HER2 positive breast cancer in older adults: (neo)adjuvant approach?

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HER2-targeted treatment for older patients with breast cancer: An expert position paper from the International Society of Geriatric Oncology

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Disclosure

I have the following the conflict(s) of interest to declare:

- Consulting fees and honoraria to my institute from Roche, Astra Zeneca, Amgen, Lilly, Novartis, Abbvie, Vifor Pharma, Pfizer, Celldex therapeutics, Janssen-CILAG.
- Unrestricted grant to my institute from Roche.
- Travel support from Roche and Pfizer.
T-DM1 adjuvant if no pCR after neoadjuvant chemotherapy

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Von Minckwitz et al NEJM 2019
**T-DM1 adjuvant** if no pCR after neoadjuvant chemotherapy

**Invasive Disease-Free Survival**

- Trastuzumab
  - No. at Risk: 743
  - Events, no. (%): 165 (22.2)
  - 3-year IDFS: 77.0%
- T-DM1
  - No. at Risk: 743
  - Events, no. (%): 91 (12.2)
  - 3-year IDFS: 88.3%

**Overall Survival**

- Trastuzumab
  - No. at Risk: 743
  - Events, no. (%): 50 (7.5)
- T-DM1
  - No. at Risk: 743
  - Events, no. (%): 42 (5.7)

**T-DM1 will likely become standard after neoadjuvant chemo without pCR**
### HER2 positive early breast cancer

#### Primary surgery

<table>
<thead>
<tr>
<th>cTNM</th>
<th>pTNM</th>
<th>Adjuvant schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1N0</td>
<td>pT1N0</td>
<td>12xPaclit+Trast 1y</td>
</tr>
<tr>
<td>cT2-4</td>
<td>pT2-4</td>
<td>4EC-&gt;12Paclit+Trast 1y</td>
</tr>
<tr>
<td>cN0</td>
<td>pN0</td>
<td>or 6 TCH</td>
</tr>
<tr>
<td>cTany</td>
<td>pTany</td>
<td>4EC-&gt;12Paclit+Trast+Perj</td>
</tr>
<tr>
<td>cNpos</td>
<td>Npos</td>
<td>or 6 TCH-P</td>
</tr>
</tbody>
</table>

#### Neoadjuvant systemic therapy

<table>
<thead>
<tr>
<th>cTNM</th>
<th>Neoadjuvant schedule</th>
<th>Adjuvant schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1N0</td>
<td>No upfront chemo proposed</td>
<td>Not applicable</td>
</tr>
<tr>
<td>cT2-4</td>
<td>4EC-&gt;12Paclit+Trast±Pert</td>
<td>If pCR:</td>
</tr>
<tr>
<td>cN0</td>
<td>or 6 TCH±P</td>
<td>- 14x Trast ± Pert</td>
</tr>
<tr>
<td>cTany</td>
<td>4EC-&gt;12Paclit+Trast+Perj</td>
<td>If no pCR:</td>
</tr>
<tr>
<td>cNpos</td>
<td>or 6 TCH-P</td>
<td>- 14x T-DM1</td>
</tr>
</tbody>
</table>

**HER2 positive early breast cancer**
HER2+: De-escalation

1. **Taxane only as chemobackbone adjuvant?**

- **Paclitaxel weekly** x12 + 1y trastuz.  (NEJM 2015, ASCO 2017 Tolaney)
  - 410 women N0, max 3 cm, 67% ER+, 20% pT1a, 9% pT2
  - 7y IDFS 99.3%, 23 relapses, 4 distant metastases (1%)

- **TC** (docetaxel-cycloph.) x 4 + 1y trastuz.  (Lancet Oncol 2011 Jones)
  - 493 women stage I-II (20% N1-2), 33% T2
  - 3y DFS 96.9%

- **TCH** (BCIRG-006): Docetaxel Carboplatin AUC 6 Trastuzuzmab
  - exclusion of ≥70y!
HER2+: De-escalation attempts:

2. Taxane only as chemobackbone neoadjuvant?

TRAIN study

HER2+ BC, Stage II-III
No prior therapy
N = 438

9 cycles of neoadjuvant therapy

3 x Pacilitaxel + carboplatin + pertuzumab + trastuzumab

3 x FEC + pertuzumab + trastuzumab

6 x Pacilitaxel + carboplatin + pertuzumab + trastuzumab

6 x Paclitaxel + carboplatin + pertuzumab + trastuzumab

PCR rate (ypT0/is, ypN0)

P = 0.75

Anthracycline free regimens are an option

SABCS 2017 Van Ramshorst
### 2. Duration of trastuzumab adjuvant

<table>
<thead>
<tr>
<th>Study</th>
<th>N pts</th>
<th>Trastuzumab duration</th>
<th>Noninferiority DFS HR</th>
<th>Observed DFS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persephone</td>
<td>4089</td>
<td>6m vs 12m</td>
<td>&lt; 1,29</td>
<td>1,07 (0.93-1.24)</td>
</tr>
<tr>
<td>Short-Her</td>
<td>1253</td>
<td>9w vs 12m</td>
<td>&lt; 1,29</td>
<td>1,13 (0.89-1.42)</td>
</tr>
<tr>
<td>Phare</td>
<td>3384</td>
<td>6m vs 12m</td>
<td>&lt; 1,15</td>
<td>1,08 (0.93-1.25)</td>
</tr>
<tr>
<td>SOLD</td>
<td>2176</td>
<td>9w vs 12m</td>
<td>&lt; 1,3</td>
<td>1,39 (1.12-1.72)</td>
</tr>
<tr>
<td>HORG</td>
<td>481</td>
<td>6m vs 12m</td>
<td>&lt; 1,53</td>
<td>1,57 (0.86-2.10)</td>
</tr>
</tbody>
</table>

**Meta-analysis**: shorter duration inferior for DFS (HR 1.19 (1.08-1.30)) and OS (HR 1.22 (1.07-1.39))

In subgroup analysis limited benefit in ER+ and N-

1 year trastuzumab still standard, but pts with low relapse risk, or at cardiac risk, may benefit from shorter duration.

**PS**: Short duration not tested with ‘Tolaney’ regimen.

Cardiac events longer duration OR = 2.48 (1.94-3.17)

3. **Omission** of classical chemotherapy neoadjuvant

- **Adjuvant trastuzumab without chemo (elderly)**
  
  - RESPECT trial (Japan), randomized phase II, n=275, age 70-80y, stage I-IIIA, adjuvant trastuzumab +/- chemo
  
  - 3y-DFS 89,2% vs 94,8% (p value ?)
  
  - AEs (all grade)
    - anorexia (7,4% vs 44.3%, p < 0.0001)
    - alopecia (2,2% vs 71.8%, p < 0.0001)
    - grade 3/4 non-haematological AEs were 11,9% vs 29.8% (p = 0.0003).

- QoL: decreased with chemo at 2 Mo and 1y, but recovery at 3y
HER2+: De-escalation attempts:

3. Omission of classical chemotherapy neoadjuvant

• Neoadjuvant regimens (all age)

<table>
<thead>
<tr>
<th>Study</th>
<th>N pts</th>
<th>Regimen</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPT</td>
<td>375</td>
<td>T-DM1</td>
<td>41,0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-DM1 + endocrine R/</td>
<td>41,5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trastuzumab + endocrine R/</td>
<td>15,1%</td>
</tr>
<tr>
<td>KRISTINE</td>
<td>444</td>
<td>TCHP</td>
<td>55,7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-DM1+Pertuzumab</td>
<td>44,4%</td>
</tr>
</tbody>
</table>

Subgroups can probably skip classical chemotherapy, but better predictive markers needed

JCO 2017 Harbeck; Lancet Oncol 2018 Hurvitz
Conclusions **HER2+ early breast cancer in older patients**

- Fit older pts can receive standard therapy
- **Deescalation** often possible for
  - Patients who desire to avoid classical chemo side effects
  - Unfit/frail patients
- Most suitable deescalation possibilities for elderly:
  - Upfront surgery -> adjuvant Paclitaxel Trastuzumab +/- Pertuzumab
  - Upfront surgery -> adjuvant trastuzumab without chemo (if chemo not feasible)
  - Neoadjuvant Paclitaxel Trastuzumab Pertuzumab -> T-DM1 if no pCR
  - Shorter duration of antiHER2 therapy
  - …