Systemic therapy of triple negative advanced breast cancer

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Breast Cancer Program
Division of Early Drug Development
• State of the Art in the management of TN advanced breast cancer
• Dealing with heterogeneity of TN breast cancer
• Targeting subtypes and clinical trials
• Targeting pathways and immune-system
### TNBC in the real life

**Patients with TN Disease Received Fewer Treatments and Stayed on Each Treatment Regimen For A Shorter Interval**

<table>
<thead>
<tr>
<th>Line of CT</th>
<th>Total</th>
<th>TNBC</th>
<th>ER+</th>
<th>HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>205</td>
<td>45 (100%)</td>
<td>102 (100%)</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>2</td>
<td>159</td>
<td>36 (80%)</td>
<td>79 (77%)</td>
<td>44 (76%)</td>
</tr>
<tr>
<td>3</td>
<td>122</td>
<td>26 (58%)</td>
<td>56 (55%)</td>
<td>69 (52%)</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>13 (29%)</td>
<td>38 (37%)</td>
<td>30 (52%)</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>8 (18%)</td>
<td>24 (24%)</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>6 (13%)</td>
<td>9 (9%)</td>
<td>19 (33%)</td>
</tr>
</tbody>
</table>

Seah et al, ASCO 2012
Median PFS to Chemotherapy in TNBC

- **Initial therapy**
- **First distant relapse**
  - First line chemo: 12 weeks
  - Second line chemo: 9 weeks
  - Third line chemo: 4 weeks

**“Time on Treatment”**
**Taxanes for TNBC**

Retrospective subgroup analyses
Placebo arm data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Setting</th>
<th>Taxane</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9342&lt;sup&gt;1&lt;/sup&gt;</td>
<td>III</td>
<td>44</td>
<td>First- or second-line metastatic</td>
<td>Paclitaxel weekly and q3w</td>
<td>ORR = 26% TTF = 2.8 months OS = 8.6 months</td>
</tr>
<tr>
<td>ECOG 2100&lt;sup&gt;2&lt;/sup&gt;</td>
<td>III</td>
<td>110</td>
<td>First-line metastatic</td>
<td>Paclitaxel weekly</td>
<td>ORR = 11.7%&lt;sup&gt;4&lt;/sup&gt; PFS = 5.3 months</td>
</tr>
<tr>
<td>AVADO&lt;sup&gt;3&lt;/sup&gt;</td>
<td>III</td>
<td>52</td>
<td>First-line metastatic</td>
<td>Docetaxel q3w</td>
<td>ORR = 23.1%&lt;sup&gt;4&lt;/sup&gt; PFS = 6.1 months</td>
</tr>
</tbody>
</table>

## Capecitabine for TNBC

### Retrospective subgroup analyses

**Placebo arm data**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Setting</th>
<th>Treatment</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
</table>
| Pooled analysis | III   | 208| Third-line or greater metastatic | Capecitabine             | ORR = 15%  
PFS = 1.7 months |
| RIBBON-1        | III   | 50 | First-line metastatic          | Capecitabine + placebo   | PFS = 4.2 months         |

## Platinum salts for TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Multiple doses</th>
<th>N</th>
<th>First Line</th>
<th>ORR(%)</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALI-1</td>
<td>Cisplatin</td>
<td>75 mg/m² q3w</td>
<td>48</td>
<td>73%</td>
<td>6 (10.3%)</td>
<td>1.5 m</td>
</tr>
<tr>
<td>BSI-201</td>
<td>Carbo - Gem</td>
<td>AUC 2 d1, 8 q3w, 1000 mg/m² d1, 8</td>
<td>62</td>
<td>59%</td>
<td>20 (32%)</td>
<td>3.3 m</td>
</tr>
<tr>
<td>TBCRC 001</td>
<td>Carbo – Cetuximab</td>
<td>AUC 2 d1, 8, 15 q4w</td>
<td>71</td>
<td>46%</td>
<td>13 (18%)</td>
<td>2.0 m</td>
</tr>
</tbody>
</table>
Targeting Triple Negative

- Bevacizumab beyond progression
  - TANIA
    (von Minckwitz et al, Lancet Oncol 2014)

- Maintenance with capecitabine and bevacizumab following response to Bevacizumab

- IMELDA (Gligorov et al, Lancet Oncol 2014)
Efficacy (ORR, pFS)
Safety profile
Impact on QoL
Comorbidity
Performance status
Target oriented
Schedule
Real life therapy

- Treatment Efficacy (ORR, PFS)
- Impact on Quality of Life
- Safety profile
- Performance Status
- Comorbidity
- Target oriented
- Convenience of the Schedule
Real life therapy

Treatment Efficacy (ORR, PFS)

Impact on Quality of Life

Safety profile

Performance Status

Comorbidity

Target oriented

Convenience of the Schedule
Real life therapy

Treatment Efficacy (ORR, PFS)

Impact on Quality of Life

Safety profile

Performance Status

Comorbidity

Target oriented

Convenience of the Schedule
Clinical Heterogeneity of TNBC

Subtype
- Basal-like 1
- Basal-like 2
- Immunomodulatory
- Mesenchymal
- Mesenchymal stem-like
- Luminal androgen receptor

Gene expression profile
- high Ki-67; DNA damage response
- GF pathways
- Immune genes
- Cell motility
- Cell motility; claudin-low
- Steroid pathways

Clinical
- BRCA-associated
- Higher pCR
- Lower DDFS
- Apocrine features, higher LRF; PI3Kmut

• Triple negative breast cancer and BRCA-mutations
  – Clinical behavior
  – Genomic instability

Stephens et al *Nature* 2009
vol. 462 (7276) pp 1005
54 Stage IV women
• Inherited BRCA1/2

Olaparib 100 mg po bid

Olaparib 400 mg po bid

• Primary endpoint = Objective response rate
• Secondary endpoints:
  – % tumor change
  – Progression-free survival

<table>
<thead>
<tr>
<th>Demographics</th>
<th>400 bid (n=27)</th>
<th>Efficacy (400 bid) (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior chemo</td>
<td>3 (1-5)</td>
<td>Overall response rate 11 (41)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>67%</td>
<td>CR 1 (4)</td>
</tr>
<tr>
<td>Triple negative</td>
<td>50%</td>
<td>PR 10 (37)</td>
</tr>
</tbody>
</table>

• 30% reduced doses, 30% delayed doses for toxicity

Tutt A et al, Lancet 2011
PARP inhibitors in metastatic TNBC

- niraparib – BRAVO Trial
- BMN 673 – EMBRACA - NCT01945775
- OLYMPIAD – Olaparib - NCT02000622

- gBRCA1 / BRCA2 Carriers
  Advanced anthracycline taxane resistant breast cancer

- Potent PARP inhibitor at MTD as continuous exposure

- Physician Choice within SOC options
  - Capecitabine
  - Vinorelbine
  - Eribulin
  - Gemcitabine

Primary endpoint
- PFS
<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Route</th>
<th>Current trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib</td>
<td>Clovis</td>
<td>IV/oral</td>
<td>BRCA+ Post neoadjuvant TNBC + cisplatin</td>
</tr>
<tr>
<td>Olaparib</td>
<td>AstraZeneca</td>
<td>Oral</td>
<td>BRCA+</td>
</tr>
<tr>
<td>Veliparib</td>
<td>Abbott</td>
<td>Oral</td>
<td>BRCA+, TNBC Temodal Paclitaxel CBDCA</td>
</tr>
<tr>
<td>Iniparib</td>
<td>BiPar/ Sanofi Aventis</td>
<td>IV</td>
<td>Dose escalation</td>
</tr>
<tr>
<td>LT673</td>
<td>Biomarin</td>
<td>Oral</td>
<td>-</td>
</tr>
<tr>
<td>INO-1001</td>
<td>Inotek/Genentech</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>MK4827</td>
<td>Merck</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>CEP 9722</td>
<td>Cephalon</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>E7016</td>
<td>Eisai/MGI Pharma</td>
<td>Oral</td>
<td></td>
</tr>
</tbody>
</table>
Cisplatin in basal like 1

ER-, PgR-/unknown & HER2- or known BRCA1/2
Metastatic or recurrent locally advanced

Exclusions include:
• Adjuvant taxane in ≤12 months
• Previous platinum treatment
• Non-anthracyclines for MBC

A Priori subgroup analyses:
• BRCA1/2 mutation
• Basal-like subgroups (PAM50 and IHC)
• Biomarkers of HRD

Tutt A et al, 2014

Carboplatin (C)
AUC 6 q3w, 6 cycles
On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles
n-376
BRCA1/2 = 9%/12%
On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles

Carboplatin (C)
AUC 6 q3w, 6 cycles
Cisplatin in basal like 1

Randomised treatment - all patients (N=376)

- Carboplatin: 59/188 (31.4%)
- Docetaxel: 67/188 (35.6%)

Absolute difference (C-D) = -4.2% (95% CI -13.7 to 5.3)
Exact p = 0.44

Crossover treatment - all patients (N=182)

- Carboplatin (Crossover=Docetaxel): 21/92* (22.8%)
- Docetaxel (Crossover=Carboplatin): 23/90* (25.6%)

Absolute difference (D-C) = -2.8% (95% CI -15.2 to 9.6)
Exact p = 0.73

*Denominator excludes those with no first progression and those not starting crossover treatment

Tutt, SABCS 2014
Cisplatin in basal like 1

Median PFS:
- Carboplatin: 3.1 mths (95% CI = 2.5 to 4.2)
- Docetaxel: 4.5 mths (95% CI = 4.1 to 5.2)

Restricted mean survival to 15 mths:
- Carboplatin: 4.8 mths
- Docetaxel: 5.2 mths

Absolute difference: -0.4 (95% CI -1.1 to 0.3)
\[ p = 0.29 \]

Number of events/at risk

<table>
<thead>
<tr>
<th></th>
<th>C: 0/188</th>
<th>90/98</th>
<th>40/56</th>
<th>32/22</th>
<th>9/13</th>
<th>5/8</th>
<th>0/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>D: 0/188</td>
<td>57/130</td>
<td>60/69</td>
<td>48/20</td>
<td>7/13</td>
<td>6/5</td>
<td>2/3</td>
<td></td>
</tr>
</tbody>
</table>
Cisplatin in basal like 1

Median OS:
Carboplatin: 12.4 mths
(95% CI = 10.4 to 15.3)
Docetaxel: 12.3 mths
(95% CI = 10.5 to 13.6)

Restricted mean survival to 15 mths:
Carboplatin: 10.7 mths
Docetaxel: 10.8 mths

Absolute difference:
-0.2 (95% CI -1.1 to 0.8)
\( p = 0.31 \)

Number of events/at risk

<table>
<thead>
<tr>
<th></th>
<th>C: 0/188</th>
<th>23/165</th>
<th>18/141</th>
<th>24/114</th>
<th>22/89</th>
<th>14/71</th>
<th>22/44</th>
</tr>
</thead>
<tbody>
<tr>
<td>D: 0/188</td>
<td>11/176</td>
<td>20/151</td>
<td>35/110</td>
<td>19/85</td>
<td>23/58</td>
<td>16/39</td>
<td></td>
</tr>
</tbody>
</table>
Cisplatin in basal like 1

**Germline BRCA 1/2 Mutation (n=43)**

- **Carboplatin**
  - 17/25 (68.0%)
- **Docetaxel**
  - 6/18 (33.3%)

**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)**

- **Carboplatin**
  - 36/128 (28.1%)
- **Docetaxel**
  - 53/145 (36.6%)

**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
Cisplatin in basal like 1

Median PFS:
- C + BRCA 1/2 mutated: 6.8 months (95% CI = 4.4 to 8.1)
- C + BRCA1/2 not mutated: 3.1 months (95% CI = 2.4 to 4.2)
Basal like 2: Growth factor signalling

Enrolled (N = 112)

Treated (n = 102)

Not treated (n = 10)
- Personal reasons (n = 4)
- Screen failure (n = 3)
- Death or progression during screening (n = 3)

Arm 1
cetuximab alone (n = 31)
- Evaluable (n = 31)
  - Early progressors (n = 2)
- Not evaluable (n = 0)
  Arm 1 crossover to cetuximab + carboplatin (n = 26)

Arm 2
cetuximab + carboplatin (n = 71)
- Evaluable (n = 65)
  - Early progressors (n = 5)
- Not evaluable (n = 6)
  Off protocol (n = 5)

Lisa A. Carey et al. JCO 2012;30:2615-2623
### Table 2. Response Within Treatment Arms and to Combined Therapy in Basal-Like Disease

<table>
<thead>
<tr>
<th>Response</th>
<th>Arm 1 (n = 31)</th>
<th>Arm 1B (n = 25)</th>
<th>Arm 2 (n = 71)</th>
<th>C + Cb* (n = 51)</th>
<th>Basal-Like Tumors†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C Only</td>
<td>C + Cb†</td>
<td>C + Cb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>4</td>
<td>11</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>16%</td>
<td>16%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>10%</td>
<td>28%</td>
<td>21%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>26</td>
<td>48</td>
<td>54</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
<td>8%</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Abbreviations: C, cetuximab; Cb, carboplatin; CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

*Combined Arms 1B and 2.
†After progression while receiving C.
‡Limited to those with confirmed basal-like disease by quantitative real-time polymerase chain reaction–based intrinsic subtype assay.
The combination of cetuximab plus Carboplatin in metastatic TNBC produced responses in fewer than 20% of patients. EGFR pathway analysis showed that most TNBCs involved activation.
Clinical Heterogeneity of TNBC

Subtype
- Basal-like 1
- Basal-like 2
- Immunomodulatory
- Mesenchymal
- Mesenchymal stem-like
- Luminal androgen receptor

Gene expression profile
- Basal-like 1: high Ki-67; DNA damage response, GF pathways, Immune genes, Cell motility
- Basal-like 2: higher pCR, Apocrine features
- Immunomodulatory: Immune genes, Cell motility; claudin-low
- Mesenchymal: Cell motility; claudin-low
- Mesenchymal stem-like: Cell motility; claudin-low
- Luminal androgen receptor: Steroid pathways

Clinical
- Basal-like 1: BRCA-associated
- Basal-like 2: Higher pCR
- Immunomodulatory: Lower DDFS
- Mesenchymal: Apocrine features, higher LRF; PI3Kmut

Evidence from clinical trials

**Pembrolizumab** (Merck)
Humanized IgG4 anti-PD-1 antibody

**MPDL3280** (Genentech)
engineered human IgG1 anti-PD-L1 antibody
Pembrolizumab in TNBC

- Recurrent or metastatic ER-/PR-/HER2- breast cancer
- ECOG PS 0-1
- PD-L1+ tumour
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

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

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aPD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
bIf clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.
Pembrolizumab in TNBC

Objective response rate: 18.5%
Stable disease: 25.9%

Nanda, SABCS 2015
Pembrolizumab in TNBC

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response\(^a\): not reached (range, 15 to 40+ weeks)
- PFS 1.9 ms; 6 ms PFS- 23%

\(^a\)Kaplan-Meier estimate.
Analysis cut-off date: November 10, 2014.
Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

<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)(^a)</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)(^b)</td>
<td>88.9% (51.7, 99.7)</td>
<td>75.0% (34.9, 96.8)</td>
<td>42.9% (9.9, 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>

Response rates were higher for patients who received atezolizumab/nab-paclitaxel treatment as 1L therapy compared to 2L+

\(^a\) Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.

\(^b\) Including investigator-assessed unconfirmed responses.

Efficacy-evaluable patients were dosed by June 1, 2015, and were evaluable for response by RECIST v1.1. Minimum efficacy follow up was ≥ 3 months.

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

- 11 of 17 responses (65%) continued on treatment at time of data cut off

Including investigator-assessed unconfirmed responses.

### Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

<table>
<thead>
<tr>
<th>PD-L1 IHC IC Status</th>
<th>Patients N = 24</th>
<th>PD-L1 IHC TC Status</th>
<th>Patients N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC3 (≥ 10%)(^a)</td>
<td>1</td>
<td>TC3 (≥ 50%)</td>
<td>1</td>
</tr>
<tr>
<td>IC2 (≥ 5% and &lt; 10%)</td>
<td>3</td>
<td>TC2 (≥ 5% and &lt; 50%)</td>
<td>0</td>
</tr>
<tr>
<td>IC1 (≥1% and &lt; 5%)</td>
<td>5</td>
<td>TC1 (≥ 1% and &lt; 5%)</td>
<td>2</td>
</tr>
<tr>
<td>IC0 (&lt; 1%)</td>
<td>7</td>
<td>TC0 (&lt; 1%)</td>
<td>13</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>Unknown</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) Percent of IC or TC staining positive for PD-L1.

- Expression of PD-L1 in TNBC is mostly restricted to IC

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

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

Including investigator-assessed unconfirmed responses.

- Responses were observed in both IC0 and IC1/2/3 patients

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

- Proliferating activated CD8+ T cells transiently peaked at the end of the first cycle of atezolizumab treatment

Phase III Study of Atezolizumab and Nab-Paclitaxel in mTNBC

- Randomized, double-blind, placebo-controlled Phase 3 trial of nab-paclitaxel ± atezolizumab as 1st line therapy in mTNBC (NCT02425891)

**Study design**

- Histologically documented locally advanced or metastatic TNBC
- No prior therapy for advanced disease
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Patients with significant CV or CNS disease (except asymptomatic brain metastases), autoimmune disease or prior checkpoint inhibitor therapy are excluded
- Target accrual: ~350 pts

**Co-primary endpoints:**
- PFS in all patients
- PFS according to PD-L1 expression

**Secondary endpoints:**
- OS
- ORR
- Response duration
- Safety/tolerability
- PK
- HR QoL

**Stratification factors:**
- Presence of liver metastases
- Prior taxane therapy
- PD-L1 expression status (centrally evaluated by IHC using the SP142 assay)

Emens et al. SABCS 2015 (abstract OT1-01-06)
Immunotherapy in TNBC

**Nivolumab** (BMS)
Human IgG4 anti-PD-1 antibody

**Pembrolizumab** (Merck)
Humanized IgG4 anti-PD-1 antibody

**MPDL3280** (Genentech)
Engineered human IgG1 anti-PD-L1 antibody

**MEDI4736** (AZ)
Human IgG1 anti-PD-L1 antibody

**Tremelimumab** (AZ)
Human IgG2 Anti-CTLA-4 antibody
## Immunotherapy in TNBC

<table>
<thead>
<tr>
<th></th>
<th>Phase</th>
<th>Setting</th>
<th>Subtype</th>
<th>PD-L1 expression as inclusion criteria</th>
<th>Combination/comparator</th>
<th>Primary EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>II</td>
<td>Metastatic TN</td>
<td>No</td>
<td></td>
<td>Monotherapy after induction with RT and CT</td>
<td>PFS</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>II</td>
<td>Metastatic IBC HER2-</td>
<td>No</td>
<td></td>
<td>monotherapy</td>
<td>Disease control rate</td>
</tr>
<tr>
<td></td>
<td>Ib/II</td>
<td>Metastatic TN</td>
<td>No</td>
<td>+ eribulin</td>
<td>DLT/ORR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Metastatic TN</td>
<td>Cohort B (positive) Cohort C (strong)</td>
<td>monotherapy</td>
<td>ORR/Safety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ib/II</td>
<td>Metastatic/LABC TN</td>
<td>Presence of PD-L1 expression</td>
<td>+ nabpaclitaxel</td>
<td>Safety/ORR</td>
<td></td>
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<tr>
<td></td>
<td>II</td>
<td>Metastatic HR+</td>
<td>No</td>
<td>+ Tamoxifen + Vorinostat</td>
<td>Safety/ORR</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>III</td>
<td>Metastatic TN</td>
<td>No</td>
<td>+ nabpaclitaxel vs nabpaclitaxel</td>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>II</td>
<td>Metastatic HER2-</td>
<td>No</td>
<td>+ tremelimumumab (AZ)</td>
<td>ORR</td>
<td></td>
</tr>
</tbody>
</table>
# Adaptive Phase II Randomized Non-comparative Trial of Nivolumab After Induction Treatment in Triple-negative Breast Cancer (TNBC) Patients: TONIC-trial (The Netherlands Cancer Institute)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Assigned intervention</th>
</tr>
</thead>
</table>
| Active Comparator: Radiation therapy  
Radiotherapy on metastatic lesion | Nivolumab 3 mg/kg, every 2 weeks after induction treatment  
Radiation: Radiation therapy  
20 Gy to metastatic lesion |
| Active Comparator: Low dose doxorubicin  
15 mg flat dose, once weekly for 2 weeks | Nivolumab 3 mg/kg, every 2 weeks after induction treatment  
Low dose doxorubicin |
| Active Comparator: Cyclophosphamide  
metronomic schedule, 50 mg daily orally for 2 weeks | Nivolumab 3 mg/kg, every 2 weeks after induction treatment  
Metronomics CTX |
| Active Comparator: Cisplatin  
40 mg/m², weekly for 2 weeks | Nivolumab 3 mg/kg, every 2 weeks after induction treatment  
Weekly cisplatin |
| Active Comparator: No induction treatment | Nivolumab 3 mg/kg, every 2 weeks after induction treatment |
Targeting stroma and inflammation

G. Curigliano et al. The Breast, 2015

19.07.2007

18.10.2007
Targeting stroma and inflammation

- **PD-L1 positivity**: Stratification factor
- **Treatment**: metronomic CT plus pembrolizumab
- **Response assessment**: Performed every 8 weeks per RECIST v1.1

**Eligibility Criteria**
- Recurrent or metastatic LBC or IBC
- ECOG PS 0-1
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

**Treatment Protocol**
- Pembro 200 mg Q3W + CTX 50 mg/die

**Response Outcomes**
- Complete Response: Discontinuation Permitted
- Partial Response or Stable Disease: Treat for 24 months or until progression or intolerable toxicity
- Confirmed Progressive Disease: Discontinue

PI G. Curigliano et al.
Immunootherapy of TNBC?

- Is there a rational for immune-based therapy in TNBC? **YES**
- Evidences from clinical data? **LIMITED**
- Can you enhance immunogenicity? **MAY BE**
- Can we monitor and to predict response? **NO, BUT...**
Clinical Heterogeneity of TNBC

**Subtype**
- Basal-like 1
- Basal-like 2
- Immunomodulatory
- Mesenchymal
- **Mesenchymal stem-like**
- Luminal androgen receptor

**Gene expression profile**
- High Ki-67; DNA damage response
- GF pathways
- Immune genes
- Cell motility
- Cell motility; claudin-low
- Steroid pathways

**Clinical**
- BRCA-associated
- Higher pCR
- Lower DDFS
- Apocrine features, higher LRF; PI3Kmut

Phase 1b Study of docetaxel + PF-03084014 in Triple-negative Breast Cancer
## Notch pathway

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PF 100 mg BID/ D 75 mg/m² (N = 8)</th>
<th>PF 100 mg BID/ D 100 mg/m² (N = 3)</th>
<th>PF 150 mg BID/ D 75 mg/m² (N = 11)</th>
<th>All Dose Levels (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age, years</td>
<td>57 (43-76)</td>
<td>43 (32-64)</td>
<td>46 (27-69)</td>
<td>50 (27-76)</td>
</tr>
<tr>
<td>ECOG PS, n (%) 0/1</td>
<td>4/4 (50/50)</td>
<td>1/2 (33/67)</td>
<td>8/3 (73/27)</td>
<td>13/9 (59/41)</td>
</tr>
<tr>
<td>Primary Diagnosis, n (%) locally recurrent/metastatic</td>
<td>1/7 (13/87)</td>
<td>0/3 (0/100)</td>
<td>3/8 (27/73)</td>
<td>4/18 (18/82)</td>
</tr>
<tr>
<td>Prior Systemic Therapies, n (%) 1st line/ 2nd line</td>
<td>4/4 (50/50)</td>
<td>3/0 (100/0)</td>
<td>7/4 (64/36)</td>
<td>14/8 (64/36)</td>
</tr>
</tbody>
</table>

G Curigliano, ASCO 2015
Clinical Heterogeneity of TNBC

Subtype
- Basal-like 1
- Basal-like 2
- Immunomodulatory
- Mesenchymal
- Mesenchymal stem-like
- Luminal androgen receptor

Gene expression profile
- Basal-like 1: high Ki-67; DNA damage response
- Basal-like 2: GF pathways
- Immunomodulatory: Immune genes
- Mesenchymal: Cell motility
- Mesenchymal stem-like: Cell motility; claudin-low
- Luminal androgen receptor: Steroid pathways

Clinical
- BRCA-associated: Higher pCR
- Lower DDFS
- Apocrine features, higher LRF; PI3Kmut

Enzalutamide Inhibits AR Signaling in 3 Different Ways

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding

AR = androgen receptor, T = testosterone.

Preclinical Activity of Enzalutamide in an AR+ TNBC Cell Line (MDA-MB-453)

DHT = dihydrotestosterone; TNBC = triple-negative breast cancer.
Cochrane DR et al. Breast Cancer Res. 2014;16:R7;
Luminal Androgen Receptor

Eligibility
- "AR positive" advanced TNBC*
- ECOG-PS ≤ 1
- Any number of prior therapies permissible
- Evaluable bone-only disease allowed
- No CNS metastases
- Sufficient tissue to enable biomarker discovery

Endpoints
- Primary
  - CBR16
- Other Key Endpoints
  - CBR24
  - Response rate
  - PFS
  - OS
  - Safety
  - AR biomarker discovery

Treatment
Enzalutamide 160 mg/day orally

Stage 1
- ≥ 3 of 26 Evaluable have CBR16
  - "Go" to Stage 2

Stage 2
- ≥ 9 of 62 Evaluable have CBR16
  - Rejection of H0

Statistical Considerations
- 85% power to detect true CBR16 = 8% tested against 1-sided alternative (CBR16 ≥ 20%); alpha = 5%

* A separate consent allowed tissue submission for central AR IHC testing at any time. "AR positive" was defined as IHC staining in >0% of tumor nuclei. Physicians and patients were blinded to actual % AR staining. AR = androgen receptor; CBR = clinical benefit rate; CBR16 = 16-week CBR; CBR24 = 24-week CBR; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; H0 = null hypothesis; IHC = immunohistochemistry; ITT = intent-to-treat.; TNBC = triple negative breast cancer

www.clinicaltrials.gov, NCT01889238.

Courtesy of J. Cortes, ECCO 2015
Response to enzalutamide

**Figure 4. Clinical Benefit Rate at 16 and 24 Weeks in Stage 1 Evaluable Patients**

<table>
<thead>
<tr>
<th></th>
<th>Evaluable</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 26</td>
<td>n = 42</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>CBR16</td>
<td>42.3%</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>24.2%–61.9%</td>
</tr>
<tr>
<td></td>
<td>n = 11</td>
<td>n = 12</td>
</tr>
<tr>
<td>Secondary</td>
<td>CBR24</td>
<td>34.6%</td>
</tr>
<tr>
<td>Endpoints</td>
<td>95% CI</td>
<td>18.3%–54.2%</td>
</tr>
<tr>
<td></td>
<td>n = 9</td>
<td>n = 10</td>
</tr>
<tr>
<td>CR or PR</td>
<td>7.7%</td>
<td>4.8%</td>
</tr>
<tr>
<td>(1 PR, 1 CR)</td>
<td>(1 PR, 1 CR)</td>
<td></td>
</tr>
</tbody>
</table>

- Clinical Progression
- Patients with PFS Event
- Patients Active on Study as of Nov 10, 2014
- CR or PR (Best Overall Response)

Length of the horizontal bars indicate duration of PFS.
Luminal Androgen Receptor

- Hierarchical clustering according to biology

- Responders clustered within a recognized and distinct pattern that includes AR\(^1-^5\)
  - 521 genes significantly different in responders at 1% false discovery rate

- A diagnostic test (PREDICT AR) was created and validated

Data Cut-off 01 July 2015

*Includes duplicates and samples from tissue collected for optional AR testing; CBR16 = clinical benefit rate at week 16; AR = androgen receptor; IHC immunohistochemistry


Parker, et al ASCO 2015

Courtesy of J. Cortes, ECCO 2015
Data cutoff 1Jul2015
ITT = intent to treat; mOS = median survival; CI = confidence interval; .

NCT01889238

Luminal Androgen Receptor

ITT Population

Patients at risk
PREDICT AR+ 56 53 49 45 42 40 32 15 11 3
PREDICT AR− 62 55 46 37 27 24 13 6 6 2

PREDICT AR+ mOS 75.6 weeks
(95% CI: 51.6, 91.4)
PREDICT AR− mOS 32.3 weeks
(95% CI: 20.7, 48.3)

PREDICT AR+ mOS 18.0 months
PREDICT AR− mOS 7.5 months

Courtesy of J. Cortes, ECCO 2015
Luminal Androgen Receptor

Overall Survival (%)

Patients at risk

PREDICT AR+

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Patients</th>
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<tbody>
<tr>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
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<tr>
<td>16</td>
<td>25</td>
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<tr>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>88</td>
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</table>

PREDICT AR−

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>16</td>
<td>29</td>
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<td>48</td>
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<td>56</td>
<td>4</td>
</tr>
<tr>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
</tr>
</tbody>
</table>

CI= confidence interval; mOS = median survival; NYR = not yet reached

Data cutoff 1Jul2015.

PREDICT AR+  mOS not yet reached

PREDICT AR−  mOS 10.1 months
Challenges

• Small phase II maybe NOT be enough to interpret data
• Run large trials in low-incidence disease to generate knowledge about drug and disease
• Change statistical hypothesis since expectations are higher now
Conclusions

- Select the right partner and validate studies with the same backbone
- Demonstrate bioactivity and not MTD
- Metastatic breast cancer is not always the right setting:
  - Neoadjuvant
  - Post-neoadjuvant can be more informative
Thank you

Slides available contacting: giuseppe.curigliano@ieo.it