Taking a Closer Look: How HR Status Affects Treatment Response in HER2+ ABC

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Edinburgh Cancer Research Centre, University of Edinburgh, UK
Disclosures

- I have non-personal (paid to my institution) relationships with GSK, Novartis, and Roche in relation to anti-HER therapies
- I have conducted research funded by GSK, Novartis, and Roche
Disclaimers

• Scientific information presented here may include data/information on investigational uses of compounds/drugs that have not yet been approved by regulatory authorities.

• The following are not EU approved for use in any indication:
  – Abemaciclib
  – Alpelisib
  – Buparlisib
  – Palbociclib
  – Pictilisib
  – Ribociclib
  – Taselisib
Factors Affecting Treatment Decisions in Advanced Breast Cancer

- HER2 and HR status
- Patient preference
- Previous therapies and their toxicities
- Clinical evidence for individual agents
- Tumor burden and disease-free interval
- Menopausal status (for endocrine therapy)
- Need for rapid disease/symptom control
- Socioeconomic/psychological factors
- Physiologic age and comorbidities
- Regional availability of therapies
- Availability of clinical trials

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- Physiologic age and comorbidities
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- Availability of clinical trials

HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
HER2 and HR Crosstalk

EGF, epidermal growth factor; EGFR, EGF receptor; ER, estrogen receptor.

Current Treatment Algorithm:¹−³
HER2+ Metastatic Breast Cancer

First line

- HR− disease
  - Pertuzumab + trastuzumab + taxane
  - Trastuzumab ± chemotherapy

Second line

- T-DM1 (preferred)
- Lapatinib + capecitabine
- Other HER2-targeted combinations
  - Trastuzumab + pertuzumab ± cytotoxic agent*
  - Lapatinib + trastuzumab

*If pertuzumab not previously received.
ET, endocrine therapy; HER2+, human epidermal growth factor receptor 2-positive; HR−, hormone receptor-negative; HR+, hormone receptor-positive; T-DM1, trastuzumab emtansine.
Current Treatment Algorithm:¹–³
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First line

HR– disease
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- Trastuzumab ± chemotherapy

Second line

T-DM1 (preferred)
- Trastuzumab + pertuzumab ± cytotoxic agent*

Lapatinib + capecitabine
- Lapatinib + trastuzumab

Other HER2-targeted combinations

HR+ disease
- HER2-targeted therapy + chemotherapy
- ET ± trastuzumab or lapatinib

HER2-targeted therapy + ET
- Other ET

HER2-targeted therapy ± chemotherapy

*If pertuzumab not previously received.
ET, endocrine therapy; HER2+, human epidermal growth factor receptor 2-positive; HR–, hormone receptor-negative; HR+, hormone receptor-positive; T-DM1, trastuzumab emtansine.
HER2-targeted Therapy + Chemotherapy: Any HR Status

• **First line:** Pertuzumab + trastuzumab + docetaxel is indicated for metastatic or locally recurrent, unresectable HER2+ breast cancer that is naive to prior anti-HER2 therapy or chemotherapy for metastatic disease\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab + trastuzumab + docetaxel</th>
<th>Trastuzumab + docetaxel</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS(^2)</strong></td>
<td>18.7 months</td>
<td>12.4 months</td>
<td>0.68 (0.58, 0.80)</td>
</tr>
<tr>
<td><strong>OS(^2)</strong></td>
<td>56.5 months</td>
<td>40.8 months</td>
<td>0.68 (0.56, 0.84)</td>
</tr>
</tbody>
</table>

- **Common treatment-related AEs ≥30% of patients in either arm** (triple vs double combination):\(^3\) diarrhea (68% vs 48%), alopecia (61% vs 61%), neutropenia (53% vs 50%), nausea (44% vs 42%), fatigue (38% vs 37%), rash (37% vs 24%), decreased appetite (30% vs 27%)

AE, adverse event; CI, confidence interval; OS, overall survival; PFS, progression-free survival.
HER2-targeted Therapy: Any HR Status

- **Second line**: **T-DM1** is indicated for metastatic or locally advanced, unresectable HER2+ breast cancer after prior trastuzumab and a taxane (separately or in combination) and after prior therapy for advanced disease or recurrence ≤6 months of completing adjuvant therapy\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>T-DM1</th>
<th>Lapatinib + capecitabine</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS(^2)</strong></td>
<td>9.6 months</td>
<td>6.4 months</td>
<td>0.65 (0.55, 0.77)</td>
</tr>
<tr>
<td><strong>OS(^2)</strong></td>
<td>30.9 months</td>
<td>25.1 months</td>
<td>0.68 (0.55, 0.85)</td>
</tr>
</tbody>
</table>

- **Common treatment-related AEs ≥25% of patients in either arm**
  (T-DM1 vs lapatinib + capecitabine):\(^2\) nausea (39% vs 45%), fatigue (35% vs 28%), thrombocytopenia (28% vs 3%), diarrhea (23% vs 80%), vomiting (19% vs 29%), PPE (1% vs 58%)

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PPE, palmar plantar erythrodysesthesia.
HER2-targeted Therapy + Chemotherapy: Any HR Status

- **Second line:** *Lapatinib + capecitabine* is indicated for advanced/metastatic HER2+ breast cancer after prior anthracyclines, taxanes, and trastuzumab in the metastatic setting\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib + capecitabine</th>
<th>Capecitabine</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP(^2)</td>
<td>6.2 months</td>
<td>4.3 months</td>
<td>0.57 (0.43, 0.77)</td>
</tr>
<tr>
<td>OS(^3)</td>
<td>75.0 weeks</td>
<td>64.7 weeks</td>
<td>0.87 (0.71, 1.08)</td>
</tr>
</tbody>
</table>

- **Common treatment-related AEs ≥25% of patients in either arm**
  (combination vs monotherapy):\(^4\) diarrhea (60% vs 39%), PPE (49% vs 49%), nausea (44% vs 42%), rash (27% vs 15%), vomiting (26% vs 24%), fatigue (18% vs 27%)

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TTP, time to progression.
**HER2-targeted Therapy + Endocrine Therapy: HR+ Disease**

- **Trastuzumab/lapatinib + AI** is indicated for postmenopausal metastatic HR+/HER2+ breast cancer that:\(^1,^2\)
  - Trastuzumab + AI: has not been previously treated with trastuzumab\(^1\)
  - Lapatinib + AI: is not currently intended for chemotherapy (EU)\(^2\)

<table>
<thead>
<tr>
<th>HR+/HER2+</th>
<th>Anti-HER2 therapy + AI</th>
<th>AI</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole ± trastuzumab(^3)</td>
<td>PFS: 4.8 months</td>
<td>PFS: 2.4 months</td>
<td>0.63 (0.47, 0.84)</td>
</tr>
<tr>
<td>Letrozole ± trastuzumab(^4)</td>
<td>TTP: 14.1 months</td>
<td>TTP: 3.3 months</td>
<td>0.67 (0.35, 1.29)</td>
</tr>
<tr>
<td>Letrozole ± lapatinib(^5)</td>
<td>PFS: 8.2 months</td>
<td>PFS: 3.0 months</td>
<td>0.71 (0.53, 0.96)</td>
</tr>
<tr>
<td>Letrozole ± lapatinib(^5)</td>
<td>OS:* 33.3 months</td>
<td>OS:* 32.3 months</td>
<td>0.74 (0.5, 1.1)</td>
</tr>
</tbody>
</table>

- **Common treatment-related AEs \(\geq20\%\) in either arm** (combination vs monotherapy):
  - **Anastrozole ± trastuzumab\(^3\)**: fatigue (21% vs 10%), diarrhea (20% vs 8%), vomiting (21% vs 5%)
  - **Letrozole ± trastuzumab\(^4\)**: bone pain (27% vs 16%), fatigue (27% vs 0), arthralgia (23% vs 16%)
  - **Letrozole ± lapatinib\(^5\)**: diarrhea (64% vs 20%), rash (45% vs 13%), nausea (31% vs 21%), arthralgia (19% vs 23%), fatigue (21% vs 17%)

*<50% OS events recorded. AI, aromatase inhibitor.
Dual Blockade of HER2: HR– Disease

- **Lapatinib + trastuzumab** is indicated for metastatic HR–/HER2+ breast cancer that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>HR–/HER2+</th>
<th>HR+/HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS(^2)</strong></td>
<td>15.4 weeks</td>
<td>8.2 weeks</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>8.2 weeks</td>
<td>7.9 weeks</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.73 (0.52, 1.03)</td>
<td>8.1 weeks</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>0.73 (0.51, 1.04)</td>
</tr>
<tr>
<td><strong>OS(^2)</strong></td>
<td>17.2 months</td>
<td>8.9 months</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>8.9 months</td>
<td>12.0 months</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.62 (0.42, 0.90)</td>
<td>11.2 months</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>0.84 (0.58, 1.23)</td>
</tr>
</tbody>
</table>

- **Common treatment-related AEs ≥10% of patients in either arm** (combination vs monotherapy):\(^2\) diarrhea (54% vs 43%), rash (19% vs 25%), nausea (19% vs 18%), fatigue (15% vs 12%), vomiting (10% vs 10%), dermatitis acneiform (5% vs 10%)

1. Tyverb EU SPC available from http://www.ema.europa.eu/ (accessed August 2015);
Importance of Molecular Re-testing

HR and HER2 status can change between primary tumor and metastases

<table>
<thead>
<tr>
<th></th>
<th>Macfarlane¹ (N=160)</th>
<th>Guarneri² (N=75)</th>
<th>Fabi³ (N=137)</th>
<th>Hoefnagel⁴ (N=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+ → HR−</td>
<td>5%</td>
<td>12%</td>
<td>−</td>
<td>11%*</td>
</tr>
<tr>
<td>HR− → HR+</td>
<td>9%</td>
<td>9%</td>
<td>−</td>
<td>3%*</td>
</tr>
<tr>
<td>HER2+ → HER2−</td>
<td>4%</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>HER2− → HER2+</td>
<td>1%</td>
<td>13%</td>
<td>9%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Using 10% threshold for receptor conversion

2015 ASCO guidelines: “Patients with accessible, newly diagnosed metastases from primary breast cancer should be offered biopsy for confirmation of disease process and testing of HR and HER2 status”⁵

- However, it is unclear whether changing anticancer treatment on the basis of change in receptor status affects clinical outcomes⁵

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Signaling Pathways Downstream of HER2$^{1–3}$

Estrogen

HER2

HER3

HER2

CDK, cyclin-dependent kinase; E2F, E2 family transcription factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; Rb, retinoblastoma.

Signaling Pathways Downstream of HER2\(^1\)\(^–\)\(^3\)

- Most patients with metastatic HER2+ breast cancer eventually acquire resistance to HER2-targeted therapies\(^4\)

CDK, cyclin-dependent kinase; E2F, E2 family transcription factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; Rb, retinoblastoma.
Signaling Pathways Downstream of HER2\textsuperscript{1–3}

- Most patients with metastatic HER2+ breast cancer eventually acquire resistance to HER2-targeted therapies\textsuperscript{4}

- Preclinical data suggest activation of the PI3K/mTOR pathway contributes to such resistance\textsuperscript{4,5}

- PI3K/mTOR pathway activation is associated with poor response to trastuzumab therapy\textsuperscript{6,7}

CDK, cyclin-dependent kinase; E2F, E2 family transcription factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; Rb, retinoblastoma.

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CDK, cyclin-dependent kinase; E2F, E2 family transcription factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; Rb, retinoblastoma.
BOLERO-3: Everolimus in Trastuzumab-resistant, HER2+ Advanced Breast Cancer

- BOLERO-3 provided proof-of-principle for the combination of HER2-targeted therapy with an inhibitor of the PI3K/mTOR pathway
  - Addition of everolimus to trastuzumab + vinorelbine significantly prolonged PFS in trastuzumab-resistant, taxane-pretreated HER2+ advanced breast cancer (7.00 vs 5.78 months, \( P=0.0067 \))
  - Greater benefit was seen in HR– vs HR+ tumors

All N=569

<table>
<thead>
<tr>
<th></th>
<th>N=569</th>
<th>Hazard ratio (95% CI): 0.78 (0.65, 0.95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR– n=250</td>
<td></td>
<td>0.65 (0.48, 0.87)</td>
</tr>
<tr>
<td>HR+ n=317</td>
<td></td>
<td>0.93 (0.72, 1.20)</td>
</tr>
</tbody>
</table>

- **Common treatment-related AEs ≥35% of patients in either arm** (everolimus vs placebo): neutropenia (81% vs 70%), stomatitis (63% vs 28%), anemia (49% vs 29%), leukopenia (46% vs 37%), fatigue (43% vs 42%), pyrexia (39% vs 23%), diarrhea (38% vs 30%), nausea (35% vs 37%)
Signaling Pathways Downstream of HER2¹⁻³

- Most patients with metastatic HER2+ breast cancer eventually acquire resistance to HER2-targeted therapies⁴

- Preclinical data suggest activation of the PI3K/mTOR pathway contributes to such resistance⁴,⁵

- PI3K/mTOR pathway activation is associated with poor response to trastuzumab therapy⁶,⁷

Phase I/II study (NCT01132664) of buparlisib (pan-PI3K inhibitor) + trastuzumab in trastuzumab-resistant locally advanced/metastatic HER2+ breast cancer\textsuperscript{1}

- RP2D was declared as 100 mg/day buparlisib with trastuzumab (2 mg/kg/week)\textsuperscript{1}
- **Common treatment-related AEs ≥20% of patients:**\textsuperscript{1} rash (39%), hyperglycemia (33%), diarrhea (28%), asthenia (22%), mood altered (22%), nausea (22%), pruritus (22%)

<table>
<thead>
<tr>
<th>Best overall response, n (%)\textsuperscript{1}</th>
<th>Full analysis set (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>2 (12)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (47)</td>
</tr>
<tr>
<td>SD ≥24 weeks</td>
<td>1 (6)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (12)</td>
</tr>
</tbody>
</table>

CR, complete response; PD, progressive disease; PR, partial response; RP2D, recommended Phase II dose; SD, stable disease.
# Ongoing Studies of PI3K Inhibitors in HER2+ Breast Cancer

<table>
<thead>
<tr>
<th>Study number</th>
<th>Study</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02038010</td>
<td>Phase I study of alpelisib + T-DM1 in metastatic HER2+ breast cancer that has progressed on prior trastuzumab and taxane-based therapy; N≈28</td>
<td>Northwestern University, IL, USA</td>
</tr>
<tr>
<td>NCT01300962</td>
<td>Parts C and D: Phase I study of buparlisib + capecitabine + trastuzumab/lapatinib in metastatic HER2+ breast cancer; N≈84 Parts A–D</td>
<td>UNC Lineberger Comprehensive Cancer Center, NC, USA</td>
</tr>
<tr>
<td>NCT02390427</td>
<td>Phase Ib study of taselisib + anti-HER2 therapies in advanced HER2+ breast cancer; N≈76</td>
<td>Dana-Farber Cancer Institute, MA, USA</td>
</tr>
<tr>
<td>NCT00960960</td>
<td>Phase Ib study of pictilisib + paclitaxel ± bevacizumab or trastuzumab in locally recurrent/metastatic breast cancer; N≈71</td>
<td>Genentech, Inc.</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov (accessed August 2015).]
Signaling Pathways Downstream of HER2\textsuperscript{1–3}

- Cyclin D–CDK4/6–Rb pathway activation promotes cell proliferation and tumor growth\textsuperscript{4}
- HER2+ luminal human breast cancer cell lines are sensitive to CDK4/6 inhibition \textit{in vitro}\textsuperscript{4}
- Cyclin D–CDK4/6–Rb pathway is downstream of many processes that drive resistance to HER2-targeted therapy\textsuperscript{5}
- CDK4/6 inhibition blocks tumor growth in models of acquired resistance to HER2-targeted therapies\textsuperscript{5}

# Ongoing Studies of CDK4/6 Inhibitors in HER2+ Breast Cancer

<table>
<thead>
<tr>
<th>Study number</th>
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</thead>
<tbody>
<tr>
<td><strong>Palbociclib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02448420</td>
<td>Phase II study of palbociclib + trastuzumab ± letrozole in postmenopausal locally advanced/metastatic HER2+ breast cancer after chemotherapy and trastuzumab treatment for metastatic disease; N≈138</td>
<td>SOLTI Breast Cancer Research Group, Spain</td>
</tr>
<tr>
<td>NCT01976169</td>
<td>Phase Ib study of palbociclib + T-DM1 in patients with recurrent/metastatic HER2+ after prior trastuzumab or other HER2-directed therapies; N≈17</td>
<td>University of Texas Southwestern Medical Center, TX, USA</td>
</tr>
<tr>
<td><strong>Abemaciclib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02308020</td>
<td>Phase II study of abemaciclib in HER2+ or HER2−, HR+ breast cancer with brain metastases; N≈120</td>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td>NCT02057133</td>
<td>Phase I study of abemaciclib in combination with different standard therapies (letrozole, anastrozole, tamoxifen, exemestane, exemestane + everolimus, or trastuzumab) in metastatic breast cancer; N≈102</td>
<td>Eli Lilly and Company</td>
</tr>
</tbody>
</table>
Summary

- HR status affects treatment decisions in metastatic HER2+ breast cancer; EMA-approved targeted therapy combinations include:
  - Pertuzumab + trastuzumab + docetaxel (any HR status)
  - Lapatinib + capecitabine (any HR status)
  - Trastuzumab + AI (HR+)
  - Lapatinib + AI (HR+)
  - Lapatinib + trastuzumab (HR–)

- Activation of the PI3K/mTOR and cyclin D–CDK4/6–Rb pathways may contribute to acquired resistance to HER2-targeted therapies

- PI3K and CDK4/6 inhibitors are in development for treatment of HER2+ advanced breast cancer in combination with HER2-targeted therapies
Interim Assessment:
Poll and Panel Discussion

Professor David Cameron (Moderator)
Edinburgh Cancer Research Centre, University of Edinburgh, UK
Case Study 1

- **June 2013:** Postmenopausal woman, aged 65 years, was diagnosed with Stage IIB HR−/HER2+ breast cancer
  - She underwent surgery and then received doxorubicin + cyclophosphamide followed by paclitaxel + trastuzumab

- **August 2014:** (14 months later) The breast cancer recurred and lung metastases were detected; patient received pertuzumab + trastuzumab + docetaxel
  - Cardiac toxicity was detected with a decrease in LVEF; patient restarted therapy after a temporary dose interruption

- **April 2015:** (8 months later) Disease progression was detected and T-DM1 was administered

- **September 2015:** (5 months later) Disease progression was detected again; the patient currently has an ECOG performance status of 2

ECOG, Eastern Cooperative Oncology Group; HER2+, human epidermal growth factor receptor 2-positive; HR−, hormone receptor-negative; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine.
Question: Which Treatment Would You Suggest?

1. Continue T-DM1
2. Lapatinib + trastuzumab
3. Lapatinib + capecitabine
4. Trastuzumab + chemotherapy*
5. Other

*Not approved for this indication; trastuzumab + chemotherapy is indicated for metastatic HER2+ breast cancer that is naive to prior chemotherapy for metastatic disease.
Case Study 2

- **March 2014:** A postmenopausal woman, aged 58 years, who previously led an active lifestyle, was diagnosed with *de novo* HR+/HER2+ advanced breast cancer
- Metastases in the bone were detected along with small volume lung disease
- Received trastuzumab + docetaxel; the combination was well tolerated and no cardiac toxicity was recorded
- After 6 cycles of docetaxel, an AI was added to trastuzumab
Question: Which First-line Treatment Would You Have Chosen?

1. Trastuzumab + chemotherapy
2. Trastuzumab + AI
3. Lapatinib + AI
4. Endocrine therapy alone
5. Pertuzumab + trastuzumab + docetaxel
6. Other
Case Study 2

- **March 2014:** A postmenopausal woman, aged 58 years, who previously led an active lifestyle, was diagnosed with *de novo* HR+/HER2+ advanced breast cancer.

- Metastases in the bone were detected along with small volume lung disease.

- Received trastuzumab + docetaxel; the combination was well tolerated and no cardiac toxicity was recorded.

- After 6 cycles of docetaxel, an AI was added to trastuzumab.

- **September 2015:** (18 months later) Disease progression was detected in the bone.
Question: Which Second-line Treatment Would You Suggest?

1. Continue trastuzumab + chemotherapy
2. T-DM1
3. Lapatinib + capecitabine
4. Endocrine therapy alone
5. Other