Quanto la selezione delle pazienti e la scelta dell'endpoint primario possono influenzare i risultati?

Lo studio CEREBEL

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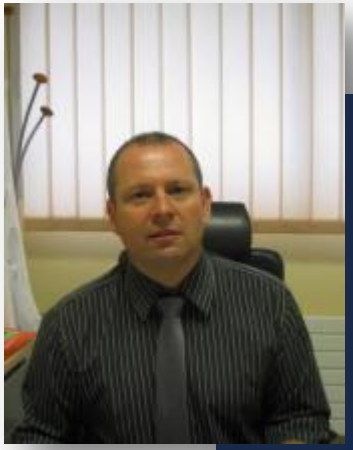
I commenti sono basati sulla presentazione ESMO



CEREBEL (EGF111438): An open-label randomised Phase III study comparing the incidence of CNS metastases in patients with HER2+ metastatic breast cancer, treated with lapatinib plus capecitabine versus trastuzumab plus capecitabine

Xavier Pivot[1], Bogdan Żurawski[2], Rozenn Allerton[3], Alessandra Fabi[4], Eva Ciruelos[5], Roma Parikh[6], Michelle DeSilvio[7], Sergio Santillana[7], Ramona Swaby[7] and Vladimir Semiglazov[8]

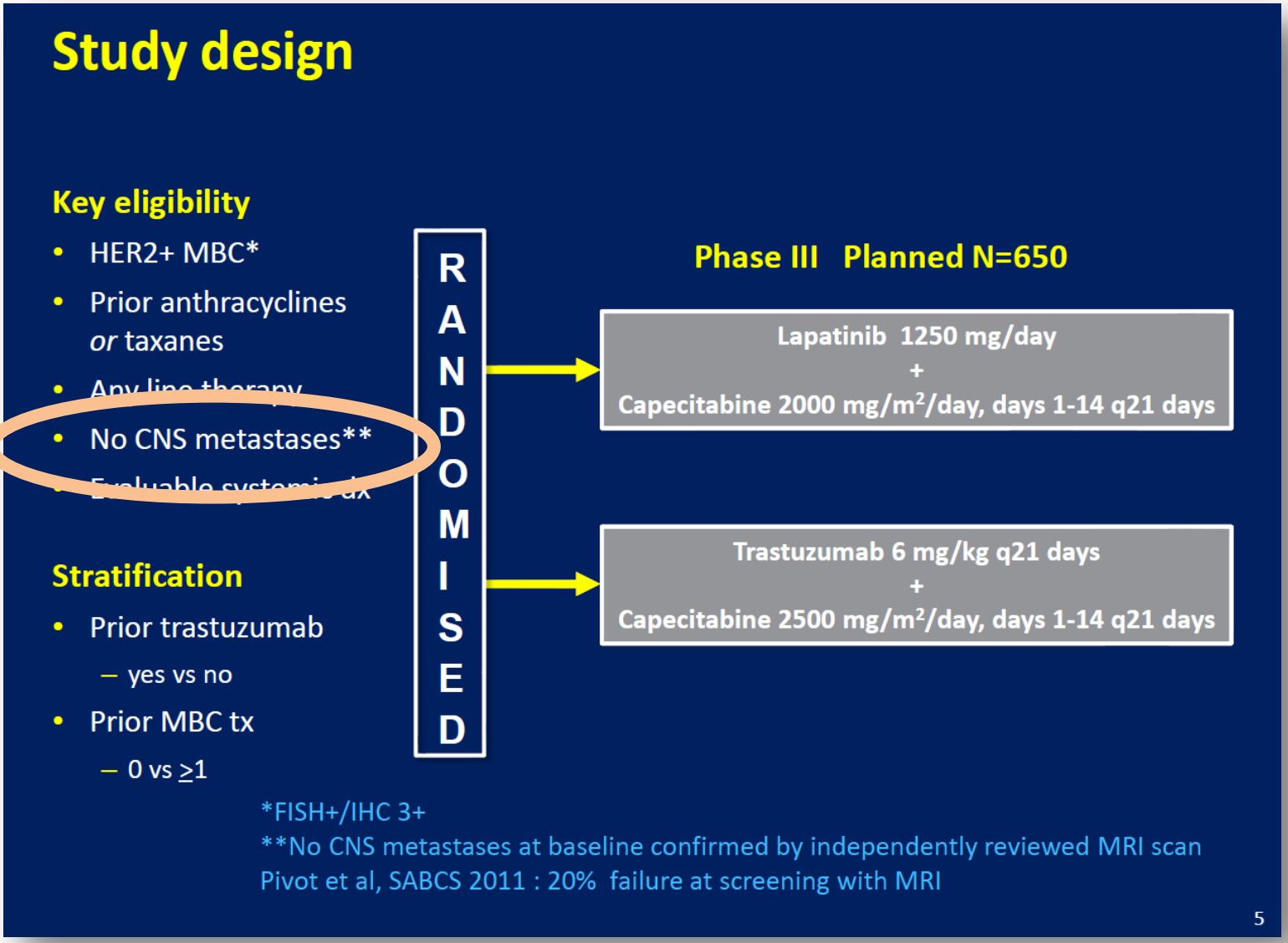
EudraCT number: 2008-000673-38
ClinicalTrials.gov Identifier: NCT00820222

[1]CHU - Hôpital Jean Minjoz, Besançon, France; [2]Centrum Onkologii im. prof. L. Lukaszczyka, Bydgoszcz, Poland; [3]The Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, United Kingdom; [4]Instituto Nazionali Tumori Regina Elena, Roma, Italy; [5]Hospital Universitario 12 de Octubre, Madrid, Spain; [6]GlaxoSmithKline, Uxbridge, United Kingdom; [7]GlaxoSmithKline, Collegeville, PA, USA; [8]Petrov Research Institute of Oncology, St. Petersburg, Russian Federation

Pivot X et al, ESMO 2012, abstract LBA11

Voleva essere uno studio focalizzato sulle metastasi cerebrali…

Ma in realtà…



Pivot X et al, ESMO 2012, abstract LBA11

Incidence Rate of Asymptomatic CNS Lesions in Patients With HER2+ Metastatic Breast Cancer Screened for EGF111438/CEREBEL Study

Xavier Pivot[1], John Hackmann[2], Alexey Manikhas[3], Roma Parikh[4], Dipak Kothari[4], Allison Florance[5], Gursel Aktan[6], Robert Coleman[7]

[1]University Hospital of Besançon, Besançon, France; [2]Marien-Hospital, Witten, Germany; [3]St. Petersburg State Medical Institution: Municipal Clinical Oncology Center, St. Petersburg, Russia; [4]GlaxoSmithKline, Uxbridge, United Kingdom; [5]GlaxoSmithKline, Research Triangle Park, NC, USA; [6]GlaxoSmithKline, Collegeville, PA, USA; [7]Weston Park Hospital, Sheffield, United Kingdom

Figure 2. EGF111438/CEREBEL brain MRI acquisition checklist.[a]

Scanner

☐ 1.5T (**minimum requirement**)

Slice thickness

☐ 3 mm, no gaps (**mandatory**)

Contrast (gadolinium) T1 only

☐ IV (**mandatory**)

Sequences

☐ Axial T1-weighted whole brain MRI without gadolinium

☐ Axial T2-weighted whole brain MRI

☐ Axial postgadolinium T1-weighted whole brain MRI

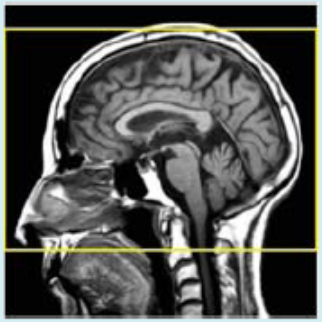
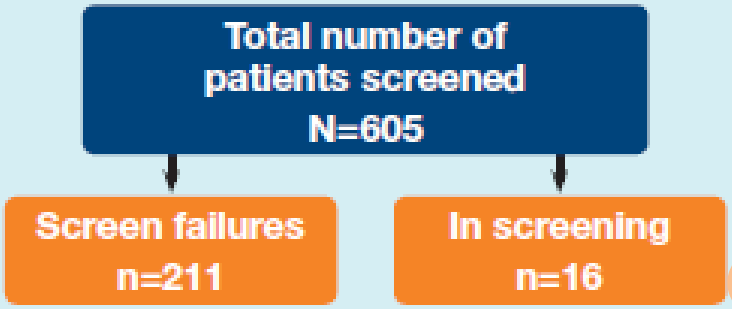


Figure 3. Study conduct.



	Number of patients n/N (%)
Screen failures due to asymptomatic brain metastases	120/211 (56.9)
Overall incidence of asymptomatic brain metastases	120/605 (19.8)

Pivot X et al, SABCS 2011, abstract P4-17-03

SABCS: Silent Brain Mets Common in Breast Cancer

This report is part of a 12-month Clinical Context series.

By Ed Susman, Contributing Writer, MedPage Today
Published: December 10, 2011
Reviewed by Vandana G. Abramson, MD; Assistant Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee and Dorothy Caputo, MA, RN, BC-ADM, CDE, Nurse Planner

- "We have clearly **underestimated** the incidence of asymptomatic brain metastases in women with advanced breast cancer", Pivot said during the SABCS.
- "Approximately **20%** of all screened patients in this study thought to be clinically free of brain lesions actually had brain metastases verified by brain MRI", Pivot reported.
- He said that he plans to follow this retrospective patient population in a prospective manner. He said that it will take a least a year of prospective study **to determine what impact these silent lesions have on overall outcomes**.

medpage TODAY

Quando l'osservato non coincide con l'atteso…

	% metastasi SNC braccio trastuzumab	% metastasi SNC braccio lapatinib
Ipotizzato	**20%**	**12%**
Osservato		

Incidenza assoluta clinicamente rilevante: 1 donna su 5

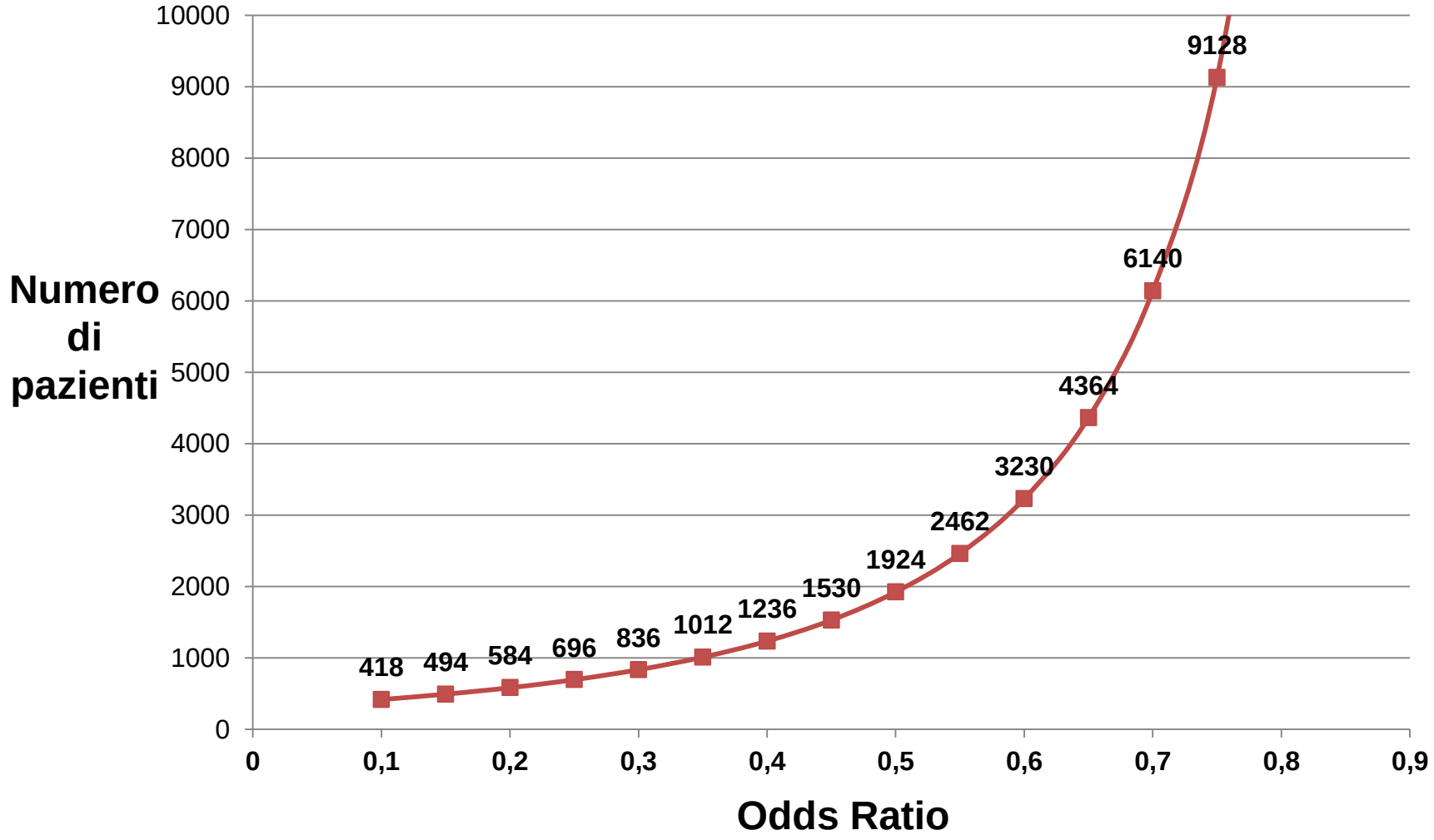
Vantaggio ipotizzato clinicamente rilevante: incidenza quasi dimezzata!

Quando l'osservato non coincide con l'atteso…

	% metastasi SNC braccio trastuzumab	% metastasi SNC braccio lapatinib
Ipotizzato	**20%**	**12%**
Osservato	**5%**	

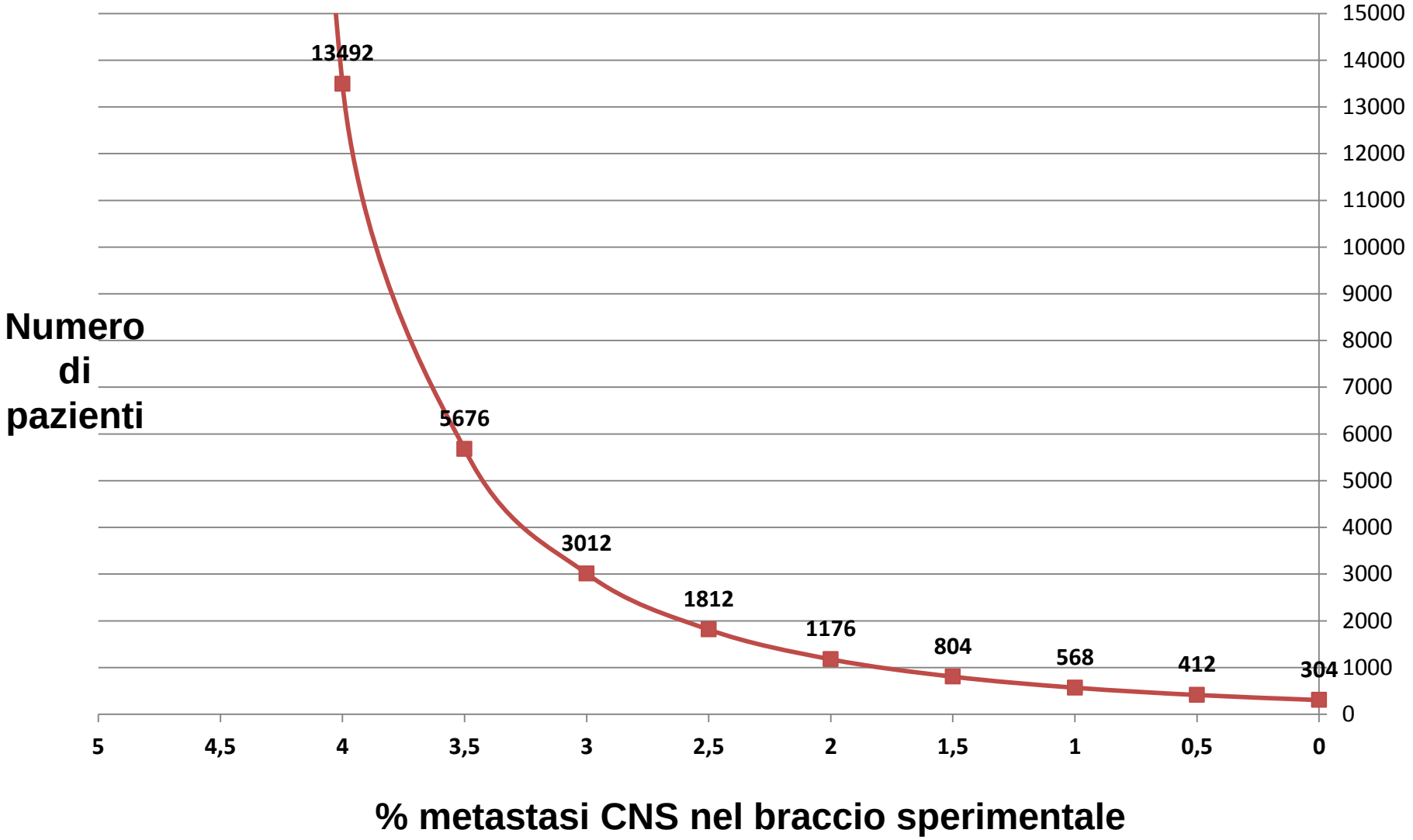
Di quante pazienti avremmo avuto bisogno?

% metastasi SNC braccio di controllo 5%, alfa 5%, potenza 80%



Di quante pazienti avremmo avuto bisogno?

% metastasi SNC braccio di controllo 5%, alfa 5%, potenza 80%



Conclusions (1)

- Inconclusive for primary endpoint (CNS as first site of relapse)
  - There was a low incidence of brain metastases as the first site of progression in both arms
  - These are the first prospective data in subjects with HER2-positive MBC showing an approximate 20% incidence of asymptomatic brain metastases

(Pivot et al 2011)

- In the ITT population, PFS was longer for those who received trastuzumab plus capecitabine
- In the trastuzumab naïve group, trastuzumab plus capecitabine had superior efficacy
- In the group previously treated by trastuzumab no superiority was observed

Pivot X, et al. San Antonio Breast Cancer Symposium 2011

Pivot X et al, ESMO 2012, abstract LBA11

Ma secondo me…

- …non è tanto un problema di **underpower** dovuto ai **criteri di esclusione**

- È invece un problema di **scelta dell'endpoint primario!**

Study objectives

- **Primary Objective**
  - Incidence of CNS as site of first relapse
- **Secondary Objectives**
  - PFS (time from randomisation to progression and/or death)
  - OS
  - ORR, CBR
  - Time to first CNS progression
  - Incidence of CNS progressions at any time
  - Safety

Pivot X et al, ESMO 2012, abstract LBA11

…perfettamente coerente con quanto richiesto dall'EMA nel 2008

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame. The results of which shall be taken into account in the risk benefit balance during the assessment of the application for a renewal.

Clinical aspects

1. To perform and submit an updated analysis of survival data for study EGF100151. A data cut-off date of August 2008 will be applied, with the results of the analysis to be submitted by Decembe[illegible] 2008.

2. To conduct a Phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate, trastuzumab-containing control arm.

   The study protocol will be finalised and submitted to the EMEA by July 2008. The final study report for the trial will by submitted by May 2013.

http://ec.europa.eu/health/documents/community-register/2008/2008061046548/anx_46548_en.pdf

Setting

HER2+ metastatic breast cancer progressed after trastuzumab-based therapy

Study	Exp arm	Std arm	Result
GBG 26/BIG 3-05 (Geyer, NEJM 2006)	Lapatinib + capecitabine	Capecitabine	Better PFS
EGF100151 (von Minckwitz, ASCO 2008)	Trastuzumab + capecitabine	Capecitabine	Better PFS

Milestones

- Conditional approval granted for lapatinib plus capecitabine in EU: June 2008
- CEREBEL was a Specific Obligation measure required by CHMP
- First patient randomised: April 2009
- IDMC meeting for preplanned IA: June 6, 2012; n=475
- Study terminated based on IDMC recommendation: June 11, 2012
- Final analysis database lock: June 11, 2012; n=540

Adesso votiamo: quale popolazione avreste scelto?

1. **HER2+, pretrattate con trastuzumab**
2. **HER2+, non pretrattate con trastuzumab**
3. **HER2+, sia pretrattate che non pretrattate con trastuzumab**

Adesso votiamo: quale endpoint avreste scelto?

1. Incidence of CNS as site of first relapse
2. PFS
3. OS
4. Objective response
5. Time to first CNS progression
6. Incidence of CNS progression at any time
7. Safety

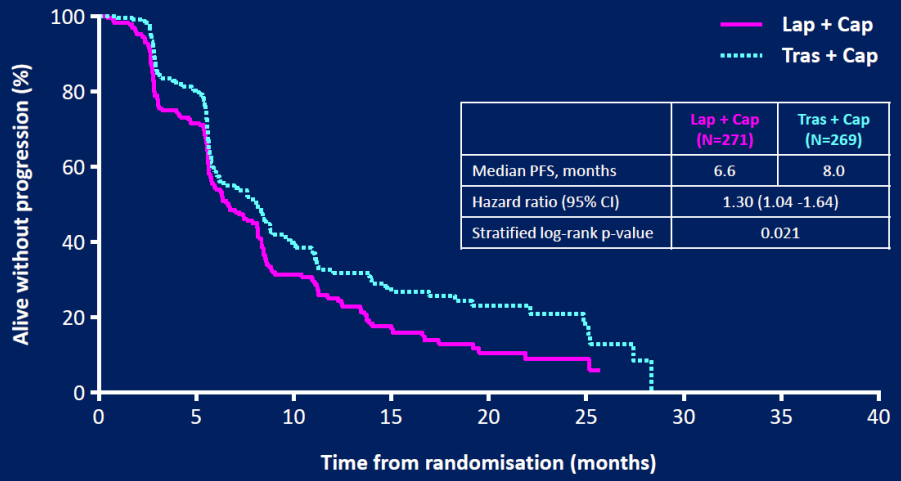
Pragmatic vs explanatory trials

- **Pragmatic research** asks whether an intervention works under real-life conditions and whether it works in terms that matter to the patient.
  - Pragmatic studies are most useful for deciding what services should be provided.
- **Explanatory research** asks whether an intervention works under ideal or selected conditions.
  - Explanatory studies are valuable for understanding questions of efficacy but are of limited value for telling us whether we should provide a service to a wide variety of patients in a wide variety of circumstances.

What are pragmatic trials? Roland and Torgerson. BMJ 1998;316:285
Can it work? Does it work? Is it worth it? Haynes. BMJ 1999;319:652-653

	Explanatory trials	Pragmatic trials
Selection criteria	Selective	Broad, similar to clinical practice
Question	Can this work? (under ideal conditions)	Does this work? (under routine conditions)
Point of view	Registrative	Clinical practice
Endpoint	Related to treatment activity	Related to treatment efficacy

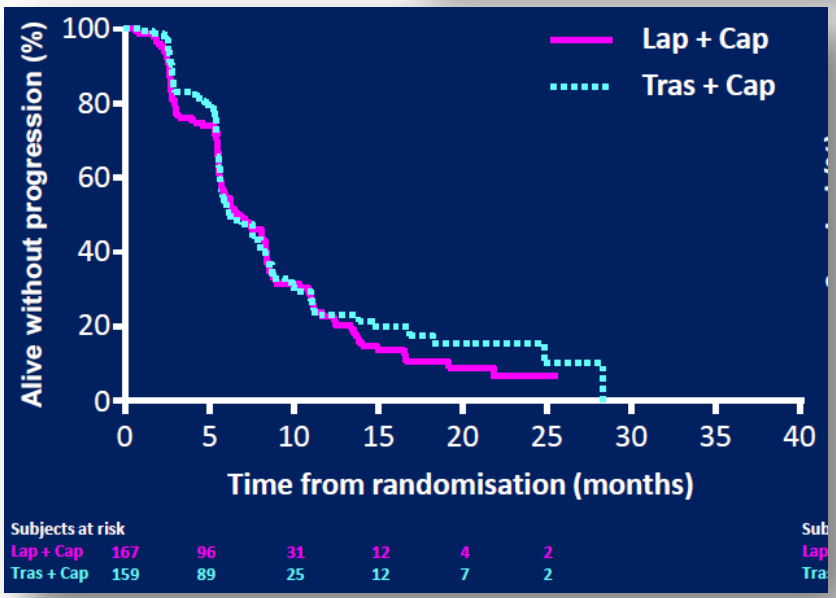
Investigator-assessed PFS (ITT population)

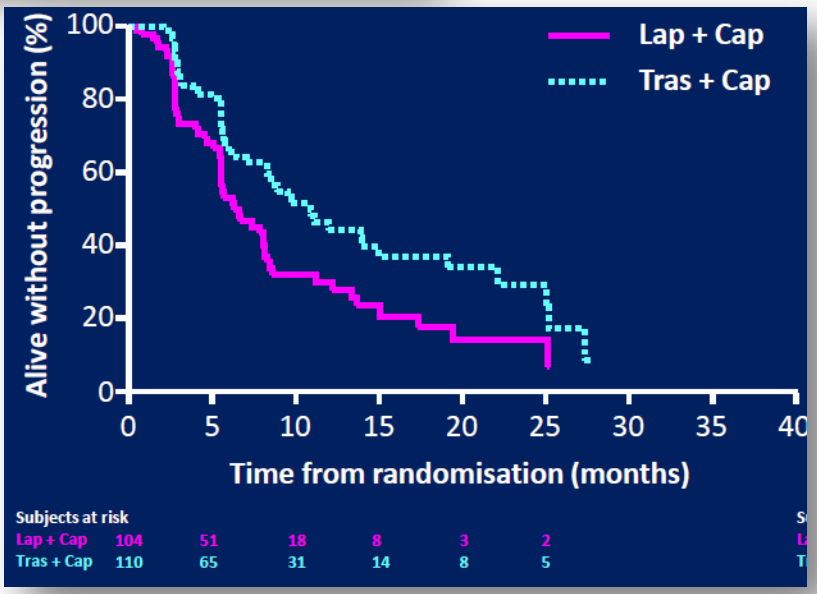


	Lap + Cap (N=271)	Tras + Cap (N=269)
Median PFS, months	6.6	8.0
Hazard ratio (95% CI)	1.30 (1.04 -1.64)	
Stratified log-rank p-value	0.021	

Subjects at risk

Lap + Cap	271	147	49	20	20	7	4
Tras + Cap	269	154	56	26	26	15	7





Pivot X et al, ESMO 2012, abstract LBA11

Conclusions (2)

- **Lapatinib in combination with capecitabine is indicated for use after progression of disease on a prior trastuzumab containing regimen in the metastatic setting**
- The safety profile of lapatinib + capecitabine was consistent with the registration study EGF100151 and the es safety profile
  - The incidence of AEs, SAEs and AEs leading to discontir and similar between treatment arms
- **Proactive diarrhoea management is important fc and quality of life**
  - 6% Grade 3/4 lapatinib + capecitabine
  - 8% Grade 3/4 trastuzumab + capecitabine

?

Pivot X et al, ESMO 2012, abstract LBA11

Grazie per l'attenzione!

Massimo Di Maio

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