NOSCM
13th Annual New Orleans Summer Cancer Meeting
New Orleans LA 2018

ER/PR Breast Disease: Early Stage, Locally Advanced and Metastatic Breast Cancer

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Outline

• Advanced stage
  – Overview
  – M-THOR inhibitors
  – CDK4/6 inhibitors

• Early stage
  – Update in adjuvant endocrine treatment
  – Genomic signatures: Mammaprint and Oncotype-DX
Current Treatment of Advanced Hormone Receptor Positive (HR+) HER2- Breast Cancer

• Nearly 75% of patients have invasive breast cancers are hormone receptor positive (HR+)

• Endocrine therapy is the standard of care for patients with HR+ breast cancer, recommended by national and international guidelines

• Several developments in the past years offer promising treatment options and better care for patients with HR+, HER2- early and advanced breast cancer
New Trials of Hormone Therapy Alone in First-Line Advanced Breast Cancer
FALCON: (Fulvestrant and Anastrozole Compared in Hormonal Therapy- naïve Advanced BC)

- Randomized, double-blind, parallel-group, international, multicenter study
- Randomization of 450 patients was planned to achieve 306 progression events; if true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test).

Primary endpoint: PFS

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

Anastrozole 1 mg (daily PO) + placebo to fulvestrant

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

- Postmenopausal women
- Locally advanced or metastatic BC
- ER+ and/or PgR+
- HER2–
- ET-naïve


BC = breast cancer; PgR = progesterone receptor; HER = human epidermal growth receptor; PO = by mouth; ORR = objective (or overall) response rate; CBR = clinical benefit rate; DoR = duration of response; EDoR = expected DoR; DoCB = duration of clinical benefit; EDoCB = expected DoCB; HRQoL = health-related quality of life; FACT-B = Functional Assessment of Cancer Therapy for BC; TOI = Trial Outcome Index.
**FALCON: Primary Endpoint, PFS**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant</td>
<td>230</td>
<td>16.6 mos</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>232</td>
<td>13.8 mos</td>
</tr>
</tbody>
</table>

HR = 0.797 (95% CI, 0.637–0.999)

*P*=0.0486

Circles represent censored observations.

**FALCON: PFS in Patients ± Visceral Disease**

**Without visceral disease**

- **Fulvestrant**
  - n: 95
  - Median PFS: 22.3 mos
  - HR = 0.59 (95% CI, 0.42–0.84)

- **Anastrozole**
  - n: 113
  - Median PFS: 13.8 mos

**With visceral disease**

- **Fulvestrant**
  - n: 135
  - Median PFS: 13.8 mos

- **Anastrozole**
  - n: 119
  - Median PFS: 15.9 mos
  - HR = 0.99 (95% CI, 0.74–1.33)

Post hoc interaction test $P<0.01$. Circles represent censored observations.

Major Challenge in Endocrine Resistance

• Approximately 30-50% of patients with HR$^+$ advanced breast cancer do not respond to initial endocrine therapy.

• The majority (if not all) of patients with HR$^+$ advanced breast cancer will ultimately progress despite endocrine therapy.

APPROACHES TO OVERCOMING RESISTANCE TO ENDOCRINE THERAPY

- Alterations of downstream signaling pathways such as PI3K, (mTOR and PI3K inhibitors)

- Alterations of the cell cycle machinery (CDK inhibitors)
Everolimus 10 mg/day + Exemestane 25 mg/day (N = 485)

Placebo + Exemestane 25 mg/day (N = 239)

Stratification:
1. Sensitivity to prior hormonal therapy
2. Presence of visceral disease

No cross-over

, Baselga et al NEJM 2012.
BOLERO-2: Primary Endpoint, PFS (18-Month Follow-Up, Local)

HR = 0.45 (95% CI: 0.38-0.54)  
Log-rank P value: <.0001

Kaplan-Meier medians
EVE 10 mg + EXE: 7.8 months  
PBO + EXE: 3.2 months

Consistent results with central analysis:  
HR = 0.38 (95% CI: 0.31-0.48); log-rank P value: <.0001  
Kaplan-Meier medians: EVE 10 mg + EXE: 11.01 months vs PBO + EXE: 4.14 months

BOLERO-2 (39 months): Final OS Analysis

HR = 0.89 (95% CI, 0.73-1.10)
Log-rank $P = .14$

Kaplan-Meier medians
EVE+EXE: 30.98 months
PBO+EXE: 26.55 months

- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 55% deaths ($n = 267$) in the EVE+EXE arm vs 60% deaths ($n = 143$) in the PBO+EXE arm

One-sided $P$ value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®.
Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; IXRS®, Interactive Voice and Web Response System; PBO, placebo.
Randomized, Open-Label, Phase II Study

- BOLERO-6 randomized 309 patients to receive EVE + EXE (n = 104), EVE alone (n = 103), or CAP (n = 102)

Eligibility Criteria
- Postmenopausal women with ER+ HER2-metastatic or recurrent BC, or locally advanced BC not amenable to curative surgery or radiotherapy
- Recurrence or progression on ANA or LET
- Measurable disease per RECIST v1.1 or bone lesions (lytic or mixed), and ECOG PS 0-2
- N = 309

Randomization (1:1:1)*
- EVE 10 mg PO QD + EXE 25 mg PO QD (n = 104)
- EVE 10 mg PO QD (n = 103)
- CAP 1250 mg/m² PO BID (2 weeks on, 1 week off) (n = 102)

Primary Objective
- Estimate HR of investigator-assessed PFS for EVE + EXE vs EVE alone

Key Secondary Objective
- Estimate HR of PFS for EVE + EXE vs CAP†

Other Secondary Endpoints
- OS,† ORR, CBR, and safety

• BOLERO-6 was not powered to perform statistical comparisons between arms

*Stratified by presence or absence of visceral disease (lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion, or malignant ascites; †Stratified multivariate Cox regression models were adjusted on treatment and the following prognostic and baseline covariates where imbalances between arms were observed: bone-only lesions (yes vs no); prior chemotherapy (yes vs no); ECOG PS (0 vs 1-2); organs involved (2 vs 1, and ≥3 vs 1); race (Caucasian vs non-Caucasian); age (<65 vs ≥65 years). ANA, anastrozole; BID, twice daily; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PO, oral administration; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
Primary Objective

Estimated HR of PFS for EVE + EXE vs EVE alone

EVE + EXE offers a PFS benefit vs EVE alone

Presented By Guy Jerusalem at 2018 ASCO Annual Meeting

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>mPFS, months</th>
<th>HR* (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVE + EXE</td>
<td>80/104</td>
<td>8.4</td>
<td>0.74 (0.57-0.97)</td>
</tr>
<tr>
<td>EVE alone</td>
<td>74/103</td>
<td>6.8</td>
<td></td>
</tr>
</tbody>
</table>

- Estimated HR of PFS for EVE + EXE vs EVE alone was 0.74 (90% CI 0.57-0.97)

- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - EVE alone arm, 18%

- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave a consistent HR (0.73; 90% CI 0.56-0.97) for EVE + EXE vs EVE alone

*EVE + EXE vs EVE alone (obtained from a stratified Cox model).

mPFS, median progression-free survival.
Key Secondary Objective

Estimated HR of PFS for EVE + EXE vs CAP

CAP may have been favored by baseline imbalances and potential informative censoring

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>mPFS, months</th>
<th>HR* (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censoring</td>
<td>80/104</td>
<td>8.4</td>
<td>1.26 (0.96-1.66)</td>
</tr>
<tr>
<td>EVE + EXE</td>
<td>68/102</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td>68/102</td>
<td>9.6</td>
<td></td>
</tr>
</tbody>
</table>

- Estimated HR of PFS for EVE + EXE vs CAP was 1.26 (90% CI 0.96-1.66)

- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - CAP arm, 20%

- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave a HR of 1.15 (90% CI 0.86-1.52) for EVE + EXE vs CAP

*EVE + EXE vs CAP (obtained from a stratified Cox model).
### Overall Survival

**EVE + EXE vs EVE alone or CAP**

<table>
<thead>
<tr>
<th></th>
<th>n/N</th>
<th>mOS, months</th>
<th>HR* (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Censoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVE + EXE</td>
<td>71/104</td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>EVE alone</td>
<td>59/103</td>
<td>29.3</td>
<td>1.27 (0.95-1.70)</td>
</tr>
<tr>
<td>CAP</td>
<td>58/102</td>
<td>25.6</td>
<td>1.33 (0.99-1.79)</td>
</tr>
</tbody>
</table>

- New antineoplastic therapies initiated at EOT:
  - EVE + EXE arm, 78%
  - EVE alone arm, 81%
  - CAP arm, 79%

- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors **gave a HR of 1.27 (90% CI 0.94-1.70)** for EVE + EXE vs EVE alone and a **HR of 1.19 (90% CI 0.88-1.62)** for EVE + EXE vs CAP

*EVE + EXE vs EVE alone or CAP (obtained from a stratified Cox model). EOT, end of treatment; mOS, overall survival.*
## Adverse Events

<table>
<thead>
<tr>
<th>AE, * %</th>
<th>EVE + EXE (n = 104)</th>
<th>EVE alone (n = 103)</th>
<th>CAP (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3-4</td>
<td>All grades</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>Stomatitis¹</td>
<td>49</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>Anemia</td>
<td>32</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Elevated GGT</td>
<td>15</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>15</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

- Most frequent all-grade AEs:
  - Stomatitis in EVE-containing arms
  - PPE syndrome and diarrhea in CAP arm

- Grade 3-4 AEs more frequent in EVE + EXE arm vs EVE alone arm, and comparable between EVE + EXE and CAP arms

*<sup>3</sup>≥ grade 3-4 events in any arm; ¹BOLERO-6 was not designed to use the SWISH protocol for stomatitis prevention.

AE, adverse event; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PPE, palmar-planter erythrodysesthesia.

Conclusions

- Median PFS with EVE + EXE (8.4 months) consistent with BOLERO-2 (7.8 months), and vs EVE alone here (6.8 months) corresponded to estimated 26% reduction of risk of disease progression or death (HR 0.74)
  - Median PFS with EVE alone numerically longer than previously reported in a small phase II study (3.5 months)
  - No new safety signals observed with EVE + EXE

- A numerical median PFS difference was observed for CAP over EVE + EXE (9.6 vs 8.4 months), which may be attributed to various baseline characteristics favoring CAP and potential informative censoring
  - Median PFS with CAP also inconsistent with previous studies (4.1–7.9 months)

Cell Cycle Control in Breast Cancer and CDK Inhibition
Regulation of G1/S Checkpoint in Breast Cancer

ERK = extracellular signal-regulated kinase; MEK = mitogen-activated protein kinase kinase; mTOR = mammalian target of rapamycin; Rb = retinoblastoma; P = phosphate; PI3K = phosphatidylinositol 3-kinase; CDK = cyclin-dependent kinase.
In Breast Cancer, Frequent Alterations in Cyclin D/CDK4/6

- Amplification of cyclin D1 (11q13) in ER+ breast cancer
  - Noncatalytic effects of cyclin D1 on transcription, DNA repair, etc.
- Cyclin dependent kinase 4 (CDK4) amplification/overexpression
- Rb loss uncommon ER+ disease
- Loss of negative regulators (p16, p27)
- Association of above with response to antiestrogens and prognosis
- Growth factor signaling (steroid and peptide) and cell cycle progression

## Summary of 1st and 2nd line CDK4/6i Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Phase</th>
<th>No.</th>
<th>PFS, Endocrine Alone (months)</th>
<th>PFS, + CDK 4/6 Inhibitor (months)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALOMA-1</td>
<td>Letrozole with or without palbociclib</td>
<td>II</td>
<td>165</td>
<td>10.2</td>
<td>20.2</td>
<td>0.488 (0.39 to 0.75)</td>
</tr>
<tr>
<td>PALOMA-2</td>
<td>Letrozole with or without palbociclib</td>
<td>III</td>
<td>666</td>
<td>14.5</td>
<td>24.8</td>
<td>0.58 (0.46 to 0.72)</td>
</tr>
<tr>
<td>MONALEESA-2</td>
<td>Letrozole with or without ribociclib</td>
<td>III</td>
<td>668</td>
<td>14.7</td>
<td>25.</td>
<td>0.56 (0.38 to 0.72)</td>
</tr>
<tr>
<td>MONARCH-3</td>
<td>NSAI with or without abemaciclib</td>
<td>III</td>
<td>493</td>
<td>NCT 3</td>
<td>21*</td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALOMA-3</td>
<td>Fulvestrant with or without palbociclib</td>
<td>III</td>
<td>521</td>
<td>4.6</td>
<td>9.5</td>
<td>0.46 (0.36 to 0.59)</td>
</tr>
<tr>
<td>MONARCH-2</td>
<td>Fulvestrant with or without abemaciclib</td>
<td>III</td>
<td>669</td>
<td>9.3</td>
<td>16.4</td>
<td>0.553 (0.49 to 0.68)</td>
</tr>
<tr>
<td>MONALEESA-3</td>
<td>Fulvestrant with or without ribociclib</td>
<td>III</td>
<td>725</td>
<td>NCT02422615</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; PFS, progression-free survival; NSAI, nonsteroidal aromatase inhibitor.

*Interim analysis reportedly met primary end point of improved PFS in the combination arm.\(^8\)
# Side effects of CDK4/6 inhibitors

<table>
<thead>
<tr>
<th>Common Adverse Event*</th>
<th>All Grades</th>
<th>Grade 3 and 4</th>
<th>All Grades</th>
<th>Grade 3 and 4</th>
<th>All Grades</th>
<th>Grade 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>74-81</td>
<td>54-67</td>
<td>74</td>
<td>59</td>
<td>46</td>
<td>27</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16-22</td>
<td>2-8</td>
<td>NR</td>
<td>NR</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37-46</td>
<td>2-4</td>
<td>37</td>
<td>2</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21-26</td>
<td>1-4</td>
<td>35</td>
<td>1</td>
<td>86</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>25-35</td>
<td>0-2</td>
<td>52</td>
<td>2</td>
<td>49</td>
<td>3</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

- **NOTE.** Data are given as percent.
- **Abbreviation:** NR, not reported; QTc, corrected QT interval.
- ***Common adverse events in phase III trials in the metastatic setting.**

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017
MONALEESA-3: Phase III placebo-controlled study of ribociclib + fulvestrant

- Postmenopausal women and men with HR+/HER2- ABC
- No or ≤1 line of prior endocrine therapy for advanced disease
- N=726

Randomization (2:1)

Stratified by:
- Presence/absence of liver/lung metastases
- Prior endocrine therapy

Ribociclib
- (600 mg/day orally; 3-weeks-on/1-week-off)
- fulvestrant (500 mg)*
  - n=484

Placebo + fulvestrant
- (500 mg)*
  - n=242

Primary endpoint
- PFS (locally assessed per RECIST v1.1)

Secondary endpoints
- Overall survival
- Overall response rate
- Clinical benefit rate
- Time to response
- Duration of response
- Time to definitive deterioration of ECOG PS
- Patient-reported outcomes
- Safety
- Pharmacokinetics

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~364 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm), and a sample size of 660 patients

ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria In Solid Tumors.
*Fulvestrant administered Intramuscularly on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every 28-day cycle thereafter.
Primary endpoint: PFS (investigator-assessed)

- The hazard ratio of 0.593 corresponds to a 41% reduction in risk of progression in the ribociclib vs placebo arm.
Conclusions

- Patients receiving ribociclib + fulvestrant had a statistically significant and clinically meaningful improvement in PFS vs placebo + fulvestrant
  - Hazard ratio: 0.593; p=0.00000041; 41% reduction in risk of disease progression vs placebo
- Ribociclib treatment benefit was consistent across patient subgroups
- Prolonged PFS was observed with first-line ribociclib + fulvestrant (hazard ratio: 0.577; 95% CI: 0.415-0.802)
  - Benefit was also observed in patients who received treatment in the second-line setting (hazard ratio: 0.565; 95% CI: 0.428-0.744)
- Ribociclib + fulvestrant demonstrated a manageable safety profile, consistent with previous Phase III ribociclib studies
- Ribociclib combined with fulvestrant may be a new first- or second-line treatment option for postmenopausal women with HR+/HER2- ABC
- This is the first study to show that CDK4/6 inhibitor + fulvestrant combinations are efficacious in patients with de novo ABC and patients with disease that relapsed >12 months after completion of prior (neo)adjuvant endocrine therapy
CDK 4/6 Single Agent Therapy in ER+ HER-2 normal Refractory Metastatic Breast Cancer
MONARCH 1: Phase 2 Study Design

Previously-treated HR+/HER2- MBC → Abemaciclib 200 mg orally Q12H → Treatment continued until unacceptable toxicity or PD

Primary objective
To evaluate abemaciclib with respect to confirmed objective response rate based on investigator assessment (per RECIST v1.1)

Secondary objectives
Duration of response, progression-free survival, overall survival, clinical benefit rate, safety

Statistical design
A sample size of 128 patients provides 82% power, assuming a true response rate of 25%, to exclude an ORR of ≤15% on the lower bound of the 95% CI at 12 months follow-up
Investigator-Assessed Response<sup>a</sup> | Abemaciclib<sup>b</sup> (N = 132)
--- | ---
Confirmed ORR (CR+PR) (95% CI) | 19.7% (13.3–27.5)
CR | 0%
PR | 19.7%
Stable disease ≥6 mos | 22.7%
CBR (CR+PR+ SD ≥6 mos) | 42.4%
DCR (CR+PR+SD) | 67.4%

<sup>a</sup>Assessments based on independent review were comparable. <sup>b</sup>200 mg monotherapy dose.

CR = complete response; PR = partial response; DCR = disease control rate; SD = stable disease.

Abemaciclib for Brain Metastases*

**Patients with brain metastases (BM)**

- **Part A:** HR+, HER2+ BC (23–56 patients)
- **Part B:** HR+, HER2– BC (23–56 patients)
- **Part D:** NSCLC (23–56 patients)
- **Part E:** melanoma (23–56 patients)

**Primary endpoint:** Objective intracranial response rate

**Exploratory**

- **Part C:** HR+ BC, NSCLC, or melanoma and clinically indicated for surgical resection (after receiving 5–14 days of therapy) (~8 patients)
- **Part F:** HR+ BC, NSCLC, or melanoma and leptomeningeal metastases (± parenchymal brain metastases) (~15 patients)

**Plasma, CSF, and resected tumor tissue unbound concentrations of ABE**

- **8.7% ORR; 17% CBR**
- Heavily-pretreated BM metastatic BC

NSCLC = non-small-cell lung cancer; CSF = cerebrospinal fluid. * Abemaciclib is not FDA-approved for this indication.

Summary: CDK4/6 Inhibitors in ER+ MBC

- The 3 CDK4/6 inhibitors seem to be consistent and comparable in prolonging PFS in combination with endocrine therapy in the metastatic setting with acceptable toxicity.
- We have no overall survival data yet in phase III trials.
- Selection of agent, sequence, and number of drugs should be patient-specific; most patients are receiving CDK4/6i + AI in US.
- Given activity in advanced setting, now moving to adjuvant setting
- Resistance is universal
  - Next generation of trials is looking at switching ET or CDKI with addition of other drugs to inhibit resistance pathways.
Take home points in HT in ER+ HER-2- MBC

• Endocrine therapy is the cornerstone of the treatment of HR+ MBC.

• Resistance to endocrine therapy is a challenge.

• Mutations of the PI3K pathway are frequent in breast cancer.
  • Aberrations in PI3K – Common mechanism of endocrine resistance.

• CDK inhibitors – basal therapy is the standard of care in first or second line setting. All agents with nearly identical activity but have different side effect profiles. "Optimal use" remains unclear and survival data is still evolving.

• Everolimus – clinical benefit when used in combination with endocrine therapy.
  – Reverse endocrine resistance
  – Represents an option in the treatment of patients with MBC.
  – Challenges: Toxicities and patient selection
MTHOR and CDK Inhibition in Early Breast Cancer
Phase III SWOG-S1207 Trial Design

HR+ and HER2– breast cancer

Surgery: number of positive nodes?

Node-negative and tumor ≥2 cm

1–3 positive

≥4 positive

Recurrence Score® evaluation

RS ≤25: Not eligible

RS >25

Adjuvant chemotherapy

Radiation therapy if indicated

Stratification factors for randomization
- Node-negative
- 1–3 positive nodes
- ≥4 positive nodes with adjuvant
- ≥4 positive nodes with neoadjuvant

Neoadjuvant chemotherapy

Surgery

≥4 positive lymph nodes

EVE: 10 mg PO

ET: physician’s choice

EVE for 1 year + ET for 5 years

PBO for 1 year + ET for 5 years

RS = recurrence score.

Patient population
• HR+ and HER−
• Stage II or III
• N = 4600

Diagnosis, surgery ± neoadjuvant/ adjuvant chemotherapy

Arm A
Palbociclib (2 years) + endocrine treatment (5 years)

Arm B
Endocrine treatment (5 years)

Trial design: PALLAS is an international open-label, phase III trial randomizing patients to 2 years of palbociclib combined with at least 5 years of provider-choice endocrine therapy versus endocrine therapy alone.

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

Arm B: standard adjuvant endocrine therapy (AI, tamoxifen, LHRH agonist).

LHRH = luteinizing hormone-releasing hormone.
NCT02513394.
MONARCH E Study Schema

- MONARCH E is a randomized, open-label phase 3 study of abemaciclib + standard adjuvant endocrine therapy versus standard adjuvant therapy alone in patients with high-risk, early stage, node-positive, HR+, HER2– breast cancer.
- Target N = 3580

**Primary outcome measure:** invasive disease-free survival (IDFS)

**Secondary Outcome Measures:** IDFS for patients with Ki67 Index ≥20%; DRFS; OS; change from baseline on FACT-B, FACT-ES, FACIT-F, EQ-5D-5L; and pharmacokinetics

- HR+, HER2– early BC
- High-risk, node-positive disease
- Women (regardless of menopausal status) and men
- ECOG status 0–1
- ≤12 weeks of standard adjuvant ET prior to randomization

**Treatment Groups:**
- **Abemaciclib** for 2 years + standard adjuvant endocrine therapy
- **Placebo** for 2 years + standard adjuvant endocrine therapy

NCT03155997.
Adjuvant Hormonal Therapy

Premenopausal HR+ Early Breast Cancer
ATLAS: Adjuvant Tamoxifen 5 vs. 10 years

5-9 years: RR 0.90 (0.79-1.02)
≥10 years: RR 0.75 (0.62-0.90)
All years: log-rank p=0.002

5-9 years: RR 0.97 (0.79-1.18)
≥10 years: RR 0.71 (0.58-0.88)
All years: log-rank p=0.01
Absolute Improvements in Freedom from Distant Recurrence with Adjuvant Endocrine Therapies for Premenopausal Women with HR+ HER2-negative Breast Cancer: Results from TEXT and SOFT

Meredith M. Regan, Prudence A. Francis, Olivia Pagani, Gini F. Fleming, Barbara A. Walley, Giuseppe Viale, Marco Colleoni, István Láng, Henry L. Gómez, Carlo Tondini, Graziella Pinotti, Angelo Di Leo, Alan S. Coates, Aron Goldhirsch, Richard D. Gelber, for the SOFT and TEXT Investigators and International Breast Cancer Study Group
SOFT and TEXT Designs

**Enrolled: Nov03 - Apr11**

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

**TEXT (n=2672)**

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

**CURRENT FOLLOW-UP**

- Median follow-up 9 years

**SOFT (n=3066)**

- Tamoxifen x 5y
- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

**MEDIAN FOLLOW-UP 8 YEARS**

OFS = ovarian function suppression
Analysis Approach

- 4891 (86%) of 5707 SOFT and TEXT patients with HER2-negative cancers
  - excluded HER2+ by local or central lab, and/or absent HRs by central lab
- Endpoint: distant recurrence-free interval (DRFI)
  - From randomization until distant recurrence (censored at last follow-up or death without recurrence)
  - 8-yr freedom from distant recurrence, by Kaplan-Meier estimate
- Assessed magnitude of absolute improvement across a continuum of risk of recurrence
- Examined 4 cohorts of patients, defined by trial and chemotherapy use
## Characteristics by Cohort (HR+/HER2-)

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<th>Category</th>
<th>N</th>
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<th>LN+</th>
<th>T-size&gt;2cm</th>
<th>PgR&lt;50%</th>
<th>Grade 3</th>
<th>Ki-67≥20%</th>
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<td><strong>Chemotherapy</strong></td>
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<td></td>
<td>30%</td>
<td>69%</td>
<td>52%</td>
<td>23%</td>
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</tr>
<tr>
<td><strong>No Chemotherapy</strong></td>
<td>991</td>
<td></td>
<td></td>
<td>16%</td>
<td>21%</td>
<td>20%</td>
<td>13%</td>
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<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Age&lt;40</th>
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<th>T-size&gt;2cm</th>
<th>PgR&lt;50%</th>
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<td><strong>TEXT</strong></td>
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<td>49%</td>
<td>58%</td>
<td>46%</td>
<td>38%</td>
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</tr>
<tr>
<td><strong>SOFT</strong></td>
<td>1353</td>
<td></td>
<td></td>
<td>9%</td>
<td>9%</td>
<td>13%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Note: The data represent the percentage of patients with each characteristic.*
Distant Recurrence-free Interval by Cohort (HR+/HER2-)

**TEXT**

*Chemo-therapy*

Absolute improvement at 8 yr, 
E+OFS v T+OFS: **5.1%**

N=1276 (159 DRs)

**SOFT**

*Chemo-therapy*

Absolute improvement at 8 yr, 
E+OFS v T: **5.2%**

T+OFS v T: **-0.7%**

N=1271 (216 DRs)

*No Chemo-therapy*

Absolute improvement at 8 yr, 
E+OFS v T+OFS: **0.9%**

N=991 (35 DRs)

**INTERNATIONAL BREAST CANCER STUDY GROUP**

Presented By Meredith Regan at 2018 ASCO Annual Meeting
Conclusions

Among premenopausal women in SOFT & TEXT with HR+/HER2-cancers, magnitude of absolute improvement in 8-yr freedom from distant recurrence varied widely according to risk of recurrence:

- Those at higher risk may experience 10-15% improvement with E+OFS vs T+OFS or T alone
- Improvement with E+OFS may be 4-5% for patients at intermediate risk, most of whom also received chemotherapy
- For those at low risk, potential benefit of escalating endocrine therapy from T-alone may be minimal, as >97% of these women were without distant recurrence at 8 years
Adjuvant Hormonal Therapy
Premenopausal Early Breast Cancer 2018

• Low risk: Tamoxifen 5 years
• High risk: Ovarian ablation or suppression plus aromatase inhibitor x 5 years
• High risk: Ovarian ablation or suppression plus aromatase inhibitor x aromatase inhibitor x 2-3 years follow by tamoxifen 2-3 years
• High risk: If poor tolerance to aromatase inhibitor, tamoxifen x 5 to 10 years
• Be aware of transitory chemotherapy-induced ovarian function failure
Adjuvant Hormonal Therapy

Postmenopausal HR+ Early Breast Cancer
Meta-Analysis of Adjuvant Tamoxifen vs. Aromatase Inhibitor Trials

N ≈ 19,000 Patients

- 5-year gain, 2.9% (SE, 0.7%)
- 8-year gain, 3.9% (SE, 1.0%)
- Log-rank 2P < .00001

5-year gain, 1.1% (SE, 0.5%)
- 8-year gain, 0.5% (SE, 0.8%)
- Log-rank 2P = .1

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

\( \text{AI}_5 \) vs \( \text{TAM}_{2-3} \rightarrow \text{AI}_{2-3} \)

Als are equally effective*

MA 27: ANA vs EXE

FACE: LET vs ANA

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

Smith I, et al.
JCO 2017; DOI: 10.1200/JCO.2016.69.2871
Adjuvant Hormonal Therapy
Postmenopausal Early Breast Cancer
2018

- Aromatase inhibitor x 5 years
- Aromatase inhibitor x 2-3 years follow by tamoxifen 2-3 years then aromatase inhibitor x 5 years
- If poor tolerance to aromatase inhibitor, tamoxifen x 5 to 10 years
- Consider aromatase Inhibitors x 10 years in high risk patients
- All new generation aromatase inhibitors have similar clinical efficacy
- Be aware of transitory chemotherapy-induced amenorrhea
Do all patients with ER+ HER-2 normal early breast cancer benefit equally from current treatments, hormonal therapy and systemic chemotherapy?

Do we have new clinical or ancillary tools to do “Precision Medicine” in 2018
Genonic Signatures

• To identify patients a low risk at baseline

• To select patients for adjuvant hormonal therapy alone

• To select patients for adjuvant chemotherapy

• To identify patients at high residual risk after 5 years of adjuvant hormonal therapy

• To select patients for extended hormonal therapy
MINDACT

Early stage breast cancer
Stratify by clinical and genomic risk

Low/Low ➔ ET, only ➔ 2634

Low/High ➔ ET ± CT ➔ 2187

High/Low ➔ RANDOMIZED

High/High ➔ CT & ET ➔ 1806

NEJM 2016;375:717-29
Definition of High Risk Clinical Assessment in MINDACT:
(Patients assessed as clinically High Risk†)

- Hormone Receptor POSITIVE, Lymph Node NEGATIVE (HR+/LN0) and:
  - \( T \geq 1\text{cm} \) & Grade 3
  - \( T \geq 2\text{cm} \) & Grade 2 or 3
  - \( T > 3\text{cm} \) & Any Grade
- Any Lymph Node POSITIVE (LN+ 1-3) ‡
- Triple NEGATIVE
- HER2 POSITIVE

† Clinical High Risk was defined in MINDACT as the level of risk of recurrence for which most clinical guidelines advise adjuvant systemic chemotherapy. Clinical Low Risk was defined as the level of risk for which there would be little or no meaningful clinical benefit from adjuvant systemic chemotherapy. Clinical Low Risk was defined using Adjuvant!Online (modified version 8.0, including HER2) as greater than 92% breast cancer specific survival at 10-years for ER- patients without adjuvant systemic chemotherapy. For ER+ patients, Clinical Low Risk was defined as 88% breast cancer specific survival at 10-years, without any systemic therapy, and 92% with endocrine therapy, to account for the 4% average absolute benefit of adjuvant endocrine therapy for ER+ patients.

‡ Patients that were LN+, Grade I and tumors \( \leq 2\text{cm} \) were classified as clinical low risk in MINDACT
The MINDACT study: Patient demographics

N = 6,693

Median age = 55y

Node - 79%
Node + 21%
T1 tumours 72%
Grade 2 49%
HR positive 88%
HER2+ 10%

N = 6,693

N = 2745 clinical Low/genomic Low

N = 592 clinical Low/genomic High

Discordant

N = 1806 clinical High/genomic High

N = 1550 clinical High/genomic Low

from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators
DMFS MINDACT population at 5-year median follow-up

**Distant Metastasis Free Survival**

% at 5 year
- cL/gL 97.6 (96.9, 98.1)
- cL/gH 94.8 (92.4, 96.4)
- cH/gL 95.1 (93.8, 96.2)
- cH/gH 90.6 (89.0, 92.0)

Number of patients at risk:

<table>
<thead>
<tr>
<th>Year</th>
<th>cL/gL</th>
<th>cL/gH</th>
<th>cH/gL</th>
<th>cH/gH</th>
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<tbody>
<tr>
<td>0</td>
<td>2745</td>
<td>592</td>
<td>1550</td>
<td>1806</td>
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<td>2</td>
<td>2628</td>
<td>550</td>
<td>1457</td>
<td>1689</td>
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<tr>
<td>4</td>
<td>2331</td>
<td>484</td>
<td>1317</td>
<td>1462</td>
</tr>
<tr>
<td>6</td>
<td>735</td>
<td>136</td>
<td>311</td>
<td>395</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

Corrected risk:
- cL/gL 33
- cL/gH 2
- cH/gL 9
- cH/gH 11

Discordant risk groups
Efficacy: CT vs no CT in discordant risk

Intent-to-treat analysis

Distant Metastasis Free Survival

c-High/g-Low

<table>
<thead>
<tr>
<th>Allocated Treatment strategy</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Hazard Ratio (adjusted Cox model) (95% CI)</th>
<th>p-value (adjusted logrank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>95.9 (94.0, 97.2)</td>
<td>0.78 (0.50, 1.21)</td>
<td>0.267</td>
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<tr>
<td>no CT</td>
<td>94.4 (92.3, 95.9)</td>
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Distant Metastasis Free Survival

c-Low/g-High

<table>
<thead>
<tr>
<th>Allocated Treatment strategy</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Hazard Ratio (adjusted Cox model) (95% CI)</th>
<th>p-value (adjusted logrank)</th>
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<tbody>
<tr>
<td>CT</td>
<td>95.8 (92.9, 97.6)</td>
<td>1.17 (0.59, 2.28)</td>
<td>0.657</td>
</tr>
<tr>
<td>no CT</td>
<td>95.0 (91.8, 97.0)</td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT Investigators
Conclusions

• In the first prospective, randomized data for lymph node positive patients (1-3+ LN), MammaPrint Low Risk patients show no statistically significant or clinically meaningful benefit of adding chemotherapy

• 46% of patients identified as high risk for recurrence according to clinical-pathological factors as described in the publication, and who therefore would be usual candidates for adjuvant chemotherapy, were reclassified as Low Risk by MammaPrint® and MINDACT shows no statistically significant or clinically meaningful benefit of chemotherapy

• In the HR+/HER2-/LN0 group, following MammaPrint results to optimize treatment decisions can result in a
  – 97.8% DMFI in MammaPrint Low Risk patients without chemotherapy
  – 94.6% DMFI for MammaPrint High Risk patients with chemotherapy
TAILORx: A Clinical Trial Assigning Individualized Options for Treatment (Rx)

Eligible 10,253 pts prospectively enrolled (2006-2010)

Published in NEJM 2015

Patients in Arm A were predominantly treated with AI (59%) and tamoxifen (34%)

RS: Recurrence Score® result

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 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

**Secondary Endpoint**

Distant Relapse-Free Interval

---

Presented by Joseph Sparano at 2018 ASCO Annual Meeting
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)

Number at risk

<table>
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<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
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<tbody>
<tr>
<td>Arm C</td>
<td>3312</td>
<td>3213</td>
<td>3134</td>
<td>3047</td>
<td>2911</td>
<td>2705</td>
<td>2405</td>
<td>1840</td>
<td>1176</td>
<td>543</td>
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<tr>
<td>Arm B</td>
<td>3399</td>
<td>3313</td>
<td>3227</td>
<td>3127</td>
<td>3010</td>
<td>2802</td>
<td>2498</td>
<td>1915</td>
<td>1245</td>
<td>568</td>
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</table>

Number at risk

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<tr>
<th>Months</th>
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<th>12</th>
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<th>36</th>
<th>48</th>
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<th>72</th>
<th>84</th>
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<tbody>
<tr>
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<tr>
<td>Arm B</td>
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<td>3260</td>
<td>3204</td>
<td>3082</td>
<td>2903</td>
<td>2400</td>
<td>1614</td>
<td>859</td>
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</table>
TAILORx Results - ITT Population: All Arms (A,B,C & D)

9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone

- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)

- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET
### TAILORx Results - ITT Population: Exploratory Analysis of Chemotherapy Treatment Interactions in RS 11-25 Arms

<table>
<thead>
<tr>
<th>No statistically significant chemo treatment interactions</th>
<th>Statistically significant chemo treatment interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RS&lt;br&gt;  • 11-15 vs. 16-20 vs. 21-25&lt;br&gt;  • 11-17 vs. 18-25&lt;br&gt;  • Tumor size (≤ 2 cm vs. &gt; 2 cm)&lt;br&gt;  • Grade (low vs. int. vs. high)&lt;br&gt;  • Menopausal status (pre vs. post)&lt;br&gt;  • Clinical risk category (high vs. low)</td>
<td>• Age (≤ 50, 51-65, &gt; 65) and chemo benefit&lt;br&gt;  • IDFS (p=0.003)&lt;br&gt;  • RFI (p=0.02)&lt;br&gt;  • Age (or menopause), RS (11-15, 16-20, 21-25), and chemo benefit&lt;br&gt;  • IDFS - Age-RS (p=0.004)&lt;br&gt;  • IDFS - Menopause-RS (p=0.02)</td>
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</table>
TAILORx Results - ITT Population: Potential Chemotherapy Benefit in Women ≤ 50 Years (N=2216) in RS 11-25 Arms

• RS 16-25 - some chemo 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

• RS 0-15 - good prognosis with endocrine therapy
  • 3% distant recurrence with ET alone
  • no evidence for chemo benefit in RS 11-15
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 25-100**: 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