Pre-Conference Workshop: HER2-Targeted Therapies

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Assistant Professor of Oncology
Johns Hopkins School of Medicine
Outline

• Where do HER2-targeted therapies fit into the continuum of cancer care?
• Review individual HER2 targeted-therapies
  – Oncologic benefits (focus primarily on breast cancer)
  – Cardiac risks
• Questions and Case
Overall Approach to Treating Breast Cancer

**Early Stage:**

- Surgery
- Neoadjuvant Systemic Therapy
- Surgery
- Adjuvant Systemic Therapy +/- Radiation

**Metastatic:**

- Palliative Systemic Therapy
- Palliative Systemic Therapy
- Palliative Systemic Therapy
HER2-Positive Breast Cancer

- ~20% of breast cancers HER2-positive
- HER2-positivity defined by:
  a) HER2 protein over-expression (assessed by immunohistochemistry) or
  b) gene amplification (based on HER2 copy number or HER2:CEP17 ratio on in situ hybridization)
- Historically, HER2 positive breast cancers more aggressive, characterized by poor prognosis
- HER2-positivity predicts response to HER2-targeted therapies
- Favorable prognosis in modern era with HER2-targeted therapies

Slamon Science 1987;235(4785):177–182
Wolff J Clin Oncol 36:2105-2122, 2018
Where Do Her2-Targeted Therapies Fit Into the Breast Cancer Treatment Paradigm?

**Early Stage HER2-Positive:**
- Surgery
- Neoadjuvant Chemo/HER2-Targeted Therapy
- Surgery
- Adjuvant Chemo/HER2-Targeted Therapy +/- Radiation +/- Endocrine Therapy

**Metastatic HER2-Positive:**
- Palliative Chemo
- Palliative HER2-Targeted Therapy +/- Radiation +/- Endocrine Therapy
- Palliative HER2-Targeted Therapy +/- Chemo
HER2-Targeted Therapy for Metastatic Gastric or GE Junction Cancer

• ~20% of gastric or GE junction tumors are HER2-positive

  – Improved outcomes with first-line chemo + HER2-targeted therapy for Metastatic HER2-Positive Gastric or GE Junction Cancer:

    1\textsuperscript{st} line Palliative HER2-Targeted Therapy + Chemo
    \rightarrow
    2\textsuperscript{nd} line Palliative systemic therapy
    \rightarrow
    3\textsuperscript{rd} line Palliative systemic therapy
    \rightarrow
    etc
The ErbB Receptor Family

- The ErbB family of receptor tyrosine kinases includes 4 HER proteins:
  - HER1 (EGFR, ErbB1)
  - HER2
  - HER3 (ErbB3)
  - HER4 (Erb4)
- Homo- or hetero-dimerization of the HER receptors leads to downstream intracellular signaling via pathways that mediate cell growth and proliferation.
- HER2 is the preferred partner for hetero-dimerization with other HER receptors
Approved HER2-Targeted Therapies

Trastuzumab

- Humanized monoclonal antibody against HER2
- Binds to extra-cellular domain 4 of HER2 → prevents its homo- and hetero-dimerization
- HER2-positivity predicts response to trastuzumab
- Mechanisms of action include:
  - Activates antibody dependent cellular cytotoxicity
  - Inhibits downstream intracellular signaling
  - Inhibits angiogenesis
  - Inhibits cleavage of the extra-cellular domain
  - Increases intracellular HER2 degradation
# Pivotal Phase III Trastuzumab Studies in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Survival, Mos</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy Alone</td>
<td>Chemotherapy + Trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Slamon: Paclitaxel or Anthracycline-based*</td>
<td>20.3</td>
<td>25.1</td>
<td>0.80 (0.64-1.00)</td>
</tr>
<tr>
<td>Marty: Docetaxel</td>
<td>22.7</td>
<td>31.2</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Patients previously treated with adjuvant anthracyclines received paclitaxel and patients not previously treated with anthracyclines received doxorubicin/cyclophosphamide.

Overall, the addition of trastuzumab to chemotherapy improves overall survival in metastatic breast cancer.

# Key Adjuvant Trastuzumab Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Median F/u</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B31</strong></td>
<td><strong>AC→T</strong></td>
<td>8.4 years</td>
<td>62.2% 10 year DFS</td>
<td>75.2% 10 year OS</td>
</tr>
<tr>
<td></td>
<td><strong>AC→TH→H (1 yr total)</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>HERA</strong></td>
<td><strong>Chemo</strong></td>
<td>11 years</td>
<td>63% 10 year DFS</td>
<td>73% 10 year OS</td>
</tr>
<tr>
<td></td>
<td><strong>Chemo → H (1 yr)</strong></td>
<td></td>
<td>69 % 10 year DFS</td>
<td>79% 10 year OS</td>
</tr>
<tr>
<td></td>
<td><strong>Chemo → H (2 yrs)</strong></td>
<td></td>
<td>69% 10 year DFS</td>
<td>80% 10 year OS</td>
</tr>
<tr>
<td><strong>BCIRG 006</strong></td>
<td><strong>AC→D</strong></td>
<td>5.4 years</td>
<td>75% 5 year DFS</td>
<td>87% 5 year OS</td>
</tr>
<tr>
<td></td>
<td><strong>TCH→H (1 yr total)</strong></td>
<td></td>
<td>84% 5 year DFS</td>
<td>92% 5 year OS</td>
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<tr>
<td></td>
<td><strong>AC→DH→H (1 yr total)</strong></td>
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<td>81% 5 year DFS</td>
<td>91% 5 year OS</td>
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</table>
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</table>

**Combined Analysis**

**Standard of care: Chemotherapy + 1 year of Her2 targeted therapy**
Reducing Therapy for Low-Risk HER2-Positive Early Breast Cancer

• APT trial:
  – Single arm
  – < 3 cm tumors
  – Paclitaxel/Trastuzumab weekly x 12 → Trastuzumab (1 year total)
  – 3 year DFS: 98.7%
Trastuzumab for HER2-Positive Metastatic Gastric or GE Junction Cancer

ToGA Trial:
- First line
- Metastatic HER2-positive gastric or GE Junction Cancer

R

Chemotherapy (Capecitabine/Cisplatin OR 5FU/Cisplatin)

Median OS 11.1 months

Chemotherapy (Capecitabine/Cisplatin OR 5FU/Cisplatin)
PLUS Trastuzumab

Median OS 13.8 months

Bang Lancet 2010
Current Indications for Trastuzumab

• Metastatic HER2-positive breast cancer:
  – Monotherapy
  – In conjunction with chemotherapy +/- pertuzumab

• Early Stage HER2-positive breast cancer:
  – In conjunction with chemotherapy +/- pertuzumab

• First line treatment of HER2-positive metastatic gastric or GE junction tumors:
  – In conjunction with chemotherapy
Cardiac Toxicity of Trastuzumab in Metastatic Breast Cancer Trials

- Initially noted in pivotal Slamon phase III trial
  - No prospective cardiac monitoring or cardiac inclusion/exclusion criteria
- Led to creation of Cardiac Review and Evaluation Committee: retrospectively reviewed records from 1219 patients treated on 6 phase II trials and 1 phase III trial evaluating trastuzumab for metastatic breast cancer:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>Proportion with cardiac dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>II</td>
<td>3-7%</td>
</tr>
<tr>
<td>Trastuzumab + Chemotherapy</td>
<td>II</td>
<td>3-6%</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>III</td>
<td>8%</td>
</tr>
<tr>
<td>Taxane</td>
<td>III</td>
<td>1%</td>
</tr>
<tr>
<td>Anthracyline+ Trastuzumab</td>
<td>III</td>
<td>27%</td>
</tr>
<tr>
<td>Taxane+Trastuzumab</td>
<td>III</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Overall proportion 9.2%
*Highest proportion of cardiotoxicity with combination of anthracycline+trastuzumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>% Class III-IV CHF</th>
<th>% Asymptomatic Decline in LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B31</strong> (Romond NEJM 2005)</td>
<td>AC→T</td>
<td>0.8%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>AC→TH→H (1 yr total)</td>
<td>4.1%</td>
<td>Not reported</td>
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<tr>
<td><strong>9831</strong> (Advani JCO 2016)</td>
<td>AC→T</td>
<td>0.3%</td>
<td>~9%</td>
</tr>
<tr>
<td></td>
<td>AC→TH→H (1 yr total)</td>
<td>3.4%</td>
<td>~18%</td>
</tr>
<tr>
<td></td>
<td>AC→T→H (1 yr)</td>
<td>2.8%</td>
<td>~14%</td>
</tr>
<tr>
<td><strong>HERA</strong> (Procter JCO 2010)</td>
<td>Chemo</td>
<td>0%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>Chemo → H (1 yr)</td>
<td>0.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>Chemo → H (2 yrs)</td>
<td>Not published</td>
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<td>11.2%</td>
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<tr>
<td></td>
<td>TCH→H (1 yr total)</td>
<td>0.4%</td>
<td>9.4%</td>
</tr>
<tr>
<td></td>
<td>AC→DH→H (1 yr total)</td>
<td>2%</td>
<td>18.6%</td>
</tr>
<tr>
<td><strong>APT</strong> (Tolaney NEJM 2015)</td>
<td>TH→H</td>
<td>0.5%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Strict cardiac eligibility criteria and cardiac monitoring utilized for adjuvant trials; Approx 6-7% of patients unable to receive trastuzumab due to decline in EF after anthracycline prior to trastuzumab.
Clinical Presentation of Trastuzumab-Related Cardiac Toxicity

- Most often asymptomatic decline in ejection fraction
- Clinical heart failure less common
- Not dose related
- Traditionally thought to be reversible (although can persist in some cases...)
- Can often re-challenge with trastuzumab
Factors Associated with Trastuzumab-Related Cardiotoxicity

- Receipt of anthracycline
- Older age
- Receipt of medications for HTN
- Low normal LVEF prior to trastuzumab (50-54%)
Cardiomyocytes express ErbB receptors

In the normal heart, neuregulin binds to HER4 → HER2:HER4 hetero-dimerization → activates downstream signaling pathways required for homeostasis

Trastuzumab blocks HER2:HER4 hetero-dimerization → inhibits downstream signaling pathways → ↑myocyte cell cycle arrest, ↓myocyte cell proliferation, ↓myocyte cell survival, accumulation of reactive oxygen species

Two-hit model may explain the increase in cardiotoxicity with the combination of anthracyclines and trastuzumab:

1. Anthracycline induces oxidative damage
2. Trastuzumab blocks neuregulin-mediated signaling required to protect against oxidative damage

Trastuzumab-Related Cardiac Toxicity: Proposed Mechanism of Action

Maurea J Cardiovasc Med 2016
Telli JCO  2007
Milano Current Drug Targets 2014
Preventing Trastuzumab-Related Cardiotoxicity

MANTICORE (Pituskin JCO 2017):
Eligibility: HER2-positive early breast cancer initiating chemo+tras (77% non-anthracycline)
Intervention: perindopril (n=33), bisoprolol (n=31) or placebo (n=30), serial cardiac MRI
Primary endpoint: Δ indexed LVEDV
Secondary endpoint: Δ LVEF
Results: No diff in mean Δ indexed LVEDV; lower mean Δ LVEF for bisoprolol arm compared to placebo and perindopril arm (-1% v -3% v -5%, p=0.001)

PRADA (Gulati Eu Heart Jnl 2016):
Eligibility: Early breast cancer initiating Anthracycline (22% also received tras)
Intervention: 2x2 factorial randomized placebo-controlled trial of candesartan and/or metoprolol (n=130), serial cardiac MRI
Primary endpoint: Δ LVEF
Results: Mean Δ LVEF -2.6 for placebo and -0.8 for candesartan. No effect of metoprolol on Δ LVEF
Monitoring Cardiac Function in Asymptomatic Patients at Risk of Cardiac Dysfunction who are Receiving HER2-Targeted Therapy

• Echocardiogram is modality of choice in most circumstances
• Typically obtain at baseline and every 3 months (in accordance with schedule used in adjuvant trials)
• May consider less frequent monitoring in patients receiving prolonged therapy

Armenian JCO 2017
Approved HER2-Targeted Therapies

Pertuzumab

- Humanized monoclonal antibody against HER2
- Binds to extra-cellular domain 2 of HER2 → prevents HER2:HER3 hetero-dimerization → inhibits downstream signaling
- Activates antibody dependent cellular cytotoxicity
- Minimal activity as a single agent → synergistic when used in combination with trastuzumab
Pertuzumab for Metastatic Breast Cancer

**CLEOPATRA TRIAL:**

- HER2-positive locally recurrent, unresectable or MBC
- ≤ 1 hormonal regimen for MBC
- Prior (neo)adjuvant systemic Rx, including trastuzumab and/or taxane allowed if followed by DFS ≥ 12 mos
- Baseline LVEF ≥ 50%; no CHF or LVEF < 50% during or after previous trastuzumab

**Primary endpoint:** Independently assessed PFS

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CLEOPATRA Trial Survival Results

Median OS:
THP: 56.5 mo
TH: 40.8 mo
HR 0.68
P<0.001

Pertuzumab in the Neoadjuvant Setting

Neosphere Trial (Gianni Lancet Oncol 2012):

<table>
<thead>
<tr>
<th>N=417</th>
<th>Docetaxel + trastuzumab</th>
<th>Docetaxel + trastuzumab + pertuzumab</th>
<th>Pertuzumab + trastuzumab</th>
<th>Docetaxel + pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>29%</td>
<td>45.8%</td>
<td>16.8%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Tryphaena Trial (Schneeweiss Ann Onc 2013):

<table>
<thead>
<tr>
<th>N=225</th>
<th>FEC+ trastuzumab + pertuzumab → docetaxel + trastuzumab + pertuzumab</th>
<th>FEC→ docetaxel + trastuzumab + pertuzumab</th>
<th>Docetaxel + carboplatin + trastuzumab + pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>61.6%</td>
<td>57.3%</td>
<td>66.2%</td>
</tr>
</tbody>
</table>

*High pCR rates with addition of pertuzumab to trast/chemo
*Concurrent anthracycline with pert/trast not associated with higher pCR
Adjuvant Pertuzumab

APHINITY: Trial Design

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

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

- **Chemotherapy**
  - 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

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Presented By Gunter Von Minckwitz at 2017 ASCO Annual Meeting
APHINITY TRIAL RESULTS: *Statistically significant improvement in invasive DFS with addition of pertuzumab. But, absolute benefit small. Greatest benefit in node positive.

Current Indications for Pertuzumab

- Metastatic HER2-positive breast cancer:
  - In conjunction with chemotherapy + trastuzumab (1st line)
- Early Stage HER2-positive breast cancer:
  - In conjunction with chemotherapy + trastuzumab (neoadjuvant) (high risk patients: >2cm, node pos)
  - In conjunction with trastuzumab (adjuvant) (high risk patients: node pos)
## Cardiac Toxicity in Pertuzumab Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arm</th>
<th>% Asymptomatic ↓LVEF</th>
<th>% grade 3-4 LV dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEOPATRA (Swain NEJM 2015)</td>
<td>Pertuzumab+Trastuzumab+Docetaxel</td>
<td>6.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab+Docetaxel</td>
<td>7.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>NEOSPHERE (Gianni Lancet 2012)</td>
<td>Docetaxel + trastuzumab</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + trastuzumab + pertuzumab</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel + pertuzumab</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab + trastuzumab</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>TRYPHAENA (Schneeweiss Ann Onc 2013) (primary focus: cardiac tolerability during neoadjuvant therapy)</td>
<td>FEC+ trastuzumab + pertuzumab → docetaxel + trastuzumab + pertuzumab</td>
<td>5.6%</td>
<td>0%</td>
</tr>
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<td>Docetaxel + carboplatin + trastuzumab + pertuzumab</td>
<td>3.9%</td>
<td>0%</td>
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<td>APHINITY</td>
<td>Chemo + trastuzumab</td>
<td>2.8%</td>
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*Low rates of cardiac toxicity in pertuzumab trials*
Approved HER2-Targeted Therapies

Ado-Trastuzumab Emtansine (T-DM1)

- Antibody-Drug Conjugate: A chemotherapy agent (DM1) covalently bound to trastuzumab (T)
- Trastuzumab component binds to extracellular domain 4 of HER2 → targeted delivery of chemotherapy to HER2+ cell
- Minimizes toxicity
EMILIA TRIAL:

*Improved PFS and OS for T-DM1 compared to lapatinib/capecitabine after progression on a trastuzumab-containing regimen

Verma NEJM 2012
**Post-Neoadjuvant T-DM1**

Katherine Trial:

*Improved iDFS with post-neo-adjuvant T-DM1 compared to trastuzumab in the setting of residual disease after neoadjuvant therapy*
Current Indications for T-DM1

• **Metastatic HER2-positive breast cancer:**
  – After progression on a trastuzumab/pertuzumab-containing regimen

• **Early Stage HER2-positive breast cancer (possible new indication):**
  – In post-neoadjuvant setting in patients with residual disease after neoadjuvant therapy
# Cardiac Toxicity of T-DM1

<table>
<thead>
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<th>Arm</th>
<th>% Asymptomatic Decline EF</th>
<th>% Grade 3-4 CHF</th>
</tr>
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<tbody>
<tr>
<td>EMILA</td>
<td>T-DM1</td>
<td>1.7%</td>
<td>0.024%</td>
</tr>
<tr>
<td></td>
<td>Capecitabine/Laptinib</td>
<td>1.6%</td>
<td>0%</td>
</tr>
<tr>
<td>KATHERINE</td>
<td>T-DM1</td>
<td>1.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>1.4%</td>
<td>0.6%</td>
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Von Minckwitz NEJM 2018
Verma NEJM 2012
Approved HER2-Targeted Therapies

Lapatinib

- Oral
- Reversible
- Dual tyrosine kinase inhibitor against HER1 and HER2
Lapatinib for Metastatic Breast Cancer

*Improved PFS with addition of lapatinib to capecitabine

Current Indications for Lapatinib

• Metastatic HER2-positive breast cancer:
  – 3rd line or later
Cardiac Toxicity of Laptainib for Treatment of Metastatic Breast Cancer

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<th>% Asymptomatic Decline EF</th>
<th>% Grade 3-4 CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>0.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Capecitabine/Laptinib</td>
<td>2%</td>
<td>0%</td>
</tr>
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</table>

Von Minckwitz NEJM 2018
Verma NEJM 2012
Approved HER2-Targeted Therapies

Neratinib

- Oral
- Irreversible
- Dual tyrosine kinase inhibitor against HER1 and HER2
Neratinib after Adjuvant Trastuzumab

- **Extenet trial**: placebo controlled trial of neratinib x 1 year after completion of (neo)adjuvant chemo/trastuzumab.
  - Improved 2 year iDFS with neratinib (93.9% vs 91.6%)
  - Minimal cardiac toxicity (1% ↓ LVEF in each arm)

Chan Lancet Onc 2016
Audience Response Question #1

Which of the following is not a HER2-targeted therapy used in the treatment of HER2 positive breast cancer?

a) Trastuzumab
b) Doxorubicin
c) Pertuzumab
d) Lapatinib
e) T-DM1
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Explanation:

- Doxorubicin is an anthracycline. Trastuzumab, Pertuzumab, Lapatinib and T-DM1 (ado-trastuzumab emtansine) are all HER2-targeted therapies used for the treatment of HER2-positive breast cancer.
Which of the following regimens used to treat early stage HER2-positive breast cancer is the most likely to be associated with cardiac toxicity?

a) TCH (docetaxel, carboplatin, trastuzumab)
b) AC-TH (doxorubicin, cyclophosphamide, paclitaxel, trastuzumab)
c) TH (paclitaxel, trastuzumab)
d) TCH/P (docetaxel, carboplatin, trastuzumab, pertuzumab)
Audience Response Question #2

Which of the following regimens used to treat early stage HER2-positive breast cancer is the most likely to be associated with cardiac toxicity?

a) TCH (docetaxel, carboplatin, trastuzumab)

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c) TH (paclitaxel, trastuzumab)
d) TCH/P (docetaxel, carboplatin, trastuzumab, pertuzumab)

Explaination:

- AC-TH is most likely to be associated with cardiac toxicity because it incorporates an anthracycline and trastuzumab.
  - In the BCIRG-006 trial, congestive heart failure and subclinical drop in ejection fraction were observed more frequently in the AC-TH arm than in the TCH arm.
- The addition of pertuzumab to a trastuzumab-containing regimen does not increase cardiac toxicity.
- The incidence of cardiac toxicity with the TH regimen is very low.
**Audience Response Question #3**

A 45 yo female has T1bN0M0 ER/PR negative, HER2-positive R-sided breast cancer. She had a lumpectomy and sentinel node biopsy. She received 12 weeks of adjuvant paclitaxel/trastuzumab (TH) and underwent radiation to the R breast. She is now receiving trastuzumab alone every 3 weeks over 9 months to complete one year of HER2-targeted therapy. What type of cardiac monitoring is appropriate during her trastuzumab therapy?

a) No cardiac monitoring required since risk of symptomatic heart failure is low with paclitaxel/trastuzumab

b) Baseline echocardiogram only; no follow-up cardiac assessment if baseline is normal

c) EKG and echocardiogram at baseline and approximately every 3 months

d) Echocardiogram at baseline and approximately every 3 months
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Explanation:
- Although the risk of cardiac toxicity is low with this regimen, cardiac monitoring to assess EF is recommended at baseline and every 3 months.
Audience Response Case

55 yo female with metastatic HER2-positive breast cancer. She has had progressive disease after receiving first line docetaxel/pertuzumab/trastuzumab. Which therapy do you recommend next?

a. Lapatinib/Capecitabine
b. T-DM1
c. Neratinib
d. Trastuzumab + another chemotherapy agent
e. Pertuzumab/Trastuzumab + another chemotherapy agent
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Explanation:
- T-DM1 is recommended for 2nd line treatment of metastatic breast cancer after progression on a trastuzumab/pertuzumab-containing regimen
Thank you