Treatment of Early-Stage HER2+ Breast Cancer

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Disclosures

- I have research funding from
  - Roche/Genentech
  - PUMA
Objectives

• Trastuzumab
  – Historical adjuvant data

• Neoadjuvant
  – NEOSPHERE
  – TRYPHAENA
  – BERENICE

• Adjuvant
  – APHINITY
  – ExteNET
  – APT, US Oncology
Trastuzumab in Adjuvant Setting

- **NSABP B-31**
  - Trastuzumab: H...x 52
- **NCCTG 9831**
  - Standard ChemoRx: H...x 52, H...x 52
- **BCIRG 006**
  - No therapy: H...x 52, H...x 52
- **HERA**
  - No therapy: H...x 52
  - Standard ChemoRx: H...x 1 year, H...x 2 years
- **FinHer**
  - Trastuzumab: H...x 9
  - Epirubicin, Vinorelbine, Fluorouracil: H...x 52
- **PACS 04**
  - No therapy: H...x 52

Color Codes:
- Red: Doxorubicin
- Yellow: Paclitaxel
- Green: Cyclophosphamide
- Blue: Docetaxel
- Black: Carboplatin
- Pink: Epirubicin
- Grey: Vinorelbine
- Blue: Fluorouracil
- Blue: Trastuzumab
# Persistent Benefit of Adjuvant Trastuzumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th>Med FU</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA ¹ (x-over 52%)</td>
<td>Chemo Chemo → H x 1 yr Chemo → H x 2 yr</td>
<td>11 yrs</td>
<td>63%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>69%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>69%</td>
<td>80%</td>
</tr>
<tr>
<td>B-31²,³ (x-over 20%)</td>
<td>ACT AC → TH→ H</td>
<td>8.4 yrs*</td>
<td>62.2%</td>
<td>75.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73.7%</td>
<td>84.0%</td>
</tr>
<tr>
<td>N 9831²,³ (x-over 20%)</td>
<td>AC → w T AC → w TH→ H AC → w T→ H</td>
<td>8.4 yrs*</td>
<td>62.2%</td>
<td>75.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73.7%</td>
<td>84.0%</td>
</tr>
<tr>
<td>BCIRG 006 ⁴ (x-over 3.1%)</td>
<td>AC → D DCbH→ H AC → DH→ H</td>
<td>10 yrs</td>
<td>67.9%</td>
<td>78.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73.0%</td>
<td>83.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>74.6%</td>
<td>85.9%</td>
</tr>
</tbody>
</table>

A=doxorubicin, C=cyclophosphamide T=pac;itaxel, D=docetaxel, Cb=carboplatin H=trastuzumab, N=not reported

*Combined analysis of B-31/N9831

2. Perez et al. JCO 2014
3. Slamon et al. SABC 2015
## Adjuvant Trastuzumab, Asymptomatic LVEF Decline and Heart Failure, and Treatment Interruption

<table>
<thead>
<tr>
<th>Study</th>
<th>Rx</th>
<th>Med FU (yrs)</th>
<th>Asx LVEF ↓&gt; 10% to &lt; 50%</th>
<th>NYHA Class III-IV</th>
<th>Med FU (yrs)</th>
<th>NYHA Class III-IV</th>
<th>Trastuzumab Discontinuation - Cardiac causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA 1-2</td>
<td>Chemo</td>
<td>3.6</td>
<td>0.9%</td>
<td>0.0%</td>
<td>11</td>
<td>0.1%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Chemo → H x 1 yr</td>
<td></td>
<td>4.1%</td>
<td>0.8%</td>
<td></td>
<td>1.0%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td>Chemo → H x 2 yr</td>
<td></td>
<td>7.2%</td>
<td>NR</td>
<td></td>
<td>1.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>B-31 3-5</td>
<td>ACT</td>
<td>2</td>
<td>NR</td>
<td>0.8%</td>
<td>7</td>
<td>1.0%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>AC → TH → H</td>
<td></td>
<td>14%</td>
<td>4.1%</td>
<td></td>
<td>4.0%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>N 9831</td>
<td>AC → w T</td>
<td>3.75</td>
<td>4%-5.1%</td>
<td>0.3%</td>
<td>9</td>
<td>0.6%</td>
<td>NA</td>
</tr>
<tr>
<td>3,6-7</td>
<td>AC → w T → H</td>
<td></td>
<td>4%-7.8%</td>
<td>2.8%</td>
<td></td>
<td>2.8%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>AC → w TH → H</td>
<td></td>
<td>5.8%-10.4%</td>
<td>3.3%</td>
<td></td>
<td>3.4%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC → D</td>
<td>5</td>
<td>11.2%</td>
<td>0.7%</td>
<td>10</td>
<td>0.7%</td>
<td>NA</td>
</tr>
<tr>
<td>8-9</td>
<td>AC → DH → H</td>
<td></td>
<td>18.6%</td>
<td>2.0%</td>
<td></td>
<td>2.0%</td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>DCbH → H</td>
<td></td>
<td>9.4%</td>
<td>0.4%</td>
<td></td>
<td>0.4%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

A=doxorubicin, C=cyclophosphamide, T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab, NR=not reported, NA=not applicable

1. Procter et al. JCO 2010
2. Cameron et al. Lancet 2017
3. Romond et al. NEJM 2005
4. Tan-Chiu et al. JCO 2005
5. Romond et al. JCO 2012
6. Perez et al. JCO 2008
7. Advani et al. JCO 2015
8. Slamon et al. NEJM 2011
9. Slamon et al. SABC 2015
Neoadjuvant and Adjuvant Anti-HER2 Therapy
CLEOPATRA
Docetaxel/Trastuzumab/Pertuzumab > Docetaxel/Trastuzumab/Placebo

PFS
12.4 vs 18.7 mo

OS
40.8 vs 56.5 mo

1. Baselga et al. NEJM 2012
2. Swain et al. NEJM 2015
MSKCC Study
Paclitaxel, Trastuzumab, Pertuzumab (THP)

PFS
Med FU of 33 mo
OS

1. Dang et al. JCO 2015
Patients with operable or locally advanced /inflammatory* HER2-positive BC

Chemo-naïve & primary tumors >2cm

Study dosing: q3w x 4

BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide
*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; D, docetaxel

Gianni et al. Lancet Oncol 2012
TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive Early Breast Cancer

- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)

EBC=early-stage breast cancer; FEC=5-fluorouracil, epirubicin, cyclophosphamide

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>pCR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEOSPHERE (N=417)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DH</td>
<td></td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>DP</td>
<td>12 w</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>DHP</td>
<td></td>
<td>45.8%</td>
<td>0.0141</td>
</tr>
<tr>
<td>HP</td>
<td></td>
<td>16.8%</td>
<td></td>
</tr>
<tr>
<td>TRYPHAENA (N=225)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FECHP → DHP</td>
<td></td>
<td>61.6%</td>
<td></td>
</tr>
<tr>
<td>FEC → DHP</td>
<td>18 w</td>
<td>57.3%</td>
<td></td>
</tr>
<tr>
<td>DCbHP</td>
<td></td>
<td>66.2%</td>
<td></td>
</tr>
</tbody>
</table>

E=epirubicin; C=cyclophosphamide; F=fluorouracil; D=docetaxel; Cb=carboplatin; H=trastuzumab; P=pertuzumab
FDA Approval
“Neoadjuvant” Setting

• Based on significant PFS/OS benefit of pertuzumab in MBC and pCR gain in neoadjuvant setting, pertuzumab was granted accelerated approval in neoadjuvant setting

• Eligible pts are those w/ stage II-III
  – Size > 2 cm
  – Node (+)
  – Locally advanced breast cancer
  – Inflammatory breast cancer

• Up to 6 cycles of pertuzumab allowed

• Safety of pertuzumab with doxorubicin containing regimen not established
Cardiac safety study – BERENICE

Cohort A

2-weekly ddAC x4

Weekly T x12

P 840 mg ➔ 420 mg 3-weekly

H 8 mg/kg ➔ 6 mg/kg 3-weekly

SURGERY

P 420 mg 3-weekly

H 6 mg/kg 3-weekly

Investigator choice

Cohort B

3-weekly FEC x4

3-weekly D x 4

P 840 mg ➔ 420 mg 3-weekly

H 8 mg/kg ➔ 6 mg/kg 3-weekly

SURGERY

P 420 mg 3-weekly

H 6 mg/kg 3-weekly

400 patients, ~200 in each cohort
Primary endpoint: cardiac safety
Secondary endpoint: total pCR

ddAC= dose-dense doxorubicin and cyclophosphamide;
FEC=5-fluorouracil, epirubicin, cyclophosphamide; T=paclitaxel;
D=docetaxel; P=pertuzumab; H=trastuzumab

Swain, Dang et al. Ann Oncol 2018
<table>
<thead>
<tr>
<th>Cohort</th>
<th>tpCR (ypT0/is ypN0)</th>
<th>NYHA Class III-IV Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddAC-THP</td>
<td>61.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>FEC-DHP</td>
<td>60.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

ddAC = dose-dense doxorubicin and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; T = paclitaxel; D = docetaxel; P = pertuzumab; H = trastuzumab

NYHA = New York Heart Association  
Swain, Dang et al. Ann Oncol 2018
Neoadjuvant Use
Trastuzumab/Pertuzumab

• Stage II-III: Yes
  – Downstage (primary tumor and/or axilla)
  – HP-based therapy

• Stage I: No
Adjuvant Pertuzumab

**Eligibility**
- Stage I-III
- HER2 (+)
- LVEF ≥ 55%

**1 yr-3 yr iDFS, 2 yr-OS, safety**

**Demographics**
- Node (-) 38%
- HR (+) 64%
- Anthracycline 78%

---

**APHINITY: Trial Design**

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

von Minckwitz et al. NEJM 2017
Primary Endpoint
3-year iDFS

- Preplanned analysis
  - LN- (97.5% vs 98.4%, p=0.64)
  - LN+ (92% vs 90.2%, HR 0.77, p=0.02)
  - ER- (92.8% vs 91.2%, p=0.08)
  - ER+ (94.8% vs 94.4%, p=0.28)

- Adjuvant Pertuzumab FDA approved 2017
  - For pts at “high risk of recurrence”

- Note:
  - Pertuzumab appropriate for LN+
  - Less clear in other subgroups

von Minckwitz et al. NEJM 2017
www.fda.org
# APHINITY: Cardiac Endpoints

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Pertuzumab n=2364</th>
<th>% Treatment difference (95% CI)</th>
<th>Placebo n=2405</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary cardiac endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure NYHA III/IV + LVEF drop*</td>
<td>17 (0.7)</td>
<td>0.4 (0.0, 0.8)</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Cardiac death**</td>
<td>15 (0.6)</td>
<td></td>
<td>6 (0.2)</td>
</tr>
<tr>
<td></td>
<td>2 (0.08)</td>
<td></td>
<td>2 (0.08)</td>
</tr>
<tr>
<td>Recovered according to LVEF</td>
<td>7</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Secondary cardiac endpoint</strong></td>
<td>64 (2.7)</td>
<td>-0.1 (-1.0, 0.9)</td>
<td>67 (2.8)</td>
</tr>
<tr>
<td>Asymptomatic or mildly symptomatic LVEF drop*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LVEF drop = ejection fraction drop ≥10% from baseline AND to below 50%;

**Identified by the Cardiac Advisory Board for the trial according to a prospective definition
**APHINITY: Common Grade ≥ 3 Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab n=2364</th>
<th>Placebo n=2405</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>385 (16.3%)</td>
<td>377 (15.7%)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>287 (12.1%)</td>
<td>266 (11.1%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>163 ( 6.9%)</td>
<td>113 ( 4.7%)</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- with chemotherapy and targeted therapy</td>
<td>232 ( 9.8%)</td>
<td>90 ( 3.7%)</td>
</tr>
<tr>
<td>- with targeted therapy (post-chemotherapy)</td>
<td>12 ( 0.5%)</td>
<td>4 ( 0.2%)</td>
</tr>
<tr>
<td>- with AC-&gt;T (N=1834; 1894)</td>
<td>137 ( 7.5%)</td>
<td>59 ( 3.1%)</td>
</tr>
<tr>
<td>- with TCH (N= 528; 510)</td>
<td>95 (18.0%)</td>
<td>31 ( 6.1%)</td>
</tr>
</tbody>
</table>
Neratinib
ExteNET

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab & chemotherapy
- Stage I-III
- Lymph node −/+ or residual invasive disease after neoadjuvant therapy
- ER/PR + or −

1:1 randomization

- Neratinib x 1 year
  240mg/day
- Placebo x 1 year

2-year follow-up for iDFS
5-year follow-up for iDFS
5+ year survival

1°-2 yr iDFS
2°-DCIS-DFS, OS, safety
Demographics
  - Node (-) 24%
  - HR (+) 57%
  - Anthracycline 78%

Chan et al. Lancet Onc 2016
Primary Endpoint: Invasive DFS (ITT)

- Disease-free survival (%)
- Months after randomization
- No. at risk
  - Neratinib
  - Placebo
- Preplanned
  - HR+ (95.4% vs 91.2%, HR 0.51, p=0.001)
  - HR- (92.0% vs 92.2%, p=0.74)
- P-value = 0.009
- HR (95% CI) = 0.67 (0.50–0.91)
- Δ 2.3%

Chan et al. Lancet Onc 2016
## Safety (Adverse Events ≥10%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>All grades</th>
<th>Grade 3–4</th>
<th>All grades</th>
<th>Grade 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neratinib (n=1408)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1343 (95.4)</td>
<td>562 (39.9)</td>
<td>499 (35.4)</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>605 (43.0)</td>
<td>26 (1.8)</td>
<td>303 (21.5)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>382 (27.1)</td>
<td>23 (1.6)</td>
<td>283 (20.1)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>369 (26.2)</td>
<td>47 (3.3)</td>
<td>113 (8.0)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Abdominal pain, general</td>
<td>340 (24.1)</td>
<td>24 (1.7)</td>
<td>144 (10.2)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>278 (19.7)</td>
<td>8 (0.6)</td>
<td>275 (19.5)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>212 (15.1)</td>
<td>11 (0.8)</td>
<td>96 (6.8)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>211 (15.0)</td>
<td>5 (0.4)</td>
<td>100 (7.1)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>170 (12.1)</td>
<td>3 (0.2)</td>
<td>40 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>159 (11.3)</td>
<td>1 (0.1)</td>
<td>45 (3.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>146 (10.4)</td>
<td>3 (0.2)</td>
<td>128 (9.1)</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>86 (6.1)</td>
<td>2 (0.1)</td>
<td>162 (11.5)</td>
<td>4 (0.3)</td>
</tr>
</tbody>
</table>
Neratinib

- FDA approved
  - As extended Rx in HER2+ pts after trastuzumab based Rx

- NCCN
  - “Consider” neratinib in pts w/ HR (+) dz “perceived” to be at high risk of recurrence

- **Note:**
  - Stage II-III (node+) → HP-based Rx (ie: AC-THP or DCbHP)
  - No data on neratinib after HP-based Rx

www.fda.org
Stage I HER2+
Outcomes for T1a/bN0 HER2+ Tumors

MDACC Series (N=98)

<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 (N=520)

For HR+ HER2+

5-yr DRFS

T1a 96% vs 100%
T1b 94% vs 96%

5-yr OS

T1a 95% vs 100%
T1b 95% vs 99%

For HR-HER2+

5-yr DRFS

T1a 93% vs 100%
T1b 100% vs 95%

5-yr OS

T1a 93% vs 100%
T1b 100% vs 95%

Gonzalez-Angulo et al. JCO 2009
Vaz-Luiz et al. JCO 2014
Adjuvant Paclitaxel and Trastuzumab (APT)

HER2+ 
ER+ or ER- 
Node Negative < 3 cm

Planned N=400

T1a-19%
1b-31%
1c-42%
T2 - 9%

Enroll

PACLITAXEL 80 mg/m² + TRASTUZUMAB 2 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 et al. NEJM 2015
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>132</td>
<td>33</td>
</tr>
<tr>
<td>50-70</td>
<td>233</td>
<td>57</td>
</tr>
<tr>
<td>≥70</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td><strong>Size of Primary Tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a ≤0.5 cm</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>T1b &gt;0.5-≤1.0</td>
<td>124</td>
<td>31</td>
</tr>
<tr>
<td>T1c &gt;1.0-≤2.0</td>
<td>169</td>
<td>42</td>
</tr>
<tr>
<td>T2 &gt;2.0-≤3.0</td>
<td>36</td>
<td>9</td>
</tr>
</tbody>
</table>

- 50% with T1a ≤0.5 cm
- 50% with T1b >0.5-≤1.0

<table>
<thead>
<tr>
<th><strong>Histologic Grade</strong></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Well differentiated</td>
<td>44</td>
<td>11</td>
</tr>
<tr>
<td>II Moderately differentiated</td>
<td>131</td>
<td>32</td>
</tr>
<tr>
<td>III Poorly differentiated</td>
<td>228</td>
<td>56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HR Status (ER and/or PR)</strong></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>272</td>
<td>67</td>
</tr>
<tr>
<td>Negative</td>
<td>134</td>
<td>33</td>
</tr>
</tbody>
</table>
Disease-Free Survival

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Point Est.</th>
<th>95% Conf. Interval</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr DFS</td>
<td>98.5%</td>
<td>97.2% to 99.7%</td>
<td>6</td>
</tr>
<tr>
<td>5-yr DFS</td>
<td>96.3%</td>
<td>94.4% to 98.2%</td>
<td>14</td>
</tr>
<tr>
<td>7-yr DFS</td>
<td>93.3%</td>
<td>90.4% to 96.2%</td>
<td>23</td>
</tr>
</tbody>
</table>

Tolaney et al. ASCO 2017
Non-Anthracycline + Trastuzumab Cardiac Toxicity

<table>
<thead>
<tr>
<th>Cardiac event</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Congestive Heart Failure*</td>
<td>2</td>
<td>0.5 (0.1-18)</td>
</tr>
<tr>
<td>Asymptomatic Declines in LVEF**</td>
<td>13</td>
<td>3.2 (1.7-5.4)</td>
</tr>
</tbody>
</table>

*Both patients had normalization of LVEF after discontinuation of trastuzumab
**11 of 13 were able to resume trastuzumab therapy after an interruption of trastuzumab

Dang et al. JAMA Oncol 2016
Phase II Study of Docetaxel, Cyclophosphamide, and Trastuzumab

- N = 493, med FU of 3 yrs
- Node Status
  - Node (-): 79.3%
  - Node (+): 20.7%
- Stage: I (57.6%), II (41.2%) III (1.2%)
- Outcomes:
  - 2 year DFS: 97.8%
  - 3 year DFS: 96.9%
  - Node (-): 97.8%
  - Node (+): 93.5%
- Symptomatic heart failure: 0.4%

Jones et al. Lancet Oncol 2014

DFS

G3-4 neutropenia: 47.1%
FN: 6.2%
Putting it together

• **Node (+)**
  – Stage 2-3 $\rightarrow$ HP-based (ie: ddAC-THP or DCbHP)
  – No data on neratinib after HP (cost, QOL)

• **Node (-)**
  – Stage 2-3 $\rightarrow$ HP-based ($\geq$T2) ?
    • No significant benefit of HP in node (-) tumors in APHINITY
    • If pts have received H-based Rx (ie: ddAC-TH, DCbH), can consider neratinib (ie: in HR+ pts)
  – Stage 1 $\rightarrow$ TH (T1, N1mi) or DCH
    • Pts in APT did well with TH alone

A=doxorubicin, C=cyclophosphamide, T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab, P=pertuzumab
NCCN
HER2 (+)

• Node (-) or N1mi:
  – \( \leq 0.5 \text{ cm} \): “Consider” Chemo + trastuzumab
  – \( \leq 0.5 \text{ cm} \) N1mi: “Consider” Chemo + trastuzumab
  – \( > 0.6 - 1.0 \text{ cm} \): “Consider” Chemo + trastuzumab
  – \( > 1.0 \text{ cm} \): Chemo + trastuzumab

• Node (+): Chemo + trastuzumab

Add endocrine Rx hormone receptor (+) disease

NCCN HER2-Positive (Neoadjuvant/Adjuvant)

- **Preferred**
  - $AC \rightarrow TH^{+/-P}$
  - $DCbH^{+/-P}$
  - $TH$

- **Other**
  - $AC \rightarrow DH^{+/-P}$
  - $DCH$

**Stage II-III**
- $AC \rightarrow TH^{+/-P}$
- $DCbH^{+/-P}$

(Consider neratinib in pts w/ HR+ “perceived” to have high-risk of recurrence after trastuzumab; no data after HP)

**Stage I**
- $TH$
- $DCH$

A=doxorubicin, E=epirubicin, C=cyclophosphamide, T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab, P=pertuzumab
Summary
Anti-HER2 Rx

- **Neoadjuvant**
  - Downstage tumor and/or axilla (ie: Stage II-III)
  - Same Rx as adjuvant

- **Stage II-III HER2 (+)**
  - Chemo + HP (ie: LN+)
    - ie: AC →THP, DCbHP
    - no data on neratinib after HP
  - Chemo + H (no P), consider neratinib in pts w/ HR+ disease “perceived” to be high-risk

- **Stage I HER2 (+)**
  - Taxane + trastuzumab (ie: TH or DCH)
Thank You!