Management of HER2-positive early breast cancer

Evandro de Azambuja, MD, PhD
with the help of Rafael Caparica, Medical Fellow
Institut Jules Bordet, Université Libre de Bruxelles (ULB)
ESMO Council Member
Chair of the Fellowship Committee
Disclosure information

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- Research grant from Roche/GNE (my institution)
- Research grant from Astra-Zeneca (my institution)
- Research grant from GSK/Novartis (my institution)
- Research grant from Servier (my institution)
Topics

- Introduction
- Adjuvant treatment
- Neoadjuvant treatment
- Post-neoadjuvant treatment
- De-escalation strategies
- Treatment algorithm
- Take home messages
HER2 Pathway in Breast Cancer

Loibl S et al, Lancet Oncol, 2017
Definition of HER2-positive

HER2 testing (invasive component) by validated single-probe ISH assay

Batch controls and on-slide controls show appropriate hybridization

Average HER2 copy number ≥ 6.0 signals/cell*

Concurrent IHC 3+ and/or concurrent dual-probe ISH group 1+

ISH positive

Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell†

Concurrent IHC 2+

Perform dual-probe ISH for final result‡

Average HER2 copy number < 4.0 signals/cell*†

Concurrent IHC 0, 1+ and/or concurrent dual-probe ISH group 5+

ISH negative

15 - 20% of breast cancers are HER2-positive

Wolff A et al. ASCO guidelines, JCO, 2018
HER2-positive BC

Not all HER2-positive breast cancers are HER2-enriched

Prat A et al, Oncotarget 2017
Cejalvo J et al, Cancer Research, 2017
Adjuvant HER2-positive BC: multiple advances

- Gene encoding HER2
- Approval of Trastuzumab for MBC in 1985
- Fail to show improvement with dual HER2 blockade (L + T) in 2005
- Approval of Adjuvant Trastuzumab in 2014
- Improved outcomes with adjuvant dual HER2 blockade with P + T in 2017
- Approval of TDM1 in RD in 2019
Single-agent Trastuzumab

HERA (3,399)  
HR: 0.76  
Absolute gain: 6.8%  
Median FU yrs: 10

B31 / N9831 (4,046)  
HR: 0.60  
Absolute gain: 11.5%  
Median FU yrs: 8.4

BCIRG AC→TH (2,147)  
HR: 0.72  
Absolute gain: 6.7%  
Median FU yrs: 10.3

BCIRG TCH (2,148)  
HR: 0.77  
Absolute gain: 5.1%  
Median FU yrs: 10.3

Adapted from I. Smith
Duration of Trastuzumab
1 year superior to short duration

Overall survival

(a)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conte et al. 2017</td>
<td>14.8%</td>
<td>1.06 [0.73, 1.54]</td>
</tr>
<tr>
<td>Earl et al. 2018</td>
<td>43.6%</td>
<td>1.14 [0.92, 1.42]</td>
</tr>
<tr>
<td>Joensuu et al. 2018</td>
<td>19.2%</td>
<td>1.36 [0.98, 1.89]</td>
</tr>
<tr>
<td>Mavroidis et al. 2015</td>
<td>2.4%</td>
<td>1.45 [0.57, 3.69]</td>
</tr>
<tr>
<td>Pivot et al. 2013</td>
<td>20.1%</td>
<td>1.46 [1.06, 2.01]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.23 [1.07, 1.42]

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 4 (P = 0.62); I² = 0%

Test for overall effect: Z = 2.86 (P = 0.004)

Disease-free survival

(b)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earl et al. 2018</td>
<td>31.7%</td>
<td>1.07 [0.91, 1.26]</td>
</tr>
<tr>
<td>Conte et al. 2017</td>
<td>18.9%</td>
<td>1.15 [0.91, 1.45]</td>
</tr>
<tr>
<td>Pivot et al. 2013</td>
<td>24.6%</td>
<td>1.28 [1.05, 1.56]</td>
</tr>
<tr>
<td>Joensuu et al. 2018</td>
<td>21.5%</td>
<td>1.39 [1.12, 1.73]</td>
</tr>
<tr>
<td>Mavroidis et al. 2015</td>
<td>3.3%</td>
<td>1.58 [0.86, 2.90]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 1.21 [1.09, 1.36]

Heterogeneity: Tau² = 0.00; Chi² = 4.89, df = 4 (P = 0.30); I² = 18%

Test for overall effect: Z = 3.41 (P = 0.0007)
Low-risk disease – APT long-term results

- HER2+ breast cancer
- Tumors ≤3cm, node-negative
- Weekly paclitaxel + trastuzumab for 12 weeks

A

DFS (probability)

Time (months)

B

DFS (probability)

Time (months)

Tolaney S et al, JCO 2019
Addition of Pertuzumab

Rationale

Addition of Pertuzumab
APHINITY

Central confirmation of HER2 status (N = 4805)

Chemotherapy* + trastuzumab + pertuzumab

Chemotherapy* + trastuzumab + placebo

Randomisation and treatment within 8 weeks of surgery

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 Intention-to-Treat Population

Invasive Disease-free Survival Rate (%)

98.6 96.4 94.1 92.3

98.8 95.7 93.2 90.6

Stratified hazard ratio, 0.81 (95% CI, 0.66–1.00)
P=0.045

No. at Risk
Pertuzumab 2400 2309 2275 2236 2199 2153 2101 1687 879
Placebo 2404 2335 2312 2274 2215 2168 2108 1674 866

Von Minckwitz G et al, NEJM, 2018
Increased rates of diarrhea (9.8 vs. 3.7%) and anemia (6.9 vs. 4.7%) AND Similar rates of cardiac toxicity (0.6% vs. 0.2%) with pertuzumab.
Neratinib

Available at https://www.bocsci.com/blog/index
ExteNET: study design

- HER2+ breast cancer
  - IHC 3+ or ISH amplified (locally determined)
  - Prior adjuvant trastuzumab + chemotherapy
  - Lymph node +/-, or residual invasive disease after neoadjuvant therapy
- Stratified by: nodal status, hormone receptor status, concurrent vs sequential trastuzumab

Randomization (1:1)

N=2840

Part A
Neratinib x 1 year
240 mg/day
2-year follow-up for iDFS

Part B
Placebo x 1 year
5-year follow-up for iDFS

Part C
Overall survival

Primary endpoint: invasive disease-free survival (iDFS)
Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety
Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)
Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

Chan et al. Lancet Oncol 2016
Diarrhea and rash were more frequent with neratinib
Grade 3 diarrhea 40% vs. 2%
ExteNET: iDFS by hormone receptor status

Δ 4.4%

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
Neratinib 816 757 731 705 642 571 565 558 554 544 523
Placebo 815 779 750 719 647 581 567 556 551 542 525

Invasive disease-free survival (%)

Months after randomization

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

Martins et al, Lancet Oncol 2017
Potential advantages of neoadjuvant treatment

- In vivo assessment of response
- Tumor downstaging → More conservative surgeries
- Early treatment of micro-metastases
- Allows post-neoadjuvant treatment
Correlation between pCR and outcomes

All patients

**Overall survival**

- 

**Time since randomisation (years)**

- HR 0.36 (95% CI 0.31–0.42)

**HER2-positive**

- HER2-positive

- HER2-positive, hormone-receptor-positive

- HER2-positive, hormone-receptor-negative

**Event-free survival (%)**

- HR 0.39 (95% CI 0.31–0.50)

- HR 0.58 (95% CI 0.42–0.82)

- HR 0.25 (95% CI 0.18–0.34)

*Cortazar P et al, Lancet Oncol, 2014*
Correlation between pCR and outcomes
NEOALTTO Landmark analysis

All patients

EFS by pCR

Tests for interaction: pCR x HR p=0.34

dezambuja A et al, Lancet Oncol, 2014
Neoadjuvant Trastuzumab NOAH

Single HER2 blockade

Breast pCR

- With H: 43%
- Without H: 22%
- Δ pCR = 21%

Total pCR

- With H: 38%
- Without H: 19%
- Δ pCR = 19%

p = 0.0007

Gianni L et al, Lancet Oncol, 2010
Addition of Pertuzumab Neosphere

Gianni L et al, Lancet Oncol, 2012
### pCR rate with dual blockade in different trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>% pCR Trastuzumab</th>
<th>% pCR Dual blockade</th>
<th>% pCR Dual blocked HR neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoALTTO (N=455)</td>
<td>29.5</td>
<td>51.3</td>
<td>61.3</td>
</tr>
<tr>
<td>Neosphere (N=417)</td>
<td>45.8</td>
<td>63.2</td>
<td></td>
</tr>
<tr>
<td>NSABP B41 (N=529)</td>
<td>52.5</td>
<td>62</td>
<td>73</td>
</tr>
<tr>
<td>CALGB 40601 (N=305)</td>
<td>46</td>
<td>56</td>
<td>79</td>
</tr>
<tr>
<td>CHERLOB (N=121)</td>
<td>41.6</td>
<td>68.8</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Guarneri V et al, J Clin Oncol 2012
- Carey LA et al, J Clin Oncol 2016
Addition of Pertuzumab

TRYPHAENA

Dual HER2 blockade

Addition of Pertuzumab impact on survival

**A**

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of patients</th>
<th>Patients with events</th>
<th>3-year disease-free survival (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>Group A 69</td>
<td>10</td>
<td>87% (79 – 95)</td>
</tr>
<tr>
<td>0.1</td>
<td>Group B 67</td>
<td>8</td>
<td>88% (80 – 86)</td>
</tr>
<tr>
<td>0.2</td>
<td>Group C 72</td>
<td>11</td>
<td>90% (82 – 97)</td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Disease-free survival (%)</th>
<th>Number of patients</th>
<th>Number of events (%)</th>
<th>5-year disease-free survival (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Group A 103</td>
<td>18 (18)</td>
<td>81% (72 – 88)</td>
<td>0.60 (0.28 – 1.27)</td>
</tr>
<tr>
<td>90</td>
<td>Group B 101</td>
<td>15 (15)</td>
<td>84% (72 – 91)</td>
<td>0.83 (0.42 – 1.64)</td>
</tr>
<tr>
<td>80</td>
<td>Group C 96</td>
<td>19 (20)</td>
<td>80% (70 – 86)</td>
<td>2.16 (1.08 – 4.32)</td>
</tr>
<tr>
<td>70</td>
<td>Group D 92</td>
<td>22 (24)</td>
<td>75% (64 – 83)</td>
<td></td>
</tr>
</tbody>
</table>

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Schneeweiss A et al, European Journal of Cancer 2018
Non-anthracycline regimens

TRAIN II study

- Treatment-naïve pts
- HER2-positive, stage II-III breast cancer

Carboplatin + Taxol + Pertuzumab q3 weeks
9 cycles

FEC-T + Pertuzumab q3 weeks

Carboplatin + Taxol + Pertuzumab q3 weeks

Surgery
Trastuzumab (1 year) and endocrine treatment

Van Ramshorst MS et al, Lancet Oncol 2019
Post-neoadjuvant Treatment
Post-neoadjuvant treatment

Early breast cancer → Neoadjuvant treatment → Residual disease

Evaluation of residual disease

- Xenografts
- LVI
- TILs
- Ki67
- Gene expression

ctDNA and NGS

Chemotherapy
Immunotherapy
PARPi
CDKi (HR+)
TDM1 (HER2+)

Caparica et al, Therapeutic advances in Medical Oncology 2019
Post-neoadjuvant – TDM1
KATHERINE

- Early HER2+ breast cancer patients
- Pertuzumab use was allowed
- Residual disease after neoadjuvant treatment with chemotherapy and trastuzumab

T-DM1
3.6mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

N=1,486

Radiation and endocrine treatment were administered according to local guidelines
Post-neoadjuvant – TDM1

A

Invasive Disease–free Survival (%)

100

80

60

40

20

0

0 6 12 18 24 30 36 42 48 54 60

Months since Randomization

No. of Patients

T-DM1  Trastuzumab

No. of Events (%)

T-DM1  743  743

Trastuzumab  91 (12.2)  165 (22.2)

3-Yr Invasive Disease–free Survival, %

T-DM1  88.3

Trastuzumab  77.0

Unstratified hazard ratio for disease recurrence or death, 0.50 (95% CI, 0.39–0.64)
P<0.001

No. at Risk

T-DM1  743  707  681  658  633  561  409  255  142  44  4

Trastuzumab  743  676  635  594  555  501  342  220  119  38  4

Von Minckwitz et al, NEJM 2019
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>T-DM1</th>
<th>Trastuzumab</th>
<th>Hazard Ratio for Invasive-Disease Event (95% CI)</th>
<th>3-Yr Invasive Disease–free Survival Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>91/743</td>
<td>165/743</td>
<td>0.50 (0.39–0.64)</td>
<td>88.3</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 yr</td>
<td>20/143</td>
<td>37/153</td>
<td>0.50 (0.29–0.86)</td>
<td>86.5</td>
</tr>
<tr>
<td>40–64 yr</td>
<td>64/542</td>
<td>113/522</td>
<td>0.49 (0.36–0.67)</td>
<td>88.8</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>7/58</td>
<td>15/68</td>
<td>0.55 (0.22–1.34)</td>
<td>87.4</td>
</tr>
<tr>
<td><strong>Clinical stage at presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inoperable breast cancer</td>
<td>42/185</td>
<td>70/190</td>
<td>0.54 (0.37–0.80)</td>
<td>76.0</td>
</tr>
<tr>
<td>Operable breast cancer</td>
<td>49/558</td>
<td>95/553</td>
<td>0.47 (0.33–0.66)</td>
<td>92.3</td>
</tr>
<tr>
<td><strong>Hormone-receptor status</strong></td>
<td></td>
<td></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>
<td>0.50 (0.33–0.74)</td>
<td>82.1</td>
</tr>
<tr>
<td>Positive (ER-positive, progesterone-receptor–positive, or both)</td>
<td>53/534</td>
<td>104/540</td>
<td>0.48 (0.35–0.67)</td>
<td>90.7</td>
</tr>
<tr>
<td>Preoperative HER2-directed therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab alone</td>
<td>78/600</td>
<td>141/596</td>
<td>0.49 (0.37–0.65)</td>
<td>87.7</td>
</tr>
<tr>
<td>Trastuzumab plus additional HER2-directed agent or agents</td>
<td>13/143</td>
<td>24/147</td>
<td>0.54 (0.27–1.06)</td>
<td>90.9</td>
</tr>
<tr>
<td><strong>Pathological nodal status after preoperative therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-positive</td>
<td>62/343</td>
<td>103/346</td>
<td>0.52 (0.38–0.71)</td>
<td>83.0</td>
</tr>
<tr>
<td><strong>Node-negative or NE</strong></td>
<td>29/400</td>
<td>62/397</td>
<td>0.44 (0.28–0.68)</td>
<td>92.8</td>
</tr>
<tr>
<td>Primary tumor stage at definitive surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0, ypT1a, ypT1b, ypT1mic, ypTis</td>
<td>40/331</td>
<td>52/306</td>
<td>0.66 (0.44–1.00)</td>
<td>88.3</td>
</tr>
<tr>
<td>ypT1, ypT1c</td>
<td>14/175</td>
<td>42/184</td>
<td>0.34 (0.19–0.62)</td>
<td>91.9</td>
</tr>
<tr>
<td>ypT2</td>
<td>25/174</td>
<td>44/185</td>
<td>0.50 (0.31–0.82)</td>
<td>88.3</td>
</tr>
<tr>
<td>ypT3</td>
<td>9/51</td>
<td>21/57</td>
<td>0.40 (0.18–0.88)</td>
<td>79.8</td>
</tr>
<tr>
<td>ypT4</td>
<td>3/12</td>
<td>6/11</td>
<td>0.29 (0.07–1.17)</td>
<td>70.0</td>
</tr>
<tr>
<td>Regional lymph-node stage at definitive surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN0</td>
<td>28/344</td>
<td>56/335</td>
<td>0.46 (0.30–0.73)</td>
<td>91.9</td>
</tr>
<tr>
<td>ypN1</td>
<td>29/220</td>
<td>50/213</td>
<td>0.49 (0.31–0.78)</td>
<td>88.9</td>
</tr>
<tr>
<td>ypN2</td>
<td>16/86</td>
<td>38/103</td>
<td>0.43 (0.24–0.77)</td>
<td>81.1</td>
</tr>
<tr>
<td>ypN3</td>
<td>17/37</td>
<td>15/30</td>
<td>0.71 (0.35–1.42)</td>
<td>52.0</td>
</tr>
<tr>
<td>ypNX</td>
<td>1/56</td>
<td>6/62</td>
<td>0.17 (0.02–1.38)</td>
<td>98.1</td>
</tr>
</tbody>
</table>

Von Minckwitz et al, NEJM 2019
Table 3. Adverse Events of Any Grade with an Incidence of at Least 15% in Either Treatment Group in the Safety Population. *

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Trastuzumab Group (N = 720)</th>
<th>T-DM1 Group (N = 740)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>243 (33.8)</td>
<td>189 (26.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>94 (13.1)</td>
<td>74 (10.3)</td>
</tr>
<tr>
<td>Decreased platelet count†</td>
<td>17 (2.4)</td>
<td>14 (1.9)</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase level</td>
<td>40 (5.6)</td>
<td>36 (5.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>122 (16.9)</td>
<td>94 (13.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>148 (20.6)</td>
<td>114 (15.8)</td>
</tr>
<tr>
<td>Radiation-related skin injury</td>
<td>199 (27.6)</td>
<td>121 (16.8)</td>
</tr>
<tr>
<td>Increased alanine aminotransferase level</td>
<td>41 (5.7)</td>
<td>35 (4.9)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25 (3.5)</td>
<td>24 (3.3)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>50 (6.9)</td>
<td>39 (5.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>59 (8.2)</td>
<td>51 (7.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>80 (11.1)</td>
<td>64 (8.9)</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>146 (20.3)</td>
<td>118 (16.4)</td>
</tr>
</tbody>
</table>

*Adverse events were reported in the safety population.
†Grade 3 events included in grade 4 events.
De-escalation strategies
De-escalation strategies
KRISTINE study

Centrally confirmed HER2 positive operable, locally advanced or inflammatory breast cancer >2cm N=444

Randomisation

Docetaxel + Carboplatin + Trastuzumab + Pertuzumab x 6

Trastuzumab + Pertuzumab x 12

Pertuzumab + T-DM1 x 6

Surgery

Pertuzumab + T-DM1 x 12

Okines A, Reviews on Recent Clinical Trials 2017
KRISTINE study
no improvement in pCR rates

Difference: −11.3 percentage points
(95% CI −20.5 to −2.0)
Stratified two-sided p=0.016*
KRISTINE study long-term outcomes

Hazard ratio, 2.61 (95% CI, 1.36 to 4.98)

Event-Free Survival (%)

Time (months)

No. at risk:
TCH+P 221 214 211 209 197 190 140 10
TCH+P 223 199 192 185 177 173 126 16

Hurvitz S, JCO 2019
De-escalation strategies
TBCR006 study

Table 2. Pathologic Response Rates

<table>
<thead>
<tr>
<th>ER Status</th>
<th>pCR No.</th>
<th>pCR %</th>
<th>ypT1a-b No.</th>
<th>ypT1a-b %</th>
<th>NR No.</th>
<th>NR %</th>
<th>Total No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>8</td>
<td>21</td>
<td>13</td>
<td>33</td>
<td>18</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>Negative</td>
<td>9</td>
<td>36</td>
<td>1</td>
<td>4</td>
<td>15</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>27</td>
<td>14</td>
<td>22</td>
<td>33</td>
<td>52</td>
<td>64</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; NR, nonpathologic response; pCR, pathologic complete response.
De-escalation strategies
TBCRC023 study

Neoadjuvant treatment

1:2 randomization

Hypothesis: a longer HER2/ER blockade would increase pCR rates

<table>
<thead>
<tr>
<th>Path CR (ypT0-N0)</th>
<th>12 weeks (n=33)</th>
<th>24 weeks (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4 (12%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>ER-positive</td>
<td>2 (9%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>ER-negative</td>
<td>2 (20%)</td>
<td>4 (18%)</td>
</tr>
</tbody>
</table>

Rimawi M, Cancer Research, 2015
De-escalation strategies
ADAPT trial (HER2+ and HR+)

Harbeck N, JCO, 2017
De-escalation strategies

ADAPT trial (HER2+ and HR-)

Nitz UA, Ann Oncol, 2017
De-escalation strategies
ADAPT trial (HER2+ and HR-)

Nitz UA, Ann Oncol, 2017
De-escalation strategies
PREDIX-HER2 trial

A Docetaxel + trastuzumab sc + pertuzumab x 6
B Trastuzumab emtansine x 6

In case of no change (NC) or progressive disease (PD), patients were offered switch of treatment arm

<table>
<thead>
<tr>
<th>All patients</th>
<th>Docetaxel, trastuzumab, pertuzumab</th>
<th>Trastuzumab emtansine</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>N = 99 (47)</td>
<td>N = 98 (45)</td>
</tr>
<tr>
<td>No pCR (SD or PR)</td>
<td>53 (54)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>(PD by radiology)</td>
<td>0</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Chi² 2.049
p = 0.359

ER and PR negative

<table>
<thead>
<tr>
<th>All patients</th>
<th>N = 33 (%)</th>
<th>N = 39 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>22 (67)</td>
<td>23 (59)</td>
</tr>
<tr>
<td>No pCR</td>
<td>11 (33)</td>
<td>16 (41)</td>
</tr>
</tbody>
</table>

Chi² 0.451
p = 0.502

ER and/or PR positive

<table>
<thead>
<tr>
<th>All patients</th>
<th>N = 66 (%)</th>
<th>N = 59 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>24 (36)</td>
<td>21 (36)</td>
</tr>
<tr>
<td>No pCR</td>
<td>42 (64)</td>
<td>38 (64)</td>
</tr>
</tbody>
</table>

Chi² 0.008
p = 0.929

Bergh JCS et al, ASCO, 2019
De-escalation strategies
PHERGain trial

- Stage II and III HER2-positive breast cancer
- Tumors > 1cm
- Treatment naive

Cortes et al, ESMO 2019
Early Breast Cancer

ER-negative

HER2-positive
- ChT + anti-HER2\textsuperscript{b} [I, A]
- ChT [I, A]
- Observation or ChT [III, B]

Ductal

Special histological types\textsuperscript{a}, N\textsubscript{0}, no other risk factors

TNBC

ER-positive

HER2-negative
- ET
  - ChT only in selected cases with high-disease burden [I, A]
  - ET ± ChT\textsuperscript{d} [I, A]

Luminal A

Luminal B

HER2-positive
- ChT\textsuperscript{a} + anti-HER2\textsuperscript{a} + ET [I, A]

Cardoso F et al, Annals of Oncology 2019
HER2-positive breast cancer

Pre-operative ChT + trastuzumab ± pertuzumab

pCR

Initially N-positive or ER-negative
- Complete 1 year of dual blockade [I, A; MCBS B] or Complete 1 year of trastuzumab [I, A]

No pCR

Other cases
- Complete 1 year of trastuzumab [I, A]

T-DM1 [I, A]
Take home messages

✓ Surgery followed by adjuvant paclitaxel and trastuzumab is safe for low risk patients (T≤2cm and node-negative)

✓ Adjuvant pertuzumab → in high-risk patients (node-positive)

✓ Neoadjuvant treatment is the standard-of-care for most HER2+ early breast cancer patients

✓ Post-neoadjuvant TDM-1 is the new standard when there is residual disease after neoadjuvant treatment