Randomized Controlled Trial Comparing Taxane-Based Chemotherapy with Lapatinib or Trastuzumab as First-Line Therapy for Women with HER2+ Metastatic Breast Cancer:

Interim Analysis of NCIC CTG MA.31/ GSK EGF 108919

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Disclosures

- **K Gelmon** Consultant/Advisor: Amgen, AstraZeneca, GSK, Novartis, Pfizer, Roche
- **F Boyle** Consultant/Advisor: GlaxoSmithKline, Roche Honoraria and Research Funding: GlaxoSmithKline
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Background

- Lapatinib is an orally active, reversible inhibitor of EGFR (ErbB1) and HER2 (ErbB2) receptor tyrosine kinases.

- It is approved in combination with capecitabine for the treatment of advanced or metastatic breast cancer in patients whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab\(^1\).

- Lapatinib has also been combined with other cytotoxic chemotherapy with improvement in efficacy \(^2,3\) but has not been directly compared to trastuzumab in the first line metastatic setting.

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Purpose of This Presentation

- MA.31/EGF 108919 has undergone an interim analysis

- An independent DSMC has recommended that:
  - these results be released
  - trial conduct be altered

- This presentation will describe:
  - these and associated results
  - future conduct of the trial
  - analyses that will subsequently become available
Study Timelines

- Activation: July 17, 2008
- Accrual: Oct 7, 2008 – Dec 1, 2011 (n=652)
- Events at IA: Nov 7, 2011 (n=195) (centrally-confirmed HER2+ patients)
- Database Lock: Apr 13, 2012 (333 PFS events by intent to treat)
- DSMC Review: Apr 27, 2012

MA.31 Steering Committee actions: May 7, 2012
Informed investigators/patients/ethics/regulatory bodies
Study Objectives

• Primary
  – To compare the Progression Free Survival (PFS) of taxane therapy plus lapatinib to taxane therapy plus trastuzumab

• Secondary:
  – Overall survival
  – Adverse events
    – Incidence of CNS metastases (first progression) and time to CNS metastases
  – Objective response rate (ORR), Clinical Benefit response rate (CB), time to response and duration of response
  – QOL
  – Correlative studies
Primary endpoint is PFS:

- Time from randomization to progression by RECIST 1.0 or death from any cause
- Primary analysis is by ITT
- Secondary analysis is by centrally-confirmed HER2+
- Sensitivity analyses to account for asymmetric follow-up
- If non-inferiority demonstrated: test for superiority
Non-inferiority margin: HR < 1.25 for LTAX/L vs TTAX/T
1 sided alpha = 2.5%; beta = 90%
390 events required
Accrue over 2 years
Follow-up 1 year
NCIC CTG holds, manages and analyzes the database
Interim Analysis

- 2-sided test for superiority
  - requires **195 (50%)** events in HER2+ centrally-confirmed
  - evaluate the ITT population
  - Lan-DeMets / O’ Brien-Fleming boundary = 0.00305
  - Adjust boundary based on actual # of events

- Actual # of events:
  - 333 in ITT population, IA stopping boundary: \( P=0.0301 \)
  - 263 events in centrally-confirmed HER2+
Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting
**MA.31/ EGF108919: Design**

<table>
<thead>
<tr>
<th>Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Standard inclusion including mandatory central HER2 testing</td>
</tr>
<tr>
<td>- Standard exclusion</td>
</tr>
<tr>
<td>- Prior (neo)adjuvant chemo / trastuzumab allowed ($\geq$ 12 mo)</td>
</tr>
<tr>
<td>- No CNS mets</td>
</tr>
</tbody>
</table>
Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting

Stratify

Standard inclusion and exclusion

- Prior (neo)adjuvant HER2 therapy
- Prior (neo)adjuvant taxane chemotherapy
- Planned taxane treatment
- Liver metastasis
Women with HER2 positive (central or local lab) metastatic breast cancer and no prior chemotherapy or HER2 targeted therapy in the metastatic setting

Stratify

Standard inclusion and exclusion

Randomize

1:1
MA.31/ EGF108919: Design

Randomize

<table>
<thead>
<tr>
<th>EXPERIMENTAL ARM</th>
<th>STANDARD ARM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24 Weeks:</strong> Lapatinib plus Taxane</td>
<td><strong>24 Weeks:</strong> Trastuzumab plus Taxane</td>
</tr>
<tr>
<td>Until PD: Lapatinib</td>
<td>Until PD: Trastuzumab</td>
</tr>
</tbody>
</table>

Primary Outcome: PFS

Sample Size: ~ 600 (536 centrally confirmed HER2+ patients)
Protocol Therapy

- **Taxane (Tax)**
  - Paclitaxel 80 mg/m² IV weekly (3 week out of 4) or
  - Docetaxel 75 mg/m² IV q3 weekly

- **Anti HER2/neu therapy:**
  - Lapatinib (L)
    - Plus taxane: 1250 mg po daily
      - If toxicity de-escalation 1250, 1000, 750 and then discontinue
    - Monotherapy 1500 mg po daily
  - Trastuzumab (T)
    - Plus taxane: loading dose followed by 6 mg/kg IV q3 weekly or 2 mg/kg IV weekly
    - Monotherapy 6 mg/kg IV q3 weekly
TREATMENT ARM

24 Weeks: Combined Therapy

Until PD: Monotherapy

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clinic visit for trastuzumab administration

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protocol visit (PE and RECIST assessment)
Study Conduct

Median follow-up: 13.6 months

(12.9 months on lapatinib arm; 14 months on trastuzumab arm)
MA.31 Flow Diagram

652 patients randomized in Dec 7, 2011

636 patients randomized Nov 7, 2011 (ITT)

318 LTAX/L

266 Centrally confirmed Her2/neu status

5 did not receive protocol therapy

42 without PFS assessment

318 in ITT PFS analysis
313 in safety analysis

318 TTAX/T

259 Centrally confirmed Her2/neu Status

1 did not receive protocol therapy

36 without PFS assessment

318 in ITT PFS analysis
317 in safety analysis
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LTAX/L (n=318)</th>
<th>TTAX/T (n=318)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – median (range)</strong></td>
<td>55.4 (27-87)</td>
<td>54.1 (29-84)</td>
</tr>
<tr>
<td><strong>ECOG 0/1</strong></td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>Prior (Neo) adjuvant anti HER2/neu therapy</strong></td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Prior (Neo) adjuvant taxane therapy</strong></td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Metastatic breast cancer at primary diagnosis</strong></td>
<td>42%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Liver metastases</strong></td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Planned 3 weekly docetaxel treatment</strong></td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Planned weekly paclitaxel treatment</strong></td>
<td>45%</td>
<td>45%</td>
</tr>
</tbody>
</table>

* ER/PR results centrally done
Results of Interim Analysis

• DSMC Review:
  – ITT PFS: HR = 1.38; P = 0.006

• DSMC recommendation was accepted according to NCIC CTG policies

• Repeat analysis using more conservative censoring:
  – ITT PFS: HR = 1.33; P = 0.01
Median PFS TTAX/T = 11.4 months
Median PFS LTAX/L = 8.8 months
HR = 1.33 (95% CI = 1.06 – 1.67), P = 0.01
Progression Free Survival
Centrally-confirmed HER2+ Analysis

Median PFS $TTAX/T = 13.7$ months
Median PFS $LTAX/L = 9.0$ months
$HR = 1.48 (95\% CI = 1.15 - 1.92), P = 0.003$
Overall Survival Intent to Treat Analysis

HR = 1.1 (95% CI = 0.75 – 1.61), P = 0.62
HR = 1.25 (95% CI = 0.81 – 1.93), P = 0.32

Overall Survival
Centrally-confirmed HER2+ Analysis

HR = 1.25 (95% CI = 0.81 – 1.93), P = 0.32
Serious Adverse Events

<table>
<thead>
<tr>
<th>EVENT</th>
<th>LTAX/L</th>
<th>Total SAE reports = 136</th>
<th>Number post amendment</th>
<th>TTAX/T</th>
<th>Total SAE reports = 78</th>
<th>Number post amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>25</td>
<td></td>
<td>Diarrhea</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>17</td>
<td>7</td>
<td></td>
<td>Febrile Neutropenia</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

* Included as one of the adverse event terms within a single SAE report

** Protocol Amendment after first 189 patients were randomized mandated primary GCSF prophylaxis for patients on docetaxel and lapatinib
<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>
<td>126 (63)</td>
</tr>
<tr>
<td>36</td>
<td>145</td>
<td>95 (66)</td>
</tr>
<tr>
<td>48</td>
<td>72</td>
<td>43 (60)</td>
</tr>
<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>
## Treatment Discontinuations

### OFF PROTOCOL TREATMENT

*(n = 382)*

<table>
<thead>
<tr>
<th>Reason</th>
<th>LTAX/L=202</th>
<th>Number (%)</th>
<th>TTAX/T=180</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 (2.5)</td>
<td></td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Intercurrent Illness</td>
<td>3 (1.5)</td>
<td></td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>143 (70.8)</td>
<td></td>
<td>121 (67.2)</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>36 (17.8)</td>
<td></td>
<td>19 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Refused Treatment</td>
<td>2 (1.0)</td>
<td></td>
<td>4 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic Progression</td>
<td>4 (2.0)</td>
<td></td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.5)</td>
<td></td>
<td>20 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>
Further Considerations

• Future analysis include:
  – Incidence of brain metastasis as site of first recurrence
  – Treatment exposure
  – Response rate
  – QOL
  – Correlative studies

• This study does not provide information on the efficacy of lapatinib versus trastuzumab or their combination
  – in second line metastatic treatment;
  – in patients refractory to trastuzumab;
  – in a population more heavily pretreated in the adjuvant setting;
  – in the setting of continuous taxane therapy.
Conclusions

• In this study comparing LTAX/L to TTAX/T, the PFS was statistically significantly better in the trastuzumab arm with a HR of 1.33 and a 2.6 month difference (median PFS) in the ITT population and a HR of 1.48 with a 4.7 month difference (median PFS) in the centrally confirmed HER2 + population.

• The toxicity pattern of the two arms was different with more rash and diarrhea in the lapatinib containing arm and a higher incidence of decrease in LVEF from baseline in the trastuzumab arm.
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