</tr>
<tr>
<td>4+ N+</td>
<td>42</td>
<td>11</td>
<td>71.8</td>
<td>60.8</td>
<td>11.0%</td>
<td>1.34 (0.62-2.91)</td>
</tr>
<tr>
<td>ER or PgR (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-</td>
<td>358</td>
<td>29</td>
<td>91.5</td>
<td>94.2</td>
<td>-2.7%</td>
<td>0.69 (0.39-1.19)</td>
</tr>
<tr>
<td>1-3 N+</td>
<td>771</td>
<td>46</td>
<td>94.3</td>
<td>92.3</td>
<td>2.0%</td>
<td>1.14 (0.77-1.69)</td>
</tr>
<tr>
<td>4+ N+</td>
<td>279</td>
<td>35</td>
<td>87.2</td>
<td>81.4</td>
<td>5.8%</td>
<td>1.46 (0.95-2.26)</td>
</tr>
</tbody>
</table>

*Suggests all groups aside from ER+ N0 benefit from A-containing regimens, especially ER- N+*
Should Stage Affect the Choice of a Treatment Regimen?

What is the optimal treatment for small, node negative TNBC tumors?

Do all patients need to be treated with AC-T?
Outcome in National Comprehensive Cancer Network
Distant Relapse Free Survival HR-HER2-

No chemotherapy

T1a = 74
T1b = 94

Chemotherapy

T1a = 25
T1b = 170

T1a 5-year estimate: 93% (84-97)
T1b 5-year estimate: 90% (81-95)

Vaz-Luis et al. JCO 2014;32:2142-2150
Options for Stage 1 TNBC

- Chemotherapy treatment options for low risk disease:
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

<table>
<thead>
<tr>
<th></th>
<th>Enthusiasm for Chemotherapy</th>
<th>Possible Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microinvasion only</td>
<td>Virtually none</td>
<td>---</td>
</tr>
<tr>
<td>T1a</td>
<td>Low to moderate</td>
<td>Simple</td>
</tr>
<tr>
<td>T1b</td>
<td>Moderate to high</td>
<td>Simple</td>
</tr>
<tr>
<td>T1c</td>
<td>High</td>
<td>Simple or selectively sequential approach</td>
</tr>
</tbody>
</table>
Is There a Role for Platinum Chemotherapy in the Neo/Adjuvant Management of Triple Negative Breast Cancer?
Randomized Trials of Preoperative Platinum Chemotherapy for TNBC

GeparSixto Schema

N=315 centrally confirmed TNBC

PM

R

PMCb

Pacitaxel 80 mg/m² q1w
Non-pegylated liposomal doxorubicin (M)
20 mg/m² q1w
Carboplatin AUC 1.5-2
Bevacizumab 15 mg/kg

GerparSixto pCR: platinum vs not

OR 1.94
[1.24 – 3.04]
P = 0.005

CALGB 40603 Schema

2 x 2 Randomization

Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
Paclitaxel 80 mg/m² wkly x 12 ddAC x 4
Carboplatin AUC 6 q3wks x 4
Carboplatin AUC 6 q3wks x 4
Carboplatin AUC 6 q3wks x 4
Carboplatin AUC 6 q3wks x 4

CALGB pCR: platinum vs not

46% (40-53%) 60% (54-66%)

Odds Ratio: 1.76
p = 0.0018

Does Addition of Preoperative Platinum Improve Survival Outcomes for TNBC?

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

GeparSixto 3Y DFS: Improved with Carbo

CALGB 40603 3Y EVS: Not Improved with Carbo

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

• Need definitive study showing improvement in DFS and/or OS

• If platinum is ultimately used, should it be added to standard therapy or substituted for one or more drugs?

• Are there triple negative subtypes that are particularly sensitive to platinum, ie biomarker driven?
ER+ Disease: Hormonal Therapy

- Premenopausal
- Postmenopausal
- Extended Duration
Premenopausal

• When to use OS?

• When to use AI?
SOFT DFS
8 years median follow-up

Francis et al, SABCS 2017
SOFT Secondary Endpoints

Distant Recurrence-Free Interval

Percent without Distant Recurrence

<table>
<thead>
<tr>
<th>Years since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>T</td>
</tr>
<tr>
<td>T+OFS</td>
</tr>
<tr>
<td>E+OFS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pts</th>
<th>Events</th>
<th>8-yr %</th>
<th>HR (95% CI) vs. T</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>1018</td>
<td>115</td>
<td>88.4</td>
</tr>
<tr>
<td>T+OFS</td>
<td>1015</td>
<td>104</td>
<td>89.4 (0.86(0.66-1.13))</td>
</tr>
<tr>
<td>E+OFS</td>
<td>1014</td>
<td>87</td>
<td>91.2 (0.73(0.55-0.96))</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Absolute Benefit at 8 years vs. T</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+OFS 1.0%</td>
</tr>
<tr>
<td>E+OFS 2.9%</td>
</tr>
</tbody>
</table>

Overall Survival

Percent Alive

<table>
<thead>
<tr>
<th>Years since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>T</td>
</tr>
<tr>
<td>T+OFS</td>
</tr>
<tr>
<td>E+OFS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pts</th>
<th>Events</th>
<th>8-yr %</th>
<th>HR (95% CI) vs. T</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>1018</td>
<td>88</td>
<td>91.5</td>
</tr>
<tr>
<td>T+OFS</td>
<td>1015</td>
<td>61</td>
<td>93.3 (0.67(0.48-0.92))</td>
</tr>
<tr>
<td>E+OFS</td>
<td>1014</td>
<td>76</td>
<td>92.1 (0.85(0.62-1.15))</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absolute Benefit at 8 years vs. T</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+OFS 1.9%</td>
</tr>
<tr>
<td>E+OFS 0.6%</td>
</tr>
</tbody>
</table>

Francis et al, SABCS 2017
SOFT Secondary Endpoints: No Chemo

SOFT Secondary Endpoints: Chemotherapy

Francis et al, SABCS 2017
Who Should Receive Ovarian Suppression +/- AI?

• High risk patients (node positive, larger node negative, higher grade)

• What about choice of OS + tam vs OS + AI
  – OS + AI is challenging treatment – may be best to start with tamoxifen
  – AI can always be substituted, though no data using switch strategy in premenopausal women apart from MA-17
Postmenopausal

• ASCO Guideline: AI should be given either upfront, after 2-3 years, or after 5 years
• Very high risk patients should start with AI
• Very low risk patients probably fine with tamoxifen
• Side effects need to be considered carefully and managed effectively
• Far better to substitute one agent for another than to risk non-adherence
Effects of Hormonal Therapy for Early Breast Cancer on Recurrence: EBCTCG Analysis

BIG 1-98: Long-term Outcomes
Initially Therapy Has Little Impact on Late Recurrence

### The Problem of Late Recurrence

#### Annual and Cumulative Risk by Subset

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women Who Were Event-free at 5 Yr</th>
<th>Annual Rate of Distant Recurrence</th>
<th>Cumulative Risk from 5 Yr to 20 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no.</td>
<td>Chemotherapy Scheduled no. (%)</td>
<td>5 to &lt;10 Yr percent</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>28,847</td>
<td>9,136 (32)</td>
<td>1.0</td>
</tr>
<tr>
<td>N1–3</td>
<td>25,292</td>
<td>17,280 (68)</td>
<td>1.9</td>
</tr>
<tr>
<td>N4–9</td>
<td>8,784</td>
<td>6,664 (76)</td>
<td>3.9</td>
</tr>
<tr>
<td>Tumor diameter in N0 only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a or T1b: ≤1.0 cm</td>
<td>5,527</td>
<td>910 (16)</td>
<td>0.5</td>
</tr>
<tr>
<td>T1c: 1.1–2.0 cm</td>
<td>13,875</td>
<td>4,034 (29)</td>
<td>0.8</td>
</tr>
<tr>
<td>T2: 2.1–3.0 cm</td>
<td>6,700</td>
<td>2,859 (43)</td>
<td>1.5</td>
</tr>
<tr>
<td>T2: 3.1–5.0 cm</td>
<td>2,745</td>
<td>1,333 (49)</td>
<td>1.7</td>
</tr>
<tr>
<td>Tumor grade in T1N0 only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3,524</td>
<td>401 (11)</td>
<td>0.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>7,363</td>
<td>1,861 (25)</td>
<td>0.7</td>
</tr>
<tr>
<td>High</td>
<td>3,054</td>
<td>1,414 (46)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

All Patients Cancer Free at 5 Years and Received Adjuvant Tamoxifen

Hayes et al NEJM 2017
Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial


Summary

Background For women with oestrogen receptor (ER)-positive early breast cancer, treatment with tamoxifen for 5 years substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis. We aimed to assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years.
Extended Letrozole After 5 yrs of Tamoxifen (MA17)

Tamoxifen for 4.5-6 yrs Postmenopausal
N=5,187

DFS

OS

PLACEBO

5 yrs rx planned

LETROZOLE

Goss et al. JNCI 2005
MA 17: Letrozole or Placebo after 5 years of Tamoxifen

DFS and OS

Contralateral BC

**A** Disease-free Survival

Women Surviving Free of Breast Cancer (%)

<table>
<thead>
<tr>
<th>Months after Randomization</th>
<th>Letrozole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
<td>50</td>
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<tr>
<td>50</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
<td>30</td>
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No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>2375</th>
<th>2308</th>
<th>1327</th>
<th>624</th>
<th>383</th>
<th>11</th>
<th>0</th>
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<td>Letrozole</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2382</td>
<td>2298</td>
<td>1295</td>
<td>610</td>
<td>380</td>
<td>11</td>
<td>0</td>
</tr>
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</table>

**P=0.001**

**B** Overall Survival

Women Surviving (%)

<table>
<thead>
<tr>
<th>Months after Randomization</th>
<th>Letrozole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
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<tr>
<td>10</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>20</td>
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<td>30</td>
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<td>40</td>
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<tr>
<td>50</td>
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<td>50</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
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</table>

No. at Risk

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<thead>
<tr>
<th>Group</th>
<th>2375</th>
<th>2328</th>
<th>1349</th>
<th>641</th>
<th>388</th>
<th>14</th>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2382</td>
<td>2328</td>
<td>1353</td>
<td>645</td>
<td>396</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

**P=0.25**


**Difference in distant recurrences is only 10 events!**
### Frequency of ctDNA ESR1 mutations in ER+ MBC

<table>
<thead>
<tr>
<th>Study</th>
<th>ESR1 mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOLERO2* (N=541)</td>
<td>28.8%</td>
</tr>
<tr>
<td>SOFeA** (N=161)</td>
<td>39.1%</td>
</tr>
<tr>
<td>PALOMA 3** (N=360)</td>
<td>25.3%</td>
</tr>
<tr>
<td>FERGI§ (N=70)</td>
<td>37%</td>
</tr>
</tbody>
</table>

*DS38G and Y537G
**E380Q, L536R, Y537C, D538G, S463P, Y537N, and Y537S

---

Gendreau S. et al. SABCS 2015

Courtesy of Mafalda Oliveira
Duration of Therapy

• 5 years adequate for many patients
• Longer duration reasonable for those at higher risk
  – 10 years of tamoxifen (in premenopause)
  – 5 years of tamoxifen followed by 5 years of AI
  – 2-3 years of tamoxifen followed by 5-8 of AI
  – 10 years of AI
Which ER+ Patients Need Chemotherapy?
RS in Node Negative Pts Treated With Tamoxifen

N = 668 treated with Tamoxifen x 5 yrs
In NSABP B-14

Low <18   6.8% (4.0-9.6%)
Intermediate (18-30)  14.3% (8.3-20.3)
High >30  30.5% (23.6-37.4)

N = 668 treated with Tamoxifen x 5 yrs
In NSABP B-14

Low 338  (51%)
Intermediate 149  (22%)
High 181  (27%)

Paik et al, NEJM 2004
Benefit of Chemotherapy By Oncotype Dx Recurrence Score In Node Negative Breast Cancer Treated With Tamoxifen

Paik S et al. JCO 2006;24:3726-3734

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Recurrence Score and Benefit from Chemotherapy in NSABP B-20

Figure 4: Linear fit of the likelihood of distant recurrence as a continuous function of recurrence score for the tamoxifen alone (TAM) and tamoxifen plus chemotherapy (TAM + chemol) treatment groups.

Paik et al, JCO2006
CAF Benefit Greatest in Higher RS for Both Nodal Subsets, with No Benefit in Lower RS

Five-Year Probability of Death or Disease Recurrence
Linear model for Recurrence Score and interactions with treatment

- Tam, 4+ nodes (n=54)
- CAF-T, 4+ nodes (n=86)
- Tam, 1-3 nodes (n=94)
- CAF-T, 1-3 nodes (n=133)

Chemo benefit 4+ nodes
Chemo benefit 1-3 nodes

Albain et al, Lancet Oncology 2011
Prospective Validation of 21-Gene RS in Node-Negative Patients: TAILORx

ER-Positive and/or PR-Positive Breast Cancer
Axillary Node-Negative
Candidate for Adjuvant Cytotoxic Therapy
in Addition to Hormonal Therapy

Secondary Study Group - 1
Recurrence Score < 11
(-29% of Population)
Patients = Registered

Primary Study Group
Recurrence Score 11-25
(-44% of Population)
Patients = Randomized

Secondary Study Group - 2
Recurrence Score > 25
(-27% of Population)
Patients = Registered

**Stratify**
- Tumor Size: ≤ 2.0 cm vs. > 2.1 cm
- Post-menopausal vs. Pre- or Peri-menopausal
- Planned chemotherapy: Taxane-containing (i.e. paclitaxel, docetaxel) vs. Non-taxane-containing
- Planned radiation therapy: whole breast, no boost planned vs. whole breast, boost planned vs. partial breast irradiation planned vs. no planned radiation therapy (for patients who have had a mastectomy)

Arm A
Hormonal Therapy

Arm B
Hormonal Therapy

Arm C
Chemotherapy Plus Hormonal Therapy

Arm D
Chemotherapy Plus Hormonal Therapy

Sparano JA et al. NEJM 2015
Prospective Validation of 21-Gene RS in Node-Negative Patients: TAILORx

Secondary Group
RS <11
Assigned to Hormonal Therapy Only

5 Year Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant Relapse Free Survival</td>
<td>99.3%</td>
</tr>
<tr>
<td>Invasive Disease Free Survival</td>
<td>93.8%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>98.0%</td>
</tr>
</tbody>
</table>
Prospective Outcome Data for 21-Gene RS in Node-POSITIVE Patients: PlanB

3-year DFS (%)

<table>
<thead>
<tr>
<th></th>
<th>RS 0-11</th>
<th>RS 12-25</th>
<th>RS &gt;25</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>97.9</td>
<td>97.2</td>
<td>89.4</td>
</tr>
<tr>
<td>N0</td>
<td>98.6</td>
<td>98.5</td>
<td>97</td>
</tr>
</tbody>
</table>

No CT

CT

N=190

1-3 positive nodes

RS < 11

Update: EBCC 2016
5 year DFS = 94%

Gluz O et al. JCO 2016
Results From Tailorx Will Be Presented At ASCO

• Most investigators expect trial will demonstrate minimal or no benefit from chemotherapy

• What will the implications be for patients with positive nodes, especially those with 1-3 nodes?

• Do we have to wait for results of Rxponder? If so, many of us may no longer be practicing medicine!
MINDACT: Survival without Distant Metastasis, Disease-free Survival, and Overall Survival in the Two Discordant-Risk Groups, According to Randomized Treatment
HER2 Signaling Pathways

Tyrosine Kinase Domains

Plasma membrane

Cytoplasm

Nucleus

Cell survival

Cell Proliferation

Mobility

Invasiveness

VEGF
Update Overall Survival and Disease-free Survival From Combined Data Analysis for N9831 and NSABP B-31 (AC-T +/- Trastuzumab)

Significant difference maintained over time in both ER- and ER+ cohorts. Late events more common in ER+ disease (not shown).

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Perez E A et al. JCO 2014;32:3744-3752
BCIRG-006 DFS Final Analysis (10.3yrs)

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

Slamon et al, SABCS 2015
Population: Node + or high risk node negative

*antibody therapy started with taxane
APHINITY: By Nodal Subgroups

+3.2%  -0.5%

Node Positive  Node Negative

Also greater impact in ER- than ER+
Adjuvant Paclitaxel/Trastuzumab Trial
Study Design

HER2+  
ER+ or ER-  
Node Negative ≤ 3 cm

Accrual N=406

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

PACLITAXEL 80 mg/m² + TRASTUZUMAB 2 mg/kg x 12

FOLLOWED BY 13 EVERY 3 WEEK DOSES  
OF TRASTUZUMAB (6 mg/kg)*

** Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney et al, NEJM 2015
APT: Updated Recurrence Free Interval

<table>
<thead>
<tr>
<th>RFI Events</th>
<th>Point Est.</th>
<th>95% Conf. Interval</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>99.2%</td>
<td>98.4% to &gt;99.9%</td>
<td>3</td>
</tr>
<tr>
<td>Local/Regional Recurrence</td>
<td>98.1%</td>
<td>96.8% to 99.5%</td>
<td>7</td>
</tr>
<tr>
<td>Distant Recurrence</td>
<td>97.5%</td>
<td>95.9% to 99.1%</td>
<td>9</td>
</tr>
<tr>
<td>Death from Breast Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tolaney et al, ASCO 2017
ATEMPT Trial Schema

Stage I
HER2+ *
ER+ or ER-
PS 0-1
Adequate organ fx

N=500

All HER2 testing centrally confirmed

Adjuvant endocrine therapy can be initiated after completion of 12 weeks of therapy

Adjuvant radiation therapy can be administered concurrently with study treatment.

ACCRUAL COMPLETED 2016
PI: Sara Tolaney, MD, MPH
Path CR is Predictive of Outcome in NSABP B-27 (and MAYBE it does not matter how path CR is achieved)

If path CR achieved with AC 82%
If path CR achieved with AC-T 84%

Rastogi, Anderson, Bear et al JCO 2008
Personal communication Terry Mamounas
pCR is Predictive of EFS and DRFS in HR−/HER2+

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

Hazard Ratio: 0.14
(95% CI: 0.04-0.51)
Log rank p: 5.09e-4

Yee et al, SABCS 2017
Maybe We Are Looking At The Role of Neoadjuvant Therapy The Wrong Way....

• Looking for new treatment approaches based on higher rates of path CR has not paid off to date (e.g. lapatinib, bevacizumab)

• Perhaps we should attempt treatment de-escalation in those with a path CR

• At the same time, we can evaluate resistance mechanisms and new treatments in those who do not obtain a path CR
A Design to Decrease Treatment, Assess Resistance, and Test New Therapies

Stage II/III HER2+

Highly Active Therapy (THP)

- pCR
- No pCR

Comprehensive Tissue/Blood Collection and Analysis

Target RFS Approximately 93-95% at 3-5 years

Sample size will depend on confidence intervals for phase II study of CR patients and phase III of high risk patients (almost certainly < 2000)

A Trans-Atlantic Collaboration is Planned
The Future...
but not so far from now
Adjuvant vs Neoadjuvant Therapy

• Increasing use of neoadjuvant therapy for majority of HER2+, triple negative, and high grade ER+ breast cancer

• Goal will be to decrease extent of surgery and guide radiation

• May be used, particularly in HER2+ setting, as an *in vivo* "experiment" that will allow escalation and de-escalation of therapy
Triple Negative Disease

• Better characterization of subtypes, particularly in terms of responsiveness to immunotherapy

• Incorporation of new agents into early stage treatment
  – Immuno-oncology agents
  – Antibody drug conjugates
  – ?? Androgen receptor antagonists
  – PARP inhibitors for patients with BRCA mutations
ER+ Disease

• Continued decline in chemotherapy use
• Ultimately, I suspect will only give chemotherapy to a relatively small minority
• Better delineation of role/need for ovarian suppression
• No new hormonal agents, except perhaps for the selective estrogen receptor degraders, on the horizon
• But...
What About the CDK 4/6 Inhibitors?

**Pallas Trial**

- Stage II/III ER+
- Chemo or not
- Completed surgery

N=6000

- Endocrine Therapy Alone
- Endocrine Therapy + Palbociclib

Trial will complete accrual in next year
Analysis in next 2-3 years

Similar Trial Being Conducted with Abemaciclib
Late Recurrence

• Hormonal therapy has not eliminated problem, and simply extending hormonal therapy is unlikely to be the primary solution
• CDK 4/6 inhibitors may lessen problem
• We need a better understanding of the biology...why are so many tumors dormant and what leads them to be awakened?
• Watch for studies in this area
HER2+ Disease

• Huge successes have been made
• Need more/better therapy for a small percentage
• For others, the major question will be how much chemotherapy can be eliminated
• Testing will likely improve
• And subsets of HER2+ disease are likely to need somewhat different treatment strategies
Getting it right for each patient...

We need to allow biologic insights and thoughtful clinical trials to lead us to “just right”
Thanks to my group at Dana-Farber

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