Sequencing of Therapy In HR+ve ABC

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Disclosures

• Speaker for Roche, Novartis, AstraZenica, Pfizer, Janssen,
HR+ve MBC
the Goal of Treatment is

↓ symptoms
↑ Survival
↑ QOL

Side effects of the treatment

Convenience, availability and Cost
HR+ve HER2-ve MBC
Which Treatment to Start?
Visceral Metastasis

Hormonal TTT?
Single or combination?

Chemotherapy?
Single or combination?
ASCO/ ABC4 guidelines: Patients with ER+/HER2- ABC

What is your evidence against 1st line chemo in these cases?

ER+/HER2- ABC
Postmenopausal

Is the patient in visceral crisis?

ET is the preferred option

Chemotherapy

YES

*Except for relapse <12 mths from finishing adjuvant AI

ABC, advanced breast cancer; AI, aromatase inhibitor; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor-2; NSAI, non-steroidal AI; PD, progressive disease

Chemotherapy vs Endocrine therapy

The Cochrane Meta-Analysis 8 trials 1st-Line Endocrine Therapy vs chemo: n=817 HR+ve MBC

**OS:** no significant differences (HR = 0.94, \( P = .5 \))

*RR:* chemotherapy > endocrine TTT (OR = 1.25, \( P = .04 \))

Single Agent Chemotherapy Results

E2100 Ph III trial
• Taxol Single agent +/-bev
• N=722

<table>
<thead>
<tr>
<th>ORR%</th>
<th>49%</th>
<th>22%</th>
<th>P&lt;0.000 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFSm</td>
<td>11</td>
<td>5.8m</td>
<td>HR 0.48</td>
</tr>
</tbody>
</table>

RIBBON1 Ph III
Capecitabine +/-Bev
Taxane or antracycline +/-bev
N=1237 MBC

<table>
<thead>
<tr>
<th>Cape +Bev</th>
<th>Cape</th>
<th>Tax or anthra +bev</th>
<th>Tax or anthra</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFSm</td>
<td>8.6</td>
<td>5.7</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Single agent Chemotherapy mPFS 5-7m

Grey etal JCO October 20, 2009, Robert et al J Clin Oncol. 2011
Two articles report market research data on the use of endocrine therapy and chemotherapy for the treatment of ABC in European countries. The indications for choosing chemotherapy over endocrine therapy is related to the need of a rapid onset of response, i.e., highly symptomatic patients or visceral crisis which occurs only in less than 10% of patients. In the 1st line setting, the percentage of ABC patients treated with chemotherapy upfront is in the range of 60-70% and endocrine therapy is used upfront in only less than 30% of patients.

This has to stop!
Principles of Endocrine Treatment

- **ET1**: No response
- **ET2**: No response
- **ET3**: No response
- **ET4**: No response

**ChT**
- **Upfront 1ry Resistance**: Improve the RR to endocrine TTT
- **Acquired 2ry Resistance**: Improve the PFS & delay Chemotherapy

How to best sequence and combine these drugs?

Defining Endocrine Sensitivity / Resistance

1st Line ET

Adjuvant endocrine ttt

Early relapse on Tx

Relapse after 2-3 ys Tx

Late relapse off Tx

0 2 5 6 Time in years

Chances of response to endocrine therapy for MBC

? De Novo Resistance

? Acquired

? Endocrine Sensitive

Cardoso et al. Annals of Oncology 2018
Endocrine Sensitive  HR+ve Her2-ve

Front Line options?
Postmenopausal: AIs vs. TAM

Time to treatment progression (ITT)


AI > Tamoxifen TTP 10m vs 5.5m

Chemotherapy results TTP 5-7m

Can we improve on the AI?
Fulvestrant is an ER antagonist without agonist effect so blockes ER & accelerates its break down → down regulates ER
Fulvestrant 500mg vs anastrozole

FALCON PIII RCT 1st Line

- Postmenopausal women
- Locally advanced or metastatic breast cancer
- ER+ and / or PgR+
- HER2-
- Endocrine therapy-naïve

Primary endpoint: PFS

Secondary endpoints:
- OS
- ORR
- HRQoL (FACT-B total and TOI)
- CBR
- DoR, EDoR
- Safety

1:1

Fulvestrant 500 mg
(500 mg IM on Days 0, 14 and 28, then every 28 days)
+ placebo to anastrozole

Anastrozole 1 mg
(daily PO)
+ placebo to fulvestrant

mPFS 16.6 vs 13.8m
p 0.04

PFS in Patients With or Without Visceral Disease

Patients without visceral met Fulvestrant 22m vs 13.8m
In visceral mets Fulv = AI
Evolution of therapy for endocrine-sensitive Her2-ve MBC

Chemotherapy 5-6 ms
Tamoxifen 6 ms
Aromatase inhibitors 10–14 ms
Fulvestrant 500 mg 16.6 ms
Fulvestrant 500 mg bone mets only 22m

Median TTP/PFS (months)

*Median PFS: Ribociclib + Letrozole: 25.3 months
Abemaciclib + NSAI: Not reached
Abemaciclib is an investigational drug and is not approved for use in Europe

Improve Endocrine Treatment

ER signaling altered

Alternative signaling altered

- Cycline/CDk
- P13K

ESR1 Mutation Background

ESR1: Gene encoding the ER
ESR1-mutations can change the function of ER leading to resistance

*ESR1*m are acquired during TTT with AI
Not with tamoxifen

ESR1 Mutations Linked With Resistance To Aromatase Inhibitors

ESR1 mutations result in constitutively activated ER and endocrine resistance → SERD more sensitive than AI or SERM
ER-Signaling and Cellular Signaling Network

![Diagram showing various signaling pathways involving IGFR, FGFR, MET, and EGFR/HER2, with interactions at the levels of Stat3, mTORC2, Akt, p21cip1, CDK4/6, and p16INK4A. The diagram also highlights E2F, ERE, and the ER, with arrows indicating the direction of signaling. There is a box labeled "Proliferation, cell survival, invasion." Growth factors and estrogen/Tamoxifen are indicated with specific colors.]
ER-Signaling and Cellular Signaling Network
ER-Signaling and Cellular Signaling Network

CDK4/6 central to growth of ER+ cells
Can we Improve on Endocrine Therapy?

Cross Talk Signaling

Addition of CDK4/6 inhibitors

Amplification of cyclin D1 in 15-20% of human breast cancers overexpression of the up to 50%

O’leary B et al Nat Rev Clin Oncol. 2016;13(7)417-430
ER & CDK4/6 are Distinct Targets for Control of Cancer Cell Growth

Inhibition of upstream ER signalling arrests ER⁺ breast cancer tumour cells in the G1 phase.
Decreases cyclin D1-CDK4/6 activity and increases CDK inhibition.

Potential synergistic effect.

Inhibition of downstream CDK4/6 restores cell cycle control, restricting growth of ER⁺ breast cancer cell lines in the G1 phase.

Dual action therapy.

Finn et al Br Cancer Res 2009
CDK4/6 I + Endocrinial TTT

- CDK4/6 I + Fulvestrant
- CDK4/6 I + AI
Fulvestrant + CDK4/6 I  
Endocrine Sensitive Disease

MONALEE 3A is the 1st study to evaluate a CDK4/6I + fulvestrant in patients who are treatment naïve in MBC (Endocrine Sensitive).

- Postmenopausal women with HR+/HER2- ABC
- No or ≤1 line of prior endocrine therapy for advanced disease

Ribociclib
(600 mg/day; 3-weeks-on/1-week-off)
+ Fulvestrant (500mg*)
N=484

Placebo
+ Fulvestrant (500mg*)
N=242

Stratified by:
- Presence/absence of liver/lung metastasis
- Prior endocrine therapy

## Prior endocrine therapy status criteria

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line + early relapsers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(i.e. treatment-naive for ABC)</strong></td>
<td><em>(i.e. received up to 1 line of prior endocrine therapy for ABC)</em></td>
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<tr>
<td>- Relapse &gt;12 months after completion of (neo)adjuvant endocrine therapy</td>
<td>- Early relapse on or ≤12 months from completion of (neo)adjuvant endocrine therapy</td>
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<tr>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>- <em>De novo</em> advanced/metastatic disease (no prior exposure to endocrine therapy)</td>
<td>- Relapse &gt;12 months from completion of (neo)adjuvant endocrine therapy with subsequent <em>progression</em> after 1 line of endocrine therapy (antiestrogen/Al) for ABC</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>- ABC at diagnosis that <em>progressed</em> after 1 line of endocrine therapy (antiestrogen/Al) for ABC</td>
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</tbody>
</table>
Patients demographics & baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Ribociclib + fulvestrant n=484</th>
<th>Placebo + fulvestrant n=242</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (31-89)</td>
<td>63 (34-86)</td>
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<tr>
<td>Race</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>406 (83.9)</td>
<td>213 (88.0)</td>
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<tr>
<td>Asian</td>
<td>45 (9.3)</td>
<td>18 (7.4)</td>
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<tr>
<td>Other†</td>
<td>33 (6.8)</td>
<td>11 (4.5)</td>
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<tr>
<td>ECOG PS§</td>
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<td></td>
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<tr>
<td>0</td>
<td>310 (64.0)</td>
<td>158 (65.3)</td>
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<tr>
<td>1</td>
<td>173 (35.7)</td>
<td>83 (34.3)</td>
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<tr>
<td>Metastatic sites</td>
<td></td>
<td></td>
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<tr>
<td>Visceral disease</td>
<td>293 (60.5)</td>
<td>146 (60.3)</td>
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<tr>
<td>Bone-only disease</td>
<td>103 (21.3)</td>
<td>51 (21.1)</td>
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<tr>
<td>Prior endocrine therapy status†</td>
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<tr>
<td>First line†</td>
<td>238 (49.2)</td>
<td>129 (53.3)</td>
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<tr>
<td>Second line + early relapsers**</td>
<td>236 (48.8)</td>
<td>109 (45.0)</td>
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<td>Prior endocrine therapy setting</td>
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<tr>
<td>(Neo)adjuvant</td>
<td>289 (59.7)</td>
<td>142 (58.7)</td>
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<tr>
<td>Advanced</td>
<td>110 (22.7)</td>
<td>40 (16.5)</td>
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<tr>
<td>Prior (neo)adjuvant chemotherapy</td>
<td>261 (53.9)</td>
<td>126 (52.1)</td>
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</table>
MONALEESA-3: PFS

ORR 40.9% vs 28.7% (P = .003).

PFS:20.5 vs 16m
HR 0.59

PFS:NR vs 18 ms
HR 0.57

PFS:14.6m vs 9 ms
HR 0.56
MONALEESA-3 PFS Benefit in all subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events, n/n</th>
<th>Favor ribociclib</th>
<th>Favor placebo</th>
<th>Hazard ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Ribociclib + fulvestrant</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td>210/484</td>
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<td></td>
<td>0.593</td>
<td>0.480-0.732</td>
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<tr>
<td>First line</td>
<td>76/238</td>
<td></td>
<td></td>
<td>0.577</td>
<td>0.415-0.802</td>
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<td>Second line + early relapsers</td>
<td>131/236</td>
<td></td>
<td></td>
<td>0.565</td>
<td>0.428-0.744</td>
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<td>Liver or lung involvement</td>
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<tr>
<td>Yes</td>
<td>116/242</td>
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<td></td>
<td>0.645</td>
<td>0.483-0.861</td>
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<td>No</td>
<td>94/247</td>
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<td>0.563</td>
<td>0.415-0.764</td>
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<td>Bone lesion only</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>36/103</td>
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<td></td>
<td>0.379</td>
<td>0.234-0.613</td>
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<tr>
<td>No</td>
<td>174/381</td>
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<td>0.658</td>
<td>0.519-0.833</td>
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<td>Age ≤65 years</td>
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<td>Yes</td>
<td>115/258</td>
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<td></td>
<td>0.607</td>
<td>0.454-0.810</td>
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<tr>
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<td>95/226</td>
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<td>0.597</td>
<td>0.436-0.818</td>
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<td>Race</td>
<td></td>
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</tr>
<tr>
<td>Asian</td>
<td>22/45</td>
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<td>1.353</td>
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<tr>
<td>Caucasian</td>
<td>174/406</td>
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<td>0.562</td>
<td>0.448-0.704</td>
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<td>Other</td>
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<td>0.881</td>
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<tr>
<td>0</td>
<td>126/310</td>
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<td></td>
<td>0.559</td>
<td>0.427-0.733</td>
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<tr>
<td>1</td>
<td>83/173</td>
<td></td>
<td></td>
<td>0.633</td>
<td>0.450-0.890</td>
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<tr>
<td>Number of metastatic sites</td>
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<tr>
<td>&lt;3</td>
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<td>0.586</td>
<td>0.447-0.768</td>
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<td>≥3</td>
<td>84/175</td>
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<td>0.621</td>
<td>0.441-0.874</td>
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<td>Prior tamoxifen</td>
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<td></td>
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<tr>
<td>Yes</td>
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<td></td>
<td>0.620</td>
<td>0.443-0.866</td>
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<tr>
<td>No</td>
<td>131/291</td>
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<td>0.562</td>
<td>0.428-0.738</td>
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<tr>
<td>Prior AI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>135/257</td>
<td></td>
<td></td>
<td>0.670</td>
<td>0.507-0.886</td>
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<tr>
<td>No</td>
<td>75/227</td>
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<td></td>
<td>0.481</td>
<td>0.345-0.669</td>
</tr>
</tbody>
</table>

*14 patients were not included in the prior endocrine therapy subgroup analysis due to missing data or criteria not being met.
*Treatment refers to ABC. Received up to 1 line of prior endocrine therapy for ABC.
Hazard ratios were estimated based on stratified Cox proportional hazards model except in the subgroups related to the stratification factors (presence or absence of lung or liver metastases and prior endocrine therapy), where an unstratified analysis was used.
CDK4/6 I in Endocrine Sensitive disease

- HR+, HER2- ABC
- Postmenopausal
- No prior systemic therapy in this setting
- If neoadjuvant/adjuvant ET DFI >12 ms since end of ET
- ECOG PS ≤1

Primary endpoint: Investigator-assessed PFS

ES MBC AI + CDK4/6 I significant ↑ in PFS 25m vs 14m & ↑ QOL
CDK 4/6 Inhibitor Combinations

Safety profiles

<table>
<thead>
<tr>
<th>Common adverse event</th>
<th>Palbociclib (125 mg per day [3 weeks on, 1 week off])</th>
<th>Ribociclib (600 mg per day [3 weeks on, 1 week off])</th>
<th>Abemaciclib (200 mg twice per day [continuous])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 and 4</td>
<td>All grades</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74–81</td>
<td>54–67</td>
<td>74</td>
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<tr>
<td>Thrombocytopenia</td>
<td>16–22</td>
<td>2–3</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37–40</td>
<td>2–4</td>
<td>37</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>21–26</td>
<td>1–4</td>
<td>35</td>
</tr>
<tr>
<td>Nausea</td>
<td>25–35</td>
<td>0–2</td>
<td>52</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>

Financial & Clinical toxicity !!

Evolution of therapy for endocrine-sensitive Her2-ve MBC

- Tamoxifen: 6 ms
- Aromatase inhibitors: 10–14 ms
- Fulvestrant 500 mg: 16.6 ms
- Fulvestrant 500 mg bone mets only: 22 ms
- Letrozole + palbociclib or abemaciclib or ribociclib: 25 months

Regardless of visceral mets!!!

- Fulvestrant + ribociclib: NR

Median TTP/PFS (months)

What is the optimal frontline therapy? Fulvestrant vs AI?

PARSIFAL

Arm A:
Palbociclib 125 mg + Fulvestrant 500 mg/5mL i.m.

Randomisation (1:1) non-blinded. Stratified by:
- Visceral / non-visceral involvement
- De novo / non-de novo

480 patients
- ER(+)/HER2(-)
- MBC

Arm B:
Palbociclib 125 mg + Letrozole 2.5 mg

1. Daily for 3 weeks followed by a week off over 28-day cycles
2. On days 1 and 14 of cycle 1; then on day 1 of subsequent 28-day cycles
3. Once daily continuously over 28-day cycles

End of study:
- Disease progression
- Symptomatic deterioration
- Unacceptable toxicity
- Death
- Withdrawal of consent

NCT02491983. Available at: www.clinicaltrials.gov.
Who should receive the combination Fulvestrant CDK4/6?
Comparable outcome of Fulvestrant single agent vs combination in front line setting ET.

- mPFS: 25, 25, 22
- CBR: 70%, 73%, 74%

**Study:**
- PALOMA-2
- MONALEESA-2
- FALCON
Who Should Receive combination CDK4/6I+ AI/Fulvestrant

With visceral disease

- Fulvestrant (n = 135)
- Anastrozole (n = 119)

PFS: 13.8m vs 15.8m

ESR1-mut

- Exemestane: Median PFS, 2.6 months (95% CI, 2.4 to 6.2)
- Fulvestrant-containing regimen: Median PFS, 5.7 months (95%CI, 3.0 to 8.5)

Combination is better PFS >25 vs 13m
PALOMA3: Palbo + Fulv. PFS benefit regardless of ESR1 mutation

CDK4/6 inhibitor: First-line or second line?

**BOOG trial (Netherlands)**

**Arm A:**
- Any AI +
- Any CDK4/6 inhibitors

**PD** ➔ **Fulvestrant**

**Primary endpoint**
- Progression-free survival after two lines of treatment (PFS2)

**Arm B:**
- Any AI

**PD** ➔ **Fulvestrant + CDK4/6 inhibitors**

**1050 patients**
- ER(+) / HER2(-)
- Advanced breast cancer
- Endocrine sensitive
- Pre and post

Randomization (1:1) non-blinded. Stratified by:
- Visceral / non-visceral involvement

NCT02271828. Available at: www.clinicaltrials.gov
Endocrine Resistance

Chances of response to endocrine therapy for MBC

- Early relapse on Tx
- Relapse after 2-3 yrs Tx
- Late relapse off Tx
- De Novo Resistance
- Acquired Resistance
- Endocrine Sensitive
Non cross resistant AI as second line endocrine TTT

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Second treatment</th>
<th>N</th>
<th>Objective response (%)</th>
<th>Clinical benefit (%)</th>
<th>Time to progression (months)</th>
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</thead>
<tbody>
<tr>
<td>Anastrozole or letrozole</td>
<td>Exemestane</td>
<td>23</td>
<td>8.7</td>
<td>43.5</td>
<td>5.1</td>
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<tr>
<td>Exemestane</td>
<td>Anastrozole or letrozole</td>
<td>18</td>
<td>22.2</td>
<td>55.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Exemestane</td>
<td>12</td>
<td>---</td>
<td>---</td>
<td>4.4</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Anastrozole</td>
<td>11</td>
<td>---</td>
<td>---</td>
<td>1.9</td>
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<tr>
<td>Anastrozole</td>
<td>Exemestane</td>
<td>50</td>
<td>8.0</td>
<td>44.0</td>
<td>5.0</td>
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<tr>
<td>Anastrozole or letrozole</td>
<td>Exemestane</td>
<td>114</td>
<td>5.0</td>
<td>46.0</td>
<td>4.5</td>
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<td>Anastrozole or letrozole</td>
<td>Exemestane</td>
<td>31</td>
<td>19.4</td>
<td>54.8</td>
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<td>Anastrozole or letrozole</td>
<td>Exemestane</td>
<td>30</td>
<td>0.0</td>
<td>46.6</td>
<td>4.0</td>
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<td>Anastrozole or letrozole</td>
<td>Exemestane</td>
<td>60</td>
<td>20.0</td>
<td>38.3</td>
<td>3.2</td>
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<tr>
<td>Anastrozole or letrozole</td>
<td>Exemestane</td>
<td>105</td>
<td>4.8</td>
<td>20</td>
<td>3.2</td>
</tr>
</tbody>
</table>

OR 6-20%, CBR 30-40% TTP 3-5m

Miller WR et al. Breast Cancer Res 2012; 14: 201
2nd Line ET in HR + ABC

<table>
<thead>
<tr>
<th>Treatments</th>
<th>CBR, %</th>
<th>ORR, %</th>
<th>TTP, mo</th>
<th>PFS, mo</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUL vs ANA</strong>(^1)</td>
<td>43.5 vs 40.9</td>
<td>19.2 vs 16.5</td>
<td>5.5 vs 4.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>EFECT: FUL vs EXE</strong>(^2)</td>
<td>32.2 vs 31.5</td>
<td>7.4 vs 6.7</td>
<td>3.7 vs 3.7</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>CONFIRM: FUL 500 mg vs FUL 250 mg</strong>(^3)</td>
<td>45.6 vs 39.6</td>
<td>9.1 vs 10.2</td>
<td>—</td>
<td>6.5 vs 5.5</td>
<td>Initial 25.1 vs 22.8 Final 26.4 vs 22.3(^4,*)</td>
</tr>
<tr>
<td><strong>SoFEA: FUL + ANA vs FUL vs EXE</strong>(^5)</td>
<td>—</td>
<td>7.4 vs 6.9 vs 3.6</td>
<td>—</td>
<td>4.4 vs 4.8 vs 3.4</td>
<td>20.2 vs 19.4 vs 21.6 (^5)</td>
</tr>
</tbody>
</table>

Evolution of therapy for endocrine-resistant MBC

2. IBRANCE EU SmPC;

Monotherapy is not enough!!
HR+, HER2- ABC
Pre/peri & Postmenopausal*
Progressed on prior endocrine therapy:
— On or within 12 mo adjuvant
— On therapy for ABC

Primary endpoint:
Investigator-assessed PFS
*Only postmenopausal

Endocrine Resistant Disease

**PALOMA3**
- HR: 0.46, p=<0.0001

**MONARCH2**
- HR: 0.55, p=<0.001

**MONALEESA -3**
- HR: 0.56

**ER: Fulv + CDK4/6i → PFS 14-16m vs 4-6**

---

In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm vs the placebo arm was 10.0 months.
MAGNITUDE OF TREATMENT EFFECT WAS MAINTAINED ACROSS ENDPOINTS

- **PAL+FUL**: mPFS=11.2 mo
- **PBO+FUL**: mPFS=4.6 mo
- **PAL+FUL**: mOS=34.9 mo
- **PBO+FUL**: mOS=28 mo

- Time (Month)
  - 6.6 months
  - 6.9 months

mOS=median overall survival; mPFS=median progression-free survival.
MAGNITUDE OF TREATMENT EFFECT WAS MAINTAINED ACROSS ENDPOINTS

- **mTCT** = median time from randomization to the start of postprogression chemotherapy
- **mTEST** = median time from randomization to the end of the immediate subsequent line of postprogression therapy
- **mTET** = median time from randomization to end of study treatment

**mPFS =** 11.2 mo
**mOS =** 34.9 mo
**mTET =** 11.0 mo
**mTCT =** 17.6 mo

**mPFS =** 4.6 mo
**mOS =** 28 mo
**mTET =** 4.6 mo
**mTCT =** 8.8 mo

**mTEST =** 18.8 mo
**mTET =** 14.1 mo

6.6 months
6.9 months
Causes of Resistance to Endocrine TTT

Cross talk between PI3K/AKT/MTOR & ER Pathway

ER & PR levels ↓ due to AKT P

PI3K inhibition increases ER expression

Bosch et al. Sci Transl Med. 2015
Efficacy limited in unselected patients. Significant toxicities with Pan-PI3K Inhibitors.

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Trial Arm1</th>
<th>Arm2</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FERGI</td>
<td>168</td>
<td>fulvestrant+ pictilisib</td>
<td>fulvestrant+ placebo</td>
<td>-ve</td>
</tr>
<tr>
<td>BELLE2</td>
<td>1147</td>
<td>fulvestrant+ buparlisib</td>
<td>fulvestrant+ placebo</td>
<td>+ve but not clinically significant;</td>
</tr>
<tr>
<td>post-mTORi</td>
<td>432</td>
<td>fulvestrant+ buparlisib</td>
<td>fulvestrant+ placebo</td>
<td>benefit in PIK3CA m</td>
</tr>
</tbody>
</table>
Fulvestrant + alpha-specific Pi3K I
HR+, Her2-, PIK3CA- mutant MBC

SOLAR-1: Ph3
Alpelisib + Fulvestrant
n = 572

SANDPIPER Ph3 P III
Taselisib + Fulvestrant

PFS 11 vs 3.7 m

Fulv + Taselisib → PFS 7 vs 5 m
HR 0.7

new option for PIK3CA-mutant HR+, HER2–ABC who have progressed on prior endocrine therapy (with/without a CDK4/6 inhibitor)
Fulvestrant + MTOR I

PrECOG 102: Ph2 Everolimus + Fulvestrant

Everolimus ↑efficacy of fulvestrant in AI-resistant, ER+ MBC

G3,4 AE 56% vs 26% (Mostly hyperglycemia, stomatitis, hyper triglyceridemia, lymphopenia, pneumonitis)


PFS =10m vs 5m
HR 0.6, P=0.02
Evolution of therapy for endocrine-resistant metastatic breast cancer

- **Exemestane**: 3.2 months
- **Fulvestrant 500 mg**: 4.6–6.5 months
- **Exemestane + everolimus**: 7.8 months
- **Fulvestrant + alpha-specific Pi3K I**: 11 months
- **Fulvestrant + palbociclib or abemaciclib or Ribociclib**: 11.2-16 months

*Median PFS: Abemaciclib + Fulvestrant: 16.4 months

Abemaciclib is an investigational drug and is not approved for use in Europe

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%)
Choosing the treatment in HR+ ABC

Disease activity
- Short DFI
- Visceral disease burden
- Symptoms

Chance to respond to ET
- Resistance type
- Intrinsic subtype
- Biomarkers?

Single agent ET
CDK4/6 inhibitors + ET?
Chemotherapy

“Low tumour burden”
Single-agent ET
ET + CDK4/6
Second line?

“Visceral disease”
ET + CDK4/6

“Visceral crisis”
Chemotherapy
ET + CDK4/6

Source: Courtesy of Prof. Peter Schmid.
## Front line Endocrine Treatment in HR+ ABC

**mPFS:**
- **Tamoxifen:** 6m
- **AI:** 10m
- **Faslodex:** 22.3m if no visceral met. 13.8m if visceral met

### MONALEESA 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mPFS</th>
</tr>
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<tbody>
<tr>
<td>Ribo + Fulv</td>
<td>NR</td>
</tr>
<tr>
<td>Fulv</td>
<td>18m</td>
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</table>

### PALOMA1,2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbo + Let</td>
<td>24.8</td>
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<tr>
<td>Let</td>
<td>14.5</td>
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</table>

### MONALLESIA-2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribo + Let</td>
<td>NR</td>
</tr>
<tr>
<td>Let</td>
<td>14.7</td>
</tr>
</tbody>
</table>

Fulvestrant > AI > Tam non Visceral met PFS 22m
If Visceral mets → CDK4/6 I + Fulv or AI → mPFS 25m vs 14m
# 2nd Line Endocrine Treatment in HR+ ABC

## PFS: Tam 3-4m  AI: 3-5m  Faslodex500mg: 6-7m

<table>
<thead>
<tr>
<th>Study</th>
<th>mPFS</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PALOMA3</td>
<td></td>
<td>Palbo + Fulv</td>
<td>9.2m</td>
<td>Fulv</td>
</tr>
<tr>
<td></td>
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<td>HR 0.46</td>
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<tr>
<td>MONALEESA-3</td>
<td></td>
<td>Ribo + Fulv</td>
<td>16m</td>
<td>Fulv</td>
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<tr>
<td></td>
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<td>HR 0.56</td>
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<tr>
<td>MONARCH -2</td>
<td></td>
<td>Abem+ Fulv</td>
<td>15m</td>
<td>Fulv</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 0.55</td>
<td></td>
</tr>
</tbody>
</table>

- Combination Fulv + CDK4/6 I > Fulv
- Combination Fulv + Everloimus > Fulv more toxic
- Combination AI + MTOR I > AI

Thank You

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