HER2-Positive Breast Cancer
Competitive Monitoring &
Strategic Analysis

State of the Art Landscape

NOTE: Hyperlinks to full records are active in presentation mode
- not slide sorter or edit modes

May 2011
Executive Summary

- Herceptin (trastuzumab) is the gold standard treatment for HER2-overexpressing (HER2-positive) breast cancer, with over $5B in 2010 global sales. Although Tykerb (lapatinib) has carved out a niche in Herceptin experienced patients, it has been unable to dethrone Herceptin (2010 global sales of Tykerb were $350M).

- In the metastatic setting, the biggest challenge to Herceptin’s dominance in the next few years will come from another Roche compound, T-DM1. Results of the head-to-head COMPLETE study may also position Tykerb as a first-line alternative.

- The addition of other targeted therapies to Herceptin (e.g., pertuzumab) may continue to produce impressive results, but the high cost of these regimens is a liability.

- In the adjuvant setting, although Herceptin is firmly entrenched (and may become more so with two-year HERA data expected next year), Tykerb is likely to emerge as a significant threat given its oral bioavailability. Subcutaneous trastuzumab would be an improvement over Herceptin in this regard, but would not be as compelling as an oral alternative.
Executive Summary (2)

- Efforts to refine our understanding of how best to use Herceptin and Tykerb are also underway. These include attempts to develop new biomarkers and predictors of response, as well as assessments of optimal agent sequencing. It is becoming clear that HER2 expression status alone does not adequately predict response to treatment.

- The best means of preventing and treating CNS metastases is unclear, but must be addressed given the high incidence of this complication in advanced HER2-positive disease.

- In breast cancer as with other therapeutic areas, regulatory risk in the U.S. should not be underestimated. The refusal of T-DM1 accelerated approval and the ongoing Avastin controversy are recent examples of regulatory setbacks.
Table of Contents

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Summary</td>
<td>2</td>
</tr>
<tr>
<td>Paradigm Evolution in HER2-Positive Breast Cancer</td>
<td>6</td>
</tr>
<tr>
<td>Future Key Data Presentations</td>
<td>8</td>
</tr>
<tr>
<td>Key 2011 Breast Cancer Meetings</td>
<td>9</td>
</tr>
<tr>
<td>HER2-Positive Breast Cancer Overview</td>
<td>10</td>
</tr>
<tr>
<td>HER2-Positive Breast Cancer Management</td>
<td>14</td>
</tr>
<tr>
<td>Current Market for HER2-Positive Breast Cancer Pharmacotherapeutics</td>
<td>23</td>
</tr>
<tr>
<td>Future Treatments &amp; Emerging Trends</td>
<td>27</td>
</tr>
<tr>
<td>Competitive Landscape: Overview of Key Compounds in Development</td>
<td>30</td>
</tr>
<tr>
<td>Approvability Index of Select Compounds</td>
<td>39</td>
</tr>
<tr>
<td>SWOT Analyses of Key Compounds</td>
<td>44</td>
</tr>
<tr>
<td>Key Clinical Trials</td>
<td>58</td>
</tr>
<tr>
<td>Institutions/Companies with Significant Activity in HER2-Positive Breast Cancer</td>
<td>67</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>71</td>
</tr>
</tbody>
</table>
Methodology

- The goal of this report is to enhance the understanding of the HER2-positive breast cancer market, including emerging pipeline agents and likely clinical developments and trends.
- To achieve this, Adis has assessed the current HER-2 positive breast cancer clinical landscape using the R&D Insight and Clinical Trials Insight databases and other available sources.
- This State of the Art report contains our assessment of unmet needs and likely shifts in treatment paradigms, analysis of approved drugs and key pipeline compounds, an overview of important trials and upcoming data milestones, and a review of HER2-positive breast cancer.
- Detailed clinical profiles of select drugs of interest can be found in the separate Dashboard report. Clinical, regulatory, and other updates will be made to the Dashboard on a monthly basis.
Paradigm Evolution in HER2-Positive Breast Cancer
Possible Treatment Scenarios to 2021

- By 2021, several new HER2-targeted therapies are likely to launch.
- Competition likely to include trastuzumab variants (SC formulation, T-DM1) but also novel agents such as dimerization inhibitors and kinase inhibitors.
- Patient selection and treatment sequencing will be driven by prognostic markers that go beyond HER2 expression status.

**Worst-case scenario**
- Pipeline agents fail to produce strong data and/or hit regulatory roadblocks and clinicians have few options to improve upon current results.

**Best-case scenario**
- Refinements in biomarkers and understanding of resistance permit clinicians to select from a variety of approved HER2-targeted therapies to maximize patient outcomes.
Future Key Data Presentations 2011/2012

- Data presented at key meetings in 2011/2012 will be catalysts for change in treatment:
  - Neoadjuvant
    - CALGB-40601: paclitaxel + Herceptin and/or Tykerb, due Jun 2010 (but still recruiting)
    - ELATE: EC90 followed by paclitaxel + Tykerb or paclitaxel + Herceptin, due Apr 2012
  - Adjuvant
    - HERA 2-year data: Herceptin (1 or 2 years) versus observation, 2012
  - 1st-line metastatic
    - NCT00667251: taxane + Tykerb or Herceptin, due Jul 2011 (but still recruiting)
    - CLEOPATRA: Herceptin + docetaxel ± pertuzumab, due Mar 2012
    - BOLERO-1: Herceptin + paclitaxel ± everolimus, due Oct 2012
  - Herceptin-exposed
    - BOLERO-3: Herceptin + vinorelbine ± everolimus, due Dec 2012
  - Maintenance after completion of neoadjuvant/adjuvant therapy
    - TEACH: Tykerb versus placebo, due Apr 2012
Key 2011 Breast Cancer Meetings

- IMPAKT Breast Cancer Conference, Brussels, May 5-7
- American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, Jun 3-7
- 2011 ASCO Breast Cancer Symposium, San Francisco, Sep 8-10
- European Multidisciplinary Cancer Congress, Stockholm, Sep 23-27
- San Antonio Breast Cancer Symposium (SABCS), San Antonio, Dec 6-10
HER2-Positive Breast Cancer Overview
HER2-Positive Breast Cancer Overview

- Breast cancer is the leading cause of cancer in women worldwide and is one of the most common cancers overall.\(^1\)\(^-\)\(^3\)
  - 5-year survival varies from between 27% and 98% depending upon disease stage at diagnosis.\(^1\)
  - There are a number of risk factors associated with developing breast cancer; the greatest one of which is increasing patient age.
- Diagnosis of breast cancer is based on clinical and radiological examinations.\(^1\)\(^,\)\(^2\)
  - Bimanual palpation of breasts and local regional lymph nodes
  - Bilateral mammography and ultrasound of the breasts
  - Chest X-ray, abdominal ultrasound and bone scintigraphy can also be used to exclude or evaluate the extent of metastatic disease
- Additional histopathological, cytogenetic and genomic tests are employed (on biopsy or surgical specimens) to aid in treatment decisions.\(^4\)\(^,\)\(^5\)
  - Tumor histological grade
  - Tumor pathology
    - TMN staging assesses the extent of nodal involvement and the presence and location of metastatic disease
  - Proliferation marker (Ki67 labeling index) evaluation
  - Hormone receptor (estrogen, progesterone) status
  - HER2 status
  - Gene expression profiling
    - E.g. Oncotype DX, a 21-gene assay, predicts the likelihood of response to chemotherapy and disease recurrence
  - Decision making tools, such as the Nottingham prognostic Index or Adjuvant! Online\(^6\), provide scores to help predict the probabilities of recurrence or death

1. ACS Cancer Statistics 2008;
4. NCCN Breast Cancer Guidelines v2.2011 (www.nccn.com);
5. Aebi et al. Ann Oncol 2010; 21 Suppl. 5: 9-14;
HER2-Positive Breast Cancer Overview (2)

- Approximately 25% of early-stage breast cancers over-express HER2\(^1\)
- HER2 is one in a family of four human epidermal growth factor receptors (also known as ErbB) which promote cell growth
  - It is a receptor tyrosine kinase normally involved in cell growth and differentiation signal transduction pathways
  - Upon ligand binding, ErbB receptors dimerize and HER2 is the preferential dimerization partner of all the other members of the ErbB receptors
- Amplification of (or a mutation in) the HER2 proto-oncogene, located on chromosome 17, can result in elevated expression of the HER2 receptor on the surface of tumor cells
- Amplification of HER2 is a strong prognostic factor for relapse and poor overall survival\(^2,3\)
  - HER2+ tumors tend to grow faster and are generally more likely to recur than HER2- tumors\(^1,2\)
  - HER2 status also strongly predicts response to treatment with anti-HER2-targeted therapies\(^4\)
  - And may be predictive of resistance to alkylator-based chemotherapy, the need for higher dose chemotherapy, benefit from adjuvant anthracyclines and tamoxifen resistance\(^5\)

2. Slamon et al. Science 1987; 235: 177-82;
4. Slamon et al. NEJM 2001; 344: 783-792;
HER2-Positive Breast Cancer Pathology

- Breast cancer tumors are routinely assessed for HER2 status by:
  - Immunohistochemistry (IHC) evaluates expression levels of the HER2 protein
    - Useful as a triage method
    - Expression levels are scored from 0 (no expression) to 3+ (over-expression)
  - Fluorescence or chromogenic in situ hybridization (FISH or CISH) evaluates HER2 gene copy number
    - FISH and CISH are definitive tests and can be used alone or to clarify ambiguous IHC2+ tumors
HER2-Positive Breast Cancer Management
Management of HER2-Positive Breast Cancer

- Management of breast cancer patients involves a multidisciplinary team including a breast surgeon, radiologist, pathologist, medical and radiation oncologists

- Surgery
  - Breast-conserving surgery (wide local excision and radiotherapy)
    - Pathologic assessment of resection margins essential
  - Mastectomy
    - Recommended for larger tumors (>5cm diameter in US or >4cm in Europe) or with positive pathologic margins
    - With or without breast reconstruction
  - Axillary staging
    - Sentinel lymph node biopsy recommended in preference to full nodal clearance
  - Risk-reducing surgery
    - Prophylactic bilateral mastectomy and reconstruction
    - Increasing in popularity amongst younger patients

- Radiation therapy
  - Strongly recommended after breast-conserving surgery
  - Recommended post-mastectomy in patients with:
    - ≥4 positive axillary nodes
    - T3-T4 tumors
    - Additional risk factors (e.g. young age, vessel invasion)

Management of HER2-Positive Breast Cancer (2)

- **Neoadjuvant therapy**\(^1,2\)
  - Recommended for locally advanced breast cancer (stages IIIA-B) and large operable tumors for reducing tumor size prior to breast-conserving surgery
  - Chemotherapy plus Herceptin is recommended in patients with HER2+ disease

- **Adjuvant therapy**\(^1,2\)
  - Adjuvant chemotherapy plus Herceptin is recommended
    - Anthracyclines are especially recommended for patients with HER2+ disease
    - Docetaxel + cyclophosphamide and cyclophosphamide + methotrexate + fluorouracil may also be appropriate

---

Management of HER2-Positive Breast Cancer (3)

- Advanced disease\(^1,^2\)
  - Patients should be treated with Herceptin with or without chemotherapy or endocrine therapy
    - Addition of anti-HER2 therapies (Herceptin or Tykerb) to hormonal treatment is beneficial for patients with HR+ and HER2+ tumors
    - Tykerb + capecitabine has activity in patients progressing while receiving Herceptin
    - Combination of anti-HER2 therapy with other targeted therapies (pan-HER, mTOR etc) may be useful in patients with disease that is resistant or refractory to Herceptin

- Cardiotoxicity
  - HER2-targeted therapies are associated with cardiotoxicity\(^3\)
    - Cardiac function should be routinely monitored in patients before and while receiving HER2-targeted agents\(^1,^2,^4\)
    - Treatment with HER2-targeted therapies should be avoided in patients with low LVEF (<50%-55%) and discontinued in those whose cardiac function deteriorates during therapy\(^1,^2,^4\)

1. NCCN Breast Cancer Guidelines v2.2011 (www.nccn.com);
2. Cardoso et al. Ann Oncol 2010; 21 Suppl. 5: 15-19;
Pharmacotherapy Principles & Guidelines

- Every patient with HER2+ breast cancer should be offered HER2-targeted therapy as soon as possible
  - In Europe, Herceptin is even recommended in patients with small (<1cm), node-negative tumors
    - It can be administered in parallel with a taxane but not concurrently with anthracyclines
    - The adjuvant use of Herceptin with endocrine therapy and without chemotherapy is not recommended
- It is unknown whether switching to Tykerb at first progression would be better than continuing Herceptin with a different chemotherapy regimen
  - Continuing Herceptin after first-disease progression with a different chemotherapy regimen is superior to discontinuation of Herceptin
- Treatment is relatively consistent across physicians and geographies, as indicated by international, national and local guidelines:
  - US: National Comprehensive Cancer Network (NCCN) 2011 guidelines
  - EU: European Society of Medical Oncology (ESMO) 2010 guidelines
    National Institute for Health and Clinical Excellence (NICE, United Kingdom) 2009 guidelines

1. NCCN Breast Cancer Guidelines v2.2011 (www.nccn.com);
2. Cardoso et al. Ann Oncol 2010; 21 Suppl. 5: 15-19;
Drivers of Treatment Selection

NOW
- Tumor staging
- HER2 status as assessed via IHC or FISH
- Cardiac functional status

FUTURE
- Refined HER2 status via more sophisticated assays
- Assessment of other tumor genetic markers, possibly including PTEN, TGF-alpha, MET, Src, IGF-1R
- Cost-effectiveness, especially for combinations of targeted agents
Current Treatment Flow Patterns

- Neoadjuvant therapy: Herceptin + chemotherapy
- Adjuvant therapy: Herceptin + chemotherapy
  - Chemotherapy even administered to patients with HR+ tumors
- First-line metastatic therapy: Herceptin + chemotherapy or endocrine therapy
  - Endocrine therapy given to patients with HR+ disease who did not receive it in the adjuvant setting
  - Tykerb may be given to patients for whom Herceptin is contraindicated (e.g., cardiac problems) or who do not respond to Herceptin
- Second- and subsequent-line metastatic therapy: HER2-targeted agent + chemotherapy
  - Herceptin + other chemotherapies
  - Herceptin + Tykerb
  - Tykerb + capecitabine
## Differences in Treatment Flow Between US and Europe

<table>
<thead>
<tr>
<th>Preferred neoadjuvant regimens</th>
<th>Preferred adjuvant regimens</th>
<th>Preferred first-line metastatic regimens</th>
<th>Upon disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td><strong>Europe</strong></td>
<td><strong>US</strong></td>
<td><strong>Europe</strong></td>
</tr>
<tr>
<td>paclitaxel + Herceptin then CEF + Herceptin</td>
<td>no specific chemotherapy regimens recommended</td>
<td>Eligibility axillary lymph node-positive, HER2+ tumors</td>
<td>Eligibility HER2+ tumors (even node-negative tumors &lt;1cm in diameter)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eligibility axillary lymph node-negative, HER2+ tumors &gt;1 cm</td>
<td>• Herceptin with paclitaxel ± carboplatin, vinorelbine or capecitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC then paclitaxel + Herceptin</td>
<td>• Herceptin + anthracycline (not concurrently)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>docetaxel + carboplatin + Herceptin</td>
<td>• docetaxel + cyclophosphamide and Herceptin (Herceptin can be given in parallel with a taxane)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMF and Herceptin</td>
<td>• CMF and Herceptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>US</strong></td>
<td><strong>Europe</strong></td>
<td><strong>US</strong></td>
<td><strong>Europe</strong></td>
</tr>
<tr>
<td>continue HER2-targeted therapy typically in combination with other chemotherapy</td>
<td>continue Herceptin and switch chemotherapy</td>
<td>Tykerb + capecitabine</td>
<td></td>
</tr>
</tbody>
</table>

Source: NCCN & ESMO Guidelines
Current Unmet Needs

- Optimal treatment management of patients with HER2+ breast cancer that has progressed after Herceptin administered either in the adjuvant or metastatic settings is as yet unclear
  - Primary and acquired Herceptin resistance may become more problematic as Herceptin moves into earlier settings (neoadjuvant/adjuvant)
  - With acquired Herceptin resistance it is currently unknown whether to continue Herceptin (change chemotherapy/add other targeted agents) or whether to switch to a different HER2-targeted agent (e.g. Tykerb)
  - Certain patient subgroups (e.g., p95HER2, loss of PTEN) may benefit from the use of other HER2-targeted therapies

- Patients with cardiac problems
  - Because of known cardiotoxicity, the benefits of administering HER2-targeted therapies must be weighed against the possible risks to the patient
    - Heart function should be evaluated both before and during treatment with HER2-targeted therapies
    - Both Herceptin and Tykerb are only recommended for use in patients with normal LVEF before initiating treatment

- Prevention/treatment of brain metastases
  - HER2+ tumors preferentially metastasize to visceral sites including the brain
  - Relative lack of CNS activity with Herceptin due to inability to cross the blood-brain barrier
  - New HER2-targeted therapies that are able to cross the blood-brain barrier and with activity are needed.
The Current Market for HER2-Positive Breast Cancer Pharmacotherapeutics
Current HER2-Positive Breast Cancer Market

- There are only two approved drugs specifically designed to treat breast cancers that overexpress HER2, Herceptin (trastuzumab) and Tykerb (lapatinib).
- Herceptin, first approved in the U.S. in 1998, remains the gold standard for HER2-positive breast cancer. In 2010, Herceptin sales totaled $5.2B.
- Tykerb, approved by FDA in 2007, has emerged as a viable option for Herceptin-refractory disease. 2010 Tykerb sales totaled $351M.
# Marketed Agents

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>MOA</th>
<th>Approvals by Country</th>
<th>Patent Expiry</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herceptin (trastuzumab)</strong> (Genentech/Roche/Chugai)</td>
<td>HER2 inhibitor</td>
<td>Breast cancer: Argentina, Australia, Brazil, Canada, Israel, Japan, Taiwan mBC: EU, USA Adjuvant therapy: Japan, EU, USA</td>
<td>2019 (US)</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Tykerb (lapatinib)</strong> (GlaxoSmithKline/Nippon Kayaku)</td>
<td>Dual EGFR/HER2 inhibitor</td>
<td>Breast cancer: India, Japan 1st-line mBC: EU, USA 2nd-line mBC: Australia, New Zealand, Switzerland, UK, USA</td>
<td>2020 (US), 2023 (EU)</td>
<td>Oral</td>
</tr>
</tbody>
</table>
## Comparison of Current Marketed Biologic Treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Target(s)</th>
<th>Use</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trastuzumab</strong></td>
<td>HER2</td>
<td>• Neoadjuvant treatment of HER2+ BC (in combination with chemotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Herceptin)</td>
<td></td>
<td>• Adjuvant treatment of early HER2+ BC (in combination with endocrine therapy for pts with HR+ disease or chemotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1st-line HER2+ mBC (in combination with endocrine therapy for pts with HR+ disease or chemotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2nd- and 3rd-line HER2+ mBC</td>
<td>• Gold standard for HER2+ breast cancer</td>
<td>• IV infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Maximum length of administration unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Associated with CHF (especially when administered in combination with anthracyclines)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Resistant/refractory disease (may become more problematic since more women are receiving Herceptin in the neoadjuvant and adjuvant settings)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Relative efficacy to other HER2-targeted therapies unknown</td>
</tr>
<tr>
<td><strong>Lapatinib</strong></td>
<td>EGFR, HER2</td>
<td>• HER2+ mBC (in combination with endocrine therapy for pts with HR+ disease, chemotherapy or Herceptin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tykerb, Tyverb)</td>
<td></td>
<td></td>
<td>• Oral</td>
<td>• True extent of cardiotoxicity unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May be useful in patients with CHF</td>
<td>• Relative efficacy to other HER2-targeted therapies unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May be useful in Herceptin-resistant/refractory disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May be useful for prevention/treatment of brain metastases</td>
<td></td>
</tr>
</tbody>
</table>
Future Treatments & Emerging Trends
Emerging Trends in HER2-Positive Breast Cancer Treatment

- Evolving trends in the management of HER2+ disease include:
  - Replacement of intravenous Herceptin with subcutaneous formulation
  - Increasing use of Tykerb in the neoadjuvant, first-line adjuvant and CNS metastatic settings
  - Introduction of novel HER2-targeted agents in first-line adjuvant and metastatic settings
  - Combination of HER2-targeted agents in first-line adjuvant and metastatic settings
  - Introduction of novel HER2-targeted agents and other targeted agents for the treatment of refractory disease
Ideal HER2-Positive Breast Cancer Drug Profile

- For metastatic disease:
  - Clinically meaningful extension of overall survival (months, not weeks)
  - Relatively well tolerated
  - Benign cardiotoxicity profile
  - Validated biomarker that allows for judicious patient selection

- For early-stage disease (adjuvant therapy):
  - Clinically meaningful prevention of disease recurrence
  - Extremely well tolerated
  - Extremely safe
  - Orally available
Competitive Landscape: Overview of Key Compounds in Development
The HER2+ BC development landscape is highly competitive, with 8 oral compounds and 14 parenteral compounds targeting the HER family of receptors in active clinical development (see following slides).

Agents targeting other signaling pathways with potential relevance in Herceptin resistance are also in development.

The main players include Roche/Genentech/Chugai, Pfizer, GlaxoSmithKline, Array Biopharma, AstraZeneca, Bristol-Myers Squibb, and Merrimack Pharmaceuticals.
### HER-Targeted Agents in Development: Phase III

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Indication</th>
<th>Phase</th>
<th>Route of Administration</th>
<th>Estimated Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Pan-HER” Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neratinib (Pfizer)</td>
<td>Early-stage BC, advanced BC</td>
<td>III</td>
<td>PO</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dual EGFR/HER2 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afatinib (Boehringer Ingelheim)</td>
<td>2nd-line mBC</td>
<td>III</td>
<td>PO</td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HER2 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertuzumab (Genentech/Roche/Chugai)</td>
<td>1st-line HER2+ mBC (in combination with Herceptin and taxane or in combination with trastuzumab-DM1); adjuvant HER2+ BC planned (in combination with trastuzumab and taxane)</td>
<td>III</td>
<td>IV</td>
<td>2012</td>
</tr>
</tbody>
</table>

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.
## HER-Targeted Agents in Development: Phase III (2)

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Indication</th>
<th>Phase</th>
<th>Route of Administration</th>
<th>Estimated Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 Inhibitors (continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab subcutaneous</strong> (Roche/Halozyme)</td>
<td>HER2+ early BC</td>
<td>III</td>
<td>SC</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Trastuzumab emtansine</strong> (Genentech/Roche/ImmuNoGen/Chugai)</td>
<td>1st- and 2nd-line HER2+ mBC</td>
<td>III</td>
<td>IV</td>
<td>2013</td>
</tr>
</tbody>
</table>

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.
**HER-Targeted Agents in Development: Phase II**

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Indication</th>
<th>Phase</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Pan-HER” Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Varlitinib</em> (Array BioPharma)</td>
<td>Advanced BC</td>
<td>II</td>
<td>PO</td>
</tr>
<tr>
<td><em>AZD 8931</em> (AstraZeneca)</td>
<td>1st-line mBC</td>
<td>II</td>
<td>PO</td>
</tr>
<tr>
<td><strong>EGFR Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Erlotinib</em> (OSI/Genentech/Roche/Chugai)</td>
<td>1st- and 2nd-line mBC (various combination therapies), neoadjuvant BC</td>
<td>II</td>
<td>PO</td>
</tr>
<tr>
<td><strong>HER2-Based Immunotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>AE 37</em> (Antigen Express/Generex)</td>
<td>2nd-line adjuvant therapy for lymph node-positive or high-risk lymph node-negative HER2+ BC</td>
<td>II</td>
<td>Parenteral</td>
</tr>
<tr>
<td><em>Anti-CD3-anti-HER2/neu-activated T cells</em>  (TransTarget)</td>
<td>3rd-line mBC</td>
<td>II</td>
<td>IV</td>
</tr>
</tbody>
</table>

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.
## HER-Targeted Agents in Development: Phase II (2)

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Indication</th>
<th>Phase</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-Based Immunotherapy (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HER2 ASCI</strong> (GlaxoSmithKline)</td>
<td>mBC</td>
<td>II</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Breast cancer vaccine HER2/neu</strong> (GlaxoSmithKline)</td>
<td>HER2+ mBC refractory to Herceptin (monotherapy and in combination with Tykerb); HER2+ mBC (in combination with chemotherapy or maintenance Herceptin)</td>
<td>II*</td>
<td>IM</td>
</tr>
</tbody>
</table>

| Multi-kinase inhibitors                        |                                                                             |       |                         |
| **BMS 690514** (Bristol Myers-Squibb)          | 1st-line mBC                                                               | II    | PO                      |
| **Vandetanib** (AstraZeneca)                    | 2nd-line mBC                                                               | II    | PO                      |

*Current status unclear

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.

---

**USER NOTE:** Click on hyperlink to see RDI drug profile
### HER-Targeted Agents in Development: Phase I/II

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Indication</th>
<th>Phase</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-Based Immunotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NeuVax (RXi)</td>
<td>HER2+ BC at risk of recurrence</td>
<td>I/II</td>
<td>Intradermal</td>
</tr>
<tr>
<td><strong>PX 1032</strong> (Bavarian Nordic)</td>
<td>2nd- or 3rd-line HER2+ mBC (± Herceptin), HER2+ mBC (in combination with chemotherapy and/or Herceptin)</td>
<td>I/II</td>
<td>SC</td>
</tr>
<tr>
<td><strong>HER3 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM 111 (Merrimack)</td>
<td>HER2+ refractory mBC (monotherapy and in combination with Herceptin)</td>
<td>I/II</td>
<td>IV</td>
</tr>
</tbody>
</table>

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.
### HER-TARGETED AGENTS IN DEVELOPMENT: PHASE I

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Indication</th>
<th>Phase</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-HER Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AC 480</strong></td>
<td>HER2+ solid tumors (monotherapy and in combination with taxane)</td>
<td>I</td>
<td>IV</td>
</tr>
<tr>
<td>(Ambit/Bristol Myers-Squibb)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual EGFR/HER2 Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CUDC 101</strong></td>
<td>Advanced solid tumors</td>
<td>I</td>
<td>IV</td>
</tr>
<tr>
<td>(Curis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARRY 380</strong></td>
<td>HER2-positive solid tumors</td>
<td>I</td>
<td>PO</td>
</tr>
<tr>
<td>(Array BioPharma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MGAH 22</strong></td>
<td>Treatment-refractory HER2+ BC</td>
<td>I</td>
<td>IV</td>
</tr>
<tr>
<td>MacroGenics/Raven</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-Based Immunotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lapuleucel-T</strong></td>
<td>HER2+ mBC</td>
<td>I</td>
<td>IV</td>
</tr>
<tr>
<td>(Dendreon)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.
### HER-Targeted Agents in Development: Preclinical

<table>
<thead>
<tr>
<th>Compound, Developer(s)</th>
<th>Phase</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DXL 702</strong> (InNexus)</td>
<td>Preclin</td>
<td>Parenteral</td>
</tr>
<tr>
<td>HER2-Based Immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VM 206</strong> (ViroMed/RecipharmCobra Biologics)</td>
<td>Preclin</td>
<td>Parenteral</td>
</tr>
<tr>
<td><strong>ADXS 31164</strong> (Advaxis)</td>
<td>Preclin</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HER2 Z00342</strong> (Affibody)</td>
<td>Preclin</td>
<td>Parenteral</td>
</tr>
<tr>
<td><strong>GlyB4</strong> (GlyTag)</td>
<td>Preclin</td>
<td>Injection</td>
</tr>
</tbody>
</table>

Note: Only includes compounds in active development in HER2-positive or HER2-unspecified patient populations.
Approvability Index of Select Compounds
### IAI Overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Indication</th>
<th>Phase of Development</th>
<th>IAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>lapatinib (Tykerb)</td>
<td>GlaxoSmithKline</td>
<td>Metastatic HER2+ breast cancer frontline therapy</td>
<td>III</td>
<td>67% (C)</td>
</tr>
<tr>
<td>lapatinib (Tykerb)</td>
<td>GlaxoSmithKline</td>
<td>HER2+ breast cancer adjuvant therapy</td>
<td>III</td>
<td>72% (B)</td>
</tr>
<tr>
<td>everolimus (Afinitor)</td>
<td>Novartis</td>
<td>Metastatic breast cancer</td>
<td>III</td>
<td>68% (C)</td>
</tr>
<tr>
<td>neratinib</td>
<td>Wyeth (Pfizer)</td>
<td>Relapsed/refractory HER2+ metastatic breast cancer</td>
<td>III</td>
<td>55% (D)</td>
</tr>
</tbody>
</table>
## IAI Overview (II)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase III Trials for IAI Analysis</th>
<th>Strengths To Date</th>
<th>Weaknesses To Date</th>
<th>IAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>lapatinib (Tykerb)</td>
<td>COMPLETE</td>
<td>• Active control in phase III&lt;br&gt;• Phase III partially enrolled</td>
<td>• No visibility on phase III dose&lt;br&gt;• Open-label phase III design</td>
<td>67% (C)</td>
</tr>
<tr>
<td>frontline</td>
<td></td>
<td></td>
<td></td>
<td>-----------</td>
</tr>
<tr>
<td>lapatinib (Tykerb)</td>
<td>TEACH ALTTO</td>
<td>• Approved for treatment of metastatic breast cancer&lt;br&gt;• Phase III fully enrolled</td>
<td>• Diarrhea/discontinuation rate in other monotherapy studies</td>
<td>72% (B)</td>
</tr>
<tr>
<td>adjuvant</td>
<td></td>
<td></td>
<td></td>
<td>-----------</td>
</tr>
<tr>
<td>everolimus (Afinitor)</td>
<td>BOLERO-1 BOLERO-2 BOLERO-3</td>
<td>• Approved for treatment of renal cell carcinoma &amp; pancreatic neuroendocrine tumors&lt;br&gt;• One of three phase III trials fully enrolled</td>
<td>• Toxicity/discontinuation rate</td>
<td>68% (C)</td>
</tr>
<tr>
<td>neratinib</td>
<td>ExteNET NEfERT/T</td>
<td>• Phase II PFS data</td>
<td>• Toxicity/discontinuation rate</td>
<td>55% (D)</td>
</tr>
</tbody>
</table>

IAI: Intensive Anti-Impression
### IAI Overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Milestone</th>
<th>Expected Timing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>lapatinib (Tykerb) frontline</td>
<td>COMPLETE data</td>
<td>Jul 2011</td>
</tr>
<tr>
<td>lapatinib (Tykerb) adjuvant</td>
<td>TEACH data</td>
<td>Apr 2012</td>
</tr>
<tr>
<td>everolimus (Afinitor)</td>
<td>BOLERO-1 data</td>
<td>Oct 2012</td>
</tr>
<tr>
<td>everolimus (Afinitor)</td>
<td>BOLERO-3 data</td>
<td>Dec 2012</td>
</tr>
<tr>
<td>everolimus (Afinitor)</td>
<td>BOLERO-2 data</td>
<td>Dec 2013</td>
</tr>
<tr>
<td>neratinib</td>
<td>NEfERT/T data</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>neratinib</td>
<td>ExteNET data</td>
<td>Sept 2016</td>
</tr>
<tr>
<td>lapatinib (Tykerb) adjuvant</td>
<td>ALTTO data</td>
<td>Apr 2018</td>
</tr>
</tbody>
</table>

*Projected data for final data collection
Source: CT.gov
Approvability Index

- The Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development.

- Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with "A" indicating significantly above average/likely to progress, "C" indicating average, and "F" indicating significantly below average/unlikely to progress.
Strengths, Weaknesses, Opportunities, & Threats (SWOT) Analyses of Select Compounds
# Herceptin SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
</table>
| - Entrenched HER2-positive market leader with demonstrated benefit in frontline metastatic and adjuvant settings | - High rates of intrinsic resistance and limited response duration  
  - Need for injection may not appeal to patients seeking adjuvant therapy  
  - Likely pleomorphic mechanism of action still incompletely understood (HER2 has no known ligand) |

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Development of enhanced biomarkers could lead to improved patient selection</td>
<td>- Concerns about cardiotoxicity, especially in adjuvant setting, could limit use</td>
</tr>
</tbody>
</table>
Trastuzumab SC SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on validated trastuzumab biology</td>
<td>Hyaluronidase technology applied to subcutaneous delivery of an antibody has yet to be fully evaluated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>This more convenient formulation may increase patient acceptance in the adjuvant setting.</td>
<td>Oral adjuvant therapies could be seen as even more patient friendly.</td>
</tr>
</tbody>
</table>
### T-DM1 SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Based on validated trastuzumab biology</td>
<td>- Most advanced data to date in refractory breast cancer stems from single-arm phase II study</td>
</tr>
<tr>
<td>- Has produced positive PFS results compared to Herceptin/docetaxel in head-to-head phase II first-line metastatic study</td>
<td>- Development of antibody-drug conjugates has been slow with many false starts related to linker technology, toxicity, and other issues.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Could overcome trastuzumab resistance</td>
<td>- Should FDA require an overall survival benefit for approval this might be a high bar</td>
</tr>
<tr>
<td></td>
<td>- Others agents, such as kinase inhibitors, in development for trastuzumab refractory breast cancer may be seen as less risky or safer</td>
</tr>
</tbody>
</table>
# Pertuzumab SWOT Analysis

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Weaknesses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Phase II studies indicate activity in breast cancer, including increase in pCR rate when added to Herceptin/docetaxel in neoadjuvant setting</td>
<td>- High cost of pertuzumab/trastuzumab combination regimens may become an issue</td>
</tr>
<tr>
<td>- Development for lung cancer suspended (reasons are unclear but activity in NSCLC might have been expected given role of EGFR)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Opportunities</strong></th>
<th><strong>Threats</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dimerization inhibition may prove to be an alternative or complementary to anti-HER2 antibody therapy</td>
<td></td>
</tr>
<tr>
<td>- Strategy may be applicable to multiple tumor types, not just breast cancer</td>
<td>- Full implications of dimerization inhibition are incompletely understood</td>
</tr>
</tbody>
</table>
## Tykerb SWOT Analysis

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Weaknesses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Marketed drug with demonstrated benefit in frontline and refractory metastatic settings</td>
<td>- Rash and other adversities could limit appeal as an adjuvant therapy</td>
</tr>
<tr>
<td>- May be superior to trastuzumab when CNS metastases are present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Opportunities</strong></th>
<th><strong>Threats</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ongoing adjuvant trials with this oral agent could expand indication and clinical use</td>
<td>- Other kinase inhibitors targeting HER2 family members in addition to EGFR and HER2 are in development</td>
</tr>
</tbody>
</table>
# MM-111 SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strong preclinical evidence of activity in relevant model systems</td>
<td>• Bispecific antibody technology is novel and clinically unproven</td>
</tr>
<tr>
<td></td>
<td>• Still relatively early in clinical development</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May help to overcome resistance to EGFR and HER2 targeted drugs</td>
<td>• Agents targeting ErbB3 without anti-HER2 functionality may be easier to study and develop</td>
</tr>
<tr>
<td>• Companion diagnostic, if successfully validated, could enhance clinical development and patient selection</td>
<td></td>
</tr>
</tbody>
</table>

---

**Adis**
## MM-121 SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strong preclinical evidence of activity in relevant model systems</td>
<td>• Still relatively early in clinical development</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May help to overcome resistance to EGFR and HER2 targeted drugs</td>
<td>• Efficacy and safety of targeting ErbB3 has yet to be established</td>
</tr>
<tr>
<td>• May work in both HER2-positive as well as HER2-negative settings</td>
<td></td>
</tr>
<tr>
<td>• Companion diagnostic, if successfully validated, could enhance clinical development and patient selection</td>
<td></td>
</tr>
</tbody>
</table>
**AC480 SWOT Analysis**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HER2 inhibition and EGFR/HER2 inhibition are validated strategies in breast cancer</td>
<td>- Anti-EGFR associated rash may limit patient acceptance as adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>- Still relatively early in clinical development</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>- May help to overcome resistance to HER2 directed therapies</td>
<td>- Inhibition of multiple kinases could increase toxicity</td>
</tr>
<tr>
<td>- Pan-HER2 receptor kinase inhibition may lead to enhanced therapeutic activity</td>
<td></td>
</tr>
<tr>
<td>- Oral formulation would be ideal for adjuvant therapy</td>
<td></td>
</tr>
</tbody>
</table>
Neratinib SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HER2 and EGFR/HER2 kinase inhibition are validated strategies in breast cancer</td>
<td>- Anti-EGFR associated rash may limit patient acceptance as adjuvant therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Irreversible inhibition may lead to optimal target suppression</td>
<td>- Inhibition of multiple kinases could increase toxicity</td>
</tr>
<tr>
<td>- May help to overcome resistance to HER2 directed therapies</td>
<td></td>
</tr>
<tr>
<td>- Inhibition of multiple HER family kinases may lead to enhanced therapeutic activity</td>
<td></td>
</tr>
<tr>
<td>- Oral formulation would be ideal for adjuvant therapy</td>
<td></td>
</tr>
</tbody>
</table>
AZD 8931 SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• EGFR kinase and dual EGFR/HER2 kinase inhibitors are FDA approved for the treatment of cancer (erlotinib, lapatinib)</td>
<td>• Still relatively early in clinical development</td>
</tr>
<tr>
<td>• ErbB3 inhibition has yet to be fully validated</td>
<td>• ErbB3 inhibition has yet to be fully validated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May be able to overcome resistance to both trastuzumab and lapatinib</td>
<td>• Targeting multiple kinases could increase toxicity</td>
</tr>
<tr>
<td>• Could play a role in management of both HER2-positive and -negative disease</td>
<td></td>
</tr>
</tbody>
</table>
## Eribulin SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Has demonstrated survival advantage in heavily pretreated patients</td>
<td>- Rationale for activity in HER2-positive disease is unclear</td>
</tr>
<tr>
<td>- FDA approved drug</td>
<td>- Neuropathy and other toxicities could limit appeal as adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td>- Some ongoing phase II studies are small and/or uncontrolled</td>
</tr>
<tr>
<td>Opportunities</td>
<td>Threats</td>
</tr>
<tr>
<td>- Could move into earlier lines of therapy if ongoing studies are successful.</td>
<td>- Long-term goal is to eliminate traditional cytotoxics from most treatment regimens</td>
</tr>
</tbody>
</table>
### Everolimus SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Evidence of activity in breast cancer seen in early stage trials</td>
<td>- Precise means by which mTOR inhibition adversely affects cancer biology is unclear</td>
</tr>
<tr>
<td>- FDA approved for renal cell carcinoma and pancreatic neuroendocrine tumors</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>- May help to overcome resistance to HER2 directed therapies</td>
<td>- Other agents aiming to overcome anti-HER2 therapy are also in development</td>
</tr>
</tbody>
</table>
BEZ235 SWOT Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evidence of antitumor activity in phase I studies</td>
<td>• Still relatively early in clinical development</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple kinase targets could enhance activity</td>
<td>• Multiple kinase targets could lead to additional toxicity</td>
</tr>
<tr>
<td>• Could play a role in management of both HER2-positive and -negative disease</td>
<td></td>
</tr>
</tbody>
</table>
Key Clinical Trials
Completed Head-to-Head Trials

- Truly informed differentiation between HER2-targeted agents requires large head-to-head studies.
- Little such data exists today, but as the HER2 pipeline matures additional trials will be conducted. Some are already underway (e.g., COMPLETE) and a few earlier stage trials have begun to generate data. These include:
  - **TDM4450g** (randomized phase II; first-line HER2+ mBC)
    - T-DM1 monotherapy produced statistically significantly longer PFS than Herceptin/docetaxel.
  - **NEOSPHERE** (randomized phase II; neoadjuvant HER2+ BC)
    - Adding pertuzumab to Herceptin/docetaxel increased the rate of tumor disappearance prior to surgery (pCR) from 29% to 46%.
Ongoing/Planned Head-to-Head Trials: Neoadjuvant Setting

- **NCT00770809**: CALGB-40601: phase III trial of paclitaxel combined with Herceptin, Tykerb, or both.  
  - **Study start**: December 2008  
  - **Recruiting**: n=400  
  - **Estimated primary completion date**: June 2010

- **NCT01205217**: ELATE: phase II trial of Tykerb + epirubicin + cyclophosphamide (EC90) followed by paclitaxel + Tykerb compared with EC90 followed by paclitaxel + Herceptin.  
  - **Study start**: November 2010  
  - **Not yet recruiting**: n=164  
  - **Estimated primary completion date**: April 2012

- **NCT00545688**: NEOSPHERE: phase II study evaluating pertuzumab and Herceptin-based neoadjuvant regimens.  
  - **Study start**: June 2006  
  - **Active, no longer recruiting**: n=416  
  - **Estimated primary completion date**: January 2015

- **NCT00486668**: NSABP-B41: phase III trial investigating Herceptin + Tykerb versus Herceptin and Tykerb alone, administered with weekly paclitaxel following doxorubicin + cyclophosphamide.  
  - **Study start**: July 2007  
  - **Recruiting**: n=522  
  - **Estimated primary completion date**: July 2015
Ongoing/Planned Head-to-Head Trials: Neoadjuvant Setting (2)

**NCT00553358**
Neo ALTTO: phase III trial investigating Tykerb, Herceptin and their combination plus paclitaxel.

- **Study start:** December 2007
- **Status:** Active, no longer recruiting
- **n:** 455
- **Estimated primary completion date:** September 2020

**NCT01104571**
EPHOS-B: phase III trial investigating surgery alone versus neoadjuvant Herceptin + surgery + adjuvant therapy versus neoadjuvant Tykerb + surgery + adjuvant therapy.

- **Study start:** April 2010
- **Status:** Recruiting
- **n:** 250
- **Estimated primary completion date:** November 2021
Ongoing/Planned Head-to-Head Trials: First-line Adjuvant Setting

**NCT00950300**  
BO22227: comparison of subcutaneous with intravenous formulations of Herceptin.  
*Study start: October 2009*  
*active, no longer recruiting*  
n=552  
*Estimated primary completion date: August 2014*

**NCT00490139**  
ALTTO: phase III study of Tykerb, Herceptin, their sequence and their combination.  
*Study start: May 2007*  
*Recruiting*  
n=8400  
*Estimated primary completion date: October 2018*
**Ongoing/Planned Head-to-Head Trials: First-line Metastatic Setting**

- **NCT00667251**
  - Study start: February 2008
  - Recruiting
  - n=536
  - Estimated primary completion date: July 2011

- **NCT00679341**
  - Study start: July 2008
  - Active, no longer recruiting
  - n=120
  - Estimated primary completion date: February 2012

- **NCT00567190**
  - Study start: February 2008
  - Active, no longer recruiting
  - n=808
  - Estimated primary completion date: March 2012

- **NCT00876395**
  - Study start: September 2009
  - Recruiting
  - n=717
  - Estimated primary completion date: October 2012
Ongoing/Planned Head-to-Head Trials: First-line Metastatic Setting (2)

**NCT00915018**
NEFERTT: phase III study of neratinib + paclitaxel compared with Herceptin + paclitaxel.

**Study start: August 2009**
- Recruiting
- n=1200

**Estimated completion date: October 2013**

**NCT00272987**
Phase III trial comparing paclitaxel + Herceptin + Tykerb versus paclitaxel + Herceptin.

**Study start: January 2006**
- Recruiting
- n=720

**Estimated completion date: September 2014**

**NCT01120184**
MARIANNE: phase III trial evaluating trastuzumab emtansine ± pertuzumab versus Herceptin + docetaxel and paclitaxel.

**Study start: July 2010**
- Recruiting
- n=1092

**Estimated completion date: July 2017**
Ongoing/Planned Head-to-Head Trials: Herceptin-exposed disease

NCT01007942
BOLERO-3: phase III trial of everolimus + Herceptin + vinorelbine versus Herceptin + vinorelbine.

Study start: October 2009
Recruiting
n=572
Estimated primary completion date: December 2012

NCT00829166
EMILIA: phase III trial comparing trastuzumab eptansine with capecitabine + Tykerb.

Study start: March 2009
Recruiting
n=980
Estimated primary completion date: August 2013

NCT01026142
PHEREXA: phase II study of Herceptin and capecitabine with or without pertuzumab.

Study start: January 2010
Recruiting
n=450
Estimated primary completion date: July 2015

NCT01160211
A phase III trial of Tykerb + Herceptin + an AI versus Herceptin + an AI versus Tykerb + an AI.

Study start: May 2011
Not yet recruiting
n=525
Estimated primary completion date: December 2017
Ongoing/Planned Head-to-Head Trials: Maintenance therapy

**Early-stage breast cancer**

- **NCT00374322**
  - TEACH: phase III trial of Tykerb versus placebo.
  - Study start: August 2006
  - Estimated primary completion date: April 2012
  - Active, no longer recruiting
  - n=3000

- **NCT00878709**
  - Phase III trial of neratinib versus placebo administered after adjuvant treatment with Herceptin.
  - Study start: July 2009
  - Recruiting
  - n=3850
  - Estimated primary completion date: September 2016

**Metastatic breast cancer**

- **NCT00968968**
  - A phase III trial of Tykerb + Herceptin versus Herceptin alone as continued HER2 suppression therapy after completion of 1st- or 2nd-line Herceptin + chemotherapy.
  - Study start: January 2010
  - Recruiting
  - n=276
  - Estimated primary completion date: August 2014
Institutions or Companies with Significant Activity in HER2-Positive Breast Cancer
### Current Activities of Key Companies/Institutions

<table>
<thead>
<tr>
<th>Company</th>
<th># Agent(s)</th>
<th>MOA (# agents)</th>
<th>Company Role</th>
<th>Agent (Development Stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advaxis</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Licensee</td>
<td>ADXS 31142 (PC)</td>
</tr>
<tr>
<td>Affibody</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>HER2 ZO0342 (PC)</td>
</tr>
<tr>
<td>Affimed</td>
<td>1</td>
<td>EGFR inhibitor</td>
<td>Owner</td>
<td>AFM 21 (PC)</td>
</tr>
<tr>
<td>Ambit Biosciences Corporation</td>
<td>1</td>
<td>pan-HER inhibitor</td>
<td>Licensee</td>
<td>AC 480 (I)</td>
</tr>
<tr>
<td>Antigen Express</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>AE 37 (II)</td>
</tr>
<tr>
<td>Apthera</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Licensee</td>
<td>Cancer vaccine E75 (I/II)</td>
</tr>
<tr>
<td>Array BioPharma</td>
<td>2</td>
<td>pan-HER inhibitor</td>
<td>Owner</td>
<td>Varlitinib (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>ARRY 38 (I)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>2</td>
<td>EGFR inhibitor</td>
<td>Owner</td>
<td>AZD 8931 (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VEGFR/EGFR antagonist</td>
<td>Owner</td>
<td>Vandetanib (II)</td>
</tr>
<tr>
<td>Bavarian Nordic</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>PX 1032 (I/II)</td>
</tr>
<tr>
<td>BN ImmunoTherapeutics</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Licensee</td>
<td>PX 1032 (I/II)</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>1</td>
<td>Dual EGFR/HER2 inhibitor</td>
<td>Owner</td>
<td>Afatinib (III)</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>2</td>
<td>pan-HER inhibitor</td>
<td>Owner</td>
<td>AC 480 (I)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pan-HER/VEGFR inhibitor</td>
<td>Owner</td>
<td>BMS 690514 (II)</td>
</tr>
<tr>
<td>Company</td>
<td># Agent(s)</td>
<td>MOA (# agents)*</td>
<td>Company Role</td>
<td>Agent (Development Stage)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>----------------------------------</td>
<td>--------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Chugai Pharmaceutical</td>
<td>4</td>
<td>EGFR inhibitor</td>
<td>Licensee</td>
<td>Erlotinib (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 inhibitors</td>
<td>Licensee</td>
<td>Trastuzumab (M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Licensee</td>
<td>Trastuzumab emtansine (III)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Licensee</td>
<td>Pertuzumab (III)</td>
</tr>
<tr>
<td>Curis</td>
<td>1</td>
<td>Dual EGFR/HER2 inhibitor</td>
<td>Owner</td>
<td>CUDC 101 (I)</td>
</tr>
<tr>
<td>Dendreon Corporation</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>Lapuleucel-T (I)</td>
</tr>
<tr>
<td>Genentech</td>
<td>4</td>
<td>HER2 inhibitors</td>
<td>Owner</td>
<td>Trastuzumab (M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Owner</td>
<td>Trastuzumab emtansine (III)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Owner</td>
<td>Pertuzumab (III)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGFR inhibitor</td>
<td>Licensee</td>
<td>Erlotinib (II)</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>3</td>
<td>Dual EGFR/HER2 inhibitor</td>
<td>Owner</td>
<td>Lapatinib (M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>HER2-antigen-specific cancer immunotherapeutic (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Owner</td>
<td>Breast cancer vaccine HER2/neu (II)</td>
</tr>
<tr>
<td>GlyTag LCC</td>
<td>1</td>
<td>ErbB4 inhibitor</td>
<td>Owner</td>
<td>GlyB4 (PC)</td>
</tr>
<tr>
<td>InNexus Biotechnology</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>DXL 702 (PC)</td>
</tr>
<tr>
<td>MacroGenics</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>MGAH 22 (I)</td>
</tr>
</tbody>
</table>
## Current Activities of Key Companies/Institutions (3)

<table>
<thead>
<tr>
<th>Company</th>
<th># Agent(s)</th>
<th>MOA (# agents)</th>
<th>Company Role</th>
<th>Agent (Development Stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merrimack Pharmaceuticals</td>
<td>2</td>
<td>HER3 inhibitors</td>
<td>Owner</td>
<td>MM 111 (I/II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Owner</td>
<td>MM 121 (II*)</td>
</tr>
<tr>
<td>OSI Pharmaceuticals</td>
<td>1</td>
<td>EGFR inhibitor</td>
<td>Owner</td>
<td>Erlotinib (II)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>1</td>
<td>pan-HER inhibitor</td>
<td>Owner</td>
<td>Neratinib (III)</td>
</tr>
<tr>
<td>Roche</td>
<td>5</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>Trastuzumab SC (III)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGFR inhibitor</td>
<td>Licensee</td>
<td>Erlotinib (II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER 2 inhibitor</td>
<td>Licensee</td>
<td>Trastuzumab (M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Licensee</td>
<td>Trastuzumab emtansine (III)</td>
</tr>
<tr>
<td>TransTarget</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>Anti-CD3 anti-HER2/neu activated T cells (II)</td>
</tr>
<tr>
<td>ViroMed Co Ltd</td>
<td>1</td>
<td>HER2 inhibitor</td>
<td>Owner</td>
<td>VM 206 (PC)</td>
</tr>
</tbody>
</table>

* Specifically targeting HER2-negative BC*
## Abbreviations

- **AC**, Doxorubicin + cyclophosphamide
- **AE(s)**, Adverse event(s)
- **AI**, Aromatase inhibitor
- **BC**, Breast cancer
- **CBR**, Clinical benefit rate
- **CEF**, Cyclophosphamide + epirubicin + fluorouracil
- **CHF**, Congestive heart failure
- **CI**, Confidence intervals
- **CISH**, Chromogenic in situ hybridization
- **CMF**, Cyclophosphamide + methotrexate + fluorouracil
- **CNS**, Central nervous system
- **CR**, Complete response
- **EGFR**, Epidermal growth factor receptor (also known as erbB1 and HER1)
- **ER**, Estrogen receptor
- **erbB3**, Human epidermal growth factor receptor 3 (also known as HER3)
- **ErbB4**, Human epidermal growth factor receptor 4 (also known as HER4)
- **FEC**, Fluorouracil, epirubicin and cyclophosphamide
- **FISH**, Fluorescence in situ hybridization
- **GI**, Gastrointestinal
- **HB-EGF**, Heparin-binding EGF-like growth factor
- **HER2**, Human epidermal growth factor receptor 2
- **HER2+, HER2-positive**
- **HER2-, HER2-negative**
- **HDLs**, HER dimerization inhibitors
- **HR**, Hazard ratio
- **HR+, Hormone receptor-positive**
- **IHC**, Immunohistochemistry
- **ITT**, Intent to treat
- **IV**, Intravenous
- **LVEF**, Left ventricular ejection fraction
- **LVSD**, Left ventricular systolic dysfunction
- **M**, Marketed
- **mBC**, Metastatic breast cancer
- **mTOR**, Mammalian target of rapamycin
- **NA**, Not applicable
- **NCCTG**, North Central Cancer Treatment Group
- **NSABP**, National Surgical Adjuvant Breast and Bowel Project
- **NSCLC**, Non-small cell lung cancer
- **ORR**, Objective response rate
- **OS**, Overall survival
- **PC**, Preclinical
- **pCR**, Complete pathologic response
- **PD**, Progressive disease
- **PFS**, Progression-free survival
- **PgR**, Progesterone receptor
- **PO**, Oral
- **PR**, Partial response
- **Preclin**, Preclinical
- **SAE(s)**, Serious adverse event(s)
- **SC**, Subcutaneous
- **SD**, Stable disease
- **TGF**, Transforming growth factor
- **TTF**, Time to treatment failure
- **TTP**, Time to progression
- **VEGFR**, Vascular endothelial growth factor receptor