Treatment of Triple Negative Breast Cancer

Giuseppe Curigliano MD, PhD
University of Milano and European Institute of Oncology
Outline

• Neoadjuvant treatment in triple negative EBC
• Picking optimal adjuvant chemotherapy for TN early breast cancer
• The post-neoadjuvant setting
• Treatment of triple negative metastatic breast cancer
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene expression profile</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like 1</td>
<td>high Ki-67; DNA damage response</td>
<td>BRCA-associated</td>
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<td>Basal-like 2</td>
<td>GF pathways</td>
<td>Higher pCR</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Immune genes</td>
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</tr>
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<td>Mesenchymal stem-like</td>
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<td>Apocrine features, higher LRF; PI3Kmut</td>
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<td>Luminal androgen receptor</td>
<td>Steroid pathways</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subtypes according to clinical-pathological and genomic risk assessment</th>
<th>Treatment recommendation</th>
<th>De-escalation</th>
<th>Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ductal triple negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy for stage II or III is the preferred initial treatment approach.</td>
<td>No routine adjuvant chemotherapy for stage pT1a pN0.</td>
<td>No consensus on post-neoadjuvant treatment in case of residual disease, nor which treatment might be preferred.</td>
<td>In BRCA1/2 associated cancers, the Panel was evenly split on whether to recommend (neo)-adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.</td>
</tr>
<tr>
<td>Chemotherapy should include anthracycline and taxanes</td>
<td>Dose-dense adjuvant chemotherapy not as necessarily preferred treatment approach.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• #1 Using NO chemotherapy

• #2 Neoadjuvant timing to minimize Rx

• #3 Using less toxic / aggressive chemotherapy

• *Future* – substituting *non-cytotoxic options to reduce risk of relapse*
Should all TNBC receive PST?

- Neoadjuvant approach

  - Advantages
    - Minimize surgery = no controversy
    - Minimize chemotherapy?

  - Disadvantages
    - Clinical staging - less accurate
    - Locoregional management less clear
(Neo)Adjuvant therapy in TN EBC

- Who needs more treatment?
- Addition of carboplatin
- Tumor infiltrating lymphocytes
- Post-neoadjuvant setting
## Carboplatin in TN

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Drugs</th>
<th>Population</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEICAM</td>
<td>94</td>
<td>EC-D</td>
<td>Basal-like</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EC-D+carbo</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>GeparSixto</td>
<td>165</td>
<td>PM/bev</td>
<td>TNBC (subset)</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMCb/bev</td>
<td></td>
<td>59%*</td>
</tr>
<tr>
<td>CALGB 40603</td>
<td>455</td>
<td>T-AC(bev)</td>
<td>TNBC</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T/carbo-AC(bev)</td>
<td></td>
<td>60%*</td>
</tr>
<tr>
<td>ADAPT-TN</td>
<td>336</td>
<td>Nab-P/wkly Gem</td>
<td>TNBC</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nab-P/wkly Carbo</td>
<td></td>
<td>46%*</td>
</tr>
</tbody>
</table>

*Alba, BCRT’12; von Minckwitz, Lancet Oncol’14; Sikov, JCO’14; Gluz, ACR-SABCS’15

Carboplatin augments pCR in TNBC
Carboplatin in TN

Study Objectives

Primary objectives:
• Pathologic complete response (pCR) in breast and ipsilateral axillary lymph nodes

Secondary objectives:
• EFS, OS, and rate of eligibility for breast conservation after therapy

AC, doxorubicin plus cyclophosphamide; Cb, carboplatin; EFS, event free survival; OS, overall survival; P, paclitaxel; V, veliparib

S. Loibl et al. The Lancet Oncology 2018
## Carboplatin in TN

<table>
<thead>
<tr>
<th>Characteristic, n%</th>
<th>V+Cb+P (n=316)</th>
<th>Cb+P (n=160)</th>
<th>P (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median [range], years</strong></td>
<td>51 [26–79]</td>
<td>49 [23–76]</td>
<td>50 [22–75]</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>140 (44.3)</td>
<td>73 (45.6)</td>
<td>79 (50.0)</td>
</tr>
<tr>
<td>Europe</td>
<td>119 (37.7)</td>
<td>65 (40.6)</td>
<td>58 (36.7)</td>
</tr>
<tr>
<td>Asian Pacific</td>
<td>57 (18.0)</td>
<td>22 (13.8)</td>
<td>21 (13.3)</td>
</tr>
<tr>
<td><strong>gBRCA status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deleterious mutation</td>
<td>45 (14.2)</td>
<td>25 (15.6)</td>
<td>23 (14.6)</td>
</tr>
<tr>
<td>No deleterious mutation</td>
<td>271 (85.8)</td>
<td>135 (84.4)</td>
<td>135 (85.4)</td>
</tr>
<tr>
<td><strong>Tumor Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>37 (11.7)</td>
<td>20 (12.5)</td>
<td>15 (9.5)</td>
</tr>
<tr>
<td>T2</td>
<td>229 (72.5)</td>
<td>107 (66.9)</td>
<td>117 (74.1)</td>
</tr>
<tr>
<td>T3-4a</td>
<td>50 (15.8)</td>
<td>33 (20.6)</td>
<td>26 (16.5)</td>
</tr>
<tr>
<td><strong>Lymph Node Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>180 (57.0)</td>
<td>92 (57.5)</td>
<td>94 (59.5)</td>
</tr>
<tr>
<td>N1-N2</td>
<td>136 (43.0)</td>
<td>68 (42.5)</td>
<td>64 (40.5)</td>
</tr>
<tr>
<td><strong>Planned Schedule of AC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 weeks</td>
<td>173 (54.7)</td>
<td>88 (55.0)</td>
<td>89 (56.3)</td>
</tr>
<tr>
<td>Q3 weeks</td>
<td>140 (44.3)</td>
<td>70 (43.8)</td>
<td>69 (43.7)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (1.0)</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Longest Tumor Diameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30 mm</td>
<td>145 (45.9)</td>
<td>71 (44.4)</td>
<td>79 (50.0)</td>
</tr>
<tr>
<td>&gt; 30 mm</td>
<td>171 (54.1)</td>
<td>89 (55.6)</td>
<td>79 (50.0)</td>
</tr>
</tbody>
</table>
Carboplatin in TN

Pathologic Complete Response
ypT0/Tis ypN0

Clinical Response Rate*

Minimal Residual Disease
Residual Cancer Burden Class 0 or I

Error bars are 95% confidence intervals based on normal approximation. p-values were calculated from Cochran-Mantel-Haenszel test versus Arm A (V+Cb+P).

*Clinical response rate after paclitaxel based treatment on serial MRI assessment

S. Loibl et al. The Lancet Oncology 2018
Carboplatin in TN

- Addition of V and Cb to P followed by AC demonstrated a significant improvement in pCR compared with P followed by AC (53.2% vs 31.0%, $p<0.001$) confirming results of I-SPY-2.

- However, addition of V and Cb to P followed by AC did not show improvement in pCR compared to Cb+P followed by AC (53.2% vs 57.5%, $p=0.36$), demonstrating improvement in pCR was due to carboplatin, without apparent contribution from veliparib at the 50 mg BID dose.

- Increase in pCR with addition of carboplatin was independent of gBRCA mutation status.
TILs

INFORM: preop cisplatin vs AC for BRCA 1/2 carriers

Stage II/III BC with BRCA1 or 2 mutation

- Multicenter study
- Designed to show 20% improvement in pCR with cisplatin over AC

N = 170; approximately 60 enrolled

Principal Investigators:
Nadine Tung and Judy Garber
TBCRRC and other sites
Post-Neoadjuvant setting

C. Liedtke JCO, 26, 8, 2008: pp. 1275-1281
Post-Neoadjuvant setting

• Theory:
  • pCR = no further therapy needed
  • Residual disease = give more treatment
Post-Neoadjuvant setting

- Preplanned interim analysis of a randomized, open-label phase III study\[1\]
  
  Stratified by ER status, age, neoadjuvant chemotherapy, use of 5-FU, institution, node status

- Pts 20-74 yrs of age with stage I-IIIB HER2- BC and residual disease (non-pCR, N+) after neoadjuvant chemotherapy* and surgery; ECOG PS 0 or 1; no previous oral fluoropyrimidines (N = 910)†

  - Primary endpoint: DFS
  - Secondary endpoints: OS, time from first day of preoperative chemotherapy to recurrence or death, safety, cost-effectiveness


- Capecitabine
  2500 mg/m²/day PO Days 1-14 Q3W for 8 cycles‡
  Hormonal therapy if ER/PgR+ (n = 455)†

- Hormonal therapy if ER/PgR+
  No further therapy if ER/PgR- (n = 455)†

*Anthracycline/taxane, anthracycline containing, or docetaxel/cyclophosphamide.
†25 pts were removed from treatment (n = 10) and control (n = 15) arms due to failure to meet eligibility criteria.
‡IDMC recommended extension to 8 cycles following interim safety analysis of first 50 pts receiving 6 cycles.[2]
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median yrs (range)</td>
<td>48 (25-74)</td>
<td>48 (25-74)</td>
</tr>
<tr>
<td>Menopausal status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>59.3</td>
<td>56.0</td>
</tr>
<tr>
<td>Post</td>
<td>40.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, IIA, IB</td>
<td>58.9</td>
<td>62.0</td>
</tr>
<tr>
<td>IIIA, IIB</td>
<td>40.5</td>
<td>37.5</td>
</tr>
<tr>
<td>Hormonal receptor status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ or PgR+</td>
<td>63.9</td>
<td>62.9</td>
</tr>
<tr>
<td>ER- and PgR-</td>
<td>33.4</td>
<td>33.5</td>
</tr>
<tr>
<td>Lymph nodes with metastatic disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39.3</td>
<td>38.7</td>
</tr>
<tr>
<td>1-3</td>
<td>37.5</td>
<td>39.1</td>
</tr>
<tr>
<td>≥ 4</td>
<td>22.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Histologic effect grading by NAC, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1a, 1b</td>
<td>56.4</td>
<td>52.6</td>
</tr>
<tr>
<td>2, 3</td>
<td>41.6</td>
<td>45.4</td>
</tr>
</tbody>
</table>

Post-Neoadjuvant setting

- Capecitabine achieved significantly higher 5-yr DFS and OS in HER2- BC pts with residual disease

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
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<tr>
<td>5-yr DFS</td>
<td>74.1</td>
<td>67.7</td>
<td>0.70 (0.53-0.93)</td>
<td>.00524</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>89.2</td>
<td>83.9</td>
<td>0.60 (0.40-0.92)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Post-Neoadjuvant setting

Masuda N, NEJM 2017
Triple negative BRCA mutated

Figure 1. OlympiA study design

- Screening

  Randomization (1:1)

  - Olaparib 300 mg bid (12 months’ duration)
  - Matched placebo (12 months’ duration)

  Invasive disease-free survival assessment (mammogram/breast MRI 6 months from randomization)

  Follow-up for local and distant recurrence and survival status
**BRAVE Protocol**

- **TNBC** → **Neoadj Chemo** → **Surgery**
  - **pCR**: 40%
  - **No pCR**: 60%

1. **Placebo**
2. **Radiotherapy**
   - 1
   - 2
   - **Avelumab**

**Principle Investigator:** Pierfranco Conte
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum routine in neo-adjuvant Rx</td>
<td>Yes (justifiable in high risk but no known EFS advantage)</td>
</tr>
<tr>
<td>Capecitabine in residual disease</td>
<td>Possible - Stage II+ who has received anthracycline/taxane-based Rx</td>
</tr>
<tr>
<td></td>
<td>Uncertain in lower risk or less comprehensively treated</td>
</tr>
<tr>
<td>Biologic subsets to tailor escalating Rx</td>
<td>No</td>
</tr>
<tr>
<td>Immunotherapy/PARPi/anti androgens or other novel strategies</td>
<td>Not off-trial</td>
</tr>
</tbody>
</table>
Adjuvant therapy in TN

• Based on direct comparisons, subset analyses and considerations of toxicity/tolerability
• Sequential anthracycline, cyclophosphamide and taxane-based therapy
• Arguably ddAC $\rightarrow$ paclitaxel in high risk
• Alternative regimens
• Preferred regimen without anthracyclines: TC
• Preferred regimen without taxanes: AC or CMF
• Neoadjuvant regimens = adjuvant regimens
Options for Stage I Disease

- Chemotherapy treatment options for low risk disease:
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Enthusiasm for Chemotherapy</th>
<th>Possible Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microinvasion only</td>
<td>Virtually none</td>
<td>---</td>
</tr>
<tr>
<td>T1a</td>
<td>Low to moderate</td>
<td>None</td>
</tr>
<tr>
<td>T1b</td>
<td>Moderate to high</td>
<td>Simple</td>
</tr>
<tr>
<td>T1c</td>
<td>High</td>
<td>Simple or selectively sequential approach</td>
</tr>
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</table>
# De-Escalating in TN EBC

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<tr>
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</tr>
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<tbody>
<tr>
<td>Clinical low risk subsets can omit chemotherapy</td>
<td>Only in very small, node-negative (T1a-bN0)</td>
</tr>
<tr>
<td>Biologic low risk subsets can omit / limit chemotherapy</td>
<td>No</td>
</tr>
<tr>
<td>Neoadjuvant Rx to reduce surgery</td>
<td>No stage I</td>
</tr>
<tr>
<td></td>
<td>Yes stage II+</td>
</tr>
<tr>
<td>Treating to pCR to de-escalate systemic therapy</td>
<td>No</td>
</tr>
<tr>
<td>Anthracyclines may be omitted</td>
<td>No (may consider in low risk)</td>
</tr>
</tbody>
</table>
Metastatic triple-negative breast cancer

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Basal like 1 TNBC

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

Stephens et al *Nature* 2009
vol. 462 (7276) pp 1005
Basal like 1 TNBC

HER2- MBC + gBRCAmt ≤2 chemo for MBC (prior A and T. No plat resistance)

2:1 randomization
N~300

~ 150 TNBC

Olaparib
300 mg tablets bid

Primary endpoint PFS

Treat until progression

Chemo TPC
• Capecitabine
• Eribulin
• Vinorelbine

70% prior chemotherapy for MBC (30% prior platinum)
• 57% BRCA1
• 50% TNBC

Robson M et al, NEJM 2017
Among patients with metastatic HER2-negative BC and a germline BRCA1/2 mutation in the OlympiAD study, the objective response rate with olaparib tablet monotherapy was double that seen with standard chemotherapy TPC.

Stable disease was for ≥5 weeks, recorded ≥6 weeks after randomization.
Chemotherapy TPC, treatment of physician’s choice (including capecitabine, eribulin or vinorelbine)

Robson M et al, NEJM 2017
Olaparib in basal like 1

**Response rate** ↑ 21% to 55%

**QoL olaparib > chemotherapy**

**ER and/or PgR positive**

**TNBC**

Robson M et al, NEJM 2017
Olaparib in basal like 1

Robson M et al, NEJM 2017

17th ESO-ESMO Masterclass in Clinical Oncology
## Olaparib in basal like 1

Although the study was not powered to detect differences in treatment effect between subgroups, the PFS benefit for olaparib over chemotherapy TPC across tumour burden and location subgroups was consistent with that seen in the overall population.

### Tumour burden

<table>
<thead>
<tr>
<th>Tumour burden</th>
<th>Olaparib 300 mg bid</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 metastatic site, n</td>
<td>46</td>
<td>25</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.4</td>
<td>4.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td><strong>0.62 (0.35, 1.13)</strong></td>
<td></td>
</tr>
<tr>
<td>≥2 metastatic sites, n</td>
<td>159</td>
<td>72</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>6.5</td>
<td>3.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td><strong>0.59 (0.43, 0.82)</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Tumour location

<table>
<thead>
<tr>
<th>Tumour location</th>
<th>Olaparib 300 mg bid</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral, n</td>
<td>165</td>
<td>84</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.9</td>
<td>3.9</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td><strong>0.64 (0.47, 0.86)</strong></td>
<td></td>
</tr>
<tr>
<td>Non-visceral, n</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>11.0</td>
<td>8.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td><strong>0.65 (0.30, 1.65)</strong></td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio. Non-visceral disease includes lymph nodes, soft tissue, cutaneous and bone only.

Veliparib in basal like 1

**Patient Population**
- Men and women ≥ 18 years of age
- Measurable metastatic breast cancer
- Documented BRCA1 or BRCA2 deleterious germline mutation

**Randomization 1:1:1**
- Veliparib BID + Temozolomide
  - N = 80
- Placebo + Carboplatin/Paclitaxel
  - N = 80
- Veliparib BID + Carboplatin/Paclitaxel
  - N = 80

**Endpoints**
- **Primary Endpoint**
  - Progression Free Survival
- **Secondary Endpoints**
  - Overall Survival
  - Clinical Benefit Rate
  - Objective Response Rate
  - Safety and Tolerability

**Primary Analysis**
- 150 PFS Events

**Interim Analyses**
- Safety: 36 subjects complete two cycles of treatment
- Futility: 30 subjects on veliparib/TMZ complete Week 27 tumor assessment
**Veliparib in basal like 1**

**Placebo + C/P**
- N = 98

**Veliparib + C/P**
- N = 95

<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
<th>Placebo + C/P</th>
<th>Veliparib + C/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3</td>
<td>(9.3–14.5)</td>
<td>14.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.789</td>
<td>(0.536–1.162)</td>
</tr>
</tbody>
</table>

**RR ↑ 61% to 78%**

**However no ↑ pCR with veliparib in neoadjuvant setting**

**Phase III BROCADE 3 pending...**

*Han et al, Annals of Oncol 2018; Geyer et al, ASCO 2017*
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

**Carboplatin (C)**
AUC 6 q3w, 6 cycles

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

n-376
BRCA1/2 = 9%/12%

**Carboplatin (C)**
AUC 6 q3w, 6 cycles

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

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%)

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
- C: 0/188 90/98 40/56 32/22 9/13 5/8 0/7
- D: 0/188 57/130 60/69 48/20 7/13 6/5 2/3
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

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
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)
PARP inhibitors in metastatic TNBC

2:1 randomization

Chemo TPC
• Capecitabine
• Eribulin
• Gemcitabine
• Vinorelbine

Primary endpoint PFS

Talazoparib (BMN 673)
1 mg po qd

Treat until progression

Niraparib
100 mg po qd

Primary endpoint PFS

Chemo TPC
Menu of 4 drugs

HER2- MBC + gBRCAmt
Prior chemo

HER2- MBC + gBRCAmt
No platinum-R

2:1
Basal like 2: Growth factor signalling

Enrolled (N = 112)

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

Treated (n = 102)

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)
- Off protocol (n = 5)

Arm 2: Cetuximab + Carboplatin (n = 71)
- Evaluable (n = 65)
  - Early progressors (n = 5)
- Not evaluable (n = 6)

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>
</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>0 0</td>
<td>0 0</td>
<td>1 1</td>
<td>1 2</td>
</tr>
<tr>
<td>PR</td>
<td>2 6</td>
<td>4 16</td>
<td>11 16</td>
<td>7 14</td>
</tr>
<tr>
<td>SD</td>
<td>3 10</td>
<td>7 28</td>
<td>15 21</td>
<td>8 16</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>1 3</td>
<td>3 12</td>
<td>10 14</td>
<td>7 14</td>
</tr>
<tr>
<td>PD</td>
<td>26 84</td>
<td>12 48</td>
<td>38 54</td>
<td>32 63</td>
</tr>
<tr>
<td>NE</td>
<td>0 0</td>
<td>2 8</td>
<td>6 8</td>
<td>3 6</td>
</tr>
</tbody>
</table>

Abbreviations: C, cetuximab; Cb, carboplatin; CR, complete response; NE, non-evaluable; 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.
Subsets of triple-negative breast cancer

<table>
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<tr>
<th>Subtype</th>
<th>Gene expression profile</th>
<th>Clinical</th>
</tr>
</thead>
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<td>GF pathways</td>
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</tr>
<tr>
<td>Luminal androgen receptor</td>
<td>Steroid pathways</td>
<td></td>
</tr>
</tbody>
</table>

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**

**Treatment:** 10 mg/kg IV Q2W

**Response assessment:** Performed every 8 weeks per RECIST v1.1

- **CR:** Discontinuation permitted
- **PR/SD:** Treat for 24 mo or until PD or toxicity
- **Confirmed PD:** Discontinue

---

**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

---

**Notes:**

a. 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 ≥1% of tumor cells were eligible for enrollment.

b. 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

Objective response rate: 18.5%
Stable disease: 25.9%

n = 32

Confirmed complete response (nodal disease)
Confirmed partial response
Stable disease
Progressive disease
Pembrolizumab in TNBC

Cohort A (N = 170):
Previously Treated,
Regardless of PD-L1 Expression

Cohort B (N = 52):
Previously Untreated,
PD-L1 Positive

ORR, %

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>23.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complete response
Partial response

Total PD-L1 Positive
PD-L1 Negative

Adams S et al. ASCO 2017
Anti PD1 and anti PDL1 in TNBC

Anti-PD-L1/PD-1 single agent in mTNBC ≥1L, PDL1+/-

- Atezolizumab (n=115):
  - 1L: 11%
  - 2L+: 26%

- Pembrolizumab (n=222):
  - 1L: 4.7%
  - 2L+: 23%

No clear relationship with PD-L1 positivity

Role of TILs in TNBC

- **Atezolizumab (Cohort A: ≥2nd line)**
  - TIL high: 19%
  - TIL low: 9%

- **Pembrolizumab (Cohort B: 1st line)**
  - TIL high: 39.1%
  - TIL low: 8.7%

Different levels by source of sample (archival vs new) and organ site sampled: LN>lung>liver

Metastatic breast cancer is a low TIL disease

# 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)&lt;sup&gt;a&lt;/sup&gt;</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)&lt;sup&gt;b&lt;/sup&gt;</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+

---

<sup>a</sup> Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.

<sup>b</sup> 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.

Including investigator-assessed unconfirmed responses.

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

**Phase III Study of Atezolizumab and Nab-Paclitaxel in mTNBC**

- Randomized, double-blind, placebo-controlled Phase 3 trial of nab-paclitaxel ± atezolizumab as 1\textsuperscript{st} 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)
Neoadjuvant paclitaxel x 12 +/- pembrolizumab followed by AC x 4
Adaptive randomization on I-SPY 2

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR rate (95% probability interval)</th>
<th>Probability pembro is superior to control</th>
<th>Predictive probability of success in phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro (Pembro)</td>
<td>Control (Control)</td>
<td></td>
</tr>
<tr>
<td>All HER2-</td>
<td>0.46 (0.34 – 0.58)</td>
<td>0.16 (0.06 – 0.27)</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>TNBC</td>
<td>0.60 (0.43 – 0.78)</td>
<td>0.20 (0.06 – 0.33)</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>0.34 (0.19 – 0.48)</td>
<td>0.13 (0.03 – 0.24)</td>
<td>&gt; 99%</td>
</tr>
</tbody>
</table>

The Bayesian model estimated pCR rates adjust to characteristics of the I-SPY 2 population. The raw pCR rates are higher than the model estimate of 0.604 in TNBC.

Nanda et al, ASCO 2017, Abstract 506
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
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)

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>
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<th>Endpoint</th>
<th>Total (n = 50)</th>
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<tbody>
<tr>
<td>Best ORR (CR + PR) iRECIST</td>
<td>24%</td>
</tr>
<tr>
<td>CBR (CR + PR + SD)</td>
<td>26%</td>
</tr>
<tr>
<td>CR</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>SD ≥24 weeks</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>ORR RECIST 1.1</td>
<td>22%</td>
</tr>
<tr>
<td>Median PFS [95% CI]</td>
<td>3.4 months [2.5-3.7]</td>
</tr>
<tr>
<td>Median time to response [range]</td>
<td>2.1 months [0.5-3.5]</td>
</tr>
<tr>
<td>Median duration of response [95% CI]</td>
<td>9.0 months [5.5-NA]</td>
</tr>
</tbody>
</table>
PARP inhibitors and IO

**Phase I**

Patients with OC or TNBC

- Dose level 1
  - Niraparib 200 mg + pembrolizumab 200 mg

- Dose level 2
  - Niraparib 300 mg + pembrolizumab 200 mg

**Phase II**

Patients with OC (target n = 48) or TNBC (target n = 48)

RP2D

Endpoint assessment

---

PARP inhibitors and IO

Clinical Heterogeneity of TNBC

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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>
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M Locatelli et al, Oncotarget 2016
### Clinical Heterogeneity of TNBC

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Luminal Androgen Receptor: Bicalutamide

ER/PR(-) (IHC ≤10%)
LABC/MBC

AR+
DAKO Ab ≥ 10%

Bicalutamide 150mg daily

• Primary endpoint = CBR24 (CR + PR + SD > 24 weeks)

Screened patients 12% AR+ (mostly TNBC)

Clinical Benefit Rate = 19% (95% CI 7-39%)
All SD

Gucalp et al CCR 2013
Luminal Androgen Receptor: Abiraterone

- MBC ER/PR ≤10%
- 138 screened → 38% AR+ (≥10%)

- Primary Endpoint = CBR24
- N = 30 evaluable patients
- ~ 2.5 prior lines Rx
- ~ 50% visceral mets

- Most common, related AEs:
  - fatigue (18%)
  - HTN (12%)
  - hypokalemia (9%)
  - nausea (6%)

CBR24 = 20% (95%CI: 8-39%)
1 confirmed CR

Bonnefoi et al, Ann Onc 2016
Luminal Androgen Receptor: Enzalutamide

ER/PR/HER2 (-) LABC/MBC → AR+ Ventana > 0% → Enzalutamide 160 mg daily

• Primary endpoint = CBR16 (CR + PR + SD > 16) weeks
• Screened patients 79% AR+ (55% by 10% cutoff)
• Median 1 prior Rx

<table>
<thead>
<tr>
<th>Evaluation (n=75 AR &gt; 10%)</th>
<th>CBR16</th>
<th>35% (24-46%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBR24</td>
<td>29% (20-41%)</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

PFS 14.7 weeks
95% CI: 8.1, 19.3
Luminal Androgen Receptor

Gene expression classifier created = “PredictAR” (Basal-, apocrine+, etc to identify LAR)

Traina et al, ASCO 2015
Luminal Androgen Receptor

Data cutoff: 1Jul2015
ITT = intent to treat; mOS = median survival; CI = confidence interval

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

ITT Population

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

NCT01889238
Median PFS to Chemotherapy in TNBC

- Initial therapy
- First distant relapse

```
<table>
<thead>
<tr>
<th>Time on Treatment</th>
<th>First line chemo</th>
<th>Second line chemo</th>
<th>Third line chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td></td>
<td>9 weeks</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>
```

Median D.F.I.
Challenges

• AR-targeting – maybe

• PARPi – Yes! My bet – will work in somatically inactivated

• I-O? See next slide
Challenges

High risk breast cancer

High TILs/immune activation signature/ PDL1+/ High TMB
Good microbiota

I-O as monotherapy or combination of I-O

Low/Intermediate TILs/immune activation signature-/PDL1-/
Bad microbiota

Low TMB

Add CT to enhance immunogenicity or STING,
TIGIT, RT

High TMB

Low TMB

No I-O
Conclusions

• Chose 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
Giuseppe Curigliano MD, PhD

giuseppe.curigliano@ieo.it