Navigating the conundrum of endocrine therapy in ABC

F. Cardoso, MD
Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal
ESMO Board of Directors & NR Committee Chair
ESO Breast Cancer Program Coordinator
EORTC Breast Group Chair
Consultant/Ad Board:

Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Teva
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. (LoE: 1 A) (93%)
**VISCERAL CRISIS** is defined as *severe organ dysfunction* as assessed by signs and symptoms, laboratory studies, and *rapid progression of disease*.

Visceral crisis is *not the mere presence of visceral metastases* but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

*(LoE: Expert opinion) (95%)*
Treatment of HR+ ABC

⇒ Direct comparisons: chemotherapy has a higher response rate

Treatment of HR+ ABC

⇒ Direct comparisons: No significant differences in overall survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>endocrine therapy n/N</th>
<th>chemotherapy n/N</th>
<th>Peto Odds Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
<th>Weight %</th>
<th>Peto Odds Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon 1992</td>
<td>18/30</td>
<td>14/30</td>
<td>4.8 %</td>
<td>0.76 [0.34, 1.66]</td>
<td></td>
</tr>
<tr>
<td>Tashiro 1990</td>
<td>23/30</td>
<td>24/26</td>
<td>8.7 %</td>
<td>0.76 [0.42, 1.36]</td>
<td></td>
</tr>
<tr>
<td>ANZBCTG 1986</td>
<td>95/113</td>
<td>100/113</td>
<td>39.1 %</td>
<td>0.85 [0.65, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Taylor 1986</td>
<td>68/99</td>
<td>69/95</td>
<td>29.0 %</td>
<td>0.84 [0.61, 1.16]</td>
<td></td>
</tr>
<tr>
<td>Clavel 1982</td>
<td>17/34</td>
<td>16/30</td>
<td>3.6 %</td>
<td>1.61 [0.65, 4.00]</td>
<td></td>
</tr>
<tr>
<td>Priestman 1978</td>
<td>40/47</td>
<td>33/45</td>
<td>14.9 %</td>
<td>1.65 [1.06, 2.57]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.94 [0.79, 1.12]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 9.22, \text{ df } = 5 (P = 0.10); I^2 = 46%$

Test for overall effect: $Z = 0.66 (P = 0.51)$

Meta-analysis: Chemotherapy vs Endocrine Therapy in MBC

Methods
- Randomized trials of chemotherapy alone vs endocrine therapy alone

Results
- No significant difference for OS in 6 trials (N = 692):
  HR: 0.94 (95% CI: 0.79-1.12; P = .5)
- Significant difference favoring chemotherapy for ORR in 8 trials (N = 817):
  HR: 1.25 (95% CI: 1.01-1.54; P = .04)
  - However, the 2 largest trials demonstrated trends in opposite directions
- Toxicity: Little information available on adverse events and QoL
  - Increased toxicity with chemotherapy (nausea, vomiting, alopecia)
  - 3 of 7 trials noted QoL aspects with differing results

Authors’ Conclusions
- “In women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.”

In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium

D. J. A. Lobbezoo¹,², R. J. W. van Kampen¹, A. C. Voogd¹,³, M. W. Dercks², F. van den Berkmortel², T. J. Smilde⁵, A. J. van de Wouw⁶, F. P. J. Peters⁷, J. M. G. H. van Riel⁸, N. A. J. B. Peters⁶, M. de Boer¹, P. G. M. Peer¹⁰ & V. C. G. Tjan-Heijnen¹¹

¹GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht; ²Department of Internal Medicine, Maxima Medical Center, Veldhoven; ³Netherlands Comprehensive Cancer Organisation, Utrecht; ⁴Department of Internal Medicine, Athem Orbis Heerlen, Heerlen; ⁵Department of Medical Oncology, Jan van Boghospitaal Den Bosch; ⁶Department of Internal Medicine, Veenhuizen Medical Center, Veenhuizen; ⁷Department of Internal Medicine, Athem Orbis Sittard, Sittard; ⁸Department of Internal Medicine, St Elisabeth Hospital, Tilburg; ⁹Department of Internal Medicine, St Jans Hospital, Weert; ¹⁰Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

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Starting with ET vs. Starting with CT

PFS

OS
ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

ET₁ → response → ET₂ → response → ET₃ → response → ET...

CT

## Endocrine-Based Therapies for Breast Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>SERMs</td>
<td>Antagonizes ER in breast tissue</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toremifene</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990s</td>
<td>Anastrozole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Letrozole</td>
<td></td>
</tr>
<tr>
<td>2000s</td>
<td>ERD</td>
<td>Impairs ER dimerization, increases ER degradation, and disrupts nuclear localization of ER</td>
</tr>
<tr>
<td></td>
<td>Fulvestrant</td>
<td></td>
</tr>
<tr>
<td>2010s</td>
<td>Combinations</td>
<td>Blockade of estrogen signaling and prosurvival or cell cycle pathways</td>
</tr>
<tr>
<td></td>
<td>Exemestane/everolimus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Letrozole/palbociclib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fulvestrant/palbociclib</td>
<td></td>
</tr>
</tbody>
</table>


Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
ER POSITIVE / HER-2 NEGATIVE MBC

For **pre-menopausal** women, for whom ET was decided, ovarian suppression/ablation combined with additional endocrine therapy is the preferred choice. *(LoE: 1 B) (93%)*

For **pre-menopausal** women, the additional endocrine agent can be **AI** or **tamoxifen**, according to type and duration of prior adjuvant endocrine therapy but AI absolutely mandates the use of ovarian suppression/ablation. *(LoE: 1 B) (95%)*

**Fulvestrant** is also a valuable option, but for the moment also mandates the use of ovarian suppression/ablation. *(LoE: 1 C) (95%)*
The preferred 1st line ET for postmenopausal patients depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant. (LoE: 1 A) (84%)
Initial Treatment of Hormone Receptor–Positive Advanced Breast Cancer

- Premenopausal SOC: ovarian suppression or ablation plus endocrine therapy as recommended for postmenopausal women\(^1\)
- Postmenopausal SOC: AIs due to improved efficacy vs tamoxifen\(^1\)

<table>
<thead>
<tr>
<th>AI</th>
<th>Parameter</th>
<th>AI vs Tamoxifen, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>TTP</td>
<td>10.7 vs 6.4</td>
</tr>
<tr>
<td>Letrozole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Fulvestrant has demonstrated similar efficacy vs tamoxifen\(^1\)
- Preliminary evidence suggests that fulvestrant may demonstrate improved efficacy vs anastrozole\(^6,7\)
  - TTP, fulvestrant vs anastrozole: 23.4 vs 13.1 mos\(^6\)

BUT: These patients were treated with Tam alone in the adjuvant setting! Different from nowadays.


Slide credit: clinicaloptions.com
Phase II FIRST: First-line Fulvestrant vs Anastrozole for Advanced Breast Cancer

- Primary endpoint: clinical benefit rate

- Postmenopausal women with previously untreated hormone receptor–positive advanced breast cancer (N = 205)

- Fulvestrant 500 mg IM injection
  Days 0, 14, 28 and every 28 days thereafter (n = 102)

- Anastrozole 1 mg/day PO
  (n = 103)

- Until disease progression or other event requiring discontinuation


Slide credit: clinicaloptions.com
**FIRST: Results**

- Clinical benefit rate and time to progression analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fulvestrant 500 mg (n = 102)</th>
<th>Anastrozole 1 mg (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR, %</td>
<td>72.5</td>
<td>67.0</td>
</tr>
<tr>
<td>mTTP, mos</td>
<td>23.4*</td>
<td>13.1</td>
</tr>
</tbody>
</table>

*P = .01

- OS analysis
  - Not a defined endpoint in original protocol

OS (%)

Median OS:
- Fulvestrant 500 mg: 54.1 mos
- Anastrozole 1 mg: 48.4 mos

HR: 0.70 (95% CI: 0.50-0.98; P = .04)

Phase III FALCON: First-line Fulvestrant vs Anastrozole for Advanced Breast Cancer

- Primary endpoint: PFS
- Secondary endpoints including: OS, ORR, DoR, CBR, and safety

Postmenopausal women with previously untreated hormone receptor–positive advanced breast cancer (N ≈ 450)

**Fulvestrant** 500 mg IM injection
- Days 1, 14, 28, and every 28 days thereafter (n ≈ 225)

**Anastrozole** 1 mg/day PO
- (n ≈ 225)

Until disease progression or other event requiring discontinuation

ClinicalTrials.gov. NCT01602380.

Slide credit: clinicaloptions.com
Optimal post-aromatase inhibitor treatment is uncertain.

Available options include, but are not limited to, tamoxifen, another AI (with a different mechanism of action), fulvestrant HD, megestrol acetate and everolimus + AI. (LoE: 1 A) (97%)

and HT + Palbociclib, where available
The combination of a nonsteroidal AI and fulvestrant as first-line therapy for post-menopausal patients resulted in significant improvement in both PFS and OS compared to AI alone in one phase III trial and no benefit in a second trial with a similar design.

Subset analysis suggested that the benefit was limited to patients without prior exposure to adjuvant ET (tamoxifen). Based on these data, combination ET may be offered to some patients with MBC without prior exposure to adjuvant ET.

(LoE: 2 B) (33% Yes, 53% No, 14% Abstain)
Mechanisms of De Novo & Acquired Endocrine Resistance

**De Novo** ET Resistance

- The lost/inactivation of ER/ER pathway
- Activation of PI3K/AKT/mTOR pathway
- Activation of the growth factor or HER pathway activation

**Acquired** ET Resistance

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%)

Note: resistance is a continuum and these definitions help mainly clinical trials and not necessarily clinical practice
ER & GROWTH FACTOR PATHWAYS & ENDOCRINE RESISTANCE

ER & GROWTH FACTOR PATHWAYS & ENDOCRINE RESISTANCE

Adapted from Denise Yardley et al, ASCO-Breast 2011
4.6 to 6.9 ms benefit PFS

No statistical significant benefit in OS

• 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
EVEROLIMUS: Adverse Events

Most Common Adverse Events (AEs)
- Fatigue
- Stomatitis
- Rash
- Anorexia
- Diarrhea

Less frequent but clinically relevant:
- Hyperglycemia

_Pneumonitis: Rare but potentially fatal_

Clinical Management Strategy
- Focus on patient awareness and early intervention
- Importance of well defined management & dose reduction/delay or drug discontinuation guidelines (they exist for stomatitis, pneumonitis, hyperglycemia)

Significant % (about 20%) of EVE–treated patients required a dose reduction
The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a non-steroidal AI, since it significantly prolongs PFS, albeit without OS benefit. The decision to treat must take into account the individual relevant toxicities associated with this combination and should be made on a case by case basis. (LoE: 1 B) (85%)

Tamoxifen can also be combined with everolimus. (LoE: 2 B) (85%)

Notes:  
a) At present, no predictive biomarker exists to identify those patients who will benefit from this approach.  
b) some studies have shown an excess in mortality with this combination in patients >70 years-old.
Palbociclib (PD 0332991; CDK4/6 inhibitor)

**Background:**
- PD 0332991, is a selective inhibitor of CDK4/6
- Prevents cellular DNA synthesis
- Luminal ER subtype,
- ↑ expression of cyclin D1 & Rb protein
- ↓ p16 expression

Finn RS, et al. SABCS 2012. Abstract S1-6
Palbociclib + Letrozole vs. Letrozole Study

Primary endpoint: PFS
Secondary endpoints: RR, OS, safety, correlative biomarker studies

• 2-part, randomized phase II study

**Part 1**
- Stratified by disease site (visceral, bone only, or other); Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)
- Postmenopausal women with ER-positive, HER2-negative advanced breast cancer (N = 66)
  - PD 0332991 125 mg QD + Letrozole 2.5 mg QD
  - Letrozole 2.5 mg QD

**Part 2**
- Stratified by disease site (visceral, bone only, or other); Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)
- Postmenopausal women with ER-positive, HER2-negative advanced breast cancer, CCND1 amp, and/or p16 loss (N = 99)
  - PD 0332991 125 mg QD + Letrozole 2.5 mg QD
  - Letrozole 2.5 mg QD

All patients continued assigned treatment until disease progression, withdrawal of consent, or unacceptable toxicity with follow-up tumor assessment every 2 mos

Finn RS, et al. SABCS 2012, Abstract S1-6
Palbociclib + Letrozole vs Letrozole: PFS (Final results)

**Progression-Free Survival (ITT)**

- **PAL + LET** (N=84)
- **LET** (N=81)

<table>
<thead>
<tr>
<th>Number of Events (%)</th>
<th>41 (49)</th>
<th>59 (73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.1, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.319 (0.748)</td>
<td>0.488 (0.319, 0.748)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival (ITT)**

- **PAL + LET** (N=84)
- **LET** (N=81)

<table>
<thead>
<tr>
<th>Number of Events (%)</th>
<th>30 (36)</th>
<th>31 (38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>37.5 (28.4, NR)</td>
<td>33.3 (26.4, NR)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.482 (1.345)</td>
<td>0.813 (0.492, 1.345)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.2105</td>
<td></td>
</tr>
</tbody>
</table>

**Objective Response Rate, % (95% CI)**

- **PAL + LET** (N=84)
- **LET** (N=81)

<table>
<thead>
<tr>
<th>Complete Response, n (%)</th>
<th>43 (32, 54)</th>
<th>33 (23, 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response, n (%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Clinical Benefit Rate*, % (95% CI)</td>
<td>81 (71, 89)</td>
<td>58 (47, 69)</td>
</tr>
</tbody>
</table>

**Stable Disease ≥24 weeks, n (%)**

- **PAL + LET** (N=84)
- **LET** (N=81)

| 32 (38%) | 20 (25%) |

Few dropouts due to toxicity. Main side effect: neutropenia (but no infection)

Finn RS, et al. AACR 2014, Abstract CT101
Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided \( \alpha = 0.025 \)

Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos

Blinded independent central review of efficacy endpoints performed as supportive analysis

PALOMA-2: Study Design (1008)

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

RANDOMIZATION

2:1

Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)

Placebo (3/1 schedule) + letrozole (2.5 mg QD)

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; \( \leq 12 \) mo, \( > 12 \) mo)
- Prior (neo)adjuvant hormonal therapy (yes, no)

\( ^a\) Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

1.clinicaltrials.gov
NCT01740427
PALOMA-2

PFS: Investigator-Assessed - (ITT Population)

Number of patients at risk
<table>
<thead>
<tr>
<th>PAL+LET</th>
<th>PCB+LET</th>
</tr>
</thead>
<tbody>
<tr>
<td>444</td>
<td>222</td>
</tr>
<tr>
<td>395</td>
<td>171</td>
</tr>
<tr>
<td>360</td>
<td>148</td>
</tr>
<tr>
<td>328</td>
<td>131</td>
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<td>295</td>
<td>116</td>
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<td>263</td>
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<td>238</td>
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<td>154</td>
<td>54</td>
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<td>69</td>
<td>22</td>
</tr>
<tr>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Number of Events, n (%)
- PAL+LET (N=444): 194 (44)
- PCB+LET (N=222): 137 (62)

Median (95% CI) PFS
- PAL+LET: 24.8 (22.1–NR)
- PCB+LET: 14.5 (12.9–17.1)

HR (95% CI); 1-sided P value
- PAL+LET: 24.8 (0.46–0.72); P<0.000001

ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.
**PALOMA3 Study Design**

- **HR+, HER2− ABC**
- **Pre- or post-menopausal**
- **Progressed on prior endocrine therapy:**
  - On or within 12 mo adjuvant
  - On therapy for ABC
- **≤1 prior chemotherapy regimen for advanced cancer**

2:1 Randomization

N=521*

- **Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)**
  - n=347

- **Placebo (3 wks on/ 1wk off) + Fulvestrant† (500 mg IM q4w)**
  - n=174

- Pre- and peri-menopausal women received concurrent ovarian function suppression with goserelin†.
- Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.
<table>
<thead>
<tr>
<th>AE, %</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>98</td>
<td>59</td>
<td>11</td>
<td>89</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79</td>
<td>53</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>46</td>
<td>25</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Fatigue</td>
<td>38</td>
<td>2</td>
<td>0</td>
<td>27</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>26</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>&lt;1</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Thrombocytopenia</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Upper respiratory infection</td>
<td>19</td>
<td>&lt;1</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Primary Endpoint: PFS (Investigator-Assessed)
ITT Population

![Graph showing progression-free survival probability over time for Placebo + Fulvestrant (n=174) and Palbociclib + Fulvestrant (n=347).]

- # Events (%): Placebo + Fulvestrant (93, 53.4%) vs Palbociclib + Fulvestrant (102, 29.4%)
- Median PFS: Placebo + Fulvestrant (3.8 months, 3.5-5.5) vs Palbociclib + Fulvestrant (9.2 months, 7.5-NE)
- Hazard Ratio: 0.422 (0.318, 0.560) with a p-value of <0.000001

Similar benefit seen in all subgroups examined.

Ci=confidence interval; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.
Clinical Implications

- Confirms findings from front-line randomized phase II that led to accelerated approval
- Provides support for combination of fulvestrant + palbociclib in second line setting
- In practice, palbociclib can be used in either the first-line or second-line setting, and can be used with either AI or fulvestrant

NO OS SURVIVAL RESULTS YET!
But due to improved QoL: ESMO MCBS score 4
The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients (except patients relapsing < 12 months from the end of adjuvant AI), provided a significant improvement in PFS (10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options, where available. OS results are still awaited.

LoE: 1A
The addition of CDK4/6 inhibitor palbociclib to Fulvestrant, beyond 1\textsuperscript{st} line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited. For pre/peri-menopausal pts, an LHRH-agonist must also be used. (LoE: 1 B) (86%)

At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these type of agents and research efforts must continue.
# CDK4/6 Inhibitors in Hormone Receptor–Positive Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target (IC&lt;sub&gt;50&lt;/sub&gt;, nM)</th>
<th>Phase III Trials</th>
<th>Phase I Dose-Limiting Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib (PD0332991)</td>
<td>CDK4 (11) CDK6 (15)</td>
<td>First-line combo:</td>
<td>Neutropenia, thrombocytopenia‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Letrozole*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Exemestane</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fulvestrant*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second-line combo:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anastrozole or letrozole</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fulvestrant</td>
<td></td>
</tr>
<tr>
<td>Abemaciclib (LY2835219)</td>
<td>CDK4 (2) CDK6 (10)</td>
<td>First-line combo:</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anastrozole or letrozole</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fulvestrant</td>
<td></td>
</tr>
<tr>
<td>Ribociclib (LEE011)</td>
<td>CDK4 (10) CDK6 (39)</td>
<td>First-line combo:</td>
<td>Neutropenia, mucositis, pulmonary embolism, asymptomatic thrombocytopenia, hyponatremia, QTcF prolongation (&gt; 500 ms), increased creatinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Letrozole</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fulvestrant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tamoxifen or NSAI†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second-line combo:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Fulvestrant</td>
<td></td>
</tr>
</tbody>
</table>

* Approved. † Premenopausal women; NSAI in combination with goserelin. ‡ Phase II grade 3/4.


Slide credit: clinicaloptions.com
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

Presented by: Maura N. Dickler, MD
## MONARCH 1: Most Common Adverse Events

<table>
<thead>
<tr>
<th>Investigator Assessed TEAEs&lt;sup&gt;a&lt;/sup&gt; &gt;20% (N=132)</th>
<th>Grade 1 %</th>
<th>Grade 2 %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
<th>All Grades %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>41.7</td>
<td>28.8</td>
<td>19.7</td>
<td>0</td>
<td>90.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21.2</td>
<td>31.1</td>
<td>12.9</td>
<td>0</td>
<td>65.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>39.4</td>
<td>20.5</td>
<td>4.5</td>
<td>0</td>
<td>64.4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>28.0</td>
<td>14.4</td>
<td>3.0</td>
<td>0</td>
<td>45.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22.0</td>
<td>14.4</td>
<td>2.3</td>
<td>0</td>
<td>38.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22.7</td>
<td>10.6</td>
<td>1.5</td>
<td>0</td>
<td>34.8</td>
</tr>
<tr>
<td>Headache</td>
<td>13.6</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
<td>20.5</td>
</tr>
</tbody>
</table>

### Lab abnormalities<sup>b</sup>

<table>
<thead>
<tr>
<th>Lab abnormality</th>
<th>Grade 1 %</th>
<th>Grade 2 %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
<th>All Grades %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased&lt;sup&gt;c&lt;/sup&gt;</td>
<td>46.9</td>
<td>50.8</td>
<td>0.8</td>
<td>0</td>
<td>98.5</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>18.5</td>
<td>44.6</td>
<td>27.7</td>
<td>0</td>
<td>90.8</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>17.7</td>
<td>43.1</td>
<td>22.3</td>
<td>4.6</td>
<td>87.7&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anemia</td>
<td>30.0</td>
<td>38.5</td>
<td>0</td>
<td>0</td>
<td>68.5</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>28.9</td>
<td>10.2</td>
<td>2.3</td>
<td>0</td>
<td>41.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>CTCAE Version 4.03, <sup>b</sup>N = 130 for lab abnormalities listed, except platelet count decreased (N=128), <sup>c</sup>Abemaciclib is a competitive inhibitor of OCT2, MATE1, and MATE2-K, efflux transporters of creatinine; cystatin C calculated GFR was not raised, <sup>d</sup>One patient who received cytotoxic chemotherapy within the 30 day follow up window experienced febrile neutropenia.

Presented by: Maura N. Dickler, MD
Conclusions – MONARCH 1

- Abemaciclib, a CDK4 & 6 inhibitor, demonstrates single agent activity in heavily pretreated patients with HR+/HER2- MBC
  - ORR of 19.7% (95% CI: 13.3, 27.5; 15% not excluded)
  - Median DoR of 8.6 mos
  - CBR of 42.4%, median PFS of 6.0 mos, median OS of 17.7 mos

- Safety and toxicity profile of twice daily continuous administration was consistent with previous experience
  - Few patients (7.6%) discontinued treatment due to adverse events

- Phase III studies of abemaciclib in combination with endocrine therapies are ongoing
  - MONARCH 2: abemaciclib plus fulvestrant in endocrine pre-treated MBC
  - MONARCH 3: abemaciclib plus an NSAI as initial treatment for MBC

Presented by: Maura N. Dickler, MD
Phase II Randomized Trial of Exemestane with or without Entinostat, a Novel HDAC Inhibitor

Previously treated HR-positive MBC (n=130)
Primary Endpoint: PFS

Exemestane + Entinostat

Exemestane + Placebo

HR, hormone receptor; MBC, metastatic breast cancer; R, randomisation

Exemestane +/- HDAC inhibitor Entinostat

PFS

OS

Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS). (A) Vertical tick marks represent the PFS time of patients without progressive disease. (B) Vertical tick marks represent the survival time of patients alive or lost to follow-up as of the last contact.

Phase III E2112: Exemestane ± Entinostat in Advanced Breast Cancer

- Entinostat: oral, histone deacetylase inhibitor

Pre/peri/postmenopausal women and men with HR+/HER2-, inoperable, locally advanced or metastatic BC, with progression on/after NSAI therapy (N ≈ 600)

Entinostat PO Days 1, 8, 15, 22 + Exemestane PO QD Days 1-28 (n ≈ 300)

Placebo PO Days 1, 8, 15, 22 + Exemestane PO QD Days 1-28 (n ≈ 300)

*Pre/perimenopausal female and all male pts receive goserelin acetate SC Day 1.

- Primary endpoints: OS, PFS
- Secondary endpoints: ORR (CR or PR), TTD, toxicity
- Other outcomes: adherence, QoL, protein lysine acetylation
The **optimal sequence** of endocrine agents after 1\textsuperscript{st} line ET is uncertain. It depends on which agents were used in the (neo)adjuvant and 1\textsuperscript{st} line ABC settings.

**Available options** include AI, tamoxifen, fulvestrant + palbociclib, AI + everolimus, tamoxifen + everolimus, fulvestrant, megestrol acetate and estradiol. 
(LoE: 1 A) (93%)

It is currently unknown how the different combinations of endocrine + biological agents compare with each other, and with single agent CT. Several trials are ongoing.
WHEN CHEMOTHERAPY IS NEEDED . . .
Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for MBC.

Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

(LoE: 1 B). (96%)

Please see also Cardoso et al, JNCI 2009; 101: 1174–1181
Cochrane meta-analysis of Combination vs. Sequential monoCT for ABC

**Progression-free survival (all trials)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba 2004</td>
<td>0.0296</td>
<td>0.1827</td>
<td>69</td>
<td>75</td>
<td>10.7%</td>
<td>1.03 [0.72, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Baker 1974</td>
<td>0.239</td>
<td>0.2295</td>
<td>46</td>
<td>30</td>
<td>6.8%</td>
<td>1.27 [0.81, 1.99]</td>
<td></td>
</tr>
<tr>
<td>Beslja 2006</td>
<td>-0.6033</td>
<td>0.2865</td>
<td>50</td>
<td>50</td>
<td>4.3%</td>
<td>0.55 [0.31, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Conte 2004</td>
<td>0.0082</td>
<td>0.139</td>
<td>106</td>
<td>92</td>
<td>18.5%</td>
<td>1.09 [0.83, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>0.2151</td>
<td>0.1579</td>
<td>90</td>
<td>93</td>
<td>14.3%</td>
<td>1.24 [0.91, 1.69]</td>
<td></td>
</tr>
<tr>
<td>Park 2010</td>
<td>0.2776</td>
<td>0.2429</td>
<td>41</td>
<td>40</td>
<td>6.0%</td>
<td>1.32 [0.82, 2.12]</td>
<td></td>
</tr>
<tr>
<td>Sledge 2003</td>
<td>0.2409</td>
<td>0.0862</td>
<td>230</td>
<td>453</td>
<td>38.5%</td>
<td>1.28 [1.06, 1.55]</td>
<td></td>
</tr>
<tr>
<td>Tomova 2010</td>
<td>-0.01625</td>
<td>0.6415</td>
<td>46</td>
<td>53</td>
<td>0.9%</td>
<td>0.85 [0.24, 2.99]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 678 886 100.0% 1.16 [1.03, 1.31]

Heterogeneity: Chi² = 9.41, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 2.52 (P = 0.01)

**Overall survival (all trials)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba 2004</td>
<td>0.2151</td>
<td>0.2834</td>
<td>69</td>
<td>75</td>
<td>4.5%</td>
<td>1.24 [0.74, 2.08]</td>
<td></td>
</tr>
<tr>
<td>Baker 1974</td>
<td>0.3716</td>
<td>0.2606</td>
<td>46</td>
<td>30</td>
<td>4.6%</td>
<td>1.45 [0.87, 2.42]</td>
<td></td>
</tr>
<tr>
<td>Beslja 2006</td>
<td>-0.6387</td>
<td>0.3182</td>
<td>50</td>
<td>50</td>
<td>3.1%</td>
<td>0.53 [0.26, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Chlebowski 1989</td>
<td>-0.1054</td>
<td>0.1282</td>
<td>129</td>
<td>93</td>
<td>19.2%</td>
<td>0.90 [0.76, 1.16]</td>
<td></td>
</tr>
<tr>
<td>Conte 2004</td>
<td>0.174</td>
<td>0.2355</td>
<td>106</td>
<td>92</td>
<td>5.7%</td>
<td>1.19 [0.75, 1.89]</td>
<td></td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>0.1989</td>
<td>0.1167</td>
<td>90</td>
<td>93</td>
<td>11.3%</td>
<td>1.22 [0.88, 1.69]</td>
<td></td>
</tr>
<tr>
<td>Park 2010</td>
<td>-0.1744</td>
<td>0.235</td>
<td>41</td>
<td>40</td>
<td>5.4%</td>
<td>0.84 [0.53, 1.33]</td>
<td></td>
</tr>
<tr>
<td>Sledge 2003</td>
<td>0.0488</td>
<td>0.0901</td>
<td>230</td>
<td>453</td>
<td>38.9%</td>
<td>1.05 [0.86, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Tomova 2010</td>
<td>0.01989</td>
<td>0.211</td>
<td>46</td>
<td>53</td>
<td>7.1%</td>
<td>1.22 [0.81, 1.84]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 807 979 100.0% 1.04 [0.93, 1.16]

Heterogeneity: Chi² = 10.54, df = 8 (P = 0.23), I² = 24%
Test for overall effect: Z = 0.76 (P = 0.45)

Dear RF et al. Combination vs. sequential single agent CT for MBC (Review) 2013
In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not need combination CT, single agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines.

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

(LoE: 1 B) (77%)
In the absence of medical contraindications or patient concerns, anthracycline or taxane based regimens, preferably as single agents, would usually be considered as first line CT for HER-2 negative MBC, in those patients who have not received these regimens as (neo)adjuvant treatment and for whom chemotherapy is appropriate. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient (LoE: 1 A) (71%).
In patients with taxane-naive and anthracycline-resistant MBC or with anthracycline cumulative dose or toxicity (i.e. cardiac) who are being considered for further CT, *taxane-based therapy*, preferably as single agents, would usually be considered as treatment of choice. Other options are, however, available and effective, such as *capecitabine and vinorelbine*, particularly if avoiding alopecia is a priority for the patient.

(LoE: 1 A) (59%).
PATIENTS IN THESE TRIALS WERE TAXANE-NAÏVE (Dogma even less valid for today’s 1st line population)

• Single-agent T significantly worse than single-agent A in PFS but not in RR nor OS.
• T-based significantly better than A-based combinations in RR and PFS, but not in OS.
Extrapolating from HER-2+ disease: Vinorelbine seems at least as good as taxane and significantly less toxic.

Vinorelbine & Capecitabine: Consistent efficacy results & NO ALOPECIA.

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane Arm</td>
<td>58%</td>
<td>6.0 months</td>
</tr>
<tr>
<td>Vinorelbine Arm</td>
<td>66%</td>
<td>8.5 months</td>
</tr>
</tbody>
</table>

Research question: BEST SEQUENCE!?
A Phase III, Open-label, Randomized, Multicenter Study Of Eribulin Mesylate Versus Capecitabine In Patients With Locally Advanced Or Metastatic Breast Cancer Previously Treated With Anthracyclines And Taxanes

Peter A. Kaufman,1 Ahmad Awada,2 Christopher Twelves,3 Louise Yelle,4 Edith A. Perez,5 Jantien Wanders,6 Martin S. Olivo,7 Yi He,7 Corina E. Dutcus,7 Javier Cortes8

1Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; 2Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium; 3Leeds Institute of Molecular Medicine and St James’s Institute of Oncology, Leeds, UK; 4Department of Medicine, University of Montreal, Montreal, Canada; 5Mayo Medical Clinic, Jacksonville, FL, USA; 6Eisai Ltd, Hatfield, UK; 7Eisai Inc., Woodcliff Lake, NJ, USA; 8Vall D’Hebron University Hospital, Barcelona, Spain
Study Design

Global, randomized, open-label Phase III trial (Study 301)

Patients (N=1102)
Locally advanced or MBC
- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Co-primary endpoint
- OS and PFS

Secondary endpoints
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

Randomization 1:1

Eribulin mesylate 1.4 mg/m²† 2- to 5-min IV Day 1 & 8 q21 days

Capecitabine 1250 mg/m² BID orally Days 1-14, q21 days

Stratification:
- Geographical region, HER2 status

†Equivalent to 1.23 mg/m² eribulin
**Overall Survival**

- **Median OS (months)**
  - Eribulin (n=554): 15.9
  - Capecitabine (n=548): 14.5

- **HR**: 0.879 (95% CI 0.770, 1.003)  
  - **p value**: =0.056

**Progression-free Survival**

- **Independent Review**
  - Median (months)
    - Eribulin (n=554): 4.1
    - Capecitabine (n=548): 4.2

- **Investigator Review**
  - Median (months)
    - Eribulin (n=554): 4.2
    - Capecitabine (n=548): 4.1

- **HR**: 1.079 (95% CI 0.932, 1.250)  
  - **p value**: =0.305

- **HR**: 0.977 (95% CI 0.857, 1.114)  
  - **p value**: =0.736

- **Median OS (months)**
  - Eribulin (n=554): 15.9
  - Capecitabine (n=548): 14.5

- **HR Cox model including geographic region and HER2 status as strata**

- **p value from stratified log-rank test based on clinical database**

- **This presentation is the intellectual property of the author.**

**San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 4-8, 2012**

- **• No major differences in outcomes**
- **• 1st drug to “as good as capecitabine” in 1st/2nd line**
- **• Different toxicity profile**
- **• A new good treatment option**
Even if given in the adjuvant setting, provided that cumulative dose has not been achieved and that there are no cardiac contra-indications, anthracyclines can be re-used in MBC, particularly if there has been at least one year of disease-free survival.

(LoE: 1 C) (93%)
Duration of each regimen and number of regimens should be tailored to each individual patient (LoE: Expert opinion). (96%)

Usually each regimen should be given until progression of disease or unacceptable toxicity (unacceptable should be defined together with the patient) (LoE: 1B). (72%)

✓ A meta-analysis of published trials (Gennari et al) concluded that longer 1st line CT duration is associated with a marginally longer OS and a substantially longer PFS.
Optimal Duration of Chemotherapy?

- Longer CT duration associated with:
  - significant and clinically meaningful improvement in PFS (HR 0.64; 95% CI 0.55 – 0.76)
  - significant improvement in OS (HR 0.91; 95% CI 0.84-0.99)

These results provide support to the clinical approach of prolonging 1st line CT in the absence of significant toxicity and disease progression (when CT is the only option...)

Role of biologics, HT, metronomic CT ?!

Gennari et al, J Clin Oncol 2011
Metronomic chemotherapy is an reasonable treatment option, for patients not requiring rapid tumor response. (LoE: 1 B) (88%)

The better studied regimen is CM (low dose oral cyclophosphamide and methotrexate); other regimens are being evaluated (including capecitabine and vinorelbine).

Randomized trials are needed to accurately compare metronomic CT with standard dosing regimens.
Bridging the Gap ABC 4

Advanced Breast Cancer
2-4 November 2017 • Lisbon, Portugal
Fourth International Consensus Conference

SAVE THE DATE

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