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)

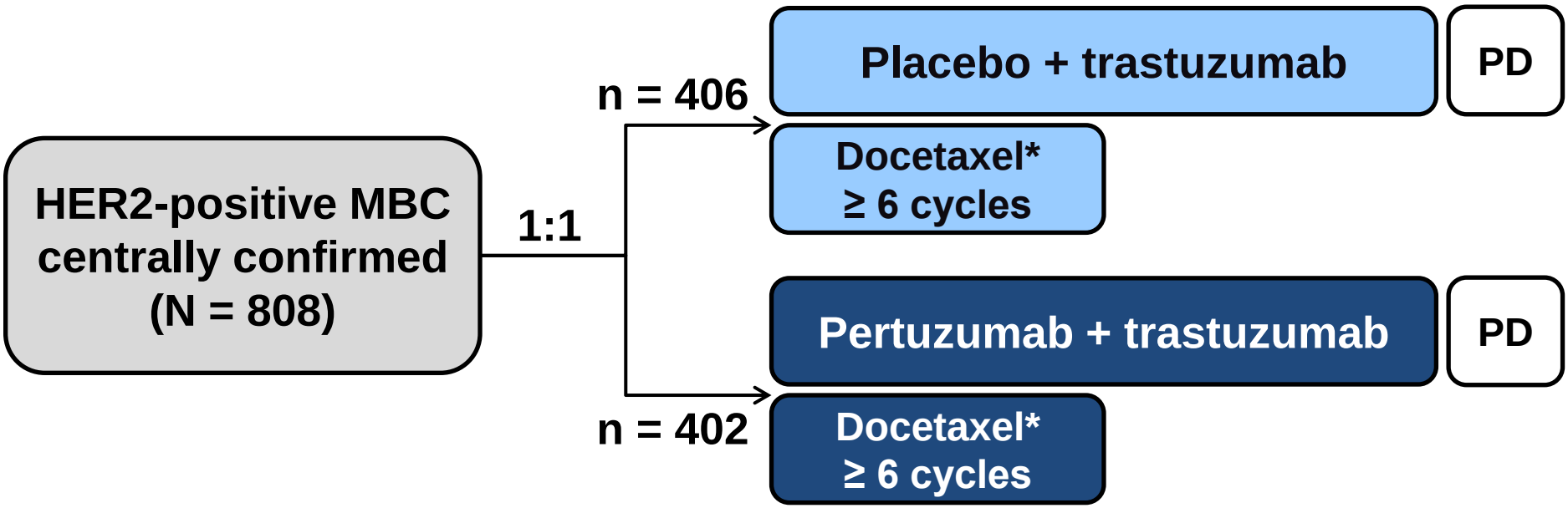
Sandra M. Swain,[1] Sung-Bae Kim,[2] Javier Cortés,[3] Jungsil Ro,[4] Vladimir Semiglazov,[5] Mario Campone,[6] Eva Ciruelos,[7] Jean-Marc Ferrero,[8] Andreas Schneeweiss,[9] Sarah Heeson,[10] Emma Clark,[10] Graham Ross,[10] Mark C. Benyunes,[11] and José Baselga[12]

[1]Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC, USA; [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Center for Breast Cancer, National Cancer Center, Goyang, South Korea; [5]NN Petrov Research Institute of Oncology, St Petersburg, Russia; [6]Centre René Gauducheau, Saint-Herblain (Nantes), France; [7]12 de Octubre University Hospital, Medical Oncology Department, Madrid, Spain; [8]Centre Antoine Lacassagne, Nice, France; [9]National Center for Tumor Diseases, University Hospital, Heidelberg, Germany; [10]Roche Products Limited, Welwyn, United Kingdom; [11]Genentech, South San Francisco, CA, USA; [12]Memorial 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



- **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/m^2 → 100 mg/m^2 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.

Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

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**

LVEF, left ventricular ejection fraction.

Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

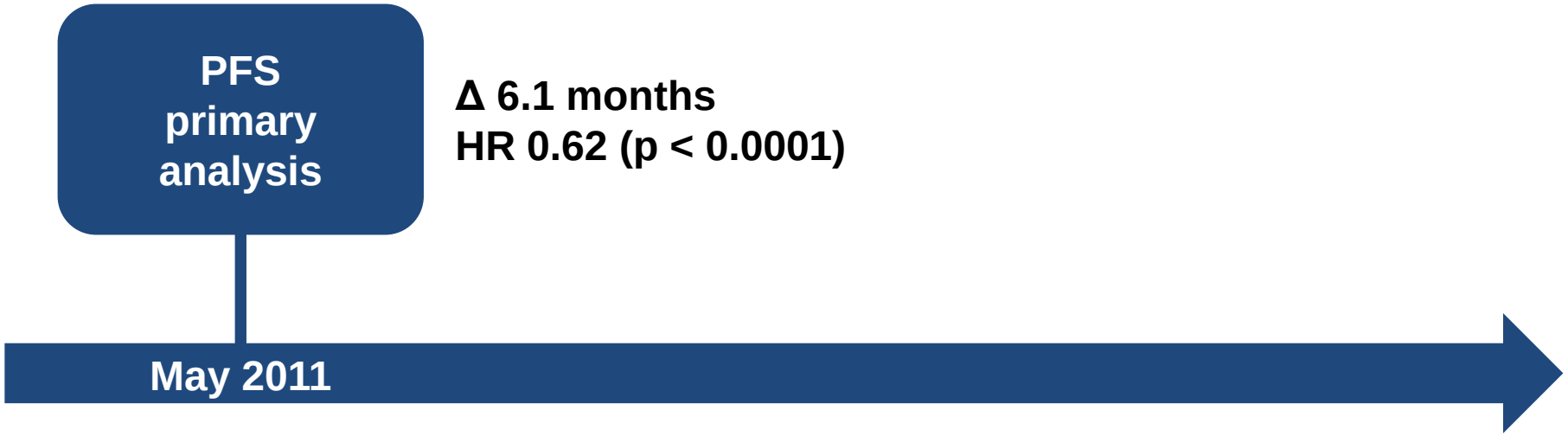
Statistical Considerations

- **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.

Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119;
Swain SM, *et al*. *Lancet Oncol* 2013; **14:**461–471.

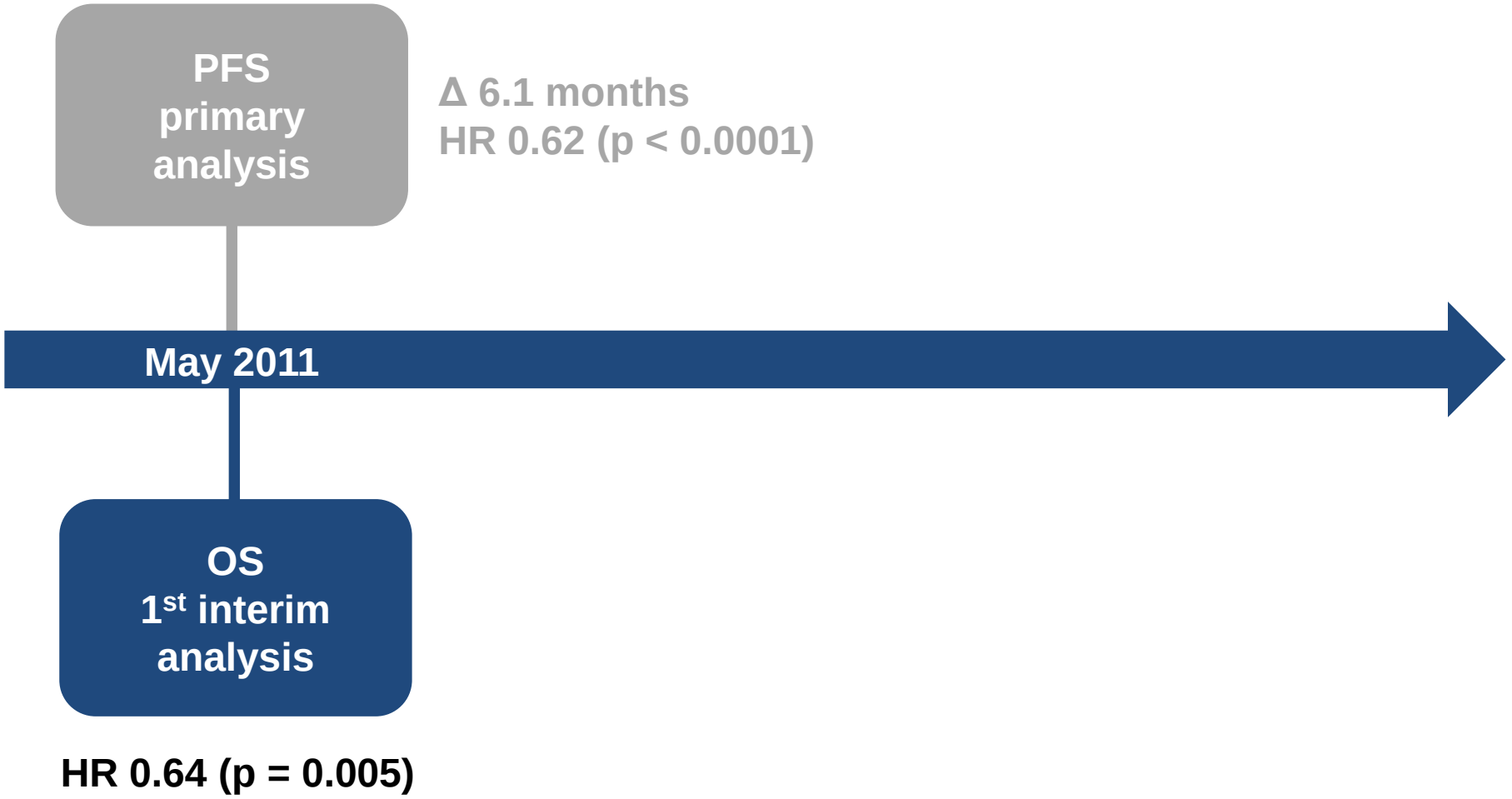
Efficacy Analysis Milestones



HR, hazard ratio.

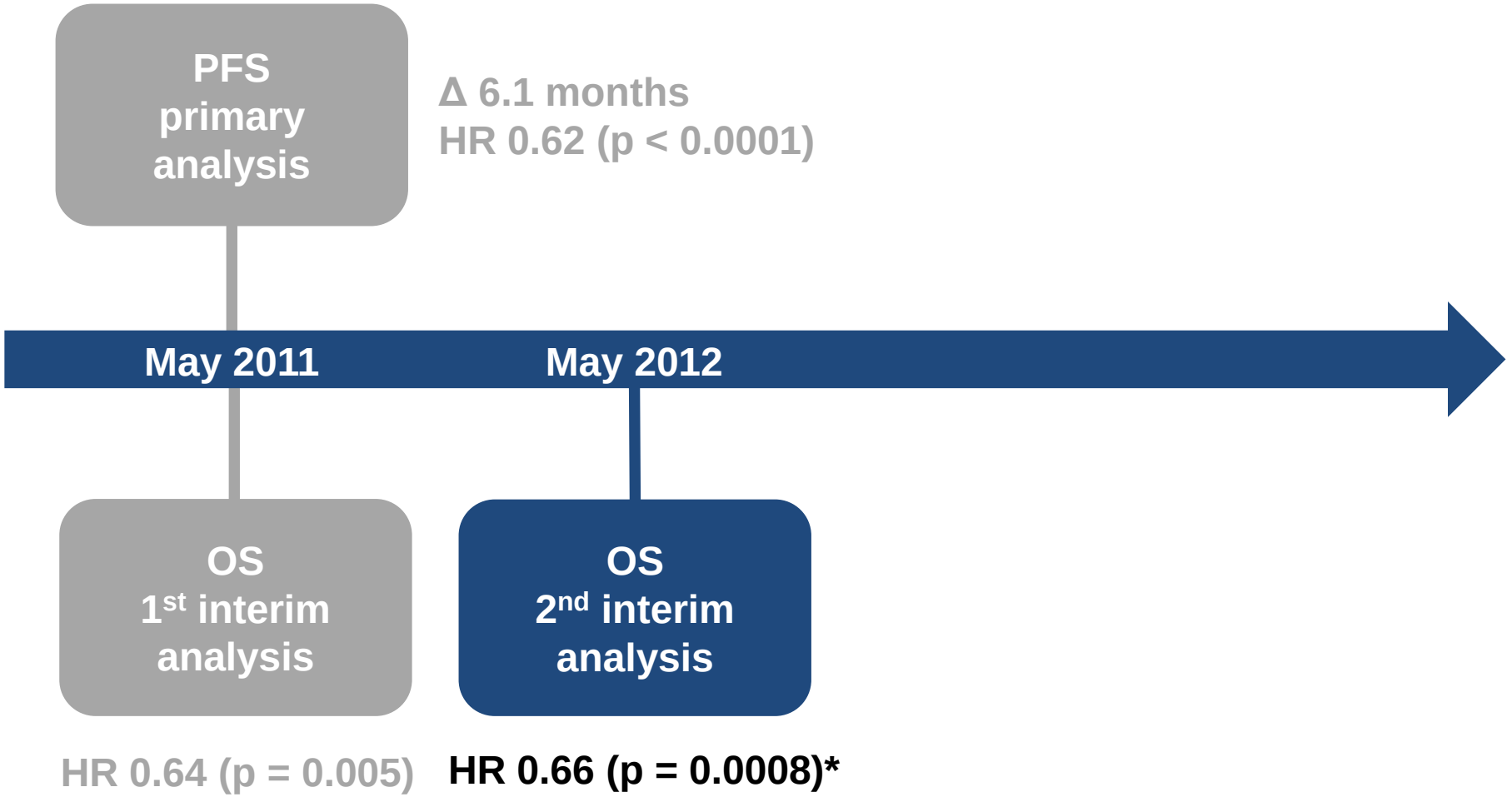
Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

Efficacy Analysis Milestones



Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

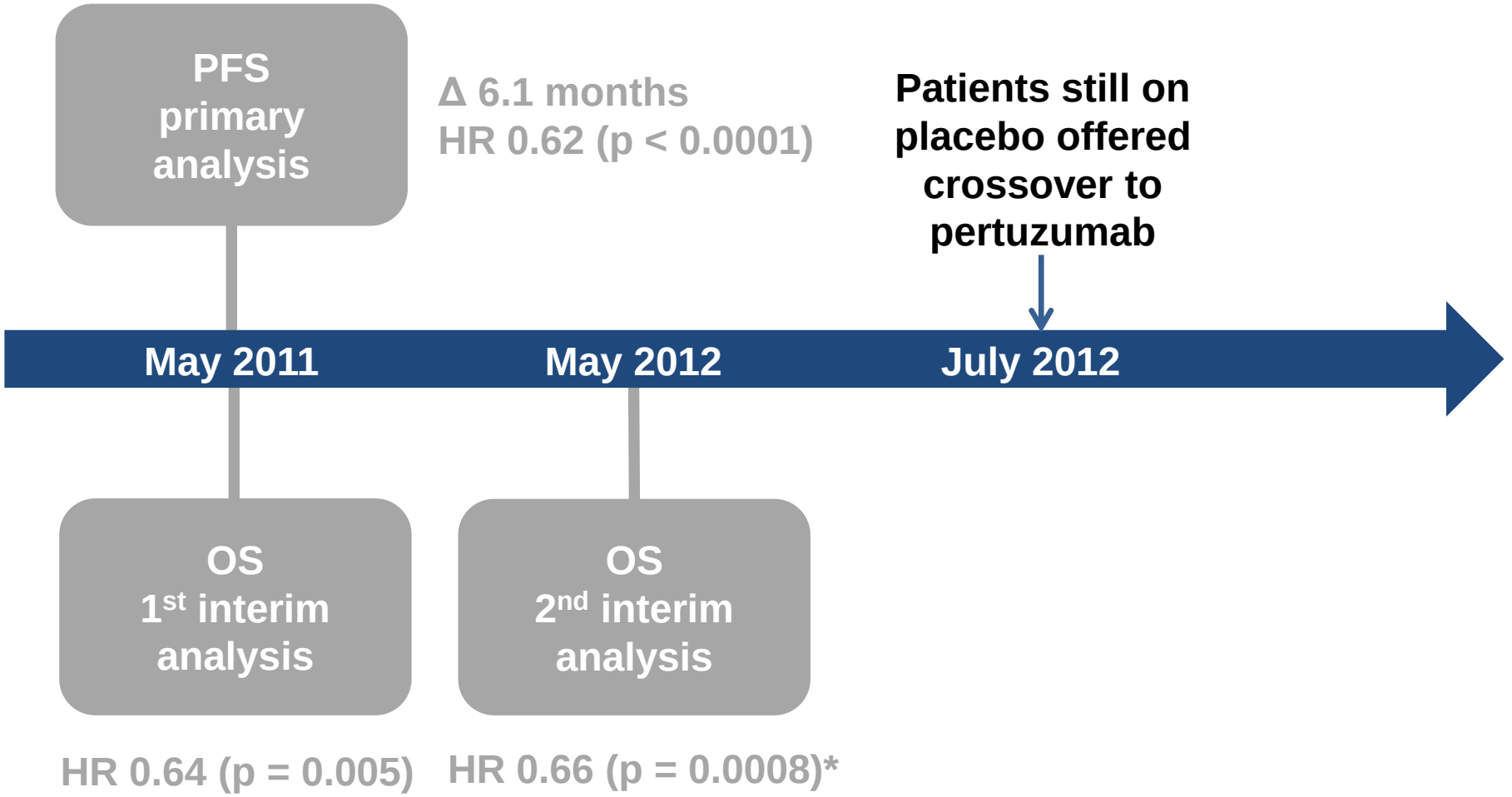
Efficacy Analysis Milestones



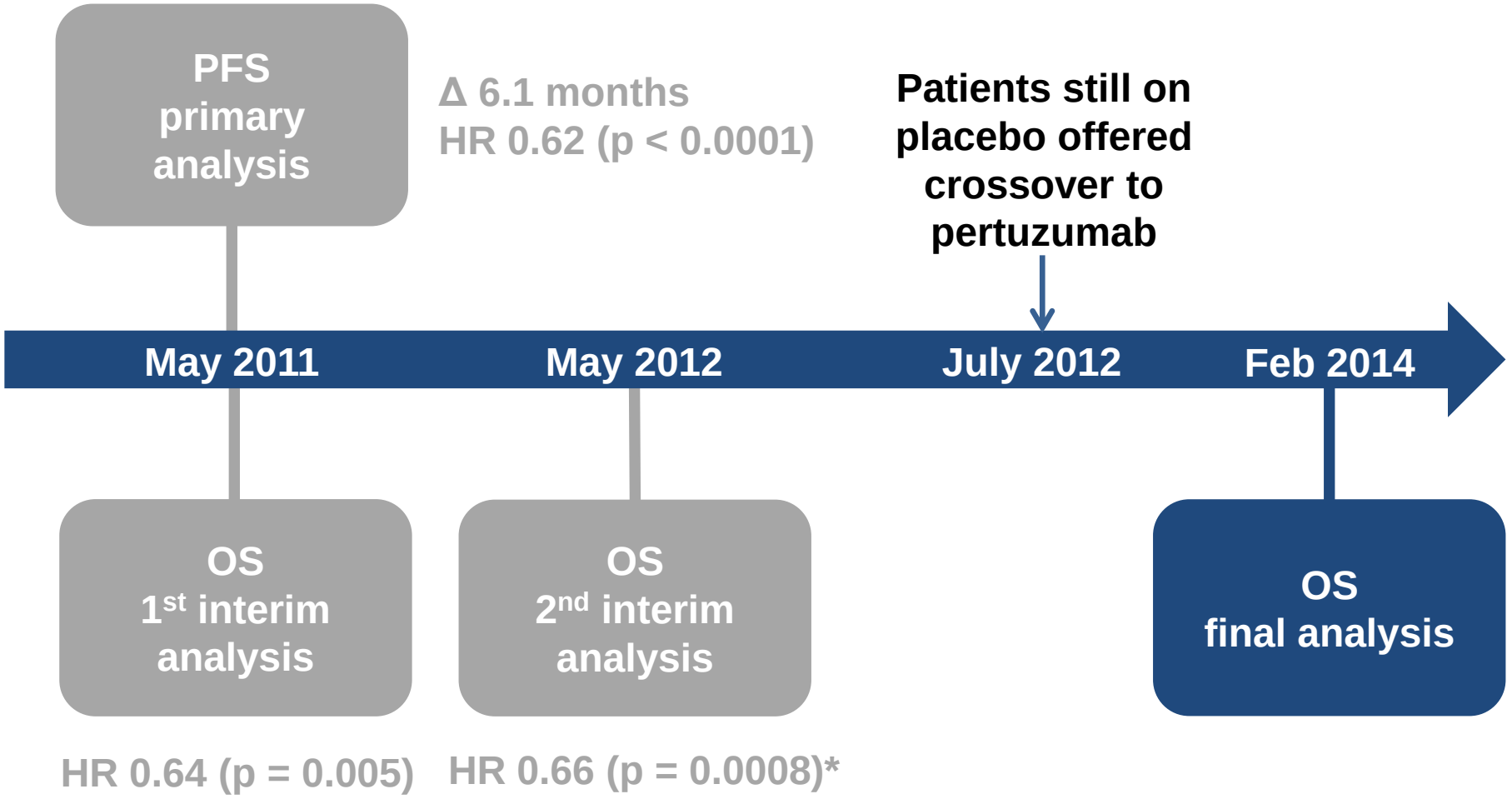
*** Crossed the prespecified O'Brien-Fleming stopping boundary (HR ≤ 0.739; p ≤ 0.0138)**

Swain SM, *et al*. *Lancet Oncol* 2013; **14:**461–471.

Efficacy Analysis Milestones



Efficacy Analysis Milestones



Baseline Characteristics

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

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

Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

Prior Therapy for Breast Cancer

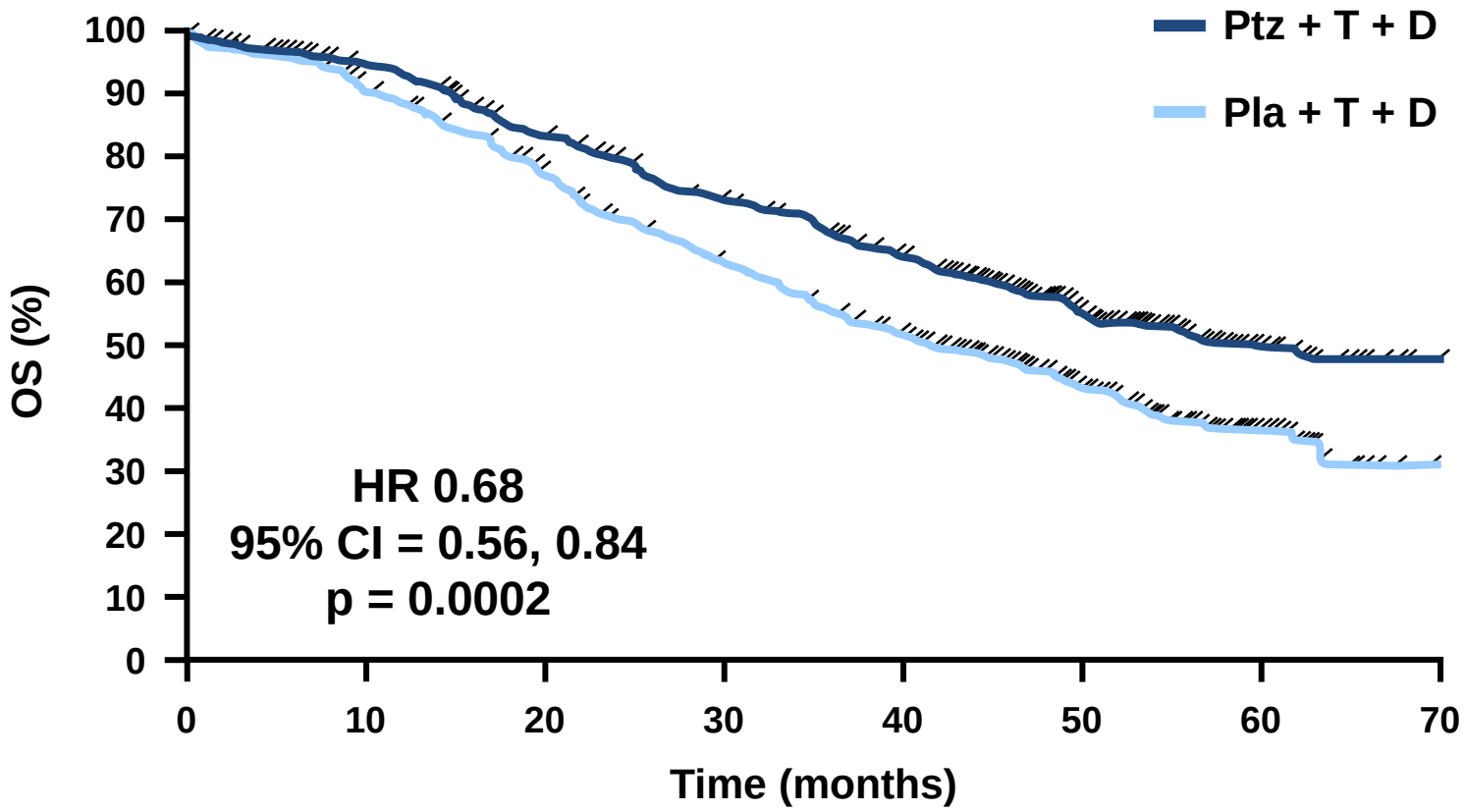
ITT population	Placebo + T + D (n = 406)		Pertuzumab + T + D (n = 402)	
Prior neo/adjuvant chemotherapy, n (%)				
Yes	192	(47.3)	184	(45.8)
No	214	(52.7)	218	(54.2)
Components of neo/adjuvant therapy*, n (%)				
Anthracyclines	164	(40.4)	150	(37.3)
Taxanes	94	(23.2)	91	(22.6)
Hormonal treatments	97	(23.9)	106	(26.4)
Trastuzumab	41	(10.1)	47	(11.7)

* Patients could have received more than one therapy.

Baselga J, *et al*. *N Engl J Med* 2012; **366:**109–119.

Final OS Analysis

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



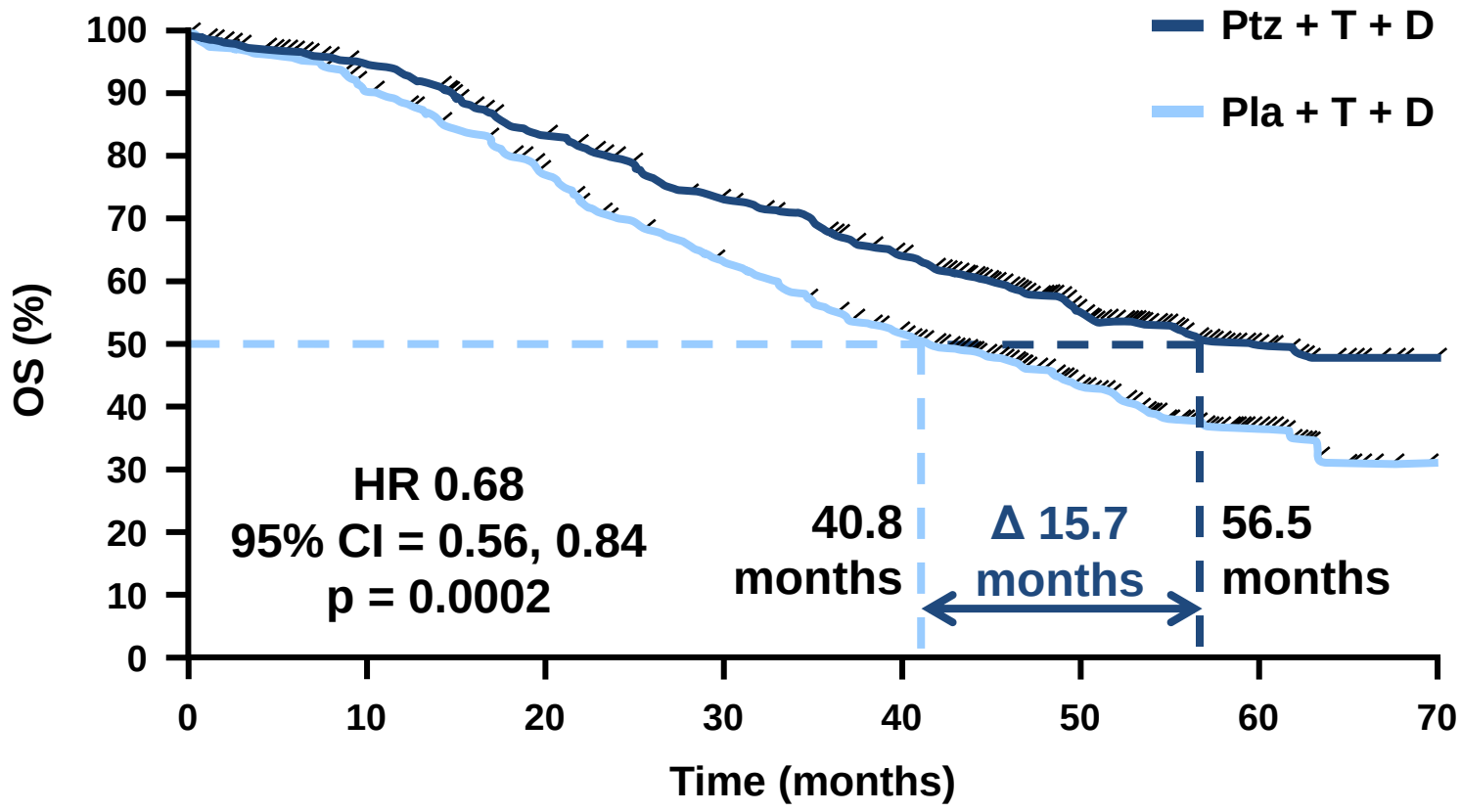
n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

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

CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Final OS Analysis

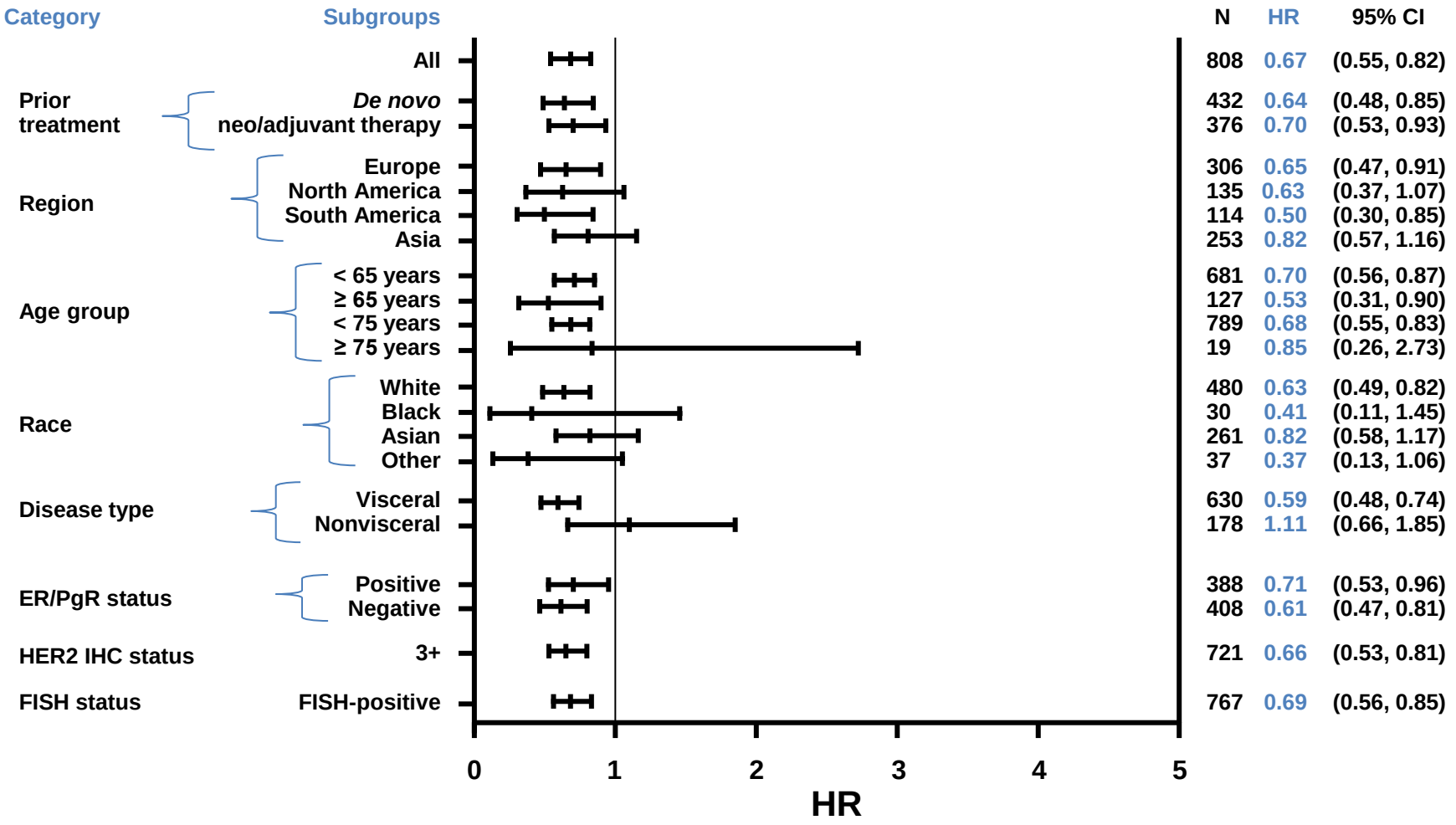
Median follow-up 50 months (range 0–70 months)



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.

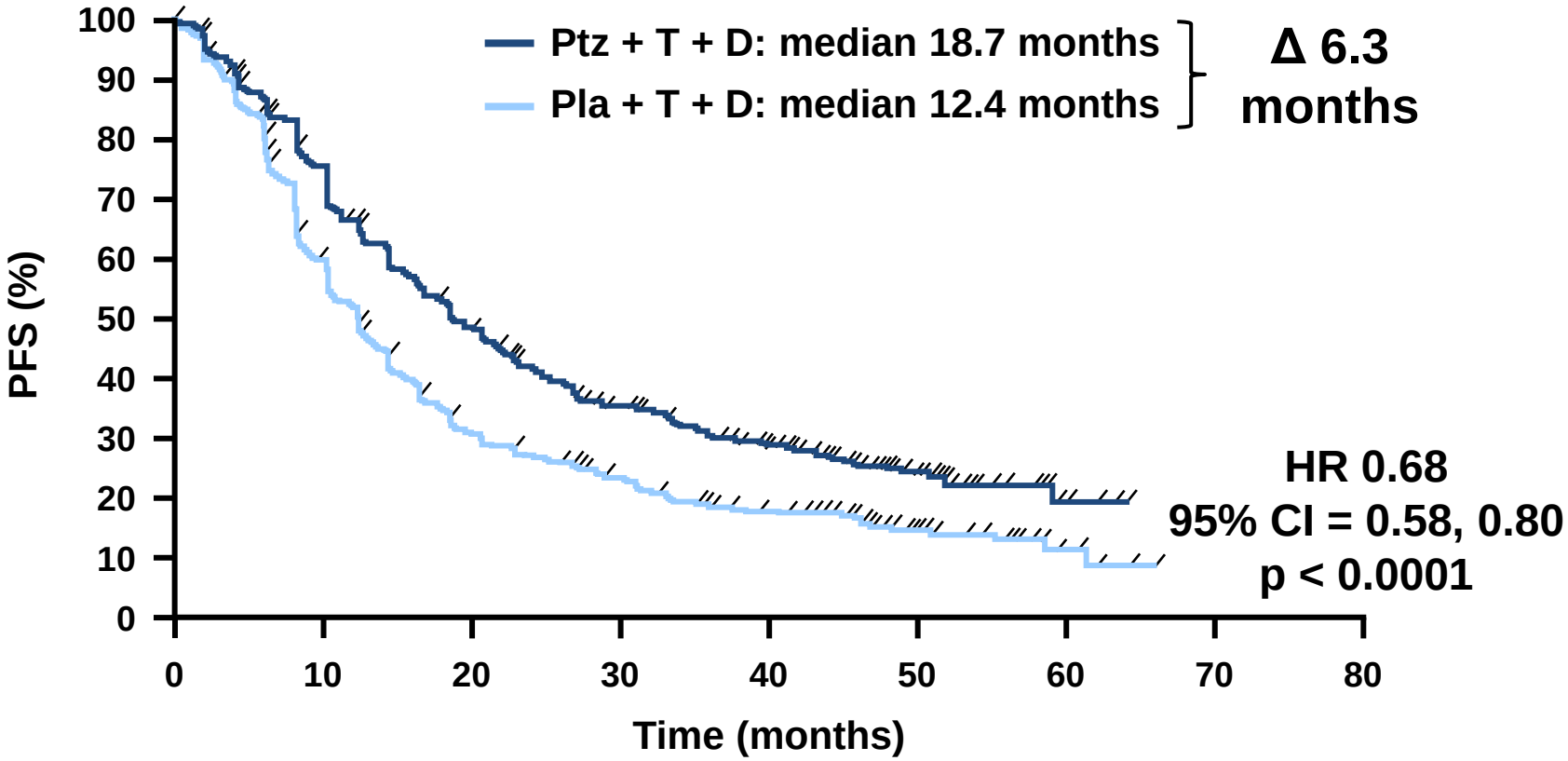
OS: Predefined Subgroups



ITT population. Nonstratified.

Updated PFS

Investigator-Assessed



n at risk									
Ptz + T + D	402	284	179	121	87	37	6	0	0
Pla + T + D	406	223	110	75	51	21	6	0	0

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

Exposure to Study Treatment

Safety population*	Placebo + T + D (n = 396)	Pertuzumab + T + D (n = 408)
Median time on study treatment, months (range)	11.4 (0.1−66.3)	17.4 (0.1−67.7)
Median number of docetaxel cycles (range)	8 (1−42)	8 (1−52)

* 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

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

Grade ≥ 3 Adverse Events

Incidence ≥ 5%

Safety population	Placebo + T + D (n = 396), %	Pertuzumab + T + D (n = 408), %
Neutropenia	46.2	49.0
Leukopenia	14.9	12.3
Febrile neutropenia	7.6	13.7
Diarrhea	5.1	9.3

- **No cumulative toxicities**

Cardiac Safety

Safety population	Placebo + T + D (n = 396), %	Pertuzumab + T + D (n = 408), %
sLVD	1.8	1.5
LVEF decline to < 50% and by ≥ 10% points from baseline*	7.4	6.1

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

* 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

Safety population	Placebo + T + D (n = 396), %	Pertuzumab + T + D (n = 408), %
PD	49.5	36.8
Febrile neutropenia or infection	1.5	1.7
Other/unknown	3.8	2.9

Treatment after Study Discontinuation

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

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 Matwiejuk, Paola Edith Price, Mirta Varela
Brazil	Jurandyr Andrade, Rodrigo Araujo, Sérgio Azevedo, Eduardo Cortes, Eduardo Costa e Silva, Daniel Cubero, Gilson Delgado, Maria del Pilar Diz, Brigitte Eyll, Fabio Franke, Roberto Hegg, Gustavo Ismael, David Jendiroba, José Luiz Pedrini, Rodrigo Pereira, Hélio Pinczowski, Paula Tokunaga, Célia Tosello
Canada	Christine Brezden-Masley
Central laboratories	Targos Molecular Pathology GmbH (Kassel, Germany), 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, 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 Angiolini, 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, Shigehira Saji, Yasutsuna Sasaki, Nobuaki Sato, Ken Shimada, Koji Takeda, Yutaka 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 Grincuka, Iveta Kudaba, Gunta Purkalne
Macedonia	Liljana Kostovska-Maneva, Petar Stefanovski
Mexico	Gloria Martinez, Gabriel Tellez
Philippines	Priscilla Caguioa, Valorie Chan, Dennis Tudtud
Poland	Malgorzata Foszczynska-Kloda, Tadeusz Pienkowski, Wojciech Polkowski, Elzbieta Starosławska, 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 Gonzalez, Javier Hornedo Muguiro, Serafin Morales, Nuria Ribelles Entrena, Susana de la Cruz Sánchez, Pedro Sanchez Rovira
Thailand	Wichit Arpornwirat, Thitiya Dejthevaporn, Jedzada Maneechavakajorn, Vichien Srimuninnimit, Virote Sriuranpong, Patrapim Sunpaweravong
UK	Rizvana Ahmad, Laura Assersohn, 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 Blachly, Kimberly Blackwell, Rita Blanchard, Paulette Blanchet, Barbara J. Bowers, Adam Brufsky, Leanne Sterbank Budde, 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, Andre 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, Alejandra Perez, Carol E. Peterson, Jonathan D. Polikoff, 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