Late Stage Breast Cancer, Including SABCS Updates

Presented by:
William J. Gradishar, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

March 11, 2016

Moderated by Rose K. Joyce
NCCN, Conferences and Meetings Department

This activity is supported by educational grants from AstraZeneca, Celgene Corporation, Genomic Health, Inc., Lilly, Novartis Oncology, and Pfizer.
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• Please use the Q&A feature on the right-hand portion of your screen for any clinical questions and logistical concerns you have regarding the session. This is the only online method of communicating questions or concerns. Should you need additional assistance please e-mail education@nccn.org or call 215-690-0300 and ask to be connected with someone in the NCCN Conferences and Meetings Department.

• While NCCN is pleased to respond to as many questions as possible during this webinar, NCCN will not be able to respond to your individual questions of a clinical nature after the webinar has concluded. We are also not able to offer recommendations on patient care regarding specific cases.

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• If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.

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• If you have not individually registered, please register at: http://www.cvent.com/d/9fqzgs.
Accreditation Information

Intended Audience
This educational program is designed to meet the educational needs of oncologists, nurses, pharmacists, and other health care professionals who manage patients with breast cancer.

Learning Objectives
Following this program, participants should be able to:

• Analyze critical clinical considerations in choosing the most appropriate treatment regimen for a given patient with advanced breast cancer.

• Compare the risks and benefits of the newer options available for the treatment of patients with HER2-positive disease to limit toxicities and optimize outcomes.

• Assess the risks and benefits of current and emerging agents in order to appropriately integrate them into the treatment of patients who have developed resistance to endocrine therapy.

Accreditation Information

Physicians
National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

National Comprehensive Cancer Network designates this web-based activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.
Accreditation Information

Pharmacists

Pharmacy Educational Objective: After completing this activity, the participant should be able to:
• Provide accurate and appropriate counsel as part of the treatment team.

Accreditation Statement
National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of Activity: Knowledge

UAN: 0836-0000-16-019-L01-P

Credit Designation: National Comprehensive Cancer Network designates this continuing education activity for 1.0 contact hour (0.10 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

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To comply with ACPE standards, pharmacists must complete all activity requirements within 30 days of the live event date.

Accreditation Information

How to Claim Credit:

Within 5 business days after this educational program, you will receive an e-mail with information on how to claim credit for this activity. A statement of credit will be issued only upon completion of the activity evaluation form & immediate post-test within 30 days of the activity date. A certificate will be electronically generated immediately upon completion of the evaluation.

All credit claiming must be done online through NCCN’s continuing education portal at education.nccn.org/node/78125.

Should you not receive an e-mail within 5 days, please contact us at education@nccn.org.
Accreditation Information

- It is required by the ACCME that all educational activities are designed to change participant competence, performance, or patient outcomes.
- To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:
  - The post-test and evaluation as indicated in e-mail you will receive within 3-5 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.
  - There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.
  - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at http://education.nccn.org. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail education@nccn.org.

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All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.
Faculty Disclosures

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Faculty Disclosures
The faculty listed below have no relevant financial relationships to disclose:

William J. Gradishar, MD

NCCN Staff Disclosures

NCCN Staff Disclosures
The activity planning staff listed below has no relevant financial relationships to disclose:

Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Deborah Moonan, RN, BSN; Liz Rieder; Shannon K. Ryan; Kathy Smith, CMP, CHCP; Jennifer McCann Weckesser

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Dorothy Shead, MS
Faculty Biography

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.

Late Stage Breast Cancer, Including SABCS Updates

Advances in Treatment of MBC: NCCN Update & SABCS 2015 Review

William J. Gradishar, MD

Betsy Bramsen Professor of Breast Oncology
Director, Maggie Daley Center for Womens’ Cancer Care
Robert H. Lurie Comprehensive Cancer Center
Center of Northwestern University
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

Case: JJ

• 58-year-old woman with a hx of stage III, HER2+, HR-breast cancer rx with adjuvant doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab 5 years ago
• She presents with persistent cough
• CT scan shows 2 right middle/lower lobe nodules (largest is 3.5 cm), 3 smaller lung nodules on left
• CT-guided biopsy of a lung nodule confirms recurrent breast cancer; HR-negative, HER2 3+ by IHC, Brain MRI negative, normal LVEF
Case: JJ

What first-line therapy is associated with the longest overall survival?

A. Capecitabine plus lapatinib
B. Trastuzumab alone
C. Trastuzumab plus chemotherapy
D. Trastuzumab plus pertuzumab plus taxane

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

First-Line Setting
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

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

Sharon H. Giordano, Sarah Torre, Jeffrey I. Kreighner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shashu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

- 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**

- **HER2+ (central) LABC or MBC (N=980)**
  - Prior taxane and trastuzumab
  - Progression on metastatic tx or within 6 mos of adjuvant tx

- **T-DM1**
  - 3.6 mg/kg q3w IV

- **Capecitabine**
  - 1000 mg/m² orally bid, days 1–14.
  - Laptinib 1250 mg/day orally daily

- **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

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**EMILIA: Overall Survival**

<table>
<thead>
<tr>
<th>Treatment</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

Efficiency stopping boundary: P=0.0937 or HR=0.727


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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, Sung-Bae Kim, Antonio Gonzalez Martin, Patricia M. LoRusso, Jean-Marc Ferrero, Tanja Badovinac-Crnjevic, Ron Yu, Melanie Smitt, Ian E. Krop

1University Hospitals Leuven, Leuven, Belgium; 2Asian Medical Center, University of Utah 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

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TH3RESA Study Schema

- HER2-positive (central) advanced BC (N=600)
  - ≥2 prior HER2-directed therapies for advanced BC
  - Prior treatment with trastuzumab, lapatinib, and a taxane

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 BIRAD 2nd intention OS results to allow patients in the TPC arm to receive T-DM1 after documented PD.

*Contact him at hans.wildiers@ulb.ac.be for permission to reprint and/or distributes.
### Treatment of Physician’s Choice Regimen

<table>
<thead>
<tr>
<th>TPC treatment regimen</th>
<th>TPC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination with HER2-directed agent</td>
<td>83.2</td>
</tr>
<tr>
<td>Chemotherapy + trastuzumab</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 + lapatinib</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Single-agent chemotherapy: 16.8%

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### Final OS Analysis

- **TPC (n=216)**
  - Median (months): 15.8
  - Stratified HR: 0.68 (95% CI: 0.54-0.85)
  - *P* = 0.0007

- **T-DM1 (n=210)**
  - Median (months): 22.7

**Pre-specified crossing boundary:** HR = 0.748; *P* = 0.012

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MARIANNE Phase III

N=1092 HER2+ MBC First-line

Taxane + Trastuzumab

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
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 (no.)</td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>—</td>
<td>0.91</td>
<td>0.72-1.13</td>
</tr>
<tr>
<td>(97.5% CI) vs HT</td>
<td></td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Stratified HR</td>
<td>—</td>
<td>0.91</td>
<td>0.72-1.13</td>
</tr>
<tr>
<td>(97.5% CI) vs T-DM1</td>
<td></td>
<td></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

DFI = disease free interval from neoadjuvant or adjuvant setting
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

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>Basal-like 1 (BL1)</td>
<td>Cell-cycle, proliferation and DNA damage response genes</td>
</tr>
<tr>
<td>Basal-like 2 (BL2)</td>
<td>Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)</td>
</tr>
<tr>
<td>Immunomodulatory (IM)</td>
<td>Immune cell &amp; cytokine signaling (overlap with medullary signature)</td>
</tr>
<tr>
<td>Mesenchymal (M)</td>
<td>Cell motility and differentiation (Wnt, ALK, TGF-β)</td>
</tr>
<tr>
<td>Mesenchymal stem-like (MSL)</td>
<td>Similar to M, but increased growth factors signaling, low proliferation, enrichment of stem cell genes</td>
</tr>
<tr>
<td>Luminal androgen receptor (LAR)</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:

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)

Ineligible for testing (n=28)

Ineligible for therapy (n=8)

Eligible for therapy: trial closed to accrual (n=15)

Ineligible post therapy (n=2)

12% AR(+)

Clinical Benefit Rate = 21%
(95% CI 7.1-42.1%)

Gucalp et al, ASCO 2012
**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**

<table>
<thead>
<tr>
<th>AR by PREDICT AR+ (n=26)</th>
<th>AR by IHC (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS 40.4 weeks (95% CI: 16.1, NVR)</td>
<td>mPFS 8.5 weeks (95% CI: 3.3–15.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AR by PREDICT AR- (n=30)</th>
<th>AR ≥ 10% (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS 17.6 weeks (95% CI: 9.0–27.4)</td>
<td>AR ≥ 10% (n=47)</td>
</tr>
</tbody>
</table>

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**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

*Prior 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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage with OR at cycle 3 or 6 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>17/25 (68.0%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>6/18 (33.3%)</td>
</tr>
</tbody>
</table>

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

No Germline BRCA 1/2 Mutation (n=273)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage with OR at cycle 3 or 6 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>36/128 (28.1%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>53/145 (36.6%)</td>
</tr>
</tbody>
</table>

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

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

Checkpoint Inhibitors
The next frontier!
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, TGFbeta, 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 costimulatory molecule, "peripheral exhaustion" can occur.

PD-L1: programmed death-ligand 1; CD: cluster of differentiation; PD-1: programmed cell death-1; APC: antigen-presenting cell; MHC: major histocompatibility complex; IL: interleukin; TGFbeta: transforming growth factor beta.

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

- PD-L1 positivity: 68% of all patients enrolled 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)](image)
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)*

- 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.

---

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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)

Courtesy of Dirix et al. SABCS 2015 abs S1-04

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

Red arrow indicates biopsy.
*A second post-dose biopsy was taken in serial biopsy cohort 4 wk after first dose of atezolizumab.

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>Confirmed ORR (95% CI)*</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>ORR (95% CI)*</td>
<td>88.9% (51.7, 99.7)</td>
<td>75.0% (34.9, 96.8)</td>
<td>42.9% (9.0, 81.6)</td>
<td>70.8% (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>IC1/2S (n = 9)</th>
<th>Unknown (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>57.1% (18.4, 90.1)</td>
<td>77.8% (40.0, 97.2)</td>
<td>75% (34.8, 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 CD28 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

Case #2

- A 67 yo WF presents with newly diagnosed bone metastases. She was originally dx with a 3 cm IDC of the left breast 4 years earlier and underwent mastectomy. The tumor was ER+/PR+/HER2- and SLN were negative. A recurrence score was low. Treatment with anastrozole was initiated.
Case #2

• She was doing well until recently when diffuse boney aches were noted not responding to NSAID
• Labs showed an elevated Alk Phos; a bone scan demonstrated several lytic lesion throughout the axial skeleton. CT CAP showed 2 suspicious 1 cm lesion in the liver
• A liver biopsy was consistent with the original dx and remained ER+

In addition to starting a bone agent (bisphosphonate or denosumab) and discontinuing anastrozole, you would:

A. Start chemotherapy
B. Start an alternative AI
C. Start an alternative AI and add palbociclib
D. Start fulvestrant
E. Start fulvestrant and palbociclib
Big Questions in ER+ MBC

- Overcoming endocrine resistance
- Role for endocrine monotherapy
- New partners for endocrine therapy
- Challenges in certain subsets (ER+/HER+)

**Estimated Cancer Deaths From ER+ Breast Cancer**

*ER+ Breast Cancer is Responsible For Approximately 30,000 Deaths Each Year*

- 26% Lung & bronchus
- 10-11% Breast Luminal
- 9% Colon & rectum
- 7% Pancreas
- 5% Ovary
- 4-5% Breast TNBC

- 4% Non-Hodgkin lymphoma
- 3% Leukemia
- 3% Uterine corpus
- 2% Liver & intrahepatic bile duct
- 2% Brain/Other nervous system
- 24% All other sites

O’Brien et al. CCR. 2010
FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE

Continue endocrine therapy until progression or unacceptable toxicity → Progression → No clinical benefit after 3 sequential endocrine therapy regimens or Symptomatic visceral disease → Yes → Chemotherapy

No → Trial of new endocrine therapy

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
The Future (and Present!) Treatment In ER+ MBC

TCGA: Comprehensive Molecular Portraits of Human Breast Tumors

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
Genomic Alterations in 128 Clinically Relevant Genes in 962 TCGA Breast Cancer Samples

Distribution of Mutations in TCGA by Breast Cancer Subtype
Phase II PALOMA-1/TRIO-18: Let +/- Palbociclib 1st line ER+ MBC

**Part 1**
- Palbociclib 125 mg QD + Letrozole 2.5 mg QD
- Same as part 1 but with CCND1 amplification and/or loss of p16

**Part 2**
- Palbociclib 125 mg QD + Letrozole 2.5 mg QD

**Stratification Factors**
- Disease site (visceral vs bone only vs other)
- Disease-free interval (>12 vs ≤12 mo from ad of adjuvant to recurrence or de novo advanced disease)

**Progression-Free Survival (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>41 (49)</td>
<td>59 (73)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.7, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.488 (0.319, 0.748)</td>
<td>0.139 (0.073, 0.261)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.
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

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. 39% 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.
Phase III PALOMA-2: Letrozole +/- Palbociclib 1st Line ER+ MBC

~450 patients
Postmenopausal women
ER+/HER2-/ 1st line

2:1 Randomization
Stratification: Disease site (visceral vs not), Disease-free interval (de novo metastatic ≤ 12 mo, > 12 mo), Prior anticancer 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
- ORR (all): 12/47 (25.5%)
- ORR (HR+): 12/36 (33.3%)
- ORR (HR-): 0/9 (0%)

Tolaney SM et al. SABCS 2014; Abstract 763.
Best Change in Tumor Size from Baseline with Abemaciclib Combined with Other Therapies


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

- LEE011 + letrozole
- BYL719 + letrozole

**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 He3, Aliaksandra Samoila1, Daoqi You1, Trusha Bhatt1, Parul Patel2, 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

<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>

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
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 genetic 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

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 (74.7% of ITT)</td>
<td>156 (28.8%)</td>
<td>83 (15.3%)</td>
<td>42 (7.8%)</td>
<td>30 (5.5%)</td>
</tr>
</tbody>
</table>

*cfDNA, cell free DNA; 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.
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>EVE + EXE</td>
<td></td>
<td>257</td>
<td>172</td>
<td>8.5 (6.9-9.9)</td>
<td>0.34 (0.2-0.0000)</td>
<td>0.01</td>
</tr>
<tr>
<td>D538G</td>
<td>EXE</td>
<td>24</td>
<td>22</td>
<td>2.7 (1.4-2.8)</td>
<td>0.34 (0.2-0.57)</td>
<td>0.95</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>0.98 (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>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

AIs, aromatase inhibitors; cfDNA, cell-free DNA; EVE, everolimus; HR+, hormone receptor-positive; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival.
**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).  
  \[
  \begin{array}{ccccc}
  \text{PI3K Isoform} & \alpha & \beta & \gamma & \delta \\
  \text{IC}_{50}, \text{nM} & 52 & 166 & 262 & 116 \\
  \end{array}
  \]

- Buparlisib has demonstrated preliminary clinical activity in combination with fulvestrant.  
- 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

- Postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer that progressed on/after AI therapy
  - N = 1147

- 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

**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 Illumina 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)


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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><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>97.6</td>
<td>98.2</td>
</tr>
<tr>
<td>1</td>
<td>40.1</td>
<td>37.0</td>
</tr>
<tr>
<td><strong>Hormone receptor status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>96.1</td>
<td>96.6</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>41.0</td>
<td>42.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>26.2</td>
<td>26.7</td>
</tr>
<tr>
<td><strong>Visceral disease present, %</strong></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>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>54.6</td>
<td>44.6</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>

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>Progressive disease</td>
<td>54.3</td>
<td>73.0</td>
</tr>
<tr>
<td>Adverse event</td>
<td>13.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Patient decision</td>
<td>8.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Physician decision</td>
<td>4.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Death</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure to study treatment</th>
<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>4.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Buparlisib/placebo median relative dose intensity, %</td>
<td>93.2</td>
<td>100</td>
</tr>
<tr>
<td>Buparlisib/placebo dose adjustments, %</td>
<td>94.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>43.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>55.8</td>
<td>31.4</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>92.5</td>
<td>33.2</td>
<td>14.1</td>
<td>93.0</td>
<td>27.4</td>
<td>7.0</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>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23.3</td>
<td>5.2</td>
<td>0.2</td>
<td>6.2</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31.8</td>
<td>4.9</td>
<td>0</td>
<td>23.8</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>20.7</td>
<td>3.7</td>
<td>0.1</td>
<td>8.9</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24.2</td>
<td>3.3</td>
<td>0</td>
<td>14.8</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.1</td>
<td>4.9</td>
<td>0.1</td>
<td>10.9</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>36.7</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>29.8</td>
<td>1.6</td>
<td>0</td>
<td>11.1</td>
<td>0.2</td>
<td>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

<table>
<thead>
<tr>
<th></th>
<th>Buparlisib + fulvestrant (N = 576)</th>
<th>Placebo + fulvestrant (N = 571)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>6.9 (6.8–7.8)</td>
<td>5.0 (4.0–5.2)</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.78 (0.67–0.89)</td>
<td>One-sided <strong>P</strong> value &lt; .001</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th></th>
<th>Buparlisib + fulvestrant (N = 188)</th>
<th>Placebo + fulvestrant (N = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>6.8 (4.9–7.1)</td>
<td>4.0 (3.1–5.2)</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.76 (0.60–0.97)</td>
<td>One-sided <strong>P</strong> value* .014</td>
</tr>
</tbody>
</table>

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

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\(^1\)-\(^4\)
- In BELLE-2, ctDNA from 587 patients was analyzed for *PIK3CA* mutations by BEAMing technology\(^4\)
  - 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 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 (4.7–8.6)</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>.542</td>
<td></td>
</tr>
</tbody>
</table>

Buparlisib + fulvestrant (n/N = 48/87) Placebo + fulvestrant (n/N = 90/113)

Buparlisib + fulvestrant (n/N = 124/199) Placebo + fulvestrant (n/N = 128/188)

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

Q&A SESSION
Upcoming Webinars — Register at NCCN.org/events

- Recognition and Management of Toxicities Associated with the Treatment of Renal Cell Carcinoma Supportive Care: Fertility Preservation & Use of Bone Modifying Agents in Patients with Breast Cancer
  Thursday, March 17 at 2:00 PM [EDT]
  Joanne Frankel Kelvin, MSN, RN, CNS, AOCN, Memorial Sloan Kettering Cancer Center
  John H. Ward, MD, Huntsman Cancer Institute at the University of Utah

- Early Stage Breast Cancer: Role of Multigene Assays & SABCS Updates on Adjuvant & Neoadjuvant Therapies
  Friday, April 8 at 2:30 PM [EDT]
  Matthew Goetz, MD, Mayo Clinic Cancer Center
  Sarika Jain, MD, MSCI, Robert H. Lurie Comprehensive Cancer Center of Northwestern University
  Cesar A. Santa-Maria, MD, Robert H. Lurie Comprehensive Cancer Center of Northwestern University

- Early Stage Breast Cancer: Adjuvant Radiation, Surgical Management, & SABCS Updates on Local Therapy
  Friday, April 22 at 8:45 AM [EDT]
  Benjamin O. Anderson, MD, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
  Seema A. Khan, MD, Robert H. Lurie Comprehensive Cancer Center of Northwestern University
  Kilian E. Salerno, MD, Roswell Park Cancer Institute

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