Current standards and practice changing studies in Luminal ABC in 2017

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ESO Breast Cancer Program Coordinator
ESMO Board of Directors & NR Committee Chair
EORTC Breast Group Past-Chair
DISCLOSURES

Consultant/Ad Board:

Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Seattle Genetics, Teva
ABC4 was held under the High Patronage of and had the Opening made by His Excellency the President of the Portuguese Republic.

1300 participants from 88 countries
SEVERAL AVAILABLE OPTIONS
FOR THE MANAGEMENT OF ER+/HER-2 neg ABC

ET alone (Tamoxifen, AI, Fulvestrant)
ET + Biological agent (Palbociclib, Ribociclib, Everolimus)
CT monotherapy
CT combination

Clinical Trial with new therapies

HOW TO CHOOSE FOR THE INDIVIDUAL PATIENT?
Treatment choice should take into account at least these factors:

- HR & HER-2 status
- Previous therapies and their toxicities
- Disease-free interval
- Tumor burden (defined as number and site of metastases)
- Biological age
- Performance status
- Co-morbidities (including organ dysfunctions)
- Menopausal status (for ET)
- Need for rapid disease/symptom control
- Socio-economic and psychological factors
- Available therapies in the patient's country
- Patient preference

(LoE: Expert opinion)

Tailoring Therapy In Metastatic Breast Cancer
TAILOR FOR THE PATIENT
TAILOR FOR THE DISEASE
both biologically and clinically
INDIVIDUALIZED TREATMENT
Target

PATIENT PREFERENCES
(Incurable setting; Quality & Quantity of Life)

PATIENT CHARACTERISTICS

DISEASE clinical CHARACTERISTICS

TUMOR CHARACTERISTICS (Biomarkers)

SEVERAL AVAILABLE OPTIONS
FOR THE MANAGEMENT OF ER+/HER-2 neg ABC

For the Disease biologically and clinically
Target

INDIVIDUALIZED TREATMENT
HOW TO TREAT ER+/HER-2 neg (LUMINAL) ABC:

MAIN QUESTIONS:

a) Do we need Chemotherapy (CT)?

b) If Endocrine Therapy (ET) which agent?

c) Can we improve treatment of Luminal ABC by combining ET with biological agents?

d) If CT: combination vs. sequential monotherapy

e) If CT: which agent (s)
1\textsuperscript{st} QUESTION

Is CT needed?
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%)
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 Berkmortel4, T. J. Smilde5, A. J. van de Wouw6, F. P. J. Peters7, J. M. G. H. van Riel8, N. A. B. Peters9, M. de Boer1, P. G. M. Peer10 & V. C. G. Tjan-Heijnen11

1GROW—School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht; 2Department of Internal Medicine, Maxima Medical Centre, Veldhoven; 3Department of Internal Medicine, Onkologisch Centrum, Maastricht; 4Department of Internal Medicine, Netherlands Comprehensive Cancer Organisation, Utrecht; 5Department of Internal Medicine, Achmea Ziekenhuizen, Heeren; 6Department of Medical Oncology, Jeroen Bosch Hospital, Den Bosch; 7Department of Internal Medicine, Meecan Medical Center, Venlo; 8Department of Internal Medicine, Ahriun Orgine, Sittard; 9Department of Internal Medicine, St. Elisabeth Hospital, Tilburg; 10Department of Internal Medicine, St. Jans Hospita, Heerlen; 11Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands.

Received 24 May 2013; revised 28 August 2013 and 14 October 2013; accepted 26 October 2013.

Starting with ET vs. Starting with CT

**PFS**

- Patients with initial chemotherapy, median PFS 5.3 months (95% CI 4.2–6.2)
- Patients with initial endocrine therapy, median PFS 13.3 months (95% CI 11.3–15.5)

**OS**

- Patients with initial chemotherapy, median OS 16.1 months (95% CI 13.7–19.7)
- Patients with initial endocrine therapy, median OS 36.9 months (95% CI 30.6–43.9)

\( P < 0.0001 \)
NEED FOR CHANGE IN REIMBURSEMENT RULES
Current rules do not facilitate oral, less toxic treatments, nor shorter treatments of radiotherapy
ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

ET₁ → ET₂ → ET₃ → ET...

CT

response response response response

no response no response no response no response

MAIN CHALLENGE: Identify small percentage of “fast progressors”

First line endocrine therapy: FALCON or PALOMA-2?

**PALOMA-2**
HR 0.58 (0.46–0.72)

**FALCON**
HR 0.797 (0.637–0.999)

Finn et al. ESMO 2016, LBA-15; Ellis et al. ESMO 2016, LBA-14

Courtesy Peter Schmid, ESMO 2016, Discussant
2\textsuperscript{nd} and 3\textsuperscript{rd} QUESTIONS

Can ET alone be given or should combination with a biological agent be considered?

Which agents to use?
## Endocrine-Based Therapies for Breast Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Mechanism</th>
</tr>
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<tbody>
<tr>
<td>1977</td>
<td>SERMs</td>
<td>Antagonizes ER in breast tissue</td>
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<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
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<td></td>
<td>Toremifene</td>
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<tr>
<td>1990s</td>
<td>AIs</td>
<td>Inhibit estrogen production in postmenopausal women</td>
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<tr>
<td></td>
<td>Anastrozole</td>
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<td></td>
<td>Exemestane</td>
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<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>
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<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>
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<tr>
<td></td>
<td>Letrozole/palbociclib</td>
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<tr>
<td></td>
<td>Fulvestrant/palbociclib</td>
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</tbody>
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Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
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%)
Phase III FALCON: First-line Fulvestrant vs Anastrozole for Advanced Breast Cancer

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

ClinicalTrials.gov. NCT01602380.

M. Ellis et al, ESMO 2016

Slide credit: clinicaloptions.com
FALCON: PRIMARY ENDPOINT, PFS

Fulvestrant (n=230) vs Anastrozole (n=232)

Small PFS benefit for Fulvestrant DE NOVO BC (what if AI pre-treated?)

Why??
Subgroup analysis!!
ER POSITIVE / HER-2 NEGATIVE MBC

Many trials in ER+ ABC have not included pre-menopausal women. Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OS/OA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies.
(LoE/GoR: Expert Opinion/A) (95%)

Future trials exploring new endocrine-based strategies should be designed to allow for enrollment of both pre- and post-menopausal women.
(LoE/GoR: Expert Opinion/A) (92%)
MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 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

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.

*Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.


Primary endpoint: PFS (investigator-assessed) ± 10 ms PFS benefit

± 40% de novo
± 57% visceral mets

Goserelin included in all combinations.
Patient-reported outcomes (EORTC QLQ-C30 – global health status)

- There was a sustained improvement in time to definitive deterioration of at least 10% for the global health status/QoL scale in the ribociclib arm vs the placebo arm.
- A clinically meaningful (>5 points) improvement from baseline in pain score was observed as early as 8 weeks in the ribociclib arm, and was sustained.

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + tamoxifen/NSAI</th>
<th>Placebo + tamoxifen/NSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>102 (30.4)</td>
<td>115 (34.1)</td>
</tr>
<tr>
<td>Median, months</td>
<td>NR (22.2–NR)</td>
<td>21.2 (15.4–23.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.699 (0.533–0.916)</td>
<td></td>
</tr>
<tr>
<td>Log-rank test p value</td>
<td>0.004</td>
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</tbody>
</table>

Events-free probability (%)

Time to deterioration (months)

No. at risk

<table>
<thead>
<tr>
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<th>Ribociclib + tamoxifen/NSAI</th>
<th>Placebo + tamoxifen/NSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + tamoxifen/NSAI</td>
<td>335 282 256 236 218 201 188 145 112 69 43 41 15 3 0</td>
<td></td>
</tr>
<tr>
<td>Placebo + tamoxifen/NSAI</td>
<td>337 260 218 198 178 158 132 97 67 38 18 17 6 1 0</td>
<td></td>
</tr>
</tbody>
</table>

QoL, quality of life.
Goserelin included in all combinations.

D. Tripathy, SABCS 2017
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade (highest grade scored)

<table>
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<tr>
<th>3</th>
<th>2</th>
<th>1</th>
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<tbody>
<tr>
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<td>X</td>
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</tbody>
</table>

Toxicity and QoL adjustment when only a PFS improvement

RIBOCICLIV 1st line:
Efficacy score: 3
Improved QoL
Provisional MCBS: 4

Annals of Oncology 26: 1547–1573, 2015
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

Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

Aromatase Inhibitor
Nonsteroidal AIs: Anastrozole, Letrozole
Steroidal Al: Exemestane

ER Downregulator
Fulvestrant

Selective ER Modulators
Tamoxifen, Toremifene

ER target gene transcription

mTOR Inhibitors
Everolimus, Sirolimus, Temsirolimus

CDK4/6 Inhibitors
Palbociclib, Abemaciclib, Ribociclib

HDAC Inhibitor
Entinostat

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.
Key eligibility criteria

- Postmenopausal women with ER+, HER2− ABC not amenable to curative treatment by surgery or radiotherapy
- No prior metastatic BC treatment
- No prior treatment with, or known hypersensitivity to, mTOR inhibitors
- Prior neoadjuvant or adjuvant NSAI therapy must have been completed >1 year prior to enrollment
- ECOG performance status 0–2

1L setting (n=202)
- EVE 10 mg/day + LET 2.5 mg/day

Patients progressing in the 1L setting had the option to receive 2L treatment at the investigator’s discretion

2L setting (n=50)
- EVE 10 mg/day + EXE 25 mg/day

Primary endpoint
- 1L PFS

Secondary endpoints
- 2L PFS
- 1L OS
- 1L/2L ORR, CBR, and safety

1L, first-line; 2L, second-line; ER+, CBR, clinical benefit rate; ECOG, Eastern Cooperative Oncology Group; estrogen receptor positive; HER2−, human epidermal growth factor receptor 2-negative LET, letrozole; ORR, overall response rate; OS, overall survival; PFS, progression-free survival. CRAD001Y24135 Study Protocol v04 (August 10, 2015).
BOLERO-4: PFS in the 1L setting

- At data cut-off, median progression-free survival was 22.0 months (95% CI 18.1–25.1) at a median duration of follow-up of 29.5 months.

PROBLEM: Single-arm study!

EVE + LET

<table>
<thead>
<tr>
<th>No. of PFS events, n (%)</th>
<th>108 (54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression, n (%)</td>
<td>103 (51)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>No. censored, n (%)</td>
<td>94 (47)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>22.0 (18.1–25.1)</td>
</tr>
</tbody>
</table>

BOLERO-4: OS in the 1L setting

- OS following 1L treatment with EVE + LET is defined as the time from the start of treatment to date of death due to any cause.

PROBLEM: Single-arm study!

EVE + LET

<table>
<thead>
<tr>
<th>No. of OS events, n (%)</th>
<th>50 (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NE (37.0–NE)</td>
</tr>
<tr>
<td>KM-estimated OS rate, % (95% CI)</td>
<td>92.8 (88.1–95.7)</td>
</tr>
<tr>
<td>12-month</td>
<td>88.5</td>
</tr>
<tr>
<td>18-month</td>
<td>88.5</td>
</tr>
<tr>
<td>24-month</td>
<td>78.7</td>
</tr>
<tr>
<td>30-month</td>
<td>73.4</td>
</tr>
</tbody>
</table>

OS following 1L treatment with EVE + LET is defined as the time from the start of treatment to date of death due to any cause.

LPFV, last patient first visit; NE, not evaluable.
EVEROLIMUS: Adverse Events

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

Less frequent but clinically relevant:
- Hyperglycemia
  *Pneumonitis: Rare but potentially fatal*

Significant % (about 20%) of EVE–treated patients required a dose reduction

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)
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 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%)

* For pre and peri with OS/OA, and post-menopausal women and men
Palbociclib + Letrozole vs Letrozole: PFS (Final results)

**Progression-Free Survival (ITT)**

- **PAL + LET (N=84)**
  - Median PFS, months: 20.2 (13.8, 27.5)
  - Hazard Ratio: 0.488 (0.319, 0.748)
  - p-value: 0.0004

- **LET (N=81)**
  - Median PFS, months: 10.2 (5.7, 12.6)
  - Hazard Ratio: 1.000 (0.990, 1.010)
  - p-value: 0.6017

**Overall Survival (ITT)**

- **PAL + LET (N=84)**
  - Median OS, months: 37.5 (28.4, NR)
  - Hazard Ratio: 0.813 (0.492, 1.345)
  - p-value: 0.2105

- **LET (N=81)**
  - Median OS, months: 33.3 (26.4, NR)
  - Hazard Ratio: 0.987 (0.531, 1.834)
  - p-value: 0.9583

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

- **PAL + LET (N=84)**
  - Complete Response, n (%): 1 (1%)
  - Partial Response, n (%): 35 (42%)

- **LET (N=81)**
  - Complete Response, n (%): 1 (1%)
  - Partial Response, n (%): 26 (32%)

**Clinical Benefit Rate*, % (95% CI)**

- **PAL + LET (N=84)**
  - 81 (71, 89)

- **LET (N=81)**
  - 58 (47, 69)

**Stable Disease ≥24 weeks, n (%)**

- **PAL + LET (N=84)**
  - 32 (38%)

- **LET (N=81)**
  - 20 (25%)

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

Finn RS, et al. AACR 2014, Abstract CT101
PALOMA-2: Study Design (1008)\(^1\)

- **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; ≤12 mo, >12 mo)
  - Prior (neo)adjuvant hormonal therapy (yes, no)

- **Sample size**
  - N=666\(^a\)

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

- **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

- **Additional notes**
  - Blinded independent central review of efficacy endpoints performed as supportive analysis

---

\(^a\)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)

**Progression-Free Survival, %**

- **Time, months**
  - 0 3 6 9 12 15 18 21 24 27 30 33
  - **Number of patients at risk**
    - PAL+LET (N=444)
      - Number of Events, n (%)
        - 194 (44)
    - PCB+LET (N=222)
      - Number of Events, n (%)
        - 137 (62)
  - **Median (95% CI) PFS**
    - PAL+LET (N=444)
      - 24.8 (22.1–NR)
    - PCB+LET (N=222)
      - 14.5 (12.9–17.1)
  - **HR (95% CI); 1-sided P value**
    - PAL+LET (N=444)
      - 0.58 (0.46–0.72); P<0.000001
    - PCB+LET (N=222)
      - 0.58 (0.46–0.72); P<0.000001

**Number of patients at risk**

- PAL+LET (N=444)
  - 444 395 360 328 295 263 238 203 154 68 29 10 2
- PCB+LET (N=222)
  - 222 171 148 131 116 98 81 54 22 12 4 2

**ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.**
Initial QoL Presentation:
no difference in QoL!
TTD in HRQOL: Both Treatment Arms Combined

Statistically significant delay in TTD in HRQOL as assessed by FACT-B and FACT-G total scores was observed in patients who had not progressed vs those who had progressed in ALL patients.

<table>
<thead>
<tr>
<th>Time to Deterioration in FACT-B Total Score</th>
<th>PAL+LET/PBO +LET (n=329)</th>
<th>PAL+LET/PBO +LET (n=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI), mo</td>
<td>28.6 (26.3–NE)</td>
<td>19.4 (16.9–25.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.533 (0.409–0.694)</td>
<td>&lt;0.0001</td>
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<tr>
<td>1-sided P value*</td>
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<tr>
<th>Time to Deterioration in FACT-G Total Score</th>
<th>PAL+LET/PBO+LET (n=329)</th>
<th>PAL+LET/PBO+LET (n=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI), mo</td>
<td>31.3 (24.9–NE)</td>
<td>18.4 (15.2–24.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.533 (0.414–0.688)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-sided P value*</td>
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</table>

*Unstratified log-rank.

Courtesy Nadia Harbeck, ABC4, 2017
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade
(highest grade scored)

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<td>3</td>
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<td>1</td>
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<tr>
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Toxicity and QoL adjustment when only a PFS improvement

PALBOCICLIB 1st line:
(Based Paloma 2; waiting for OS & final QoL)
MCBS = 3

Annals of Oncology 26: 1547–1573, 2015
MONALEESA-2: A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF RIBOCICLIB + LETROZOLE

- Postmenopausal women with HR+/HER2– advanced breast cancer
- No prior therapy for advanced disease
- N=668

Randomization (1:1)
Stratified by the presence/absence of liver and/or lung metastases

Ribociclib (600 mg/day) 3-weeks-on/1-week-off + Letrozole (2.5 mg/day) n=334

Placebo + Letrozole (2.5 mg/day) n=334

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

Secondary endpoints
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio ≤0.56 and p<0.0000129

PFS, progression-free survival.
MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).
**Monaleesa 2 - Updated results ASCO 2017**

- **PFS results by independent central review:** hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)

- **Probability of Progression-free Survival (%):**
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- **Number of events, n (%):**
  - Ribociclib + Let: 93 (28)
  - Placebo + Let: 150 (45)

- **Median PFS, months (95% CI):**
  - Ribociclib + Let: NR (19.3–NR)
  - Placebo + Let: 14.7 (13.0–16.5)

- **Hazard ratio (95% CI):**
  - 0.556 (0.429–0.720)

- **One-sided p value:** 0.00000329

---

**Hortobagyi et al, ESMO 2016, updated ASCO 2017**

**NEJM 2017**
HR QoL Monaleesa 2 (no significant differences)

Change From Baseline in Global Health Patient-reported Outcomes, by Treatment Arm – EORTC QLQ-C30 Questionnaire

Time to definitive deterioration of the global health status/QoL scale score of the EORTC QLQ-C30 questionnaire by at least 10%

Verma et al. ASCO 2017
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade (highest grade scored)

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Toxicity and QoL adjustment when only a PFS improvement

RIBOCICLIB 1st line:
Efficacy score: 3
No improved QoL
MCBS: 3

Annals of Oncology 26: 1547–1573, 2015
**MONARCH 3: Study Design**

- **HR+, HER2- ABC**
- Postmenopausal
- Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

### Randomization

2:1

**Primary endpoint:**
Investigator-assessed PFS

**Secondary endpoint:**
OS, Response rates, Safety

**Stratification factors:**
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

- Abemaciclib: 150 mg BID (continuous schedule) plus Anastrozole: 1 mg or
  Letrozole: 2.5 mg QD until PD
- Placebo: BID (continuous schedule) plus Anastrozole: 1 mg or
  Letrozole: 2.5 mg QD until PD

---

**Statistics:** Study powered to 80% at one-sided alpha of 0.025 assuming a hazard ratio of 0.67 with analyses at 189 and 240 PFS events. Positive study at the interim required a hazard ratio <0.56 and two-sided p<0.0005.

**Enrollment:** From November 2014 to November 2015 patients enrolled in 158 centers from 22 countries

**Median follow-up:** 17.8 months

Di Leo et al, ESMO 2017
**MONARCH 3: Primary Endpoint: PFS (ITT)**

**Median PFS**
- **abemaciclib + NSAI**: not reached
- **placebo + NSAI**: 14.7 months

**HR (95% CI)**: 0.543 (0.409, 0.723)  
**p** = 0.000021

PFS benefit confirmed by blinded independent central review: HR (95% CI): 0.508 (0.359, 0.723); p = 0.000102

Di Leo et al, ESMO 2017
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade
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Toxicity and QoL adjustment when only a PFS improvement

ABEMACICLIB 1st line: (waiting for OS & QoL)
MCBS = 3

Annals of Oncology 26: 1547–1573, 2015
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%)

* For pre and peri with OS/OA, and post-menopausal women and men

Notes for manuscript:

a) Problems with QoL studies and methodology used
b) General availability of new drugs very uneven around the world
c) Discuss class effect of different CDKi and differences in toxicities which may influence treatment decision
**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**

**Stratification:**
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

- **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 goserelin¹.
- Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.
Primary Endpoint: PFS (Investigator-Assessed) ITT Population

- Placebo + Fulvestrant (n=174):
  - # Events (%): 93 (53.4)
  - Median PFS: 3.8 (3.5, 5.5)
  - Hazard Ratio: 0.422 (0.318, 0.560)

- Palbociclib + Fulvestrant (n=347):
  - # Events (%): 102 (29.4)
  - Median PFS: 9.2 (7.5, NE)
  - Hazard Ratio: <0.000001

Similar benefit seen in all subgroups examined.

CI=confidence interval, ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.
Conclusions

Compared to placebo + fulvestrant, addition of palbociclib to fulvestrant in endocrine resistant HR+/HER2- MBC patients was associated with:

- Significantly higher on treatment overall Global QOL scores
- Significantly greater improvement from baseline in emotional functioning and pain scores
- Significant delay in deterioration of pain
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade (highest grade scored)

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Toxicity and QoL adjustment when only a PFS improvement

PALBOCICLIB 2nd line:
Efficacy score: 3
Improved QoL
MCBS: 4

Annals of Oncology 26: 1547–1573, 2015
MONARCH 2: Abemaciclib in Combination with Fulvestrant in Patients with HR+/HER2- Advanced Breast Cancer Who Progressed On Endocrine Therapy

- HR+/HER2- ABC
- Pre/peri-\(^a\) or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET
  - Progressed on first-line ET
- No chemo for MBC
- No more than 1 ET for MBC
- ECOG PS \(\leq 1\)

N=669

Randomization 2:1

- abemaciclib: 150 mg\(^b\) BID (continuous schedule)
- fulvestrant: 500 mg\(^c\)
- placebo: BID (continuous schedule)
- fulvestrant: 500 mg\(^c\)

Primary endpoint: Investigator-assessed PFS
Secondary endpoint: OS, Response, Clinical Benefit Rate, Safety
Stratification factors:
- Metastatic site
- ET resistance (primary vs secondary)\(^4,5\)

- Statistics: 378 events for 90% power at one-sided \(\alpha\) of .025 assuming a true HR of .703
- Patients enrolled in 142 centers in 19 countries

\(^a\)Required to receive GnRH agonist
\(^b\)Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled
\(^c\)Fulvestrant administered per label

MONARCH 2: Primary Endpoint: PFS (ITT)

Median PFS
abemaciclib + fulvestrant: 16.4 months
placebo + fulvestrant: 9.3 months

HR (95% CI): .553 (.449, .681)
P < .0000001

PFS benefit confirmed by blinded independent central review (HR: .460; 95% CI: .363, .584; P < .000001)

Courtesy G. Sledge et al
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade
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Toxicity and QoL adjustment when only a PFS improvement

ABEMACICLIB 2nd line:
(waiting for OS & QoL)
MCBS = 3

Annals of Oncology 26: 1547–1573, 2015
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%)

* For pre and peri with OS/OA, and post-menopausal women and men

Notes for manuscript: a) Discuss class effect of different CDKi and differences in toxicities which may influence treatment decision; b) this is an appropriate option in patients who progressed less than one year after adjuvant AI
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%)

It is currently unknown how the different combinations of endocrine + targeted agents compare with each other, and with single agent CT. Trials are ongoing.

* For pre and peri with OS/OA, and post-menopausal women and men
# Main differences in PK, PD, dosing, and toxicity between the three CDKi

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib</th>
<th>Ribociclib</th>
<th>Abemaciclib</th>
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<tbody>
<tr>
<td><strong>PK</strong></td>
<td>$T_{\text{max}}$ 4.2–5.5 hours  $t_{1/2}$ 25.9–26.7 hours</td>
<td>$T_{\text{max}}$ 4 hours  $t_{1/2}$ 24–36 hours</td>
<td>$T_{\text{max}}$ 4–6 hours  $t_{1/2}$ 17–38 hours (Crosses blood:brain barrier)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>Reduced Rb phosphorylation in paired tumour biopsies, along with reduced fluorothymidine-PET uptake</td>
<td>Reduced Rb phosphorylation and Ki67 expression in paired tumour biopsies</td>
<td>Reduced Rb phosphorylation and TOPO IIα expression in paired tumour and skin biopsies</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>125 mg daily (3 weeks, 1-week drug holiday)  or 200 mg daily (2 weeks, 1-week drug holiday)</td>
<td>600 mg daily (3 weeks, 1-week drug holiday)</td>
<td>200 mg twice daily (continuous dosing)</td>
</tr>
<tr>
<td><strong>Major dose-limiting toxicities</strong></td>
<td>Neutropenia, thrombocytopenia</td>
<td>Neutropenia, thrombocytopenia</td>
<td>Fatigue</td>
</tr>
<tr>
<td><strong>Other reported adverse events</strong></td>
<td>Anaemia, nausea, anorexia, fatigue, diarrhoea</td>
<td>Mucositis  Prolonged ECG QTc interval  Elevated creatinine  Nausea</td>
<td>Diarrhoea  Neutropenia</td>
</tr>
</tbody>
</table>

PD, pharmacodynamics; PET, positron emission tomography; PK, pharmacokinetics; TOPO IIα, topoisomerase IIα.
So what do we do back in the clinic?

2 different treatment strategies; choice should probably rely on BIOLOGY (i.e. primary vs acquired ET resistance…

PFS in Months

Total
AI 1st line
CDK4/6i + Fulv 2nd line
mTORi + AI 3rd line

Total
CDK4/6i + AI 1st line
Fulv 2nd line
mTORi + AI 3rd line

Courtesy Ingrid Mayer
First line therapy: ET alone or ET + CDK4/6 or Chemotherapy

Disease activity
- Short DFI
- Visceral disease burden
- Symptoms

Probability to respond to ET
- Resistance Type (I⁰/II⁰)
- Intrinsic Subtype
- Biomarkers?

“Low Risk”
Single agent ET *
(ET + CDK4/6)

“Intermediate Risk”
ET + CDK4/6
(Single agent ET) (Chemo)

“High Risk”
Chemo
ET + CDK4/6

Visceral/non-visceral?

*ESR1 Mutation and choice of ET

Courtesy Peter Schmid, ESMO 2016, Discussant
THE QUEST FOR BIOMARKERS. . .
Many genetic biomarkers have shown little or no association with response to therapy

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Clinical studies</th>
<th>Findings (mutant/amplified/loss vs wildtype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>BOLERO-2, PALOMA-3, FERGI</td>
<td>PIK3CA: no significant difference in treatment effect</td>
</tr>
<tr>
<td>CCND1</td>
<td>BOLERO-2, PALOMA-1</td>
<td>CCND1 (BOLERO-2): no significant difference in treatment effect</td>
</tr>
<tr>
<td>p16</td>
<td>PALOMA-1</td>
<td>CCND1/p16 (PALOMA-1): changes in copy number did not improve patient selection beyond ER/HER2 status</td>
</tr>
<tr>
<td>FGFR</td>
<td>BOLERO-2</td>
<td>FGFR: no significant difference in treatment effect</td>
</tr>
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</table>

ESR1 mutations seem to be associated with resistance to AIs

**Biomarker**
- ESR1

**Clinical studies**
- PALOMA-3
- SoFEA
- BOLERO-2
- Schiavon et al

**Findings (mutant/amplified/loss vs wildtype)**
- PALOMA-3: no difference between mut vs wt
- SoFEA: treatment less effective in mut vs wt
- BOLERO-2: improved OS and PFS in wt vs mut*
- Schiavon et al: ESR1 mutations predict resistance to subsequent AI therapy**

*no statistical analysis carried out; **small sample size (n=45); mut = mutant; wt = wildtype

Potential Mechanisms of Acquired Resistance to CDK4/6 Inhibitors

- RB loss*
- Cyclin E1 over-expression* 
- Lineage plasticity** (via epigenetics)

sensitivity to CDK4/6 inhibitors may potentially be retained


The RBsig Predicts Resistance to Palbociclib

*In Vitro* and Clinical Outcome

**in vitro**

METABRIC dataset

Luminal A, endocrine treated

- HR = 2.67 (1.8-3.9, P = 1.1e-06)

Luminal B, endocrine treated

- HR = 2.31 (1.3-4.1, P = .0017)

Add comments with highlights, sticky tools

OPEN QUESTIONS

1) How do agents aiming at delaying/avoiding endocrine resistance (CDKi, Everolimus) compare with each other?

2) How do CDKi/Everolimus compare with CT?

3) Role of triple combinations (CDKi/mTORi/Pi3Ki)

4) When is ET alone a good (even best) option?

5) Which is the best sequence of endocrine agents and ET + Biologics? (both CDKi and Everolimus are efficacious in 1st and 2nd line)

6) How to choose between all available options, for each individual patient? – BIOMARKERS needed!

7) COST!
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%)

ALL guidelines are in agreement for this recommendation
• GOAL: to treat for as long as possible with a good QoL

• Then:
  – **TOXICITY PROFILE** is crucial
  – **DOSE REDUCTIONS** are acceptable and often needed (and better than interruptions)
  – **ORAL** vs IV (convenient, cost-effective, maintain work responsibilities...)
  – **PATIENT PREFERENCES** (oral treatment approaches and time saving drug delivery strategies are usually preferred by the patients)
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.
Clinical Efficacy of Cytotoxic Agents

Research question:

BEST SEQUENCE!??
Which agents?
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.
HERNATA Trial of Docetaxel/Trastuzumab vs Vinorelbine/Trastuzumab

Median PFS (months) D+T: 12.4 V+T: 15.3
P=0.67 HR 0.94 (95%CI 0.71-1.25)

Anderssen et al EBCC 2010
In press J Clin Oncol

N=284
Docetaxel + trastuzumab
Vinorelbine + trastuzumab

HER-2+ disease:
Vinorelbine seems at least as good as taxane and significantly less toxic

TRAVIOTA:
Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab

Vinorelbine & Capecitabine:
Consistent efficacy results & NO ALOPECIA

Paclitaxel or Docetaxel + Trastuzumab
Vinorelbine + Trastuzumab

P=0.09

First-line MBC
No prior trastuzumab
Measurable Disease
N=81

RR
TTP

Taxane Arm
58%
6.0 months

Vinorelbine Arm
66%
8.5 months

LIPOSOMAL TECHNOLOGY
“Old” agents with new technology

Doxorubicin
Liposomal Doxorubicin
Pegylated Liposomal Doxorubicin
The ABC Global Alliance

Continuing the work of the
ABC Consensus Conference and Guidelines
ABC Global Alliance

Who We Are:
• A multi-stakeholder platform for all those interested in collaborating in common projects relating to advanced breast cancer (ABC) around the world
• Continuation of the work developed through the ABC International Consensus Conference and Guidelines
• Launched during the World Cancer Congress in Paris on 3 November 2016

Our Vision/Mission:
• To improve and extend the lives of women and men living with ABC in all countries worldwide and to fight for a cure
• To raise awareness of advanced breast cancer and lobby worldwide for the improvement of the lives of ABC patients

Website www.abcglobalalliance.org
Email ABCGlobalAlliance@eso.net
Social media @ABCGlobalAll
ABC GLOBAL CHARTER
10 goals for the next 10 years

1. Double median overall survival for patients with ABC by 2025
2. Improve Quality of Life for patients with ABC in clinical practice
3. Improve availability of robust epidemiology and outcomes data for ABC
4. Increase availability and access to multidisciplinary care, including palliative, supportive, and psychosocial assistance for patients, families, and caregivers to ensure patients are receiving the best treatment experience
5. Strive for all patients with ABC to have financial support for treatment, care and assistance if unable to work
6. Offer communication skills training to all healthcare providers
7. Provide accurate and up-to-date ABC-specific information tools to all patients who want them
8. Increase public understanding of ABC
9. Improve access to non-clinical supportive services for ABC
10. Protect workforce rights for patients with ABC
Advanced Breast Cancer

Fifth International Consensus Conference

14-16 November 2019
Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT

RECEIVE UPDATES AT WWW.ABC-LISBON.ORG | #ABCLISBON

SAVE THE DATE
BACK-UP
Abemaciclib penetrates BBB