New Data for HER2 Driven Metastatic Breast Cancer

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Overview

- New mechanisms of Trastuzumab and Lapatinib Resistance
- New Therapies and Combinations
New Mechanisms of Resistance
Mechanisms of Action and Biological Significance of HER2 Mutations in HER2-Overexpressing Breast Cancer

Delphine R. Boulbes, Quanri Jin, Stefan T. Arold, John E. Ladbury, Dihua Yu, Francisco J. Esteva

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MD Anderson Cancer Center
The *her2* gene is amplified in 20% of invasive breast cancers

*Her2* amplification is a predictive marker of response to trastuzumab and lapatinib therapy

Response to trastuzumab and lapatinib is heterogeneous

- 15-20% of patients with early-stage breast cancer develop metastatic disease despite adjuvant trastuzumab

- Most patients with HER2 positive metastatic breast cancer develop progressive disease and die despite trastuzumab- and lapatinib-based therapy
Identification of molecular mechanisms of resistance to HER2-targeted therapy is an area of active investigation.

EGFR and HER2 mutations are predictive of response to tyrosine kinase inhibitors in lung cancer cells.

Limited data on her2 mutations in breast cancer.

Hypothesis: mutations in the her2 kinase domain predict response to targeted therapy in HER2-positive breast cancers.
78 HER2-positive primary invasive breast cancers from patients who subsequently received trastuzumab for metastatic disease

Sequenced kinase domain of her2 using the Sanger method

Identified 3 mutations: D808N, V794M, L726F (each mutation on a different tumor)
Localization of HER2 mutations

L726F is located at the entrance of the ATP binding cleft.

D808N is close to nucleotide binding site.

V794M is at the interface between ‘activator’ and ‘acceptor’ molecules.
Methods (Cont.)

- Site-directed mutagenesis
- Cell Lines
  - MCF10A: non-tumorigenic
  - MDA-MB-175: HER2 overexpressed
  - SKBR3 and BT474: Her2 gene amplified
- Anchorage-independent growth (soft-agar)
- Mammosphere formation
- Invasion assay (matrigel)
- Cell survival during drug incubation
L726F & V794M show a dramatic lack of phosphorylation.

**IP: HER2**
Kinase assay

**Anti-P-Y**

**Ph1248-Her2**

**Her2**

**Actin**

**p-Erk1/2 wt**

**Erk1/2 wt**

**Actin**

**PLVX**

**WT**

**L726F**

**P-877 Her2**

**P-1196 Her2**

**P-1221-1222 Her2**

**P-1248 Her2**

**cmyc**

**Her2**
Impaired Cellular Localization of the L726F mutant in Primary Breast Cancer Tissue

- Y1248 altered phosphorylation status has been shown to be involved in intracellular localization (Ramsauer VP et al., J Biol Chem 278, 30142-7)
L726F mutation confers lapatinib resistance

Colony formation in soft-agar treated with Lapatinib 0.1uM

MDA-MB-175

SKBR3

BT474-M1

Colony formation in soft-agar treated with Lapatinib 0.1uM
L726F location at the entrance of the ATP binding cleft probably hamper binding of lapatinib and similar drugs.
All three HER2 kinase mutations are associated with aggressive phenotypes

- D808N: promotes anchorage independence, invasion and impairs formation of normal acini
- V794M: promotes invasion and mammosphere formation and impairs formation of normal acini
- L726F: promotes invasion and mammosphere formation and impairs formation of normal acini

L726F mutation confers resistance to lapatinib in HER2-Overexpressing breast cancer cell lines
Association of PTEN Loss and PIK3CA Mutations on Outcome in HER2+ Metastatic Breast Cancer Patients Treated With First-Line Lapatinib Plus Paclitaxel or Paclitaxel Alone

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Predictive Relevance of Biomarkers Downstream of HER2 Not Proven

# Effect of PTEN Loss/PIK3CA Mutations on Lapatinib Efficacy

<table>
<thead>
<tr>
<th>Articles</th>
<th>Study Population</th>
<th>Patient No.</th>
<th>Treatment</th>
<th>PTEN Loss</th>
<th>PIK3CA Mutation</th>
<th>AKT or PTEN Loss/PIK3CA Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spector et al, 2008</td>
<td>HER2+ IBC</td>
<td>45</td>
<td>Lap</td>
<td></td>
<td>–</td>
<td>No impact on Lap efficacy</td>
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<tr>
<td>Toi et al, 2009</td>
<td>HER2+ MBC</td>
<td>100</td>
<td>Lap</td>
<td></td>
<td>–</td>
<td>No impact on Lap efficacy</td>
</tr>
<tr>
<td>Chang et al, 2011</td>
<td>HER2+ BC/HER2+ cell lines</td>
<td>49</td>
<td>Lap→Tra/Dox</td>
<td></td>
<td>–</td>
<td>No impact on Lap efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tra→Dox</td>
<td></td>
<td>–</td>
<td>Impact on Lap efficacy</td>
</tr>
<tr>
<td>Xu et al, 2011</td>
<td>HER2+ MBC</td>
<td>38</td>
<td>Lap + Cap</td>
<td></td>
<td>–</td>
<td>No impact on Lap efficacy</td>
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<tr>
<td>Hu et al, 2011</td>
<td>HER2+ MBC</td>
<td>57</td>
<td>Lap + Cap</td>
<td></td>
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<td>No impact on Lap efficacy</td>
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<tr>
<td>Baselga et al, 2008</td>
<td>HER2+ BC cell lines</td>
<td>N/A</td>
<td>Lap</td>
<td></td>
<td>–</td>
<td>No impact on Lap efficacy</td>
</tr>
<tr>
<td>Slamon et al, 2010</td>
<td>HER2+ BC cell lines</td>
<td>N/A</td>
<td>Lap or Tra</td>
<td></td>
<td>–</td>
<td>No impact on Lap efficacy</td>
</tr>
</tbody>
</table>
Biomarker Study Aim

Evaluate the predictive and prognostic value of PIK3CA mutations or PTEN loss in HER2+ metastatic breast cancer patients receiving first-line treatment with paclitaxel alone or in combination with lapatinib.
EGF104535 Study Schema

Key Inclusion
- HER2 FISH+
- No prior treatment for MBC
- Stage IV

Stratification
- ER/PgR+ and/or ER/PgR-
- Any visceral site or nonvisceral only

Randomize

Pac
80 mg/m² IV
3/4 weekly + Lap 1500 mg oral, once daily (n=222)

Treatment Period
(until disease progression, death, unacceptable toxicity, or patient withdrawal)

Survival Follow-Up Phase

Open-Label Extension Phase
Lap monotherapy available to patients following disease progression

Efficacy assessments: every 8 weeks
Safety assessments: every 4 and 8 weeks
Laboratory assessments: weekly

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary endpoints</td>
<td>PFS, ORR, CBR, biomarker assessment, safety</td>
</tr>
</tbody>
</table>
Primary Endpoint: OS (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Lap + Pac (n=222)</th>
<th>Plac + Pac (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died from any cause, n (%)</td>
<td>120 (54)</td>
<td>143 (64)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>27.8 (23.2, 32.2)</td>
<td>20.5 (17.9, 24.3)</td>
</tr>
<tr>
<td>Pike estimator of the HR (95% CI)</td>
<td>0.74 (0.58, 0.94)</td>
<td>0.0124</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; HR=hazard ratio; LR=log-rank.
### Secondary Efficacy Endpoints (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Lap + Pac (n=222)</th>
<th>Plac + Pac (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI), months</td>
<td>9.7 (9.2, 11.1)</td>
<td>6.5 (5.5, 7.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.52 (0.42, 0.64)</td>
<td></td>
</tr>
<tr>
<td>Stratified LR (P) value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>ORR,(^a) n (%)</td>
<td>154 (69)</td>
<td>110 (50)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.30 (1.54, 3.47)</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CBR,(^b) n (%)</td>
<td>166 (75)</td>
<td>124 (56)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.34 (1.54, 3.58)</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Confirmed CR or PR.
\(^b\)Confirmed CR or PR, or SD ≥24 weeks.

Abbreviations: CR=complete response; PR=partial response; SD=stable disease.
PTEN expression was not prognostic in this population, $P > 0.47$
In the PIK3CA wild-type subgroup, treatment with Lap+Pac reduced the risk of progression compared with Pac alone (n=106; HR=0.44; 95% CI=0.28, 0.69; P<0.0001); OS was not significant (P>0.7)
Effect of PTEN Loss on Lapatinib Efficacy

In both PTEN subgroups, patients treated with Lap+Pac had significant improvement in PFS in compared with Pac alone ($P < 0.05$).
Summary and Conclusions

- In a randomized phase III study with prospective tumor sample collection
  - Prevalence of PIK3CA mutations was consistent with other reports (30.1%, reported ~25%)
  - Prevalence of PTEN IHC 0 cases was lower than reported (12.4%, reported ~30%-40%)

- PIK3CA mutation
  - PIK3CA mutations were significantly associated with worse survival in this HER2+ breast cancer population
  - A trend in PFS improvement was observed in the PIK3CA mutation subgroup with the addition of lapatinib

- Loss of PTEN
  - OS was significantly improved in the PTEN loss group with addition of lapatinib
  - PFS was significantly improved in patients treated with Lap+Pac regardless of PTEN status
New Therapies and Combinations
Targeting cancer with a novel anti-HER3 antibody

An anti-HER3 antibody that stabilizes the inactive conformation inhibits both HER2 and ligand driven tumor growth.

Andy Garner

SABCS 2011
HER3 is a key signaling node in HER2+ cancer

- HER3 is activated by ligands such as Neuregulin (NRG)
- HER2 preferentially dimerizes with HER3
- In HER2+ cancer, assembly of HER2/HER3 heterodimers is ligand-independent
- Persistent HER3 signaling is a common mechanism of therapeutic resistance

**Therapeutic Hypothesis**
Targeting ligand-independent HER3 signaling will improve the activity of trastuzumab in HER2+ cancer
Targeting the HER2/HER3 oncogenic signaling complex

Goal: Inhibition of ligand-independent HER3 signaling

Ligand blocking antibodies do not inhibit HER2/HER3 driven growth

![Graph showing growth inhibition](image)

Schoeberl, Canc Res (2010)

Novartis Approach: Target ligand-independent HER3 signaling

**Phage Display (Human)** → Antigens → **Screening**

- HER2 driven Signaling/ Proliferation
- Ligand driven Signaling/ Proliferation

**GNF Hybridoma (Humanization)**
The identification of dual-blocking HER3 antibodies

Ligand-independent signaling/growth

Ligand-dependent signaling/growth

<table>
<thead>
<tr>
<th></th>
<th>HER3 SET $K_D$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human</td>
</tr>
<tr>
<td>$\alpha$-HER3</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Conclusion:
- Family 15 antibodies uniquely target multiple mechanisms of HER3 activation.
Can a HER3 antibody inhibit HER3 signaling in vivo?

Single dose (20mg/kg) pharmacodynamic study

Ligand-independent
(BT474, HER2 amp)

- pHER3
  - Control
  - α-HER3

- pAkt
  - Control
  - α-HER3

Ligand-dependent
(BxPC3)

- pHER3
  - Control
  - α-HER3

- pAkt
  - Control
  - α-HER3

Conclusion:
- α-HER3 inhibits HER2 & NRG driven HER3 signaling in vivo

Saxena, Li, Chen
HER2/ HER3 combinations are efficacious in vivo

**HER2 amplified (BT474/ NSG mice)**
Compromised ADCC

![Graph showing tumor volume over days post implantation](image)

- IgG (20mg/kg, q2d)
- Trastuzumab (10mg/kg, 2qw)
- α-HER3 (20mg/kg, q2d)
- α-HER3/ Trastuzumab

**Conclusions:**
- HER3 antibodies can combine with trastuzumab to improve efficacy in trastuzumab resistant models
α-HER3 mAb:

- Stabilizes the inactive conformation of HER3
- Targets both HER2 & NRG driven HER3 activation
- First anti-HER3 mAb to demonstrate efficacy in HER2 amplified models
- Active in combination with trastuzumab and PI3Ki

α-HER3 mAb exhibits a unique profile and will shortly enter the clinic
AVEREL, a randomized phase III trial to evaluate bevacizumab in combination with trastuzumab + docetaxel as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer

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1Ospedale San Raffaele, Milan, Italy; 2Centre Régionale de Lutte contre le Cancer, Val d'Aurelle, Montpellier, France; 3N N Blokhin Russian Oncology Research Center, Moscow, Russian Federation; 4Fundação Pio XII Hospital de Câncer de Barretos, Barretos, Brazil; 5University Hospital of Udine, Udine, Italy; 6University Hospital Jean Minjoz, Besançon, France; 7Medical Radiological Science Center, Obninsk, Russian Federation; 8Fondazione IRCCS, Istituto Nazionale Tumori, Milan, Italy; 9Gustave Roussy Institute, Villejuif, France; 10Mount Hospital, Perth, Australia; 11Republican Clinical Oncology Dispensary, Ufa, Russian Federation; 12Nottingham University Hospitals NHS Trust, Nottingham, UK; 13The Christie, Manchester, UK; 14III Medizinische Universitätsklinik Salzburg, Salzburg, Austria; 15CHA-Hôpital du Saint Sacrement, Quèbec, Canada; 16F Hoffmann-La Roche Ltd, Basel, Switzerland; 17N N Petrov Research Institute of Oncology, St Petersburg, Russian Federation
**Background**

- Strong preclinical rationale for combining trastuzumab (H) and bevacizumab (BEV):
  - VEGF expression is positively regulated by HER2\(^1,2\)
  - VEGF levels correlate with HER2 overexpression\(^3,4\)
  - H and BEV are synergistic in *in vivo* models\(^5\)
- Single-arm phase II studies of H + BEV (± chemotherapy) in LR/mBC showed encouraging activity\(^6,7\)

LR/mBC = locally recurrent/metastatic breast cancer; VEGF = vascular endothelial growth factor

Study schema

Previously untreated HER2-positive LR/mBC
- Centrally confirmed IHC 3+ or IHC 2+ and FISH/CISH+
- Measurable or evaluable disease
- ECOG PS 0/1
- No CNS metastases

Stratification variables
- Prior (neo)adjuvant taxane (yes vs no [no chemotherapy/relapse <12 months vs ≥12 months since last chemotherapy])
- Adjuvant H (yes vs no)
- ER/PgR status (positive vs negative)
- Measurable disease (yes vs no)

H: 8→6 mg/kg
DOC: 100 mg/m²
both q3w

H: 8→6 mg/kg
DOC: 100 mg/m²
BEV: 15 mg/kg
all q3w

- H and BEV continued to PD or unacceptable toxicity
- DOC given until PD or unacceptable toxicity (planned minimum of 6 cycles)

CISH = chromogenic in situ hybridization; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; PD = progressive disease; PgR = progesterone receptor
Study endpoints

• Primary: Investigator-assessed PFS

• Secondary:
  – Efficacy (OS, ORR [RECIST v1.0], duration of response, time to treatment failure)
  – Safety (NCI CTCAE v3.0)
  – Quality of life (FACT-B)

• Exploratory:
  – IRC-assessed PFS (for US regulatory purposes)
  – Translational research (participation optional; blood and tumor biomarker assessment)

IRC = Independent Review Committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
Investigator-assessed PFS (unstratified\textsuperscript{a})

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>H + DOC (n=208)</th>
<th>H + DOC + BEV (n=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>208</td>
<td>216</td>
</tr>
<tr>
<td>0</td>
<td>216</td>
<td>192</td>
</tr>
<tr>
<td>6</td>
<td>173</td>
<td>134</td>
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<tr>
<td>12</td>
<td>106</td>
<td>82</td>
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<td>18</td>
<td>65</td>
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<td>30</td>
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<td>12</td>
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<tr>
<td>36</td>
<td>10</td>
<td>8</td>
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<tr>
<td>42</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Events, n (%):**
- H + DOC: 154 (74.0)
- H + DOC + BEV: 153 (70.8)

**Median PFS, months (95% CI):**
- H + DOC: 13.7 (11.4–16.3)
- H + DOC + BEV: 16.5 (14.1–19.1)

**HR, unstratified (95% CI):**
- H + DOC: 0.82 (0.65–1.02)
- H + DOC + BEV: 0.82

**Log-rank p-value:** 0.0775

\textsuperscript{a}Primary analysis per protocol
IRC-assessed PFS\textsuperscript{a} (stratified, censored for non-protocol therapy)

<table>
<thead>
<tr>
<th></th>
<th>H + DOC (n=208)</th>
<th>H + DOC + BEV (n=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>114 (54.8)</td>
<td>111 (51.4)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>13.9 (11.2–16.7)</td>
<td>16.8 (14.1–19.5)</td>
</tr>
<tr>
<td>HR, stratified (95% CI)</td>
<td>0.72 (0.54–0.94)</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td></td>
<td>0.0162</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Prespecified in the statistical analysis plan for US regulatory purposes

No. at risk: 208 149 75 39 24 14 7 2 1 0

216 173 101 58 32 15 10 7 2 0
Objective response rates

**Investigator assessed**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient % with PR</th>
<th>Patient % with CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>H + DOC (n=176)</td>
<td>64.2%</td>
<td>5.7%</td>
</tr>
<tr>
<td>H + DOC + BEV (n=183)</td>
<td>68.9%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

4.4% p=0.3492

**IRC assessed**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient % with PR</th>
<th>Patient % with CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>H + DOC (n=176)</td>
<td>65.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>H + DOC + BEV (n=183)</td>
<td>76.5%</td>
<td>10.6%</td>
</tr>
</tbody>
</table>

10.6% p=0.0265

*Patients with measurable disease at baseline*
Exploratory biomarker study

• In HER2-negative LR/mBC (AVADO):
  – High baseline plasma VEGF-A levels were associated with poorer prognosis in the control (DOC monotherapy) arm\(^1\)
  – Patients with high baseline plasma VEGF-A levels derived a more pronounced PFS improvement from BEV in combination with DOC than those with low plasma VEGF-A levels\(^1\)

• In AVEREL, an exploratory analysis of PFS according to baseline plasma VEGF-A levels was conducted

1. Miles et al. SABCS 2010
PFS according to baseline plasma VEGF-A

Plasma VEGF-A | HR (95% CI) | H + DOC + BEV better | H + DOC better
--- | --- | --- | ---
≤ median | 0.83 (0.50–1.36) | | |
> median | 0.70 (0.43–1.14) | | |

H + DOC low VEGF-A (n=45) | H + DOC + BEV low VEGF-A (n=36) | H + DOC high VEGF-A (n=37) | H + DOC + BEV high VEGF-A (n=43)

Time (months) | Estimated probability
--- | ---
0 | 1.0
6 | 0.8
12 | 0.6
18 | 0.4
24 | 0.2
30 | 0.0
36 | 0.0
42 | 0.0
48 | 0.0
54 | 0.0

H + DOC low VEGF-A (n=45): Time to event = 8.5 months
H + DOC high VEGF-A (n=37): Time to event = 13.6 months
H + DOC + BEV low VEGF-A (n=36): Time to event = 16.6 months
H + DOC + BEV high VEGF-A (n=43): Time to event = 16.5 months
Conclusions

• AVEREL demonstrated longer median PFS when BEV was combined with H + DOC in patients with HER2-positive LR/mBC
  – Investigator-assessed PFS (primary endpoint) HR 0.82 (p=0.0775)
  – IRC-assessed PFS HR 0.72 (p=0.0162)
• No difference in OS (immature data)
• No new safety signals were observed
Perspectives

• In AVEREL, exploratory analyses of plasma VEGF-A suggest a potentially predictive effect (greater benefit with high VEGF-A levels), consistent with observations in HER2-negative LR/mBC

  – Global biomarker study GO25632 (MERiDiAN) is planned: BEV + paclitaxel with stratification by plasma VEGF-A level

• The BETH adjuvant trial will provide further data on BEV in patients with HER2-positive breast cancer
A Phase 2, Randomized, Open-label Study of Neratinib (HKI-272) Versus Lapatinib Plus Capecitabine for 2nd/3rd-line Treatment of HER2+ Locally Advanced or Metastatic Breast Cancer

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*This author was employed at Pfizer during the conduct of this study, but has since become employed at another company.
Background

- Neratinib is an orally active, irreversible pan-ErbB receptor tyrosine kinase inhibitor with activity against HER1, -2, and -4

- As a single agent, neratinib showed clinical activity in patients with advanced and metastatic HER2+ breast cancer (BC)
  - In trastuzumab-naive patients, the objective response rate (ORR) was 56% and the median progression-free survival (PFS) was 39.6 weeks\(^1\)
  - In pretreated patients, the ORR was 24%, and the median PFS was 22.3 weeks\(^2\)
  - The most common adverse event was diarrhea

Patients were randomized 1:1 to neratinib or L + C
- Neratinib was administered orally at 240 mg/day continuously
- L 1,250 mg/day was administered orally continuously; C 2,000 mg/m² was administered orally on Days 1 to 14 of each 21-day cycle
Incidences of Diarrhea and PPE: Safety Population

\[ P = 0.002 \]

- **Neratinib**
  - 85% all grades
  - 28% grade 3/4
  - \( n = 116 \)

- **L + C**
  - 68% all grades
  - 10% grade 3/4
  - \( n = 115 \)

\[ P < 0.001 \]

- **Neratinib**
  - 65% all grades
  - 14% grade 3/4
  - \( n = 116 \)

- **L + C**
  - 5% all grades
  - 0% grade 3/4
  - \( n = 115 \)

PPE, palmar-plantar erythrodysesthesia syndrome; L, lapatinib; C, capecitabine.
PFS: ITT Population

![Graph showing the probability of progression-free survival (PFS) over time for two groups: Neratinib and L + C.](image)

- **Neratinib**
  - n: 117
  - Median PFS: 4.5 mo
  - 95% CI: 3.1–5.7 mo
  - P value: 0.231

- **L + C**
  - n: 116
  - Median PFS: 6.8 mo
  - 95% CI: 5.9–8.2 mo

L, lapatinib; C, capecitabine; PFS, progression-free survival; CI, confidence interval.
Overall Survival: ITT Population

![Survival Curve Graph](image)

**Probability of OS (%)**

**Time since randomization (mo)**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median OS</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib</td>
<td>117</td>
<td>19.7 mo</td>
<td>18.2 mo–NE</td>
<td>0.280</td>
</tr>
<tr>
<td>L + C</td>
<td>116</td>
<td>23.6 mo</td>
<td>18.0 mo–NE</td>
<td></td>
</tr>
</tbody>
</table>

L, lapatinib; C, capecitabine; OS, overall survival; CI, confidence interval; NE, not estimable.
Conclusions

- Neratinib did not demonstrate non-inferiority versus L + C in terms of PFS
- The median PFS was numerically, but not statistically, superior in L + C (4.5 mo for neratinib vs 6.8 mo for L + C)
- In addition, the antitumor activity of neratinib monotherapy in heavily pretreated patients with advanced or metastatic HER2+ BC was robust (ORR of 29%) and consistent with results from the preceding single-arm trial

A Phase III, Randomized, Double-Blind, Placebo-Controlled Registration Trial to Evaluate the Efficacy and Safety of Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel in Patients with Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA)

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Introduction

- Trastuzumab-based therapy improves progression-free and overall survival in HER2-positive MBC. However, disease progression still occurs in a majority of patients.

- Pertuzumab is a humanized monoclonal antibody and HER2 dimerization inhibitor that binds HER2 at a different epitope from trastuzumab.

- Phase II trials in patients with HER2-positive breast cancer have shown improved activity, and a good safety profile with pertuzumab-trastuzumab-based therapy.

References:
Pertuzumab and trastuzumab have complementary mechanisms of action

**Pertuzumab**
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

**Trastuzumab**
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

ADCC, antibody-dependent cell-mediated cytotoxicity; ECD, extracellular domain
Study design

Patients with HER2-positive MBC centrally confirmed (N = 808)

Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

Study dosing q3w:
- Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
- Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
- Docetaxel: 75 mg/m², escalating to 100 mg/m² if tolerated

* <6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

MBC, metastatic breast cancer; PD, progressive disease
Key patient eligibility criteria

- Centrally confirmed HER2-positive (IHC 3+ and/or FISH-positive; ratio ≥2.0) locally recurrent, unresectable, or metastatic breast cancer
- Measurable and/or non-measurable disease
- No more than one hormonal regimen for MBC prior to randomization
- Prior (neo)adjuvant systemic breast cancer chemotherapy including trastuzumab and/or taxanes allowed if followed by a disease-free interval of ≥12 months
- LVEF ≥50% at baseline; no history of CHF or LVEF decline to <50% during or after prior trastuzumab therapy

CHF, congestive heart failure; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer
## Prior therapy for breast cancer

<table>
<thead>
<tr>
<th>Prior (neo)adjuvant chemotherapy, n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n = 406)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>192 (47.3)</td>
<td>184 (45.8)</td>
</tr>
<tr>
<td>No</td>
<td>214 (52.7)</td>
<td>218 (54.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Components of (neo)adjuvant therapy*, n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n = 406)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline</td>
<td>164 (40.4)</td>
<td>150 (37.3)</td>
</tr>
<tr>
<td>Hormones</td>
<td>97 (23.9)</td>
<td>106 (26.4)</td>
</tr>
<tr>
<td>Taxane</td>
<td>94 (23.2)</td>
<td>91 (22.6)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>41 (10.1)</td>
<td>47 (11.7)</td>
</tr>
</tbody>
</table>

* Numbers add up to more than 100% because patients could have received more than one therapy
Efficacy results
Primary endpoint: Independently assessed PFS

\[ n = 433 \text{ PFS events} \]

\[ \text{Ptz} + T + D: \text{median 18.5 months} \]
\[ \Delta = 6.1 \text{ months} \]
\[ \text{Pla} + T + D: \text{median 12.4 months} \]

\[ \text{HR} = 0.62 \]
\[ 95\% \text{ CI 0.51–0.75} \]
\[ p < 0.0001 \]

Progression-free survival (%)

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Stratified by prior treatment status and region
Independently and investigator-assessed PFS

![Graph showing progression-free survival (PFS) for Pertuzumab + T + D vs Placebo + T + D.]

**Independent assessment**
- HR = 0.62
- 95% CI, 0.51–0.75; p<0.0001

**Investigator assessment**
- HR = 0.65
- 95% CI, 0.54–0.78; p<0.0001

D, docetaxel; PFS, progression-free survival; T, trastuzumab
Independently assessed PFS in predefined subgroups

ER, estrogen receptor; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; PgR, progesterone receptor; PFS, progression-free survival.
## Independently assessed PFS by prior trastuzumab therapy in patients with (neo)adjuvant therapy

<table>
<thead>
<tr>
<th>Prior (neo)adjuvant trastuzumab treatment (n = 88)</th>
<th>Placebo + trastuzumab + docetaxel Median PFS, months</th>
<th>Pertuzumab + trastuzumab + docetaxel Median PFS, months</th>
<th>Hazard ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior (neo)adjuvant trastuzumab treatment</td>
<td>10.4</td>
<td>16.9</td>
<td>0.62 (0.35–1.07)</td>
</tr>
<tr>
<td>No prior (neo)adjuvant trastuzumab treatment</td>
<td>12.6</td>
<td>21.6</td>
<td>0.60 (0.43–0.83)</td>
</tr>
</tbody>
</table>

PFS, progression-free survival
Independently reviewed objective response
*In patients with measurable disease at baseline*

<table>
<thead>
<tr>
<th></th>
<th>Placebo + trastuzumab + docetaxel (n = 336)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, n (%)</td>
<td>233 (69.3)</td>
<td>275 (80.2)</td>
</tr>
<tr>
<td>Complete response rate, n (%)</td>
<td>14 (4.2)</td>
<td>19 (5.5)</td>
</tr>
<tr>
<td>Partial response rate, n (%)</td>
<td>219 (65.2)</td>
<td>256 (74.6)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>70 (20.8)</td>
<td>50 (14.6)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>28 (8.3)</td>
<td>13 (3.8)</td>
</tr>
<tr>
<td>Unable to assess or no assessment, n (%)</td>
<td>5 (1.5)</td>
<td>5 (1.5)</td>
</tr>
</tbody>
</table>

* The statistical test result is deemed exploratory
Overall survival: Predefined interim analysis

Median follow-up: 19.3 months, n = 165 OS events

HR = 0.64*
95% CI 0.47–0.88
p = 0.0053*

* The interim OS analysis did not cross the pre-specified O'Brien-Fleming stopping boundary (HR ≤0.603; p ≤0.0012)

D, docetaxel; OS, overall survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab
Safety results
## Cardiac tolerability

<table>
<thead>
<tr>
<th></th>
<th>Placebo + trastuzumab + docetaxel (n = 397)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic LVSD*</td>
<td>1.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Independently adjudicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic LVSD*</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Fall in LVEF to &lt;50% and by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 percentage points from</td>
<td>6.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LVSD was defined as NYHA class III/IV

LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction
## Adverse events (all grades) ≥25% incidence or ≥5% difference between arms

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n = 397)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n = 407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>184 (46.3)</td>
<td>272 (66.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>240 (60.5)</td>
<td>248 (60.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>197 (49.6)</td>
<td>215 (52.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>165 (41.6)</td>
<td>172 (42.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>146 (36.8)</td>
<td>153 (37.6)</td>
</tr>
<tr>
<td>Rash</td>
<td>96 (24.2)</td>
<td>137 (33.7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>105 (26.4)</td>
<td>119 (29.2)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>79 (19.9)</td>
<td>113 (27.8)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>120 (30.2)</td>
<td>106 (26.0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>119 (30.0)</td>
<td>94 (23.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>99 (24.9)</td>
<td>61 (15.0)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>30 (7.6)</td>
<td>56 (13.8)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>17 (4.3)</td>
<td>43 (10.6)</td>
</tr>
</tbody>
</table>
Summary and conclusions

• CLEOPATRA met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in PFS (HR = 0.62) in patients with HER2-positive MBC
  – Median PFS increased by 6.1 months from 12.4 to 18.5 months
  – The PFS improvement was consistent across subgroups and supported by the secondary endpoints of ORR and OS (immature)

• The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin
  – These adverse events were primarily grades 1–2, manageable, and occurred during docetaxel therapy
  – There was no increase in cardiac adverse events or LVSD

• This new regimen may be practice-changing in HER2-positive first-line MBC
Take Home Messages

- New predictive markers of trastuzumab and lapatinib response and resistance have been defined - PI3K mutations and PTEN loss.

- New therapies should become rapidly available
  - Ab to HER3
  - Neratinib
  - Pertuzumab
  - DM-1