News in the management of ABC in young patients

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DISCLOSURES

Consultant/Ad Board:
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4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†


1300 participants from 88 countries
Luminal-like ABC
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%)
ADEQUATE OVARIAN FUNCTION SUPPRESSION (OFS) IN THE CONTEXT OF ABC

Adequate OFS for ABC premenopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or ovarian function ablation through pelvic radiotherapy (this latter is not always effective and therefore is the least preferred option). (LoE/GoR: I/A) (85%)

If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS. (LoE/GoR: II/B) (85%)

Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, specially if an AI is administered. (LoE/GoR: Expert Opinion/B)

As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient’s wish for potentially preserving fertility, compliance with frequent injections over along period of time, and cost.
MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin

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

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

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

Secondary endpoints:
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety
- Patient-reported outcomes

No prior endocrine therapy for advanced disease
- 335

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

Received treatment
- n=335

Goserelin included in all combinations.

Ribociclib
- + Tamoxifen
- n=248

Safety set
- n=90

Placebo
- + Tamoxifen
- n=337

± 40% de novo
± 57% visceral mets

± 10 ms PFS benefit

Ribbon Title: San Antonio Breast Cancer Symposium, December 5–9, 2017

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D. Tripathy, SABCS 2017
Patient-reported outcomes (EORTC QLQ-C30 – global health status)

- There was a **sustained improvement in time to definitive deterioration** of at least 10% for the global health status/QoL scale in the ribociclib arm vs the placebo arm.
- A clinically meaningful (>5 points) improvement from baseline in pain score was observed as early as 8 weeks in the ribociclib arm, and was sustained.
Evaluation form 2b: treatments with non-curative intent, primary endpoint PFS or TTP

Preliminary magnitude of clinical benefit grade
(highest grade scored)

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Toxicity and QoL adjustment when only a PFS improvement

RIBOCICLIB 1st line:
Efficacy score: 3
Improved QoL
Provisional MCBS: 4
MONARCH 2: PFS in Pre/Peri-menopausal Population

**Patients at risk:**
- abemaciclib: 72
- placebo: 42

**Progression-free Survival (%)**

**Time (months):**
- abemaciclib + fulvestrant: not reached
- placebo + fulvestrant: 10.5 months

**HR (95% CI):** .446 (.264, .754) p = .002

**PFS benefit confirmed by blinded independent central review HR: .432; 95% CI: .236, .793 p < .005**
MONARCH 2 in Pre/Peri-menopausal Population

Conclusions

♦ Abemaciclib plus fulvestrant and a GnRH agonist significantly improved PFS (median NR vs 10.5 months; HR: 0.446) and ORR (60.8% vs 28.6% in patients with measurable disease) in pre/peri-menopausal women with ABC. These results are consistent with the ITT population.

♦ Abemaciclib and fulvestrant delayed the time to initiation of subsequent chemotherapy in the ITT population. Similar results were observed in pre/peri-menopausal patients.

♦ Abemaciclib dosed on a continuous schedule plus fulvestrant demonstrated a manageable safety profile consistent with other studies of abemaciclib. No additional toxicities were observed by adding a GnRH agonist to abemaciclib plus fulvestrant.
The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.

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

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

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
The addition of a **CDK4/6 inhibitor to fulvestrant**, in patients **previously exposed** to ET, provided significant improvement in median PFS (6 to 7 months) as well as improvement of QoL, and is one of the preferred **treatment options**, if a CDK4/6 inhibitor was not previously used.

OS results are awaited.

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

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

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**ER POSITIVE / HER-2 NEGATIVE ABC**
ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

$ET_1$ → $ET_2$ → $ET_3$ → $ET...$

$CT$
MAIN CHALLENGE:
Identify small percentage of “fast progressors”

First line endocrine therapy: FALCON or PALOMA-2?

**PALOMA-2**
HR 0.58 (0.46–0.72)

**FALCON**
HR 0.797 (0.637-0.999)

Finn et al. ESMO 2016, LBA-15; Ellis et al. ESMO 2016, LBA-14
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
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 HER2 negative disease also apply for triple negative ABC.

(LoE/GoR: I/A) (98%)
In triple-negative ABC patients (regardless of BRCA status), previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared to docetaxel, and is therefore an important treatment option.

(LoE/GoR: I/A) (91%)
Hereditary ABC
A PARP inhibitor (olaparib or talozaparib) is a reasonable treatment option for patients with BRCA-associated triple negative or luminal (after progression on endocrine therapy) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL and a favorable toxicity profile.

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

(LoE/GoR: I/B) (80%)
PARP Inhibitors in BRCA+ ABC

OLYMPIAD study design

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

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

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

Olaparib 300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician’s choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

PFS

Progression/deaths, n (%)

Median PFS, months

Olaparib 300 mg bd

Chemotherapy TPC

163 (79.5) 71 (73.2)

7.0 4.2

HR 0.58

95% CI 0.43 to 0.80; P=0.0009

At risk, n

205 177 154 107 94 69 40 23 21 11 4 3 2 1 0

0 0 Olaparib 300 mg bd

Chemotherapy TPC
EMBRACA

**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

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**EMBRACA**

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

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<th>Overall PCT (n= 144)</th>
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<td>Events, no. (%)</td>
<td>186 (65%)</td>
<td>83 (56%)</td>
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<td>Median, mo (95% CI)</td>
<td>6.6 (7.2, 9.3)</td>
<td>5.6 (4.2, 6.7)</td>
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Hazard ratio: 0.54, 95% CI: 0.41, 0.71; \( P < 0.001 \)

1-Year PFS 37% vs 20%; \( HR:0.54(95\% CI, 0.41,0.71); P<0.001 \)

OS data is immature
PRECISION MEDICINE

• **NOT RECOMMENDED** for ROUTINE CLINICAL PRACTICE:
  
  • Multigene panels
  
  • Circulating tumour DNA (ctDNA) assessment
  
  • Immunotherapy
Advanced Breast Cancer

Fifth International Consensus Conference

14-16 November 2019
Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT

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