GRUPPO A

Nelle pazienti con carcinoma mammario HER2+ metastatico senza metastasi viscerali, l'aggiunta del pertuzumab al trastuzumab + taxano è raccomandabile rispetto al trastuzumab + taxano?

Presentazione del quesito strutturato e relativa tavola delle evidenze

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QUESITO STRUTTURATO
il metodo PICO

P Popolazione

I Intervento

C Confronto

O Outcome (beneficio/danno)

- importanti ed essenziali (critici)
- importanti ma non essenziali
- non importanti

SCELTA DEGLI OUTCOMES

Rating **(mediana del voto)**	**Importanza**	**Incluso in**
7 8 9	*outcome* importanti ed essenziali	tabelle sulla qualità delle prove: SÌ raccomandazione: SÌ
4 5 6	*outcome* importanti ma non essenziali	tabelle sulla qualità delle prove: SÌ raccomandazione: NO
1 2 3	*outcome* non importanti	tabelle sulla qualità delle prove: NO raccomandazione: NO

P Pazienti con carcinoma mammario HER2+ metastatico senza metastasi viscerali

I Intervento

C Confronto

O Outcome (beneficio/danno)

P Pazienti con carcinoma mammario HER2+ metastatico senza metastasi viscerali

I Aggiunta di pertuzumab al trastuzumab + taxano

C Confronto

O Outcome (beneficio/danno)

P Pazienti con carcinoma mammario HER2+ metastatico senza metastasi viscerali

I Aggiunta di pertuzumab al trastuzumab + taxano

C Trastuzumab + taxano

O Outcome (beneficio/danno)

P Pazienti con carcinoma mammario HER2+ metastatico senza metastasi viscerali

I Aggiunta di pertuzumab al trastuzumab + taxano

C Trastuzumab + taxano

Prima scelta reale?

O Outcome (beneficio/danno)

P Pazienti con carcinoma mammario HER2+ metastatico senza metastasi viscerali

I Aggiunta di pertuzumab al trastuzumab + taxano

C Trastuzumab + taxano

O Outcome PROPOSTI – OS e PFS (beneficio); cardiotossicità e tossicità inaccettabile (danno)

LA VOTAZIONE DEI 12 PANELISTS

BENEFICIO												
OS	8	7	8	8	8	9	8	8	8	9	8	7
PFS	5	9	9	8	9	8	7	7	9	9	7	9
DANNO												
Cardio tox	9	9	9	8	9	8	9	9	9	8	7	7
Tox inaccettabile	8	9	7	6	8	7	7	8	8	8	9	8

LA VOTAZIONE DEI 12 PANELISTS

BENEFICIO												
OS	8	7	8	8	8	9	8	8	8	9	8	7
	Mediana : 8											
PFS	5	9	9	8	9	8	7	7	9	9	7	9
	Mediana : 8											
DANNO												
Cardio tox	9	9	9	8	9	8	9	9	9	8	7	7
	Mediana : 9											
Tox inaccettabile	8	9	7	6	8	7	7	8	8	8	9	8
	Mediana : 8											

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 12, 2012 VOL. 366 NO. 2

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

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Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M
Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M
and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

ABSTRACT

BACKGROUND
The anti–human epidermal growth factor receptor 2 (HER2) humanized monoclo-
nal antibody trastuzumab improves the outcome in patients with HER2-positive met-
astatic breast cancer. However, most cases of advanced disease eventually progress.
Pertuzumab, an anti-HER2 humanized monoclonal antibody that inhibits receptor
dimerization, has a mechanism of action that is complementary to that of trastu-
zumab, and combination therapy with the two antibodies has shown promisin
tivity and an acceptable safety profile in phase 2 studies involving patient
HER2-positive breast cancer.

METHODS
We randomly assigned 808 patients with HER2-positive metastatic br
receive placebo plus trastuzumab plus docetaxel (control group)
plus trastuzumab plus docetaxel (pertuzumab group) as first-lin
the time of disease progression or the development of toxic ef
be effectively managed. The primary end point was indep
gression-free survival. Secondary end points included overa
free survival as assessed by the investigator, the objective

RESULTS
The median progression-free survival was 12.4 month
pared with 18.5 months in the pertuzumab group
death, 0.62; 95% confidence interval, 0.51 to 0.7
overall survival showed a strong trend in favor
docetaxel. The safety profile was generally si
in left ventricular systolic dysfunction; the
of grade 3 or above were higher in the pe

CONCLUSIONS
The combination of pertuzumab pl
placebo plus trastuzumab plus do
positive metastatic breast canc
with no increase in cardiac t
tech; ClinicalTrials.gov num

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*

ABSTRACT

BACKGROUND
In patients with metastatic breast cancer that is positive for human epidermal growth factor receptor 2 (HER2), progression-free survival was significantly improved after first-line therapy with pertuzumab, trastuzumab, and docetaxel, as compared with placebo, trastuzumab, and docetaxel. Overall survival was significantly improved with pertuzumab in an interim analysis without the median being reached. We report final prespecified overall survival results with a median follow-up of 50 months.

METHODS
We randomly assigned patients with metastatic breast cancer who had not received previous chemotherapy or anti-HER2 therapy for their metastatic disease to receive the pertuzumab combination or the placebo combination. The secondary end points of overall survival, investigator-assessed progression-free survival, independently assessed duration of response, and safety are reported. Sensitivity analyses were adjusted for patients who crossed over from placebo to pertuzumab after the interim analysis.

RESULTS
The median overall survival was 56.5 months (95% confidence interval [CI], 49.3 to not reached) in the group receiving the pertuzumab combination, as compared with 40.8 months (95% CI, 35.8 to 48.3) in the group receiving the placebo combination (hazard ratio favoring the pertuzumab group, 0.68; 95% CI, 0.56 to 0.84; P<0.001), a difference of 15.7 months. This analysis was not adjusted for crossover to the pertuzumab group and is therefore conservative. Results of sensitivity analyses after adjustment for crossover were consistent. Median progression-free survival as assessed by investigators improved by 6.3 months in the pertuzumab group (hazard ratio, 0.68; 95% CI, 0.58 to 0.80). Pertuzumab extended the median duration of response by 7.7 months, as independently assessed. Most adverse events occurred during the administration of docetaxel in the two groups, with long-term cardiac safety maintained.

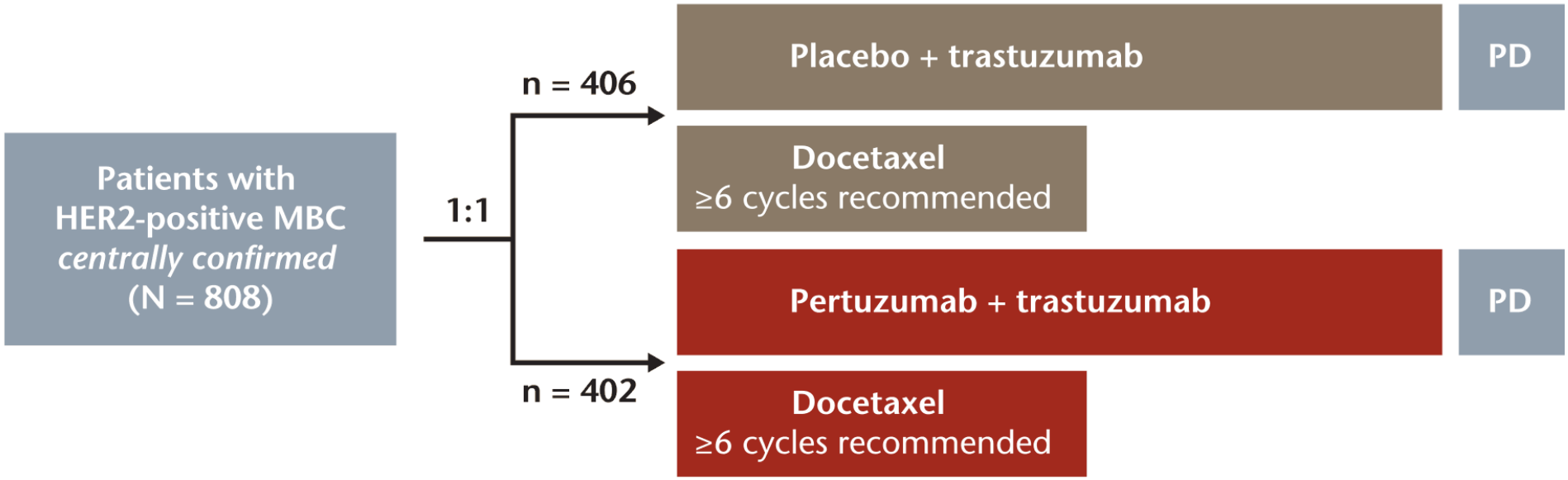
CONCLUSIONS
In patients with HER2-positive metastatic breast cancer, the addition of pertuzumab to trastuzumab and docetaxel, as compared with the addition of placebo, significantly improved the median overall survival to 56.5 months and extended the results of previous analyses showing the efficacy of this drug combination. (Funded by F. Hoffmann–La Roche and Genentech; CLEOPATRA ClinicalTrials.gov number, NCT00567190.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Swain at the Washington Cancer Institute, MedStar Washington Hospital Center, 110 Irving St., Washington, DC 20010, or at sandra.m.swain@medstar.net.

*A complete list of investigators in the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2015;372:724-34.
DOI: 10.1056/NEJMoa1413513

CLEOPATRA: disegno dello studio



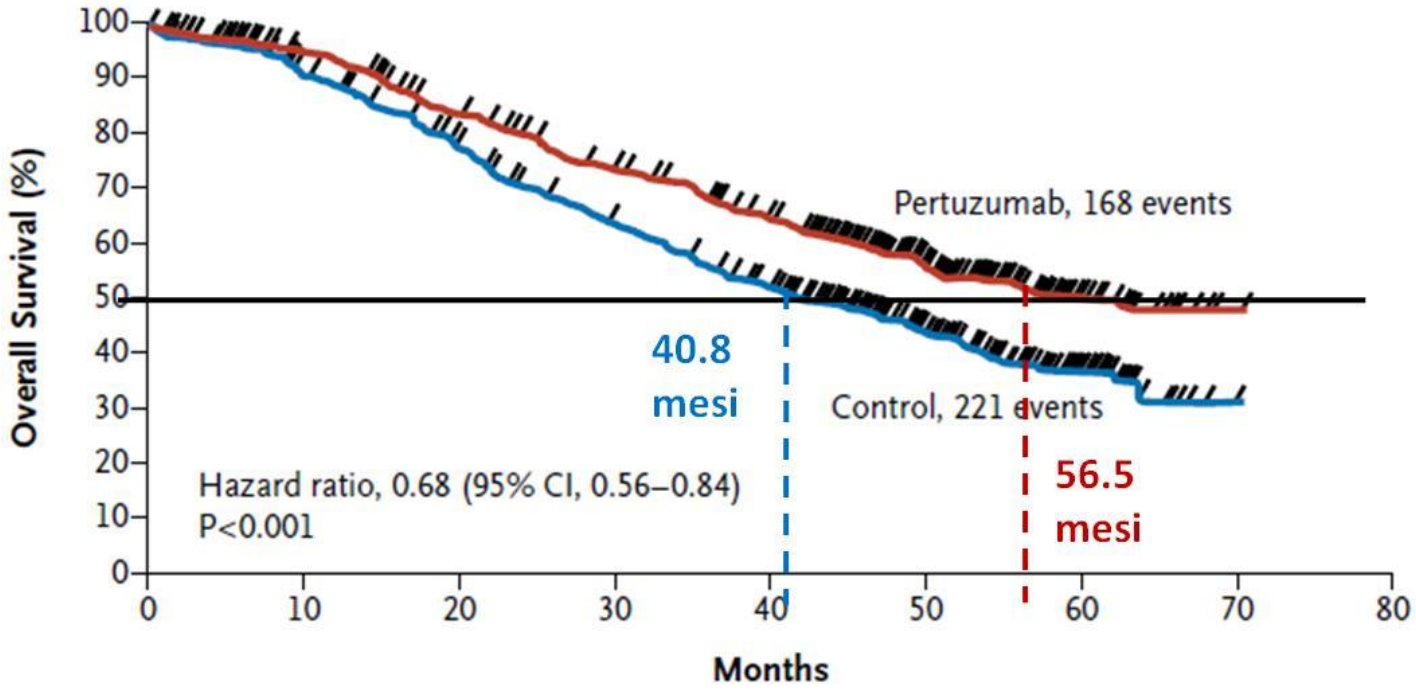
Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

HER2 = human epidermal growth factor receptor 2; MBC = metastatic breast cancer; N/n = number of patients; PD = progressive disease

Characteristic	Placebo plus Trastuzumab plus Docetaxel (N = 406)	Pertuzumab plus Trastuzumab plus Docetaxel (N = 402)
Age — yr		
Median	54.0	54.0
Range	27–89	22–82
ECOG performance status — no. (%)‡		
0	248 (61.1)	274 (68.2)
1	157 (38.7)	125 (31.1)
≥2	1 (0.2)	3 (0.7)
Disease type at screening — no. (%)		
Nonvisceral	90 (22.2)	88 (21.9)
Visceral	316 (77.8)	314 (78.1)
Hormone-receptor status — no. (%)		
ER-positive, PgR-positive, or both	199 (49.0)	189 (47.0)
ER-negative and PgR-negative	196 (48.3)	212 (52.7)
Unknown	11 (2.7)	1 (0.2)

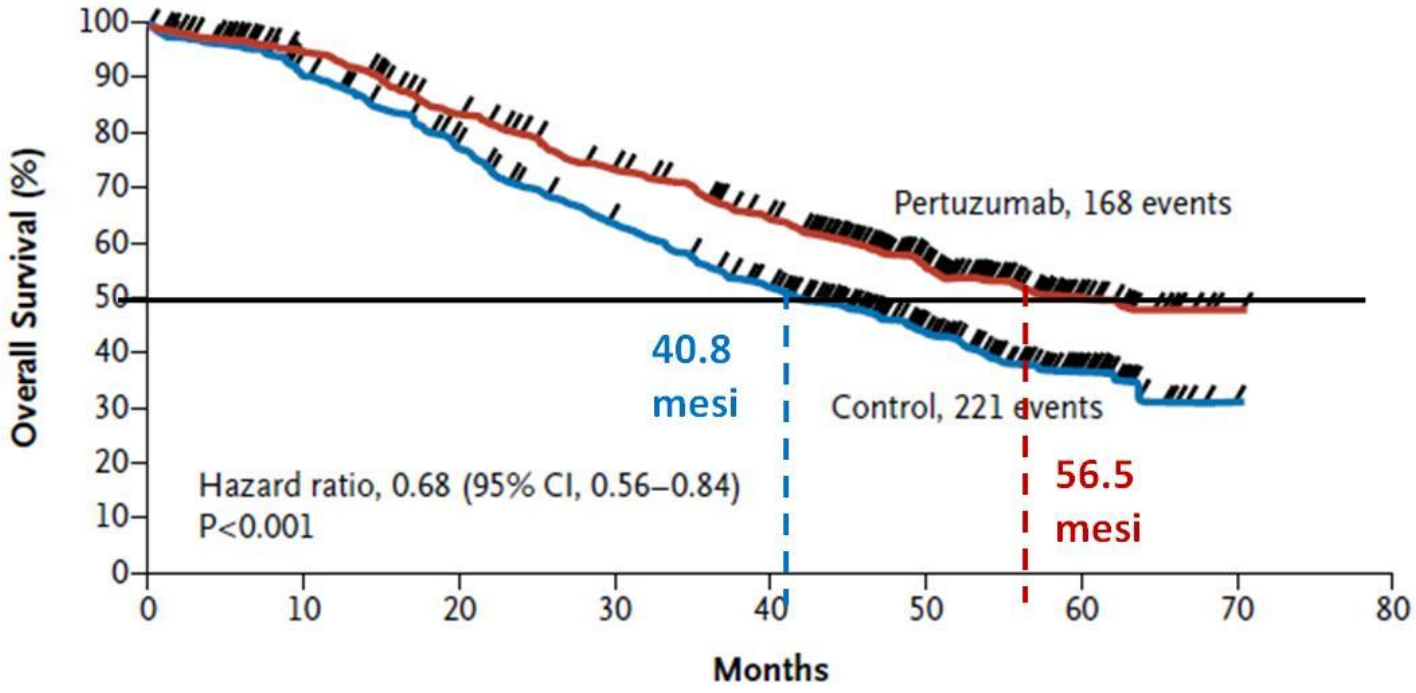
Stratificazione per area geografica di provenienza (Asia, Europa, Nord America o Sud America) e trattamento precedente (adiuvante, neoadiuvante o nessuno)

OS: follow up mediano di 50 mesi



No. at Risk								
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	406	350	289	230	179	91	23	0	0

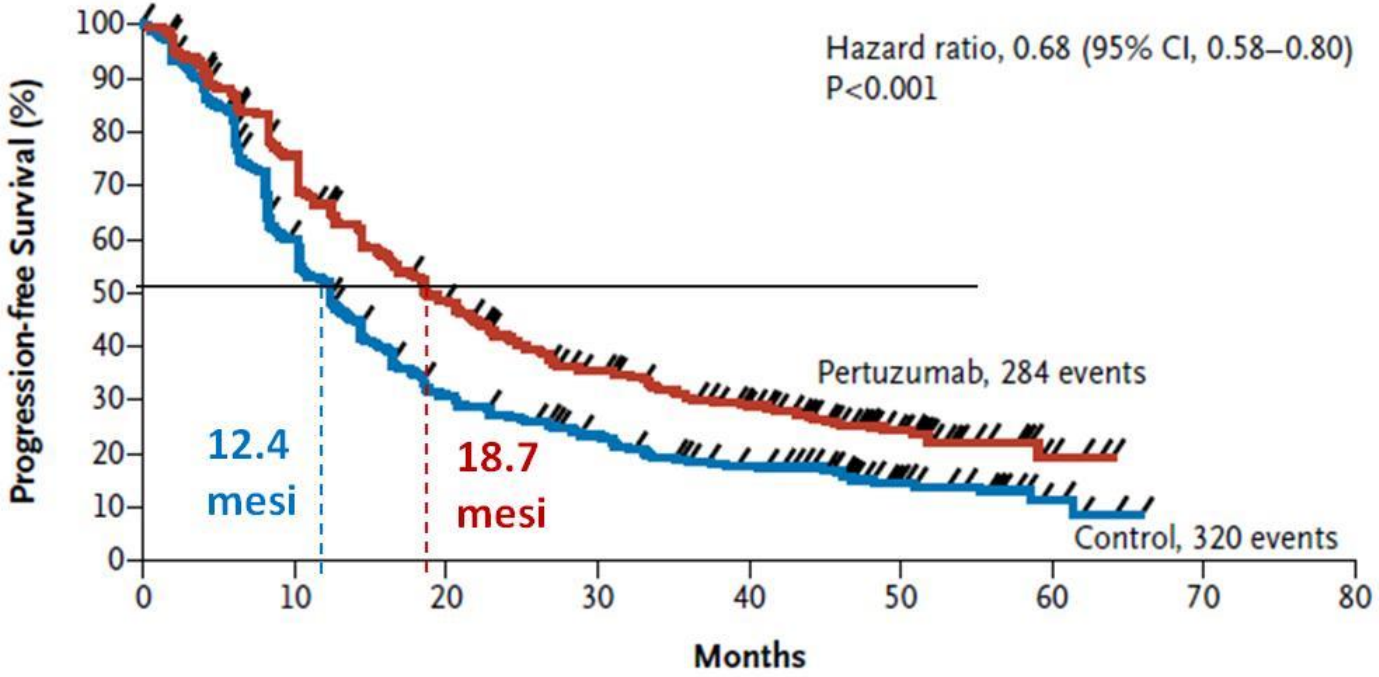
OS: follow up mediano di 50 mesi



No. at Risk									
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	406	350	289	230	179	91	23	0	0

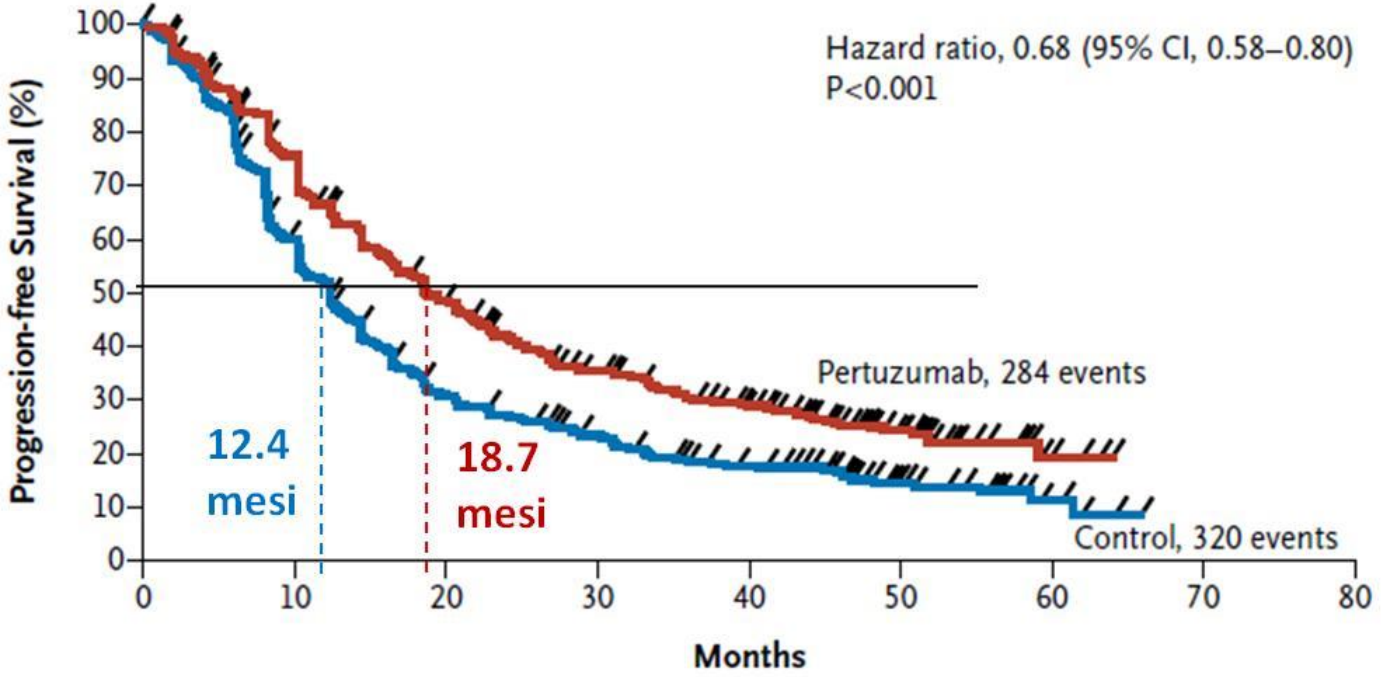
Disease type				0.03
Visceral	630		0.59 (0.48–0.74)	
Nonvisceral	178		1.11 (0.66–1.85)	

PFS: follow up mediano di 50 mesi



No. at Risk									
Pertuzumab	402	284	179	121	87	37	6	0	0
Control	406	223	110	75	51	21	6	0	0

PFS: follow up mediano di 50 mesi



No. at Risk

Pertuzumab	402	284	179	121	87	37	6	0	0
Control	406	223	110	75	51	21	6	0	0

Disease type			0.19
Visceral	630		0.64 (0.53–0.76)
Nonvisceral	178		0.83 (0.58–1.18)

PFS: follow up 20 vs. 50 mesi

Pazienti senza malattia viscerale

Follow-up di ~ 20 mesi

HR 0.96; 95%CI 0.61 – 1.52

Follow-up di ~ 50 mesi

HR 0.83; 95%CI 0.58 – 1.18

Pazienti con malattia viscerale

Follow-up di ~ 20 mesi e di ~ 50 mesi

nessuna differenza

CARDIOTOSSICITA’

Follow-up 20 mesi

Left ventricular systolic dysfunction (any grade) was reported more frequently in the control group than in the pertuzumab group (8.3% vs. 4.4%).

CARDIOTOSSICITA'

Follow-up 20 mesi

Left ventricular systolic dysfunction (any grade) was reported more frequently in the control group than in the pertuzumab group (8.3% vs. 4.4%).

Follow-up 50 mesi

The rate of left ventricular dysfunction, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, and the New York Heart Association,[6] was somewhat lower in the pertuzumab group than in the control group (6.6% [27 of 408 patients] vs. 8.6% [34 of 396 patients]).

TOSSICITA' INACCETTABILE