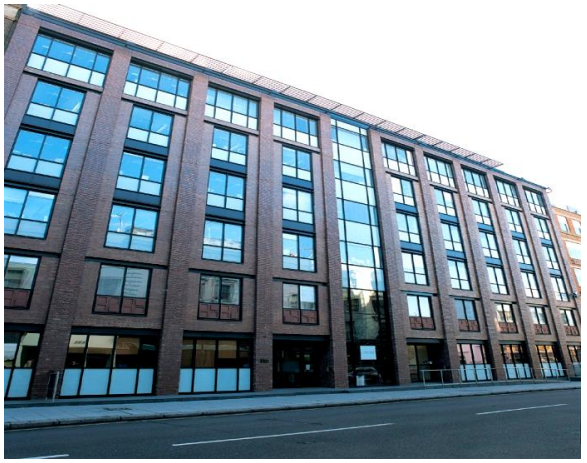
Endocrine Therapy for Metastatic Breast Cancer



Ian E Smith

Royal Marsden Hospital and Institute of Cancer Research, London

ESMO Madrid September 2014

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ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.

SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SU
GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGE
TO THE UNIVERSITY OF EDINBURGH.

Sir George Beatson
1848 - 1933

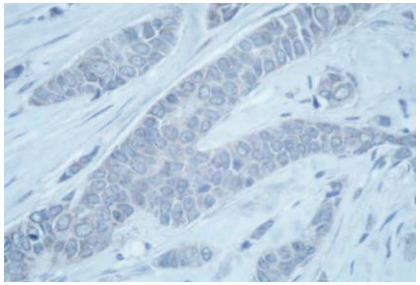
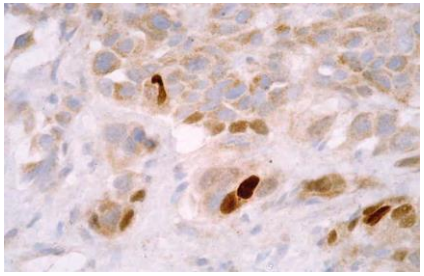
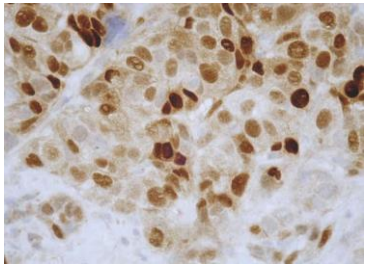
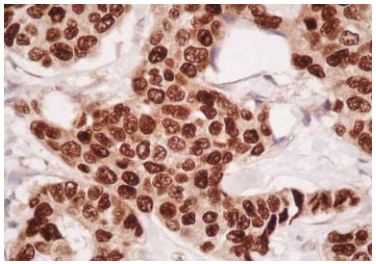
I HAVE no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such

Oestrogen Receptor (ER)
Jensen and Jacobsen (1962)

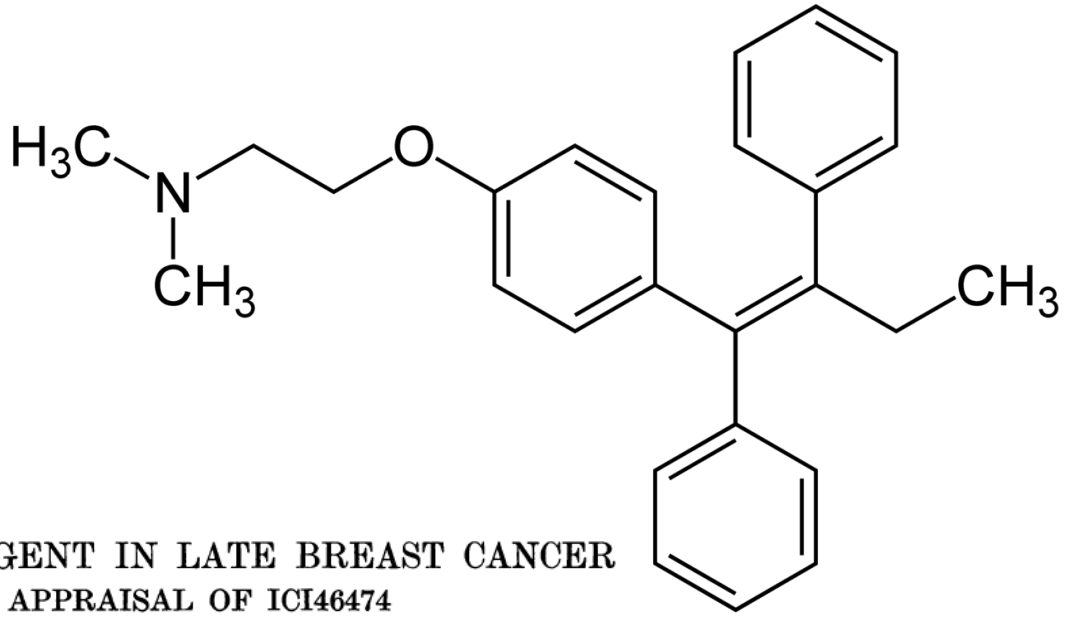
^{3}H-estrogen bound by target tissues in rats
- uterus, vagina, pituitary

Could the binding of estrogen by breast cancer determine endocrine response?

Would the absence of estrogen binding (ER-negative) indicate poor likelihood of response?

Tamoxifen



A NEW ANTI-OESTROGENIC AGENT IN LATE BREAST CANCER
AN EARLY CLINICAL APPRAISAL OF ICI46474

M. P. COLE, C. T. A. JONES AND I. D. H. TODD

From the Christie Hospital and Holt Radium Institute, Manchester M20 9BX

Received for publication April 7, 1971

SUMMARY.—An introductory clinical trial of the anti-oestrogenic agent ICI46474 in late or recurrent carcinoma of the breast is described.

Forty-six patients have been treated, of whom 10 have shown a good response. This is of the same order as that seen with oestrogens and androgens.

The particular advantage of this drug is the low incidence of troublesome side effects.

Br J Cancer. 1971 June; 25(2): 270–275

Tamoxifen Efficacy

- In ER+ve metastatic breast cancer:
- 86 clinical studies involving 5353 patients
- 30% response rate; 20% stable disease
- Median Response Durations 15 - 24 months

Litherland S and Jackson IM Cancer Treat Rev 1988;15:183–94.

When Should Endocrine Therapy Be Used in Metastatic Breast Cancer?

- **ASCO Clinical Practice Guidelines for Treatment of Metastatic Breast Cancer**
- **Co –Chairs Partridge A and Smith IE**

- **Recommendation 1**

  Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for advanced/metastatic breast cancer patients with ER+ve disease, except for immediately life threatening disease

  -The main benefit is less toxicity and better quality of life for the patient associated with endocrine therapy compared with chemotherapy (potential benefit: high).

  - The quality of the evidence is intermediate, and is based on the NCCC systematic review

  - The strength of this recommendation is strong and is supported by the evidence and expert consensus

Partridge et al JCO 2014

What Is the Optimal Endocrine Therapy for Metastatic Breast Cancer?

- SERMs
  - Tamoxifen
  - Toremifene
- SERDs
  - Fulvestrant
- Aromatase inhibitors
  - Anastrozole
  - Letrozole
  - Exemestane
- Progestins
  - Megestrol acetate
  - Medroxyprogesterone acetate
- Estrogens
  - Estradiol
  - DES (diethylstilbestrol)
- Androgens
  - Fluoxymesterone
- LHRH analogs
  - Goserelin
  - Leuprolide
  - Buserelin

SERM = selective endocrine receptor modulator; SERD = selective estrogen receptor down-regulator;

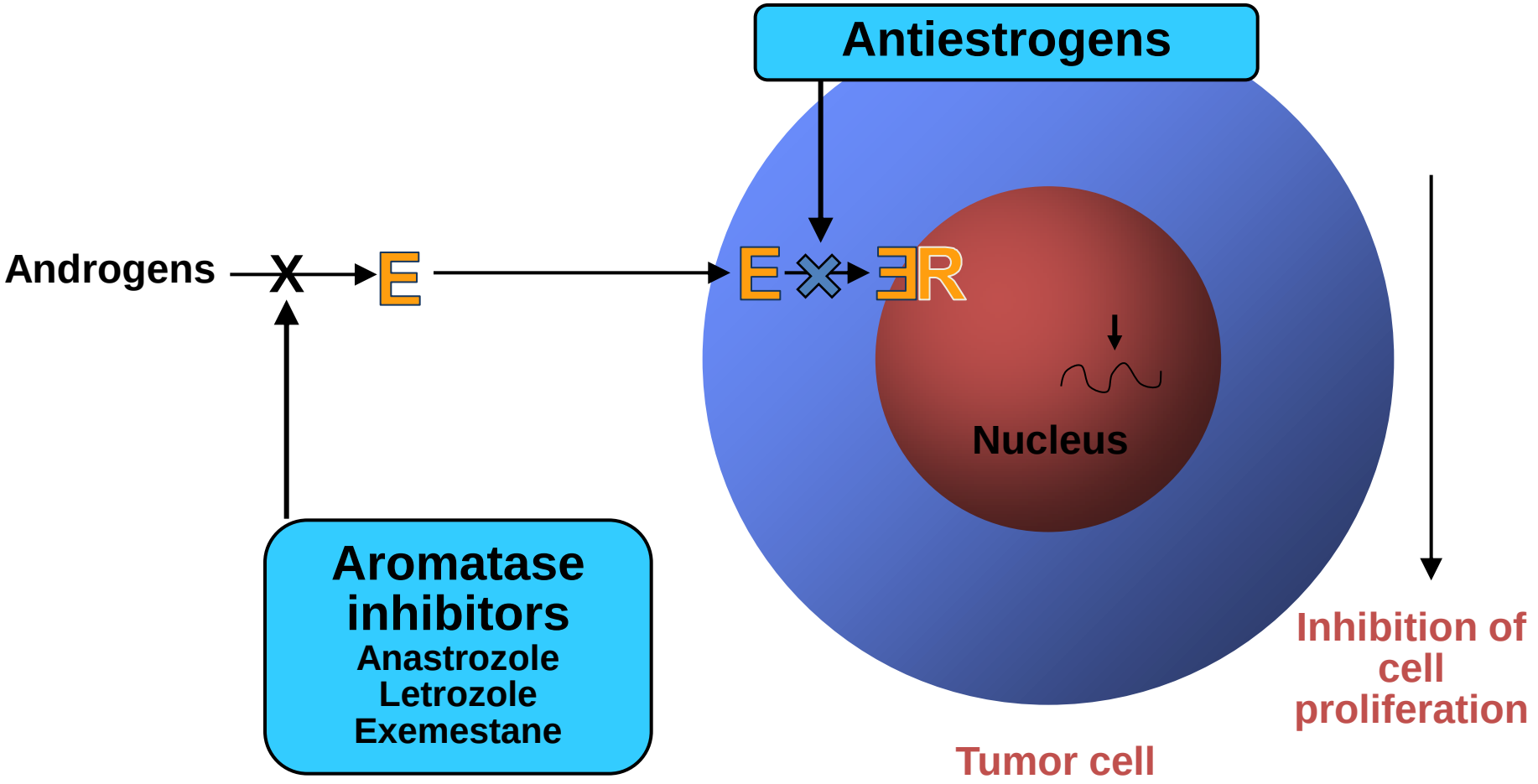
First-Line Comparative Tamoxifen Trials in Advanced Breast Cancer 1981-96 (2004)

		n=17
Tamoxifen v	Progestagens	6
	Estrogens	1
	Androgens	1
	Anti-Estrogens	2
	AG	3
	Formestane	1
	Fadrozole	2
	Fulvestrant	1

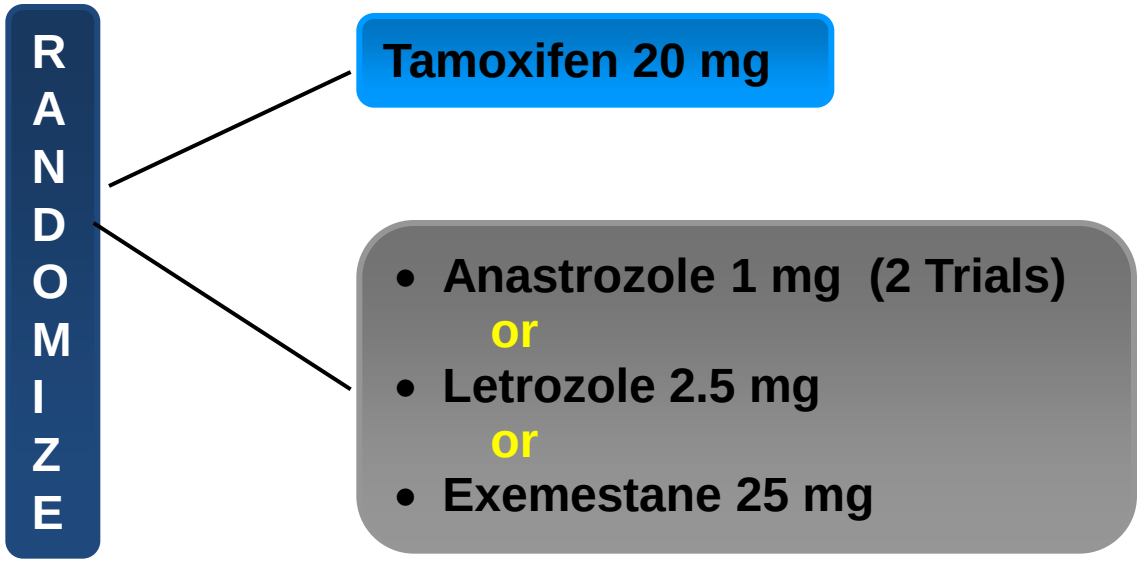
Tamoxifen always better or at least as good

Schiavon and Smith Hematol Oncol Clin North Am. 2013 Aug;27(4):715-36

Inhibiting the Effects of Estrogen



First Line Trials of AI v Tamoxifen in Metastatic Breast Cancer



- 4 Trials 3320 patients
- 2 (letrozole and exemestane) better for Overall Response
- 3 better for Time To Progression
- None better for Overall Survival

.Mouridsen H, JCO 2001 and JCO 2003 Nabholtz JM et al JCO 2000 Bonneterre J et al JCO 2000 Bonneterre al Cancer 2001 ., Paridaens R et al. Ann Oncol 2003 Paridaens R et al. JCO 2008

What Is the Optimal Endocrine Therapy in Metastatic Breast Cancer After an Adjuvant AI?

- These endocrine trials in metastatic breast cancer were done BEFORE the era of adjvant AIs (ATAC; BIG 1-98; TEAM)

- What is the best endocrine therapy for a patient with mbc who has relapsed during or after an adjuvant AI?

- Options: Exemestane
  Tamoxifen
  Fulvestrant
  Progestogens
  Estrogens

How Good Is Exemestane After a Non-Steroidal AI?

Data from Trials v Fulvestrant 591 pts

	Response	Clinical Benefit
• EFFECT[1]		
Exemestane (342 pts)	6.7%	31.5%
• SOFEA[2]		
Exemestane (249 pts)	2.8%	39.8%

[1]Chia S, et al. JCO 2008

[2]Johnston et al, LBA2 - EBCC Vienna 2012

How About Tamoxifen after AI Failure?

Not a lot of data

Anastrozole v. Tamoxifen[1]:

Retrospective crossover data for tamoxifen

TAMRAD[2]:

Tamoxifen + Everolimus v Tamoxifen alone in patients with previous AI exposure

[1]Thurlimann, et al. Eur J Cancer 2003
[2]Bachelot T, et al. SABCS 2010. Abstract S1-6

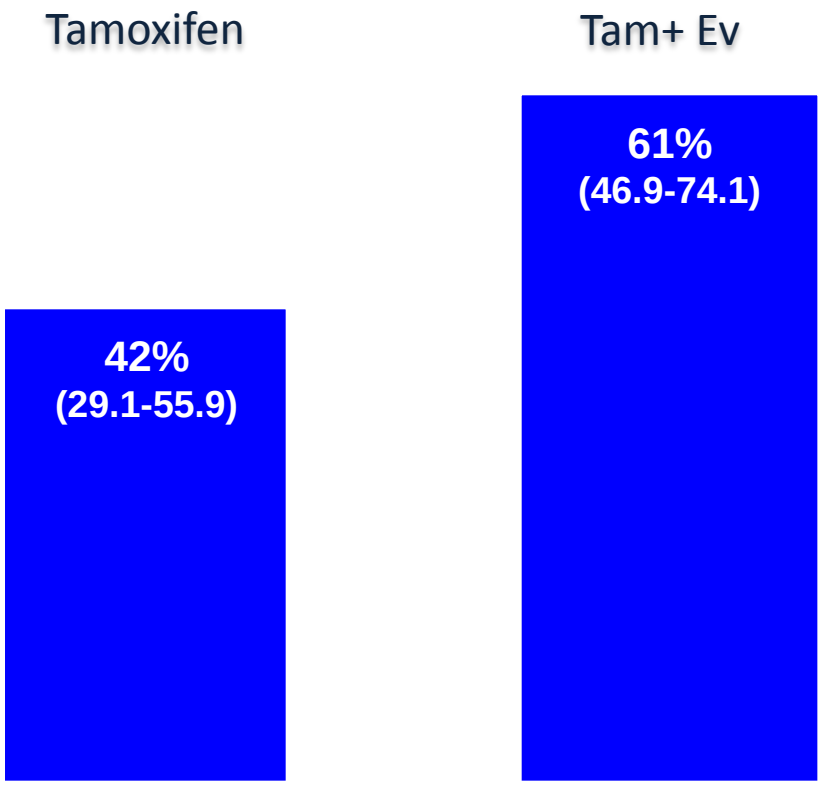
Anastrozole v Tamoxifen Trials in MBC
Tamoxifen Cross-Over after Anastrozole

- 2 trials. 511 patients randomised to anastrozole
- Questionnaire data were available for 119 patients crossed-over to tamoxifen after anastrozole
- 58 (49%) gained clinical benefit
- 12 (10%) had an objective response

Thurlimann et al Eur J.Cancer 39 (2003) 2310–2317

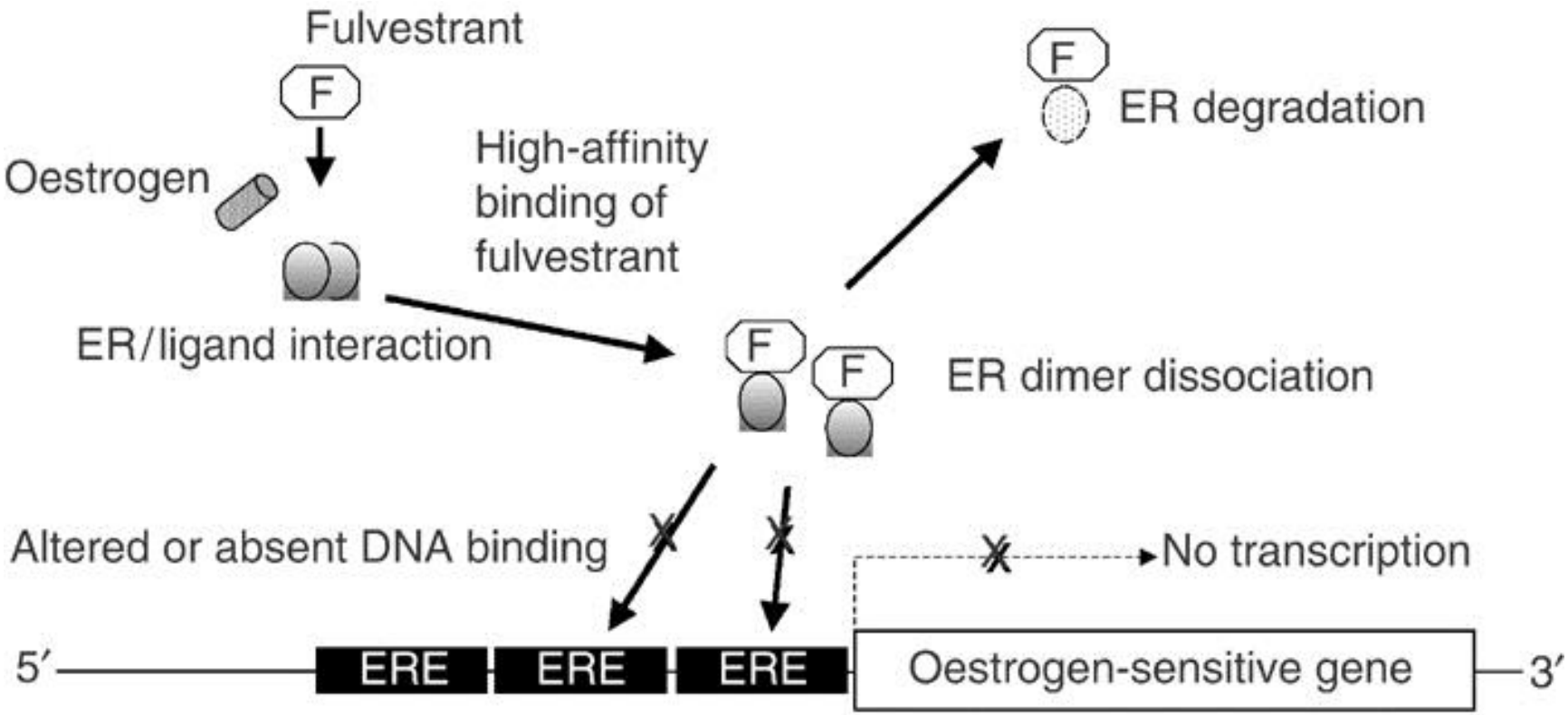
TAMRAD: Tam v Tam + Everolimus
Primary Endpoint: Clinical Benefit Rate

P = 0.045 (exploratory analysis)



Bachelot T, et al. *J Clin Oncol.* 2012 May 7 [Epub ahead of print].

Fulvestrant: Mechanism of Action.



Osborne et al British Journal of Cancer (2004) 90, S2–S6

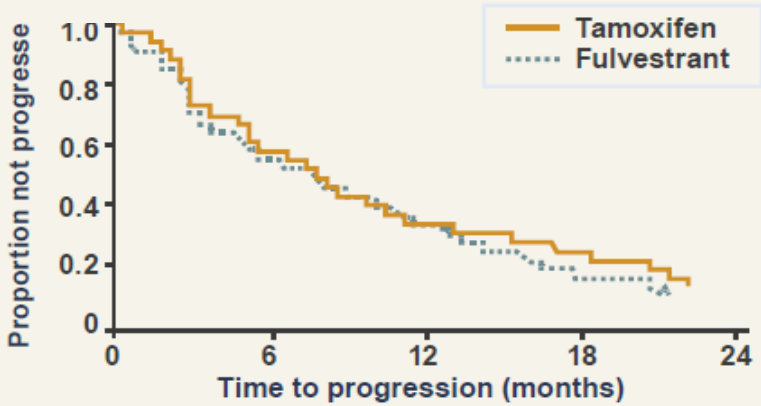
ERE Estrogen response element; ER estrogen receptor; F fulvestrant

Fulvestrant versus Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer

- **Objective tumor response to treatment in patients with ER-and/or PR-positive tumors**

	Fulvestrant (n=247)	Tamoxifen (n=212)	*p*-value
Complete response	8.90%	5.70%	NR
Partial response	24.3%	25.5%	NR
Stable disease ≥ 24 wk	23.9%	31.6%	NR
Objective response rate	33.2%	31.1%	0.64
Clinical benefit rate*	57.1%	62.7%	0.22
Time to progression	8.2 mo	8.3 mo	0.39

NR = not reported



Kaplan-Meier plot for time to progression (patients with estrogen receptor-positive and/or progesterone receptor-positive tumors)

Howell A et al. *J Clin Oncol 2004*

Does Fulvestrant Enhance the Efficacy of AIs?
Experimental Rationale Using Xenografts

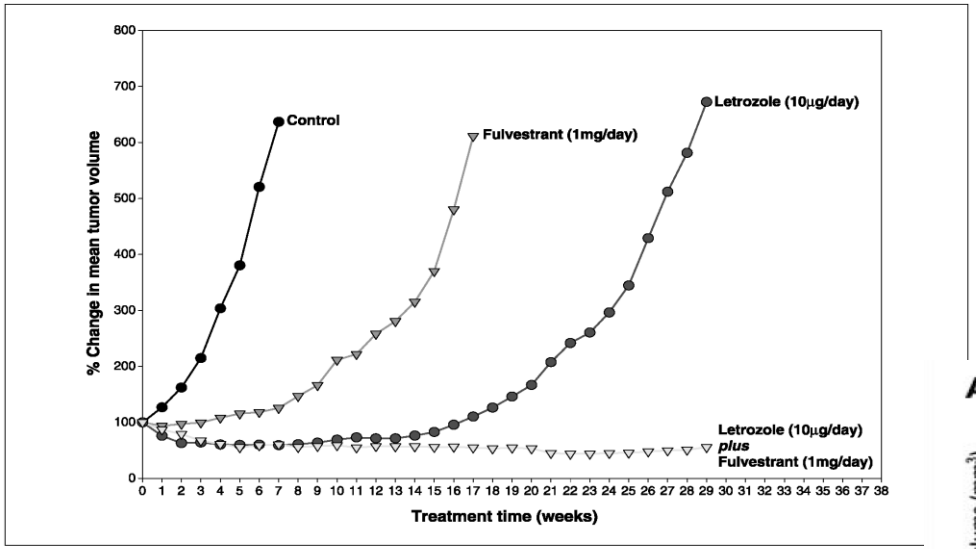
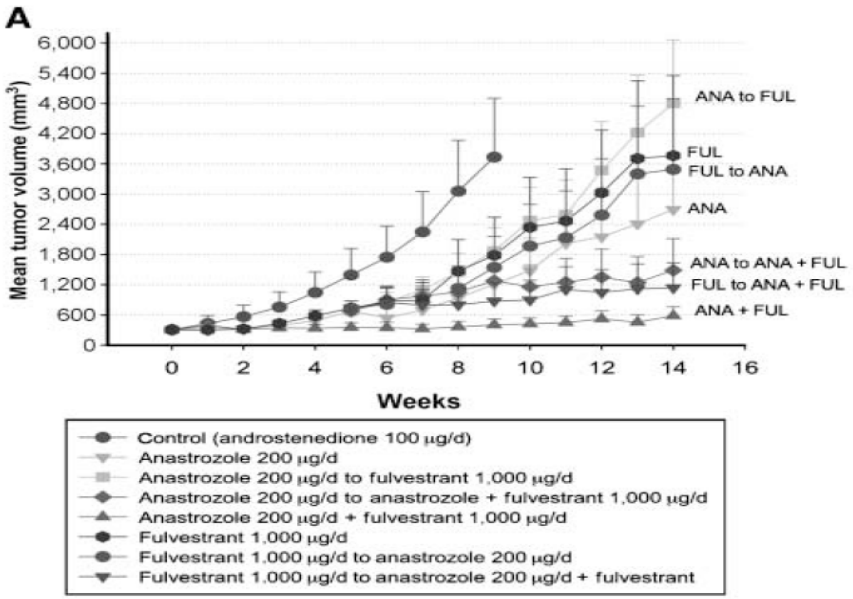


Figure 1. The effect of letrozole (10 μg/d) and fulvestrant (1 mg/d) alone or in the combination on the growth of MCF-7Ca breast tumor xenografts in female ovariectomized athymic nude mice. When tumors reached ~300 mm^3, animals were divided into four groups and injected s.c. daily with vehicle (control; n = fulvestrant (1 mg/d; n = 7), letrozole (10 μg/d; n = 18), or letrozole (10 μg/d) plus fulvestrant (1 mg/d; n = 5). Tumor volumes were measured weekly and expre the percent change in mean tumor volume relative to the initial size at week 0.

Brodie A et al, Cancer Res 65:5439-44, 2005



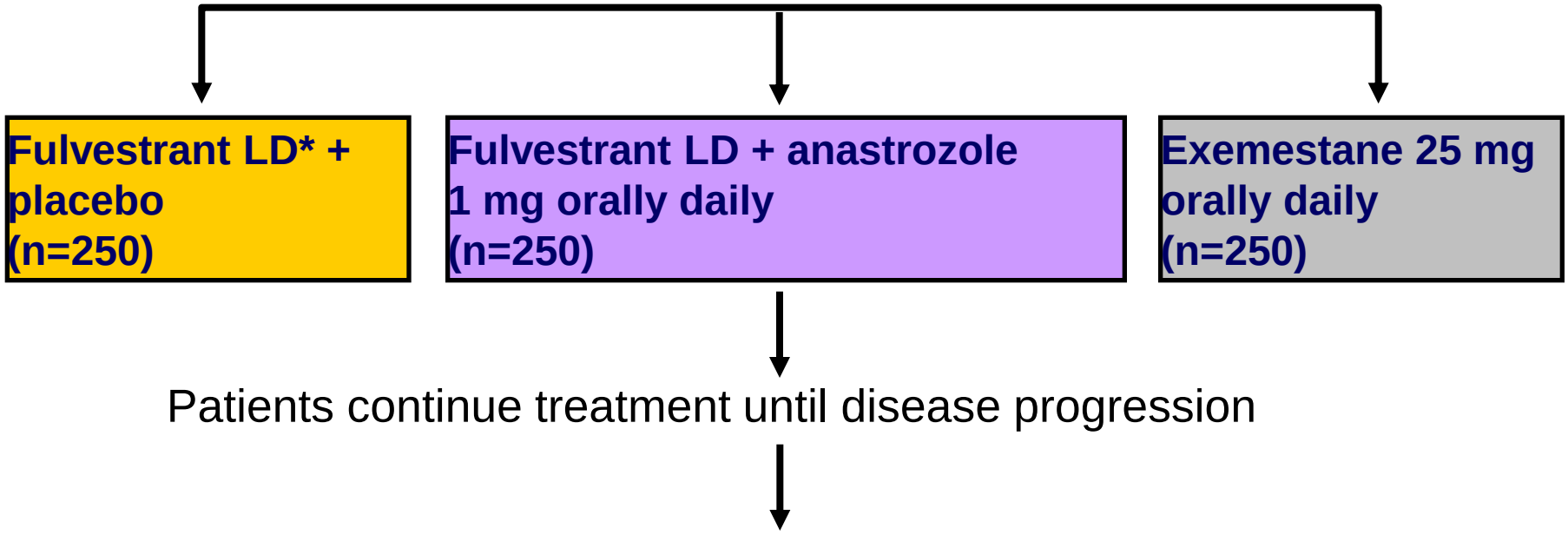
Macedo et al, Cancer Res 68, 3516-22, 2008

SOFEA- Study design

ER &/or PgR +ve postmenopausal patients with locally advanced (LABC) / metastatic breast cancer (MBC) <u>following progression on NSAIs</u> as adjuvant treatment for at least 12 months

Or as 1st line therapy for LABC or MBC for at least 6 months

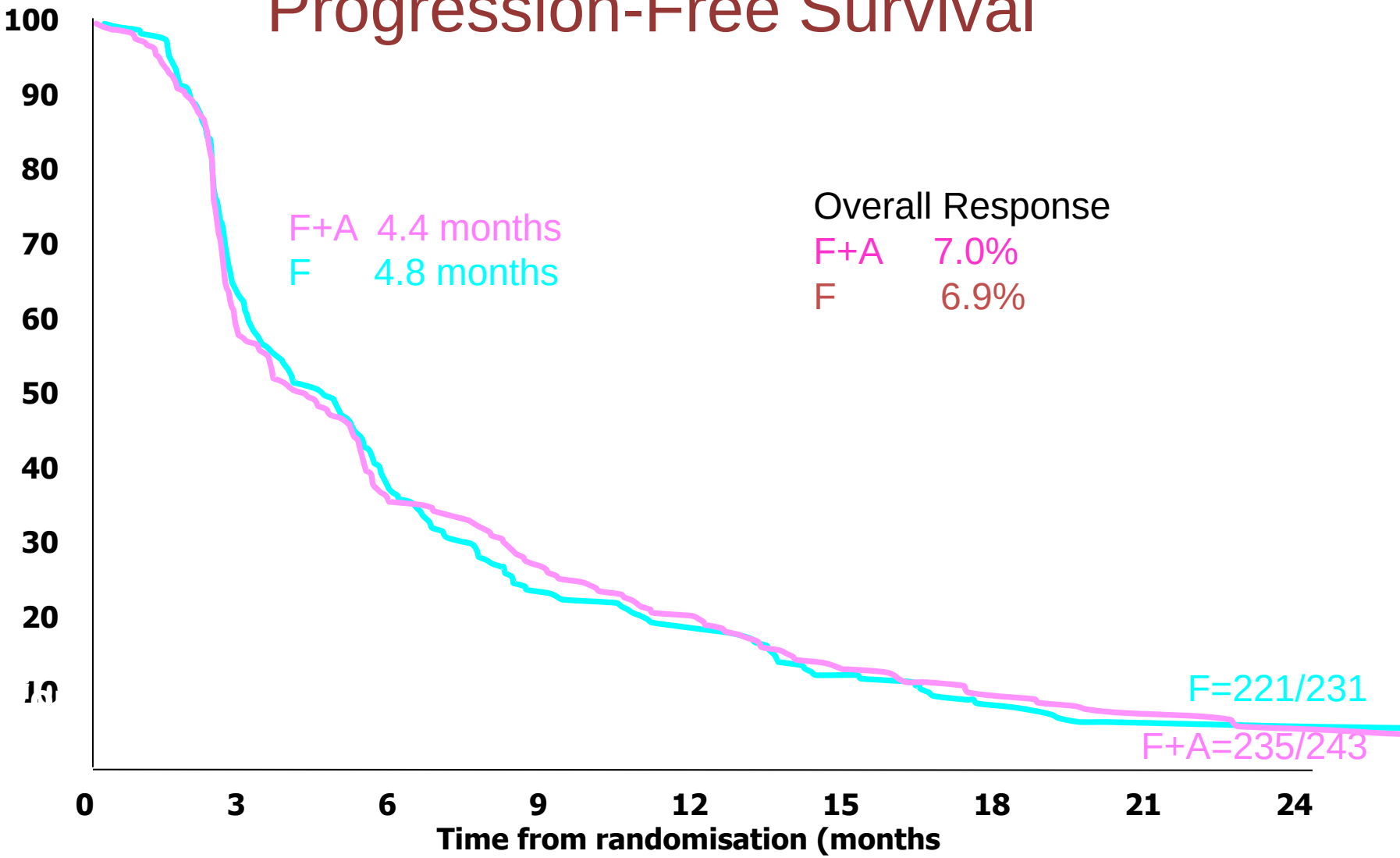
2nd-line non-steroidal AI failures



*500 mg Day 1,
250 mg Days 14 & 28, and monthly

Johnston et al LBA2– EBCC March 2012

SOFEA: Fulvestrant(F) +Anastrozole versus F
Progression-Free Survival



Johnston SRD et al, LBA2 - EBCC Vienna 2012

Fulvestrant Trials

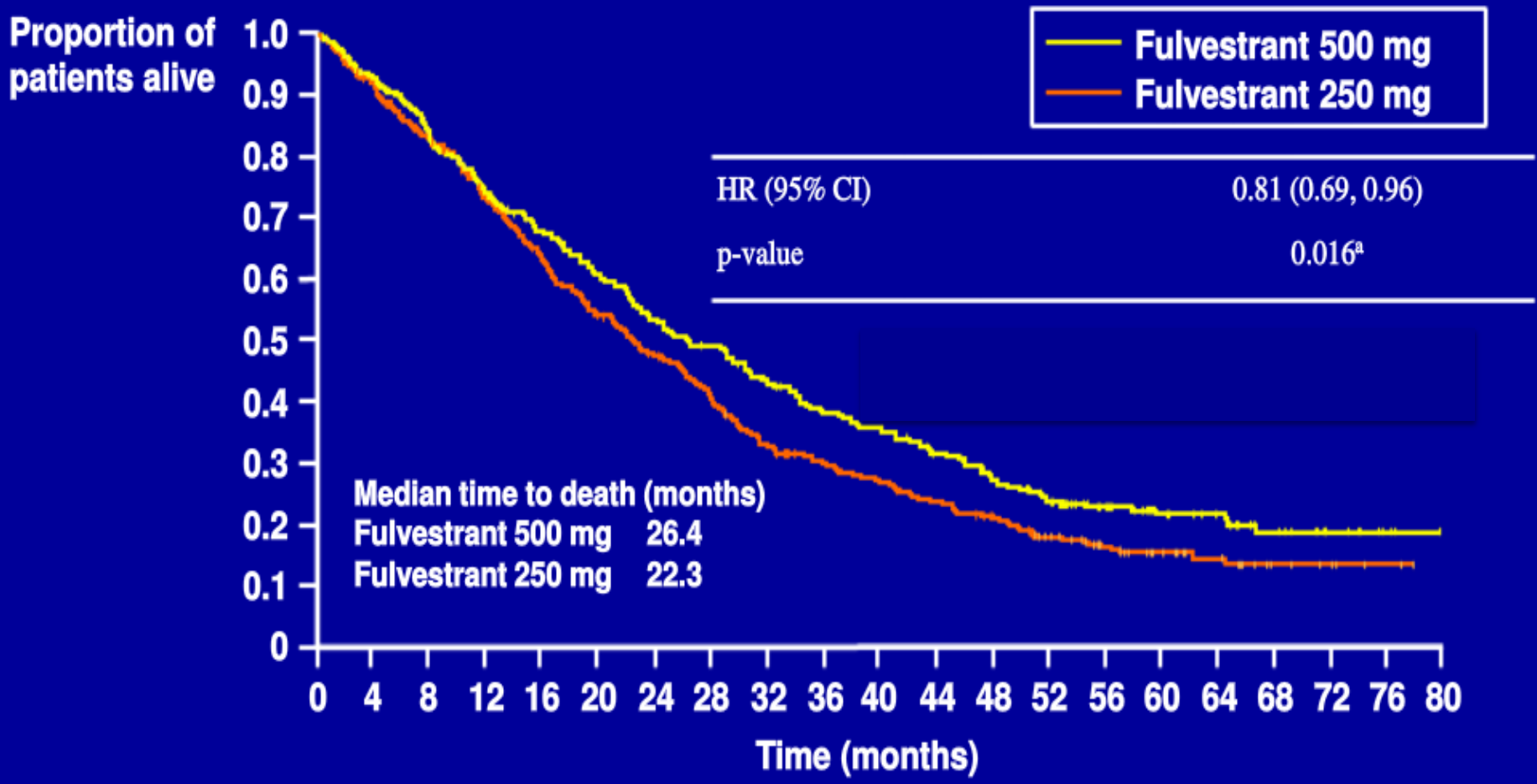
Study	Arms	n	Median TTP (mo)	Median OS (mo)
FACT (1st line) [1]	**FULV LD + Ana** **Ana**	258 256		37.8 38.2
SWOG S0226 (1st line) [2]	**FULV LD + Ana** **Ana**	355 352	15 (P<.007)* 13.5	47.7 (P=.049)* 41.3
FIRST (1st line) [3]	**FULV HD** **Ana**	102 103	23.4 (P=.01) 13.1	- -
EFECT (3rd line or more) [4]	**FULV LD** **Exe**	351 342		nr nr
SOFEA (acquired AI resistance) [5]	**FULV LD + Ana** **FULV LD** **Exe**	243 231 249		- - -
CONFIRM (2nd line) [6]	**Fulv HD 500mg** **Fulv AD 250mg**	362 374	6.5 (P=.006) 5.5	25.2 22.8

*benefits restricted to tamoxifen-naive patients (n=414, 60%, unplanned subgroup analysis)

HD (high dose) = 500mg i.m. at day 0 + 500mg i.m. at days 14 and 28, thereafter 500mg i.m. monthly until PD
AD (approved dose) = 250mg i.m. monthly
LD (loading dose regimen) =500mg i.m. at day 0, 250mg at days 14, 28, and 250mg monthly thereafter

1. Bergh J, et al. JCO 2012
2. Mehta RS, et al. SABCS 2011. Abstract S1-1
3. Robertson JF, et al. JCO 2009
4. Chia S, et al. JCO 2008
5. Johnston S, et al. EBCC-8 2012
6. Di Leo A, et al. JCO 2010

CONFIRM Overall survival (final analysis at 75% maturity – full analysis set)



Patients at risk:

500 mg	362	333	288	254	227	202	178	163	141	123	114	98	81	64	47	30	26	15	8	1	0
250 mg	374	338	299	261	223	191	164	137	112	96	87	74	64	48	37	22	14	8	3	2	0

Di Leo et al JCO 2010 Update

Fulvestrant: Conclusions

- Equivalent to tamoxifen as first-line treatment (study 0025)
- Equivalent to anastrozole first line (FIRST), maybe better (FACT;SO226)
- Equivalent to exemestane post NSAI (EFECT;SOFEA)
- Superior PFS comparing 500mg vs 250mg as second-line therapy (CONFIRM)

Estradiol after Aromatase Inhibitors
Phase 2 High v Low Dose

Estrogen deprivation therapy with AIs has been hypothesized to sensitize ER+ve breast cancer tumor cells to low-dose estradiol

Clinical benefit rate:

30mg 28% (9/32 pts)

6mg 29% (10/34 pts)

Adverse event rate (≥grade 3):

30mg 34% (11/32 pts)

6mg 18% (4/34 pts) *P*=.03

The efficacy of the lower dose should be further examined in phase III clinical trials

Ellis et al, SABCS 2008 Abstract 16; Ellis M et al, JAMA 2009

Case Study 59yr old

- **Mar 2011** 5cm L breast carcinoma. Core biopsy - Grade II invasive ductal carcinoma. ER8/8, PgR 8/8, HER-2 negative, axillary node cytology C5. CT scan and bone scan metastatic bone disease including collapse T5.
- Letrozole and zoledronate radiotherapy to T4.
  Stable Disease

- **Feb 2013** Progressive bone disease on MRI scan CA15-3 up.
  Exemestane and Everolimus Clinical improvement CA 15-3 down
  .
- **May 2014** Progression bone disease, pain and CA15-3 up

- **Next Treatment?**

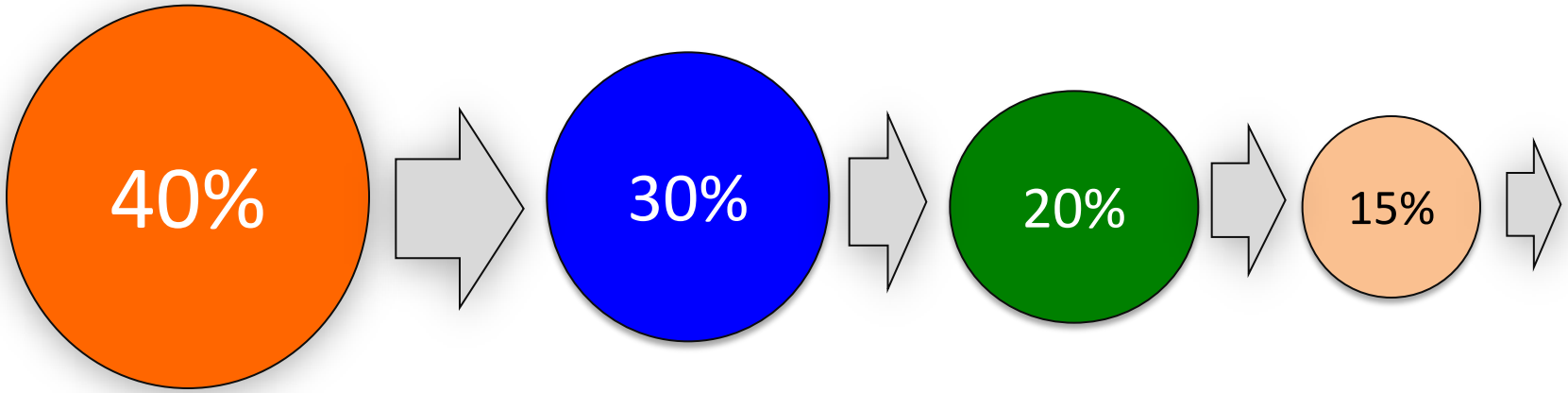
Case Study 59yr old (cont)

- **June 2014** Tamoxifen
- **July 2014** CA 15-3 rapidly up then down
- **Sept 2014** Symptom-free. CA15-3 continues to fall

- **Moral** – don't forget tamoxifen!

Sequential Endocrine Treatment

The optimal sequence has not been defined



NCCN Guidelines (2012): Endocrine Therapy for MBC

Both premenopausal and postmenopausal women with metastatic breast cancer who have responded to endocrine therapy will benefit from additional endocrine therapy at the time of disease progression

Postmenopausal The optimal sequence has yet to be determined

Second-line in postmenopausal women: one option is **fulvestrant** = **anastrozole** after disease progression on tamoxifen[1]

Second- or third-line following a NSAI: **fulvestrant** = **exemestane** in terms of TTP and response[2]

Optimal dosing of fulvestrant remains unclear, with the suggestion of increased benefit with 500-mg intramuscularly monthly dosing[3]

Premenopausal Previous anti-estrogen therapy within the previous year: ovarian suppression with LHRH agonist

Ver 1.2012, 01/20/2012, NCCN Guidelines, Breast Cancer Recommendations 2A

1.Osborne 2002; Howell 2002
2.Chia 2008
3.DiLeo 2010; Bergh 2009

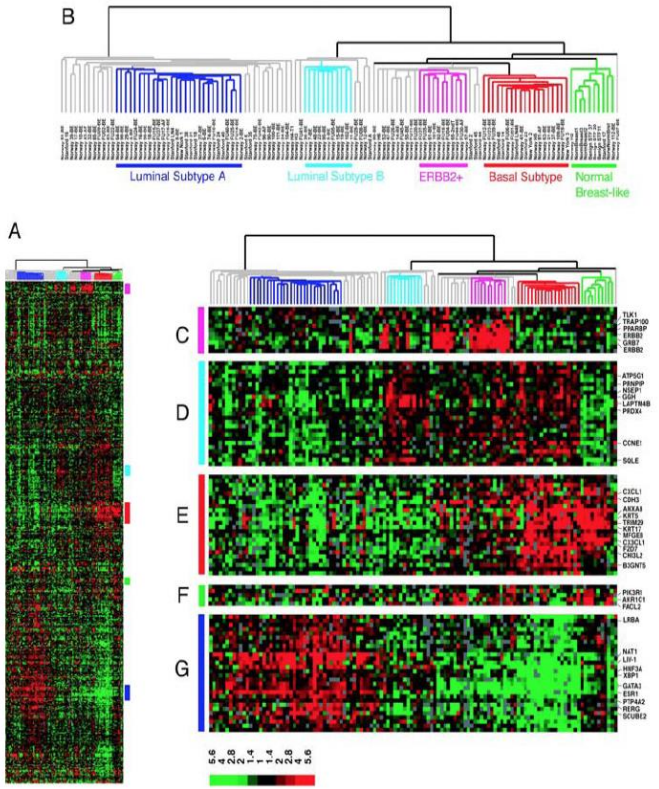
Endocrine Therapy in Metastatic Breast Cancer: My Suggested Guidelines

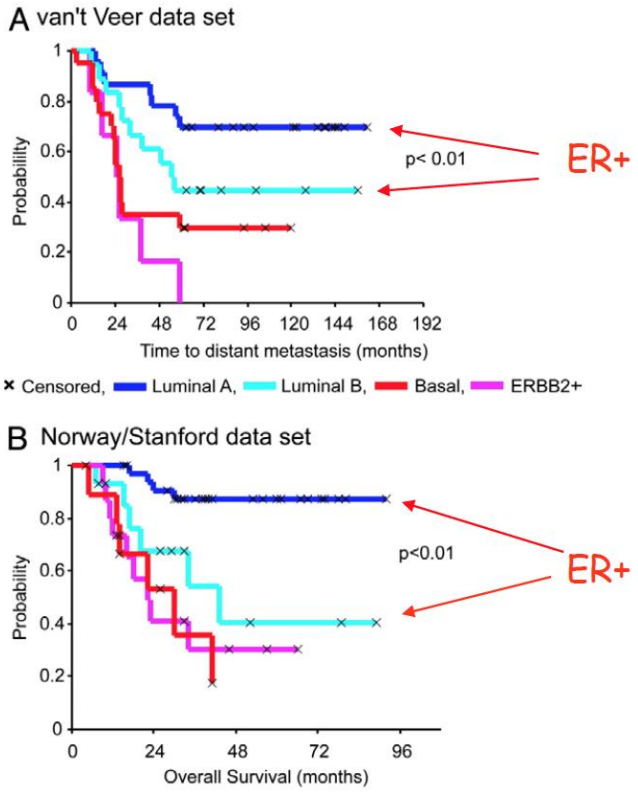
- No Previous AI
  - Use an AI (or tamoxifen if side effects)
- Previous AI
  - Tamoxifen and Fulvestrant of some benefit
  - Exemestane – some clinical benefit but OR rare - Optimal order not known
  - Progestogens and Estrogens may be of benefit
- Premenopausal (After tamoxifen)
  - AI with ovarian suppression

Why Do ER+ve Breast Cancers Not Always Respond to Endocrine Therapy?

What Is the Basis for De Novo and Acquired Resistance?

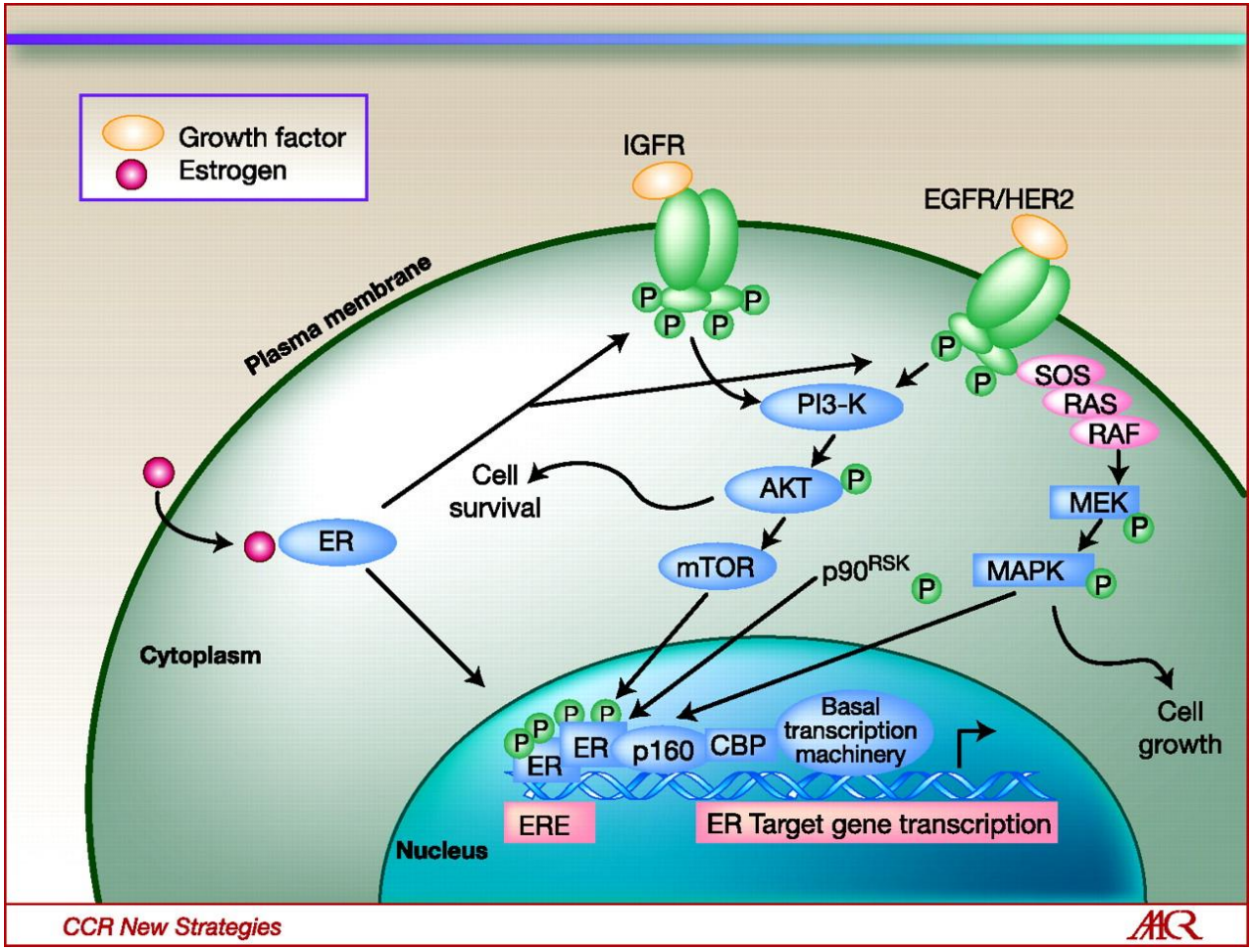
ER-positive Cancers Are Heterogeneous at Diagnosis and at Recurrence





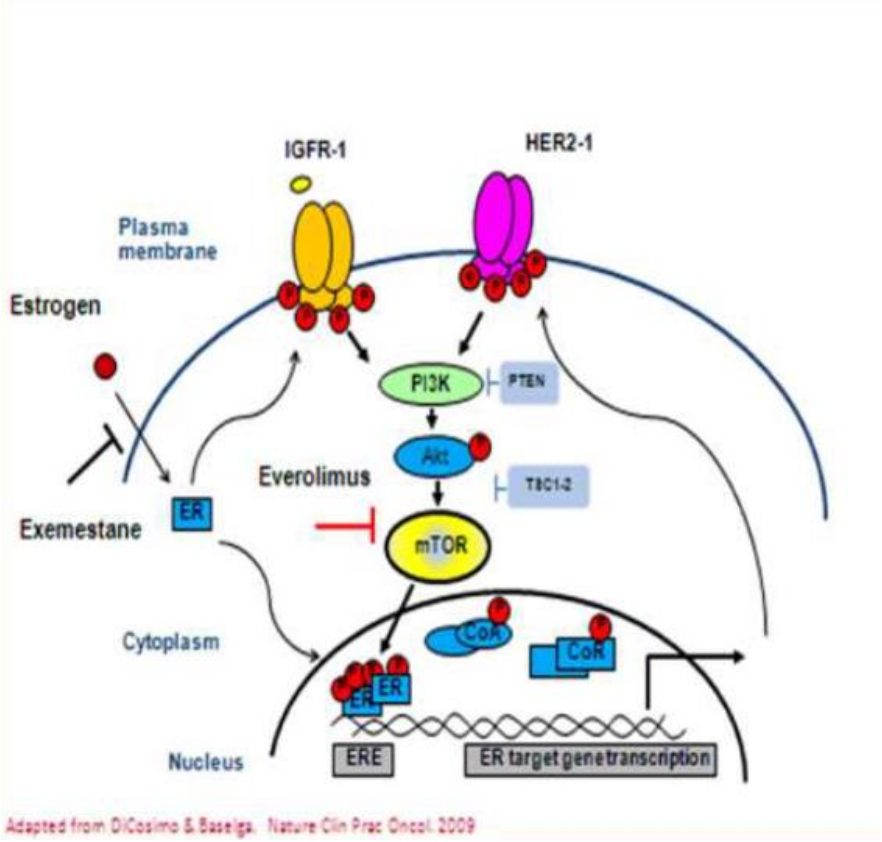
Sorlie et al PNAS 2003

Can We Improve on Endocrine Therapy? Cross-Talk Signalling



Johnston S R Clin Cancer Res 2010;16:1979-1987

Crosstalk between ER and mTOR Signalling

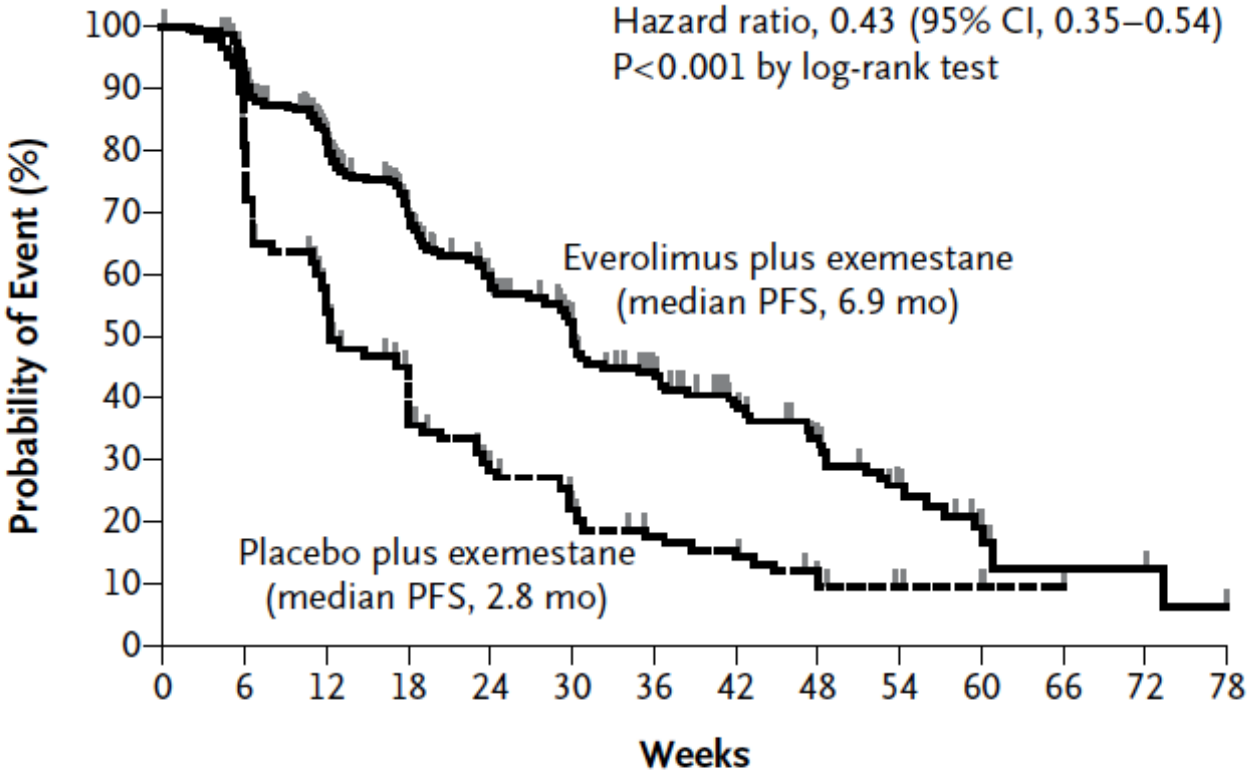


- mTORC1 activates ER in a ligand-independent fashion
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine resistant breast cancer cells
- mTOR is a rational target to enhance the efficacy of hormonal therapy
- Everolimus is one of a group of mTOR inhibitors

Yamnik, RL. J Biol Chem 2009; 284(10):6361-636
Crowder, RJ. Cancer Res 2009;69:3955-62
Miller, TW. J Clin Invest 2010; 120(7):2406-2413

BOLERO-2: A Phase 3 Trial (724 patients*) of Exemestane ± Everolimus

Primary Endpoint, PFS



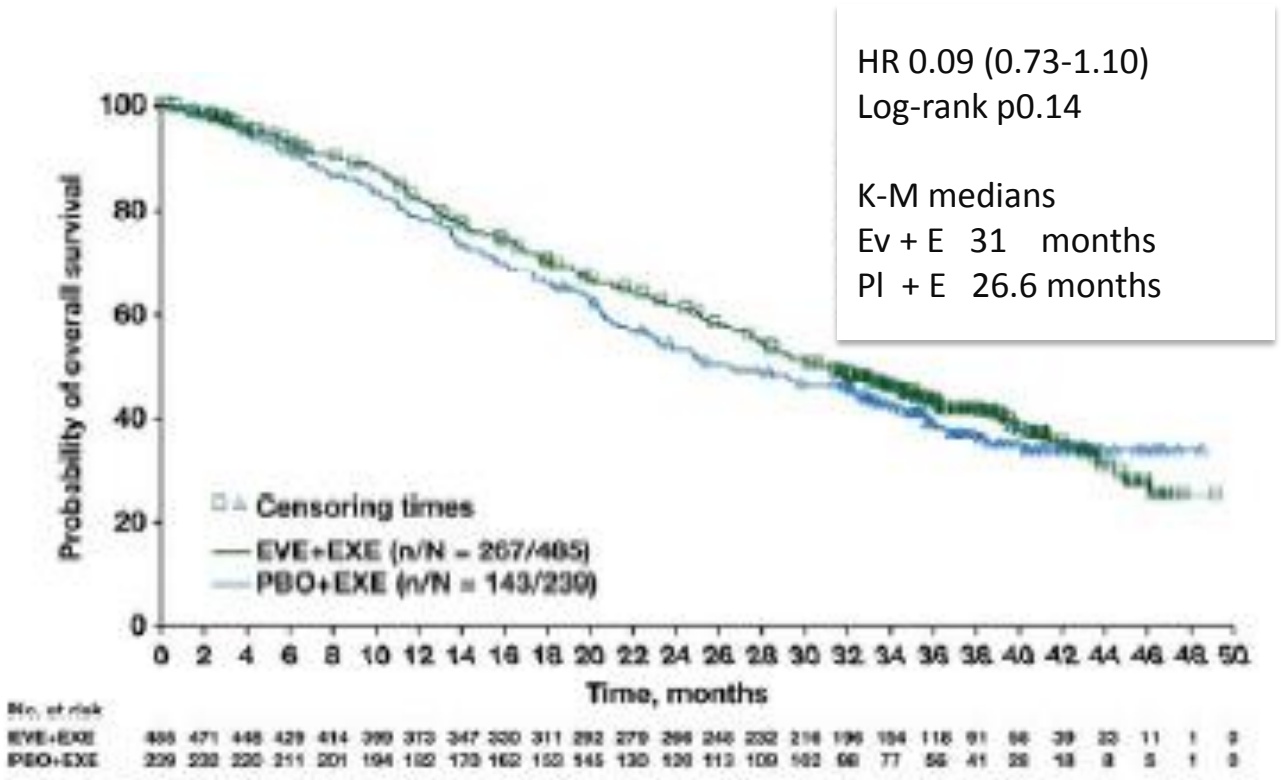
No. at Risk

Everolimus	485	398	294	212	144	108	75	51	34	18	8	3	3	0
Placebo	239	177	109	70	36	26	16	14	9	4	3	1	0	0

* Refractory to anastrozole or letrozole

Baselga J, et al. *N Engl J Med.* 2012;366(6):520-529.

BOLERO-2: Exemestane+/-Everolimus
Update: Overall Survival



Piccart et al Ann Oncol Sept 2014

HORIZON: Letrozole ± Temsirolimus

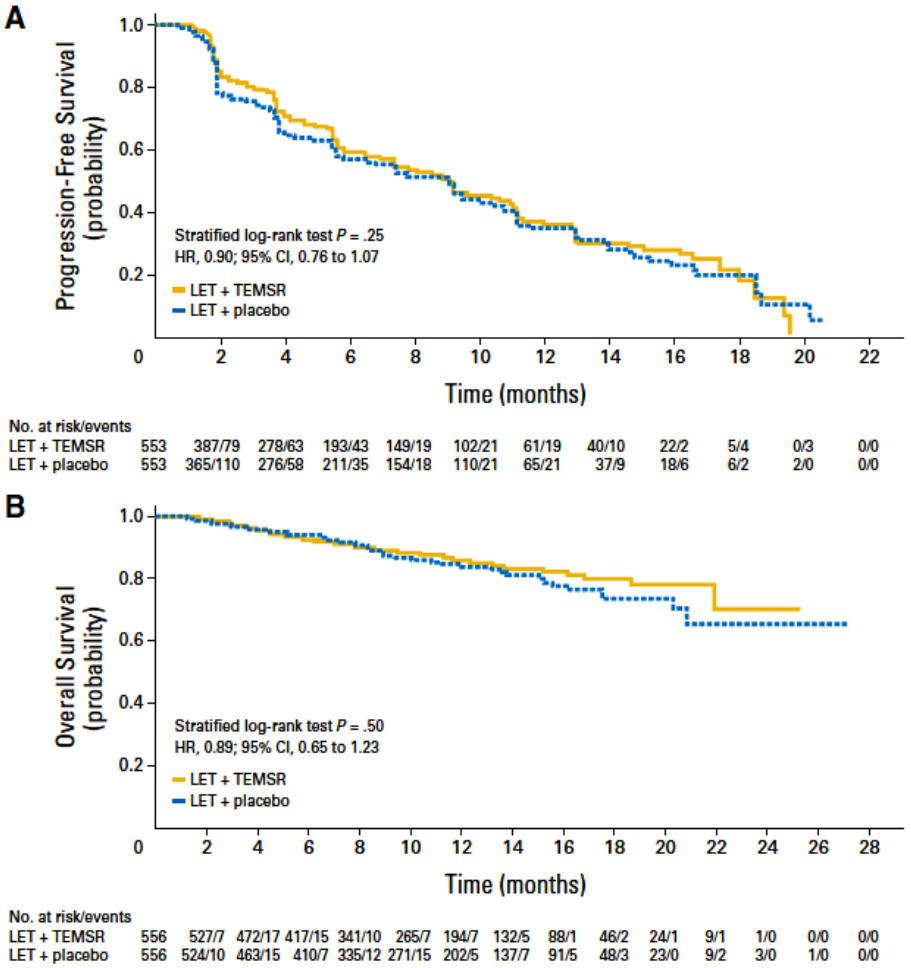
Phase 3 Placebo controlled study
N =1.112

Postmenopausal women with ER+ advanced breast cancer

AI naïve

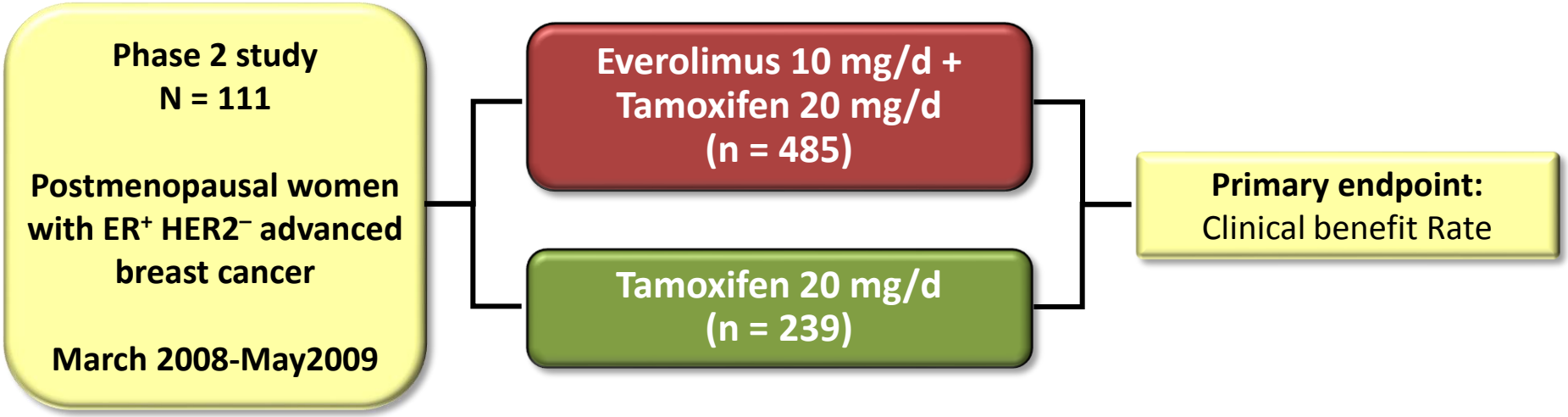
Letrozole 2.5mg/day + Temsirolimus 30 mg/d 5 days q2 weeks

Letrozole 2.5 mg/day + Placebo



Wolff AC, et al. *J Clin Oncol*. 2013;2:197.

TAMRAD: Phase II trial in Metastatic Postmenopausal women with ABC with previous exposure to AIs



Stratification: Primary or Secondary Resistance

Primary: Relapse during adjuvant AI; progression within 6 months of starting AI treatment in metastatic setting

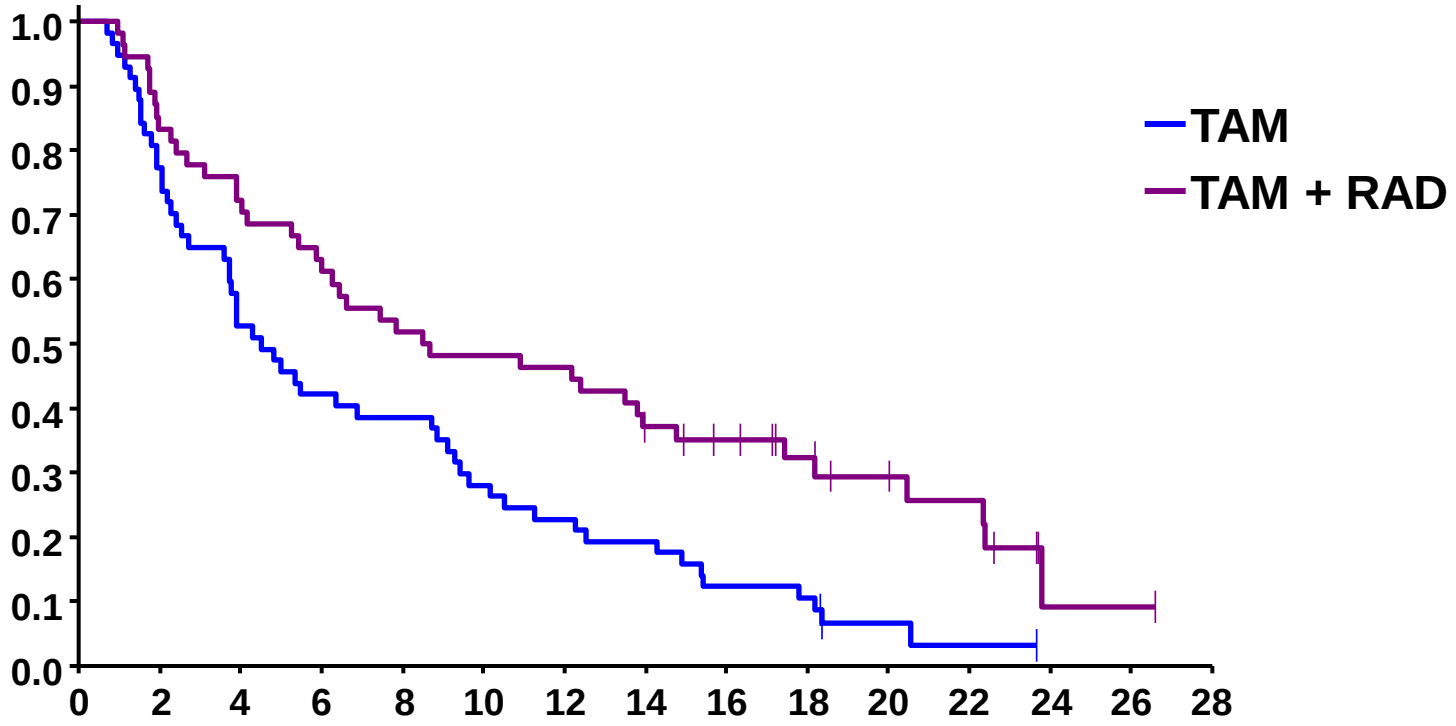
Secondary: Late relapse (≥ 6 months) or prior response and subsequent progression to metastatic AI treatment

Bachelot T, et al. *J Clin Oncol.* 2012 May 7 [Epub ahead of print].

TAMRAD: Tam v Tam + Everolimus Phase 2 (Prior AI): Time to Progression

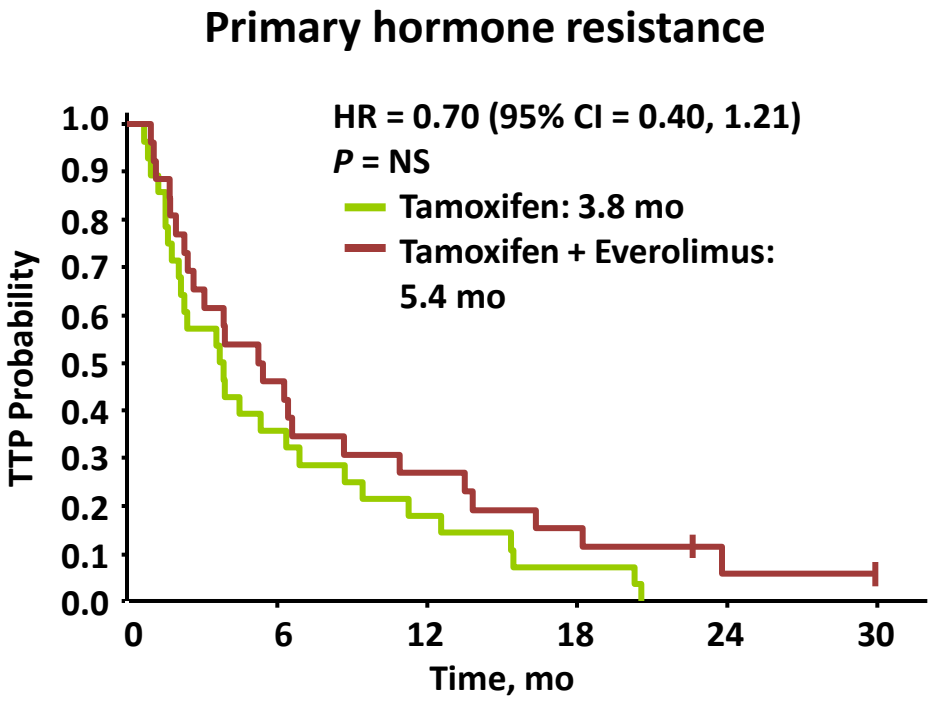
TAM: 4.5 mo.
TAM + RAD: 8.6 mo.

Hazard Ratio (HR) = 0.53; 95% CI (0.35-0.81)
Exploratory log-rank: *P* = 0.0026

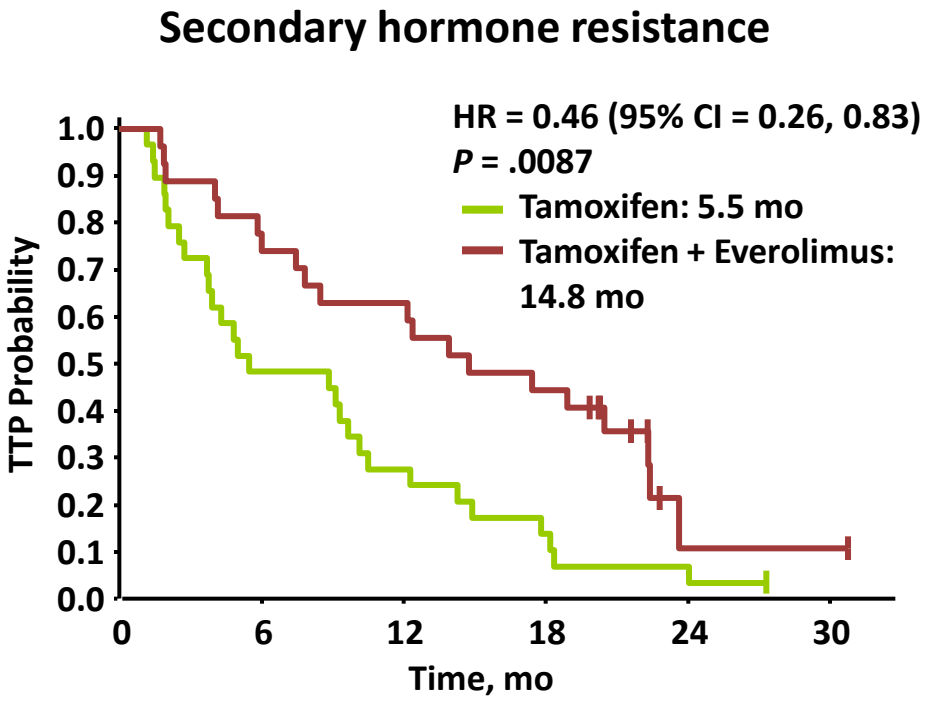


Bachelot T, et al. *J Clin Oncol.* 2012 May 7

TAMRAD: TTP as a Function of Intrinsic Hormone Resistance



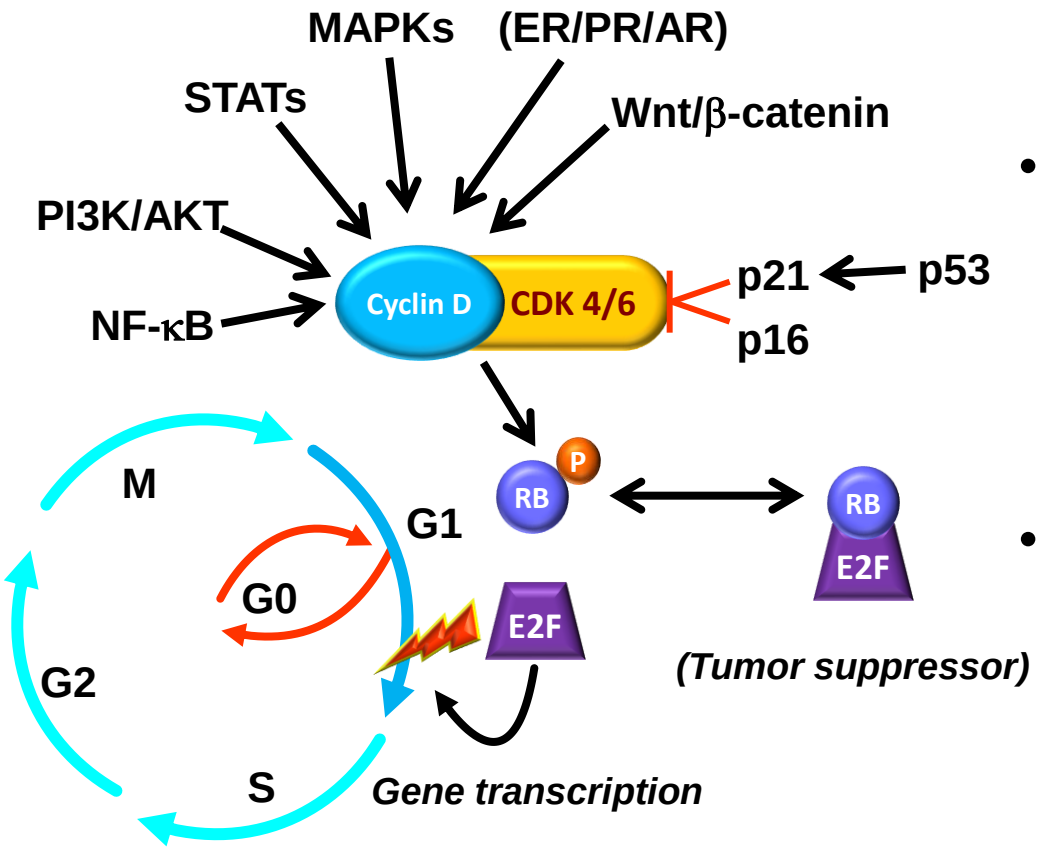
Primary Resistance
Relapse during adjuvant AI; progression within 6 months of starting AI treatment in the metastatic setting



Secondary Resistance
Late relapse (≥ 6 months) or prior response and subsequent progression to metastatic AI treatment

Bachelot T, et al. *J Clin Oncol.* 2012 May 7 [Epub ahead of print].

Targeting the Cell Cycle: Cyclin D1/CDK 4-6

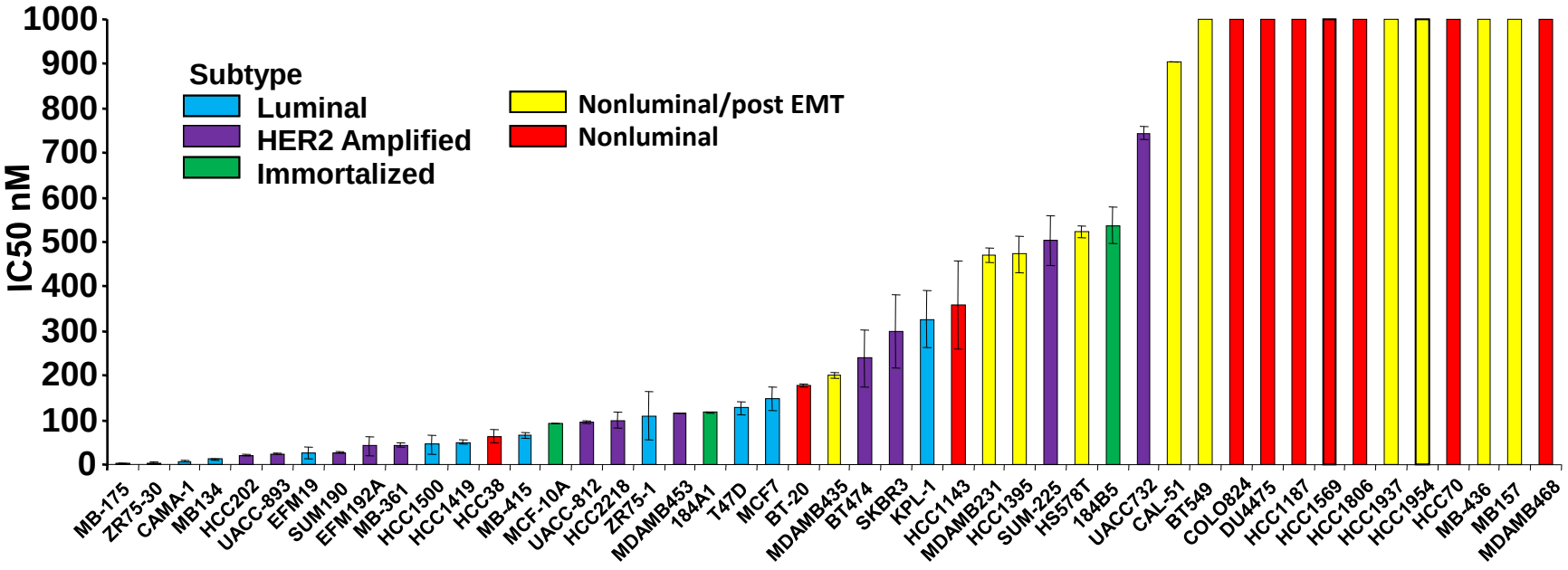


- In AI resistance models ER drives a CDK 4/E2F dependent transcriptional program
- CDK 4-6 inhibition reduces cell proliferation in both ER-dependent and ER-independent, AI resistance breast cancer models
- PD 0332991 (palbociclib), a selective inhibitor of CDK-4/6, prevents DNA synthesis by blocking cell cycle progression

Miller TW, et al. *Cancer Discovery.* 2011;1(4):338-351.
Lange CA, et al. *Endocr Relat Cancer*. 2011;18:C19-C24.

Palbociclib: CDK 4/6 Inhibitor

Preferential activity on ER+ luminal breast cancer cell lines with or without HER2 amplification

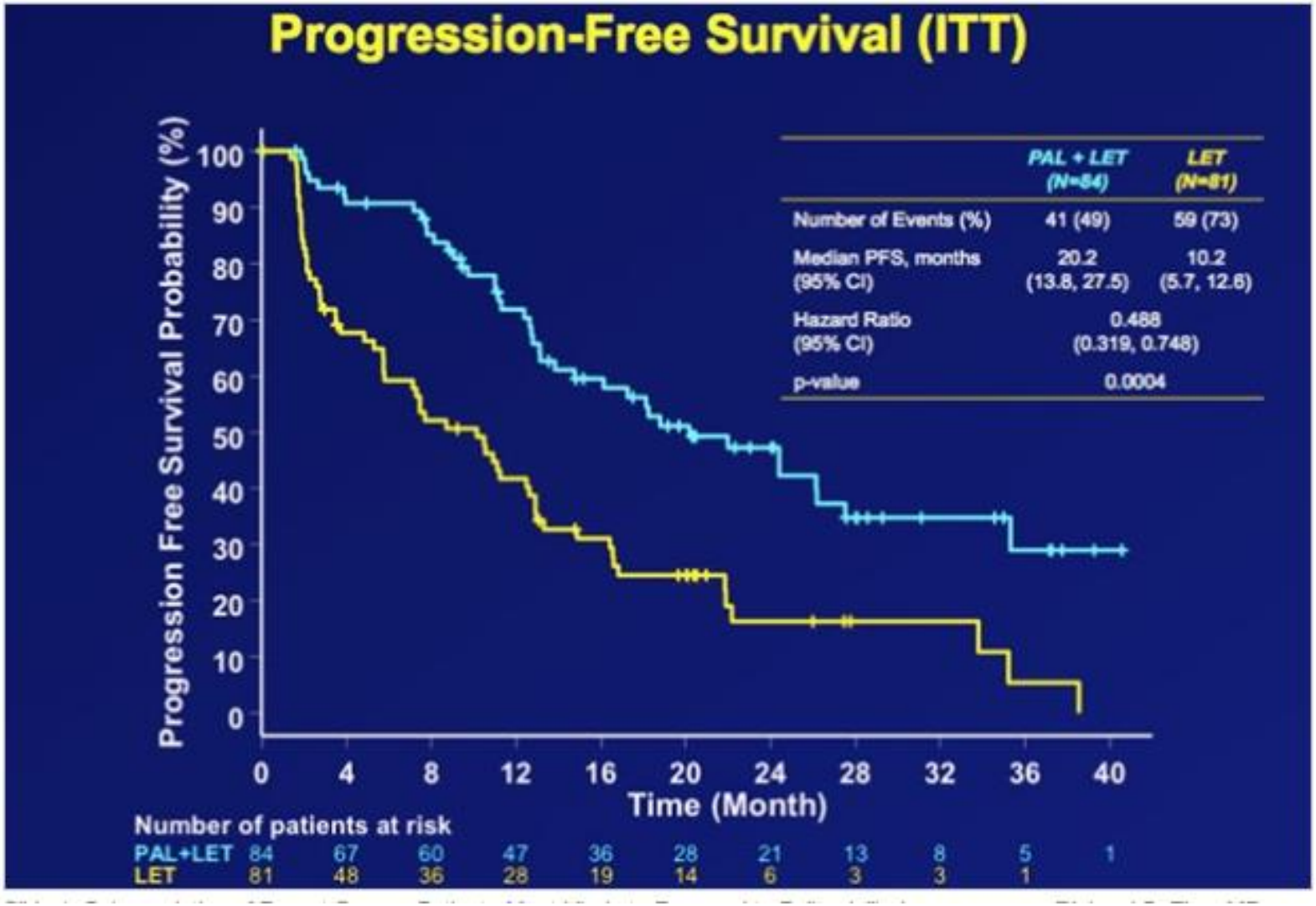


- Resistance to Pallbociclib in many of the nonluminal breast cancer cell lines may be explained by the absence of pRb.
- Lack of pRb in basal-like breast cancer tissue can result in the characteristic epithelial-to-mesenchymal transition changes

Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77.

PD 0332991 (Palbociclib): CDK 4/6 Inhibitor

First Line Phase 2 Trial: Palbociclib + Letrozole v Letrozole



Finn RS et al.AACR 2014 abstr CT101

PD 0332991 (Palbociclib): CDK 4/6 Inhibitor

Phase 2 Trial: Palbociclib + Letrozole v Letrozole

- Response rate 27%* v 23%
- Clinical Benefit 59%* v 44%
- Commonest side effects*
  neutropenia, leukopenia,fatigue

* Combination arm

Palbociclib(P) : Next Steps

- PALOMA 2 Phase 3 P + Letrozole v letrozole
- PALOMA 3 Phase 3 P + Fulvestrant v Fulvestrant
- PALLET Phase 2 Neoadjuvant P + letrozole
  Which patients are most likely to benefit?

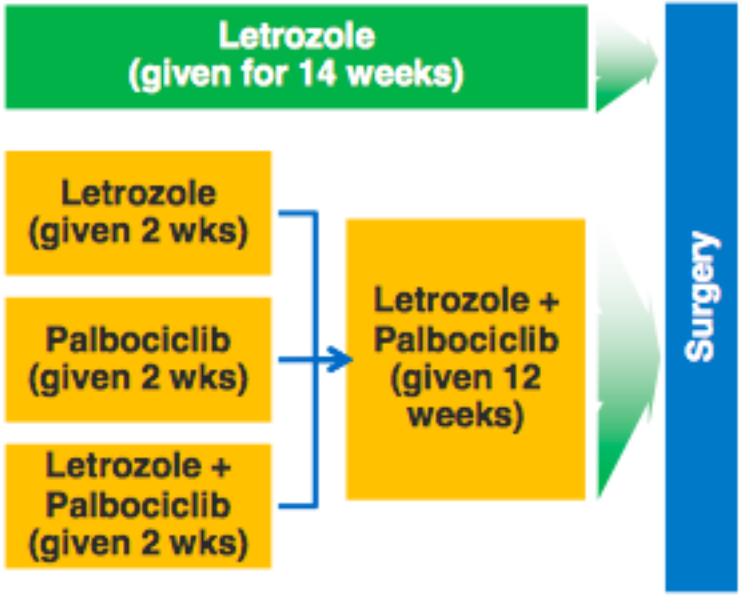
PALLET Trial Design: Ph2 Study of Palbociclib with Letrozole in the Neoadjuvant Treatment of ER+ BC

Ph2 Study Design

Ph2 Study (ICR-CTSU & NSABP): To Support Patient Selection for Ph 3

Patients Characteristics

- Postmenopausal women with localized ER+HER2- invasive early breast cancer suitable for neoadjuvant therapy with letrozole



- To perform gene expression profile analysis by a commercially available assay such as PAM 50, Oncotype Dx etc. and identify with tumor subsets (such as luminal B, or RS >=18) that benefit from palbociclib treatment

- N=301 Open label, Multicenter (UK & USA), Active controlled, Ph2
- Primary Endpoints: Decrease in Ki67 at wk 14; Clinical response at 3 mo
- Secondary Endpoints: Ki67 at 2 weeks, pCR after 14 weeks
- Stratification Factors: by country

- PIs - Johnston, Dowsett, Osborne, Wolmark)

Conclusions:

Endocrine Therapy for ER+ve Metastatic Breast Cancer

- When it works endocrine therapy is still the best treatment in terms of duration of benefit and low toxicity
- First line treatment except for immediatley life-threatening visceral disease
- AIs best for postmenopausal women if no previous treatment

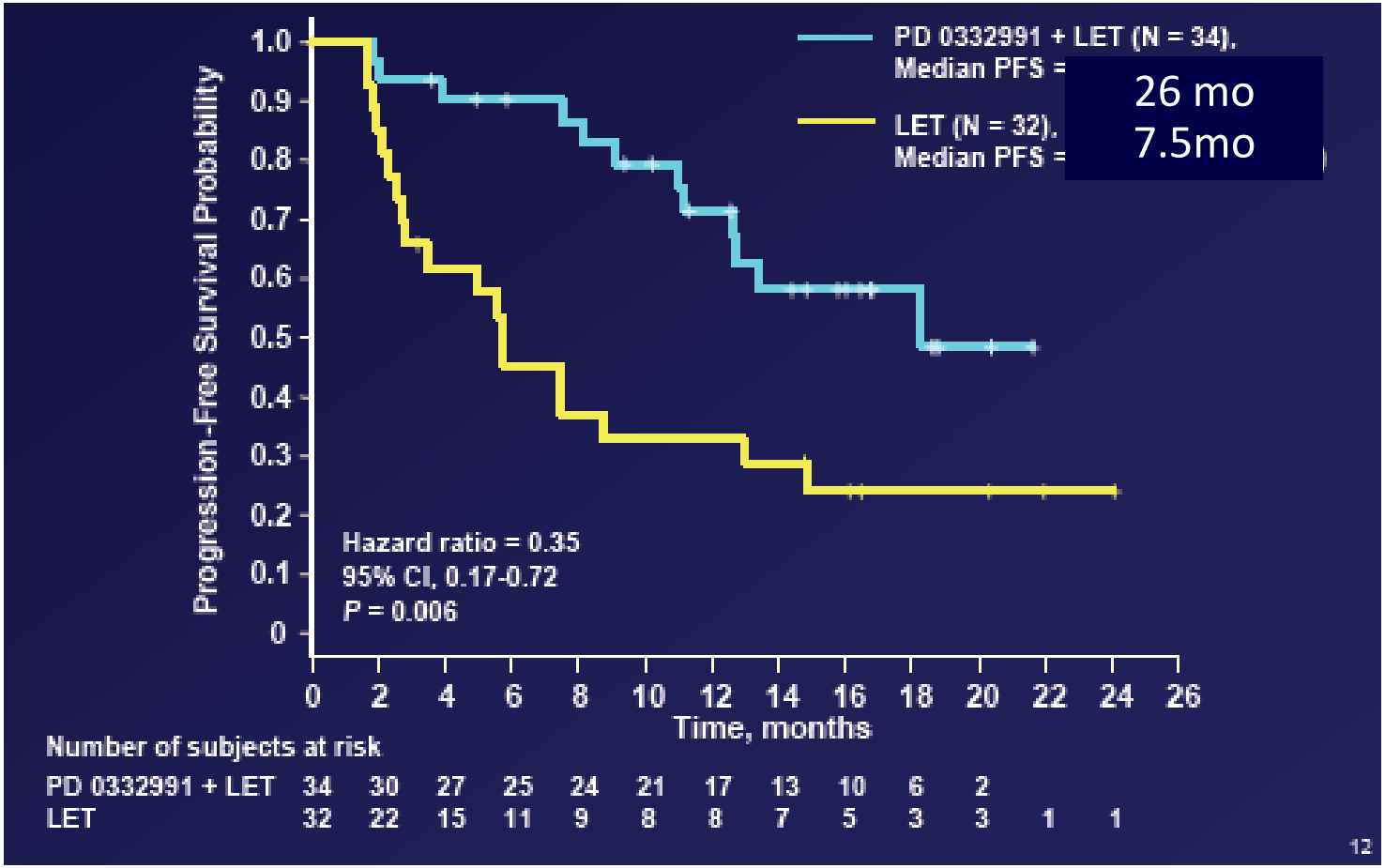
Conclusions:

Endocrine Therapy for ER+ve Metastatic Breast Cancer

- After AIs, no single best second line, but don't forget tamoxifen
- If previous responses, keep trying sequential therapies
- Edge of a new era in which targeted therapies will help overcome resistant disease

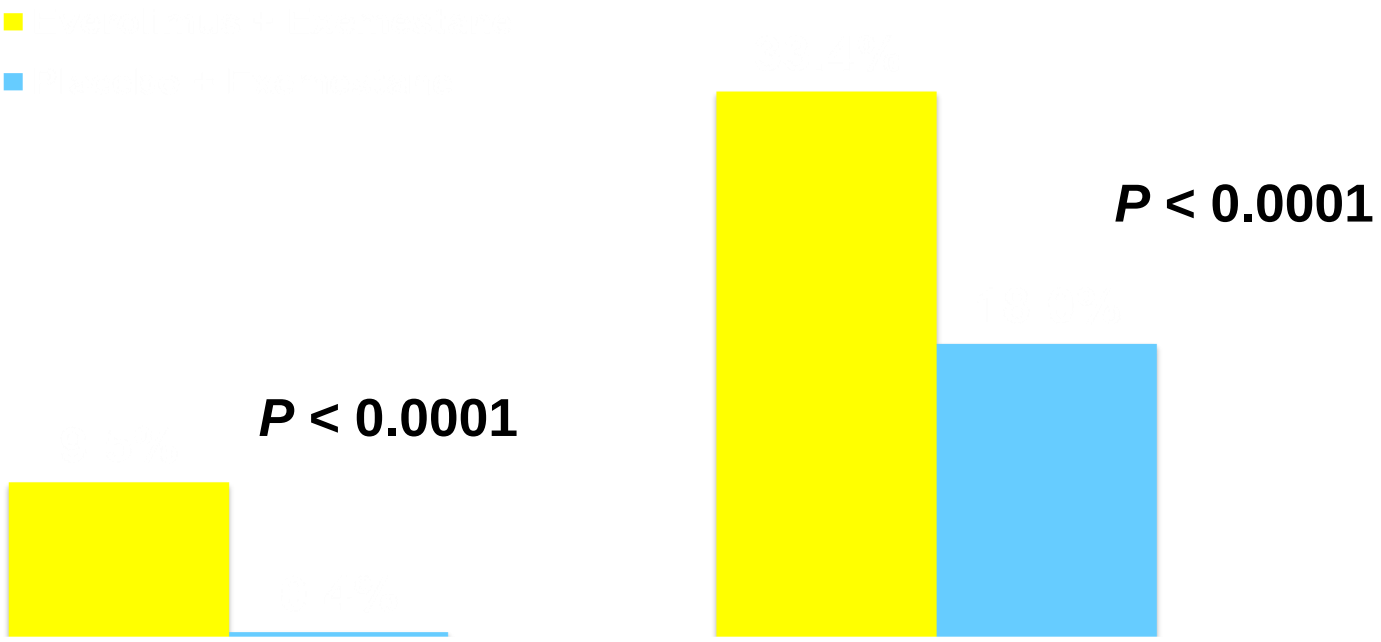
PD 0332991 (Palbociclib): CDK 4/6 Inhibitor

P + Let v Let. Progression-Free Survival



Finn RS, et al. Abstract. S1-6. 2012 (SABCS),

BOLERO-2: Overall Response Rate and Clinical Benefit Rate by Local Assessment



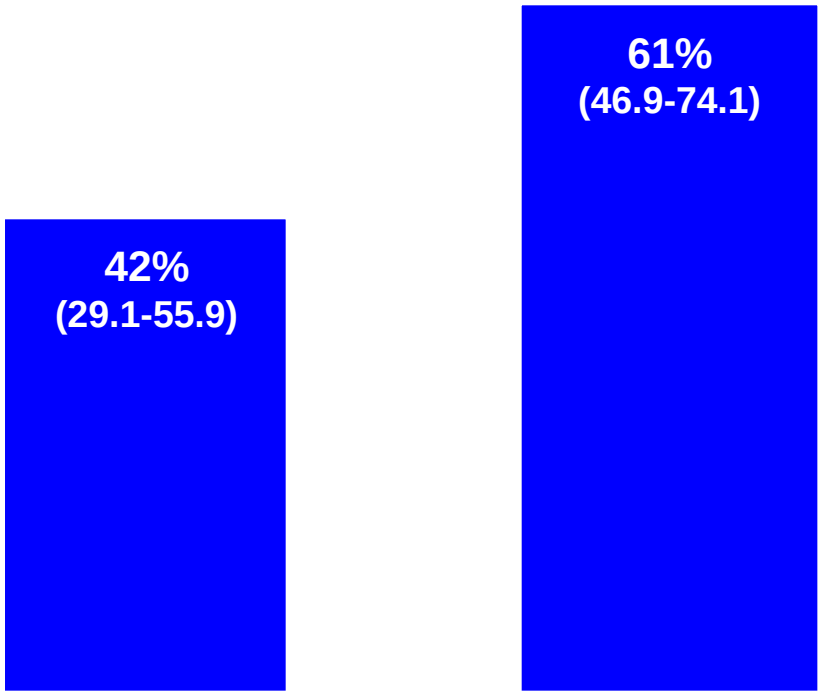
Central assessment:

- **Response rate: 7.0% vs 0.4%**
- **Clinical benefit rate: 30.9% vs 15.1%**

Presented by J. Baselga at the 2011 European Multidisciplinary Cancer Congress (ECCO/ESMO), September 26, 2011. Abstract: 9LBA.

TAMRAD: Tam v Tam + Everolimus
Primary Endpoint: Clinical Benefit Rate

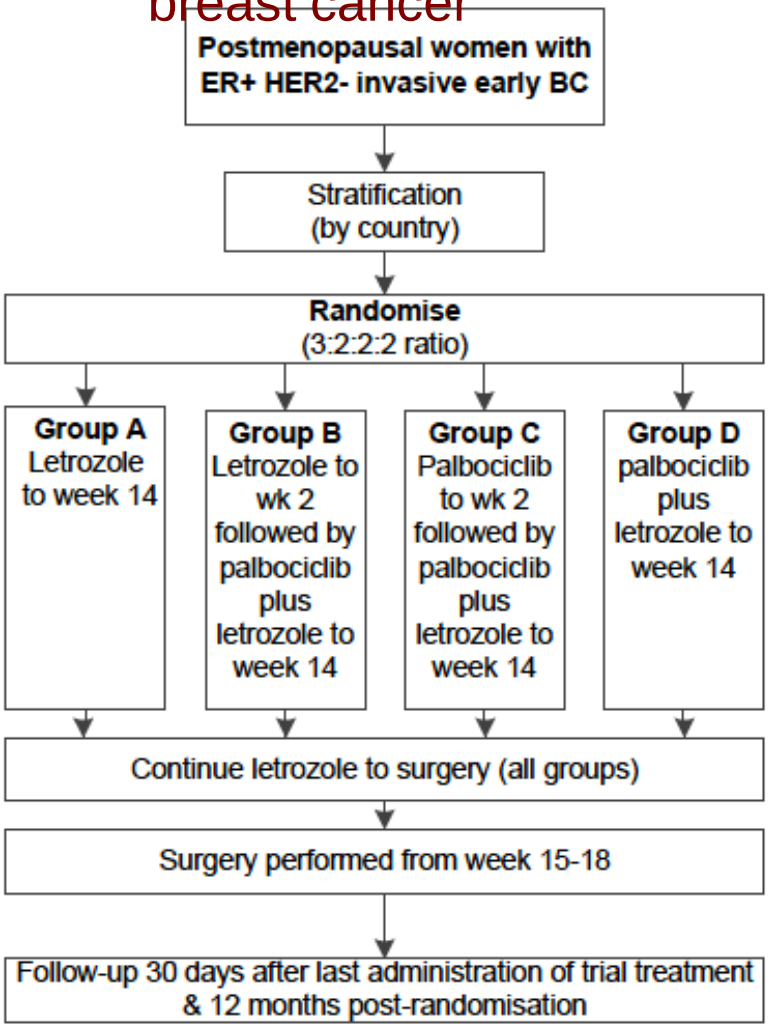
P = 0.045 (exploratory analysis)



PALLET

A phase II randomised study evaluating the biological and clinical effects of the combination of palbociclib with letrozole as neoadjuvant therapy in post-menopausal women with ER+ primary breast cancer

RECRUITMENT TARGET
306 patients (global),
100-200 patients (UK)



ASCO 2013

- A phase II trial of an oral CDK 4/6 inhibitor, PD0332991, in advanced breast cancer.
- **2013 ASCO Annual Meeting** abstr 519
- **Author(s):**
- Angela DeMichele, Amy Sanders Clark, Daniel Heitjan, Sophia Randolph, Maryann Gallagher, Priti Lal, Michael D Feldman, Paul J. Zhang, Allison Schnader, Kelly Zafman, Susan M. Domchek, Keerthi Gogineni, Stephen Michael Keefe, Kevin R. Fox, Peter J. O'Dwyer; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Hospital of the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; Pfizer Oncology, San Diego, CA; University of Pennsylvania Health System, Philadelphia, PA
- **Abstract:**
- **Background:** The G1/S checkpoint of the cell cycle is frequently dysregulated in breast cancer (BC). Initial efficacy of PD0332991, a potent oral inhibitor of cyclin-dependent kinases (CDKs) 4/6 was shown in a variety of solid tumors and in combination with letrozole in a randomized phase II trial. **Methods:** We performed a phase II, single arm trial of PD0332991 in women with advanced BC. The primary objectives were safety and efficacy. Eligible patients had histologically-confirmed, stage IV BC with primary or metastatic tumor positive for retinoblastoma (Rb) protein expression, measureable disease by RECIST and adequate organ function/performance status. PD0332991 was given at 125 mg orally, days 1 – 21 of a 28-day cycle. Tumor was assessed every 2 cycles. A two-stage statistical design was employed. Secondary objectives included predictive biomarker assessment. **Results:** 36 patients were enrolled; 28 who completed cycle 1 are reported: 18 (64%) HR+/Her2-, 2 (7%) HR+/Her2+ and 8 (29%) HR-/Her2-. 90% had prior chemotherapy for metastatic disease (median 3 lines); 78% had prior hormonal therapy (median 2 lines). Grade 3/4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). One episode of neutropenic sepsis occurred in cycle 1 in patient with 6 prior chemo regimens. All other toxicities were grade 1/2. Treatment was interrupted in 7 (25%) and dose reduced in 13 (46%) pts for cytopenias. For response data see table. Responses occurred at dose levels as low as 50 mg. Median PFS (months, 95% CI) was 4.1 (2.3,7.7) for ER+/Her2-, 18.8 (5.1,∞) for ER+/Her+ and 1.8 (0.9,∞) for ER-/Her2-. 27/28 patients discontinued study for progressive disease (PD); 1 due to patient preference. **Conclusions:** Therapy with PD0332991 alone is well-tolerated and demonstrates response or prolonged stable disease (SD) in patients with BC despite prior hormonal and chemotherapy. Expansion within subtypes and molecular predictors of response are being investigated. Clinical trial information: **NCT01037790**.

Response	HR+/Her2- (n=18)	HR+/Her2+ (n=2)	HR-/Her2- (n=8)	Total (n=28)
Partial response (PR)	1 (6%)	1 (50%)	0	2 (7%)
SD > 6 months	3 (17%)	0	1 (13%)	4 (14%)
SD < 6 months	9 (50%)	1 (50%)	0	10 (36%)
PD	5 (27%)	0	7 (87%)	12 (43%)
Clinical benefit (PR + SD>6 months)	4 (23%)	1 (50%)	1 (13%)	6 (21%)

AACR 2014

I need to find the kaplan meie

- **Abstract Number:** CT101
- **Presentation Title:** Final results of a randomized Phase II study of PD 0332991, a cyclin-dependent kinase (CDK)-4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (PALOMA-1; TRIO-18)
- **Presentation Time:** Sunday, Apr 06, 2014, 10:15 AM -10:35 AM
- **Author Block:** *Richard S. Finn*, *et al.*

- **Abstract Body:** Background: PD 0332991 (palbociclib), a selective inhibitor of CDK-4/6, prevents DNA synthesis by blocking cell cycle progression. Preclinical studies identified luminal ER+ breast cancer cell lines with elevated expression of cyclin-D1, Rb and reduced p16 expression as being associated with palbociclib sensitivity (Finn et al. 2009). In addition, synergistic activity was seen in vitro when combined with tamoxifen. As a result of these data Phase Ib safety testing was performed, and led to this randomized Phase II study using a recommended Phase II dose of palbociclib (P) 125 mg QD for 3 weeks followed by 1 week off plus letrozole (L) 2.5 mg QD continuously.
- Methods: This Phase II trial was designed as a two-part study evaluating P+L in front-line ER+/HER2- metastatic breast cancer (MBC). Part 1 enrolled post-menopausal patients (pts) with this subtype using ER+/HER2- biomarkers while Part 2 enrolled pts with the same MBC subtype additionally screened for CCND1 amplification and/or loss of p16. The primary endpoint was investigator assessed progression-free survival (PFS) defined as time from randomization to objective progression or death. Secondary endpoints included objective response rate, overall survival, safety, and correlative biomarker studies. In both parts, post-menopausal women with ER+/HER2- MBC were randomized 1:1 to receive either P+L or L alone. Pts continued until disease progression, unacceptable toxicity, or consent withdrawal and were followed for tumor assessments every 2 months. The trial had 80% power to detect a 50% improvement in median PFS (hazard ratio 0.67 [P+L vs. L] with a 1-sided alpha=0.10).
- Results: A total of 165 pts were randomized in this Phase II study; 66 pts in Part 1 and 99 pts in Part 2. Baseline characteristics were balanced between treatment arms. The final analysis of primary endpoint showed a statistically significant improvement in PFS for the P+L arm (20.2 months) vs. L arm (10.2 months) with hazard ratio (HR)=0.488 (95% CI: 0.319, 0.748) and 1-sided p=0.0004. The treatment effects were also demonstrated when Part 1 and Part 2 were analyzed separately (HR=0.299 [95% CI: 0.156, 0.572]; 1-sided p=0.0001 for Part 1 and HR=0.508 [95% CI: 0.303, 0.853]; 1-sided p=0.0046 for Part 2). The OS analysis with 61 events demonstrated a trend in favor of P+L vs. L (37.5 months vs. 33.3 months, respectively; HR=0.813; p=0.2105). The most common adverse events in the P+L arm were neutropenia, leukopenia, fatigue, and anemia.
- Conclusions: P+L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P+L in this same MBC population is ongoing.

ASCO 2013

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PD 0332991 (palbociclib)

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- In addition, synergistic activity was seen in vitro when combined with tamoxifen.

Randomized Phase II study palbociclib (P) 125 mg QD for 3 weeks followed by 1 week off plus letrozole (L) 2.5 mg QD continuously.

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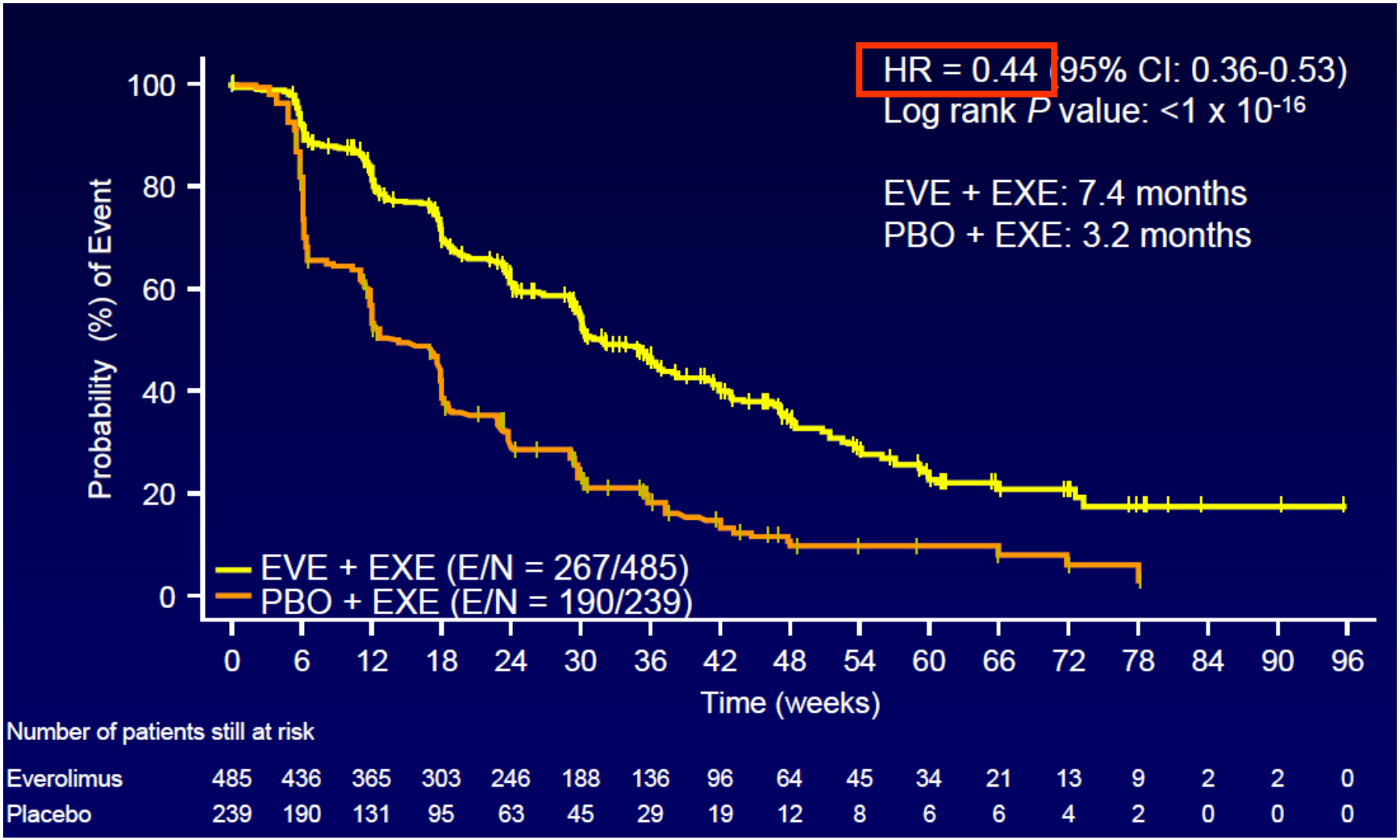
BOLERO-2: Exemestane+/-Everolimus

Phase 3 Trial 724 post menopausal patients recurrence after letrozole or anastrozole



Baselga et al N Engl J Med 2012;366:520-9.

Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg

Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka,
Igor N. Bondarenko, Rustem Khasanov, Didier Verhoeven, José L. Pedrini,
Iva Smirnova, Mikhail R. Lichinitser, Kelly Pendergrass, Sally Garnett,
Yuri Rukazenkov, Miguel Martin, on behalf of the CONFIRM investigators

Fulvestrant (Faslodex) is an oestrogen receptor antagonist without known agonistic properties that downregulates cellular levels of ER in a dose-dependent manner.

Trial design and main eligibility criteria

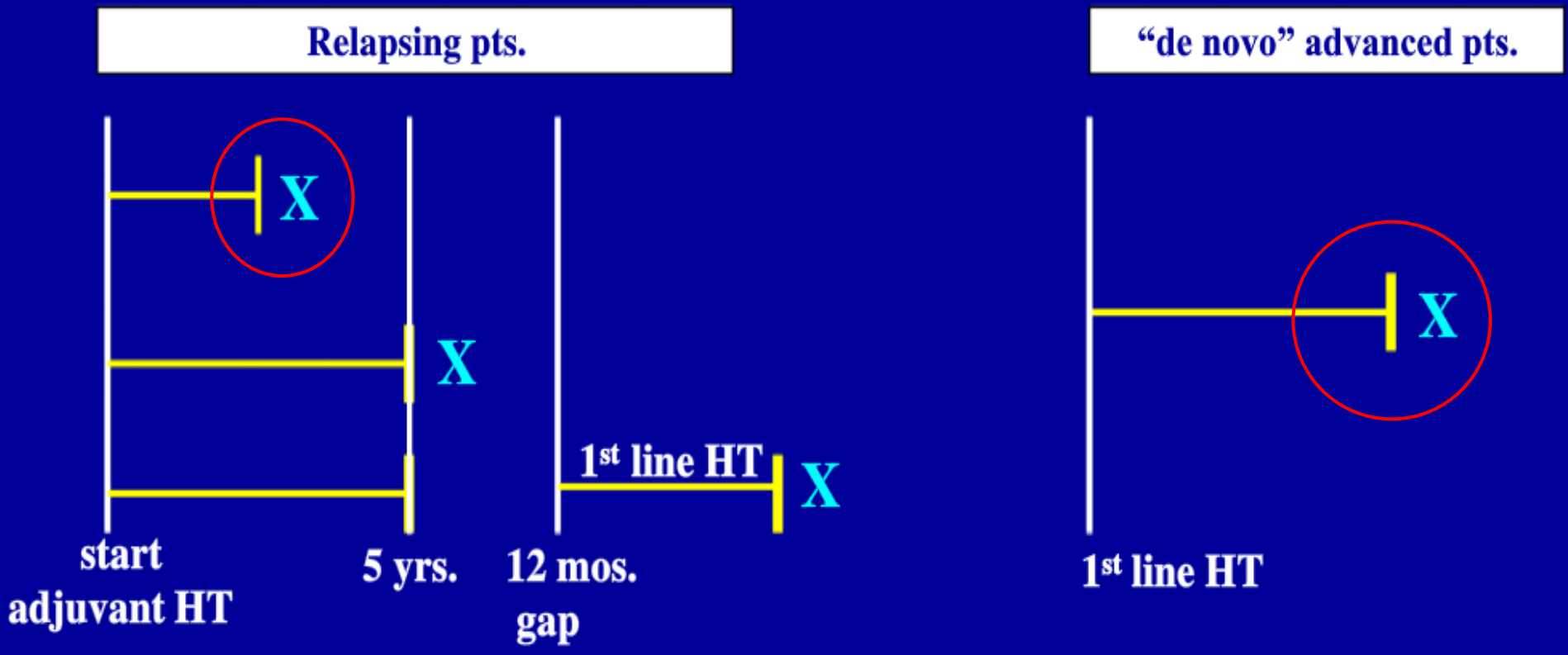
- Post-menopausal
- Advanced disease
- ER+

N=736

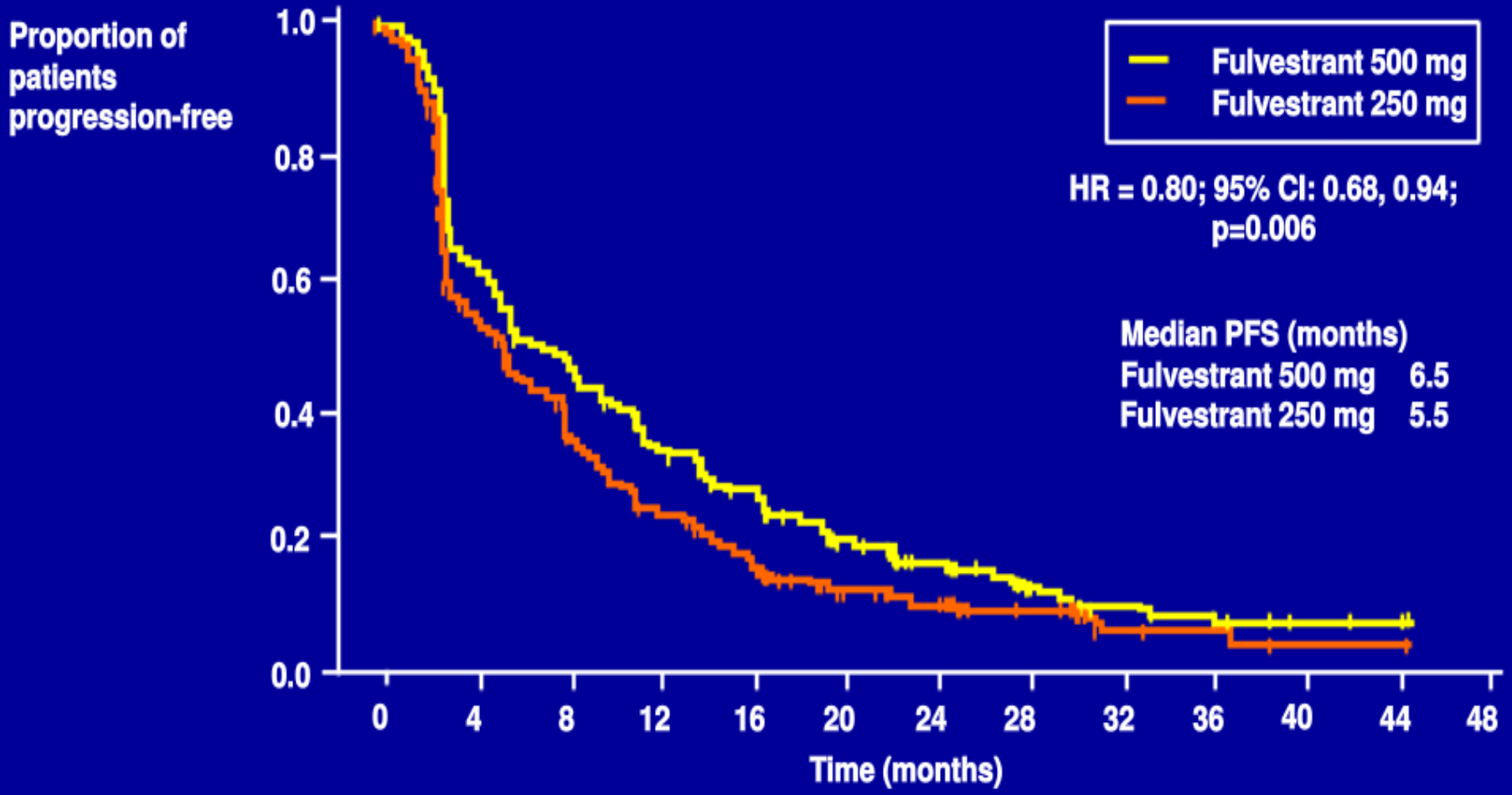
Fulvestrant 250 mg (1 injection i.m.) + placebo (1 injection i.m.) days 0, 14 (2 placebo injections), 28, and every 28 days thereafter

Fulvestrant 500 mg (2 injections 250 mg i.m.) days 0, 14, 28, and every 28 days thereafter

Allowed prior hormonotherapy (HT)



Primary endpoint: progression-free survival

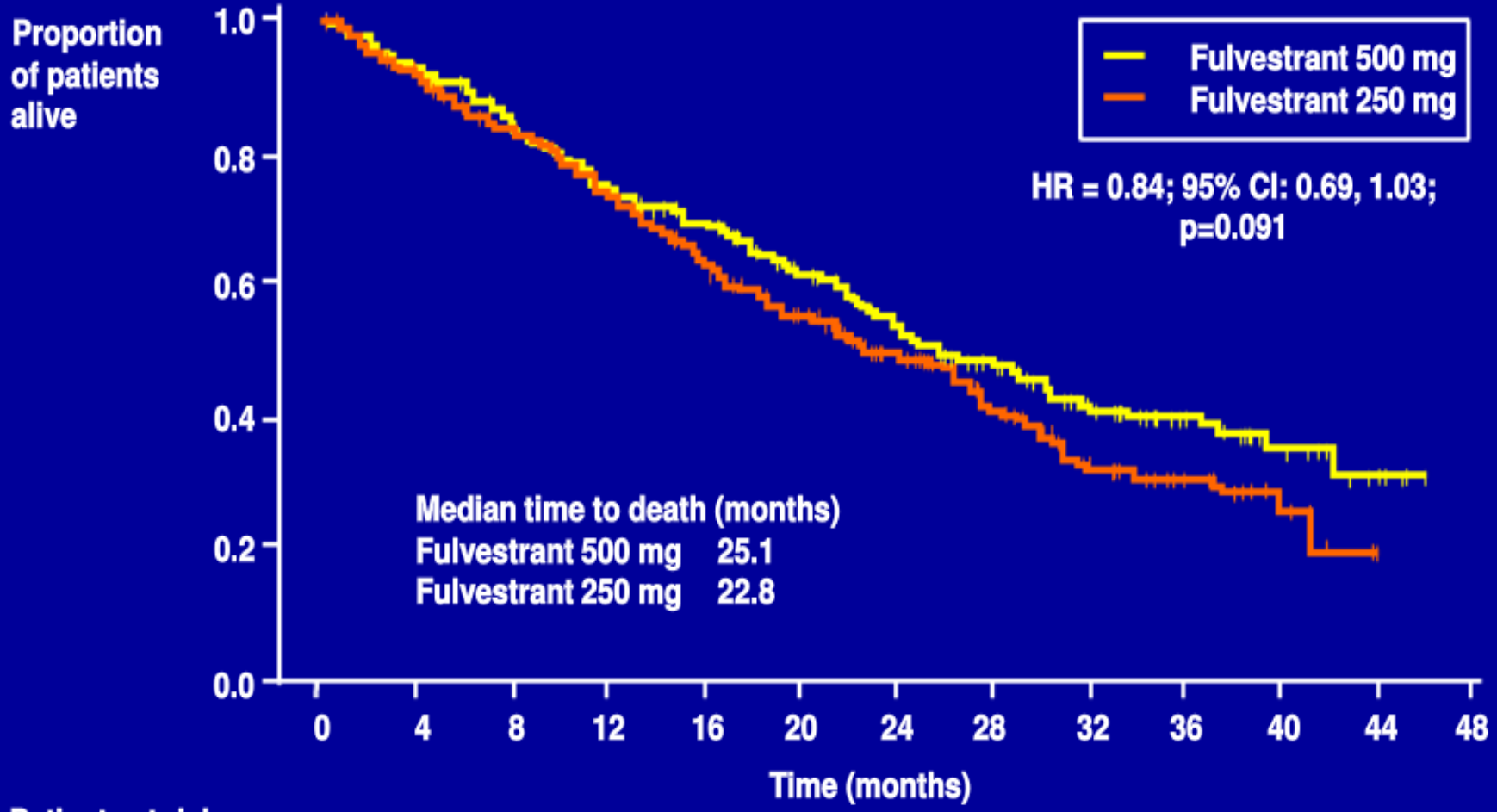


Patients at risk:													
500 mg	362	216	163	113	90	54	37	19	12	7	3	2	0
250 mg	374	199	144	85	60	35	25	12	4	3	1	1	0

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

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

Secondary endpoint: overall survival (first analysis at 50% maturity – full analysis set)

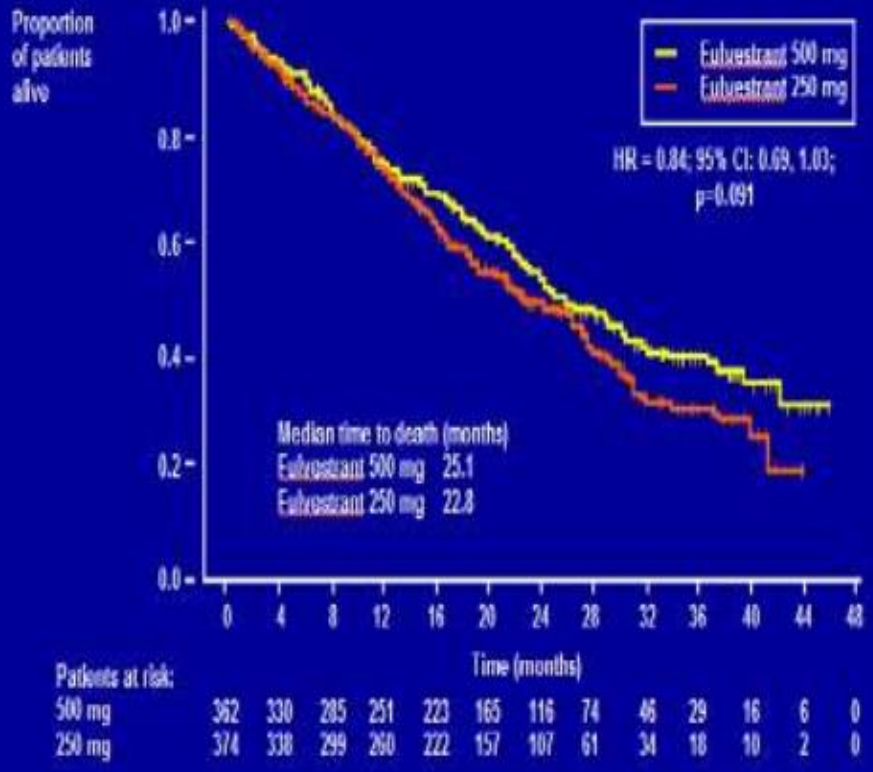


Patients at risk:													
500 mg	362	330	285	251	223	165	116	74	46	29	16	6	0
250 mg	374	338	299	260	222	157	107	61	34	18	10	2	0

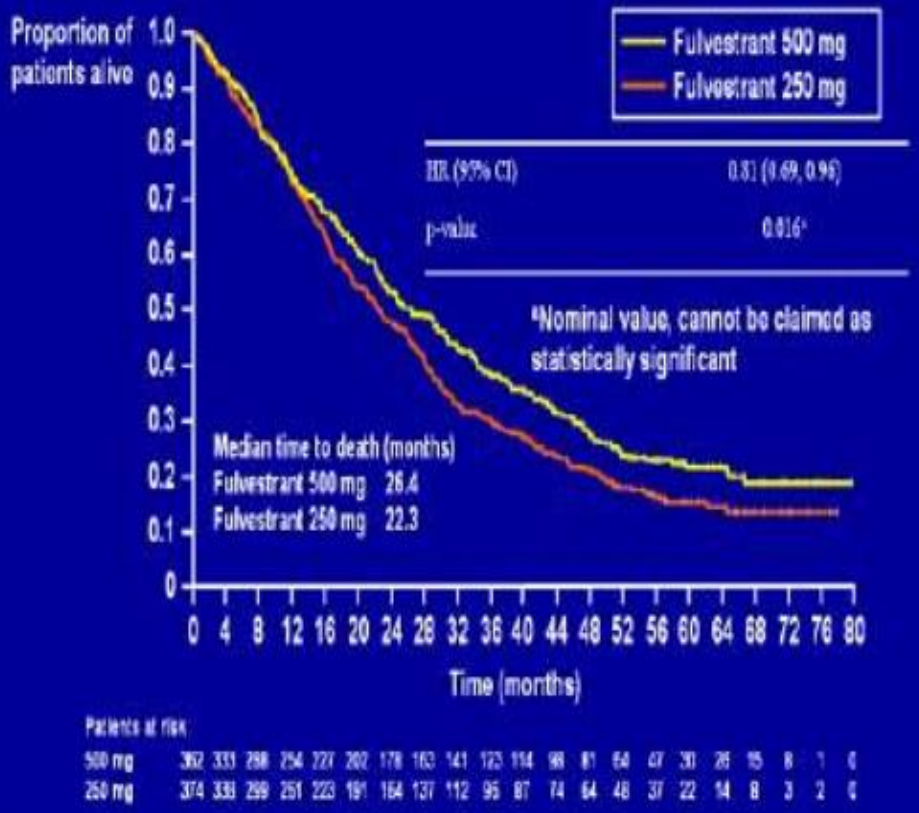
Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

Overall survival: first (50% events) and final (75% events) analyses

50% events



75% events



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

First subsequent therapies

	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-HER-2	59 / -	59 / 0.4
- % endocrine therapy other than fulvestrant*	35	31
% objective response / clinical benefit	8 / 33	8 / 41

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

SAEs with outcome of death during the whole treatment period

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 (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

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: 4594-00, 2010)
- Analysis of 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