Biosimilari da anticorpi monoclonali: le evidenze derivanti da studi randomizzati

Commento metodologico

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- Obiettivo e disegno dello studio
- Scelta dell’endpoint
- Scelta del margine di equivalenza
- Modalità di analisi

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2012
EMA/CHMP/BMWP/403543/2010
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues

Draft Agreed by Similar Biological Medicinal Products Working Party	**October 2010**
Adoption by CHMP for release for consultation	18 November 2010
End of consultation (deadline for comments)	31 May 2011
Final agreed by BMWP	March 2012
Adoption by CHMP	30 May 2012
Date for coming into effect	1 December 2012

Keywords	***Biosimilars, monoclonal antibodies, similar biological medicinal products, relevant animal model, non-clinical studies, in vitro studies, clinical use, clinical endpoints, extrapolation***

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

Cosa dice l'EMA…

Normally, similar clinical efficacy should be demonstrated in **adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind, normally equivalence trials**.

[…]

The guiding principle is **to demonstrate similar clinical efficacy and safety** compared to the reference medicinal product, not patient benefit *per se,* which has already been shown for the reference medicinal product.

European Medicines Agency
Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues
30 May 2012

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Obiettivo dello studio

Study Aims & Objective

- **Study Aims:** To demonstrate equivalence of CT-P6 and trastuzumab, both given in combination with paclitaxel, as first-line treatment in women with HER2-positive MBC.

Im YH *et al*, ASCO 2013

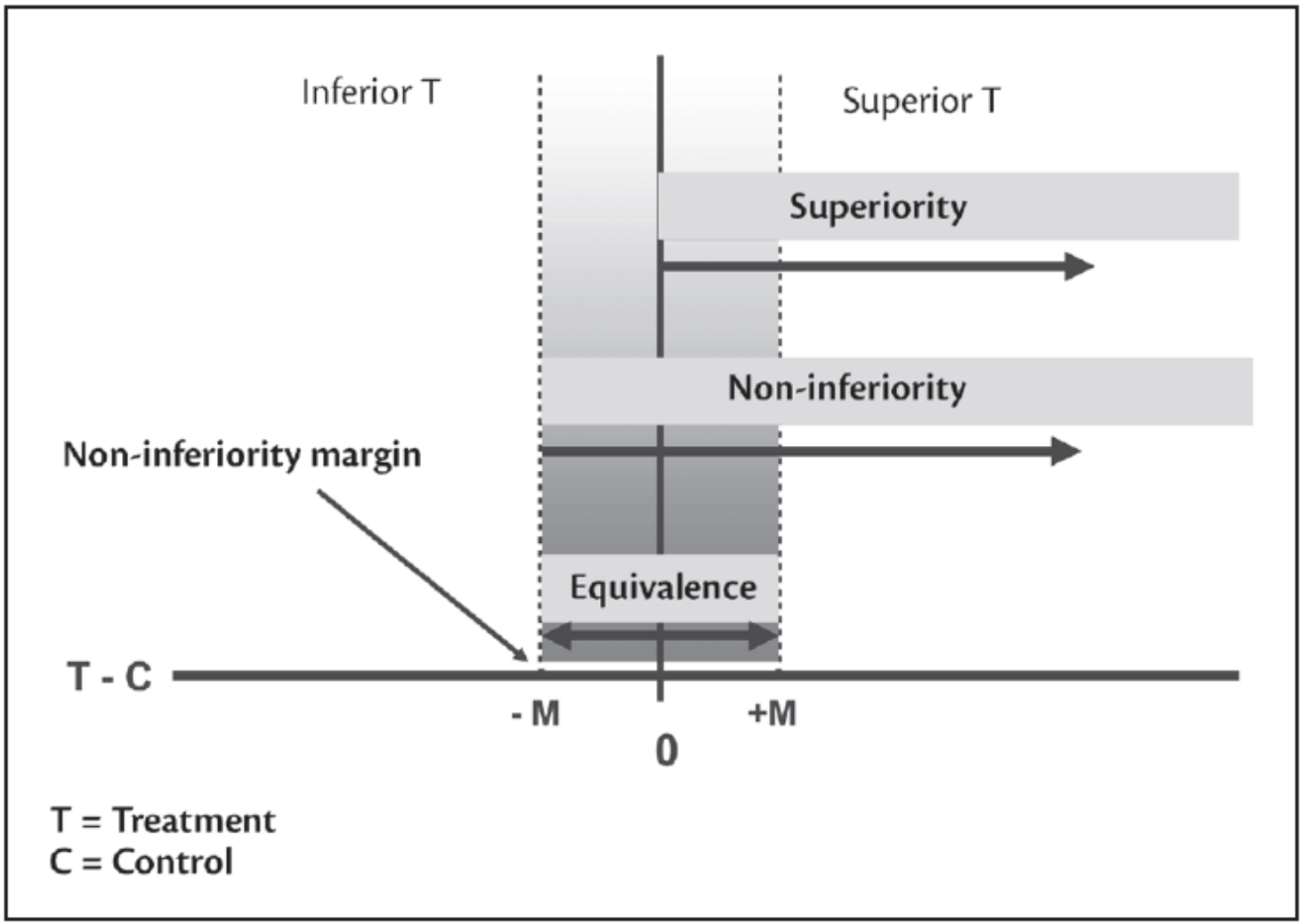


Figure 1 – T: treatment; C: control. T is superior to C if the confidence interval of the difference is entirely at the right of zero, non-inferior if entirely at the right of -M and equivalent if contained in the equivalence zone between -M and +M

CT-P6 vs trastuzumab: pooled analysis di due studi

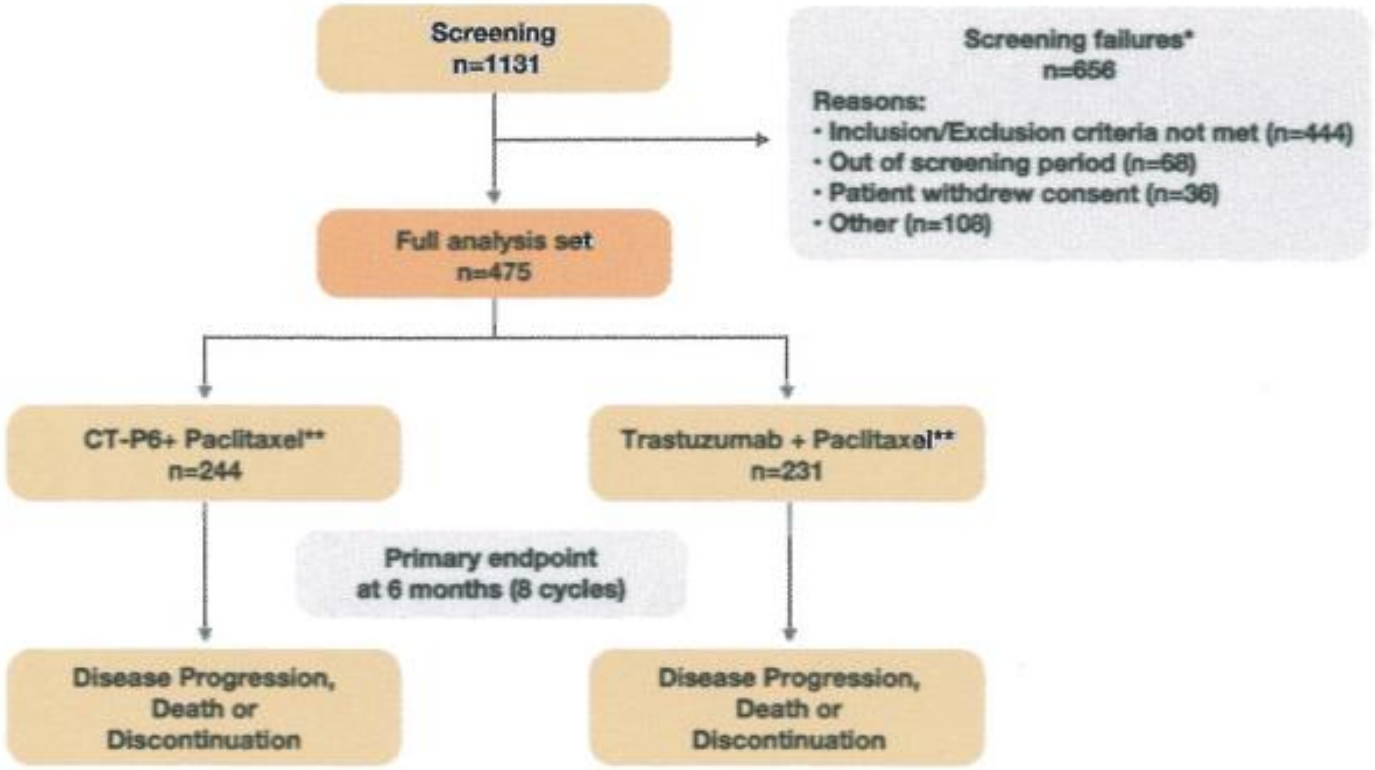
ClinicalTrials.gov	Phase	Endpoint	Pts.
NCT01084863	I-II	Pharmacokinetics	174
NCT01084876	III	Efficacy	383
Total			557

- Same design
- Both double blind
- Same inclusion criteria

Source: clinicaltrials.gov
(March 4, 2014)

Disegno dello studio

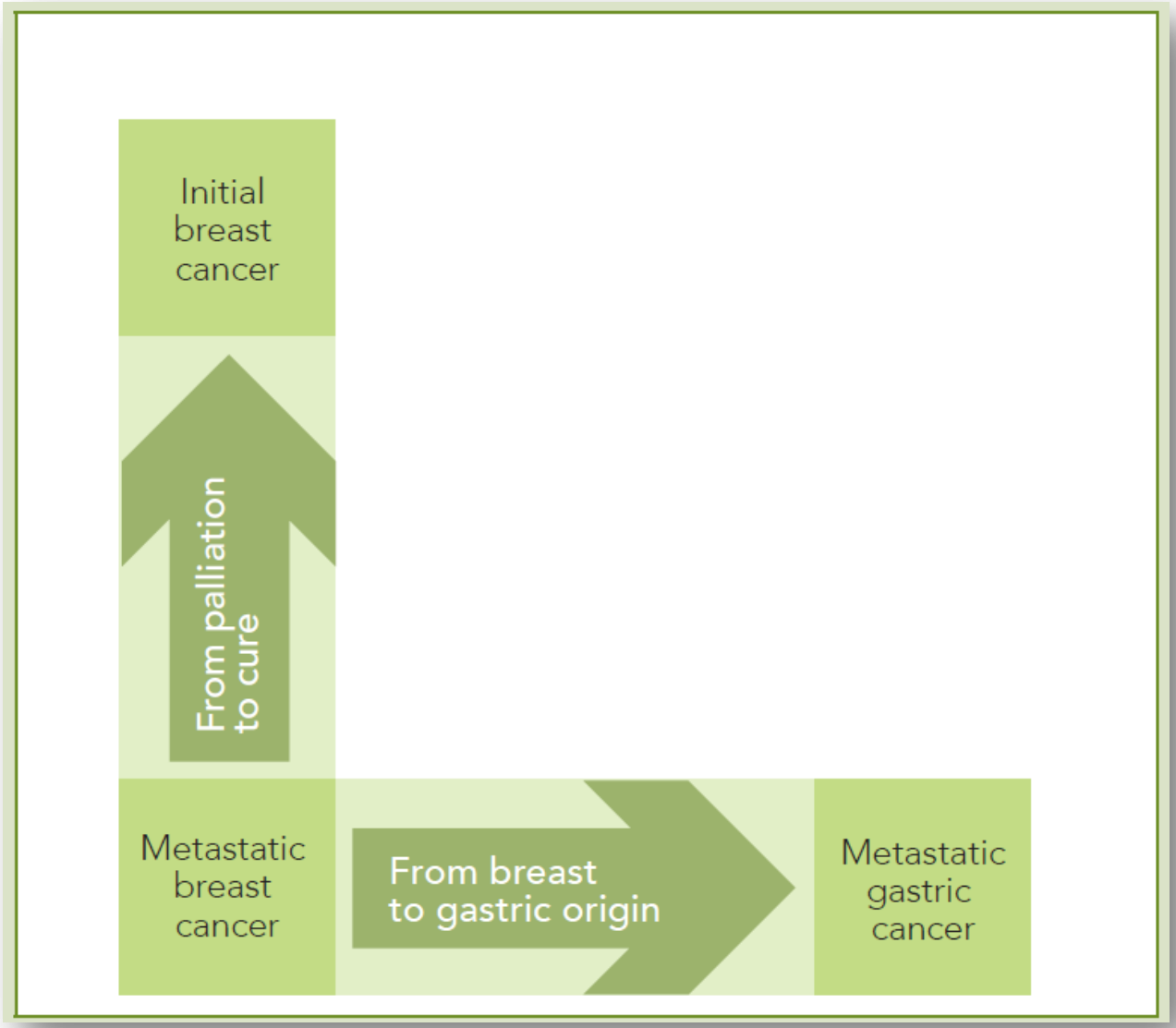
Figure 1. Study design



** Potentially ineligible 82 patients were excluded from analyses.*
*** CT-P6/trastuzumab: 8 mg/kg IV loading (day 1), followed by 6 mg/kg every 3 weeks, Paclitaxel : 175 mg/m2 IV every 3 weeks*

Im YH *et al*, ASCO 2013

Possible extrapolation jumps of a trastuzumab biosimilar…



Courtesy of F. Perrone, 2014

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Cosa dice l'EMA…

In general **the most sensitive patient population and clinical endpoint** is preferred to be able to detect product-related differences, if present and, at the same time, to reduce patient and disease-related factors to a minimum in order to increase precision.

A clinical trial in a **homogeneous patient population with a clinical endpoint that measures activity as primary endpoint** may be considered.

An example may be Overall Response Rate.

[…]

Scelta dell'endpoint

Study Aims & Objective

- **Study Aims:** To demonstrate equivalence of CT-P6 and trastuzumab, both given in combination with paclitaxel, as first-line treatment in women with HER2-positive MBC.
- **Efficacy Objectives**
  - Primary Endpoint: Overall response rate (ORR) (complete response [CR] or partial response [PR]) at 6 months, as assessed by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1.
  - Secondary Endpoints: Time to progression (TTP) by RECIST 1.1; change in target lesion size.

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Margine di equivalenza

When defining comparability margins, clinical considerations need to be taken into account; the selected margins should represent **the largest difference in efficacy that would not matter in clinical practice**.
Treatment differences within these margins would thus be acceptable because they have no clinical relevance.

Weise M et al
Biosimilars: what clinicians should know
Blood, *Dec 20, 2012 vol. 120, no. 26: 5111-5117*

CONSORT modified for equivalence and non-inferiority

The **margin of non-inferiority Δ** should be specified and preferably justified on clinical grounds.

If Δ is too large, there will be too great a risk of accepting a truly inferior treatment as non-inferior.

[…]

If Δ is chosen to be a proportion of the difference between reference treatment and placebo in previous trials (ratio approach), that should be noted.

Piaggio G et al.
Reporting of Noninferiority and Equivalence Randomized Trials Extension of the CONSORT 2010 Statement
JAMA, December 26, 2012—Vol 308, No. 24: 2594-2604

Rates and Durations of Responses.

TABLE 3. RATES AND DURATIONS OF RESPONSES.*

VARIABLE	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Complete response — no. (%)	18 (8)	8 (3)	11 (8)	6 (4)	7 (8)	2 (2)
Partial response — no. (%)	100 (43)	66 (28)	69 (48)	52 (38)	31 (34)	14 (15)
Complete and partial responses — no. (% [95% CI])	118 (50 [44–57])	74 (32 [26–38])	80 (56 [48–64])	58 (42 [34–50])	38 (41 [31–51])	16 (17 [9–24])
P value	<0.001		0.02		<0.001	
Median duration of response — mo	9.1	6.1	9.1	6.7	10.5	4.5
P value	<0.001		0.005		<0.01	

*The analysis included all 469 patients. A complete response was defined as the disappearance of all tumors on the basis of radiographic evidence, visual inspection, or both. A partial response was defined as a decrease in the dimensions of all measurable lesions of more than 50 percent. The duration of response was defined as the time from the first response to disease progression or death. The response-evaluation committee assessed the tumor response in 446 patients: 99 percent of the 452 patients who had an assessment after the base-line evaluation and 95 percent of the 469 patients who enrolled in the study. In the group given paclitaxel and trastuzumab, the response rate was higher among patients who had a Karnofsky score of 90 to 100 at base line. CI denotes confidence interval.

Aggiunta del trastuzumab al paclitaxel
Response rate 16.7% -> 41.3%
(+24.6%, 95%CI +11.7%; +36.6%)

Slamon DJ et al. N Engl J Med 2001;344:783-792.

The NEW ENGLAND JOURNAL of MEDICINE

Statistical analysis for primary endpoint

Table 1. Statistical analysis for primary endpoint

Randomized population, no	557
Target population, no	466
Primary endpoint	**ORR (at cycle 8)**
Statistical assumptions	• Equivalence margin: 15% with alpha = 0.05 • Drop-out rate: 13% • Primary population: randomized patients receiving any study drug, having ≥1 post-baseline assessment
Analytical method for Primary endpoint	• 95% CI for difference in proportion of patients randomized to CT-P6 who have objective response (CR or PR as per RECIST 1.1 criteria) and proportion of patients randomized to trastuzumab who have objective response

• Equivalence margin: 15% with alpha = 0.05

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Statistical analysis for primary endpoint

Equivalence margin	Number of patients (power 80%)	Number of patients (power 90%)
15%	450	556
12.5%	702	868
10%	1010	1248
7.5%	2060	2548
5%	4038	4992

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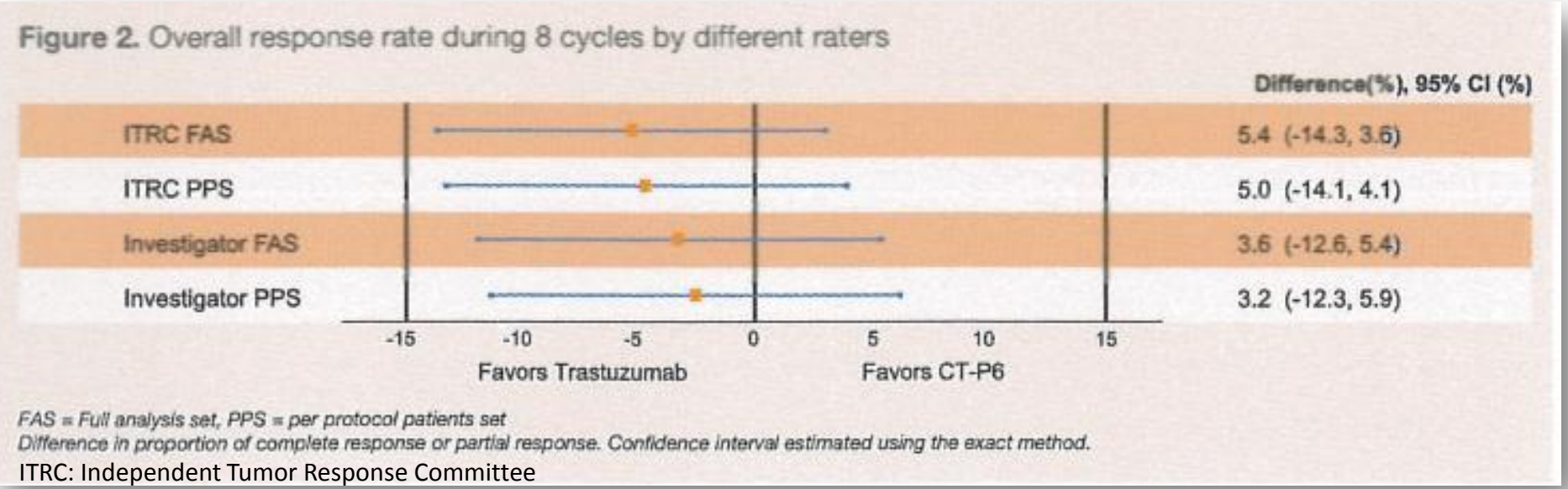
- **Modalità di analisi**

Independent *vs* Investigator
Intention to treat *vs* per protocol



ITRC: Independent Tumor Response Committee

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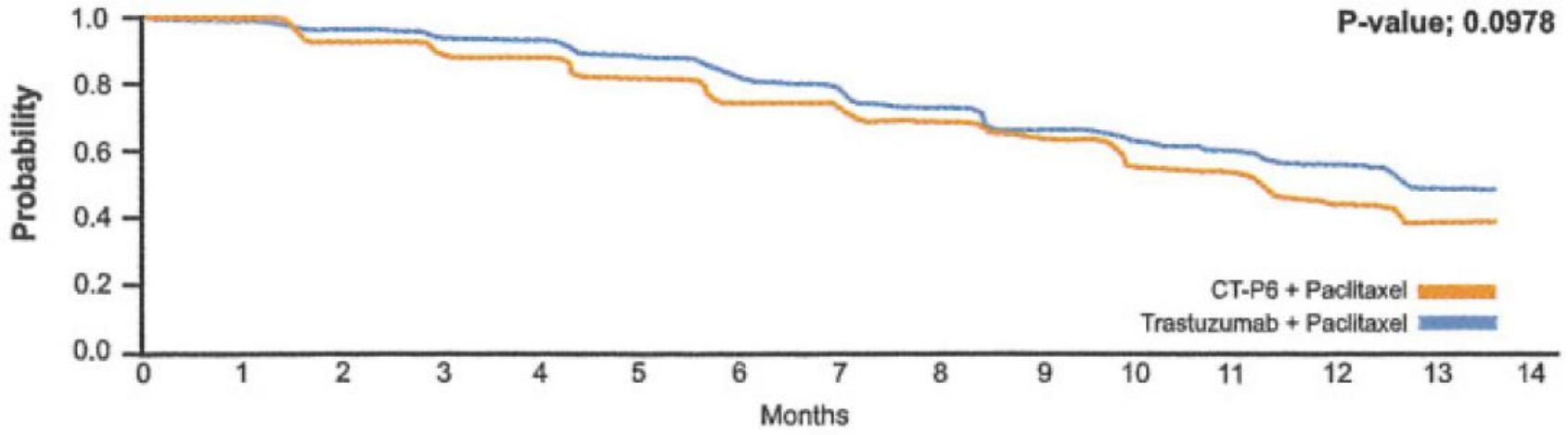
Endpoints secondari: progression-free survival

Figure 3. Kaplan Meier plots of time to progression in the responder group by ITRC (Full analysis set, 1 year data)



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Endpoints secondari: progression-free survival

- Lo studio **NON** era dimensionato per escludere **differenze potenzialmente rilevanti** di PFS

- Uno studio di non inferiorità dimensionato sulla PFS richiederebbe **numeri di pazienti molto maggiori**:

  (Slamon 2001: PFS 7.4 *vs* 4.6 mesi)

  per Δ 1.5 mesi:

  – potenza 80%: 625 eventi

  – potenza 90%: 866 eventi

Aspettando il lavoro *in extenso…*

Conclusions

- **Equivalence of CT-P6 and trastuzumab was observed for efficacy in this phase III trial:**
  - The overall response rate (primary endpoint, complete response [CR] or partial response [PR]) as assessed by RECIST 1.1 of CT-P6 + paclitaxel was equivalent to that of trastuzumab + paclitaxel during 8 cycles as determined.
  - Results for the primary endpoint were supported by the results of the secondary efficacy endpoints.
- **CT-P6 was well tolerated with a safety profile comparable to that of trastuzumab.**

Im YH *et al*, ASCO 2013

Grazie per l'attenzione!

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