The newest and most promising treatments

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ESO Breast Cancer Program Coordinator
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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%)*
The Effect of Hospital Volume on Breast Cancer Mortality
Rachel A. Greenup, MD, MPH,† Samilia Obeng-Gyasi, MD, MPH,‡ Samantha Thomas, MS,‡ K. Houck, MS,† Whitney O. Lane, MD,§ Rachel C. Blitzblau, MD, PhD,‡ Terry Hyslop, PhD,‡ and E. Shelley Hwang, MD, MPH†

Annals of Surgery 2016

FIGURE 2. Scatter plot of log HR by average annual hospital volume with restricted cubic spline fit. Relationship between risk of death and annual hospital volume after adjustment for known covariates. Black dashed line represents the restricted cubic spline (RCS) fit with knots indicated by black dots. Gray dotted lines represent the 95% confidence interval for the RCS fit.

FIGURE 3. Unadjusted Kaplan-Meier curve for overall survival (N = 1,058,198). Relationship between hospital volume and unadjusted overall survival by months (log-rank P < 0.0001).
Conclusion: Survival benefits reported in high-volume hospitals suggest a better application of recommended processes of care, justifying the centralization of breast cancer care in such hospitals.
RESEARCH ARTICLE

Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer

Alexis Prat, Joel S. Parker, Olga Karginova, Cheng Fan, Chad Livasy, Jason I. Herschkowitz, Xiaping He, Charles A. Perou

Reach to Recovery International Conference 2019
## MOLECULAR CLASSIFICATION OF BREAST CANCER - SURROGATES

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Histological characteristics SURROGATES</th>
<th>Biology/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Luminal A</strong></td>
<td>• ER+</td>
<td>• indolent behaviour</td>
</tr>
<tr>
<td></td>
<td>• low grade/low proliferation</td>
<td>• sensitive to hormonal therapy</td>
</tr>
<tr>
<td><strong>Luminal B</strong></td>
<td>• ER+ (lower expression than in luminal A)</td>
<td>• more aggressive behaviour than luminal A</td>
</tr>
<tr>
<td></td>
<td>• high grade/high proliferation</td>
<td>• less sensitive to hormonal therapy than luminal A</td>
</tr>
<tr>
<td><strong>Basal-like</strong></td>
<td>• “Triple negative” (ER-, PR -, HER 2-)</td>
<td>• aggressive behaviour</td>
</tr>
<tr>
<td></td>
<td>• high grade/high proliferation</td>
<td>• sensitive to chemotherapy</td>
</tr>
<tr>
<td><strong>Her-2 enriched</strong></td>
<td>• HER 2+</td>
<td>• aggressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• sensitive to anti-HER-2 therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• sensitive to chemotherapy</td>
</tr>
</tbody>
</table>
A tumor cell in the Seventies

![Diagram](https://via.placeholder.com/150)

*Courtesy of T. Tursz*
GENERAL RECOMMENDATIONS

TREATMENT

THE 2 MAIN PROBLEMS IN ONCOLOGY TODAY

✓ PATIENT SELECTION

✓ TUMOR RESISTANCE
THE MAJOR PROBLEM OF TUMOR RESISTANCE TO THERAPY
BIOPSY OF METASTATIC DISEASE

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.
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 BIOPSIES are very difficult
PERFORM MINIMAL OR NON-INVASIVE SERIAL EVALUATIONS OF DISEASE STATUS/BIOLOGY

IMAGING & FUNCTIONAL IMAGING

LIQUID BIOPSIES
NANOTECHNOLOGY
THE « WEAPONS » OF MEDICAL ONCOLOGY

The “bomb”

Chemotherapy

Tumor cell in division

The “missiles”

Endocrine Therapy

Tumor cell with hormonal receptors
(about 2/3 of BC)

Ant-HER-2 therapy

Tumor cell with HER-2 receptors
(about 1/5 of BC)
The newest and most promising treatments for Metastatic/Advanced Breast Cancer
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**
- **Patient preference**

**(LoE/GoR: Expert opinion/A) (100%)**

**Tailoring Therapy In Metastatic Breast Cancer**

**TAILOR FOR THE PATIENT**

**TAILOR FOR THE DISEASE**

both biologically and clinically

**INDIVIDUALIZED TREATMENT**

**Target**

Reach to Recovery International Conference 2019
ENDOCRINE THERAPY

1st example of TARGETED THERAPY

ER: estrogen receptor

THE TARGET

THE LIGAND

Tamoxifen
Fulvestrant

Aromatase inhibitors
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%)
ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

**ET\(_1\)**  \(\rightarrow\) **ET\(_2\)**  \(\rightarrow\) **ET\(_3\)**  \(\rightarrow\) **ET...**

- **CT**

**MAIN RESEARCH QUESTION:**

OPTIMAL SEQUENCE

## Endocrine-Based Therapies for Breast Cancer

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


Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
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
**ER & GROWTH FACTOR PATHWAYS & ENDOCRINE RESISTANCE**

- **Anti-HER-2 agents**
- **HDAC inhibitors** (Entinostat)
- **M-TOR inhibitor** (Everolimus, Sirolimus)
- **Growth factor receptor**
- **PI3K**
- **Akt**
- **m-TOR**
- **MEK**
- **MAPK**
- **ER & GROWTH FACTOR PATHWAYS**
- **Estrogen**
- **Aromatase Inhibitors**
- **Tamoxifen**

Adapted from Denise Yardley et al, ASCO-Breast 2011
CDK 4/6 INHIBITORS (Palbociclib, Ribociclib, Abemaciclib)

They delay ET resistance by regulating the cell cycle (i.e., the cell clock).

Restriction point – to divide or not to divide

- Entry into G1
- Exit into G0 (quiescence)


Courtesy B. Sousa
1st Line CDK 4/6 INHIBITORS: EFFICACY

### PALOMA-2

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

<table>
<thead>
<tr>
<th></th>
<th>PCB+LET</th>
<th>PAL+LET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events, n (%)</td>
<td>194 (64)</td>
<td>137 (62)</td>
</tr>
<tr>
<td>Median (95% CI) PFS</td>
<td>24.8 (22.1–NR)</td>
<td>14.5 (12.3–17.1)</td>
</tr>
<tr>
<td>HR (95% CI); 1-sided P value</td>
<td>0.59 (0.46–0.72); P&lt;0.000001</td>
<td></td>
</tr>
</tbody>
</table>

**Number of patients at risk**

- PCB+LET: 257
- PAL+LET: 233

Hazard ratio (95% CI) 0.55 (0.44–0.69), p<0.0001

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

Di Leo et al, ESMO 2017

### 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\(^1\,^2\)

Di Leo et al, ESMO 2017

### MONARCH 3: Primary Endpoint: PFS (ITT)

- Median PFS: abemaciclib + NSAI: not reached
- Placebo + NSAI: 14.7 months

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

Monaleesa 2 - Updated results ASCO 2017

Hortobagyi et al, ESMO 2016, updated ASCO 2017 NCI 2017
1st Line CDK 4/6 INHIBITORS: IMPACT ON QoL

Abemaciclib: no QoL yet reported

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

**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%.*
MONALEESA-7 Study Design

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

- Pre/perimenopausal women \(^a\) with HR+/HER2– ABC
- No prior ET for ABC \(^b\) ≤ 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\(^c\) + GOS\(^d\)
  \(n = 335\)

**Placebo**

- 3 weeks on/1 week off
- + NSAI/TAM\(^c\) + GOS\(^d\)
  \(n = 337\)

**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.

\(^a\) 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.

\(^b\) 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.

\(^c\) Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed.

\(^d\) TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg, and ANA dose was 1 mg. 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
2nd Line CDK 4/6 INHIBITORS: EFFICACY

**FINAL PROGRESSION-FREE SURVIVAL IN PALOMA-3 (ITT)**

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

**MONALEESA-3: FINAL PFS**

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

P. Fasching, ESMO 2018

**MONARCH 2: Primary Endpoint: PFS (ITT)**

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

Cistolafanilli et al, ESMO 2018

**PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS**

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

P. Fasching, ESMO 2018
OVERALL SURVIVAL IN PALOMA-3 (ITT)

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

Stratified HR=0.81
95% CI (0.64–1.03)
1-sided $P=0.043$

Unstratified HR=0.79
95% CI (0.63–1.00)
1-sided $P=0.025$

Cristofanilli et al, ESMO 2018
Reach to Recovery International Conference 2019
**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

**GLOBAL HRQoL**

**QoL similar in both arms**

Abemaciclib: no QoL yet reported
CDK 4/6 INHIBITORS (Palbociclib, Ribociclib, Abemaciclib)

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

COST: ~ 5.000 €/cycle
Everolimus (mTOR inhibitor)
4.6 to 6.9 ms benefit PFS

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

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

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

• 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)*.
Everolimus

6 MONTHS BENEFIT IN PFS in 2\textsuperscript{nd} line
NO OS BENEFIT SEEN

COST: \(\sim 3.500 \, \text{€/cycle}\)
NEW DRUGS ARRIVING...
Modified from Ma et al, Nat Rev Cancer 2015; ASCO 2018

<table>
<thead>
<tr>
<th>Subtype</th>
<th>HR+ HER2-</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA mut</td>
<td>40%</td>
<td>7-9%</td>
</tr>
<tr>
<td>PTEN mut/loss</td>
<td>2-4%</td>
<td>30-40%</td>
</tr>
<tr>
<td>PIK3R1 mut</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>AKT1 mut</td>
<td>2-3%</td>
<td>Rare</td>
</tr>
</tbody>
</table>
SOLAR-1 (NCT02437318, Alpelisib) Primary endpoint: Locally assessed PFS in the PIK3CA-mutant cohort

PI3K inhibitors

6 Months benefit PFS

Only ~ 7% pretreated with CDK 4/6i

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=168)</th>
<th>Placebo + fulvestrant (N=171)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>282 (99.3)</td>
<td>264 (92.0)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>181 (63.7)</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>164 (57.7)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>127 (44.7)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>101 (35.6)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>101 (35.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>77 (27.1)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>76 (26.8)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>70 (24.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69 (24.3)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>58 (20.4)</td>
<td>5 (1.8)</td>
</tr>
</tbody>
</table>

*Safety profiles were similar to the PIK3CA-mutant and PIK3CA non-mutant cohorts.

F. André et al, ESMO 2018
How do HDAC inhibitors work?

We can re-write our epigenetic code via writers, erasers and readers
HDACi can reprogram the carcinogenic epigenetic changes

Histone code is mediated by writers, erasers, and readers of histone marks

ACE (Chidamide) Trial: PFS in ITT Population

HDAC inhibitors
Chidamide? Entinostat?

4 Months benefit PFS

Not pretreated with CDK 4/6i

Phase III E2112: Exemestane ± Entinostat in Advanced Breast Cancer

- Entinostat: oral, histone deacetylase inhibitor

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

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

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

Until disease progression or unacceptable toxicity

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

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

Pre/Recovery International conference 2019
2nd EXAMPLE OF TARGETED THERAPY: HER-2 RECEPTOR & TRASTUZUMAB
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)
DUAL BLOCKADE: TRANSTUZUMAB + PERTUZUMAB

Trastuzumab

Subdomain IV of HER2

Pertuzumab

Dimerisation domain of HER2
Lapatinib: TKI, small molecule, acts in the intracellular domain

MAPK pathway (Ras/Raf/MEK/ERK)

PI3K/Akt pathway

Ligands

Other ErbB

ErbB2

Lapatinib

Proliferation

Cell cycle, Survival

STOP

GO

Cell death

STOP

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

T-DM1 binds to the HER2 protein on cancer cells

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

Trastuzumab-DM1
**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
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:**
- \( \uparrow \) Affinity for activating Fc\(\gamma\)RIIIA (CD16A)
- \( \downarrow \) Affinity for inhibitory Fc\(\gamma\)RIIB (CD32B)

**Margetuximab Binding to Fc\(\gamma\)R 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

# Abstract

**Arm 1**

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

**Arm 2**

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

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

**HER2+ advanced breast cancer**
- ≥2 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastasis ok if treated and stable

**Investigator’s choice of chemotherapy**
- Capecitabine, eribulin, gemcitabine, or vinorelbine

**1:1 Randomization (N=536)**

**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**

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

**HR=hazard ratio; CBA=central blinded analysis.**

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

- ITT population: N=536. CI=confidence interval.

H. Rugo, ASCO 2019
DS-8201a: a HER2-targeting Antibody-drug Conjugate

- 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”
Overall survival according to subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Events n (%)</th>
<th>Median OS months (95% CI)</th>
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<tbody>
<tr>
<td>HR-pos./HER2-neg.</td>
<td>269 (60.7%)</td>
<td>33.8 (30.2 - 40.2)</td>
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<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>
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</tbody>
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Heterogeneity of TRIPLE NEGATIVE BC:
TNBC Classification

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

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%)*
PARP INHIBITORS—mechanism of action (SYNTHETIC LETHALITY)

Reach to Recovery International Conference 2019
The principle of synthetic lethal tumour targeting

Normal tissue cells

- DNA repair
  - Homologous recombination (HR) repair

BRCA1/BRCA2 deficient Tumor cells

- DNA repair
  - Base excision DNA repair

Few normal tissue effects

- HR repair

Specific tumor cell killing

- PARP inhibitor
  - Base excision DNA repair

How does PARP inhibition compare with CT in ABC?

**gBRCA1 / BRCA2 Carriers**

- Advanced anthracycline taxane resistant breast cancer

**Primary endpoint**

- PFS

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

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

**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 BRCA1/2g

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

✓ 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
PARP Inhibitors in BRCA+ ABC

3 MONTHS DIFFERENCE IN PFS BUT BETTER QoL IMPACT ON OS?
COST: ~ 7,000 €/month
PRECISION MEDICINE

- NOT RECOMMENDED for ROUTINE CLINICAL PRACTICE:
  - Multigene panels
  - Circulating tumour DNA (ctDNA) assessment
  - Immunotherapy
**Checkpoint inhibitors:** ABC and EBC are totally different immune settings

Atezolizumab approval was based in a 2.5 months PFS difference
WHEN CHEMOTHERAPY IS NEEDED . . .
The cell cycle is the target of chemotherapy

Courtesy B. Sousa
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)
Which agents?
Clinical Efficacy of Cytotoxic Agents

Research question:
BEST SEQUENCE!? 

LIPOSOMAL TECHNOLOGY
“Old” agents with new technology

Doxorubicin  Liposomal Doxorubicin  Pegylated Liposomal Doxorubicin
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 EUSOMA, AACR, and other organizations
The ABC5 conference is held under the auspices of ASCO and is endorsed by ESO, ESTRO, OECI, UICC, and other organizations

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