Highlights of

Metastatic & Advanced Breast Cancer
Financial Disclosure(s)

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Speaker’s Bureau: Novartis
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SABCS Review: Metastatic & Advanced Breast Cancer

List of Selected Abstracts

- Bardia et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate... Abs. GS1-07
- Tripathy et al. First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized phase III MONALEESA-7 trial. Abs. GS2-05
- Goetz et al. The benefit of amemaciclib in prognostic groups: An exploratory analysis of combined data from the MONARCH 2 and 3 studies. GS6-02
- Schmid P et al. MANTA - A randomized phase II study of fulvestrant in combination with the dual mTOR inhibitor AZD2014 or everolimus or fulvestrant alone in estrogen receptor-positive advanced or metastatic breast cancer. GS2-07
- Couch et al. Cancer risks and response to targeted therapy associated with BRCA2 variants of uncertain significance. GS4-06
- Singh et al. A U.S. Food and Drug Administration pooled analysis of outcomes of older women with hormone-receptor positive metastatic BC treated with CDK4/6 inhibitor as initial endocrine based therapy. GS5-06
- GS6-07 EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician’s choice of therapy in patients with advanced germline BRCA-mutation breast cancer
First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial 

Debu Tripathy,¹ Joohyuk Sohn,² Seock-Ah Im,³ Marco Colleoni,⁴ Fabio Franke,⁵ Aditya Bardia,⁶ Nadia Harbeck,⁷ Sara Hurvitz,⁸ Louis Chow,⁹ Keun Seok Lee,¹⁰ Saul Campos-Gomez,¹¹ Rafael Villanueva Vazquez,¹² Kyung Hae Jung,¹³ Gary Carlson,¹⁴ Gareth Hughes,¹⁵ Ivan Diaz-Padilla,¹⁶ Caroline Germa,¹⁴ Samit Hirawat,¹⁴ Yen-Shen Lu¹⁸
Background

• Endocrine therapy with ovarian suppression is the recommended first-line treatment for premenopausal women with HR+, HER2– ABC; however, resistance and disease progression ultimately occur

• CDK4 and CDK6 are cyclin-dependent kinases that are typically deregulated and overactive in cancer cells
  – CDK4/6 inhibitors, such as palbociclib and ribociclib, help block of cell-cycle progression in mid-G1 by activating the tumor suppressor, Rb
  – Adding ribociclib to letrozole significantly prolonged PFS compared with letrozole alone in postmenopausal women with de novo and/or recurrent HR+, HER2– ABC (Hortobagyi et al. N Engl J Med 2016)

• MONALEESA-7 is the first Phase III trial investigating CDK4/6 inhibitor-based regimens as a front-line treatment specifically for premenopausal women with ABC
Cell Cycle Progression and Cyclin-Dependent Kinases

Cyclin B-CDK1

Cyclin A-CDK1

G_0

Mitogenic signals

Cyclin D-CDK4
Cyclin D-CDK6

INK4 family proteins (eg, p16)

Growth inhibitory signals

Cyclin A-CDK2

Cyclin E-CDK2

R point


Slide credit: clinicaloptions.com
Mechanism of Action of CDK4/6 Inhibitors

- **Mitogenic signaling**
  - G1 → S phase transition

- **S phase transcription program**
  - CDK4/6
  - Cyclin D

- **Nucleus**
  - RB not phosphorylated
  - E2F transcription inhibited
  - Arrest of cell cycle at G1/S transition restriction point

- **Restriction point blockade of G1/S transition**
  - S phase transcription program


Slide credit: clinicaloptions.com
CDK 4/6 inhibitors approved by the FDA

- **Palbociclib**
  - PD 0332991
  - ![Chemical structure of Palbociclib]

- **Ribociclib**
  - LEE011
  - ![Chemical structure of Ribociclib]

- **Abemaciclib**
  - LY2835219
  - ![Chemical structure of Abemaciclib]
Comparative Potency of Selective CDK4/6 Inhibitors

- These agents show little or no inhibitory activity for CDK1, CDK2, CDK5, or CDK7

<table>
<thead>
<tr>
<th>Agent</th>
<th>CDK4 (nM)</th>
<th>CDK6 (nM)</th>
<th>CDK9 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abemaciclib</td>
<td>2</td>
<td>9.9</td>
<td>57</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>11</td>
<td>15</td>
<td>NR</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>10</td>
<td>39</td>
<td>NR</td>
</tr>
</tbody>
</table>
Senescence or Apoptosis With CDK4/6 Inhibition

- Preclinical mouse models suggest that CDK4/6 inhibitors may lead to alternative mechanisms of tumor cell disruption
  - Dependent on reliance on different cyclin D-CDK4/6 combinations
- CDK4/6 inhibition is associated with quiescence that is reversible or senescence that is irreversible in different tumor cell types
- In liposarcoma cells, senescence is correlated with MDM2 degradation

Phase II PALOMA-1: Study Design

Stratified by disease site and disease-free interval

Postmenopausal women with ER+/HER2-advanced BC and no prior systemic therapy (N = 165)*

- **Palbociclib 125 mg QD**
  - 3 wks on/1 wk off +
  - **Letrozole 2.5 mg QD**
  - (n = 84)

- **Letrozole 2.5 mg QD**
  - (n = 81)

*ITT population; enrolled in 2 sequential cohorts.

- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** ORR, CBR (CR, PR, or SD for ≥ 24 wks), DoR, OS, pt-reported outcomes, safety


Slide credit: clinicaloptions.com
PALOMA-1: PFS

Median PFS:
- Palbociclib plus letrozole \((n = 84)\): 20.2 mos (95% CI: 13.8-27.5)
- Letrozole \((n = 81)\): 10.2 mos (95% CI: 5.7-12.6)

HR: 0.488 (95% CI: 0.319-0.748; 1-sided \(P = .0004\))

- Median follow-up: 29.6 mos

PALOMA-2 & MONALEESA-2: Design of Phase III Studies

**PALOMA 2**

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

**Randomize**

- Primary endpoint: PFS
- Secondary endpoints:
  - Response, OS, safety, biomarkers, PROs
  - PRO, patient-reported outcome; qd, once daily

**MONALEESA-2**

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

**Randomize**

- Primary endpoint: PFS
- Secondary endpoints:
  - OS (key), ORR, CBR, safety

- Palbociclib (125 mg qd, 3/1 schedule) + letrozole (2.5 mg qd)
- Placebo + letrozole (2.5 mg qd)

- Ribociclib (600 mg qd, 3 wk on/1 wk off schedule) + letrozole (2.5 mg qd)
- Placebo + letrozole (2.5 mg qd)

## PALOMA-2 & MONALEESA-2: Toxicity

### PALOMA-2

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib + Letrozole n = 444</th>
<th>Placebo + Letrozole n = 222</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>433 (98.9)</td>
<td>276 (62.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>369 (85.0)</td>
<td>289 (55.6)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>173 (39.0)</td>
<td>107 (24.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>166 (37.4)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>156 (35.1)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>148 (33.3)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>148 (32.9)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>116 (26.1)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>111 (25.0)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>107 (24.1)</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>96 (21.6)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>95 (21.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>93 (20.9)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>86 (19.4)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>79 (17.8)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>75 (16.9)</td>
<td>10 (2.3)</td>
</tr>
</tbody>
</table>

### MONALEESA-2

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib + Letrozole n = 334</th>
<th>Placebo + Letrozole n = 330</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>331 (99.4)</td>
<td>232 (69.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>204 (61.4)</td>
<td>169 (49.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>178 (53.3)</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>138 (41.3)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>128 (38.3)</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>115 (34.4)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>112 (33.5)</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>111 (33.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>93 (27.8)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>90 (26.9)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>82 (24.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>81 (24.3)</td>
<td>10 (3.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>77 (23.1)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>72 (21.6)</td>
<td>53 (15.9)</td>
</tr>
</tbody>
</table>

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

Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter

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

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

Ribociclib
(600 mg/day; 3-weeks-on/1-week-off)
+ tamoxifen/NSAI + goserelin
n=335

Placebo
+ tamoxifen/NSAI + goserelin*
n=337

Randomization (1:1)

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

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
MONALEESA7 Primary endpoint: PFS (investigator-assessed)

Goserelin included in all combinations.

<table>
<thead>
<tr>
<th>PFS (Investigator assessment)</th>
<th>Ribociclib + tamoxifen/NSAI n=335</th>
<th>Placebo + tamoxifen/NSAI n=337</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>131 (39.1)</td>
<td>187 (55.5)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>23.8 (19.2–NR)</td>
<td>13.0 (11.0–16.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.553 (0.441–0.694)</td>
<td></td>
</tr>
<tr>
<td>One-sided p value</td>
<td>9.83×10⁻⁸</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
<th>26</th>
<th>28</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + tamoxifen/NSAI</td>
<td>335</td>
<td>301</td>
<td>284</td>
<td>264</td>
<td>245</td>
<td>235</td>
<td>219</td>
<td>178</td>
<td>136</td>
<td>90</td>
<td>54</td>
<td>40</td>
<td>20</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Placebo + tamoxifen/NSAI</td>
<td>337</td>
<td>273</td>
<td>248</td>
<td>230</td>
<td>207</td>
<td>183</td>
<td>165</td>
<td>124</td>
<td>94</td>
<td>62</td>
<td>31</td>
<td>24</td>
<td>13</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
## PFS subgroup analysis*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>Favors ribociclib</th>
<th>Favors placebo</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>672 (100)</td>
<td></td>
<td></td>
<td>0.553</td>
<td>0.441–0.694</td>
</tr>
<tr>
<td><strong>Endocrine therapy partner</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>177 (26)</td>
<td></td>
<td></td>
<td>0.585</td>
<td>0.387–0.884</td>
</tr>
<tr>
<td>NSAI</td>
<td>496 (74)</td>
<td></td>
<td></td>
<td>0.569</td>
<td>0.438–0.743</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>186 (28)</td>
<td></td>
<td></td>
<td>0.443</td>
<td>0.293–0.671</td>
</tr>
<tr>
<td>≥40 years</td>
<td>486 (72)</td>
<td></td>
<td></td>
<td>0.590</td>
<td>0.449–0.777</td>
</tr>
<tr>
<td><strong>Race‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>196 (29)</td>
<td></td>
<td></td>
<td>0.401</td>
<td>0.258–0.625</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>413 (61)</td>
<td></td>
<td></td>
<td>0.657</td>
<td>0.492–0.877</td>
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<tr>
<td><strong>ECOG performance status§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>500 (74)</td>
<td></td>
<td></td>
<td>0.549</td>
<td>0.417–0.721</td>
</tr>
<tr>
<td>≥1</td>
<td>186 (25)</td>
<td></td>
<td></td>
<td>0.495</td>
<td>0.320–0.765</td>
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<tr>
<td><strong>ER/PgR status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and PgR+</td>
<td>572 (85)</td>
<td></td>
<td></td>
<td>0.574</td>
<td>0.446–0.739</td>
</tr>
<tr>
<td>Other</td>
<td>100 (15)</td>
<td></td>
<td></td>
<td>0.444</td>
<td>0.268–0.786</td>
</tr>
<tr>
<td><strong>Liver and/or lung involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>329 (49)</td>
<td></td>
<td></td>
<td>0.642</td>
<td>0.454–0.907</td>
</tr>
<tr>
<td>Yes</td>
<td>343 (51)</td>
<td></td>
<td></td>
<td>0.503</td>
<td>0.375–0.677</td>
</tr>
<tr>
<td><strong>Bone-only disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>513 (76)</td>
<td></td>
<td></td>
<td>0.533</td>
<td>0.415–0.686</td>
</tr>
<tr>
<td>Yes</td>
<td>159 (24)</td>
<td></td>
<td></td>
<td>0.703</td>
<td>0.414–1.194</td>
</tr>
<tr>
<td><strong>Prior chemotherapy for advanced disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>578 (85)</td>
<td></td>
<td></td>
<td>0.566</td>
<td>0.443–0.724</td>
</tr>
<tr>
<td>Yes</td>
<td>94 (14)</td>
<td></td>
<td></td>
<td>0.547</td>
<td>0.314–0.954</td>
</tr>
<tr>
<td><strong>Disease-free interval</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12 months</td>
<td>36 (5)</td>
<td></td>
<td></td>
<td>0.560</td>
<td>0.210–1.490</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>366 (54)</td>
<td></td>
<td></td>
<td>0.815</td>
<td>0.455–0.832</td>
</tr>
<tr>
<td>De novo</td>
<td>270 (40)</td>
<td></td>
<td></td>
<td>0.428</td>
<td>0.287–0.640</td>
</tr>
</tbody>
</table>

*Locally assessed PFS; ‡Non-Asian race includes Caucasian, Black, and Native American; §ECOG performance status missing for n=6; †patient had an ECOG performance status of 2.

ER, estrogen receptor; PgR, progesterone receptor.
Conclusions

• Progression free survival with 23.8 months in the ribociclib arm compared to 13.0 months in the placebo arm (HR 0.553)
• Subgroup analysis favored treatment with ribociclib compared to placebo in all groups
• Choice of endocrine therapy backbone, tamoxifen or an aromatase inhibitor, did not show a significant difference in PFS
• Overall survival data were immature at the data cut-off and will be presented at a later date.
• Dose density was high in both groups, 94% in the ribociclib arm and 100% in the placebo arm
• Patient-reported outcomes were assessed and favored the treatment arm with ribociclib
• Cytopenias were more common in the ribociclib arm with 9.9% of patients having grade 4 neutropenia in the ribociclib group compared to 0.6% in the placebo group.
  — However, febrile neutropenia was rare at 2.1% in the ribociclib group
• The authors concluded ribociclib in combination with tamoxifen or an AI with ovarian suppression should be considered as potential new treatment option for premenopausal women with hormone receptor positive, HER2 negative advanced breast cancer.
The benefit of abemaciclib in prognostic subgroups: An exploratory analysis of combined data from the MONARCH 2 and 3 studies

Matthew P. Goetz¹, Joyce O’Shaughnessy², George W. Sledge Jr.³, Miguel Martin⁴, Yong Lin⁵, Tammy Forrester⁵, Colleen Mockbee⁵, Ian C. Smith⁵, Angelo Di Leo⁶, Stephen Johnston⁷
Background

• Clinical and pathological factors are known to predict the activity of endocrine monotherapy in the adjuvant and metastatic settings\textsuperscript{1-4}

• CDK 4/6 inhibitors have shown benefit as initial treatment for endocrine-sensitive advanced BC (extended PFS)\textsuperscript{5-10}, \~one-third may not need a CDK 4/6 inhibitor as initial treatment

• Currently there is little insight into whether clinical and pathological factors can guide clinical decision making for the use of endocrine monotherapy versus combination therapy with a CDK4 & 6 inhibitor

• Abemaciclib is a CDK 4/6 inhibitor that has shown efficacy as a monotherapy and in combination with endocrine therapy\textsuperscript{8-10}

• In an earlier analysis, patients with more challenging disease characteristics, such as liver metastases, patients benefited substantially from the addition of abemaciclib

• This analysis combines data from two phase III studies of abemaciclib in combination with endocrine therapy to identify possible factors that may guide when and in whom to use abemaciclib
MONARCH 2 and 3 Study Design

**MONARCH 2 (N=669)**

- HR+, HER2- ABC
- Pre/peri-\(^a\) or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET\(^b\)
  - Progressed on first-line ET
- No chemo for MBC
- No more than 1 ET for MBC
- ECOG PS ≤ 1

\(\text{abemaciclib: } 150 \text{ mg}^{c} \text{ BID (continuous schedule) plus fulvestrant: } 500 \text{ mg}^{d}\)

\(\text{placebo: BID (continuous schedule) plus fulvestrant: } 500 \text{ mg}^{d}\)

**MONARCH 3 (N=493)**

- HR+, HER2- ABC
- Postmenopausal
- Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS ≤ 1

\(\text{abemaciclib: } 150 \text{ mg BID (continuous schedule) plus anastrozole: } 1 \text{ mg or }^{e} \text{ letrozole: } 2.5 \text{ mg QD}\)

\(\text{placebo: BID (continuous schedule) plus anastrozole: } 1 \text{ mg or }^{e} \text{ letrozole: } 2.5 \text{ mg QD}\)

\(2:1\)

\({}^{a}\text{Required to receive GnRH agonist}\)

\({}^{b}\text{Most patients entered after progressing while receiving prior ET, with only 8.8% who had disease that progressed within 1 year after completing adjuvant therapy}\)

\({}^{c}\text{Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled}\)

\({}^{d}\text{Fulvestrant administered per label}\)

\({}^{e}\text{Per physician’s choice: 79.1% received letrozole, 19.9% received anastrozole}\)
MONARCH 2: PFS

Median PFS, Mos
Abemaciclib + fulvestrant: 16.4
Placebo + fulvestrant: 9.3
HR: 0.55 (95% CI: 0.449-0.681; P < .0000001)

- PFS benefit with addition of abemaciclib to fulvestrant observed across all pt subgroups, except those with nonvisceral soft tissue metastases
- ORR, abemaciclib cohort vs placebo cohort: 35.2% vs 16.1%

Primary Endpoint (PFS) Met at Interim Analysis

Median PFS
abemaciclib + NSAi: not reached
placebo + NSAi: 14.7 months

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

Patients at Risk:
- abemaciclib arm: 328, 271, 234, 205, 125, 25, 1, 0
- placebo arm: 165, 127, 105, 82, 45, 7, 0, 0

PFS benefit confirmed by blinded independent central review: HR (95% CI): 0.508 (0.359, 0.723); p = .000102

Di Leo et al. ESMO 2017
Exploratory PFS Analysis: Treatment-Free Interval (TFI)

**TFI <36 months**
- Median PFS: abemaciclib + NSAi: not reached
- Placebo + NSAi: 9.0 months
- HR (95% CI): 0.48 (0.25, 0.91)

**TFI ≥36 months**
- Median PFS: abemaciclib + NSAi: not reached
- Placebo + NSAi: not reached
- HR (95% CI): 0.83 (0.46, 1.52)

<table>
<thead>
<tr>
<th>Arm</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>abemaciclib (n=42)</td>
<td>77.5%</td>
<td>64.8%</td>
<td>53.0%</td>
</tr>
<tr>
<td>Placebo (n=32)</td>
<td>58.6%</td>
<td>37.9%</td>
<td>30.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>abemaciclib (n=94)</td>
<td>82.4%</td>
<td>73.7%</td>
<td>59.4%</td>
</tr>
<tr>
<td>Placebo (n=40)</td>
<td>83.5%</td>
<td>66.2%</td>
<td>53.9%</td>
</tr>
</tbody>
</table>

Di Leo et al ESMO 2017
## MONARCH 2: Treatment-Emergent AEs

<table>
<thead>
<tr>
<th>Treatment-Emergent AE Occurring in ≥ 20% in Either Arm, %</th>
<th>Abemaciclib + Fulvestrant (n = 441)</th>
<th>Placebo + Fulvestrant (n = 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any</td>
<td>98.6</td>
<td>60.5</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>86.4</td>
<td>13.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>46.0</td>
<td>26.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>45.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>35.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>29.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Headache</td>
<td>20.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Incidence of diarrhea greatly reduced after starting abemaciclib dose amended from 200 mg to 150 mg.


Slide credit: clinicaloptions.com
### Starting Variables

<table>
<thead>
<tr>
<th>MONARCH 2</th>
<th>MONARCH 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET Resistance (Primary vs Secondary)</td>
<td>De Novo Metastatic Disease (Yes vs No)</td>
</tr>
<tr>
<td>Number of Prior ETs (1 vs 2)</td>
<td>Time from Diagnosis to Recurrence (≤10 vs &gt;10 yrs)</td>
</tr>
<tr>
<td>ET for Metastatic Disease (Yes vs No)</td>
<td>Treatment-free Interval after ET (&lt;36 vs ≥36 mo)</td>
</tr>
</tbody>
</table>

**Variables identified as prognostic (p<.05) by univariate analysis of PFS, based on a univariate Cox model stratified by treatment arm**

- Treatment-free Interval after ET (<36 vs ≥36 mo)
## Objective Response Rates (Measurable Disease)

### MONARCH 2

<table>
<thead>
<tr>
<th></th>
<th>placebo arm (%)</th>
<th>abemaciclib arm (%)</th>
<th>delta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PgR - Negative</td>
<td>9.68</td>
<td>43.94</td>
<td>34.26</td>
</tr>
<tr>
<td>Liver Metastases - Yes</td>
<td>15.25</td>
<td>48.65</td>
<td>33.39</td>
</tr>
<tr>
<td>High Grade</td>
<td>20.83</td>
<td>51.32</td>
<td>30.48</td>
</tr>
<tr>
<td>Bone-only Disease - No</td>
<td>21.79</td>
<td>49.50</td>
<td>27.70</td>
</tr>
<tr>
<td>Low/intermediate Grade</td>
<td>19.51</td>
<td>47.06</td>
<td>27.55</td>
</tr>
<tr>
<td>ECOG PS - 0</td>
<td>20.59</td>
<td>47.47</td>
<td>26.89</td>
</tr>
<tr>
<td>ECOG PS - 1</td>
<td>22.58</td>
<td>49.17</td>
<td>26.59</td>
</tr>
<tr>
<td>PgR - Positive</td>
<td>25.40</td>
<td>50.00</td>
<td>24.60</td>
</tr>
<tr>
<td>Liver Metastases - No</td>
<td>24.76</td>
<td>47.83</td>
<td>23.06</td>
</tr>
</tbody>
</table>

### MONARCH 3

<table>
<thead>
<tr>
<th></th>
<th>placebo arm (%)</th>
<th>abemaciclib arm (%)</th>
<th>delta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Metastases - Yes</td>
<td>20.69</td>
<td>54.17</td>
<td>33.48</td>
</tr>
<tr>
<td>PgR - Negative</td>
<td>27.59</td>
<td>59.02</td>
<td>31.43</td>
</tr>
<tr>
<td>High Grade</td>
<td>39.29</td>
<td>69.09</td>
<td>29.80</td>
</tr>
<tr>
<td>ECOG PS - 1</td>
<td>42.86</td>
<td>65.18</td>
<td>22.32</td>
</tr>
<tr>
<td>Low/intermediate Grade</td>
<td>43.84</td>
<td>64.29</td>
<td>20.45</td>
</tr>
<tr>
<td>Bone-only Disease - No</td>
<td>42.98</td>
<td>60.32</td>
<td>17.34</td>
</tr>
<tr>
<td>PgR - Positive</td>
<td>48.51</td>
<td>59.31</td>
<td>10.80</td>
</tr>
<tr>
<td>ECOG PS - 0</td>
<td>44.44</td>
<td>54.84</td>
<td>10.40</td>
</tr>
<tr>
<td>Liver Metastases - No</td>
<td>50.50</td>
<td>60.27</td>
<td>9.77</td>
</tr>
</tbody>
</table>

*Note: Response rates are not reported for bone-only disease since the majority of lesions were not measurable.*
This exploratory analysis of over 1,000 patients treated on monarch 2 and 3 demonstrated that while all subgroups benefited from amemaciclib, patient that benefited the most from the addition of amemaciclib to endocrine therapy were those with:

- good performance status
- progesterone receptor negative tumors
- high grade tumors
- metastatic disease to the liver
- bone only metastatic disease
- Patients a short treatment free interval (less than 36 months)

The authors suggest that these clinical and tumor characteristics may help select patients who will benefit the most from dual CDK 4/6 inhibitor and endocrine therapy vs. endocrine monotherapy.
Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, as ≥3rd-line Therapeutic Option for Patients With Relapsed/Refractory Metastatic Triple-Negative Breast Cancer (mTNBC): Efficacy Results

Aditya Bardia,1 Linda T. Vahdat,2,† Jennifer R. Diamond,3 Kevin Kalinsky,4 Joyce O’Shaughnessy,5 Rebecca L. Moroose,6 Steven J. Isakoff,6 Sara M. Tolaney,7 Alessandro D. Santin,8 Vandana Abramson,9 Nikita C. Shah,6 Serengulam V. Govindan,10 Pius Maliakal,10 Robert M. Sharkey,10 William A. Wegener,10 David M. Goldenberg,10 Ingrid A. Mayer9

*EBCTCG, Lancet 2012
Anti-Trop-2-SN-38

Trop-2, a cell surface protein is widely expressed in a variety of epithelial cancers (Figure 1). This cell surface protein is presents in 90% of triple-negative breast cancer patients. Trop-2 is a signal-transducing receptor that results in transient elevated intracellular Ca++ levels. In epithelial ovarian cancer (EOC), Trop-2 protein overexpression correlates with an aggressive malignant phenotype. Overexpression of wild-type Trop-2 was shown to be necessary and sufficient to drive cancer growth in a widely invariant manner across cell type and species.
Sacituzumab Govitecan Shows Promise for TNBC

- Trop-2 is an epithelial antigen expressed on many solid cancers, including mTNBC
- Bardia and colleagues presented the results of a 24 month study on 110 patients

Sacituzumab govitecan is a humanized antibody that targets Trop-2
### Key Eligibility Criteria

- Adults, ≥18 years of age
- ECOG 0-1
- ≥2 prior therapies in metastatic setting or ≥1 therapy if progressed within 12 months of (neo)adjuvant therapy
- Prior taxane therapy
- Measurable disease

### Evaluations

- Response evaluation by investigators
- Blinded independent central review of all CRs, PRs, and ≥20% tumor reductions
- Other evaluations: safety, immunogenicity, Trop-2 expression
Sacituzumab Govitecan (IMMU-132)
A next-generation irinotecan of interest in TNBC

- Trop-2 expressed in >90% of TNBC
- IMMU-132 is an antibody-drug conjugate of humanized anti-Trop-2 coupled with SN-38, the active metabolite of irinotecan
- Phase I/II ongoing
  - N = 60 patients with TNBC
  - ≥2 prior chemotherapy regimens; median of 5 priors
  - ORR = 31% (18/58); CBR24 = 45%
  - Median PFS 6 months (95% CI: 4.1-9.4mo)
  - Most common side effects: low white cells, diarrhea, fatigue, anemia
  - Serious diarrhea 3% (relatively rare)

Bardia et al, Abstract #1016; ASCO 2015; SABCS 2015
Progression-Free and Overall Survival

Progression-free survival

- Median (95% CI): 5.5 months (4.8, 6.6)
  - 85/110 (77%) number of events

Overall survival

- Median (95% CI): 12.7 months (10.8, 13.6)
  - 71/110 (64%) deaths reported

Based on local assessment
<table>
<thead>
<tr>
<th></th>
<th>Blinded ICR*</th>
<th>Locally Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>31% (6 CRs, 28 PRs)</td>
<td>34% (3 CRs, 34 PRs)</td>
</tr>
<tr>
<td>Median DOR(Duration of response)</td>
<td>9.1 months</td>
<td>7.6 months</td>
</tr>
</tbody>
</table>

In addition to a robust median duration of response, 9 responders were progression free for more than 1 year from start of sacituzumab govitecan treatment, 4 of which were longer than 2 years. As of data cutoff on June 30, 2017, 12 responding patients were still receiving sacituzumab govitecan.
<table>
<thead>
<tr>
<th>Subgroups</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>37% (20/54)</td>
</tr>
<tr>
<td>≥55</td>
<td>30% (17/56)</td>
</tr>
<tr>
<td><strong>Onset of metastatic disease</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 years</td>
<td>29% (16/55)</td>
</tr>
<tr>
<td>≥1.5 years</td>
<td>38% (21/55)</td>
</tr>
<tr>
<td><strong>Prior regimens for metastatic disease</strong></td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line</td>
<td>36% (16/45)</td>
</tr>
<tr>
<td>≥4&lt;sup&gt;th&lt;/sup&gt; line</td>
<td>32% (21/65)</td>
</tr>
<tr>
<td><strong>Visceral Involvement at study entry</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30% (26/88)</td>
</tr>
<tr>
<td>No</td>
<td>50% (11/22)</td>
</tr>
<tr>
<td><strong>Trop-2 IHC (N = 62)</strong></td>
<td></td>
</tr>
<tr>
<td>0-1 (weak, absent)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>2-3 (moderate, strong)</td>
<td>40% (23/57)</td>
</tr>
<tr>
<td>No Trop-2 IHC</td>
<td>29% (14/48)</td>
</tr>
<tr>
<td><strong>Prior checkpoint inhibitors</strong></td>
<td>47% (9/19)</td>
</tr>
</tbody>
</table>
Clinical Response to Sacituzumab Govitecan

- Patient with mTNBC, including metastasis to liver
- 2 prior regimens including paclitaxel and carboplatin

After 5 cycles, target lesion size reduced from 11x9 mm to 7x6 mm
Conclusions

• Sacituzumab govitecan demonstrated significant clinical activity as ≥3rd-line therapy in patients with relapsed/refractory mTNBC
  — Confirmed ORR*: 34%; clinical benefit rate (6 months)*: 45%

• Safety profile was judged as predictable and manageable, suggestive that this agent may hold potential for this patient population

• ASCENT Phase III study is recruiting and has a primary completion date as end of 2019

• “Given relapsed or refractory mTNBC is currently an unmet clinical need and standard therapies provide a very limited benefit of 10-15% ORR and about 2-3 months progression-free survival, we are very encouraged with the efficacy and safety data sacituzumab govitecan has consistently been showing in this late-stage setting,” commented Aditya Bardia, MD, MPH, Director of Precision Medicine and attending physician at Center for Breast Cancer, Massachusetts General Hospital, Harvard Medical School, Boston, MA, who presented the single-arm study in an oral presentation during the 2017 San Antonio Breast Cancer Symposium.

A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician’s choice of therapy in patients with advanced breast cancer and a germline BRCA-mutation

Background
OlympiAD: Olaparib vs SOC for *gBRCA*1/2+, HER2- MBC

- Randomized, open-label phase III study

  Pts with HER2-negative MBC with suspected or confirmed deleterious *gBRCA* mutation; TNBC or HR+ disease; ≤ 2 prior lines of CT* for MBC; if HR+, not suitable for ET or progressed on ≥ 1 ET (N = 302)

  - Olaparib 300 mg BID (n = 205)
  - SOC CT† on 21-day cycles (n = 97)

  *Stratified by prior CT for metastatic disease (yes vs no), HR status (HR+ vs TNBC), prior platinum tx (yes vs no)*

- Primary endpoint: PFS per mRECIST v1.1 (BICR)

- Secondary endpoints: time to second progression/death, OS, ORR, safety, HRQoL

*Either (neo)adjuvant treatment or treatment for metastatic disease with an anthracycline (unless contraindicated) and taxane. If received platinum-based tx, pt either could not have progressed on tx in metastatic setting or must be ≥ 12 mos since (neo)adjuvant tx.

†Physician’s choice of: capecitabine 2500 mg/m² PO Days 1-14; eribulin mesylate 1.4 mg/m² IV Days 1, 8; vinorelbine 30 mg IV Days 1, 8.

OlympiAD: PFS by BICR (Primary Endpoint)

**Progression/deaths, n (%)**
- Olaparib: 163 (79.5)
- CT: 71 (73.2)

**Median PFS, mos**
- Olaparib: 7.0
- CT: 4.2

**HR:** 0.58 (95% CI: 0.43-0.80; \(P < .001\))

OlympiAD: OS by Investigator Assessment

Deaths, n (%)
Olaparib: 94 (45.9)
CT: 46 (47.4)

Median OS, mos
Olaparib: 19.3
CT: 19.6

HR: 0.90 (95% CI: 0.63-1.29; P = .57)

OlympiAD: Adverse Events

Any-Grade AEs in ≥ 15% of Pts

- Nausea: 58
- Anemia: 40
- Vomiting: 30
- Fatigue: 29
- Neutropenia: 27
- Diarrhea: 21
- Headache: 20
- Cough: 17
- Decreased white blood cells: 16
- Decreased appetite: 16
- Pyrexia: 14
- Increased ALT: 11
- Increased AST: 9
- Hand–foot syndrome: 1

Grade ≥ 3 AEs in ≥ 2% of Pts

- Anemia: 16
- Neutropenia: 9
- Decreased white blood cells: 10
- Fatigue: 3
- Leukopenia: 2
- Decreased platelet count: 2
- Increased AST: 2
- Dyspnea: 1
- Headache: 1
- Hand–foot syndrome: 2

Phase II ABRAZO: Talazoparib in \textit{gBRCA1/2} Mutation–Positive MBC

- A 2-stage study of talazoparib (1.0 mg/day) in pts with \textit{gBRCA1/2} mutation–positive MBC and ECOG PS 0-1; primary endpoint: ORR
  - Cohort 1: Response to platinum-based therapy, PD > 8 wks after last dose (n = 48)
  - Cohort 2: ≥ 3 cytotoxic regimens (n = 35); no prior platinum for metastatic disease

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Cohort 1 (n = 48)</th>
<th>Cohort 2 (n = 35)</th>
<th>Total (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>21 (10-35)</td>
<td>37 (22-55)</td>
<td>28 (18-39)</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2 (4)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (17)</td>
<td>13 (37)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>SD</td>
<td>18 (38)</td>
<td>18 (51)</td>
<td>36 (43)</td>
</tr>
<tr>
<td>PD</td>
<td>18 (38)</td>
<td>4 (11)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (4)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>
ABRAZO: Survival in Pts With Prior Platinum (Cohort 1)

**PFS**
- Subjects, N: 49
- Events, n (%): 44 (89.8)
- Censored, n (%): 5 (10.2)
- Median PFS, mos (95% CI): 4.0 (2.8-5.4)

**OS**
- Subjects, N: 49
- Events, n (%): 36 (73.5)
- Censored, n (%): 13 (26.5)
- Median OS, mos (95% CI): 12.7 (9.6-15.8)
ABRAZO: Survival in Pts With ≥ 3 Lines but No Prior Platinum (Cohort 2)

**PFS**

- Subjects, N: 35
- Events, n (%): 30 (85.7)
- Censored, n (%): 5 (14.3)
- Median PFS, mos (95% CI): 5.6 (5.5-7.8)

**OS**

- Subjects, N: 35
- Events, n (%): 22 (62.9)
- Censored, n (%): 13 (37.1)
- Median OS, mos (95% CI): 14.7 (11.0-24.4)
Positive Results with the oral PARP inhibitor, talazoparib

• Talazoparib (TALA) is a highly potent dual-mechanism PARP inhibitor
  – Inhibits the PARP enzyme; preventing repair of DNA damage, and, resulting in cell death

• Phase 2 ABRAZO trial showed encouraging efficacy/safety in patients with germline BRCA1/2 mutations and prior platinum therapy or at least 3 prior cytotoxic regimens
  • ORR of 21% (10, 35) in patients with prior platinum therapy (n = 48); 37% (22, 55) in patients with ≥ 3 Lines, No Platinum (n = 35)

• EMBRACA is the largest randomized trial evaluating a PARP inhibitor in patients with advanced breast cancer and a germline BRCA1/2 mutation

Study Design: EMBRACA

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline BRCA1 or BRCA2 mutation*†

Stratification factors:
- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

Primary endpoint
- Progression-free survival by RECIST by central review

Key secondary efficacy endpoints
- Overall survival
- ORR by investigator
- Safety

Exploratory endpoints
- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

Phase 3, international, open-label, randomized study conducted in 16 countries and 145 sites

**Primary Endpoint: PFS by Central Review**

<table>
<thead>
<tr>
<th></th>
<th>TALA (n = 287)</th>
<th>Overall PCT (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>186 (65%)</td>
<td>83 (58%)</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>8.6 (7.2-9.3)</td>
<td>5.6 (4.2-6.7)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.54, 95% CI 0.41-0.71</td>
<td>P &lt; .0001</td>
</tr>
</tbody>
</table>

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Conclusions

• With a median follow up of 11.2 months, the PFS in the talazoparib group was 8.6 months compared to 5.6 months in the PCT group. (HR of 0.54 and a p<0.0001)
• Subgroup analysis all favored treatment with talazoparib.
• In preplanned subgroup analysis of patients with previously treated CNS metastases, the PFS in the talazoparib group was significantly longer at 5.7 months versus 1.6 months in the PCT group (HR 0.32).
• Secondary endpoint of overall survival did not meet statistical significance, however, there was a late separation of the curve and OS will be re-evaluated with a longer duration of follow up.
• 12 (5.5%) complete responses in the talazoparib group compared to none in the PCT group.
• Objective response rate in the talazoparib arm was 62.6% compared to 27.2% in the PCT arm.
• The primary adverse events for talazoparib is anemia and neutropenia
  – rate of febrile neutropenia was very low (0.3%).
  – common nonhematologic toxicities included fatigue, nausea, alopecia and headaches, the majority being grade 1 and 2
• Patient reported global health status showed an improvement in patients on the talazoparib versus a decrease in the global health status in patients treated in the PCT arm
• Authors concluded that talazoparib met its primary endpoint with increase in PFS compared to PCT
When to Test for *BRCA1/2* Mutations in MBC

- Pts diagnosed at young age, with specific subtypes, or with family history of breast or ovarian cancer should be referred for genetic testing and counseling

<table>
<thead>
<tr>
<th>Pt Factors</th>
<th>Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 yrs of age at diagnosis of BC</td>
<td>First-degree relative diagnosed with BC at &lt; 50 yrs of age</td>
</tr>
<tr>
<td>≤ 60 yrs of age at diagnosis of TNBC</td>
<td>≥ 2 first- or second-degree relatives diagnosed with BC at any age</td>
</tr>
<tr>
<td>Diagnosis of bilateral BC</td>
<td>Any male relative diagnosed with BC</td>
</tr>
<tr>
<td>History of ovarian cancer at any age or in any first- or second-degree relative</td>
<td>≥ 1 grandparent of Ashkenazi Jewish heritage</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
CALGB 40502/NCCTG N063H: Randomized Phase III Trial of Weekly Paclitaxel Compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel or Ixabepilone ± Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Rugo HS et al. *Proc ASCO 2012; Abstract CRA1002.*
CALGB 40502–NCCTG N063H Trial Design

Eligibility (n = 799)
- No prior chemotherapy for advanced breast cancer (BC)
- ≥12 mo from adjuvant taxanes
- Peripheral neuropathy ≤Grade 1
- Treated/stable brain metastases
- ECOG PS ≤1

1:1:1

Nab paclitaxel
150 mg/m² (qwk) + bevacizumab
10 mg/kg (q2wk)

Restage q2 cycles until PD

Paclitaxel
90 mg/m² (qwk) + bevacizumab
10 mg/kg (q2wk)

Ixabepilone
16 mg/m² (qwk) + bevacizumab
10 mg/kg (q2wk)

 Patients could stop CT and continue bevacizumab alone after 6 cycles if stable or responding disease

Rugo HS et al. Proc ASCO 2012;Abstract CRA1002.
Assessed for eligibility (N = 799)

Randomly assigned (n = 799)

Allocated to paclitaxel arm (n = 283)
- Received intervention (n = 275)
- Did not receive intervention (n = 8)

Allocated to nab-paclitaxel arm (n = 271)
- Received intervention (n = 267)
- Did not receive intervention (n = 4)

Allocated to ixabepilone arm (n = 245)
- Received intervention (n = 241)
- Did not receive intervention (n = 4)

Lost to follow-up (n = 13)
- Withdrew consent (n = 13)
- Unknown reason (n = 0)

Discontinued intervention (n = 258)
- Progression or death (n = 137)
- Adverse event (n = 39)
- Withdrew consent (n = 35)
- Alternative therapy (n = 12)
- Complicating illness (n = 6)
- Other (n = 29)

Lost to follow-up (n = 9)
- Withdrew consent (n = 9)
- Unknown reason (n = 0)

Discontinued intervention (n = 259)
- Progression or death (n = 118)
- Adverse event (n = 70)
- Withdrew consent (n = 36)
- Alternative therapy (n = 6)
- Complicating illness (n = 4)
- Other (n = 25)

Lost to follow-up (n = 8)
- Withdrew consent (n = 7)
- Unknown reason (n = 1)

Discontinued intervention (n = 238)
- Progression or death (n = 139)
- Adverse event (n = 17)
- Withdrew consent (n = 35)
- Alternative therapy (n = 7)
- Complicating illness (n = 4)
- Other (n = 5)

Analyzed (n = 275)

Analyzed (n = 267)

Analyzed (n = 241)
Updated data on SABCS 2017

Interaction tests: 1. p=0.0018; 2. p=0.0073; 3. p=0.96; 4. p=0.92 mo: months; HR: hazard ratio

<table>
<thead>
<tr>
<th></th>
<th>P (mo)</th>
<th>NP (mo)</th>
<th>NP to P; HR (95% CI)</th>
<th>Ix (mo)</th>
<th>Ix to P, HR (95% CI)</th>
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<tbody>
<tr>
<td>TNBC, PFS</td>
<td>6.4</td>
<td>7.4</td>
<td>0.79 (0.55-1.12)</td>
<td>5.6</td>
<td>1.39 (0.99-1.96)</td>
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<tr>
<td>HR+, PFS</td>
<td>12.2</td>
<td>9.6</td>
<td>1.29 (1.04-1.59)</td>
<td>8</td>
<td>1.5 (1.21-1.86)</td>
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<tr>
<td>TNBC, OS</td>
<td>15.3</td>
<td>21</td>
<td>0.74 (0.51-1.07)</td>
<td>15.1</td>
<td>1.28 (0.9-1.82)</td>
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<tr>
<td>HR+, OS</td>
<td>33.2</td>
<td>26.6</td>
<td>1.25 (0.99-1.58)</td>
<td>25.4</td>
<td>1.35 (1.07-1.71)</td>
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PANACEA Trial

Screening: unresectable locoregional or metastatic breast cancer overexpressing HER2

Submit an FFPE block from core biopsy for central testing

Central Testing:
HER2 by IHC

HER2 neg: not eligible
HER2 pos: Central PD-L1 testing

PD-L1 neg: enroll 15 patients in phase II
PD-L1 positive: enroll 40 patients in phase II

Phase Ib: dose finding for MK-3475 in 3+3 design — Phase II 200mg

Treatment in 3 week cycles:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 etc.</th>
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<tbody>
<tr>
<td>T</td>
<td>T</td>
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<td>M</td>
</tr>
</tbody>
</table>

T: trastuzumab 6mg/kg
M: MK-3475 200mg

Tissue Samples:
at enrollment:
FFPE block Fresh frozen block *
* if feasible

Blood samples:
whole blood plasma prior to cycles 1, 3, 5 and then every 3 cycles, and 30 days after end of tx

PANACEA (SG 45-13/BIG 4-13/KEYNOTE-014) accrued patients with centrally confirmed HER2-positive breast cancer, ECOG performance status of 0 or 1, and measurable disease per RECIST 1.1. There was no limit on the number of prior systemic therapies, and patients had to have progressed on trastuzumab (Herceptin) or T-DM1 (ado-trastuzumab emtansine; Kadcyla).
The combination of pembrolizumab (Keytruda) and trastuzumab (Herceptin) reached an objective response rate (ORR) of 15.2% in patients with trastuzumab-resistant, PD-L1–positive, HER2-positive breast cancer.

Results from the phase Ib/II PANACEA trial also showed that pembrolizumab/trastuzumab achieved a disease control rate of 24% in PD-L1–positive patients. Further, stromal tumor infiltrating lymphocytes (sTILs) were identified as a potential predictive marker. Among patients with sTIL levels ≥5%, ORR was 39% versus 5% in patients with sTIL levels <5%.
Figure 3: Overall study design
MANTA trial

- Adding vistusertib (AZD2014) to fulvestrant did not improve progression-free survival (PFS) among women with estrogen receptor–positive (ER+) advanced or metastatic breast cancer, according to findings from the phase 2 MANTA trial presented at the 2017 San Antonio Breast Cancer Symposium.1

- The authors noted no PFS benefit after adding the dual mTORC1/2 inhibitor to fulvestrant, though they did find that adding everolimus to fulvestrant improved PFS.

- In addition to MANTA Study, everolimus + fulvestrant has shown benefit in other well-designed trials: TAMROD and BOLERO-2.
GS5-06. A U.S. Food and Drug Administration pooled analysis of outcomes of older women with hormone-receptor positive metastatic BC treated with **CDK4/6 inhibitor** as initial endocrine based therapy.

- Little is known about the safety and efficacy of CDK 4/6 inhibitors in patients > 70 years old, as older patients are historically underrepresented in BC clinical trials, including those for CDK 4/6 inhibitor agents.

- This pooled analysis of outcomes of older women with HR positive, HER2 negative, metastatic BC found that this patient population benefits from use of CDK4/6 inhibitors as initial endocrine based therapy. As expected, the severity of adverse events and rates of dose modifications and interruptions increased with patients over 65 years, and even more so with patients over 70 years old.