William J. Gradishar, MD, is the Betsy Bramsen Professor of Breast Oncology in the Division of Hematology and Medical Oncology, Department of Medicine at the Feinberg School of Medicine at Northwestern University and a member of Robert H. Lurie Comprehensive Cancer Center of Northwestern University. He serves as Director of the Maggie Daley Center for Women’s Cancer Care. He also has served as Chair of the Annual Lynn Sage Comprehensive Breast Cancer Symposium since its inception.

Dr. Gradishar received his medical degree from the University of Illinois Abraham School of Medicine. He later completed a residency and chief residency in internal medicine at Michael Reese Hospital and Medical Center and a fellowship in medical oncology at the University of Chicago. He is board-certified in internal medicine and medical oncology.

Dr. Gradishar has published in the area of breast cancer therapeutics, with a focus on new endocrine therapy, chemotherapy, and biologic agents. A Fellow of the American College of Physicians, Dr. Gradishar also is a member of the American Association for Cancer Research, the American Federation for Clinical Research, and the Association of Subspecialty Professors. He is a Fellow of the American Society of Clinical Oncology (ASCO) and past-Chair of ASCO’s Nominating Committee, Professional Development Committee, Oncology Training Program Committee, and Communications Committee.

Additionally, Dr. Gradishar serves as a consultant to the Oncology Drug Advisory Committee of the FDA. He has served on the Committee on Cancer for the American College of Surgeons. He also has served on numerous study sections including NIH, NCI, ACS, Komen, and Alberta Cancer Board. Dr. Gradishar was awarded the Betsy Bramsen Endowed Chair of Breast Oncology at Northwestern University.

Dr. Gradishar is an editorial board member for numerous journals, including the Journal of Clinical Oncology, Oncology, Clinical Breast Cancer, Journal Watch, the European Journal of Clinical and Medical Oncology, and Clinical Cancer Research.

Dr. Gradishar currently serves as Chair of the NCCN Breast Cancer Panel and as a member of the NCCN Breast Cancer Risk Reduction Panel.
OUTLINE

• The HER2 Algorithm
  – Theresa update
  – Marianne
• TNBC
  – No evidence based standard, still chemo
  – Emerging data with checkpoint inhibitors
• ER+
  – New partners?
  – Molecular clues for resistance providing insights to Precision Medicine

Trastuzumab Has Changed the Natural History of HER2-Positive Breast Cancer

• Patients with HER2-positive metastatic breast cancer (MBC) now have comparable outcomes with HER2-negative MBC

![Graph showing survival probability for HER2-positive and HER2-negative breast cancer patients with and without trastuzumab (TRAS).]

TRAS, trastuzumab

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First-Line Setting

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other agents for HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents
CLEOPATRA: Study Design

• Primary endpoint: PFS (independently assessed)
• Secondary endpoints: PFS (investigator assessment), ORR, OS, Safety

Women with previously untreated, HER2-positive locally recurrent/metastatic breast cancer
(N = 808)

Trastuzumab 6 mg/kg q3w* +
Docetaxel 75-100 mg/m² q3w† +
Pertuzumab (PTZ) 420 mg q3w‡
(n = 402)

Trastuzumab 6 mg/kg q3w* +
Docetaxel 75-100 mg/m² q3w† +
Placebo q3w
(n = 406)

Treatment until disease progression or unacceptable toxicity

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


CLEOPATRA Overall Survival


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Hormonal Therapy in HER2-Positive Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR, %</th>
<th>Median PFS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (N = 114; HER2 positive, n = 79)(^1)</td>
<td>26</td>
<td>3.5-3.8</td>
</tr>
<tr>
<td>Anastrozole/trastuzumab (n = 103)(^2)</td>
<td>20</td>
<td>4.8</td>
</tr>
<tr>
<td>Anastrozole (n = 104)(^2)</td>
<td>7</td>
<td>2.4</td>
</tr>
<tr>
<td>Lapatinib/letrozole (n = 642)(^3)</td>
<td>28</td>
<td>8.2</td>
</tr>
<tr>
<td>Letrozole (n = 644)(^3)</td>
<td>15</td>
<td>3.0</td>
</tr>
<tr>
<td>Lapatinib (N = 138)(^4)</td>
<td>24</td>
<td>NA</td>
</tr>
</tbody>
</table>


ORR, overall response rate; PFS, progression-free survival

• Clinicians should recommend combination of trastuzumab, pertuzumab and a taxane for first-line treatment, unless contraindication to taxane use
• If ER+, can consider endocrine therapy + trastuzumab or lapatinib in selected cases


Summary: Optimal Choice First-Line Setting 2016

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline


• Clinicians should recommend combination of trastuzumab, pertuzumab and a taxane for first-line treatment, unless contraindication to taxane use
• If ER+, can consider endocrine therapy + trastuzumab or lapatinib in selected cases

EMILIA Study Design

- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell et al., ASCO 2012
Verma et al., NEJM 2012

EMILIA: Overall Survival

<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=0.68 (95% CI, 0.55, 0.85); P<0.001

Efficacy stopping boundary P=0.0137 or HR=0.727

Verma et al., NEJM, 2012.
Trastuzumab emtansine (T-DM1) improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: final overall survival results from the phase 3 TH3RESA study

Hans Wildiers,1 Sung-Bae Kim,2 Antonio Gonzalez Martin,3 Patricia M. LoRusso,4 Jean-Marc Ferrero,5 Tanja Badovinac-Crnjic,6 Ron Yu,7 Melanie Smit7, Ian E. Krop8

1University Hospitals Leuven, Leuven, Belgium; 2Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; 3MD Anderson Cancer Center, Madrid, Spain; 4Yale Cancer Center, Yale University Medical Center, New Haven, CT, USA; 5Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; 6F. Hoffmann-La Roche, Ltd, Basel, Switzerland; 7Genentech, Inc, South San Francisco, CA, USA; 8Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

TH3RESA Study Schema

Stratification factors: World region, number of prior regimens for advanced BC, presence of visceral disease
Co-primary endpoints: PFS by investigator and OS
Key secondary endpoints: ORR by investigator and safety

*First patient in: Sept, 2011. Study amended: Sept, 2012 following EMILIA 2nd interim OS results to allow patients in the TPC arm to receive T-DM1 after documented PD.
Treatment of Physician’s Choice Regimen

<table>
<thead>
<tr>
<th>TPC treatment regimen</th>
<th>TPC (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination with HER2-directed agent, %</td>
<td>83.2</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>68.5</td>
</tr>
<tr>
<td>Lapatinib + trastuzumab</td>
<td>10.3</td>
</tr>
<tr>
<td>Hormonal therapy + trastuzumab</td>
<td>1.6</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2.7</td>
</tr>
<tr>
<td>Single-agent chemotherapy, %</td>
<td>16.8</td>
</tr>
</tbody>
</table>

*Includes patients who received study treatment. Excludes one patient who was randomized to the TPC arm but received two cycles of T-DM1 by mistake.

**The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.

Final OS Analysis

- TPC (n=198): Median = 15.8 months
- T-DM1 (n=404): Median = 22.7 months

Stratified HR = 0.68 (95% CI: 0.54-0.85) P=0.0007

(Pre-specified crossing boundary: HR=0.748; P=0.012)
### MARIANNE Phase III

**Taxane + Trastuzumab**

- **N=1092 HER2+ MBC**
- **First-line**

**TDM1**

**TDM1+ Pertuzumab**

1° Endpoint: PFS
2° Endpoints: OS, TTF, DOR, ORR, CBR

**T** = paclitaxel 80 m/m weekly or docetaxel at 75-100 m/m q 3 w

**H** = trastuzumab 2 mg/kg q w or 6 mg/kg q 3 w

**P** = pertuzumab at 840 mg load → 420mg q 3 w

**TDM** = trastuzumab/DM1 at 3.6 mg/kg q 3 w

---

<table>
<thead>
<tr>
<th>Nonhematologic AEs, %</th>
<th>TPC (n=184)</th>
<th>T-DM1 (n=403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>Grade ≥3</td>
<td>Any grade</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>17.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12.5</td>
<td>2.7</td>
</tr>
<tr>
<td>AST increased</td>
<td>7.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26.1</td>
<td>2.7</td>
</tr>
<tr>
<td>ALT increased</td>
<td>5.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Shading indicates grade ≥3 AEs with >1% difference between the TPC and T-DM1 arms.

*The incidence of grade ≥3 neutropenia of any type (granulocytopenia) was 42% (T-DM1) and 55% (TPC).*
Progression-Free Survival by IRF

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo)</td>
<td>13.7</td>
<td>14.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Events (mo)</td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
<tr>
<td>Stratiﬁed HR (97.5% CI) vs HT</td>
<td>—</td>
<td>0.91 (0.73–1.13)</td>
<td>0.67 (0.68–1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p=0.31)</td>
<td>(p=0.14)</td>
</tr>
<tr>
<td>Stratiﬁed HR (97.5% CI) vs T-DM1</td>
<td>—</td>
<td>0.91 (0.73–1.13)</td>
<td></td>
</tr>
</tbody>
</table>

DFI = disease free interval from neoadjuvant or adjuvant setting

Key Differences Between CLEOPATRA and MARIANNE

**MARIANNE**
- Poorer prognosis population
  - Shorter DFI required: > 6m
  - Less de novo MBC
  - More patients have prior taxane exposure
  - More patients have previous trastuzumab exposure

**CLEOPATRA**
- Better prognosis population
  - Longer DFI required: > 12m
  - More de novo MBC
  - Fewer patients have prior taxane exposure
  - Fewer patients have previous trastuzumab exposure
Triple-Negative Disease Compared with Other Phenotypes in the California Cancer Registry Study

Parise et al. The Breast Journal 2009: 15: 593

- Population-based study
  - 6370 with “triple-negative” disease compared with 44,704 “other” cases (12% of all cases)
- TNBC more likely to be associated with
  - Younger age (<40): OR 1.53
  - Non-Hispanic black race (OR 1.77) or Hispanic ethnicity (OR 1.23)
  - Higher grade (72% grade 3)
  - More advanced stage (66% >/= stage II vs. 50% ER+HER2-)
  - Poorer 5 year RFI irrespective of stage
    - TNBC: 76% (similar to 76% for HER2-Pos)
    - HR-Pos, HER2-Neg: 94%
  - Greater propensity for lung and brain mets
Annual Hazard Rate of Recurrence by Breast Cancer Subtype in E1199: Node-Positive & High-Risk Node Negative Breast Cancer Treated with AC-Taxane Chemotherapy Plus Endocrine Therapy

Recurrence hazard rate

Years Since Randomization

TNBC Subtypes
21 publicly available gene expression breast cancer datasets, 587 TNBCs

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal-like 1 (BL1)</strong></td>
<td>Cell-cycle, proliferation and DNA damage response genes</td>
</tr>
<tr>
<td><strong>Basal-like 2 (BL2)</strong></td>
<td>Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)</td>
</tr>
<tr>
<td><strong>Immunomodulatory (IM)</strong></td>
<td>Immune cell &amp; cytokine signaling (overlap with medullary signature)</td>
</tr>
<tr>
<td><strong>Mesenchymal (M)</strong></td>
<td>Cell motility and differentiation (Wnt, ALK, TGF-β)</td>
</tr>
<tr>
<td><strong>Mesenchymal stem-like (MSL)</strong></td>
<td>Similar to M, but increased growth factors signaling, low proliferation, enrichment of stem cell genes</td>
</tr>
<tr>
<td><strong>Luminal androgen receptor (LAR)</strong></td>
<td>Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)</td>
</tr>
</tbody>
</table>

Exploitation of the Heterogeneity of TNBC:

Therapeutic Strategies
- DNA damage and repair
- Hormone receptor modulation
- Immune modulation
- Signaling pathway inhibition
- ....

TBCRC 011: Bicalutamide in AR+ TNBC

Consented for AR testing (n=452)
- Screened for AR expression (n=424)
  - AR(+) (n=51)
    - On study (n=28)
      - Eligible on study (n=26)
      - Clinical Benefit Rate = 21% (95% CI 7.1-42.1%)

Ineligible for testing (n=28)
- AR(-) (n=373)
  - Ineligible for therapy (n=8)
    - Eligible for therapy: trial closed to accrual (n=15)
    - Ineligible post therapy (n=2)

12% AR(+)
MDV3100-11: PFS Is Driven by AR Genomic Signature, Not IHC, in Patients with 0–1 Prior aTNBC Treatment
Enzalutamide in AR+ Metastatic TNBC Patients

**AR by PREDICT AR**
- AR ≥ 10% (n=47)
  - mPFS 17.6 weeks
  - (95% CI, 9.0–27.4)
- AR < 10% (n = 15)
  - mPFS 8.5 weeks
  - (95% CI, 6.9–20.4)

**AR by IHC**
- AR ≥ 10% (n=47)
  - mPFS 17.6 weeks
  - (95% CI, 9.0–27.4)
- AR < 10% (n = 15)
  - mPFS 8.5 weeks
  - (95% CI, 6.9–20.4)

---

**TNT Trial design**

**Tutt et al**
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

On progression, crossover if appropriate
- Carboplatin (C) AUC 6 q3w, 6 cycles
- Docetaxel (D) 100mg/m² q3w, 6 cycles
- BRCA1/2 = 9%/12%

n-376
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)**

- Germline BRCA 1/2 Mutation: 34.7% (95% CI 6.3 to 63.1) Exact p = 0.03
- No Germline BRCA 1/2 Mutation: -8.5% (95% CI -19.6 to 2.6) Exact p = 0.16

**Interaction: randomised treatment & BRCA 1/2 status: p = 0.01**

Tutt, SABCS 2014

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**Checkpoint Inhibitors**

*The next frontier!***
PD-1/PD-L1

PD-1–PD-L1 binding leads to peripheral CD8+ T cell "exhaustion" phenotype

In a state of chronic antigen presentation, such as malignancy, the chronic presence of antigen or pro-inflammatory cytokines (IL-12, IFN-γ, etc.) can upregulate PD-1 expression on the T cell; tumor clones can also select for PD-L1 expression. With PD-1/PD-L1 binding, even in the presence of the co-stimulatory molecule, "peripheral exhaustion" can occur.

PD-L1: programmed death-ligand 1; CD: cluster of differentiation; PD-1: programmed cell death-1; APC: antigen-presenting cells; MHC: major histocompatibility complex; IL: interleukin; IFN-γ: interferon gamma.

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A Phase Ib Study of Pembrolizumab (MK-3475) in Patients With Advanced TNBC
KEYNOTE-012: Triple-Negative Breast Cancer Cohort

- Recurrent or metastatic ER- PR-hormone receptor breast cancer
- ECOG PS 0–1
- PD-L1+ tumor
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

- PD-L1 positivity: 58% of all patients screened had PD-L1-positive tumors
- Treatment: 10 mg/kg IV Q2W
- Response assessment: Performed every 8 weeks per RECIST v1.1

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PD-1 & Breast Cancer

- SABCS 2014 presentation
  - Phase IB study
  - 27 patients with heavily pretreated metastatic TNBC treated with the humanized IgG4κ isotype mAb against PD-1, pembrolizumab
    - 18.5% response rate (1 CR, 4 PR)
    - 7 patients had stable disease
    - Median PFS “just under 2 months”
    - 3 pts remained on treatment for at least 11 months
    - 1 pt died of treatment-related DIC

Time to and Durability of Response
(RECIST v1.1, Central Review)

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response*: not reached (range, 15 to 40+ weeks)

*Kaplan-Meier estimate
Analysis cut-off date: November 10, 2014
courtesy: Rita Nanda, MD
Inhibition of PD-L1 by MPDL3280A leads to clinical activity in TNBC
Emens et al. AACR 2015 Abst. 2859

- Metastatic TNBC expansion cohort as part of Phase Ia study
- N =27
- ORR =24% (3 PR; 2 CR)
- 24 week PFS = 33%
- Toxicity tolerable
- 0.1-41.6 week duration; median duration not reached

Avelumab (MSB0010718C), an anti-PD-L1 Antibody, in Patients with Locally Advanced or Metastatic Breast Cancer: a Phase IB JAVELIN Solid Tumor Trial

Courtesy of Dirix et al. SABCS 2015 abs S1-04
JAVELIN: Phase Ib Study Design

Pts with refractory or progressive locally advanced or MBC (N = 168)*

Avelumab 10 mg/kg IV Q2W
Dosing until progression

• Primary endpoint: DLT
• Secondary endpoints: clinical activity, immune response, safety
• PD-L1 expression assessed by IHC

*Pts eligible if ≤ 3 previous cytotoxic regimens, previous treatment with taxane + anthracycline, biopsy/tissue sample taken within 90 days of avelumab initial dose, ECOG PS 1 or 2, ≥ 1 quantifiable lesion, life expectancy ≥ 3 mos.
Pts unselected for PD-L1 expression, HER2/ER/PR subtype.

JAVELIN: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Pts (N = 168)</th>
<th>Pts With TNBC (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>55 (31-81)</td>
<td>52.5 (31-80)</td>
</tr>
<tr>
<td>Female, %</td>
<td>99.4</td>
<td>100</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 0</td>
<td>49.4</td>
<td>56.9</td>
</tr>
<tr>
<td>• 1</td>
<td>50.6</td>
<td>43.1</td>
</tr>
<tr>
<td>Molecular subtype, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TNBC</td>
<td>34.5</td>
<td>100</td>
</tr>
<tr>
<td>• HER2-/ER+ or HER2-/PgR+</td>
<td>42.9</td>
<td>--</td>
</tr>
<tr>
<td>• HER2+</td>
<td>15.5</td>
<td>--</td>
</tr>
<tr>
<td>• Unknown</td>
<td>7.1</td>
<td>--</td>
</tr>
<tr>
<td>Previous regimens,* %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ 3</td>
<td>52.4</td>
<td>22.4</td>
</tr>
<tr>
<td>• 2</td>
<td>20.8</td>
<td>27.6</td>
</tr>
<tr>
<td>• ≤ 1</td>
<td>26.8</td>
<td>50.0</td>
</tr>
<tr>
<td>Median time since Dx of MBC, mos (range)†</td>
<td>21.6 (0.7-176.8)</td>
<td>13.2 (0.7-176.8)</td>
</tr>
</tbody>
</table>

*Excluding neoadjuvants. †Missing data in 8 pts.

Courtesy of Dirix et al. SABCS 2015 abs S1-04
JAVELIN: Antitumor Activity

<table>
<thead>
<tr>
<th>Best Overall Response, %</th>
<th>All Pts (N = 168)</th>
<th>Pts With TNBC (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>4.2</td>
<td>8.6</td>
</tr>
<tr>
<td>SD*</td>
<td>23.2</td>
<td>22.4</td>
</tr>
<tr>
<td>PD</td>
<td>63.1</td>
<td>65.5</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>8.9</td>
<td>3.4</td>
</tr>
<tr>
<td>ORR</td>
<td>4.8 (95% CI: 2.1-9.2)</td>
<td>8.6 (95% CI: 2.9-19.0)</td>
</tr>
<tr>
<td>DCR†</td>
<td>28.0</td>
<td>31.0</td>
</tr>
</tbody>
</table>

*Defined as SD at first assessment after 6 wks.
†Defined as response plus SD.
JAVELIN: ORR According to PD-L1 Expression

- ORR increased in pts with PD-L1–positive tumors
  - Pts with PD-L1 expression by immune cells showed greater response than pts with PD-L1–negative immune cells (33.3% [4/12] vs 2.4% [3/124])
  - PD-L1 expression also appeared associated with ORR in subgroup with TNBC (4 of 9 PD-L1 positive vs 1/39 PD-L1 negative)


Safety and Clinical Activity pf Atezolizumab (anti-PDL1) in Combination with nab-Paclitaxel in Patients with Metastatic Triple-Negative Breast Cancer


Courtesy of Adams et al. SABCS 2015 P2-11-06
Treatment & Biopsy Schedule

Table 3. Summary of Best Overall Responses by RECIST v1.1

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>1L (n = 9)</th>
<th>2L (n = 8)</th>
<th>3L+ (n = 7)</th>
<th>All Patients N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR (95% CI)</strong></td>
<td>66.7% (29.9, 92.5)</td>
<td>25% (3.2, 65.1)</td>
<td>28.6% (3.7, 71.0)</td>
<td>41.7% (22.1, 63.4)</td>
</tr>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>88.9% (51.7, 99.7)</td>
<td>75.0% (34.9, 96.8)</td>
<td>42.0% (9.9, 81.6)</td>
<td>70.9% (48.9, 87.4)</td>
</tr>
<tr>
<td>CR</td>
<td>11.1%</td>
<td>0</td>
<td>0</td>
<td>4.2%</td>
</tr>
<tr>
<td>PR</td>
<td>77.8%</td>
<td>75.0%</td>
<td>42.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>SD</td>
<td>11.1%</td>
<td>25.0%</td>
<td>28.6%</td>
<td>20.8%</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>28.6%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

* Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.
* Including investigator-assessed unconfirmed responses.
Table 5. Objective Response Rate by PD-L1 Expression Level

<table>
<thead>
<tr>
<th></th>
<th>IC0 (n = 7)</th>
<th>IC1/2/3 (n = 9)</th>
<th>Unknown (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>57.1% (18.4, 90.1)</td>
<td>77.8% (40.0, 97.2)</td>
<td>75% (34.9, 96.8)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>12.5%</td>
</tr>
<tr>
<td>PR</td>
<td>57.1%</td>
<td>77.8%</td>
<td>62.5%</td>
</tr>
<tr>
<td>SD</td>
<td>42.9%</td>
<td>22.2%</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Including investigator-assessed unconfirmed responses.

Courtesy of Adams et al. SABCS 2015 P2-11-06

CTLA-4

CTLA-4 acting as physiologic "brake" on costimulation of CD8+ T cell

CTLA4 outcompetes CD8 for CD80 and CD86, and the costimulatory signal ceases as the target is eliminated, reducing the release of pro-effector cytokines such as IL-12 and cytotoxic enzymes such as perforin and granzyme B. Homeostasis is restored.


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NU 15B01
PI: Cesar Santa-Maria

• Non-randomized, open-label, pilot phase II clinical trial of the PD-L1 inhibitor, durvalumab (MEDI4736), in combination with the CTLA-4 inhibitor, tremelimumab, in patients with stage IV HER2-negative breast cancer (hormone-refractory & TNBC)

NU 15B01

• Durvalumab (MEDI4736)
  – Human IgG1κ monoclonal antibody directed against human PD-L1
  – Currently being evaluated in three phase I clinical trials

• Tremelimumab
  – IgG2κ isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) aka CD152
  – 10 clinical studies
  – Response rates generally low (~10%)
  – Responses are durable, lasting months to years even in subjects with aggressive tumors, such as refractory metastatic melanoma
Key Inclusion Criteria

- Stage IV HER2-negative breast cancer
- TNBC: must have progressed through at least 1 prior chemotherapy regimen in the metastatic setting or within 12 months of last adjuvant systemic tx
- ER positive disease: must have received prior therapy with palbociclib (in addition to 1 line of chemotherapy and standard hormone therapy options) prior to enrollment in the study
- ECOG PS 0-2
- Willing to provide fresh biopsies prior to enrollment & after 2 cycles of treatment

Big Questions in ER+ MBC

- Overcoming endocrine resistance
- Role for endocrine monotherapy
- New partners for endocrine therapy
- Challenges is certain subsets (ER+/HER+)
ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

Postmenopausal Patients
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator ( exemestane)
- Exemestane + everolimus
- Palbociclib + letrozole
- Palbociclib + fulvestrant (category 1)
- Fulvestrant
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

BINV-N
Distribution of Mutations in TCGA by Breast Cancer Subtype

Phase II PALOMA-1/TRIO-18:
Let +/- Palbociclib 1st line ER+ MBC

Stratification Factors:
- Disease site (visceral vs bone only vs either)
- Disease-free interval (>12 vs ≤12 mo from and of adjuvant to recurrence or de novo advanced disease)
PALOMA3: A Double-Blind, Phase III Trial of Fulvestrant with or without Palbociclib in Pre- and Post-Menopausal Women with Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer that Progressed on Prior Endocrine Therapy

Phase III PALOMA-3: Fulvestrant +/- Palbociclib 2nd line ER+ MBC

- 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

腭

2:1 Randomization
N=521

Palbociclib
(125 mg QD;
3 wks on/1 wk off)
- Fulvestrant
(500 mg IM q4w)

Placebo
(3 wks on/1 wk off)
- Fulvestrant
(500 mg IM q4w)

n=347
n=174

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

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

Nicholas Turner at 2015 ASCO Annual Meeting

Progression-free Survival.

Central Assessment

Palbociclib–fulvestrant (N=147)
Median progression-free survival, NE

Placebo–fulvestrant (N=64)
Median progression-free survival, 3.7 mo (95% CI, 1.4–7.2)

Hazard ratio, 0.27 (95% CI, 0.16–0.46)
P<0.001

No. at Risk
Palbociclib–
fulvestrant
Placebo–
fulvestrant
147 118 53 24 7 2
64 37 12 4 1 1


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Summary of Key Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib + Fulvestrant (n=347), % of patients</th>
<th>Placebo + Fulvestrant (n=174), % of patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>10.4</td>
<td>6.3</td>
<td>0.1582</td>
</tr>
<tr>
<td>CBR*</td>
<td>34.0</td>
<td>19.0</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

* CBR is underestimated.
36% of palbociclib and 24% of placebo pts remain on study treatment with <24 weeks of follow up.

At the time of the interim analysis, OS data was immature with 28 deaths.

CBR=clinical benefit rate (CR+PR+SD>24 wk); CR=complete response; ORR=objective response (CR+PR); OS=overall survival; PR=partial response; SD=stable disease.

Phase III PALOMA-2: Letrozole +/- Palbociclib 1st Line ER+ MBC

~450 patients
Postmenopausal women
ER(*)/HER2( ) MBC
1st line

2:1 Randomization
Stratification: Disease site (visceral vs. not)
Disease-free interval (de novo metastatic, ≤12 mo, >12 mo)
Prior anti-cancer therapy (hormonal vs not)

Palbociclib (125 mg qd 21 d on, 7 d off) + Letrozole (2.5 mg daily)  
Placebo (21 d on, 7 d off) + Letrozole (2.5 mg daily)
Abemaciclib Monotherapy in Advanced or Metastatic Breast Cancer

Change in tumor size at best response

<table>
<thead>
<tr>
<th>Category</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (all)</td>
<td>12/47 (25.5%)</td>
</tr>
<tr>
<td>ORR (HR+)</td>
<td>12/36 (33.3%)</td>
</tr>
<tr>
<td>ORR (HR-)</td>
<td>0/9 (0%)</td>
</tr>
</tbody>
</table>

Best Change in Tumor Size from Baseline with Abemaciclib Combined with Other Therapies


* For this patient, change in tumor size is greater than 100%.
**PENELOPE-B Phase III Trial**

N = 800 pts. with HR+/HER2- breast cancer
no PCR and
CPS-EG score ≥ 3

Neoadjuvant Chemotherapy → Surgery +/- Radiotherapy → R

Palbociclib
125 mg once daily p.o.
d1-21, q28d for 13 cycles

Placebo
d1-21, q28d for 13 cycles

All patients will receive concomitantly endocrine therapy according to local standards

**PALLAS Phase III Trial**

Patient Population
- N = 4000
- Inclusion Criteria:
  - HR+ and HER2-
  - Stage II or III

Randomize

Arm A: Palbociclib at a dose of 125 mg once daily, day 1-21 in a 28-day cycle for total duration of 2 years, in addition to standard adjuvant endocrine therapy

Arm B: Standard adjuvant endocrine therapy (AI, tamoxifen, LHRH agonist)

Stratification Factors:
- disease stage (IIIA vs IIIB)
- estrogen receptor (ER)-positive (≥1% vs <1%)
- age (≥ 50 yrs vs < 50 yrs)
- Geographic region (North America vs Europe vs Asia)

NCT01864746
CDK 4/6 Inhibitor Abemaciclib: Ongoing trials

- MONARCH 2 (NCT02327703) Phase III 1st or 2nd line
  - abemaciclib + fulvestrant
  - placebo + fulvestrant

- NCT0205133 Phase I 2 arms are 2nd line therapy
  - abemaciclib + luteinizing
d  - abemaciclib + anastrozole
d  - abemaciclib + goserelin

- MONARCH 3 (NCT01009654) Phase III
  - abemaciclib + anastrozole
  - abemaciclib + letrozole
  - placebo + anastrozole
  - placebo + letrozole

- MONARCH 1 (NCT0216350) Phase II
  - abemaciclib + exemestane
  - abemaciclib + exemestane + everolimus

CDK 4/6 Inhibitor Ribociclib (LEE011): Ongoing trials

- LEE011 + letrozole
- LEE011 + fulvestrant
- LEE011 + buparlisib + letrozole

- NCT01877289 Phase Ib/II
  - LEE011 + letrozole
  - BYL719 + letrozole
  - LEE011 + BYL719 + letrozole

- NCT01947183 Phase Ib/II
  - LEE011 + everolimus + exemestane

- NCT02147276 Phase I 1st or 2nd line
  - LEE011 + buparlisib + letrozole

- NCT03045587 Phase Ib/II
  - LEE011 + bmk120 + fulvestrant

- NCT03058989 Phase Ib/II
  - LEE011 + BYL719 + fulvestrant + anastrozole
  - LEE011 + fulvestrant
cfDNA Analysis From BOLERO-2 Plasma Samples Identifies a High Rate of ESR1 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 Patel², Maurizio Vo², 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.

eTOR, mammalian target of rapamycin.
**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 month advanced)

**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>P &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

*cfDNA, cell-free DNA; ddPCR, digital polymerase chain reaction; HR+, hormone receptor-positive; HER2−, human epidermal growth factor receptor-negative; NSAIs, non-steroidal aromatase inhibitors; OS, overall survival; PFS, progression-free survival.
Detection and Quantification of ESR1 Mutations by ddPCR

**Y537S mutant droplets**

**Wild type droplets**

Detection and Quantification of ESR1 Mutations by ddPCR

**Frequency of ESR1 Mutations**

- High ESR1 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 (28.8%)</td>
<td>83 (15.3%)</td>
<td>42 (7.8%)</td>
<td>30 (5.5%)</td>
</tr>
<tr>
<td>(74.7% of ITT)</td>
<td></td>
<td></td>
<td></td>
<td></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 ESR1
  - 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)
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></td>
<td></td>
</tr>
<tr>
<td>MT</td>
<td>156</td>
<td>112</td>
<td>20.7 (17.7 - 28.1)</td>
<td>1.40 (1.2 - 1.65)</td>
<td>0.000037</td>
</tr>
<tr>
<td>D538G</td>
<td>83</td>
<td>57</td>
<td>26.0 (19.2-32.4)</td>
<td>1.25 (1.02-1.54)</td>
<td>0.033</td>
</tr>
<tr>
<td>Y537S</td>
<td>42</td>
<td>30</td>
<td>20.0 (13.0-29.3)</td>
<td>2.31 (1.34-3.97)</td>
<td>0.0024</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

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></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>0.16</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 (0.75-1.75)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; MT, mutation; OS, overall survival; WT, wild-type.
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></td>
<td>EVE + EXE</td>
<td>257</td>
<td>172</td>
<td>8.5 (6.9-9.9)</td>
<td>0.34 (0.2-0.0000)</td>
<td>01</td>
</tr>
<tr>
<td>D538G</td>
<td>EXE</td>
<td>24</td>
<td>22</td>
<td>2.7 (1.4-2.8)</td>
<td>0.57</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>EVE + EXE</td>
<td>59</td>
<td>45</td>
<td>5.8 (4.2-8.4)</td>
<td>0.98 (0.49-1.94)</td>
<td>0.95</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></td>
<td>EVE + EXE</td>
<td>21</td>
<td>19</td>
<td>4.2 (1.4-5.4)</td>
<td>0.53 (0.23-1.25)</td>
<td>0.15</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>0.53 (0.23-1.25)</td>
<td>0.15</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
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

Abstract #S6-01


Rationale for Combination of Fulvestrant With Buparlisib

- The PI3K/mTOR pathway is the most frequently altered oncogenic pathway in ER+ breast cancer. PIK3CA mutations present in approximately 35% of ER+ breast cancer1
- PI3K/mTOR pathway activation is a hallmark of HR+/HER2- breast cancer cells that have developed resistance to endocrine therapy2,3
- PI3K inhibitors upregulate ER expression and transcriptional activity3
- Therefore, dual blockade of the PI3K/mTOR and ER pathways may act synergistically and help overcome resistance to endocrine therapies2,4,5


Rationale for Combination of Fulvestrant With Buparlisib

- Buparlisib (BKM120) is an oral pan-class I PI3K inhibitor that targets all four isoforms of PI3K (α, β, γ, δ)\(^1\)
- 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

<table>
<thead>
<tr>
<th>PI3K Isoform</th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</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>

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 full population
- 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)

**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†

BELLE-2: ClinicalTrials.gov NCT01610284.
*PI3K pathway activation (activated, non-activated, unknown) was assessed in archival tumor tissue provided at screening, defined as PIK3CA mutation by Sanger sequencing (any mutations in exons 1, 7, 9, or 20) and/or loss of PTEN expression by immunohistochemistry (1+ expression in <10% of cells); †ctDNA PIK3CA status was assessed by Sequenom technology.

BELLE-2 Key Inclusion and Exclusion Criteria

**Key Inclusion Criteria**

- Postmenopausal women with ER+ and/or PgR+ and HER2– inoperable locally advanced or metastatic breast cancer
- Disease progression on/after AI therapy:
  - Recurrence during or ≤12 months from end of adjuvant AI therapy
  - Progression on AI therapy for advanced/metastatic disease
- Measurable disease or non-measurable lytic or mixed bone lesions (RECIST v1.1)
- Tumor tissue for analysis of PI3K-related biomarkers

**Key Exclusion Criteria**

- Prior therapy with a PI3K, AKT, or mTOR inhibitor, or fulvestrant
- More than one prior chemotherapy line for metastatic disease
- History of, or active, anxiety, depression, or other major psychiatric disorders (measured using validated questionnaires)


BELLE-2 Statistical Assumptions

<table>
<thead>
<tr>
<th>Population</th>
<th>Assumed median PFS improvement, months</th>
<th>One-sided alpha*</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full population</td>
<td>7.5 vs 5.0</td>
<td>0.014</td>
<td>99.9%</td>
</tr>
<tr>
<td>Main population</td>
<td>7.5 vs 5.0</td>
<td>0.02</td>
<td>91.8%</td>
</tr>
<tr>
<td>PI3K activated group</td>
<td>8.33 vs 5.0</td>
<td>0.01</td>
<td>93.6%</td>
</tr>
</tbody>
</table>

Statistical significance would be achieved if hazard ratio is <0.86 in the full population

*Alpha allocation was split using a graphical gate-keeping approach to test the multiple primary endpoints, conserving the overall type-1 error at one-sided α = 0.025


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## Patient Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buparlisib + fulvestrant (n = 576)</th>
<th>Placebo + fulvestrant (n = 571)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62 (26–90)</td>
<td>61 (31–90)</td>
</tr>
<tr>
<td>ECOG performance status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>97.6</td>
<td>96.2</td>
</tr>
<tr>
<td>1</td>
<td>40.1</td>
<td>37.6</td>
</tr>
<tr>
<td>Hormone receptor status, %</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>PI3K pathway activation status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated</td>
<td>32.6</td>
<td>32.4</td>
</tr>
<tr>
<td>Non-activated</td>
<td>41.6</td>
<td>42.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>26.9</td>
<td>25.7</td>
</tr>
<tr>
<td>Visceral disease present, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>59.2</td>
<td>59.6</td>
</tr>
<tr>
<td>Prior therapy in metastatic setting, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hormonal therapy</td>
<td>72.6</td>
<td>76.1</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>Prior lines of hormonal therapy in metastatic setting, %</td>
<td>27.4</td>
<td>24.9</td>
</tr>
<tr>
<td>≥2</td>
<td>19.4</td>
<td>22.4</td>
</tr>
</tbody>
</table>


## BELLE-2 Patient Disposition and Exposure to Study Treatment

<table>
<thead>
<tr>
<th>Patient disposition, %</th>
<th>Buparlisib + fulvestrant (n = 576)</th>
<th>Placebo + fulvestrant (n = 571)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment phase ongoing</td>
<td>16.1</td>
<td>16.5</td>
</tr>
<tr>
<td>Treatment discontinued</td>
<td>83.5</td>
<td>83.2</td>
</tr>
<tr>
<td>Primary reason for treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression of disease</td>
<td>54.3</td>
<td>55.7</td>
</tr>
<tr>
<td>Adverse event</td>
<td>16.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Patient decision</td>
<td>8.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Death</td>
<td>4.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Exposure to study treatment

<table>
<thead>
<tr>
<th>Buparlisib + fulvestrant (n = 573)</th>
<th>Placebo + fulvestrant (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment exposure, months</td>
<td></td>
</tr>
<tr>
<td>Buparlisib/placebo median relative dose intensity, %</td>
<td>93.2</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>46.4</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>55.8</td>
</tr>
</tbody>
</table>

BELLE-2 Safety Profile Was Characterized by Transaminitis, Hyperglycemia, 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>93.6</td>
<td>27.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>40.1</td>
<td>10.7</td>
<td>6.8</td>
<td>6.8</td>
<td>1.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>37.3</td>
<td>15.0</td>
<td>3.0</td>
<td>9.3</td>
<td>2.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>43.1</td>
<td>16.2</td>
<td>0.2</td>
<td>7.7</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>32.1</td>
<td>7.7</td>
<td>0.2</td>
<td>6.3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22.3</td>
<td>5.2</td>
<td>0.2</td>
<td>5.2</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31.9</td>
<td>4.9</td>
<td>0.0</td>
<td>23.9</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Depression</td>
<td>26.2</td>
<td>3.0</td>
<td>0.0</td>
<td>8.9</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34.2</td>
<td>3.7</td>
<td>0.7</td>
<td>14.6</td>
<td>1.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.1</td>
<td>2.8</td>
<td>0.0</td>
<td>10.5</td>
<td>1.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21.6</td>
<td>2.1</td>
<td>0.0</td>
<td>6.5</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>36.7</td>
<td>1.7</td>
<td>0.0</td>
<td>23.2</td>
<td>1.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>29.8</td>
<td>1.6</td>
<td>0.0</td>
<td>11.1</td>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- Serious adverse events occurred in 23.4% of patients in the buparlisib arm vs 15.8% in the placebo arm
- 12 on-treatment deaths (2.1%) were reported in each arm in the full population, the majority due to disease progression


BELLE-2 Met the Primary Endpoint for PFS Improvement in the Full Population

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided P value .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 Improvement in the PI3K Activated Group Was Not Statistically Significant

- **Median PFS, months (95% CI)**
  - Buparlisib + fulvestrant: 6.8 (4.9–7.1)
  - Placebo + fulvestrant: 4.0 (3.1–5.2)

- **HR (95% CI)**: 0.76 (0.60–0.97)
  - One-sided *P*-value*: .014

BELLE-2 Prospectively Evaluated PIK3CA Mutation Status in ctDNA

- There are substantial limitations in utilizing archival tumor tissue for PI3K testing in patients with metastatic disease, including tumor evolution under selective pressure, sample bias, and tumor heterogeneity
  - Approximately 80% of archival tissue biopsy samples were obtained from the primary tumor
  - ctDNA obtained from blood samples has emerged as a sensitive, reliable, and minimally invasive way to measure current PIK3CA mutation status

- In BELLE-2, ctDNA from 587 patients was analyzed for PIK3CA mutations by BEAMing technology
  - Baseline patient characteristics were generally balanced in the full and ctDNA populations; based on sensitivity analyses, any imbalances did not influence the efficacy outcome

BEAMing, beads, emulsification, amplification, and magnets; ctDNA, circulating tumor DNA.


Buparlisib Plus Fulvestrant Produced A Clinically Meaningful PFS Improvement in Patients With ctDNA PIK3CA Mutations

<table>
<thead>
<tr>
<th>ctDNA PIK3CA Mutant n = 200</th>
<th>Buparlisib + fulvestrant n = 87</th>
<th>Placebo + fulvestrant n = 113</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</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;.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ctDNA PIK3CA Non-mutant n = 387</th>
<th>Buparlisib + fulvestrant n = 199</th>
<th>Placebo + fulvestrant n = 188</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.8 (4.7–8.5)</td>
<td>6.8 (4.7–8.6)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.05 (0.82–1.34)</td>
<td></td>
</tr>
<tr>
<td>One-sided nominal P value</td>
<td>.642</td>
<td></td>
</tr>
</tbody>
</table>


Buparlisib Plus Fulvestrant Resulted in Higher Response Rates in Patients With ctDNA PIK3CA Mutations

Conclusions

- The BELLE-2 study met its primary endpoint, demonstrating a modest PFS improvement for combined buparlisib and fulvestrant in postmenopausal women with HR+/HER2– advanced breast cancer that had progressed after prior AI therapy
- Frequent discontinuations due to adverse events reduced treatment duration in the buparlisib arm, potentially limiting the efficacy of combination therapy
- Patients with tumors harboring PIK3CA mutations in ctDNA performed poorly on fulvestrant monotherapy, achieving a clinically meaningful PFS improvement with the combination
  - 3.8 month PFS improvement was supported by higher response rates (18.4% vs 3.5%) in this patient population
- The BELLE-2 study suggests that assessment of PIK3CA mutations in ctDNA may help select patients who would benefit from adding a PI3K inhibitor to endocrine therapy
- Phase III studies with PI3Kα-selective inhibitors are underway to confirm the predictive value of PIK3CA mutations detected in ctDNA and tumor tissue


Conclusions:
SABCS 2015/NCCN 2016

- Significant progress in HER2 + disease with new agents under evaluation
- TNBC remains a huge challenge, molecular interrogation of the tumor may lead to better options; Immunologic strategies in their infancy
- Monotherapy for ER+ disease is now losing to a strategy of combining with novel agents