Standards of Care and Optimal Choices in HER2+ ABC

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Disclosures

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Advisory or consultant role (no personal compensation): G1 Therapeutics, GSK, Innocrin, Lilly, Novartis, Seattle Genetics.
HER2+ Breast Cancer is Molecularly Heterogeneous

Intrinsic subtype in pooled analysis 40 trials

<table>
<thead>
<tr>
<th></th>
<th>LumA</th>
<th>LumB</th>
<th>HER2-E</th>
<th>Basal-like</th>
<th>Normal-like</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2+</td>
<td>42%</td>
<td>25%</td>
<td>28%</td>
<td>2%</td>
<td>3%</td>
<td>2336</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>28%</td>
<td>2%</td>
<td>71%</td>
<td>14%</td>
<td>7%</td>
<td>1591</td>
</tr>
</tbody>
</table>

Courtesy T. Pascual, A. Prat
# Treating HER2+: Many Steps Forward

<table>
<thead>
<tr>
<th>Metastatic disease approvals</th>
<th>trastuzumab</th>
<th>lapatinib</th>
<th>pertuzumab</th>
<th>T-DM1</th>
<th>? neratinib</th>
<th>? tucatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>2005</td>
<td>2012-13</td>
<td>&gt;1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td></td>
<td>2020+</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(Neo)adjuvant approvals</th>
<th>Trastuzumab (H)</th>
<th>Pertuzumab (added to H)</th>
<th>Neratinib (after H)</th>
<th>T-DM1</th>
<th>In RD</th>
</tr>
</thead>
</table>

Changes in (neo)adjuvant will alter the MBC Rx paradigm

Questions Regarding Optimal Rx HER2+ MBC

1. Should ER+ HER2+ be treated differently from ER- HER2+?
2. How long / when should chemotherapy be used?
3. What are the implications of changes in the adjuvant setting for treatment of MBC?
4. Should those with CNS metastases be treated differently?
First-Line Therapy
Primary antibody-based therapy = trastuzumab
Synergy provided by pertuzumab
Immune-mediated effects of trastuzumab increasingly recognized
Underperform when used alone (but some activity)
**CLEOPATRA: Phase III Trial Adding Pertuzumab in First-Line**

**HER2-positive MBC**
(53% no prior chemo, 10% prior trastuzumab)

N=800

Docetaxel + trastuzumab + placebo

Docetaxel + trastuzumab + pertuzumab

1º endpoints: PFS / OS

<table>
<thead>
<tr>
<th>THP</th>
<th>TH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>18.5m</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.62 (95% CI, 0.51–0.75) P<0.001

6 cycles docetaxel required:
- Median 8 cycles chemo, 17-18 cycles H(P)
Does chemo duration matter?

Baselga J et al. NEJM 2012
CLEOPATRA: Mature Overall Survival (secondary endpoint)

- 16 month OS $\Delta$
- OS $\sim$ 5.5 years from metastasis
- 25% without PD @ 8y f/u

Trastuzumab + Docetaxel + Pertuzumab

Trastuzumab + Docetaxel + Placebo

57m 41m

Hazard ratio, 0.68 (95% CI, 0.56–0.84)
P $< 0.001$

<table>
<thead>
<tr>
<th>ER or PgR status</th>
<th>388</th>
<th>408</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Swain, NEJM 2015; Swain, ASCO 2019
HER2-Targeting Added To Endocrine Therapy

**anastrozole vs anastrozole + trastuzumab**
*Kaufman B et al, JCO 2009*

<table>
<thead>
<tr>
<th>Events</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>Hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>4.8 months</td>
<td>3.7 to 7.0</td>
<td>0.63</td>
<td>.0016</td>
</tr>
<tr>
<td>99</td>
<td>2.4 months</td>
<td>2.0 to 4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**letrozole vs letrozole + lapatinib**
*Johnston S et al, JCO 2009*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>Hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole 2.5 mg + lapatinib 1,500 mg</td>
<td>8.2 months</td>
<td>7.0 to 8.9</td>
<td>0.57</td>
<td>.019</td>
</tr>
<tr>
<td>Letrozole 2.5 mg + placebo</td>
<td>3.0 months</td>
<td>2.3 to 3.7</td>
<td></td>
<td>.047</td>
</tr>
</tbody>
</table>

**Adds toxicity but improves outcome.**

**Note poor PFS in ER+ HER+ (2.4-8.2m)**

**ET alone reasonable in individual patients but with caution.**
PERTAIN: Pertuzumab Added to ET + Trastuzumab

Rimawi et al, JCO 2018
PERTAIN: Results

**Median PFS**
- **H+P+Al**: 18.9m (14-28m)
- **H+Al**: 15.8m (11-19m)

**OS**
- Not yet reported

**HR**
- 0.65 (0.48-0.89)

*Rimawi et al, JCO 2018*
PERTAIN Results by Induction THP or Not

No Induction (N=112)
HR 0.55 (0.34-0.88)

Induction (N=146)
HR 0.75 (0.50-1.13)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>(T)ET/HP</th>
<th>(T)ET/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Induction T/HP</td>
<td>21.7m</td>
<td>12.4m</td>
<td></td>
</tr>
<tr>
<td>Induction T/HP</td>
<td>16.9m</td>
<td>16.8m</td>
<td></td>
</tr>
</tbody>
</table>

Favors ET/HP from outset. Why?
• Difference in cohorts? YES!
• In Induction group:
  • Those benefiting from T (early d/c)?
  • Those benefiting from ET (late initiation)?
• Subset analysis “red herring”?

Rimawi et al, JCO 2018
Decision Points: First-line HP added to ET or to Chemo?

ER- HER2+

• Standard = THP. Likely ok to substitute another taxane (nab pac, paclitaxel).
• Whether dropping chemotherapy is a good idea is unknown.
  • Continuous vs interrupted chemo: efficacy ↑ with continuous. Less studied in HER2+.

ER+ HER2+

• Either ET/H(P) or T/HP is reasonable. No OS data ET/HP.
  • Not clear T/HP → ET/HP is optimal approach.
  • Decision can be made on basis of prior ET, prior (neo)adjuvant Rx, frailty and comorbidities.
Second-Line and Later
Antibody-Drug Conjugate(s)

Key elements:

• Highly specific antibody vs highly expressed target. Does not need independent activity.
• Potent cytotoxic not subject to efflux pumps. Favorable drug-to-antibody ratio (DAR).
• Linker:
  • noncleavable (released intracellularly, e.g. TDM1) or
  • cleavable (↓ specificity but ? ↑ bystander effect, e.g. DS8201a)
EMILIA: Phase III Trial T-DM1 versus XL = 2\textsuperscript{nd} Line Rx

Pre-treated HER2+

<table>
<thead>
<tr>
<th></th>
<th>TDM1</th>
<th>XL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>9.6m</td>
<td>6.4m</td>
</tr>
<tr>
<td>OS</td>
<td>29.9m</td>
<td>25.9m</td>
</tr>
</tbody>
</table>

HR=0.650, p<0.001

Toxicity better (and different) with T-DM1: grade 3+ 57% vs 41%
- T-DM1 – thrombocytopenia, LFT↑
- XL – N/V, hand-foot syndrome

*Verma S, NEJM 2012; Dieras, Lancet Oncol 2017*
T-DM1

Excellent 2\textsuperscript{nd} line option. Emerging evidence of good outcomes in THP-treated.

If received in adjuvant setting, will need to reconsider depending on interval.

Not optimal 1\textsuperscript{st} line (MARIANNE)
## Hoofbeats of other ADC...

<table>
<thead>
<tr>
<th>Agent</th>
<th>Anti-HER2 MAb/payload (target)</th>
<th>Drug to antibody ratio</th>
<th>Linker drug</th>
<th>Phase of development</th>
<th>ORR in HER2-positive</th>
<th>ORR in HER2 low (IHC1+/2+/ISH-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab-DM1 (T-DM1)⁷</td>
<td>Trastuzumab/DM1 (anti-tubulin)</td>
<td>3.5</td>
<td>Noncleavable</td>
<td>US FDA Approved</td>
<td>43.6%</td>
<td>— — —</td>
</tr>
<tr>
<td>Trastuzumab duruxtecan</td>
<td>Trastuzumab/exatecan derivative [topoisomerase I inhibitor]</td>
<td>8</td>
<td>Cleavable</td>
<td>II/III</td>
<td>54.5%</td>
<td>50%</td>
</tr>
<tr>
<td>(DS-8201a)³⁹</td>
<td></td>
<td></td>
<td></td>
<td>NCT03248492 NCT03529110 NCT03523585</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYD985⁴⁰</td>
<td>Duocarmycin derivative [alkylating agent]</td>
<td>2.8</td>
<td>Cleavable</td>
<td>III</td>
<td>33%</td>
<td>HR + 27% HR – 40%</td>
</tr>
<tr>
<td>XMT-1522⁴¹</td>
<td>XMT-1519/ monomethyl auristin (anti-tubulin)</td>
<td>12</td>
<td>Cleavable</td>
<td>I</td>
<td>unknown</td>
<td>unknown</td>
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<tr>
<td>ARX788</td>
<td>Anti-HER2 MAb/ auristatin analog 269 (AS269) (anti-tubulin)</td>
<td>1.9</td>
<td>Non-cleavable</td>
<td>I</td>
<td>unknown</td>
<td>unknown</td>
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<tr>
<td>DHES0815A</td>
<td>Trastuzumab/ alkylator</td>
<td>2</td>
<td>Cleavable</td>
<td>I</td>
<td>unknown</td>
<td>unknown</td>
</tr>
</tbody>
</table>

_Pernas, Ther Adv Med Oncol 2019_
AntiHER2 Small Molecules

Small molecule kinase inhibitors

Neratinib (Tucatinib)

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Small Molecule HER2 Inhibitors

Lapatinib – reversible HER1/HER2 inhibitor
- After EMILIA, capecitabine + lapatinib = 3rd+ line Rx
- Lapatinib + trastuzumab > trastuzumab alone = all-biologic late-line Rx

Irreversible inhibitors:
- Neratinib (approved in early breast cancer). Toxicity an issue.
- Tucatinib (newer kid on the block)
- Both have evidence of better CNS activity
NALA: Phase III Trial Neratinib vs Lapatinib

Inclusion criteria
- Metastatic breast cancer (MBC)
- Centrally confirmed HER2+ disease
- ≥2 lines of HER2-directed therapy for MBC
- Asymptomatic and stable brain metastases permitted

R (1:1) n=621

Neratinib 240 mg/d + Capecitabine 1500 mg/m² 14/21 d
Loperamide (cycle 1)\textsuperscript{a}
No endocrine therapy permitted

Lapatinib 1250 mg/d + Capecitabine 2000 mg/m² 14/21 d

70% 3\textsuperscript{rd} line, ~ 60% HR+
Did not require pertuzumab or TDM1 exposure

\textsuperscript{a}
NALA Results

**HR 0.76 (0.63-0.93)**

<table>
<thead>
<tr>
<th></th>
<th>XN</th>
<th>XL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>8.8m</td>
<td>6.6m</td>
</tr>
<tr>
<td>OS</td>
<td>24.0m</td>
<td>22.2m</td>
</tr>
</tbody>
</table>

**Grade 3 Diarrhea:**
- XN: 24%
- XL: 13%

Rx discontinued due to treatment-emergent AEs:
- XN: 10.9%
- XL: 14.5%

**HR status**
- HR− 254: 0.42 (0.31–0.57) <0.001
- HR+ 367: 1.08 (0.84–1.40)

Saura, ASCO 2019
HER2CLIMB: Phase II Tucatinib added to XH

Key Eligibility Criteria
- HER2+ MBC
- Prior trastuzumab, pertuzumab, and T-DM1
- Brain MRI: no mets or mets not needing immediate local Rx

Tucatinib + Trastuzumab + Capecitabine
Placebo + Trastuzumab + Capecitabine

R* (2:1)
N=410
N=202

Press release 10/2019:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>0.54 (0.42-0.71)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>OS</td>
<td>0.66 (0.50-0.88)</td>
<td>0.0048</td>
</tr>
<tr>
<td>CNS PFS</td>
<td>0.48 (0.34-0.69)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Toxicity: diarrhea, LFT abnl

Presentation at SABCS!
CNS Metastasis

There are no standards of care and limited but emerging data.

Drug efficacy similar for existing CNS metastases (disrupted BBB):
• T-DM1 = XL in EMILIA, > TPC in TH3RESA
• Neratinib > lapatinib in NALA (29% vs 22% requiring Rx)
• Tucatinib 50% reduction in CNS progression

This may differ for prevention of CNS metastases (intact BBB):
• KATHERINE: same % metastases in CNS with TDM1 and trastuzumab

Guideline for CNS-only progression in HER2+:
Treat locally, continue same HER2-directed therapy

Krop, Ann Oncol 2015; Krop, Lancet Oncol 2017; Saura, ASCO 2019; von Minckwitz, NEJM 2019; Ramakrishna, JCO 2018
Treatment Approach HER2+ MBC in 2019 (adapted from ABC4)

**HR-**

1\(^{st}\)
- Taxane + trastuzumab + pertuzumab
  
2\(^{nd}\)
- TDM-1
  
3\(^{rd}\)
- ? Capecitabine + neratinib?
- ? Tucatinib + capecitabine + trastuzumab?
  
Later
- Other ChT + trastuzumab
- Lapatinib + trastuzumab

**HR+**

ET + trastuzumab (+ pertuzumab, lapatinib)

1\(^{st}\)
- Taxane + trastuzumab + pertuzumab
  
2\(^{nd}\)
- TDM-1 (post THP)
- Other ET + trastuzumab or lapatinib
  
3\(^{rd}\)
- ? Capecitabine + neratinib?
- ? Tucatinib + capecitabine + trastuzumab?
  
Later
- Other ET + trastuzumab
- Other ET + lapatinib + trastuzumab
- Other ChT + trastuzumab

Cardoso, Ann Oncol 2018
Thank you!
HER2-Targeting: The First Generation

Multiple chemotherapy partners for HER2-targeting

- Platinums, vinorelbine, gemcitabine, capecitabine
- What is optimal?

Post-trastuzumab progression, ongoing HER2-targeting works

- Lapatinib
- TDM1
- Trastuzumab!

ER+ HER2+ disease benefits from dual targeting

- AI + either trastuzumab or lapatinib
- Ok to omit HER2-targeting in strongly ER+, indolent, asymptomatic.
Trastuzumab-emtansine (T-DM1), HER2 Antibody-Drug Conjugate

- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab – similar to gemtuzumab (Myelotarg)
- Will it allow omission of separate cytotoxic?

![Diagram of Trastuzumab-emtansine](image)

**Average number DM1 molecules/monoclonal antibody = 3.5**

**T-MCC-DM1**

- HER2-mediated internalization
- Lysosomal degradation

**T-Lysine-MCC-DM1**

Active metabolite can’t cross plasma membrane (no bystander effect)
## Next Generation of HER2-Targeting

<table>
<thead>
<tr>
<th>Trial</th>
<th>Line</th>
<th>Regimens</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEOPATRA</td>
<td>1</td>
<td>TH + Pert</td>
<td><strong>19 v. 12m</strong> (HR 0.69*)</td>
<td><strong>56 v. 41m</strong> (HR 0.68*)</td>
</tr>
<tr>
<td>MARIANNE&amp;</td>
<td>1</td>
<td>TH v. TDM1 v. TDM1+P</td>
<td><strong>ns</strong></td>
<td>-</td>
</tr>
<tr>
<td>NEfERTT&amp;</td>
<td>1</td>
<td>TH v. TN</td>
<td><strong>17 v. 17m</strong> (ns)</td>
<td>?fewer CNS with TN?</td>
</tr>
<tr>
<td>BOLERO-1</td>
<td>1</td>
<td>TH + Eve</td>
<td><strong>15 v. 14m</strong></td>
<td>-</td>
</tr>
<tr>
<td>EMILIA</td>
<td>2</td>
<td>TDM1 v. XL</td>
<td><strong>10 v. 6m</strong> (HR 0.65*)</td>
<td><strong>31 vs 29m</strong> (HR 0.68*)</td>
</tr>
<tr>
<td>BOLERO-3</td>
<td>2</td>
<td>VH + Eve</td>
<td><strong>7 v. 6m</strong> (HR 0.78*)</td>
<td>-</td>
</tr>
<tr>
<td>TH3RESA</td>
<td>3+</td>
<td>TDM1 v. MD choice</td>
<td><strong>6 v. 3m</strong> (HR 0.53)</td>
<td><strong>HR 0.55</strong> (interim)</td>
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</tbody>
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* significant

T=taxane; N=neratinib; V=vinorelbine; E=everolimus

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# Next Generation of HER2-Targeting

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<td></td>
<td>-</td>
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</tr>
<tr>
<td>BOLERO-3</td>
<td>+</td>
<td></td>
<td>6 v. 3m (HR 0.53)</td>
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<td></td>
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</tbody>
</table>

* significant

T=taxane; N=neratinib; V=vinorelbine; E=everolimus

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1st line: T+H+P wins (~$10,000/m)

2nd+ line: TDM1 wins (~$10,000/m)
Oncogene Addiction:

HER2 is Still a Relevant Target After Progression on Trastuzumab
# Summary: Metastatic Options for HER2+

<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Regimen Options</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Chemotherapy-based</strong></td>
</tr>
<tr>
<td>First</td>
<td>Taxane + trast + pert</td>
</tr>
<tr>
<td>Second</td>
<td>T-DM1</td>
</tr>
<tr>
<td>Third</td>
<td>Capecitabine + lapatinib</td>
</tr>
<tr>
<td>Later</td>
<td>Other drugs + trastuzumab</td>
</tr>
</tbody>
</table>

Median survival increasing
Multiple drug choices

How do we treat most thoughtfully?

Mariotto AB et al, Cancer Epid Biomark Prev 2017
Trastuzumab (H)

- Effective partner for chemotherapy of many kinds as well as for ET
- Works across lines of therapy and after progression on H

Original trial chemo ± H

Endocrine Rx ± H

H post-progression on H
(ongoing HER2-targeting post PD)

Slamon, NEJM 2001; Kaufman, JCO 2009; von Minckwitz, JCO 2009
AntiHER2 Antibody Drug Conjugates

Summary TDM1 creation, nature etc
Note re DS8201a
Summary

• At what point does targeting HER2 no longer play a role?
EORTC 75111-10114: Phase II 1st Line HP + Oral CM in Elderly

Small study (N=80)
Age ≥ 70 or ≥ 60 but frail
1º endpoint: 6m PFS
- Median age ~ 76
- PFS @ 6m 46% vs 73%

Consistent findings:
- HP alone tends to underperform
- “Chemotherapy” good partner

Wildiers, Lancet Oncol 2018
PERTAIN Forest Plots

May be important:
- Recent ET (less benefit of adding pertuzumab to ET)

Don’t appear important:
- Age
- Visceral vs not
- Prior adjuvant therapies (ET, chemo, trastuzumab)
Trastuzumab Added To Chemotherapy

Slamon DJ, et al. NEJM 2001

<table>
<thead>
<tr>
<th></th>
<th>Chemo + H (paclitaxel or AC)</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>7.4m</td>
<td>4.6m</td>
</tr>
<tr>
<td>OS*</td>
<td>25m</td>
<td>20m</td>
</tr>
</tbody>
</table>

* Despite crossover

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Capecitabine + Trastuzumab: Time To Progression (after prior trastuzumab)

Product-Limit Survival Estimates
With Number of Subjects at Risk

X : 5.6 (4.2 - 6.3) mos
XH : 8.2 (7.3 - 11.2) mos

HR=0.69 (two-sided p=0.034)

Median Follow Up: 15.6 months

von Minckwitz G et al, JCO 2009

ORR 48% vs 27%, p=0.0011
TH3RESA: TDM-1 vs TPC = Late line Rx

Prior trastuzumab and lapatinib, PD on > 2 HER2-directed Rx

HR 0.58
Censored for crossover

<table>
<thead>
<tr>
<th></th>
<th>TDM1</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>6.2m</td>
<td>3.3m</td>
</tr>
<tr>
<td>OS</td>
<td>22.7m</td>
<td>15.8m</td>
</tr>
</tbody>
</table>

Krop, Lancet Oncol 2014; Krop, Lancet Oncol 2017
Targeting HER2

Humanized monoclonal Ab to HER2 extracellular domain

Antibody-drug conjugate (TDM1= maytansine analogue conjugated to trastuzumab)

Small molecule kinase inhibitors

Neratinib (Tucatinib)
MARIANNE: T-DM1 (P) = Not First-Line

- 1st Line HER2+ LABC/MBC
- >6 months from prior chemo

N = 1095

Trastuzumab + taxane

T-DM1 + placebo

T-DM1 + pertuzumab

Similar outcomes
Less toxicity
Comparator = TH not THP
Remained at 2nd line

Note heterogeneity of HER2+ disease

Perez, JCO 2017
HER2+ Natural History

Without HER2-targeting
Frequent and early relapse
Visceral and CNS involvement

<table>
<thead>
<tr>
<th></th>
<th>Bone</th>
<th>Soft Tissue</th>
<th>Viscera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple negative</td>
<td>13%</td>
<td>13%</td>
<td>74%</td>
</tr>
<tr>
<td>ER+</td>
<td>39%</td>
<td>7%</td>
<td>54%</td>
</tr>
<tr>
<td>HER2+</td>
<td>7%</td>
<td>12%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CNS ~40%</td>
</tr>
</tbody>
</table>