QUANTO LA SELEZIONE DELLE PAZIENTI E LA SCELTA DELL'ENDPOINT PRIMARIO POSSONO INFLUENZARE I RISULTATI?

Lo studio Cerebel

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ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

PM

Persona informata sui fatti

Giudice (impatto sul clinicalpractice)

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

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

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ARRUOLAMENTO


Russia

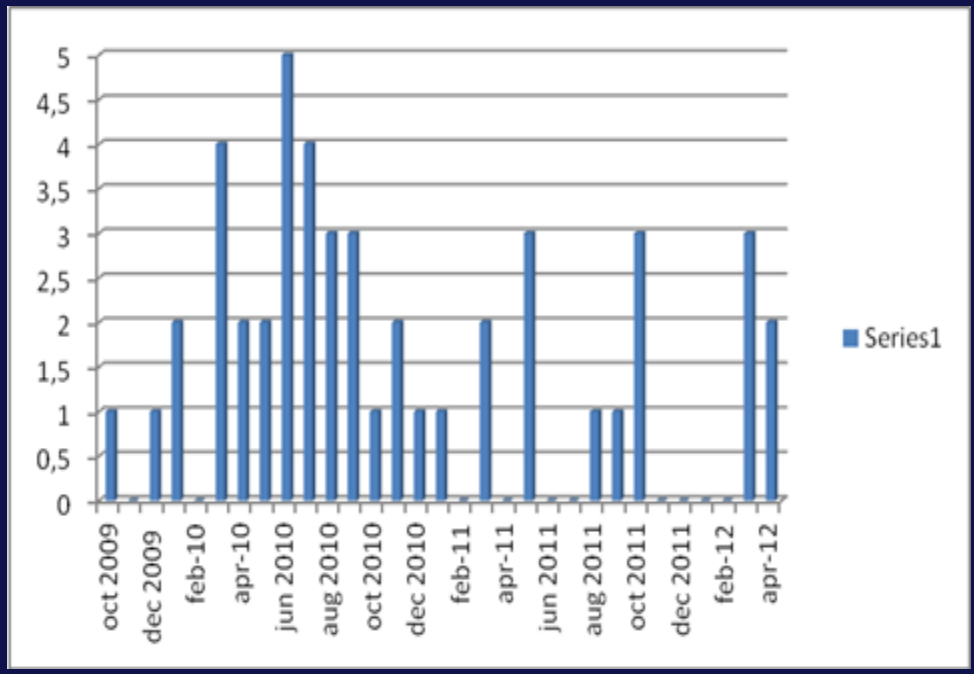
Polonia

UK → 64
Italia


ARRUOLAMENTO ITALIANO

Centri
Fabi
Martoni
Bidoli
Gori
Puglisi
Ravaioli
Giardina
Amadori
Brandes
Barni
Falcone
Ferro
TOTALE

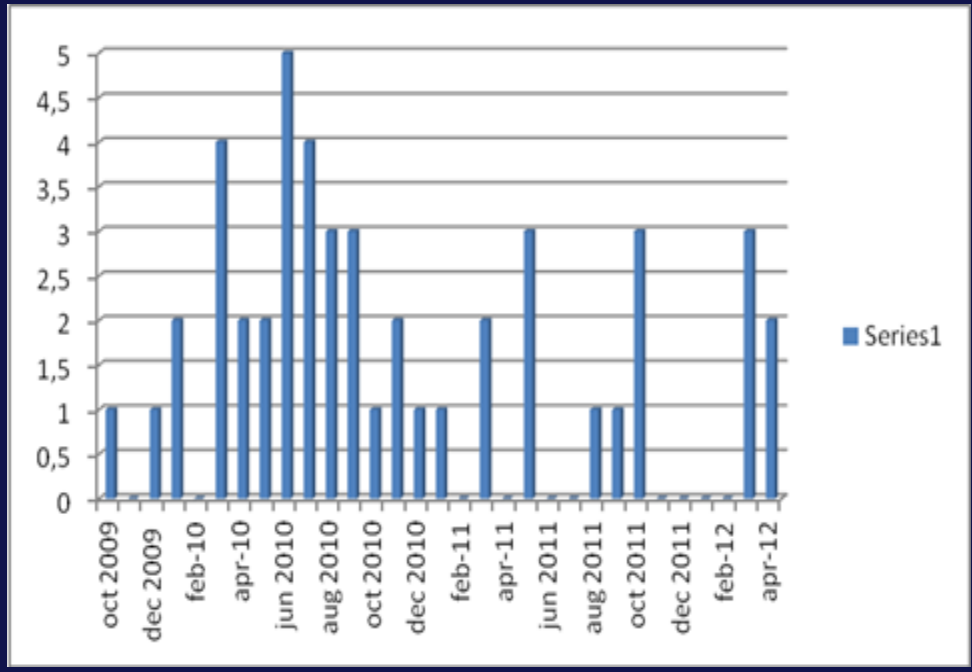
Andamento dell'arruolamento



ARRUOLAMENTO

ARRUOLAMENTO ITALIANO

Andamento dell'arruolamento



Background

- **Lapatinib and capecitabine**
  - Is approved for the treatment of patients with HER2+ MBC who have progressed on prior trastuzumab therapy in the metastatic setting (Geyer et al 2006; Cameron et al 2008)
- **Trastuzumab and capecitabine**
  - Clinical activity in patients with HER2+ MBC (Von Minckwitz et al 2009)
- **CNS metastases** constitute a major clinical concern in 28–43% of trastuzumab-treated HER2+ MBC patients (Bendell et al 2003; Clayton et al 2004)
  - Lapatinib and capecitabine demonstrated a lower incidence of CNS metastases (Cameron et al 2008)
  - EMA requested a confirmatory study

Geyer CE, et al. N Engl J Med 2006;355:2733-43; Cameron D, et al. Breast Cancer Res Treat 2008;112:533-43; Von Minckwitz G, et al. J Clin Oncol 2009;27:1999-2006; Bendell JC, et al. Cancer 2003;97:2972-7; Clayton AJ, et al. Br J Cancer 2004;91:639-43

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

Milestones…….and the dates

- Additional approved granted for lapatinib/capecitabine in EU: **June 2008**

- Cerebel was a specific Obligation measure required by CHMP

- The study enrolled the first patient on **14 April 2009**.

- Based upon recommendations of the CEREBEL IDMC **(convened on 6 June 2012)**, following analysis of the interim safety and efficacy data of 475 randomised patients, the study was terminated on **11 June 2012** (final analysis 540 pts).

Anotherpoint….

The protocol was subsequently amended to include an independent review of baseline and on-study CNS MRI scans to both confirm eligibility as well as recurrence, because 39 of the first 199 accrued patients showed abnormalities on their baseline MRI that could not be adjudicated.

Study design

Key eligibility

- HER2+ MBC*
- Prior anthracyclines *or* taxanes
- Any line therapy
- No CNS metastases**
- Evaluable systemic dx

Stratification

- Prior trastuzumab
  - yes vs no
- Prior MBC tx
  - 0 vs ≥1

RANDOMISED

Phase III Planned N=650

Lapatinib 1250 mg/day
+
Capecitabine 2000 mg/m²/day, days 1-14 q21 days

Trastuzumab 6 mg/kg q21 days
+
Capecitabine 2500 mg/m²/day, days 1-14 q21 days

*FISH+/IHC 3+

**No CNS metastases at baseline confirmed by independently reviewed MRI scan

Pivot et al, SABCS 2011 : 20% failure at screening with MRI

Statistical design

- 650 subjects were required to detect an absolute decrease in the incidence of CNS as site of 1st relapse of 8%
  - Assuming an incidence of 20% CNS metastases in the trastuzumab + capecitabine arm, and
  - Resulting in an incidence of 12% CNS metastases in the lapatinib + capecitabine arm
  - Provide 80% power with a 2-sided α=0.05
- Incidence of CNS based on adjusted odds ratio estimate from the logistic regression model
- CNS metastasis incidence assumptions based on unscreened patient population

Results: patient demographics and tumour characteristics

	Lapatinib + capecitabine (N=271)	Trastuzumab + capecitabine (N=269)
Age in years, median (range)	53 (27–83)	56 (31–79)
ECOG status at baseline, n (%)		
n	269	266
0/1	260 (96)	261 (98)
2	9 (3)	5 (2)
Race, n (%)		
Caucasian/White	266 (98)	261 (97)
HER2 status, n(%)		
IHC 3+ only	235 (87)	223 (83)
FISH+	62 (23)	63 (23)
Oestrogen receptor status, n(%)		
ER+	133 (49)	122 (45)
ER-	135 (50)	144 (54)
Unknown	3 (1)	3 (1)
Progesterone receptor status, n(%)		
PR+	98 (36)	80 (30)
PR-	158 (58)	173 (64)
Unknown	15 (6)	16 (6)

Results: patient demographics and tumour characteristics

	Lapatinib + capecitabine (N=271)	Trastuzumab + capecitabine (N=269)
Stage IV at initial diagnosis	52 (19)	44 (16)
Visceral disease, n(%)	173 (64)	164 (61)
# of Involved sites		
≥3	77 (28)	78 (29)
<3	194 (72)	191 (71)
Patients who have received prior trastuzumab, n (%)	167 (62)	159 (59)
Adjuvant	81 (30)	70 (26)
Metastatic	96 (35)	93 (35)

Exposure to study treatment

	Lapatinib + capecitabine (N=269)		Trastuzumab + capecitabine (N=267)	
	Lapatinib 1250 mg daily	Capecitabine 2000 mg/m²	Trastuzumab q3 weekly*	Capecitabine 2500 mg/m²
Daily dose (mg), median (range)	1250 (678–1427)	1336 (691–2120)	8.0 cycles (1–40)	1630 (698–2500)
Patients with dose reductions, n (%)	29 (11)	113 (42)	-	120 (45)
Number of dose reductions, n (%)				
0	240 (89)	156 (58)	-	147 (55)
1	27 (10)	70 (26)		71 (27)
2	1 (<1)	37 (14)		32 (12)
3 or more	1 (<1)	6 (2)		17 (6)
Patients with dose interruptions, n (%)	111 (41)	180 (67)	109 (41)	204 (76)

*No dose reductions for trastuzumab were permitted per protocol

Overview of safety profile

	Lapatinib + capecitabine (N=269)	Trastuzumab + capecitabine (N=267)
All AEs, n (%)	245 (91)	245 (92)
Serious AEs, n (%)	34 (13)	45 (17)
Fatal AEs, n (%)	4 (1)	1 (<1)
AEs leading to study treatment discontinuation, n (%)	29 (11)	35 (13)

Key AEs by maximum toxicity grade

AE, n (%)	Lapatinib + capecitabine (N=269)				Trastuzumab + capecitabine (N=267)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4 (1)	24 (9)	7 (3)	2 (<1)	3 (1)	25 (9)	11 (4)	4 (1)
Febrile neutropenia	-	-	0	0	-	-	0	0
Anaemia	3 (1)	12 (4)	3 (1)	0	3 (1)	18 (7)	4 (1)	0
PPE	60 (22)	47 (17)	25 (9)	0	56 (21)	58 (21)	40 (15)	1 (<1)
Diarrhoea	67 (25)	38 (14)	16 (6)	0	51 (19)	33 (12)	21 (8)	0
Rash	46(17)	9 (3)	4 (1)	0	13 (5)	5 (2)	1 (<1)	0
Stomatitis	11 (4)	4 (1)	1 (<1)	0	9 (3)	10 (4)	4 (1)	0
ALT	13 (5)	17 (6)	3 (1)	0	9 (3)	18 (7)	6 (2)	0
Hyperbilirubinemia	4 (1)	24 (9)	4 (1)	0	4 (1)	15 (6)	3 (1)	0
Vomiting	18 (7)	11 (4)	4 (1)	0	15 (6)	6 (2)	3 (1)	0
Cardiac*	3 (1)	1(<1)	0	0	1 (<1)	3 (1)	2 (<1)	0

PPE, palmar-plantar erythrodysaesthesia syndrome; *cardiac refers to all LV dysfunction, EF decrease, and/or ventricular dysfunction

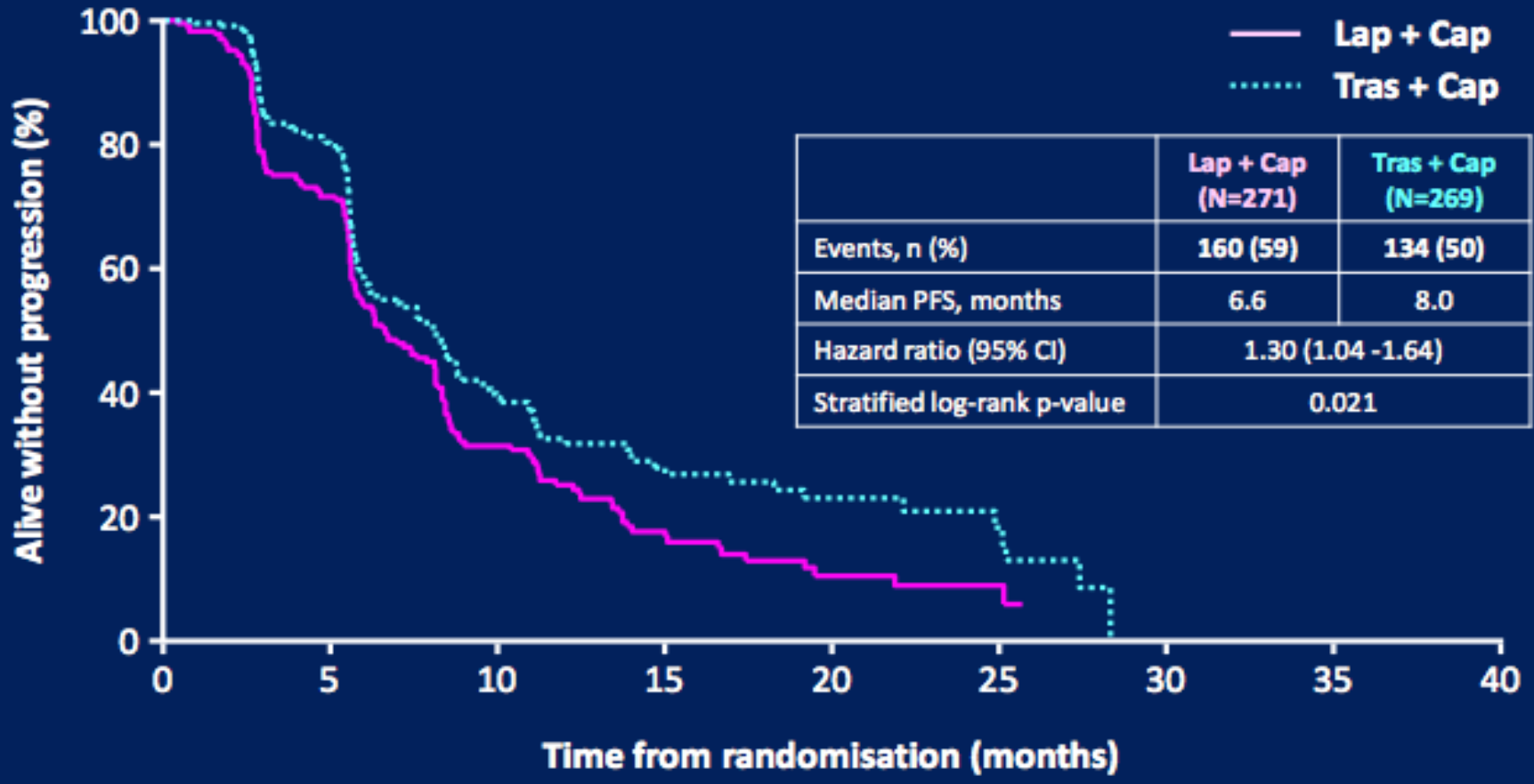
Primary endpoint: CNS endpoints (modified ITT)

	Lapatinib + capecitabine (N=251)	Trastuzumab + capecitabine (N=250)	OR (95% CI)	p-value

Primary endpoint: CNS endpoints (modified ITT)

	Lapatinib + capecitabine (N=251)	Trastuzumab + capecitabine (N=250)	OR (95% CI)	p-value
CNS as first site of relapse, n (%)	8 (3)	12 (5)	0.65 (0.26, 1.63)	0.360
Incidence of CNS progression at any time, n (%)	17 (7)	15 (6)	1.14 (0.52, 2.51)	0.8646
Time to first CNS progression, median (range)	5.7 (2–17)	4.4 (2–27)	-	-

Investigator-assessed PFS (ITT population)

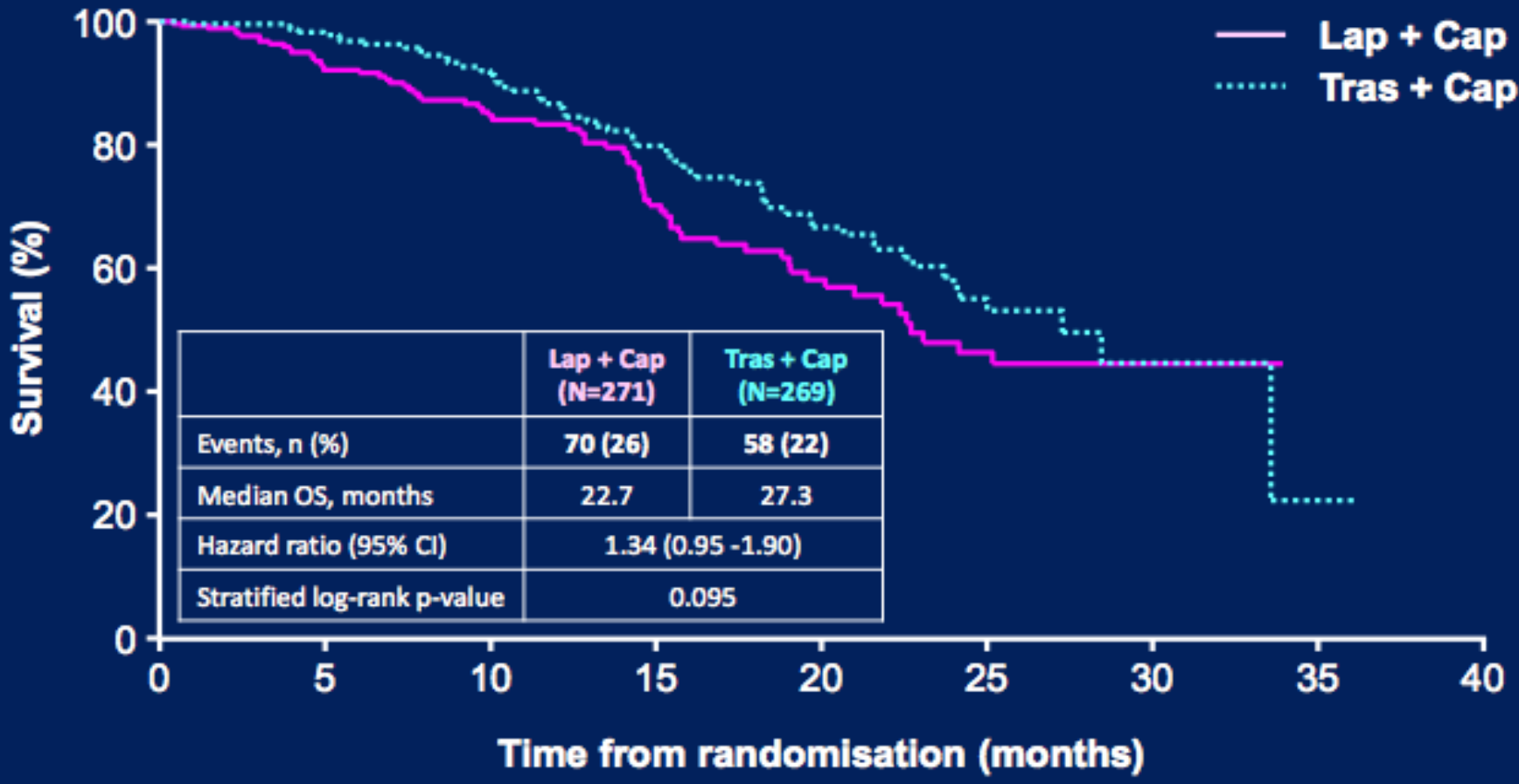


	Lap + Cap (N=271)	Tras + Cap (N=269)
Events, n (%)	160 (59)	134 (50)
Median PFS, months	6.6	8.0
Hazard ratio (95% CI)	1.30 (1.04 -1.64)	
Stratified log-rank p-value	0.021	

Subjects at risk

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

OS (ITT population)



	Lap + Cap (N=271)	Tras + Cap (N=269)
Events, n (%)	70 (26)	58 (22)
Median OS, months	22.7	27.3
Hazard ratio (95% CI)	1.34 (0.95 -1.90)	
Stratified log-rank p-value	0.095	

Subjects at risk

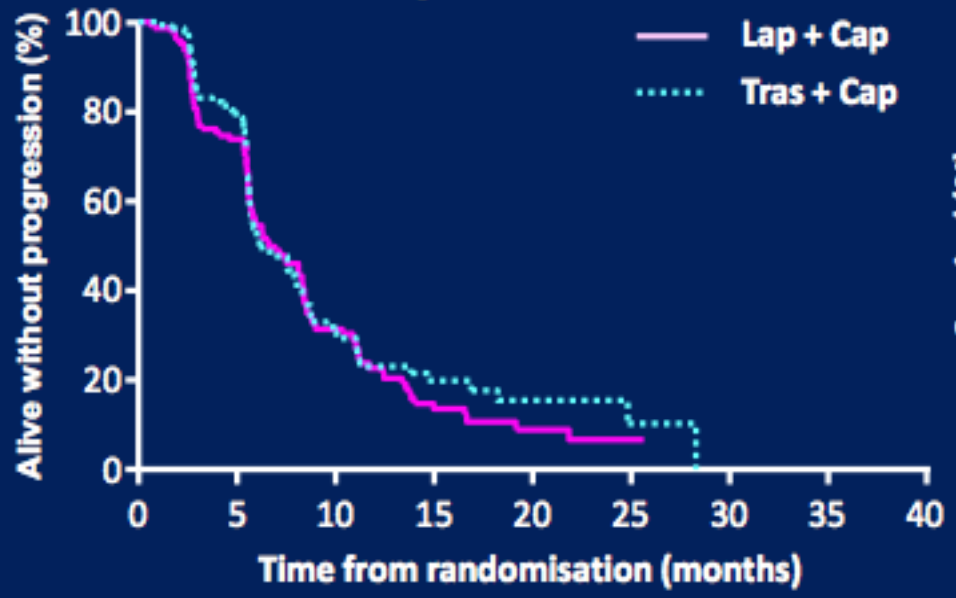
Lap + Cap	271	194	129	79	48	27	7
Tras + Cap	269	207	140	97	61	29	6	1

Response efficacy (ITT population)

	Lapatinib + capecitabine (N=271)	Trastuzumab + capecitabine (N=269)
ORR, n (%)	73 (27)	85 (32)
CR, n (%)	8 (3)	12 (4)
PR, n (%)	65 (24)	73 (27)
SD, n (%)	97 (36)	104 (39)
SD ≥24weeks, n (%)	39 (14)	33 (12)
CBR, n (%)	112 (41)	118 (44)
PD as best response, n (%)	49 (18)	38 (14)

PFS and OS in patients with prior trastuzumab treatment (ITT)

Investigator-assessed PFS

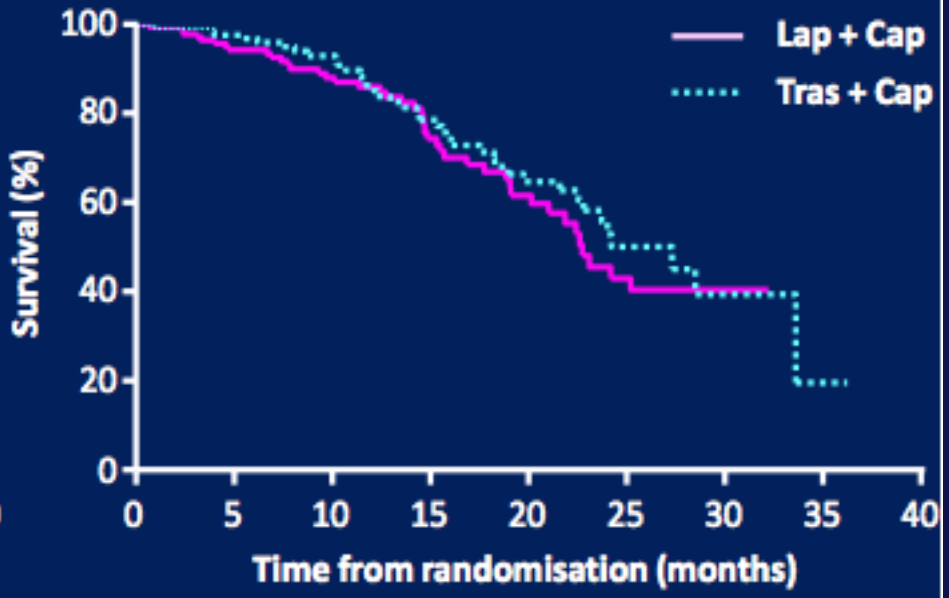


Subjects at risk

Lap + Cap	167	96	31	12	4	2
Tras + Cap	159	89	25	12	7	2

	Lap + Cap (N=167)	Tras + Cap (N=159)
Events, n (%)	103 (62)	86 (54)
Median PFS, months	6.6	6.1
Hazard ratio (95% CI)	1.13 (0.85, 1.50)	

OS



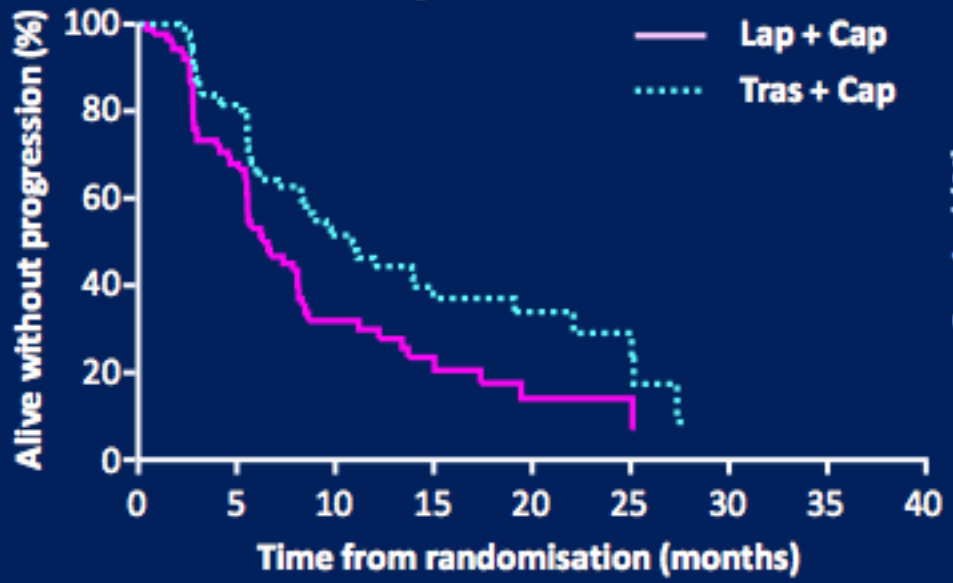
Subjects at risk

Lap + Cap	167	127	87	53	34	17	5
Tras + Cap	159	126	86	57	38	17	5	1

	Lap + Cap (N=167)	Tras + Cap (N=159)
Events, n (%)	43 (26)	38 (24)
Median OS, months	22.7	27.3
Hazard ratio (95% CI)	1.18 (0.76, 1.83)	

PFS and OS in patients with no prior trastuzumab treatment (ITT)

Investigator-assessed PFS

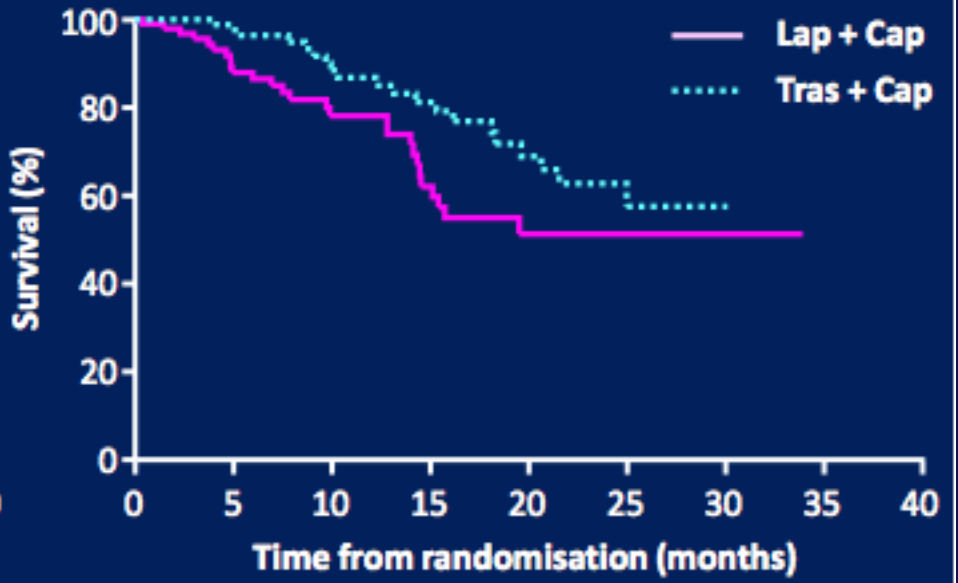


Subjects at risk

Lap + Cap	104	51	18	8	3	2
Tras + Cap	110	65	31	14	8	5

	Lap + Cap (N=104)	Tras + Cap (N=110)
Events, n (%)	57 (55)	48 (44)
Median PFS, months	6.3	10.9
Hazard ratio (95% CI)	1.70 (1.15, 2.50)	

OS



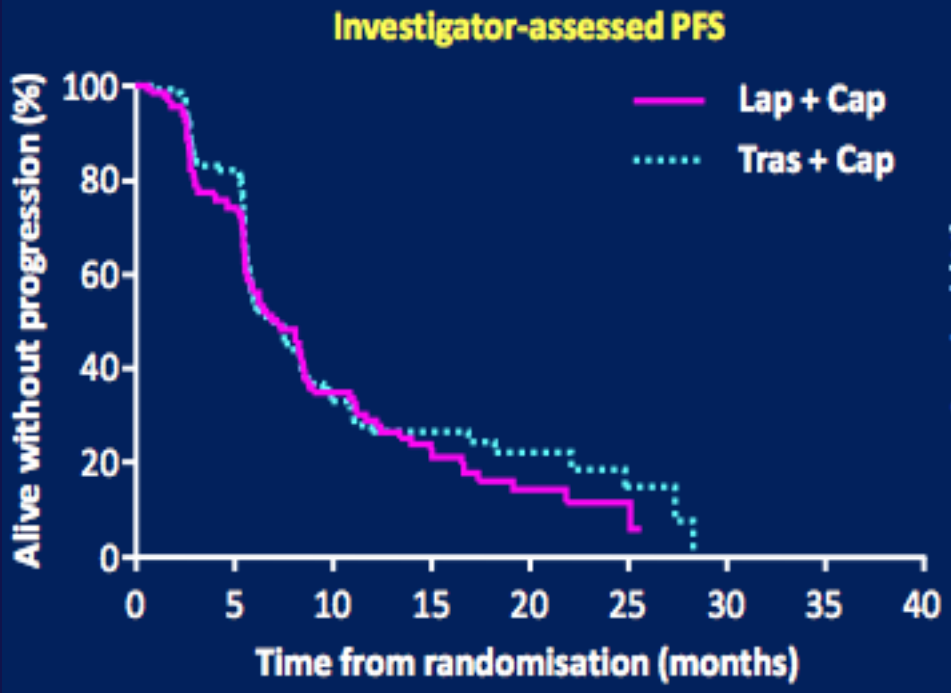
Subjects at risk

Lap + Cap	104	67	42	26	14	10	2
Tras + Cap	110	81	54	40	23	12	1

	Lap + Cap (N=104)	Tras + Cap (N=110)
Events, n (%)	27 (26)	20 (18)
Median OS, months	NR	NR
Hazard ratio (95% CI)	1.67 (0.94, 2.96)	

NR, not reached

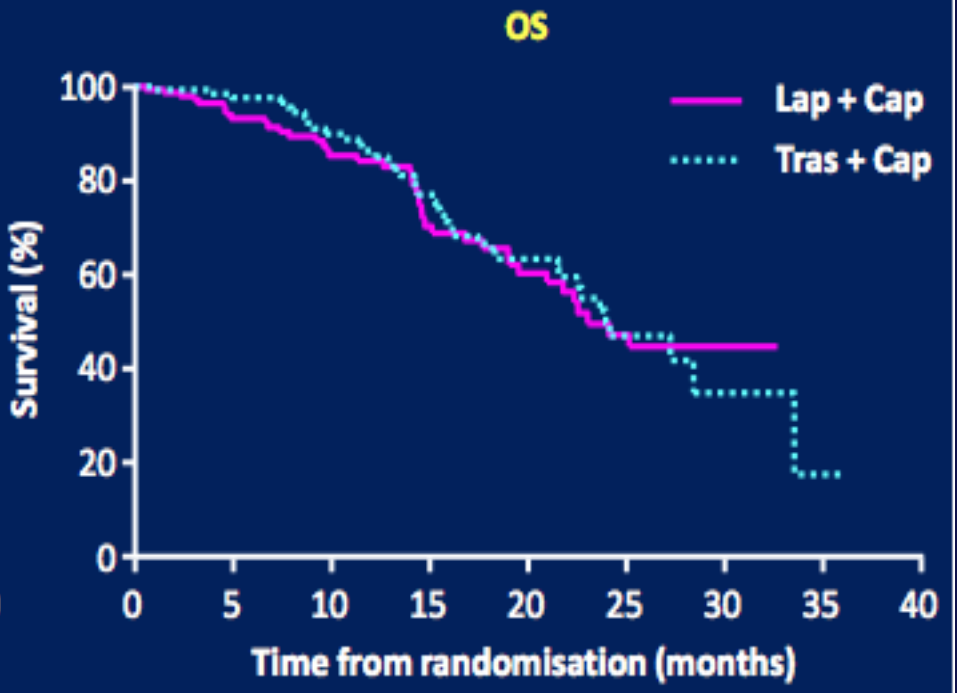
PFS and OS in patients with ≥1 line of previous metastatic therapy (ITT)



Subjects at risk

Lap + Cap	154	89	32	16	5	3
Tras + Cap	148	83	26	14	9	4

	Lap + Cap (N=154)	Tras + Cap (N=148)
Median PFS, months	7.2	6.9
Hazard ratio (95% CI)	1.11 (0.82, 1.50)	

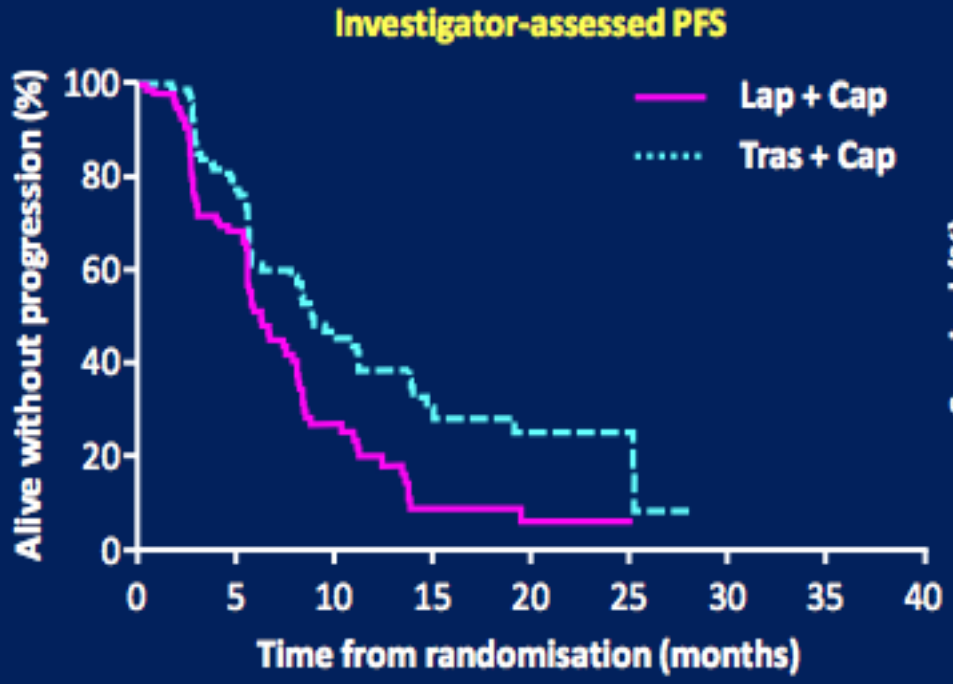


Subjects at risk

Lap + Cap	154	113	78	48	34	19	4
Tras + Cap	148	115	76	55	36	16	5	1

	Lap + Cap (N=154)	Tras + Cap (N=148)
Median OS, months	23.1	24.0
Hazard ratio (95% CI)	1.09 (0.70, 1.69)	

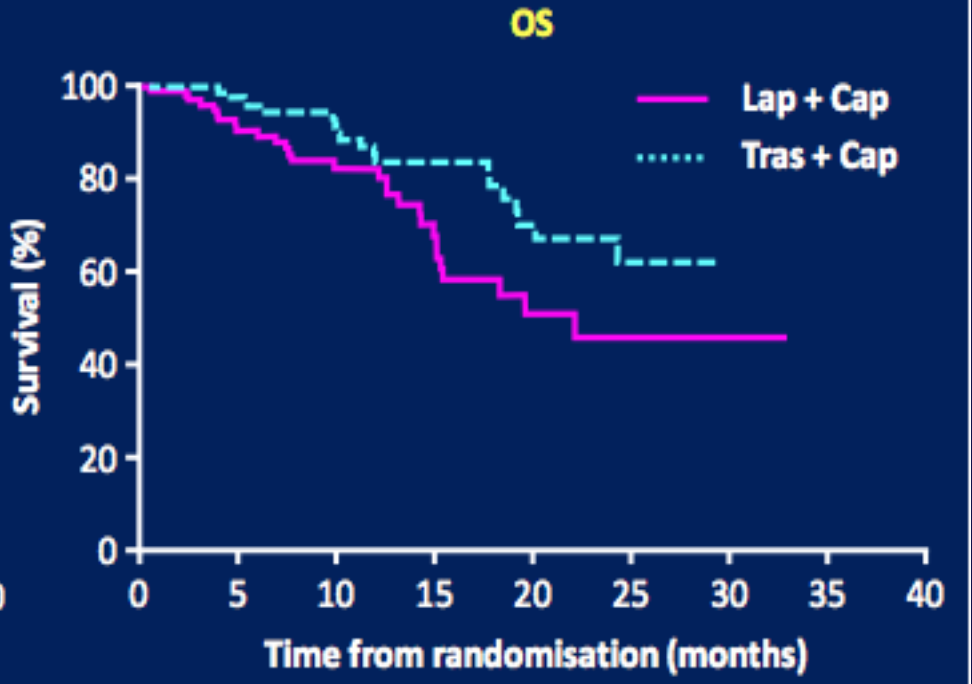
PFS and OS in patients with no previous metastatic therapy (ITT)



Subjects at risk

Lap + Cap	117	58	17	4	2	1
Tras + Cap	121	71	30	12	6	3

	Lap + Cap (N=117)	Tras + Cap (N=121)
Median PFS, months	6.2	8.9
Hazard ratio (95% CI)	1.61 (1.13, 2.29)	



Subjects at risk

Lap + Cap	117	81	51	31	14	8	3
Tras + Cap	121	92	64	42	25	13	1

	Lap + Cap (N=117)	Tras + Cap (N=121)
Median OS, months	22.7	NR
Hazard ratio (95% CI)	1.89 (1.07, 3.35)	

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

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 established safety profile
  - The incidence of AEs, SAEs and AEs leading to discontinuation was low and similar between treatment arms
- **Proactive diarrhoea management is important for tolerability and quality of life**
  - 6% Grade 3/4 lapatinib + capecitabine
  - 8% Grade 3/4 trastuzumab + capecitabine

..... La parola PM