Development of lurbinectedin in BRCA2 mutation-associated breast cancer

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Stanford University School of Medicine

April 24, 2017
My background

- Academic medical oncologist focused on breast cancer

- Interests in clinical development of novel treatment approaches for:
  - Hereditary breast cancer
  - Triple-negative breast cancer

- Pertinent appointments/memberships:
  - NCCN Breast Cancer Guidelines Panel
  - Komen Scholar
  - FORCE, Scientific Advisory Board Member
Talk Outline

- Clinical features of hereditary breast cancer
  - BRCA1
  - BRCA2
  - Others

- Lurbinectedin in advanced BRCA mutated breast cancer

- Future landscape of BRCA2 therapy

- Importance of hereditary cancer community advocacy

Q & A will follow at the end of the presentations
Hereditary Breast and Ovarian Cancer

Most hereditary breast and ovarian cancers are due to germline $BRCA1$ & $BRCA2$ mutations.
The Problem:

- Information from BRCA1/2 testing does **NOT** guide treatment decisions at present

- Responses to standard therapies in carriers not well characterized

- PARP inhibitors active in advanced BRCA+ breast cancer, but no drugs approved
  - Landscape changing with expectation of olaparib approval in 2017

- Many patients with hereditary predisposition do not know it
Clinical features of *BRCA1/2* mutated breast cancer

- *BRCA1/2* mutated cancers are compromised in DNA repair resulting in genomic instability & higher grade features

- Majority of *BRCA1*+ tumors are triple-negative; majority of *BRCA2*+ are hormone receptor-positive
  - HER2 positivity is rare in both

- *BRCA1/2* mutated breast cancer continues to be treated systemically according to the same algorithm for the treatment of sporadic breast cancer

- Strong rationale for development of DNA damaging therapeutics in this disease
Homologous recombination (HR) DNA repair defects in breast cancer

- HR deficiency characterizes breast cancers in *BRCA1/2* mutation carriers
  - Due to loss of heterozygosity at *BRCA1* or *BRCA2*
- Beyond *BRCA1/2*, there are other HR pathway genes implicated in hereditary breast cancer
  - *PALB2, ATM, CHEK2*, others

HBOC: *BRCA1*, *BRCA2* and beyond

Case Scenario: **BRCA2+ Breast Cancer**

- A 42 year-old woman presents with a clinical T2N1M0 Stage IIB high grade invasive ductal carcinoma
  - ER 90%, PR 20%, HER2 negative, Ki-67 50%

- Multiplex panel testing reveals a deleterious **BRCA2** mutation

- Treated with neoadjuvant AC-T chemotherapy, followed by oophorectomy and adjuvant aromatase inhibitor

- 22 months later, she relapses with bone, nodal and lung metastases
  - Started on fulvestrant and palbociclib with progression at 8 months
  - Started on tamoxifen with rapid progression after 2 months
  - Recommended for clinical trial versus standard chemotherapy (capecitabine/taxane/carboplatin)
Anti-tumor activity of PM01183 (lurbinectedin) in BRCA 1/2-associated metastatic breast cancer patients: Results of a single-agent phase II trial

J. Balmaña\(^1\), C. Cruz\(^1\), B. Arun\(^2\), M. Telli\(^3\), J. Garber\(^4\), S. Domchek\(^5\), C. Fernandez\(^6\), C. Kahatt\(^6\), S. Szyldergemajn\(^6\), A. Soto Matos\(^6\), A. Perez de la Haza\(^6\), J. Pérez Fidalgo\(^7\), A. Lluch\(^7\), S. Antolin\(^8\), N. Tung\(^9\), L. Vahdat\(^10\), R. Lopez\(^11\), S. Isakoff\(^12\)

\(^1\)Hospital Vall d’Hebron and Vall d’Hebron Institute of Oncology, Barcelona, Spain; \(^2\)MD Anderson Cancer Center, Houston, USA; \(^3\)Stanford University Medical Center, Stanford, USA; \(^4\)Dana Farber Cancer Institute, Boston, USA; \(^5\)University of Pennsylvania, Philadelphia, USA; \(^6\)Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain; \(^7\)Hospital Clínico de Valencia, Valencia, Spain; \(^8\)Complejo Universitario Hospitalario La Coruña, La Coruña, Spain; \(^9\)Beth Israel Deaconess Medical Center, Boston, USA; \(^10\)Weill Cornell Medicine, New York, USA; \(^11\)Complejo Hospitalario Universitario Santiago de Compostela, Santiago de Compostela, Spain; \(^12\)Massachusetts General Hospital, Boston, USA.
Lurbinectedin

Lurbinectedin (PM01183) is a trabectedin analog with an unique mechanism of action (1):

- *Inhibits active transcription* (RNA Pol II blockade and degradation)
- Binds to CG-rich motifs
- Generates double strand DNA breaks
- Affects tumor microenvironment

Deficient homologous recombination system favors PM01183-induced apoptosis (2)

Antitumor activity observed in patients resistant to platinum compounds (3)

Two Phase III trials are currently ongoing, one as a single agent in platinum resistant ovarian cancer, and one in combination with doxorubicin in 2nd line SCLC

3. Poveda A. et al. ASCO 2014, oral presentation
Overview trial design and current status

MBC
- Ductal/Lobular
- Up to 3 prior advanced chemotherapy regimens
- PS: 0-1
- Asymptomatic, non steroid requiring CNS metastasis
- Measurable disease by RECIST v.1.1

BRCA1/2 mutation (Arm A)

Futility analysis (20 pts)

BRCA 1/2 mutation after PARPi (Arm A1)

53 pts

Further development: ≥ 17 confirmed responses

Non (or UNK) BRCA1/2 mutation (Arm B)

Futility analysis (30 pts)

20 pts

64 pts

Statistical hypotheses:
- H0: ORR ≤ 20% vs. H1: ORR ≥ 40%
- α=0.025 (one-sided); Power = 90%

Statistical hypotheses:
- H0: ORR ≤ 10% vs. H1: ORR ≥ 25%
- α=0.025 (one-sided); Power = 90%

Statistical hypotheses:
- Lower bound CI95% ≥ 5%

Balmaña, SABCS 2014, poster P3-13-01
Cruz, ESMO 2016, abstract 1520O
Study Endpoints

Primary endpoint:
• Overall confirmed response rate (ORR)

Secondary endpoints:
• Duration of response
• Clinical benefit (response or stable disease > 3 months)
• Exploratory ORR in specific MBC subpopulations
• PFS and one year-OS
• Safety profile
• Pharmacokinetics, pharmacodynamics and pharmacogenomics analysis
Initial recommended dose (IV, q3wk)

PM1183-B-003-11 Dosing

Initial recommended dose:
- 7 mg FD*
- 6 mg FD
- 5 mg FD
- 4 mg/m²

DL-1
- 6 mg FD = 3.5 mg/m²

DL-2
- 5 mg FD = 2.6 mg/m²
- 2.0 mg/m²

Arm A (BRCA +):
- 35 patients
- 19 patients

* FD: Fixed Dose

Amendment #2 starting dose

DL-1

DL-2
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients (n: 54) (100%)</th>
<th>BRCA1 (n: 31) (57%)</th>
<th>BRCA2 (n: 23) (43%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median (range)</td>
<td>43 (29-73)</td>
<td>40 (29-67)</td>
</tr>
<tr>
<td><strong>PS</strong></td>
<td>0/1</td>
<td>31 (57%) / 23 (43%)</td>
<td>15(48%) / 16(52%)</td>
</tr>
<tr>
<td><strong>Receptor Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple neg</td>
<td>33 (61%)</td>
<td>26 (84%)</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>HR+ / HER2 -</td>
<td>19 (35%)</td>
<td>5 (16%)</td>
<td>-</td>
</tr>
<tr>
<td>HER2+</td>
<td>2 (4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sites of Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>28 (52%)</td>
<td>12 (39%)</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>CNS</td>
<td>3 (6%)</td>
<td>2 (7%)</td>
<td>-</td>
</tr>
<tr>
<td>≥ 3 sites involved</td>
<td>27 (50%)</td>
<td>13 (42%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Prior Treatments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>43 (80%)</td>
<td>28 (90%)</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>47 (87%)</td>
<td>29 (94%)</td>
<td>18 (78%)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>18 (33%)</td>
<td>6 (19%)</td>
<td>12 (52%)</td>
</tr>
<tr>
<td>Platinum</td>
<td>27 (50%)</td>
<td>21 (67%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>PARP inhibitor</td>
<td>9 (17%)</td>
<td>4 (13%)</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Advanced CT lines</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Safety - Most common related AEs

<table>
<thead>
<tr>
<th></th>
<th>7 mg FD (n: 35)</th>
<th>3.5 mg/m² (n: 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3</td>
</tr>
<tr>
<td><strong>Any Related AE</strong></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Any Related AE</strong></td>
<td>35 (100)</td>
<td>11 (31)</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>33 (94)</td>
<td>7 (20)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>32 (91)</td>
<td>6 (17)</td>
</tr>
<tr>
<td><strong>Neutrophil count decreased</strong></td>
<td>31 (89)</td>
<td>7 (20)</td>
</tr>
<tr>
<td><strong>Platelet count decreased</strong></td>
<td>26 (74)</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Transaminases increased</strong></td>
<td>31 (89)</td>
<td>8 (23)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>28 (80)</td>
<td>3 (9)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>17 (49)</td>
<td>2 (6)</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td>10 (29)</td>
<td>7 (20)</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>8 (23)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
# Clinical efficacy: ORR

<table>
<thead>
<tr>
<th>Treatment (n=54)</th>
<th>PM01183</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Overall Response (RECIST)</td>
<td>7 mg FD (n=35) or 3.5 mg/m² (n=19) 1-h i.v. infusion, q3wk</td>
</tr>
<tr>
<td>(n evaluable: 54 pts)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR (Confirmed Responses)</strong></td>
<td>22 (40.7%)</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(27.6 - 55.0)</td>
</tr>
<tr>
<td>• CR</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>• PR</td>
<td>21 (38.9%)</td>
</tr>
<tr>
<td>• SD*</td>
<td>23* (42.6%)</td>
</tr>
<tr>
<td>• PD</td>
<td>9 (16.7%)</td>
</tr>
<tr>
<td>Median duration of response (95% CI)</td>
<td>6.7 months</td>
</tr>
<tr>
<td></td>
<td>(3.0 - 13.0)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD) n (%)</td>
<td>45 (83%)</td>
</tr>
<tr>
<td>Clinical benefit (CR+PR+SD ≥ 3 mo) n (%)</td>
<td>33 (61%)</td>
</tr>
</tbody>
</table>

* including 4 patients with unconfirmed PR
Waterfall - Sum of target lesions and time on treatment

- 5 out of 22 responding patients had ongoing responses at the time of data cutoff
- 7 patients had durable responses (> 10 months)
- Median number of cycles was 6 (1-24)
### Best ORR in specific subpopulations

<table>
<thead>
<tr>
<th>Prior Platinum</th>
<th>BRCA</th>
<th>Hormone Status</th>
<th>Prior advanced CT lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n: 27)</td>
<td>1 n: 31</td>
<td>2 Triple Negative (n: 33)</td>
<td>0-1 (n: 31)</td>
</tr>
<tr>
<td>Yes (n: 27)</td>
<td>2 (n: 23)</td>
<td>HR+ (n: 21*)</td>
<td>2-3 (n: 23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORR (95% CI)</th>
<th>Duration of Response (95% CI)</th>
<th>Disease control rate</th>
<th>Clinical benefit (CR+PR+SD ≥ 3 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>56%</strong> (35.3-74.5)</td>
<td><strong>10.2 m</strong> (3.0-13.5)</td>
<td><strong>25 (93%)</strong></td>
<td><strong>19 (70%)</strong></td>
</tr>
<tr>
<td><strong>26%</strong> (11.1-46.3)</td>
<td><strong>5.9 m</strong> (2.8-12.8)</td>
<td><strong>19 (70%)</strong></td>
<td><strong>14 (52%)</strong></td>
</tr>
<tr>
<td><strong>26%</strong> (11.9-44.6)</td>
<td><strong>6.6 m</strong> (2.8-12.8)</td>
<td><strong>23 (74%)</strong></td>
<td><strong>14 (45%)</strong></td>
</tr>
<tr>
<td><strong>61%</strong> (38.5-80.3)</td>
<td><strong>6.7 m</strong> (3.4-13.5)</td>
<td><strong>22 (96%)</strong></td>
<td><strong>19 (83%)</strong></td>
</tr>
<tr>
<td><strong>36%</strong> (20.4-54.9)</td>
<td><strong>7.7 m</strong> (2.8-12.8)</td>
<td>26 (79%)</td>
<td>29 (88%)</td>
</tr>
<tr>
<td><strong>48%</strong> (25.7-70.2)</td>
<td><strong>6.7 m</strong> (2.8-13.4)</td>
<td>19 (90%)</td>
<td>14 (67%)</td>
</tr>
<tr>
<td><strong>52%</strong> (33.1-69.9)</td>
<td><strong>8.5 m</strong> (3.0-12.8)</td>
<td>27 (87%)</td>
<td>21 (68%)</td>
</tr>
<tr>
<td><strong>26%</strong> (10.2-48.4)</td>
<td><strong>3.4 m</strong> (2.8-20.5)</td>
<td>18 (78%)</td>
<td>12 (52%)</td>
</tr>
</tbody>
</table>

* Including 2 patients also HER-2 +
Progression-Free Survival

Median PFS BRCA 1/2: 4.1 months 95% CI (2.8-5.9)
BRCA 1: 2.7 95% CI (2.1-4.6)
BRCA 2: 5.9 95% CI (4.1-7.9)

p-value=0.0064
Overall Survival

Median OS BRCA 1/2:
20.0 months 95% CI (10.9-31.8)

BRCA 1: 11.8 95% CI (6.5-20.0)
BRCA 2: 31.8 95% CI (20.7-38.9)

p-value=0.0038
Take Away Thoughts

- Lurbinectedin is active and well tolerated in patients with BRCA1/2 mutated MBC
  - ORR: 40.7%
  - Significant activity observed in BRCA2 patients

- Convenient 1 hour infusion every 3 weeks
  - Absence of alopecia, neuropathy
  - Myelosuppression manageable with growth factors

- Activity in platinum resistance important
  - PARP inhibitors have absent - minimal response rates in platinum resistance
Current **BRCA2 Landscape**

- Endocrine therapy +/- CDK inhibitor initial therapy for relapsed ER+/HER2- MBC
  - My experience is that **BRCA2** mutated patients develop endocrine resistance more rapidly than sporadic disease though data on this is lacking
- Given rarity of HER2 positivity, HER2 treatment algorithms not generally applicable
- Cytotoxic chemotherapy:
  - TNT trial showed higher ORR with carboplatin vs. docetaxel in **BRCA1/2** mutated mTNBC
  - Limited uptake currently in ER+ disease
- PARP inhibitor approval expected this year
  - OlympiaD trial reached PFS endpoint per press release
TNT Trial: Carboplatin vs. Docetaxel in Frontline mTNBC

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%)

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01
Olaparib in advanced BRCA mutant breast cancer: Initial proof-of-concept

Olaparib: Superior activity at higher dose

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 400 mg twice daily (n=27)</th>
<th>Olaparib 100 mg twice daily (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>11 (41%; 25–59)</td>
<td>6 (22%; 11–41)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (4%; 1–18)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (37%; 22–56)</td>
<td>6 (22%; 11–41)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (44%; 28–63)</td>
<td>12 (44%; 28–63)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (15%; 6–32)</td>
<td>9 (33%; 19–53)</td>
</tr>
</tbody>
</table>

Data are number (%; 95% CI).

Tutt A. Lancet. Published online July 6, 2010
Responses in *BRCA 1/2* Carriers irrespective of subtype

<table>
<thead>
<tr>
<th>Olaparib 400 mg twice daily (n=27)</th>
<th>BRCA1 (n=18)</th>
<th>BRCA2 (n=9)</th>
<th>Triple negative (n=13)</th>
<th>Non-triple negative (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>9 (50%)</td>
<td>2 (22%)</td>
<td>7 (54%)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (44%)</td>
<td>2 (22%)</td>
<td>7 (54%)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7 (39%)</td>
<td>5 (56%)</td>
<td>4 (31%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (11%)</td>
<td>2 (22%)</td>
<td>2 (15%)</td>
<td>2 (14%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Olaparib 100 mg twice daily (n=27)</th>
<th>BRCA1 (n=16)</th>
<th>BRCA2 (n=11)</th>
<th>Triple negative (n=16)</th>
<th>Non-triple negative (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>3 (19%)</td>
<td>3 (27%)</td>
<td>4 (25%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (19%)</td>
<td>3 (27%)</td>
<td>4 (25%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (56%)</td>
<td>3 (27%)</td>
<td>7 (44%)</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (25%)</td>
<td>5 (45%)</td>
<td>5 (31%)</td>
<td>5 (45%)</td>
</tr>
</tbody>
</table>

Tutt A. Lancet. Published online July 6, 2010
Phase III OLympiAD Trial (OLaparib in Advanced Disease)

- Metastatic germline BRCA+ breast cancer
- Prior anthracycline / taxane
- 0-2 prior tx for mBC
- No prior platinum*

Physician’s choice (capecitabine, vinorelbine, eribulin)

- Olaparib
- Primary endpoint: PFS (no cross-over)
- Secondary: OS, PFS2
- Planned sample size: 310 patients

* Amended to allow patients with prior adjuvant platinum or no progression on platinum in advanced setting
Concluding Remarks

- Lurbinectedin has significant activity in *BRCA1/2* mutant breast cancer

- ORRs higher in *BRCA2* compared with *BRCA1*

- Provides rationale for development in *BRCA2* mutant MBC
  - Unmet clinical need exists in this space

- Given similarities with *BRCA2+ MBC*, potential role in *PALB2+ MBC*, others
Concluding Remarks

- Activity of lurbinectedin in platinum resistant disease of significant clinical interest
  - Cross-resistance of platinum and PARPi will likely be clinically very significant
  - Evaluation of lurbinectedin in PARPi resistance ongoing

- New clinical algorithms for specific treatment of hereditary breast cancers increasingly expected
  - Development of additional active therapies beyond platinum chemotherapy and PARP inhibitors important
  - Optimal sequencing of these agents is a high priority
Importance of Advocacy

- Facing Our Risk of Cancer Empowered (FORCE) is a leading national nonprofit dedicated to hereditary cancer
- Partnership with FORCE and other groups critical to disseminate information about active clinical trial and therapeutic options
- Credited with greatly increased awareness of hereditary breast cancer
Thank you