Pearls from ESMO 2016

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Napoli 10-11 Marzo 2017
ESMO 2016: the “record meeting”

• ESMO 2016 has broken records of attendance
  • 20,522 participants

• 1,640 studies presented, including 47 late-breaking trials
  • A record number of research published in major medical journals such as NEJM, The Lancet Oncology and JAMA

• Several practice-changing studies with positive results
  • ENGOT-OV16/NOVA concerning landmark study for patients with recurrent ovarian cancer
  • Keynote-024 and Keynote-021 presenting new immunotherapeutic options for advanced lung cancer
  • Monaleesa 2 in HER2 negative advanced breast cancer
  • EORTC 18071 with good survival results for patients with stage III melanoma
  • Checkmate 141 study of patient reported outcomes in head and neck cancers
Pearls from ESMO 2016

**Advanced Breast Cancer**

- **ER+ Disease**
  - Single agent ET
  - Combination Strategies
    - CDK 4/6 inhibition

- **HER2+ Disease**
  - Trastuzumab biosimilars

- **New Directions**
  - New potential agents
  - New potential targets

**Early Breast Cancer**

- **Neoadjuvant therapy**
  - Interim results of neoMONARCH study

- **Adjuvant therapy**
  - Concurrent vs. sequential trastuzumab

- **Molecular marker assays and patient outcome**

- **Identification of higher risk population**
Pearls from ESMO 2016

**Advanced Breast Cancer**

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**Early Breast Cancer**
FALCON Trial
Study Design

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

N = 450 patients for 306 progression events;
If true PFS HR was 0.69 this would provide 90% power at the 5% two-sided level (log-rank test)
Subgroup analysis of PFS for pre-defined baseline covariates

Stratification factors:
- Prior chemo for MBC
- Measurable disease
- Locally advanced vs. MBC

Fulvestrant 500 mg
(500 mg IM on days 0, 14, 28 then every 28 days) + Placebo

Anastrozole 1 mg + Placebo

Primary endpoint: PFS
Secondary: OS, ORR, CBR, DoR, DoCB, HRQoL, Safety

<table>
<thead>
<tr>
<th></th>
<th>Total (N=462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior chemotherapy, n (%)</td>
<td>160 (34.6%)</td>
</tr>
<tr>
<td>Advanced disease</td>
<td>79 (17.1%)</td>
</tr>
<tr>
<td>Adjuvant / neoadjuvant</td>
<td>62 / 27 (13.4%/5.8%)</td>
</tr>
<tr>
<td>Receptor status, n (%)</td>
<td></td>
</tr>
<tr>
<td>ER+ / PgR+</td>
<td>354 (76.6%)</td>
</tr>
<tr>
<td>ER+ / PgR-</td>
<td>87 (18.8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (3.7%)</td>
</tr>
<tr>
<td>Overall disease classification, n (%)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced disease</td>
<td>60 (13.0%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>402 (87.0%)</td>
</tr>
<tr>
<td>Visceral disease, n (%)</td>
<td>254 (55.0%)</td>
</tr>
<tr>
<td>Measurable disease, n (%)</td>
<td>389 (84.2%)</td>
</tr>
</tbody>
</table>

Ellis et al., ESMO 2016
FALCON Trial
Results

Primary Endpoint met: Benefit in PFS
16.6 vs 13.8 months, HR 0.797

Ellis et Al., ESMO 2016
Pearls from ESMO 2016

Advanced Breast Cancer

• ER+ Disease
  • Single agent ET
  • Combination Strategies
    • CDK 4/6 inhibition

• HER2+ Disease
  • Trastuzumab biosimilars

• New Directions
  • New potential agents
  • New potential targets

Early Breast Cancer
The Role of CDK4/6 in HR+ Breast Cancer

- Rb binding inactivates E2F, which regulates genes important for transition through the G1/S cell cycle restriction point\(^1,2\)
- Phosphorylation of Rb by CDK4/6 leads to dissociation of E2F from Rb and cell cycle progression\(^1,2\)
- Increased CDK4/6 activity driven by perturbations of other pathways is associated with endocrine therapy resistance\(^1,2\)

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MONALEESA-2
Study Design

- Postmenopausal women with HR+/HER2– advanced breast cancer
- No prior therapy for advanced disease
- N=668

Randomization (1:1)
Stratified by the presence/absence of liver and/or lung metastases

Ribociclib (600 mg/day)
3-weeks-on/1-week-off
+ Letrozole (2.5 mg/day)
n=334

Placebo
+ Letrozole (2.5 mg/day)
n=334

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

Secondary endpoints
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio ≤0.56 and p<0.0000129

PFS, progression-free survival.
MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).

Hortobagyi G et al ESMO 2016 LBA 1
MONALEESA-2
Interim Analysis on Primary Endpoint

Median follow-up: 15.3 months

<table>
<thead>
<tr>
<th>PFS (Investigator Assessment)</th>
<th>Ribociclib + Let n=334</th>
<th>Placebo + Let n=334</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>93 (28)</td>
<td>150 (45)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (19.3–NR)</td>
<td>14.7 (13.0–16.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.556 (0.429–0.720)</td>
<td>0.00000329</td>
</tr>
<tr>
<td>One-sided p value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS results by independent central review: hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)

Let, letrozole; NR, not reached.

Hortobagyi G et al ESMO 2016 LBA 1
### MONALEESA-2 Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>Favor Ribociclib + Let</th>
<th>Favor Placebo + Let</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>668 (100)</td>
<td></td>
<td></td>
<td>0.556 (0.429–0.720)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>373 (56)</td>
<td></td>
<td></td>
<td>0.523 (0.378–0.723)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>295 (44)</td>
<td></td>
<td></td>
<td>0.608 (0.394–0.937)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>51 (7.6)</td>
<td></td>
<td></td>
<td>0.387 (0.166–0.906)</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>568 (85)</td>
<td></td>
<td></td>
<td>0.607 (0.459–0.804)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>407 (61)</td>
<td></td>
<td></td>
<td>0.588 (0.422–0.820)</td>
</tr>
<tr>
<td>1</td>
<td>261 (39)</td>
<td></td>
<td></td>
<td>0.528 (0.348–0.801)</td>
</tr>
<tr>
<td><strong>ER/PgR status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and PgR+</td>
<td>546 (82)</td>
<td></td>
<td></td>
<td>0.616 (0.461–0.823)</td>
</tr>
<tr>
<td>Other</td>
<td>122 (18)</td>
<td></td>
<td></td>
<td>0.358 (0.196–0.647)</td>
</tr>
<tr>
<td><strong>Liver or lung involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>295 (44)</td>
<td></td>
<td></td>
<td>0.547 (0.360–0.832)</td>
</tr>
<tr>
<td>Yes</td>
<td>373 (56)</td>
<td></td>
<td></td>
<td>0.569 (0.409–0.792)</td>
</tr>
<tr>
<td><strong>Bone-only disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>521 (78)</td>
<td></td>
<td></td>
<td>0.541 (0.405–0.723)</td>
</tr>
<tr>
<td>Yes</td>
<td>147 (22)</td>
<td></td>
<td></td>
<td>0.690 (0.381–1.249)</td>
</tr>
<tr>
<td><strong>De novo disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>441 (66)</td>
<td></td>
<td></td>
<td>0.603 (0.447–0.814)</td>
</tr>
<tr>
<td>Yes</td>
<td>227 (34)</td>
<td></td>
<td></td>
<td>0.445 (0.267–0.750)</td>
</tr>
<tr>
<td><strong>Prior (neo)adjuvant endocrine therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAI and others†</td>
<td>53 (7.9)</td>
<td></td>
<td></td>
<td>0.448 (0.193–1.038)</td>
</tr>
<tr>
<td>Tamoxifen or exemestane</td>
<td>293 (44)</td>
<td></td>
<td></td>
<td>0.570 (0.393–0.826)</td>
</tr>
<tr>
<td>None</td>
<td>322 (48)</td>
<td></td>
<td></td>
<td>0.570 (0.380–0.854)</td>
</tr>
<tr>
<td><strong>Prior (neo)adjuvant chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>377 (56)</td>
<td></td>
<td></td>
<td>0.548 (0.373–0.806)</td>
</tr>
<tr>
<td>Yes</td>
<td>291 (44)</td>
<td></td>
<td></td>
<td>0.548 (0.384–0.780)</td>
</tr>
</tbody>
</table>

*NSAI, non-steroidal aromatase inhibitor.  
†Excludes patients who had received tamoxifen.
PALOMA-2
Biomarker Analysis

Postmenopausal ER+ HER2– advanced breast cancer with no prior treatment for advanced disease AI-resistant patients excluded N=666

Randomised 2:1

- Primary endpoint: PFS (investigator assessed)
- Secondary endpoints: Response, OS, safety, biomarkers, PROs

Finn R, et al. ASCO 2016, Abstract 504 (oral abstract)
### PALOMA-2

**Subgroup Analysis: PFS by biomarker**

#### Qualitative Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
</tr>
<tr>
<td>ER+</td>
<td>504</td>
<td>0.57 (0.44–0.74)</td>
</tr>
<tr>
<td>ER-</td>
<td>62</td>
<td>0.41 (0.22–0.75)</td>
</tr>
<tr>
<td>Rb+</td>
<td>512</td>
<td>0.53 (0.42–0.68)</td>
</tr>
<tr>
<td>Rb-</td>
<td>51</td>
<td>0.68 (0.31–1.48)</td>
</tr>
<tr>
<td>Cyclin D1+</td>
<td>549</td>
<td>0.56 (0.44–0.71)</td>
</tr>
<tr>
<td>Cyclin D1-</td>
<td>15</td>
<td>1.0 (0.29–3.46)</td>
</tr>
<tr>
<td>p16+</td>
<td>466</td>
<td>0.52 (0.40–0.67)</td>
</tr>
<tr>
<td>p16-</td>
<td>84</td>
<td>0.73 (0.39–1.36)</td>
</tr>
<tr>
<td>Ki-67 ≤20%</td>
<td>318</td>
<td>0.53 (0.38–0.74)</td>
</tr>
<tr>
<td>Ki-67 &gt;20%</td>
<td>235</td>
<td>0.57 (0.41–0.79)</td>
</tr>
</tbody>
</table>

#### Quantitative Analysis

<table>
<thead>
<tr>
<th>Percentile</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
</tr>
<tr>
<td>ER status</td>
<td>≤25%</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td>&gt;25% to &lt;75%</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>≥75%</td>
<td>142</td>
</tr>
<tr>
<td>Rb status</td>
<td>≤25%</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>&gt;25% to &lt;75%</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>≥75%</td>
<td>249</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>≤25%</td>
<td>141</td>
</tr>
<tr>
<td>status</td>
<td>&gt;25% to &lt;75%</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>≥75%</td>
<td>247</td>
</tr>
<tr>
<td>p16 status</td>
<td>≤25%</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>&gt;25% to &lt;75%</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>≥75%</td>
<td>152</td>
</tr>
</tbody>
</table>

---

HR=hazard ratio; LET=letrozole; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Finn R et al. ESMO 2016 LBA15
PALOMA-2
Impact of Palbociclib on Quality of Life

No significant differences between the treatment groups in change from baseline scores for Physical, Social/Family, Emotional, and Functional Well-Being were observed.

Data consistent with PALOMA-3 (Annals Oncol)

Rugo et al. ESMO 2016, 225PD
Pearls from ESMO 2016

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Early Breast Cancer
Biological Complexity of Monoclonal Antibodies

Intrinsic Complexity
- Size
- Structure
- Physiochemistry
- Heterogeneity

Additional Complexity
- Manufacturing process
- Formulation
- Handling
- Route of administration

Immunogenicity
- Host related: genetic predisposition by MHC alleles, immunosuppression
- Product related: Structural properties, glycosylation, impurities, formulation, storage, aggregates
Trastuzumab Biosimilar Studies
Design

Heritage Study – Trastuzumab MYL-1401O Biosimilar

N=458

Part 1: Combined Treatment/PK analysis
- MYL-1401O Loading dose 8 mg/kg
- Maintenance dose 6 mg/kg Q3W
- The day after trastuzumab infusion
- Decrease 75 mg/m^2 Q3W cycles
- or Paclitaxel 80 mg/m^2 weekly
- 30 min after trastuzumab infusion

Part 2: Single Treatment
- MYL-1401O Maintenance dose until disease progression
- Stable disease after 8 cycles

Stable disease can continue with Part 1 beyond Cycle 8

Herceptin® Loading dose 8 mg/kg
- Maintenance dose 6 mg/kg Q3W
- Stable disease after 8 cycles

Up to 28 days
- Cycle 1
- Cycles 2-8

R = Randomization

Rugo H et Al., ESMO 2016. Abstract #LBA

Trastuzumab BCD-022 Biosimilar

N=110

Randomization

Cycle 1
- Response evaluation
- Progression or unacceptable toxicity
- Treatment discontinuation

Cycle 2
- Response evaluation

Cycle 3
- Response evaluation

Cycle 4
- Response evaluation

Cycle 5
- Response evaluation

Cycle 6
- Response evaluation

Shustova M et Al., ESMO 2016. Abstract 224 PD
# Trastuzumab Biosimilar Studies

## Results

### Heritage Study – Trastuzumab MYL-1401O Biosimilar

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MYL-1401O + Taxane (N=230)</th>
<th>Herceptin + Taxane (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate n (%)</td>
<td>160 (69.6)</td>
<td>146 (64.0)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(63.62, 75.51)</td>
<td>(57.81, 70.26)</td>
</tr>
<tr>
<td>Ratio of ORR: MYL-1401O/Herceptin (FDA)</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>90% CI</td>
<td>(0.974, 1.211)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.954, 1.237)</td>
<td></td>
</tr>
<tr>
<td>Difference in ORR: MYL-1401O-Herceptin (EMEA)</td>
<td>5.53</td>
<td></td>
</tr>
<tr>
<td>90% CI</td>
<td>(-1.70, 12.69)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(-3.08, 14.04)</td>
<td></td>
</tr>
</tbody>
</table>

### Trastuzumab BCD-022 Biosimilar

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 54)</th>
<th>Group 2 (n = 56)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>30</td>
<td>29</td>
<td>0.8622</td>
</tr>
<tr>
<td>53.57</td>
<td>(40.70 - 65.98)</td>
<td>53.70</td>
<td>(40.60 - 66.31)</td>
</tr>
</tbody>
</table>

Difference in ORR -0.13% (-19.83% – 18.35%)

1. Yates-corrected Pearson’s χ² test

### Secondary outcome measures

![Graph showing secondary outcome measures for Group 1 and Group 2](image)

Rugo H et al., ESMO 2016. Abstract #LBA

Shustova M et al., ESMO 2016. Abstract 224 PD
Pearls from ESMO 2016

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Early Breast Cancer
Phase II, PM01183 Monotherapy in Metastatic Breast Cancer

Lurbinectedin (PM01183) is a trabectedin analog:
- Inhibits active transcription (RNA Pol II degradation) (1):
  - Generates double strand DNA breaks
  - Affects tumor microenvironment

Deficient homologous recombination system favors PM01183-induced apoptosis (2)

Antitumor activity observed in patients resistant to platinum compounds (3)

Two Phase III trials are currently ongoing, one as a single agent in platinum resistant ovarian cancer, and one in combination with doxorubicin in 2\textsuperscript{nd} line SCLC

3. Poveda A. et al. ASCO 2014, oral presentation
Phase II, PM01183 Monotherapy In Metastatic Breast Cancer (MBC) – 7mg Flat Dose Amended To 3.5mg/m²

**BRCA1/2 mutation (Arm A)**

- **MBC**
  - Ductal/Lobular
  - Up to 3 prior advanced chemotherapy regimens
  - PS: 0-1
  - Asymptomatic, non-steroid requiring CNS metastasis
  - Measurable disease by RECIST v1.1

**BRCA 1/2 mutation after PARPi (Arm A1)**

- **Statistical hypotheses:**
  - $H_0$: ORR ≤ 20% vs. $H_1$: ORR ≥ 40%
  - α=0.025 (one-sided); Power = 90%

- **Further development:**
  - ≥ 17 confirmed responses

**Non (or UNK) BRCA1/2 mutation (Arm B)**

- **Statistical hypotheses:**
  - Lower bound CIR% ≥ 5%

- **Balmaña, SABCS 2014, poster P3-13-01 Cruz. ESMO 2016. abstract 15200**
## Response Data For Specific Subpopulations

<table>
<thead>
<tr>
<th></th>
<th>Prior Platinum</th>
<th>BRCA</th>
<th>Hormone Status</th>
<th>Prior Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n: 27)</td>
<td>Yes (n: 27)</td>
<td>1 (n: 31)</td>
<td>2 (n: 23)</td>
</tr>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>56% (35.3-55.6)</td>
<td>26% (11.1-25.9)</td>
<td>26% (11.9-25.8)</td>
<td>61% (38.5-60.9)</td>
</tr>
<tr>
<td><strong>Duration of Response (95% CI)</strong></td>
<td>10.2 m (3.0-13.5)</td>
<td>5.9 m (2.8-12.8)</td>
<td>6.6 m (2.8-12.8)</td>
<td>6.7 m (3.4-13.5)</td>
</tr>
<tr>
<td><strong>Disease control rate</strong></td>
<td>25 (93%)</td>
<td>19 (70%)</td>
<td>23 (74%)</td>
<td>22 (96%)</td>
</tr>
<tr>
<td><strong>Clinical benefit (CR+PR+SD ≥ 3 mo)</strong></td>
<td>19 (70%)</td>
<td>14 (52%)</td>
<td>14 (45%)</td>
<td>19 (83%)</td>
</tr>
</tbody>
</table>

*Including 2 patients also HER-2 +*  
Balmana J et al. ESMO 2016 Abstract 2230
Single Agent Activity Of Her2 Antibody Drug-Conjugate DS-8201A

Structure of DS-8201a compared with T-DM1

<table>
<thead>
<tr>
<th></th>
<th>DS-8201a</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>Anti-HER2 Ab</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Payload</td>
<td>Topoisomerase I inhibitor (DXd)</td>
<td>Tubulin inhibitor (DM1)</td>
</tr>
<tr>
<td>DAR*</td>
<td>7-8</td>
<td>3.5</td>
</tr>
</tbody>
</table>

* DAR: Average drug-to-antibody Ratio

Overall response was PD due to new lesion
Current IHC status although there were prior HER2 therapies

Tamura K et al. ESMO 2016 Abstract LBA 17
## Pathways Altered in Breast Carcinomas

**N=8564**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>ERBB Pathway</th>
<th>Hormone Therapy Resistant (ESR1 Mut)</th>
<th>HR Deficient</th>
<th>IO Sensitive</th>
<th>PI3K/AKT/mTOR Pathway</th>
<th>FGFR Pathway</th>
<th>CDK Pathway</th>
<th>Other Kinases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cases</td>
<td>1294</td>
<td>796</td>
<td>1266</td>
<td>419</td>
<td>4375</td>
<td>2650</td>
<td>2685</td>
<td>630</td>
</tr>
<tr>
<td>% Total Cases</td>
<td>15%</td>
<td>9%</td>
<td>15%</td>
<td>5%</td>
<td>51%</td>
<td>31%</td>
<td>31%</td>
<td>7%</td>
</tr>
<tr>
<td>Unique Cases</td>
<td>274</td>
<td>109</td>
<td>309</td>
<td>48</td>
<td>1442</td>
<td>226</td>
<td>231</td>
<td>87</td>
</tr>
<tr>
<td>% Unique Cases</td>
<td>3%</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
<td>17%</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Therapy Examples</td>
<td>Trastuzumab, Pertuzumab, Afatinib, Lapatinib, Neratinib</td>
<td>[Fulvestrant, Tamoxifen]</td>
<td>Olaparib</td>
<td>Pembrolizumab, Nivolumab, Atezolizumab, Ipilimumab</td>
<td>Everolimus, Temsirolimus</td>
<td>Pazopanib, Ponatinib</td>
<td>Palbociclib</td>
<td>Sorafenib, Regorafenib, Dabrafenib, Vemurafenib, Crizotinib, Cabozantinib, Sunitinib</td>
</tr>
</tbody>
</table>

Ross JR et al. ESMO Abstract 229PD
Pearls from ESMO 2016

Advanced Breast Cancer

- ER+ Disease
  - Single agent ET
  - Combination Strategies
    - CDK 4/6 inhibition

- HER2+ Disease
  - Trastuzumab biosimilars

- New Directions
  - New potential agents
  - New potential targets

Early Breast Cancer

- Neoadjuvant therapy
  - Interim results of neoMONARCH study

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  - Concurrent vs. sequential trastuzumab

- Molecular marker assays and patient outcome

- Identification of higher risk population
**NeoMONARCH**

**Study Design**

**neoMONARCH: Phase II study design**

- Abemaciclib 150 mg BID is tolerable when dosed on a continuous schedule with endocrine therapy

- The most common adverse event has been diarrhea
  - Typically occurred within the first 7 days of treatment
  - Manageable with use of loperamide or dose reduction

- Loperamide was administered prophylactically for the first 28 days then at discretion of investigator

---

**Post-menopausal women (N=220) HR+, HER2-breast cancer stage: I (T ≥1 cm), II, IIIA or IIIB suitable for neoadjuvant endocrine therapy**

**Core biopsy at baseline**

**Randomization**

- Anastrozole 1 mg QD
- Abemaciclib 150 mg Q12H + Anastrozole 1 mg QD
- Abemaciclib 150 mg Q12H

**Core biopsy after 2 weeks of treatment**

**Primary endpoint:** Compare the change from baseline in Ki67 expression after 2 weeks of therapy

- Abemaciclib 150 mg Q12H + Anastrozole 1 mg QD

**Core biopsy after 14 weeks of treatment**

**Surgery (optional)**

---


**Abbreviations:**

- HER2 = human epidermal growth factor receptor 2
- HR = hormone receptor
- Q12H = every 12 hours
- QD = once daily

*Participants receive loperamide with each dose of abemaciclib*

*Participants who experience benefit following 14 weeks may remain on neoadjuvant therapy for up to 8 additional weeks*
NeoMONARCH
Change in Ki67

- Study met the boundary for statistical significance at the interim analysis (boundary p < 0.03)

Geometric Mean Change

Complete Cell Cycle Arrest
Ki67 index <2.7% at 2 weeks

- OR = 7.8 (2.0, 30.8)
- 7.2 (2.0, 26.2)

Mean Change in Ki67 Expression (%)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>n</th>
<th>Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole 1 mg</td>
<td>22</td>
<td>-71.0%</td>
</tr>
<tr>
<td>Abemaciclib 150 mg</td>
<td>23</td>
<td>-93.5%</td>
</tr>
<tr>
<td>Abemaciclib 150 mg +</td>
<td>19</td>
<td>-93.1%</td>
</tr>
</tbody>
</table>

Complete Cell Cycle Response Rate (%)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Responders</th>
<th>Complete Cell Cycle Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole 1 mg</td>
<td>5</td>
<td>22.7%</td>
</tr>
<tr>
<td>Abemaciclib 150 mg</td>
<td>16</td>
<td>69.6%</td>
</tr>
<tr>
<td>Abemaciclib 150 mg +</td>
<td>13</td>
<td>68.4%</td>
</tr>
</tbody>
</table>

Abbreviations: GMR = geometric mean ratio, OR = odds ratio
*Geometric Mean Ratio (GMR), 2-sided 90% confidence interval (CI), p-value, p-values are based on a one-sided hypothesis test from a linear model with treatment, PR status (positive versus negative/unknown) and tumor size (<2 cm versus ≥2 cm and <5 cm versus ≥5 cm) as fixed effects.
*A responder is identified as a patient with a ln(Ki67) value of less than 1. Odds ratio (OR), 2-sided 90% CI, p value. p-value is calculated by Fisher’s Exact test of a one-sided hypothesis.
Pearls from ESMO 2016

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Sequential vs. Concurrent Trastuzumab in EBC
NCCTG Trial

The P value (.02) did not cross the prespecified O'Brien-Fleming boundary (.00116) for the planned interim analysis

Sequential and concomitant adjuvant trastuzumab in HER2+ EBC
Results from the SIGNAL/PHARE prospective cohort

Total 5,502 patients with HER2+ EBC

PHARE
3400 patients HER2+
(NCT00381901)

SIGNAL
3000 patients HER2+
6000 patients HER2-
(RECF 1098)

SIGNAL2-ICGC
500 tumours HER2+
2000 tumours HER2-

May 2006
July 2010

May 2009
July 2011

Pivot et al, ESMO 2016
Sequential and concomitant adjuvant trastuzumab in HER2+ EBC
Results from the SIGNAL/PHARE prospective cohort

Kaplan-Meier Plot

Disease Free Survival probability

<table>
<thead>
<tr>
<th>Time since first treatment (Months)</th>
<th>1: concomitant</th>
<th>2: sequential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3566</td>
<td>3492</td>
</tr>
<tr>
<td>2</td>
<td>1893</td>
<td>1878</td>
</tr>
</tbody>
</table>

Logrank p=0.2026
HR=1.08 95%CI(0.96-1.21)

Pivot et al, ESMO 2016
Pearls from ESMO 2016

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FIRST PROSPECTIVELY-DESIGNED OUTCOME STUDY IN ESTROGEN RECEPTOR (ER)+ BREAST CANCER (BC) PATIENTS (PTS) WITH N1MI OR 1-3 POSITIVE NODES IN WHOM TREATMENT DECISIONS IN CLINICAL PRACTICE INCORPORATED THE 21-GENE RECURRENCE SCORE (RS) RESULT

S.M. Stemmer, et al.
Risk of Distant Recurrence by RS Group

- The overall number of patients with distant recurrence by RS risk group (Low/Intermediate/High): 14/379, 20/258, 13/72, respectively.

- The rate of distant recurrence in the low RS group was 3.2% within 5 years compared to 16.9% for the high RS group.

Stemmer SM et Al., ESMO 2016. Abstract 3040
BREAST CANCER-SPECIFIC SURVIVAL IN PATIENTS WITH LYMPH NODE-POSITIVE HORMONE RECEPTOR POSITIVE INVASIVE BREAST CANCER AND 21-GENE RECURRENCE SCORE RESULTS IN THE SEER DATABASE

D.P. Miller, et al.

Abstract: 4013
### 5-year Breast Cancer-specific Survival (95% CI), by RS Group and Number of Positive Lymph Nodes – Total N=6,768

<table>
<thead>
<tr>
<th># Positive Nodes</th>
<th>RS &lt;18 (N=3,919; 23.8% CT Use*)</th>
<th>RS 18-30 (N=2,380; 49.0% CT Use*)</th>
<th>RS ≥31 (N=469; 77.0% CT Use*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>5-y BCSS</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Micrometastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,644</td>
<td>98.9% (97.4%, 99.6%)</td>
<td>998</td>
</tr>
<tr>
<td>2</td>
<td>1549</td>
<td>99.4% (98.4%, 99.8%)</td>
<td>893</td>
</tr>
<tr>
<td>3</td>
<td>458</td>
<td>97.1% (91.3%, 99.0%)</td>
<td>268</td>
</tr>
<tr>
<td>4+</td>
<td>139</td>
<td>95.1% (87.0%, 98.2%)</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td>129</td>
<td>92.8% (73.5%, 98.2%)</td>
<td>117</td>
</tr>
</tbody>
</table>

*Chemotherapy (CT) use reported as ‘yes’ (vs. ‘no/unknown’)
Pearls from ESMO 2016

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Prognostic Role for Derived Neutrophil-to-Lymphocyte Ratio in EBC

Study design

Stratification factors
✓ Nodes
  ▪ 1-3
  ▪ 4+
✓ Center
✓ Menopausal status

R

F  E  C

Paclitaxel
600 mg/m²
90 mg/m²
600 mg/m²
Every 3 weeks

100 mg/m²
Weekly

dNLR expression
✓ The dNLR was constructed as follows (1):

\[
dNLR = \frac{\text{neutrophil count}}{\text{white cells} - \text{neutrophil count}} \ (10^9/L)
\]

Ocana A., ESMO 2016. Abstract 3576
Prognostic Role for Derived Neutrophil-to-Lymphocyte Ratio in EBC

Association of dNLR with outcome

By PAM50 subtypes (Luminal A, Luminal B, HER2-enriched, Basal-like)

✓ For the non luminal subgroups (HER2-enriched, basal-like), elevated levels of dNLR (median cut-off) were associated with worse prognosis regardless of treatment arm.

DFS

OS

p=0.036

p=0.042
Prognostic Role for Derived Neutrophil-to-Lymphocyte Ratio in EBC

Association of dNLR with outcome

By PAM50 subtypes

✓ For the HER2-enriched subgroup, elevated dNLR was significantly associated with DFS and non-significantly associated with OS regardless of treatment arm.

DFS

OS

\[ p=0.029 \]

\[ p=0.091 \]
GESTATIONAL BREAST CANCER: DISTINCTIVE MOLECULAR AND CLINICO-EPIDEMIOLOGICAL FEATURES. GEICAM/2012-03 STUDY

J. de la Haba, et al.

Abstract: 3679
esmo.org
Gestational BC: Distinctive Molecular and Clinico-Epidemiological Features

GEICAM/2012-03 Study

Conclusions: Our study suggests that GBC patients have tumors of a particularly aggressive biology, with a higher rate of basal-like subtypes and a lower proportion of luminal subtypes compared to non-GBC patients of similar age.