SABCS 2015: Hormone receptor-positive breast cancer
GASCO Annual SABCS Review
January 9th 2016, Atlanta, GA

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Hematology and Medical Oncology,
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University of Wisconsin

Topics to cover

• Early stage ER-positive breast cancer
  – Lack of chemotherapy benefit (Abstract 1-06)
  – Adjuvant denosumab (Abstract 2-02)

• Metastatic ER-positive breast cancer
  – PI3-kinase inhibition (Abstract 6-01)
  – ESR mutations in hormone-resistance (Abstracts 2-06, 6-02)

• Novel therapeutic approaches
  – Pembrolizumab (Abstract 5-07)
  – Pre-operative palbociclib (Abstract 6-05)
High risk premenopausal Luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B randomized trial

Presenter: Torsten O. Nielsen, MD/PhD, FRCP
University of British Columbia, Canada

Abstract 1-06

Maj-Britt Jensen - Statistical Office, Danish Breast Cancer Group
Dongxia Gao, Samuel CY Leung, Samantha Burugu and Shuzhen Liu - Genetic Pathology Evaluation Centre, Vancouver Coastal Health Research Institute
Charlotte Levin Tykjaer Jorgensen and Eva Balslev - Department of Pathology, Herlev University Hospital
Bent Ejlertsen - Medical Oncologist and Director, Danish Breast Cancer Group

The DBCG77B Trial

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DBCG77B Trial: Prognosis by subtype

Disease-Free Survival (\%)

Overall Survival (\%)

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**San Antonio Breast Cancer Symposium - December 8-12, 2015**

**DBCG77B Trial: Prediction by subtype**

**Key Eligibility Criteria**
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)
- Age 18-75 years
- No PBI planned

**Statistical Design**
- RS 11-25: non-inferiority
  - 90% vs. <87% iDFS
  - 835 DFS events
- RS < 11
  - 95% vs. <93% DRFI at 10 years
  - 75 DRFI events

**Recurrence Score = 11**
- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

**Recurrence Score = 25**
- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%
Patient Characteristics and Treatment

<table>
<thead>
<tr>
<th></th>
<th>RS &lt; 11</th>
<th>RS 11-25</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. eligible patients</td>
<td>1626</td>
<td>6897</td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>58 years</td>
<td>55 years</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>70%</td>
<td>64%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Median tumor size</td>
<td>1.5 cm</td>
<td>1.5 cm</td>
<td>N.S.</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>34%</td>
<td>29%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>59%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>7%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>ER Expression</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
<td>N.S.</td>
</tr>
<tr>
<td>PgR Expression</td>
<td>98%</td>
<td>92%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>68%</td>
<td>72%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

- **Endocrine therapy in low RS group**: AI in 59%, tamoxifen in 34%, sequential tamoxifen-AI in 1%, OFS plus other therapy (3%), or other/unknown (3%)
- **Chemotherapy given to 6 patients in low RS group**: (1 of whom recurred)

Results: Kaplan Meier Plots and 5 Year Event Rates

5-year event rate in cancers with recurrence scores 10 or less did not receive chemotherapy

- 5 year iDFS Rate: 93.8% (95% CI 92.4%, 94.9%)
- 5 year DRFI Rate: 99.3% (95% CI 98.7%, 99.6%)
- 5 year RFI Rate: 98.7% (95% CI 97.9%, 99.2%)
- 5 year OS Rate: 98.0% (95% CI 97.5%, 98.6%)
Correlation between recurrence score and intrinsic subtype

<table>
<thead>
<tr>
<th>Recurrence Score</th>
<th>Luminal A (n = 123)</th>
<th>Luminal B (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>36</td>
<td>50</td>
</tr>
</tbody>
</table>

No benefit from chemotherapy  
Fan et al NEJM 2006

The Impact of Adjuvant Denosumab on Disease-Free Survival  
Results from 3,425 Postmenopausal Patients of the ABCSG-18 Trial  
Michael Gnant  
Abstract 2-02
Trial Design ABCSG-18

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 - 2013 (3,425 postmenopausal patients)
- Primary endpoint: Time to first clinical fracture (reached March 2014)
- Secondary endpoints:
  - Fracture related secondary endpoints (Primary Analysis March 2015)
  - Disease outcome related endpoints
  - DFS - time driven analysis of disease free survival
  - OS, BMFS (will be analyzed at EoS)
- Inclusion criteria:
  - Postmenopausal women with non-metastatic adenocarcinoma of the breast
  - ER+ and/or PR+; adjuvant non-steroidal aromatase inhibitor therapy
- Exclusion criteria:
  - Prior or concurrent treatment with SERMs
  - Current or prior IV bisphosphonate administration
  - Known history of:
    - Paget’s disease
    - Cushings’ disease
    - hyperprolactinemia
    - hypercalcaemia or hypocalcaemia
    - other active metabolic bone disease

Denosumab 60 mg SC Q6M
Placebo SC Q6M
randomized placebo-controlled double-blind 1:1 (N = 3,425)

Gnant et al, Lancet 2015; 386: 433-43
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ABCSG-18 Primary Endpoint Results (ASCO 2015)

<table>
<thead>
<tr>
<th>Number of Fractures / Patients</th>
<th>Hazard ratio vs Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>176 / 1,709</td>
<td>0.50 (0.39 - 0.65)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>92 / 1,711</td>
<td></td>
</tr>
</tbody>
</table>
ABCSG-18 Demographics and Safety

• 3,425 postmenopausal patients on adjuvant AI
  • Median age: 64 years (38-91)
  • Tumor size <2 cm: 72% Node-negative disease: 71%
  • Grading: G3 19% Ductal invasive histology: 74%
  • Both ER and PR positive: 83% HER-2 overexpressing: 6%
  • (Neo)adjuvant Chemotherapy: 25%

• Adverse and serious adverse events
  – Mainly associated with known AI profile (Hot flushes, arthralgia, bone pain)
  – No measurable difference between denosumab and placebo in this double-blind trial
  – No case of ONJ despite proactive screening for this condition
  – No case of atypical fracture

Gnant et al, Lancet 2015; 386: 433-43

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ABCSD-18 DFS ITT: Subgroups

Entire population

<table>
<thead>
<tr>
<th>HR status</th>
<th>ER status</th>
<th>Prior chemo. therapy</th>
<th>Grade</th>
<th>T-stage</th>
<th>Nodal status</th>
<th>Baseline BMD</th>
<th>Age</th>
<th>T-score</th>
<th>Prior chemotherapy</th>
<th>AI prior to randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER- or PR-</td>
<td>ER+ and PR+</td>
<td>none</td>
<td>G1</td>
<td>T0/Tis/T1</td>
<td>negative</td>
<td>&lt;60</td>
<td>≥-1</td>
<td>&lt; 60</td>
<td>no</td>
<td>97 / 2071</td>
</tr>
<tr>
<td></td>
<td></td>
<td>none</td>
<td>G2/GX</td>
<td>T2/T3/T4</td>
<td>positive</td>
<td>60 to 69</td>
<td>≥-1</td>
<td>≥70</td>
<td>yes</td>
<td>93 / 2070</td>
</tr>
<tr>
<td></td>
<td></td>
<td>none</td>
<td>G3</td>
<td>T0/Tis/T1</td>
<td>negative</td>
<td>&lt; 60</td>
<td>≥-1</td>
<td>&lt; 60</td>
<td>no</td>
<td>98 / 2071</td>
</tr>
<tr>
<td></td>
<td></td>
<td>none</td>
<td>G2/GX</td>
<td>T2/T3/T4</td>
<td>positive</td>
<td>60 to 69</td>
<td>≥-1</td>
<td>≥70</td>
<td>yes</td>
<td>93 / 2070</td>
</tr>
</tbody>
</table>

Hazard ratio

Denosumab: Placebo Hazard ratio

92.6% 88.9% 87.0% 80.3%

ABCSD 18- Subgroup Tumor Size >2 cm

Placebo vs Denosumab

HR (95% CI) P value

0.663 (0.47 - 0.93) 0.0171 Cox

0.0163 Log-rank

Follow-up:

0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90

Time since randomization, months

Patients at risk:

Denosumab 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495 49 / 495

ABCSD 18- Subgroup Tumor Size >2 cm

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Summary of ABCSG-18

• These time-driven DFS analyses of ABCSG-18 indicate that adjuvant denosumab improves DFS
  – ITT analysis (Cox HR=0.816, p=0.0515, log rank p=0.0510)
  – Sensitivity analyses indicate that the estimate of the DFS difference in the ITT analysis is conservative

• Adjuvant denosumab is a safe treatment in ABCSG-18
  – No measurable differences between denosumab and placebo in terms of SAEs or AEs
  – No case of confirmed ONJ
  – No case of atypical fracture
Clinical Conclusions ABCSG-18

- Adjuvant denosumab 60mg/Q6M s.c. reduces risk of disease recurrence or death in postmenopausal breast cancer patients
- The observed DFS benefit of adjuvant denosumab in ABCSG-18 is similar to the EBCTCG bisphosphonate meta-analysis
- This benefit comes in addition to significantly reducing clinical (and vertebral) fractures and improving BMD
- Adjuvant denosumab 60 mg/Q6M should be offered to postmenopausal breast cancer patients on adjuvant aromatase inhibitor therapy

PIK3CA Status in Circulating Tumor DNA Predicts Efficacy of Buparlisib Plus Fulvestrant in Postmenopausal Women With Endocrine-resistant HR+/HER2- Advanced Breast Cancer: First Results From the Randomized, Phase III BELLE-2 Trial

José Baselga,1 Seock-Ah Im,2 Hiroji Iwata,3 Mark Clemons,4 Yoshinori Ito,5 Ahmad Awada,6 Stephen Chia,7 Agnieszka Jagiello-Gruszfeld,8 Barbara Pistilli,9 Ling-Ming Tseng,10 Sara Hurvitz,11 Norikazu Masuda,12 Javier Cortés,13 Michele De Laurentiis,14 Carlos L. Arteaga,15 Zefei Jiang,16 Walter Jonat,17 Soulef Hachemi,18 Sylvie Le Mouhaër,18 Emmanuelle Di Tomaso,19 Patrick Urban,20 Cristian Massacesi,18 Mario Campone21

Abstract 6-01
The PI3K Pathway is Activated in Breast Cancer

- PI3K/mTOR pathway activation is a hallmark of HR+/HER2– breast cancer cells that have developed resistance to endocrine therapy\(^1\).\(^2\)
- The ER pathway is upregulated in tumors from patients treated with PI3K inhibitors\(^1\).
- Dual blockade of the PI3K/mTOR and ER pathways may therefore restore sensitivity to endocrine therapy\(^1\).\(^3\).\(^4\)

ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.


Clinical Rationale for BELLE-2

- Buparlisib (BKM120) is an oral pan-class I PI3K inhibitor that targets all four isoforms of PI3K (\(\alpha\), \(\beta\), \(\gamma\), \(\delta\))\(^1\).

<table>
<thead>
<tr>
<th>PI3K Isoform</th>
<th>(\alpha)</th>
<th>(\beta)</th>
<th>(\gamma)</th>
<th>(\delta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC(_{50}), nM</td>
<td>52</td>
<td>166</td>
<td>262</td>
<td>116</td>
</tr>
</tbody>
</table>

- Buparlisib has demonstrated preliminary clinical activity in combination with fulvestrant\(^2\).
- BELLE-2 is the first randomized Phase III study to assess the safety and efficacy of a pan-PI3K inhibitor combined with fulvestrant in HR+/HER2– advanced breast cancer.

ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

BELLE-2 Study Design and Endpoints

**Primary Endpoints**
- PFS in the main population (PI3K activated and non-activated, excluding status unknown*)
- PFS in the PI3K activated group* (PIK3CA mutation and/or PTEN loss in archival tissue)
- PFS in the full population (local assessment)

**Key Secondary Endpoint**
- Overall survival

**Other Secondary Endpoints**
- Overall response rate
- Clinical benefit rate
- Safety, pharmacokinetics, quality of life

**Exploratory Endpoint**
- PFS by ctDNA PIK3CA mutation status†

**Randomization (1:1)**
Stratification by PI3K pathway* and visceral disease status

Buparlisib (100 mg/day) + fulvestrant (500 mg) n=576
Placebo + fulvestrant (500 mg) n=571

**BELLE-2 Key Inclusion and Exclusion Criteria**

**Key Inclusion Criteria**
- Postmenopausal women with ER+/HER2- locally advanced or metastatic breast cancer that progressed on/after AI therapy N=1147
- Disease progression on/after AI therapy:
  - Recurrence during or ≤12 months from end of adjuvant AI therapy
  - Progression during or ≤1 month from end of AI therapy for locally advanced/metastatic breast cancer
- Measurable disease or non-measurable lytic or mixed bone lesions (RECIST v1.1)
- Adequate tumor tissue (archival/new) for analysis of PI3K-related biomarkers

**Key Exclusion Criteria**
- Prior therapy with a PI3K, AKT, or mTOR inhibitor, or fulvestrant
- >1 prior chemotherapy line for metastatic disease
- Anxiety (CTCAE Grade ≥3) or history/evidence of depression or other mood disorders
- GAD-7 mood scale score ≥15, PHQ-9 score ≥12, or positive response to PHQ-9 question 9 relating to suicidal ideation

*Buparlisib is an inhibitor of phosphatidylinositol 3-kinase (PI3K). AI, Aromatase inhibitor; BEAMing, beads, emulsification, amplification, and magnets; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase Catalytic Alpha Subunit; PTEN, Phosphatase and Tensin Homolog; PHQ, 9-item Patient Health Questionnaire; GAD, Generalized Anxiety Disorder; RECIST, Response Evaluation Criteria in Solid Tumors.
## Patient Demographics and Disease Characteristics Were Well Balanced Between Treatment Arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buparlisib + Fulvestrant (n=576)</th>
<th>Placebo + Fulvestrant (n=571)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>62 (29–90)</td>
<td>61 (31–90)</td>
</tr>
<tr>
<td><strong>ECOG performance status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57.8</td>
<td>60.2</td>
</tr>
<tr>
<td>1</td>
<td>40.1</td>
<td>37.0</td>
</tr>
<tr>
<td>2-3</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Hormone receptor status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>99.1</td>
<td>98.6</td>
</tr>
<tr>
<td>PgR+</td>
<td>74.8</td>
<td>74.1</td>
</tr>
<tr>
<td><strong>PI3K pathway activation status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated</td>
<td>32.6</td>
<td>32.2</td>
</tr>
<tr>
<td>Non-activated</td>
<td>41.5</td>
<td>42.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>25.9</td>
<td>25.7</td>
</tr>
<tr>
<td><strong>Visceral disease present, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.2</td>
<td>59.0</td>
</tr>
<tr>
<td><strong>Prior therapy in metastatic setting, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hormonal therapy</td>
<td>72.6</td>
<td>75.1</td>
</tr>
<tr>
<td>Any aromatase inhibitors</td>
<td>69.4</td>
<td>71.5</td>
</tr>
<tr>
<td>Any chemotherapy</td>
<td>24.5</td>
<td>31.0</td>
</tr>
<tr>
<td><strong>Prior lines of hormonal therapy in metastatic setting, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27.4</td>
<td>24.9</td>
</tr>
<tr>
<td>1</td>
<td>53.1</td>
<td>52.7</td>
</tr>
<tr>
<td>≥2</td>
<td>19.4</td>
<td>22.4</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor-positive; PgR+, progesterone receptor-positive; PI3K, phosphatidylinositol 3-kinase.

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## BELLE-2 Safety Profile Was Characterized by Hyperglycemia, Transaminitis, Rash, and Mood Disorders

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>All grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>99.5</td>
<td>63.2</td>
<td>14.1</td>
<td>93.0</td>
<td>27.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>40.1</td>
<td>18.7</td>
<td>6.8</td>
<td>6.8</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>37.3</td>
<td>15.0</td>
<td>3.0</td>
<td>9.3</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>43.1</td>
<td>15.2</td>
<td>0.2</td>
<td>7.7</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>32.1</td>
<td>7.7</td>
<td>0.2</td>
<td>6.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>22.3</td>
<td>5.2</td>
<td>0.2</td>
<td>8.2</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31.9</td>
<td>4.9</td>
<td>0</td>
<td>23.9</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>26.2</td>
<td>3.7</td>
<td>0.7</td>
<td>8.9</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34.2</td>
<td>3.7</td>
<td>0</td>
<td>14.6</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.1</td>
<td>2.8</td>
<td>0</td>
<td>10.5</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21.6</td>
<td>2.1</td>
<td>0</td>
<td>6.5</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>38.7</td>
<td>1.7</td>
<td>0</td>
<td>23.2</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>28.9</td>
<td>1.6</td>
<td>0</td>
<td>11.1</td>
<td>0.2</td>
<td>0</td>
</tr>
</tbody>
</table>

- Adverse events occurred in 22.4% in the buparlisib arm vs 15.8% in the placebo arm.
- ≥2 on treatment adverse (p=0.04) were reported in each arm in the full population, the majority due to disease progression.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
BELLE-2 Met the Primary Endpoint for Statistically Significant PFS Improvement in the Full and Main Population

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided P value 0.003)

- Follow-up for OS analysis is ongoing, with a pre-specified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

PFS Increase in the PI3K Activated Group was not Statistically Significant

- Targeted PFS improvement from 5.0 to 7.5 months, HR of 0.67

*PFS in the PI3K activated group was tested at a one-sided α=0.01 level of significance.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Belle-2 Prospectively Evaluated PIK3CA Mutation Status in ctDNA

- In clinical trials, archival tumor biopsy samples typically represent the primary tumor at the time of initial diagnosis
  - Recent evidence suggests that tumor mutation status can change due to disease progression or exposure to prior treatments\(^1,2\)
- ctDNA obtained from blood samples has emerged as a sensitive, reliable, and minimally invasive way to measure current PIK3CA mutation status\(^3,4,5\)
- In Belle-2, blood samples for ctDNA analysis were collected for 51.2% of enrolled patients
  - PIK3CA status in ctDNA was prospectively analyzed in 587 patients using BEAMing technology to detect mutations in exon 9 (E545K) or exon 20 (H1047R/L)\(^5\)
  - Baseline patient characteristics were generally balanced in the full and ctDNA populations; based on sensitivity analyses, any imbalances did not influence the efficacy outcome

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Buparlisib and Fulvestrant Produced a Clinically meaningful PFS Improvement in Patients With ctDNA PIK3CA Mutations

<table>
<thead>
<tr>
<th>ctDNA PIK3CA Mutant</th>
<th>Buparlisib + Fulvestrant (n=87)</th>
<th>Placebo + Fulvestrant (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.0 (5.0–10.0)</td>
<td>3.2 (2.0–5.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.56 (0.39–0.80)</td>
<td></td>
</tr>
<tr>
<td>One-sided nominal P value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.
Buparlisib and Fulvestrant produced a clinically meaningful PFS improvement in patients with ctDNA PIK3CA Mutations

<table>
<thead>
<tr>
<th>ctDNA PIK3CA</th>
<th>Buparlisib + Fulvestrant</th>
<th>Placebo + Fulvestrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutant</td>
<td>n=200</td>
<td>n=87</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.0 (5.0–10.0)</td>
<td>3.2 (2.0–5.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.56 (0.39–0.80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Buparlisib and Fulvestrant resulted in higher response rates in the ctDNA PIK3CA mutant group

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>PIK3CA Mutant (ctDNA)</th>
<th>PIK3CA Non-mutant (ctDNA)</th>
<th>PI3K Pathway Activated (Archival Tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR,*</td>
<td>Buparlisib + Fulvestrant n=87</td>
<td>Placebo + Fulvestrant n=113</td>
<td>Buparlisib + Fulvestrant n=199</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>18.4 (10.9–28.1)</td>
<td>3.5 (1.0–8.8)</td>
<td>11.6 (7.5–16.8)</td>
</tr>
<tr>
<td>CBR,**</td>
<td>47.1 (36.3–58.1)</td>
<td>31.9 (23.4–41.3)</td>
<td>42.7 (35.7–49.9)</td>
</tr>
</tbody>
</table>

*ORR is defined as best overall response (CR+PR); **CBR is defined as best overall response (CR+PR, or partial response, SD, stable disease) lasting for at least 24 weeks.
Conclusions

• The BELLE-2 study met its primary endpoint, demonstrating prolonged PFS for combined buparlisib and fulvestrant in postmenopausal women with HR+/HER2– advanced breast cancer that had progressed after prior AI therapy.

• Patients with tumors harboring PIK3CA mutations in ctDNA performed poorly on fulvestrant monotherapy, achieving a clinically meaningful PFS improvement with combined buparlisib and fulvestrant.
  – 3.8 month PFS improvement was supported by higher response rates in this patient population.

• Frequent discontinuations due to AEs reduced treatment duration in the buparlisib arm, potentially limiting the efficacy of combination therapy.

• Further studies of PI3K inhibitor and endocrine therapy combinations in this setting are ongoing.

AEs, adverse events; CBR, clinical benefit rate; CI, confidence interval; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; ORR, objective response rate; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

cfDNA Analysis From BOLERO-2 Plasma Samples Identifies a High Rate of ESRI Mutations: Exploratory Analysis For Prognostic And Predictive Correlation of Mutations Reveals Different Efficacy Outcomes of Endocrine Therapy-based Regimens

Sarat Chandarlapaty1, Patricia Sung1, David Chen2, Wei He2, Aliaksandra Samoila1, Daoqi You1, Trusha Bhatt1, Parul Patel1, Maurizio Voi2, Michael Gnant3, Gabriel Hortobagyi4, Jose Baselga1, and Mary Ellen Moynahan1

1Memorial Sloan Kettering Cancer Center, New York, United States; 2Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States; 3Dept. Of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; 4The University of Texas MD Anderson Cancer Center, Houston, United States
Introduction And Rationale

- Y537S and D538G mutations in Estrogen Receptor (ESR1) are observed in metastatic breast cancer (MBC) and promote ligand-independent receptor activation.
- ESR1 mutation could be a predictive marker for early patient selection for endocrine based therapies.

BOLERO-2: Study Design and Primary Results

- N = 724
  - Postmenopausal HR+, HER2—unresectable locally advanced or metastatic breast cancer
  - Recurring or progressing during/after NSAIs (within 12 mo adjuvant or 1 mo advanced)
- R 2:1
- Key endpoints
  - Primary: PFS
  - Secondary: OS

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Arms</th>
<th>Events/N</th>
<th>PFS (mo)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>EVE + EXE</td>
<td>310/485</td>
<td>7.8</td>
<td>0.45 (0.38-0.54)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>PBO + EXE</td>
<td>200/239</td>
<td>3.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Methodology and Statistical Analysis

Patients with HR+, HER2- MBC whose disease recurred or progressed on/after prior NSAIs were enrolled in BOLERO-2
N = 724

Consent for genomic testing

cfDNA* extraction from archival plasma samples
Evaluable samples N = 541

cfDNA analysis for ESR1 D538G and Y537S mutations by ddPCR

Statistical Analysis:
- Cox-proportional hazards model was used to assess
  - Prognostic effect on OS in patient subgroups defined by ESR1 mutation or specific mutations
  - Predictive effect on PFS in patient subgroups defined by ESR1 mutation or specific mutations

Detection and Quantification of ESR1 Mutations by ddPCR

Y537S mutant droplets
Wild type droplets

ddPCR, droplet digital PCR; HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor-negative; MBC, metastatic breast cancer; NSAIs, non-steroidal aromatase inhibitors; OS, overall survival; PFS, progression free survival.
Frequency of *ESRI* Mutations

- High *ESRI* mutation frequency in cfDNA samples
  - Some double mutations were detected

<table>
<thead>
<tr>
<th></th>
<th>D538G and/or Y537S mutation</th>
<th>D538G mutation</th>
<th>Y537S mutation</th>
<th>Double mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, N = 541</td>
<td>156</td>
<td>83</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>(74.7% of ITT)</td>
<td>(28.8%)</td>
<td>(15.3%)</td>
<td>(7.8%)</td>
<td>(5.5%)</td>
</tr>
</tbody>
</table>

ddPCR on cfDNA vs NGS on Archival Tumor DNA

- 541 cfDNA were analyzed by ddPCR and 302 archival tumor DNA by next generation sequencing (NGS)
- 236 paired samples with assessment of Y537S and D538G mutations in *ESRI*
  - 3 (1.3%) archival tumor samples had one of the two mutations
  - 67 (28.4%) cfDNA samples had one of the two mutations
- 247 paired samples with assessment of H1047R, E545K, E542K mutations in *PIK3CA*
  - 85 (34.4%) tumor samples had at least one of the three mutations
  - 114 (46.2%) cfDNA samples had at least one of the three mutations
ESR1 Mutation Frequency by Clinical Covariates

- ESR1 mutation frequency is not significantly different based on race or patient age or site of disease (visceral vs soft tissue/bone-only).

![Graph showing ESR1 mutation frequency by clinical covariates]

ESR1 Mutation Frequency by Clinical Covariates

<table>
<thead>
<tr>
<th>cDNA pop</th>
<th>(158/541)</th>
<th>P = 0.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>(21/102)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>(128/417)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>(7/22)</td>
<td></td>
</tr>
<tr>
<td>ECOG0</td>
<td>(80/311)</td>
<td></td>
</tr>
<tr>
<td>ECOG1,2</td>
<td>(75/218)</td>
<td></td>
</tr>
<tr>
<td>AI adjuvant only</td>
<td>(11/97)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>AI met</td>
<td>(145/444)</td>
<td></td>
</tr>
</tbody>
</table>

ESR1 Mutation Frequency by Clinical Covariates

Prognostic Effect of ESR1 Mutation on OS

<table>
<thead>
<tr>
<th>Mutations</th>
<th>N</th>
<th>Events</th>
<th>Median OS (95%CI) (months)</th>
<th>HR (95%CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>385</td>
<td>217</td>
<td>32.1 (28.1 - 36.4)</td>
<td>1.40 (1.2 - 1.65)</td>
<td>0.000037</td>
</tr>
<tr>
<td>MT</td>
<td>156</td>
<td>112</td>
<td>20.7 (17.7 - 28.1)</td>
<td>1.25 (1.02-1.54)</td>
<td>0.033</td>
</tr>
<tr>
<td>D538G</td>
<td>83</td>
<td>57</td>
<td>26.0 (19.2 - 32.4)</td>
<td>2.31 (1.34-3.97)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Y537S</td>
<td>42</td>
<td>30</td>
<td>20.0 (13.0-29.3)</td>
<td>1.77 (1.31-2.39)</td>
<td>0.00018</td>
</tr>
<tr>
<td>Double MT</td>
<td>30</td>
<td>24</td>
<td>15.2 (10.9-27.4)</td>
<td>1.77 (1.31-2.39)</td>
<td>0.00018</td>
</tr>
</tbody>
</table>

- Both D538G and Y537S mutations were poor prognostic factors associated with shorter OS.
- In a multivariate analysis adjusting for sensitivity to prior hormonal therapy, visceral disease and ECOG status, the effect of ESR1 mutation (compared to wild-type) on OS remained significant.

*All p-values were unadjusted for multiple testing.
### Impact of ESR1 Mutations on EXE Treatment

<table>
<thead>
<tr>
<th>Alteration</th>
<th>N</th>
<th>Events</th>
<th>Median PFS (95% CI) (months)</th>
<th>HR (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>128</td>
<td>116</td>
<td>3.94 (2.76-4.17)</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>MT</td>
<td>61</td>
<td>51</td>
<td>2.76 (1.41-4.14)</td>
<td>1.18 (0.94-1.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>D538G</td>
<td>24</td>
<td>22</td>
<td>2.69 (1.35-2.83)</td>
<td>1.44 (1.04-1.99)</td>
<td>0.029</td>
</tr>
<tr>
<td>Y537S</td>
<td>21</td>
<td>16</td>
<td>4.14 (1.38-6.7)</td>
<td>0.92 (0.44-1.93)</td>
<td>0.83</td>
</tr>
<tr>
<td>Double MT</td>
<td>15</td>
<td>12</td>
<td>2.78 (1.41-6.87)</td>
<td>1.15 (0.69-1.75)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*All p-values were unadjusted for multiple testing

### Impact of ESR1 Mutations on EVE treatment

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median PFS (95% CI) (months)</th>
<th>HR (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>EXE</td>
<td>128</td>
<td>116</td>
<td>3.9 (2.8-4.2)</td>
<td>0.4 (0.31-0.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D538G</td>
<td>EXE</td>
<td>24</td>
<td>22</td>
<td>2.6 (1.4-2.8)</td>
<td>0.34 (0.2-0.57)</td>
<td>0.00006</td>
</tr>
<tr>
<td>Y537S</td>
<td>EXE</td>
<td>21</td>
<td>16</td>
<td>4.1 (1.4-6.7)</td>
<td>0.98 (0.49-1.94)</td>
<td>0.95</td>
</tr>
<tr>
<td>Double MT</td>
<td>EXE</td>
<td>15</td>
<td>12</td>
<td>2.78 (1.41-6.87)</td>
<td>0.53 (0.23-1.25)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>EVE + EXE</td>
<td>15</td>
<td>14</td>
<td>5.42 (2.46-7.82)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- cfDNA analysis of archival plasma samples is feasible for mutation detection

- ESR1 mutation frequency in cfDNA samples is higher than identified with tumor sequencing
  - The 28% mutation frequency for D538G and Y537S ESR1 mutations assayed likely underestimates the frequency for all activating ESR1 mutations
  - The occurrence of multiple ESR1 mutations is not uncommon

- ESR1 mutations are identified in HR+ MBC prior to first-line therapy; frequency markedly increases in patients treated with AIs in the metastatic setting

- D538G and Y537S mutations appear to be associated with a more aggressive disease biology as demonstrated by a shorter OS

- Differential effects of the Y537S and D538G mutations on treatment
  - In the EXE only arm, patients with D538G mutation had a shorter PFS as compared to wild-type
  - Patients with D538G mutation demonstrate PFS benefit with the addition of EVE, whereas those with Y537S mutation did not

---

Occurrence of natural ESR1 mutations during acquisition of endocrine resistance in breast cancers and widely used ER+ cell lines

Pascal Gellert1,2, Ricardo Ribas1, Sunil Pancholi1, Elena Lopez-Knowles1,2, Belinda Yeo2, Isaac Garcia-Murillas1, Charlotte Fribbens1, Alex Pearson1, Ian Smith2, Nicholas Turner1,2, Mitch Dowsett1,2, Lesley-Ann Martin1

1Breast Cancer Now at The Institute of Cancer Research, London, UK
2Royal Marsden Hospital, London, UK

Abstract 6-02
Aims

• To identify changes in the mutational profile of ER+ breast cancers at progression on Aromatase Inhibitor treatment

• To identify concomitant mutations occurring in cell line models of resistance to E-deprivation

ER+ Breast Cancer

• Mutational landscape of ER+ primary BC well described

• Few studies on mutational landscape of metastatic BC

• Landscape changes between primary and metastatic BC likely to determine the integration of diagnostic and treatment

Frequently mutated genes in ER+ primary BC

Gellert et al, SABCS 2014
TCGA, Nature 2012
The Hallmarks of AI resistance

- **ER pathway**
  - Loss of ER expression
  - *ESR1* mutation or amplification

- **Tumor microenvironment**
  - ECM & Cellular components

- **Growth factor receptor pathway**
  - e.g. HER2 mutation or amplification

- **Apoptosis and senescence**
  - e.g. mutation of TP53

- **Cell cycle machinery**
  - e.g. amplification of *CCND1*

- **Epithelial-mesenchymal transition**
  - Notch, Hedgehog, WNT, TWIST1

Modified from Ma et al, Nature 2015

---

**ESR1 mutations in metastases**

- **Primary disease**
  - DNA binding domain
  - Ligand binding domain
  - C- terminus
  - Frameshift
  - Missense
  - Insertion

- **Potential factors**
  - Time, treatment, metastasis, mutational driver

- **Metastatic disease**
  - DNA binding domain
  - Ligand binding domain
  - C- terminus

Samples | % ESR1 mutated | Pairs
--- | --- | ---
261 primary | 3.3% primary | 47 pairs
195 mets | 13.3% mets |

Modified from Segal and Dowsett, CCR 2014

- Small number of pairs
- Great treatment heterogeneity
Patients and Methods

Arnedos M et al, Annals Oncology 2014:
- 55 patients selected retrospectively (2004-2009, Royal Marsden Hospital)
- Paired primary and recurrences available
- ER+
- Locally advanced or metastatic setting
- Relapsed or progression during AI treatment

Immunohistochemical analysis:
- 7% ER- in metastases
- Decrease of PgR
- Higher Ki67
- 5% gained HER2 amplification

51 FFPE blocks pre and post AI
48 pairs for targeted sequencing

Genes of Interest

modified from Ma et al, Nature 2015
Results

- Good quality data was available on 41 pairs
- Median depth was 782-fold
- A total of 87 tier 1 mutations were identified
- No significant difference in the number of mutations between the pre and post AI lesions

Mutational overview

Mutations were found in 29 patients

- 12 patients with private mutations
- Mutations found in post only for HER2, MAP2K4 and ESR1
- No mutations found in 12 patients, loss/reduction of ER and gain of HER2 amplification in these
**In vitro model for AI resistance**

- Long term estrogen deprivation (LTED) to model relapse on an AI
- Study mutational changes of ESR1 between wild type and resistant breast cancer cell lines

---

**Acquisition of ESR1 mutations in vitro**

**SUM44**

- Basal proliferation
- Proliferation in response to E2
- Digital droplet PCR

1.3x10⁶ WT-SUM44 were WT for ESR1, suggesting the mutation is absent or at extremely low VAF.
Acquisition of ESR1 mutations in vitro SUM44

Expression of endogenous E-regulated genes

Phenotypic analysis

RIME shows altered ER-proteome

ChIP-seq WT versus LTED

Acquisition of ESR1 mutations in vitro MCF7

1.34x10^6 WT-MCF7 were WT for ESR1, suggesting the mutation is absent or at extremely low VAF
Conclusions

- Recurrences after AI but not primary ER+ tumors may contain ESRI mutations that could influence clinical decision making.
- Other than ESRI there are no consistent acquisition of mutations.
- High variability of genotype and phenotype requires individual interpretation for personalised treatment.
- In vitro ESRI mutations can be acquired under estrogen deprivation resulting in a ligand independent phenotype
- Anti-proliferative effect of SERDs remains effective
KEYNOTE-028: ER+/HER2- Breast Cancer Cohort

Patients
- ER+/HER2- tumors
- Locally advanced or metastatic disease
- Failure of or inability to receive standard therapy
- ECOG PS 0 or 1
- 1 measurable lesion
- PD-L1 positive

Response Assessment
- Complete or partial response or stable disease
- Treat for 24 months or until progression or intolerable toxicity

Response Assessment*
- Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 by investigator and safety
Secondary end points: PFS, OS, duration of response

*Defined by institutional standards. If clinically stable, patients were to remain on pembrolizumab until progressive disease was confirmed or a second scan performed 24 weeks later. Only patients who discontinued pembrolizumab for complete response or after 12 months of continuous treatment without evidence of disease progression were eligible for up to 1 year of additional pembrolizumab.

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Patients Screened for Tumor PD-L1 Expression in the ER+/HER2- Breast Cancer Cohort

Nonevaluable
- Inadequate tissue sample (n = 19)

Samples Evaluable for PD-L1
n = 248

PD-L1-Positive Tumors
n = 48

Patients Treated as of July 1, 2015
N = 25

19.4% PD-L1+
### Antitumor Activity (N =25)
(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
<td>0.0-0.31</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (16.0)</td>
<td>4.5-36.1</td>
</tr>
<tr>
<td>Clinical benefit rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (20.0)</td>
<td>6.9-40.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (60.0)</td>
<td>38.7-78.9</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
</tbody>
</table>

In the 22 patients with at least one scan after baseline, ORR was 14% and CBR was 23%

---

<sup>a</sup> All patients with partial response received 12 lines of therapy in the metastatic setting.

<sup>b</sup> Complete response + partial response + stable disease for 22 weeks. “No assessment” signifies patients who discontinued therapy before the first post-baseline scan. Data cut off date: July 1, 2015.

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### S6-04
A phase II trial of neoadjuvant palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with anastrozole for clinical stage 2 or 3 estrogen receptor positive HER2 negative (ER+HER2-) breast cancer (BC)

Dr. Ma has disclosed that she receives clinical trial research support from Pfizer related to palbociclib.
Statistical Design

- **Fleming's single-stage phase II design**
  - To test the hypothesis that adding palbociclib would result in at least 50% improvement in the complete cell cycle arrest (CCCA) rate over AI alone, with 80% power and at 1-sided 0.05 significance.
  - Estimates were 44% with AI alone* versus 66% with the combination.
  - The study was initially only open to the PIK3CA WT cohort.
    - A sample size of 33 patients was required.
    - The primary endpoint is met if at least 20 of 33 had CCCA.
  - A subsequent protocol amendment allowed patients with mutant or non-diagnostic PIK3CA status to enroll to the study in separate cohorts.

*Ellis, MJ, et al JCO 2011

---

Primary Endpoint:
Complete Cell Cycle Arrest (CCCA: Ki67≤2.7%) Rate at C1D15

<table>
<thead>
<tr>
<th>Study Population</th>
<th>C1D15 CCCA, N (%), 90% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=45)</td>
<td>39 (87%, 75-94%)</td>
</tr>
<tr>
<td>PIK3CA WT (n=28)</td>
<td>22 (79%, 62-90%)</td>
</tr>
<tr>
<td>PIK3CA Mut (n=15)</td>
<td>15 (100%, 82-100%)</td>
</tr>
<tr>
<td>PIK3CA Undetermined (n=2)</td>
<td>2 (100%, NE)</td>
</tr>
</tbody>
</table>

**Study objective:** Demonstrate a CCCA rate of 66%.
If at least 20 of 33-patient cohort achieved CCCA on C1D15 biopsy, the primary endpoint of the study is met.
Conclusions

- Palbociclib provides enhanced cell cycle control over that achieved by anastrozole alone.
- Palbociclib enhanced cell cycle control regardless of PIK3CA mutation status or luminal A or B status.
- The combination was ineffective in the two patients with non-luminal breast cancers and a subset of luminal B cancers.
- The combination of palbociclib and anastrozole was well tolerated.
- These results support the evaluation of this combination in the adjuvant setting for ER+ HER2- BC.
- Rebound Ki67 values at surgery after an average of 4 weeks of palbociclib washout indicates that palbociclib is, like endocrine therapy, a maintenance treatment.
Abstract 4-06

TRANS-AIOG HER2 meta-analysis:

Objective
- To determine by individual patient data (IPD) meta analysis the use of HER2 as a biomarker for selection of upfront aromatase inhibitors (AIs) compared to tamoxifen in the first 2-3 years of treatment in patients treated for early breast cancer.

Hypothesis
- HER2 is a predictive biomarker for greater AI benefit in HER2-ve patients during the first 2-3 years of endocrine therapy than in patients with HER2+ve disease
  - i.e. differential benefit from AIs vs tamoxifen is not seen in patients with HER2+ve disease during the first 2-3 years of treatment.
TRANS-AIOG HER2 meta-analysis:

Objective
• To determine by individual patient data (IPD) meta-analysis the use of HER2 as a biomarker for selection of upfront aromatase inhibitors (AIs) compared to tamoxifen in the first 2-3 years of treatment in patients treated for early breast cancer.

Hypothesis
• HER2 is a predictive biomarker for greater AI benefit in HER2-ve patients during the first 2-3 years of endocrine therapy than in patients with HER2+ve disease
  • i.e. differential benefit from AIs vs tamoxifen is not seen in patients with HER2+ve disease during the first 2-3 years of treatment.

Patient characteristics:

<table>
<thead>
<tr>
<th></th>
<th>TEAM (N=4203)</th>
<th>ATAC (N=1064)</th>
<th>BIG-1-98 (N=6102)</th>
<th>Overall (N=12129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>43.8%</td>
<td>48.9%</td>
<td>49.9%</td>
<td>49.8%</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>50.2%</td>
<td>51.1%</td>
<td>50.1%</td>
<td>50.2%</td>
</tr>
<tr>
<td><strong>Tumour Size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20mm</td>
<td>48.3%</td>
<td>66.0%</td>
<td>62.3%</td>
<td>58.0%</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>49.9%</td>
<td>32.7%</td>
<td>37.0%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2.8%</td>
<td>0.4%</td>
<td>0.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Nodal Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>25.7%</td>
<td>55.6%</td>
<td>57.2%</td>
<td>47.3%</td>
</tr>
<tr>
<td>Positive</td>
<td>57.6%</td>
<td>30.2%</td>
<td>41.8%</td>
<td>45.7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>15.7%</td>
<td>4.2%</td>
<td>1.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>11.3%</td>
<td>26.0%</td>
<td>20.6%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>51.2%</td>
<td>51.0%</td>
<td>56.6%</td>
<td>54.0%</td>
</tr>
<tr>
<td>Poor</td>
<td>31.4%</td>
<td>16.3%</td>
<td>22.3%</td>
<td>24.6%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.2%</td>
<td>5.8%</td>
<td>0.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td><strong>Central HER2 status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 Negative</td>
<td>87.7%</td>
<td>89.4%</td>
<td>93.7%</td>
<td>91.0%</td>
</tr>
<tr>
<td>HER2 Positive</td>
<td>12.3%</td>
<td>10.6%</td>
<td>6.3%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

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Primary endpoint Distant recurrence free interval: Treatment by marker interaction (adjusted):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Events/Patients</th>
<th>HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAM</td>
<td></td>
<td>2.75 (1.36, 5.68)</td>
<td>46.16</td>
</tr>
<tr>
<td>ABC</td>
<td></td>
<td>1.44 (0.80, 2.64)</td>
<td>16.95</td>
</tr>
<tr>
<td>BG198</td>
<td></td>
<td>0.87 (0.60, 1.23)</td>
<td>36.09</td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p =

Overall (I² = 54.5%, p = 0.099)

Significant treatment by marker effect (p < 0.05)

Heterogeneity: not statistically significant

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Distant recurrence free interval

HER2-ve AI vs T HR = 0.70 (0.64-0.94)
HER2+ve AI vs T HR = 1.13 (0.75-1.71)

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Practice changing?

• Perhaps?
  – Denosumab in patients receiving Ais

• Confirmatory
  – Lack of chemotherapy benefit in luminal A cancers

• Requires further evaluation
  – Palbociclib in adjuvant setting
  – Buparlisib in AI-resistant ER-positive MBC
  – Pembrolizumab (maybe - disappointing results)

• Interesting
  – Acquired ESR mutations in cfDNA