Current standards and practice changing studies in Advanced Breast Cancer in 2018

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DISCLOSURES

Financial disclosures:
*Personal financial interest in form of consultancy role for:* Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics, Teva.

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Non-Financial disclosures:
*Chair ABC Global Alliance and ABC Consensus Conference and Guidelines. Member/Committee Member of ESMO, ESO, EORTC-BCG, IBCSG, SOLTI, ASCO, AACR, EACR, SIS, ASPIC*
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
THE POWER OF LOBBYING
Continuing the work of the ABC Consensus Conference and Guidelines

Members as of 12 Dec 2018
147 members from 82 countries

Website www.abcglobalalliance.org
Email ABCGlobalAlliance@eso.net
Social media @ABCGlobalAll

ABC Global Alliance members
Members represented through Europa Donna - The European Breast Cancer Coalition (full list of countries available at www.europadonna.org)
mBA Alliance represents all its members in the ABC Global Alliance (full list of members available at www.mbcalliance.org)

Full list of members available on the Alliance website
ABC Global Charter
10 goals for the next 10 years

COMPREHENSIVE NEEDS ASSESSMENT DEFINES MOST URGENT AND ACTIONABLE GOALS
Done with (almost) all different stakeholders involved in ABC

1. HELP PATIENTS WITH ABC LIVE LONGER BY DOUBLING ABC MEDIAN OVERALL SURVIVAL BY 2025
2. ENHANCE OUR UNDERSTANDING ABOUT ABC BY INCREASING THE COLLECTION OF HIGH QUALITY DATA
3. IMPROVE THE QUALITY OF LIFE (QOL) OF PATIENTS WITH ABC
4. ENSURE THAT ALL PATIENTS WITH ABC RECEIVE THE BEST POSSIBLE TREATMENT AND CARE BY INCREASING AVAILABILITY OF ACCESS TO CARE FROM A MULTIDISCIPLINARY TEAM
5. IMPROVE COMMUNICATION BETWEEN HEALTHCARE PROFESSIONALS (HCP) AND PATIENTS WITH ABC THROUGH THE PROVISION OF COMMUNICATION SKILLS TRAINING FOR HCPS
6. MEET THE INFORMATIONAL NEEDS OF PATIENTS WITH ABC BY USING EASY TO UNDERSTAND, ACCURATE AND UP-TO-DATE INFORMATION MATERIALS AND RESOURCES
7. ENSURE THAT PATIENTS WITH ABC ARE MADE AWARE OF AND ARE REFERRED TO NON-CLINICAL SUPPORT SERVICES
8. COUNTERACT THE STIGMA AND ISOLATION ASSOCIATED WITH LIVING WITH ABC BY INCREASING PUBLIC UNDERSTANDING OF THE CONDITION
9. ENSURE THAT PATIENTS WITH ABC HAVE ACCESS TO TREATMENT REGARDLESS OF THEIR ABILITY TO PAY
10. HELP PATIENTS WITH ABC CONTINUE TO WORK BY IMPLEMENTING LEGISLATION THAT PROTECTS THEIR RIGHTS TO WORK AND ENSURE FLEXIBLE AND ACCOMMODATING WORKPLACE ENVIRONMENTS
HOW MANY ABC PATIENTS EXIST?

If 1 third would be MBC: about 2.2 million MBC patients

BUT it is just a very rough estimation

GLOBOCAN 2018 data*

Evolution of OS over time

Observed Overall Survival From Diagnosis of Metastatic Disease
All Patients

National cohort of 19,898 MBC pts diagnosed between 01/2008 and 12/2016 and treated in 18 Comprehensive Cancer centers

Median FU for the whole cohort is 4.05 yrs [95 CI: 3.98-4.12]

<table>
<thead>
<tr>
<th>Period</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI)(yrs)</td>
<td>3.12</td>
<td>2.94</td>
<td>3.09</td>
<td>3.23</td>
<td>3.09</td>
<td>3.29</td>
</tr>
</tbody>
</table>

[2.92-3.31] [2.78-3.09] [2.94-3.24] [3.02-3.48] [2.89-3.25] [3.09-ND]
Overall survival and sequential treatment of patients with MBC

- 134 sites, 298 oncologists, all over Germany
- > 3,700 pts/1409 ABC pts
- (goal: 4,500 BC pts/2250 ABC pts by end 2015)

In press, The Breast 2017

Luminal is the most frequent subtype in ABC as well.

If a drug/class of drugs improves OS, it will change substantially the median OS of ABC

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>HR pos HER2 pos</td>
<td>19%</td>
</tr>
<tr>
<td>HR neg HER2 pos</td>
<td>10%</td>
</tr>
<tr>
<td>triple neg</td>
<td>13%</td>
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</tbody>
</table>
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 a rapid disease/symptom control,
- socio-economic and psychological factors,
- available therapies in the patient’s country and patient preference.

*(LoE: Expert opinion) (100%)*
ABC diagnostic work-up and staging

**Diagnosis**

- LABC: Core biopsy to evaluate histology and biomarker expression (ER, PgR, HER2, proliferation/grade)
- ABC: Biopsy of metastatic lesion to confirm ABC diagnosis, particularly if first incidence of metastatic disease

**Staging**

- Minimal staging work-up: history and physical examination, haematology, biochemistry and imaging of chest, abdomen and bone with CT, bone scan or PET-CT* 

*Discuss indications. Brain MRI not indicated unless there are symptoms
Includes 2 clinical situations:

1. **Inoperable Locally Advanced Breast Cancer (LABC)**, that has not yet spread to distant sites

2. **Metastatic Breast Cancer**, that has spread to distant sites (most common are bone, liver, lung, brain, lymph nodes); also called Stage IV breast cancer.
CLINICAL PRACTICE GUIDELINES

Treatment of LABC

Multimodality treatment strongly indicated in almost all cases

Initial therapy should be systemic

Initial therapy depends on tumour and patient characteristics

HR+ HER2- LABC

Non-inflammatory

Endocrine therapy

Operable tumour

Non-inflammatory

BCS if appropriate

RT (if not given previously)

Adjuvant endocrine therapy/continuation of anti-HER2 (if appropriate)

Mastectomy

Inflammatory

ChT

Operable tumour

Further systemic treatment (if appropriate)

RT

Tumour remains inoperable

ChT + anti-HER2 therapy

Tumour remains inoperable

Palliative care

HER2+ LABC

ChT

Operable tumour

Further systemic treatment (if appropriate)

RT
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)
1st 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%)
ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

ET_1 → response → ET_2 → response → ET_3 → response → ET...

CT → no response → ET_1 → no response → ET_2 → no response → ET_3 → no response → CT

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
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)
2nd and 3rd QUESTIONS

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

Which agents to use?
Treatment of ER-positive / HER2-negative ABC

Endocrine Therapy (ET)

Genetic counselling and BRCA mutation status testing to be discussed with selected patients

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/ Breast-Cancer/4th-ESO-ESMO-International-Consensus-Guidelines-for-Advanced-Breast-Cancer-ABC-4
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%)

Combinations with biological agents described in other statements
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

- Pre/perimenopausal women with HR+, HER2- ABC
- No prior endocrine therapy for advanced disease
- ≤ 1 line of chemotherapy for advanced disease
- N=672

Primary analysis planned after ~329 PFS events

Randomization (1:1)

Stratified by:
- Presence/absence of liver/lung metastases
- Prior chemotherapy for advanced disease
- Endocrine therapy partner (tamoxifen vs NSAI)

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)\(^1,2\), and a sample size of 660 patients

N=672

- Placebo
- + tamoxifen/NSAI + goserelin*  
  n=337

- Ribociclib
  - 600 mg/day; 3-weeks-on/1-week-off
  - + tamoxifen/NSAI + goserelin*  
  n=335

+ Tamoxifen
  n=87
+ NSAI
  n=248

† Received treatment

‡ Goserelin included in all combinations.

+ Tamoxifen
  + NSAI

± 10 ms PFS benefit

\[ \text{Median PFS, months (95\% CI)} \]

\[ \begin{array}{ll}
\text{Ribociclib + ET} & 23.8 (19.2–NR) \\
\text{Placebo + ET} & 13.0 (11.0–16.4)
\end{array} \]

\[ \text{Hazard ratio (95\% CI)} \]

\[ 0.55 (0.44–0.69), p<0.0001 \]

MONALEESA-7: RESULTS

\[ \pm 40\% \text{ de novo} \]
\[ \pm 57\% \text{ visceral mets} \]

\[ \text{MONALEESA-7:} \]

- Ribociclib + ET reduced the risk of progression by 45% vs the placebo arm \((p<0.0001)\)\(^1,2\)
- Manageable safety profile consistent with prior studies of ribociclib\(^1,2\)

D. Tripathy, SABCS 2017
N. Harbeck, ESMO 2018
**TTD ≥10% IN GLOBAL HRQoL WAS DELAYED WITH RIBOCICLIB VS PLACEBO**

N. Harbeck et al, ESMO 2018

*Patients censored at progression; Similar results obtained with TTD ≥5%, ≥10%, and ≥15%.*
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS

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 Pre-menopausal:

Efficacy score: 3 (PFS)
Improved QoL
MCBS: 4

Annals of Oncology 28: 2340–2366, 2017
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

References:
1st Line CDK 4/6 INHIBITORS: EFFICACY

**PALOMA-2**

PFS: Investigator-Assessed - (ITT Population)

**MONALEESA 2: PRIMARY ENDPOINT WAS MET EARLY**

**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 (0.369, 0.723); **p = 0.000102**

Di Leo et al, ESMO 2017

Hortobagyi et al, ESMO 2016, updated ASCO 2017

NEJM 2017

No. of patients at risk

- **Ribociclib + Let:** 334
- **Placebo + Let:** 334

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

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

No. of patients at risk

- **Ribociclib + Let:** 294
- **Placebo + Let:** 279

MONALEESA 2: PRIMARY ENDPOINT WAS MET EARLY

One-sided p value

- 0.00000012

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

Hortobagyi et al, ESMO 2016, updated ASCO 2017

NEJM 2017
1st Line CDK 4/6 INHIBITORS: IMPACT ON QoL

Initial QoL Presentation: no difference in QoL!

Abemaciclib: no QoL yet reported

Verma et al. ASCO 2017
1st Line CDK 4/6 INHIBITORS: ESMO-MCBS Score

Evaluation form 2b: non-curative intent, primary endpoint PFS

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Efficacy

Toxicity and QoL adjustment when only a PFS improvement

10 MONTHS BENEFIT IN PFS
COST: ~ 5.000 €/cycle

PALBOCICLIB 1st line:
Efficacy score: 3 (PFS)
No improved QoL
MCBS = 3

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

ABEMACICLIB 1st line:
Efficacy score: 3 (PFS)
No QoL reported
MCBS = 3
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 OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
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 OFS/OFA, and post-menopausal women and men
**FINAL PROGRESSION-FREE SURVIVAL IN PALOMA-3 (ITT)**

- **Palbociclib+Fulvestrant (N=347)**
  - Median PFS=11.2 months
  - 95% CI (9.5, 12.9)
  - HR=0.497
  - 95% CI (0.398, 0.620)
  - 1-sided p<0.000001

- **Placebo+Fulvestrant (N=174)**
  - Median PFS=4.6 months
  - 95% CI (3.5, 5.6)

---

**Absolute improvement in median PFS was 6.6 months**

---

**Number of patients at risk**

- **PAL+FUL**
  - 347 276 245 215 189 168 137 69 38 12 2 1

- **PBO+FUL**
  - 174 112 83 62 51 43 29 15 11 4 1 1

---

FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; PAL=palbociclib; PBO=placebo.
1. Ibrance Summary of Product Characteristics; Pfizer Ltd; Kent, UK; 2018. Data cutoff date: 23 October 2015.

Cristofanilli et al, ESMO 2018
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
OVERALL SURVIVAL IN PALOMA-3 (ITT)

Absolute improvement in median OS was 6.9 months
BUT
NOT STATISTICALLY SIGNIFICANT

Cristofanilli et al, ESMO 2018
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS

Preliminary magnitude of clinical benefit grade (highest grade scored)

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7 MONTHS BENEFIT IN PFS
NO STATISTICAL SIGNIFICANT BENEFIT IN OS
COST: ~ 5,000 €/cycle

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

Annals of Oncology 28: 2340–2366, 2017
Ribociclib + fulvestrant reduced the risk of progression by 41% vs placebo + fulvestrant (p<0.001)\textsuperscript{1,2}

\begin{itemize}
  \item Ribociclib + fulvestrant
  \item Placebo + fulvestrant
\end{itemize}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{No. at risk} & 0 & 2 & 4 & 6 & 8 & 10 & 12 & 14 & 16 \\
\hline
\textbf{Ribociclib + fulvestrant} & 484 & 403 & 365 & 347 & 324 & 305 & 282 & 259 & 235 \\
\textbf{Placebo + fulvestrant} & 242 & 195 & 168 & 156 & 144 & 134 & 116 & 106 & 95 \\
\hline
\end{tabular}
\end{table}

\begin{itemize}
  \item \textbf{PFS}\textsuperscript{a,1,2}:
  \item Ribociclib + fulvestrant \textbf{N}=484
  \item Placebo + fulvestrant \textbf{N}=242
  \item \textbf{Median PFS, months (95% CI)}:
    \begin{itemize}
      \item Ribociclib + fulvestrant: 20.5 (18.5–23.5)
      \item Placebo + fulvestrant: 12.8 (10.9–16.3)
    \end{itemize}
  \item \textbf{HR (95% CI)}:
    \begin{itemize}
      \item Ribociclib + fulvestrant: 0.59 (0.48–0.73), p<0.001
    \end{itemize}
\end{itemize}

\textsuperscript{1}Investigator assessed.
\textsuperscript{2}Slamon DJ et al. ASCO 2018; abst 1000 (oral); 2. Slamon DJ et al. \textit{J Clin Oncol} 2018;36:2465–2472.
PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS

First line\textsuperscript{a}

Second line +
early relapse\textsuperscript{b}

\begin{tabular}{|c|c|c|}
\hline
Riboceibl + fulvestrant & Placebo + fulvestrant \\
\hline
PFS\textsuperscript{1,2} & 236 & 109 \\
Median PFS, months & 14.6 & 9.1 \\
HR (95% CI) & 0.57 (0.43–0.74) & \\
\hline
\end{tabular}

\footnotesize{\textsuperscript{a}No prior endocrine therapy for ABC; \textsuperscript{b}Up to one line of prior endocrine therapy for ABC or relapse on/within 12 months of (neo)adjuvant endocrine therapy; \textsuperscript{c}Investigator assessed.}

GLOBAL HRQoL

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Ribociclib + Fulvestrant</th>
<th>Placebo + Fulvestrant</th>
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<tbody>
<tr>
<td>0</td>
<td>139 (28.7%)</td>
<td>79 (32.6%)</td>
</tr>
<tr>
<td>6</td>
<td>228 (47.5%)</td>
<td>205 (84.9%)</td>
</tr>
<tr>
<td>12</td>
<td>177 (36.2%)</td>
<td>155 (63.9%)</td>
</tr>
<tr>
<td>18</td>
<td>105 (21.8%)</td>
<td>90 (36.8%)</td>
</tr>
<tr>
<td>24</td>
<td>49 (10.2%)</td>
<td>15 (6.1%)</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.80 (0.60–1.05)

No. at risk
Ribociclib + Fulvestrant: 484, 351, 316, 300, 283, 251, 240, 218, 216, 185
Placebo + Fulvestrant: 242, 175, 149, 133, 133, 116, 105, 96, 84, 82

GLOBAL HRQoL IMPROVED/MAINTAINED VS BASELINE WHILE ON TREATMENT IN BOTH ARMS

QoL similar in both arms
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS

Preliminary magnitude of clinical benefit grade (highest grade scored)

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Toxicity and QoL adjustment when only a PFS improvement

RIBOCICLIB + Fulvestrant:
Efficacy score: 3 (PFS)
No improvement in QoL
MCBS = 3

Annals of Oncology 28: 2340–2366, 2017
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

Preliminary magnitude of clinical benefit grade (highest grade scored)

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Toxicity and QoL adjustment when only a PFS improvement

ABEMACICL LIB 2nd line:
Efficacy score: 3 (PFS)
Waiting for QoL
MCBS = 3

Annals of Oncology 28: 2340–2366, 2017
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

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
4.6 to 6.9 ms benefit PFS

BOLERO-2 (18-ms FU): PFS Central

HR = 0.38 (95% CI: 0.31-0.48)
Log-rank P value: <.0001

Kaplan-Meier medians
EVE 10 mg + EXE: 11.0 months
PBO + EXE: 4.1 months

Number of patients still at risk
HR = 0.38 (95% CI: 0.31-0.48)
Log-rank P value: <.0001
Kaplan-Meier medians
EVE 10 mg + EXE: 11.0 months
PBO + EXE: 4.1 months

Number of patients still at risk
EVE 10 mg + EXE
PBO + EXE

Censoring times
EVE 10 mg + EXE (n/N = 188/485)
PBO + EXE (n/N = 132/239)

4 months “absolute difference” in OS
BUT
NOT STATISTICAL SIGNIFICANT

Everolimus 2nd line:
Efficacy score: 3 (OS)
Decreased QoL/Toxicity: loose 1
MCBS = 2

• 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


Piccart M, et al, EBCC 2014, LBA
Management of MUCOSITIS/STOMATITIS

**Steroid mouthwash** should be used for prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5mg/5ml dexamethasone, 10 ml to swish x 2 minutes then spit out qid). *(LoE/GoR: I/B)*

Early intervention is recommended. For > Grade 2 stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended. Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis. Consider adding steroid dental paste to treat developing ulcerations. *(LoE/GoR: Expert opinion/B).*

**MCBS = 3**
BOLERO 6: Randomized, Open-Label, Phase II Study

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

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

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

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

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

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

*Stratified by presence or absence of visceral disease (lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion, or malignant ascites; †Stratified multivariate Cox regression models were adjusted on treatment and the following prognostic and baseline covariates where imbalances between arms were observed: bone-only lesions (yes vs no); prior chemotherapy (yes vs no); ECOG PS (0 vs 1-2); organs involved (2 vs 1, and ≥3 vs 1); race (Caucasian vs non-Caucasian); age (<65 vs ≥65 years).

ANA, anastrozole; BID, twice daily; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PO, oral administration; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors.

BOLERO 6: Key Secondary Objective
Estimated HR of PFS for EVE + EXE vs CAP

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

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

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

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

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

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

*≥5% grade 3–4 events in any arm; †BOLERO-6 was not designed to use the SWISH\(^1\) protocol for stomatitis prevention.

### Other Safety

- **Serious AEs more frequent with EVE + EXE vs EVE alone or CAP**
- **Incidence of AEs leading to discontinuation comparable in each arm**

- Most frequent all-grade AEs:
  - Stomatitis in EVE-containing arms
  - PPE syndrome and diarrhea in CAP arm
- Grade 3–4 AEs more frequent in EVE + EXE arm vs EVE alone arm, and comparable between EVE + EXE and CAP arms

---

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 OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
At present, no validated predictive biomarker other than hormone receptor status exist to identify patients who will/will not benefit from the addition of a targeted agent (i.e. CDK4/6 inhibitor, mTOR inhibitor) to endocrine therapy and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.

(LoE/GoR: I/E) (95%)
WHEN CHEMOTHERAPY IS NEEDED . . .
Treatment of ER-positive / HER2-negative ABC

Chemotherapy (ChT)

Genetic counselling and BRCA mutation status testing to be discussed with selected patients
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...) *(remember metronomic CT)*

  – **PATIENT PREFERENCES** (oral treatment approaches and time saving drug delivery strategies are usually preferred by the patients)
Treatment of ER-negative / HER2-positive ABC

CLINICAL PRACTICE GUIDELINES

Previously untreated with anti-HER2 therapy

- ChT + trastuzumab + pertuzumab (ChT + trastuzumab only if pertuzumab not available)

Previously treated (neo)adjuvantly with anti-HER2 therapy

- ChT + pertuzumab + trastuzumab or ChT + trastuzumab

Patients unsuitable for ChT or with long disease-free interval, minimal disease burden

- Trastuzumab alone or dual blockade alone (trastuzumab + pertuzumab or trastuzumab + lapatinib)

No progression

Anti-HER2 as maintenance therapy

- If complete remission, optimal duration of maintenance anti-HER2 therapy is unknown

- Stopping therapy after several years of complete remission may be an option

Progression

T-DM1 if available (no data available on use after dual blockade)

- Trastuzumab in combination with an unused ChT agent

- Trastuzumab + lapatinib

Additional anti-HER2 therapy and ChT

Note: Include in clinical trials when available
**CLINICAL PRACTICE GUIDELINES**

**Treatment of ER-positive / HER2-positive ABC**

- **First line**
  - Previously untreated with anti-HER2 therapy:
    - ChT + trastuzumab + pertuzumab
    (ChT + trastuzumab only if pertuzumab not available)
  - No progression:
    - ET + anti-HER2 as maintenance therapy
  - If complete remission, optimal duration of maintenance anti-HER2 therapy is unknown:
    - Stopping anti-HER2 therapy after several years of complete remission may be an option

- **Second lines**
  - Previously treated (neo)adjuvantly with anti-HER2 therapy:
    - ChT + pertuzumab + trastuzumab
    or ChT + trastuzumab
  - Progression:
    - T-DM1 if available (no data available on use after dual blockade)
  - Trastuzumab in combination with an unused ChT agent or with ET (if appropriate)
  - Trastuzumab + lapatinib + ET, if not previously used
  - Maintenance ET + anti-HER2 therapy
  - Additional anti-HER2 therapy and ChT or ET

**Note:** Include in clinical trials when available

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### Comparison of patient populations

**Limited prior Adjuvant Trastuzumab Therapy**

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo</strong></td>
<td>Docetaxel/Paclitaxel</td>
<td>Docetaxel</td>
<td>Paclitaxel</td>
<td>Taxane</td>
</tr>
<tr>
<td><strong>Anti-HER2 regimens tested</strong></td>
<td>T-DM1 or T-DM1 + Pertuzumab</td>
<td>Trastuzumab + Pertuzumab <em>(vs TRAS)</em></td>
<td>Trastuzumab + Everolimus 10mg OD <em>(vs TRAS)</em></td>
<td>Lapatinib <em>(vs TRAS)</em></td>
</tr>
<tr>
<td><strong>De novo metastatic</strong></td>
<td>55%</td>
<td>53%</td>
<td>≈ 50%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Prior adj. trast. (and interval &gt;1y)</strong></td>
<td>31%</td>
<td>11%</td>
<td>10%</td>
<td>18%</td>
</tr>
</tbody>
</table>

The results of most of these trials are relevant today only for de novo metastatic patients

Adapted from M. Piccart St. Gallen 2015 & R. Dent ESMO Asia 2015
Trastuzumab suppresses HER2 activity
• Flags cells for destruction by the immune system

Pertuzumab inhibits HER2 heterodimerization
• Suppresses multiple HER signaling pathways
• Flags cells for destruction by the immune system

DUAL BLOCKADE: TRASTUZUMAB + PERTUZUMAB

15 MONTHS BENEFIT IN OS in previously untreated patients
COST: ~ 6,500 €/cycle
Trastuzumab-DM1

Receptor-T-DM1 complex is internalized into HER2-positive cancer cell

T-DM1 binds to the HER2 protein

Potent antimicrotubule agent is released once inside the HER2-positive tumor cell

5 MONTHS BENEFIT IN OS
COST: ~ 4,000 €/cycle
HER-2 POSITIVE MBC: 1\textsuperscript{st} line

CT + trastuzumab and pertuzumab
or
CT + trastuzumab
or
ET + trastuzumab +/- pertuzumab or lapatinib

HER-2 POSITIVE MBC: 2\textsuperscript{nd} line and beyond

T-DM1
or
CT + trastuzumab
or
ET + trastuzumab
Treatment of advanced TNBC

- Genetic counseling and BRCA mutation status testing should be discussed with patient.
- Combination ChT (patients with rapid progression, visceral crisis, need for rapid symptom/disease control).
  - Preferred regimens: Carboplatin + gemcitabine OR Cisplatin + 5-FU/ or capecitabine.
- Sequential single-agent ChT.
  - Previously untreated with anthracycline or taxanes:
    - Anthracycline or taxanes.
  - Previously treated with anthracycline and/or taxanes:
    - BRCA mutation:
      - PARPI
      - Carboplatin
      - Capecitabine
      - Eribulin
      - Vinorelbine
    - BRCA wild-type:

A PARP inhibitor (olaparib or talozaparib) is a reasonable treatment option for patients with BRCA-associated triple negative or luminal (after progression on endocrine therapy) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL and a favorable toxicity profile.

OS results are awaited. It is unknown how PARP inhibitors compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumors.

(LoE/GoR: I/B) (80%)
OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≥2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
  - If prior platinum use
    - No evidence of progression during treatment in the advanced setting
    - ≥12 months since (neo)adjuvant treatment

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

Primary endpoint: progression-free survival by BICR

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression/deaths, n (%)</td>
<td>163 (79.5)</td>
<td>71 (73.2)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.0</td>
<td>4.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.43 to 0.80; P=0.0009</td>
<td></td>
</tr>
</tbody>
</table>

At risk, n:
- Olaparib 300 mg bd: 205, 177, 154, 107, 94, 69, 40, 23, 11, 4, 1, 1, 1, 1, 1, 1, 0
- Chemotherapy TPC: 97, 63, 44, 25, 21, 11, 8, 4, 4, 4, 1, 1, 1, 1, 0
OLYMPIAD: Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>130 (63)</td>
<td>62 (64)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>19.3</td>
<td>17.1</td>
</tr>
<tr>
<td>HR</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.66–1.23; P=0.513</td>
<td></td>
</tr>
<tr>
<td>Alive at 6 months, %</td>
<td>93.1</td>
<td>85.8</td>
</tr>
<tr>
<td>Alive at 18 months, %</td>
<td>54.1</td>
<td>48.0</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>18.9</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Preliminary OS data

3 MONTHS DIFFERENCE IN PFS BUT BETTER QoL
IMPACT ON OS?
COST: ~ 7.000 €/month

Nominal P values calculated using a likelihood ratio test; OS stratification factors were prespecified but not alpha controlled
1L, first line; 2/3L, second or third line; NS, not significant

Courtesy of Mark Robson
**Hypothesis:** Addition of PARP inhibitor improves outcomes in pts with gBRCA ABC

**1st EP:** PFS

**Inclusion criteria:** ABC with BRCA1/2g

**Follow-up/n:** 11.2 months / n= pts

---

**EMBRACA**

**Primary Endpoint:** PFS by Blinded Central Review

- **TALA**
- **Overall PCT**

<table>
<thead>
<tr>
<th>Events, no. (%)</th>
<th>TALA (n=231)</th>
<th>Overall PCT (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>186 (85%)</td>
<td>82 (56%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median, mo (95% CI)</th>
<th>TALA</th>
<th>Overall PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.6 (5.2, 9.3)</td>
<td>5.6</td>
<td>(4.2, 6.7)</td>
</tr>
</tbody>
</table>

- Hazard ratio: 0.54 (95% CI, 0.41, 0.71); *P* = .0001

- 1 year PFS improvement with TALA 37% vs 20%; **HR: 0.54 (95% CI, 0.41, 0.71); P<0.001**

- OS data is immature
• **NOT RECOMMENDED** for ROUTINE CLINICAL PRACTICE:
  
  • Multigene panels
  
  • Circulating tumour DNA (ctDNA) assessment
  
  • Immunotherapy (not yet! Even after Impassion!)
TAKE-HOME MESSAGES

- Survival of ABC in “rich” countries has not improved much, except for HER2+ ABC
- Expensive medicines are not the priority! Except TRASTUZUMAB, which is now an WHO essential medicine
- FOCUS ON:
  - QUALITY PATHOLOGY
  - ACCESS TO OPIOIDS/SUPPORTIVE and PALLIATIVE CARE
  - RADIOTHERAPY (e.g. brain, bone mets)
  - BIOSIMILARS and GENERICS (if approved and high-quality)
  - FIGHT FOR TRASTUZUMAB
  - STOP PRESCRIBING SO MUCH UNECESSARY CT IN LUMINAL ABC – PREFER ENDOCRINE THERAPY!
  - DON’T WASTE RESOURCES on “fashionable things”
Advanced Breast Cancer

Fifth ESO-ESMO International Consensus Conference

14-16 November 2019 | Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT
Co-Chairs: G. Curigliano, IT - S.A. Mertz, US
Scientific Committee Members: K. Gelmon, CA
F. Penault-Llorca, FR - E. Senkus, PL - C. Thomssen, DE

The ABC5 guidelines will be developed by ESO and ESMO
The ABC5 conference and guidelines are endorsed by

The ABC5 conference is held under the auspices of
with official representatives of
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BACK-UP
IMPROVING SURVIVAL

• STOP ACCEPTING PFS BENEFIT ALONE AS THE MAIN GOAL
• OS MUST BE AT LEAST A CO-PRIMARY
• INVEST IN LESS BUT “BIGGER” (SUFFICIENTLY POWERED) TRIALS
• COLLECT POST-PROGRESSION DATA
• USE REAL WORLD AND BIG DATA
IMPROVING QUALITY OF LIFE

• STOP PRESCRIBING SO MUCH UNECESSARY CT
• NOT ALL PATIENTS NEED COMBINATION OF ET + TARGETED
• ADEQUATE SYMPTOM CONTROL (Opioids access)

• DEVELOP BETTER AND SPECIFIC QoL TOOLS
• ASK EXPERTS FOR HELP WHEN CHOOSING QoL TOOLS AND ENDPOINTS
NEED FOR CHANGE IN REIMBURSEMENT RULES

In many countries, current rules do not facilitate oral, less toxic treatments, nor shorter treatments of radiotherapy.
IMPROVING COST-EFFECTIVENESS

- INVEST WISELY
- STOP WASTING RESOURCES
- USE BIOSIMILARs and GENERICS (if approved and high-quality)
- USE AVAILABLE TOOLS TO PRIORITIZE (ESMO-MCBS)