(NEO-)ADJUVANT THERAPY FOR HER-2+ BREAST CANCER

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Disclosures

• Advisory Boards, Honorariums or Travel
  – Astra Zeneca, Eisai, Genentech, Merck, Novartis, Pfizer, Roche
Introduction of new treatment modalities over time has improved recurrence outcomes in the ADJUVANT setting

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Improvement in recurrence rate after 5 years</th>
<th>RR 5 years vs. tam 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>+9.9%</td>
<td>RR = 0.70</td>
</tr>
<tr>
<td>CMF</td>
<td></td>
<td>RR = 0.89</td>
</tr>
<tr>
<td><strong>Anthracyclines</strong></td>
<td></td>
<td>RR = 0.84</td>
</tr>
<tr>
<td><strong>Anthracycline + taxane combination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td>+11.4%</td>
<td>RR = 0.69</td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td></td>
<td>RR = 0.80</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab + chemo</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; CMF, cyclophosphamide, methotrexate and fluorouracil; HR, hazard ratio; RR, risk ratio.

Consistent & significant benefit of adjuvant trastuzumab
Four pivotal trials (>12,000 pts) established 18 cycles (1 year) of adjuvant trastuzumab as the SoC for HER2-positive eBC


IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation; SoC, standard of care.
These adjuvant trials demonstrated consistent DFS and OS benefit with 1 year of trastuzumab versus observation.

<table>
<thead>
<tr>
<th>Study</th>
<th>FU (yrs)</th>
<th>N</th>
<th>DFS</th>
<th>HR</th>
<th>OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA1–5</td>
<td>1</td>
<td>3387</td>
<td></td>
<td>0.54</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3401</td>
<td></td>
<td>0.64</td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>CT* ± RT→H (1 year) vs.</td>
<td>4</td>
<td>3401</td>
<td></td>
<td>0.76</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>CT* ± RT</td>
<td>8</td>
<td>3401</td>
<td></td>
<td>0.76</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3399</td>
<td></td>
<td>0.76</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>AC→TH vs. AC→T</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>TCH vs. AC→T</td>
<td>10.3</td>
<td>3222</td>
<td></td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint analysis7–9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>(NCCTG N9831/NSABP B-31)</td>
<td>2</td>
<td>3351</td>
<td></td>
<td>0.48</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>4045</td>
<td></td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC→PacH vs. AC→Pac</td>
<td>8.4</td>
<td>4046</td>
<td></td>
<td>0.60</td>
<td></td>
<td>0.88</td>
</tr>
</tbody>
</table>

* Selected from a list of approved regimens consisting of ≥4 cycles.
AC, doxorubicin plus cyclophosphamide; CT, chemotherapy; DFS, disease-free survival; FU, follow-up; H, trastuzumab; OS, overall survival; Pac, paclitaxel; RT, radiotherapy; T, docetaxel; TCH, docetaxel, carboplatin.

Optimal Chemotherapy regimen?
(anthracyclines: to give or not give!)
BCIRG 006 - > can we avoid anthracycline?

BCIRG 006: DFS final analysis (10.3 years’ MFU)

MFU, median follow-up

**Table 2. Therapeutic Index for Critical Clinical Events.**

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>AC-T</th>
<th>AC-T plus Trastuzumab</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>201</td>
<td>146</td>
<td>149</td>
</tr>
<tr>
<td>Distant breast-cancer recurrence</td>
<td>188</td>
<td>124</td>
<td>144</td>
</tr>
<tr>
<td>Grade 3 or 4 congestive heart failure</td>
<td>7</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>6</td>
<td>1</td>
<td>1†</td>
</tr>
</tbody>
</table>

*This therapeutic index is a compilation of the numbers of distant breast-cancer recurrences, cases of congestive heart failure, and cases of acute leukemia. AC-T denotes doxorubicin and cyclophosphamide followed by docetaxel, and TCH docetaxel, carboplatin, and trastuzumab.

†This case of acute leukemia developed after the patient received an anthracycline as part of a combination chemotherapy regimen for a diffuse large B-cell lymphoma that occurred after she received treatment with TCH for breast cancer.
Clinical Implications of BCIRG 006

- We don’t know how safe it is to withhold anthracyclines and in which pts (trial not powered to show equivalence; trial hypothesis (TCH better) not proven)

- TCH associated with less cardiotoxicity and less leukemia (associated with A or C??!!)

**ONLY POSSIBLE CLINICAL RECOMMENDATION:**

- TCH is a very good option and should be chosen when cardiac risk factors or c.i. for anthracyclines are present
What about **duration** of trastuzumab?

1 vs. 2 years: HERA

9 weeks: FinHER (Finland)

1 year vs. 3 ms: E 2198 (US)

1 year vs. 9 weeks: ShortHER

1 year vs. 9 weeks: SOLD

1 year vs. 6 ms: PHARE (France)

1 year vs. 6 ms: HeCOG (Greece)

1 year vs. 6 ms: Persephone (UK)
HERA: Longer duration of trastuzumab did not improve outcomes

- No added benefit for 2 years
- Independent of ER status
- Higher cardiac toxicity for 2 years


CI, confidence interval; obs, observation.
PHARE failed to show non-inferiority of 6 months vs. 1 year of trastuzumab treatment

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>2-yr DFS (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab 1 yr</td>
<td>175</td>
<td>93.8% (92.6–94.9)</td>
<td>1.28 (1.05, 1.56)</td>
<td>0.29</td>
</tr>
<tr>
<td>Trastuzumab 6 mo</td>
<td>219</td>
<td>91.1% (89.7–92.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Short-HER: Study Design

Stratification factors: HR status, Nodal status
Radiotherapy and hormonal therapy started at the completion of ChemoRx, when indicated

EUDRACT number: 2007-004326-25
NCI ClinicalTrials.gov number: NCT00629278

Non-inferiority study:
HR = 1.29,
Alpha: 0.05 (one tail)
Power: 80%

n = 1250 pts
SHORTHer Primary Objective of DFS

5.2 yrs Follow-up N = 1253

HR = 1.15 (0.91 – 1.46); 0.78 probability 5yr DFS (87.5% LONG vs. 85.4% SHORT)

Subset Analyses:

<table>
<thead>
<tr>
<th>Subset</th>
<th>Ratio of HRs (90%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III vs I+II</td>
<td>2.30 (1.35, 3.94)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nodal status N2+N3 vs N0+N1</td>
<td>2.25 (1.33, 3.83)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HR>1.0 favors LONG

No difference in 5 yr OS (95.1 vs 95%)

Anders ASCO 2017
ShortHER: Cardiac Adverse Events

<table>
<thead>
<tr>
<th>Grade</th>
<th>Long N=627</th>
<th>Short N=626</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>69 (11.0)</td>
<td>22 (3.5)</td>
</tr>
<tr>
<td>3</td>
<td>12 (1.9)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>4</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>82 (13.1)</td>
<td>27 (4.3)</td>
</tr>
</tbody>
</table>

HR = 0.32 (95% CI 0.21;0.50) p<0.0001

Anders ASCO 2017
Duration of adjuvant trastuzumab: **DON’T CHANGE YOUR PRACTICE**

Duration of adjuvant trastuzumab: **STORY NOT FINISHED**

In total about **15,000 pts** enrolled to answer duration question!

Need to identify biomarkers to allow to identify de-escalate!
(Aleix Prat ASCO 2018, Her2 Enriched)
Outcomes for T1a/bN0 HER2+ Tumors

MD Anderson Series

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>n</th>
<th>5 yr RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>98</td>
<td>77.1%</td>
</tr>
<tr>
<td>HER2-</td>
<td>867</td>
<td>93.7%</td>
</tr>
</tbody>
</table>

NCCN Series

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>n</th>
<th>5 yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>255</td>
<td>83.3%</td>
</tr>
<tr>
<td>HER2-</td>
<td>3127</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

Gonzalez-Angulo A M et al. JCO 2009;27:5700-5706
Vaz-Luis, I et al. ASCO Meeting 2013, abstract 1006

Tolaney ASCO 2017
Risk of Disease Recurrence at 5 yrs

- Definitions vary
- With these caveats, without treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>2 – 10%</td>
</tr>
<tr>
<td>T1b</td>
<td>5 – 20%</td>
</tr>
<tr>
<td>T1c</td>
<td>10 – 25%</td>
</tr>
</tbody>
</table>
APT (Tolaney) trial: Adjuvant paclitaxel and trastuzumab for low-risk HER2-positive breast cancer

- HER2-positive
- ER+ or ER–
- Node-negative tumour ≤3 cm

N = 406

Primary endpoint: Invasive DFS

Paclitaxel (80 mg/m²) + trastuzumab (2 mg/kg) x 12 weeks (q1w)**

Q3w doses of trastuzumab (6 mg/kg) x 13‡

Total 18 cycles of trastuzumab

NOTE: This is a single-arm, single-centre study, so is unable to provide definitive data on treatment benefit

* Loading dose of 4 mg/kg IV trastuzumab on Day 1;
† Radiation and hormonal therapy was initiated after completion of paclitaxel;
‡ Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks; qxw, every x weeks.
ER, oestrogen receptor

Tolaney NEJM 2015
APT Trial
7 year Update ASCO 2017

Tolaney SM et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC).
Poster discussion at ASCO 2017, 2–6 June, Chicago, IL, USA (Abstract 511).
APT (Tolaney) trial: IDFS rates in small, node-negative tumours

Tolaney SM, et al. ASCO 2017 (Abstract 511). PR, progesterone receptor
Docetaxel/Cyclophosphamide/Trastuzumab for Early Stage HER2+ Cancers

Stage I – II HER2-positive Early breast cancer → Docetaxel/Cyclophosphamide/Trastuzumab X 4 → Trastuzumab

Jones Lancet Oncol 2013
ATEMPT Trial Schema

Stage I
HER2+*  
ER+ or ER-  
PS 0-1  
Adequate organ fx

N=500

3

Trastuzumab-DM1 q3weeks X17
N=375

1

Paclitaxel + Trastuzumab x12  
Trastuzumab q3weeks x13

N=125

*HER2-positive defined as IHC 3+ or FISH≥2.0; will be confirmed by central HER2 testing prior to study enrollment
Adjuvant endocrine therapy can be initiated after completion of 12 weeks of therapy
Adjuvant radiation therapy can be administered concurrently with study treatment.

Presented By Sara Tolaney at 2017 ASCO Annual Meeting
International guidelines recommend the APT treatment regimen in patients with small, node-negative tumours

**Adjuvant therapy: HER2 targeted therapy**
Paclitaxel and trastuzumab is an effective regimen for stage I breast cancers with low rates of recurrence.

**Adjuvant systemic treatment**
Luminal B HER2-positive tumours are treated with chemotherapy, endocrine therapy and trastuzumab [I, A].* No randomised data exist to support omission of chemotherapy in this group. However, in small, node-negative tumours, combination of single-agent paclitaxel and trastuzumab provides excellent results.

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* Level of evidence I: Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity; Grade of recommendation A: strong evidence for efficacy with a substantial clinical benefit, strongly recommended.

Adjuvant Therapy For Stage 1 HER2+ Disease

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Action</th>
<th>ER Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mm</td>
<td>SELECTIVELY</td>
<td>ER-</td>
</tr>
<tr>
<td>0.1-0.5 cm</td>
<td>YES</td>
<td>ER-</td>
</tr>
<tr>
<td>0.6-1.0 cm</td>
<td>YES</td>
<td>ER+</td>
</tr>
<tr>
<td>1.1-2.0 cm</td>
<td>YES</td>
<td>ER+</td>
</tr>
</tbody>
</table>

Group of patients with small tumors represent optimal group to begin to evaluate reductions in chemotherapy and non-chemotherapy options.
Advantages of neoadjuvant over adjuvant therapy in breast cancer

- Increased rates of BCS and fewer mastectomies\(^1\)–\(^4\)
- Smaller patient population required and more rapid results:\(^5\) new therapies available to patients quicker
- Assessment of pCR allows early evaluation of therapeutic effect\(^4\)
  - pCR predictive of survival benefit\(^4,6\)
- Comparable survival benefit\(^1,2\)

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**Adjuvant trial:**


**Neoadjuvant trial:**

BCS, breast-conserving surgery;

pCR, pathological complete response.
Impact on pCR rates from the addition of trastuzumab to neoadjuvant chemotherapy in patients with HER2-positive EBC

**MD Anderson**
- H+(T→FEC)
- T→FEC
  - n = 45
  - n = 19
  - 26*
  - p = not reported

**NOAH**
- H+(AC→T→CMF)
- AC→T→CMF
  - n = 117
  - n = 118
  - 22†
  - p < 0.0007

**GeparQuattro**
- H+(EC→T[(X)])
  - EC→T→X (HER2-negative)
  - n = 445
  - n = 1050
  - 32*
  - p = not reported

**German trials meta-analysis**
- Chemotherapy+H
  - Chemotherapy
  - n = 662
  - n = 665
  - 27*
  - p = not reported

**CTNeoBC meta-analysis**
- Chemotherapy+H
  - Chemotherapy (hormone receptor-positive)
  - n = 385
  - n = 701
  - 30†
  - p = not reported

  - Chemotherapy (hormone receptor-negative)
  - n = 364
  - n = 471
  - 31†
  - p = not reported

* No evidence of residual invasive cancer, in breast or axilla
† No evidence of residual disease in breast tissue
‡ Absence of invasive cancer in the breast and axillary nodes; absence of DCIS/absence of invasive cancer in the breast and axillary nodes; DCIS allowed/absence of invasive cancer in the breast and DCIS allowed; regardless of nodal involvement

---

4. Loibl S, *et al.* SABCS 2011 (Abstract S5-4; oral presentation);
FDA CT NeoBC Meta-analysis

There was no correlation between magnitude of pCR difference and EFS/OS

*It can not be considered a surrogate endpoint*


\[
\text{pCR=ypT0/is ypN0} \quad \quad \quad \text{* Nominal p-value}
\]
Summary

• Is pCR a relevant surrogate endpoint for patients receiving anti-Her2 Therapy?
  – pCR is associated with an improved event free survival (EFS) for patients receiving neoadjuvant trastuzumab
  – There is a stronger association for ER-ve/Her2 positive patients
  – However, it can not be considered as a surrogate endpoint for EFS or OS.
TAKE HOME MESSAGE

If CT is needed, use the neoadjuvant setting

NEoadjuvant ChemoTherapy
HER-POSITIVE TUMORS

• Should neoadjuvant chemotherapy and anti HER2 therapy be the preferred option for HER2 positive Stage II-III patients? **94% YES**
Dual Anti Her 2 neoadjuvant trials
Key differences in design

- Inclusion of IBC/LABC
- Definition of pCR
- Choice of chemo backbone
- Duration of targeted therapy
- Completion of protocol specified therapy
- Sample Size
NeoALTTO Study Design

- Invasive operable HER2+ BC
- T >2 cm (inflammatory BC excluded)
- LVEF ≥50%

N = 450

Stratification
- T≤5 cm vs T>5 cm
- ER or PgR+ vs ER & PgR-
- N0-1 vs N≥2
- Conservative surgery or not

52 weeks of anti-HER2 therapy

IBC exclusion criteria

NeoALTTO: Overall Clinical Response at 6 weeks (w/o chemo) and at surgery

L = lapatinib; T = trastuzumab

At Week 6 (w/o chemo)
- L: N = 154, % Response = 52.6
- T: N = 149, % Response = 30.2
- L+T: N = 152, % Response = 67.1

At surgery
- L: N = 154, % Response = 74
- T: N = 149, % Response = 70.5
- L+T: N = 152, % Response = 80.3

P < .001
P = .49
P = .049

**NeoALTTO trial**

**Overall Survival Analysis by treatment arm**

**MEDIAN FU: 6.7 years**

Jens Huober et al, ESMO 2017

Tests for interaction:
- L + T vs T x HR p = 0.45
- L vs T x HR p = 0.72

Results of first analysis of EFS/OS are shown in square brackets to provide comparison with this update. De Azambuja et al. Lancet Oncol 2014
Landmark Analysis: OS by PCR

**Tests for interaction:** pCR x HR p=0.33

Results of first analysis of EFS/OS are shown in square brackets to provide comparison with this update. De Azambuja et al. Lancet Oncol 2014.
Operable Breast Cancer HER-2 neu Positive

Tissue for Biomarkers

AC → WP+T

AC → WP+L

AC → WP+T+L

WP=Weekly Paclitaxel

SURGERY

Trastuzumab for a total of 1 year

Accrued 529 patients from July 16, 2007 to June 30, 2011
NSABP B-41
pCR Breast by Hormone Receptor Status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>HR (vs. T)</th>
<th>P (vs. T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→WP+T</td>
<td>179</td>
<td>10</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>AC→WP+L</td>
<td>171</td>
<td>17</td>
<td>1.52 (0.69, 3.35)</td>
<td>0.11</td>
</tr>
<tr>
<td>AC→WP+T+L</td>
<td>172</td>
<td>7</td>
<td>0.63 (0.24, 1.67)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Overall log-rank test: P=0.07

# At Risk
<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→WP+T</td>
<td>179</td>
<td>177</td>
<td>173</td>
<td>172</td>
<td>160</td>
<td>102</td>
</tr>
<tr>
<td>AC→WP+L</td>
<td>171</td>
<td>169</td>
<td>163</td>
<td>155</td>
<td>143</td>
<td>81</td>
</tr>
<tr>
<td>AC→WP+T+L</td>
<td>172</td>
<td>169</td>
<td>165</td>
<td>163</td>
<td>152</td>
<td>94</td>
</tr>
</tbody>
</table>
**ALTTO trial**

**Efficacy Results: OS**

- \( N = 6281 \rightarrow \) excluding patients in the lapatinib-alone arm, stopped for futility

**Disease-Free Survival (DFS) Analysis**

- No significant difference in overall survival (OS) among treatment arms

By permission of Piccart-Gebhart M et al. J Clin Oncol ASCO 2014;32(18_suppl)LBA4

**MCBS:**

No Evaluable Benefit

ALTTO investigators
ALTTO study: Adjuvant lapatinib and trastuzumab
Intrinsic Subtype Heterogeneity in Clinically HER2+ disease

- Basal-like
- HER2-enriched
- Luminal A
- Luminal B

ER+/HER2+ (N=1,648)
- Basal-like: 2.2%
- HER2-enriched: 30.0%
- Luminal A: 36.0%
- Luminal B: 31.8%

ER-/HER2+ (N=1,213)
- Basal-like: 7.4%
- HER2-enriched: 14.8%
- Luminal A: 2.7%
- Luminal B: 75.1%

Courtesy Aleix Prat
pCR by Tumor and Microenvironmental Variables

Intrinsic Subtype
- HER2E (n=82): 70%
- LumA (n=80): 80%
- LumB (n=80): 71%

Taxane and trastuzumab + lapatinib

Immune Cell Activation
- High (n=109): 36%
- Int (n=76): 40%
- Low (n=80): 17%

Carey, JCO 2016

Presented By Lisa Carey at 2018 ASCO Annual Meeting
Patients with operable or locally advanced/inflammatory* HER2-positive breast cancer

Chemo-naïve and primary tumors >2 cm (N = 417)

NeoSphere Study Design

TH (n = 107) docetaxel + trastuzumab

THP (n = 107) docetaxel + trastuzumab + pertuzumab

HP (n = 107) trastuzumab + pertuzumab

TP (n = 96) docetaxel + pertuzumab

BC, breast cancer; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel

*Locally advanced = T2-3, N2-3, M0 or T4a-c, any N, M0; operable = T2-3, N0-1, M0; inflammatory = T4d, any N, M0

NeoSphere: pCR Rates (ITT Population)

pCR, % ± 95% CI

TH: 29.0 [27.0, 31.0]
THP: 45.8 [42.0, 50.0]
HP: 16.8 [14.0, 19.0]
TP: 24.0 [20.0, 27.0]

P = .0198
P = .0141
P = .003

CI, confidence interval; H, trastuzumab; P, pertuzumab; pCR, pathologic complete response; T, docetaxel

Long term outcome (EFS): NeoSPHERE

Neoadjuvant pertuzumab added to TH

EFS HR in ER+ = 0.86
EFS HR in ER- = 0.60

Gianni, Lancet Oncol 2016
TRAIN-2: Study Design

- Multicenter, randomized phase III study in the Netherlands
  - Stratified by cT (0-2 vs 3-4), cN (neg vs pos), ER (neg vs pos), and age (< 50 vs ≥ 50 yrs)

- Primary endpoint: pCR (ypT0/is, ypN0) by local assessment
- Secondary endpoints: RFS, BCSS, OS, toxicity

*21-day cycles: PTC + pertuzumab Day 1, P Day 8; paclitaxel 80 mg/m², carboplatin AUC 6 mg-min/mL
†21-day cycles. 5-fluorouracil 500 mg/m², epirubicin 90 mg/m², cyclophosphamide 500 mg/m².
Trastuzumab 6 mg/kg with 8-mg/kg loading dose, pertuzumab 420 mg with 840-mg loading dose.
‡To complete 1 yr of adjuvant trastuzumab; endocrine therapy for ER+ and/or PgR+ tumors.

van Ramshorst MS, et al. Lancet Oncol 2018
TRAIN-2: pCR

- **FEC-T + Pertuzumab**
  - All Pts: 67% (68%)
  - ER- and PR-: 89% (84%)
  - ER+ and/or PgR+: 51% (55%)
  - *P* value for interaction: .32

- **PTC + Pertuzumab**

van Ramshorst MS, et al. Lancet Oncol 2018
NEOADJUVANT TRIALS OF DUAL BLOCKADE
TAKE HOME MESSAGES

• Dual blockage beneficial particularly in ER negative disease, in terms of pCR rates
  – Anthracycline-free options but in whom?
• Interesting RR of 2 anti-HER-2 agents alone (with no CT)
• Benefit in long term outcome NOT FULLY CONFIRMED IN THE LARGE ADJUVANT TRIALS
**APHINITY: Trial Design**

**Surgery**
- Central confirmation of HER2 status (N = 4805)
- Randomisation and treatment within 8 weeks of surgery

**Chemotherapy**
- Chemotherapy* + trastuzumab + pertuzumab
- Chemotherapy* + trastuzumab + placebo

**Follow-up**
- Anti-HER2 therapy for a total of 1 year (52 weeks) (concurrent with start of taxane)
- Radiotherapy and/or endocrine therapy may be started at the end of adjuvant chemotherapy

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

---

**APHINITY trial**

**Central confirmation of HER2 status (N = 4805)**

**Randomisation and treatment within 8 weeks of surgery**

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- Chemotherapy* + trastuzumab + pertuzumab
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**APHINITY: Intent-to-Treat Primary Endpoint Analysis**

**Invasive Disease-free Survival**

Provisional MCBS: B

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G. von Minckwitz et al, ASCO 2017, NEJM 2017
APHINITY: Study Design

- International, randomized, double-blind, placebo-controlled phase III trial\(^1\)

  - Patients with HER2+ EBC, no prior invasive BC or anticancer tx or RT, N+ any tumor size (no T0) or N0 tumor size > 1 cm, \(^*\) BL LVEF ≥ 55% (N = 4805)

  - Pertuzumab + Trastuzumab + CT\(^\dagger\) (n = 2400)

  - Placebo + Trastuzumab + CT\(^\dagger\) (n = 2405)

- Primary endpoint: IDFS per modified STEEP definition\(^2\) (excludes second primary non-BC as event)

- Secondary endpoints: IDFS per STEEP definition,\(^2\) OS, distant recurrence-free survival, DFS, recurrence-free interval, safety, cardiac safety, health-related QoL


\(^*\) Or node negative with tumors > 0.5 to ≤ 1 cm + at least 1 of following: histologic/nuclear grade 3; ER negative and PgR negative; aged < 35 yrs. Node-negative enrollment capped after first 3655 patients randomized. \(^\dagger\) Tx initiated ≤ 8 wks post surgery. Permitted CT: standard anthracycline or nonanthracycline regimens. Endocrine and/or radiotherapy
APHINITY: IDFS by Nodal Status

Node Positive

- Pertuzumab (n = 897), 32 events
- Placebo (n = 902), 29 events

Unstratified HR: 1.13 (95% CI: 0.68-1.86; \( P = .064 \))

Node Negative

- Pertuzumab (n = 1503), 139 events
- Placebo (n = 1502), 181 events

Unstratified HR: 0.77 (95% CI: 0.62-0.96; \( P = .02 \))

APHINITY: IDFS by Hormone Receptor Status

Hormone Receptor Positive

- Pertuzumab (n = 1536), 100 events
- Placebo (n = 1546), 119 events

Unstratified HR: 0.86 (95% CI: 0.66-1.13; \(P = .277\))

Hormone Receptor Negative

- Pertuzumab (n = 864), 71 events
- Placebo (n = 858), 91 events

Unstratified HR: 0.76 (95% CI: 0.56-1.04; \(P = .085\))


Slide credit: clinicaloptions.com
APHINITY: IDFS in subgroup with HR-negative disease

A. Hormone receptor-negative

How do NNTs for DFS in the APHINITY trial compare with other trials?

<table>
<thead>
<tr>
<th>Study arm</th>
<th>HERA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>BCIRG-006&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>Joint analysis&lt;sup&gt;4&lt;/sup&gt;</th>
<th>APHINITY&lt;sup&gt;6&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Observati</td>
<td>AC-T</td>
<td>AC-T</td>
<td>H + chemo</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>NNTs for DFS</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
<th>8 years</th>
<th>10 years</th>
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<tbody>
<tr>
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<td>143</td>
<td>112</td>
<td>59</td>
<td>–</td>
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</tr>
</tbody>
</table>

Interim OS results are still immature and have not yet reached statistical significance

Strata: nodal status and protocol version, intended adjuvant chemotherapy regimen and central hormone receptor status

Hazard ratios were estimated by Cox regression

NOTE: The adjusted two-sided significance level for the first interim analysis of OS is <0.00001


Strata: nodal status and protocol version, intended adjuvant chemotherapy regimen and central hormone receptor status

Hazard ratios were estimated by Cox regression

NOTE: The adjusted two-sided significance level for the first interim analysis of OS is <0.00001

ExteNET 5-Yr Update: Neratinib vs Placebo After Adjuvant Trastuzumab in HER2+ EBC

Primary endpoint: IDFS at 2 yrs

Primary analysis of 2-yr IDFS rate: neratinib, 93.9%; placebo, 91.6% (HR: 0.67; 95% CI: 0.50-0.91; \( P = .0091 \))

ExteNET: 5-Yr IDFS Analysis

HR: 0.73 (95% CI: 0.57-0.92; \( P = .0083 \))

Patients at Risk, n
Neratinib 1420 1316 1272 1225 1106 978 965 949 938 920 88
Placebo 1420 1354 1298 1248 1142 1029 1011 991 978 958 5

ExteNET: 5-Yr IDFS Analysis by Hormone Receptor Status

Hormone Receptor Positive

- Patients at Risk, n
  - Neratinib: 816, 815, 757, 779, 816, 757
  - Placebo: 815, 779, 750, 779

- IDFS (%) at 60 months:
  - Neratinib: 98.1%, 96.1%, 91.7%, 89.8%, 88.5%, 86.8%
  - Placebo: 97.5%, 94.7%, 92.8%, 91.8%, 90.8%, 90.4%

HR: 0.60 (95% CI: 0.43-0.83)

Hormone Receptor Negative

- Patients at Risk, n
  - Neratinib: 604, 559, 541, 520, 464, 407, 400, 391, 384, 376, 362
  - Placebo: 605, 575, 548, 529, 495, 448, 444, 435, 427, 416, 402

- IDFS (%) at 60 months:
  - Neratinib: 97.5%, 94.7%, 92.8%, 90.8%, 89.9%
  - Placebo: 94.7%, 91.8%, 90.4%, 89.3%, 88.8%

HR: 0.95 (95% CI: 0.66-1.35)

Considerations for Management of Neratinib-Induced Diarrhea: Prophylaxis

**Loperamide at First Dose of Neratinib**

- Give patients instructions for use of loperamide (potential to adjust dose if constipation occurs)

**Neratinib Dose Modifications**

Hold if grade 2 lasting ≥ 5 days or grade 3 lasting ≥ 2 days or any grade with complicated features*

<table>
<thead>
<tr>
<th>Time</th>
<th>Loperamide Dose</th>
<th>Dose Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wks 1-2</td>
<td>4 mg</td>
<td>3 times per day</td>
</tr>
<tr>
<td>Wks 3-8</td>
<td>4 mg</td>
<td>2 times per day</td>
</tr>
<tr>
<td>Wks 9+</td>
<td>4 mg</td>
<td>As needed, no more than 16 mg/day</td>
</tr>
</tbody>
</table>

*Includes dehydration, fever, hypotension, renal failure, or grade 3/4 neutropenia.

Resume neratinib

- at same dose (Wks 1-2 & Wks 3-8)
- at reduced dose (Wks 9+)

Resume neratinib at reduced dose (200/160/120 mg/day)

Resume neratinib at same dose (Wks 1-2 & Wks 3-8)

Resume neratinib at same dose (Wks 9+)

Resume neratinib at reduced dose (200/160/120 mg/day)

**ADAPT HER2+ / HR+ TRIAL**

- **International, prospective, randomized phase II trial**

- **Primary endpoint:** pCR (no invasive carcinoma in breast/nodes)
- **Secondary endpoints:** dynamic testing evaluation, EFS, OS, safety

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

**Treatment arms:**
- **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)**

**Wk 12**

**Surgery†**

*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

- 12-wk T-DM1 increased pCR rate vs trastuzumab + ET in women with HER2+/HR+ EBC
  - 41% vs 15%, respectively ($P < .001$)
  - Addition of ET to T-DM1 did not raise pCR rate
  - Menopausal status had minimal bearing on results
- Tolerable safety profile with low toxicity
- Early response significantly associated with increased pCR rate
  - Detectable after 3 wks
  - Authors conclude further investigation of T-DM1 in pts with EBC warranted

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

Based on NeoSphere, NeoAltto, Tryphaena

Courtesy G. Curigliano
What about de-escalation?

WSG-ADAPT HER2+/HR- phase II Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Subset</th>
<th>pCR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + Pertuzumab + Navelbine</td>
<td>ypT0/is, ypN0</td>
<td>38/42 (90.5%)</td>
</tr>
<tr>
<td>Trastuzumab + Pertuzumab</td>
<td>ypT0, ypN0</td>
<td>33/42 (78.6%)</td>
</tr>
</tbody>
</table>

- Standard chemotherapy/completion of tyr Trastuzumab obligatory in all cases except pCR at surgery (optionally 1 yr trastuzumab only)

Nitz et al. Annals of Oncology Sep 2017
Evolving Standard of HER2 Treatment

More or Less

De-escalation of Treatment

- T1a/T1b/T1c
- Node Negative
- ? Patients achieving pCR
- ? Immunomodulatory host factors

Escalation (incorporation of newer tx)

- Node positive
- LABC/Inflammatory
- ? no pCR
- ? Resistant Phenotype/Signatures
How are we going to get there?

The biological complexity of HER2+ breast cancer

- HER2+ disease today
  - HER2 +3
  - HER2 ISH+
  - ER-positive
  - ER-negative

- HER2+ tumor cell features
  - mRNA
  - microRNA
  - Protein
  - DNA Copy Number
  - DNA Methylation
  - DNA Mutations

- HER2+ tumor microenvironment
  - Tumor Infiltrating Lymphocytes (TILs)

Courtesy of Dr. Pedro Fernández

*TCGA Nature 2012*

*Courtesy Aleix Prat*
Katherine: Study Schema

SURGERY

Preoperative therapy: Trastuzumab/ Taxane ± Anthracycline

Residual tumor

T-DM1

Target
3 yr IDFS

N=1484

HR 0.75

Trastuzumab