What’s new for HER2 positive Early Breast Cancer?

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• Review of recent clinical trial results of HER2 positive EBC
  • Escalation : KATHERINE
  • De-escalation: PERSEPHONE, RESPECT, PerElisa

• Ongoing trials and future perspectives
HER2 positive early breast cancer

- HR of relapse in patients with biopsy proven stage I ~ III breast cancer: improvement in HER2+ patients most striking

Between 1986 and 1992

Between 2004 and 2008

Even better outcome with dual blockade – APHINTY trial IDFS

Biomarker!

HR 0.81; 95% CI 0.66–1.00; p = 0.0446

Needs more therapy - Escalation

Needs Less therapy – De-escalation
non-pCR in HER2 positive BC

Association between pCR and long term outcomes strongest in TNBC & HER2+ BC who received trastuzumab
HR: 0.39 (95% CI: 0.31-0.50) : poor prognosis with non-pCR pts

Cortazar P et al, Lancet 2014;384: 164–72
Katherine: Phase III adjuvant study

HER2(+), non-metastatic BC T1-4, N0-3 at presentation (n=1484)

Preoperative therapy
Taxane ± Anthracycline

Residual tumor

T-DM1
14 cycles

Trastuzumab
14 cycles

3 year IDFS

Stratification factors;
Inoperable vs operable
HR (+) vs HR (-) or unknown
Preoperative T vs T + other HER2 targeted agents
ypN (+) vs ypN0/not done

At least 6 cycles, including at least 9 weeks of taxane and trastuzumab

## Baseline demographics & clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trastuzumab Group</th>
<th>T-DM1 Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=743</td>
<td></td>
<td>N=743</td>
</tr>
<tr>
<td>Median Age (range) - yr</td>
<td>49 (23-80)</td>
<td>49 (24-79)</td>
</tr>
<tr>
<td>Clinical stage at presentation – no of pts (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inoperable breast cancer</td>
<td>190 (25.6)</td>
<td>185 (24.9)</td>
</tr>
<tr>
<td>Operable breast cancer</td>
<td>553 (74.4)</td>
<td>558 (75.1)</td>
</tr>
<tr>
<td>HR status – no of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER negative and PR negative</td>
<td>203 (27.3)</td>
<td>209 (28.1)</td>
</tr>
<tr>
<td>ER positive, PR positive or both</td>
<td>540 (71.7)</td>
<td>534 (71.9)</td>
</tr>
<tr>
<td>Previous use of anthracyclines – no of pts (%)</td>
<td>564 (75.9)</td>
<td>579 (77.9)</td>
</tr>
<tr>
<td>Neoadjuvant HER2 targeted therapy – no of pts (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab alone</td>
<td>596 (80.2)</td>
<td>600 (80.8)</td>
</tr>
<tr>
<td>Trastuzumab plus pertuzumab</td>
<td>139 (18.7)</td>
<td>133 (17.9)</td>
</tr>
<tr>
<td>Trastuzumab plus other HER2 targeted therapy</td>
<td>8 (1.1)</td>
<td>10 (1.3)</td>
</tr>
</tbody>
</table>
KATHERINE: Invasive DFS

HR : 0.50 (95% CI: 0.39-0.64; P < 0.001)
### Subgroup analysis of IDFS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>T-DM1</th>
<th>Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. of patients with an invasive-disease event/total no.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>91/743</td>
<td>165/743</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 yr</td>
<td>20/143</td>
<td>37/153</td>
</tr>
<tr>
<td>40–64 yr</td>
<td>64/542</td>
<td>113/522</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>7/58</td>
<td>15/68</td>
</tr>
<tr>
<td>Clinical stage at presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inoperable breast cancer</td>
<td>42/185</td>
<td>70/190</td>
</tr>
<tr>
<td>Operable breast cancer</td>
<td>49/558</td>
<td>95/553</td>
</tr>
<tr>
<td>Hormone-receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (ER-negative and progesterone-receptor–negative or unknown)</td>
<td>38/209</td>
<td>61/203</td>
</tr>
<tr>
<td>Positive (ER-positive, progesterone-receptor–positive, or both)</td>
<td>53/334</td>
<td>104/540</td>
</tr>
<tr>
<td>Preoperative HER2-directed therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab alone</td>
<td>78/600</td>
<td>141/596</td>
</tr>
<tr>
<td>Trastuzumab plus additional HER2-directed agent or agents</td>
<td>13/143</td>
<td>24/147</td>
</tr>
<tr>
<td>Pathological nodal status after preoperative therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-positive</td>
<td>62/343</td>
<td>103/346</td>
</tr>
<tr>
<td>Node-negative or NE</td>
<td>29/400</td>
<td>62/397</td>
</tr>
<tr>
<td>Primary tumor stage at definitive surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0, ypT1a, ypT1b, ypT1mic, ypTiS</td>
<td>40/331</td>
<td>52/306</td>
</tr>
<tr>
<td>ypT1, ypT1c</td>
<td>14/175</td>
<td>42/184</td>
</tr>
<tr>
<td>ypT2</td>
<td>25/174</td>
<td>44/185</td>
</tr>
<tr>
<td>ypT3</td>
<td>9/51</td>
<td>21/57</td>
</tr>
<tr>
<td>ypT4</td>
<td>3/12</td>
<td>6/11</td>
</tr>
<tr>
<td>Regional lymph-node stage at definitive surgery</td>
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<td></td>
</tr>
<tr>
<td>ypN0</td>
<td>28/344</td>
<td>56/335</td>
</tr>
<tr>
<td>ypN1</td>
<td>29/220</td>
<td>50/213</td>
</tr>
<tr>
<td>ypN2</td>
<td>16/86</td>
<td>38/103</td>
</tr>
<tr>
<td>ypN3</td>
<td>17/37</td>
<td>15/30</td>
</tr>
<tr>
<td>ypNX</td>
<td>1/56</td>
<td>6/62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio for Invasive-Disease Event (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1</td>
<td>0.50</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>0.39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3-Yr Invasive Disease–free Survival Rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1</td>
<td>88.3</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>86.5</td>
</tr>
</tbody>
</table>

T-DM1 Better vs Trastuzumab Better

0.20 0.50 1.00 2.00 5.00
Risk of first invasive-disease event by neoadjuvant HER2-targeted therapy in the ITT population

No prior pertuzumab
Unstratified HR = 0.489
(95% CI, 0.371-0.645)

Prior pertuzumab
Unstratified HR = 0.498
(95% CI, 0.249-0.995)
Secondary endpoints DRFS and OS

- HR : 0.60 (95% CI: 0.45-0.79)
- 3 year freedom from recurrence: 89.7% vs 83%

- HR: 0.70 (95% CI: 0.47-1.05)
Summary of AEs in the safety population

Grade 3 adverse event that occurred in ≥ 1% of patients

Summary & discussion

• T-DM1 significantly prolonged IDFS compared with trastuzumab in HER2+ EBC with residual invasive disease after neoadjuvant chemotherapy and HER2 targeted therapy
  • HR: 0.50 (95% CI: 0.39-0.64; P < 0.001)
  • Benefit with T-DM1 across all subgroups, including patients with prior pertuzumab in the neoadjuvant setting

• More AEs, SAEs, AE leading to discontinuation but no unexpected safety signals

• Recommended in NCCN guideline: “If HER-2 positive If residual disease: T-DM1 (Category 1) alone for 14 cycles. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (Category 1) ± pertuzumab to complete on year of therapy”
## Shorter duration of anti-HER2 treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemo Backbone</th>
<th>Duration</th>
<th>N</th>
<th>DFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARE&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Investigator choice</td>
<td>6 mos</td>
<td>1690</td>
<td>84.9% (48m)</td>
<td>1.28 (1.05-1.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 mos</td>
<td>1690</td>
<td>87.8%</td>
<td></td>
</tr>
<tr>
<td>Short-HER&lt;sup&gt;2&lt;/sup&gt;</td>
<td>TH#3-FEC#3</td>
<td>9 weeks</td>
<td>626</td>
<td>85.4%</td>
<td>1.15 (0.91-1.46)</td>
</tr>
<tr>
<td></td>
<td>AC/FEC#4-TH#4-H</td>
<td>12 mos</td>
<td>627</td>
<td>87.5%</td>
<td></td>
</tr>
<tr>
<td>SOLD&lt;sup&gt;3&lt;/sup&gt;</td>
<td>TH#3-FEC#3</td>
<td>9 wks</td>
<td>1085</td>
<td>88.0% (5y)</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>TH#3-FEC#3-H</td>
<td>12 mos</td>
<td>1089</td>
<td>90.5%</td>
<td></td>
</tr>
<tr>
<td>Hellenic group&lt;sup&gt;4&lt;/sup&gt;</td>
<td>ddFEC-T</td>
<td>6 vs 12 months</td>
<td>481</td>
<td>93.3% vs 95.7% (3yr)</td>
<td>1.57 (0.86-2.10)</td>
</tr>
<tr>
<td>Persephone&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Investigator choice</td>
<td>6 vs 12 months</td>
<td>4000</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

PERSEPHONE: 6 vs 12 mo of adjuvant trastuzumab, non-inferiority trial

HER2(+) EBC
Known HR
Consent before 10th
trastuzumab (n=4088)

Stratification
ER status
Chemo (A vs T vs
A & T vs other)
Adj / neoadj
Concurrent/
sequential T

R

Trastuzumab
6 months

Trastuzumab
12 months

DFS

4 y DFS with 12 months of
Trastuzumab: estimated at
80%, 1 sided significance 5%
Power 85%, non inferiority:
no worse than 3% below

Earl H, et al. ASCO 2018
Disease free survival

Earl H, et al. ASCO 2018
DFS: Pre-defined subgroup analysis

**ER**

- **Negative**
  - Events/Patients: $121/632$ (19.1%) at 6 months, $99/633$ (15.6%) at 12 months
  - Hazard Ratio & CI: 1.26 (0.97, 1.64)

- **Positive**
  - Events/Patients: $144/1411$ (10.2%) at 6 months, $148/1412$ (10.5%) at 12 months
  - Hazard Ratio & CI: 0.96 (0.76, 1.20)

**CT Type**

- **Anthracine-based**
  - Events/Patients: $93/846$ (11.0%) at 6 months, $108/854$ (12.6%) at 12 months
  - Hazard Ratio & CI: 0.86 (0.65, 1.13)

- **Taxane-based**
  - Events/Patients: $28/203$ (13.8%) at 6 months, $11/200$ (5.5%) at 12 months
  - Hazard Ratio & CI: 2.47 (1.31, 4.62)

- **Anthracine+Taxane**
  - Events/Patients: $144/901$ (16.0%) at 6 months, $127/869$ (14.8%) at 12 months
  - Hazard Ratio & CI: 1.14 (0.90, 1.44)

- **Neither**
  - Events/Patients: $0/3$ (0%) at 6 months, $1/2$ (50%) at 12 months
  - Hazard Ratio & CI: 1.07 (0.90, 1.28)

**CT Timing**

- **Adjuvant**
  - Events/Patients: $194/1731$ (11.2%) at 6 months, $197/1737$ (11.3%) at 12 months
  - Hazard Ratio & CI: 0.98 (0.81, 1.20)

- **Neo-adjuvant**
  - Events/Patients: $71/312$ (22.8%) at 6 months, $81/308$ (26.2%) at 12 months
  - Hazard Ratio & CI: 1.43 (1.00, 2.04)

- **Stratified**
  - Events/Patients: $265/2043$ (13.0%) at 6 months, $247/2045$ (12.1%) at 12 months
  - Hazard Ratio & CI: 1.07 (0.90, 1.28)

**Trastuzumab Timing**

- **Concurrent (with CT)**
  - Events/Patients: $123/652$ (18.9%) at 6 months, $82/851$ (9.8%) at 12 months
  - Hazard Ratio & CI: 1.53 (1.16, 2.01)

- **Sequential (after CT)**
  - Events/Patients: $142/1091$ (13.0%) at 6 months, $165/1094$ (15.1%) at 12 months
  - Hazard Ratio & CI: 0.84 (0.68, 1.06)

- **Unstratified**
  - Events/Patients: $265/2043$ (13.0%) at 6 months, $247/2045$ (12.1%) at 12 months
  - Hazard Ratio & CI: 1.07 (0.90, 1.27)

*Interaction between 2 groups $\chi^2 = 2.3; p = 0.13$*

*Heterogeneity between 4 groups $\chi^2 = 11.1; p = 0.01$*

*Interaction between 2 groups $\chi^2 = 3.2; p = 0.07$*

*Interaction between 2 groups $\chi^2 = 10.8; p = 0.001$*
Overall survival

Earl H, et al. ASCO 2018
Summary of PERSEPHONE

• 6 months of adjuvant trastuzumab is non-inferior to 12 months (4yr DFS: 89.4% vs 89.8%; HR = 1.07)

• Reduced cardiac & other toxicities, and costs both to patients and healthcare systems

• Valuable results for low-resource countries

• stopped trastuzumab because of cardiotoxicity: 8% (12mo) vs 4% (6mo), p < 0.0001

• 6 months group had more rapid recovery of cardiac function
RESPECT: adjuvant trastuzumab monotherapy in older patients

HER2(+) BC 70-80 yrs old Stage1 (pT > 0.5cm), 2A, 2B, 3A (n=274) → Trastuzumab

HER2(+) BC 70-80 yrs old Stage1 (pT > 0.5cm), 2A, 2B, 3A (n=274) → Trastuzumab + chemotherapy

Investigator’s choice (PTx, DTx, AC, EC, FEC, CMF, TC, TcbH) → DFS
DFS at 3 yrs: 94.8% in H+CT vs 89.2% in H arm (HR = 1.42; 95% CI, 0.68 to 2.95, P = 0.35). FACT-G score: H: 42.9% vs H+CT: 25.3%, P = 0.021.

Sawaki M, et al. 2018 ASCO
RESPECT

- Older patients do benefit from standard treatment
- Attempt of de-escalation does not always succeed
- Inclusion of ‘older patients’ : not just based on chronologic age

- Still, there are patients who can do very well with even single agent trastuzumab : 3 year DFS 89.2% with trastuzumab alone – need robust biomarker to select candidates for de-escalation

CALGB 49907: CMF or AC vs capecitabine in older women ≥ 65 y

PerELISA neoadjuvant study

- Histologically confirmed, IDC, stage II-III A, HR positive (ER ≥ 10%), HER2 positive, postmenopausal, LVEF within normal range, adequate organ function)

- Paclitaxel
- Trastuzumab
- Pertuzumab
- Letrozole
- Trastuzumab
- Pertuzumab

Diagnostic Core Biopsy

2 wks

Core needle biopsy for molecular response

Molecular responders

Letrozole

Trastuzumab

Pertuzumab

Molecular non-responders

Paclitaxel

Trastuzumab

Pertuzumab

Molecular response: ↓ Ki67 > 20% from baseline

pCR

Guarneri V, et al. 2018 ASCO
Outcome: pCR according to molecular response

Molecular non responders

- pCR (breast & axilla): 81.3%
- Breast OR (US): 94%
- BCS: 62.5%
- Conversion from...

Molecular responders

- pCR (breast & axilla): 20.5%
- Breast OR (US): 74%
- BCS: 65.9%
- Conversion from...

Guarneri V, et al. 2018 ASCO
PAM50 and molecular response

Guarneri V, et al. 2018 ASCO
Summary of PerELISA trial

• In molecular responding patients, letrozole + trastuzumab and pertuzumab resulted in 20% breast and axillary LN pCR

• Baseline TILs and PIK3CA mutational status were not associated with molecular response or pCR

• Intrinsic subtype by PAM50 was significantly associated with molecular response and response with pCR

  • HER2 enriched subtype further enriches for patients most likely benefit from the de-escalated approach.

Guarneri V, et al. 2018 ASCO
ATEMPT

Stage 1 HER2+ BC
ER+ or ER-
PS 0-1
Adequate organ function
(N = 500)

Paclitaxel + Trastuzumab x 12
→
Trastuzumab q 3 weeks x 13

T-DM1 q 3 weeks x 17

R

Paclitaxel + Trastuzumab x 12 →
Trastuzumab q 3 weeks x 13
Curative surgery
HER2 positive
LN positive or >2cm (n=1484)

R

FEC AC EC

FEC AC EC

T-DM1 + Pertuzumab

Taxane + Trastuzumab + pertuzumab

IDFS IDFS in LN(+)
Summary

• Excellent outcome of HER2 positive EBC with recent study results
  • Addition of adjuvant pertuzumab, extension of neratinib
  • T-DM1 in patients with residual invasive disease after neoadjuvant treatment

• Still escalation and de-escalation strategies are needed to further improve outcome & reduce toxicities in the treatment of HER2+ EBC

• 1 year of adjuvant anti-HER2 treatment still standard but 6 months treatment can be valuable option for resource limited settings & to reduce cardiotoxicities

• Biomarker to reliably identify those who need de-escalation strategies (such as endocrine plus anti-HER2 therapy or anti-HER2 therapy only) needed