TRIPLE NEGATIVE BREAST CANCER IS STILL AN UNMET NEED

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Istituto Oncologico Veneto IRCCS, Padova, Italy
OUTLINE

- Introduction:
  - Definition, epidemiology, clinical behaviour

- State of the art
  - Neoadjuvant/Adjuvant
  - Advanced disease

- How to improve on CT

- Heterogeneity: exploiting TNBC diversity to identify druggable pathways
Triple negative breast cancer (TNBC) definition:
- lack of expression of estrogen receptor and progesterone receptor
- HER2 not overexpressed/amplified

10-20% of all breast cancers

Most BRCAmut carriers develop TNBC

TNBC includes rare histologies
- Metaplastic, medullary, adenoid cystic carcinoma

High cell proliferation, poor cellular differentiation, many recurrent copy number imbalances, and mutations in the TP53
TNBC: INTRODUCTION

- Triple negative breast cancer is the most lethal form of breast cancer
- TNBC is heterogeneous and harbours several molecular alterations
- The prevalence of TNBC is higher in women of Afro–American ethnicity
- TNBC is more frequently diagnosed in younger women
- Higher risk of earlier relapse
- High risk for visceral involvement (CNS included)
- Median survival from the time of developing metastases rarely >1 year
- Endocrine therapy and anti-HER2 treatments are not effective; high chemosensitivity
HAZARD RATES OF PROGRESSION AND DEATH: TNBC VS. OTHERS

Liedtke C, et al., J Clin Oncol 2008;26;1275–81. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.
METASTATIC BEHAVIOUR OF BC SUBTYPES

3,726 EBC patients diagnosed between 1986-1992

<table>
<thead>
<tr>
<th>Subtype</th>
<th>10-yr survival</th>
<th>Median OS (from first distant mets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>70%</td>
<td>2.2</td>
</tr>
<tr>
<td>Luminal B</td>
<td>54.4%</td>
<td>1.6</td>
</tr>
<tr>
<td>Luminal/HER2</td>
<td>46.1%</td>
<td>1.3</td>
</tr>
<tr>
<td>HER2 enriched</td>
<td>48.1%</td>
<td>0.7</td>
</tr>
<tr>
<td>Basal Like</td>
<td>52.6%</td>
<td>0.5</td>
</tr>
<tr>
<td>TN non basal</td>
<td>62.6%</td>
<td>0.9</td>
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</table>

# Visceral Involvement According to BC Subtype

<table>
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<tr>
<th>Subtype</th>
<th>n</th>
<th>Brain</th>
<th>Liver</th>
<th>Lung</th>
<th>Bone</th>
<th>Distant Nodal</th>
<th>Pleural/Peritoneal</th>
<th>Other</th>
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<td>Luminal A</td>
<td>458</td>
<td>7.6</td>
<td>28.6</td>
<td>23.8</td>
<td>66.6</td>
<td>15.9</td>
<td>28.2</td>
<td>13.5</td>
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<tr>
<td>Luminal B</td>
<td>378</td>
<td>10.8</td>
<td>32.4</td>
<td>30.4</td>
<td>71.4</td>
<td>23.3</td>
<td>35.2</td>
<td>19.3</td>
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<tr>
<td>Luminal/HER2</td>
<td>117</td>
<td>15.4</td>
<td>4.4</td>
<td>36.8</td>
<td>65</td>
<td>22.2</td>
<td>34.2</td>
<td>13.7</td>
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<tr>
<td>HER2 enriched</td>
<td>136</td>
<td>28.7</td>
<td>45.6</td>
<td>47.1</td>
<td>59.6</td>
<td>25</td>
<td>31.6</td>
<td>16.9</td>
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<tr>
<td>Basal Like</td>
<td>159</td>
<td>25.2</td>
<td>21.4</td>
<td>42.8</td>
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<td>39.6</td>
<td>29.6</td>
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<tr>
<td>TN non basal</td>
<td>109</td>
<td>22</td>
<td>32.1</td>
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<td>43.1</td>
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<tr>
<td>p</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>0.006</td>
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CHEMOSENSITIVITY OF TNBC: pCR AND LONG-TERM OUTCOME

OUTLINE

- Introduction:
  - Definition, epidemiology, clinical behaviour

- State of the art
  - Neoadjuvant/Adjuvant setting
  - Advanced disease

- How to improve on CT

- Heterogeneity: exploiting TNBC diversity to identify druggable pathways
Triple-negative tumours benefit from adjuvant chemotherapy, with possible exclusion of low-risk “special histological subtypes” such as secretory juvenile, apocrine or adenoid cystic carcinomas [I,A].

Chemotherapy usually consists of four to eight cycles of anthracycline- and/or taxane-based regimen. Sequential use of anthracyclines and taxanes, instead of concomitant, is recommended [I, B].
PROGRESS IN ADJUVANT CT

Anthracycline vs. no CT

- 2076 women, ER-poor (73% N+)
- Control 41.9%
- Anthracycline 34.8%
- RR 0.80 (0.69–0.93)
- Logrank 2p = 0.003
- 10-y gain 7.1% (SE 2.3%)

Anthra+Tax vs. no Tax

- 11258 women, ER-poor (81% N+)
- RR 0.86 (0.79–0.94)
- Logrank 2p = 0.0005
- 8-y gain 3.7% (SE 1.1%)
- Control 27.7%
- Anthra+Tax 24.0%
- Tax + anthracycline 21.4%
PROGRESS IN ADJUVANT CT: EFFECT FOR TNBC

British Columbia Cancer Agency stage I-III BC (7,178 patients) → 1,132 (15.8%) patients with ER neg and HER2 neg BC

Cohort 1: 1986 - 1992

Cohort 2: 2004 - 2008

Cossetti RJD, et al., J Clin Oncol 2015;33:65–73. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.
ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH SMALL TNBC

No chemotherapy

Chemotherapy

5yrs DFS
T1a: 96%
T1b: 93%

5yrs DFS
T1a: 100%
T1b: 96%
**Guideline statements**

Sequential monotherapy is the preferred choice for MBC. Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

<table>
<thead>
<tr>
<th>Guideline statements</th>
<th>LoE</th>
<th>Consensus</th>
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<tr>
<td>Sequential monotherapy is the preferred choice for MBC. Combination CT should be</td>
<td>IA</td>
<td>96% (25) yes</td>
</tr>
<tr>
<td>reserved for patients with rapid clinical progression, life-threatening visceral</td>
<td></td>
<td>4% (1) abstain</td>
</tr>
<tr>
<td>metastases, or need for rapid symptom and/or disease control.</td>
<td></td>
<td>(26 voters)</td>
</tr>
<tr>
<td>In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline</td>
<td>IB</td>
<td>77.1% (27) yes</td>
</tr>
<tr>
<td>and a taxane, and who do not need combination chemotherapy, single-agent capecitabine, vinorelbine, or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient references, and country availability.</td>
<td></td>
<td>20.0% (7) abstain (35 voters)</td>
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</table>
HOW TUMOUR BIOLOGY DRIVES OUR THERAPEUTIC CHOICES

MBC

HR +
- HER2–
  - AI + trastuzumab
  - AI + lapatinib
  - SERMs
  - SERD
  - AI
  - OFS
  - AI + everolimus
  - AI + CDK4/6 inh.
- HER2+
  - Trastuzumab + taxane
  - TDM-1
  - Lapatinib + trastuzumab
  - Lapatinib + capecitabine

HR –
- HER2+
  - Trastuzumab + Pertuzumab + taxane
  - (Poly)chemoRx
  - Paclitaxel+Beva
- HER2–
  - DNA damaging CT
  - PARPi
- BRCA mutated

Chemotherapy

HOW TUMOUR BIOLOGY DRIVES OUR THERAPEUTIC CHOICES
LINES OF CHEMOTHERAPY AND DURATION ACCORDING TO BC SUBTYPE

Number of lines of chemotherapy

Proportion of patients receiving chemotherapy

HR⁺
TNBC
HER2⁺

Duration of chemotherapy (mo)

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Chemotherapy is the mainstay of treatment in both early and advanced settings. Treatment options have mostly remained unchanged over years.

Recent attempts to further exploit TN chemosensitivity:

1. NEO/ADJUVANT setting:
   - Schedule
   - Maintenance
   - New cytotoxics/new formulations

2. ADVANCED setting:
   - New cytotoxics/new formulations

3. THE PLATINUM SALTS STORY

4. THE BEVACIZUMAB STORY
Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer

Sparano J, et al., J Clin Oncol 2015;33:2353–60. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.
GIM-2: ADJUVANT DOSE-DENSE CHEMOTHERAPY FOR N+ BC PTS

(F)EC Q2 vs. (F)EC Q3: Disease-free survival
N=335 HR-

CMM MAINTENANCE AFTER ADJUVANT CHEMOTHERAPY

IBCSG Trial 22-00 (CM Maintenance)

Hormone receptor negative (< 10% positive cells by IHC) by locally-determined ER and PgR

Stratify
• Institution
• Menopausal status
• Induction regimen

RANDOMIZE

Induction Chemotherapy ➔
4-6 mos.

CM Maintenance Chemotherapy (CMM)
12 mos.

Induction Chemotherapy ➔
4-6 mos.

Observation (OBS)

1086 patients enrolled Jan 2001 - Dec 2012

*Any time from start of induction to within 8 weeks after first day of last course of induction

1081 patients in ITT population; Median follow-up 6.9 years

75% TNBC

CMM MAINTENANCE AFTER ADJUVANT CHEMOTHERAPY

All patients

- CMM vs Observation
- 5-yr DFS 78.1% vs 74.7%

TN patients

- CMM vs Observation
- 5-yr DFS 78.7% vs 74.6%

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<td>CMM</td>
<td>542</td>
<td>124</td>
<td>0.84</td>
<td>0.66-1.06</td>
<td>0.14</td>
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<tr>
<td>OBS</td>
<td>539</td>
<td>147</td>
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<th>Events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
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<td>0.80</td>
<td>0.60-1.06</td>
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<td>OBS</td>
<td>406</td>
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Number at Risk

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<td>1</td>
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<td>2</td>
<td>429</td>
<td>430</td>
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<tr>
<td>3</td>
<td>373</td>
<td>376</td>
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<td>4</td>
<td>321</td>
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<td>5</td>
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<td>6</td>
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<td>194</td>
<td>181</td>
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<td>8</td>
<td>143</td>
<td>123</td>
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Number at Risk

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<th>CMM</th>
<th>OBS</th>
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<tr>
<td>0</td>
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<td>406</td>
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<td>4</td>
<td>236</td>
<td>246</td>
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<td>5</td>
<td>197</td>
<td>204</td>
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<td>6</td>
<td>165</td>
<td>166</td>
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<tr>
<td>7</td>
<td>132</td>
<td>130</td>
</tr>
<tr>
<td>8</td>
<td>94</td>
<td>85</td>
</tr>
</tbody>
</table>

**FINAL STUDY DESIGN**

(AFTER 400 PATIENTS RECRUITED)

**Core biopsy**
- (before study entry)
- N=60
  - (HER2 positive)

**Core biopsy**
- (after anti-HER2 treatment / before study entry)

**R**
- 6 weeks

N=1200

**Arm A**
- Paclitaxel 80 mg/m²
  - weekly
- nab-Paclitaxel 125 mg/m²
  - weekly
- Epirubicin 90 mg/m²
- Cyclophosphamide 600 mg/m²

**Arm B**
- Paclitaxel 125 mg/m²
  - weekly
- Epirubicin 90 mg/m²
- Cyclophosphamide 600 mg/m²

12 weeks

**Surgery**

If HER2 positive:
- Trastuzumab 8 mg/kg (loading dose) followed by 6 mg/kg
- Pertuzumab (absolute dose per application) 840 mg (loading dose) followed by 420 mg

**Core biopsy**
- optional

*Centrally confirmed:
- Subtypes HER 2/ HR
- Ki67
- SPARC

*Randomizations carried out simultaneously

# GEPAR7: SUBGROUP ANALYSIS


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>Test for interaction p value</th>
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<tbody>
<tr>
<td>SPARC</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>SPARC negative</td>
<td>1015</td>
<td>1.49 (1.15-1.94)</td>
<td>0.0028</td>
<td>0.66</td>
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<tr>
<td>SPARC positive</td>
<td>191</td>
<td>1.73 (0.949-3.14)</td>
<td>0.074</td>
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<tr>
<td>Ki67</td>
<td></td>
<td></td>
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<tr>
<td>Ki67 ≤20%</td>
<td>373</td>
<td>1.46 (0.895-2.38)</td>
<td>0.13</td>
<td>0.78</td>
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<tr>
<td>Ki67 &gt;20%</td>
<td>833</td>
<td>1.58 (1.19-2.09)</td>
<td>0.0015</td>
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<tr>
<td>Biological subtype</td>
<td></td>
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<tr>
<td>HER2-, HR+</td>
<td>534</td>
<td>1.40 (0.854-2.29)</td>
<td>0.18</td>
<td>0.20</td>
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<tr>
<td>HER2-, HR-</td>
<td>276</td>
<td>2.61 (1.57-4.33)</td>
<td>0.00020</td>
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<tr>
<td>HER2+, HR+</td>
<td>289</td>
<td>1.31 (0.826-2.09)</td>
<td>0.25</td>
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<tr>
<td>HER2+, HR-</td>
<td>107</td>
<td>1.47 (0.634-3.39)</td>
<td>0.37</td>
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<tr>
<td>HER2</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>HER2-</td>
<td>810</td>
<td>1.82 (1.30-2.56)</td>
<td>0.00053</td>
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<td>HER2+</td>
<td>396</td>
<td>1.39 (0.931-2.07)</td>
<td>0.11</td>
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<td>HR</td>
<td></td>
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<tr>
<td>HR-</td>
<td>383</td>
<td>2.20 (1.46-3.31)</td>
<td>0.00017</td>
<td>0.029</td>
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<tr>
<td>HR+</td>
<td>823</td>
<td>1.24 (0.916-1.69)</td>
<td>0.16</td>
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<tr>
<td>Overall</td>
<td>1206</td>
<td>1.53 (1.20-1.95)</td>
<td>0.00054</td>
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</tr>
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</table>
SCHEME OF THE PHASE III RANDOMISED ETNA TRIAL

Scheme of the Phase III randomized ETNA trial

- HER-2 negative, operable or locally advanced unilateral breast cancer: Triple Negative or Luminal B-like
- Paclitaxel (P) 90 mg/m² weekly for 3 q 4 wks for 4 cycles followed by A(E)C or FEC for 4 cycles
- nab-Paclitaxel (nab-P) 125 mg/m² weekly for 3 q 4 wks for 4 cycles followed by A(E)C or FEC for 4 cycles

*Estrogen receptor, progesterone receptor, HER2 and Ki67 were centrally assessed before randomization

Endocrine Therapy if HR positive tumors

Tumour & Blood Banked for Correlative Studies

Subgroup Analysis: pCR rate

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>nab-P %</th>
<th>P %</th>
<th>nab-P</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>22.5</td>
<td>18.8</td>
<td></td>
<td></td>
<td>0.77 (0.52 - 1.13)</td>
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<tr>
<td></td>
<td>Luminal B-like</td>
<td>13.9</td>
<td>10.0</td>
<td></td>
<td></td>
<td>0.69 (0.39 - 1.21)</td>
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<tr>
<td></td>
<td>Triple negative</td>
<td>41.3</td>
<td>37.3</td>
<td></td>
<td></td>
<td>0.85 (0.49 - 1.45)</td>
</tr>
<tr>
<td>Tumor</td>
<td>Non-locally advanced</td>
<td>23.1</td>
<td>20.7</td>
<td></td>
<td></td>
<td>0.87 (0.57 - 1.31)</td>
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<tr>
<td>subtype</td>
<td>Locally advanced</td>
<td>20.7</td>
<td>12.5</td>
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<td>0.55 (0.24 - 1.25)</td>
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<td>Stage</td>
<td>&lt;=50</td>
<td>22.0</td>
<td>20.7</td>
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<td>0.90 (0.53 - 1.51)</td>
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<td>&gt;50</td>
<td>23.1</td>
<td>16.1</td>
<td></td>
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<td>0.63 (0.35 - 1.14)</td>
</tr>
</tbody>
</table>

Chemotherapy is the mainstay of treatment in both early and advanced settings. Treatment options have mostly remained unchanged over years.

Recent attempts to further exploit TN chemosensitivity:

1. NEO/ADJUVANT setting:
   - Schedule
   - Maintenance
   - New cytotoxics/new formulations

2. ADVANCED setting:
   - New cytotoxics/new formulations

3. THE PLATINUM SALTS STORY

4. THE BEVACIZUMAB STORY
In advanced breast cancer patients already treated with anthracyclines and taxanes (301 study)

- **Patients (N=1102)**
  - Locally advanced or metastatic breast cancer
    - ≤3 prior chemotherapy regimens (≤2 for advanced disease)
    - Prior anthracycline and taxane in (neo-) adjuvant setting or for locally advanced or metastatic breast cancer
  - **Eribulin mesylate**
    - (n=554)
    - 1.4 mg/m² for 2- to 5-min IV Days 1 & 8 q21 days
  - **Co-primary endpoints**
    - Overall survival and progression-free survival
  - **Secondary endpoints**
    - Quality of life
    - Objective response rate
    - Duration of response
    - 1-, 2- and 3-year survival
    - Tumor-related symptom assessments
    - Safety parameters
    - Population pharmacokinetics (eribulin arm only)

- **Capecitabine**
  - (n=548)
  - 1250 mg/m² BID orally Days 1–14, q21 days

---

1. Equivalent to 1.23 mg/m² eribulin (expressed as free base)
2. BID, twice daily; IV, intravenous

E301: OVERALL SURVIVAL

<table>
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<th></th>
<th>Events/n</th>
<th>Median, months</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Eribulin</td>
<td>446/554</td>
<td>15.9</td>
<td>15.2 to 17.6</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>459/548</td>
<td>14.5</td>
<td>13.1 to 16.0</td>
</tr>
</tbody>
</table>

HR, 0.88; 95% CI, 0.77 to 1.00

$P = .056$

E301: PRE-SPECIFIED SUBGROUPS ANALYSIS

### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Eribulin Median (months)</th>
<th>Capecitabine Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>0.879 (0.770, 1.003)</td>
<td>15.9</td>
<td>14.5</td>
</tr>
<tr>
<td><strong>HER2 status</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>0.965 (0.688, 1.355)</td>
<td>14.3</td>
<td>17.1</td>
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<td>Negative</td>
<td>0.838 (0.715, 0.983)</td>
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<td>0.927 (0.795, 1.081)</td>
<td>17.5</td>
<td>16.6</td>
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</table>

Kaufmann PA, ASCO 2013 (abstract 1049^)
POOLED ANALYSIS OF EMBRACE AND 301: OS BY PATIENT SUBGROUPS

Overall population
(erbulin, n = 1,602; control, n = 802)

HER2-positive
(erbulin, n = 169; control, n = 123)

HER2-negative
(erbulin, n = 748; control, n = 572)

HER2-negative and hormone-receptor-positive
(erbulin, n = 496; control, n = 379)

ER-positive
(erbulin, n = 595; control, n = 449)

ER-negative
(erbulin, n = 378; control, n = 288)

Triple-negative
(erbulin, n = 243; control, n = 185)

Non-triple-negative
(erbulin, n = 707; control, n = 543)

≤ 2 organs involved
(erbulin, n = 544; control, n = 386)

> 2 organs involved
(erbulin, n = 516; control, n = 415)

Visceral disease
(erbulin, n = 880; control, n = 694)

Non-visceral disease
(erbulin, n = 171; control, n = 101)

Taxane-refractory
(erbulin, n = 530; control, n = 401)

Non-taxane-refractory
(erbulin, n = 532; control, n = 401)
Chemotherapy is the mainstay of treatment in both early and advanced settings. Treatment options have mostly remained unchanged over years.

Recent attempts to further exploit TN chemosensitivity:

1. NEO/ADJUVANT setting:
   - Schedule
   - Maintenance
   - New cytotoxics/new formulations

2. ADVANCED setting:
   - New cytotoxics/new formulations

3. THE PLATINUM SALTS STORY
4. THE BEVACIZUMAB STORY
DRUG-SPECIFIC CHEMOTHERAPY FOR TNBC?

DNA damage

DNA damage kinases

BRCA1 - Cell cycle arrest to repair DNA damage

G1  S  G2

Mitosis - Prophase

DNA damage checkpoint DNA repair

RESISTANCE to DNA damaging agents

DNA damage

DNA damage kinases

BRCA1

G1  S  G2

Mitosis - Prophase

NO DNA damage checkpoint NO DNA repair

SENSITIVE to DNA damaging agents
pCR RATES (BREAST/AXILLA) IN TNBC

GEPARSIXTO: DFS IN TNBC

Logrank $p=0.0325$

HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), $p=0.0350$

PM 36/157 events

PMCb 21/158 events
CALGB 40603 (ALLIANCE)
EVENT FREE SURVIVAL

HR=0.84 (0.58-1.22), p=0.36

pCR RATES BY gBRCA STATUS AND CARBOPLATIN IN TNBC

pCR RATES BY TREATMENT AND ACCORDING TO HR DEFICIENCY STATUS (ypT0 ypN0)

pCR Rates by Treatment and According to HR Deficiency Status (ypT0 ypN0)

- **HR non-deficient**
  - OR 1.68 (0.50-5.69)
  - P=0.399
  - PM: N=30
  - PM+Cb: N=27
  - Mean 24.6% Δ 9.6%

- **HRD score high tBRCA intact**
  - OR 3.69 (1.46-9.37)
  - P=0.005
  - PM: N=41
  - PM+Cb: N=38
  - Mean 46.8% Δ 31.5%

- **tBRCA mutant**
  - OR 3.74 (1.18-11.82)
  - P=0.022
  - PM: N=21
  - PM+Cb: N=33
  - Mean 57.4% Δ 31.6%
Trial design

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

Carboplatin (C)
AUC 6 q3w, 6 cycles

On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles

On progression, crossover if appropriate

Docetaxel (D)
100mg/m² q3w, 6 cycles

Carboplatin (C)
AUC 6 q3w, 6 cycles

Tutt A, et al., SABCS 2014
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%)

Absolute difference (C-D)
- Carboplatin vs Docetaxel:
  - Germline: 34.7% (95% CI 6.3 to 63.1)
  - Exact p = 0.03
  - No Germline: -8.5% (95% CI -19.6 to 2.6)
  - Exact p = 0.16

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01

Tutt A, et al., SABCS 2014
TNT PHASE III TRIAL FOR TN METASTATIC BC

**PFS – BRCA 1/2 status**

- Carboplatin + BRCA1/2 mutated
- Carboplatin + BRCA1/2 not mutated

**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)

Tutt A, et al., SABCS 2014
TNT PHASE III TRIAL FOR TN METASTATIC BC

PFS – BRCA 1/2 status

- Carboplatin + BRCA1/2 mutated
- Carboplatin + BRCA1/2 not mutated
- Docetaxel + BRCA1/2 mutated
- Docetaxel + BRCA1/2 not mutated

Median PFS:
- D + BRCA 1/2 mutated: 4.8 (95% CI = 2.2 to 7.2)
- D + BRCA1/2 not mutated: 4.6 (95% CI = 4.2 to 5.5)

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)

Tutt A, et al., SABCS 2014
SYSTEMIC TREATMENT FOR TNBC: CURRENT STATUS

Chemotherapy is the mainstay of treatment in both early and advanced settings. Treatment options have mostly remained unchanged over years.

Recent attempts to further exploit TN chemosensitivity:

1. NEO/ADJUVANT setting:
   - Schedule
   - Maintenance
   - New cytotoxics/new formulations

2. ADVANCED setting:
   - New cytotoxics/new formulations

3. THE PLATINUM SALTS STORY

4. THE BEVACIZUMAB STORY
HYPOXIA-RELATED FEATURES AND BASAL-LIKE TUMOURS

Antiangiogenic approaches work in TNBC at least as well as other subtype, possibly more.

# POOLED ANALYSIS OF FIRST-LINE BEVACIZUMAB: PFS

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>$n$</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>BEV better</th>
<th>Non-BEV better</th>
<th>Median PFS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2447</td>
<td>0.64</td>
<td>0.58–0.71</td>
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<td></td>
<td>9.2</td>
</tr>
<tr>
<td>Age (years)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 65</td>
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<td>0.62</td>
<td>0.56–0.70</td>
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<tr>
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<td>No</td>
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POOLED ANALYSIS OF FIRST-LINE BEVACIZUMAB: OS

<table>
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<tr>
<th>Baseline risk factor</th>
<th>$n$</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>BEV better</th>
<th>Non-BEV better</th>
<th>Median OS, months</th>
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<tbody>
<tr>
<td>All patients</td>
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<td>Disease-free interval</td>
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<tr>
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<td>1525</td>
<td>0.87</td>
<td>0.76–1.00</td>
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NEOADJUVANT CHEMOTHERAPY AND BEVACIZUMAB FOR HER2-NEGATIVE BC

BEVACIZUMAB ADDED TO NEOADJUVANT CHEMOTHERAPY FOR BREAST CANCER

### GEPIR5

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of pts</th>
<th>Odds Ratio (95% CI)</th>
<th>Test for interaction</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1925</td>
<td>1.29 (1.02-1.65)</td>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;40 yr</td>
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<td>1.71 (0.99-2.95)</td>
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</tr>
<tr>
<td>≥40 yr</td>
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<td>1.20 (0.92-1.58)</td>
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<tr>
<td>Tumour stage</td>
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</tr>
<tr>
<td>cT1-cT3</td>
<td>1690</td>
<td>1.30 (1.01-1.67)</td>
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<td>cT4a-cT4d</td>
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<td>Lymph-node stage</td>
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<td>cN0</td>
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<td>cN1-cN3</td>
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<td>Disease stage</td>
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<td>Operable</td>
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<td>Locally advanced</td>
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<td>2.43 (0.96-6.15)</td>
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<tr>
<td>Histologic type</td>
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</tr>
<tr>
<td>Ductal or other</td>
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<td>1.31 (1.02-1.68)</td>
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<td>Lobular</td>
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<td>1 or 2</td>
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</tr>
<tr>
<td>3</td>
<td>829</td>
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<td>Hormone-receptor status</td>
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<td>Negative</td>
<td>663</td>
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<tr>
<td>Positive</td>
<td>1262</td>
<td>0.99 (0.66-1.50)</td>
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### NSABP-B40

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<th>Subgroup</th>
<th>Odds Ratio (95% CI)</th>
<th>Day test</th>
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<tbody>
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<td>1.29 (0.98, 1.92)</td>
<td>0.76</td>
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<tr>
<td>Clinical tumour size</td>
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<tr>
<td>2-4 cm</td>
<td>1.24 (0.85, 1.83)</td>
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</tr>
<tr>
<td>&gt;4 cm</td>
<td>1.35 (0.93, 1.96)</td>
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<td>Positive</td>
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<tr>
<td>Negative</td>
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<tr>
<td>Hormone receptor status</td>
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<td>1.67 (1.07, 2.58)</td>
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<tr>
<td>Negative</td>
<td>1.18 (0.82, 1.72)</td>
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<td>&lt;50 yr</td>
<td>1.29 (0.9, 1.83)</td>
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<tr>
<td>≥50 yr</td>
<td>1.30 (0.89, 1.93)</td>
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<tr>
<td>Tumour grade</td>
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<td>Low</td>
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<tr>
<td>Intermediate</td>
<td>1.21 (0.67, 2.2)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.4 (1.00, 1.91)</td>
<td></td>
</tr>
</tbody>
</table>

CALGB 40603: RESULTS BEV/NO BEV

Sikov WM, et al., J Clin Oncol 2014;33:13–21. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.
OUTLINE

- Introduction:
  - Definition, epidemiology, clinical behaviour

- State of the art
  - Neoadjuvant/Adjuvant
  - Advanced disease

- How to improve on CT

- Heterogeneity: exploiting TNBC diversity to identify druggable pathways
THE GENOMIC COMPLEXITY OF TNBC

**TNBC TYPE**

- **Basal-like 1 and Basal-like 2**
- **Immunomodulatory**
- **Mesenchymal-like and Mesenchymal stem-like**
- **Luminal AR**

- Cell proliferation, DNA damage response
- Immune signalling
- EMT, motility and growth-factor pathways
- Androgen receptor signaling

PARP INHIBITION AND TUMOUR-SELECTIVE SYNTHETIC LETHALITY

DNA damage (SSBs)

DNA replication
(accumulation of DNA DSBs)

PARP inhibition

Normal cell
with functional HR pathway

HR-mediated DNA repair

Cell survival

HR-deficient tumour cell

Impaired HR-mediated DNA repair

Cell death

Tumour-selective cytotoxicity

DSB, double-strand break; HR, homologous recombination
SSB, single-strand break

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial

Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Banu Arun, Niklos Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

Olaparib 400 mg twice daily.

Olaparib 100 mg twice daily.
PHASE III TRIALS OF PARP INHIBITORS IN HER2NEG BRCA1/2MUT BC PATIENTS

Primary endpoint PFS

Potent PARP inhibitor at MTD as continuous exposure

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

Olaparib – OLYMPIAD - NCT02000622

Talazoparib (BMN 673)
– EMBRACA - NCT01945775

Niraparib – EORTC / BIG BRAVO Trial

gBRCA1 / BRCA2 Carriers
Advanced anthracycline taxane resistant breast cancer

R
POOLED INDIVIDUAL PATIENT DATA ANALYSIS OF TILS IN PRIMARY TNBC TREATED WITH ADJUVANT CT

Overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>No of events</th>
<th>Hazard Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIG 2.98</td>
<td>269</td>
<td>86</td>
<td>0.79 [0.67, 0.94]</td>
</tr>
<tr>
<td>E1199</td>
<td>291</td>
<td>86</td>
<td>0.84 [0.71, 1.00]</td>
</tr>
<tr>
<td>E2197</td>
<td>190</td>
<td>56</td>
<td>0.72 [0.53, 0.98]</td>
</tr>
<tr>
<td>finHER</td>
<td>134</td>
<td>25</td>
<td>0.84 [0.66, 1.06]</td>
</tr>
<tr>
<td>GR</td>
<td>107</td>
<td>25</td>
<td>0.97 [0.81, 1.16]</td>
</tr>
<tr>
<td>All studies</td>
<td>991</td>
<td>278</td>
<td>0.84 [0.77, 0.92]</td>
</tr>
</tbody>
</table>

Q = 3.90 (p = 0.42)
I² = 0.00

Loi S, SABCS 2015. Reproduced courtesy of Sherene Loi
Prognostic value of tumor-infiltrating lymphocytes on residual disease after primary chemotherapy for triple-negative breast cancer: a retrospective multicenter study

5yr-MFS: 81.5% vs. 46%
HR 0.24, 95% CI 0.09-0.64

5yr-OS: 91% vs. 55%
HR 0.19, 95% CI 0.06-0.61

Dieci MV, et al., Ann Oncol. 2014;25:611–8. © The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved.
Recurrent/metastatic TNBC
ECOG PS 0-1
PD-L1+*

Pembrolizumab 10 mg/kg q2weeks

CR
Discontinuation allowed

PR or SD
Treat for 24 mos or until PD or toxicity

PD
Discontinue

*PD-L1 positivity definition: PD-L1 expression on >1% of tumour cells (58% of screened patients)
On treatment

Discontinued treatment

Objective response rate: 18.5%
Stable disease: 25.9%

Nanda R, et al., SABCS 2014. Reproduced courtesy of Rita Nanda
MPDL3280 in n=21 TNBC (PD-L1 IC scores 2/3)

<table>
<thead>
<tr>
<th>IC2/3 patients, n</th>
<th>ORR (95% CI)</th>
<th>24-Week PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>19% (5-42)</td>
<td>27% (7-47)</td>
</tr>
</tbody>
</table>

**Change in sum of largest diameters from baseline (%)**

- **CR/Pr (n=4)**
- **SD (n=3)**
- **PD (n=9)**
- **Discontinued**
- **New lesion**

**Time on study (days)**

Emens LA, et al., AACR 2015
Phase Ia trial of atezolizumab in combination with nab-paclitaxel in
patients with metastatic triple-negative breast cancer (mTNBC)

Sylvia Adams, Jennifer Diamond, Erika Hamilton, Paula Pohlmann, Sara M. Tolaney, Luciana
Moliner, Xian He, Daniel Waterkamp, Roel Funke, John Powderly

Results

DOR<sup>a</sup>

- Of 12 responders (38%), 6 remain on atezolizumab, 1 of whom has been on treatment for > 17 months
- PFS is not mature and median duration of response has not been reached
- 2 patients experienced decrease in tumor burden after an initial increase or the appearance of new lesions
Unique subclass of ER-PgR- human tumours characterised by a hormonally regulated transcriptional programme and response to androgen
PHASE II STUDY OF ENZALUTAMIDE IN ADVANCED AR+ TNBC (MDV3100-11)

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 180 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

Screened patients* (n = 165)

AR IHC > 0%
ITT Population (n = 118)

AR IHC < 10% (n = 29)

AR IHC ≥ 10% (n = 90)

AR IHC ≥ 10% No post-baseline assessment (n = 14)

AR IHC ≥ 10% and ≥ 1 post-baseline assessment
Evaluable Population (n = 75)

Study populations for analysis

- ITT = AR IHC > 0% by central assessment and received ≥ 1 dose of enzalutamide
- Evaluable = AR IHC ≥ 10% and ≥ 1 post-baseline tumor assessment

Traina T, et al., 2015 ASCO Annual Meeting. Reproduced courtesy of Tiffany Traina
PHASE II STUDY OF ENZALUTAMIDE IN ADVANCED AR+ TNBC (MDV3100-11)

**PFS in Evaluable and ITT Populations**

**Evaluable (n = 75)**
- **PFS median 14.7 weeks**
- 95% CI: 8.1, 19.3

**ITT (n = 118)**
- **PFS median 12.6 weeks**
- 95% CI: 8.1, 15.7

*Data cut off 24 March 2015.*

**Evaluable** = AR IHC ≥ 10% and ≥1 post-baseline tumor assessment

**ITT** = AR IHC > 0% by central assessment and received ≥1 dose of enzalutamide.

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Traina T, et al., 2015 ASCO Annual Meeting. Reproduced courtesy of Tiffany Traina
CLINICAL BENEFIT ACCORDING TO PREDICT AR

ITT (n = 118)

PREDICT AR+
mOS NYR
(95% CI: 55.4, NYR)

PREDICT AR−
mOS 32.1 weeks
(95% CI: 20.7, 48.3)

53 total death events (45%)
- 17 events in PREDICT AR+
- 36 events in PREDICT AR−

Median follow-up for survival 48 weeks

Traina T, et al., 2015 ASCO Annual Meeting. Reproduced courtesy of Tiffany Traina
CONCLUSIONS

- Chemotherapy remains the mainstay of treatment:
  - Anthracycline+taxanes: first choice in the neo-/adjuvant setting (the schedule matters!)
  - BRCA-mut (or BRCAwt with BRCAness features?): chance for tailored-chemotherapy with platinum salts

- Novel targets and approaches:
  - Dissecting the diversity of TNBC helps identifying druggable pathways
  - PARP inhibitors hold great promises for BRCA-mut patients
  - Immunotherapy on the horizon: what about predictive markers?
THANK YOU!