Neoadjuvant/adjuvant chemotherapy and biological agents

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SIC – Interdisciplinary Cancer Service
ESO Deputy Scientific Director

8th ESO Masterclass ARAB AND SOUTHERN EUROPEAN COUNTRIES
Outline

- Principles of neoadjuvant systemic therapy
- Deescalating adjuvant chemotherapy
- Biological agents- adjuvant anti-Her2 therapy
Heterogeneity of candidates for neoadjuvant therapy

Stage IIA
- Locally Advanced
- T3, N1
- Goal is to convert to operability

Stage IIB
- Operable: goal is to conserve the breast
- T3, N1
- T2, N0-1

Stage IIIC
- T4, N1, N2
- Goal is to conserve the breast
The NSABP data
OPERABLE breast cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>cCR</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-18</td>
<td>36%</td>
<td>13%</td>
</tr>
<tr>
<td>4 x AC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=1506</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-27</td>
<td>60%</td>
<td>26%</td>
</tr>
<tr>
<td>4 x AC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ 4x Docetaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=2411</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Neoadjuvant pCR Metaanalysis

- Patients achieving pCR have better outcome (DFS, OS)
- Her2 + and TNBC have the highest pCR
- Definition of pCR: eradication of invasive cancer from breast and axilla, no M1
  - DCIS not prognostically important
  - dichotomous: either pCR, or NOT
- BUT: predictive value is good, not great
  - 15-20% of pCR relapse/die
  - 40-50% non pCR never relapse

Cortazar et al, Lancet 2014; 384:164-172
The Panel strongly endorsed the use of NST as the preferred approach to stage 2 or 3 TNBC and HER2 positive tumors.
Evaluation prior to primary systemic therapy

- Clinical examination:
  - Clinical size of tumor
  - Skin changes: erythema, edema, ulceration, and dimpling
  - Lymph node status
- Photo documentation (inflammatory, T4's...)
- Elicitation of symptoms suggestive for distant metastasis
- Natural history of the disease (rapid growing <6 months versus neglected tumor to differentiate T4d from T4b)
Evaluation prior to primary systemic therapy

BEFORE starting any therapy, a core biopsy providing histology and biomarker (ER, PR, HER-2, proliferation/grade) expression is indispensable to guide treatment decisions. (LoE: I B) (97%)

- Adequate breast imaging: extent of disease
  - Mammography
  - Ultrasound for T and N (FNA of suspicious nodes)
  - MRI if available for response assessment

Since LABC patients have a significant risk of metastatic disease, a full staging workup, including a complete history, physical examination, lab tests and imaging of chest and abdomen (preferably CT) and bone, prior to initiation of systemic therapy is highly recommended. (LoE: I B) (100%)

PET-CT, if available, may be used (instead of and not on top of CTs & bone scan). (LoE: II B) (100%)
NOAH: trastuzumab in the neoadjuvant setting in ErbB2+ LABC

ErbB2+ LABC
IHC 3+ or FISH positive
n=115

ErbB2-negative LABC
IHC 1+ or 0
n=99

T + AP q3w x 3
AP q3w x 3
Surgery followed by RTx
T continued q3w to week 52

T + P q3w x 4
P q3w x 4
Surgery followed by RTx

T q3w x 4 + CMF q4w x 3
CMF q4w x 3
Surgery followed by RTx

RTx = radiation therapy; T, Trastuzumab; A, doxorubicin; P, paclitaxel; R, randomise.
NOAH, the NeoAdjuvant Herceptin study; q, every; IHC, immunohistochemical staining; FISH, fluorescence in-situ hybridisation; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.

Neoadjuvant NOAH
Event-Free Survival

Gianni et al. Lancet 375(9714), 2010
Dual HER2 Blockade with Taxanes, Trastuzumab and Pertuzumab

NeoSphere Study Design

- TH (n = 107) docetaxel + trastuzumab
- THP (n = 107) docetaxel + trastuzumab + pertuzumab
- HP (n = 107) trastuzumab + pertuzumab
- TP (n = 96) docetaxel + pertuzumab

SURGERY

- TH: FEC q3w x 3 Trastuzumab q3w cycles 5-17
- THP: FEC q3w x 3 Trastuzumab q3w cycles 5-17
- HP: Docetaxel q3w x 4 → FEC q3w x 3 Trastuzumab q3w cycles 5-17
- TP: FEC q3w x 3 Trastuzumab q3w cycles 5-21

TRYPHAENA: Study Design

- Cycles 1-3: FEC, Pertuzumab + trastuzumab
- Cycles 4-6: Docetaxel + Pertuzumab + trastuzumab

Study dosing q3w:
- FEC: 500 mg/m², 106 mg/m², 660 mg/m²
- Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)
- Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
- Pertuzumab: 940 mg loading dose, 420 mg maintenance
- Carboplatin: ATC 6

胸前壁，乳腺癌，HER2阳性，化疗，新辅助治疗

- HER2-positive EBC patients (n = 529)
- TH: FEC q3w x 3 Trastuzumab q3w cycles 5-17
- THP: FEC q3w x 3 Trastuzumab q3w cycles 5-17
- HP: Docetaxel q3w x 4 → FEC q3w x 3 Trastuzumab q3w cycles 5-17
- TP: FEC q3w x 3 Trastuzumab q3w cycles 5-21

Progression-free survival (%)
- tpCR: 94 (41)
- No tpCR: 323 (23)

Surgery

- Cycles 1-3: FEC, Pertuzumab + trastuzumab
- Cycles 4-6: Docetaxel + Pertuzumab + trastuzumab

Trastuzumab to complete 1 year

- HER2-positive EBC patients (n = 529)
- TH: FEC q3w x 3 Trastuzumab q3w cycles 5-17
- THP: FEC q3w x 3 Trastuzumab q3w cycles 5-17
- HP: Docetaxel q3w x 4 → FEC q3w x 3 Trastuzumab q3w cycles 5-17
- TP: FEC q3w x 3 Trastuzumab q3w cycles 5-21

Surgery
Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>OR (95% CI)</th>
<th>Platinum</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEICAM/2006-03</td>
<td>2012</td>
<td>0.97 (0.40, 2.35)</td>
<td>14/47</td>
<td>14/46</td>
</tr>
<tr>
<td>GeparSixto GBG66</td>
<td>2014</td>
<td>1.78 (1.14, 2.78)</td>
<td>90/158</td>
<td>67/157</td>
</tr>
<tr>
<td>CALGB 40603 Alliance</td>
<td>2014</td>
<td>1.68 (1.15, 2.45)</td>
<td>119/221</td>
<td>87/212</td>
</tr>
<tr>
<td>UMIN000003355</td>
<td>2014</td>
<td>4.60 (1.72, 12.27)</td>
<td>23/37</td>
<td>10/38</td>
</tr>
<tr>
<td>Aguilar Martinez et al.</td>
<td>2015</td>
<td>2.38 (0.85, 6.64)</td>
<td>18/30</td>
<td>12/31</td>
</tr>
<tr>
<td>NCT01276769</td>
<td>2016</td>
<td>3.88 (1.35, 11.15)</td>
<td>17/44</td>
<td>6/43</td>
</tr>
<tr>
<td>GeparOcco GBG84</td>
<td>2017</td>
<td>1.14 (0.77, 1.68)</td>
<td>105/203</td>
<td>97/200</td>
</tr>
<tr>
<td>WSG-ADAPT</td>
<td>2018</td>
<td>2.11 (1.33, 3.35)</td>
<td>67/146</td>
<td>51/178</td>
</tr>
<tr>
<td>BrighT Necss</td>
<td>2018</td>
<td>3.01 (1.90, 4.77)</td>
<td>92/160</td>
<td>49/158</td>
</tr>
</tbody>
</table>

Random effect (I-squared = 56.3%, p = 0.019) | 1.96 (1.46, 2.62) | 545/1046 | 393/1063
Platinum in the neo-adjuvant setting for BRCA+

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>pCR</th>
<th>DFS (med f/u – 35 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparSixto</td>
<td>Liposomal Doxorubicin + Paclitaxel +/-Carboplatin*</td>
<td>wtBRCA (n=241) 36.4% vs 55% p=0.004</td>
<td>73.5% vs 85.3% p=0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA+ (n=50) 66.7% vs 65.4% p=0.92</td>
<td>82.5% vs 86% NS</td>
</tr>
</tbody>
</table>

* Also randomization to bevacizumab

BrightNess
Paclitaxel +/-Carboplatin +/-Veliparib
→ ACx4
No outcome data

Loibl et al, Lancet Oncology, 2018

Hahnen et al, JAMA Oncology, 2017

<table>
<thead>
<tr>
<th>Germline BRCA status</th>
<th>Paclitaxel + carboplatin + veliparib</th>
<th>Paclitaxel + carboplatin + veliparib placebo</th>
<th>Paclitaxel + carboplatin placebo + veliparib placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>168/316 (53%)</td>
<td>92/160 (58%)</td>
<td>49/158 (31%)</td>
</tr>
<tr>
<td>Mutation in BRCA1 or BRCA2, or both</td>
<td>26/46 (57%)</td>
<td>12/24 (50%)</td>
<td>9/22 (41%)</td>
</tr>
<tr>
<td>No mutation in BRCA1 or BRCA2, or both</td>
<td>142/270 (53%)</td>
<td>80/136 (59%)</td>
<td>40/136 (29%)</td>
</tr>
<tr>
<td></td>
<td>AC-T</td>
<td>Platinum+</td>
<td>IO</td>
</tr>
<tr>
<td>----------------------</td>
<td>------</td>
<td>-----------</td>
<td>----</td>
</tr>
<tr>
<td>Poggio F et al.</td>
<td>47%</td>
<td>52%</td>
<td>-</td>
</tr>
<tr>
<td>Ann Oncol 2018</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
## CORALLEEN trial Design

### Key secondary endpoints at surgery

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy n=52</th>
<th>Ribociclib + letrozole n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>95% IC</td>
</tr>
<tr>
<td>ROR score median (IQR)</td>
<td>25 (12.0-45.0)</td>
<td></td>
</tr>
<tr>
<td>Central Ki67 IHC median (IQR)</td>
<td>10 (3.0-20.0)</td>
<td></td>
</tr>
<tr>
<td>RCB 0-1 rate</td>
<td>6 (11.8%)</td>
<td>4.5-27.8</td>
</tr>
<tr>
<td>pCR rate</td>
<td>3 (5.8%)</td>
<td>1.4-16.6</td>
</tr>
<tr>
<td>PEPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (17.3%)</td>
<td>8.6-31.4</td>
</tr>
<tr>
<td>1-3</td>
<td>24 (46.1%)</td>
<td>33.6-62.6</td>
</tr>
<tr>
<td>≥4</td>
<td>17 (32.7%)</td>
<td>21.2-48.7</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (3.9%)</td>
<td></td>
</tr>
</tbody>
</table>

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CREATE-X: Trial Design

HER2-
NAC Surgery
Pathology Non-pCR or node + (n=900)

Control:
Standard therapy
Standard therapy + Capecitabine

Subgroup Analysis for DFS

### Category (n) HR (95%CI)

<table>
<thead>
<tr>
<th>Total (885)</th>
<th>0.70 (0.53-0.93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age -50 (531)</td>
<td>0.72 (0.50-1.03)</td>
</tr>
<tr>
<td>50- (354)</td>
<td>0.68 (0.45-1.04)</td>
</tr>
<tr>
<td>HR+ (561)</td>
<td>0.84 (0.57-1.23)</td>
</tr>
<tr>
<td>HR- (296)</td>
<td>0.58 (0.39-0.87)</td>
</tr>
<tr>
<td>ypNO (345)</td>
<td>0.88 (0.48-1.62)</td>
</tr>
<tr>
<td>ypN1 (339)</td>
<td>0.54 (0.36-0.83)</td>
</tr>
<tr>
<td>ypN2 or 3 (199)</td>
<td>0.82 (0.52-1.39)</td>
</tr>
<tr>
<td>Path grade 0-1b (482)</td>
<td>0.63 (0.45-0.88)</td>
</tr>
<tr>
<td>by NAC 2,3 (385)</td>
<td>0.84 (0.52-1.34)</td>
</tr>
<tr>
<td>Taxane + (849)</td>
<td>0.70 (0.53-0.93)</td>
</tr>
<tr>
<td>(36)</td>
<td>0.87 (0.12-6.24)</td>
</tr>
<tr>
<td>SFU containing + (529)</td>
<td>0.74 (0.52-1.04)</td>
</tr>
<tr>
<td>- (356)</td>
<td>0.65 (0.42-1.02)</td>
</tr>
<tr>
<td>Japanese (599)</td>
<td>0.74 (0.53-1.02)</td>
</tr>
<tr>
<td>Korean (286)</td>
<td>0.63 (0.37-1.05)</td>
</tr>
</tbody>
</table>

Free Survival

| 5yr DFS | 74.1% Capecitabine |
| 67.7% Control |

Capcitabine better
Control better

*General rules for clinical and pathological recording of breast cancer, from the Japanese breast cancer society
KATHERINE Trial: Phase III Trial of T-DM1 vs Trastuzumab in Patients with HER2+ Breast Cancer with Residual Disease after Preop Therapy

**Preop Therapy:**
- At least 6 cycles, including at least 9 weeks of taxane and trastuzumab

**Surgery:**
- Residual tumor in breast or axilla

**Primary endpoints:** invasive DFS

**Unstratified hazard ratio for disease recurrence or death:**
- T-DM1: 0.50 (95% CI, 0.39–0.64)
- Trastuzumab: 0.70 (95% CI, 0.47–1.05)

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of Events (%)</th>
<th>3-Yr Invasive Disease–free Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1</td>
<td>743</td>
<td>91 (12.2)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>743</td>
<td>165 (22.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1</td>
<td>743 707 681 658 633 561 409 255 142 44 4</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>743 676 635 594 555 501 342 220 119 38 4</td>
</tr>
</tbody>
</table>

**Overall Survival (%):**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1</td>
<td>743</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>743</td>
</tr>
</tbody>
</table>

Take Home Messages: Neoadjuvant Therapy

- Systemic therapy is the first indication for stage II and III (majority of patients!)
- Anthra plus taxanes = standard backbone
- pCR is prognostic
- Use platinum in TNBC ( ? BRCA mutated maybe not?)
- Anti-Her2 primary therapy: use trastuzumab! (plus pertuzumab if reimbursed)
- Taxane alone might be acceptable (if double blockade)
- Post-neoadjuvant T-DM1 for residual disease
- Unsolved questions:
  - Who needs double blockade, and which one?
  - Do pCR patients need adjuvant anti-Her2 therapy?
  - is CT always needed? which one (T versus A and T)?
Chemotherapy Update: EBCTCG Overview Data

**Taxanes > Anthra > CMF > No Chemo**

- **Control**: 36.4%  
  - **4.2%**
- **CMF**: 32.2%  
  - **4.3%**
- **Anthra**: 27.0%  
  - **5.1%**
- **CMF**: 31.3%

- **Taxane**: 25.9%

---

EBCTCG 2005-06 Overview Peto SABCS 2007
Adjuvant Capecitabine: For Whom, and When?

CBCSG-10: concomitant administration of Cape with T/A significantly improved DFS in TNBC

**Clinical Implications**

- Routine use for unselected patients as part of neo/adjuvant regimen
  - TNBC
    - Use response to neoadjuvant chemotherapy to identify eligible patients so as to limit exposure and toxicity to those at the highest risk
    - Adjuvant capecitabine in setting of residual disease following neoadjuvant taxane/alkylator and anthracycline chemotherapy recommended by NCCN and St. Gallen Guidelines
      - DFS and OS 18% and 22%, respectively
Using TAILOR-X and MINDACT data

• TAILORx results are in line with the EORTC MINDACT trial results, thus confirming that not all ER+ N-negative (or up to 3 LND-positive according to MINDACT) patients benefit from toxic chemotherapy!
• TAILORx confirms excellent prognosis of ER+ N0 patients with low RS < 11 with ET alone and supports omitting Cht in patients with RS up to 25.
• TAILORx did not address identification of a group in which genomic test is not necessary while MINDACT trial shows that genomic test is not needed in all patients.
• Under 50? (ASCO and SABCS 2019 data?)- OFS??
  ▪ Practice changing data!
# Adjuvant Trastuzumab Improves DFS and OS in HER+ EBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Treatment Arm</th>
<th>DFS Absolute values HR (95% CI; p)</th>
<th>OS Absolute values HR (95% CI; p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>Observation</td>
<td>1,698</td>
<td></td>
<td>11-year DFS: 63.0%</td>
<td>12-year OS: 72.9%</td>
</tr>
<tr>
<td></td>
<td>Sequential</td>
<td>1,703</td>
<td></td>
<td>0.76 (0.68-0.86; &lt;0.0001)</td>
<td>0.74 (0.64-0.86; &lt;0.0001)</td>
</tr>
<tr>
<td>NCCTG</td>
<td>Sequential</td>
<td>2,018</td>
<td></td>
<td>8-year DFS: 62.0%</td>
<td>8-year OS: 75.2%</td>
</tr>
<tr>
<td></td>
<td>CT + trastuzumab 1 yr</td>
<td>2,028</td>
<td></td>
<td>0.60 (0.53-0.68; &lt;0.001)</td>
<td>0.63 (0.54-0.73; &lt;0.001)</td>
</tr>
<tr>
<td>BCIRG</td>
<td>Sequential</td>
<td>1,073</td>
<td></td>
<td>10-year DFS: 67.9%</td>
<td>10-year OS: 78.7%</td>
</tr>
<tr>
<td></td>
<td>T CH trastuzumab 1 yr</td>
<td>1,074</td>
<td></td>
<td>0.72 (0.62-0.85; &lt;0.0001)</td>
<td>0.63 (0.62-0.79; &lt;0.0001)</td>
</tr>
</tbody>
</table>

**Adjuvant trastuzumab 1 year:**
- **Risk of relapse (DFS)** by 23%-40% (absolute benefit 6%-12%)
- **Risk of death (OS)** by 24%-37% (absolute benefit 7%-9%)

**Change in natural history of EBC:**
- DFS and OS for trastuzumab-treated Her2+ early better are similar or better than Her2 negative
Need for escalation: 20% of patients still relapse

Cameron et al, Lancet 389, 2017
How can we de-escalate?

- **Cured with usual care (De-escalation)**
- **No benefit from intervention (De-escalation)**

Benefit from Intervention

Kaplan-Meier survival probability

Usual care vs. Intervention

P = 0.033
Escalation and De-escalation of Adjuvant Anti-HER2 Therapy

Escalating targeted agents
- BETH: H + Bevacizumab (negative)
- ExteNET: H -> neratinib (positive)
- ALTTO: H -> L or H+L (negative)
- APHINITY: H + pertuzumab (positive)
- KAITLIN: T-DM1 + pertuzumab (on-going)

Non-anthracycline-based CT
- BCIRG 006: TCH regimen (positive)
- APT: weekly P + H (positive)

"CT-free" regimen
- ATEMPT: T-DM1 (on-going)

"CT-free" regimen
- PHARE: H for 6 months (negative)
- HORG trial: H for 6 months (negative)
- SHORT-HER: H for 3 months (negative)
- PERSEPHONE: H for 6 months (positive)
- SOLD: H for 9 weeks (on-going)

POST Neoadjuvant for residual disease (no pCR)
- KATHERINE: T-DM1 (positive)

Prolonging duration of adjuvant H
- HERA: H for 2 years (negative)

Reducing duration of adjuvant H
- PHARE: H for 6 months (negative)
- HORG trial: H for 6 months (negative)
- SHORT-HER: H for 3 months (negative)
- PERSEPHONE: H for 6 months (positive)
- SOLD: H for 9 weeks (on-going)

ExteNET: 1 year Neratinib after 1 year of Trastuzumab vs 1 year Trastuzumab alone

ESMO-MCBS: A

- Positive DFS data persist with longer FU (5-year DFS, Martin M, Lancet Oncol 2017).
- OS data are still pending!
- Substantial toxicity (40% G3/4 diarrhea)
- Anti-diarrhea prophylaxis may be used (CONTROL trial, Hurwitz S, et al. Cancer Res 2018).

Subsets

<table>
<thead>
<tr>
<th>HR Status</th>
<th>DFS Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node-negative</td>
<td>0.83 (ns)</td>
<td></td>
</tr>
<tr>
<td>1–3+ nodes</td>
<td>0.75 (ns)</td>
<td></td>
</tr>
<tr>
<td>4+ nodes</td>
<td>0.67*</td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>0.60*</td>
<td></td>
</tr>
<tr>
<td>ER-</td>
<td>0.95 (ns)</td>
<td></td>
</tr>
</tbody>
</table>

5yr DFS absolute benefit = 2.6%

➢ Effect due to treatment extension or to HR and HER2 signaling co-targeting?

IDFS = invasive disease-free survival.

NNT (4y): 23
APHINITY: 1 year Trastuzumab plus Pertuzumab vs 1 year Trastuzumab plus Placebo - NODE POSITIVE SUBGROUP

ESMO-MCBS: B

APHINITY Updated descriptive analysis 74.1 months median FU
Time to first IDFS event by treatment regimen and nodal status

The node positive cohort continues to derive clear benefit from addition of pertuzumab.
APHINITY Updated descriptive analysis 74.1 months median FU
Time to first IDFS event by treatment regimen and hormone receptor status

Treatment benefit of pertuzumab is also seen in the hormone positive cohort.

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Hormone Receptor negative cohort, ITT population

- 3 years:
  - Pertuzumab (n = 864): 92.8%
  - Placebo (n = 858): 91.2%
- 6 years:
  - Pertuzumab (n = 864): 89.5%
  - Placebo (n = 858): 87.0%

Hormone Receptor positive cohort, ITT population

- 3 years:
  - Pertuzumab (n = 1536): 94.4%
  - Placebo (n = 1546): 91.2%
- 6 years:
  - Pertuzumab (n = 1536): 88.2%
  - Placebo (n = 1546): 88.2%

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Unstratified HR (95% CI):
- Hormone Receptor negative cohort: PERT 0.83 (0.63, 1.01)
- Hormone Receptor positive cohort: PERT 0.73 (0.59, 0.92)

6 year duration:
- Difference in Event Free Rate (%): 2.5
- 95% CI for Difference: (-0.7, 5.6)
- Difference in Event Free Rate (%): 3.0
- 95% CI for Difference: (0.8, 5.2)

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No. of patients at risk
- Hormone Receptor negative cohort:
  - Pertuzumab: 864
  - Placebo: 858

No. of patients at risk
- Hormone Receptor positive cohort:
  - Pertuzumab: 1536
  - Placebo: 1546
St Gallen 2017: Paclitaxel plus one year of trastuzumab “sufficient for most stage I patients”
TBCRC 033: A Randomized Phase 2 Trial of Adjuvant Trastuzumab Emtansine (T-DM1) vs. Paclitaxel with Trastuzumab for Stage 1 HER2+ Breast Cancer (ATEMPT)

Sara Tolaney et al.

Co-Primary Endpoints:
- 3-year DFS in T-DM1 arm
- Compare clinically relevant toxicities between the 2 arms

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>ATTEMPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T ≤ 1 cm</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>(11% T1a)</td>
</tr>
<tr>
<td>HR+</td>
<td>75%</td>
</tr>
<tr>
<td>N1mic</td>
<td>NR</td>
</tr>
</tbody>
</table>

Stage I HER2+
N0 or N1mic
ER+ or ER-
N=497

Median f/u 3.1 years

T-DM1 x 1yr is not de-escalated therapy compared to the APT regimen

Need longer follow up - 75% HR+
## De-escalating duration of HER2-directed Adjuvant Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Treatment Arm</th>
<th>DFS Absolute Values</th>
<th>OS Absolute Values</th>
<th>Cardiac Events</th>
<th>Heart Rate CV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHARE Phase 3</strong></td>
<td>1690</td>
<td>CT + trastuzumab for 1 year</td>
<td>2-year: 93.8%</td>
<td>NR</td>
<td>5.7%*</td>
<td></td>
</tr>
<tr>
<td>Pivot X, et al.</td>
<td>1690</td>
<td>CT + trastuzumab for 6 months</td>
<td>2-year: 91.1%</td>
<td>NR</td>
<td>1.28 (1.05-1.56; 0.29)</td>
<td>1.46 (1.06-2.01; 0.03)</td>
</tr>
<tr>
<td><strong>HORG Phase 3</strong></td>
<td>241</td>
<td>ddFEC -&gt; ddDocetaxel + trastuzumab for 1 year</td>
<td>3-year: 95.7%</td>
<td>NR</td>
<td>2 cases</td>
<td></td>
</tr>
<tr>
<td>Mavroudis D, et al.</td>
<td>240</td>
<td>ddFEC -&gt; ddDocetaxel + trastuzumab for 6 months</td>
<td>3-year: 93.3%</td>
<td>NR</td>
<td>0 cases</td>
<td></td>
</tr>
<tr>
<td><strong>Short-HER Phase 3</strong></td>
<td>627</td>
<td>CT + trastuzumab for 1 year</td>
<td>5-year: 87.5%</td>
<td>NR</td>
<td>16%*</td>
<td></td>
</tr>
<tr>
<td>Conte PF, et al., ASCO 2017, Abstr 501.</td>
<td>626</td>
<td>CT + trastuzumab for 9 weeks</td>
<td>5-year: 85.4%</td>
<td>NR</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>PERSEPHONE Phase 3</strong></td>
<td>2045</td>
<td>CT + trastuzumab for 1 year</td>
<td>4-year: 89.8%</td>
<td>NR</td>
<td>12%*</td>
<td></td>
</tr>
<tr>
<td>Earl H, et al. ASCO 2018, Abstr 506</td>
<td>2043</td>
<td>CT + trastuzumab for 6 months</td>
<td>4-year: 89.4%</td>
<td>NR</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td><strong>SOLD Phase 3</strong></td>
<td>1089</td>
<td>CT + trastuzumab for 1 year</td>
<td>5-year: 90.5%</td>
<td>NR</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Joensuu H, et al. JAMA Oncol 2018</td>
<td>1085</td>
<td>CT + trastuzumab for 9 weeks</td>
<td>5-year: 88.0%</td>
<td>NR</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>
**PERSEPHONE: 6 vs 12 months of trastuzumab**

**Disease-free survival**

![Graph showing disease-free survival rates for 6 and 12 months of trastuzumab treatment.](image)

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>#events</th>
<th>HR</th>
<th>90% CI</th>
<th>Non-inferiority p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>247</td>
<td>1.07</td>
<td>0.93-1.24</td>
<td>0.01</td>
</tr>
<tr>
<td>6 months</td>
<td>265</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- **HR:** Hazard Ratio
- **90% CI:** 90% Confidence Interval
- **Non-inferiority p:** Probability of non-inferiority

**Graph Notes:**
- Non-inferiority limit: Hazard Ratio = 1.31
- No. at Risk:
  - 12 months: 2045, 2013, 1887, 1666, 1304, 1012
  - 6 months: 2043, 2007, 1879, 1647, 1316, 1016
PERSEPHONE and SHORT-HER Subgroups Analysis

PERSEPHONE: Subgroups for which 12 m might be superior

- ER-
- Taxane-based

No inferiority margin 1.31

SHORT-HER: Subgroups for which 6 m might be non-inferior

- Stage I, II
- N0-1

No inferiority margin 1.29

➢ Shorter trastuzumab treatment duration might be equally effective in low stage, ER+ disease.
➢ However, in all other scenarios 1 year of trastuzumab remains the gold standard!
Putting it all together: HER2+ EBC

T1a?
- HER2+ cT1 AND cN0
  - Any HR status
    - Surgery
      - pN0
        - pT1
          - Adjuvant Paclitaxel + Trastuzumab
        - pT >2
          - Standard chemo + Trastuzumab + Pertuzumab
            - Consider Neratinib (ER+)
      - pN >1
        - Standard chemo + Trastuzumab + Pertuzumab
          - Consider stopping Pertuzumab

HER2+ cT2 and/or cN >1
- Any HR status
  - Neoadjuvant chemotherapy + Trastuzumab AND Pertuzumab
    - Surgery
      - PCR
        - cN0
          - Complete 1 year Trastuzumab
        - cN >1
          - Complete 1 year Trastuzumab + Pertuzumab
      - No PCR
        - T-DM1
          - HER TKI?

56% of all distant recurrences were in CNS
<table>
<thead>
<tr>
<th>Risk</th>
<th>Hormone therapy</th>
<th>Chemotherapy</th>
<th>Factors to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (T1, N0, Grade 1, or low “gen risk”)</td>
<td>PRE TAM</td>
<td>No chemo</td>
<td>No Ovarian Sup. 5 years enough</td>
</tr>
<tr>
<td></td>
<td>POST TAM or AI</td>
<td>No chemo</td>
<td>5 years enough AI in Lobular C</td>
</tr>
<tr>
<td>Interm risk (pN0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High/interm HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1c, pT2, pN0 or G2/G3, interm “gen risk”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE OFS + AI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POST AI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interm risk (pN1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High/interm HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1c, pT2, pN1 (1-3) or G2/G3, interm “gen risk”</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PRE OFS + AI (benefit &lt;35y)</td>
<td></td>
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<tr>
<td>POST AI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>High risk (low/interm HR)</td>
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<td></td>
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</tr>
<tr>
<td>pT3, pN2-3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High grade</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Younger</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PRE OFS + AI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POST AI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER positive
Her2 negative
EARLY BREAST CANCER

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<table>
<thead>
<tr>
<th>Risk</th>
<th>Treatment recommendation</th>
<th>De-escalation</th>
<th>Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC, pT1a N0</td>
<td>-</td>
<td>No routine systemic therapy</td>
<td></td>
</tr>
</tbody>
</table>

**HER2 POSITIVE EARLY BREAST CANCER**

- **TNBC, pT1a N0**: No routine systemic therapy
- **Her2 Positive, pT1b,c N0**: Chemotherapy + trastuzumab. Consider Paclitaxel + 1 y of trastuzumab without anthracyclines
- **Her2 Positive, Higher T, N**: Neoadjuvant for stage II, III, T+P Anthra + taxanes concomitant with 1 y trastuzumab (no anthracyclines)
- **T-DM1 for residual**
- **Dual blockade P+T in some pts at higher risk (N+)**
- **Her2 Positive as above plus hormonal treatment**
- **Chemo in many cases**
- **Extended Neratinib may improve outcome in HR+**