Current standards and practice changing studies in Advanced Breast Cancer in 2019

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ESMO Guidelines and Public Policy Steering Committees
ESO Scientific Committee
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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
5 year survival rates for mBC still around 25%


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.
What we can learn from EBC to apply in ABC

EGUIDELINES

ESO-ESMO ABC4 GUIDELINES

MULTIDISCIPLINARY TEAM
Indispensable for
EBC
LABC
MBC

In CLINICAL PRACTICE & RESEARCH

MULTIDISCIPLINARY CARE
GET TOGETHER!
COLLABORATE!
SHARE RESOURCES AND KNOWLEDGE!

Website www.abcglobalalliance.org
Email rventura@abcglobalalliance.org
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
INEQUALITIES IN ACCESS TO CARE
Between countries but also within each country

AN EXAMPLE
The worrisome situation of
New Zealand
Figure 3: Survival time for metastatic breast cancer
Changes in survival through time

Table 3: Median, one and five-year survival after MBC diagnosis, for people diagnosed in each period

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median survival (months)</td>
<td>10.6 (6.8, 19.9)</td>
<td>14 (11.4, 16.7)</td>
<td>18.8 (15.9, 21.4)</td>
</tr>
<tr>
<td>One-year survival</td>
<td>46% (34, 58)</td>
<td>54% (48, 60)</td>
<td>62% (58, 67)</td>
</tr>
<tr>
<td>Five-year survival</td>
<td>12% (05, 20)</td>
<td>11% (08, 15)</td>
<td>15% (11, 19)</td>
</tr>
</tbody>
</table>
Figure 5: Median survival after metastatic diagnosis by subtype

<table>
<thead>
<tr>
<th>Luminal A</th>
<th>Luminal B1</th>
<th>Luminal B2</th>
<th>HER2 enriched</th>
<th>Triple Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.3 (21.4, 30.6)</td>
<td>15.9 (13, 20.8)</td>
<td>24 (18.3, 28)</td>
<td>13.3 (10, 17.7)</td>
<td>6.6 (5.8, 8.7)</td>
</tr>
</tbody>
</table>

**PRIORITY!**
CAN EASILY BE IMPROVED!
INEQUALITIES IN ACCESS TO CARE
Between countries but also within each country

AN EXAMPLE
The situation of New Zealand

LOBBYING WORKS!
T-DM1 and CDK4/6i have been approved
ABC Guidelines are being implemented
Treatment choice should take into account at least these factors:

- HR & HER-2 status, and germline BRCA status
- PIK3CA in HR+ and PD-L1 in TNBC, if targeted therapies are accessible
- 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

CLINICAL PRACTICE GUIDELINES

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.
HOW TO TREAT ER+/HER-2 neg (LUMINAL-like) ABC: The standard and novelties

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)
Endocrine-based therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis.

(LoE/GoR: I/A) (93%)
**VISCERAL CRISIS** is defined as *severe organ dysfunction* as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies *important ORGAN compromise* leading to a clinical indication for the most rapidly efficacious therapy.

*Examples:*
*Liver visceral crisis*: rapidly increasing bilirubin >1.5x ULN, in the absence of Gilbert’s Syndrome or biliary tract obstruction
*Lung visceral crisis*: rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion

(LoE: Expert opinion/NA) (97%)

To be discussed in manuscript: “impending visceral crisis”, clinical situation very difficult to objectively define
BIOLOGICAL HETEROGENEITY OF LUMINAL TUMOURS

Adapted from F. Penault-Llorca

mut PIK3CA 40% (45% A, 29% B)
mut/loss of PTEN 18%
INPP4B loss 12%
mut AKT1 3%
ampl 11q13 37%
ampl CDK4 19%
CDKN1B 2A, 2B loss 11%
mut RB1 1%
mut TP53 22% (13% A, 66% B)
gain MDM2 22%
mut TPS3 7% (8% A, 5% B)
lum B hypermethyl 8%
mut ESR1 1% (up to 19% mets)
ampl 8p11-12 10%
ampl FGFR1 10% (up to 27% B)

HT Adaptation

HDAC inhibitors

PI3K inhibitors

CDK4/6 inhibitors

FGFR, TKIs inhibitors

MDM2 inhibitors

HT ALONE

ALL OTHERS

LOW BURDEN & LESS AGGRESSIVE BIOLOGY (15%) 

VISCERAL CRISIS (10-15%) 

CHEMO

“Impending visceral crisis”

CLINICAL HETEROGENEITY OF LUMINAL TUMOURS

Implications for therapeutic decisions – 1st line

Impending visceral crisis

CHEMO

HT + CDKi

HT ALONE

ALL OTHERS

CLINICAL HETEROGENEITY OF LUMINAL TUMOURS

Implications for therapeutic decisions – 1st line

“Impending visceral crisis”
The preferred 1st line endocrine agent *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
A CDK4/6 inhibitor combined with endocrine therapy is the **standard of care** for patients with ER+/HER-2 neg ABC, since it achieves substantial PFS benefit, significantly increases OS and either maintains or improves QoL.

The CDK4/6 inhibitor *can be combined with an AI or with Fulvestrant, in de novo or recurrent ABC*, in 1*st* or 2*nd* line, and in cases of primary or secondary resistance (as defined per ABC guidelines).

This recommendation applies to post-menopausal women, to premenopausal women in combination with an LHRH agonist, and to men preferably in combination with an LHRH agonist.

(LoE/GoR : I/A) (97%)
**1st Line CDK 4/6 INHIBITORS: EFFICACY**

**Consistent ± 10 MONTHS BENEFIT IN PFS**

- Ribociclib + ET reduced the risk of progression by 45% vs the placebo arm ($p<0.00001$).²
- Manageable safety profile consistent with prior studies of ribociclib.¹²

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

**Monaleesa 2 - Updated results ASCO 2017**

**PALOMA-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: RESULTS**

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

- **MONALISA-7: RESULTS**

- **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)

$p=0.000021$

**Di Leo et al, ESMO 2017**
1st Line CDK 4/6 INHIBITORS: EFFICACY
Overall Survival
OS BENEFIT

• ~ 29% relative reduction in risk of death

Landmark Analysis (3.5 years)

Kaplan-Meier Estimate

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + ET</th>
<th>Placebo + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>71.9%</td>
<td>64.9%</td>
</tr>
<tr>
<td>42 months</td>
<td>70.2%</td>
<td>46.0%</td>
</tr>
</tbody>
</table>

Interesting shape of the curve!
Hypothesis: acquired resistance to ET?
1st Line CDK 4/6 INHIBITORS: IMPACT ON QoL
Only 1 study showed improved QoL (ML7). Why?

Initial QoL Presentation:
o no difference in QoL!
2nd Line CDK 4/6 INHIBITORS: Efficacy
Consistent 6.5 TO 7.5 MONTHS BENEFIT IN PFS

**MONALEESA-3: FINAL PFS**

- Ribociclib + fulvestrant reduced the risk of progression by 41% vs placebo + fulvestrant ($p<0.001$).

**PFS BENEFIT CONSISTENT ACROSS TREATMENT SETTINGS**

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

Absolute improvement in median PFS was 6.6 months.

**MONARCH 2 UPDATED PFS (ESMO 2019)**
2nd Line CDK 4/6 INHIBITORS: EFFICACY

OS BENEFIT

Absolute improvement in median OS was 6.9 months

BUT

NOT STATISTICALLY SIGNIFICANT

Criscianilli et al, ESMO 2018

Overall Survival

The reduction in relative risk of death with RIB was 28%

MONALEESA-3 Trial

OS results with median FU of 39.4 months

Sledge et al, ESMO 2019

OS IN PALOMA-3 (ITT)

MONARCH 2

Overall Survival Probability (%)

Overall Survival by Line of Therapy

OS by line of therapy was consistent with overall population

FUL, fulvestrant; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival; PBO, placebo; RIB, ribociclib.
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
It remains unclear if CDK4/6 inhibitors should be preferably administered in the 1st line or in the 2nd line setting. However, the majority of panelists preferred giving a CDK4/6 inhibitor in the 1st line setting for the majority of their patients. 

(LoE/GoR : Expert Opinion/NA) (100%)
OTHER OPTIONS OF ET + TARGETED THERAPY?
When to use them?
What is the best option after a CDK4/6i?
ER POSITIVE / HER-2 NEGATIVE MBC

The addition of everolimus to an AI is a valid option for some patients previously exposed to or naïve of (in case CDK4/6i are not available) 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%)

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)

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
COST: ~ 3.500 €/cycle
New data 2019: premenopausal pts
PI3K inhibitors
ALPELISIB
Only ~ 7% pretreated with CDK 4/6i

ALPELISIB with fulvestrant is a treatment option for patients with PIK3CA-mutant tumors (in exons 9 or 20), previously exposed to an AI and with appropriate HbA1c levels, since it provided about 5 months benefit in median PFS.

The decision to give alpelisib should take into consideration the inclusion/exclusion criteria in the study SOLAR-1 (re: pre-existing diabetes & baseline HbA1c), as well as the toxicity profile of alpelisib.

Its efficacy after exposure to CDK4/6 inhibitors is unknown, since only 7% of patients in the Solar-1 trial had been previously treated with those agents.

(LoE/GoR: I/B) (88%)

ESMO-MCBS: 2

Note: For PIK3CA mutation testing, see Precision Medicine statements

In manuscript: Need to elaborate about inclusion/exclusion criteria in study and how this should guide which patients should/shouldn't receive drug
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), duration of response to those agents, burden of the disease, patients’ preference and availability.

Available options for 1\textsuperscript{st} and 2\textsuperscript{nd} line include AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus, fulvestrant + alpelisib (for PIK3CA mut), AI, tamoxifen, fulvestrant.

(LoE/GoR : Expert Opinion) (100%)

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

**MAIN TAKE-HOME MESSAGES**

- Use several lines of ET, before moving to CT
- Give the same options to premenopausal (with LHRH/ovariectomy) and men (with LHRH)
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)

MAIN TAKE-HOME MESSAGES

• When moving to CT, use single agent, favor oral, discuss type of side effects/patient preferences
HOW TO TREAT HER-2+ ABC: The standard and novelties

Treatment of HER2+ ABC: Progress over time

TRASTUZUMAB + PERTUZUMAB + CT
15 MONTHS BENEFIT IN OS in previously untreated patients
COST: ~ 6.500 €/cycle

T-DM1
5 MONTHS BENEFIT IN OS
COST: ~ 4.000 €/cycle

1 Slamon et al. NEJM 2001; 2 Swain et al. NEJM 2015; 3 Geyer et al. NEJM 2011; 4 Verma et al. NEJM 2012
5 Geyer et al. SABCS 2015. mod. from Löbl SABCS 2015
Treatment of ER-negative / HER2-positive ABC

Note: Include in clinical trials when available
Treatment of ER-positive / HER2-positive ABC

Note: Include in clinical trials when available
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

MAIN TAKE-HOME MESSAGES

• The biggest benefit and the most cost-effective is TRASTUZUMAB
• Crucial to keep blocking HER2 pathway even after several progressions
HER-2 POSITIVE ABC: NEW AGENTS

Antibody
- Margetuximab
  - BTRC4017A
  - GBR 1302
  - MCLA-128
  - PRS-343
  - ZW-25
  - ZW-49

Bispecific antibody

ADC
- A166
- ARX788
- DHES0815A
- DS 8201a
  - Trastuzumab deruxtecan
- SYD-985

Novel TKI
- Poziotinib
- Pyrotinib
- Tucatinib

New recommendations on
NERATINIB, MARGETUXIMAB, TUCATINIB, TRASTUZUMAB DERUXTECAN

Courtesy G. Curigliano
NEW Anti-HER-2 AGENTS
Recommendations AGAINST use

NALA study design

Inclusion criteria:
- Metastatic breast cancer (MBC)
- Centrally confirmed HER2+ disease
- ≥2 lines of HER2-directed therapy for MBC
- Asymptomatic and stable brain metastases permitted

Stratification variables:
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints:
- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

No endocrine therapy permitted

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

NALA STUDY (NERATINIB)
Major design problem: Comparator is a suboptimal regimen (should have been compared to trastuzumab + capecitabine)
Very small difference (2 ms); small benefit in response on brain mets
NEW Anti-HER-2 AGENTS

Recommendations AGAINST use

SOPHIA STUDY (MARGETUXIMAB)

Very small difference (1 ms)

Potential new biomarker to be explored: CD16A genotype as a predictor of anti-HER2 antibody efficacy and selection of anti-HER2 agent
NEW Anti-HER-2 AGENTS

Recommendation: POSSIBLE OPTION

HER2CLIMB Trial Design (Tucatinib)

R. Murthy, SABCS 2019

https://clinicaltrials.gov/ct2/show/NCT02614794

Tucatinib + Trastuzumab + Capecitabine

Treatment (21-day cycle)

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m² PO BID (Days 1–14)

Placebo + Trastuzumab + Capecitabine

Treatment (21-day cycle)

Placebo (Pbo) +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m² PO BID (Days 1–14)

Key Eligibility Criteria

- Measurable or non-measurable HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- Brain MRI at baseline
  - No evidence of brain metastases, or
  - Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy

*Stratification Factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region of world (US or Canada or rest of world)

- 35% de novo pts
- 60% ER/PR+
- 48% BRAIN METS
- Median prior lines in MBC: 3

Progression-Free Survival in the Primary Endpoint Population

• 2.2 ms difference in PFS
• 4.5 ms difference in OS

Overall Survival in the Total Study Population

• 4.5 ms difference in OS

HER2CLIMB STUDY (TUCATINIB)

Still a small difference (2.2 ms), even for brain mets!
Bigger difference in OS (4.5 ms), in heavily pretreated pts
Higher toxicity than Trastuzumab-based
NEW Anti-HER-2 AGENTS
Recommendation: POTENTIALLY PRACTICE-CHANGING (BUT WAITING FOR PHASE 3 TRIALS)

DESTINY-Breast01 Study Design:
An Open-Label, Multicenter, Phase 2 Study

DESTINY-Breast 01 STUDY (TRASTUZUMAB DERUXTECAN)

Trastuzumab Deruxtecan (DS-8201) is a Novel ADC Designed to Deliver an Optimal Antitumor Effect1-4

Payload MOA: topoisomerase I inhibitor
NEW Anti-HER-2 AGENTS

Recommendation: POTENTIALLY PRACTICE-CHANGING (BUT WAITING FOR PHASE 3 TRIALS)

Best Change in Tumor Size

**ORR: 61%**

| Best % Change From Baseline in the Sum of Diameters of Measurable Tumors |
|-----------------------------|-----------------------------|
| -100                        | 0                           |
| 20                          | 40                          |
| 60                          | 80                          |
| 100                         | 120                         |

Confirmed ORR: 60.9%∗
(95% CI, 53.4%–68.0%)
11 CRs

I. Krop, SABCS 2019

DESTINY-Breast01 TRIAL (Trastuzumab-Deruxtecan DS-8201)

Overall Safety Summary

<table>
<thead>
<tr>
<th>Type of Adverse Event, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td>Any TEAE</td>
</tr>
<tr>
<td>TEAE grade ≥3</td>
</tr>
<tr>
<td>Serious TEAE</td>
</tr>
<tr>
<td>Dose adjustments</td>
</tr>
<tr>
<td>TEAE associated with disruption</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td>TEAE associated with dose reduction</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td>TEAE associated with dose interruption</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Drug-related</td>
</tr>
</tbody>
</table>

†Medication duration, 12.0 months (range, 0.7-24.1 months)

| TEAEs that led to discontinuation in ≥2 patients included pneumonitis, pleural effusion, interstitial lung disease (ILD)

Treatment-emergent Adverse Events in >15% of Patients

<table>
<thead>
<tr>
<th>Type of ADR</th>
<th>Grade 1 or 2</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>86 (45.7)</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>37 (20.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>33 (17.7)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Decreased WBC count</td>
<td>29 (15.7)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28 (15.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>27 (14.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24 (13.2)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (5.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (5.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (4.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>8 (4.3)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (7.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (9.2)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

MAJOR TOXICITY:
Potentially fatal Interstitial Lung Disease (ILD) / Pneumonitis (4 toxic deaths)

I. Krop, SABCS 2019
HOW TO TREAT TRIPLE NEGATIVE ABC:
The standard and novelties

Treatment of advanced TNBC

Clinical Practice Guidelines

Diagnosis of advanced TNBC

Genetic counselling 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 Capecitabine + 5-FU or capecitabine

Sequential single-agent ChT

Previously untreated with anthracycline or taxanes

Anthracycline or taxanes

Previously treated with anthracycline and/or taxanes

Note: Include in clinical trials when available.

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**IMMUNOTHERAPY FOR TRIPLE NEGATIVE ABC**

Atezolizumab + nab-paclitaxel is an option for 1st line therapy for PD-L1+* triple negative ABC, either de novo or at least 12 months since (neo)adjuvant chemotherapy.

MCBS: 3

(LoE/GoR: I/B) (95%)

Checkpoint inhibitor monotherapy in later lines for triple negative ABC is not recommended, due to low response rates.

(LoE/GoR: I/E) (89%)

**MAJOR PROBLEM: COST**

For patients with a germline BRCA mutation single agent PARP inhibitor (olaparib or talazoparib) is a preferred treatment option for those with triple negative ABC.

(LoE/GoR: I/A) (78%)

In ER+ gBRCA-associated ABC, the optimal sequence between PARPi and ET with or without CDK4/6i is unknown. Given the OS benefit seen with CDK4/6i, the panel recommends their use before a PARPi.

(LoE/GoR: Expert Opinion/B) (78%)

Single agent PARP inhibitors (olaparib or talozaparib) are associated with a PFS benefit, improvement in QoL and a favorable toxicity profile.

Results suggest that any benefit in OS may be limited to the 1st line setting.

MCBS: 4
PRECISION MEDICINE

• NOT RECOMMENDED for ROUTINE CLINICAL PRACTICE:
  • Multigene panels (possibly small targeted ones)
  • Circulating tumor DNA (ctDNA) assessment for prognosis or response assessment (can be used for detection of PIK3CA mutations)

• RECOMMENDED for ROUTINE CLINICAL PRACTICE BUT ONLY IF ACCESS TO THE THERAPEUTIC AGENTS:
  • PD-L1
  • PIK3CA mutation
The ABC community is aware of the limitations that are being imposed worldwide, as a consequence of the opioid use disorders in certain areas of the world.

The ABC community is united in insisting that cancer patients should not have restrictions placed that will limit their access to adequate pain control.

(LoE/GoR: Expert Opinion/NA) (100%)
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, and if possible CDK4/6 INHIBITORS
• 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

Sixth International Consensus Conference

SAVE THE DATE
4-6 November 2021
Lisbon, Portugal

Coordinating Chair:
F. Cardoso, PT

www.abc-lisbon.org