HER-2-Positive Breast Cancer

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Objectives

• Evolution of HER2 Directed Therapies
• Definition of HER2 Positivity
• Treatments for Metastatic Disease
• Treatments for Early Stage Disease
  – Adjuvant
  – Neoadjuvant
Trastuzumab 1st line Rx of HER2+ MBC with paclitaxel; monotherapy

Lapatinib approved for 2nd line Rx of MBC with capecitabine

Pertuzumab approved for 1st line Rx of MBC with docetaxel and trastuzumab

Trastuzumab approved for adjuvant Rx of high risk node- BC

Ado Trastuzumab Emtansine (T-DM1) approval for 2nd line Rx of MBC

BC = breast cancer; MBC = metastatic breast cancer, Rx=treatment
HER2 “Positive”: Definitions

- **Amplification**: an abnormal increase in the number of HER2 gene copies in the cell nucleus
- **Overexpression**: an abnormal increase in the number of HER2 protein receptors on the cell surface

Normal breast epithelium
(~ 20,000 receptor molecules)

HER2 positive
(Up to 2 million receptor molecules)
HER2 Tests

• HER2 test should be done on invasive breast cancer sample when being treated in:
  – Adjuvant or neoadjuvant setting
  – Metastatic setting

• HER2-positive if invasive tumor is
  – HER2 over-expressed: Immunohistochemistry (IHC) 3+ “or”
  – HER2 amplified: Fluorescent in situ hybridization (FISH) ratio >/= 2.0
Metastatic First-Line
Inhibits HER1 HER2 and HER4 at intracellular tyrosine kinase domains

Published online 2011 February 10. doi: 10.5306/wjco.v2.i2.125.
CLEOPATRA Study Design

HER2-positive MBC centrally confirmed (N = 808)

1:1

n = 406

Placebo + trastuzumab

Docetaxel*

≥ 6 cycles

PD

n = 402

Pertuzumab + trastuzumab

Docetaxel*

≥ 6 cycles

PD

• Randomization stratified by geographic region and neo/adjuvant chemotherapy

• Study dosing q3w:
  – Pertuzumab/placebo: 840 mg loading → 420 mg maintenance
  – Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance
  – Docetaxel: 75 mg/m² → 100 mg/m² escalation if tolerated

* < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.

HER2, human epidermal growth factor receptor 2;
MBC, metastatic breast cancer;
PD, progressive disease.

CLEOPATRA Results

• Docetaxel/trastuzumab/pertuzumab > docetaxel/trastuzumab/placebo in terms of:
  – Progression-free survival
    • period free from cancer growth
  – Survival

• Side effects: tolerable
  – No increased risk of heart failure w/ addition of pertuzumab

• Approved as 1\textsuperscript{st}-line Rx
Paclitaxel, Trastuzumab, Pertuzumab (THP)
Memorial Sloan Kettering Cancer study

- Paclitaxel (T) at 80 mg/m² q week
- Pertuzumab (P) at 840 mg load → 420 mg q 3 weeks
- Trastuzumab (H) at 8 mg/kg load → 6 mg/kg q 3 weeks

Cardiac biomarkers every 2 cycles

N = 69
HER2 +
0-1 prior Rx
1° endpoint = 6 mo PFS

Dang et al. JCO 2015
PFS = progression-free survival
Conclusions

• Study met 1° endpoint in terms of efficacy (benefit) of drugs

• Well tolerated
  – No fevers from low white blood count

• Paclitaxel/trastuzumab/pertuzumab (THP) is another 1\textsuperscript{st}-line option for patients with HER2+ metastatic breast cancer
  – Endorsed by National Comprehensive Cancer Network (NCCN)
NCCN Guidelines

• NCCN guidelines for 1\textsuperscript{st}-line\textsuperscript{1}:
  – Docetaxel + HP (CLEOPATRA study)\textsuperscript{2}
  – Paclitaxel + HP (MSKCC study)\textsuperscript{3}

H=trastuzumab, P=pertuzumab

3. Dang. JCO 2015
Metastatic
Second-Line and Beyond
Ado Trastuzumab Emtansine
T-DM1
T-DM1

• In 2\textsuperscript{nd}-line
  • T-DM1 $>$ capecitabine/lapatinib (standard option)

• In 3\textsuperscript{rd}-line and beyond
  – T-DM1 $>$ other standard options

• Well tolerated
  – No hair loss

• Low risk of heart failure
Other 3rd-line and Beyond Options

• Trastuzumab + capecitabine
• Lapatinib + capecitabine
• Trastuzumab + lapatinib
• Trastuzumab + other chemo
• Trastuzumab + hormone Rx
• Lapatinib + hormone Rx
• Pertuzumab-based Rx if not received in 1st-line
Clinical Pathway: HER2 Positive MBC

1st Line

Taxane + Trastuzumab + Pertuzumab

2nd Line

Ado Trastuzumab Emtansine (T-DM1)

3rd Line and beyond

- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + Lapatinib
- Trastuzumab + other chemo
- Trastuzumab + hormone Rx (for HR+)
- Lapatinib + hormone Rx (for HR+)
- Ado Trastuzumab Emtansine (T-DM1) if not received in 2nd line
- Pertuzumab-based if not received in 1st line

HR = hormone receptor

Giordano et al. JCO 2014
Adjuvant
Node (+) and Node (-) High Risk
Trastuzumab in Adjuvant Setting
Early Breast Cancer

- **NSABP B-31**: Doxorubicin x 52
- **NCCTG 9831**: Cyclophosphamide x 52
- **HERA**: Paclitaxel x 52
- **HERA**: Docetaxel x 52
- **HERA**: Carboplatin x 52
- **HERA**: Epirubicin x 52
- **HERA**: Vinorelbine x 52
- **HERA**: Fluorouracil x 52
- **HERA**: Standard ChemoRx (x 52): 12 cycles
- **HERA**: No therapy (x 1 year)
- **HERA**: No therapy (x 2 years)
- **HERA**: H Trastuzumab x 52

- **BCIRG 006**: Doxorubicin x 52
- **BCIRG 006**: Cyclophosphamide x 52
- **BCIRG 006**: Paclitaxel x 52
- **BCIRG 006**: Docetaxel x 52
- **BCIRG 006**: Carboplatin x 52
- **BCIRG 006**: Epirubicin x 52
- **BCIRG 006**: Vinorelbine x 52
- **BCIRG 006**: Fluorouracil x 52
- **HERA**: Standard ChemoRx (x 52): 12 cycles
- **HERA**: No therapy (x 1 year)
- **HERA**: No therapy (x 2 years)
- **HERA**: H Trastuzumab x 52

- **FinHer**: Doxorubicin x 9
- **FinHer**: Cyclophosphamide x 9
- **FinHer**: Paclitaxel x 9
- **FinHer**: Docetaxel x 9
- **FinHer**: Carboplatin x 9
- **FinHer**: Epirubicin x 9
- **FinHer**: Vinorelbine x 9
- **FinHer**: Fluorouracil x 9
- **HERA**: Standard ChemoRx (x 9): 12 cycles
- **HERA**: No therapy (x 1 year)
- **HERA**: No therapy (x 2 years)
- **HERA**: H Trastuzumab x 9

- **PACS 04**: Doxorubicin x 52
- **PACS 04**: Cyclophosphamide x 52
- **PACS 04**: Paclitaxel x 52
- **PACS 04**: Docetaxel x 52
- **PACS 04**: Carboplatin x 52
- **PACS 04**: Epirubicin x 52
- **PACS 04**: Vinorelbine x 52
- **PACS 04**: Fluorouracil x 52
- **HERA**: Standard ChemoRx (x 52): 12 cycles
- **HERA**: No therapy (x 1 year)
- **HERA**: No therapy (x 2 years)
- **HERA**: H Trastuzumab x 52

**Treatments & Cycles**
- **NSABP B-31**: 1 year
- **BCIRG 006**: 2 years
- **NCCTG 9831**: 1 year
- **HERA**: 2 years
- **FinHer**: 1 year
- **PACS 04**: 2 years

**Chemotherapies**
- **Doxorubicin** (red)
- **Cyclophosphamide** (yellow)
- **Paclitaxel** (light blue)
- **Docetaxel** (dark blue)
- **Carboplatin** (gray)
- **Epirubicin** (pink)
- **Vinorelbine** (purple)
- **Fluorouracil** (green)

**Trastuzumab** (H) is used in the adjuvant setting for early breast cancer.
Adjuvant Trastuzumab

• With up to 10 years of follow-up, there is a sustained benefit of trastuzumab added to standard chemo

• 1 year remains standard
  – 6 month-duration was not as effective
  – 2 year-duration was not better

• Is dual antibody therapy (with trastuzumab and pertuzumab) being studied?
Adjuvant Study-APHINITY
Anthracycline Based

Centrally Confirm HER2

Arm A

AC/EC x 4 or FEC/FAC x 3-4
T x 3-4
Trastuzumab q 3 wks x 52 wks
Placebo q 3 wks x 52 wks

Arm B

AC/EC x 4 or FEC/FAC x 3-4
T x 3-4
Trastuzumab q 3 wks x 52 wks
Pertuzumab q 3 wks x 52 wks

1-year anti-HER2 Rx

Completed Data in 2017

A=doxorubicin, E=epirubicin, C=cyclophosphamide, T= taxane (paclitaxel or docetaxel), F=5-fluorouracil, H=trastuzumab, P=pertuzumab
Adjuvant Node (-) Low Risk
Adjuvant Paclitaxel and Trastuzumab (APT) Trial

HER2+ ER+ or ER- Node Negative ≤ 3 cm

Planned N=400

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. NEJM 2015
Results of APT Trial

• The 3 year disease free survival was 98.7%
• Well tolerated Rx
• Low heart failure rate of 0.5%
• Paclitaxel and trastuzumab is standard option for patients w/ stage I HER2+ breast cancer
• Note: T-DM1 is currently being evaluated against paclitaxel/trastuzumab in ATEMPT study for patients with stage I HER2 (+) breast cancer
Neoadjuvant
Neoadjuvant Therapy

• Reasons to have neoadjuvant Rx: downstage
  – Convert inoperable → operable breast cancer
  – Convert mastectomy → lumpectomy

• Two studies demonstrated that when combined w/ standard chemo, trastuzumab/pertuzumab (HP) led to high pathologic complete response (pCR) rates\(^1\)-\(^2\)
  – Patients enrolled had stage II-III disease

• pCR=no residual invasive cancer in breast (at time of surgery)

FDA Approval of Pertuzumab in Neoadjuvant Setting

• Patients w/ stage II-III
  – Size > 2 cm “or”
  – Node (+)
  – Locally advanced breast cancer
  – Inflammatory breast cancer

• Up to 6 cycles of pertuzumab allowed in neoadjuvant setting

http://www.fda.gov
NCCN Recommendations

• Pertuzumab-containing regimen can be given to patients in “neoadjuvant” or “adjuvant” setting
  – Stage II-III

• Patients who have not received a “neoadjuvant” pertuzumab-containing regimen can receive “adjuvant” pertuzumab.

Summary

• **Metastatic**
  - 1\textsuperscript{st}-line
    • Taxane + trastuzumab + pertuzumab
  - 2\textsuperscript{nd}-line
    • T-DM1
  - 3\textsuperscript{rd}-line and beyond
    • Capecitabine + trastuzumab
    • Capecitabine + lapatinib
    • Trastuzumab + lapatinib
    • Trastuzumab+ other chemo
    • Trastuzumab + hormone Rx
    • Lapatinib + hormone Rx
    • T-DM1 (if not received as 2\textsuperscript{nd}-line)
    • Pertuzumab-based Rx (if not received in 1\textsuperscript{st}-line)
Summary

• **Adjuvant**
  - One year trastuzumab is standard
  - Sustained benefit of trastuzumab w/ longer follow-up
  - High-Risk (node +, stage II-III)
    • Chemo + trastuzumab (pertuzumab allowed)
      – Anthracycline → taxane/trastuzumab +/- pertuzumab
      – Taxane/trastuzumab +/- pertuzumab
  - Low risk (node-, stage I)
    • Taxane + trastuzumab (ie: paclitaxel + trastuzumab)

H=trastuzumab, P=pertuzumab,
Summary

• Neoadjuvant
  – Pertuzumab w/ trastuzumab for up to 6 cycles (as part of complete Rx) indicated for pts w/ stage II-III
  – FDA approved and NCCN endorsed
  – Rx options
    • Anthracycline → taxane/trastuzumab/pertuzumab
    • Taxane/trastuzumab/pertuzumab
Thank You!