SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

Highlitghs in MBC

First and second line endocrine treatments

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Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

1st International consensus guidelines for advanced breast cancer (ABC 1)

F. Cardoso [a,*], A. Costa [b], L. Norton [c], D. Cameron [d], T. Cufer [e], L. Fallowfield [f], P. Francis [g], J. Gligorov [h], S. Kyriakides [i], N. Lin [j], O. Pagani [k], E. Senkus [l], C. Thomssen [m], M. Aapro [n], J. Bergh [o], A. Di Leo [p], N. El Saghir [q], P.A. Ganz [r], K. Gelmon [s], A. Goldhirsch [t], N. Harbeck [u], N. Houssami [v], C. Hudis [w], B. Kaufman [x], M. Leadbeater [y], M. Mayer [z], A. Rodger [aa], H. Rugo [bb], V. Sacchini [cc], G. Sledge [dd], L. van't Veer [ee], G. Viale [ff], I. Krop [gg], E. Winer [gg]

ER +/HER-2 negative ABC.

Guideline statement	LoE
19) Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, *even in the presence of visceral disease*, unless there is concern or proof of endocrine resistance or there is disease needing a fast response.	1 A

Which clinical scenario have to face with today?

- First line therapy
  - Untreated metastatic breast cancer (*endocrine sensitive*)
  - Pretreated with adjuvant hormones
    - Early relapse (during or shortly after adjuvant hormonal phase – TAM or NSAI) (*endocrine resistant*)
    - Late relapse (after 12-24 months from the end of adjuvant hormones – TAM or NSAI) (*endocrine sensitive*)

- Second line after prior hormones for MBC (*endocrine resistant*)

NSAI in tamoxifen resistant patients

Autore	Trattamento	N. pazienti	Follow-up mediano (mesi)	ORR (%)	TTP mediano (mesi)	OS mediana (mesi)
Buzdar et al.[11]a	Anastrozolo 1 mg/die	263	31	12,6	4,8	26,7*b
	Anastrazolo 10 mg/die	248		12,5	5,3	25,5
	MA 40 mg × 4/die	253		12,2	4,6	22,5
Dombernowsky et al.[12]	Letrozolo 0,5 mg/die	188	33	12,8	5,1	21,8
	Letrozolo 2,5 mg/die	174		23,6*c	5,6*d	25,7*c
	MA 40 mg × 4/die	189		16,4	5,5	21,8
Buzdar et al.[13]	Letrozolo 0,5 mg/die	202	18	21,0	5,6*	33
	Letrozolo 2,5 mg/die	199		16,0	3,2	29
	MA 40 mg × 4/die	201		15,0	3,4	26
Kaufmann et al.[14]	Exemestane 25 mg/die	366	12,5	15,0	5,1*	Non raggiunta
	MA 40 mg × 4/die	403		12,4	4,2	31

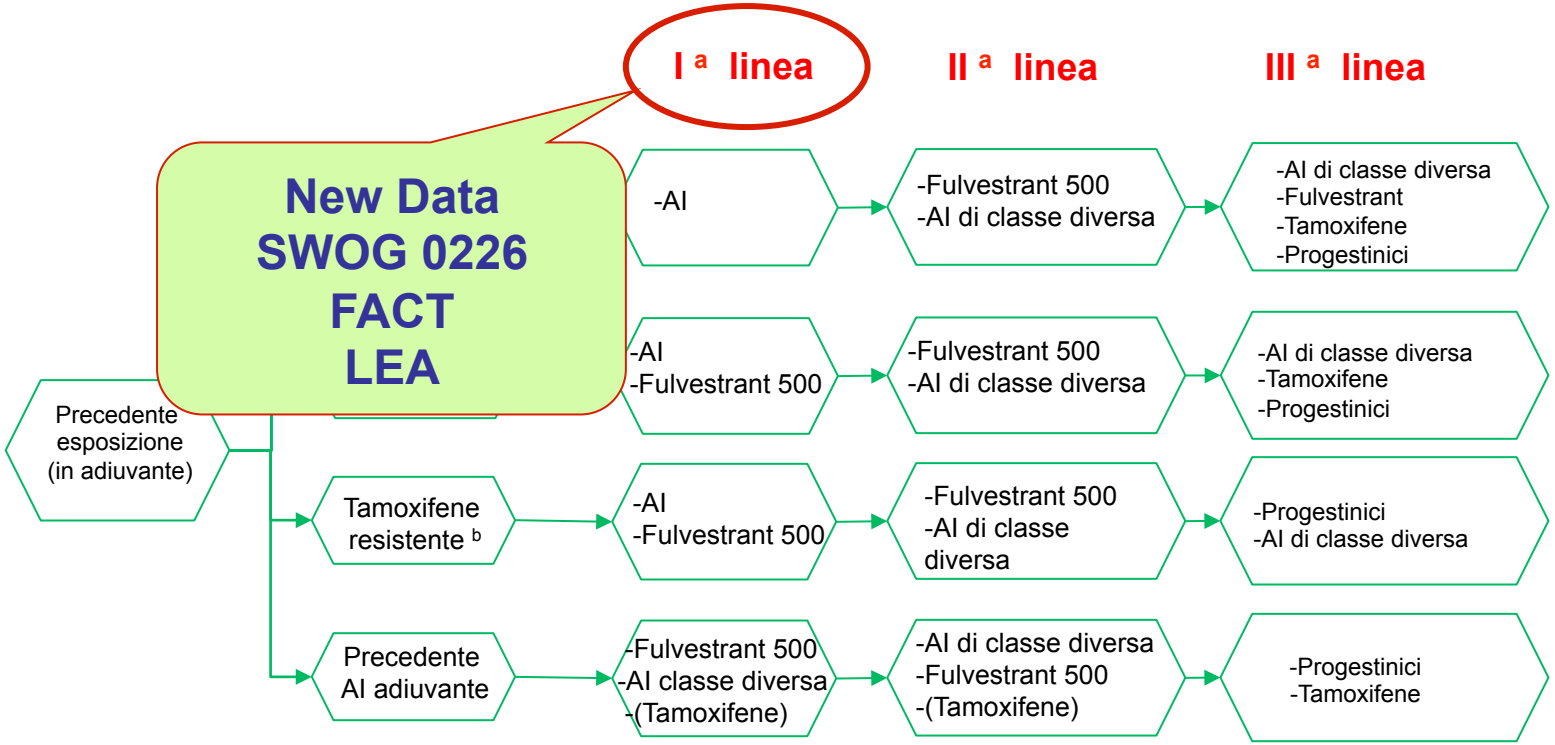
Trials with fulvestrant

Trial	TAM	Line	Comp	Pts	OR %	TTP mos	Signif
0025	**N**	**I**	**TAM**	**587**	**31.6 vs 31.9**	**6.8 vs 8.3**	**0.09**
0020*	**P**	**II**	**ANA**	**451**	**20.7 vs 15.7**	**5.5 vs 5.4**	**0.84**
0021**	**P**	**II**	**ANA**	**400**	**17.5 vs 17.5**	**5.4 vs 3.4**	**0.43**
0020 + 0021	**P**	**II**	**ANA**	**851**	**19.2 vs 16.5**	**5.5 vs 4.1**	**0.48**

N= naive; P= pretreated

* 56% received ET for ABC; 53% for EBC. **53% received ET for ABC; 59% for EBC

LG AIOM 2012 - CARCINOMA MAMMARIO METASTATICO
Terapia ormonale in post-menopausa



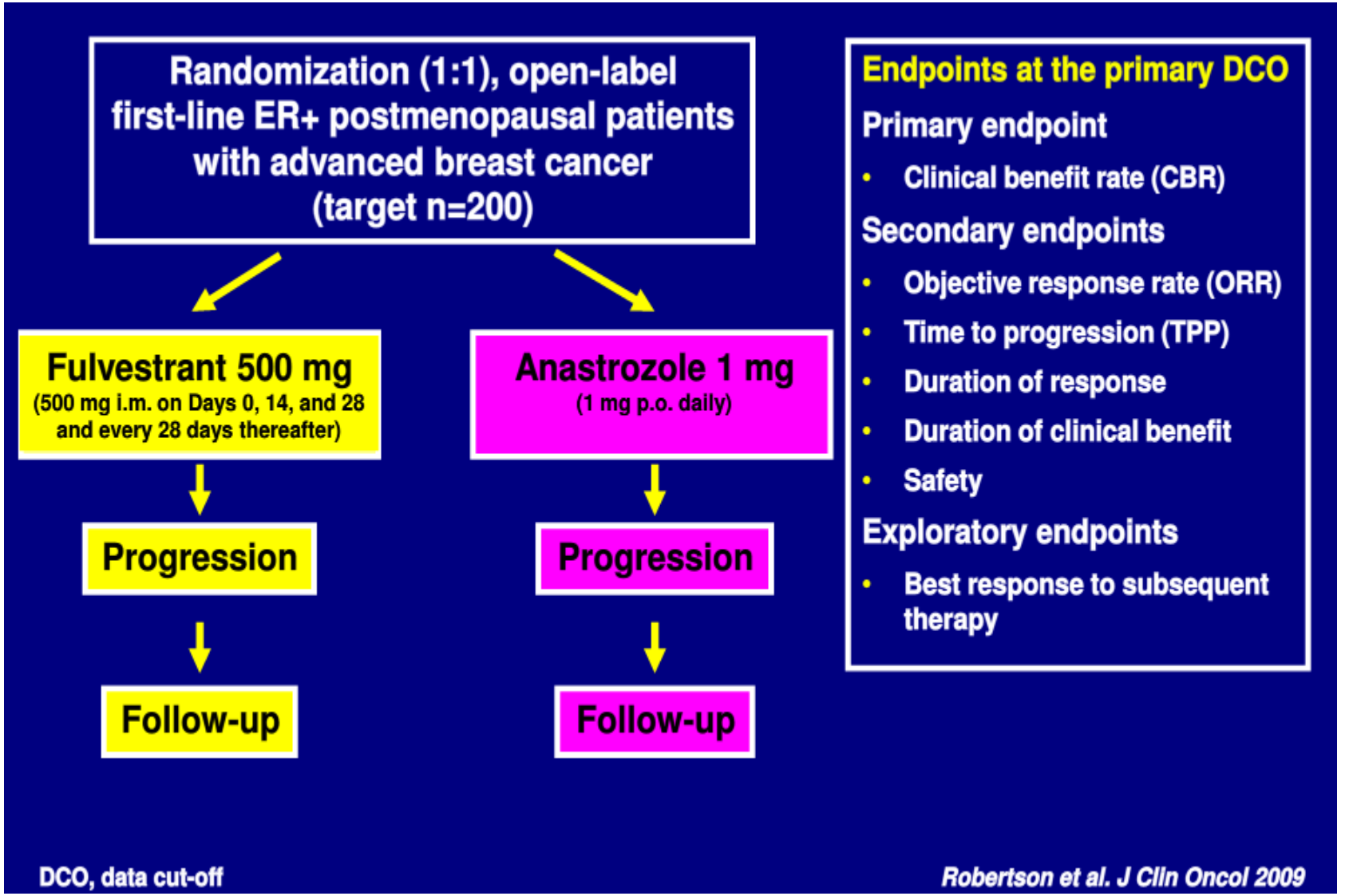
Nota a -Tamoxifene sensibile: Intervallo tra la fine del trattamento con tamoxifene adiuvante e la comparsa di metastasi >12 mesi.
Nota b - Tamoxifene resistente: Comparsa di metastasi durante il trattamento o entro 12 mesi dalla fine del trattamento adiuvante con tamoxifene.

Endocrine sensitive breast cancer

Trials in patients with endocrine-sensitive tumors

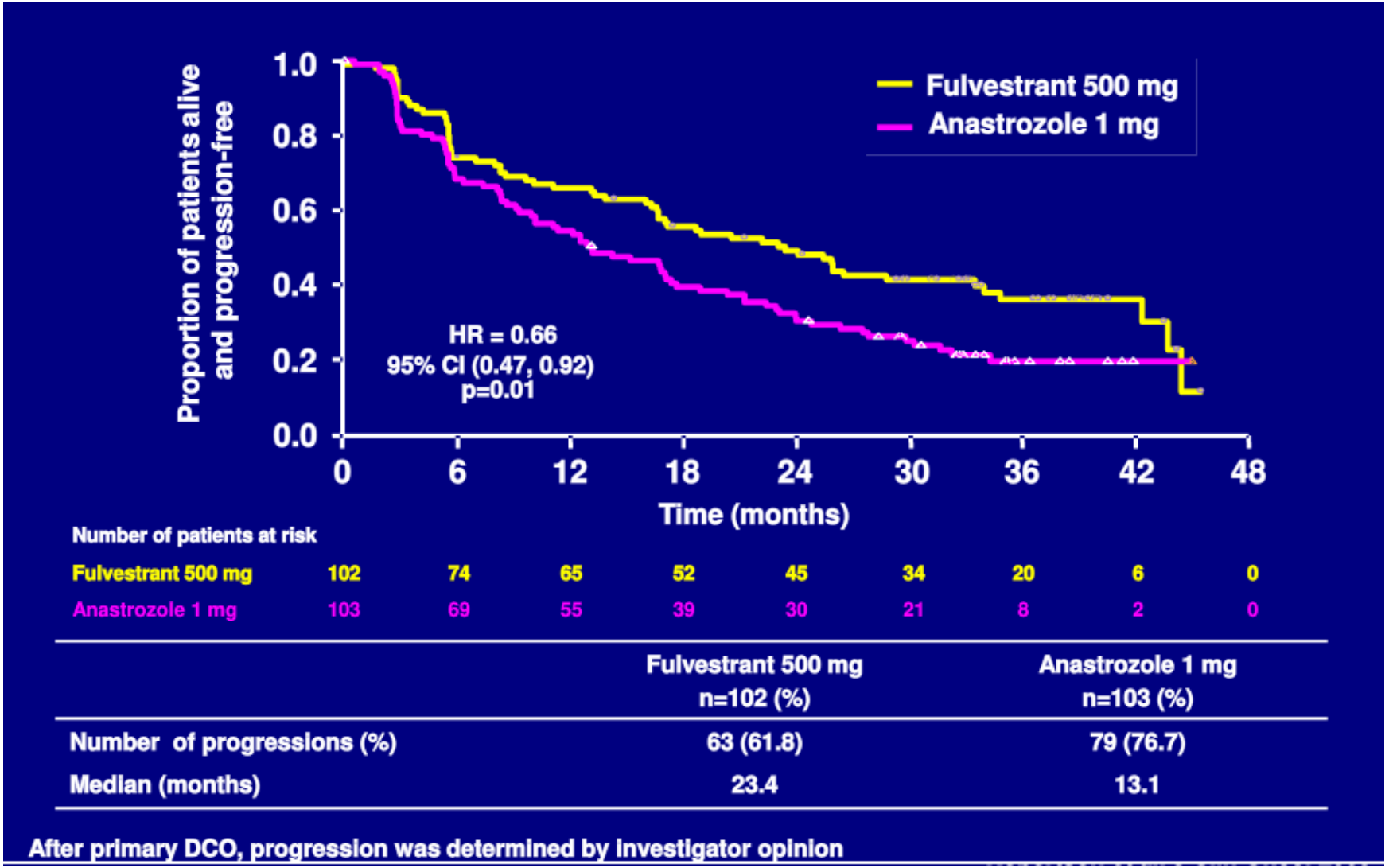
Autore	Trattamento	N. pazienti	Follow-up mediano	ORR (%)	TTP mediano (mesi)	OS mediano (mesi)
Mouridsen et al.[15]	Letrozolo 2,5 mg/die	458	32 mesi	32*	9,4*	34
	Tamoxifene 20 mg/die	458		21	6,0	30
Bonneterre et al.[16]	Anastrozolo 1 mg/die	340	19 mesi	33	8,2	
	Tamoxifene 20 mg/die	328		33	8,3	
Nabholtz et al.[17]	Anastrozolo 1 mg/die	171	17,7 mesi	21	11,1*	-
	Tamoxifene 20 mg/die	182		17	5,6	-
Paridaens et al.[18]	Exemestane 25 mg/die	182	29 mesi	46*	9,9*	37,2
	Tamoxifene 20 mg/die	189		31	5,8	43,3

The “FIRST” trial



75% of patients endocrine naive

FIRST updated analysis

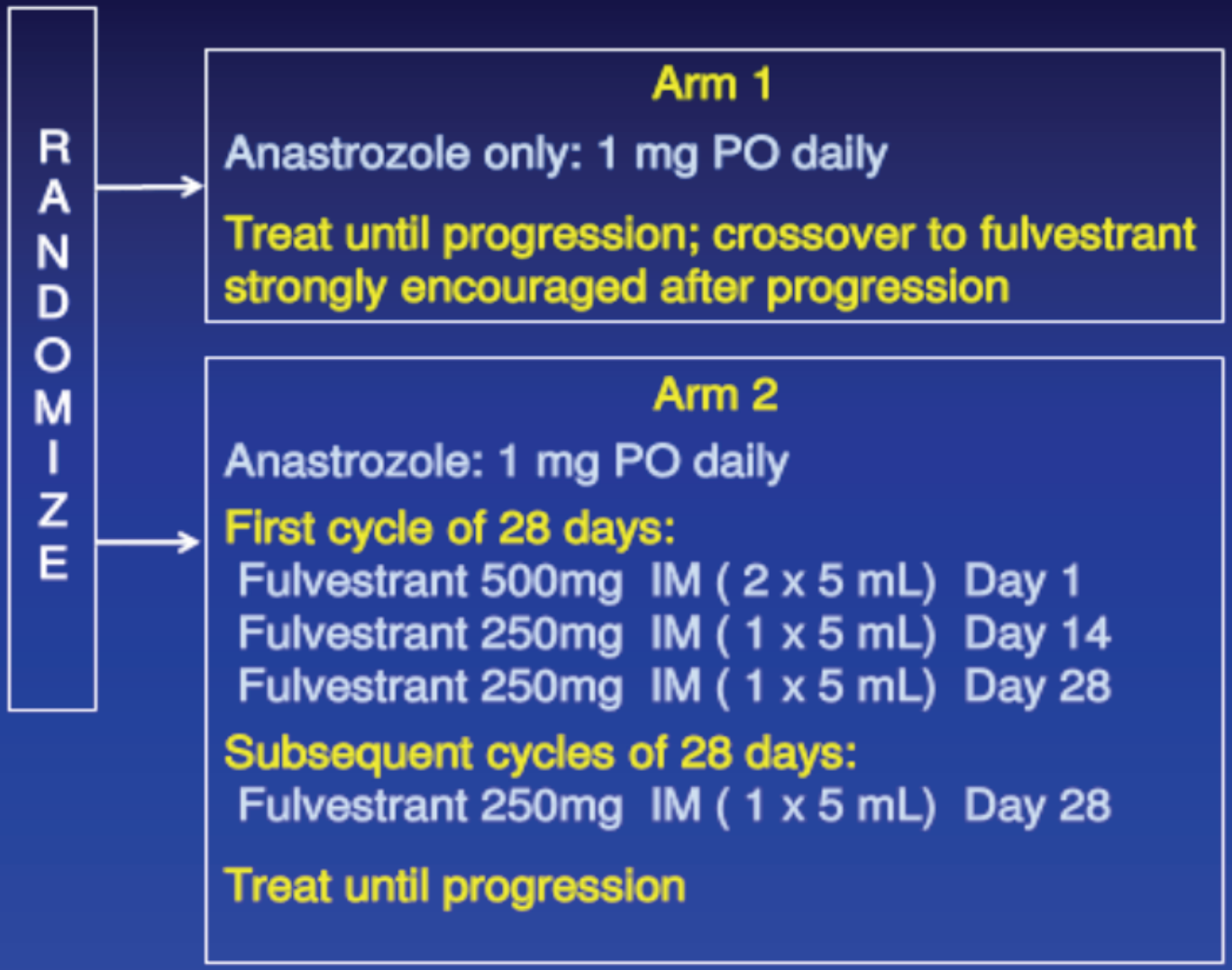


Number of patients at risk									
Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

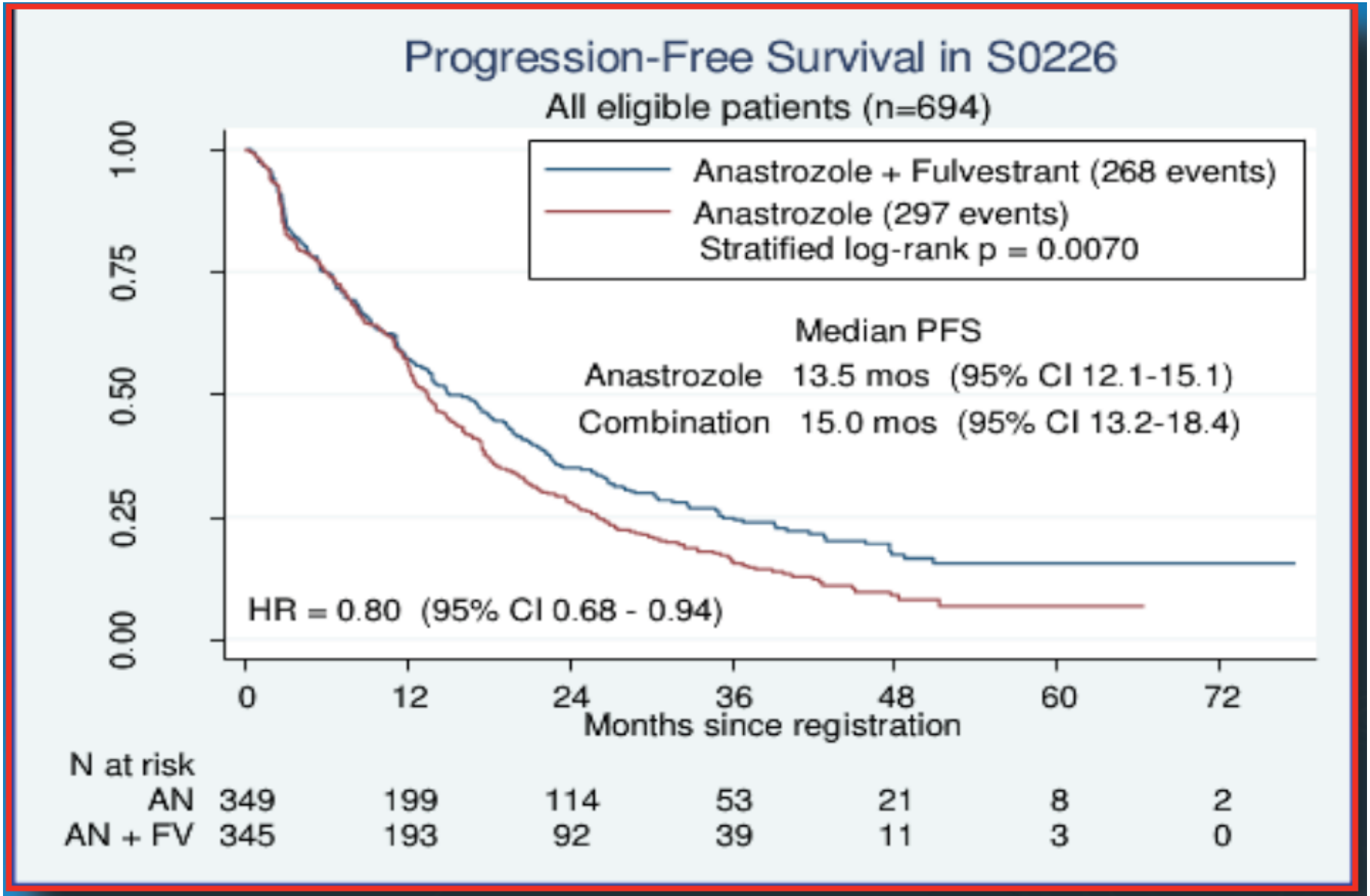
	Fulvestrant 500 mg n=102 (%)	Anastrozole 1 mg n=103 (%)
Number of progressions (%)	63 (61.8)	79 (76.7)
Median (months)	23.4	13.1

After primary DCO, progression was determined by investigator opinion

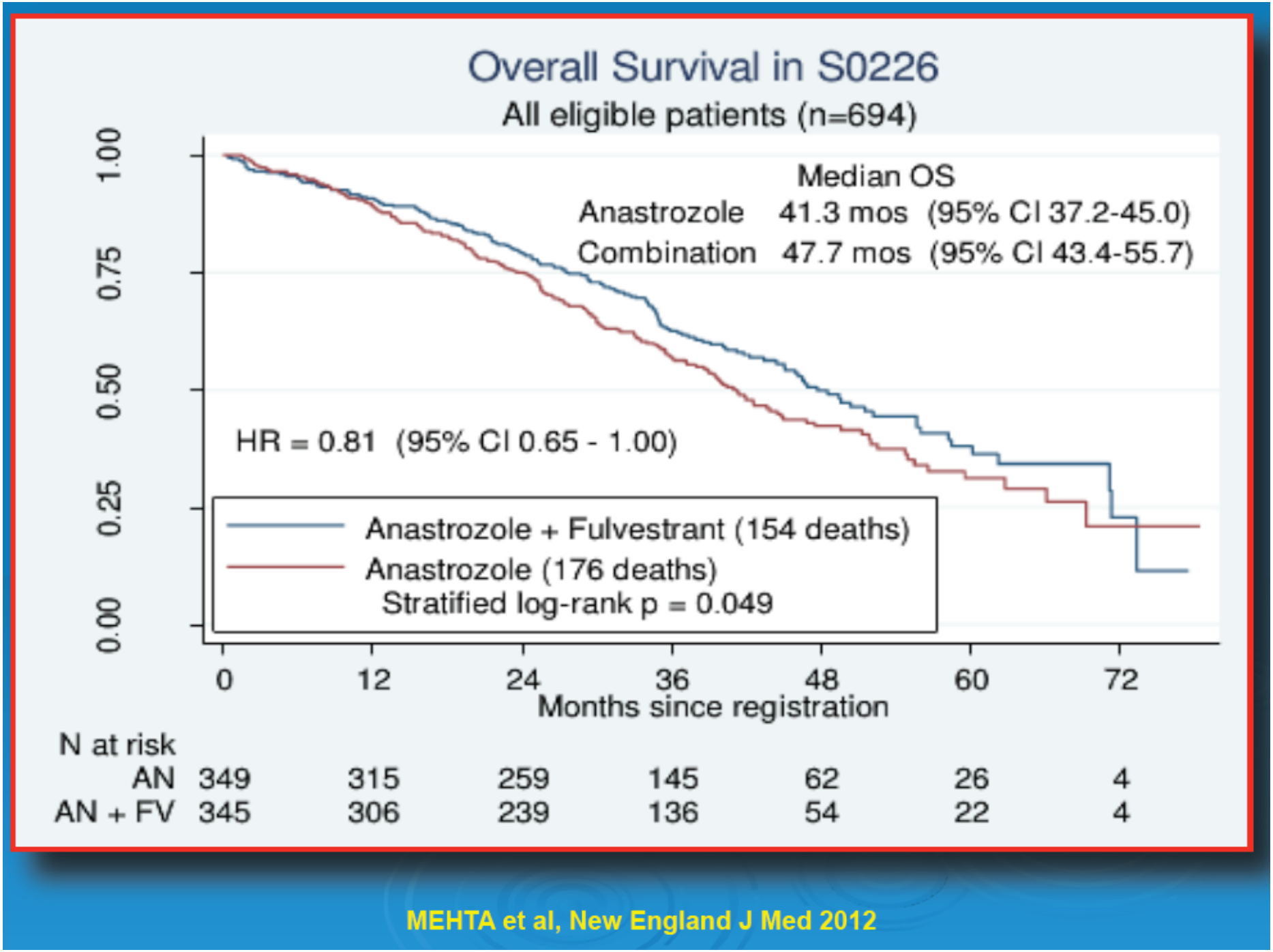
S0226: Schema



MEHTA et al, New England J Med 2012



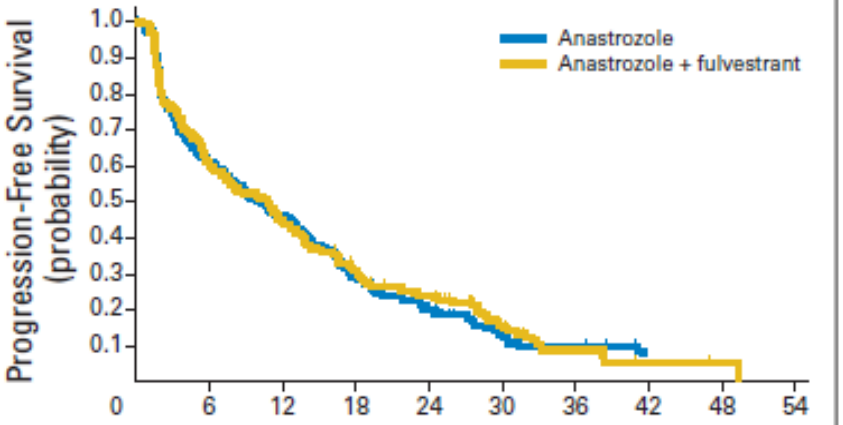
MEHTA et al, New England J Med 2012



MEHTA et al, New England J Med 2012

FACT: An Open-Label Randomized Phase III Study of Fulvestrant and Anastrozole in Combination Compared With Anastrozole Alone As First-Line Therapy for Patients With Receptor-Positive Postmenopausal Breast Cancer

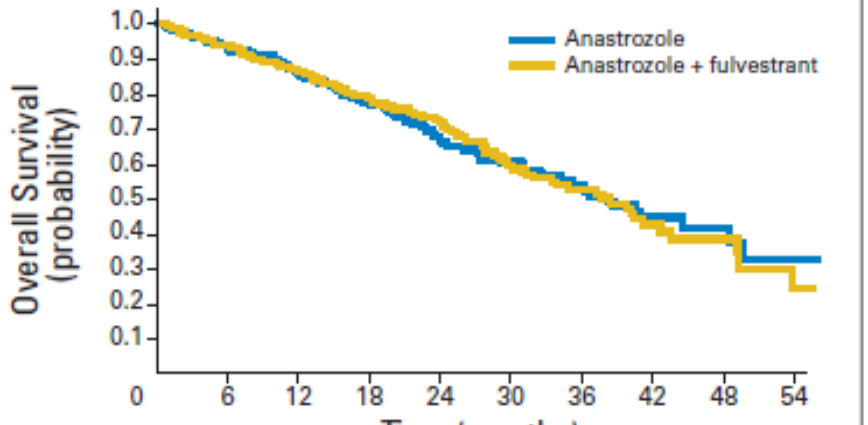
Jonas Bergh, Per-Ebbe Jönsson, Elisabet Kerstin Lidbrink, Maureen Trudeau, Wolfgang Eiermann, Daniel Brattström, Justin P.O. Lindemann, Fredrik Wiklund, and Roger Henriksson



No. at risk

Anastrozole	256	148	108	57	31	16	10	5	4	1
Anastrozole + fulvestrant	258	149	107	55	40	20	6	2	1	0

	Fulvestrant + anastrozole (n = 258)	Anastrozole (n = 256)
No. of patients with progression (%)	200 (77.5)	200 (78.1)
Median TTP in months	10.8	10.2
Primary TTP analysis (log-rank test):		
Hazard ratio* (95% CI)	0.99 (0.81 to 1.20)	
P	0.91	



No. at risk

Anastrozole	256	238	215	165	117	79	49	22	11	4
Anastrozole + fulvestrant	258	239	220	159	119	73	45	23	10	4

	Anastrozole + fulvestrant (n = 258)	Anastrozole (n = 256)
No. of deaths (%)	102 (39.5)	102 (39.8)
Median OS, months	37.8	38.2
Primary OS analysis (log-rank test):		
Hazard ratio* (95% CI)	1.00 (0.76 to 1.32)	
P	1.00	

J Clin Oncol 30:1919-1925. © 2012

VOLUME 30 · NUMBER 16 · JUNE 1 2012
JOURNAL OF CLINICAL ONCOLOGY E D I T O R I A L

Polyendocrine Treatment in Estrogen Receptor–Positive Breast Cancer: A "FACT" Yet to Be Proven

Angelo Di Leo, *Hospital of Prato, Istituto Toscano Tumori, Prato, Italy*
Luca Malorni, *Hospital of Prato, Istituto Toscano Tumori, Prato, Italy; Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, TX*

The most relevant difference between the two study populations is the number of patients who were naive to tamoxifen: 60% (414 patients) in the SWOG trial and 33% (171 patients) in the FACT trial.

VOLUME 31 · NUMBER 2 · JANUARY 10 2013
JOURNAL OF CLINICAL ONCOLOGY E D I T O R I A L

Improving Endocrine Therapy for Breast Cancer: It's Not That Simple

E. Claire Dees and Lisa A. Carey, *Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC*

A high-profile recent study of fulvestrant plus anastrozole demonstrated a 6-month improvement in overall survival. This study included a population of primarily endocrine therapy–naive patients treated in the first line setting. In fact, the population benefiting from the combination appeared to be limited to those who were entirely endocrine therapy-naive, even in the adjuvant setting, not a typical contemporary metastatic population. It is unclear if any other subset of the study population derived benefit from the combination.[23] By contrast, the FACT study,[24] another randomized trial of anastrazole with or without fulvestrant that enrolled endocrine-pretreated patients showed no benefit to the combination.

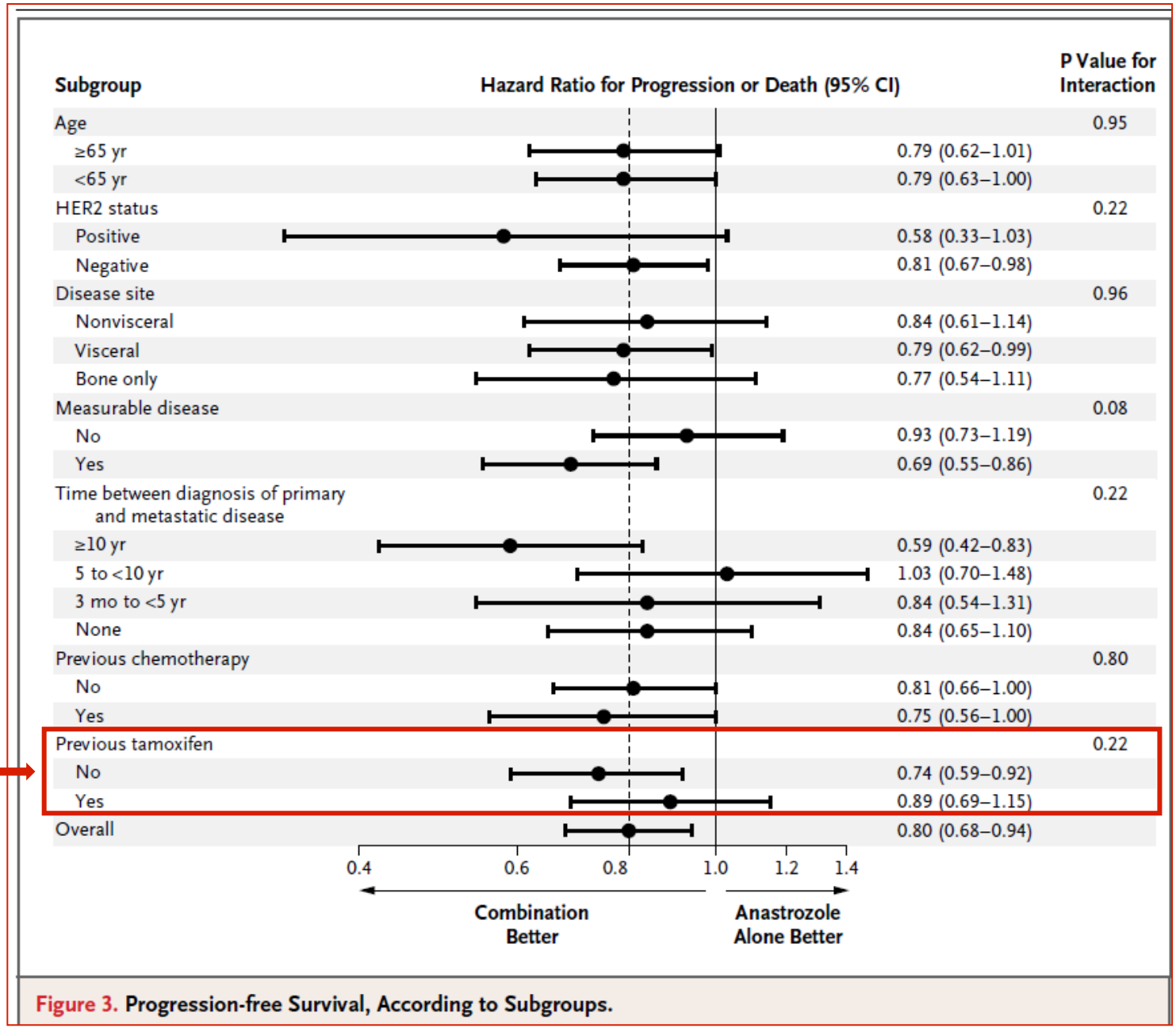
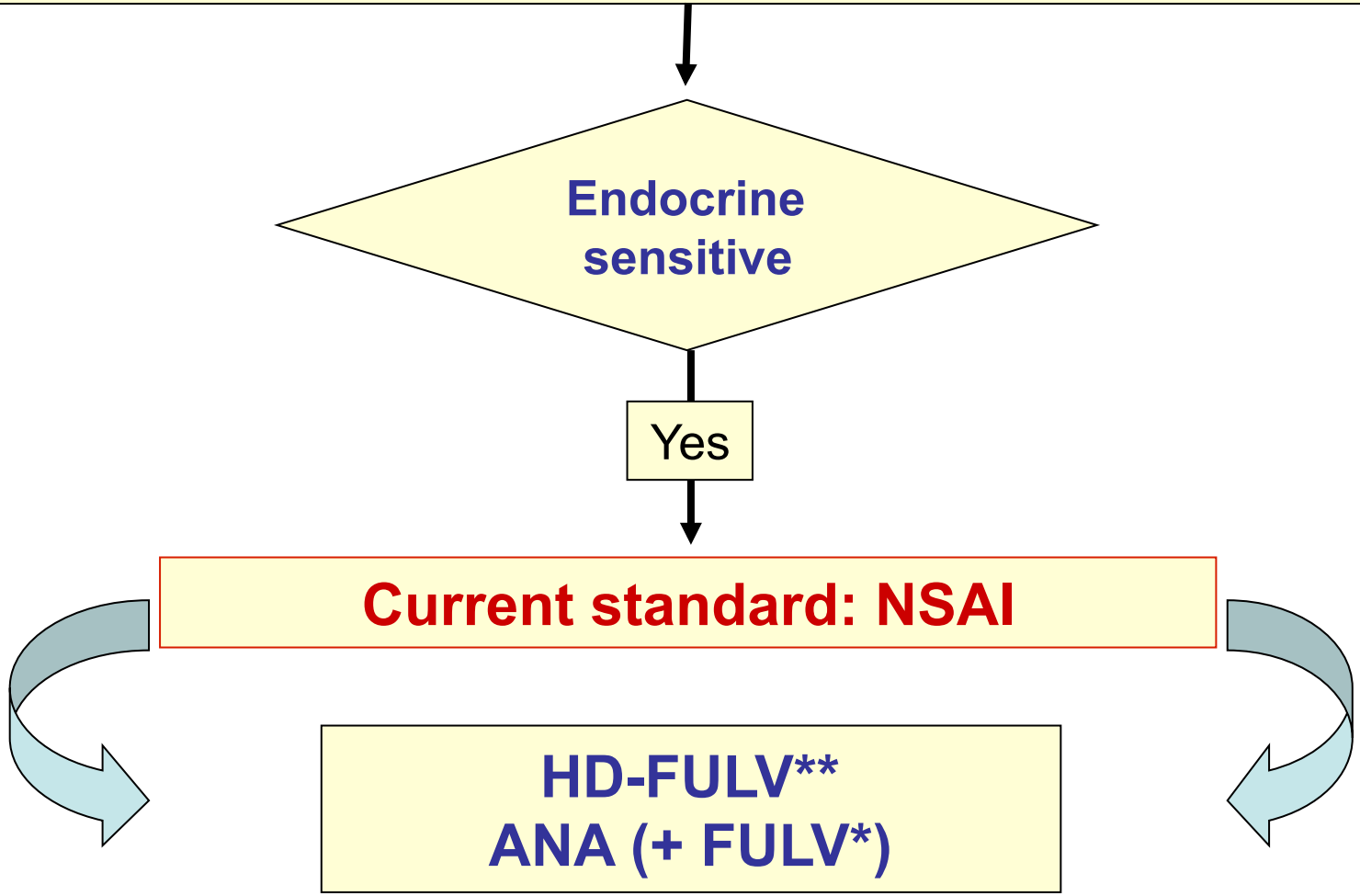


Figure 3. Progression-free Survival, According to Subgroups.

Prior Tamoxifen: 280/707 (40,3%)

Mehta N Engl J Med 2012;367:435-44.

First line endocrine therapy



*Ph III: FULV 500-250-250, 60% HT naive; PFS 13.5 mos – HR 0.74
**Ph II: FULV 500-500-500, 75% HT naive; PFS 23.4 mos – HR 0.66

San Antonio Breast Cancer Symposium – December 4–8, 2012. Abstract # 866

Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer – First efficacy results from the LEA study.

Miguel Martin[1*], Sibylle Loibl[2*], Gunter von Minckwitz[2], Serafín Morales[3], Carmen Crespo[4], Antonio Anton[5], Ángel Guerrero[6], Bahriye Aktas[7], Winfried Schoenegg[8], Montserrat Muñoz[9], José Ángel Garcia-Saenz[10], Miguel Gil[11], Manuel Ramos[12], Eva Carrasco[13], Cornelia Liedtke[14], Grischa Wachsmann[15], Keyur Mehta[2], Juan R De la Haba[16], On behalf of GEICAM (Spanish Breast Cancer Research Group) and GBG (German Breast Group).
*contributed equally

[1]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain; [2]GBG (German Breast Group), Neu-Isenburg, Germany; [3]H. Arnau Vilanova de Lérida, Spain; [4]Hospital U. Ramón y Cajal, Spain; [5]Hospital Universitario Miguel Servet, Spain; [6]Instituto Valenciano de Oncología, Spain; [7]University Women´s Hospital Essen, Germany; [8]Medical Practice Berlin, Germany; [9]Hospital Clinic i Provincial, Spain; [10]Hospital Clínico U. San Carlos, Spain; [11]Instituto Catala d' Oncología Hospitalet, Spain; [12]Centro Oncológico de Galicia, Spain; [13]GEICAM (Spanish Breast Cancer Research Group), Spain; [14]University Women´s Hospital Muenster, Germany; [15]Klinikum Boeblingen, Germany and [16]Hospital U. Reina Sofía, Spain.

Rationale for Bevacizumab in *hormone sensitive BC*

- Estrogen is a potent modulator of angiogenesis and directly regulates new blood vessel formation through effects on endothelial cells.
- Estrogen-induced angiogenesis is mediated by VEGF
- Estrogen withdrawal reduces VEGF expression in oophorectomized animals
- In MCF-7 cell lines, estrogen increases levels of VEGF and aromatase inhibition lowered VEGF expression in a mouse model

VOLUME 28 · NUMBER 4 · FEBRUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Feasibility Trial of Letrozole in Combination With Bevacizumab in Patients With Metastatic Breast Cancer

Tiffany A. Traina, Hope S. Rugo, James F. Caravelli, Sujata Patil, Benjamin Yeh, Michele E. Melisko, John W. Park, Stephanie Geneus, Matthew Paulson, Jill Grothusen, Andrew D. Seidman, Monica Fornier, Diana Lake, Chau Dang, Mark Robson, Maria Theodoulou, Carlos D. Flombaum, Larry Norton, Clifford A. Hudis, and Maura N. Dickler

ABSTRACT

Purpose

Preclinical models suggest that the use of anti–vascular endothelial growth factor (anti-VEGF) therapy with antiestrogens may prevent or delay the development of endocrine therapy resistance. We therefore performed a feasibility study to evaluate the safety of letrozole plus bevacizumab in patients with hormone receptor–positive metastatic breast cancer (MBC).

Methods

Patients with locally advanced breast cancer or MBC were treated with the aromatase inhibitor (AI) letrozole (2.5 mg orally daily) and the anti-VEGF antibody bevacizumab (15 mg/kg intravenously every 3 weeks). The primary end point was safety, defined by grade 4 toxicity using the National Cancer Institute Common Toxicity Criteria, version 3.0. Secondary end points included response rate, clinical benefit rate, and progression-free survival (PFS). Prior nonsteroidal AIs (NSAIs) were permitted in the absence of progressive disease.

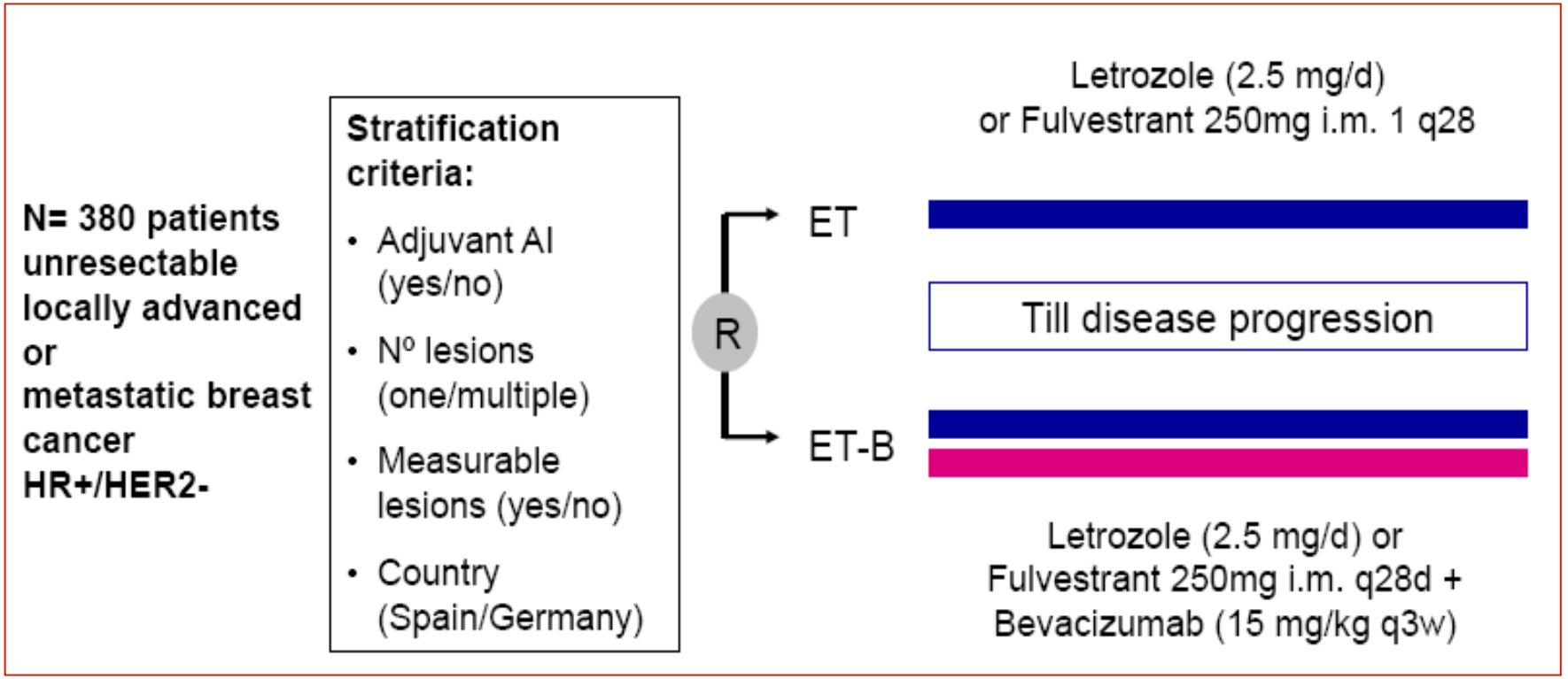
Results

Forty-three patients were treated. After a median of 13 cycles (range, 1 to 71 cycles), select treatment-related toxicities included hypertension (58%; grades 2 and 3 in 19% and 26%), proteinuria (67%; grades 2 and 3 in 14% and 19%), headache (51%; grades 2 and 3 in 16% and 7%), fatigue (74%; grades 2 and 3 in 19% and 2%), and joint pain (63%; grades 2 and 3 in 19% and 0%). Eighty-four percent of patients had at least stable disease on an NSAI, confounding efficacy results. Partial responses were seen in 9% of patients and stable disease ≥ 24 weeks was noted in 67%. Median PFS was 17.1 months.

Conclusion

Combination letrozole and bevacizumab was feasible with expected bevacizumab-related events of hypertension, headache, and proteinuria. Phase III proof-of-efficacy trials of endocrine therapy plus bevacizumab are in progress (Cancer and Leukemia Group B 40503).

Study design



Primary Endpoint: PFS

Other Endpoints: OS, TTF, OR, CB, Safety, Biomarkers

Letrozole 90%, Fulvestrant 10%)

Martin, SABCS 2012

Patient characteristics

	ET n= 189	ET-B n= 191
Age in years,		
≤ 64	46%	52.8%
65-69	19%	17.8%
>70	34.9%	29.3%
Country		
Spain	71.4%	70.7%
Germany	28.6%	29.3%
ECOG PS		
0	71.4%	72.8%
1	28.6%	26.7%
Unknown	0	0.5%
Previous adjuvant chemotherapy		
Taxane, anthras or both	35.4%	34.5%
CMF	11.1%	9.4%
None	52.9%	55.5%
Previous adjuvant endocrine therapy		
Antiestrogens	31.2%	33.5%
Aromatase inhibitor	7.4%	4.2%
Both	12.7%	14.7%
None	48.7%	47.6%

Patient characteristics

	ET n= 189	ET-B n= 191
Stage of disease at study entry		
Locally Advanced disease	3.2%	3.1%
Metastatic disease	82%	80.1%
Unknown	14.8%	16.8%
Number of metastatic sites		
Single	38%	42%
Multiple	62%	58%
Visceral disease		
Yes	48%	48%
No	52%	52%
Types of metastatic sites		
Lung	37%	32%
Liver	20%	21%
Bone	65%	65%
Other	61%	53%
Measurable disease		
Yes	79%	75%
No	21%	25%

Toxicity

Toxicity NCI-CTCAE 3.0, (n %)	Grade	ET	ET-B	P-Value
Fatigue	1-4	51 (29.0)	95 (50.5)	<0.001
	3-4	1 (0.6)	4 (2.1)	0.373
Hypertension	1-4	28 (15.9)	111 (59.0)	<0.001
	3-4	0	6 (3.2)	0.030
Hemorrhage	1-4	3 (1.7)	35 (18.6)	<0.001
	3-4	0	0	N.A.
Liver enzyme elevation (ASAT)	1-4	49 (28.0)	87 (46.5)	<0.001
	3-4	0	3 (1.6)	0.249
Proteinuria	1-4	5 (2.8)	57 (30.3)	<0.001
	3-4	0	2 (1.1)	0.499
Thromboembolic events	1-4	1(0.6)	4(2.1)	0.373
	3-4	0 (0.0)	4 (2.1)	0.124

Loibl S et al. ESMO 2012 # 323

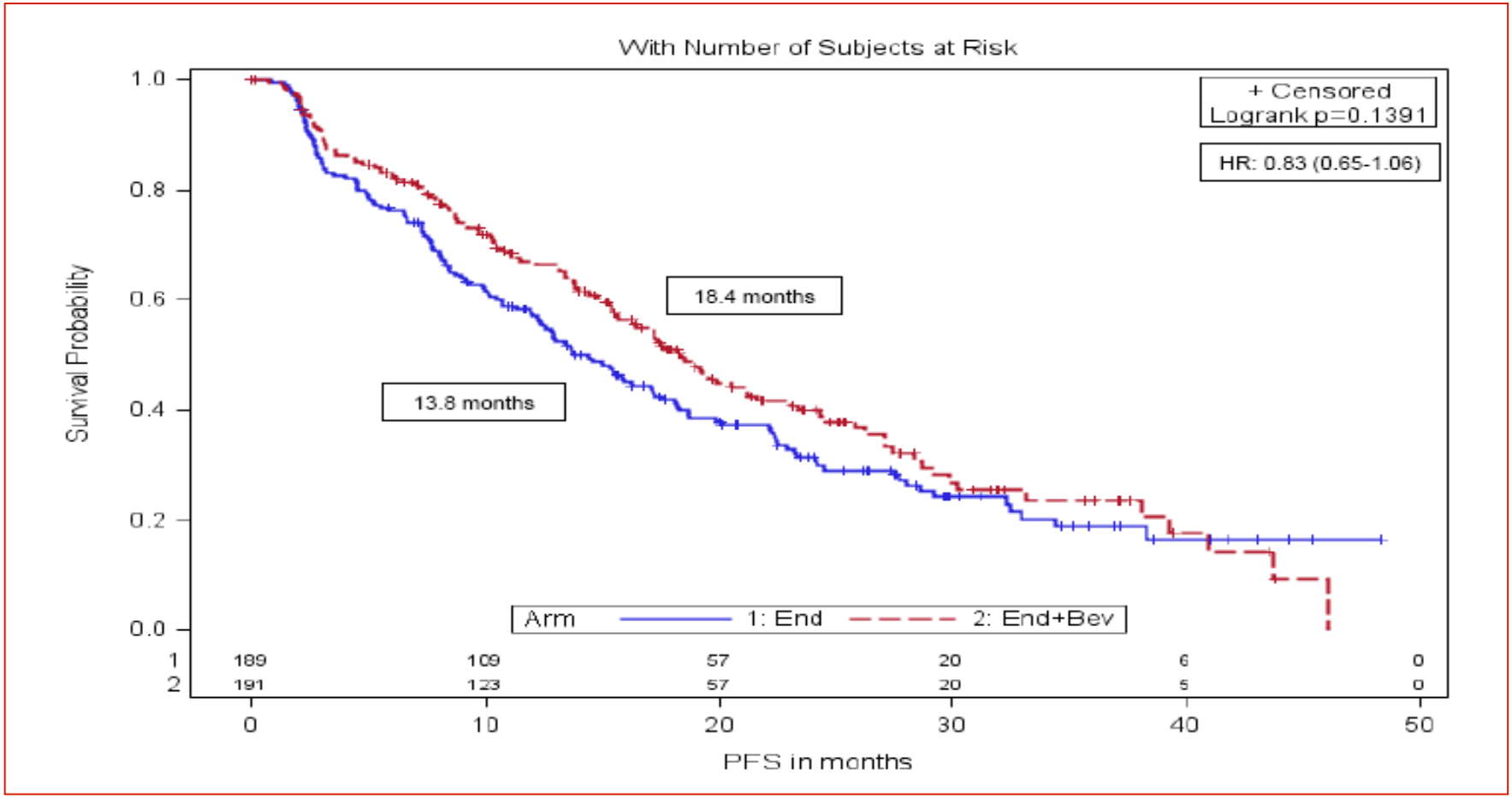
Events

Events	ET n= 189	ET-B n= 191
PFS, median (months)	13.8	18.4
P-value, log-rank HR (95% CI)	0.14 0.83 (0.65-1.06)	
PFS events (Total)	131	117*
Censored	58	74

PFS: Progression-free survival, time from the date of randomization to the first date of documented progression or death from any cause for all randomized patients; CI: confidence interval

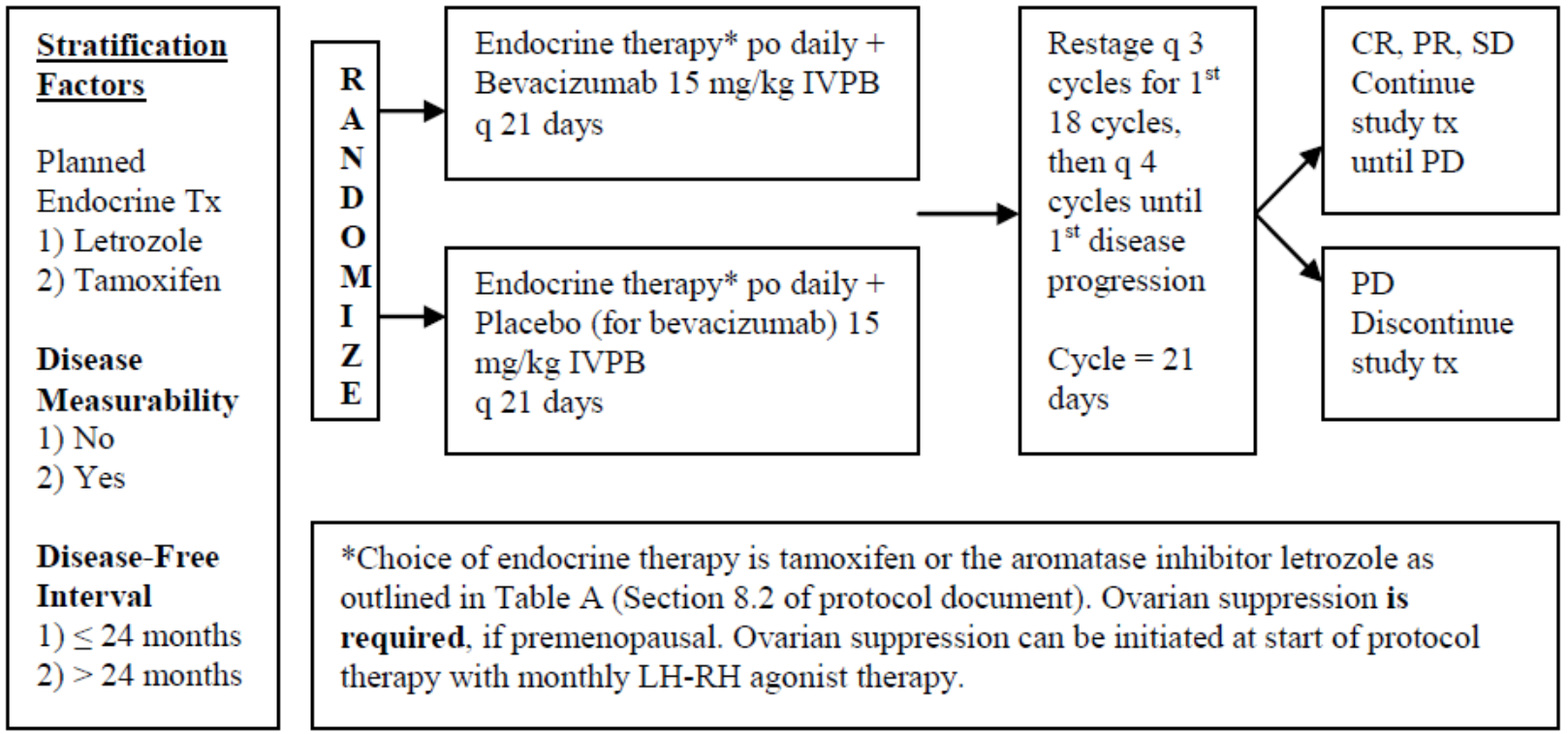
* Seven while on treatment (3 cardiac, 1 pulmonary embolism, 1 cerebellar hemorrhage, 1 sudden death, 1 liver failure)

Progression Free Survival



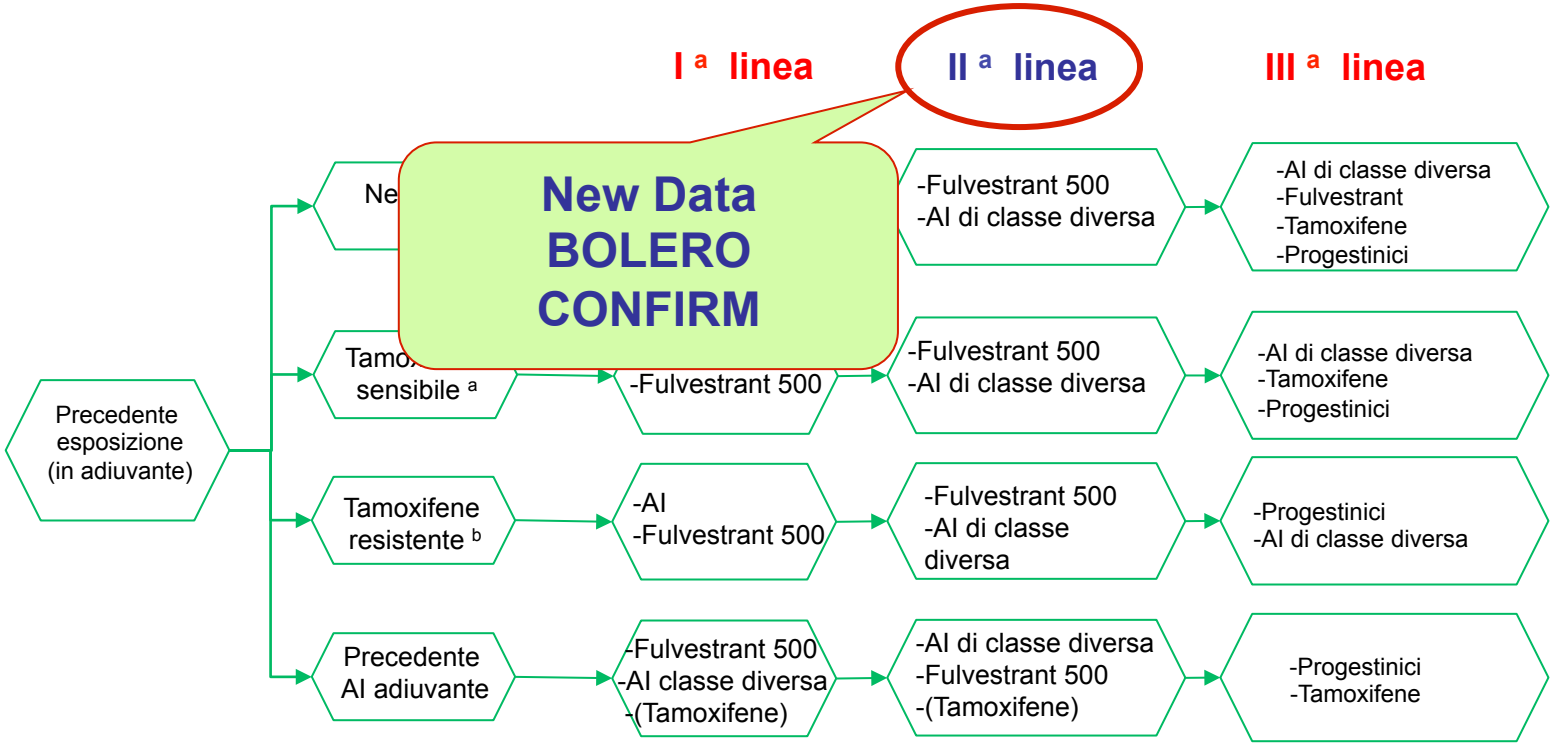
Median Overall Survival: 42 vs 41 mos. HR:1.18

Phase III CALGB 40503 trial
Endocrine therapy ± Bevacizumab



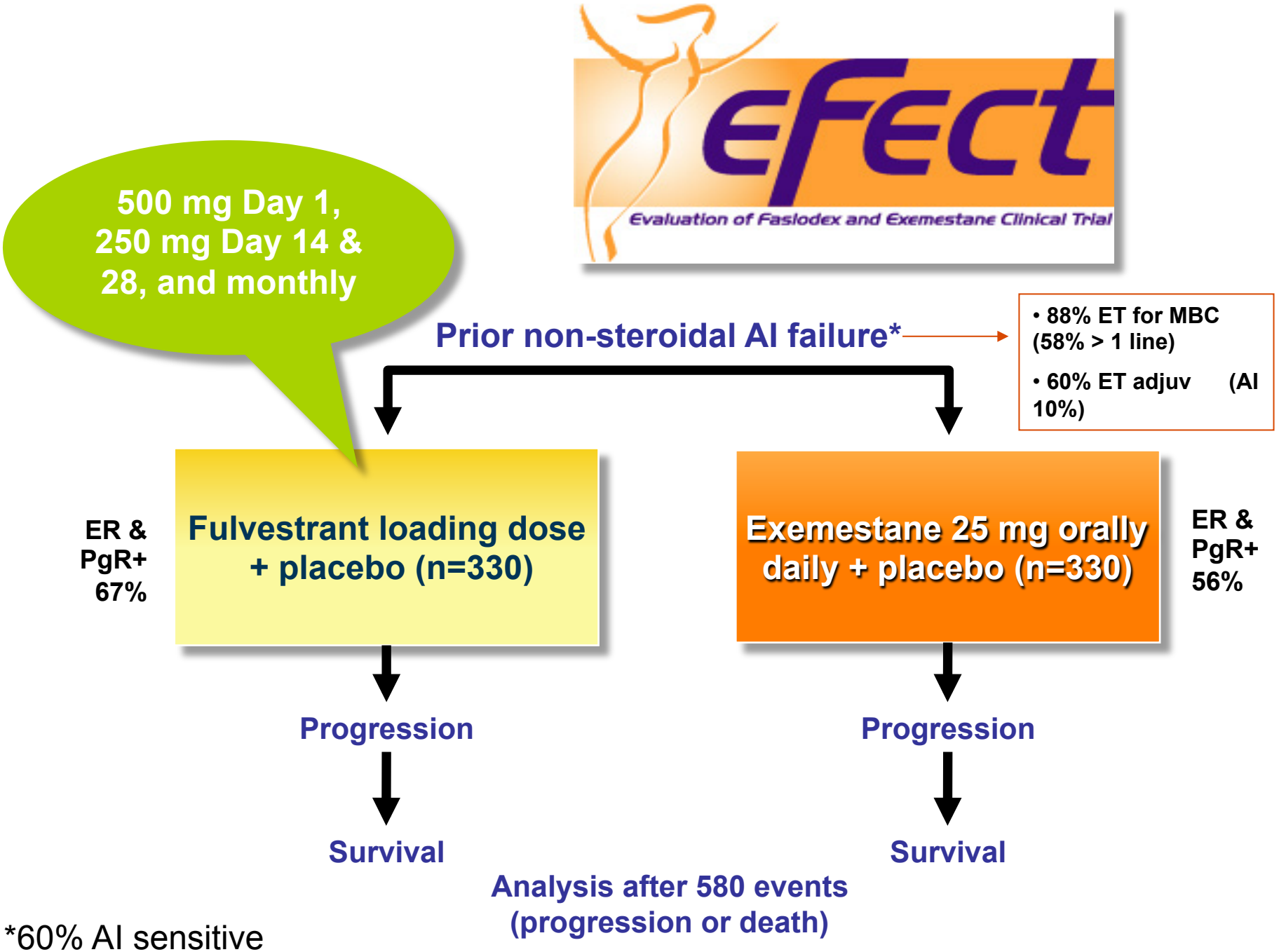
ACTIVATED May 15, 2008
ENROLLMENT 502 patients
CLOSED

LG AIOM 2012 - CARCINOMA MAMMARIO METASTATICO
Terapia ormonale in post-menopausa



Nota a -Tamoxifene sensibile: Intervallo tra la fine del trattamento con tamoxifene adiuvante e la comparsa di metastasi >12 mesi.
Nota b - Tamoxifene resistente: Comparsa di metastasi durante il trattamento o entro 12 mesi dalla fine del trattamento adiuvante con tamoxifene.

Endocrine resistant breast cancer


eFect
Evaluation of Faslodex and Exemestane Clinical Trial
500 mg Day 1,
250 mg Day 14 &
28, and monthly
Prior non-steroidal AI failure*
• 88% ET for MBC (58% > 1 line)
• 60% ET adjuv (AI 10%)
ER & PgR+ 67%
Fulvestrant loading dose + placebo (n=330)
Exemestane 25 mg orally daily + placebo (n=330)
ER & PgR+ 56%
Progression
Progression
Survival
Survival
Analysis after 580 events (progression or death)
*60% AI sensitive

EFECT trial: clinical endpoints

Efficacy Measure	Fulvestrant n = 351	Exemestane n = 342
ORR	**7.4%**	**6.7%**
Median TTP	**3.7 months**	**3.7 months**
Median duration of clinical benefit	**9.3 months**	**8.3 months**
Clinical benefit rate	**32.2%**	**31.5%**
Efficacy Measure	Fulvestrant n = 351	Exemestane n = 342

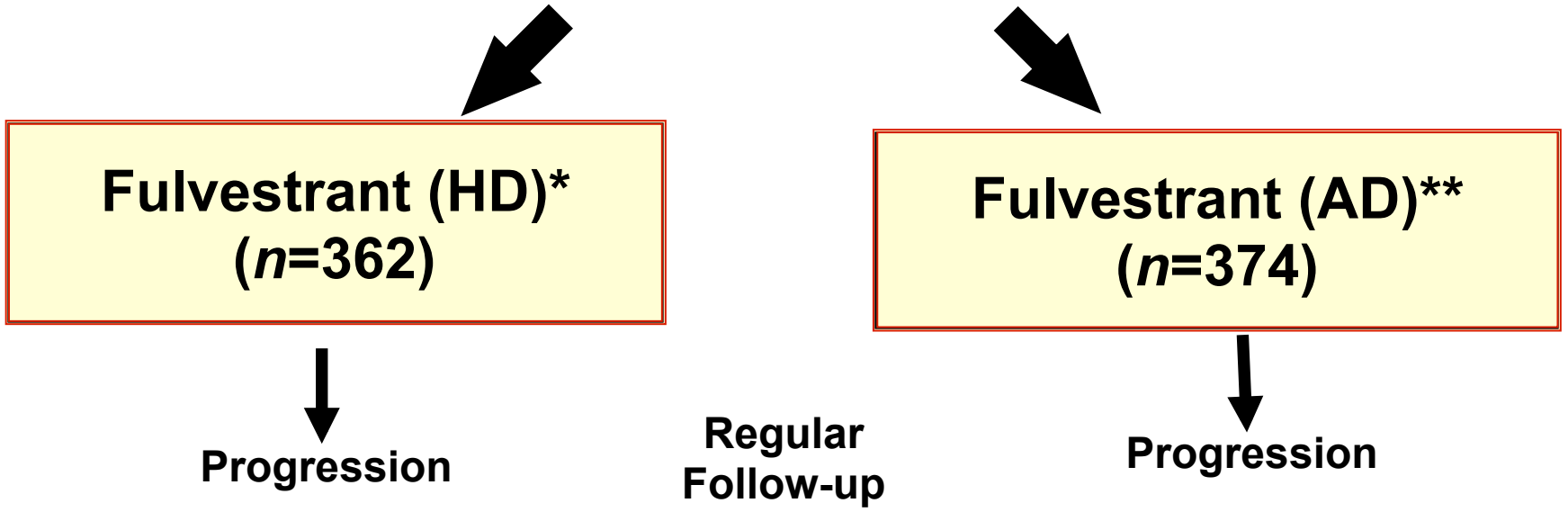
Similar results in the SOFEA trial, for EXA or SD-Fulv in patients progressing on NSAI: 3.4 vs 4.8 mos

CONFIRM

Final analysis of Overall Survival

Di Leo, et al: SABCS 2012

736 postmenopausal women with ER-positive MBC or LABC after failure on one prior endocrine therapy



* **HD** = high dose (500mg i.m. 2 injections at day 0 + 500mg i.m. at days 14 and 28, thereafter 500mg i.m. monthly until progression)

** **AD** = approved dose (250mg i.m. Monthly + Placebo)

Primary objective: PFS

Secondary objectives: ORR, CBR, duration of response and CB, OS, tolerability, QoL

Characteristics of the patients

Characteristic	Fulvestrant 500 mg (n = 362) No. of Patients	%	Fulvestrant 250 mg (n = 374) No. of Patients	%
Median age, years	61		61	
ER positive	362	100	374	100
PgR status				
Positive	241	66.6	266	71.1
Negative	92	25.4	96	25.7
Unknown	29	8	12	3.2
Locally advanced disease	4	1.1	11	2.9
Metastatic disease	358	98.9	363	97.1
Visceral involvement	239	66	232	62
No. of disease sites				
Median	2		2	
Range	1-6		0-7	
Time from diagnosis to random assignment, months				
Median	60.5		59.9	
Range	0.9-338.6		1.9-418.4	
Relapse/progression				
During adjuvant endocrine therapy	175	48.3	169	45.2
0-12 months after completion of adjuvant endocrine therapy	16	4.4	27	7.2
> 12 months after completion of adjuvant endocrine therapy and after progression on first-line endocrine therapy for advanced disease	36	9.9	52	13.9
Patients presenting with de novo advanced disease and experiencing progression on first-line endocrine therapy	130	35.9	125	33.4
Other	5	1.4	1	0.3

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

Di Leo A et al. JCO 2010;28:4594-4600

Response rate

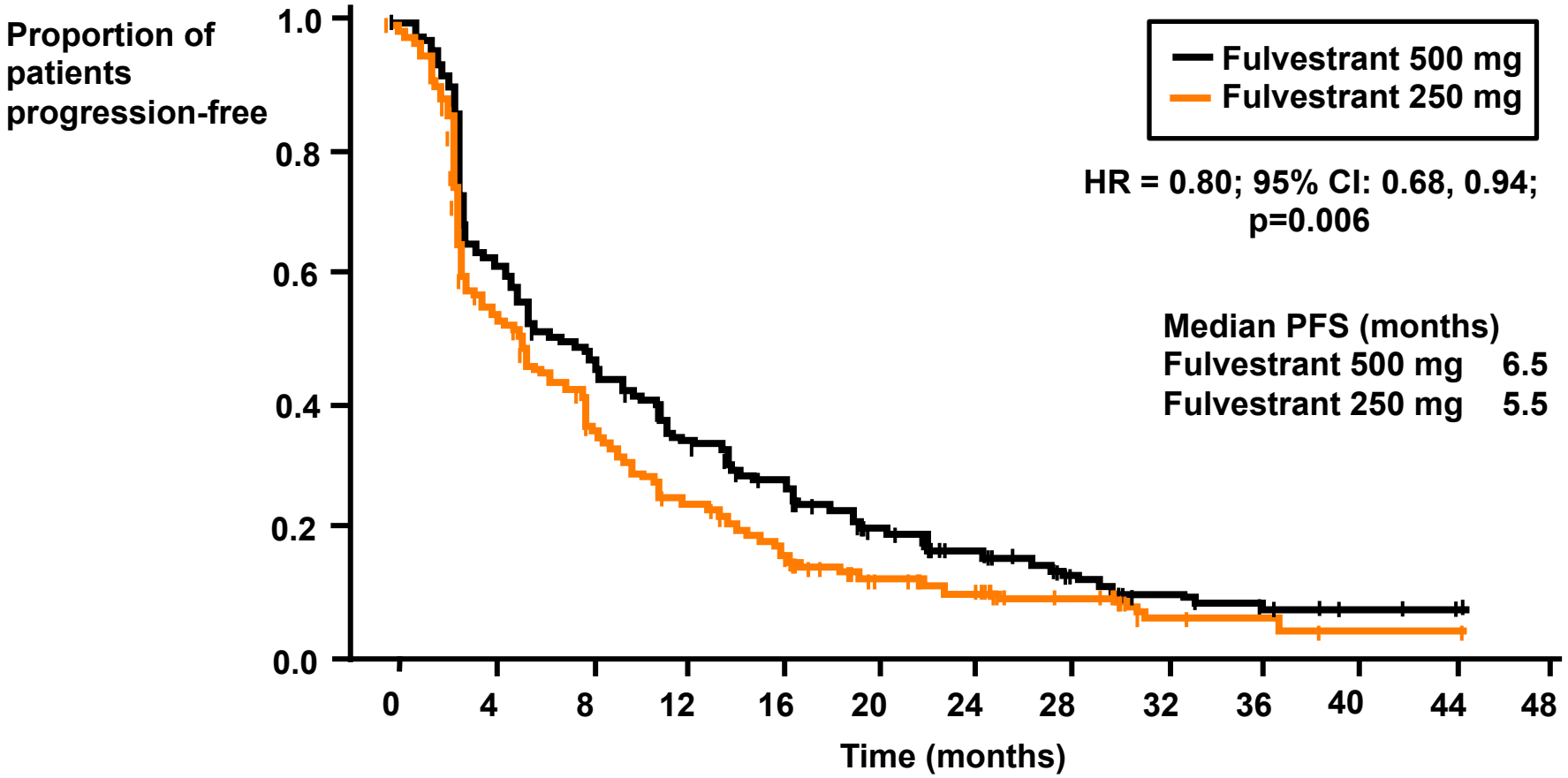
Response	Fulvestrant 500 mg (n = 362)		Fulvestrant 250 mg (n = 374)	
	No. of Patients	%	No. of Patients	%
Complete response	4	1.1	1	0.3
Partial response	29	8	37	9.9
Objective response*	33	9.1	38	10.2
Stable disease ≥ 24 weeks	132	36.5	110	29.4
Clinical benefit†	165	45.6	148	39.6
Stable disease < 24 weeks	47	13	52	13.9
Progressive disease	140	38.7	167	44.7
Not evaluable	10	2.8	7	1.9

*The complete response plus partial response rate in patients with measurable disease was 13.8% (33 of 240 patients) with fulvestrant 500 mg and 14.6% (38 of 261 patients) with fulvestrant 250 mg.

† Clinical benefit defined as complete response + partial response + stable disease ≥ 24 weeks.

Di Leo A et al. JCO 2010;28:4594-4600

Primary endpoint: progression-free survival



Patients at risk:													
500 mg	362	216	163	113	90	54	37	19	12	7	3	2	0
250 mg	374	199	144	85	60	35	25	12	4	3	1	1	0

CI, confidence interval; HR, hazard ratio;
PFS, progression-free survival

Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

Overall survival: final analysis at 75% maturity

- Following the reporting of the first survival data, an amendment to the SAP to allow for a 75% survival analysis was initiated by the study Steering Committee with a commitment for the data to be shared with the European Medicines Agency

- Exploratory analysis:
  - analysis by log-rank, confirmed by cox regression, summarised by Kaplan-Meier curves
  - no alpha was retained for this analysis (the 5% error was used for the 1st OS analysis)
  - Accordingly, adjustment for multiplicity was not feasible

- During the survival follow-up phase,
  - all patients continued to have their survival status monitored every 12+/-2 weeks until cut-off for the final 75% OS analysis
  - SAEs were reported for those patients still receiving randomized treatment
  - details of the first subsequent systemic breast cancer therapy, as well as the best response to this therapy, were collected

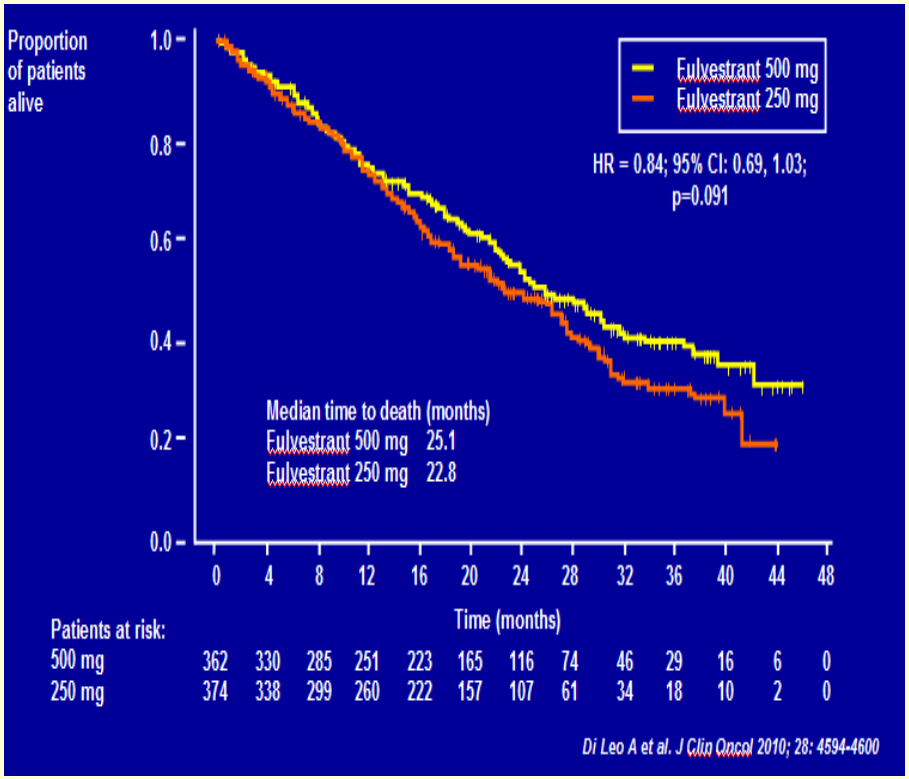
Survival status

Survival status	Number (%) of patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Ongoing in survival FU, on study treatment	13 (3.6)	8 (2.1)
Ongoing in survival FU, not on study treatment	45 (12.4)	37 (9.9)
Dead at data cut-off	261 (72.1)	293 (78.3)
Lost to FU	33 (9.1)	30 (8.0)
Withdrawn consent	10 (2.8)	6 (1.6)

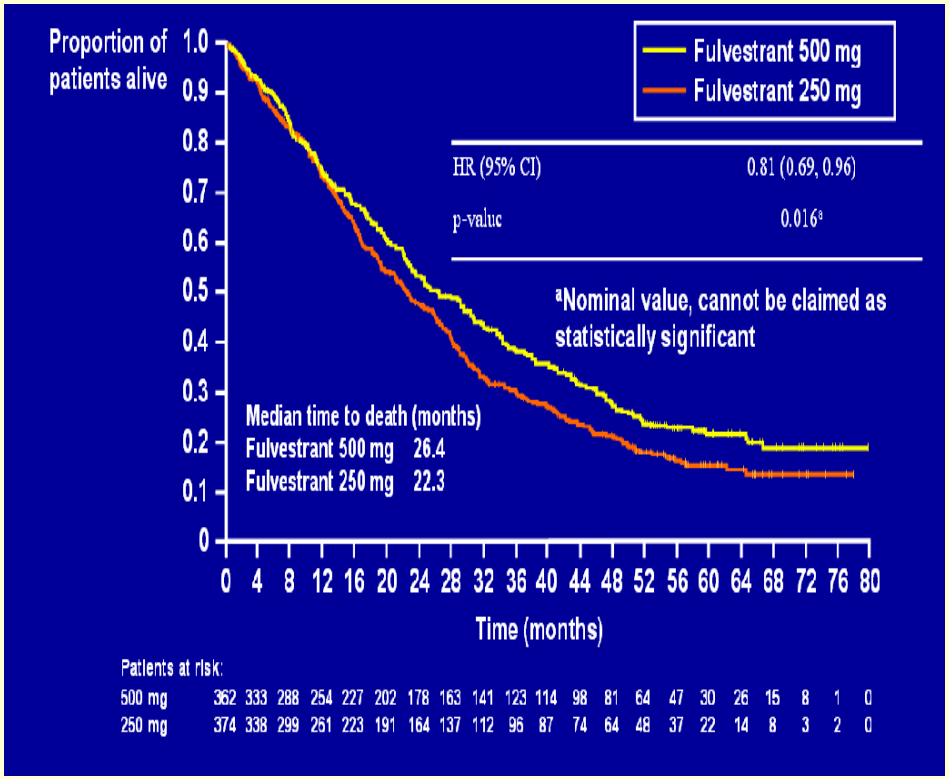
Di Leo A et al. SABCS 2012

Overall survival: first and final analyses

50% events



75% events



Di Leo, SABCS 2012

First subsequent therapy

	Fulvestrant 500 N=362	Fulvestrant 250 N=374*
% pts with available information	63 (N=230)	64 (N=239)
Type of 1st subsequent therapy - % chemotherapy/anti-HER2 - % endocrine therapy other than fulvestrant*	 59/ - 35	 59/ 0.4 31
% objective response/ clinical benefit	8/ 33	8/ 41

* **8 0ut of 374** patients (**2.1%**) shifted from fulvestrant 250 mg to 500 mg

Deaths during the treatment

Preferred term	Number (%) of patients	
	FULVESTRANT 500 mg N= 361	FULVESTRANT 250 mg N=374
Acute myocardial infarction	0	2 (0.5)
Acute renal failure	0	1 (0.3)
Aspiration	0	1 (0.3)
Cardiopulmonary failure	1 (0.3)	0
Suicide	0	1 (0.3)
Death (cause unknown)	1 (0.3)	0
Dyspnea	2 (0.6)	0
Hypertension	0	1 (0.3)
Intestinal adenocarcinoma	1 (0.3)	0
Meningitis	0	1 (0.3)

All events occurring after first dose are summarized
Patient numbers are not mutually exclusive

Di Leo A et al. SABCS 2012

Conclusions

- Final OS analysis at 75% maturity shows that fulvestrant 500 mg is associated with 4.1 month increase in median OS and a 19% reduction in the risk of death compared with fulvestrant 250 mg

- These results are consistent with the previously reported PFS and OS data (J Clin Oncol 28: 4594 4600,2010)

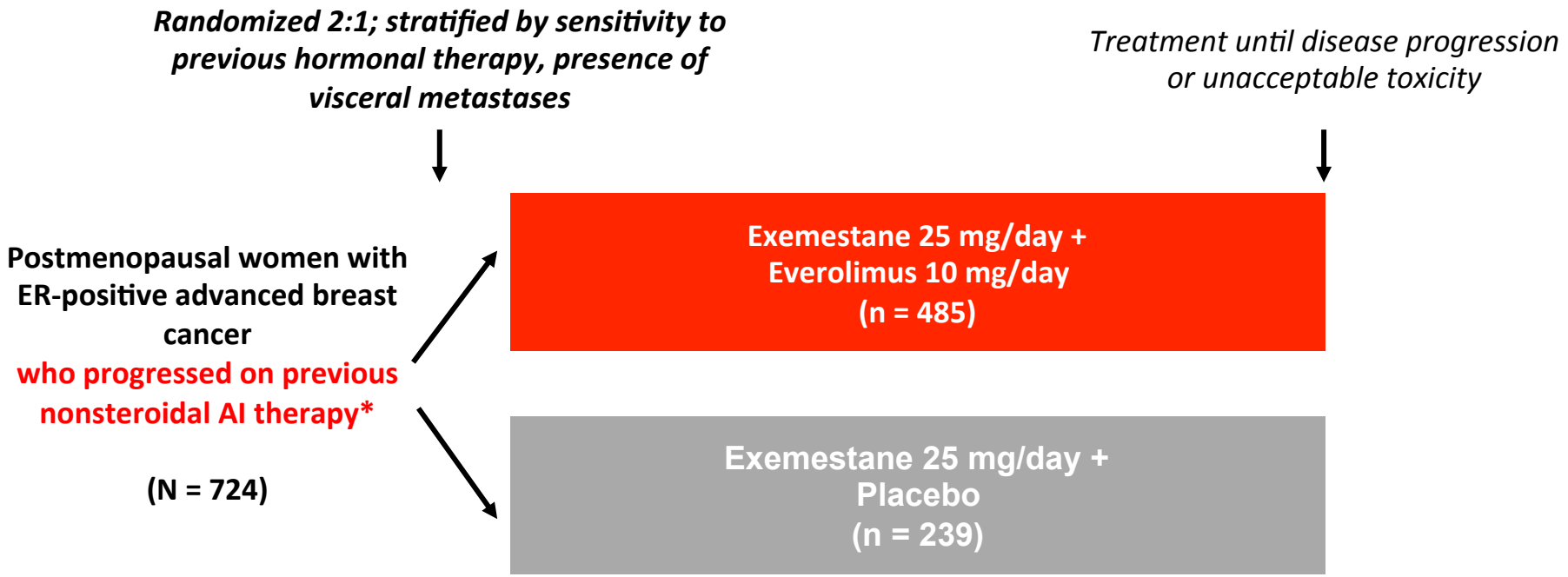
- Analysis at 1st subsequent therapies does not support any imbalance between the two study arms

- Only 2% of patients crossed-over from 250 to 500 mg. However, activity for 500 mg after pre-treatment with 250 mg is unknown

- The safety results do not support any clinically relevant difference between fulvestrant 250 and 500 mg and they are consistent with the previously reported safety profile of fulvestrant 500 mg

BOLERO-2: Study Design

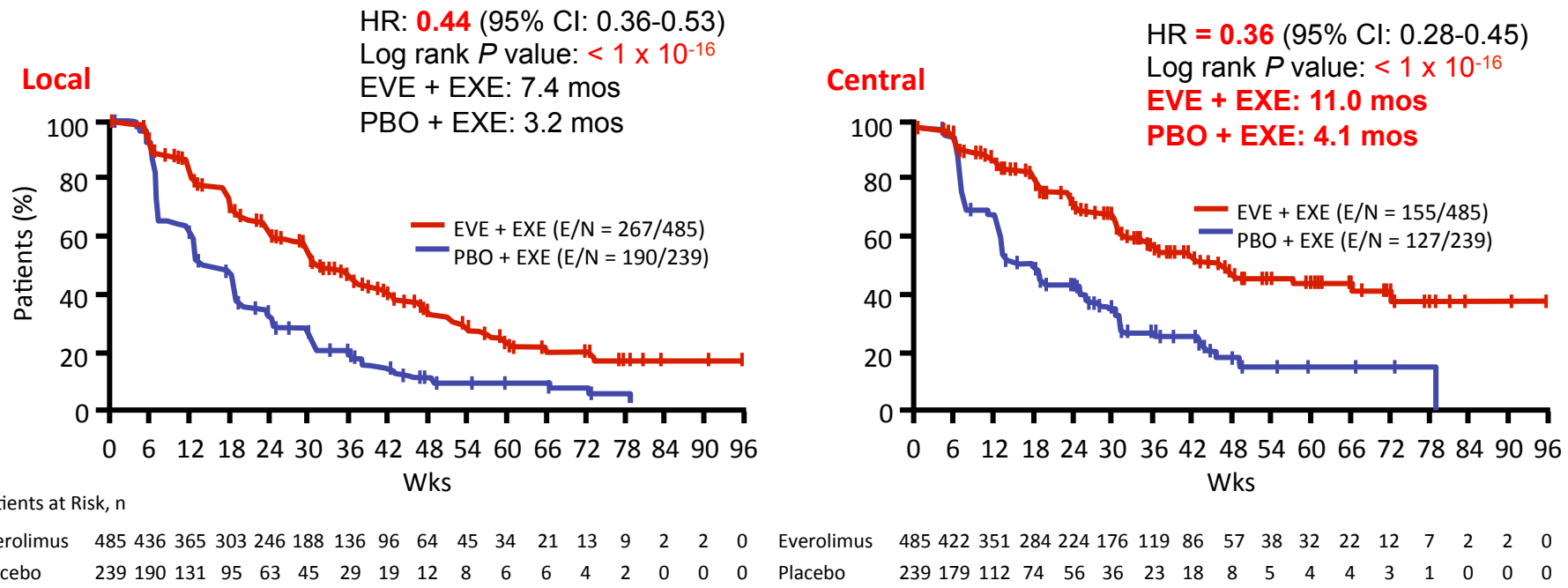
- Primary endpoint: PFS (investigator assessment)
- Secondary endpoints: OS, ORR, clinical benefit rate, safety



***> 50% of patients in each arm with ≥ 3 previous therapies**

Hortobagyi GN, et al. SABCS 2011. Abstract S3-7.

BOLERO-2 : PFS



Patients at Risk, n

Everolimus	485	436	365	303	246	188	136	96	64	45	34	21	13	9	2	2	0
Placebo	239	190	131	95	63	45	29	19	12	8	6	6	4	2	0	0	0

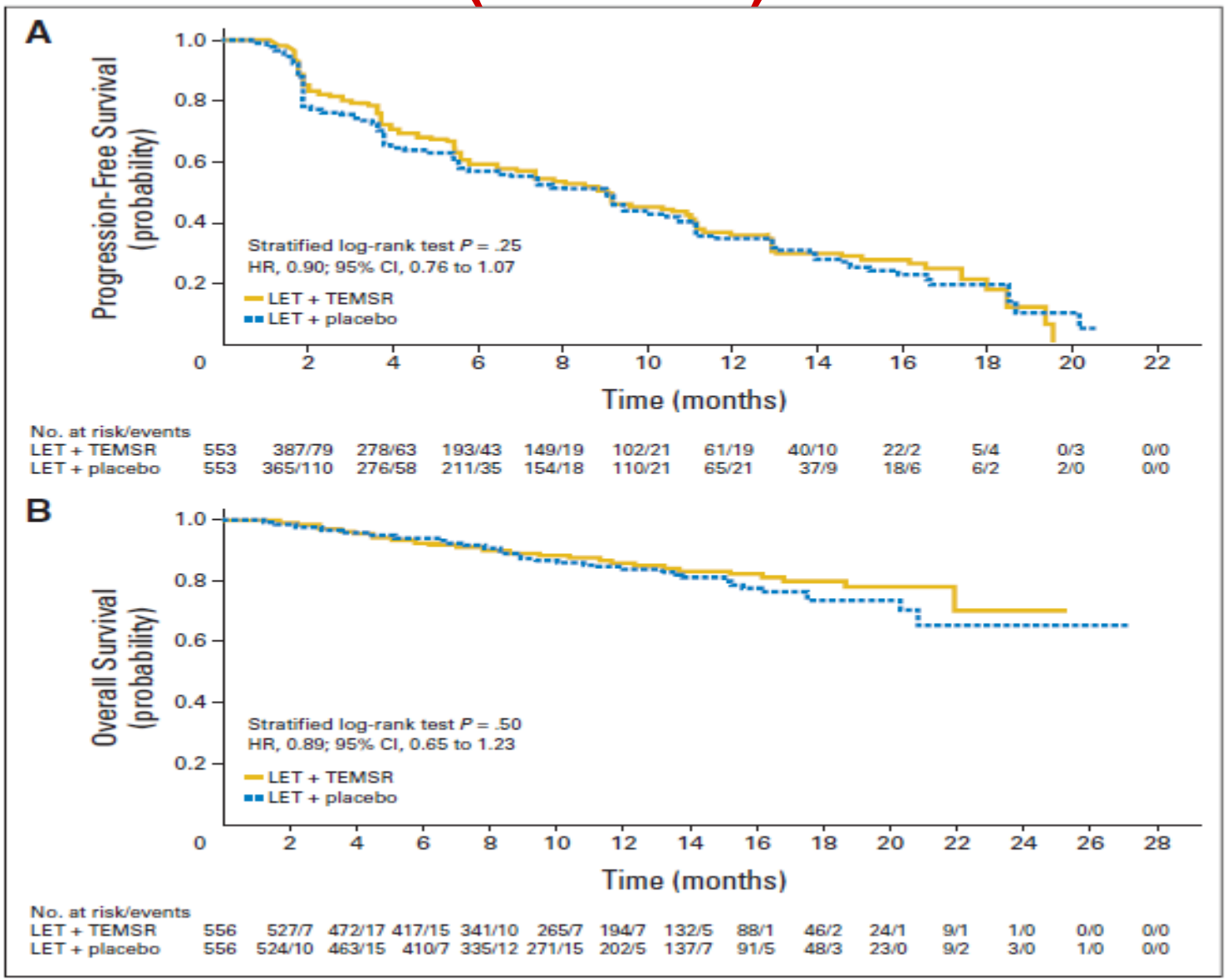
Everolimus	485	422	351	284	224	176	119	86	57	38	32	22	12	7	2	2	0
Placebo	239	179	112	74	56	36	23	18	8	5	4	4	3	1	0	0	0

NEJM: HR 0.43; 6.9 vs 2.8 mos; p < 0.001 HR 0.36; 10.6 vs 4.1 mos; p < 0.001

PSF in 2nd/3rd line similar to 1st line

Hortobagyi GN, et al. SABCS 2011. Abstract S3-7.

First line Letrozole + Temsirolimus (Horizon)



Wolff, JCO 2013

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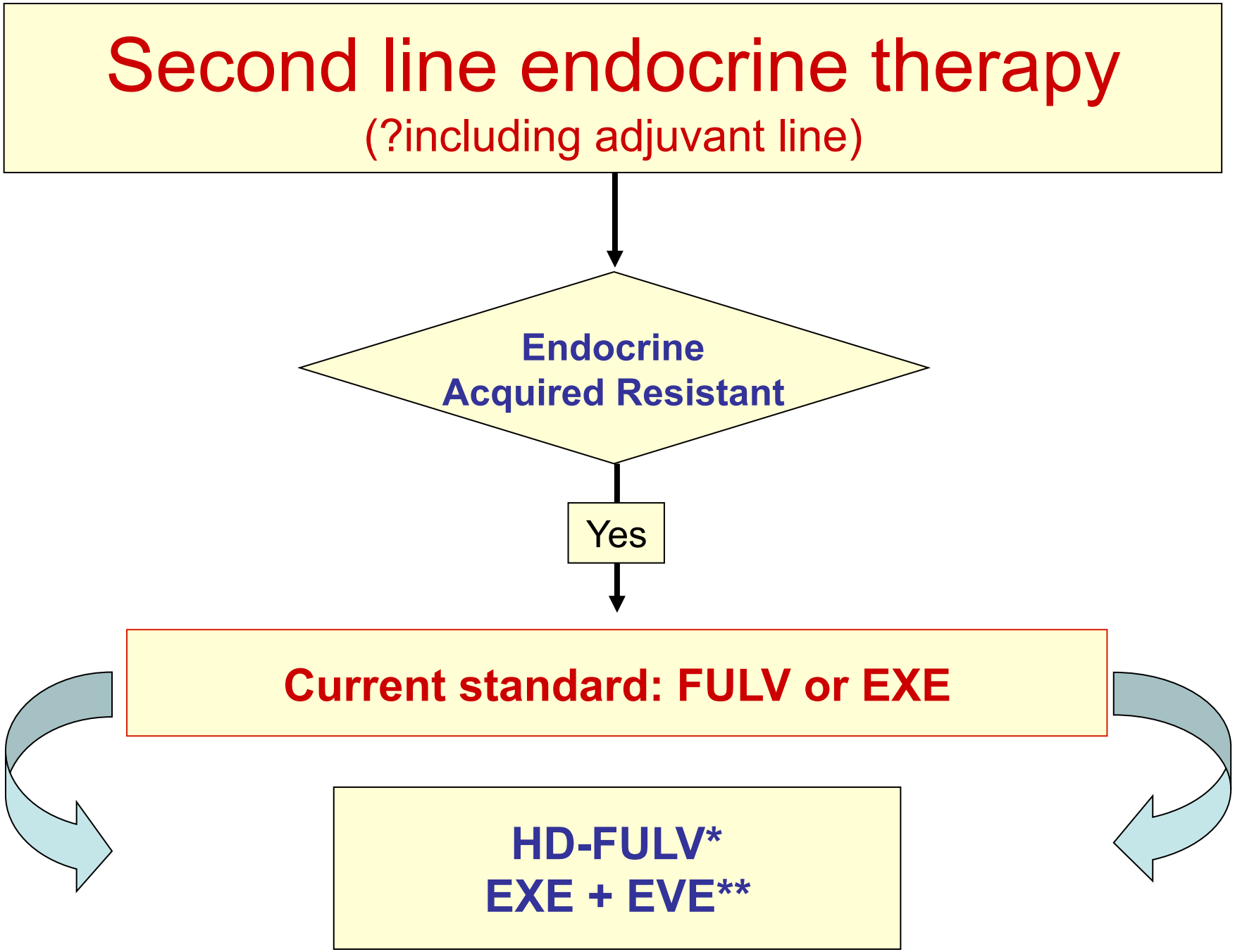
E D I T O R I A L

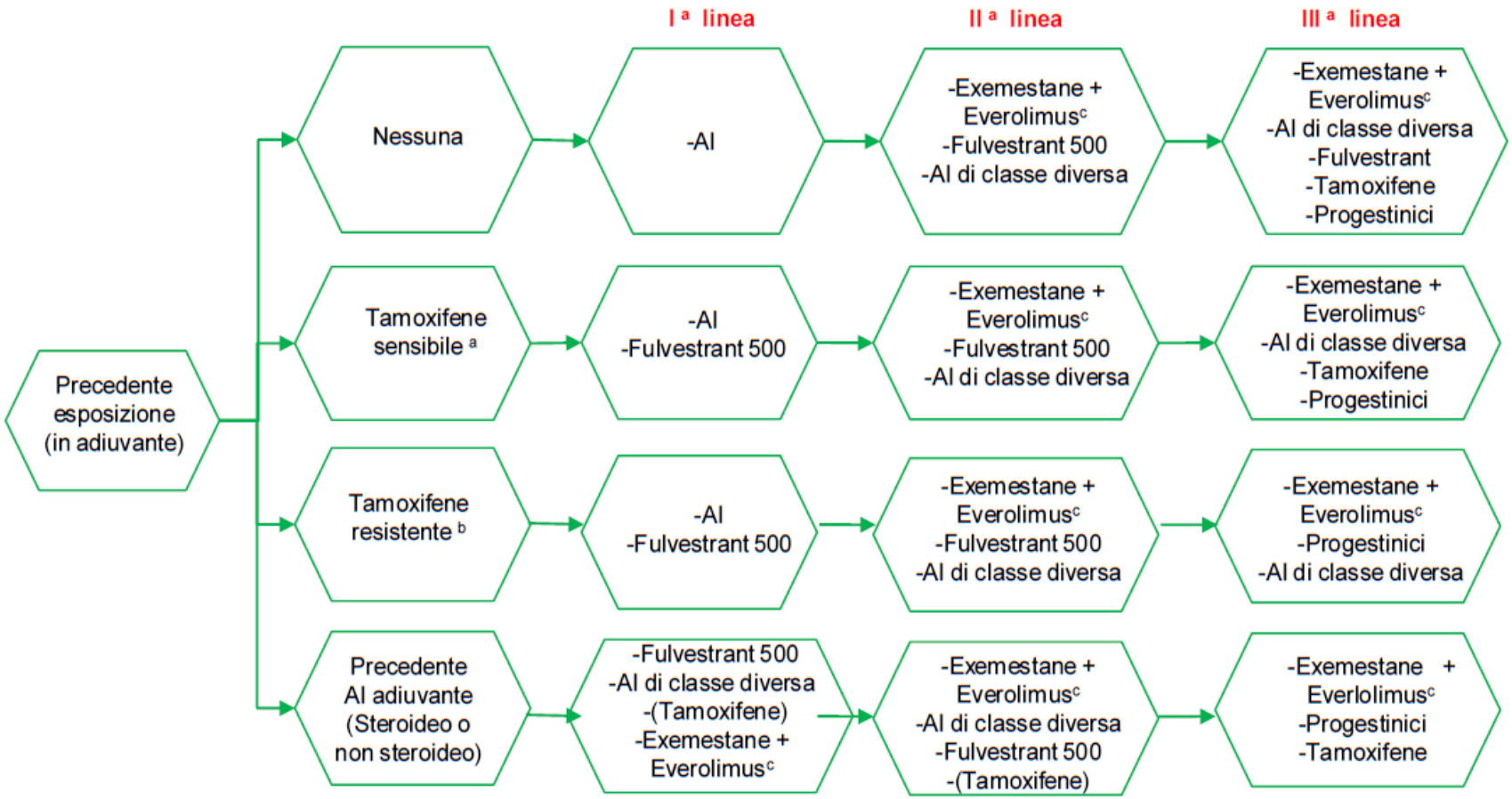
Improving Endocrine Therapy for Breast Cancer: It's Not That Simple

E. Claire Dees and Lisa A. Carey, *Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC*

In conclusion, the HORIZON study reminds us that we may learn as much from negative studies as from positive ones and that it is important to apply results to the clinical population shown to benefit from the intervention. At this point the cumulative experience suggests that targeting mTOR should be limited to populations with acquired AI resistance and should use everolimus, not others in the class. From a research perspective, we know that careful choice of


Second line endocrine therapy
(?including adjuvant line)
Endocrine
Acquired Resistant
Yes
Current standard: FULV or EXE
HD-FULV*
EXE + EVE**

AIOM Guidelines 2013



Legenda - AI= inibitore dell'aromatasi; **classe di AI=** classe molecolare di AI:non steroideo o steroideo.

Nota a -Tamoxifene sensibile: Intervallo tra la fine del trattamento con tamoxifene adiuvante e la comparsa di metastasi >12 mesi.
Nota b - Tamoxifene resistente: Comparsa di metastasi durante il trattamento adiuvante oppure entro 12 mesi dalla fine del trattamento adiuvante con tamoxifene.
Nota c – INDICAZIONI AIFA luglio 2013: " in carcinoma mammario avanzato con stato recettoriale ormonale positivo, HER2-negativo, in donne in postmenopausa in assenza di malattia viscerale sintomatica, dopo recidiva o progressione a seguito di trattamento con AI non steroideo".