Innovations in the Targeted Treatment of Malignancy: Focus on Breast Cancer

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Director, Breast Oncology Program
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Breast Cancer: Lecture Objectives

• Molecular characterization of breast cancer
• Hormone receptor positive breast cancer
  – Endocrine therapy: Tam vs AI’s
  – The future? CDK4/6 inhibitors?
• HER2+ breast cancer
  – HER2-targeted therapy
  – Metastatic: Pertuzumab, T-DM1
• PARP inhibitors: BRCA mutated cancer
Evolving understanding of molecular subtypes
Breast Cancer: The first cancer described?

- Edwin Smith Papyrus
- Egypt 1600 BC
- Treatment: cautery with “Fire drill” or removal with sharpened instruments

Plates vi & vii of the Edwin Smith Papyrus; Rare Book Room, New York Academy of Medicine
Classification: Histologic vs. Biologic Subtypes

Rudolf Ludwig Karl Virchow (1821-1902)

Die Krankhaften Geschwülste 1863
<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Frequency</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrating Ductal</td>
<td>70-80%</td>
<td>When DCIS is associated, goal is to obtain surgical margins clear of both invasive tumor and DCIS to reduce risk of recurrence</td>
</tr>
<tr>
<td>Invasive Lobular</td>
<td>5-10%</td>
<td>LCIS or DCIS; higher freq bilateral &amp; multicentric, spread to unusual locations (meninges, peritoneum, GI)</td>
</tr>
<tr>
<td>Mucinous/Colloid</td>
<td>2.4%</td>
<td>Well circumscribed, tumor cells dispersed in large pools of extracellular mucus; uniform, low grade nuclei, prognostically favorable variant of invasive breast carcinoma.</td>
</tr>
<tr>
<td>Metaplastic</td>
<td>&lt;5%</td>
<td>Poorly differentiated ductal carcinoma combined with squamous cell carcinoma and/or various forms of sarcomatous differentiation; tends to be resistant to chemotherapy</td>
</tr>
<tr>
<td>Tubular</td>
<td>&lt;5%</td>
<td>Well differentiated, low-grade, unusual pre-mmg era, now more common, indolent and rarely metastasizes</td>
</tr>
<tr>
<td>Medullary</td>
<td>&lt;5%</td>
<td>Poorly differentiated, lymphoplasmacytic infiltrate, prognosis more favorable despite aggressive histologic features, associated with BRCA1, usually ER-PR-</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>&lt;5%</td>
<td>Aggressive with lymph node metastases even when small</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>&lt;5%</td>
<td>Rare, morphologically identical to that of salivary glands, tends to be favorable prognosis,</td>
</tr>
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Revolutionary Realization:
Breast Cancer is Not All One Disease

Sorlie et al PNAS 2001
A major shift in how we classify cancers is leading to a major change in how we treat cancers.

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<td><em>Tumors classified by how they look under the microscope and their organ of origin</em></td>
<td><em>Tumors treated with chemotherapy that kills all rapidly dividing cells</em></td>
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<td><strong>Present &amp; Future</strong></td>
<td><em>Tumors classified by the molecular problems that cause them to behave like cancer</em></td>
<td><em>Tumors treated with therapy that is rationally targeted toward the molecular defect in tumor cells, thus leaving normal cells alone</em></td>
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Hormonally Driven Cancers
Endocrine Therapy: Hormone Receptors

- ~60-75% breast ca ER+
- Tamoxifen blocks the estrogen receptor
- Ais interfere with the peripheral production of estradiol
Adjuvant Endocrine Therapy

• (Anti)Hormonal Therapy - first kind of targeted therapy

• First recognized in the **1890**, by a Scottish surgeon George Beatson. Learned from Scottish farmers that the removal of ovaries from cows alters their ability to lactate.

• Removed ovaries from 3 women with breast cancer - the breast tumors shrank dramatically, however when repeated on a larger scale in London - only 2/3 of the patients responded.

• Estrogen discovered by Doisy in **1920**

• Estrogen receptor discovered by Elwood Jensen in **1968**
ESTROGEN BLOCKADE: TAMOXIFEN

- **Tamoxifen** is a Selective Estrogen Receptor Modulator—discovered in 1962
  - Blocks the effects of estrogen/competes with estrogen for the receptor binding
  - Has anti-estrogenic effects in the breast
  - Pro-estrogenic effect in the bone
  - Pro-estrogenic effect in the uterus

- Used in both pre/post menopausal women
- Standard of care in premenopausal women (5 years), who make most estrogen in the ovaries
- Teratogenic
5 years of tamoxifen versus no tamoxifen*

**RECURRENT**

<table>
<thead>
<tr>
<th>ER+</th>
<th>Control 46.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>33.0%</td>
</tr>
<tr>
<td>≈ 5 years tamoxifen</td>
<td></td>
</tr>
<tr>
<td>15-y gain 13.0% (SE 1.1)</td>
<td>Logrank 2p &lt; 0.000001</td>
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**BREAST CANCER MORTALITY**

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<tr>
<th>ER+</th>
<th>Control 32.7%</th>
</tr>
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<tr>
<td>5 years</td>
<td>23.6%</td>
</tr>
<tr>
<td>≈ 5 years tamoxifen</td>
<td></td>
</tr>
<tr>
<td>15-y gain 9.1% (SE 1.0)</td>
<td>Logrank 2p &lt; 0.000001</td>
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*EBCTCG, Lancet 2011; 378: 771–84*
10 years tamoxifen reduces breast cancer mortality by a third in first decade and half in second decade

<table>
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<tr>
<th></th>
<th>Tam 5 vs 0 yrs EBCTCG meta-analysis N=10645</th>
<th>Tam 10 vs 5 yrs ATLAS (n=6846)</th>
<th>Tam 10 vs 0 Estimated effect (product of two RRs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Cancer Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years 0-4</td>
<td>RR 0.53 (0.48 -0.57) 2p&lt;0.00001</td>
<td>(1.0)</td>
<td>RR=0.53 (0.48-0.57) 2p&lt;0.00001</td>
</tr>
<tr>
<td>Years 5-9</td>
<td>0.68 (0.60-0.78) P&lt;0.00001</td>
<td>0.90 (0.79-1.02)</td>
<td>0.61 (0.51-0.73) 2p&lt;0.00001</td>
</tr>
<tr>
<td>Years 10+</td>
<td>0.94 (0.79-1.12)</td>
<td>0.75 (0.62-0.90) 2p&lt;0.01</td>
<td>0.70 (0.54-0.91) 2p&lt;0.01</td>
</tr>
<tr>
<td><strong>Breast Cancer Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years 0-4</td>
<td>0.71 (0.62-0.80) P&lt;0.00001</td>
<td>1.0</td>
<td>0.71 (0.62-0.81) P&lt;0.00001</td>
</tr>
<tr>
<td>Years 5-9</td>
<td>0.66 (0.58-0.75) P&lt;0.00001</td>
<td>0.97 (0.79-1.18)</td>
<td>0.64 (0.50-0.82) P=0.0001</td>
</tr>
<tr>
<td>Years 10+</td>
<td>0.73 (0.62-0.86) P=0.0001</td>
<td>0.71 (0.58-0.88) P=0.0016</td>
<td>0.52 (0.40-0.68) P&lt;0.00001</td>
</tr>
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Davies, SABCS 2012
Side effects and therapeutic effects of 10 years of tamoxifen on 15-year mortality in meta-analysis & ATLAS

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<th>Tam 5 vs 0 Meta-analysis (n=10,645)</th>
<th>Tam 10 vs 5 ATLAS (n=6846)</th>
<th>Tam 10 vs 0 (estimated as product of RRs)</th>
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<tr>
<td>Endometrial cancer and PE mortality</td>
<td>0.2% loss</td>
<td>0.2% loss</td>
<td>0.4% loss</td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>9% gain</td>
<td>3% gain</td>
<td>12% gain</td>
</tr>
</tbody>
</table>

Estimated effects of 10 years tamoxifen compared to 0 on 15 year mortality: absolute gain is approx 30 times the absolute loss

Davies, SABCS 2012
Estrogen Production in Post-Menopausal Women

- Produced in small amounts through aromatization of androgens, testosterone, and androstenedione

- Low levels of estrogen production in adrenals, fat, bone, liver and muscle (cancer cells may also have aromatase)

- Aromatase inhibitors block this conversion reducing levels to undetectable

- Women with ovarian function are not candidates for this therapy because ovarian function is not blocked and AI can actually stimulate estrogen production
Adjuvant Endocrine Trials: Efficacy

• Aromatase Inhibitors Began testing in 1990s
  • Anastrozole (Arimidex)
  • Letrozole (Femara)
  • Exemestane (Aromasin)

• Appropriate only for post-menopausal women with ER+ and/or PR+ tumors

• Multiple large randomized phase III clinical trials have been performed, all of which show a 2-6% reduction in the risk of breast cancer recurrence compared to tamoxifen
AIs versus tamoxifen: benefit/risk

- ↓ Osteoporosis risk
- ↓ Musculoskeletal syndrome
- ↓ Cost
- ↓ Neurocognition
- ↓ Sexual function
- ↓ Hyperlipaemia
- ↓ Cardiovascular disease
- ↓ DVT
- ↓ Stroke
- ↓ Endometrial cancer
- ↓ Hot flashes

Patient history

TAMOXIFEN

AI

What may be coming soon for early ER+ breast cancer?

A look at new insights from metastatic ER+ breast cancer:
CDK4/6 inhibitors
Rb as Master-Regulator of the R-point

**Diagram:**
- **G1** to **M**: The cell cycle progresses from G1 to M phase.
- **R point**: The critical point in the cell cycle where Rb regulation occurs.
- **hyperphosphorylation** and **dephosphorylation** pathways are indicated.
- **Target of PD 0332991**: Inactivates Rb and allows progression.

**Key Points:**
- **Extent of pRb phosphorylation**
- **Rb** regulation at the R-point is crucial for cell cycle progression.
- **CDK2 and CDC2** enzymes play a role in the regulation of Rb phosphorylation.

**Annotations:**
- **G1** to **S**: Transition from G1 to S phase.
- **M** to **G1**: Transition from M to G1 phase.

**Symbols:**
- **A** and **B**: Indicate regulatory inputs to the system.
- **D** and **E**: Indicate regulatory outputs of the system.
PD 0332991 Preferentially Inhibits Proliferation of Luminal Estrogen Receptor-Positive Human Breast Cancer Cell Lines in Vitro

Phase 2 Design

**Part 1**

- **N = 66**
- **Randomization**
  - ER+, HER2– BC
  - 1:1
  - PD 0332991 125 mg QD<sup>a</sup> + Letrozole 2.5 mg QD
  - Letrozole 2.5 mg QD

**Part 2**

- **N = 99**
- **Randomization**
  - ER+, HER2– BC with **CCND1 amp and/or loss of p16**
  - 1:1
  - PD 0332991 125 mg QD<sup>a</sup> + Letrozole 2.5 mg QD
  - Letrozole 2.5 mg QD

**Primary Endpoint PFS**

**Stratification Factors**

- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

<sup>a</sup> Schedule 3/1.
Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>PD 991 + LET (n = 84)</th>
<th>LET (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>21 (25)</td>
<td>40 (49)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>26.1 (12.7, 26.1)</td>
<td>7.5 (5.6, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.37 (0.21, 0.63)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients at risk

- PD991+LET: 84, 75, 60, 53, 43, 35, 25, 18, 15, 14, 9, 5, 3, 1
- LET: 81, 57, 38, 29, 22, 17, 11, 6, 5, 4, 3, 3, 1
Ongoing Phase 3 trial of PD-0332991 (Palbociclib)

Next Steps for CDK 4/6 Inhibition

- Primary endpoint
  - PFS

- Secondary endpoints
  - OS
  - Response
  - Response duration
  - Disease control
  - Safety
  - Safety
  - PK/PD
  - Biomarkers
  - QoL

~450 patients

- Postmenopausal women aged ≥18 years
- Locoregionally recurrent or metastatic, ER(+) / HER2(−) advanced BrCa
- No prior systemic treatment for advanced disease

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)

Disease assessments every 12 wk ± 7 d from randomization date

Repeat bone scans every 24 wk ± 7 d from randomization date

HER2-driven breast cancer
The HER-2/neu Alteration

Significance of HER-2/neu

**Overall Survival**

- **Median Survival:**
  - Her2/neu Negative: 6-7 yrs
  - Her2/neu Positive: 3 yrs

**Disease Free Survival**

- Not amplified ($n=52$)
- Amplified ($n=11$) > 5 copies

*Slamon Science 1987*
Trastuzumab (anti-HER2 antibody)

**Extracellular effects of trastuzumab**
- Inhibition of cleavage of HER2 extracellular domain
- Interference with homodimer and heterodimer formation between HER-family receptors
- Antibody-dependent immune mechanisms

**Intracellular effects of trastuzumab**
- Induction of apoptosis
- Decreased cell proliferation
- HER2 down-regulation, dephosphorylation, or both
- Decreased VEGF production
- Potentiation of chemotherapy
- Modulation of downstream signal paths
- Altered cross-talk with other signal paths

Amplified number of HER2 genes on chromosome 17

*Burstein NEJM 2005; 353*
## Trastuzumab in Metastatic Breast Cancer
### The Pivotal Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate</th>
<th>Time to Progression</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>32%</td>
<td>4.6 mos</td>
<td>20.3 mos</td>
</tr>
<tr>
<td>Chemo + Trastuzumab</td>
<td>50%</td>
<td>7.4 mos</td>
<td>25.1 mos</td>
</tr>
</tbody>
</table>

Slamon, NEJM, 2001; 344: 783
Trastuzumab Has Changed the Natural History of HER2+ Metastatic Breast Cancer

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

Trastuzumab has changed the natural history of HER2+ early breast cancer

- 1458 patients with operable, non-metastatic breast cancer from Italy (Registry)
- 1210 (83%) HER2 negative (blue line)
- 219 (15%) HER2+
  - 53 received trastuzumab (green line)
  - 161 did not receive trastuzumab (red line)

Musolino, et al. Cancer 2010
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>ARMS</th>
<th># Pts</th>
<th>DFS</th>
<th>OS</th>
<th>HR</th>
<th>F/U</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int N9831 + NSABP B31</td>
<td>AC→Taxol® (T)  AC→TH  AC→T→H</td>
<td>3351</td>
<td>4-yr 86% AC-TH 74% AC-T P&lt;0.001</td>
<td>4-yr 93% AC-TH 86% AC-T P&lt;0.001</td>
<td>OS 0.61 DFS 0.52</td>
<td>4 yr</td>
<td>H qwk</td>
</tr>
<tr>
<td>HERA</td>
<td>Std chemo then: Observ vs. H x 1 yr (Vs. H x 2 yr)</td>
<td>3401 (5090 incl 2 year)</td>
<td>8-yr DFS events: 471 H 1 yr 570 no H P&lt;0.0001</td>
<td>8-yr OS events: 278 H 1 yr 350 no H P=0.005</td>
<td>OS 0.76 DFS 0.76</td>
<td>8 yr</td>
<td>1/3 pts LN neg, H q3wk, 1/4 prior taxane, x-over allowed</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC→Taxotere® (T) AC→TH T/Carboplatin/H</td>
<td>3222</td>
<td>5-yr DFS 84% AC-TH 81% TCH 75% AC-T</td>
<td>5-yr OS 92% AC-TH 91% TCH 87% AC-T</td>
<td>OS: 0.63 AC-TH 0.77 TCH</td>
<td>65 mo</td>
<td>After chemo, H given q3wk</td>
</tr>
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Trastuzumab Resistance

• Resistance to trastuzumab, both primary and secondary, is a major clinical concern
  – ~50% no response
  – Half of patients who respond to treatment have their disease grow back/worsen in 12 months
• Delaying resistance to trastuzumab (and future HER2-targeted therapies) AND treatments that overcome resistance are needed
The HER family of receptors

HER1/EGFR  HER2  HER3  HER4
Effects of ligand binding to the HER3 receptor

Ligand binds
Conformational change from “closed” to “open” state
Exposes the dimerization domain and allows the formation of dimers
Triggers intracellular signaling pathways through transphosphorylation
Effects of ligand binding to the HER3 receptor

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HER3
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Conformational change from “closed” to “open” state

Exposes the dimerization domain and allows the formation of dimers

Triggers intracellular signaling pathways through transphosphorylation

HER2  HER3

P13K

angiogenesis

proliferation

cell cycle control

survival

↓ apoptosis

mTOR

Cyclin Dp27

BAD

GSK3β

NFκB
Pertuzumab: a HER dimerization inhibitor

- A mechanism of action designed to bind to the HER dimerization domain
- By targeting HER2, the preferred pairing partner for HER1, HER3 and HER4, pertuzumab may inhibit multiple HER signaling pathways

**Diagram:**
- HER2
- HER3
- Pertuzumab

**Pathways:**
- AKT
- PDK1
- Cyclin D1
- p27
- BAD
- GSK3β
- NFκB
- mTOR
- P13K
- angiogenesis
- proliferation
- cell cycle control
- apoptosis
- survival
CLEOPATRA: First-line HER2+ BC

- **CLEOPATRA** – basis of FDA approval for pertuzumab

**Patients with HER2+ metastatic BC centrally confirmed (N = 808)**

- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated

- 1 prior line of hormonal therapy allowed for pts with ER+/PgR+ BC
- Only ~10% of pts had prior TRAS as neo/adjuvant therapy
- <50% of pts had prior chemotherapy
- No crossover allowed
- Study powered at 80% to detect a 33% increase in OS

![Diagram showing study design and outcomes](image.png)

Abbreviations: BC, breast cancer; ER, estrogen receptor; PgR, progesterone receptor; pts, patients.

*< 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.

Independently and Investigator-Assessed PFS

- **Independent assessment**
  - HR = 0.62
  - 95% CI, 0.51-0.75; P<0.0001

- **Investigator assessment**
  - HR = 0.65
  - 95% CI, 0.54-0.78; P<0.001

CLEOPATRA: OS

Overall Survival (%)

1 year: 94%
2 years: 81%
3 years: 66%
1 year: 94%
2 years: 81%
3 years: 66%

Ptz + T + D: 113 events; median not reached
Pta + T + D: 154 events; median 37.6 months

Time (months)

No. at Risk

Ptz + T + D: 402 387 371 342 317 230 143 84 33 9 0 0
Pta + T + D: 406 383 350 324 285 198 128 67 22 4 0 0

HR = 0.66
95% CI 0.52 - 0.84
P = 0.0008

T-DM1: Mechanism of Action

Adapted from LoRusso PM et al. Clin Cancer Res. 2011;17:6437-6447.
TDM1 Response Profile in Breast Panel

TDM1 Ranked Response and HER2 status - Breast Panel
TDM1 vs Trastuzumab

TDM1 and Trastuzumab Response in HER2 Amplified Breast Lines

Cell Line

- Trastuzumab Resistant
- Trastuzumab Sensitive
TDM1 vs Lapatinib

TDM1 Ranked Response and Lapatinib Sensitivity - Breast Panel

TDM1 IC50s in ug/ml (log scale)

Cell Line

- Lapatinib Resistant (IC50 > 1uM)
- Lapatinib Sensitive (IC50 < 1uM)

* - HER2 Amplified
**TDM4450 Study Design**

- Randomized, phase II, international, open-label study\(^b\)
- Stratification factors: World region, prior adjuvant trastuzumab therapy, disease-free interval
- Primary end points: PFS by investigator assessment, and safety
- Data analyses were based on clinical data cut of Nov 15, 2010 prior to T-DM1 crossover
- Key secondary end points: OS, ORR, DOR, CBR, and QOL

\(^a\)Patients were treated until PD or unacceptable toxicity.
\(^b\)This was a hypothesis generating study; the final PFS analysis was to take place after 72 events had occurred.
Kaplan-Meier estimates of progression-free survival (PFS) in the overall study population.

![Graph showing Kaplan-Meier estimates of PFS with data points for HT and T-DM1 groups.]

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, n</th>
<th>months</th>
<th>HR</th>
<th>95% CI</th>
<th>Log-rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT</td>
<td>70</td>
<td>9.2</td>
<td>0.59</td>
<td>0.36 to 0.97</td>
<td>0.035</td>
</tr>
<tr>
<td>T-DM1</td>
<td>67</td>
<td>14.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:
- HT: 70, 66, 63, 53, 43, 27, 12, 4, 2, 2, 0
- T-DM1: 67, 60, 51, 46, 42, 35, 22, 15, 6, 3, 0

Hurvitz S A et al. JCO 2013;31:1157-1163
TDM4450: Kaplan-Meier estimates of duration of response (DOR) by investigator.

Hurvitz S A et al. JCO 2013;31:1157-1163
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<tr>
<th></th>
<th>Trastuzumab + docetaxel (n=66)(^a), n (%)</th>
<th>T-DM1 (n=69)(^a,b), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade ≥3 AE</td>
<td>59 (89.4)</td>
<td>32 (46.4)</td>
</tr>
<tr>
<td>AE leading to discontinuation of any study treatment component (any grade)</td>
<td>19 (28.8)</td>
<td>5 (7.2)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>1 (1.5)(^c)</td>
<td>1 (1.4)(^d)</td>
</tr>
<tr>
<td>Serious AEs (any grade)</td>
<td>17 (25.8)</td>
<td>13 (18.8)</td>
</tr>
</tbody>
</table>

\(^a\)Two patients mistakenly received a dose of T-DM1 and were thus included in the T-DM1 arm for safety analyses.

\(^b\)Includes 3 patients who received at least 1 dose of trastuzumab alone or trastuzumab plus docetaxel.

\(^c\)Due to cardiopulmonary failure.

\(^d\)Due to sudden death.
**EMILIA: TDM-1 Phase 3 Trial Design**

**Key endpoints**

**Primary:** Progression-free survival (PFS, central assessment), safety, overall survival

**Secondary:** Objective response, duration of objective response, PFS (investigator review)

**Stratification factors:** World region, number of prior chemo regimens for ABC or unresectable LABC, presence of visceral disease

---

**EMILIA**

N = 978

- Postmenopausal
- ABC
- Prior taxane and progression on TRAS
- Cardiac ejection fraction ≥50%
- ECOG PS ≤ 1

**T-DM1**

(3.6 mg/kg IV q3w)

**Lapatinib + Capecitabine**

(L: 1250 mg/d PO)
(C: 1000 mg/m² PO bid, days 1-14q3w)

---


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**Estimated Study Completion Date:** April 2014
EMILIA: PFS by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
<th>No. events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP + LAP</td>
<td>6.4</td>
<td>304</td>
</tr>
<tr>
<td>T-DM1</td>
<td>9.6</td>
<td>265</td>
</tr>
</tbody>
</table>

Stratified HR = 0.65 (95% CI, 0.55, 0.77)  
\( P < 0.001 \)

Abbreviation: CAP, capecitabine; LAP, lapatinib; PFS, progression-free survival.
EMILIA: Overall Survival

Overall Survival, %

Stratified hazard ratio, 0.68
(95% CI, 0.55-0.85)  \( P < .001 \)
Efficacy stopping boundary, \( P = .0037 \) or hazard ratio, 0.73

LAP + CAP
T-DM1

Median No. of Months
No. of Events

25.1
182

30.9
149

No. at risk:

LAP + CAP
T-DM1

496 471 453 435 403 368 297 240 204 159 133 110 86 63 45 27 17 7 4

T-DM1

495 485 474 457 439 418 349 293 242 197 164 136 111 86 62 38 28 13 5

CAP, capecitabine; LAP, lapatinib
PARP inhibitors for Breast Cancer
Mechanisms of DNA Repair

DNA DAMAGE

Environmental factors
(UV, radiation, chemicals)
Normal physiology
(DNA replication, ROS)
Chemotherapy
(alkylating agents, antimetabolites)
Radiotherapy

MAJOR DNA REPAIR PATHWAYS

Single Strand Breaks
- Nucleotide excision repair
- Base excision repair
  - PARP1

Double Strand Breaks
- Non-homologous end-joining
- Homologous recombination
  - BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

Replication Lesions
- Base excision repair
  - PARP1

DNA Adducts/Base Damage
- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
  - PARP1

Cell Death

Homologous Recombination

• ATM & CHEK2 signal presence of ds-DNA breaks by phosphorylating BRCA1 protein
• BRCA1 moves to site for DNA repair
• BRCA2 carries DNA-recombination enzyme RAD51 to site of repair (guided by Dss1)
• This is an error free system
• If BRCA 1 or 2 deficient, breaks in dsDNA repaired by error-prone mechanisms. Leading to chromosomal aberrations and increased mutation.
PARP
[Poly (ADP-Ribose) Polymerase]

SSBs are normally rapidly repaired by PARP-mediated SSB repair (through base excision repair, BER).

If PARP is inhibited, unrepaired SSBs may be converted to DSBs during DNA replication and channeled into HR repair.

HR repair is absent in BRCA-defective cells, resulting in cell death.

BRCA1$^{-/-}$ and BRCA2$^{-/-}$ cells are extremely sensitive to PARP inhibition.

No difference in sensitivity between heterozygous and wild-type BRCA cells.

Targeted inhibition → selective and less toxic therapy

Farmer et al. Nature 2005; 434:917-21
PARPi in BRCA deficient tumors

- In normal cells with normal BRCA1/2 function, homologous recombination (HR) leads to chromosomal stability/cell survival.
- In normal tissue of BRCA1/BRCA2 carriers, homologous recombination works so inhibiting PARP shouldn’t lead to cell death.
- But in BRCA 1/2 deficient tumors, blocking PARP blocks BER and gives tumor-specific lethality.

*Tutt et al. Proc ASCO 2009 Abst CRA501*
Not all PARPi are alike in cell killing activity

- PARP inhibitors act as poisons that trap PARP on DNA
- The potency of trapping PARP differs markedly among inhibitors. Pattern not correlated with catalytic inhibitory properties of each drug.

BMN673

- Most potent PARPi reported
- Single digit nM inhibition carrying BRCA mutation
- High oral bioavailability, long half-life
Summary of *in vitro* BMN673 Activity

<table>
<thead>
<tr>
<th></th>
<th>PARP-1 Enzyme Inhibition(^1) IC(_{50}) (nM)</th>
<th>Cellular PAR Synthesis(^2) EC(_{50}) (nM)</th>
<th>Temozolomide Potentiation(^3) GI(_{50}) (nM)</th>
<th>Capan-1 (brca2(-/)) Cytotoxicity(^4) IC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib</td>
<td>4.73</td>
<td>5.94</td>
<td>6203</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>1.98</td>
<td>4.69</td>
<td>144</td>
<td>609</td>
</tr>
<tr>
<td>Olaparib</td>
<td>1.94</td>
<td>3.56</td>
<td>237</td>
<td>259</td>
</tr>
<tr>
<td>BMN 673</td>
<td>0.57</td>
<td>2.5</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

- BMN673 is a potent PARP inhibitor tested in Temozolomide potentiation and as a single agent in BRCA2 negative Capan-1 cells
- 50-1000x selectivity for BRCA mutant cells vs normal fibroblasts
- BMN673 potency in tumor cell killing is unique
BMN673: 300-1000x more potent than other PARP inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Lowest dose with reported clinical response</th>
<th>Clinical Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMN-673</td>
<td>0.1 milligrams qd</td>
<td>1 milligram qd</td>
</tr>
<tr>
<td>olaparib</td>
<td>100 milligrams bid</td>
<td>400 milligrams bid</td>
</tr>
<tr>
<td>niraparib</td>
<td>60 milligrams qd</td>
<td>300 milligrams qd</td>
</tr>
<tr>
<td>rucaparib</td>
<td></td>
<td>≥480 milligrams bid</td>
</tr>
</tbody>
</table>
First-in-human trial of novel oral PARP inhibitor BMN 673 in patients with solid tumors

Johann de Bono,1 Lida A. Mina, 2 Michael Gonzalez, 1 Nicola J. Curtin, 3 Evelyn Wang, 4 Joshua W. Henshaw, 4 Manpreet Chadha, 5 Jasgit C. Sachdev, 5 Daniela Matei, 2 Gayle S. Jameson, 5 Michael Ong, 1 Bristi Basu, 1 Zev A. Wainberg, 6 Lauren Byers, 7 Rashmi Chugh, 8 Andrew Dorr, 4 Stanley B. Kaye, 1 Ramesh K. Ramanathan; 5

Institute of Cancer Research, Royal Marsden NHS Foundation Trust, Sutton, UK; 1 Indiana University, Indianapolis, IN; 2 Northern Institute for Cancer Research, Newcastle University, UK; 3 BioMarin Pharmaceutical, Novato, CA; 4 Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ; 5 David Geffen School of Medicine at University of California, Los Angeles, CA; 6 University of Texas MD Anderson Cancer Center, Houston, TX; 7 University of Michigan, Ann Arbor, MI; 8

ASCO 2013 – Abstract 2580
Objectives

- **Primary Objective:**
  - Establish the maximum tolerated dose (MTD) of oral, daily BMN 673

- **Secondary Objectives:**
  - Characterize the safety and PK of BMN 673
  - Establish the recommended phase 2 dose
  - Obtain preliminary anti-tumor activity of single agent BMN 673
  - Characterize PARP inhibition in peripheral blood mononuclear cells

*deBono et al. ASCO 2013 Abs 2580*
Study Design

- Standard 3 + 3 dose escalation followed by expansion at MTD in cohorts with selected tumor types to further characterize safety and anti-tumor activity
- BMN 673 taken daily in 28-day cycles
- Starting dose: 25 µg/day

deBono et al. ASCO 2013 Abs 2580
## Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation</th>
<th>Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>33/6</td>
<td>27/4</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>58 (19-81)</td>
<td>45 (18-77)</td>
</tr>
<tr>
<td>Median PS (range)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Median # prior chemo regimens (range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ovarian</td>
<td>4 (1-13)</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>- Breast</td>
<td>4 (2-10)</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>- 3 (1-8)</td>
<td>2 (0-4)</td>
<td></td>
</tr>
<tr>
<td>Ovarian / Peritoneal</td>
<td>21/2</td>
<td>10/1</td>
</tr>
<tr>
<td>Breast</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Ewing’s Sarcoma</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SCLC</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>BRCA1 Mutation (Deleterious)</td>
<td>17 (16)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>BRCA2 Mutation (Deleterious)</td>
<td>9 (8)</td>
<td>13 (13)</td>
</tr>
</tbody>
</table>

deBono et al. ASCO 2013 Abs 2580
All patients, all cycles, related adverse events, (n=70)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of total patients (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>All Grades</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (17)</td>
<td>8 (11)</td>
<td>1 (1)</td>
<td>0</td>
<td>21 (30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (26)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>20 (29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>13 (19)</td>
<td>2 (3)</td>
<td>0</td>
<td>0</td>
<td>15 (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (1)</td>
<td>4 (6)</td>
<td>9 (13)</td>
<td>0</td>
<td>14 (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>9 (13)</td>
<td>1 (1)</td>
<td>13 (19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>4 (6)</td>
<td>0</td>
<td>8 (11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 11 patients have had dose reductions for myelosuppression
- No discontinuations for adverse events
## Germline BRCA Mutation – Breast Cancer

<table>
<thead>
<tr>
<th>Deleterious Mutation</th>
<th>N</th>
<th>PR</th>
<th>CR</th>
<th>SD ≥ 12 weeks</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA 1</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>BRCA 2</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>6*</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

• RECIST response: 7/18 (39%)
• Clinical benefit (CR, PR, SD ≥ 12 weeks) = 12/18 (67%)
• Too early to evaluate clinical benefit at 24 weeks

deBono et al. ASCO 2013 Abs 2580
BMN 673 (de Bono ASCO 2013)

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Germline BRCA Mutation – Breast Cancer Duration on Treatment

Treatment Duration (Weeks)

Dose (µg/day)
- 900
- 1000
- 1100
- PD

SD
PR
CR
PD

> Treatment ongoing
* Not yet confirmed

BRCA 1
BRCA 2

0 10 20 30 40 50 60

Treatment Duration (Weeks)
Germline BRCA – Breast Cancer Response by Prior Platinum Exposure

- 2 of 2 patients with prior response to platinum responded to BMN 673
- 0 of 4 patients with non-response to prior platinum responded to BMN 673
- 5 of 12 with no prior platinum exposure responded to BMN 673

deBono et al. ASCO 2013 Abs 2580
BMN673-301

A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of BMN 673 versus Physician’s Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received No More than 2 Prior Chemotherapy Regimens for Metastatic Disease
Randomized, phase III, international, open-label study, 100 sites

Does not allow pts to have received prior PARPi or prior platinum (platinum in adjuvant setting ok if >12 mos since relapse); must have received prior anthracycline and/or taxane; No HER2+

Stratification factors: No. of prior chemo, triple negative vs non-TN, h/o CNS mets vs no h/o CNS mets

Primary end points: PFS

Key secondary end points: OS, ORR, DOR, CBR, and QOL
Treatment Approach to Early Breast Cancer

**Local-Regional Treatment**
- Surgery (MRM or BCT)
- Radiation (if BCT or if MRM and ≥ 4+ LN)

**Systemic Treatment**
- Tamoxifen 5-10 yrs
- AI’s 5 yrs (if ER+)
- Cytotoxic Chemotherapy (if ER/PR neg or large tumor or LN positive)

**Goal:** Prevent disease from coming back in breast/surrounding tissues. Some impact on survival.

**Targeted/Biologics**
- Trastuzumab
- T-DM1?
- Pertuzumab?
- Palbociclib?
Treatment Approach to Advanced Breast Cancer

**PALLIATION**

- **Bisphosphonates** *(control bone metastases)*
- **Tamoxifen**
- **Aromatase Inhibitors** *(if ER+)*
- **Cytotoxic Chemotherapy**
- **Radiation** *(For symptomatic bone or brain metastases)*

**Targeted/Biologics**
- Trastuzumab
- Pertuzumab
- Lapatinib
- Everolimus? Palbociclib?
- T-DM1

**RANK-ligand inhibitors**
Her2 Positive or BRCA mutation Carriers Breast Cancer

NeoAdjuvant HER2+
- Trio 21
  - Phase II
  - TCH vs T-DM1-P
  - Hurvitz

Adjuvant HER2+
- Digni-Caps
  - Non-randomized
  - Stage I-II breast cancer getting TCHx4-6
  - UCLA only
  - Hurvitz

BRCA+ (HER2 neg)
- BMN673
  - Phase III open-label
  - Must be HER2 neg
  - PARPi vs MD-choice chemo 2:1
  - Up to 2 prior chemo ok
  - Stable CNS ok
  - No prior platinum allowed
  - Hurvitz

Metastatic HER2+
- Puma-Ner 1301
  - Phase III
  - Neratinib/capecitabine vs lapatinib/capecitabine
  - No prior lapat/cape allowed
  - 3rd line or greater
  - Hurvitz

- Trio-B09
  - CNS metastases, Ph II, single arm
  - Lapatinib+
  - Everolimus+
  - Capecitabine
  - Hurvitz

For trial eligibility & enrollment info, contact:
- Renee Robinson: 310-206-3539
- Sara Hurvitz, MD: 310-829-5471