4TH ESO-ESMO LATIN-AMERICAN MASTERCLASS IN CLINICAL ONCOLOGY

18-22 April 2018
Mexico City, Mexico

Chairs:
A. Cervantes, ES - N. Pavlidis, GR
R.A. Stahel, CH

Scientific Co-ordinators:
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Under the auspices of

CMO
SMEO

LATIN-AMERICA PROGRAMME
(Neo-) Adjuvant chemotherapy and biological agents

Giuseppe Curigliano MD, PhD
University of Milano and European Institute of Oncology
• Neoadjuvant treatment in triple negative and HER2 positive early breast cancer
• The post-neoadjuvant setting
• Picking optimal adjuvant chemotherapy for TN and HER2 positive early breast cancer
## Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Pathology and molecular biology</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal “triple negative”</td>
<td>ER, PgR and HER2 negative</td>
</tr>
<tr>
<td>“Basal like” tumor</td>
<td>Genomic testing</td>
</tr>
<tr>
<td>ER negative and HER2-positive</td>
<td>ASCO/CAP Guidelines</td>
</tr>
<tr>
<td>ER positive and HER2-positive</td>
<td>ASCO/CAP guidelines; ER and/or PgR positive &gt;= 1%</td>
</tr>
<tr>
<td>“HER2-enriched” tumor</td>
<td>Genomic testing</td>
</tr>
</tbody>
</table>

St Gallen 2017
The Panel strongly endorsed the use of neoadjuvant therapy for stage II or III, HER2 positive or triple-negative breast cancer as the preferred initial treatment approach, particularly when there is any suggestion that treatment response might enable de-escalation of surgery or radiotherapy.
Neoadjuvant therapy

**Pro:**
- Conservative surgery
- Pathologic complete response
- New drug development

**Contras:**
- Low rate of pCR in some subtype (ER+)
- Enrich by subtypes
- Implication for surgeon and radiation therapist

In TN and HER2 positive EBC should be the preferred approach
Pathological complete response

- Absence of invasive tumor in breast and nodes
- Absence of invasive tumor in breast and nodes with residual carcinoma *in situ*.
pCR and outcome

(N=11,955)
### Clinical Heterogeneity of TNBC

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene expression profile</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like 1</td>
<td>high Ki-67; DNA damage response</td>
<td>BRCA-associated</td>
</tr>
<tr>
<td>Basal-like 2</td>
<td>GF pathways</td>
<td>Higher pCR</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Immune genes</td>
<td>Lower DDFS</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Cell motility</td>
<td>Apocrine features, higher LRF; PI3Kmut</td>
</tr>
<tr>
<td>Mesenchymal stem-like</td>
<td>Cell motility; claudin-low</td>
<td></td>
</tr>
<tr>
<td>Luminal androgen receptor</td>
<td>Steroid pathways</td>
<td></td>
</tr>
</tbody>
</table>

Should all TNBC receive PST?

• **Neoadjuvant approach**

  • **Advantages**
    – *Minimize surgery = no controversy*
    – *Minimize chemotherapy?*

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

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

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

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

Carboplatin augments pCR in TNBC
Study Objectives

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

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

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

Pathologic Complete Response
ypT0/Tis ypN0

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>V + Cb + P</td>
<td>53.2</td>
</tr>
<tr>
<td>Cb + P</td>
<td>57.5</td>
</tr>
<tr>
<td>P</td>
<td>31.0</td>
</tr>
</tbody>
</table>

p = 0.001

Clinical Response Rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>V + Cb + P</td>
<td>83.4</td>
</tr>
<tr>
<td>Cb + P</td>
<td>83.3</td>
</tr>
<tr>
<td>P</td>
<td>55.7</td>
</tr>
</tbody>
</table>

p = 0.001

Minimal Residual Disease
Residual Cancer Burden Class 0 or I

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>V + Cb + P</td>
<td>68.3</td>
</tr>
<tr>
<td>Cb + P</td>
<td>70.0</td>
</tr>
<tr>
<td>P</td>
<td>47.2</td>
</tr>
</tbody>
</table>

p = 0.74

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

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

S. Loibl et al. The Lancet Oncology 2018
Addition of V and Cb to P followed by AC demonstrated a significant improvement in pCR compared with P followed by AC (53.2% vs 31.0%, \( p<0.001 \)) confirming results of I-SPY-2.

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

Increase in pCR with addition of carboplatin was independent of gBRCA mutation status.
INFORM: preop cisplatin vs AC for BRCA 1/2 carriers

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

Stage II/III BC with BRCA1 or 2 mutation

N = 170; approximately 60 enrolled

Principal Investigators:
Nadine Tung and Judy Garber
TBCRRC and other sites
Neoadjuvant therapy in HER2+ EBC

LESSONS LEARNED FROM NEOADJUVANT TRIALS

I. First generation

Trastuzumab + chemo > chemo alone
Trastuzumab and chemotherapy

- No evidence of residual invasive cancer, both in breast and axilla
- No evidence of residual disease in breast tissue
- pCR, pathological complete response; H, trastuzumab; T, taxane
- FEC, 5-fluorouracil+epirubicin+cyclophosphamide; AT, doxorubicin+paclitaxel
- CMF, cyclophosphamide+methotrexate+5-fluorouracil; EC, epirubicin+cyclophosphamide

2. Gianni L, et al. 2010
Improved pCR rate translates into improved outcome with Trastuzumab

5-year event-free survival

5-year overall survival

*EFS, Event–free survival; HR, Hazard ratio; OS, Overall survival.

LESSONS LEARNED FROM NEOADJUVANT TRIALS

II. Second generation

Dual HER2 blockade + chemo > single HER2 blockade + chemo
Pertuzumab and trastuzumab

Study dosing: q3w x 4

TH (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

Neoadjuvant docetaxel + trastuzumab + pertuzumab was FDA approved!
Overview of dual blockade
Dual blockade better

Increase in pCR

- Long CHT + dual anti-HER2 therapy
  - 74%
- Long CHT + Trastuzumab similar to short CHT + dual anti-HER2
  - 65%
- Short CHT + Trastuzumab
  - 48%
- CHT alone
  - 45%
- CHT alone
  - 38%
- CHT alone
  - 25%
- CHT alone
  - 20%
- CHT alone
  - 15%
Beyond dual blockade

LESSONS LEARNED FROM NEOADJUVANT TRIALS

III. Third generation

Identify the subset which can benefit from a chemo-sparing regimen
HER2+ /HR- disease

Based on NeoSphere, NeoAltto, Tryphaena

Who are these patients with HER2+ HR- disease who perhaps do not need chemo?
HER2+ /HR- disease

- PIK3CA mutations/
  PTEN loss

- Improved tailoring

- TIL’s Immune signatures
Chemofree Therapy in HER2+ patients

**Neosphere**

**THP (n=107)**
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

**HP (n=107)**
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

**TBCRC 0023**

12 weeks of HL +/- ET
24 weeks of HL +/- ET

**TBCRC006**

Trastuzumab Emtansine ± ET vs Trastuzumab + ET in HER2+/HR+

- International, prospective, randomized phase II trial

- Primary endpoint: pCR (no invasive carcinoma in breast/nodes)

- Secondary endpoints: dynamic testing evaluation, EFS, OS, safety

Pts with ER+ and/or PgR+, HER2+, cT1c - cT4a-c, cN, cM0 BC and adequate organ function, LVEF ≥ 50%, normal ECG (N = 375)

T-DM1 3.6 mg/kg Q3W (n = 119)

T-DM1 3.6 mg/kg Q3W + ET* (n = 127)

Trastuzumab 8 mg/kg loading dose, then 6 mg/kg Q3W + ET* (n = 129)

Surgery†

Wk 12

* Tamoxifen if premenopausal; aromatase inhibitor (of investigator’s choice) if postmenopausal.
† Standard chemotherapy (1-yr trastuzumab) recommended after surgery or 12-wk biopsy (if clinical non-pCR).

## ADAPT Trial

<table>
<thead>
<tr>
<th>Outcome, n/N (%)</th>
<th>T-DM1</th>
<th>T-DM1 + ET</th>
<th>Trastuzumab + ET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR (ypT0 or ypT0/is, ypN0)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts*</td>
<td>48/117 (41.0)</td>
<td>51/123 (41.5)</td>
<td>18/119 (15.1)</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td>22/58 (37.9)</td>
<td>24/63 (38.1)</td>
<td>8/59 (13.6)</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>26/59 (44.1)</td>
<td>27/60 (45.0)</td>
<td>10/60 (16.7)</td>
</tr>
<tr>
<td><strong>Near pCR (ypT1a)</strong></td>
<td>14/117 (12.0)</td>
<td>14/123 (11.4)</td>
<td>5/119 (4.2)</td>
</tr>
<tr>
<td><strong>Early response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponders</td>
<td>9/36 (25.0)</td>
<td>6/25 (24.0)</td>
<td>5/40 (12.5)</td>
</tr>
<tr>
<td>Responders</td>
<td>24/61 (39.3)</td>
<td>36/76 (47.4)</td>
<td>11/62 (17.7)</td>
</tr>
</tbody>
</table>

*P < .001 for comparison between each T-DM1 arm vs trastuzumab + ET.

†Low cellularity (< 500 tumor cells) or Ki67 decline ≥ 30% in 3-wk biopsy.

Neoadjuvant summary

✓ Neoadjuvant therapy is a standard for these two EBC subtypes
  ✓ Evidence-based therapy options differ from adjuvant setting
  ✓ pCR correlated with outcome; non-pCR: options investigated

✓ **TNBC**: Anthracyclines and taxanes are standard
  ✓ Platinum increases pCR (independent of BRCA status)

✓ **HER2+**: Standard CTx backbone: anthracycline+taxane vs. TCb
✓ Dual antibody blockade (T+P) are standard
Neoadjuvant summary

- pCR: Adjuvant therapy to be redefined
- Non-pCR: Effective additional therapy options needed
- Role of targeted therapies (e.g. immune therapy, PARPi, etc.)
- **HER2+**: Therapy concepts for luminal vs. non-luminal tumors
- Multidisciplinary concept including loco-regional therapy
Adjuvant therapy

Treatment decision

Who needs more?
Prognostic Factors

Which is the Best therapy?
Predictive factors
Post-Neoadjuvant setting TN

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

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

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

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

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

  *Anthraclycine/taxane, anthracycline containing, or docetaxel/cyclophosphamide.

  \(^\dagger\)25 pts were removed from treatment (n = 10) and control (n = 15) arms due to failure to meet eligibility criteria.

  \(^\ddagger\)IDMC recommended extension to 8 cycles following interim safety analysis of first 50 pts receiving 6 cycles.\(^2\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Capecitabine (n = 440)</th>
<th>No Capecitabine (n = 445)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median yrs (range)</td>
<td>48 (25-74)</td>
<td>48 (25-74)</td>
</tr>
<tr>
<td>Menopausal status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>59.3</td>
<td>56.0</td>
</tr>
<tr>
<td>Post</td>
<td>40.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, IIA, IB</td>
<td>58.9</td>
<td>62.0</td>
</tr>
<tr>
<td>IIIA, IIIB</td>
<td>40.5</td>
<td>37.5</td>
</tr>
<tr>
<td>Hormonal receptor status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ or PgR+</td>
<td>63.9</td>
<td>62.9</td>
</tr>
<tr>
<td>ER- and PgR-</td>
<td>33.4</td>
<td>33.5</td>
</tr>
<tr>
<td>Lymph nodes with metastatic disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39.3</td>
<td>38.7</td>
</tr>
<tr>
<td>1-3</td>
<td>37.5</td>
<td>39.1</td>
</tr>
<tr>
<td>≥ 4</td>
<td>22.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Histologic effect grading by NAC, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1a, 1b</td>
<td>56.4</td>
<td>52.6</td>
</tr>
<tr>
<td>2, 3</td>
<td>41.6</td>
<td>45.4</td>
</tr>
</tbody>
</table>

Post-Neoadjuvant setting

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

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

Post-Neoadjuvant setting

Masuda N, NEJM 2017
Triple negative BRCA mutated

Figure 1. OlympiA study design

- **Screening**
- **Randomization (1:1)**
  - **Olaparib 300 mg bid (12 months' duration)**
  - **Matched placebo (12 months’ duration)**
- **Invasive disease-free survival assessment**
  (mammogram/breast MRI 6 months from randomization)
- **Follow-up for local and distant recurrence and survival status**
Triple negative IO

BRAVE Protocol

TNBC → Neoadj Chemo → Surgery → pCR (40%) → R → 1 → Placebo
No pCR (60%) → R → 2 → Avelumab

Radiotherapy

Principle Investigator: Pierfranco Conte
## Escalating in TN EBC

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum routine in neo-adjuvant Rx</td>
<td>Yes (justifiable but no known EFS advantage)</td>
</tr>
<tr>
<td>Capecitabine in residual disease</td>
<td>An option - Stage II+ who has received anthracycline/taxane-based Rx</td>
</tr>
<tr>
<td></td>
<td>Uncertain in non adequately treated</td>
</tr>
<tr>
<td>Biological subsets to tailor escalating Rx</td>
<td>No</td>
</tr>
<tr>
<td>Immunotherapy/PARPi/anti androgens or other novel strategies</td>
<td>Not off-trial</td>
</tr>
</tbody>
</table>
Adjuvant therapy in TN

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

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

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

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical low risk subsets can omit chemotherapy</td>
<td>Only in very small, node-negative (T1a pN0)</td>
</tr>
<tr>
<td>Biologic low risk subsets can omit / limit chemotherapy</td>
<td>No</td>
</tr>
<tr>
<td>Neoadjuvant Rx to reduce surgery</td>
<td>No stage I</td>
</tr>
<tr>
<td></td>
<td>Yes stage II+</td>
</tr>
<tr>
<td>Treating to pCR to de-escalate systemic therapy</td>
<td>No</td>
</tr>
<tr>
<td>Anthracyclines may be omitted</td>
<td>No (may consider in low risk)</td>
</tr>
</tbody>
</table>
Optimal Adjuvant Therapy in 2016 for the ‘average’ patient with HER2-positive breast cancer
First generation trials

**HERA (ex-USA)**
- IHC / FISH (n=5102)
- Observation
  - 1 year
  - 2 years

**NCCTG N9831 (USA)**
- IHC / FISH (n=3505)
  - 1 year

**BCIRG 006 (global)**
- FISH (n=3222)
  - 1 year
  - 1 year
  - 1 year

**NSABP B-31 (USA)**
- IHC / FISH (n=2030)
  - 1 year

- Standard CTx
- Doxorubicin + cyclophosphamide
- Docetaxel
- Docetaxel + carboplatin
- Herceptin®
- Paclitaxel

*IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation*
### Long-term DFS benefit with adjuvant Trastuzumab for 1 year

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up (years)</th>
<th>N</th>
<th>HR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>1</td>
<td>3387</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>(CT+/−RT→H vs. AC→T)</td>
<td>2</td>
<td>3401</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>(CT+/−RT)</td>
<td>4</td>
<td>3401</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3401</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AC→TH→H vs. AC→T)</td>
<td>5</td>
<td>3222</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>(TCH vs. AC→T)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined analysis&lt;sup&gt;6-8&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NCCTG N9831/NSABP B-31)</td>
<td>2</td>
<td>3351</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>(AC→TH→H vs. AC→T)</td>
<td>4</td>
<td>4045</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>4046</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio

1. Longer trastuzumab duration (Hera 2y arm)

2. Adding bevacizumab to trastuzumab (Beth)

3. Dual HER2 blockade
   - Lapatinib + trastuzumab (ALTTO)
   - Pertuzumab + trastuzumab (APHINITY)

4. T-DM1 after neoadjuvant CT + trastuzumab in case of residual disease (Katherine)
HERA 2 years

2 year adjuvant trastuzumab treatment does not improve clinical outcome!!

Goldhirsch A et al. The Lancet Volume 382, No. 9897, p1021–1028, 21 September 2013
Adding bevacizumab

Node positive or high-risk node negative HER2+

Cohort 1
Non-Anthracycline
N= 3231
TCH → H

Arm 1A
TCH → H

Arm 1B
TCH Bev → H Bev

Cohort 2
Anthracycline
N= 278
TH → FEC → H

Arm 2A
TH → FEC → H Bev

Arm 2B
TH Bev → FEC → H Bev

Slamon D et al, SABCS 2-13, abstract #S1-03
<table>
<thead>
<tr>
<th></th>
<th>No Bevacizumab</th>
<th>+ Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>92%</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>97%</td>
<td>96%</td>
<td></td>
</tr>
</tbody>
</table>

Slamon D et al, SABCS 2-13, abstract #S1-03

**Addition of Bevacizumab does not improve clinical outcome!!**
Adding lapatinib

Anti-HER2 therapy: 4 groups assigned by randomization

- Trastuzumab (T) x 52 weeks
- Lapatinib (L) x 52 weeks
- T x 12 wks  L x 34 weeks  6 weeks
- Trastuzumab and Lapatinib x 52 weeks

3 modalities of adjuvant CT administration per physician’s choice

- **Design 1**
  - Chemotherapy
    - 12 to 18 weeks
  - Anti-HER2 therapy
    - 52 weeks

- **Design 2a**
  - Anthracycline
    - 9 to 12 weeks
  - Taxane
    - 12 weeks
  - Anti-HER2 therapy
    - 52 weeks

- **Design 2b**
  - Docetaxel + Carboplatin
    - 18 weeks
  - Anti-HER2 therapy
    - 52 weeks

* R: refers to the timing of randomization
Adding lapatinib

MFU = 4.5 yrs

M. Piccart et al. JCO 2015
Extended Neratinib

HER2+ Stage II-IIIIC node positive BC following CT + 12 months of trastuzumab (adj) (N=2821)

R

Neratinib
240 mg orally daily for 1 year

Placebo
Orally daily for 1 year

DFS

DFS

CT, chemotherapy; adj, adjuvant; DFS, disease-free survival; BC, breast cancer.

Press release - Puma Biotechnology
July 22nd, 2014

Extended DFS by 33% compared with placebo (HR = 0.67; P = .0046)
ExteNET

Intention-to-treat population

Disease-free survival (%)

P-value = 0.009
HR (95% CI) = 0.67 (0.50–0.91)

No. at risk
Neratinib 1420 1291 1260 1229 1189 1150 1108 1033 662
Placebo 1420 1367 1324 1292 1243 1209 1163 1090 704

Chan et al. Lancet Oncol 2016
ExteNET

Hormone receptor-positive

Disease-free survival (%)

- Months after randomization
- No. at risk
  - Neratinib: 816, 737, 721, 698, 677, 653, 629, 591, 380
  - Placebo: 815, 784, 761, 741, 716, 699, 699, 622, 401
- P = 0.001
- HR (95% CI) = 0.51 (0.33–0.77)

Hormone receptor-negative

Disease-free survival (%)

- Months after randomization
- No. at risk
  - Neratinib: 604, 554, 539, 531, 512, 497, 479, 442, 282
  - Placebo: 605, 583, 563, 551, 527, 510, 494, 468, 303
- P = 0.74
- HR (95% CI) = 0.93 (0.60–1.43)

Chan et al. Lancet Oncol 2016
**ExteNET**

Invasive disease-free survival (%)

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Neratinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>97.9%</td>
<td>95.5%</td>
</tr>
<tr>
<td>12</td>
<td>94.3%</td>
<td>91.7%</td>
</tr>
<tr>
<td>18</td>
<td>92.2%</td>
<td>90.2%</td>
</tr>
<tr>
<td>24</td>
<td>91.2%</td>
<td>89.1%</td>
</tr>
<tr>
<td>30</td>
<td>90.2%</td>
<td>87.7%</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HR (95% CI)** = 0.73 (0.57–0.92)

Two-sided P = 0.008

**No. at risk**

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Neratinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1420</td>
<td>1420</td>
</tr>
<tr>
<td>6</td>
<td>1316</td>
<td>1354</td>
</tr>
<tr>
<td>12</td>
<td>1272</td>
<td>1298</td>
</tr>
<tr>
<td>18</td>
<td>1225</td>
<td>1248</td>
</tr>
<tr>
<td>24</td>
<td>1106</td>
<td>1142</td>
</tr>
<tr>
<td>30</td>
<td>978</td>
<td>1029</td>
</tr>
<tr>
<td>36</td>
<td>965</td>
<td>1011</td>
</tr>
<tr>
<td>42</td>
<td>949</td>
<td>991</td>
</tr>
<tr>
<td>48</td>
<td>938</td>
<td>978</td>
</tr>
<tr>
<td>54</td>
<td>920</td>
<td>958</td>
</tr>
<tr>
<td>60</td>
<td>885</td>
<td>927</td>
</tr>
</tbody>
</table>

Intention-to-treat population. Cut-off date: March 1, 2017

**ExteNET**

### HR-positive subgroup

- **HR** (95% CI) = 0.60 (0.43–0.83)
- Two-sided *P* = 0.002

### HR-negative subgroup

- **HR** (95% CI) = 0.95 (0.66–1.35)
- Two-sided *P* = 0.762

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Neratinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neratinib</strong></td>
<td>816 757 731 705 642 571 565 558 554 544 523</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>815 779 750 719 647 581 567 556 551 542 525</td>
<td></td>
</tr>
</tbody>
</table>

Intention-to-treat population. Cut-off date: March 1, 2017

• A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed

Number needed to treat: 112
Katherine

Neoadjuvant CT + trastuzumab

Residual invasive cancer

R

T-DM1

Trastuzumab

Primary endpoint: IDFS

≈ 900/1400 patients recruited as of today
1300/2500 women recruited...

Worrysome: taxane + trastuzumab = T-DM1 = T-DM1 + pertuzumab in the first line metastatic MARIANNE trial!
### Escalation attempts: preliminary conclusions

<table>
<thead>
<tr>
<th>Failed</th>
<th>Succeeded</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Trastuzumab x 2y</td>
</tr>
<tr>
<td>V</td>
<td>Trastuzumab + bevacizumab</td>
</tr>
<tr>
<td>V</td>
<td>Trastuzumab + lapatinib</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab followed by neratinib</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab + pertuzumab</td>
</tr>
<tr>
<td>❓</td>
<td>T-DM1 after neoadj CT + trast</td>
</tr>
</tbody>
</table>
De-Escalation

Study Design (APT Trial)

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400

Enroll

Paclitaxel 80 mg/m² + Trastuzumab 3 mg/kg x 12

Followed by 13 every 3 week doses of Trastuzumab (6 mg/kg)

Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks

Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney S, NEJM 2015
pT1-pT3 pN0 HER2+

Disease-Free Survival by Tumor Size

Tolaney S, NEJM 2015
## De-Escalation attempts: preliminary conclusions

<table>
<thead>
<tr>
<th>Failed</th>
<th>Succeeded</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mathbf{V}$ (so far...)</td>
<td></td>
</tr>
<tr>
<td>Shorten trastuzumab duration</td>
<td></td>
</tr>
<tr>
<td>Eliminate the anthracycline component</td>
<td>$\mathbf{V}$ (in selected pts !)</td>
</tr>
<tr>
<td>Use T-DM1 + pertuzumab instead of taxane + trastuzumab + pertuzumab</td>
<td>?</td>
</tr>
</tbody>
</table>
# Adjuvant therapy in HER2 + EBC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Terapia medica</th>
<th>De-escalation</th>
<th>Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER negative &amp; HER2-positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1a pN0</td>
<td>No therapy</td>
<td>No therapy</td>
<td>Pertuzumab/trastuzumab?</td>
</tr>
<tr>
<td>pT1b,c pN0</td>
<td>Chemotherapy plus trastuzumab</td>
<td>Consider trastuzumab and paclitaxel plus one year trastuzumab without anthracyclines</td>
<td></td>
</tr>
<tr>
<td><strong>Higher T and N stage</strong></td>
<td>Neoadjuvant therapy for stage II or III is the preferred initial treatment approach. Anthracycline/taxane with concurrent trastuzumab continued to 12 months</td>
<td></td>
<td>Dual anti-HER2 therapy with pertuzumab and trastuzumab with chemotherapy as the preferred option in the neoadjuvant setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Data with dual blockade in the adjuvant setting are pending</td>
</tr>
<tr>
<td><strong>ER positive &amp; HER2-positive</strong></td>
<td>As above plus endocrine therapy appropriate to menopausal status as below</td>
<td></td>
<td>Extended adjuvant therapy with neratinib after one year of trastuzumab</td>
</tr>
</tbody>
</table>
1. Adjuvant trastuzumab treatment for 1 year is the standard of care.

2. Longer or shorter durations of adjuvant trastuzumab treatment are not justified by currently available data.

3. Dual HER2 blockade with the incorporation of pertuzumab is standard of care in “high risk” patients applied in clinical practice.

4. We still lack a “validated biomarker” beyond HER2 for improved treatment tailoring.

We need to:

1. Identify patients with disease resistant to HER2 blockade.
2. Identify patients not needing intensified regimens.
3. Identify patients candidate for “chemotherapy-free” regimens.
Where we are

Targeted therapy

Ch
Chirurgia
RT

Chemo
Targeted therapy

Endocrine therapy

Duration of treatment: from 1 day to > 10 years!
Escalation

- More Patients Treated
- Longer Drug Exposure
- More Drugs

Therapeutic Escalation
De-Escalation: Surgery

- **1890**
- **1993**
- **2009**
- **2016**
- **????**

- **Mastectomy and axillary dissection**
- **QUAD and axillary dissection only if SN+**
- **Sentinel node up to 2 SN+**
- **No surgery on the axilla**

No surgery on the axilla
De-Escalation: Radiotherapy

The graph shows the duration in days for different radiotherapy methods:

- Standard RT
- AWBI
- APBI
- IORT
- No RT

The duration ranges from 0 to 35 days.
Clinical research in the future

Drug treatment
de-escalation
- Governments
- EU
- [Charities]

Drug treatment
escalation
- Pharma
Thank you