Triple Negative Breast Cancer and Novel Therapies
WAHO Best of SABCS 2018

Ruth M. O’Regan, MD
Professor and Division Chief
Hematology and Medical Oncology,
Department of Medicine,
University of Wisconsin
Chief Scientific Officer,
Big Ten Cancer Research Consortium
My disclosures

• Advisor: Novartis, Pfizer, Lilly, Biotheranostics, Genomic Health, Macrogenics, Immunomedics, PUMA, Genentech

• Travel/accommodations: Genomic Health, Macrogenics, Immunomedics, PUMA

• Research funding: Novartis, Eisai, Pfizer, Seattle Genetics
Topics to cover

• Optimal time to adjuvant chemotherapy in TNBC (Abstract GS2-5)

• Implications of PCR in TNBC and role of “adjuvant therapy”
  • Outcomes based on PCR (Abstract GS2-3)
  • Tailoring of therapy based on PCR (Abstract GS5-5)
  • Adjuvant capecitabine (Abstract GS2-4)

• Immunotherapy
  • Biomarkers for atezolizumab and nab-paclitaxel (Abstract GS1-5)
Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer

Zaida Morante, MD, Rossana Ruiz, MD, Gabriel de la Cruz – Ku, MD, Fernando Namuché, MD, Raul Mantilla, Maria Guadalupe Luján, MS, Hugo Fuentes, MD, Jesus Schwarz, MD, Alfredo Aguilar, MD, Silvia Neciosup, MD-PhD, Henry Gomez, MD-PhD
• 6,827 women diagnosed with BC stages I to III.

• TTC 61 days after surgery was associated with adverse outcomes.
  • Stage II → DFRS (HR, 1.20; 95% CI: 1.02 to 1.43)
  • Stage III → OS (HR, 1.76; 95% CI: 1.26 to 2.46), RFS (HR, 1.34; 95% CI: 1.01 to 1.76) and DFRS (HR, 1.36; 95% CI: 1.02 to 1.80)

• Patients with TNBC/HER-2 who started chemotherapy 61 days after surgery had worse survival.
  • TNBC → (HR, 1.54; 95% CI, 1.09 to 2.18)
  • HER-2 → (HR, 3.09; 95% CI, 1.49 to 6.39)

• 24,843 patients diagnosed with BC stages I to III.

• TTC 91 or more days after surgery experienced worse overall survival and worse breast cancer–specific survival.

Subgroup analysis according to subtype

• Longer TTC caused patients with triple-negative breast cancer to have worse overall survival (HR, 1.53; 95% CI, 1.17-2.00) and worse breast cancer–specific survival (HR, 1.53; 95% CI 1.17-2.07).
Objectives

We evaluated the influence of time to adjuvant chemotherapy (TTC) on the survival (OS – DFS - DRFS) of TNBC patients diagnosed at the Instituto Nacional de Enfermedades Neoplasicas (Lima, Peru) between 2000 to 2014.

Inclusion criteria
- ER (-), PR (-) and HER2 (-) tumors.
- CS I, II and III TNBC diagnosed and treated at INEN
- Upfront treatment: surgery
- Complete adjuvant chemotherapy
- Complete tumor and treatment information on clinical record

Exclusion criteria (N=1320)
- Inflammatory breast cancer
- Unknown tumor size or surgery type
- Incomplete or unknown chemotherapy or surgery dates
- Neoadjuvant chemotherapy

• TTC was defined as the number of days between surgery and the first dose of chemotherapy.
• Patients were categorized into 4 groups: ≤30 days; 31-60 days; 61-90 days; ≥91 days
Distribution of patients according to TTC

N=687

- <= 30 days: 189 patients (27.5%)
- 31-60 days: 329 patients (47.9%)
- 61-90 days: 115 patients (16.7%)
- >= 91 days: 54 patients (7.9%)
Distribution of patients diagnosed by year according to TTC

- **2000 - 2004**:
  - n=195
  - >=91: 5%
  - 61-90: 9%
  - 31-60: 47%
  - <=30: 39%

- **2005 - 2009**:
  - n=287
  - >=91: 9%
  - 61-90: 15%
  - 31-60: 45%
  - <=30: 32%

- **2010 - 2014**:
  - n=205
  - >=91: 10%
  - 61-90: 27%
  - 31-60: 53%
  - <=30: 10%

*p < 0.001*
Outcomes estimated curves by TTC

DFS

<table>
<thead>
<tr>
<th>TTC (days)</th>
<th>Total</th>
<th>Events</th>
<th>12mo</th>
<th>60mo</th>
<th>120mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>189</td>
<td>36</td>
<td>97.3%</td>
<td>86.5%</td>
<td>81.4%</td>
</tr>
<tr>
<td>31-60</td>
<td>329</td>
<td>96</td>
<td>91.5%</td>
<td>72.9%</td>
<td>68.6%</td>
</tr>
<tr>
<td>61-90</td>
<td>115</td>
<td>33</td>
<td>92.9%</td>
<td>70.8%</td>
<td>70.8%</td>
</tr>
<tr>
<td>≥91</td>
<td>54</td>
<td>16</td>
<td>85.2%</td>
<td>70.9%</td>
<td>68.1%</td>
</tr>
</tbody>
</table>

p=0.005

OS

<table>
<thead>
<tr>
<th>TTC (days)</th>
<th>Total</th>
<th>Events</th>
<th>12mo</th>
<th>60mo</th>
<th>120mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>189</td>
<td>37</td>
<td>99.5%</td>
<td>86.2%</td>
<td>82%</td>
</tr>
<tr>
<td>31-60</td>
<td>329</td>
<td>105</td>
<td>98.8%</td>
<td>76.2%</td>
<td>67.4%</td>
</tr>
<tr>
<td>61-90</td>
<td>115</td>
<td>37</td>
<td>97.4%</td>
<td>71.3%</td>
<td>67.1%</td>
</tr>
<tr>
<td>≥91</td>
<td>54</td>
<td>20</td>
<td>94.4%</td>
<td>75.8%</td>
<td>65.1%</td>
</tr>
</tbody>
</table>

p=0.003
Distant disease-free survival estimated curves by TTC

<table>
<thead>
<tr>
<th>TTC (days)</th>
<th>Total</th>
<th>Events</th>
<th>12mo</th>
<th>60mo</th>
<th>120mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>189</td>
<td>39</td>
<td>97.9%</td>
<td>85.7%</td>
<td>80.2%</td>
</tr>
<tr>
<td>31-60</td>
<td>329</td>
<td>112</td>
<td>94.5%</td>
<td>72.2%</td>
<td>64.9%</td>
</tr>
<tr>
<td>61-90</td>
<td>115</td>
<td>38</td>
<td>93%</td>
<td>68.7%</td>
<td>67.5%</td>
</tr>
<tr>
<td>≥91</td>
<td>54</td>
<td>24</td>
<td>87%</td>
<td>68.4%</td>
<td>58.6%</td>
</tr>
</tbody>
</table>

P < 0.001
Influence of TTC according to nodal status in 10-year OS (%)

<table>
<thead>
<tr>
<th>Nodal Status</th>
<th>Kaplan-Meier</th>
<th>Cox-regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>N0</td>
<td>11.8%</td>
<td>1.701 (1.023-2.827)</td>
</tr>
<tr>
<td>N1</td>
<td>20.1%</td>
<td>2.498 (1.023-4.510)</td>
</tr>
<tr>
<td>N2-N3</td>
<td>19.3%</td>
<td>2.065 (0.723-5.899)</td>
</tr>
</tbody>
</table>
Conclusion

• In patients with TNBC, the greater the delay in initiating adjuvant chemotherapy, the worse the outcomes.

• Delayed initiation of adjuvant chemotherapy over 30 days is associated with decreased DFS, DRFS and OS rates.

• The difference of 10-year overall survival between patients receiving chemotherapy within 30 days after surgery and after 30 days was more than 10%.

• These results represent a feasible opportunity for improving the outcomes of TNBC patients.
Pathological complete response (pCR) after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage:
Patient-level meta-analyses of over 27,000 patients.

Laura M. Spring MD\textsuperscript{1,3}; Geoffrey Fell MS\textsuperscript{2}; Andrea Arfe MS\textsuperscript{5}; Rachel Greenup MD, MPH\textsuperscript{6}; Kerry L. Reynolds MD\textsuperscript{1,3}; Barbara L. Smith MD, PhD\textsuperscript{1,3}; Beverly Moy MD, MPH\textsuperscript{1,3}; Steven J. Isakoff MD, PhD\textsuperscript{1,3}; Lorenzo Trippa PhD\textsuperscript{2,4}; Giovanni Parmigiani PhD\textsuperscript{2,4}; Aditya Bardia MD, MPH\textsuperscript{1,3}

1. Massachusetts General Hospital Cancer Center, Boston, MA
2. Dana-Farber Cancer Institute, Boston, MA
3. Harvard Medical School, Boston, MA
4. Harvard TH Chan School of Public Health, Boston, MA
5. Bocconi University, Milan, Italy
6. Duke University, Durham, NC
Study Objectives

To conduct a comprehensive meta-analysis of studies on neoadjuvant chemotherapy for localized breast cancer using recapitulated patient level data to evaluate:

➢ association between pCR and clinical outcomes (EFS and OS) by breast cancer subtype,

➢ impact of adjuvant chemotherapy on association between pCR and clinical outcomes,

➢ magnitude of change in pCR (Δ pCR) and corresponding change in clinical outcomes (Δ EFS)
Methods

• Librarian-led systematic search in PubMed from inception until September 2016 (PRISMA guidelines)

• Inclusion criteria included:
  ➢ published studies of localized breast cancer with 25 patients or more featuring neoadjuvant chemotherapy that reported pCR (ypT0 ypN0 or ypT0/is ypN0) results as well as recurrence and/or survival based on pathologic outcome

• Exclusion criteria included:
  ➢ studies reporting local recurrence only
  ➢ studies featuring neoadjuvant endocrine therapy or neoadjuvant radiation

• Relevant data extracted by two independent reviewers
Impact of PCR on EFS and OS in overall population

5-year EFS pCR vs RD: 88% vs 67%
5-year OS pCR vs RD: 94% vs 75%

Blue: pCR group
Orange: Residual disease (RD) group
Impact of PCR on EFS by Subtype

**Similar results seen with OS**

**Blue**: pCR group  
**Orange**: Residual disease (RD) group
Impact of adjuvant chemotherapy in patients achieving a PCR

5-year EFS in patients with pCR followed by adjuvant chemotherapy: 86%; pCR without additional adjuvant chemotherapy: 88%

<table>
<thead>
<tr>
<th>Adjuvant Chemotherapy</th>
<th>Hazard Ratio (pCR and EFS)</th>
<th>95% PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes¹</td>
<td>0.36</td>
<td>0.19-0.67</td>
</tr>
<tr>
<td>No²</td>
<td>0.36</td>
<td>0.27-0.54</td>
</tr>
</tbody>
</table>

pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups³.

¹ >90% of patients received adjuvant chemotherapy  
² No more than 10% of patients received adjuvant chemotherapy  
³ Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 0.60)
### ΔEFS vs. ΔpCR

<table>
<thead>
<tr>
<th>Change in (Δ) pCR*</th>
<th>Corresponding HR (EFS)</th>
<th>95% PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>0.1</td>
<td>0.90</td>
<td>0.88-0.92</td>
</tr>
<tr>
<td>0.2</td>
<td>0.81</td>
<td>0.78-0.84</td>
</tr>
<tr>
<td>0.3</td>
<td>0.72</td>
<td>0.68-0.77</td>
</tr>
<tr>
<td>0.4</td>
<td>0.65</td>
<td>0.60-0.70</td>
</tr>
<tr>
<td>0.5</td>
<td>0.58</td>
<td>0.52-0.64</td>
</tr>
<tr>
<td>0.6</td>
<td>0.52</td>
<td>0.46-0.58</td>
</tr>
<tr>
<td>0.7</td>
<td>0.46</td>
<td>0.39-0.53</td>
</tr>
<tr>
<td>0.8</td>
<td>0.40</td>
<td>0.34-0.48</td>
</tr>
<tr>
<td>0.9</td>
<td>0.36</td>
<td>0.28-0.43</td>
</tr>
<tr>
<td>1</td>
<td>0.31</td>
<td>0.24-0.39</td>
</tr>
</tbody>
</table>

Assuming pCR is a valid surrogate endpoint (i.e. it mediates all treatment effects) and average* pCR of 50%, the magnitude of pCR change is predictive of treatment effects on EFS within a certain amount of uncertainty, based on the model.
Conclusions

• Achieving pCR following neoadjuvant chemotherapy is associated with significantly improved EFS and overall survival, particularly for triple negative and HER2+ breast cancer.

• The similar outcomes with or without adjuvant chemotherapy in patients who attain pCR after neoadjuvant chemotherapy likely reflects tumor biology and suggests adjuvant chemotherapy could potentially be omitted.

• Further research is needed to evaluate the clinical utility of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response.
No survival benefit of chemotherapy escalation in patients with pCR and “high-immune” triple-negative early breast cancer in the neoadjuvant WSG-ADAPT-TN trial

Oleg Gluz1,2, Ulrike Nitz1,2, Cornelia Kolberg-Liedtke3, Aleix Prat4,5, Matthias Christgen6, Friedrich Feuerhake6, Madlen Garke7, Eva-Maria Grischke8, Helmut Forstbauer9, Michael Braun10, Mathias Warm11, John Hackmann12, Christoph Uller13, Bahriye Aktas14,15, Claudia Schumacher16, Sherko Kuemmel17, Enrico Pelz18, Daniel Gebauer18, Laia Paré4,5, Ronald Kates1, Rachel Wuerstlein1,19, Hans Heinrich Kreipe6, Nadia Harbeck1,19 on behalf of the ADAPT investigators

1 West German Study Group, Moenchengladbach, Germany; 2 Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany; 3 University Clinics Charité, Women’s Clinic, Berlin, Germany; 4 Department of Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain; 5 Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; 6 Hannover Medical School, Institute of Pathology, Hannover, Germany; 7 University Hospital Luebeck, Luebeck, Germany; 8 University Clinics Tuebingen, Women’s Clinic, Tuebingen, Germany; 9 Practice Network Troisdorf, Troisdorf, Germany; 10 Rotkreuz Clinics Munich, Breast Center, Munich, Germany; 11 City Hospital Holweide, Breast Center, Cologne, Germany; 12 Marien Hospital, Breast Center, Witten, Germany; 13 Practice of Gynecology and Oncology, Hildesheim, Germany; 14 University Clinics Essen, Women’s Clinic, Essen, Germany; 15 University Clinics Leipzig, Women’s Clinic, Leipzig, Germany; 16 St. Elisabeth Hospital, Breast Center, Cologne, Germany; 17 Clinics Essen Mitte, Breast Center, Essen, Germany; 18 Institute of Pathology Viersen, Viersen, Germany; 19 Breast Center, Dept. OB&GYN, University of Munich (LMU) and CCCLMU, Munich, Germany
ADAPT HR-/HER2-:
Trial Design

- Centrally confirmed TNBC (ER/PR<1%)
- cT1c-cT4c or cN+
- M0
- Adequate organ function
- n = 336

Standard chemotherapy (4xEC) recommended after surgery / 12-week biopsy (in case of clinical non-pCR)
ADAPT HR-/HER2-:
Translational Research Methods

- Sufficient tissue for TR in 306/336 patients
  - Tumor bank collective is representative
- Using the nCounter platform*:
  - Expression of 119 breast cancer-related genes and 5 housekeeping genes (ACTB, MRPL19, PSMC4, RPLP0 and SF3A1)
  - Basal and other subtypes by PAM50
  - Scores for Proliferation, HER2, ROR-S, ROR-P**, ER, and hypoxia
- sTILs were evaluated by pathologist (two-observer approach) on digital sections on H&E staining

---

1 Salgado et al. Ann Oncol 2014
* Nanostring Technologies, Seattle, WA, US
** Risk of relapse-subtype/proliferation
ADAPT HR-/HER2-: Superiority of Nab-Paclitaxel / Carboplatin for pCR and survival impact of pCR

Gluz et al. SABCS 2015 and JNCI 2018; Gluz et al. ASCO 2018

pCR; ypT0/is, ypN0) and total pCR (ypT0/ypN0) by treatment arms

Event-free survival by pCR status
ADAPT HR-/HER2-: Survival impact of Carboplatin vs. Gemcitabine-containing NACT

Gluz et al. ASCO 2018

Event-free survival

Overall survival

This presentation is the intellectual property of the WSG. Contact them at oleg.gluz@wsg-online.com for permission to reprint and/or distribute.
ADAPT HR-/HER2-: Survival impact of additional 4xEC in patients with pCR after 12 weeks of NACT

Event-free survival

Overall survival
ADAPT HR-/HER2-: Effect of additional 4xEC on EFS in patients with pCR after 12 weeks of NACT, by arm
### ADAPT HR-/HER2-: Predictive markers for pCR

<table>
<thead>
<tr>
<th>Marker</th>
<th>OR</th>
<th>LCL</th>
<th>UCL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>basal subtype (vs. other)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN (cN+ vs. cN0)</td>
<td>2.45</td>
<td>1.17</td>
<td>5.13</td>
<td>0.015</td>
</tr>
<tr>
<td>cT (cT2-4c vs. cT1)</td>
<td>0.73</td>
<td>0.42</td>
<td>1.26</td>
<td>0.260</td>
</tr>
<tr>
<td>sTIL's</td>
<td>0.46</td>
<td>0.29</td>
<td>0.75</td>
<td>0.002</td>
</tr>
<tr>
<td>ANGPTL4</td>
<td>1.85</td>
<td>1.21</td>
<td>2.81</td>
<td>0.004</td>
</tr>
<tr>
<td>CD8</td>
<td>0.69</td>
<td>0.46</td>
<td>1.04</td>
<td>0.080</td>
</tr>
<tr>
<td>CDC20</td>
<td>1.35</td>
<td>0.9</td>
<td>2.04</td>
<td>0.140</td>
</tr>
<tr>
<td>CENPF</td>
<td>1.27</td>
<td>0.84</td>
<td>1.9</td>
<td>0.250</td>
</tr>
<tr>
<td>EMP3</td>
<td>1.33</td>
<td>0.88</td>
<td>2</td>
<td>0.170</td>
</tr>
<tr>
<td>FGFR4</td>
<td>0.73</td>
<td>0.48</td>
<td>1.1</td>
<td>0.130</td>
</tr>
<tr>
<td>HER2 Score</td>
<td>0.48</td>
<td>0.31</td>
<td>0.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Ki-67 (IHC)</td>
<td>2.7</td>
<td>1.72</td>
<td>4.24</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

None of them was predictive for EFS benefit for carboplatin vs. gemcitabine-containing arm

<table>
<thead>
<tr>
<th>Marker</th>
<th>OR</th>
<th>LCL</th>
<th>UCL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROR_P</td>
<td>1.68</td>
<td>1.23</td>
<td>2.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ROR_S</td>
<td>1.92</td>
<td>1.26</td>
<td>2.94</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>TYMS</td>
<td>1.31</td>
<td>0.87</td>
<td>1.97</td>
<td>0.190</td>
</tr>
<tr>
<td>VEGFA</td>
<td>0.74</td>
<td>0.5</td>
<td>1.12</td>
<td>0.160</td>
</tr>
</tbody>
</table>

Contact them at oleg.gluz@wsg-online.com for permission to reprint and/or distribute.
ADAPT HR-/HER2-:
Prognostic markers for EFS

<table>
<thead>
<tr>
<th>continuous variables (*)</th>
<th>Univariable</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>LCL</td>
<td>UCL</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>sTILs</td>
<td>0.39</td>
<td>0.16</td>
<td>0.91</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Ki-67 (by IHC)</td>
<td>1.83</td>
<td>0.78</td>
<td>4.30</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>Proliferation score</td>
<td>1.41</td>
<td>0.55</td>
<td>3.65</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>ROR_P score</td>
<td>1.01</td>
<td>0.99</td>
<td>1.02</td>
<td>.59</td>
<td></td>
</tr>
<tr>
<td>ROR_S score</td>
<td>1.00</td>
<td>0.98</td>
<td>1.03</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>HER2 score</td>
<td>0.97</td>
<td>0.41</td>
<td>2.31</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>PD1</td>
<td>0.36</td>
<td>0.15</td>
<td>0.86</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>PDL1</td>
<td>0.50</td>
<td>0.21</td>
<td>1.19</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td>0.48</td>
<td>0.20</td>
<td>1.15</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>ANGPTL4</td>
<td>1.11</td>
<td>0.47</td>
<td>2.62</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>TYMS</td>
<td>1.20</td>
<td>0.78</td>
<td>1.86</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>binary variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN (cN+ vs. cN0)</td>
<td>1.77</td>
<td>1.29</td>
<td>2.42</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>cT (cT2-4c vs. cT1)</td>
<td>1.82</td>
<td>1.05</td>
<td>3.16</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>basal subype (vs. other)</td>
<td>1.12</td>
<td>0.61</td>
<td>2.05</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>pCR</td>
<td>0.24</td>
<td>0.11</td>
<td>0.49</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>interaction with pCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD1*pCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*) fractionally ranked: hazard ratios refer to 75th vs. 25th percentile
ADAPT HR-/HER2-: Prognostic impact of pCR and PD1 status

Event-free survival

- no pCR and pd1 low
- no pCR and pd1 high
- pCR and pd1 low
- pCR and pd1 high

$n$ at risk

- no pCR and pd1 low: 106, 101, 98, 84, 74, 63, 45, 24, 8
- no pCR and pd1 high: 91, 84, 79, 70, 63, 54, 35, 10, 2
- pCR and pd1 low: 49, 46, 45, 41, 35, 31, 22, 10, 3
- pCR and pd1 high: 60, 59, 58, 57, 55, 51, 38, 15, 0

$P > 0.001$

$P = 0.6$
ADAPT HR-/HER2-: Effect of additional chemotherapy (4xEC) according to PD1 status in patients with pCR

PD1 expression < median

PD1 expression ≥ median
ADAPT HR-/HER2-:
Conclusions

• In TNBC, due to an excellent efficacy and safety profile, 12 weeks of nab-paclitaxel/carboplatin seem to be a promising approach for chemotherapy de-escalation

• No predictive markers for survival benefit from carboplatin were identified by our exploratory analyses

• In TNBC, early pCR can be used to adapt further treatment (de-) escalation:
  • Patients with high baseline PD1 (by mRNA) seem to be ideal candidates for further investigation of de-escalated therapy approaches
  • In non-pCR, clinical factors (cN, Ki-67) have strong prognostic impact and may thus be suitable for further risk stratification
Efficacy results from GEICAM/2003-11_CIBOMA/2004-01 study: a randomized phase III trial assessing adjuvant capecitabine after standard chemotherapy for patients with early triple negative breast cancer

Professor Miguel Martin
Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, Madrid, Spain

Authors: Miguel Martín, Carlos H Barrios, Laura Torrecillas, Manuel Ruiz-Borrego, Jose Bines, Jose Segalla, Amparo Ruiz, Jose A García-Sáenz, Roberto Torres, Juan de la Haba, Elena García-Martínez, Henry L Gómez, Antonio Llombart, Maria Rodríguez de la Borbolla, José M Baena, Agustí Barnadas, Lourdes Calvo, Laura Pérez-Michel, Manuel Ramos, Javier Castellanos, Álvaro Rodríguez-Lescure, Jesús Cárdenas, Jeferson Vinholes, Eduardo Martínez de Dueñas, Maria J Godes, Miguel A Seguí, Antonio Antón, Pilar López-Álvarez, Jorge Moncayo, Gilberto Amorim, Esther Villar, Salvador Reyes, Carlos Sampaio, Bernardita Cardemil, Maria J Escudero, Susana Bezares, Eva Carrasco, Ana Lluch, on behalf of CIBOMA (Iberoamerican Coalition for Research in Breast Oncology), LACOG (Latin American Cooperative Oncology Group) and GEICAM Spanish Breast Cancer Group.

- 6 cycles of standard CT mandatory except for N0 tumors (4 cycles of AC allowed).
- Primary endpoint: Disease-Free Survival (DFS).
- Secondary endpoints: Overall Survival (OS), subgroup analyses, safety, biomarkers.

<table>
<thead>
<tr>
<th>Patient and Tumor Characteristics</th>
<th>Capecitabine (n=448)</th>
<th>Observation (n=428)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>50 (20-79)</td>
<td>49 (23-82)</td>
</tr>
<tr>
<td>Type of CT, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adjuvant (only)</td>
<td>353 (78.8)</td>
<td>352 (82.2)</td>
</tr>
<tr>
<td>• Neoadjuvant (+/- adjuvant)</td>
<td>89 (19.9)</td>
<td>75 (17.5)</td>
</tr>
<tr>
<td>• Missing data</td>
<td>6 (1.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>pCR in patients with neoadjuvant CT*, n (%)</td>
<td>22 (24.7)</td>
<td>19 (25.3)</td>
</tr>
<tr>
<td>CT regimens, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anthracyclines-based</td>
<td>147 (32.8)</td>
<td>138 (32.2)</td>
</tr>
<tr>
<td>• Anthracyclines and Taxanes-based</td>
<td>301 (67.2)</td>
<td>290 (67.8)</td>
</tr>
<tr>
<td>Nodal status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Negative</td>
<td>244 (54.5)</td>
<td>242 (56.5)</td>
</tr>
<tr>
<td>• 1–3 positive nodes</td>
<td>121 (27.0)</td>
<td>124 (29.0)</td>
</tr>
<tr>
<td>• ≥4 positive nodes</td>
<td>77 (17.2)</td>
<td>61 (14.3)</td>
</tr>
<tr>
<td>• Not available</td>
<td>6 (1.3)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
Disease-Free Survival (ITT)

Log-rank p-value: 0.135

Median follow-up: 7.34 years

<table>
<thead>
<tr>
<th>Group</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>105</td>
</tr>
<tr>
<td>Observation</td>
<td>120</td>
</tr>
</tbody>
</table>

HR: 0.82 (95% CI: 0.63, 1.06, p=0.136)

Adjusted HR*: 0.79 (95% CI: 0.61, 1.03, p=0.082)

*Adjusted HR for stratification variables: Spain vs. LA, previous neo/adjuvant treatment (anthracyclines vs. anthracyclines and taxanes), number of involved nodes (0 vs. 1-3 vs. ≥4) and TN phenotype by IHC (basal vs. non-basal).

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>448</td>
<td>428</td>
</tr>
<tr>
<td>1</td>
<td>396</td>
<td>379</td>
</tr>
<tr>
<td>2</td>
<td>365</td>
<td>347</td>
</tr>
<tr>
<td>3</td>
<td>344</td>
<td>329</td>
</tr>
<tr>
<td>4</td>
<td>334</td>
<td>313</td>
</tr>
<tr>
<td>5</td>
<td>323</td>
<td>290</td>
</tr>
<tr>
<td>6</td>
<td>304</td>
<td>262</td>
</tr>
<tr>
<td>7</td>
<td>248</td>
<td>204</td>
</tr>
<tr>
<td>8</td>
<td>154</td>
<td>123</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Overall Survival (ITT)

Log-rank p-value: 0.623
Median follow-up: 7.34 years

<table>
<thead>
<tr>
<th>Group</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>71</td>
</tr>
<tr>
<td>Observation</td>
<td>73</td>
</tr>
</tbody>
</table>

HR: 0.92 (95% CI: 0.66, 1.28)

Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>448</th>
<th>417</th>
<th>393</th>
<th>367</th>
<th>354</th>
<th>347</th>
<th>324</th>
<th>267</th>
<th>170</th>
<th>71</th>
<th>24</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>428</td>
<td>407</td>
<td>375</td>
<td>350</td>
<td>339</td>
<td>318</td>
<td>296</td>
<td>232</td>
<td>145</td>
<td>73</td>
<td>28</td>
<td>2</td>
</tr>
</tbody>
</table>

Overall Survival Probability

86.2%
Subgroup Analysis of DFS (ITT)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Subgroup</th>
<th>Hazard Ratio</th>
<th>No. of events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>n=876 (100%)</td>
<td>0.819 (0.630-1.065)</td>
<td>Capecit. 105</td>
<td>Observ. 120</td>
</tr>
<tr>
<td>Menopausal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>276 (32)</td>
<td>0.686 (0.408-1.153)</td>
<td>24 35</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>600 (68)</td>
<td>0.867 (0.639-1.176)</td>
<td>81 85</td>
<td></td>
</tr>
<tr>
<td>Phenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>628 (72)</td>
<td>0.942 (0.697-1.272)</td>
<td>84 86</td>
<td></td>
</tr>
<tr>
<td>Non-basal</td>
<td>248 (28)</td>
<td>0.530 (0.307-0.913)</td>
<td>21 34</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>164 (19)</td>
<td>1.006 (0.586-1.727)</td>
<td>29 24</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>705 (80)</td>
<td>0.747 (0.552-1.012)</td>
<td>74 96</td>
<td></td>
</tr>
<tr>
<td>Type of CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>285 (33)</td>
<td>0.884 (0.551-1.418)</td>
<td>33 36</td>
<td></td>
</tr>
<tr>
<td>No taxanes</td>
<td>591 (67)</td>
<td>0.798 (0.583-1.093)</td>
<td>72 84</td>
<td></td>
</tr>
<tr>
<td>N0 vs. N+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>444 (51)</td>
<td>0.685 (0.445-1.057)</td>
<td>34 52</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>420 (49)</td>
<td>0.878 (0.628-1.228)</td>
<td>70 67</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>532 (61)</td>
<td>0.750 (0.534-1.053)</td>
<td>60 75</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>344 (39)</td>
<td>0.934 (0.618-1.413)</td>
<td>45 45</td>
<td></td>
</tr>
</tbody>
</table>

Capecitabine Observation

<-Capecitabine Observation->
Subgroup Analysis of DFS (ITT)

Basal (EGFR and/or CK5/6 positive)

Log-rank p-value: 0.696
HR: 0.94 (95% CI: 0.70, 1.27)

Non-basal (EGFR and CK5/6 negative)

Log-rank p-value: 0.020
HR: 0.53 (95% CI: 0.31, 0.91)

Group | Events | Group | Events
---|---|---|---
Capecitabine | 84 | Capecitabine | 21
Observation | 86 | Observation | 34

Number of patients at risk

Cape. | 329 | 119 | 110 | 318 | 110 | 3
| 290 | 106 | 92 | 287 | 84 | 2
| 266 | 99 | 84 | 274 | 77 | 7
| 274 | 97 | 76 | 241 | 71 | 67
| 232 | 93 | 71 | 223 | 62 | 50
| 223 | 91 | 70 | 186 | 62 | 21
| 126 | 93 | 67 | 52 | 33 | 9
| 52 | 14 | 28 | 14 | 3 | 3

Obs. | 318 | 310 | 310 | 318 | 310 | 3
| 287 | 287 | 287 | 287 | 287 | 3
| 263 | 263 | 263 | 263 | 263 | 3
| 252 | 252 | 252 | 252 | 252 | 3
| 237 | 237 | 237 | 237 | 237 | 3
| 219 | 219 | 219 | 219 | 219 | 3
| 195 | 195 | 195 | 195 | 195 | 3
| 154 | 154 | 154 | 154 | 154 | 3
| 102 | 102 | 102 | 102 | 102 | 3
| 49 | 49 | 49 | 49 | 49 | 3
| 22 | 22 | 22 | 22 | 22 | 3

p-value interaction test: 0.0694
Subgroup Analysis of OS (ITT)

Basal (EGFR and/or CK5/6 positive)

- OS Probability: 84.9%
- Log-rank p-value: 0.286

- Capecitabine: 58 Events
- Observation: 46 Events

HR: 1.23 (95% CI: 0.84, 1.82)

Non-basal (EGFR and CK5/6 negative)

- OS Probability: 89.5%
- Log-rank p-value: 0.007

- Capecitabine: 13 Events
- Observation: 27 Events

HR: 0.42 (95% CI: 0.21, 0.81)

Number of patients at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Cape.</th>
<th>Obs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>329, 307, 286, 263, 256, 249, 238, 200, 139, 64</td>
<td>318, 301, 284, 268, 259, 242, 223, 179, 123, 64</td>
</tr>
<tr>
<td>Observation</td>
<td>307, 286, 263, 256, 249, 238, 200, 139, 64, 21</td>
<td>318, 301, 284, 268, 259, 242, 223, 179, 123, 64</td>
</tr>
</tbody>
</table>

Number of patients at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Cape.</th>
<th>Obs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>119, 110, 107, 104, 98, 86, 67, 31, 8, 3</td>
<td>110, 106, 91, 82, 80, 76, 73, 53, 22, 9, 3</td>
</tr>
<tr>
<td>Observation</td>
<td>110, 106, 91, 82, 80, 76, 73, 53, 22, 9, 3</td>
<td>110, 106, 91, 82, 80, 76, 73, 53, 22, 9, 3</td>
</tr>
</tbody>
</table>

p-value interaction test: 0.0052
Conclusions

• This study failed to show a statistically significant increase in DFS by adding capecitabine to standard neo/adjuvant chemotherapy in early TNBC:
  — 5-year DFS with capecitabine vs observation: 79.6% vs 76.8% (\( \Delta 2.8\% \), HR: 0.82, p=0.14, adjusted HR: 0.79, p=0.082).

• In a prospective subset analysis, TNBC patients with non-basal like phenotype (IHC) had a statistically significant increase in DFS and OS with extended adjuvant capecitabine:
  — 5-year DFS with capecitabine vs observation: 82.6% vs 72.9% (HR 0.53, p=0.02, \( \Delta 9.7\% \)).
  — 5-year OS with capecitabine vs observation: 89.5% vs 79.6% (HR 0.42, p=0.007, \( \Delta 9.9\% \)).

• Tolerance of extended adjuvant capecitabine was as expected, with a median dose intensity of 86.3% and 75.2% of patients completing the planned 8 cycles.
IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + nab-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

Leisha A. Emens,1 Sherene Loi,2 Hope S. Rugo,3 Andreas Schneeweiss,4 Véronique Diéras,5 Hiroji Iwata,6 Carlos H. Barrios,7 Marina Nechaeva,8 Luciana Molinero,9 Anh Nguyen Duc,10 Roel Funke,9 Stephen Y Chui,9 Amreen Husain,10 Eric P. Winer,11 Sylvia Adams,12 Peter Schmid13

1UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; 2Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; 3University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; 4University Hospital Heidelberg, Heidelberg, Germany; 5Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; 6Aichi Cancer Center Hospital, Aichi, Japan; 7Department of Medicine, PUCRS School of Medicine, Porto Alegre, Brazil; 8Arkhangelsk Regional Clinical Oncology Dispensary, Arkhangelsk, Russia; 9Genentech, Inc., South San Francisco, CA; 10F. Hoffmann-La Roche AG, Basel, Switzerland; 11Dana-Farber Cancer Institute, Boston, MA; 12New York University Langone Medical Center, New York, NY; 13Barts Cancer Institute, Queen Mary University of London, London, UK
IMpassion130 study design:
Prespecified analyses in the ITT and PD-L1 IC+ population

Phase III study IMpassion130

Previously untreated metastatic or inoperable locally advanced TNBC
N = 902 patients randomized

Stratification factors:
1. Prior taxane use
2. Liver metastases
3. PD-L1 on IC

Atezo + nab-P arm

Plac + nab-P arm

Key study endpoints
- Co-primary: PFS (ITT and PD-L1 IC+)
  OS (ITT and PD-L1 IC+)
- Secondary: ORR and DOR
- Safety and tolerability

ITT population: n = 451
PD-L1 IC+ patients: n = 185 (41%)

ITT population: n = 451
PD-L1 IC+ patients: n = 184 (41%)

Double blind; no crossover

R 1:1

- NCT02425891. * Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.

- N = 902 patients randomized

- PD-L1 IC+ patients: n = 185 (41%)

- ITT population: n = 451

- PD-L1 IC+ patients: n = 184 (41%)

- R 1:1

- Stratifiation factors:
  1. Prior taxane use
  2. Liver metastases
  3. PD-L1 on IC

- Key study endpoints
  - Co-primary: PFS (ITT and PD-L1 IC+)
    OS (ITT and PD-L1 IC+)
  - Secondary: ORR and DOR
  - Safety and tolerability

- Phase III study IMpassion130

- Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
IMpassion130 primary analysis\textsuperscript{1,2}: Clinically meaningful PFS and OS benefit in the PD-L1+ population

**ITT population**

- **ITT PFS**
  - Stratified HR, 0.80
  - (95% CI: 0.69, 0.92)
  - \( P = 0.0025 \)
  - Median follow-up (ITT): 12.9 months.

- **ITT OS**
  - Stratified HR, 0.84
  - (95% CI: 0.69, 1.02)
  - \( P = 0.0840\textsuperscript{b} \)
  - Median follow-up (ITT): 12.9 months.

**PD-L1+ population\textsuperscript{a}**

- **PD-L1+ PFS**
  - Stratified HR, 0.62
  - (95% CI: 0.49, 0.78)
  - \( P < 0.0001 \)

- **PD-L1+ OS**
  - Stratified HR, 0.62
  - (95% CI: 0.45, 0.86)\textsuperscript{c}

\textsuperscript{a}PD-L1+: PD-L1 in ≥ 1% of IC.
\textsuperscript{b}Not significant.
\textsuperscript{c}Not formally tested per hierarchical study design.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program GS1-04).
IMpassion130 biomarker analyses

- Pre-existing immune biology, including PD-L1 expression on TC, CD8+ T cells and stromal TILs, has also been associated with clinical benefit from anti–PD-L1/PD-1\(^1,2\)

- In this exploratory analysis, we sought to evaluate whether this immune biology and \textit{BRCA1/2} mutation status were associated with clinical benefit from atezolizumab + \textit{nab}-paclitaxel

- Biomarkers were centrally analyzed in pre-treatment biopsies
  - PD-L1 on IC and TC by VENTANA SP142 IHC assay\(^a\)
  - Intratumoral CD8+ T cells by IHC (Dako clone C8/144B) and stromal TILs by H&E\(^b\)
  - \textit{BRCA1/2} mutation status by FoundationOne assay

---

\[\text{PD-L1 IHC (SP142) Assay by Ventana Medical Systems}\]

\begin{tabular}{l|l}
<table>
<thead>
<tr>
<th>PD-L1 on IC</th>
<th>PD-L1 on TC</th>
</tr>
</thead>
</table>
\end{tabular}

\(\text{PD-L1 IHC (SP142) Assay by Ventana Medical Systems}\)

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

---

\(\text{H&E, hematoxylin and eosin staining; IHC, immunohistochemistry.}\)

\(^a\) PD-L1 scoring: IC0: < 1%; IC1: \(\geq 1\%\) and < 5%; IC2: \(\geq 5\%\) and < 10%; IC3: \(\geq 10\%\); TC-: < 1% PD-L1 on tumor cells; TC+: \(\geq 1\%\) PD-L1 on tumor cells.

\(^b\) Pre-specified cutoffs for CD8 IHC and stromal TILs are based on references 1 and 2.

In IMpassion130, PD-L1 in TNBC is expressed mainly on tumor-infiltrating immune cells.

**Prevalence of PD-L1 IC subgroups**
- PD-L1 IC+ (IC1/2/3) 41%
- PD-L1 IC– (IC0) 59%

**Prevalence of PD-L1 TC subgroups**
- PD-L1 TC+ 9%
- PD-L1 TC– 91%

The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population.

BEP: biomarker-evaluable population.
BEP (TC): n = 900. PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC+: ≥ 1% PD-L1 on tumor cells; TC–: < 1% PD-L1 on tumor cells.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + nab-paclitaxel

Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values except for PD-L1 IC+ PFS are nominal P values. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + nab-paclitaxel

Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values except for PD-L1 IC+ PFS are nominal P values. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant.

PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel.

PD-L1 IC status (positive vs negative) predicts PFS benefit with atezolizumab + nab-paclitaxel

- Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values except for PD-L1 IC+ PFS are nominal P values. Data cutoff: April 17, 2018.
• A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant

• PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values are nominal. Data cutoff: April 17, 2018.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant.

PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel.

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values are nominal. Data cutoff: April 17, 2018.
A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant.

PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel.

Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All P values are nominal. Data cutoff: April 17, 2018.
Consistent clinical benefit with atezolizumab + nab-paclitaxel was observed across all PD-L1 IC+ subgroups

<table>
<thead>
<tr>
<th>PD-L1 IC Status</th>
<th>n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC0</td>
<td>532</td>
<td>A + nP: 5.6</td>
<td>P + nP: 5.6</td>
<td>0.93 (0.77, 1.12)</td>
</tr>
<tr>
<td>IC1</td>
<td>243</td>
<td>A + nP: 7.4</td>
<td>P + nP: 3.9</td>
<td>0.59 (0.44, 0.78)</td>
</tr>
<tr>
<td>IC2/3</td>
<td>125</td>
<td>A + nP: 9.3</td>
<td>P + nP: 5.7</td>
<td>0.64 (0.42, 0.97)</td>
</tr>
<tr>
<td>All</td>
<td>900</td>
<td>A + nP: 7.2</td>
<td>P + nP: 5.5</td>
<td>0.79 (0.68, 0.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.02 (0.79, 1.31)</td>
<td>0.90</td>
</tr>
<tr>
<td>0.56 (0.38, 0.82)</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>0.71 (0.39, 1.30)</td>
<td>0.26</td>
</tr>
<tr>
<td>0.83 (0.68, 1.02)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Adjusted for prior taxane treatment and liver metastases.
A multivariate analysis was performed to account for imbalances in baseline characteristics between PD-L1 IC–expressing subgroups (IC1, IC2 and IC3).
IC0: < 1% PD-L1; IC1: ≥ 1% and < 5% PD-L1; IC2/3: ≥ 5% PD-L1. All P values are nominal. Data cutoff: April 17, 2018.
CD8+ IHC has clinical benefit if co-occurring with PD-L1 IC+

<table>
<thead>
<tr>
<th>CD8−/PD-L1 IC+ (n = 37)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.33 (0.13, 0.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>OS</td>
<td>0.25 (0.06, 1.02)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD8+/PD-L1 IC+ (n = 280)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.61 (0.46, 0.80)</td>
<td>≤ 0.005</td>
</tr>
<tr>
<td>OS</td>
<td>0.55 (0.38, 0.80)</td>
<td>≤ 0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD8+/PD-L1 IC− (n = 220)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.89 (0.66, 1.20)</td>
<td>0.45</td>
</tr>
<tr>
<td>OS</td>
<td>0.77 (0.50, 1.17)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* PD-L1 IC+ are enriched in CD8+ (P < 0.0001) and CD8+ are enriched in PD-L1 IC+ (P < 0.0001)*

* Patients with CD8+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+

**BEP (CD8):** n = 720. A CD8+ cutoff of 0.5% was selected based on Phase Ib study in TNBC (Adams JAMA Oncol 2018). All P values are nominal.

* Data derived from contingency table with Fisher exact tests.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+

- **TIL−/PD-L1 IC+** (n = 176)
  - **PFS**: HR (95% CI) 0.74 (0.54, 1.03), P Value 0.07
  - **OS**: HR (95% CI) 0.65 (0.41, 1.02), P Value 0.06

- **TIL+/PD-L1 IC+** (n = 190)
  - **PFS**: HR (95% CI) 0.53 (0.38, 0.74), P Value ≤ 0.005
  - **OS**: HR (95% CI) 0.57 (0.35, 0.92), P Value 0.02

- **TIL+/PD-L1 IC−** (n = 94)
  - **PFS**: HR (95% CI) 0.99 (0.62, 1.57), P Value 0.97
  - **OS**: HR (95% CI) 1.53 (0.76, 3.08), P Value 0.24

* TIL+ were enriched for PD-L1 IC+ (P < 0.0001) but PD-L1 IC+ were not enriched for TIL+ (P = ns)
* Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+

---

BEP (TILs): n = 893. Cutoff of 10% was used to distinguish low vs intermediate/high levels of TILs (Denkert Lancet Oncol 2018). All P values are nominal.

* Data derived from contingency table with Fisher exact test.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)
The clinical benefit derived by PD-L1 IC+ patients was independent of their \textit{BRCA1/2} mutation status

- \textit{BRCA1/2} mutants and PD-L1 IC+ are independent from each other \((P = \text{ns})^a\)
- \textit{Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+}^b

\begin{align*}
\text{BRCA1/2 non-mut/PD-L1 IC+ (n = 257)} & \quad \text{BRCA1/2 mut/PD-L1 IC– (n = 44)} \\
\text{HR (95% CI)} & \quad \text{HR (95% CI)} \\
PFS & 0.63 (0.48, 0.83) \quad & \text{PFS} & 0.77 (0.37, 1.61) \quad \leq 0.005 \quad & 0.49 \\
\text{OS} & 0.62 (0.43, 0.91) \quad & \text{OS} & 0.85 (0.29, 2.43) \quad & 0.76 \\
\end{align*}

\begin{align*}
\text{BRCA1/2 mut/PD-L1 IC+ (n = 45)} \\
\text{HR (95% CI)} & \quad \text{P Value} \\
PFS & 0.45 (0.21, 0.96) \quad & 0.04 \\
\text{OS} & 0.87 (0.26, 2.85) \quad & 0.82 \\
\end{align*}

\footnotesize{BEP (BRCA1/2): n = 612. Per FoundationOne BRCA1/2 testing, BRCA1/2 mutant: known and likely mutations. All P values are nominal.}  
\footnotesize{a Data derived from contingency table with Fisher exact tests.} \footnotesize{b Data interpretation limited by small number of \textit{BRCA1/2}-mutant patients.}  

\footnotesize{Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)}
Conclusions

• In the Phase III IMpassion130 study, PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + nab-paclitaxel treatment for mTNBC
  • PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1% (by VENTANA SP142 IHC assay)
  • A treatment effect was not seen for adding atezolizumab to chemotherapy in the PD-L1–negative subgroup

• PD-L1 expression on TC did not provide additional information beyond PD-L1 IC status
  • Prevalence of tumor-cell PD-L1 expression was low, and the majority of these tumors were also PD-L1 IC+

• PD-L1 IC expression was the best predictor of clinical benefit as the patient subgroups with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T cells (CD8+) derived clinical benefit with atezolizumab + nab-paclitaxel if their tumors were also PD-L1 IC+

• PFS and OS results were consistent regardless of BRCA1/2 mutation status

• Patients with newly diagnosed metastatic and unresectable locally advanced TNBC should be routinely tested for PD-L1 IC status to determine whether they might benefit from atezolizumab + nab-paclitaxel
Monday morning implications

- Adjuvant chemotherapy for TNBC should be started **within 30 days** of surgery where possible
  - Suggests use of neo-adjuvant chemotherapy may be optimal where appropriate?

- “Adjuvant” chemotherapy not indicated in patients with TNBC who achieve a PCR
  - Biomarkers will be useful (PD-1)
  - Capecitabine not effective in “adjuvant” setting (but this is not the same patient population as in CREATE-X)
  - Therapy de-escalation based on PCR requires further validation

- Addition of atezolizumab to nab-paclitaxel efficacy appears restricted to PD-L1 IC expressing cancers
  - Further combinations with chemotherapy and other agents, including PARP inhibitors, awaited
NO SHORTS