CÁNCER DE MAMA TRIPLE NEGATIVO.PRESENTE Y FUTURO

Dr. Pedro Sánchez Rovira
Complejo Hospitalario de Jaén.

Panticosa
11 al 14 de junio de 2014

FORO DEBATE ONCOLOGÍA
TRIPLE NEGATIVO

Ausencia de expresión de los tres receptores

RE (-)    RP (-)    C-erbB-2 (-)
TNBC prognosis is poor

- High risk of early death (between 3–5 years)²
- Rapid rise in risk of recurrence following diagnosis
- Peak risk of recurrence at 1–3 years
- Rapid progression from distant recurrence to death

- Large, high-grade tumours
- Greater propensity to metastasise to viscera

Survival for women with TNBC is worse than for other subtypes of stage III/IV disease\(^1\)
## Types of NAC regimen

<table>
<thead>
<tr>
<th>Type of NAC Regimen</th>
<th>Events</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline-based</td>
<td>19 (1, 8, 9, 12-14, 16-18, 25-34)</td>
<td>3.19 (2.63, 3.88)</td>
<td>26.8 (24.1, 29.6)</td>
<td>39.3</td>
</tr>
<tr>
<td>Taxane-containing</td>
<td>10 (8, 13, 18, 19, 21, 25, 26, 29, 33, 45)</td>
<td>3.29 (2.41, 4.48)</td>
<td>0</td>
<td>30.5 (25.9, 35.5)</td>
</tr>
<tr>
<td>Platinum-containing</td>
<td>4 (1, 7, 19, 21, 45)</td>
<td>3.10 (1.59, 6.03)</td>
<td>0</td>
<td>44.2 (30.8, 58.5)</td>
</tr>
</tbody>
</table>
Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Marcador</th>
<th>Reactividad</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Estrógenos</td>
<td>-</td>
</tr>
<tr>
<td>R Progestetrona</td>
<td>-</td>
</tr>
<tr>
<td>Her2</td>
<td>-</td>
</tr>
<tr>
<td>EGFR (receptor de Factor de Crecimiento)</td>
<td>+</td>
</tr>
<tr>
<td>Citoqueratinas basales (5/6)</td>
<td>+</td>
</tr>
</tbody>
</table>
FENOTIPO TN / Basal

• TN y Basal no equivalentes.

• Ca mama en BRCA1 frec. TN y/o Basal

• Puede defectos BRCA1 en carcinomas TN / Basales esporádicos

• Frecuentes recidivas y metástasis tempranas.

• No tto específico
# Targeting triple-negative breast cancer: optimising therapeutic outcomes

K. Gelmon\(^1,2\*\), R. Dent\(^3,4\), J. R. Mackey\(^5,6\), K. Laing\(^7,8\), D. McLeod\(^9\) & S. Verma\(^10,11\)

## PARP inhibitors

<table>
<thead>
<tr>
<th>O'Shaughnessy [31], Rd phase II</th>
<th>First-line(^+)</th>
<th>(0–3 prior regimens)</th>
<th>Gemcitabine 1000 mg/m(^2) d1, 8, q3w; carboplatin AUC 2 d1, 8, q3w; iniparib 5.6 mg/kg d1, 4, 8, 11, q3w</th>
<th>61</th>
<th>56 (34–76)</th>
<th>52 (P = 0.02) 5.9; 0.59 [0.39–0.90] (P = 0.01)</th>
<th>12.3; 0.57 [0.36–0.90] (P = 0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Shaughnessy [37], Rd phase III</td>
<td>First-line(^+)</td>
<td>(0–2 prior regimens)</td>
<td>Gemcitabine 1000 mg/m(^2) d1, 8, q3w; carboplatin AUC 2 d1, 8, q3w; iniparib 5.6 mg/kg d1, 4, 8, 11, q3w</td>
<td>261</td>
<td>53</td>
<td>34 5.1; 0.79 [0.65–0.98] (P = 0.027)(^f)</td>
<td>11.8; 0.88 [0.69–1.12] (P = 0.28)(^g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gemcitabine 1000 mg/m(^2) d1, 8, q3w; carboplatin AUC 2 d1, 8, q3w(^c)</td>
<td>258</td>
<td>54</td>
<td>30 4.1</td>
<td>11.1</td>
</tr>
</tbody>
</table>
Oncología de cáncer de mama
Comunidad Valenciana

Estadio IV

Receptores Hormonales+
y metástasis evolución lenta* e intervalo libre enfermedad largo

Hormonoterapia

Respuesta

Ante progresión, seguir hormonoterapia ó 2ª línea

Receptores Hormonales –
ó metástasis evolución rápida y viscerales.
ó resistencias hormonoterapia ó intervalo libre enfermedad corto.

HER-2 +

Quimioterapia

No respuesta

Trastuzumab +/− quimioterapia

*p piel, tejidos blandos, huesos, ganglios y nódulos.
QUIMIOTERAPIA
Her-2 negativo

Metástasis viscerales muy sintomáticas carga tumoral alta

POLIQUIMIOTERAPIA

ANTRACICLINAS PREVIAS

COMBINACIONES TAXANOS:
- DOCETAXEL/CAPECITABINA
- PACLITAXEL/GEMCITABINA
- TAXANOS/A. LIPOSOMIALES

COMBINACIONES SIN TAXANOS

VINORELBINA/GENCITABINA
CISPLATINO/GEMCITABINA
CMF

PROGRESIÓN ENFERMEDAD

VALORACIÓN
2ª, 3ª LINEAS

Metástasis p.blandas
Metástasis óseas
Edad avanzada
Comorbididad

MONOQUIMIOTERAPIA
OT SECUENCIAL

ANTRACICLINAS LIPOSOMIALES
Docetaxel, Paclitaxel semanal,
Vinorelbina, Capecitabina,
Gemicitabina, Etoposido,
Salaes Platino

COMBINACIONES TAXANOS/ANTRA

TAC, ETC, AT, ...

ANTRACICLINAS SIN TAXANOS

AC, EC, FAC, FEC, ...
Chemotherapy is the standard treatment for patients with triple negative as well as for ER-positive MBC patients not amenable to endocrine therapy by either resistance or aggressiveness criteria. To date, the molecular phenotype is not a valid criterion to allocate for a particular regimen or agent. In general, chemotherapy should not be given concomitantly with endocrine agents, but sequencing endocrine therapy after completing chemotherapy is a valid option.
SEOM Clinical Guidelines for the systemic treatment of early breast cancer 2013

Triple-negative tumours

Triple-negative pT1pN0 or pN+ represents a subgroup with a high risk of recurrence, justifying treatment with chemotherapy containing anthracyclines and taxanes [4].
Table 1. Ongoing adjuvant trials in triple-negative breast cancer

<table>
<thead>
<tr>
<th>ClinicalTrials.gov identifier (study name where appropriate)</th>
<th>Phase</th>
<th>Treatment</th>
<th>Primary end point</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00528567 (BEATRICE)</td>
<td>III</td>
<td>Standard chemotherapy (anthracycline +/- taxane or taxane only) versus bevacizumab plus standard chemotherapy</td>
<td>Invasive disease-free survival</td>
<td>Hoffmann-La Roche</td>
</tr>
<tr>
<td>NCT00130533 (CIBOMA)</td>
<td>III</td>
<td>Maintenance capecitabine following standard adjuvant chemotherapy</td>
<td>Disease-free survival</td>
<td>Spanish Breast Cancer Research Group</td>
</tr>
<tr>
<td>NCT00630032 (FNCLCC-PACS-08)</td>
<td>III</td>
<td>Combination chemotherapy (cyclophosphamide, epirubicin, fluorouracil) followed by docetaxel or ixabepilone</td>
<td>Disease-free survival</td>
<td>Federation Nationale des Centres de Lutte Contre le Cancer</td>
</tr>
<tr>
<td>NCT00789581 (TITAN)</td>
<td>III</td>
<td>Doxorubicin/cyclophosphamide (AC) followed by ixabepilone versus AC followed by paclitaxel</td>
<td>Disease-free survival</td>
<td>Sarah Cannon Research Institute; Bristol-Myers Squibb</td>
</tr>
<tr>
<td>NCT01112826</td>
<td>III</td>
<td>Standard adjuvant chemotherapy +/- capcitabine for 1 year</td>
<td>Disease-free survival</td>
<td>Sun Yat-sen University</td>
</tr>
<tr>
<td>NCT01150513</td>
<td>III</td>
<td>Docetaxel plus carboplatin versus epirubicin plus cyclophosphamide followed by docetaxel</td>
<td>Disease-free survival</td>
<td>Chinese Academy of Medical Sciences</td>
</tr>
<tr>
<td>NCT01216111</td>
<td>III</td>
<td>Paclitaxel plus cisplatin versus cyclophosphamide, epirubicin, fluorouracil (CEF) followed by docetaxel</td>
<td>Disease-free survival</td>
<td>Fudan University</td>
</tr>
<tr>
<td>NCT01289353</td>
<td>I/II</td>
<td>Concurrent carboplatin and radiation</td>
<td>Grade 2–3 dermatitis 60 days post-radiation</td>
<td>New York University School of Medicine</td>
</tr>
</tbody>
</table>
**Triple-negative breast cancer: bridging the gap from cancer genomics to predictive biomarkers**

S. Lindsey Davis, S. Gail Eckhardt, John J. Tentler and Jennifer R. Diamond

Table 2. Biomarker evaluations with classical chemotherapeutic agents in the treatment of triple-negative breast cancer in the neoadjuvant setting.

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Potential biomarker(s)</th>
<th>pCR rate</th>
<th>Method of testing</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel and epirubicin [Li et al. 2011]</td>
<td>Basal-like markers negative Nm23-H1 positive</td>
<td>72.7%</td>
<td>IHC</td>
<td>Prospective</td>
</tr>
<tr>
<td>Cisplatin [Byrski et al. 2010]</td>
<td>BRCA1 mutation</td>
<td>83%</td>
<td>PCR</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Docetaxel and doxorubicin [Keam et al. 2011]</td>
<td>High Ki-67</td>
<td>18.2%</td>
<td>IHC</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Anthracycline-based therapy [Bidard et al. 2008]</td>
<td>p53 positive</td>
<td>22.5%*</td>
<td>IHC</td>
<td>Retrospective</td>
</tr>
<tr>
<td>TAC [Von Minckwitz et al. 2011]</td>
<td>High cytoplasmic PARP</td>
<td>41%</td>
<td>IHC</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Anthracycline and taxane combinations [Darb-Esfahani et al. 2012]</td>
<td>High TMSB15A expression</td>
<td>47.2% and 36.8%**</td>
<td>qRT-PCR</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Various regimens [Dennison et al. 2013]</td>
<td>High LDHB expression</td>
<td>45.5% and 36.6%**</td>
<td>Microarray</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Anthracycline or taxane-based therapy [Ono et al. 2012]</td>
<td>High tumor-infiltrating lymphocytes</td>
<td>37%</td>
<td>Histopathologic evaluation</td>
<td>Retrospective</td>
</tr>
</tbody>
</table>

* Not statistically significant increase.
19p13.1 locus and the MDM4 locus has been associated with TNBC, but not other forms of breast cancer, suggesting that these are TNBC-specific loci.
Molecular Characterization of Basal-Like and Non-Basal-Like

A

TRIPLE-NEGATIVE

PAM50
- Basal-like
- HER2E
- Luminal
- Normal

Claudin-low
Others

FAP
CAV1
CD36
AR
FOXA1
ESR1

CD8A
CD3D
LY96
KRT5
KRT14

B

Lehmann et al.

UP
NA
DOWN

IM
BL1
M
BL2
MSL
LAR
Triple Negative Subtype GE Patterns are Reproducible

Clinical Cancer Research

Differ triple
Hiroko M
Clin Canc

Distribution (%)

Proportion of patients DMFS

Proportion of patients surviving

P=0.371

P=0.287

Days

Days
<table>
<thead>
<tr>
<th>TNBC subtypes</th>
<th>Molecular characteristics</th>
<th>Potential therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like 1</td>
<td>Cell cycle function</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Proliferation</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td></td>
<td>DNA damage response</td>
<td></td>
</tr>
<tr>
<td>Basal-like 2</td>
<td>Cell cycle function</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Proliferation</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td></td>
<td>Growth factor signaling</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>EMT</td>
<td>Src inhibitor</td>
</tr>
<tr>
<td></td>
<td>Cell motility</td>
<td>PI3K pathway inhibitor</td>
</tr>
<tr>
<td></td>
<td>Differentiation</td>
<td>Wnt pathway inhibitor</td>
</tr>
<tr>
<td></td>
<td>Proliferation</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal stem-like</td>
<td>EMT</td>
<td>Src inhibitor</td>
</tr>
<tr>
<td></td>
<td>Cell motility</td>
<td>PI3K pathway inhibitor</td>
</tr>
<tr>
<td></td>
<td>Differentiation</td>
<td>Wnt pathway inhibitor</td>
</tr>
<tr>
<td></td>
<td>Growth factor signaling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Luminal androgen receptor</td>
<td>AR signaling</td>
<td>AR antagonist</td>
</tr>
<tr>
<td></td>
<td>Luminal cytokeratine</td>
<td>Hsp90 inhibitor</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Immune cell processes</td>
<td>PI3K pathway inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immune targeted agents</td>
</tr>
</tbody>
</table>

AR, androgen receptor; EMT, epithelial mesenchymal transition; PARP, poly ADP ribose polymerase; TNBC, triple-negative breast cancer.
TNBC

20-30%  70-80%

non-Basal-like  Basal-like

Luminal (A+B)  HER2-enriched  Claudin-low  Basal-like

Endocrine therapies?  anti-HER2 therapies?  Platinum-based chemotherapy?
P13K inhibitors?  anti-EGFR therapies?  Anti-angiogenic therapies?
anti-androgen therapies?  PARP inhibitors?
Anti-immune cell therapies?
Chemotherapy With or Without Trastuzumab After Surgery in Treating Women With Invasive Breast Cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Receptor-negative Breast Cancer</td>
<td>Drug: doxorubicin hydrochloride</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Estrogen Receptor-positive Breast Cancer</td>
<td>Drug: docetaxel</td>
<td></td>
</tr>
<tr>
<td>HER2-positive Breast Cancer</td>
<td>Drug: cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>Progesterone Receptor-negative Breast Cancer</td>
<td>Biological: trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Progesterone Receptor-positive Breast Cancer</td>
<td>Drug: paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Recurrent Breast Cancer</td>
<td>Other: laboratory biomarker analysis</td>
<td></td>
</tr>
<tr>
<td>Stage IA Breast Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IB Breast Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II Breast Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA Breast Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIC Breast Cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ClinicalTrials.gov Identifier: NCT01275677
Table 1. Relative Risks of Disease Progression and Death among Patients in the ACTH Group as Compared with the ACT Group.∗

<table>
<thead>
<tr>
<th>End Point and Central HER2 Assay†</th>
<th>ACT</th>
<th>ACTH</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>P Value for the Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of events/total no. of events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-positive</td>
<td>163/875</td>
<td>85/804</td>
<td>0.47 (0.37–0.62)</td>
<td>&lt;0.001</td>
<td>0.47</td>
</tr>
<tr>
<td>HER2-negative</td>
<td>20/92</td>
<td>7/82</td>
<td>0.34 (0.14–0.80)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-positive</td>
<td>55/875</td>
<td>38/804</td>
<td>0.66 (0.43–0.99)</td>
<td>0.047</td>
<td>0.08</td>
</tr>
<tr>
<td>HER2-negative</td>
<td>10/92</td>
<td>1/82</td>
<td>0.08 (0.01–0.64)</td>
<td>0.017</td>
<td></td>
</tr>
</tbody>
</table>
**BEATRICE: Phase III Trial of Adjuvant Bevacizumab in Triple-Negative Breast Cancer**

- **BEATRICE study design**

  - **Eligibility criteria:**
    - Resected triple-negative (centrally confirmed) invasive early breast cancer

  - **Primary endpoint:** DFS
  - **Secondary endpoints:** OS, breast cancer-free interval, DFS, distant DFS, safety, biomarkers

  - **Randomization:**
    - 4-8 cycles of standard chemotherapy (investigator’s choice)
    - 4-8 cycles of standard chemotherapy (investigator’s choice) + bevacizumab 5 mg/kg/wk equivalent for 1 year duration

  - **Chemotherapy options:**
    - Taxane-based (≥4 cycles)
    - Anthracycline-based (≥4 cycles)
    - Anthracycline + taxane (3-4 cycles each)

Cameron et al., SABCS 2012; abstract S6-5
BEATRICE: Phase III Trial of Adjuvant Bevacizumab in Triple-Negative Breast Cancer

• Efficacy results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chemo alone (n=1290)</th>
<th>Chemo + bevacizumab (n=1301)</th>
<th>HR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr invasive DFS</td>
<td>82.7%</td>
<td>83.7%</td>
<td>0.87 (0.72-1.07)</td>
<td>.18</td>
</tr>
<tr>
<td>OS</td>
<td>--</td>
<td>--</td>
<td>0.84 (0.64-1.12)</td>
<td>.23</td>
</tr>
</tbody>
</table>

  - None of the subgroups examined (age, baseline ECOG performance status, region, race, menopausal status, tumor size, # of positive LNs, adjuvant chemotherapy, HR status, and surgery) showed a significant effect on invasive DFS

• Safety results

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Chemo alone (n=1271)</th>
<th>Chemo + bevacizumab (n=1288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>57%</td>
<td>72%</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>0.2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>AE leading to chemo and/or bev discontinuation</td>
<td>2%</td>
<td>20%</td>
</tr>
<tr>
<td>AE leading to bev discontinuation</td>
<td>--</td>
<td>18%</td>
</tr>
</tbody>
</table>
### BEATRICE Trial: Biomarker Results

- Biomarker analysis performed to investigate potential predictive markers of benefit from adjuvant bevacizumab
- Sub-study included 45% of total patient population
- Evaluated correlation of biomarkers with invasive disease-free survival

<table>
<thead>
<tr>
<th>Baseline Plasma Concentration</th>
<th>HR*</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median VEGF-A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.89</td>
<td>.7415</td>
</tr>
<tr>
<td><strong>3rd Quartile VEGF-A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.64</td>
<td>.3551</td>
</tr>
<tr>
<td>Low</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td><strong>Median VEGFR-2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>.61</td>
<td>.0291</td>
</tr>
<tr>
<td>Low</td>
<td>1.24</td>
<td></td>
</tr>
</tbody>
</table>

* HR <1.0 indicates CT plus Bev better than CT alone

Carmeliet et al., SABCS 2012; abstract P3-06-34
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Regimen</th>
<th>Eligibility</th>
<th>pCR Breast &amp; Axilla (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alba\textsuperscript{21}</td>
<td>94</td>
<td>Epirubicin 90 mg/m\textsuperscript{2} + cyclophosphamide 600 mg/m\textsuperscript{2} every 21 d x 4 cycles followed by docetaxel 100 mg/m\textsuperscript{2} every 21 d x 4 or docetaxel 75 mg/m\textsuperscript{2} + carboplatin AUC 6 every 21 d x 4 cycles</td>
<td>Stage II-III ER\textsuperscript{-}, PR\textsuperscript{-}, HER2\textsuperscript{-} and CK 5/6 or EGFR-positive breast cancer</td>
<td>30% with Cp, 30% no Cp</td>
</tr>
<tr>
<td>von Minckwitz\textsuperscript{22}</td>
<td>315</td>
<td>Paclitaxel 80 mg/m\textsuperscript{2} every 7 d + nonpegylated liposomal doxorubicin 20 mg/m\textsuperscript{2} every 7 d + bevacizumab 15 mg/kg IV every 21 d ± carboplatin AUC 1.5 every 7 d x 18 cycles</td>
<td>Stage II-III TNBC</td>
<td>59% with Cp, 38% no Cp</td>
</tr>
<tr>
<td>Sikov\textsuperscript{29}</td>
<td>443</td>
<td>Paclitaxel 80 mg/m\textsuperscript{2} every 7 d x 12 cycles followed by doxorubicin 60 mg/m\textsuperscript{2} + cyclophosphamide 600 mg/m\textsuperscript{2} every 2 wk x 4 cycles ± carboplatin AUC 6 every 21 d x 4 cycles (with paclitaxel) ± bevacizumab 10 mg/kg every 2 wk x 9 cycles (with paclitaxel and doxorubicin/cyclophosphamide)</td>
<td>Stage II-III TNBC</td>
<td>54% with Cp, 41% no Cp, 52% with bev, 44% no bev</td>
</tr>
<tr>
<td><strong>Single-arm trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gronwald\textsuperscript{17}</td>
<td>25</td>
<td>Cisplatin 75 mg/m\textsuperscript{2} IV every 21 d x 4 cycles</td>
<td>Stage I-II BRCA\textsuperscript{-} mutant breast cancer (80% TNBC)</td>
<td>72%</td>
</tr>
<tr>
<td>Silver\textsuperscript{19}</td>
<td>28</td>
<td>Cisplatin 75 mg/m\textsuperscript{2} IV every 21 d x 4 cycles</td>
<td>Stage II A-IIIC TNBC (T ≥ 1.5 cm)</td>
<td>21%</td>
</tr>
<tr>
<td>Ryan\textsuperscript{20}</td>
<td>51</td>
<td>Cisplatin 75 mg/m\textsuperscript{2} IV every 21 d x 4 cycles + bev 15 mg/kg IV every 3 wk x 3 cycles</td>
<td>T1-3 TNBC</td>
<td>15%</td>
</tr>
<tr>
<td>Teligi\textsuperscript{23}</td>
<td>80</td>
<td>Gemcitabine 1000 mg/m\textsuperscript{2} IV d 1,8 + carboplatin AUC 2 IV d1,8 + iniparib 5.6 m/kg IV d 1, 4, 8, 11 every 21 d x 6 cycles</td>
<td>Stage I-IIIA TNBC or BRCA\textsuperscript{1/2}-mutant breast cancer (T ≥ 1 cm)</td>
<td>36%, BRCA\textsuperscript{wt} = 33%, BRCA\textsuperscript{mut} = 56%</td>
</tr>
</tbody>
</table>
Results: From the 94 enrolled pts, we processed 46 pre-treatment tumor samples in a central lab and isolated high-quality RNA for microarray analysis in 39 (42%); 7 samples are still pending to be analyzed. Tumors were classified as follows: 4 BL1, 2 BL2, 8 IM, 5 LAR, 3 M, 3 ML with 7 pts that couldn’t be assigned to any subtype and were not included in this analysis. Three (75%) of the BL1 subtype pts achieved a pCR (p-value=0.075). In contrast, IM and LAR achieved the lowest pCR rates (12% and 20%, respectively). In the carboplatin-treated patients, 100% of BL1 patients showed pCR (p-value=0.033) in contrast with none of the IM and LAR pts. Conclusions: Our preliminary findings suggest that TNBC subtypes can predict tumor response to neoadjuvant CHT, supporting their potential clinical utility in diagnosis, treatment selection and drug development, bringing TNBC pts a step closer to personalized medicine.
**Differential response of neoadjuvant chemotherapy with taxane-carboplatin versus taxane-epirubicin in patients with locally advanced triple-negative breast cancer.**

Results: In total, 92 patients were enrolled between January 2009 and December 2012. Of these, 43 patients were assigned to TC group, and 49 to TE group. The pCR rate was higher in TC group than in TE group (37.2% versus 16.1%, p=0.032)
With a median follow-up of 9 months, 1-yr DFS was similar (~76%) in both treatment groups. BROCA identified deleterious mutations in 22/101 (22%) pts (8 BRCA 1, 12 BRCA 2, 2 BRIP1). 1-yr DFS in the 22 pts with mutations was ~85% compared to 79% without mutations. Whole transcriptome sequencing of paired pre vs. post preoperative chemotherapysamples will be reported separately (Radovich et al, ASCO 2014). **Conclusions:** The addition of low dose rucaparib (current phase II monotherapy dose 600 mg orally twice daily) did not impact the toxicity of cisplatin or improve 1-yr DFS. Comparison to predicted DFS based on residual cancer burden (RCB) is planned to investigate potential benefit from cisplatin. Genetic testing was underutilized in this high risk population with only 30% of BRCA1 and BRCA2 mutations identified as part of routine clinical care. Clinical trial information: **NCT01074970.**
Veliparib/carboplatino más tratamiento neoadyuvante estandar para pacientes triple negativas: I-SPY 2 TRIAL
**I-SPY 2 TRIAL:**

Learn, Drop, Graduate, and Replace Agents Over Time

**Patient is on Study**

**HER 2 (+)**
- Paclitaxel + Trastuzumab
- Paclitaxel + Trastuzumab* + New Agent A
- Paclitaxel + Trastuzumab* + New Agent B

**HER 2 (-)**
- Paclitaxel
- Paclitaxel + New Agent F
- Paclitaxel + New Agent GH
- Paclitaxel + New Agent E

**AC** → **Surgery**

Learn and adapt from each patient as we go along

*Investigational agent may be used in place

Key
- MRI
- Residual Disease (Pathology)
I-SPY 2: the first graduate
Rugo et al, #S5-02, SABCS, 2013

- Primary end point: pCR
- Graduate regimens have >85% Bayesian predictive probability of success in a 300-pts biomarker-linked neoadjuvant phase III trial
- Veliparib+carbo met the 85% predictive probability criterion in HR-/HER2- and all HER2- pts

<table>
<thead>
<tr>
<th>%</th>
<th>pCR</th>
<th>p V+Cb better</th>
<th>p of successful phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HER2-</td>
<td>35 vs 20</td>
<td>97%</td>
<td>71%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>14 vs 15</td>
<td>44%</td>
<td>16%</td>
</tr>
<tr>
<td>TNBC</td>
<td>52 vs 24</td>
<td>99%</td>
<td>92%</td>
</tr>
</tbody>
</table>

- V/Cb graduated with a TNBC signature and recommended for future trial
- Biomarker study? (lesson from iniparib)
Phase III study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy in subjects with early-stage triple-negative breast cancer (TNBC).

Gunter Von Minckwitz MD

Opened in Jan 2014.  NCT02032277
A phase II study of tivantinib (ARQ-197) for metastatic triple-negative breast cancer. (c-met)

Sara M. Tolaney MD, MPH

**Conclusions:** This represents the first study of tivantinib for the treatment of metastatic triple-negative breast cancer. These results suggest that tivantinib is well tolerated, but is *largely inactive* when used as monotherapy to treat metastatic triple-negative breast cancer.

NCT01542996.
A Phase II, Randomized, Open-label, Neoadjuvant Study of LCL161, an Oral Antagonist of Inhibitors of Apoptosis Proteins, in Combination With Paclitaxel in Patients With Triple-negative Breast Cancer

A. Lloci-Hernández,1 Ana Paro-Ruiz Simon,1 Chun-Sheng Huang,1 Javier Cortés,1 Manuel Ruiz-Borrego,1 Melinda Tell,2 Roohi Iyvafi-Khan,2 Marina Parnon,3 Ling-Ming Tseng,4 Shin-Chieh Chen,4 Peter Schmidt,5 Ingrid Mayer,6 Sara Harritz,7 Laura García-Esplee,9 Rolando Atienza,9 Suman Son,1 Scott Cameron,1 J-Theodore Beck,1 Aithya Bandle9

1Hospital Clinico Universitario de Valencia, Valencia, Spain; 2Instituto Valenciano de Oncología, Valencia, Spain; 3National Taiwan University Hospital, Taipei, Taiwan; 4Vall d’Hebron University Hospital, Barcelona, Spain; 5Hospital Virgen de Fátima, Baeza, Spain; 6Stanford University Medical Center, Stanford, CA; 7H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; 8The Royal Marsden Hospital and Institute of Cancer Research, London, UK; 9Taye’s Memorial General Hospital, Taipei, Taiwan; 10Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan; 11Royal Sussex County Hospital, Brighton, UK; 12Wonderful University Medical Centre, NaviMumbai, NY; 13University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; 14Hospital de Sandroiros, Málaga, Spain; 15Novartis Pharmaceuticals Corp., Cambridge, MA and Farhan Park Bandaranaike Hospital, Colombo, Sri Lanka.

CLCL161A2201
Study Design

Enroll patients with gene signature positive disease; 50 pts per arm

Randomize

Tumor biopsy for caspase 3

LCL161 once weekly

QW paclitaxel 80 mg/m² × 12

Surgery

Investigator’s Choice

FEC, FAC, AC

Interim analysis after 50 patients

Biopsy Genomics/Signature

LCL161 dose: 1800 mg

Pathologic CR Endpoint, Genomics

QW paclitaxel 80 mg/m² × 12

LCL161A2201
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Pathologic CR Endpoint, Genomics

NOVARTIS ONCOLOGY
A phase Ib dose escalation, open label, multicenter study evaluating LDE225 in combination with docetaxel in Triple Negative (TN) Advanced Breast Cancer (ABC) patients

EDALINE Study

Sponsor: GEICAM (Spanish Breast Cancer Research Group Foundation)  
Sponsor Study Code: GEICAM/2012-12 (EudraCT: 2013-001750-96)  
Medication code: CLDE225XES01T  
Protocol version: 2.0  
Protocol version date: 15 February 2014

A phase Ib dose escalation, open label, multicenter study evaluating LDE225 in combination with docetaxel in Triple Negative (TN) Advanced Breast Cancer (ABC) patients

EDALINE Study

Coordinating Investigator: Dr. Miguel Martín, H. General Universitario Gregorio Marañón, Madrid

selective smoothened inhibitor
Immunotherapeutic approaches in triple-negative breast cancer: latest research and clinical prospects

John Stagg and Bertrand Allard

Immunosuppressive molecules
- IL-10, IL-23, TGFβ, adenosine, PGE2, VEGF-A,

Immunosuppressive enzymes
- IDO, arginase I, ecto-5'-nucleotidase (CD73)

Activated T cells
- CD137
- OX40

Tumor vaccines
(MUC-1, NY-ESO-1)

Adoptive T-cell therapy
(CAR T cells)
Gene Signatures to define tumor immune cell subsets

Teff/CTL: CD8, IFNg, CXCL9, GZMB, PRF, EOMES
Tregs: FOXP3
Th2: IL13, IL4
B-cell: CD20
TH17: IL17A, IL17F, RORC
IB: PD1, PDL1, PDL2, CTLA4, B7H4, BTLA, Tim3, LAG3
Immune signature associated with good prognosis in Adjuvant TNBC
Mechanism of action of combined PD-1 and CTLA-4 blockade

MHC = major histocompatibility complex; TCR = T-cell receptor

Margaret K. Callahan ASCO 2014
Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthi, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.
T helper responses are maintained by basal-like breast cancer cells and confer to immune modulation via upregulation of PD-1 ligands.
Phase 1/2, Open-Label Study of Nivolumab (Anti-PD-1; BMS-936558, ONO-4538) as Monotherapy or Combined With Ipilimumab in Advanced or Metastatic Solid Tumors

Margaret K. Callahan, 1 Johanna Bendell, 2 Emily Chan, 3 Michael Morse, 4 Rathi N. Pillai, 5 Petri Bono, 6 Dirk Jaeger, 7 T. R. Jeffry Evans, 8 Ian Chau, 9 Emiliano Calvo, 10 Dung T. Le, 11 Patrick A. Ott, 12 Matthew Taylor, 13 Padmanee Sharma, 14 Scott Antonia, 15 Brian Sharkey, 16 Olaf Christensen, 16 Asim Amin 17

1Department of Medicine at Memorial Sloan-Kettering Cancer Center, New York, NY, USA; 2Sarah Cannon Research Institute, Nashville, TN, USA; 3Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; 4Duke University Medical Center, Durham, NC, USA; 5Winship Cancer Institute at Emory University, Atlanta, GA, USA; 6Cancer Center, Helsinki University Central Hospital, Helsinki, Finland; 7National Center for Tumor Diseases, University Medical Center Heidelberg, Heidelberg, Germany; 8Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; 9The Royal Marsden Hospital, London and Surrey, UK; 10START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; 11Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; 12Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; 13Oregon Health and Science University, Portland, OR, USA; 14The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 15H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; 16Bristol-Myers Squibb, Princeton, NJ, USA; 17Levine Cancer Institute, Charlotte, NC, USA

Email: callaham@mskcc.org
EL CÁNCER DE MAMA TRIPLE NEGATIVO CONSTITUYE UN GRUPO HETEROGÉNEO DE SUBTIPOS CON DISTINTOS MECANISMOS BIOMOLECULARES.

DEBEMOS PONER EN MARCHA LOS MECANISMOS NECESARIOS PARA LA IMPLEMENTACIÓN DEL DIAGNÓSTICO MOLECULAR EN ESTE SUBGRUPO DE PACIENTES.

CON ELLO, EL TRATAMIENTO BASADO EN LA COMBINACIÓN DE ANTRACICLÍNAS Y TAXANOS PODRÍA INDIVIDUALIZARSE (INCLUSIÓN DE PLATINOS, ANTIANGIOGÉNICOS, INHIBIDORES DE PARP…)

CONSTITUYE UNO DE LOS PRINCIPALES DESAFÍOS EN CÁNCER DE MAMA QUE NOS OBLIGA A PARTICIPAR EN LAS DISTINTAS LINEAS DE INVESTIGACIÓN.

GRACIAS