ESMO-ESO Medical Students Course

*Advanced Breast Cancer*

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DISCLOSURES SLIDE

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
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.
Goals of the Treatment in ABC

- Balancing treatment efficacy and toxicity is the main objective
- Goals of treatment:
  - Improve survival (very few agents achieve it!)
  - Delay disease progression
  - Prolong duration of response
  - Palliate symptoms
  - Improve or maintain quality of life
  - Transform into a chronic disease
Here & Now is a pan-European ABC awareness initiative from Novartis Oncology. The campaign aims to improve understanding of the high degree of unmet need, including the social and psychological impact of ABC, ultimately to improve support and care for patients across Europe.

Campaign ambassadors

Cardoso et al. Evolving psychosocial, emotional, functional, and support needs of women with advanced breast cancer: Results from the Count Us, Know Us, Join Us and Here & Now surveys. The Breast 28: 5-12, 2016.
5 year survival rates for mBC still around 25%


Analysis suggests limited improvement in quality of life for patients with mBC over the last decade

• An analysis of the trends in quality of life for mBC* indicates that there has not been significant improvement over the past decade²
• In fact, there has been a slight decrease in quality of life²

*Analysis was based on a review of 132 articles, of which a quantitative analysis was conducted of 14 studies reporting QoL measures for mBC. Values are weighted based on sample size. This analysis indicates a numerical decrease over time. It does not intend to demonstrate statistical significance


Have things really changed?

Yes ... but not as much as needed!
CAN WE DO BETTER?
HOW?
In the early 2000’s...

2 SURVEYS ON LIVING WITH ABC STARTED TO CHANGE THE SCENE...

- Most women do not feel that healthcare professionals, researchers, the media, women with EBC, and the governments pay enough attention to MBC.

- Throughout the survey there is a worrying picture of feelings of guilt, abandonment, isolation, and loneliness during the hard journey through MBC.

- 44% of respondents reported being afraid to talk open about their disease and 52% said their friends and family were uneasy talking about the disease.

Seminars in Oncology Nursing (26) 3, 2010; Community Oncology, Sep. 2010
TIME TO CHANGE!
ESO-MBC International Task Force

1300 attendees from 88 countries
MAIN PRINCIPLES OF ABC RECOMMENDATIONS

✓ Apply the main principles of modern oncology:
  ✓ Multidisciplinary treatment
  ✓ Specialized breast cancer units
  ✓ Evidence-based medicine
    (please STOP “eminence-based” medicine!!)
  ✓ Individualized (tailored) therapy

✓ Remember the specificities of ABC setting

✓ Patient’s preferences & active participation

✓ Identify areas of UNMET NEEDS & RESEARCH PRIORITIES
In ABC Patient/Advocates are full and equal partners
ESO-ESMO ABC4 GUIDELINES

SPECIAL ARTICLE

4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†


www.abc-lisbon.org

https://oncologypro.esmo.org/Guidelines/
WHY ARE GUIDELINES IMPORTANT?

• Unfortunately not all medical decisions can be based on level 1 evidence. Guidance is necessary.

• There is a wealth of (new) data in oncology that needs to be “digested”, put into perspective and applied to clinical practice.

• Patients in routine clinical practice are often very different from a clinical trial population.

• Many cancer patients are still treated totally outside the recommendations and available data!

• If all cancer patients would be treated according to the current knowledge, survival would substantially increase!
Several online presentations: e-ESO sessions, Peer Voice Program, Advocates Online Sessions, Breast Cancer TV, …
The ABC Global Alliance
Continuing the work of the ABC Consensus Conference and Guidelines

Members as of 20 May 2019
177 members from 84 countries

The power of lobbying!
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

**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**
The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial. (LoE/GoR: Expert opinion/A) (100%)
96% of HCPs agree that a multidisciplinary team approach improves the level of care for patients with ABC\textsuperscript{10}

\textbf{BUT...}

Over a quarter (26%) of the HCPs surveyed do not work as part of a multidisciplinary team\textsuperscript{10}
### The Challenges of Extreme Societal Opinions about mBC

<table>
<thead>
<tr>
<th>Death sentence</th>
<th>mBC Attitudes</th>
<th>Curable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some believe people with mBC will die very soon</td>
<td>Others overly positive, thinking people can &quot;beat&quot; mBC</td>
<td>Typically driven by visibility of success stories in eBC</td>
</tr>
<tr>
<td>Driven by perception that all cancer is terrible / imminently fatal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Or by perception that once cancer spreads, end of life must be close</td>
<td>Patients themselves may believe their mBC can be cured</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– in some cases, the medical team appears to have painted an overly positive picture</td>
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48–76% of the general public **believe** that advanced/metastatic breast cancer is curable

**FIGHT STIGMA!**
Public perceptions may perpetuate the stigma and isolation for mBC patients. On average, 28% of the general population indicated that patients with mBC should keep it a secret and not discuss it with anyone other than their physician.

Percentage of respondents that felt people with advanced or metastatic breast cancer should not talk about it with anyone other than their physician.

24% in UK, 22% in France, 27% in Germany, 33% in Poland, 29% in Brazil, 26% in Mexico, 18% in Argentina, 23% in Chile, 22% in Colombia, 42% in Turkey, 49% in India, 35% in Taiwan, 21% in Japan, 26% in South Africa.

14 Country Study: 14,315 respondents

mBC General Population Survey, commissioned by Pfizer. August 2015
Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances).

This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.

(LoE/GoR: Expert opinion/A) (97%)
From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care. The approach must be personalized to meet the needs of the individual patient.

(LoE: Expert opinion/A) (100%)
Patients (and their families, caregivers or support network, if the patient agrees) should be invited to participate in the decision-making process at all times.

When possible, patients should be encouraged to be accompanied by persons who can support them and share treatment decisions (e.g. family members, caregivers, support network).

(LoE/GoR: Expert opinion/A) (100%)
Patients with mBC need realistic, compassionate and individualized communication.

Of 582 surveyed oncologists and other healthcare practitioners in the U.S., Europe, Latin America and Australia...

Less than 50% of healthcare professionals report having received training on how to bring bad news to patients and families.

There is a need for patients to proactively seek involvement in decision making.

Healthcare professionals reported that only half of their patients voice their treatment goals.

Earlier discussion on end-of-life is needed to prepare patients.

In 65% of cases, end-of-life discussions are held too late - first arising after multiple changes in treatment have already occurred.

www.breastcancervision.com
www.abc-lisbon.org
CAN WE MANAGE PROPERLY WHAT WE CAN’T MEASURE?

• What is the prevalence of ABC? (most cancer registries capture diagnosis and mortality but not relapse!)

• What is the best endpoint for advanced cancer?
If 1 third would be MBC: about 2.2 million MBC patients
BUT it is just a very rough estimation

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>
<tr>
<td></td>
<td>[2.92-3.31]</td>
<td>[2.78-3.09]</td>
<td>[2.94-3.24]</td>
<td>[3.02-3.48]</td>
<td>[2.89-3.25]</td>
<td>[3.09-ND]</td>
</tr>
</tbody>
</table>
# Prospective German TMK cohort study

## Overall survival according to subtype

![Survival Probability Graph](https://example.com/survival_graph.png)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Events n (%)</th>
<th>Median OS months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-pos./HER2-neg.</td>
<td>269 (60.7%)</td>
<td>33.8 (30.2 - 40.2)</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>164 (59.2%)</td>
<td>38.2 (31.3 - 43.0)</td>
</tr>
<tr>
<td>Triple negative</td>
<td>90 (76.9%)</td>
<td>16.8 (11.5 - 22.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number at risk</th>
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<tr>
<td>HR-pos./HER2-neg.</td>
</tr>
<tr>
<td>HER2-positive</td>
</tr>
<tr>
<td>Triple negative</td>
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</tbody>
</table>

Prognosis of de novo & recurrent MBC diverges over time

De novo MBC
mean survival = 5.03 yrs.

Recurrent MBC
mean survival = 2.81 yrs.
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)

- 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

In press, The Breast 2017

Oral Presentation, ABC 2
Marschner, N, et al, TMK Registry Group
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
Which is/are best endpoint(s) for advanced cancer?

**DOES PFS BENEFIT MATTER IF NOT ASSOCIATED WITH OS BENEFIT?**

Depends!

- **on the type of disease:**
  - PD not always linked to symptoms (ovarian ≠ breast)
  - Available therapies

- **on the type of drug:**
  - Toxicity / QoL
  - Affordability
Which is/are best endpoint(s) for MBC?

**OS**

**Pros:**
1) The most objective endpoint
2) The most desired endpoint (both for patients & physician)

**Cons:**
1) May be influenced by subsequent therapies
2) Needs longer follow-up
3) May be influenced by subsequent therapies

**COMPOSITE ENDPOINTS**

**Pros:**
1) Obtained faster

**Cons:**
1) Is not a good surrogate for OS benefit
2) Not always associated with clinically meaningful benefit (only when associated with symptom control and/or low toxicity)
3) More subjective endpoint (specially in situations where response assessment is difficult (e.g. bone disease))
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
Ongoing project:
Development of a QoL tool specific for ABC

Ongoing project:
Development of Quality Indicators for ABC/MBC
NEED FOR CHANGE IN REIMBURSEMENT RULES

In many countries, current rules do not facilitate oral, less toxic treatments, nor shorter treatments of radiotherapy.
Minimal staging workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone. (LoE/GoR: II/A) (67%)

Notes:
✓ Biochemistry tests including liver function tests, renal function, electrolytes, calcium, total proteins and albumin
✓ A PET-scan should NOT be part of the minimal staging workup but it is very useful in specific situations (e.g. high suspicion of metastases that cannot be found in previous exams)
Brain imaging should NOT be routinely performed in asymptomatic patients. This approach is applicable to all patients with MBC including those patients with HER-2+ and/or TNBC MBC. (LoE/GoR: II/D) (94%)

BUT

✓ Careful evaluation of signs and symptoms is needed, particularly among patients with HER-2+ or TN MBC, since clinical manifestations of brain metastases may sometimes be quite subtle.

✓ In the setting of suggestive signs or symptoms, a lower threshold to image such patients should be considered given the higher pre-test probability for CNS involvement.
The clinical value of tumor markers is not well established for diagnosis or follow-up after adjuvant therapy, but their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. A change in tumor markers alone should not be used to initiate a change in treatment.

(LoE/GoR: II/C) (89%)
Evaluation of response to therapy should generally occur every 2-4 months for ET or after 2-4 cycles for CT, depending on the dynamics of the disease, the location and extent of metastatic involvement, and type of treatment.

Imaging of a target lesion may be sufficient in many patients. In certain patients, such as those with indolent disease, less frequent monitoring is acceptable.

Additional testing should be performed in a timely manner, irrespective of the planned intervals, if PD is suspected or symptoms appear.

Thorough history and physical examination must always be performed.

(LoE/GoR: Expert opinion/B) (81%)
GENERAL RECOMMENDATIONS
TREATMENT

THE 2 MAIN PROBLEMS IN ONCOLOGY TODAY

✓ PATIENT SELECTION
✓ TUMOR RESISTANCE
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 dysfunction).
- Menopausal status (for ET).
- Need for rapid disease/symptom control.
- Socio-economic factors.
- Available therapies in the patient's country.
- Patient preference.

**SEVERAL AVAILABLE OPTIONS**

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

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

**PATIENT CHARACTERISTICS**

**DISEASE clinical CHARACTERISTICS**

**TUMOR CHARACTERISTICS** (Biomarkers)

**INDIVIDUALIZED TREATMENT**
THE 2 MAIN PROBLEMS IN ONCOLOGY TODAY

✓ TUMOR RESISTANCE

- Why it occurs
- How to overcome it
THE MAJOR PROBLEM OF TUMOR RESISTANCE TO THERAPY

J. Ribeiro & F. Cardoso
A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time. (LoE/GoR: I/B) (98%)

Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible. (LoE/GoR: I/B) (98%)

Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.
If the results of tumour biology in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing.

(LoE/GoR: Expert opinion/B) (87%)
SHOULD WE TREAT METASTATIC CANCER BASED ON THE BIOLOGY OF THE PRIMARY OR BIOPSY?

REASSESS BIOLOGY AT TIME OF RECURRENCE IS CRUCIAL

- Biology changes every time we give a new treatment

ONGOING EVALUATION OF DISEASE STATUS & BIOLOGY

But, SERIAL BIOPSY ES are very difficult
PERFORM MINIMAL OR NON-INVASIVE SERIAL EVALUATIONS OF DISEASE STATUS/BIOLOGY

IMAGING & FUNCTIONAL IMAGING

LIQUID BIOPSIES

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

- Many available options today
- Major questions:
  - Best sequence for each individual patient
  - Best therapy after CDK4/6 inhibitors

HOW TO TACKLE HETEROGENEITY OF LUMINAL-LIKE ABC?
Are there ready-to-use (bio)markers to individualize sequence of therapies?
HOW TO TACKLE HETEROGENEITY OF LUMINAL-LIKE ABC?

• **PATIENT HETEROGENEITY:**
  - age/menopausal status, preferences, genetics and pharmaco-genomics (and other determinants for toxicity)

• **DISEASE HETEROGENEITY**
  - visceral/non-visceral metastases/visceral crisis

• **TUMOR BIOLOGICAL HETEROGENEITY**
  - ESR1 mutations, PI3K mutations, AKT/mTOR, HER pathway activation, other resistance mechanisms
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) Is a targeted agent also necessary or is ET alone sufficient?
d) If CT: combination vs. sequential monotherapy?
e) If CT: which agent(s)?
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/GoR: I/A) (93%)

ALL guidelines are in agreement for this recommendation.
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/NA) (95%)
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. Voogd³,⁴, M. W. Dercksen², F. van den Berkmortel⁵, T. J. Smilde⁶, A. J. van de Wouw⁷, F. P. J. Peters⁷, J. M. G. H. van Riel⁸, N. A. J. B. Peters⁹, M. de Boer¹⁰, P. G. M. Peer¹⁰ & V. C. G. Tjan-Heijnen¹¹

¹GRON¹ – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht; ²Department of Internal Medicine, Maastricht Medical Centre, Veldhoven; ³Netherlands Comprehensive Cancer Organisation, Utrecht; ⁴Department of Internal Medicine, Arnhem-Orbis Hekeren, Heerlen; ⁵Department of Medical Oncology, Jeroen Bosch Hospital, Den Bosch; ⁶Department of Internal Medicine, VU/MC Medical Center, Vrije Universiteit; ⁷Department of Internal Medicine, Arnhem-Orbis Sticht, Sittard; ⁸Department of Internal Medicine, St Elisabeth Hospital, Tilburg; ⁹Department of Internal Medicine, St Jan’s Hospital, Venlo; ¹⁰Department of Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands

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Starting with ET vs. Starting with CT

**PFS**

**OS**
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
2nd and 3rd QUESTIONS

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

Which agents to use?
The preferred 1st line ET 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/GoR: I/A) (84%)

* for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
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:
Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

Aromatase Inhibitor
- Nonsteroidal Alts: Anastrozole, Letrozole
- Steroidal AI: Exemestane

ER Downregulator
- Fulvestrant

Selective ER Modulators
- Tamoxifen, Toremifene

mTOR Inhibitors
- Everolimus, Sirolimus, Temsirolimus

CDK4/6 Inhibitors
- Palbociclib, Abemaciclib, Ribociclib

HDAC Inhibitor
- Entinostat

1st Line CDK 4/6 INHIBITORS: EFFICACY

**MONALEESA-7: RESULTS**

- 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\(^1,2\)

**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) \(p=0.000021\)

**MONALEESA-7**

- Ribociclib + ET
  - Placebo + ET
- Median PFS (95% CI)
  - Ribociclib + ET: 23.8 (19.2–NR)
  - Placebo + ET: 13.0 (11.0–16.4)
- Hazard ratio (95% CI)
  - Ribociclib + ET: 0.55 (0.44–0.69), \(p=0.00001\)

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

**PALOMA-2**

**PFS: Investigator-Assessed - (ITT Population)**

- Number of Events, n (%)
  - Placebo + ET: 194 (58)
  - Ribociclib + ET: 137 (42)
- Median (95% CI) PFS
  - Placebo + ET: 24.8 (22.1– NR)
  - Ribociclib + ET: 14.5 (12.3–17.1)
- HR (95% CI): 1-sided P value
  - Placebo + ET: 0.58 (0.46–0.72), \(p<0.000001\)

**MONALEESA**

- Placebo + letrozole; NR, not reached.

**MONALEESA - Updated results ASCO 2017**

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

**Abstract ID 2627: Rugo et al**

Impact of Palbociclib Plus Letrozole on Health-Related Quality of Life Compared With Letrozole Alone in Treatment-Naive Postmenopausal Patients With ER+/HER2- Advanced/Metastatic Breast Cancer: Results From PALOMA-2

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

**Randomization**

- Palbociclib: 125 mg QD
- Letrozole: 2.5 mg QD
- Placebo: 0.45 mg QD

**Trial registration:** NCT01740427

**Initial QoL Presentation:**

no difference in QoL!

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

**Abemaciclib: no QoL yet reported**

**TTD ≥10% IN GLOBAL HRQoL WAS DELAYED WITH RIBOCICLIB VS PLACEBO**

- Patients censored at progression
- Similar results obtained with TTD ≥5%, ≥10%, and ≥15%

**N. Harbeck et al, ESMO 2018**

*Patients censored at progression. *Similar results obtained with TTD ≥5%, ≥10%, and ≥15%.
The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.

OS results are still awaited. QoL was comparable to that with ET alone.

*(LoE/GoR : I/A) (90%)

ESMO-MCBS: 3

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

ATTENTION: WILL BE UPDATED AT ABC5 IN VIEW OF OS RESULTS OF MONALEESA 7
**MONALEESA-7 Study Design**

**First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients**

- **Pre/perimenopausal women** with HR+/HER2− ABC
- No prior ET for ABC, ≤ 1 prior CT for ABC
- N = 672

**Stratification Factors**

- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

**Randomized 1:1**

**Ribociclib**

- 600 mg/day;
- 3 weeks on/1 week off
- + NSAI/TAM<sup>°</sup> + GOS<sup>d</sup>
- n = 335

**Placebo**

- 3 weeks on/1 week off
- + NSAI/TAM<sup>°</sup> + GOS<sup>d</sup>
- n = 337

**Primary endpoint**

- PFS (local)

**Key secondary endpoint**

- OS

**Select secondary endpoints**

- HRQOL
- ORR
- TTDD of ECOG PS
- Safety

---

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.

<sup>a</sup> Premenopausal status was defined as either patient had last menstrual period ≤ 12 months or if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range or in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age.

<sup>b</sup> Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed.

<sup>c</sup> TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg, and ANA dose was 1 mg.

<sup>d</sup> GOS 3.6 mg was administered by subcutaneous injection.

S. Hurvitz, ASCO 2019
Overall Survival

RIBOCICLIB 1st line Pre-menopausal: MCBS: 5

- ≈ 29% relative reduction in risk of death

S. Hurvitz, ASCO 2019
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 (OFS/OFA) 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, and men. (LoE/GoR: Expert Opinion/A) (92%)
2nd Line CDK 4/6 INHIBITORS: EFFICACY

FINAL PROGRESSION-FREE SURVIVAL IN PALOMA-3 (ITT)^1

- Ribociclib + fulvestrant reduced the risk of progression by 41% vs placebo + fulvestrant (p<0.001)^1,2

MONALEESA-3: FINAL PFS

PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS
OVERALL SURVIVAL IN PALOMA-3 (ITT)

Absolute improvement in median OS was 6.9 months

**BUT**

NOT STATISTICALLY SIGNIFICANT
2nd Line CDK 4/6 INHIBITORS: IMPACT ON QoL

**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

**Abemaciclib: no QoL yet reported**

**QoL similar in both arms**
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

ESMO-MCBS: 4
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), a non-statistically-significant improvement in OS (7 months) and an improvement in QoL, and is the preferred treatment option, if a CDK4/6 inhibitor was not previously used.

(LoE/GoR : I/A)

* For pre and peri with OFS/OFA, and post-menopausal women and men

ESMO-MCBS: 4

ATTENTION: PROPOSED CHANGES. NOT YET VOTED NOR APPROVED!
CDK 4/6 INHIBITORS (Palbociclib, Ribociclib, Abemaciclib)

10 MONTHS BENEFIT IN PFS 1\textsuperscript{st} line
OS BENEFIT 1\textsuperscript{st} line in Pre-menopausal
6 MONTHS BENEFIT IN PFS in 2\textsuperscript{nd} line

COST: $\sim 5.000$ €/cycle
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%)

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

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

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

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


Piccart M, et al, EBCC 2014, LBA

• 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
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**
6 MONTHS BENEFIT IN PFS in 2nd line
NO OS BENEFIT SEEN

COST: ~ 3.500 €/cycle

Everolimus
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 exists 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%)
ESR1 mutations seem to be associated with resistance to AIs

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Clinical studies</th>
<th>Findings (mutant/amplified/loss vs wildtype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PALOMA-3</td>
<td>PALOMA-3: no difference between mut vs wt</td>
</tr>
<tr>
<td></td>
<td>SoFEA</td>
<td>SoFEA: treatment less effective in mut vs wt</td>
</tr>
<tr>
<td></td>
<td>BOLERO-2</td>
<td>BOLERO-2: improved OS and PFS in wt vs mut*</td>
</tr>
<tr>
<td></td>
<td>Schiavon et al</td>
<td>Schiavon et al: ESR1 mutations predict resistance to subsequent AI therapy**</td>
</tr>
</tbody>
</table>

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

NEW DRUGS ARRIVING . . .
SOLAR-1 (NCT02437318, Alpelisib) Primary endpoint: Locally assessed PFS in the PIK3CA-mutant cohort

PI3K inhibitors ALPELISIB

Only ~ 7% pretreated with CDK 4/6i

F. André et al, ESMO 2018

The primary endpoint crossed the pre-specified Haybittle-Peto boundary (one-sided p≤0.0199)

F. André et al, ESMO 2018

SOLAR 1
Adverse events in the total population*

<table>
<thead>
<tr>
<th>AEs ≥20% in either arm</th>
<th>Alpelisib + fulvestrant (N=284)</th>
<th>Placebo + fulvestrant (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All 4</td>
<td>All 4</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>282 (99.3)</td>
<td>183 (64.4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>181 (63.7)</td>
<td>93 (32.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>164 (57.7)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>127 (44.7)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>101 (35.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>101 (35.6)</td>
<td>28 (9.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>77 (27.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>78 (26.8)</td>
<td>15 (3.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>70 (24.6)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69 (24.3)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>58 (20.4)</td>
<td>5 (1.8)</td>
</tr>
</tbody>
</table>

- Eighteen patients (6.3%) discontinued alpelisib due to hyperglycemia and 9 patients (3.2%) discontinued alpelisib due to rash; no patients discontinued placebo due to either hyperglycemia or rash

F. André et al, ESMO 2018

SOLAR 1
Treatment exposure and dose adjustments

<table>
<thead>
<tr>
<th>Treatment exposure</th>
<th>PIK3CA-mutant*</th>
<th>PIK3CA-non-mutant*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpelisib + fulvestrant (N=169)</td>
<td>Placebo + fulvestrant (N=170)</td>
<td></td>
</tr>
<tr>
<td>Alpelisib + fulvestrant (N=115)</td>
<td>Placebo + fulvestrant (N=116)</td>
<td></td>
</tr>
</tbody>
</table>

- The data cut-off for both groups was June 12, 2018.
- The patient in the placebo arm of the PIK3CA-mutant cohort did not receive fulvestrant or placebo.

F. André et al, ESMO 2018
HDAC inhibitors
Chidamide? Entinostat?

Not pretreated with CDK 4/6i

ACE (Chidamide) Trial: PFS in ITT Population

Phase III E2112: Exemestane ± Entinostat in Advanced Breast Cancer

- Entinostat: oral, histone deacetylase inhibitor
- Primary endpoints: OS, PFS
- Secondary endpoints: ORR (CR or PR), TTD, toxicity
- Other outcomes: adherence, QoL, protein lysine acetylation

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/peri/peri lesional female and all male pts receive goserelin acetate SC Day 1.

No febrile neutropenia was reported

ClinicalTrials.gov: NCT02115282
MANAGEMENT OF LUMINAL ABC

Diagnosis of ER+/HER2- disease

Endocrine therapy (preferred treatment option)
- Pre-menopausal
- Peri-menopausal
- Post-menopausal

Ovarian ablation/ suppression

Prior perioperative (or (neo)adjuvant) endocrine therapy (preferred treatment option)
- AI + CDK4/6 inhibitor (if > 12 months since AI)
- AI
- Tamoxifen
- Fulvestrant
- Combination endocrine therapy (AI and fulvestrant)

No prior perioperative (or (neo)adjuvant) endocrine therapy
- AI, tamoxifen, fulvestrant + palbociclib, different AI + everolimus, tamoxifen + everolimus, fulvestrant, estradiol, megestrol acetate

ChT (patients with visceral crisis, endocrine resistance)

Combination ChT (patients with rapid progression, visceral crisis, need for rapid symptom/ disease control)

Sequential single-agent ChT
- Previously untreated
- Previously treated with anthracycline or taxanes

Anthracycline or taxanes
- Capecitabine
- Eribulin
- Vinorelbine

ChT to maximum response or toxicity

Maintenance endocrine therapy after ChT to maintain benefit

ABC, advanced breast cancer; AI, aromatase inhibitor; ChT, chemotherapy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

F Cardoso et al, Annals of Oncology 2018
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/GoR: I/A) (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/GoR: Expert opinion/A) (96%)*

Usually each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity. What is considered unacceptable should be defined together with the patient. *(LoE/GoR: I/B) (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.
EXAMPLE OF TARGETED THERAPY: HER-2 RECEPTOR & TRASTUZUMAB

HER-2 receptor

Ligand binding

Activated receptor

TRASTUZUMAB

Cell membrane

Signal transmission

STOP

Proliferation

Survival

Migration

Tumor Growth and Metastases
Chemotherapy ± trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

H0648g trial

- Longer OS: 25.1 vs. 20.3 ms (p=0.046)
- Longer TTP: 7.4 vs. 4.6 ms (p<0.001)
- Higher RR: 50 vs. 32% (p<0.001)
- Longer duration: 9.1 vs. 6.1 ms (p<0.001)

MCBS: 5
MAIN MESSAGES:

Anti-HER2 therapy should be offered *early* (as 1st line) to all patients with HER2+ ABC, except in the presence of contraindications to the use of such therapy.  
(LoE/GoR: I/A) (98%)

Patients progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered *additional anti-HER2 therapy* with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway.  
(LoE/GoR: I/A) (91%)

**CHANGE IN PARADIGM IN ONCOLOGY!**
DUAL BLOCKADE: TRANSTUZUMAB + PERTUZUMAB

- 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

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

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

T-DM1 binds to the HER2 protein

5 MONTHS BENEFIT IN OS

COST: ~ 4.000 €/cycle
HER-2 POSITIVE ABC: 1\textsuperscript{st} line

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

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

T-DM1
or
CT + trastuzumab
or
ET + trastuzumab
ANTI-HER2 THERAPIES

OS SURVIVAL BENEFIT IN ALL LINES

TRASTUZUMAB:
COST: ~ 2.200 €/cycle

PERTUZUMAB:
COST: ~ 6.500 €/cycle

TDM-1:
COST: ~ 4.000 €/cycle
Treatment of HER2+ ABC: Progress over time

**First-line**
- CT
- CT + Trastuzumab: 20.3 mos.
- D + Trastuzumab: 25.1 mos., 40.8 mos., 2015
- D + Trastuzumab + Pertuzumab: 2015

**Second line**
- Capecitabine: 16.2 mos., 2010
- Capecitabine + Lapatinib: 18.8 mos., 2012
- Capecitabine + Lapatinib: 25.1 mos.
- T-DM1: 30.9 mos., 2015

**Third / Later line**
- Physicians choice: 15.8 mos., 2015
- T-DM1: 22.7 mos.

---

NEW DRUGS ARRIVING . . .
Margetuximab: Fc-engineered to Activate Immune Responses

**Trastuzumab**

**Fab:**
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival

**Fc:**
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

---

**Margetuximab**

**Fab:**
- Same specificity and affinity
- Similarly disrupts signaling

**Fc engineering:**
- ↑ Affinity for activating FcγRIIIA (CD16A)
- ↓ Affinity for inhibitory FcγRIIB (CD32B)

**Margetuximab Binding to FcγR Variants:**

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Receptor</th>
<th>Allelic Variant</th>
<th>Relative Fc Binding</th>
<th>Affinity Fold-Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating</td>
<td>CD16A</td>
<td>158F</td>
<td>Lower</td>
<td>6.6x ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>158V</td>
<td>Higher</td>
<td>4.7x ↑</td>
</tr>
<tr>
<td></td>
<td>CD32A</td>
<td>131R</td>
<td>Lower</td>
<td>6.1x ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131H</td>
<td>Higher</td>
<td>↔</td>
</tr>
<tr>
<td>Inhibitory</td>
<td>CD32B</td>
<td>232I/T</td>
<td>Equivalent</td>
<td>8.4x ↓</td>
</tr>
</tbody>
</table>

H. Rugo, ASCO 2019

**Study CP-MGAH22-04 (SOPHIA) Design**

**臂1**

Margetuximab (15 mg/kg Q3W) + chemotherapy in 3-week cycles

**臂2**

Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) + chemotherapy in 3-week cycles

**STRATIFICATION:**
- Chemotherapy choice
- Prior therapies (≤2 vs >2)
- Metastatic sites (≤2 vs >2)

**Sequential Primary Endpoints**
- PFS (by CBA; n=257; HR=0.67; α=0.05; power=90%)
- OS (n=385; HR=0.75; α=0.05; power=80%)

**Secondary Endpoints**
- PFS (Investigator assessed)
- Objective response rate (by CBA)
- Clinical benefit rate (CBR), duration of response (DoR)
- Safety profile, antidrug antibody
- Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

**Tertiary/Exploratory Endpoints**
- Hazard ratio; CBA=central blinded analysis.


H. Rugo, ASCO 2019
SOPHIA TRIAL: PFS Analysis in ITT Population

24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=266)</th>
<th>Trastuzumab + Chemotherapy (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of events</td>
<td>130</td>
<td>135</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>5.8 months (5.52–6.97)</td>
<td>4.9 months (4.17–5.59)</td>
</tr>
</tbody>
</table>

HR by stratified Cox model, 0.76 (95% CI, 0.59–0.98)
Stratified log-rank P=0.033

H. Rugo, ASCO 2019

ITT population: N=536. CI=confidence interval.
DS-8201a: a HER2-targeting Antibody-drug Conjugate

DS-8201a Structure and Mechanism of Action

- DS-8201a was designed with the goal of improving critical attributes of an ADC

- DS-8201 is a humanized HER2 antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide-based linker
- Designed to deliver CT inside cancer cells and reduce systemic exposure in comparison to traditional CT
- Activity in HER2+ and “HER2 low”
Heterogeneity of TRIPLE NEGATIVE BC: TNBC Classification

- Basal-like (BL) TNBC
- Immune-associated (IM) TNBC
- Mesenchymal-like TNBC (ML-TNBC)
- Immune signature
- DNA damage
- Cell cycle
- Growth factor signaling
- EMT signature: cell motility, growth factor signaling (TFG6, Notch, Wnt/β-catenin, Hedgehog)
- Angiogenesis
- Cell cycle DNA damage
- Claudin-Low
- Normal
- LA/LB
- HER2e
- HER2-enriched (HER2e) TNBC
- Luminal/apocrine (LA) TNBC
- Luminal (LAR)

- Le Du F. Oncotarget. 2015;6:12890-12908. This work is licensed under a Creative Commons Attribution 3.0 Unreported License.

Slide credit: clinicaloptions.com
Management of Advanced TNBC, in real life...

<table>
<thead>
<tr>
<th>Line of CT</th>
<th>Total</th>
<th>TNBC</th>
<th>ER+</th>
<th>HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>205</td>
<td>45 (100%)</td>
<td>102 (100%)</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>2</td>
<td>159</td>
<td>36 (80%)</td>
<td>79 (77%)</td>
<td>44 (76%)</td>
</tr>
<tr>
<td>3</td>
<td>122</td>
<td>26 (58%)</td>
<td>56 (55%)</td>
<td>69 (52%)</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>13 (29%)</td>
<td>38 (37%)</td>
<td>30 (52%)</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>8 (18%)</td>
<td>24 (24%)</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>6 (13%)</td>
<td>9 (9%)</td>
<td>19 (33%)</td>
</tr>
</tbody>
</table>

Patients with TN Disease Received Fewer Treatments and Stayed on Each Treatment Regimen For A Shorter Interval

Courtesy G. Curigliano

Seah et al, ASCO 2012
For non-BRCA-associated triple negative ABC, there are no data supporting different or specific CT recommendations. Therefore, all CT recommendations for HER-2 negative disease also apply for triple negative ABC.

(LoE/GoR: I/A) (98%)
In patients with **BRCA-associated triple negative or endocrine-resistant ABC** previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a **platinum regimen** is the preferred option, if not previously administered and no suitable clinical trial is available.

*(LoE/GoR: I/A) (86%)*

All other treatment recommendations are similar to sporadic ABC.
A PARP inhibitor (olaparib or talozaparib) is a reasonable treatment option for patients with BRCA-associated triple negative or luminal (previously exposed to 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%)
The principle of synthetic lethal tumour targeting

Normal tissue cells
- DNA repair
- Base excision DNA repair
- Homologous recombination (HR) repair

Few normal tissue effects
- HR repair
- PARP inhibitor
- Base excision DNA repair

BRCA1/BRCA2 deficient Tumor cells
- HR repair
- PARP inhibitor
- Base excision DNA repair

Specific tumor cell killing

How does PARP inhibition compare with CT in ABC?

- **gBRCA1 / BRCA2 Carriers**
  - Advanced anthracycline taxane resistant breast cancer

- **Potent PARP inhibitor at MTD as continuous exposure**

- **Physician Choice within SOC options**
  - Capecitabine
  - Vinorelbine
  - Eribulin
  - Gemcitabine

- **Primary endpoint**
  - PFS

**Niraparib – BRAVO Trial EORTC / BIG**

**Talazoparib – EMBRACA - NCT01945775**

**Olaparib - OLYMPIAD NCT02000622**

Hypothesis: Addition of PARP inhibitor improves outcomes in pts with gBRCA ABC

**1^EP**: PFS

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

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

**EMBRACA**

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

- 1-Year PFS 37% vs 20%; HR: 0.54 (95% CI, 0.41, 0.71); P<0.001
- OS data is immature
PARP Inhibitors in BRCA+ ABC

3 MONTHS DIFFERENCE IN PFS BUT BETTER QoL IMPACT ON OS?
COST: ~ 7,000 €/month
For the purpose of these recommendations, LABC means INOPERABLE, LOCALLY ADVANCED BREAST CANCER THAT HAS NOT SPREAD TO DISTANT SITES

PLEASE CHECK SLIDES
Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan. 
(LoE/GoR: I/A) (100%)

**Early** introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority. 
(LoE/GoR: I/A) (100%)

Access to effective pain treatment (including morphine, which is inexpensive) is necessary to all patients in need. 
(LoE/GoR: I/A) (100%)
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 and is endorsed by

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ABC STATEMENTS FOR LABC

For the purpose of these recommendations, LABC means INOPERABLE, NON-METASTATIC LOCALLY ADVANCED BC
BEFORE starting any therapy, a core biopsy providing histology and biomarker (ER, PR, HER2, proliferation/grade) expression is indispensable to guide treatment decisions.

(LoE/GoR: I/A) (97%)
Since LABC patients have a significant risk of metastatic disease, a full staging workup, including a complete history, physical examination, lab tests and imaging of chest and abdomen (preferably with CT-scan) and bone, prior to initiation of systemic therapy is highly recommended. 
(LoE/GoR: I/A) (100%)

PET-CT, if available, may be used (instead of and not on top of CT-scans and bone scan).
(LoE/GoR: II/B) (100%)
Systemic therapy (not surgery or radiotherapy) should be the initial treatment. 
(LoE/GoR: III/A) (100%)

If LABC remains inoperable after systemic therapy and eventual radiation, “palliative” mastectomy should not be done, unless the surgery is likely to result in an overall improvement in quality of life. 
(LoE/GoR: Expert opinion/D) (100%)

A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and radiotherapy) is strongly indicated in the vast majority of cases. 
(LoE/GoR: I/A) (100%)
Options for HR+ LABC include an anthracycline- and taxane-based chemotherapy regimen, or endocrine therapy. (LoE/GoR: I/A) (85%)

The choice of CT versus ET, as initial treatment, will depend on tumor (grade, biomarker expression) and patient (menopausal status, performance status, comorbidities, preference) considerations. (LoE/GoR: Expert Opinion/A) (85%)
Anthracycline- and-taxane-based chemotherapy is recommended as initial treatment.

(LoE/GoR: I/A) (85%)
Concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pCR.
(LoE/GoR: I/A) (92%)

Anthracycline-based chemotherapy should be incorporated in the treatment regimen.
(LoE/GoR: I/A) (72%)

When an anthracycline is given, it should be administered sequentially with the anti-HER2 therapy.
(LoE/GoR: I/A) (87%)
For patients with HER-2+ LABC (Inflammatory or non-inflammatory), without distant metastases, who are in complete remission after appropriate neoadjuvant systemic therapy and appropriate loco-regional therapy, and being treated with a potential curative intent, the approved adjuvant duration of 1 year of anti-HER2 therapy should be used.

(LoE/GoR: I/A) (85%)
Following effective neoadjuvant systemic therapy with or without radiotherapy, surgery will be possible in many patients. This will consist of mastectomy with axillary dissection in the vast majority of cases, but in selected patients with a good response, breast conserving surgery may be possible.

(LoE/GoR: II/A) (98%)
In patients with axillary low burden of disease at presentation (previously cN0-cN1) with complete response after systemic treatment (ycN0), sentinel lymph node biopsy can be an option, provided all the recommendations for sentinel node after primary systemic treatment are followed (i.e. dual tracer, clipping/marking positive nodes, minimum of three sentinel nodes).

(LoE/GoR: III/B) (62%)
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment. *(LoE/GoR: I/A) (93%)*

Mastectomy with axillary dissection is recommended in almost all cases, even when there is good response to primary systemic therapy. *(LoE/GoR: I/A) (95%)*

Immediate reconstruction is generally not recommended in patients with inflammatory LABC. *(LoE/GoR: IV/E) (95%)*

Loco-regional radiotherapy (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy. *(LoE/GoR: I/A) (98%)*