Systemic Treatment of Luminal Early and Advanced Breast Cancer

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Adjuvant Tamoxifen: EBCTCG Oxford Meta-analysis

N>10,000, 44% N+, 51% chemotherapy

Effect on Recurrence Rate and Survival Irrespective of Age, Stage, Grade, PR and Tumor Diameter.

EBCTCG, Lancet 2011
The longer – The better

Absolute benefit of extended adjuvant endocrine therapy with tamoxifen: ATLAS and aTTom

EBCTCG Metaanalysis, Lancet, 2011
MAJOR PUBLISHED STUDIES OF ADJUVANT ENDOCRINE THERAPY WITH AN AI IN POSTMENOPAUSAL WOMEN

« STANDARD THERAPY »

N=8010

N=4742

N=3123

N=5187

N=856

N=28177

Challenged by

1) Upfront AI ATAC
   BIG 1-98

2) Early sequential AI IES
   (BIG 2-97)
   ABCSG + ARNO

3) Late sequential AI MA17
   (BIG 1-97) ABCSG – 6A

Tamoxifen x 5y

Anastrozole x 5 years

Letrozole x 5 years

Tamoxifen x 2-3y

Exemestane x 3-2y

Tam x 2y

Anastrozole x 3y

Tamoxifen x 5y

Letrozole x 5y

Anastrozole* x 3y

N=6241

N=28177

*Anastrozol is not approved for extended therapy
Aromatase inhibitors vs. Tamoxifen meta-analysis

Tam→AI (5y) vs. Tam (5y)

AI (5y) vs. Tam (5y)

Dowsett et al, JCO, 2010
Adverse Events: Meta-Analysis
Tamoxifen vs Aromatase inhibitors

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AI, %</th>
<th>Tamoxifen, %</th>
<th>OR (95% CI)</th>
<th>( p ) Value</th>
<th>NNH, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone fractures</td>
<td>7.5</td>
<td>5.2</td>
<td>1.47</td>
<td>&lt; .001</td>
<td>46 (AI)</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>4.2</td>
<td>3.4</td>
<td>1.26</td>
<td>&lt; .001</td>
<td>132 (AI)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1.6</td>
<td>3.1</td>
<td>0.55</td>
<td>&lt; .001</td>
<td>69 (tamoxifen)</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>1.5</td>
<td>1.4</td>
<td>1.01</td>
<td>.93</td>
<td>-</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>0.1</td>
<td>0.5</td>
<td>0.34</td>
<td>&lt; .001</td>
<td>250 (tamoxifen)</td>
</tr>
<tr>
<td>Other second cancers</td>
<td>4.7</td>
<td>4.8</td>
<td>0.98</td>
<td>.83</td>
<td>--</td>
</tr>
</tbody>
</table>

- Compared with TAM, AIs are associated with an increased risk of cardiovascular events and bone fractures, decreased risk of venous thromboembolism and endometrial cancer
- Data suggest an increase in the risk of death without BC recurrence associated with the use of either TAM or AI alone
- Switching from TAM to AI or vice versa might be an optimal strategy for offsetting adverse events of individual drugs

Amir et al, JNCI, 2011
Effect of additive “T+N score” (range 1-6)

Score: 1/2 for T1/T2, plus 0/1/4 for N0/N1-3/N4-9

- 47% T2N4-9 (score=6)
- 41% T1N4-9
- 29% T2N1-3
- 22% T1N1-3 or T2N0
- 14% T1N0 (score=1)

Graph showing distant recurrence over years.
MA.17R Trial Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

Any duration of prior Tamoxifen

4.5-6 yrs of Aromatase Inhibitor

Let Plac

Subjects who had a DFS event

<table>
<thead>
<tr>
<th></th>
<th>Let</th>
<th>Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 (7.0%)</td>
<td>98 (10.2%)</td>
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</table>

Distant recurrence

<table>
<thead>
<tr>
<th></th>
<th>Let</th>
<th>Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>42 (4.4%)</td>
<td>53 (5.5%)</td>
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</table>

Loco-regional recurrence

<table>
<thead>
<tr>
<th></th>
<th>Let</th>
<th>Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>30</td>
<td></td>
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</table>

Bone

<table>
<thead>
<tr>
<th></th>
<th>Let</th>
<th>Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

Contralateral breast cancer § CBC

<table>
<thead>
<tr>
<th></th>
<th>Let</th>
<th>Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (1.4%)</td>
<td>31 (3.2%)</td>
<td></td>
</tr>
</tbody>
</table>

5-year DFS: 95% LET vs. 91% PLAC

HR DFS: 0.66

p = 0.01

Letrozole 2.5 mg po od

Placebo
SOFT and TEXT Designs

**Enrolled**: Nov03 - Apr11

**TEXT** (n=2672)
- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

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

**SOFT** (n=3066)
- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (47%)
  OR
- Remain premenopausal ≤ 8 mos after chemo (53%)

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

**Current Follow-up**
- Median follow-up 9 years

**OFS=ovarian function suppression**

**2018 ASCO ANNUAL MEETING**

**INTERNATIONAL BREAST CANCER STUDY GROUP**

Presented By Meredith Regan
For women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes.

Francis, NEJM, 2015, 2018 (SOFT trial)
In premenopausal women with hormone-receptor–positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression, as compared with a tamoxifen plus ovarian suppression, significantly reduced recurrence.

Pagani, NEJM, 2014 (TEXT trial)  
Francis, NEJM, 2018 (TEXT trial)
ER+ breast cancer - *circa* 2018

<table>
<thead>
<tr>
<th>Risk</th>
<th>Hormone therapy</th>
<th>Chemotherapy</th>
<th>Factors to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td>PRE TAM</td>
<td>No chemo</td>
<td>No Ovarian Sup. 5 years enough</td>
</tr>
<tr>
<td>T1, N0, Grade 1, or low “gen risk”</td>
<td>POST TAM or AI</td>
<td>No chemo</td>
<td>5 years enough AI in Lobular C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
If the results of tumour biology in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing (LoE: Expert opinion) (87%).

PRIMARY ENDOCRINE RESISTANCE is defined as:

- Relapse while on the first 2 years of adjuvant ET, or
- PD within first 6 months of 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:

- Relapse while on adjuvant ET but after the first 2 years, or
- Relapse within 12 months of completing adjuvant ET, or
- PD ≥ 6 months after initiating ET for MBC, while on ET

(LoE: Expert opinion) (67%)
**First line Hormonal therapy**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>aromarase inhibitor n/N</th>
<th>tamoxifen n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
<th>ORR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paridaens 2008</td>
<td>83/182</td>
<td>59/189</td>
<td>1.56 (1.17-2.07)</td>
<td>18.26</td>
<td>1.85 [1.21, 2.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1323</td>
<td>1327</td>
<td></td>
<td>100.00</td>
<td>1.56 [1.17, 2.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 436</td>
<td>(aromarase inhibitor), 330 (tamoxifen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>OS</td>
</tr>
<tr>
<td>Test for heterogeneity: χ² = 11.94, df = 5 (P = 0.04), I² = 58.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>OS</td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.05 (P = 0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>OS</td>
</tr>
</tbody>
</table>

Significant difference in favouring AIs over TAM ORR (OR, 1.56; 95% CI, 1.17-2.07; P = 0.002) and CB (OR, 1.70; 95% CI, 1.24-2.33; P = 0.0009)

Trend toward an improved OS not significant (OR, 1.95; 95% CI, 0.88-4.30; P = 0.10)

Test for heterogeneity: χ² = 19.28, df = 2 (P < 0.0001), I² = 89.6%
Test for overall effect: Z = 1.65 (P = 0.10)
FALCON: Phase III Study Design

- Postmenopausal women
- Locally advanced or metastatic breast cancer
- ER+ and / or PgR+
- HER2-
- Endocrine therapy-naïve

1:1

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

Anastrozole 1 mg
(daily PO)
+ placebo to fulvestrant

Primary endpoint: PFS

Secondary endpoints
- OS
- ORR
- CBR
- DoR, EDoR
- Safety

PFS in Patients With or Without Visceral Disease

Without visceral disease
- Fulvestrant (n = 95)
- Anastrozole (n = 113)

HR 0.59 (95% CI 0.42, 0.84)
Median PFS
Fulvestrant: 22.3 months
Anastrozole: 13.8 months

With visceral disease
- Fulvestrant (n = 135)
- Anastrozole (n = 119)

HR 0.99 (95% CI 0.74, 1.33)
Median PFS
Fulvestrant: 13.8 months
Anastrozole: 15.9 months

Post hoc interaction test P<.01
A circle represents a censored observation
Combining Other Targeted Agents and Endocrine Therapy

Growth Factor
Estrogen
Tamoxifen

Plasma Membrane

Cytoplasm

Nucleus

Cell Cycle

Transcription Silencing

CDK 4/6 Inhibitors
HDAC Inhibitor Entinostat

EGF30008

P13-K
Akt
mTOR
p90RSK
MAPK
MEK
EGFR/HER2
IGFR
IGFR
EGFR

ER
ER
CBP
p160
ERE

Basal Transcription Machinery

Tamoxifen
Tam

BOLERO TAMRAD HORIZON

P90RSK

HDAC Inhibitor Entinostat
BOLERO-2 (39-mo): Final OS Analysis

- 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

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

Censoring times
- EVE+EXE (n/N = 267/485)
- PBO+EXE (n/N = 143/239)

No. at risk
- EVE+EXE: 485 471 448 429 414 399 373 347 330 311 292 279 266 248 232 216 196 154 118 91 58 39 23 11 1 0
- PBO+EXE: 239 232 220 211 201 194 182 170 162 153 145 130 120 113 109 102 98 77 56 41 28 18 8 5 1 0

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; IXR§, Interactive Voice and Web Response System; PBO, placebo.
CDK4 & 6 in Breast Cancer

• D type cyclins activate CDK4 & 6 which phosphorylate Rb resulting in G1 to S progression

• Estrogen stimulates cyclin D1 in HR+ breast cancer

• Continuous inhibition of CDK4 & 6: prolonged cell cycle arrest

• Hypothesis: continuous target inhibition may be an effective strategy

1Altucci L et al. 1996 Oncogene 12:2315-24
2Gelbert et al. 2014 Invest New Drugs 32: 825-37
3Beckman et al. AACR Annual Meeting 2016
**Study Design**

- **Placebo**: (3/1 schedule) + letrozole (2.5 mg QD)
- **Palbociclib**: (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)

**Inclusion Criteria**
- Postmenopausal
- ER+, HER2– advanced breast cancer
- No prior treatment for advanced disease
- AI-resistant patients excluded

**Randomization**
- **Primary endpoint**: Investigator-assessed PFS
- **Secondary endpoints**: Response, OS, safety, biomarkers, patient-reported outcomes

**Stratification factors**
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic; ≤12 mo, >12 mo)
- Prior (neo)adjuvant hormonal therapy (yes, no)

**Table**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Any</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, %</td>
<td>99</td>
<td>62</td>
<td>14</td>
<td>95</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>80</td>
<td>56</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Leukopeniaa</td>
<td>39</td>
<td>24</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemiaa</td>
<td>24</td>
<td>5</td>
<td>&lt;1</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopeniaa</td>
<td>16</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

**Number of patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>244</th>
<th>224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pal + Let</td>
<td>395</td>
<td>295</td>
</tr>
<tr>
<td>PCB + Let</td>
<td>263</td>
<td>81</td>
</tr>
</tbody>
</table>
# First-line Metastatic ER+/HER2- Breast Cancer
PALOMA-2, MONALEESA 2, and MONARCH 3

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>Al-Placebo</th>
<th>Al-CDK4/6i</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALOMA 2</td>
<td>0.58</td>
<td>14.5 m</td>
<td>24.8 m</td>
</tr>
<tr>
<td>(Palbociclib)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONALEESA 2</td>
<td>0.56</td>
<td>14.7 m</td>
<td>Not Reached</td>
</tr>
<tr>
<td>(Ribociclib)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONARCH 3</td>
<td>0.54</td>
<td>14.7 m</td>
<td>Not Reached</td>
</tr>
<tr>
<td>(Abemaciclib)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONALEESA-3</td>
<td>0.57</td>
<td>18.7</td>
<td>Not Reached</td>
</tr>
<tr>
<td>(Ribociclib)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ORR: 55.3%**

**Primary endpoint: PFS (investigator-assessed)**

**ORR: 32.4**

**ORR: 59.2%**
## Cross-Trial Comparison of Toxicity: PALOMA-2, MONALEESA 2, and MONARCH 3

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Palbociclib plus Letrozole</th>
<th>Ribociclib + Letrozole</th>
<th>Abemaciclib plus Al</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any (%)</td>
<td>G 3 (%)</td>
<td>G 4 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79.5</td>
<td>56.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26.1</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>35.1</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.5</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>&lt;0.01</td>
<td>15.6</td>
<td>7.5</td>
</tr>
</tbody>
</table>

VTE: abemaciclib (4.9%)

Prolonged QTcF: Ribociclib (2.7%)
Primary Endpoint: PFS (ITT Population)

- **PALOMA 3**
  - Fulvestrant vs CDK4/6 inh +
  - Fulvestrant
  - MONARCH 3
  - MONALEESA 3 - second line

**MONARCH 1: Response Summary**
- **Investigator Assessed Response***
- **Abemaciclib 200 mg**
  - N = 132
  - Confirmed Objective Response Rate (ORR = CR + PR)
    - 19.7% (13.3, 27.5)
  - CR
    - 0%
  - PR
    - 19.7%
  - Stable Disease ≥ 6 months
    - 22.7%
  - Clinical Benefit Rate (CBR = ORR + SD ≥ 6 mos)
    - 42.4%

**Disease Control Rate (CR + PR + SD) = 97.4%**

*Assessments based on independent review were comparable*

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**Primary Endpoint: PFS (ITT)**

**MONARCH 2**
- Median PFS:
  - Abemaciclib + fulvestrant: 16.4 months
  - Placebo + fulvestrant: 9.3 months
- HR (95% CI): 0.553 (0.449, 0.681)
- P < .000001

**MONALEESA 3 - second line**
- Second line + early relapsers*

*PFS benefit confirmed by blinded independent central review (HR: 4.8; 95% CI: 0.363, 5.84; P < .000001)
FDA pooled CDKi Analysis

Gao et al., Abstract #1024

All Clinical Subsets Benefit From CDKi

**Average cost of CDK inh:**
- 13,500 USD per month
  - = 162,000 USD per year
- AI: 500 USD/month
- TAM: 150 USD/month
Endocrine therapy (ET) is the preferred option for HR+ disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response.

The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), the burden of the disease, patients’ preference, costs and availability.

Available options include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and estradiol, as well as repetition of previously used agents, may be used.

(LoE/GoR : I/A) (95%)
The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination. OS results are still awaited. QoL was comparable to that with ET alone.

(LoE/GoR : I/A) (90%)  
ESMO-MCBS: 3

The addition of a CDK4/6 inhibitor to fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6 to 7 months) as well as improvement of QoL, and is one of the preferred treatment options, if a CDK4/6 inhibitor was not previously used. OS results are awaited.

(LoE/GoR : I/A) (90%)  
ESMO-MCBS: 4
The addition of everolimus to an AI is a valid option for some patients previously exposed to endocrine therapy, since it significantly prolongs PFS, albeit without evidence of OS benefit. The decision to treat must take into account the toxicities associated with this combination, lack of statistical significant OS benefit, cost and availability. (LoE/GoR : I/B) (88%)

Tamoxifen or fulvestrant can also be combined with everolimus. (LoE/GoR : II/B) (80%)

Adequate prevention, close monitoring and proactive treatment of adverse events is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the Bolero-2 trial. (LoE/GoR : I/B) (97%) ESMO-MCBS: 2

Everolimus and CDK4/6 inhibitors should NOT be used after disease progression on that specific agent (i.e. beyond progression). (LoE/GoR : NA/E) (74%)