New Evidence reports on presentations given at ASCO 2012

New Targeted Agents Demonstrate Greater Efficacy and Tolerability in the Treatment of HER2-positive Breast Cancer
Presentations at ASCO 2012 — Breast Cancer

- Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) vs. capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane (Blackwell KL, et al. ASCO Annual Meeting Abstracts 2012;30:LBA1)

- Cardiac tolerability of pertuzumab compared with placebo when combined with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study (Ewer M, et al. ASCO Annual Meeting Abstracts 2012;30:533^)


^ = Denotes abstracts that were granted an exception in accordance with ASCO’s Conflict of Interest Policy.
An open-label, randomized, phase III trial comparing taxane-based chemotherapy with lapatinib or trastuzumab as a first-line therapy for women with HER2-positive metastatic breast cancer (Gelmon KA, et al. ASCO Annual Meeting Abstracts 2012;30:LBA671)


Cardiac safety in a phase II study of trastuzumab emtansine (T-DM1) following anthracycline-based chemotherapy as adjuvant or neoadjuvant therapy for early-stage HER2-positive breast cancer (Dang CT, et al. ASCO Annual Meeting Abstracts 2012;30:532)
Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane

Clinical efficacy and safety of the HER2-directed treatments for MBC — T-DM1 and lapatinib in combination with capecitabine — have been well studied.

Capecitabine plus lapatinib is the only currently approved combination therapy for trastuzumab-refractory HER2-positive MBC.

EMILIA was designed to compare the safety and efficacy of T-DM1 vs. capecitabine plus lapatinib to determine the viability of T-DM1 as an alternative therapy for patients with trastuzumab-refractory HER2-positive MBC.

Results build on findings from two phase II trials in which T-DM1 was well-tolerated and effective in patients with MBC who had received prior HER2-directed treatments and chemotherapies.
Study design

- Patients (n = 980) with confirmed first-, second-, or third-line HER2-positive LABC or MBC randomized and treated with one of the following until disease progression or unmanageable toxicity:
  - T-DM1 (n = 490) 3.6 mg/kg iv q3w;
  - Capecitabine plus lapatinib (n = 488):
    - Capecitabine 1,000 mg/m² orally twice a day, on days 1–14 q3w;
    - Lapatinib 1,250 mg orally each day.

HER2 = human epidermal growth factor receptor 2; iv = intravenous; LABC = locally advance breast cancer; MBC = metastatic breast cancer; q3w = once every three weeks; T-DM1 = trastuzumab emtansine

**Study design (cont’d)**

HER2+ (central)  
LABC or MBC  
(n = 980)  
Prior taxane and trastuzumab  
Progression on metastatic tx or within 6 months of adjuvant tx

1:1

T-DM1  
3.6 mg/kg iv q3w

Capecitabine  
1,000 mg/m² orally bid, days 1–14 q3w  
+  
Lapatinib  
1,250 mg/day orally qd

PD

PD

*bid = twice a day; HER2+ = human epidermal growth factor receptor 2-positive; iv = intravenously; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; PD = progressive disease; q3w = dosage given every 3 weeks; qd = every day; T-DM1 = trastuzumab emtansine; tx = treatment*

Study design: endpoints

- Primary endpoints:
  - PFS assessed by IRC;
  - OS;
  - Safety.

- Secondary endpoints:
  - PFS assessed by the investigator;
  - ORR;
  - DOR;
  - Patient-reported outcome of time to symptom progression.

DOR = duration of response; IRC = independent review committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival

Key findings: progression-free survival

- At a median follow-up of 12.4 months for capecitabine plus lapatinib and 12.9 months for T-DM1, T-DM1 significantly extended the duration of PFS, (assessed by IRC) compared with capecitabine plus lapatinib:
  - 9.6 vs. 6.4 months, HR = 0.650; 95% CI: 0.55–0.77; \( p < 0.0001 \).

- PFS results assessed by the investigator consistent with IRC assessment:
  - HR = 0.658; 95% CI: 0.56–0.77; \( p < 0.0001 \).

- Subgroup analyses of PFS by baseline characteristics revealed T-DM1 better than capecitabine plus lapatinib in every category, except for those \( \geq 65 \) years:
  - HR = 1.06; 95% CI: 0.68–1.66.
Key findings: progression-free survival by independent and investigator review

Key findings: overall response rate and duration of response

- ORR significantly higher in the T-DM1 group compared with the capecitabine plus lapatinib group:
  • 43.6% vs. 30.8%, 95% CI: 6.0–19.4%; \( p = 0.0002 \).

- DOR longer in the T-DM1 group compared with capecitabine plus lapatinib group:
  • 12.6 months (95% CI: 8.4–20.8) vs. 6.5 months (95% CI: 5.5–7.2).

CI = confidence interval; DOR = duration of response; ORR = overall response rate; T-DM1 = trastuzumab emtansine
Key findings: objective response rate and duration of response

Key findings: overall survival

- OS results not yet mature, however:
  - Interim analysis showed a trend favouring T-DM1 (median OS n.y.r.) vs. 23.3 months for capecitabine plus lapatinib:
    - HR = 0.621, 95% CI: 0.48–0.81; p = 0.0005.
  - At one- and two-year follow-ups, OS trends favoured T-DM1:
    - One-year follow-up: 84.7% vs. 77.0%;
    - Two-year follow-up: 65.4% vs. 47.5%.
  - Efficacy stopping boundary had not yet been reached:
    - HR = 0.617 or p = 0.0003.


CI = confidence interval; HR = hazard ratio; n.y.r = not yet reached; OS = overall survival; T-DM1 = trastuzumab emtansine
Key findings: overall survival — interim analysis

```
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (months)</th>
<th>No. events</th>
</tr>
</thead>
<tbody>
<tr>
<td>X + L</td>
<td>23.3</td>
<td>129</td>
</tr>
<tr>
<td>T-DM1</td>
<td>NR</td>
<td>94</td>
</tr>
</tbody>
</table>
```

Stratified HR = 0.621 (95% CI: 0.48–0.81); p = 0.0005

Efficacy stopping boundary: p = 0.0003 or HR = 0.617

*CI = confidence interval; HR = hazard ratio; No. = number; NR = not reached; T-DM1 = trastuzumab emtansine; X + L = capecitabine and lapatinib*
Key findings: safety

- Grade ≥3 AEs (57.0% vs. 40.8%) and AEs leading to treatment discontinuation (10.7% vs. 5.9%) were higher in the capecitabine plus lapatinib group.

- Percentage of grade ≥3 non-hematologic AEs of nearly every kind higher in the capecitabine plus lapatinib group.
  - AST and ALT higher in the T-DM1 group.

- Occurrence of grade ≥3 neutropenia and febrile neutropenia higher in the capecitabine plus lapatinib group.
  - Grade ≥3 anemia and thrombocytopenia higher in the T-DM1 group.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T-DM1 = trastuzumab emtansine
Key findings: non-hematologic adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>X + L (n = 488)</th>
<th></th>
<th>T-DM1 (n = 490)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79.7</td>
<td>20.7</td>
<td>23.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>58.0</td>
<td>16.4</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29.3</td>
<td>4.5</td>
<td>19.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8.6</td>
<td>4.1</td>
<td>8.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.9</td>
<td>3.5</td>
<td>35.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>44.7</td>
<td>2.5</td>
<td>39.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.1</td>
<td>2.3</td>
<td>6.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>9.4</td>
<td>0.8</td>
<td>22.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>8.8</td>
<td>1.4</td>
<td>16.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>

AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; n = number of patients; T-DM1 = trastuzumab emtansine; X + L = capecitabine and lapatinib
Key findings: hematologic adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>X + L (n = 488)</th>
<th>T-DM1 (n = 490)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>8.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

n = number of patients; T-DM1 = trastuzumab emtansine; X + L = capecitabine and lapatinib

Key conclusions

- T-DM1 offered a significant and clinically meaningful improvement in PFS over capecitabine and lapatinib.
- ORR, DOR, and the safety profile support T-DM1 as an active and well tolerated novel therapy for patients with HER2-positive MBC.

DOR = duration of response; HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; ORR = overall response rate; PFS = progression-free survival; T-DM1 = trastuzumab emtansine
Cardiac tolerability of pertuzumab compared with placebo when combined with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study

Background

- Cardiac dysfunction is associated with anthracycline and trastuzumab therapy (especially their concomitant administration) in patients with HER2-positive MBC.

- Majority of trastuzumab-related cardiac events are reversible after treatment discontinuation, in contrast to anthracycline therapy.

- CLEOPATRA:
  - Randomized, double-blind, placebo-controlled, phase III trial;
  - Tested the safety and efficacy of combining docetaxel and trastuzumab with pertuzumab (a HER2 dimerization inhibitor with a distinct binding epitope) or placebo as a first-line therapy in patients with HER2-positive MBC.


CLEOPATRA = Clinical Evaluation of Pertuzumab and Trastuzumab; HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer
Study design: treatment

- Patients (n = 808) received:
  - Pertuzumab plus trastuzumab and docetaxel, n = 406; or
  - Placebo plus trastuzumab and docetaxel, n = 402.

- Study drugs administered iv q3w until disease progression or unmanageable toxicity:
  - Pertuzumab/placebo: 840 mg initial dose, then 420 mg doses;
  - Trastuzumab: 8 mg/kg initial dose, then 6 mg/kg doses;
  - Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated (≥six cycles recommended).


iv = intravenous; q3w = once every three weeks
Study design: inclusion criteria

- Baseline LVEF ≥50%;
- No history of CHF;
- No LVEF decline to <50% during/after prior trastuzumab.


CHF = congestive heart failure; LVEF = left ventricular ejection fraction
Study design: assessments

- LVEF assessed by ECHO or MUGA at baseline, q9w during treatment, at discontinuation, and up to three years thereafter.
- AEs monitored continuously and graded according to NCI-CTCAE v3.0.
- Symptomatic LVSD reported as a serious AE and graded according to the NCI-CTCAE v3.0 and NYHA classifications.

AE = adverse event; ECHO = echocardiography; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; MUGA = multigated acquisition; NCI-CTCAE v3.0 = National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0; NYHA = New York Heart Association; q9w = every nine weeks

Key findings: cardiac safety

- Incidence of any cardiac disorder (grade \( \geq 1 \)), as assessed by investigators, was similar for both groups:
  - Placebo: 16.4%;
  - Pertuzumab: 14.5%.

- Two patients in the placebo arm died due to an MI.

- LVSD grade \( \geq 1 \) was the most frequent cardiac AE.
  - More common in the placebo group compared with the pertuzumab group: 8.3% vs. 4.4%.


AE = adverse event; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction
## Key findings: LVSD adverse events

<table>
<thead>
<tr>
<th>LVSD, n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n = 397)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-CTCAE all grades</td>
<td>33 (8.3)</td>
<td>18* (4.4)</td>
</tr>
<tr>
<td>NCI-CTCAE grade 2</td>
<td>15 (3.8)</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>NCI-CTCAE grade ≥3†</td>
<td>11 (2.8)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Symptomatic LVSD†</td>
<td>7 (1.8)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>3 (0.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>3 (0.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>1 (0.3)</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

LVSD = left ventricular systolic dysfunction; NCI-CTCAE = National Cancer Institute-Common Toxicity Criteria for Adverse Events; n= number of patients; NYHA = New York Heart Association

* Assessment of NCI-CTCAE grade was missing for one patient.

† All symptomatic LVSD events (n = 11) were reported as LVSD grade ≥3. However, there were five patients with LVSD grade 3 (placebo arm: n = 4; pertuzumab arm: n = 1) that was not deemed to be symptomatic by the investigator.

Key findings: left ventricular systolic dysfunction

- At data cut-off, eight of the 11 symptomatic LVSD events had resolved; none were fatal:
  - Placebo group: seven events;
  - Pertuzumab group: four events.

- All patients who developed symptomatic LVSD had one or more potential cardiac risk factors (prior exposure to anthracyclines, trastuzumab, and radiation, smoking, diabetes, hypertension, etc.).
Key findings: comparison of risk factors between symptomatic LVSD and overall patient populations

<table>
<thead>
<tr>
<th></th>
<th>Patients who developed symptomatic LVSD (both arms combined, n = 11)</th>
<th>Entire study population (both arms combined, n = 808)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>55.0 (38–82)</td>
<td>54.0 (22–89)</td>
</tr>
<tr>
<td>&gt;75 years, n (%)</td>
<td>1 (9.1)</td>
<td>19 (2.4)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>72.0 (60–85)</td>
<td>64.9 (39–142)</td>
</tr>
<tr>
<td>Baseline LVEF, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>64.0 (50–85)</td>
<td>65.0 (50–88)</td>
</tr>
<tr>
<td>Past or current smoker, n (%)</td>
<td>3 (27.3)</td>
<td>179 (22.2)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (27.3)</td>
<td>207 (25.6)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>0 (0.0)</td>
<td>52 (6.4)</td>
</tr>
<tr>
<td>Prior anthracyclines, n (%)</td>
<td>8 (72.7)</td>
<td>314 (38.9)</td>
</tr>
<tr>
<td>Prior radiotherapy, n (%)</td>
<td>8 (72.7)</td>
<td>346 (42.8)</td>
</tr>
</tbody>
</table>

*LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; n = number of patients*

Key findings: left ventricular systolic dysfunction

- Compared with the overall patient population the only potentially important risk factors in patients who developed symptomatic LVSD were:
  - Prior anthracycline exposure:
    - HR = 2.21; 95% CI 1.27–3.86; \( p = 0.0053 \).
  - Prior radiation exposure:
    - HR = 2.43; 95% CI 1.37–4.31; \( p = 0.0025 \).
- Prior exposure to anthracyclines and radiation had no influence on the overall analysis of the time to first asymptomatic or symptomatic LVSD event.


CI = confidence interval; HR = hazard ratio; LVSD = left ventricular systolic dysfunction
Key findings: left ventricular ejection fraction

- LVEF decline to <50% and by ≥10% points from baseline was more frequent in the placebo group:
  - 6.6% vs. 3.8%.

- Most patients recovered LVEF ≥50% on or after stopping treatment:
  - Placebo group: 72.0%;
  - Pertuzumab group: 86.7%.

LVEF = left ventricular ejection fraction

Key findings: LVEF assessment

<table>
<thead>
<tr>
<th></th>
<th>Placebo + trastuzumab + docetaxel (n = 397)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with post-baseline LVEF assessment, n</td>
<td>379</td>
<td>393</td>
</tr>
<tr>
<td>LVEF decline to &lt;50% and by ≥10% points from baseline, n/N (%)</td>
<td>25/379 (6.6)</td>
<td>15/393 (3.8)</td>
</tr>
<tr>
<td>LVEF recovered to ≥50% on treatment*, n/N (%)</td>
<td>12/25 (48.0)</td>
<td>6/15 (40.0)</td>
</tr>
<tr>
<td>LVEF recovered to ≥50% after stopping treatment†, n/N (%)</td>
<td>6/25 (24.0)</td>
<td>7/15 (46.7)</td>
</tr>
<tr>
<td>Total number of patients with LVEF recovery to ≥50%, n/N (%)</td>
<td>18/25 (72.0)</td>
<td>13/15 (86.7)</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; n/N = number of patients
* On treatment is defined as on or before the day of the latest assessment date within 42 days following the last valid assigned study treatment.
† After stopping treatment is defined as after the day of the latest assessment date within 42 days following the last valid assigned study treatment.

Key conclusion

- CLEOPATRA provides evidence that pertuzumab, when combined with trastuzumab and docetaxel, does not increase the frequency of overall cardiac disorders compared with placebo.


CLEOPATRA = Clinical Evaluation of Pertuzumab and Trastuzumab
Quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer

Background

- Studies have shown that the combination of two HER2-targeted agents in the treatment of HER2-positive MBC improves efficacy vs. one targeted agent alone.

- New therapies need to demonstrate clinical efficacy and show no adverse impact on the patient’s HRQoL.

- CLEOPATRA tested the safety and efficacy of combining docetaxel and trastuzumab with pertuzumab or placebo as a first-line therapy for patients with HER2-positive MBC.
  - Addition of pertuzumab vs. placebo significantly improved PFS from 12.4 to 18.5 months.

- At ASCO 2012, Cortés et al. presented their analysis of HRQoL data from the CLEOPATRA study.


CLEOPATRA = Clinical Evaluation of Pertuzumab and Trastuzumab; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; MBC = metastatic breast cancer; PFS = progression-free survival
Study design

- Female patients completed the FACT-B questionnaire every third cycle of therapy within three days before each tumour assessment until independently determined progressive disease.

- Time to deterioration in the BCS (a measurement of symptoms and issues relevant in breast cancer) was recorded once patients reported a decrease from baseline of $\geq 2$ points.

- Time to deterioration of HRQoL was measured when a decrease from baseline of $\geq 5$ points occurred in the TOI-PFB composite score.

BCS = breast cancer scale; FACT-B = Functional Assessment of Cancer Therapy for breast cancer; HRQoL = health-related quality of life; TOI-PFB = Trial Outcome Index-Physical/Functional/BCS

Key findings: health-related quality of life

- Compliance with completion of the FACT-B questionnaire was ≥75% beyond the first year in both treatment arms.

- Similar percentage of patients in both groups experienced deterioration of HRQoL during the study:
  - Placebo: 56.7%;
  - Pertuzumab: 59.5%.

- Median time to deterioration of HRQoL was approximately six cycles of treatment for both groups:
  - HR = 0.97; p = 0.7161.

FACT-B = Functional Assessment of Cancer Therapy for breast cancer; HR = hazard ratio; HRQoL = health-related quality of life
Key findings: time to symptom progression

Key findings: TOI-PFB

- At the sixth cycle, the mean reduction in the TOI-PFB score from baseline was:
  - Placebo group: –3.5;
  - Pertuzumab group: –3.0.

- At subsequent cycles, when most patients had discontinued docetaxel, mean reductions were smaller suggesting that after an early decline, patients’ scores improved slightly.
  - Overall, mean changes were small in both arms.

- From approximately cycle 21 on, the mean change from baseline in TOI-PFB scores improved in the pertuzumab group and worsened in the placebo group.
  - Number of patients with an evaluable score decreased over time.


TOI-PFB = Trial Outcome Index-Physical/Functional/BCS
Key findings: mean change from baseline in TOI-PFB over time

Key findings: breast cancer score

- An exploratory analysis suggested that time to deterioration in the BCS score was delayed in the pertuzumab group:
  - 18.3 vs. 26.7 weeks; HR 0.77; \( p = 0.0061 \).

- Mean change from baseline in BCS scores remained stable around zero.
  - However at cycle 21, the scores improved in the pertuzumab group and worsened slightly in the placebo group.

- The number of patients with an evaluable score decreased over time.
Key conclusions

- The combination of pertuzumab with trastuzumab and docetaxel as a first-line therapy for HER2-positive MBC appeared to have no detrimental effect on patient-reported HRQoL.

- Adding pertuzumab to the first-line therapy appears to be associated with a delay in the time to deterioration in the BCS score.


BCS = breast cancer score; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; MBC = metastatic breast cancer
An open-label, randomized, phase III trial comparing taxane-based chemotherapy with lapatinib or trastuzumab as a first-line therapy for women with HER2-positive metastatic breast cancer

Gelmon KA, et al. ASCO Annual Meeting Abstracts 2012;30:LBA671
Background

- Lapatinib, an orally active, reversible inhibitor of EGFR and HER2 tyrosine kinases, is approved for use in combination with capecitabine as therapy for patients who have received prior treatment for HER2-positive LABC or MBC.

- As a first-line therapy for patients with HER2-positive MBC, lapatinib has been shown to improve efficacy over placebo when used in combination with paclitaxel.

- This trial compared the efficacy and safety of a first-line therapy using lapatinib or trastuzumab in combination with taxane-based chemotherapy for patients with HER2-positive MBC.


EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; LABC = locally advanced breast cancer; MBC = metastatic breast cancer
Study design

- A multicentre, international, open-label, randomized, phase III clinical trial.

- Patients (n = 636) with MBC and no prior chemotherapy or HER2-targeted therapy for MBC were randomized and treated with either:
  - LTax/L;
    or
  - TTax/T.


HER2 = human epidermal growth factor receptor 2; LTax/L = lapatinib with a taxane followed by lapatinib monotherapy; MBC = metastatic breast cancer; TTax/T = trastuzumab with a taxane followed by trastuzumab monotherapy
Study design: treatment

- Dosages of study drugs administered for the first 24 weeks of therapy were a taxane:
  - Paclitaxel 80 mg/m^2 iv weekly for the first three weeks, then q4w for six courses;
  or
  - Docetaxel 75 mg/m^2 iv on day 1, then q3w for eight courses (plus GCSF prophylaxis for patients taking lapatinib).

- Taxanes given in combination with a HER2-directed agent:
  - Lapatinib 1,250 mg orally each day;
    or
  - Trastuzumab 4 mg/kg iv initial dose, then 2 mg/kg iv weekly or 8 mg/kg iv initial dose, then 6 mg/kg iv q3w.

GCSF = granulocyte colony-stimulating factor; HER2 = human epidermal growth factor receptor 2; iv = intravenous; q3w = once every three weeks; q4w = once every four weeks
Study design: treatment (cont’d)

- After the first 24 weeks of treatment, patients received monotherapy with the HER2-directed agent:
  - Lapatinib 1,500 mg orally qd;
  or
  - Trastuzumab 6 mg/kg iv q3w.

- Treatment corresponded to the patient’s initial therapy for four years or until PD.


PD = progressive disease; qd = once per day; q3w = every three weeks
Study design: endpoints

- **Primary endpoint:**
  - PFS determined by RECIST 1.0 or death from any cause and analyzed by ITT.

- **Secondary analysis of PFS** was performed with patients who had centrally confirmed HER2-positive tumours.

- **Secondary endpoints:**
  - OS;
  - Safety.

HER2 = human epidermal growth factor receptor 2; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors

Key findings: progression-free survival

- After median follow-up of 12.9 months in the lapatinib arm and 14 months in the trastuzumab arm, ITT analysis indicated median time of PFS in the LTax/L arm was inferior compared with the TTax/L arm:
  - LTax/L: 8.8 months, 95% CI: 8.3–10.6;
  - TTax/L: 11.4 months, 95% CI: 10.8–13.7, HR = 1.33 (95% CI: 1.06-1.67); \( p = 0.01 \).


CI = confidence interval; HR = hazard ratio; ITT = intention to treat; LTax/L = lapatinib with a taxane followed by lapatinib monotherapy; PFS = progression-free survival; qd = once per day; q3w = every three weeks; TTax/T = trastuzumab with a taxane followed by trastuzumab monotherapy.
Key findings: PFS — analysis of intent-to-treat and centrally confirmed HER2+ populations

Key findings: secondary analysis of PFS

- Secondary analysis of PFS (only included patients with centrally-confirmed HER2-positive tumours) showed LTax/L inferior to TTax/T:
  - 9.0 vs. 13.7 median months, HR = 1.48, 95% CI: 1.15–1.92; \( p = 0.003 \).

Key findings: overall survival

- No difference in OS between the treatment arms when comparing LTax/L with TTax/T, regardless of whether it was analyzed by:
  - ITT: HR = 1.1, 95% CI: 0.75–1.61; p = 0.62;
  - HER2-positive status: HR = 1.25, 95% CI: 0.81–1.93; p = 0.32.

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; ITT = intention to treat; LTax/L = lapatinib with a taxane followed by lapatinib monotherapy; OS = overall survival; TTax/T = trastuzumab with a taxane followed by trastuzumab monotherapy.

Overall survival: analysis of intent-to-treat and centrally confirmed HER2+ populations

Key findings: safety

- Safety data profiles differed between the two treatment arms:
  - Overall, more SAEs were reported in the LTax/L group (136 vs. 78), with a greater number of cases of diarrhea (32 vs. 5).
  - Higher frequency of two grade ≥3 AEs occurred in patients receiving LTax/L:
    - Diarrhea: 19.3% vs. 1.3%;
    - Rash: 8.9% vs. 0.3%.
  - Greater percentage of patients treated with TTax/T experienced a decrease of ≥20% of LVEF from baseline over the course of the study.
  - Ten deaths on treatment took place in the TTax/T arm compared with five deaths in the LTax/L arm.


AE = adverse event; LTax/L = lapatinib with a taxane followed by lapatinib monotherapy; LVEF = left ventricular ejection fraction; SAE = serious adverse event; TTax/T = trastuzumab with a taxane followed by trastuzumab monotherapy.
Key findings: LVEF decrease from baseline while on treatment

<table>
<thead>
<tr>
<th>Week</th>
<th>LTax/L (n = 312)</th>
<th>TTax/T (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute decrease (%)</td>
<td>Absolute decrease (%)</td>
</tr>
<tr>
<td></td>
<td>0–&lt;20</td>
<td>20 or more</td>
</tr>
<tr>
<td>12</td>
<td>255</td>
<td>158 (62)</td>
</tr>
<tr>
<td>24</td>
<td>199</td>
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<td>48</td>
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<td>43 (60)</td>
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<tr>
<td>60</td>
<td>42</td>
<td>28 (67)</td>
</tr>
<tr>
<td>72</td>
<td>26</td>
<td>14 (54)</td>
</tr>
</tbody>
</table>

0 – <20 = 0 to less than 20; LTax/L = lapatinib plus taxane followed by lapatinib; n = number of patients; TTax/T = trastuzumab plus taxane followed by trastuzumab

Key conclusions

- Patients receiving TTax/T compared with LTax/L had a statistically significant increase in PFS, as indicated by median differences of 2.6 months overall and 4.7 months in those with HER2-positive tumours.

- The two therapies produced different safety data profiles:
  - Diarrhea and rash occurred more frequently with LTax/L;
  - In the TTax/T arm, a greater percentage of patients experienced a ≥20% decrease in LVEF.


HER2 = human epidermal growth factor receptor 2; LTax/L = lapatinib with a taxane followed by lapatinib monotherapy; LVEF = left ventricular ejection fraction; PFS = progression-free survival; TTax/T = trastuzumab with a taxane followed by trastuzumab monotherapy
Evaluation of lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer: NSABP protocol B-41

Background

- Standard neoadjuvant therapy for HER2-positive operable breast cancer is doxorubicin and cyclophosphamide combined with weekly paclitaxel and trastuzumab leading up to surgery.

- Lapatinib, combined with a cytotoxic agent, is used to treat patients with MBC whose tumours have progressed on trastuzumab.

- This phase III clinical trial attempted to determine whether substitution of, or addition to, the HER2-targeted component of standard neoadjuvant therapy, trastuzumab, with lapatinib might improve outcomes for patients with HER2-positive operable breast cancer.

Robidoux A, et al. ASCO 2012;30:LBA506. HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer
Study design: inclusion criteria

- A palpable tumour ≥2 cm;
- Diagnosis by core needle biopsy;
- LVEF ≥50%;
- Confirmation of a HER2-positive tumour.

HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction
Study design: treatment

- All patients (n = 529) received part of the standard neoadjuvant treatment regimen consisting of doxorubicin and cyclophosphamide followed by weekly paclitaxel, combined with trastuzumab, lapatinib, or both trastuzumab and lapatinib.

- Study drugs administered as follows:
  - Doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² iv every 21 days for cycles 1–4;
  - Weekly paclitaxel 80 mg/m² iv on days 1, 8, and 15 every 28 days for cycles 5–8.
Study design: treatment (cont’d)

- While taking weekly paclitaxel, patients were also administered the HER2-targeted agents:
  - Trastuzumab 4 mg/kg iv initial dose, 2 mg/kg iv subsequent dose weekly until one week before surgery;
  - Lapatinib 1,250 mg orally qd until one day before surgery;
  - Trastuzumab plus lapatinib: trastuzumab (same dosage) and lapatinib (750 mg orally qd until one day before surgery).

iv = intravenous; qd = once daily

Study design: endpoints

- Primary endpoint:
  - pCR in the breast.

- Secondary outcome measures:
  - cCR;
  - pCR in the breast and negative nodes;
  - Cardiac and non-cardiac toxicities.


cCR = complete clinical response; pCR = pathologic complete response
Key findings: complete clinical response

- Percentage of patients fully completing the protocol-defined neoadjuvant therapies was significantly different among the treatment groups:
  - Trastuzumab: 78%;
  - Lapatinib: 68%;
  - Trastuzumab plus lapatinib: 63%; \( p = 0.01 \).

- Achievement of a cCR was decreased with lapatinib vs. trastuzumab:
  - 69.9% vs. 82%, \( p = 0.014 \).

- Trastuzumab plus lapatinib compared with trastuzumab alone did not confer any difference in the percentage of patients with a cCR:
  - 76.8% vs. 82.0%, \( p = 0.3 \).

cCR = complete clinical response
Key findings: complete clinical response (cont’d)

Key findings: pathological complete response

- Lapatinib or trastuzumab plus lapatinib vs. trastuzumab did not significantly change the percentage of patients achieving a pCR in the breast:
  - Lapatinib vs. trastuzumab: 53.2% vs. 52.5%, \( p = 0.99 \);  
  - Trastuzumab plus lapatinib vs. trastuzumab: 62% vs. 52.5%; \( p = 0.095 \).

- When hormone receptor status (positive or negative) was compared, there was no difference in the percentage of patients achieving a pCR in the breast.

- Percentage of patients with a pCR in the breast and negative nodes remained unchanged in the trastuzumab vs. lapatinib groups: 49.4% vs. 47.4%.
  - In the trastuzumab plus lapatinib group vs. trastuzumab there was a marginal increase: 60.2% vs. 49.4%, \( p = 0.056 \).


pCR = pathological complete response
Key findings: pathological complete response (cont’d)

- Dividing the treatment groups into two categories of HER2 expression levels by IHC low (0+, 1+, and 2+) and IHC 3+, revealed that a greater percentage of patients with IHC 3+ levels of HER2 attained a pCR when treated with trastuzumab plus lapatinib compared with trastuzumab:
  - 71% vs. 54.7%; $p = 0.006$.

- An interaction of pCR with IHC levels was detected in the trastuzumab plus lapatinib vs. trastuzumab groups, $p = 0.021$.
Key findings: safety

- Overall grade ≥3 AEs, specifically diarrhea, occurred with greater frequency in patients in both of the lapatinib-treated groups compared with trastuzumab:
  - Trastuzumab: 2%;
  - Lapatinib: 20%;
  - Trastuzumab plus lapatinib: = 27%; \( p < 0.001 \).

AE = adverse event

Key conclusions

- Substitution of lapatinib for trastuzumab in neoadjuvant therapy for operable breast cancer was as efficacious as trastuzumab in nearly every outcome measure except cCR.

- Combination of the two HER2-directed agents, trastuzumab and lapatinib, may be more effective than trastuzumab alone as a neoadjuvant therapy for patients with operable breast cancer that expresses high levels of HER2.

- Main difference in AEs was an increased frequency of diarrhea in both lapatinib-containing treatment regimens compared with the standard trastuzumab regimen.


AE = adverse event; cCR = complete clinical response; HER2 = human epidermal growth factor receptor 2
Cardiac safety in a phase II study of trastuzumab emtansine (T-DM1) following anthracycline-based chemotherapy as adjuvant or neoadjuvant therapy for early-stage HER2-positive breast cancer

Dang CT, et al. ASCO Annual Meeting Abstracts 2012;30:532
Background

- Considerable interest exists in exploring the use of T-DM1 in patients with early-stage disease given its clinical efficacy and favourable safety profile as a single agent in patients with MBC.

- Monitoring the frequency and severity of cardiotoxicity associated with trastuzumab treatment is of special concern as women with early-stage breast cancer can expect long-term survival.

- This phase II study assessed the cardiac safety and clinical feasibility of T-DM1 following anthracycline-based chemotherapy in the adjuvant or neoadjuvant setting for early-stage HER2-positive breast cancer.


HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; T-DM1 = trastuzumab emtansine
Study design

- Between October 2010 to June 2011, 153 patients were enrolled with 148 receiving at least one dose of T-DM1 as of the cut-off date.
- A prechemotherapy LVEF $\geq 55\%$ by MUGA/ECHO was required for enrolment.
- A prespecified cardiac event was defined as death from a cardiac cause or severe CHF (NYHA class III or IV) with a decrease in LVEF of $\geq 10$ absolute percentage points from baseline to an LVEF $<50\%$.

CHF = congestive heart failure; ECHO = echocardiography; LVEF = left ventricular ejection fraction; multigated acquisition = MUGA; NYHA = New York Heart Association; T-DM1 = trastuzumab emtansine

Study design: treatment

- Patients were administered one of two chemotherapy regimens:
  - AC (A: 60 mg/m²; C: 600 mg/m² q2w or q3w for four cycles);
  - FEC (F: 500 mg/m²; E: 100 mg/m²; C: 600 mg/m² q3w for three to four cycles).
- Chemotherapy regimens followed by T-DM1 3.6 mg/kg iv q3w for up to 17 cycles.

A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; iv = intravenous; q2w= once every two weeks; q3w= once every three weeks; T-DM1 = trastuzumab emtansine;

Study design: primary endpoints

- Safety;
- An allowable incidence rate of prespecified cardiac events $\leq 6\%$ following initiation of T-DM1 treatment.


T-DM1 = trastuzumab emtansine
Key findings: cardiac adverse events

- Mean LVEF of patients (n = 147) prechemotherapy was 67.1% and changed very little over the course of treatment.
  - Values had greater variation approaching the end of treatment because fewer patients had reached that point at clinical cut-off.
- No symptomatic decreases in LVEF but 2.0% of patients experienced an asymptomatic decrease in LVEF.
- Neither prespecified cardiac events nor T-DM1 discontinuations due to cardiac AEs had occurred at cut-off.
  - However, 3.4% of patients experienced T-DM1-related cardiac AEs, such as atrial fibrillation, tricuspid valve incompetence, or palpitations.

AE = adverse event; LVEF = left ventricular ejection fraction; T-DM1 = trastuzumab emtansine

Key findings: mean LVEF in T-DM1-treated patients over time

CI = confidence interval; LVEF = left ventricular ejection fraction; n = number of patients; RT = radiation therapy; T-DM1 = trastuzumab emtansine

* After the end of T-DM1 cycle 4, patients may have received optional chemotherapy, RT, trastuzumab, or surgery prior to recommencing T-DM1 treatment. Some patients missed protocol-specified LVEF assessments.

Key findings: adverse events

- Most common T-DM1-related AEs (all grades) were nausea, headache, epistaxis, asthenia, and pyrexia.

- Over one quarter of patients (26.4%) had grade 3 or 4 T-DM1-related AEs; no deaths occurred.

- Most common grade ≥3 AEs were thrombocytopenia, increased AST, and increased ALT.

- Some patients (3.4%) had T-DM1-related serious AEs with 4.1% of patients overall experiencing AEs leading to T-DM1 discontinuation.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T-DM1 = trastuzumab emtansine
Key conclusion

- Early results indicate that T-DM1 following anthracycline-based chemotherapy was not associated with cardiac toxicity in patients with early-stage HER2-positive breast cancer.


HER2 = human epidermal growth factor receptor 2; T-DM1 = trastuzumab emtansine