Università degli Studi
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Cleopatra & Embrace
Clinical Practice

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Formal starting point
FDA APPROVAL

- **Eribulin, November 2010**
  - for the treatment of patients with metastatic breast cancer who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting, and at least two chemotherapeutic regimens for the treatment of metastatic disease.

- **Pertuzumab, June 2012**
  - for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Actual (practical) starting point…

Current therapies for

metastatic breast cancer generally result in delay of further spread of disease or prolongation of life, not cure

Most women are candidates for multiple lines of therapy

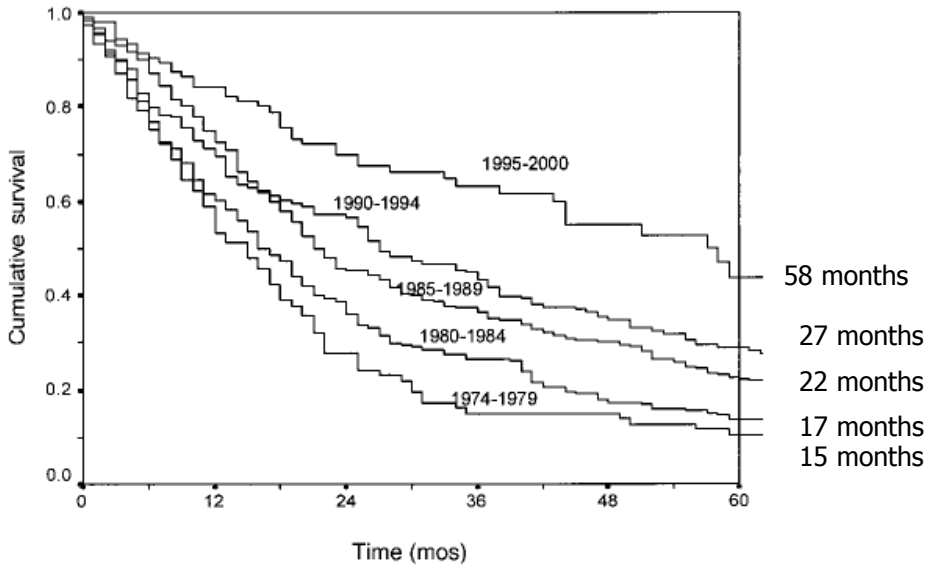
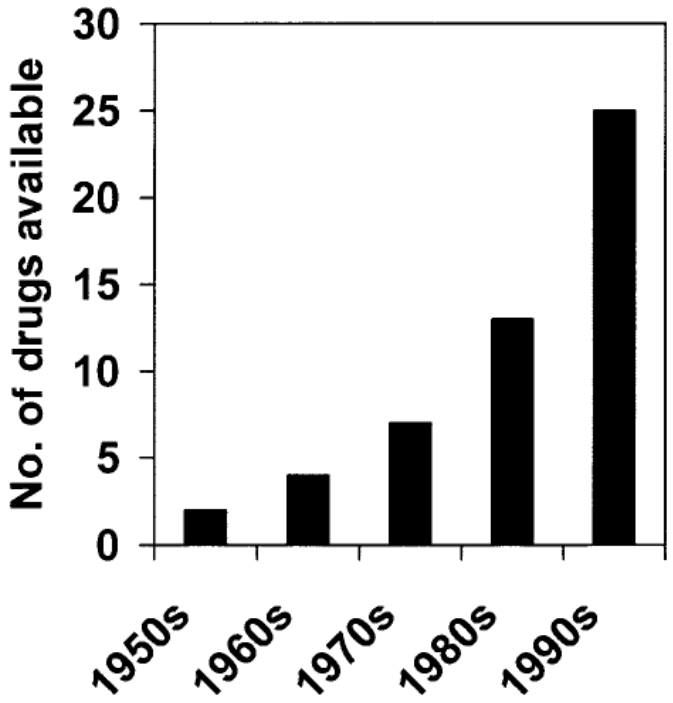


FIGURE 1. Overall survival from time of recurrence.



5-year OS

- 1974-79: 10%
- 1980-84: 14%
- 1985-89: 22%
- 1990-94: 29%
- 1995-00: 44%

•1950s: cyclophosphamide, methotrexate
•1960s: 5-fluorouracil, vinblastine, vincristine, fluoxymesterone
•1970s: doxorubicin, mitomycin-C, tamoxifen
•1980s: mitoxantrone, etoposide, aminoglutethimide, megestrol acetate, goserelin, leuprolide
•1990s: paclitaxel, docetaxel, vinorelbine, gemcitabine, trastuzumab, capecitabine, epirubicin, pamidronate, toremifene, anastrozole, letrozole, exemestane

Sharon H. Giordano. Cancer 2004; 100: 44-52

The Impact of New drugs in a Population-Based Cohort (British Columbia Cancer Agency)

2151 patients with MBC; multivariate analysis

Period	Drugs	HR for Death	P Value
I (91–92)	Baseline	1.00	–
II (94–95)	Paclitaxel, Vinorelbine	0.97	0.65
III (97–98)	Docetaxel, AIs	0.84	0.011
IV (99–01)	Trastuzumab, Capecitabine	0.71	<0.001

From 1991 to 2001, the median OS increased from 435 days to 661 days → more than a 7-month improvement.

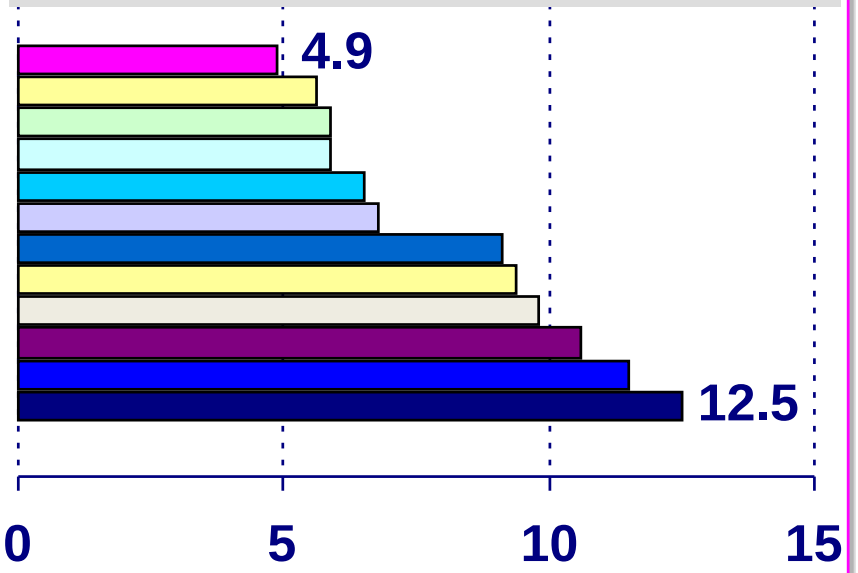
Chia et al. Cancer 2007

Network Meta-analysis of Chemotherapy and Targeted Therapy in Advanced Breast Cancer

- Anthra single agent
- Novel non-taxane agents + lapatinib
- Anthra combo
- Taxanes single agent
- Antra + novel non-taxane agents
- Anthra + Taxanes
- Taxanes + Lapatinib
- Anthra + Taxanes + novel non-taxane agents
- Anthra + Trastuzumab
- Taxanes combo
- Taxanes + Trastuzumab
- Novel non-taxane agents + taxanes*

Absolute prolongation of survival with various regimens for a patient with an anticipated survival on an old agent (single agent) of 1 y

Calculation: [(12/HR) - 12] mo



*Albain JCO 2008, O'Shaughnessy JCO 2002, Beslija ASCO 2006

Mauri D, J Natl Cancer Inst 2008

First-line chemotherapy
a systematic review of randomized trials

36 first-line chemotherapy trials for MBC published from 1999 to 2009

- Mean for Median PFS: 7.6 months (6.0-9.0)
- Mean for Median SPP: 14 months (10.8-15.6)
- Mean for Median OS: 21.7 (18.2-24.0)
- Mean for Median ratio OS/PFS: 3 (2.4-3.5)
- Mean 1-year survival: 73% (69-78%)
- Mean 2-year survival: 45% (38-50%)
- Mean 5-year survival*: 12% (7-17%)

*information available only in 14 trials

Kiely BE, et al. J Clin Oncol 2011;29:456-63.

Recent phase III first-line trials

TREATMENT	STUDY	OS (PFS) in months
Paclitaxel + Bevacizumab	E-2100	26.7 (11.8)
Docetaxel + Bevacizumab	AVADO	30.8 (9)
Capecitabine + Bevacizumab	Ribbon-1	29 (8.6)
Docetaxel + Trastuzumab + Pertuzumab	Cleopatra	not reached (18.7) -37.6, placebo arm-

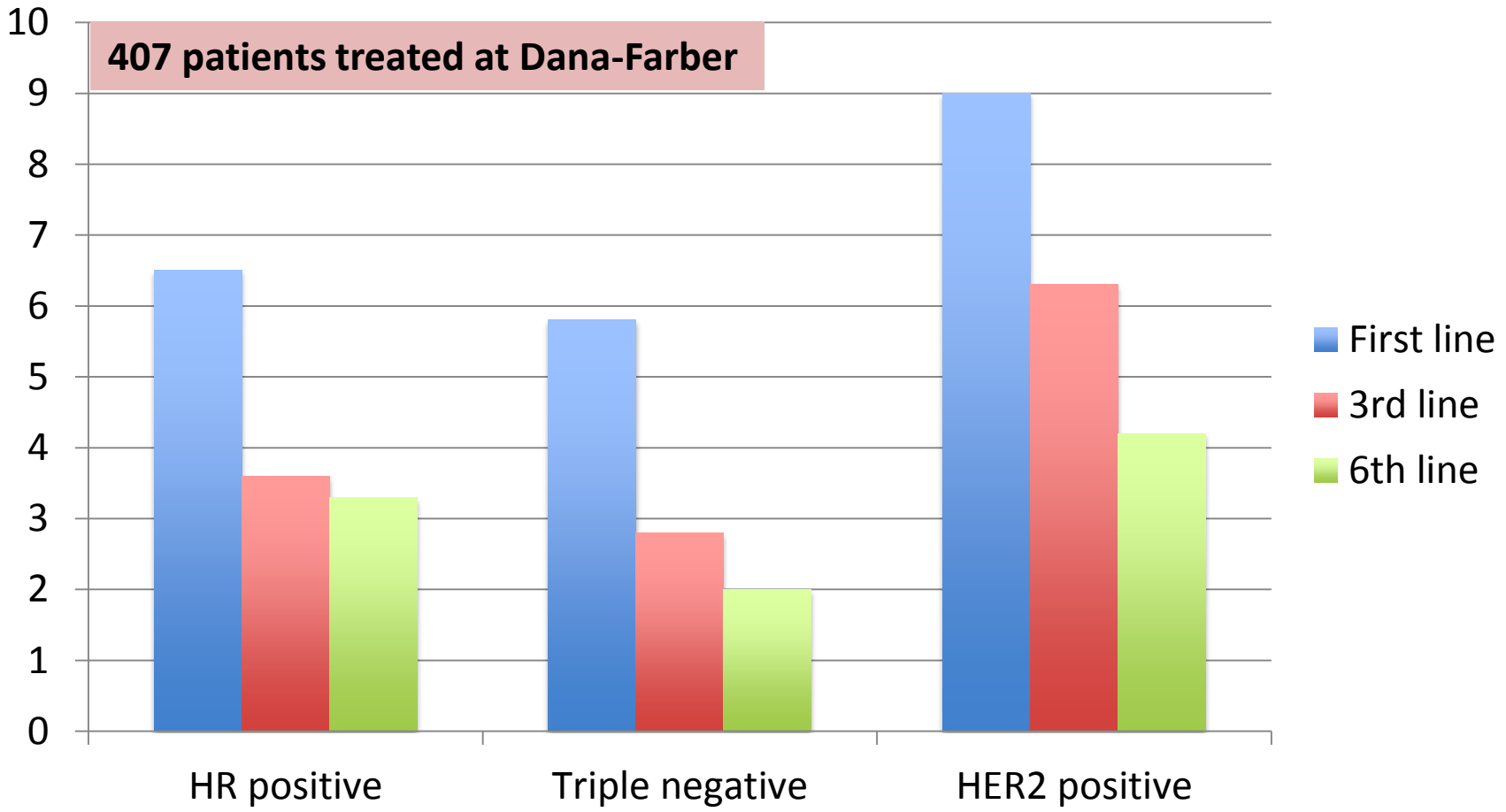
40% of patients achieve disease control for more than 6 months with third line therapy

Dufresne A, et al. Impact of chemotherapy beyond the first-line in patients with metastatic breast cancer. *Breast Cancer Res Treat 2008; 107:275-9*

ADVANCES HAVE BEEN DIFFERENT IN DIFFERENT SUBTYPES

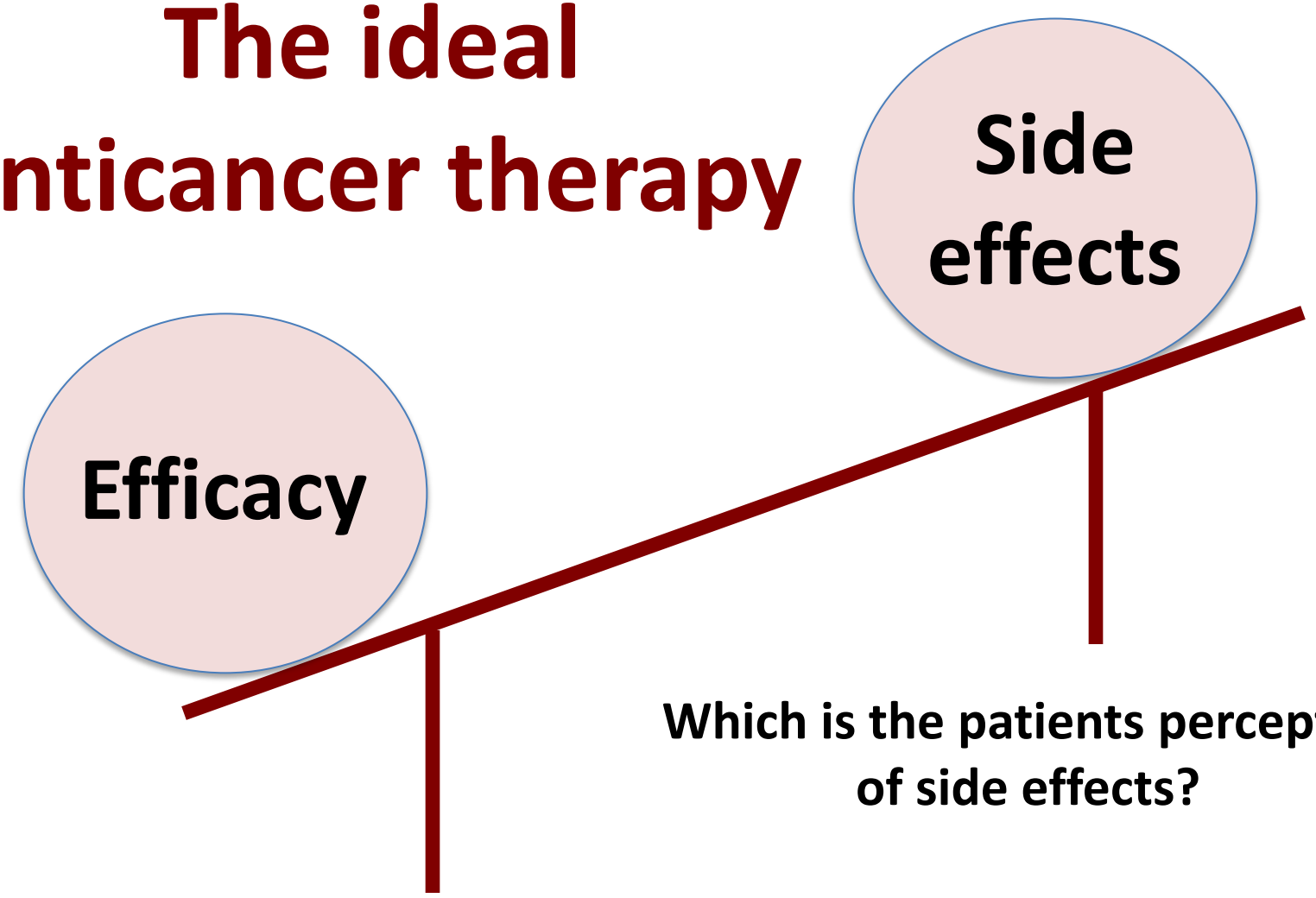
HER2-positive *vs* **HR-positive** *vs* **Triple Negative**

Use and duration of chemotherapy in pts with MBC according to tumor subtype and line of therapy



Seah DS et al. *Proc ASCO* 2012; abstract 6089

The ideal anticancer therapy



Which is the patients perception of side effects?

How do you measure efficacy?

Trade-offs

- Cancer-related symptoms
- Benefits of therapy
- The hope that comes with doing something

- Side effects of therapy, especially chronic side effects
  - fatigue,
  - neuropathy
  - GI discomfort
- The tyranny of the infusion room

NCCN Guidelines Version 2.2013
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:

Trastuzumab with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

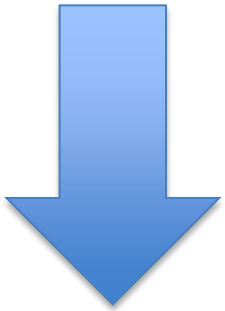
[1]There is no compelling evidence that combination regimens are superior to sequential single agents.

[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Eribulin

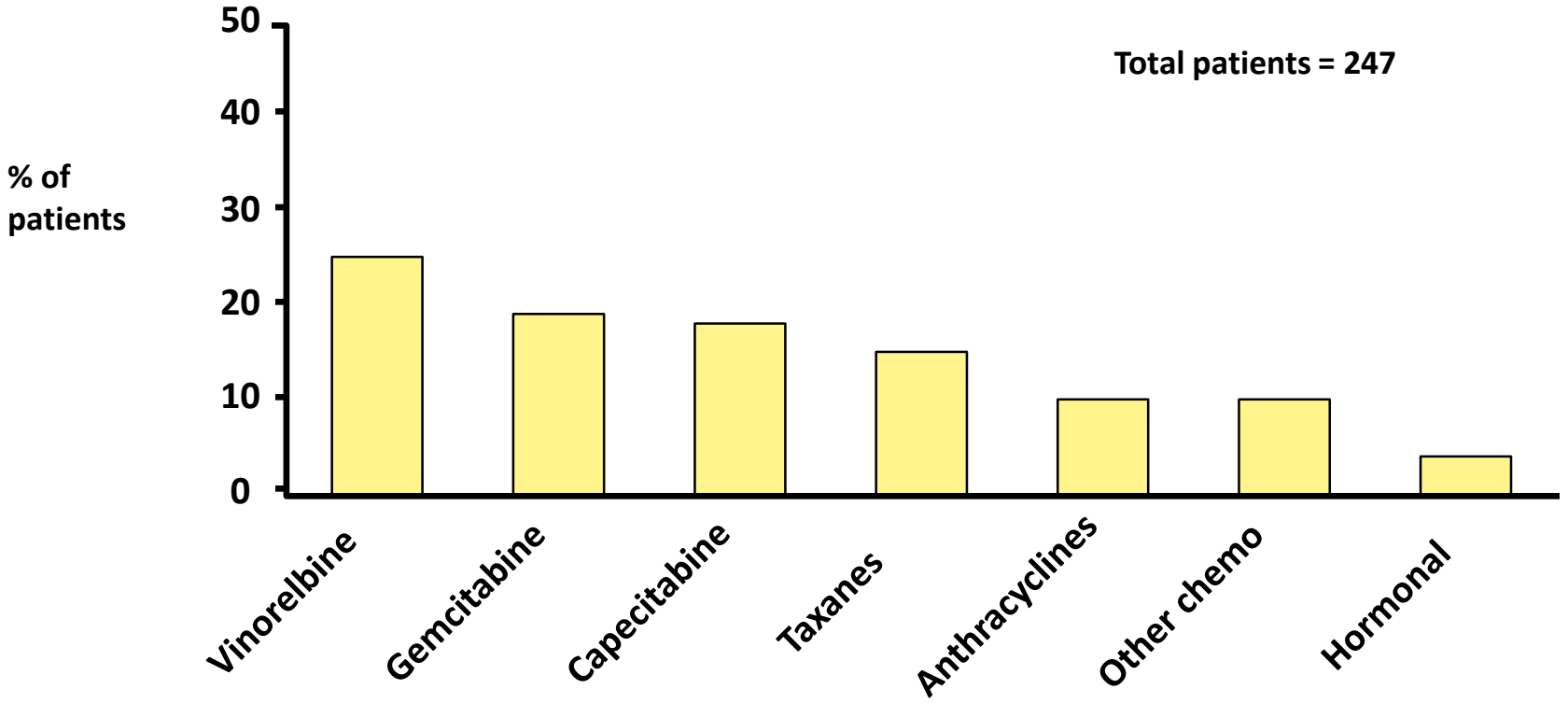
No obvious single standard of care for the treatment of metastatic breast cancer in third-line setting



The use of a physician's choice design for the control arm is reasonable (it reflects the "real-word" choice made by phisicians and their patients)

EMBRACE: TPC treatment received

96% of patients treated with chemotherapy



No patient received best supportive care or 'biological' therapies only

Taxanes: paclitaxel, docetaxel, abraxane, ixabepilone

Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone

C. Twelves, ESMO 2010

EMBRACE

Main characteristics at a glance

- Median Age: 55 years
- HER2 positive disease: 16%
- HR positive disease: 64%
- Triple negative: 19%
- N of previous chemotherapy regimens: 4 (1-7)
- > 3 previous chemotherapy regimens for MBC: 25%
- Previous capecitabine: 73%
- Progressed on or within 6 months to:
  - Taxane 81%
  - Capecitabine 68%
  - Anthracycline 58%

Cortes J, et al. Lancet 2011; 377:914-23.

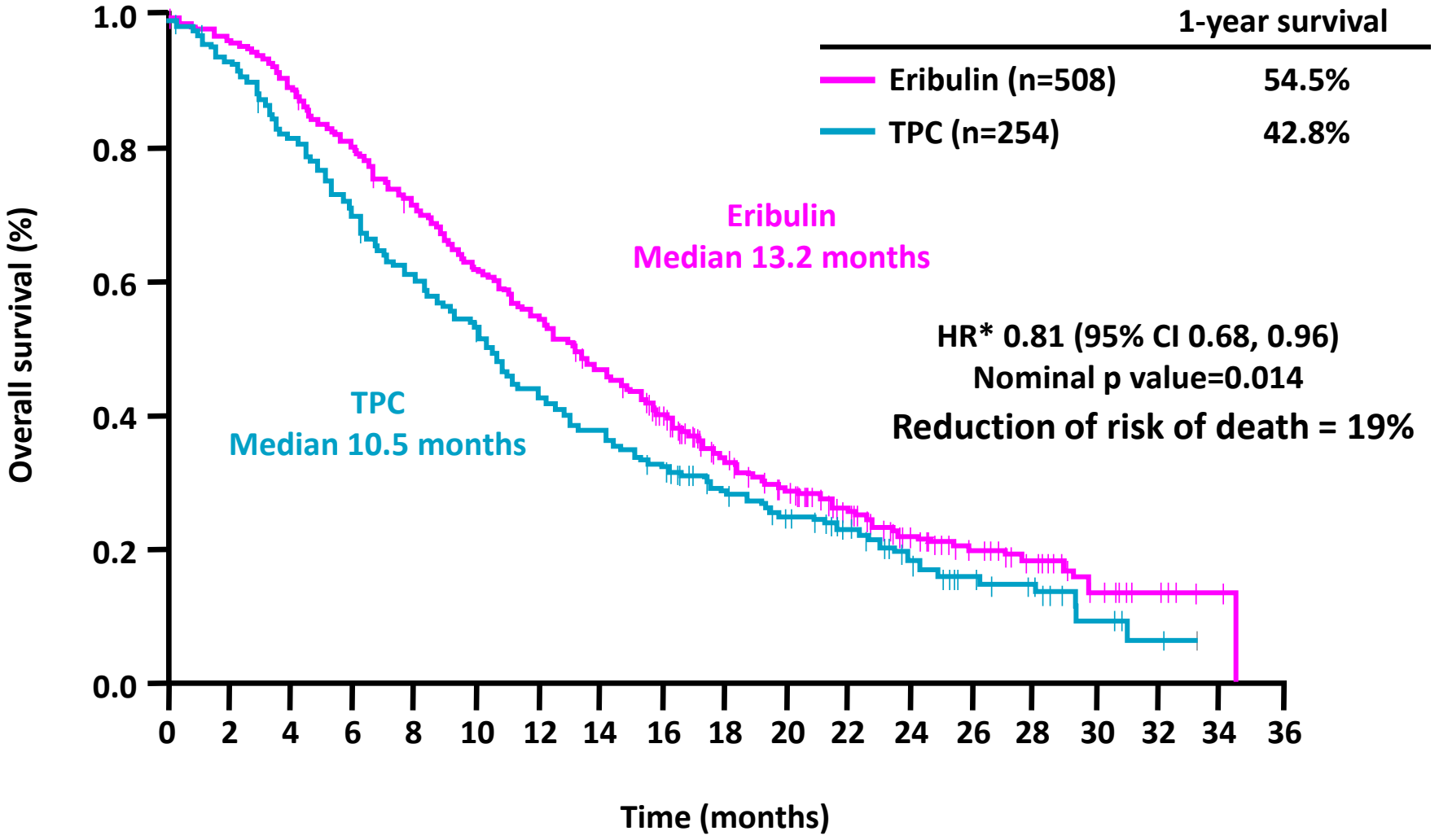
The median duration of the last chemotherapy prior study entry

- 3.6 months (eribulin arm)
- 3.5 months (control arm)

The median duration of PFS

- 3.7 months (eribulin arm)
- 2.2 months (control arm)

Overall Survival (ITT Population)
Update 3 March 2010



Update analysis requested by FDA and EMA: 586 events vs 422 events of the previous analysis

Cortes J, et al. Lancet 2011; 377:914-23

EMBRACE: Grade 3 and 4 Hematologic Events

Adverse Events, %	Grade 3		Grade 4	
	Eribulin (n=503)	TPC (n=247)	Eribulin (n=503)	TPC (n=247)
Neutropenia	21	14	24	7
Leukopenia	12	5	2	1
Anemia	2	3	0.2	0.4
Febrile neutropenia	3	1	1	0.4

Cortes J, *et al. Lancet*. 2011; **377**:914-923.

EMBRACE
Non-hematologic events Events

Adverse event, %	Eribulin (n=503)			TPC (n=247)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Peripheral neuropathy	35	8	<1	16	2	0
Alopecia	45	N/A	N/A	10	N/A	N/A
Hand-foot syndrome	1	<1	0	14	4	0

Cortes J, *et al. Lancet*. 2011; **377:**914-923.

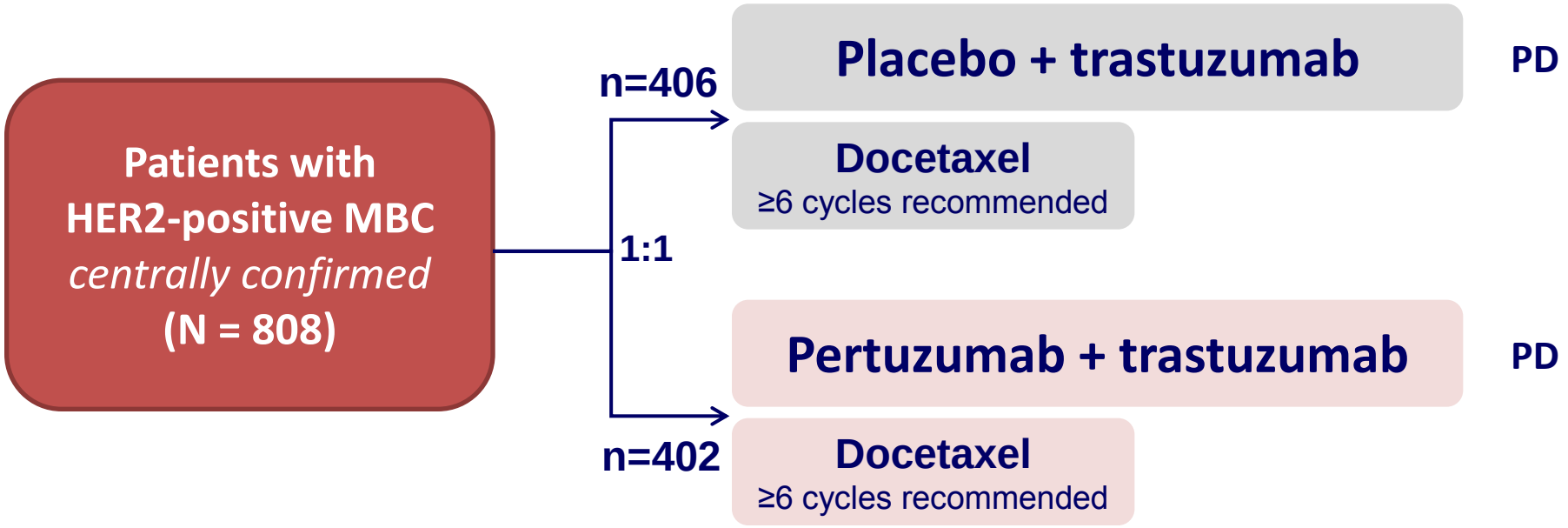
Key points

- Eribulin is the only agent that has been shown, when administered as monotherapy, to prolong OS in pretreated pts with MBC
- Manageable toxicity profile
- TPC as comparator arm is clinically relevant because the results reflect real-life choices made by clinicians and their patients

Pertuzumab

The first-in-class HER3-HER2 dimerization inhibitor

CLEOPATRA: Study design



- **Primary endpoint:** Independently assessed progression-free survival (PFS)
- **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/m^2, escalating to 100 mg/m^2 if tolerated**

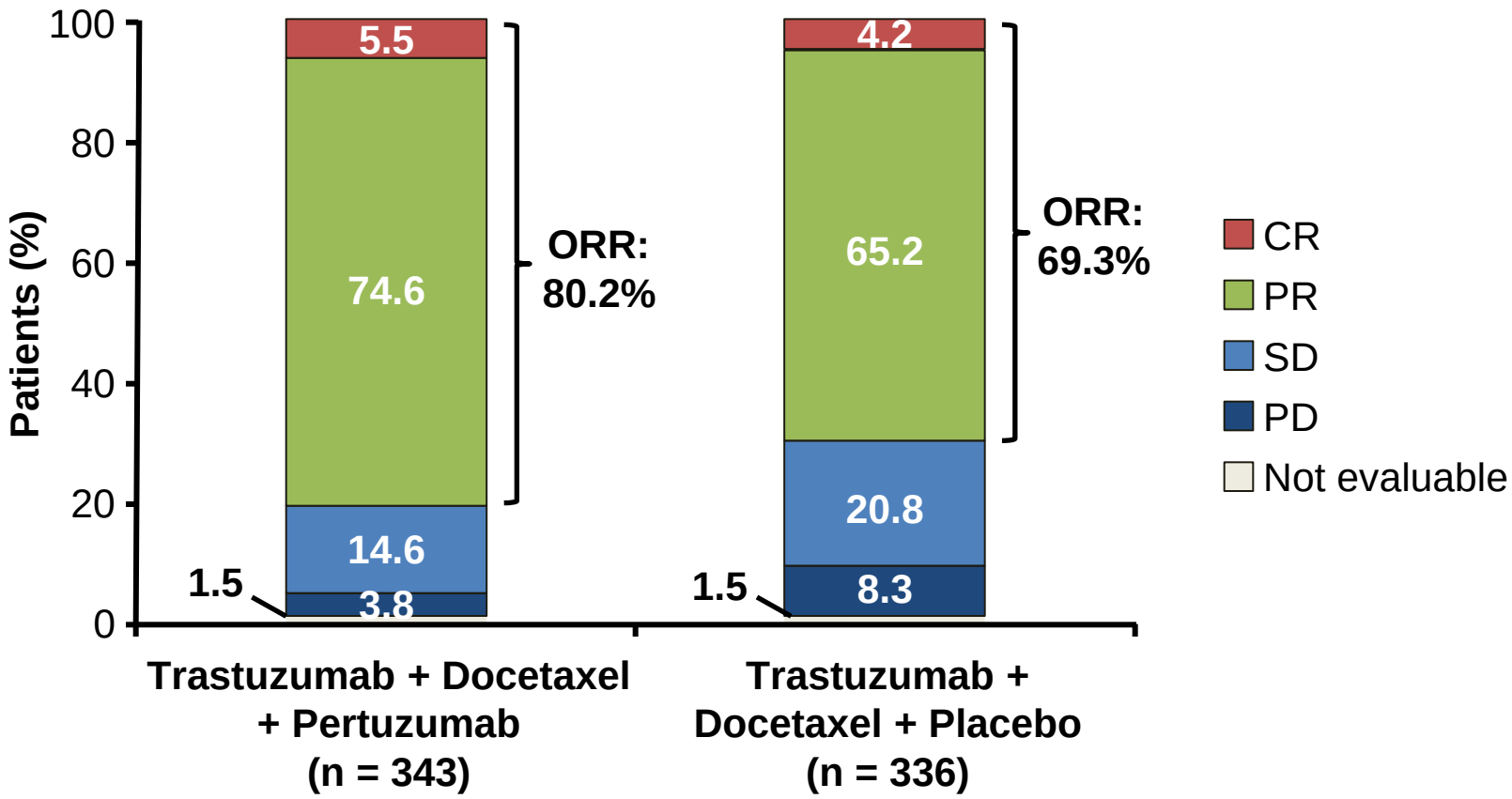
Baselga J, et al. N Engl J Med. 2012;366:109-119.

Independently assessed PFS by prior trastuzumab therapy in patients with (neo)adjuvant therapy

	Placebo + trastuzumab + docetaxel Median PFS, months	Pertuzumab + trastuzumab + docetaxel Median PFS, months	Hazard ratio (CI)
Prior (neo)adjuvant trastuzumab treatment (n = 88)	10.4	16.9	0.62 (0.35–1.07)
No prior (neo)adjuvant trastuzumab treatment (n = 288)	12.6	21.6	0.60 (0.43–0.83)

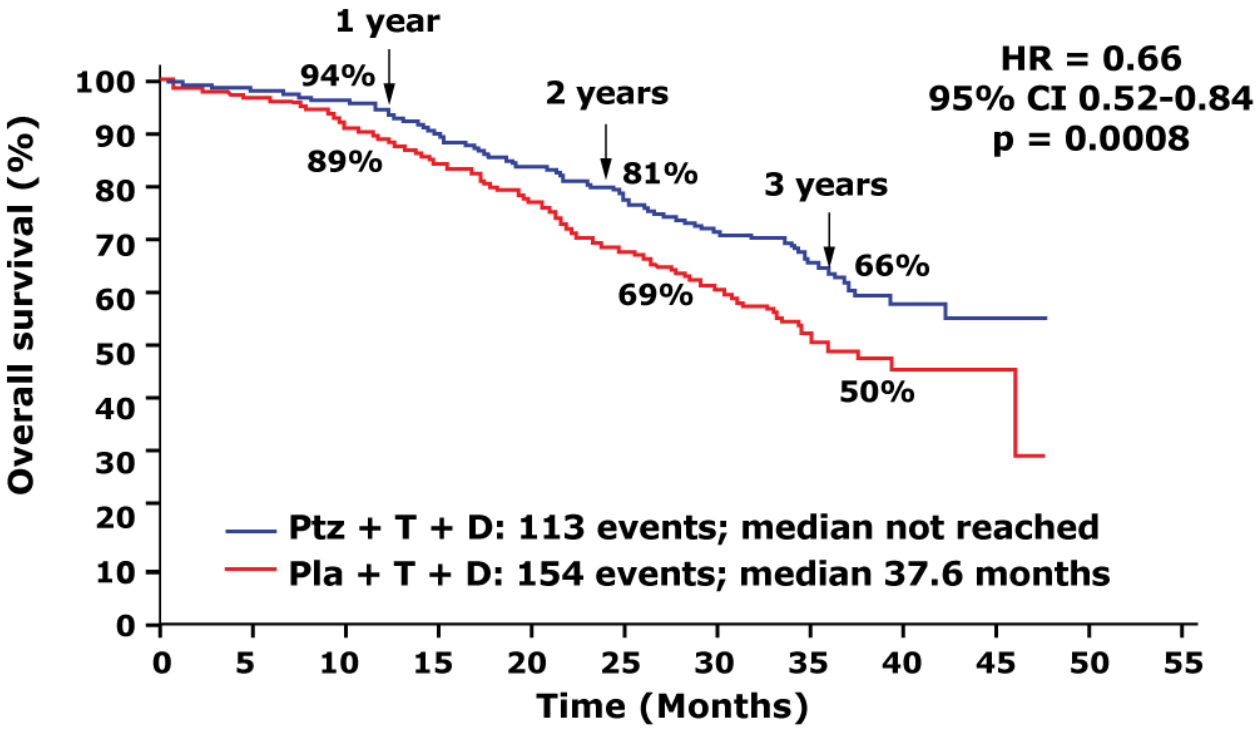
Baselga J, et al. SABCS 2011. Abstract S5-5.

CLEOPATRA: Response Data



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

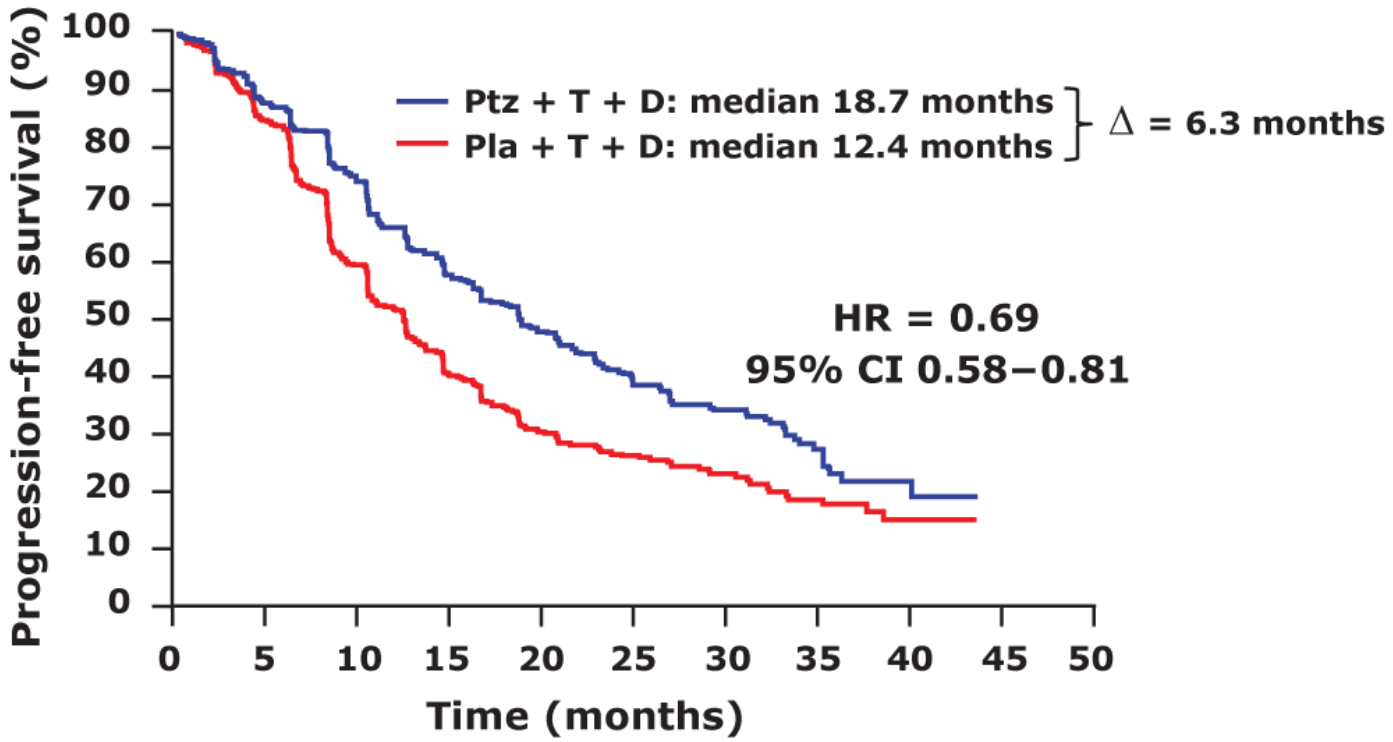
CLEOPATRA: Overall Survival (Confirmatory Analysis)



- Crossed O'Brien-Fleming stopping boundary and was therefore deemed statistically significant.
- Analysis was performed after 267 deaths and 69% of the prespecified total number of events for the final analysis had occurred.
- Median follow-up in both arms = 30 months

Swain SM et al. *Proc SABCS* 2012;Abstract P5-18-26.

CLEOPATRA: Follow-Up Analysis — Updated Investigator-Assessed PFS



- At the time of the data cutoff, 296 (72.9%) patients on the placebo arm and 257 (63.9%) on the pertuzumab arm had experienced a PFS event. These results were exploratory only.
- This updated analysis of investigator-assessed PFS was consistent with the results from the primary PFS analyses.

Swain SM et al. *Proc SABCS* 2012;Abstract P5-18-26.

CLEOPATRA: Grade ≥3 Adverse Events

Grade ≥3 adverse events (incidence ≥5%)	Ptz + T + D (n = 408)	Pla + T + D (n = 396)
Neutropenia	49.0%	46.0%
Febrile neutropenia	13.7%	7.6%
Leukopenia	12.3%	14.9%
Diarrhea	9.1%	5.1%

Mucosal inflammation (Grade ≥3) was reported in 1% of patients in the placebo arm and 1.5% of patients in the pertuzumab arm.

Swain SM et al. *Proc SABCS* 2012;Abstract P5-18-26.

CLEOPATRA
patient population and key questions

- Approximately one half had received previous adjuvant or neoadjuvant chemotherapy,
  - including a taxane in 24% to 26%
  - including trastuzumab in 10% to 12%

- All patients were required to have experienced an interval of at least 12 months between the end of adjuvant/neoadjuvant chemotherapy with or without trastuzumab and the time of diagnosis of metastatic disease.

Is Pertuzumab appropriate for use outside

Docetaxel

a constrained companion?

Not always fit