Novel Therapies for Triple Negative, HER2+ and ER+ Breast Cancer

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Baylor University Medical Center
Texas Oncology
US Oncology
## Comprehensive molecular portraits of human breast tumours

*The Cancer Genome Atlas Network*

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Basal-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER(^+)/HER2(^-) (%)</td>
<td>10</td>
</tr>
<tr>
<td>HER2(^+) (%)</td>
<td>2</td>
</tr>
<tr>
<td>TNBCs (%)</td>
<td>80</td>
</tr>
<tr>
<td>TP53 pathway</td>
<td>TP53 mut (84%); gain of MDM2 (14%)</td>
</tr>
<tr>
<td>PIK3CA/PTEN pathway</td>
<td>PIK3CA mut (7%); PTEN mut/loss (35%); INPP4B loss (30%)</td>
</tr>
<tr>
<td>RB1 pathway</td>
<td>RB1 mut/loss (20%); cyclin E1 amp (9%); high expression of CDKN2A; low expression of RB1</td>
</tr>
<tr>
<td>mRNA expression</td>
<td>Basal signature; high proliferation</td>
</tr>
<tr>
<td>Copy number</td>
<td>Most aneuploid; high genomic instability; 1q, 10p gain; 8p, 5q loss; MYC focal gain (40%)</td>
</tr>
<tr>
<td>DNA mutations</td>
<td>TP53 (84%); PIK3CA (7%)</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>Hypomethylated</td>
</tr>
<tr>
<td>Protein expression</td>
<td>High expression of DNA repair proteins, PTEN and INPP4B loss signature (pAKT)</td>
</tr>
</tbody>
</table>
Subtypes of TNBC and targeted therapy selection

No TNBC subtyping approach is yet of proven clinical utility

Basal1
Basal2
Immune Module
Mesenchymal
Mesenchymal Stem-like
Luminal Apocrine

Cell cycle, DNA damage
GFR, glycolysis, p63
B/TCR, cytokines, JAK/STAT
ECM receptors
TGF-β
Rho
Wnt/β-Cat
EMT
Stem cell markers
Luminal CK’s
AR
FOXA1
XBP1

Summary – Triple Negative Breast Cancer

- **Systemic neo/adjuvant chemotherapy**
  - Adjuvant anthracycline (TaxAC vs 6TC) improves DFS in TNBC
  - Addition of carboplatin to paclitaxel improves pCR rate with as yet unknown effects on DFS – reasonable for high risk pts
  - In patients who do not develop a pCR with preoperative chemotherapy, adjuvant treatment with capecitabine is a reasonable option

- **Promising Approaches**
  - Nab paclitaxel/carboplatin first-line metTNBC
  - PARP inhibitors gBRCA pts
  - AKT inhibitors
  - AR inhibitors
  - PD-1/PD-L1 inhibitors
ABC Trials Schema

Node+ or High Risk Node-Negative Stratification Variables
Number of + Nodes (0, 1-3, 4-9, 10+); Hormone Receptor (ER or PgR+, Both Negative)

ARM 1 (TaxAC Options)
A
TAC q 3 wk
B
AC q 3 wk
C
AC q 2 wk
D
AC q 2 wk

ARM 2 (TC)

TC q 3 wk

Arm 1 Options Per Study
- USOR 06-090 - 1A only
- NSABP B-46I/USOR 07132 - 1A only
- NSABP B-49 - investigator choice 1A-1D

Endocrine therapy for ER+ or PgR+ patients for minimum of 5 years

Presented by: Joanne L. Blum, MD, PhD.
ABC Trials: Invasive Disease Free Survival

Presented by: Joanne L. Blum, MD, PhD.

Years from Randomization

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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</thead>
<tbody>
<tr>
<td>Alive and Inv. Disease-free (%)</td>
<td>1575</td>
<td>1014</td>
<td>847</td>
<td>566</td>
<td>317</td>
<td>132</td>
<td></td>
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<tr>
<td></td>
<td>1599</td>
<td>1014</td>
<td>858</td>
<td>594</td>
<td>358</td>
<td>136</td>
<td></td>
</tr>
</tbody>
</table>

Alive and Inv. Disease-free (%)

- TC: 2094, 220 events, 88.2%
- TaxAC: 2062, 179 events, 90.7%

Δ = 2.5%

4 yr

Treatment | N   | Events | IDFS |
----------|------|--------|------|
TC        | 2094 | 220    | 88.2%|
TaxAC     | 2062 | 179    | 90.7%|

HR = 1.23, 95% CI (1.01-1.50) P = 0.04
ABC Trials: IDFS by Hormone and Nodal Status
Exploratory Analysis

HR Negative

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>N- TaxAC</td>
<td>459</td>
<td>37</td>
</tr>
<tr>
<td>N- TC</td>
<td>488</td>
<td>52</td>
</tr>
<tr>
<td>1-3N+ TaxAC</td>
<td>153</td>
<td>21</td>
</tr>
<tr>
<td>1-3N+ TC</td>
<td>119</td>
<td>28</td>
</tr>
<tr>
<td>4+N+ TaxAC</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>4+N+ TC</td>
<td>40</td>
<td>16</td>
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</table>

HR Positive

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>N- TaxAC</td>
<td>358</td>
<td>29</td>
</tr>
<tr>
<td>N- TC</td>
<td>378</td>
<td>22</td>
</tr>
<tr>
<td>1-3N+ TaxAC</td>
<td>771</td>
<td>46</td>
</tr>
<tr>
<td>1-3N+ TC</td>
<td>789</td>
<td>53</td>
</tr>
<tr>
<td>4+N+ TaxAC</td>
<td>279</td>
<td>35</td>
</tr>
<tr>
<td>4+N+ TC</td>
<td>280</td>
<td>49</td>
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</table>
## Role of Neoadjuvant Platinum in TNBC: Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>Backbone Regimen</th>
<th>No Carbo</th>
<th>Carboplatin</th>
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<tbody>
<tr>
<td>GeparSixto</td>
<td>315</td>
<td>Weekly paclitaxel + liposomal dox + bev</td>
<td>38%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>C406063</td>
<td>433</td>
<td>Sequential weekly paclitaxel – AC +/- bev</td>
<td>41%</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.0029</td>
</tr>
<tr>
<td>Tamura et al</td>
<td>75</td>
<td>Sequential weekly pacl +/- Carb AUC5 - CEF</td>
<td>26%</td>
<td>62%</td>
</tr>
<tr>
<td>Alba et al</td>
<td>94</td>
<td>EC – Doc +/- Carbo AUC6</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Von Minckwitz et al. Lancet Oncol 2014; Sikov et al. JCO 2014; Alba et al. BRCT 2012; Tamura et al. ASCO 2014, Abstract 1107
DFS: Effect of Carboplatin in TNBC

Logrank p = 0.0325
HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), p = 0.0350

PM 36/157 events
PMCb 21/158 events

3 yrs DFS 85.8%
3 yrs DFS 76.1%
CALGB 40603 – EFS for carboplatin vs. not

HR = 0.84 (0.58-1.22), p = 0.36

Proportion Event-Free

Years from Study Entry

<table>
<thead>
<tr>
<th>No Cb</th>
<th>Cb</th>
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<tbody>
<tr>
<td>218</td>
<td>225</td>
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<tr>
<td>185</td>
<td>202</td>
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<td>145</td>
<td>162</td>
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<td>94</td>
<td>101</td>
</tr>
<tr>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
NRG-BR003

Node-Positive or High-Risk Node-Negative Triple Negative Breast Cancer

Randomization

ACx4 → Paclitaxel qwk x 12

ACx4 → Paclitaxel qwk x 12 + Carboplatin beginning with WP

AC: 60 mg/m² /600 mg/m² (Std or DD AC); Paclitaxel: 80 mg/m² IV weekly; Carboplatin: AUC of 5 IV q3 weeks for 4 cycles
Efficacy of neoadjuvant carboplatin plus docetaxel in triple negative breast cancer: Combined analysis of two cohorts

**PATIENTS AND METHODS:**
- 190 patients with stage I-IIITNBC treated uniformly on two independent prospective cohorts (KU, Spain)
- Treatment regimen: Cb (AUC 6) + D (75mg/m2) given every 21 days X 6 cycles
  - all received pegfilgrastim or filgrastim

**RESULTS:**
- Median tumor size 35mm, 52% node pos, 16% BRCA1/2 mutation
- Stage: 33% stage III, 56% stage II, 11% stage I.
- pCR and RCB 0+1 rates were 55% and 68%, respectively
- Multivariable analysis - stage III disease (OR 0.35, p<0.001), T3-4 lesion (OR 0.39, p=0.003), associated with a lower pCR, but not age, BRCA ½ mutation, clinical nodal status; KU site associated with higher rate (OR 1.93, p=0.046)
- Toxicity - 21% 7% of patients, respectively, experienced at least one grade 3 or 4 adverse event.

**Reasonable option**
- Prior anthracycline or concern about anthracycline therapy
- Need for more convenient 3 weekly regimen
- Preexisting low grade neuropathy or high risk of neuropathy from weekly paclitaxel (eg, black race, diabetes)

CREATE-X: Trial Design

HER2-

NAC  Surgery

Pathology Non-pCR or node + (n=900)

Control: Standard therapy + Capecitabine

Stratification factors:
ER, Age, NAC, ypN, 5FU and institution

Capecitabine Therapy

Capecitabine (X): 2,500 mg/m²/day, po, day 1-14
Repeat every 3 weeks for 8 cycles

According to the safety interim analysis of the first 50 pts treated with 6 cycles of X, the IDMC recommended extending X to 8 cycles.

Toi M et al. Proc ASCO, 2016
Disease Free Survival

HR (95%CI) 0.70 (0.53-0.93)
One-sided p=0.00524 < 0.00671

5yr DFS
74.1% Capecitabine
67.7% Control

Toi M et al. Proc ASCO, 2016
<table>
<thead>
<tr>
<th>Category (n)</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (885)</td>
<td>0.70 (0.53-0.93)</td>
</tr>
<tr>
<td>Age &lt;50 (531)</td>
<td>0.72 (0.50-1.03)</td>
</tr>
<tr>
<td>Age 50- (354)</td>
<td>0.68 (0.45-1.04)</td>
</tr>
<tr>
<td>HR+ (561)</td>
<td>0.84 (0.57-1.23)</td>
</tr>
<tr>
<td>HR- (296)</td>
<td>0.58 (0.39-0.87)</td>
</tr>
<tr>
<td>ypNO (345)</td>
<td>0.88 (0.48-1.62)</td>
</tr>
<tr>
<td>ypN1 (339)</td>
<td>0.54 (0.36-0.83)</td>
</tr>
<tr>
<td>ypN2or3 (199)</td>
<td>0.82 (0.52-1.29)</td>
</tr>
<tr>
<td>Path grade 0-1b (482)</td>
<td>0.63 (0.45-0.88)</td>
</tr>
<tr>
<td>by NAC 2,3 (385)</td>
<td>0.84 (0.52-1.34)</td>
</tr>
<tr>
<td>Taxane + (849)</td>
<td>0.70 (0.53-0.93)</td>
</tr>
<tr>
<td>- (36)</td>
<td>0.87 (0.12-6.24)</td>
</tr>
<tr>
<td>5FU containing + (529)</td>
<td>0.74 (0.52-1.04)</td>
</tr>
<tr>
<td>- (356)</td>
<td>0.65 (0.42-1.02)</td>
</tr>
<tr>
<td>Japanese (599)</td>
<td>0.74 (0.53-1.02)</td>
</tr>
<tr>
<td>Korean (286)</td>
<td>0.63 (0.37-1.05)</td>
</tr>
</tbody>
</table>

Toi M et al. Proc ASCO, 2016
Overall Survival

HR (95%CI) 0.60 (0.40-0.92)

One-sided p<0.01

5yr OS
89.2% Capecitabine
83.9% Control

Toi M et al. Proc ASCO, 2016
Pt is On Study

Stratifying Biomarkers

Randomized

HER2 (+)

Weekly paclitaxel &
Trastuzumab
±
New Agent A, B, or C

AC → Surgery

Randomized

HER2 (−)

Weekly paclitaxel
±
New Agent C, D, or E

AC → Surgery

Stratifying Biomarkers (Established/Approved/IDE)

ER, PR
HER2 (IHC, FISH, RPPA, 44K-microarray)
MammaPrint 44K microarray
Preoperative MK-2206 AKT inhibitor

- 93 pts MK-2206 + weekly paclitaxel (then AC)
- 59 pts weekly paclitaxel alone (then AC)

- pCR TNBC pts 40% with MK-2206 vs 22% control

- 76% probability success MK-2206 phase 3 TNBC – GRADUATED

- RPPA biomarker analyses ongoing

Tripathy D. ASCO 2015
### Preoperative Neratinib

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR Rate (95% probability interval)</th>
<th>Probability Neratinib is Superior to Control</th>
<th>Predictive Probability of Success in Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neratinib</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>36% (29-43%)</td>
<td>30% (23-38%)</td>
<td>72%</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>55% (46-64%)</td>
<td>32% (22-43%)</td>
<td>94%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>14% (8-19%)</td>
<td>16% (10-21%)</td>
<td>39%</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>31% (24-37%)</td>
<td>17% (10-24%)</td>
<td>91%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ROC Established RIU Cutoff Value</th>
<th>pCR Rate Control Group</th>
<th>pCR Rate Neratinib Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TN samples in Neratinib Arms</td>
<td></td>
<td>30% (8/27)</td>
<td>37.5% (12/32)</td>
</tr>
<tr>
<td>TN samples in this study</td>
<td></td>
<td>31% (6/19)</td>
<td>40% (12/30)</td>
</tr>
<tr>
<td>EGFR Y1173 biomarker positive</td>
<td>4400</td>
<td>45.4% (4/11)</td>
<td>63% (10/16)</td>
</tr>
<tr>
<td>ERBB2 Y1248 biomarker positive</td>
<td>3100</td>
<td>36% (5/14)</td>
<td>62.5% (10/16)</td>
</tr>
</tbody>
</table>

Wulfskühle JD et al  ASCO 2015
### Veliparib/Carboplatin Graduates in the Triple Negative Signature

<table>
<thead>
<tr>
<th>SIGNATURE</th>
<th>Estimated pCR Rate</th>
<th>Probability Veliparib + Carbo is Superior to Control</th>
<th>Predictive Probability of Success in Phase 3</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimated pCR Rate (95% probability interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Veliparib/Carbo</td>
<td>Concurrent Control</td>
<td></td>
</tr>
<tr>
<td>All HER2-</td>
<td>33% (22-43%)</td>
<td>22% (10-35%)</td>
<td>92%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>14% (4-27%)</td>
<td>19% (6-35%)</td>
<td>28%</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>52% (35-69%)</td>
<td>26% (11-40%)</td>
<td>99%</td>
</tr>
</tbody>
</table>

I-SPY 2    Rugo et al, NEJM 2016
Novels Therapies for Metastatic Disease
**Trial design**

**TNT Trial**

ER-, PgR-/unknown & HER2- or known BRCA1/2
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

A Priori subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

---

**Carboplatin (C)**
AUC 6 q3w, 6 cycles
On progression, crossover if appropriate

---

**Docetaxel (D)**
100mg/m² q3w, 6 cycles
On progression, crossover if appropriate

---

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

---

**Carboplatin (C)**
AUC 6 q3w, 6 cycles

---

*Tutt et al. SABCS 2014; S3-01*
Objective response

**Randomised treatment - all patients (N=376)**

- Carboplatin: 59/188 (31.4%)
- Docetaxel: 67/188 (35.6%)

Absolute difference (C-D): -4.2% (95% CI -13.7 to 5.3)
Exact p = 0.44

**Crossover treatment - all patients (N=182)**

- Carboplatin: 21/92* (22.8%)
- Docetaxel (Cross over from Carboplatin): 23/90* (25.6%)

Absolute difference (D-C): -2.8% (95% CI -15.2 to 9.6)
Exact p = 0.73

*Denominator excludes those with no first progression and those not starting crossover treatment.

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Objective response – BRCA 1/2 status

Germline BRCA 1/2 Mutation (n=43)
- Carboplatin: 17/25 (68.0%)
- Docetaxel: 6/18 (33.3%)

No Germline BRCA 1/2 Mutation (n=273)
- Carboplatin: 36/128 (28.1%)
- Docetaxel: 53/145 (36.6%)

Absolute difference (C-D)
- 34.7% (95% CI 6.3 to 63.1) Exact p = 0.03
- -8.5% (95% CI -19.6 to 2.6) Exact p = 0.16

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01
Metastatic TNBC Exceptional Responders to First-Line Platinum

| Table 3. Clinical, Genetic, and Tumor Molecular Features of Long-Term Responders |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient | BRCA | Subtype | PIK3CA | p53 | p63/p73 | OS (months)* | Adjuvant Therapy | Therapy | Best Response | Site of Disease | Therapy After Platinum Treatment |
| 7 | WT | B | Missense mutation | Missense mutation | < 2 | 69 | None | Cisplatin | CR | Breast, lymph nodes | Surgery, chemotherapy, and radiation |
| 28 | WT | N | WT | WT | > 2 | 58 | Anthracycline-taxane | Cisplatin | PR | Lymph nodes | None |
| 45 | WT | X | WT | WT | X | 48 | None | Cisplatin | CR | Lung, breast, lymph nodes | Surgery, chemotherapy, and radiation |
| 53 | WT | B | WT | WT | Missense mutation | < 2 | 40 | Anthracycline-taxane | Cisplatin | PR | Lung | None |
| 69 | X | X | X | X | X | 41 | Anthracycline-taxane | Carboplatin | PR | Lung, lymph nodes | Radiation |
| 77 | WT | N | WT | Missense mutation | X | 34 | Anthracycline-taxane | Carboplatin | CR | Lymph nodes | Stereotactic radiosurgery to brain metastasis, chemotherapy |

4/34  highly durable ORR 11.7%  First-line cisplatin (overall ORR 35%)
2/35  highly durable ORR  5.7%  First-line carboplatin (overall ORR 23%)

TnAcity: Randomized Phase II Trial of Chemotherapy Doublets for First Line metTNBC

Figure 1. Study Design

STUDY DESIGN

First-line mTNBC
Female, age ≥ 18 y
ECOG PS 0 - 1
Measurable by RECIST
No grade ≥ 2 peripheral neuropathy

Stratification factors
- Phase II: DFI (≤ 1 year vs > 1 year)
- Phase III: DFI (≤ 1 year vs > 1 year); prior adjuvant/neoadjuvant taxane treatment (yes/no)

Yardley D et al. SABCS 2016, abst 874
TnAcity: PFS and OS First Line metTNBC

**Figure 2. Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>nab-P/C</th>
<th>nab-P/G</th>
<th>G/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, median, months</td>
<td>7.4</td>
<td>5.4</td>
<td>6.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>—</td>
<td>0.60 (0.39 - 0.93)*</td>
<td>0.61 (0.39 - 0.94)*</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>12-month PFS rate, %</td>
<td>27</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

**Figure 3. Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>nab-P/C</th>
<th>nab-P/G</th>
<th>G/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median, months</td>
<td>16.4</td>
<td>12.1</td>
<td>12.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>—</td>
<td>0.66 (0.42 - 1.04)*</td>
<td>0.74 (0.48 - 1.16)*</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>0.07</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Yardley D et al. SABCS 2016, abst 874
PARP inhibitors in gBRCA mutated cancer

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial

Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Banu Arun, Niklas Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

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Efficacy and tolerability of veliparib + carboplatin + paclitaxel in patients with BRCA1 or BRCA2 mutations in mBC

- Breast cancers with BRCA1/2 mutations -- defects in homologous recombination DNA repair mechanisms, are sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors
- The PARP inhibitor veliparib effective in early trials in combination with carboplatin and paclitaxel
- BROCADE is a randomised, placebo-controlled Phase II trial of veliparib, carboplatin and paclitaxel in locally recurrent or mBC with a BRCA1/2 mutation

**LR or mBC with BRCA1/2 mutation (N = 290)**

- Veliparib + carboplatin + paclitaxel (n=97)
- Placebo + carboplatin + paclitaxel (n=99)
- Veliparib + temozolomide (n=94)

**HS Han, et al. Oral presentation, Abstract S2-05  SABCS 2016**
Veliparib + carboplatin + paclitaxel: PFS

Primary analysis

<table>
<thead>
<tr>
<th>Placebo + C/P</th>
<th>Veliparib + C/P</th>
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</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>12.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(9.3–14.5)</td>
</tr>
<tr>
<td>HR</td>
<td>0.789</td>
</tr>
<tr>
<td>p value</td>
<td>(0.536–1.162)</td>
</tr>
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</table>

Number at risk

<table>
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<tr>
<th>Placebo + C/P</th>
<th>Veliparib + C/CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 98</td>
<td>n = 95</td>
</tr>
<tr>
<td>Number at risk</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>95</td>
</tr>
</tbody>
</table>
Stage 1 Phase II Trial of Enzalutamide in AR+ metTNBC

71 yo TNBC 5-year DFI
2 prior regimens MBC
CR 32+ weeks on Rx

73 yo TNBC 6-year DFI
First Line MBC
48+ weeks on RX

Figure 4. Clinical Benefit Rate at 16 and 24 Weeks in Stage 1 Evaluate Patients

A Prescreened population: 79% of TNBC tissue expressed some AR; 55% of TNBC tissue expressed AR ≥ 10%
Summary – Triple Negative Breast Cancer

- **Systemic neo/adjuvant chemotherapy**
  - Adjuvant anthracycline (TaxAC vs 6TC) improves DFS in TNBC
  - Addition of carboplatin to paclitaxel improves pCR rate with as yet unknown effects on DFS – reasonable for high risk pts
  - In patients who do not develop a pCR with preoperative chemotherapy, adjuvant treatment with capecitabine is a reasonable option

- **Promising Approaches**
  - Nab paclitaxel/carboplatin first-line metTNBC and ?neoadjuvant
  - PARP inhibitors gBRCA pts
  - AKT, AR and PD-1/PD-L1 inhibitors
  - ADCs against Trop2 (sacituzumab) and GPNMB (glembatumumab)
Optimizing Therapy for HER2+ Breast Cancer
HER2+ Breast Cancer Following Adjuvant Trastuzumab: Risk of Locoregional or Distant Recurrence

- Approximately 20% of patients diagnosed with breast cancer are HER2+\(^a\) (~35,000 patients annually in the US\(^b\))

- Trastuzumab has dramatically improved the outcome of HER2+ breast cancer\(^c\)

- Despite these advances,
  - 16-20+% pts recur with invasive breast cancer within 8 to 10 years after initial diagnosis\(^d,e\)

- No proven curative therapy for locally recurrent or metastatic HER2+ breast cancer following adjuvant trastuzumab

Focal HER2 Amplification
CEP17

HER2
Current HER2+ Targeted Treatments

Trastuzumab
Ado-trastuzumab emtansine
Pertuzumab
Lapatinib

HER2
HER1/3/4
PI3K
AKT
mTOR

Angiogenesis
Growth and proliferation
Metabolism

ER
CoA
ERE

Gene transcription

B-31/N9831 Cumulative Incidence of Distant Recurrence as a First Event

ER and/or PR Positive

ER and PR Negative

San Antonio Breast Cancer Symposium, December 4-8, 2012
Standard Trastuzumab-Based Adjuvant Therapy in HER2+ Breast Cancer (BCIRG 006)

Disease Free Survival

One-quarter of patients remain at risk for DFS event after adjuvant trastuzumab therapy

Pertuzumab and trastuzumab have complementary mechanisms of action.

**Trastuzumab:**
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

**Pertuzumab:**
- Inhibits ligand-dependent HER2 dimerization and signaling
- Suppresses multiple HER signalling pathways
- Activates ADCC

Patients with HER2-positive MBC centrally confirmed (N=808)

Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

Study dosing q3w:
- Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
- Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
- Docetaxel: 75 mg/m2, escalating to 100 mg/m2 if tolerated

HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PD, progressive disease
Significant improvement in OS in favour of Pertuzumab arm
Confirmatory Overall survival analysis
(Median follow-up: 30 month)

HR=0.66
95% CI 0.52–0.84
p=0.0008

* Stopping boundary for concluding statistical significance at this second interim analysis was p≤0.0138
NeoSphere: Adjuvant Component Study Design

Patients with operable or locally advanced/inflammatory HER2-positive BC

Chemo-naive & primary tumors >2 cm (N=417)

Study dosing: q3w x 4

TD (n=107)
trastuzumab (8® 6 mg/kg)
docetaxel (75® 100 mg/m²)

PTD (n=107)
pertuzumab (840® 420 mg)
trastuzumab (8® 6 mg/kg)
docetaxel (75® 100 mg/m²)

PT (n=107)
pertuzumab (840® 420 mg)
trastuzumab (8® 6 mg/kg)

PD (n=96)
pertuzumab (840® 420 mg)
docetaxel (75® 100 mg/m²)

FEC q3w x 3
trustuzumab q3w cycles 5–17

docetaxel q3w x 4
FEC q3w x 3
trustuzumab q3w cycles 5–17

FEC q3w x 3
trustuzumab q3w cycles 5–21


FEC, 5-fluorouracil, epirubicin, and cyclophosphamide
# NEOSPHERE: Baseline Characteristics

*High-risk population, balanced across arms*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>50</td>
<td>50</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Hormone receptor negative, %</td>
<td>53.3</td>
<td>53.3</td>
<td>51.9</td>
<td>52.1</td>
</tr>
<tr>
<td>Median tumor size, (cm)</td>
<td>5.0</td>
<td>5.5</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Node-positive, %</td>
<td>70.1</td>
<td>70.1</td>
<td>70.8</td>
<td>70.8</td>
</tr>
<tr>
<td>Locally advanced/inflammatory, %</td>
<td>40.1</td>
<td>39.2</td>
<td>39.2</td>
<td>37.5</td>
</tr>
</tbody>
</table>

NEOSPHERE

Hormone receptor status – tpCR rates higher with P+H+T
Aphinity (IBCSG 39-11 / BIG 4-11)
Rationale for Extended Adjuvant Neratinib

Neratinib is active against metastatic HER2+ BC previously treated with trastuzumab\textsuperscript{a}

\textsuperscript{a}Burstein H et al. J Clin Oncol 28:1301-7, 2010
ExteNET: final study design

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab & chemotherapy
- Completed trastuzumab ≤1 year prior to study entry
- Lymph node positive or non-pCR after neoadjuvant therapy
- ER/PR status known

1:1 randomization

Part A
1-year follow-up for iDFS
Neratinib x 1 year
240 mg/day

Part B
5-year follow-up for iDFS
Placebo x 1 year

Part C
Overall survival

Primary analysis: invasive DFS (iDFS) in ITT population (n=2840)
- iDFS at 2 years: HR=0.67 (0.50–0.91); p=0.009
  - Hormone receptor-positive (n=1631; 57.4%); HR=0.51; p=0.001
  - Centrally-confirmed HER2-positive 60% (n=1463; 51%); HR=0.51; p=0.002

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3-year iDFS analysis: Hormone receptor status

Hormone receptor-positive

Two-sided *P-value = 0.003
HR (95% CI) = 0.57 (0.39–0.82)

Disease-free survival (%)

Months after randomization

No. at risk
Neratinib 816 746 710 682 651 581 454 445 418 353
Placebo 815 777 745 709 637 594 494 472 445 367

Hormone receptor-negative

Two-sided *P-value = 0.938
HR (95% CI) = 0.98 (0.67–1.45)

Disease-free survival (%)

Months after randomization

No. at risk
Neratinib 604 556 537 514 426 329 316 292 247
Placebo 605 573 542 514 458 362 350 328 274

* p value descriptive

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3-year iDFS analysis:
Hormone receptor-positive & centrally confirmed HER2+

Two-sided *P-value <0.001
HR [95% CI] = 0.43 (0.26–0.70)

No. at risk
Neratinib 455 426 410 398 342 258 252 237 200
Placebo 448 426 406 385 336 275 262 245 205

* p value descriptive
Trastuzumab Emtansine (T-DM1): Mechanism of Action

Trastuzumab-specific MOA
- Antibody-dependent cellular cytotoxicity (ADCC)
- Inhibition of HER2 signaling
- Inhibition of HER2 shedding

Antibody-dependent cellular cytotoxicity (ADCC)

Inhibition of HER2 signaling

Inhibition of HER2 shedding

## Overall Survival: T-DM1 vs capecitabine/lapatinib

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>25.1</td>
<td>182</td>
</tr>
<tr>
<td>T-DM1</td>
<td>30.9</td>
<td>149</td>
</tr>
</tbody>
</table>

Stratified HR=0.682 (95% CI, 0.55, 0.85); \( P=0.0006 \)

Efficacy stopping boundary \( P=0.0037 \) or HR=0.727

---

**Data cut-off July 31, 2012; Unstratified HR=0.70 (\( P=0.0012 \)).**
Katherine Study – NSABP/German Breast Group

- HER2+, T1c-T4 / N0-3 / M0
- Neoadjuvant therapy
  - 6 cycles/16 weeks
  - Trastuzumab x 9 weeks
- Residual Invasive disease

- Trastuzumab
  - 6 mg/kg q 3 weeks x 14
- T-DM1
  - 3.6 mg/kg q 3 weeks x 14

N = 1484

Enrollment: completed

Primary Endpoint: Invasive-Free Survival
Secondary Endpoints: DFS, OS, DDFS, Safety, QOL
A ≥30% reduction in the SLDs of target CNS lesions was observed in 43% of patients.

CBR responder
- Yes (n=54)
- No (n=72)

CBR, the proportion of patients whose best response was CR, PR or SD ≥6 months.
25 Patients with HER2 Somatic Mutations

- Each blue circle represents a patient.
- From 8 publications with a total of 1,499 patients.
- 20% of patients have mutations at amino acids 309 or 310.
- 68% of patients have mutations at amino acids 755-781.
27% new HER2 Alterations met ILC

ERBB2-mutant breast cancer (Neratinib monotherapy): Tumor assessments

Breast Cancer Cohort

RECIST

PET Response Criteria

* Denotes patient that progressed with amplified ERBB2
Summary: HER2+ Breast Cancer

- Alternate chromosome 17 probes can resolve equivocal FISH cases
- Preoperative TCHP for T2+ or N1+ disease – APHINITY results soon
- Neratinib extended therapy improves PFS in ER+ HER2+ disease
- Taxane + trastuzumab + pertuzumab standard first line MBC Rx
- T-DM1 second line Rx (no data post-THP)
- Capecitabine + lapatinib or trastutumab + lapatinib --- continue HER2-targeted therapy throughout metastatic course
- HER2 mutations/amplicons detected in MBC – HER2-directed Rx may be of benefit
Clinical Markers Predictors of Resistance to Endocrine Therapy

- Disease free interval from adjuvant therapy
- Duration of response
- Prior treatment
- HER2 amplification
- Lower ER expression
Need for improved hormone therapy with minimal toxicity

**FACT**: TTP

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Anastrozole</th>
<th>Anastrozole + fulvestrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>256</td>
<td>258</td>
</tr>
<tr>
<td>1</td>
<td>148</td>
<td>149</td>
</tr>
<tr>
<td>3</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>48</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**SWOG 0226**: PFS

- Median Progression-free Survival
  - Combination, 15.0 mo (95% CI, 13.2–18.4)
  - Anastrozole, 13.5 mo (95% CI, 12.1–15.1)

- Hazard ratio, 0.80 (95% CI, 0.68–0.94)

- P = 0.007 by stratified log-rank test

---

## Comparison of First Line AI ± Fulvestrant Trials

<table>
<thead>
<tr>
<th></th>
<th>FACT¹</th>
<th>SWOG 0226²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Patients</strong></td>
<td>514</td>
<td>707</td>
</tr>
<tr>
<td><strong>De Novo Metastatic Disease</strong></td>
<td>13%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Prior Adjuvant Chemotherapy</strong></td>
<td>45%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Prior Adjuvant Endocrine Therapy (TAM)</strong></td>
<td>68%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Prior Adjuvant AI</strong></td>
<td>1.5%</td>
<td>excluded</td>
</tr>
<tr>
<td><strong>Median TTP/PFS Range (mo)</strong></td>
<td>10–11</td>
<td>13–15</td>
</tr>
<tr>
<td><strong>PFS Benefit</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Median OS Benefit, (mo)</strong></td>
<td>No, 37.8 vs. 38.2 mos</td>
<td>Yes, 41.3 vs 47.7 mos</td>
</tr>
</tbody>
</table>

Fulvestrant 500 mg IM on Day 0 followed by 250 mg IM Day 14 and 28 then 250 mg every 28 days

FALCON: (Fulvestrant and Anastrozole Compared in hormonal therapy Naïve advanced breast cancer)

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

Randomised, double-blind, parallel-group, international, multicentre study

Follow-up for disease progression and survival

Randomisation of 450 patients was planned to achieve 306 progression events; if the true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test)

Stratification factors: prior chemotherapy for advanced disease (yes / no); measurable vs. non-measurable disease (at baseline); locally advanced vs. metastatic disease

Subgroup analysis of PFS for pre-defined baseline covariates

Primary endpoint: PFS\(^a\)

Secondary endpoints

- OS\(^b\)
- ORR
- CBR
- DoR, EDoR
- DoCB, EDoCB

- HRQoL (FACT-B total and TOI)
- Safety

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

Primary endpoint:
- PFS\(^a\)

Secondary endpoints

- OS\(^b\)
- ORR
- CBR
- DoR, EDoR
- DoCB, EDoCB

- HRQoL (FACT-B total and TOI)
- Safety

\(^a\)Assessed via RECIST 1.1, surgery / radiotherapy for disease worsening, or death; \(^b\)Interim analysis at the time of PFS analysis

EDoCB, expected duration of clinical benefit; EDoR, expected duration of response; FACT-B, Functional Assessment of Cancer Therapy – Breast; TOI, Trial Outcome Index
FALCON: PRIMARY ENDPOINT, PFS

HR 0.797 (95% CI 0.637, 0.999); p=0.0486

Median PFS
Fulvestrant: 16.6 months
Anastrozole: 13.8 months

Proportion of patients alive and progression free

Number of patients at risk:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fulvestrant</th>
<th>Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>230</td>
<td>232</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

A circle represents a censored observation
FALCON: PFS IN PATIENTS WITH OR WITHOUT VISCERAL DISEASE

Without visceral disease

- Fulvestrant (n=95)
- Anastrozole (n=113)

HR 0.59 (95% CI 0.42, 0.84)
Median PFS
- Fulvestrant: 22.3 months
- Anastrozole: 13.8 months

With visceral disease

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

HR 0.99 (95% CI 0.74, 1.33)
Median PFS
- Fulvestrant: 13.8 months
- Anastrozole: 15.9 months

Post hoc interaction test p<0.01
A circle represents a censored observation
**N = 724**
- Postmenopausal women
- ER+, HER2-unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole

**Endpoints**
- **Primary**: PFS (local assessment)
- **Secondary**: OS, ORR, CBR, QOL, safety, PK
- **Exploratory**: Biomarkers

**Stratification:**
- Sensitivity to prior hormone therapy
- Presence of visceral metastases

Abbreviations: BC, breast cancer; CBR, clinical benefit rate; ER+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; HER2−, human epidermal growth factor receptor-2-negative; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.

BOLERO-2 (18-mo): Final PFS Analysis Based on Local Assessment—Met Primary Endpoint (4.6-mo Prolongation of PFS)

HR = 0.45 (95% CI, 0.38-0.54)
Log-rank $P < .0001$

Kaplan-Meier medians
EVE+EXE: 7.8 months
PBO+EXE: 3.2 months

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

PrECOG 0102

- Evaluated everolimus and fulvestrant vs fulvestrant + placebo (N=131)
- Advanced ER+, HER2-, post menopausal
- Previously treated with AI, or relapsing on AI
- PFS: 10.4 mos vs 5.1 mos (p=0.02)
- Expected toxicities
Reversible Histone Acetylation Regulates Gene Expression

Histone acetylation

Pol2

Activated Chromatin (hyper-acetylated histones)

HAT

Transcriptional Factors

Core histones

Acetyltransferases (HAT)

Histone acetylation

Repressed Chromatin (hypo-acetylated histones)

HDACs

Histone deacetylation

HDAC Inhibitor

mRNA

Cofactors

Repressed Chromatin

Yoo CB and Jones PA. Nat Rev Drug Discov. 2006;5:37
Entinostat and Exemestane

- Post-menopausal ER+ advanced breast cancer
- Progressed on/or relapsed while taking a NSAI

1:1

exemestane + entinostat

N = 130

NSAI setting
Bone only Region

Yardley et al 2013
Entinostat and Exemestane

PFS: 2.3 mos to 4.3 mos
HR 0.73 95% CI 0.5-1.07

mOS: 19.8 mos to 28.1 mos
HR 0.59 95% CI 0.36-0.97

Yardley et al 2013
Entinostat and Exemestane: Toxicity

Table 2. Most Common Adverse Events In the Safety Population

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Exemestane Plus Entinostat (n = 63)</th>
<th>Exemestane Plus Placebo (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any No. of Patients %</td>
<td>Grade 3 No. of Patients %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 48</td>
<td>7 11</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 40</td>
<td>3 5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 30</td>
<td>8 13</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13 21</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 21</td>
<td>3 5</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 19</td>
<td>1 2</td>
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<tr>
<td>Dyspnea</td>
<td>12 19</td>
<td>2 3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 19</td>
<td>1 2</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>12 19</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 17</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>10 16</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>10 16</td>
<td>1 2</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10 16</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 11</td>
<td>1 2</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 10</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

Yardley et al 2013
Entinostat and Exemestane: Phase III

**Stratify:**
- Setting in which patient developed resistance to prior non steroidal AI treatment (adjuvant vs. metastatic)
- Geographic region (USA vs. other)
- Visceral disease (yes vs. no)

**Randomize**

**Arm A**
- Exemestane 25 mg po, days 1-28
- Entinostat 5 mg po, days 1, 8, 15, and 22
- Treatment continued until progressive disease or unacceptable toxicity

**Arm B**
- Exemestane 25 mg po, days 1-28
- Placebo 5 mg po, days 1, 8, 15, and 22
- Treatment continued until progressive disease or unacceptable toxicity
Palbociclib: CDK 4/6 Inhibitor – Breast Panel

Subtype

- Luminal
- HER2 amplified
- Non-luminal/post EMT
- Non-luminal
- Immortalized

Palbociclib and Letrozole in Advanced Breast Cancer

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A Investigator Assessment

- Hazard ratio, 0.58 (95% CI, 0.46–0.72)
- Two-sided P<0.001

B Central Assessment

- Hazard ratio, 0.65 (95% CI, 0.51–0.84)
- Two-sided P=0.001

No. at Risk

- Palbociclib–Letrozole: 444, 395, 360, 328, 295, 263, 238, 154, 69, 29, 10, 2
- Placebo–Letrozole: 222, 171, 148, 131, 116, 98, 81, 54, 22, 12, 4, 2
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Palbociclib–Letrozole</th>
<th>Placebo–Letrozole</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomly assigned patients</td>
<td>444 (100)</td>
<td>222 (100)</td>
<td>0.58 (0.46–0.72)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>263 (59.2)</td>
<td>141 (63.3)</td>
<td>0.57 (0.43–0.74)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>181 (40.8)</td>
<td>81 (36.3)</td>
<td>0.57 (0.39–0.84)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>344 (77.5)</td>
<td>172 (77.3)</td>
<td>0.58 (0.45–0.74)</td>
</tr>
<tr>
<td>Asian</td>
<td>65 (14.6)</td>
<td>30 (13.3)</td>
<td>0.48 (0.27–0.87)</td>
</tr>
<tr>
<td>Site of metastatic disease at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>214 (48.2)</td>
<td>110 (49.5)</td>
<td>0.63 (0.47–0.85)</td>
</tr>
<tr>
<td>Nonvisceral</td>
<td>230 (51.8)</td>
<td>112 (50.5)</td>
<td>0.50 (0.36–0.70)</td>
</tr>
<tr>
<td>Prior hormonal therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>249 (56.1)</td>
<td>126 (56.8)</td>
<td>0.53 (0.40–0.70)</td>
</tr>
<tr>
<td>No</td>
<td>195 (43.9)</td>
<td>96 (43.2)</td>
<td>0.63 (0.44–0.90)</td>
</tr>
<tr>
<td>Disease-free interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly metastatic disease</td>
<td>167 (37.6)</td>
<td>81 (36.5)</td>
<td>0.67 (0.46–0.99)</td>
</tr>
<tr>
<td>≤12 mo</td>
<td>99 (22.3)</td>
<td>48 (21.6)</td>
<td>0.50 (0.33–0.76)</td>
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<tr>
<td>&gt;12 mo</td>
<td>178 (40.1)</td>
<td>93 (41.9)</td>
<td>0.52 (0.36–0.73)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>168 (37.8)</td>
<td>99 (44.6)</td>
<td>0.60 (0.43–0.85)</td>
</tr>
<tr>
<td>Europe</td>
<td>212 (47.7)</td>
<td>95 (42.8)</td>
<td>0.57 (0.41–0.80)</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>64 (14.4)</td>
<td>28 (12.6)</td>
<td>0.49 (0.27–0.87)</td>
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<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>257 (57.9)</td>
<td>102 (45.9)</td>
<td>0.65 (0.47–0.90)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>187 (42.1)</td>
<td>120 (54.1)</td>
<td>0.53 (0.39–0.72)</td>
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<tr>
<td>Bone-only disease at baseline</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>103 (23.2)</td>
<td>48 (21.6)</td>
<td>0.36 (0.22–0.59)</td>
</tr>
<tr>
<td>No</td>
<td>341 (76.8)</td>
<td>174 (78.4)</td>
<td>0.65 (0.51–0.84)</td>
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<tr>
<td>Measurable disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>338 (76.1)</td>
<td>171 (77.0)</td>
<td>0.66 (0.52–0.85)</td>
</tr>
<tr>
<td>No</td>
<td>106 (23.9)</td>
<td>51 (23.0)</td>
<td>0.35 (0.22–0.57)</td>
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<tr>
<td>Prior chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>213 (48.0)</td>
<td>109 (49.1)</td>
<td>0.53 (0.40–0.72)</td>
</tr>
<tr>
<td>No</td>
<td>231 (52.0)</td>
<td>113 (50.9)</td>
<td>0.61 (0.44–0.84)</td>
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<tr>
<td>Most recent therapy</td>
<td></td>
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<tr>
<td>Aromatase inhibitor</td>
<td>91 (20.5)</td>
<td>44 (19.8)</td>
<td>0.55 (0.34–0.88)</td>
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<td>Antiestrogen</td>
<td>154 (34.7)</td>
<td>75 (33.8)</td>
<td>0.56 (0.39–0.80)</td>
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<tr>
<td>No. of disease sites</td>
<td></td>
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<tr>
<td>1</td>
<td>138 (31.1)</td>
<td>66 (29.7)</td>
<td>0.51 (0.34–0.77)</td>
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<tr>
<td>≥2</td>
<td>306 (68.9)</td>
<td>156 (70.3)</td>
<td>0.61 (0.47–0.79)</td>
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<td>Histopathological classification</td>
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<td></td>
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<tr>
<td>Ductal carcinoma</td>
<td>356 (80.2)</td>
<td>184 (82.9)</td>
<td>0.59 (0.46–0.75)</td>
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<td>Lobular carcinoma</td>
<td>68 (15.3)</td>
<td>30 (13.3)</td>
<td>0.46 (0.26–0.78)</td>
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</tbody>
</table>

Finn RS et al NEJM 2016
### Qualitative Analysis

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>Favors PAL+LET</th>
<th>Favors PCB+LET</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>66</td>
<td>0.58 (0.46–0.72)</td>
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<tr>
<td>ER+</td>
<td>504</td>
<td>0.57 (0.44–0.74)</td>
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<tr>
<td>ER-</td>
<td>62</td>
<td>0.41 (0.22–0.75)</td>
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<tr>
<td>Rb+</td>
<td>512</td>
<td>0.53 (0.42–0.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rb-</td>
<td>51</td>
<td>0.68 (0.31–1.48)</td>
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<td></td>
</tr>
<tr>
<td>Cyclin D1+</td>
<td>549</td>
<td>0.56 (0.44–0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclin D1-</td>
<td>15</td>
<td>1.0 (0.29–3.46)</td>
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<tr>
<td>p16+</td>
<td>466</td>
<td>0.52 (0.40–0.67)</td>
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<tr>
<td>p16-</td>
<td>84</td>
<td>0.73 (0.39–1.36)</td>
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<tr>
<td>Ki-67 ≤20%</td>
<td>318</td>
<td>0.53 (0.38–0.74)</td>
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<tr>
<td>Ki-67 &gt;20%</td>
<td>235</td>
<td>0.57 (0.41–0.79)</td>
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<tr>
<td>HR= hazard ratio; LET= letrozole; PAL= palbociclib; PCB= placebo; PFS= progression-free survival</td>
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</table>

### Quantitative Analysis

<table>
<thead>
<tr>
<th>Percentile</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>Favors PAL+LET</th>
<th>Favors PCB+LET</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>666</td>
<td>0.58 (0.46–0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER status ≤25th</td>
<td>14</td>
<td>0.50 (0.32–0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>28</td>
<td>0.53 (0.37–0.74)</td>
<td></td>
<td></td>
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<tr>
<td>≥75th</td>
<td>14</td>
<td>0.65 (0.41–1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rb status ≤25th</td>
<td>15</td>
<td>0.57 (0.36–0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>24</td>
<td>0.46 (0.32–0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75th</td>
<td>16</td>
<td>0.63 (0.42–0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclin D1 status ≤25th</td>
<td>14</td>
<td>0.41 (0.26–0.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25th to &lt;75th</td>
<td>1</td>
<td>0.69 (0.48–1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75th</td>
<td>17</td>
<td>0.52 (0.34–0.78)</td>
<td></td>
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</tr>
<tr>
<td>p16 status ≤25th</td>
<td>14</td>
<td>0.74 (0.46–1.20)</td>
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<tr>
<td>&gt;25th to &lt;75th</td>
<td>25</td>
<td>0.62 (0.44–0.89)</td>
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<td></td>
</tr>
<tr>
<td>≥75th</td>
<td>8</td>
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</table>
Design of Phase III Study in Recurrent MBC (1023)-PALOMA-3

- HR+, HER2– ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

2:1 Randomization
N=521

Stratification:
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

Palbociclib
(125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)
n=347

Placebo
(3 wks on/ 1wk off) + Fulvestrant† (500 mg IM q4w)
n=174

- Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.

*All received goserelin.

†administered on Days 1 and 15 of Cycle 1.
PALOMA3: Primary Endpoint: PFS (ITT Population)

**Median PFS, months (95% CI)**
- **Palbociclib + Fulvestrant**: 9.2 (7.5, NE)
- **Placebo + Fulvestrant**: 3.8 (3.5, 5.5)

**HR (95% CI)**
- **0.422 (0.318, 0.560)**

**2-sided P value**
- **<0.000001**

Turner N et al NEJM 2015
NON-HEMATOLOGIC ADVERSE EVENTS
Regardless of study treatment relationship

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ribociclib + Letrozole n=334</th>
<th>Placebo + Letrozole n=330</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Nausea</td>
<td>52</td>
<td>2.4</td>
</tr>
<tr>
<td>Infections</td>
<td>50</td>
<td>3.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>2.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35</td>
<td>1.2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>33</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>3.6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>27</td>
<td>0.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>1.2</td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>0.3</td>
</tr>
<tr>
<td>Hot flush</td>
<td>21</td>
<td>0.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>20</td>
<td>2.1</td>
</tr>
<tr>
<td>Cough</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>1.5</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>0.6</td>
</tr>
<tr>
<td>ALT increased</td>
<td>16</td>
<td>7.5</td>
</tr>
<tr>
<td>AST increased</td>
<td>15</td>
<td>4.8</td>
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</table>

- In the ribociclib arm 10 (3.0%) patients experienced Grade 2 QTcF (481–500 ms) and 1 (0.3%) patient experienced Grade 3 QTcF (>500 ms); no dose reductions were required
A Phase III Randomized Double-blind, Placebo-controlled Study of Ribociclib in Combination With Fulvestrant for the Treatment of Postmenopausal Women With HR+/HER2– Advanced Breast Cancer Who Have Received No or Only One Line of Prior Endocrine Treatment

Postmenopausal women with HR+/HER2– ABC
No more than one line of endocrine therapy for advanced disease
No prior chemotherapy for advanced disease; (neo)adjuvant treatment allowed
No visceral crisis
N≈660

Randomization (2:1)
Stratification by:
- Presence of liver and/or lung metastases
- Prior endocrine therapy

Ribociclib (600 mg QD; 3-wks-on/1-wk-off) + fulvestrant (500 mg IM q4w)*
n≈440

Placebo (3-wks-on/1-wk-off) + fulvestrant (500 mg IM q4w)*
n≈220

Enrolment status: Ongoing
Study start date: Jun 2015
Estimated study completion: Apr 2020
Estimated primary completion date: Apr 2020

NCT02422615
A Phase III Randomized, Double-blind, Placebo-controlled Study of Ribociclib or Placebo in Combination With Tamoxifen and Goserelin or a Non-steroidal Aromatase Inhibitor (NSAI) and Goserelin for the Treatment of Premenopausal Women With HR+/HER2- Advanced Breast Cancer

Premenopausal women with HR+/HER2- ABC
No prior hormonal therapy for advanced disease
N=660

Randomization (1:1)

Stratification by:
- Presence of liver and/or lung metastases
- Prior chemotherapy for advanced disease
- Endocrine combination partner (tamoxifen or NSAI)

Ribociclib (600 mg QD; 3-wks-on/1-wk-off) + goserelin (3.6 mg SC q4w) + tamoxifen (20 mg QD) or NSAI (letrozole [2.5 mg QD] or anastrozole [1 mg QD])*
n≈330

Placebo (3-wks-on/1-wk-off) + goserelin (3.6 mg SC q4w) + tamoxifen (20 mg QD) or NSAI (letrozole [2.5 mg QD] or anastrozole [1 mg QD])*
n≈330

Enrolment status: Ongoing
Study start date: Nov 2014
Estimated study completion: Feb 2018
Estimated primary completion date: Feb 2018
MONARCH 1: Phase 2 Study Design

Previously-treated HR+/HER2- MBC

Abemaciclib 200 mg orally Q12H

Treatment continued until unacceptable toxicity or PD

♦ Primary objective
  • To evaluate abemaciclib with respect to confirmed objective response rate based on investigator assessment (per RECIST v1.1)

♦ Secondary objectives
  • Duration of response, progression-free survival, overall survival, clinical benefit rate, safety

♦ Statistical design
  • A sample size of 128 patients provides 82% power, assuming a true response rate of 25%, to exclude an ORR of ≤15% on the lower bound of the 95% CI at 12 months follow-up

♦ Clinical trial ID: NCT02102490
Median number of prior systemic regimens (any setting) was 5 (range 2-11)

100% of patients received taxanes in any setting

Median number of prior systemic regimens for metastatic disease was 3 (range 1-8)

<table>
<thead>
<tr>
<th>Endocrine Therapy for Metastatic Disease</th>
<th>N=132 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Regimens</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48 (36.4)</td>
</tr>
<tr>
<td>2</td>
<td>25 (18.9)</td>
</tr>
<tr>
<td>3</td>
<td>24 (18.2)</td>
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<table>
<thead>
<tr>
<th>Chemotherapy for Metastatic Disease</th>
<th>N=132 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Regimens</td>
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</tr>
<tr>
<td>1</td>
<td>67 (50.8)</td>
</tr>
<tr>
<td>2</td>
<td>64 (48.5)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.8)</td>
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</table>

Taxanes 91 (68.9)
Disease Control Rate (CR + PR + SD) = 67.4%

confirmed objective response rate (ORR = CR + PR) (95% CI)
CR: 0%
PR: 19.7%
stable disease ≥ 6 months: 22.7%
clinical benefit rate (CBR = ORR + SD ≥ 6 mos): 42.4%

progressive disease (n = 34)
stable disease (n = 63)
partial response (n = 26)
not assessed (n = 9)

assessments based on independent review were comparable

Abemaciclib 200 mg (N = 132)
confirmed objective response rate (ORR = CR + PR)
(95% CI) 19.7% (13.3, 27.5)

Dickler M. et al. J Clin Oncol 34, 2016 (suppl; abstr 510)
**A. Progression-free Survival**

- Patients/Events: 132/100
- Median, months: 5.95
- 95% CI: 4.21, 7.50

**B. Overall Survival**

- Patients/Events: 132/62
- Median, months: 22.32
- 95% CI: 17.7, NR

*Pts = patients, NR = not reached*
<table>
<thead>
<tr>
<th>Investigator Assessed TEAEs(a &gt;20%) (N=132)</th>
<th>Grade 1 %</th>
<th>Grade 2 %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
<th>All Grades %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>41.7</td>
<td>28.8</td>
<td>19.7</td>
<td>0</td>
<td>90.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>39.4</td>
<td>21.2</td>
<td>4.5</td>
<td>0</td>
<td>65.2</td>
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<tr>
<td>Fatigue</td>
<td>20.5</td>
<td>30.3</td>
<td>13.6</td>
<td>0</td>
<td>64.4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>28.0</td>
<td>14.4</td>
<td>3.0</td>
<td>0</td>
<td>45.5</td>
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<tr>
<td>Abdominal pain</td>
<td>22.0</td>
<td>14.4</td>
<td>2.3</td>
<td>0</td>
<td>38.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23.5</td>
<td>10.6</td>
<td>1.5</td>
<td>0</td>
<td>35.6</td>
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<tr>
<td>Headache</td>
<td>13.6</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
<td>20.5</td>
</tr>
<tr>
<td>Pain</td>
<td>12.1</td>
<td>6.8</td>
<td>1.5</td>
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</table>

<table>
<thead>
<tr>
<th>Lab abnormalities(b) TEAEs(a &gt;40%)</th>
<th>Grade 1 %</th>
<th>Grade 2 %</th>
<th>Grade 3 %</th>
<th>Grade 4 %</th>
<th>All Grades %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased(c) (CTCAE v 4.03: over baseline)</td>
<td>46.9</td>
<td>50.8</td>
<td>0.8</td>
<td>0</td>
<td>98.5</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>20.0</td>
<td>44.6</td>
<td>27.7</td>
<td>0</td>
<td>92.3</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>16.9</td>
<td>43.8</td>
<td>22.3</td>
<td>4.6</td>
<td>87.7(d)</td>
</tr>
<tr>
<td>Anemia</td>
<td>30.0</td>
<td>39.2</td>
<td>0</td>
<td>0</td>
<td>69.2</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4.6</td>
<td>23.1</td>
<td>13.8</td>
<td>0.8</td>
<td>42.3</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>28.9</td>
<td>10.2</td>
<td>2.3</td>
<td>0</td>
<td>41.4</td>
</tr>
</tbody>
</table>

\(a\) Abemaciclib is a competitive inhibitor of OCT2, MATE1, and MATE2-K, efflux transporters of creatinine; cystatin C calculated GFR was not raised. 
\(b\) Lab abnormalities listed, except platelet count decreased (N = 128). 
\(c\) Over baseline. 
\(d\) A patient who received cytotoxic chemotherapy within the 30-day follow-up period.
Abemaciclib (LY2835219): MONARCH 2

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without LY2835219, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

Women with HR+, HER2- Locally Advanced or Metastatic Breast Cancer (N=550)

Primary endpoint: Progression-Free Survival (PFS)

LY2835219 + Fulvestrant until PD

Placebo + Fulvestrant until PD

2:1

MARCH 20, 2017: Met its Primary Endpoint

NCT02107703
Evolution of ER+ Breast Cancer

- **Tamoxifen** (1977)
- **Astrazole** (1995)
- **Toremifene** (1997)
- **Letrozole** (1997)
- **Examestane** (1999)
- **Fulvestrant 250 mg** (2002)
- **Fulvestrant 500 mg** (2010)
- **Everolimus** (2012)
- **Palbociclib** (2015)
- **Toremifene 250 mg** (2002)
- **Fulvestrant 500 mg** (2010)

*Modified from Chmowski epub 2012*