
# Vantaggio significativo in OS negli studi di fase III: qualche volta si ottiene?

## Commento sulla metodologia

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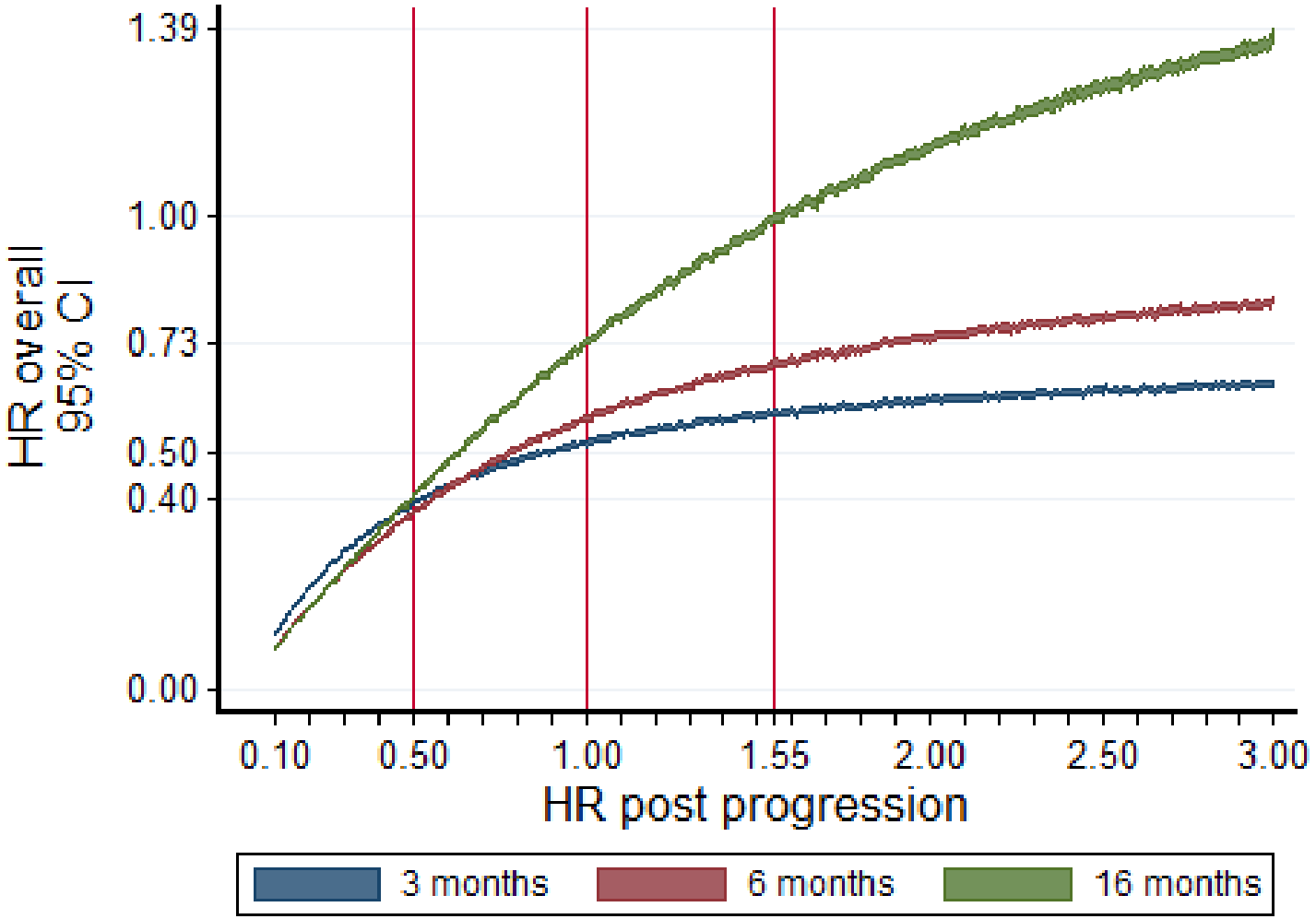
- Efficacia
  - Beneficio clinico per il paziente che può essere dimostrato per mezzo di miglioramenti su outcome clinici, quali
    - Sopravvivenza
    - Funzione
    - Sintomi
    - Endpoint surrogati ‘validati’
- Questi outcome sono utilizzati come endpoint di studi clinici accettati dagli enti regolatori per la valutazione di evidenza di efficacia.

- In casi particolari
  - In malattie life-threatening e/o senza opzioni terapeutiche è accettato l'utilizzo di endpoint surrogati meno validati rispetto a quelli utilizzati per l'approvazione regolare, sui quali si dimostri un vantaggio
- L'approvazione accelerata può essere data, ma lo sponsor si deve fare carico di dimostrare in studi successivo l'efficacia sull'endpoint clinico.

- Disegno
  - Indispensabile randomizzato, controllato
  - Non indispensabile il cieco
- Vantaggi
  - Accettato universalmente come misura diretta di beneficio
  - Misurabile facilmente e con precisione
  - Maggiore precisione nella valutazione indicatori secondari
- Svantaggi
  - Dimensioni grandi del campione
  - Diluizione di effetto per crossover o terapie attive
  - Morti non correlate alla patologia

## Assunzioni per il braccio CTR:
## Mediana PFS = 6 mesi; PFS: HR EXP vs. CTR=0.5



- Disegno
  - Indispensabile randomizzato, controllato
  - Non indispensabile il cieco/blinded review raccomandata
- Vantaggi
  - Rispetto ad OS meno pazienti e minor durata
  - Include la misura della durata della malattia stabile
  - Non influenzato dal crossover o da terapie successive
  - Basato in genere su una valutazione oggettiva e quantitativa
- Svantaggi
  - Non validato come surrogato di OS in tutti i setting
  - Soggetto a bias
  - Il tempo di valutazione deve essere simile nei gruppi a confronto
  - Necessità di esami frequenti
  - Definizione non consistente tra gli studi

- PFS come EP surrogato
  - CRC ++
  - Ovaio +
  - Polmone +/-
  - Mammella –
- Limiti criteri RECIST
- PFS ha valore clinico?
  - frequenza esami simile alla pratica clinica
  - correlazione con i sintomi

# Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

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ABSTRACT

BACKGROUND

The anti–human epidermal growth factor receptor 2 (HER2) humanized monoclonal antibody trastuzumab improves the outcome in patients with HER2-positive metastatic 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 trastuzumab, and combination therapy with the two antibodies has shown promising activity and an acceptable safety profile in phase 2 studies involving patients with HER2-positive breast cancer.

METHODS

We randomly assigned 808 patients with HER2-positive metastatic breast cancer to receive placebo plus trastuzumab plus docetaxel (control group) or pertuzumab plus trastuzumab plus docetaxel (pertuzumab group) as first-line treatment until the time of disease progression or the development of toxic effects that could not be effectively managed. The primary end point was independently assessed progression-free survival. Secondary end points included overall survival, progression-free survival as assessed by the investigator, the objective response rate, and safety.

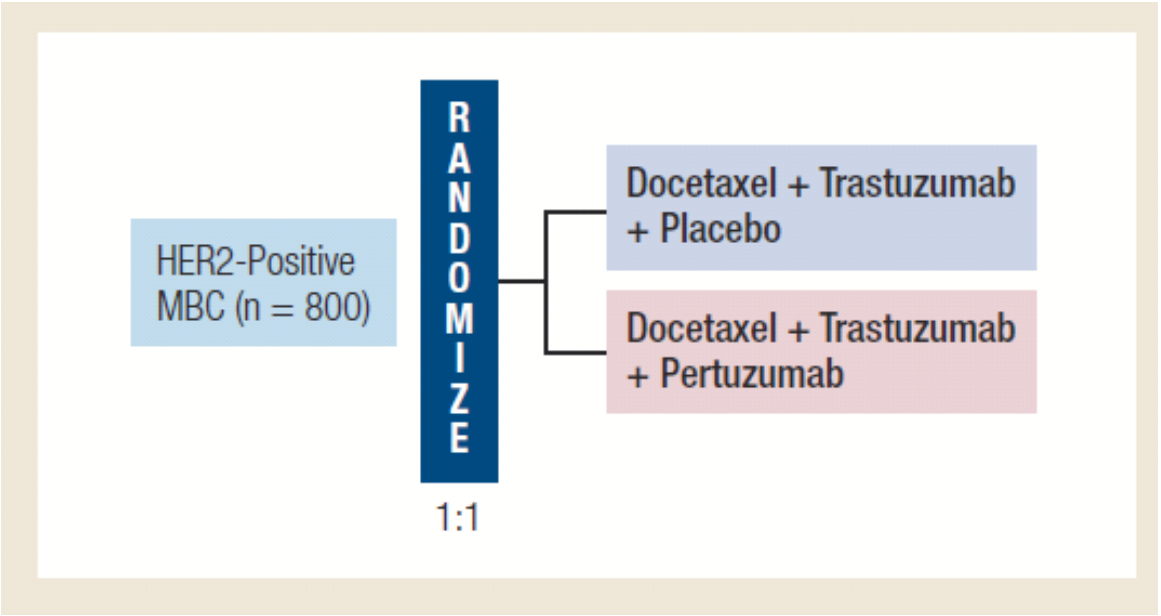
RESULTS

The median progression-free survival was 12.4 months in the control group, as compared with 18.5 months in the pertuzumab group (hazard ratio for progression or death, 0.62; 95% confidence interval, 0.51 to 0.75; P<0.001). The interim analysis of overall survival showed a strong trend in favor of pertuzumab plus trastuzumab plus docetaxel. The safety profile was generally similar in the two groups, with no increase in left ventricular systolic dysfunction; the rates of febrile neutropenia and diarrhea of grade 3 or above were higher in the pertuzumab group than in the control group.

CONCLUSIONS

The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged progression-free survival, with no increase in cardiac toxic effects. (Funded by F. Hoffmann–La Roche/Genentech; ClinicalTrials.gov number, NCT00567190.)

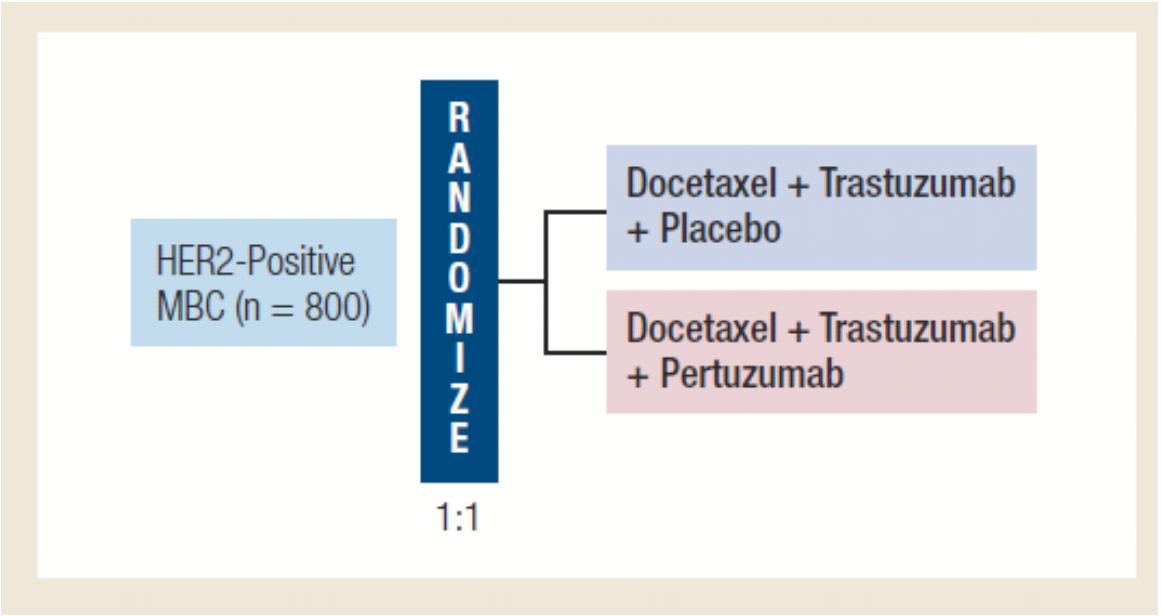
Studio CLEOPATRA – NEJM 2012




## Assessments

Routine tumor assessments, based on RECIST, were performed every 9 weeks by the investigator and by personnel at the independent review facility; these assessments were performed until the time of independently assessed disease progression or death.

Decisions regarding treatment were made by the investigator, solely on the basis of the investigator's assessment of disease progression.




## *Statistical Considerations for PFS*

The study accrual goal is approximately 800 patients from 250 centers worldwide.

The final analysis for the primary endpoint will take place when approximately 381 IRF-assessed PFS events have occurred.

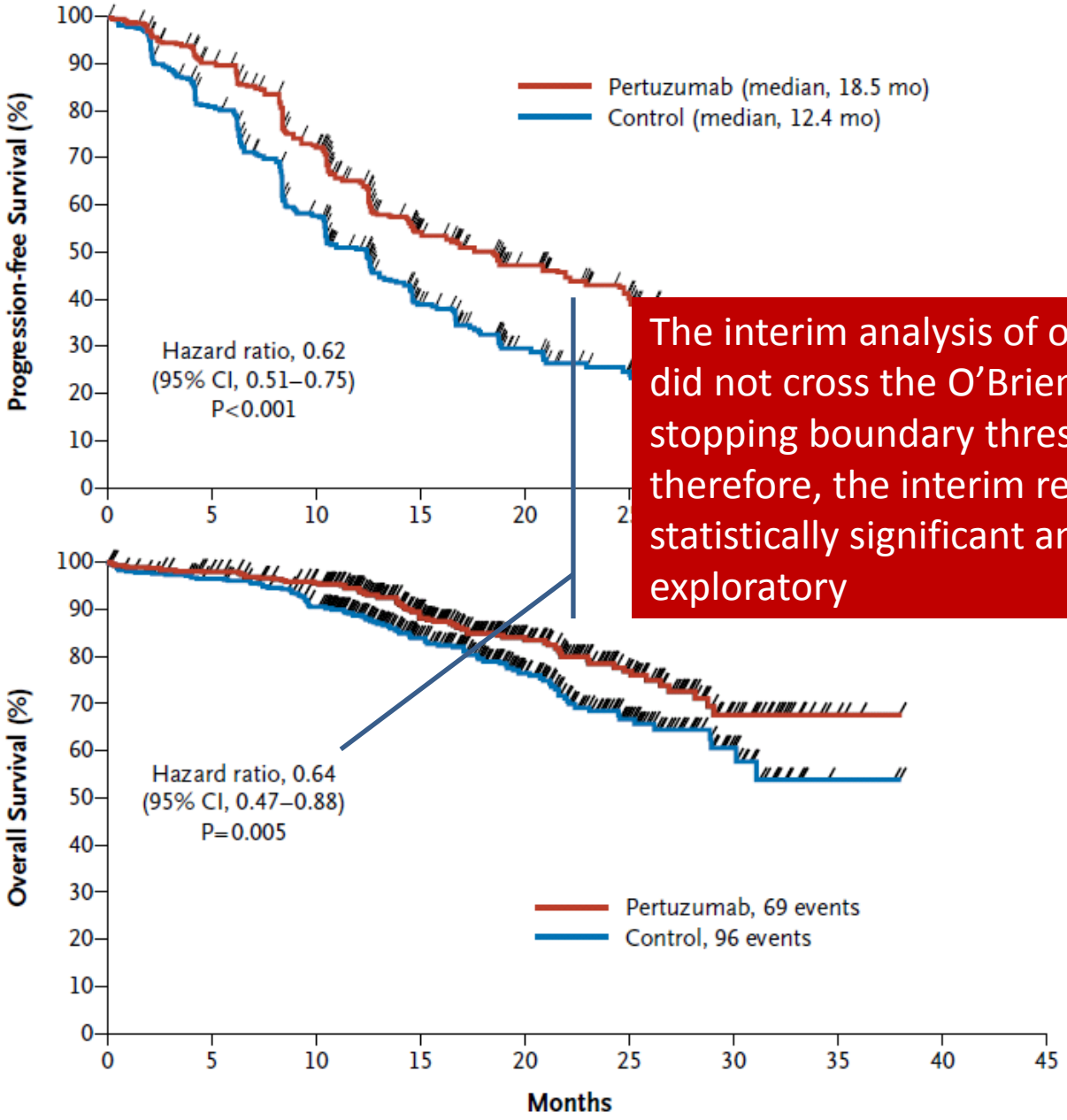
This will provide approximately 80% power to detect a 33% improvement in PFS at 5% 2 sided $\alpha$ error.

## *Statistical Considerations for OS*

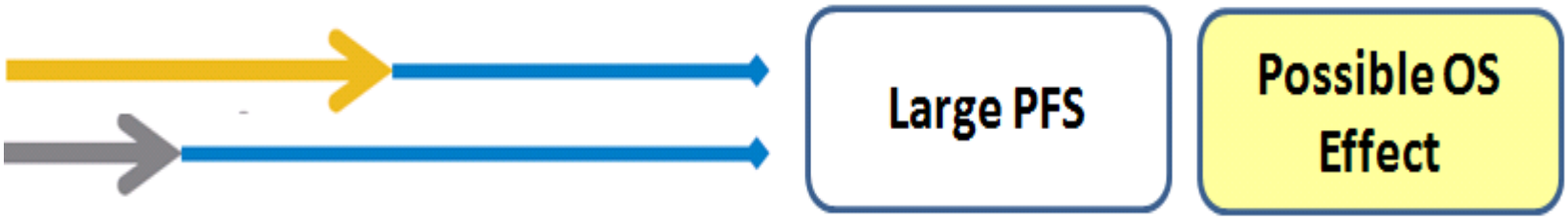
A prespecified interim analysis of overall survival was performed at the time of the primary analysis of independently assessed progression-free survival.

A Lan–DeMets $\alpha$–spending function with the O'Brien–Fleming stopping boundary was applied to the interim analysis of overall survival. If the stopping boundary was not crossed, patients were to continue to receive the study therapy (with group assignments remaining concealed) until the final analysis of overall survival, which is to be performed after 385 deaths have occurred.

With this number of deaths, we estimate that the study will have 80% power to detect a 33% improvement in overall survival in the pertuzumab group.




The interim analysis of overall survival did not cross the O'Brien–Fleming stopping boundary threshold; therefore, the interim result is not statistically significant and is deemed exploratory




- Effetti simili tra $HR_{PFS}$ e $HR_{OS}$
  - $HR_{PPS}$ ≈1
  - Se andamento mantenuto
    - all'analisi finale $HR_{0S}$
      - ≈ 0.75 se PPS=15 mesi
      - ≈ 0.80 se PPS=20 mesi
- Impatto significativo su OS possibile per mancanza cross-over

# Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

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## Summary

**Background** Treatments with survival benefit are greatly needed for women with heavily pretreated metastatic breast cancer. Eribulin mesilate is a non-taxane microtubule dynamics inhibitor with a novel mode of action. We aimed to compare overall survival of heavily pretreated patients receiving eribulin versus currently available treatments.

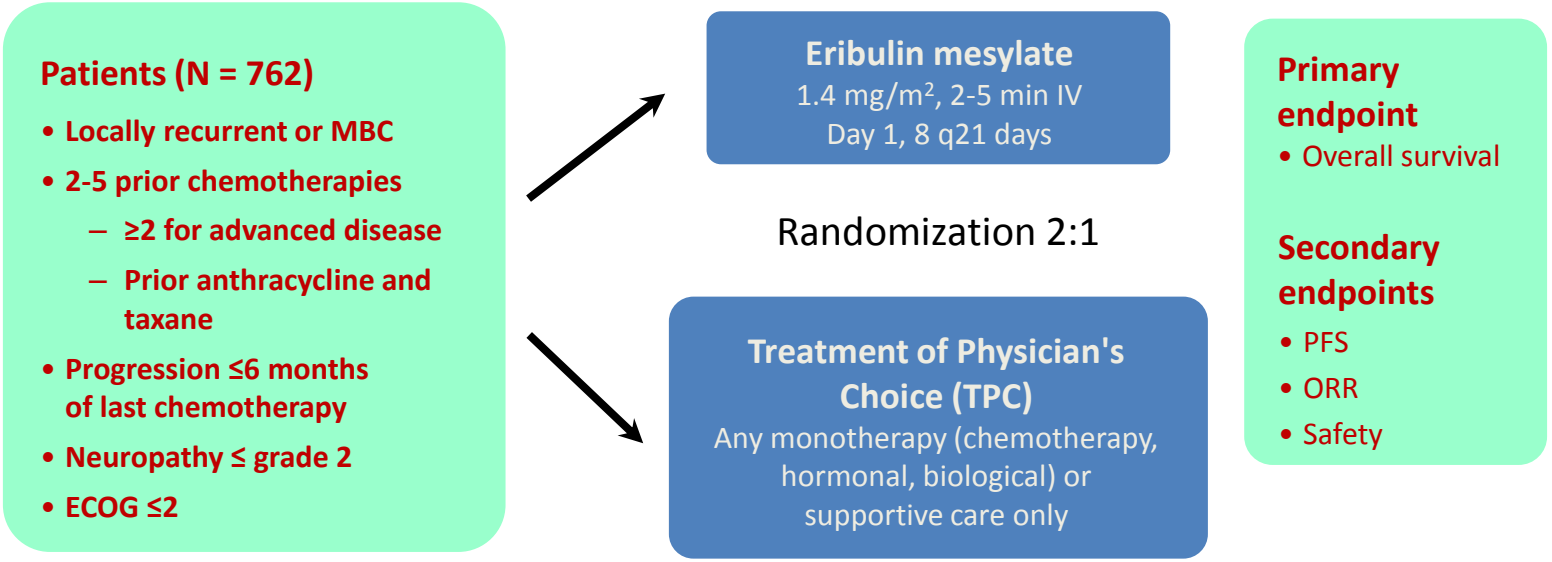
**Methods** In this phase 3 open-label study, women with locally recurrent or metastatic breast cancer were randomly allocated (2:1) to eribulin mesilate (1·4 mg/m² administered intravenously during 2–5 min on days 1 and 8 of a 21-day cycle) or treatment of physician's choice (TPC). Patients had received between two and five previous chemotherapy regimens (two or more for advanced disease), including an anthracycline and a taxane, unless contraindicated. Randomisation was stratified by geographical region, previous capecitabine treatment, and human epidermal growth factor receptor 2 status. Patients and investigators were not masked to treatment allocation. The primary endpoint was overall survival in the intention-to-treat population. This study is registered at ClinicalTrials.gov, number NCT00388726.

**Findings** 762 women were randomly allocated to treatment groups (508 eribulin, 254 TPC). Overall survival was significantly improved in women assigned to eribulin (median 13·1 months, 95% CI 11·8–14·3) compared with TPC (10·6 months, 9·3–12·5; hazard ratio 0·81, 95% CI 0·66–0·99; p=0·041). The most common adverse events in both groups were asthenia or fatigue (270 [54%] of 503 patients on eribulin and 98 [40%] of 247 patients on TPC at all grades) and neutropenia (260 [52%] patients receiving eribulin and 73 [30%] of those on TPC at all grades). Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin, occurring in 24 (5%) of 503 patients.

**Interpretation** Eribulin showed a significant and clinically meaningful improvement in overall survival compared with TPC in women with heavily pretreated metastatic breast cancer. This finding challenges the notion that improved overall survival is an unrealistic expectation during evaluation of new anticancer therapies in the refractory setting.

**Funding** Eisai.

Studio EMBRACE – The Lancet 2011




- Global, randomized, open-label Phase III trial (Study 305, EMBRACE)
- Final analysis after 422 deaths
  - Median age 55.2 yrs, 16% HER2+, 19% TNBC, median 4 prior agents

## *Assessment*

Progression-free survival,objective response rate, and duration of response were based on independent masked review of tumour assessments. We also did sensitivity analyses of these assessments on the basis of the investigator's review.
Tumour response was assessed with RECIST 15 every 8 weeks (within 1 week), or sooner if disease progression was suspected.

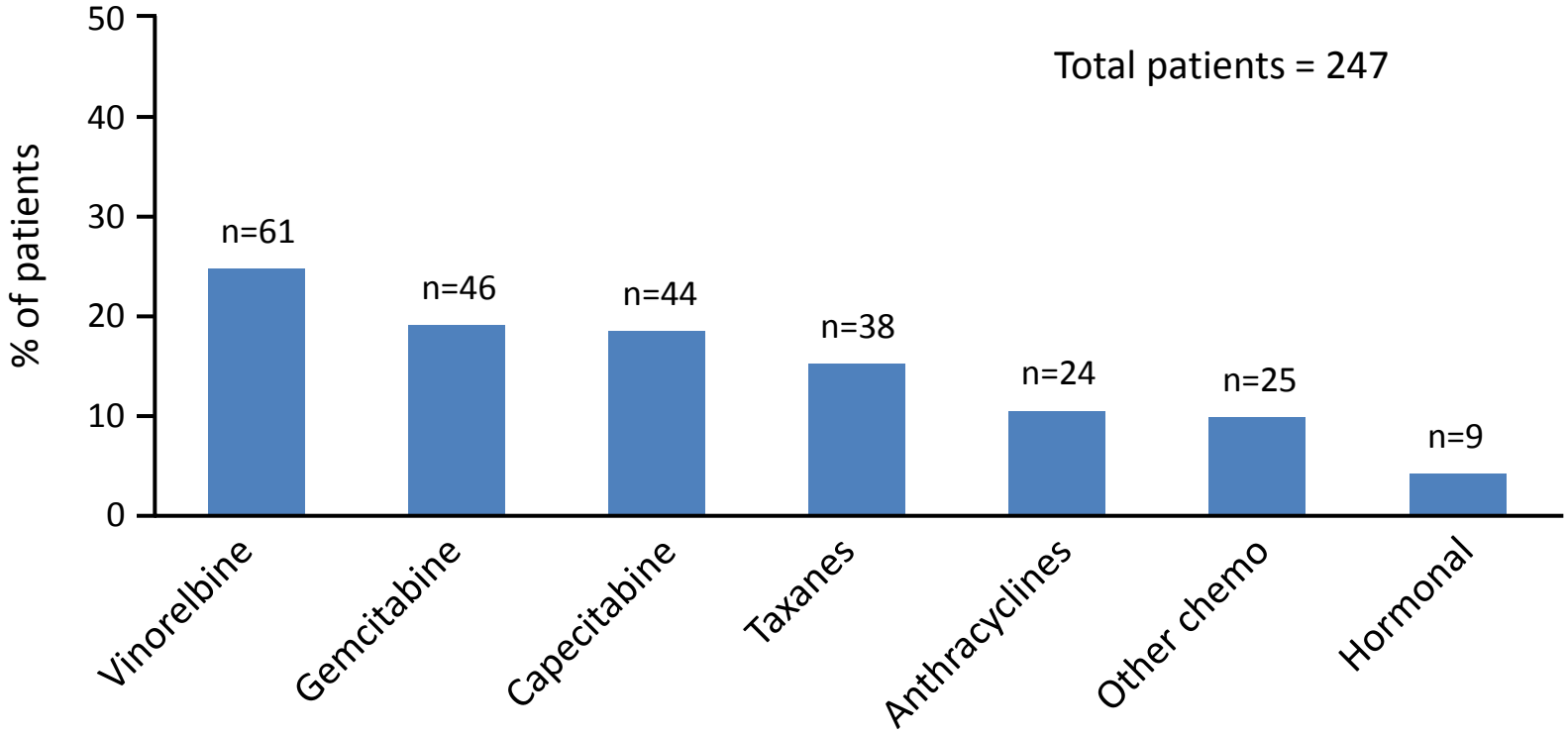
Patients and investigators were not masked to treatment allocation

***Statistical consideration***

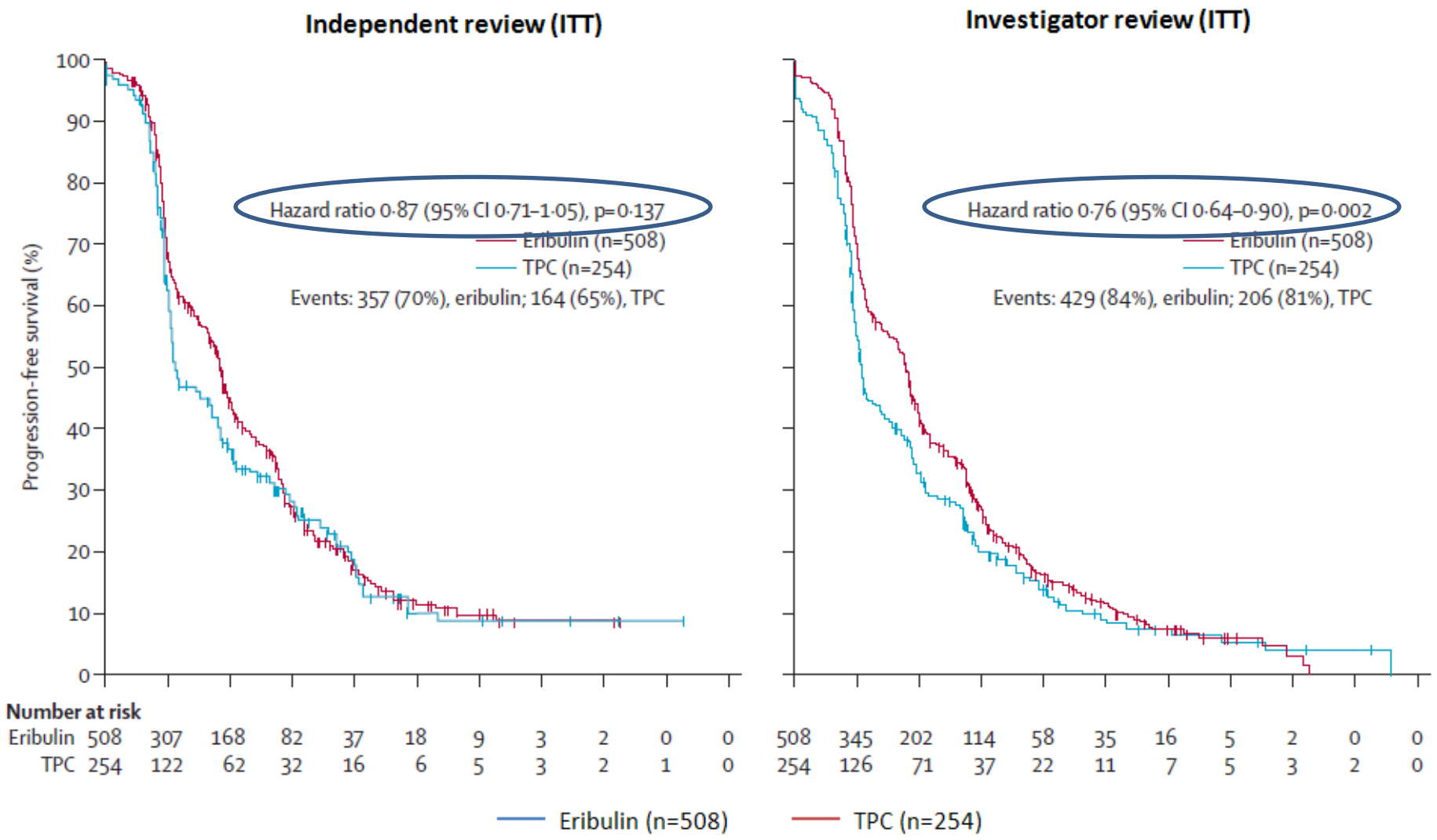
Originally planned to enroll 630 patients to achieve the 411 events (deaths) that were needed for the primary analysis. This number was later increased to a maximum of 1000 patients when the masked evaluation of the overall event rate suggested that deaths were occurring slower than expected. No change was made to the number of events needed for final analysis.

Primary analysis of overall survival included the intention-to-treat (ITT) population with a two-sided stratified log-rank test at a nominal significance level of 0.049 (adjusted for interim analysis). We used a Cox regression model to calculate the hazard ratio (HR). Progression-free survival was analysed with similar methods to overall survival, but with a 5% signifi cance level.

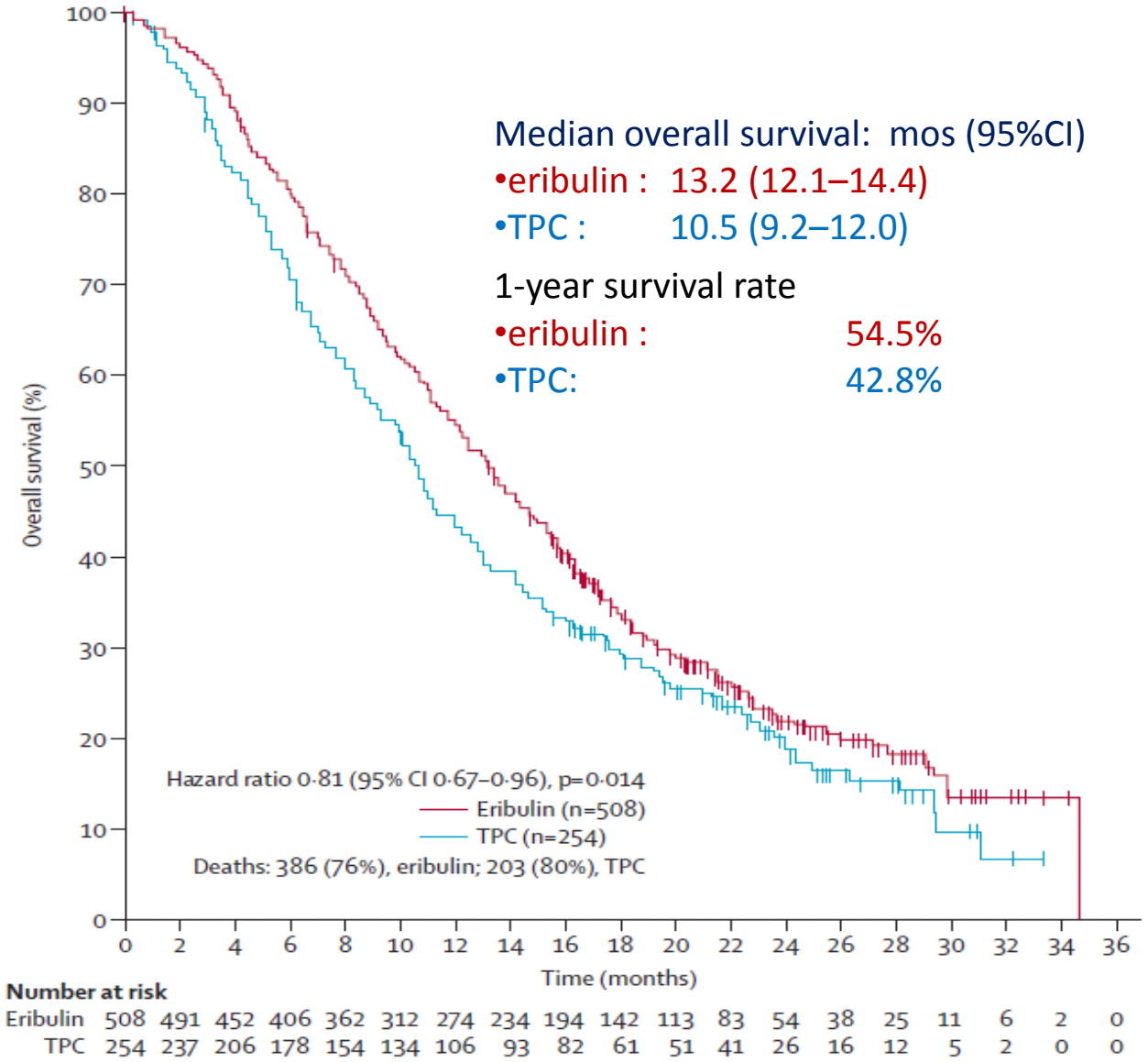
96% of patients treated with chemotherapy




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




# EMBRACE: PFS by Independent and Investigator Review




Median overall survival: mos (95%CI)

- eribulin : 13.2 (12.1–14.4)
- TPC : 10.5 (9.2–12.0)

1-year survival rate

- eribulin : 54.5%
- TPC: 42.8%

## *Side effects*

There was more myelosuppression with eribulin but a lower rate of neutropenic infection and complications.

There was a higher incidence of neuropathy, as is the case with other microtubule inhibitors, but a break in treatment would resolve the neuropathy.

| | Eribulin (n=503) | | | TPC (n=247) | | |
|---|---|---|---|---|---|---|
| | All grades | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 |
| **Haematological** | | | | | | |
| Neutropenia | 260 (52%) | 106 (21%) | 121 (24%) | 73 (30%) | 35 (14%) | 17 (7%) |
| Leucopenia | 116 (23%) | 59 (12%) | 11 (2%) | 28 (11%) | 12 (5%) | 2 (1%) |
| Anaemia | 94 (19%) | 9 (2%) | 1 (<1%) | 56 (23%) | 8 (3%) | 1 (<1%) |
| **Non-haematological** | | | | | | |
| Peripheral neuropathy | 174 (35%) | 39 (8%) | 2 (<1%) | 40 (16%) | 5 (2%) | 0 |

- Bilancio beneficio/danno: ogni 100 pts trattati:
  - ↑14 survivors a 2 anni
  - ↑ 5 casi di neurotossicità
  - ↑17 casi di neutropenia severa
- Impatto significativo su OS reso possibile da mancanza di efficacia delle chemioterapie convenzionali in questa fase di trattamento.