Systemic therapy of triple negative advanced breast cancer

Giuseppe Curigliano MD, PhD
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

<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>

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

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

Initial therapy

First distant relapse

Median D.F.I.

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 9342¹</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 2100²</td>
<td>III</td>
<td>110</td>
<td>First-line metastatic</td>
<td>Paclitaxel weekly</td>
<td>ORR = 11.7%⁴ PFS = 5.3 months</td>
</tr>
<tr>
<td>AVADO³</td>
<td>III</td>
<td>52</td>
<td>First-line metastatic</td>
<td>Docetaxel q3w</td>
<td>ORR = 23.1%⁴ 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\(^1\) | III   | 208| Third-line or greater metastatic | Capecitabine         | ORR = 15%  
PFS = 1.7 months                   |
| RIBBON-1\(^2\) | III   | 50 | First-line metastatic    | Capecitabine + placebo| PFS = 4.2 months                        |

2. Glaspy, et al. EBCC 2010
# 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</td>
<td>62</td>
<td>59%</td>
<td>20 (32%)</td>
<td>3.3 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 mg/m² d1, 8</td>
<td></td>
<td></td>
<td></td>
<td></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)

- Manteinance with capecitabine and bevacizumab following response to Bevacizumab

- IMELDA (Gligorov et al, Lancet Oncol 2014)
Ideal drug

- 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
- Concomitant Therapy
- 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

Demographics 400 bid (n=27)

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

- **gBRCA1 / BRCA2 Carriers**
  - Advanced anthracycline taxane resistant breast cancer

- **Primary endpoint PFS**

- **Potent PARP inhibitor at MTD as continuous exposure**

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

- **Niraparib – BRAVO Trial**
  - BMN 673 – EMBRACA - NCT01945775
  - OLYMPIAD – Olaparib - NCT02000622
# PARP inhibition in basal like 1

<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

On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles
BRCA1/2 = 9%/12%

Carboplatin (C)
AUC 6 q3w, 6 cycles
n=376

Tutt A et al, 2014
Cisplatin in basal like 1

Randomised treatment - all patients (N=376)

Carboplatin
59/188 (31.4%)

Docetaxel
67/188 (35.6%)

% with OR at cycle 3 or 6 (95% CI)

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%)

% with OR at cycle 3 or 6 (95% CI)

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></td>
<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>
</tr>
</tbody>
</table>
Cisplatin in basal like 1

Number of events/at risk

\[
\begin{array}{cccccccc}
C: & 0/188 & 23/165 & 18/141 & 24/114 & 22/89 & 14/71 & 22/44 \\
D: & 0/188 & 11/176 & 20/151 & 35/110 & 19/85 & 23/58 & 16/39 \\
\end{array}
\]

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)
  - \( p = 0.31 \)

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)
  - \( p = 0.31 \)
Cisplatin in basal like 1

Germline BRCA 1/2 Mutation (n=43)

Carboplatin

17/25 (68.0%)

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

Docetaxel

6/18 (33.3%)

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

Carboplatin

36/128 (28.1%)

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

Docetaxel

53/145 (36.6%)

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01
Cisplatin in basal like 1

Median PFS:
- Carboplatin + BRCA 1/2 mutated: 6.8 months (95% CI = 4.4 to 8.1)
- Carboplatin + BRCA1/2 not mutated: 3.1 months (95% CI = 2.4 to 4.2)

Tutt, SABCS 2014
### 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C Only</td>
<td>C + Cb†</td>
<td>C + Cb</td>
<td>Basal-Like Tumors†</td>
</tr>
<tr>
<td>CR</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>10</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>PD</td>
<td>26</td>
<td>84</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>NE</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</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
- 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

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

*PD-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.

*If 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

n = 32

Confirmed complete response (nodal disease)
Confirmed partial response
Stable disease
Progressive disease

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.

Nanda, SABCS 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>
</table>
| Confirmed ORR (95% CI)
a | 66.7% (29.9, 92.5) | 25% (3.2, 65.1) | 28.6% (3.7, 71.0) | 41.7% (22.1, 63.4) |
| ORR (95% CI)b | 88.9% (51.7, 99.7) | 75.0% (34.9, 96.8) | 42.9% (9.9, 81.6) | 70.8% (48.9, 87.4) |
| CR | 11.1% | 0 | 0 | 4.2% |
| PR | 77.8% | 75.0% | 42.9% | 66.7% |
| SD | 11.1% | 25.0% | 28.6% | 20.8% |
| PD | 0 | 0 | 28.6% | 8.3% |

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 $(\geq 10%)^a$</td>
<td>1</td>
<td>TC3 $(\geq 50%)$</td>
<td>1</td>
</tr>
<tr>
<td>IC2 $(\geq 5%$ and $&lt; 10%)$</td>
<td>3</td>
<td>TC2 $(\geq 5%$ and $&lt; 50%)$</td>
<td>0</td>
</tr>
<tr>
<td>IC1 $(\geq 1%$ and $&lt; 5%)$</td>
<td>5</td>
<td>TC1 $(\geq 1%$ 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><strong>ORR (95% CI)</strong></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><strong>CR</strong></td>
<td>0</td>
<td>0</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>57.1%</td>
<td>77.8%</td>
<td>62.5%</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>42.9%</td>
<td>22.2%</td>
<td>0</td>
</tr>
<tr>
<td><strong>PD</strong></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

Nab-paclitaxel 100 mg/m² QW 3/4 + Atezolizumab 840 mg Q2W

R
1:1

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>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</td>
<td>TN</td>
<td>No</td>
<td>Monotherapy after induction with RT and CT</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>II</td>
<td>Metastatic IBC</td>
<td>HER2-</td>
<td>No</td>
<td>monotherapy</td>
</tr>
<tr>
<td></td>
<td>Ib/II</td>
<td>Metastatic</td>
<td>TN</td>
<td>No</td>
<td>+ eribulin</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Metastatic</td>
<td>TN</td>
<td>Cohort B (positive) Cohort C (strong)</td>
<td>monotherapy</td>
</tr>
<tr>
<td></td>
<td>Ib/II</td>
<td>Metastatic/LABC</td>
<td>TN</td>
<td>Presence of PD-L1 expression</td>
<td>+ nabpaclitaxel</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Metastatic</td>
<td>HR+</td>
<td>No</td>
<td>+ Tamoxifen + Vorinostat</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>III</td>
<td>Metastatic</td>
<td>TN</td>
<td>No</td>
<td>+ nabpaclitaxel vs nabpaclitaxel</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>II</td>
<td>Metastatic</td>
<td>HER2-</td>
<td>No</td>
<td>+ tremelimumab (AZ)</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>
<tbody>
<tr>
<td>Active Comparator: Radiation therapy</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>Radiotherapy on metastatic lesion</td>
<td>Radiation: Radiation therapy 20 Gy to metastatic lesion</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Comparator: Low dose doxorubicin</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>15 mg flat dose, once weekly for 2 weeks</td>
<td>Low dose doxorubicin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Comparator: Cyclophosphamide</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>metronomic schedule, 50 mg daily orally for 2 weeks</td>
<td>Metronomics CTX</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Comparator: Cisplatin</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>40 mg/m2, weekly for 2 weeks</td>
<td>Weekly cisplatin</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Comparator: No induction treatment</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
</tbody>
</table>
Targeting stroma and inflammation

19.07.2007

G. Curigliano et al. The Breast, 2015
Targeting stroma and inflammation

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

PI G. Curigliano et al.
• 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
<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
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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

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

AR = androgen receptor  T = testosterone.

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>Endpoint</th>
<th>Evaluable</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBR 16</td>
<td>42.3%</td>
<td>28.6%</td>
</tr>
<tr>
<td>95% CI</td>
<td>n = 11</td>
<td>n = 12</td>
</tr>
<tr>
<td></td>
<td>24.2%–61.9%</td>
<td>15.6%–43.9%</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBR 24</td>
<td>34.6%</td>
<td>23.8%</td>
</tr>
<tr>
<td>95% CI</td>
<td>n = 9</td>
<td>n = 10</td>
</tr>
<tr>
<td></td>
<td>18.3%–54.2%</td>
<td>12.3%–39.0%</td>
</tr>
<tr>
<td>CR or PR (1 PR, 1 CR)</td>
<td>7.7%</td>
<td>4.8%</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

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


Data Cut-off 01 July 2015

**PREDICT AR**

AR IHC

<table>
<thead>
<tr>
<th>CBR16</th>
<th>PREDICT AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td>No</td>
<td>Negative</td>
</tr>
<tr>
<td>Not treated</td>
<td></td>
</tr>
</tbody>
</table>

≥ 1% ■ □
<1% ■ □

Parker, et al ASCO 2015

Courtesy of J. Cortes, ECCO 2015
Luminal Androgen Receptor

Data cutoff 1 Jul 2015

ITT = intent to treat; mOS = median survival; CI = confidence interval.

Patients at risk

<table>
<thead>
<tr>
<th></th>
<th>PREDICT AR+</th>
<th>PREDICT AR−</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>16</td>
<td>49</td>
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<tr>
<td>24</td>
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<td>33</td>
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<td>41</td>
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<tr>
<td>49</td>
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</tr>
<tr>
<td>61</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>64</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>68</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

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

PREDICT AR+  mOS 75.6 weeks
(95% CI: 51.6, 91.4)

PREDICT AR−  mOS 32.3 weeks
(95% CI: 20.7, 48.3)

Courtesy of J. Cortes, ECCO 2015
Luminal Androgen Receptor

Patients at risk
<table>
<thead>
<tr>
<th></th>
<th>PREDICT AR+</th>
<th>PREDICT AR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>29</td>
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<td>25</td>
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</tr>
<tr>
<td>24</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff 1Jul2015.
CI= confidence interval; mOS = median survival; NYR = not yet reached

PREDICT AR+  mOS not yet reached
PREDICT AR−  mOS 10.1 months

n = 63

Courtesy of J. Cortes, ECCO 2015
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