Final overall survival (OS) analysis from the CLEOPATRA study of first-line (1L) pertuzumab (Ptz), trastuzumab (T), and docetaxel (D) in patients with HER2-positive metastatic breast cancer (MBC)

Sandra M. Swain, Sung-Bae Kim, Javier Cortés, Jungsil Ro, Vladimir Semiglazov, Mario Campone, Eva Ciruelos, Jean-Marc Ferrero, Andreas Schneeweiss, Sarah Heeson, Emma Clark, Graham Ross, Mark C. Benyunes, and José Baselga

1Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC, USA; 2Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; 3Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain; 4Center for Breast Cancer, National Cancer Center, Goyang, South Korea; 5NN Petrov Research Institute of Oncology, St Petersburg, Russia; 6Centre René Gauducheau, Saint-Herblain (Nantes), France; 712 de Octubre University Hospital, Medical Oncology Department, Madrid, Spain; 8Centre Antoine Lacassagne, Nice, France; 9National Center for Tumor Diseases, University Hospital, Heidelberg, Germany; 10Roche Products Limited, Welwyn, United Kingdom; 11Genentech, South San Francisco, CA, USA; 12Memorial Sloan-Kettering Cancer Center, Memorial Hospital, New York, NY, USA
Disclosures

• SMS: Consultant/advisory relationship with Genentech/Roche; research funding from Genentech/Roche, Pfizer (Puma), Sanofi-Aventis, and Bristol-Myers Squibb
• S-BK: Research funding from Novartis
• JC: Consultant/advisory relationship with Celgene and Roche; honoraria from Novartis, Celgene, Roche, and Eisai
• JR: None
• VS: None
• MC: Consultant/advisory relationship with Novartis and Servier
• EvC: None
• J-MF: Consultant/advisory relationship with Sanofi; honoraria from Roche and Novartis
• AS: Consultant/advisory relationship with Roche, Celgene, and Medac; honoraria from Roche, Celgene, Eisai, AstraZeneca, GlaxoSmithKline, Novartis, and Pfizer; research funding from Roche and Celgene
• SH: Roche employee; owns Roche shares
• EmC: Roche employee; owns AstraZeneca shares
• GR: Roche employee; owns Roche shares
• MCB: Genentech employee
• JB: Consultant/advisory relationship with Roche
• This study was funded by F. Hoffmann-La Roche Ltd (Basel, Switzerland) and Genentech, Inc. (South San Francisco, CA, USA)
CLEOPATRA Study Design

HER2-positive MBC centrally confirmed (N = 808)

1:1

n = 406

Placebo + trastuzumab

Docetaxel* ≥ 6 cycles

PD

n = 402

Pertuzumab + trastuzumab

Docetaxel* ≥ 6 cycles

PD

- Randomization stratified by geographic region and neo/adjuvant chemotherapy
- Study dosing q3w:
  - Pertuzumab/placebo: 840 mg loading → 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance
  - Docetaxel: 75 mg/m² → 100 mg/m² escalation if tolerated

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

HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PD, progressive disease.

Eligibility Criteria

• HER2-positive (centrally confirmed)
• Metastatic, locally recurrent, or unresectable BC
• Measurable or non-measurable disease
• ≤ 1 hormonal regimen for MBC prior to randomization
• Disease-free interval ≥ 12 months since prior neo/adjuvant treatment
• LVEF ≥ 50% at baseline

Statistical Considerations

• Primary endpoint
  – Independently assessed PFS
    • At 381 events
• Secondary endpoints
  – Investigator-assessed PFS
  – Objective response rate
  – Safety
  – OS
    • Final analysis planned at 385 deaths, with two interim analyses

OS, overall survival; PFS, progression-free survival.

Efficacy Analysis Milestones

Δ 6.1 months
HR 0.62 (p < 0.0001)

PFS
primary analysis

May 2011

HR, hazard ratio.

Efficacy Analysis Milestones

- PFS primary analysis
  - Δ 6.1 months
  - HR 0.62 (p < 0.0001)

- OS 1st interim analysis
  - HR 0.64 (p = 0.005)

Efficacy Analysis Milestones

- PFS primary analysis
  - Δ 6.1 months
  - HR 0.62 (p < 0.0001)

- OS 1\textsuperscript{st} interim analysis
  - HR 0.64 (p = 0.005)

- OS 2\textsuperscript{nd} interim analysis
  - HR 0.66 (p = 0.0008)*

* Crossed the prespecified O’Brien-Fleming stopping boundary (HR ≤ 0.739; p ≤ 0.0138)

Efficacy Analysis Milestones

- **May 2011**: PFS primary analysis
- **Δ 6.1 months**
  - HR 0.64 (p = 0.005)
- **May 2012**: OS 1st interim analysis
  - HR 0.64 (p = 0.005)
  - Δ 6.1 months
  - HR 0.62 (p < 0.0001)
  - HR 0.66 (p = 0.0008)*
  - Patients still on placebo offered crossover to pertuzumab

* Indicates significance level.
Efficacy Analysis Milestones

- **PFS primary analysis**
  - Δ 6.1 months
  - HR 0.62 (p < 0.0001)

- **OS 1st interim analysis**
  - HR 0.64 (p = 0.005)

- **OS 2nd interim analysis**
  - HR 0.66 (p = 0.0008)*

- **Patients still on placebo offered crossover to pertuzumab**

- **OS final analysis**
  - May 2011
  - May 2012
  - July 2012
  - Feb 2014
## Baseline Characteristics

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 406)</th>
<th>Pertuzumab + T + D (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>54.0 (27–89)</td>
<td>54.0 (22–82)</td>
</tr>
<tr>
<td><strong>Region, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>128 (31.5)</td>
<td>125 (31.1)</td>
</tr>
<tr>
<td>Europe</td>
<td>152 (37.4)</td>
<td>154 (38.3)</td>
</tr>
<tr>
<td>North America</td>
<td>68 (16.7)</td>
<td>67 (16.7)</td>
</tr>
<tr>
<td>South America</td>
<td>58 (14.3)</td>
<td>56 (13.9)</td>
</tr>
<tr>
<td><strong>Hormone receptor status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER- and/or PgR-positive</td>
<td>199 (49.0)</td>
<td>189 (47.0)</td>
</tr>
<tr>
<td>ER- and PgR-negative</td>
<td>196 (48.3)</td>
<td>212 (52.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (2.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Disease type at screening, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvisceral</td>
<td>90 (22.2)</td>
<td>88 (21.9)</td>
</tr>
<tr>
<td>Visceral</td>
<td>316 (77.8)</td>
<td>314 (78.1)</td>
</tr>
</tbody>
</table>

D, docetaxel; ER, estrogen receptor; PgR, progesterone receptor; T, trastuzumab.

## Prior Therapy for Breast Cancer

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 406)</th>
<th>Pertuzumab + T + D (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior neo/adjuvant chemotherapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><em><em>Components of neo/adjuvant therapy</em>, n (%)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>164 (40.4)</td>
<td>150 (37.3)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>94 (23.2)</td>
<td>91 (22.6)</td>
</tr>
<tr>
<td>Hormonal treatments</td>
<td>97 (23.9)</td>
<td>106 (26.4)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>41 (10.1)</td>
<td>47 (11.7)</td>
</tr>
</tbody>
</table>

* Patients could have received more than one therapy.
Final OS Analysis

Median follow-up 50 months (range 0–70 months)

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

CI, confidence interval; Pla, placebo; Ptz, pertuzumab.
Final OS Analysis

Median follow-up 50 months (range 0–70 months)

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

40.8 months
Δ 15.7 months
56.5 months

n at risk
Ptz + T + D  402  371  318  268  226  104  28  1
Pla + T + D  406  350  289  230  179  91  23  0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.
OS: Predefined Subgroups

ITT population. Nonstratified.
Updated PFS

*Investigator-Assessed*

![Graph showing PFS results](image)

- **Ptz + T + D**: median 18.7 months
- **Pla + T + D**: median 12.4 months

Δ 6.3 months

HR 0.68
95% CI = 0.58, 0.80
p < 0.0001

**n at risk**

<table>
<thead>
<tr>
<th></th>
<th>Ptz + T + D</th>
<th>Pla + T + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>402</td>
<td>284</td>
<td>179</td>
</tr>
<tr>
<td>121</td>
<td>87</td>
<td>37</td>
</tr>
<tr>
<td>87</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>37</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
**Exposure to Study Treatment**

<table>
<thead>
<tr>
<th>Safety population*</th>
<th>Placebo + T + D (n = 396)</th>
<th>Pertuzumab + T + D (n = 408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time on study treatment, months (range)</td>
<td>11.4 (0.1–66.3)</td>
<td>17.4 (0.1–67.7)</td>
</tr>
<tr>
<td>Median number of docetaxel cycles (range)</td>
<td>8 (1–42)</td>
<td>8 (1–52)</td>
</tr>
</tbody>
</table>

*All patients who received any amount of study medication (pertuzumab/placebo, T, and/or D).
Adverse Events (All Grades) with ≥ 25% Incidence or ≥ 5% Difference between Groups Overall

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>60.6</td>
<td>60.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48.7</td>
<td>68.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50.0</td>
<td>53.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>42.4</td>
<td>44.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.4</td>
<td>38.0</td>
</tr>
<tr>
<td>Rash</td>
<td>24.0</td>
<td>37.5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>30.8</td>
<td>27.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26.8</td>
<td>29.7</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24.5</td>
<td>26.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>25.0</td>
<td>24.3</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.9</td>
<td>27.2</td>
</tr>
<tr>
<td>Headache</td>
<td>19.2</td>
<td>25.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>25.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14.4</td>
<td>20.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10.1</td>
<td>17.6</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5.1</td>
<td>10.3</td>
</tr>
</tbody>
</table>
**Grade ≥ 3 Adverse Events**

*Incidence ≥ 5%*

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>46.2</td>
<td>49.0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.1</td>
<td>9.3</td>
</tr>
</tbody>
</table>

- No cumulative toxicities
Cardiac Safety

- One new sLVD event in the pertuzumab group after 40 months (resolved)
- LVEF declines reversed in 88% of pertuzumab patients

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>sLVD</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>LVEF decline to &lt; 50% and by ≥ 10% points from baseline*</td>
<td>7.4</td>
<td>6.1</td>
</tr>
</tbody>
</table>

* In patients with post-baseline assessment; n = 378 in the placebo group and 394 in the pertuzumab group.

sLVD, symptomatic left ventricular dysfunction.
## Causes of Death

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>49.5</td>
<td>36.8</td>
</tr>
<tr>
<td>Febrile neutropenia or infection</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>3.8</td>
<td>2.9</td>
</tr>
</tbody>
</table>
## Treatment after Study Discontinuation

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 369 withdrawn), %</th>
<th>Pertuzumab + T + D (n = 335 withdrawn), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>78.9</td>
<td>77.0</td>
</tr>
<tr>
<td>Any HER2-targeted treatment</td>
<td>n = 291</td>
<td>n = 258</td>
</tr>
<tr>
<td>Any</td>
<td>71.5</td>
<td>72.9</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>41.6</td>
<td>45.3</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>48.8</td>
<td>48.1</td>
</tr>
<tr>
<td>Trastuzumab emtansine</td>
<td>11.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>58.4</td>
<td>55.0</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>30.2</td>
<td>26.0</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>19.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>16.8</td>
<td>15.9</td>
</tr>
<tr>
<td>Taxanes</td>
<td>19.2</td>
<td>15.1</td>
</tr>
<tr>
<td>Hormonal treatments</td>
<td>19.2</td>
<td>26.7</td>
</tr>
</tbody>
</table>
CLEOPATRA Conclusions

• The addition of pertuzumab to standard 1L therapy significantly improved median OS by **15.7 months**
  – Benefit consistent across subgroups

• Investigator-assessed PFS benefit maintained

• No new safety concerns
  – Long-term cardiac safety maintained
CLEOPATRA Conclusions

• The addition of pertuzumab to standard 1L therapy significantly improved median OS by **15.7 months**
  - Benefit consistent across subgroups

• Investigator-assessed PFS benefit maintained

• No new safety concerns
  - Long-term cardiac safety maintained

The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC
Thanks

To all the patients who participated in the trial, and their families

To the investigators, clinicians, and research staff at the 204 centers in 25 countries
Acknowledgments

Argentina
María Alejandra Bártoli, María Inés Bianconi, Mauricio Kotliar, Juan
Angel Lacava, Mario Matwiejk, Paola Edith Price, Mirta Varela

Brazil
Jurandyr Andrade, Rodrigo Araujo, Sérgio Azevedo, Eduardo Cortes,
Eduardo Costa e Silva, Daniel Cubero, Gilson Delgado, María del Pilar
Diz, Brigitte Eyll, Fabio Franke, Roberto Hegg, Gustavo Ismael, David
Jendiropa, José Luiz Pedrini, Rodrigo Pereira, Hélio Pinczowski,
Paula Tokunaga, Célia Tosello

Canada
Christine Brezden-Masley

Central
Targos Molecular Pathology GmbH (Kassel, Germany),
laboratories
Roche Translational Research Sciences (Basel, Switzerland)

China
Ying Cheng, Xuenong Ouyang, Zhenzhou Shen, Xiaojia Wang, Liwei
Wang, Tsz Kok Yau, Winnie Yeo

Costa Rica
Douglas Otero

Croatia
Zeljko Soldic, Damir Vrbanec

Ecuador
Tannia Soria

Finland
Pirkko Kellokumpu-Lehtinen, Seppo Pyrhönen

France
Mario Campone, Bruno Coudert, Jean-Marc Ferrero, Frank Priou

Germany
Bahriye Aktas, Walter Aulitzky, Michael Clemens, Eva-Maria Grischke,
UK
Maik Hauschild, Marianne Just, Andreas Kirsch, Sherko Kümmel,
Christoph Maintz, Alexander Marmé, Volkmar Müller, Marcus Schmidt,
Andreas Schneeweiß, Claudia Schumacher, Christoph Thomssen,
Birgitta Wesenberg

Guatemala
Hugo Castro-Salguero, Cesar Hernandez Monroy, Luis Miguel Zetina-
Toache

Italy
Dino Amadori, Catia Angioli, Laura Biganzoli, Saverio Cinieri, Teresa
Gamucci, Stefano Iacobelli, Luciano Latini, Filippo Montemurro, Edda
Simoncini

Japan
Kenjiro Aogi, Hirofumi Fujii, Jun Horiguchi, Kenichi Inoue, Yoshinori
Ito, Hiroji Iwata, Masahiro Kashiwaba, Norio Kohno, Katsumasa Kuroi,
Norikazu Masuda, Kazuhiko Nakagami, Takahiro Nakayama, Reiki
Nishimura, Haruki Ogata, Yoshiaki Rai, Shigezira Saji, Yasutsuna
Sasaki, Nobuaki Sato, Ken Shimada, Koji Takeda, Yuuta Tokuda,
Koichiro Tsugawa, Takayuki Ueno, Junichiro Watanabe

Korea
Young-Hyuck Im, Seock-Ah Im, Sung-Bae Kim, Yong Wha Moon,
Jungsil Ro, Joo Hyuk Sohn

Latvia
Elza Grincukā, Iveta Kudaba, Gunta Purkalne

Macedonia
Liljana Kostovska-Manevo, Petar Stefanovski

Mexico
Gloria Martínez, Gabriel Teles

Philippines
Priscilla Caguioa, Valorie Chan, Dennis Tudtud

Poland
Małgorzata Foszczyńska-Kloda, Tadeusz Pienkowski, Wojciech
Polkowsi, Elżbieta Starosławski, Piotr Tomczak

Russia
Vera Gorbunova, Evgeny Gotovkin, Igor Kiselev, Mikhail Kopp, Mikhail
Lichinitser, Vladimir Merkulov, Laslo Roman, Vladimir Semiglazov,
Vadim Shirinkin

Singapore
Soo Chin Lee, Zee Wan Wong

Spain
Emilio Alba Conejo, Norberto Batista, Lourdes Calvo, Eva Ciruelos,
Javier Cortés, Miguel Gil i Gil, Antonio González, Javier Hernedo
Muguiro, Serafin Morales, Nuria Ribelles Entrena, Susana de la Cruz
Sánchez, Pedro Sanchez Roxira

Thailand
Wichit Arpornwirat, Tithiya Dejheavapor, Jedzada Maneechakajorn,
Vichien Srimuninnimit, Virote Siiranpong, Patrapim Sunpawarawong
Rizvana Ahmad, Laura Assersson, Ion Boiangiu, Neville Davidson,
Chris Gallagher, Alison Jones, David Miles, Susan O’Reilly, Anne
Robinson, Duncan Wheatley, Daniel Clyde (Health Interactions,
Manchester, UK) provided third-party writing assistance, with funding
from F. Hoffmann-La Roche Ltd.

US
Richy Agajanian, Jess F. Armor, M. William Audeh, José Baselga,
Ahmed Soliman Behairy, Ruemu Birhiray, Ronald Blachy, Kimberly
Blackwell, Rita Blanchard, Paulette Blanchet, Barbara J. Bowers,
Adam Brufsky, Leanne Sterbank Buddle, Robert R. Carroll, Veena
Charu, Shaker Dakhil, Brooke Daniel, John Allan Ellerton, Louis
Fehrenbacher, Patrick Flynn, Sandra Franco, Nathan Green, Vincent
Hansen, Jeffrey Hargis, Carolyn Hendricks, Robert C. Hermann, André
Kallab, Mark Karwal, Giraldo Kato, Peter Kaufman, Peter S. Kennedy,
Paula Klein, Eric P. Lester, Christopher F. Lobo, Richard A.
Michaelson, James A. Neidhart, Jeffrey D. Neidhart, An D. Nguyen,
Timothy O’Rourke, Ravi Patel, Taral Patel, Alessandra Perez, Carol E.
Peterson, Jonathan D. Pollikoff, Sue J. Prill, Robert C. Quackenbush,
Robert Robles, Gladys Rodriguez, Francis Senecal, Priyanka Sharma,
Raymond Smith, Darcy Spicer, Sandra M. Swain, Julie A. Taguchi,
Charles L. Vogel, David M. Waterhouse, Sanjay Yadav, Denise Aysel
Yardley