Lo studio BOLERO 1 Commento sulla metodologia

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BOLERO-1/TRIO 019: Study Design

N = 719

- Locally advanced or metastatic HER2+ breast cancer
- No prior therapy for advanced or metastatic disease (except endocrine therapy)
- Prior (neo)adjuvant TRAS and/or chemotherapy allowed[1]
- Measurable disease or presence of bone lesions (lytic or mixed)

Randomized 2:1

Stratification factors:
- Prior neo/adjuvant TRAS
- Visceral metastases

Everolimus (10 mg PO daily) + Paclitaxel[2] + Trastuzumab[3]

Placebo + Paclitaxel[2] + Trastuzumab[3]

Therapy until disease progression or intolerable toxicity[4]

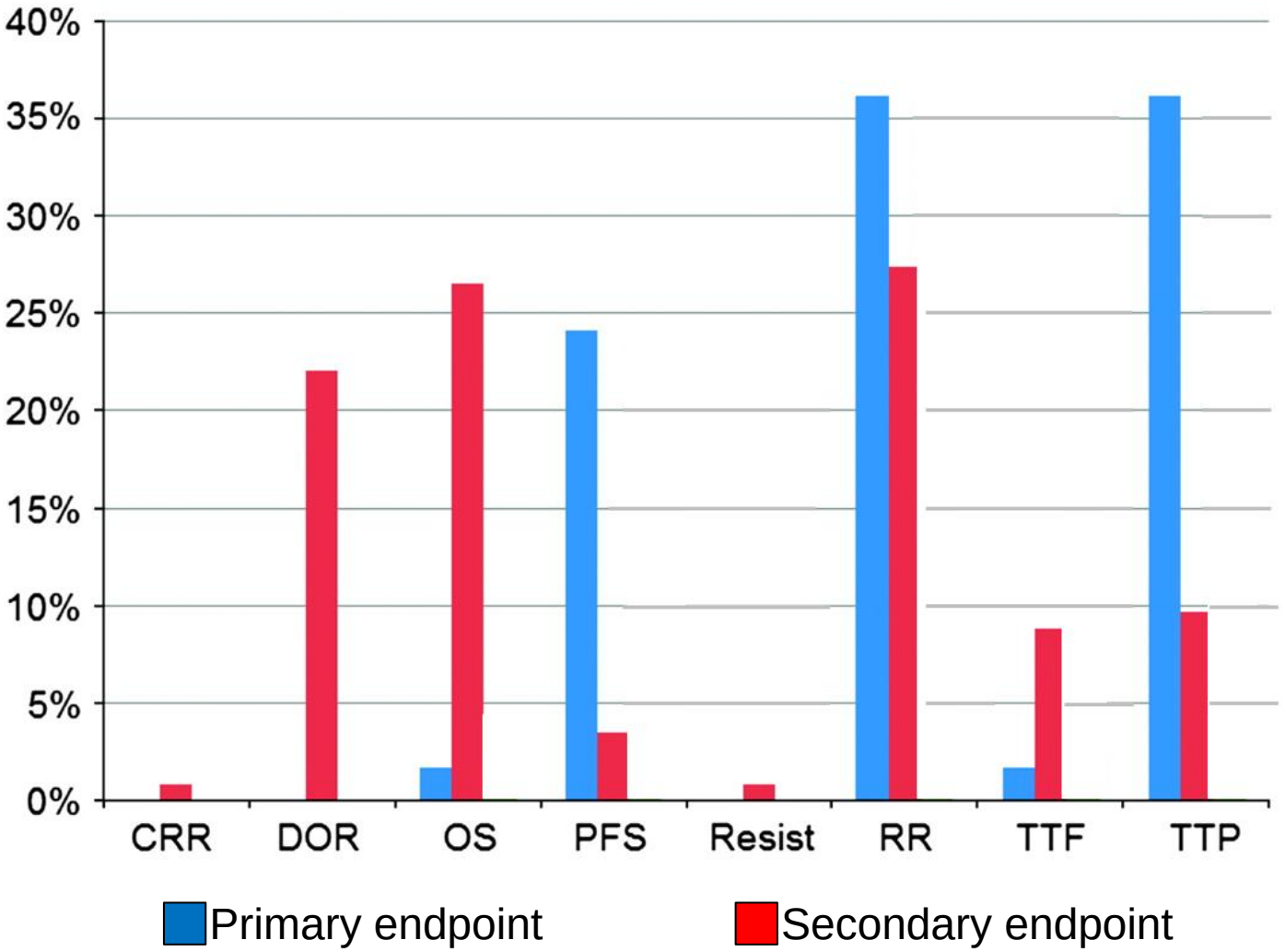
Endpoints

- **Primary: PFS (investigator-assessed)**
  - **Overall population and**
  - **HR⁻ subpopulation**
- Secondary:
  - OS, ORR, CBR, Time to response, Safety, Duration of response

[1]Discontinued > 12 mo before randomization;
[2]Paclitaxel: 80 mg/m² weekly;
[3]Trastuzumab: 4 mg/kg loading dose on day 1 at cycle 1 followed by 2 mg/kg weekly doses
[4]Patients could discontinue any study treatment due to AEs; other study treatments continued until disease progression or intolerable toxicity

ABC, advanced breast cancer; CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

Use of efficacy end points in randomized clinical trials in advanced breast cancer



Saad ED, Katz A. Ann Oncol 2008;20:460-464

VOLUME 28 · NUMBER 11 · APRIL 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Overall Survival and Post-Progression Survival in Advanced Breast Cancer: A Review of Recent Randomized Clinical Trials

Everardo D. Saad, Artur Katz, and Marc Buyse

Saad ED et al, J Clin Oncol 2010; 28: 1958-1962

Table 4. Median PFS, OS, and PPS, and the Proportion of OS Accounted for by PPS for Selected Recent Studies in Breast Cancer

Trial	Median (months)			Proportion of OS Accounted for by PPS (%)
	PFS	OS	PPS	
Chemotherapy (first-line)[5]	4.6	20.3	15.7	77.3
Chemotherapy + trastuzumab (first-line)[5]	7.4	25.1	17.7	70.5
Capecitabine (second-line)[7]	4.4	15.6	11.2	71.8
Capecitabine + lapatinib (second-line)[7]	8.4	15.4	7.0	45.5
Capecitabine (second-line)[35]	5.6	20.4	14.8	72.5
Capecitabine + trastuzumab (second-line)[35]	8.2	25.5	17.3	67.8
Paclitaxel (first-line)[8]	5.9	25.2	19.3	76.6
Paclitaxel + bevacizumab (first-line)[8]	11.8	26.7	14.9	55.8
Capecitabine (first-line)[10]	5.7	21.2	15.5	73.1
Capecitabine + bevacizumab (first-line)[10]	8.6	29.0	20.4	70.3
Anthracycline or taxane (first-line)[10]	8.0	23.8	15.8	66.4
Anthracycline or taxane + bevacizumab (first-line)[10]	9.2	25.2	16.0	63.5
Chemotherapy[36]	3.3	5.7	2.4	42.1
Chemotherapy + BSI-201[36]	6.9	9.2	2.3	25

Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

Saad ED et al, J Clin Oncol 2010; 28: 1958-1962

Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival

Kristine R. Broglio, Donald A. Berry

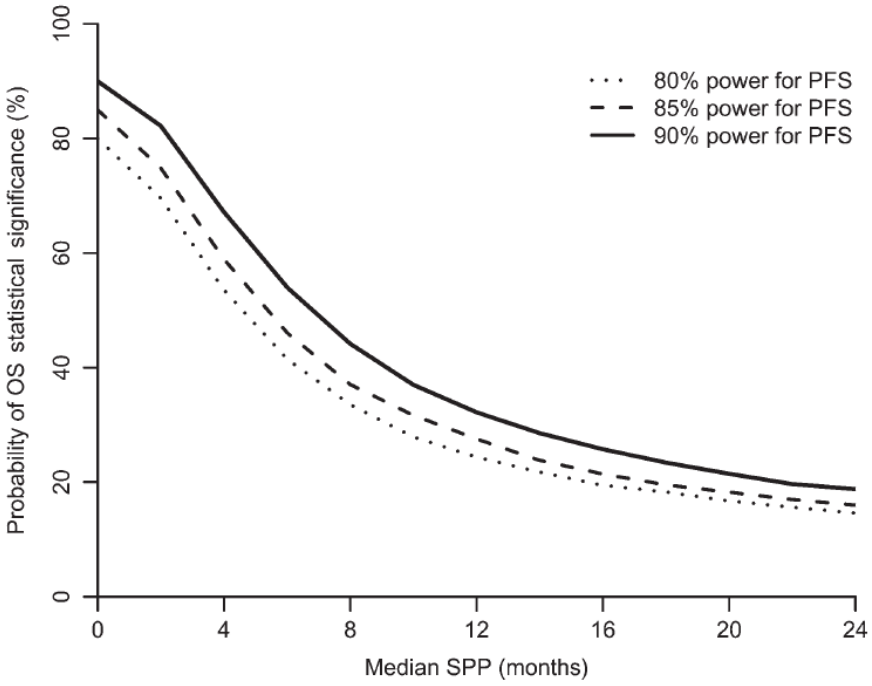


Figure 2. Probability of statistically significant differences in overall survival (OS) as a function of median survival postprogression (SPP). The **three curves** were indexed by the power for detecting the actual median progression-free survival (PFS) benefit that was simulated, 6 vs 9 months (ie, powers of 90%, 85%, and 80%).

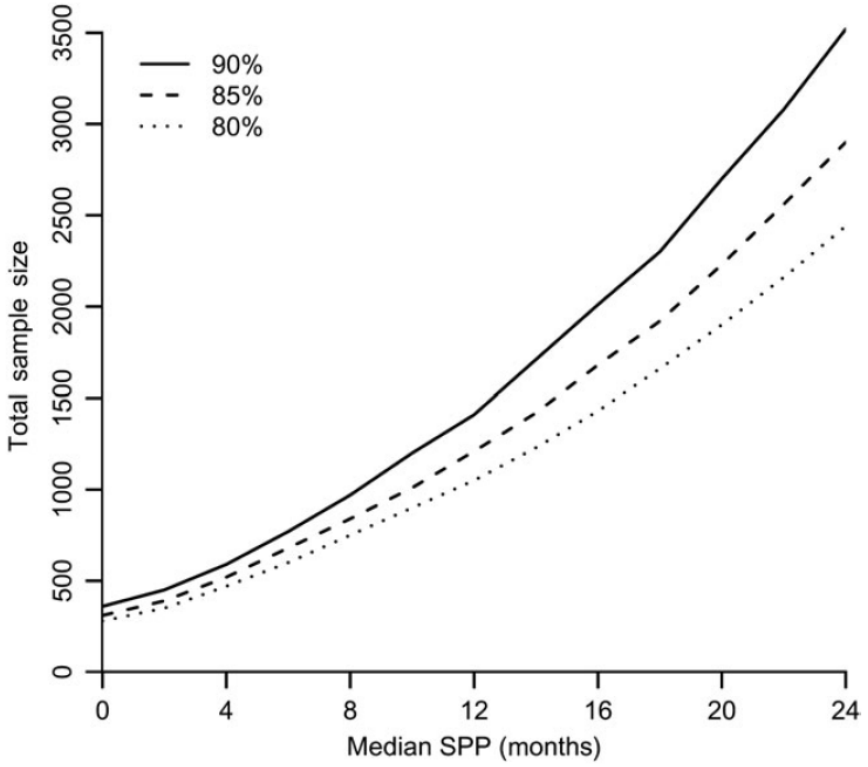


Figure 3. Sample sizes required for detecting a statistically significant difference in overall survival by median survival postprogression (SPP). The **three curves** were indexed by the power for overall survival (ie, powers of 90%, 85%, and 80%).

Broglio KR, Berry DA. J Natl Cancer Inst 2009; 101: 1642-1649

Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival

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"*For clinical trials with a PFS benefit, lack of statistical significance in OS does not imply lack of improvement in OS, especially for diseases with long survival post-progression (SPP)*

OS is a reasonable endpoint when SPP is short but is too high a bar when median SPP is long"

Broglio KR, Berry DA. J Natl Cancer Inst 2009; 101: 1642-1649

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ABC, advanced breast cancer; CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression free survival.

E’ tutta una questione di p value?

Quando l'evidenza si modifica durante la conduzione dello studio…

Clinical Rationale For Evaluating HR– subpopulation

- Extensive cross-talk between ER and HER2 pathways; inhibition of HER2 signaling increases activation of ER transcription which may act as an escape mechanism from HER2-directed agents[1]
  - Co-inhibition of the ER and HER2 pathways might be required to improve treatment outcomes in these cancers[1]
- In the pivotal phase 3 BOLERO-3 trial, clinical benefit was more pronounced in the HR– subpopulation[2]
  - Hazard ratio for PFS was 0.65 (95% CI: 0.48-0.87) in the HR– subpopulation versus 0.93 (95% CI: 0.72-1.20) in the HR+ subpopulation[2]

Possibili opzioni:

- **Se lo studio fosse stato ancora aperto all'accrual**:
  - Fermare l'accrual delle pazienti HR+ e limitare l'accrual alle sole pazienti HR-, fino al raggiungimento del numero prestabilito;
  - Aumentare il numero delle sole pazienti HR-, per garantire una potenza maggiore al confronto nel sottogruppo;
- **Essendo l'accrual chiuso**:
  - Emendare (senza conoscere i risultati) per prevedere formalmente il confronto anche nel sottogruppo HR-.

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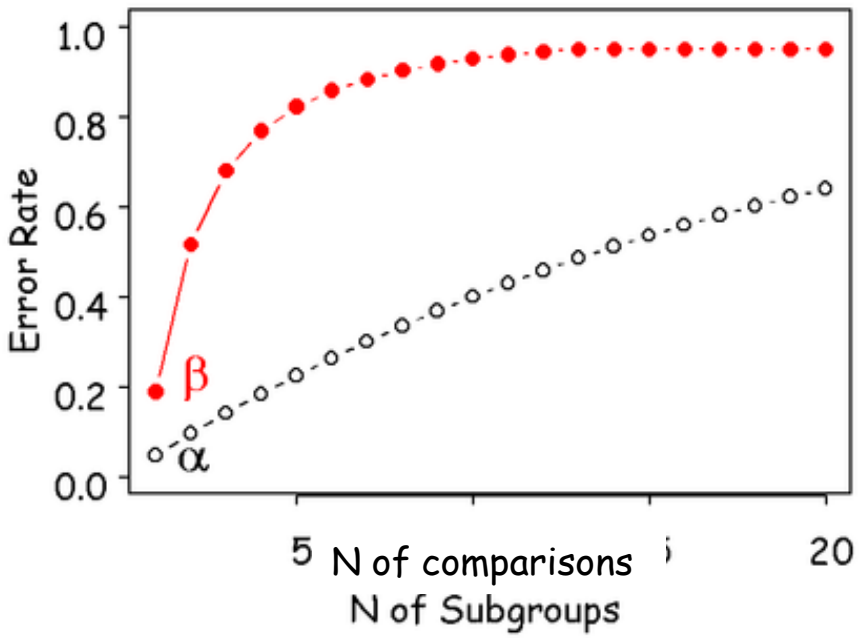
- To prospectively validate the hypothesis of differential efficacy of everolimus in patients with HR– disease, the study was amended (3/26/2014) to include PFS analyses in the HR– subpopulation as a second primary objective

1. Nahta R, et al. *Breast Cancer Res Treat.* 2012;135(1):39-48; 2. Andre F, et al. *Lancet Oncol.* 2014;15(6):580-91; 3. Blackwell KL, et al. *J Clin Oncol.* 2012;30(21):2585-2592; 4. Baselga J, et al. *N Engl J Med.* 2012;366(2):109-19; 5. Verma S, et al. *N Engl J Med.* 2012;367(19):1783-91.

Quando si pianificano confronti multipli…

Il rischio di un risultato falso positivo

Aumento della probabilità di risultati positivi (statisticamente significativi) per il solo effetto del caso....



N.ro confronti	P (≥ 1 FP)
1	5%
2	10%
5	23%
10	40%
20	64%

Subgroup analyses in randomized controlled trials

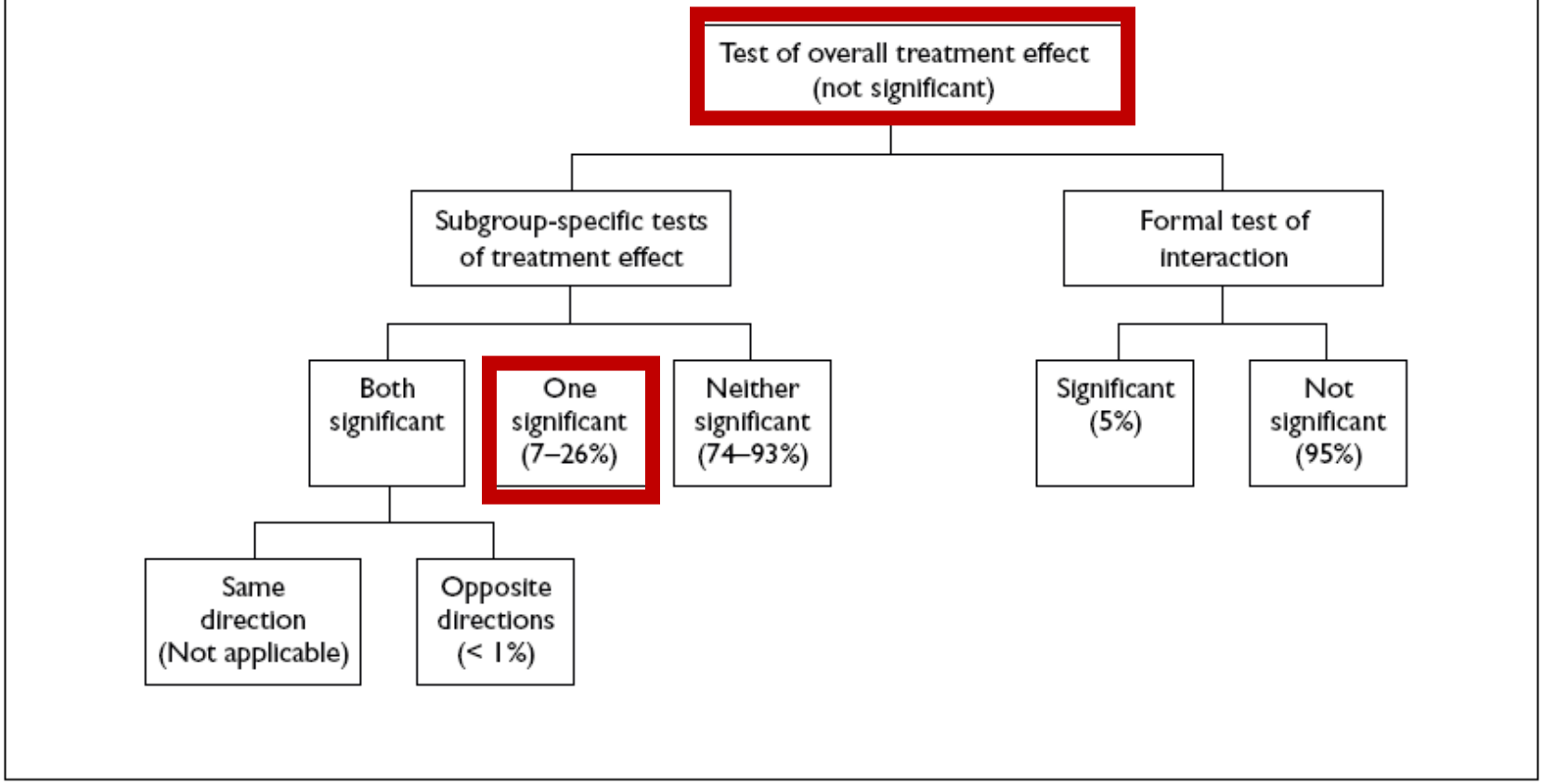


FIGURE 21 *Summary of results for the simplest case (overall test result not significant). This figure combines the results from data simulated with no overall treatment effect and with a true overall treatment effect detectable at nominal powers of 50, 80, 90 and 95%*

Brookes ST et al. Health Technology Assessment 2001; Vol.5: No. 33

Possibili opzioni:

α

α confronto nella full population

α Confronto nel sottogruppo HR-

α confronto nella full population

α Confronto nel sottogruppo HR-

Statistical Considerations For Efficacy Endpoints

- Patients were enrolled between September 2009 to December 2011
- The amended study was designed with dual primary objectives (study positive if either met):
  - Comparison of PFS in the full study population and in the HR– subpopulation
- For the primary PFS analyses, patients were censored if they received further anti-neoplastic therapy prior to progression/death
- The Type I error rate (α) for testing two primary statistical tests was controlled via weighted Hochberg procedure with the chosen α split weighted heavily on the full population:
  - 80% α for full population (α = 0.02) (To preserve maximum power)
  - 20% α for HR– population (α = 0.005) (To provide statistical validity independent of full population)

In aggiunta… la correzione per le analisi ad interim

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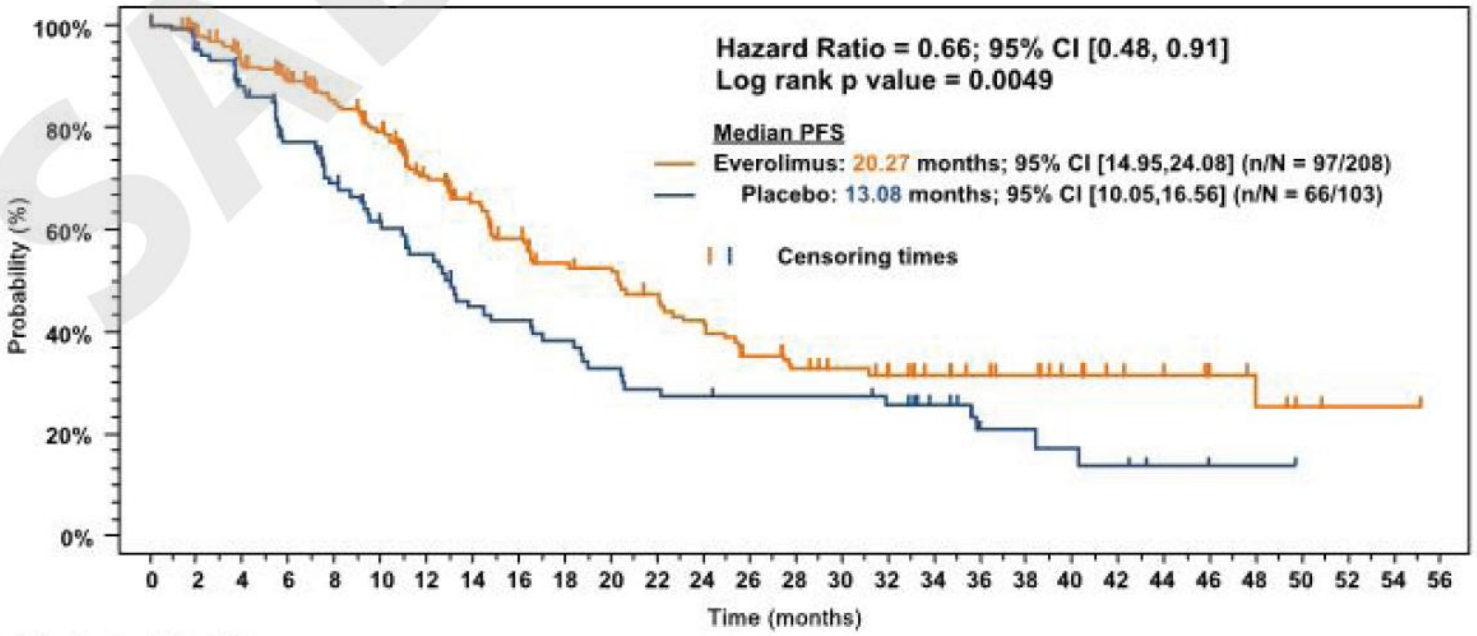
  - 80% α for full population (α = 0.02) (To preserve maximum power)
  - 20% α for HR– population (α = 0.005) (To provide statistical validity independent of full population)
- Multiplicity arising from group sequential design (interim + final analysis) controlled via use of 2 independent α-spending functions leading to the following statistical significance thresholds
  - **Full population: p = 0.0174**
  - **HR– subpopulation: p = 0.0044**

BOLERO-1/TRIO 019: PFS HR– Subpopulation
(Investigator Assessment)



No. of patients still at risk

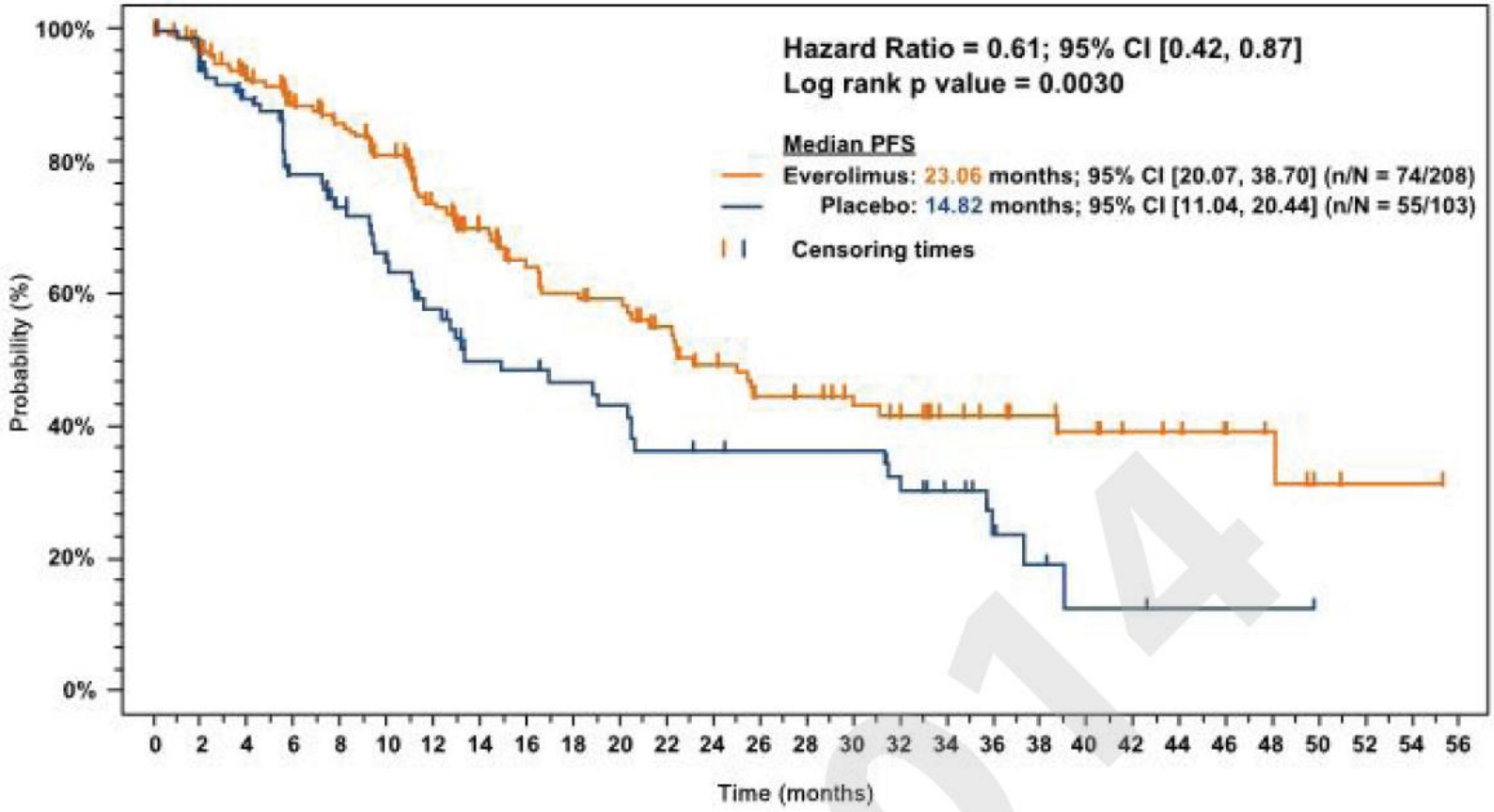
Everolimus	208	183	166	151	138	125	100	84	73	64	62	55	49	40	35	32	30	24	21	19	15	11	10	7	5	2	1	1	0
Placebo	103	96	83	68	58	49	43	34	32	28	24	21	20	19	19	19	17	13	7	6	5	4	2	1	1	0	0	0	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

- Sensitivity analysis without censoring patients at the start of new antineoplastic therapy:
  - Median PFS and 95% CIs
    - 20.27 mo (14.82, 24.08) for everolimus [n = 102]
    - 12.88 mo (10.94, 16.56) for placebo [n = 68]
  - HR=0.66 [0.48, 0.9], p = 0.0043

BOLERO-1/TRIO 019: PFS HR– Subpopulation

(Central Assessment)



No. of patients still at risk

Everolimus	208	174	156	139	131	118	96	78	65	60	57	49	42	36	34	30	28	22	20	18	15	10	9	6	5	2	1	1	0
Placebo	103	93	81	63	55	46	39	31	30	27	25	21	20	19	19	19	15	12	6	4	2	2	1	1	1	0	0	0	0

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 November 2011
EMA/916257/2011
Human Medicines Development and Evaluation

Expert workshop on subgroup analysis

Workshop report

Report of the workshop held on 18 November 2011 at the European Medicines Agency

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the investigation of subgroups in confirmatory clinical trials

DRAFT

Draft Agreed by Biostatistics Working Party	September 2013
Adoption by CHMP for release for consultation	23 January 2014
Start of public consultation	03 February 2014
End of consultation (deadline for comments)	31 July 2014

With the advent of genomics, the concept of **subgroup** has gradually been elevated to **subpopulation** due to the belief of potentially more accurately defined molecular targets.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Expert workshop on subgroup analysis – Workshop report EMA/916257/2011

Interpreting subgroup analyses presents particular methodological challenges, whereas not exploring subgroups because of these challenges would be an unsatisfactory solution as it would place excessive reliance on assumptions (e.g. homogeneity of response to treatment) that cannot be substantiated.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Expert workshop on subgroup analysis – Workshop report EMA/916257/2011

The participants of the workshop agreed that ultimately it is essential for the benefit of patients that **subgroup analyses are based on rigorous methodology, balanced with pharmacological and clinical plausibility,** such that conclusions are guided by the overall strength of evidence.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Expert workshop on subgroup analysis – Workshop report EMA/916257/2011

BOLERO-1/TRIO 019: Summary

- Primary objective of PFS was not met
- Median PFS prolonged by 7 mo in the HR-negative subpopulation (20 mo everolimus arm vs 13 mo placebo arm, HR 0.66, p=0.0049)
  - However, protocol prespecified analysis did not cross the statistical significance threshold (p=0.0044)
- Safety profile was consistent with results previously reported in BOLERO-3
- Higher rate of AE-related on-treatment deaths was reported for everolimus (3.6% vs 0% with placebo)
  - All but one AE-related on-treatment deaths occurred within 15 mo of study start
  - Proactive monitoring and early management of AEs in patients treated with everolimus and chemotherapy is critical
- OS follow-up will be ongoing until 438 events are reported

Grazie per l'attenzione!

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