Hormonal treatment of metastatic ER+/HER2- breast cancer

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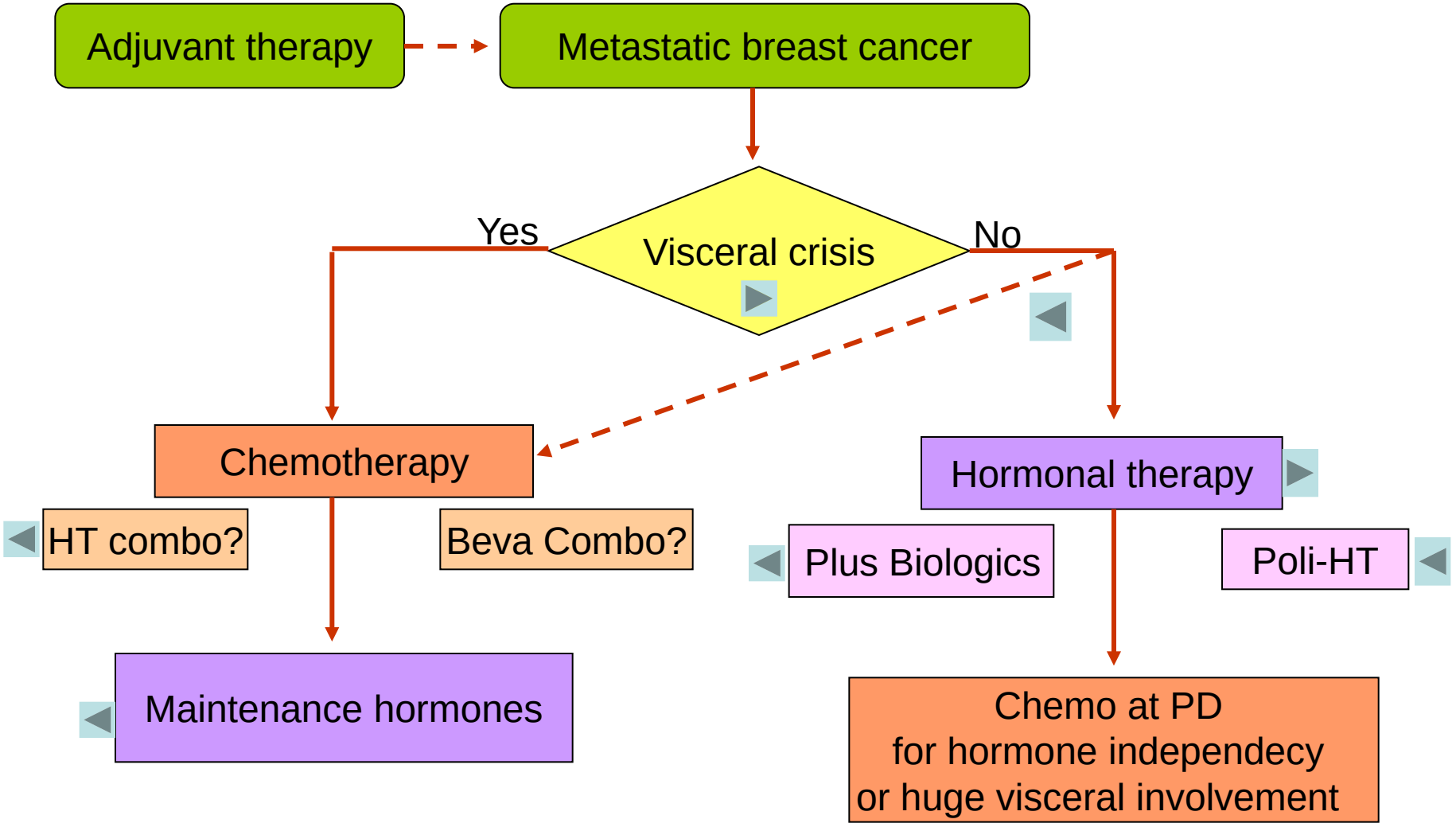
Treating metastatic breast cancer

- Only 7% of breast cancers are metastatic at the diagnosis
- The majority are recurrence of cancer diagnosed in an early stage.

- Treatment choices depend on biological tumor characteristics (ER/HER2 status), on clinical tumor characteristics (extent and site of metastates, DFI) and patient characterististics (PS, comorbidities, preferences)

Treatment options in ER+/HER2- ABC

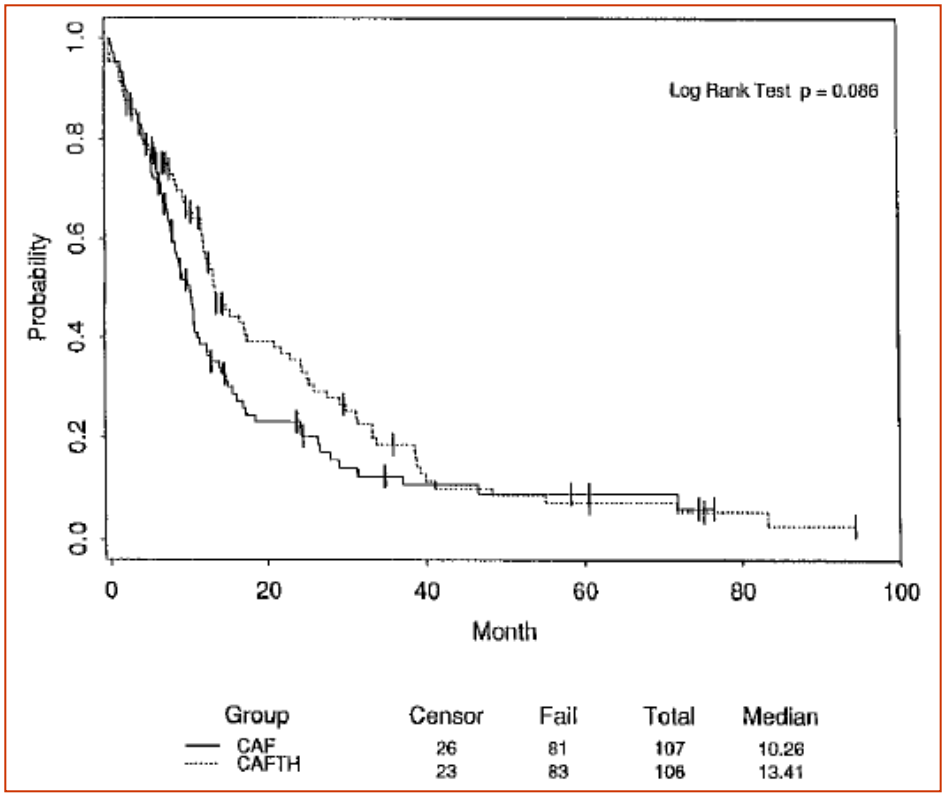


Visceral crisis definition

Guideline statements	LoE	Consensus
Visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases, but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.	Expert opinion	95.0% (38) yes 5.0% (2) abstain (40 voters)

ABC2 Ann Oncol 2014

No rooms for chemo plus hormones?



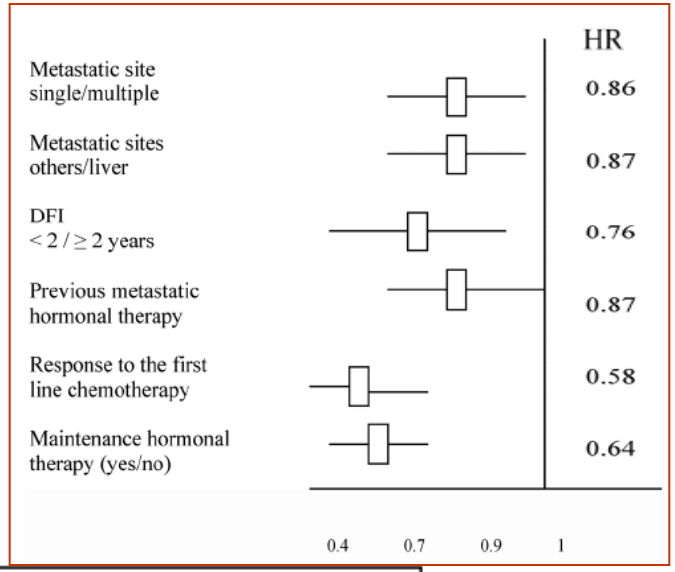
ECOG randomized trial

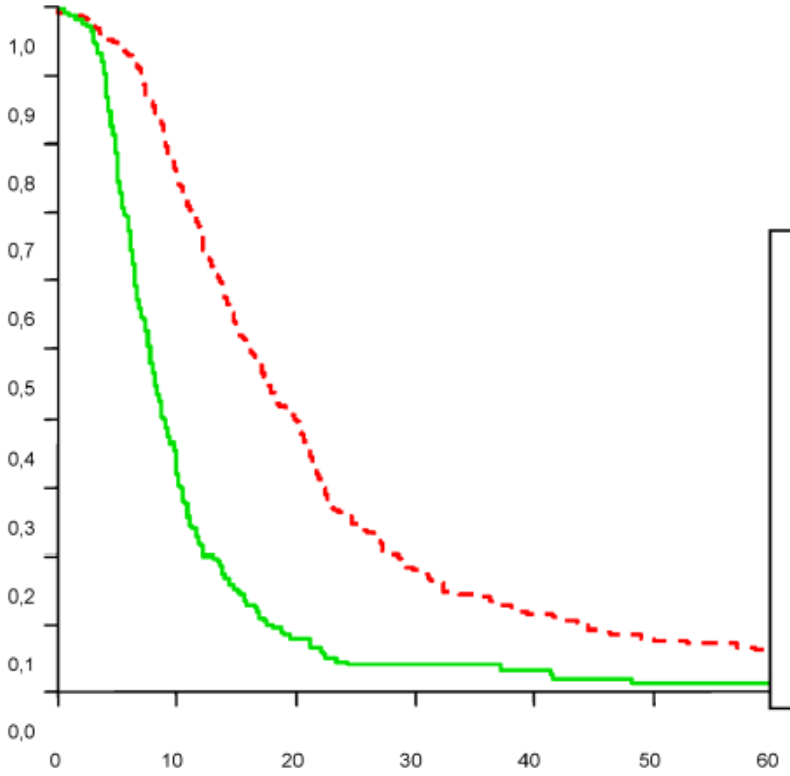
The response rates with CAF and CAFTH were similar (69.2% v 68.9%, respectively). TTF was slightly longer for chemohormonal (13.4 v 10.3 mos, P .087), and was significantly longer in ER-positive compared with ER-negative patients (17.4 v 10.3 mos, P= .048).
ER status had no effect on OS (30.0 v 29.3 mos)

Sledge, JCO 2002

Hormone maintenance after chemo

Maintenance hormonal therapy was given after chemotherapy in 308/506 patients. The hormonal treatment was TAM (94), AI (153), FULV (47) and MA (14).





Log Rank p < 0,0001
Wilcoxon p < 0,0001

– – – Subset with maintenance hormonotherapy (Median PFS 16,3 months)

——— Subset without maintenance hormonotherapy (Median PFS: 7,77 months)

Dufresne, Int J Med Sci 2008

Effect of chemotherapy is weaker in ER+ BC

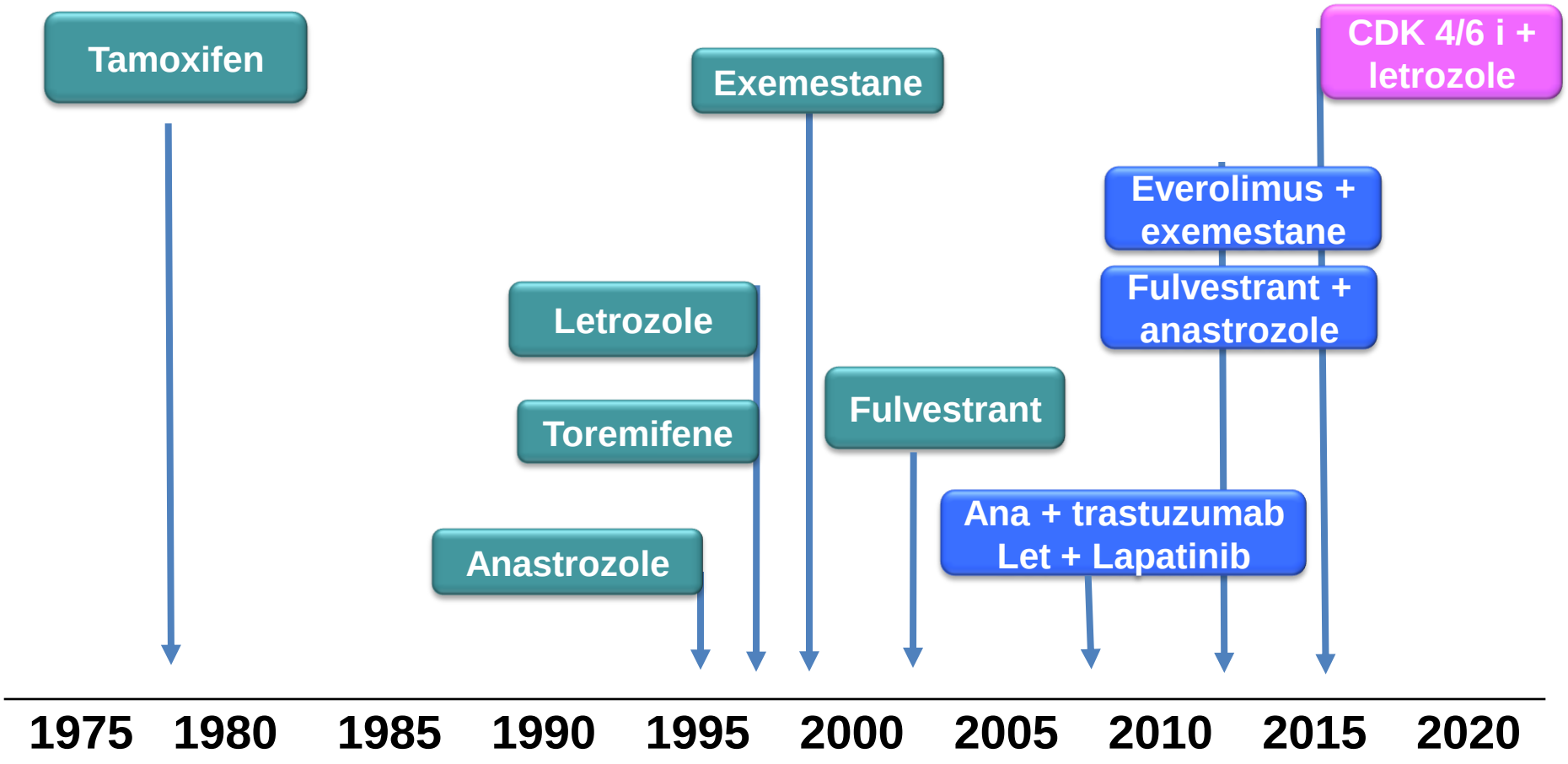
Molecular Classification	pCR (%)	P-value
Luminal A/B	2/30 (7)	P<0.001
Normal Breast Like	0/10 (0)	
ErbB2 +	9/20 (45)	
Basal Subtype	10/22 (45)	

Rouzier, Clin Can Res 2005

Efficacy of chemotherapy in first line ER unselected MBC

All (mostly HER2 –ve)	PFS/TTP(mos)	OS (mos)
DCape vs D	**6.1** vs 4.2	**14.5** vs 11.5
PacG vs Pac	**5.4** vs 3.5	**18.5** vs 15.8
Doc vs Pac	**5.7** vs 3.6	**15.4** vs 12.7
NabPac vs Pac	**5.7** vs 4.2	16.2 vs 13.9
Capecitabine vs CMF	6.0 vs 7.0	**22** vs 18
Pac+Bv vs Pac	**11.8** vs 5.9	26.7 vs 25.2
Doc+Bv vs Doc	**8.8/.8.7/** 8.0	83/78/ 73 (% at 1 y)
Ribbon1 Cape+Bv vs Cape	**8.6** vs 5.7	29 vs 21.2
Ribbon1 T/A+Bv vs T/A	**9.2** vs 8	25.2 vs 23.8

Hormonal therapy history in HR+ ABC

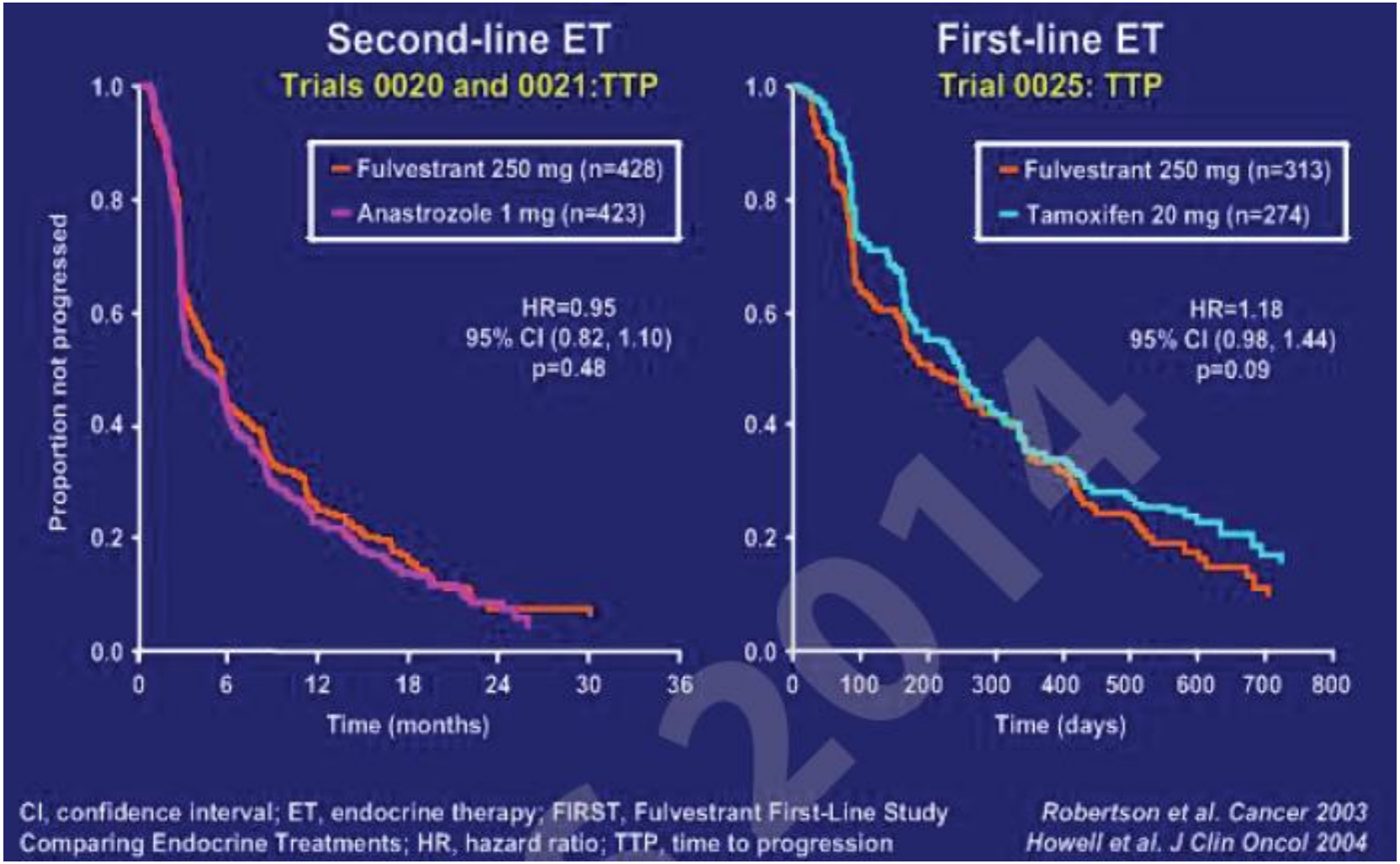


Hormonal therapy of endocrine-sensitive tumors

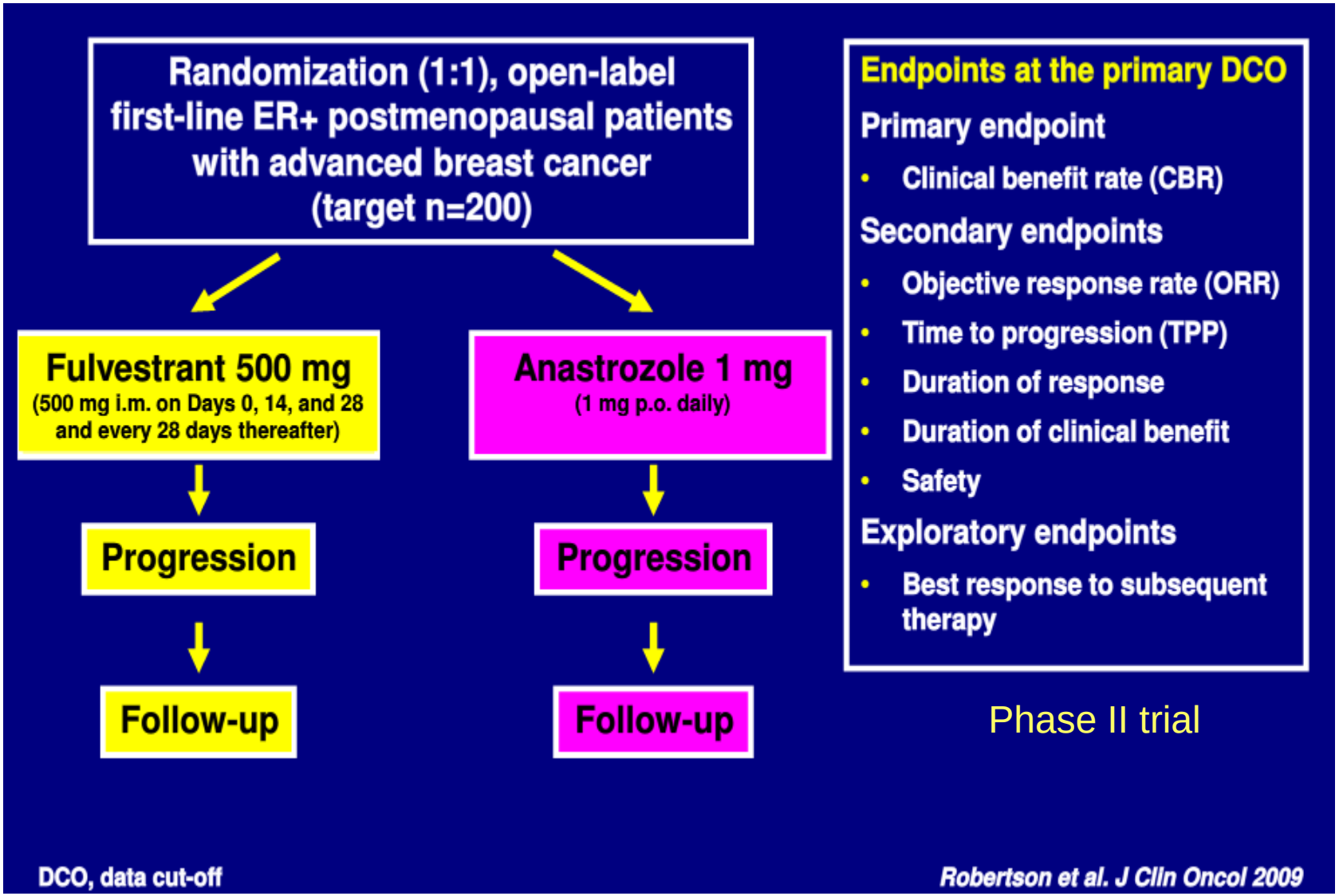
Autore	Trattamento	N. pazienti	Follow-up mediano	ORR (%)	TTP m	OS mediano (mesi)
Mouridsen et al.[15]	Letrozolo 2,5 mg/die	458	32 mesi		9,4*	34
	Tamoxifene 20 mg/die	458		21	6,0	30
Bonneterre et al.[16]	Anastrozolo 1 mg/die		19 mesi	33	8,2	
	Tamoxifene	328		33	8,3	
Nabholtz et al.[17]	mg/die	171	17,7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

NSAIs gain more benefit than tamoxifen

Improving endocrine response targeting ER



Improving endocrine response targeting ER



Patient characteristics and response to fulvestrant

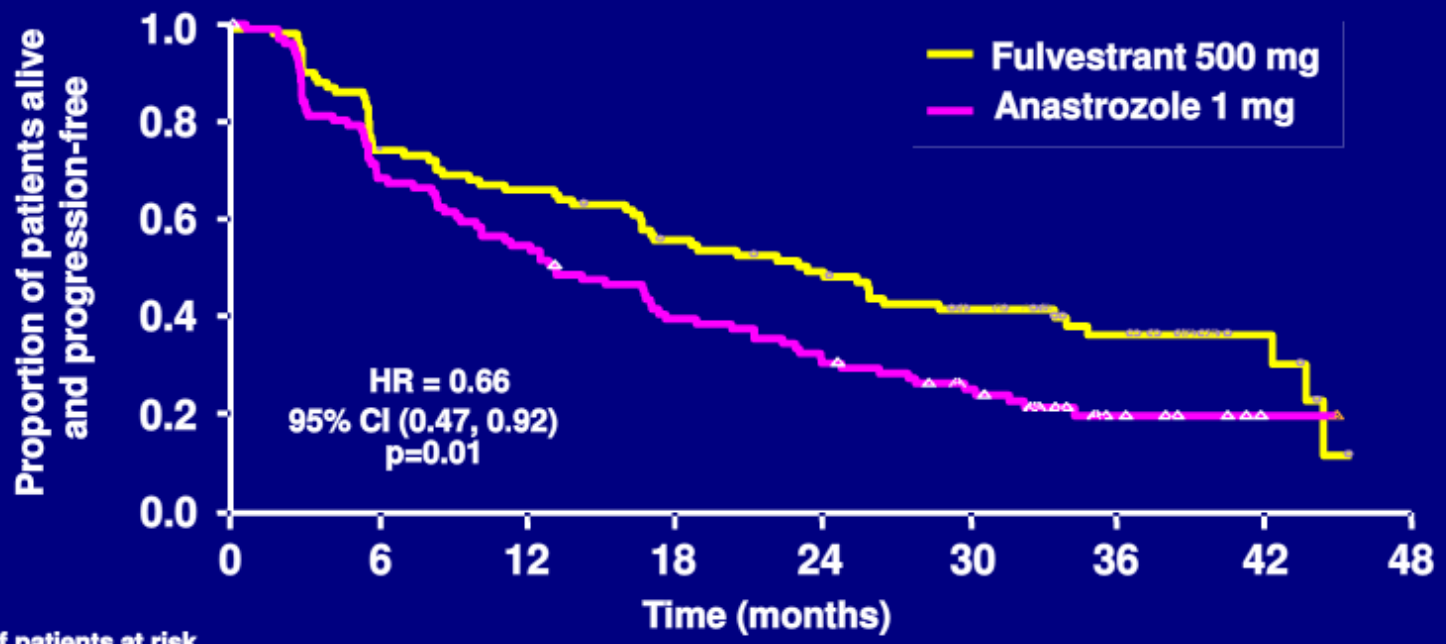
	Number (%) of patients	
	Fulvestrant 500 mg n=102	Anastrozole 1 mg n=103
Median age	66 years	68 years
Disease stage		
Locally advanced only	19 (18.6)	18 (17.5)
Metastatic	83 (81.4)	85 (82.5)
Measurable disease	89 (87.3)	93 (90.3)
Prior endocrine treatment		
No prior endocrine treatment	73 (71.6)	80 (77.7)
Completed endocrine treatment for early disease >12 months prior to randomization	28 (27.5)[a]	23 (22.3)
Prior adjuvant chemotherapy received for early breast cancer	29 (28.4)	25 (24.3)
Previously received chemotherapy and endocrine treatment	19 (18.6)	13 (12.6)

[a]In addition, one patient in the fulvestrant group received prior adjuvant endocrine treatment within 12 months of randomization

Primary endpoint

Clinical benefit rate				
Fulvestrant 500 mg % (total with CB/n)	Anastrozole 1 mg % (total with CB/n)	Odds ratio (95% CI)	p-value	Absolute difference (95% CI)
72.5% (74/102)	67.0% (69/103)	1.30 (0.72, 2.38)	0.386	5.6% (-7.8%, 15.8%)

Fulvestrant resulted in better TTP



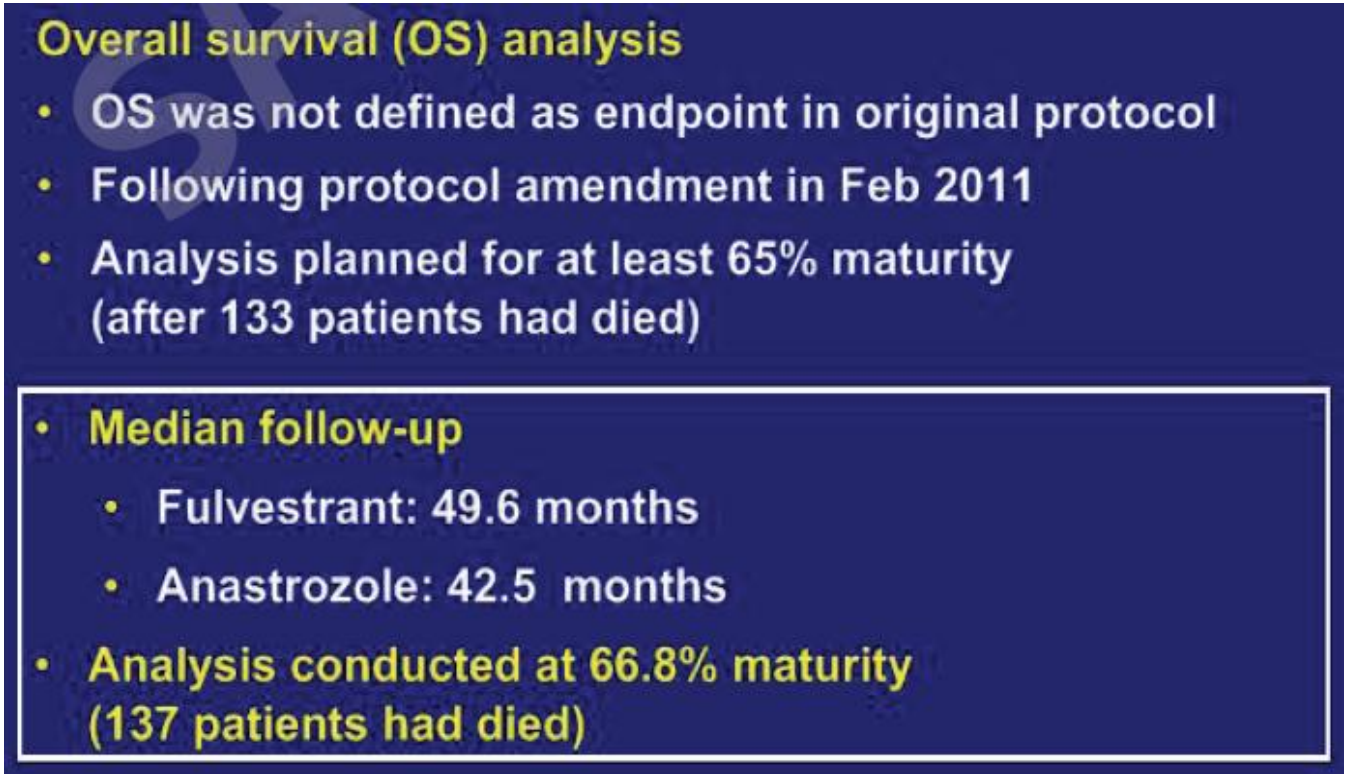
Number of patients at risk									
Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

	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

SABCS 2010

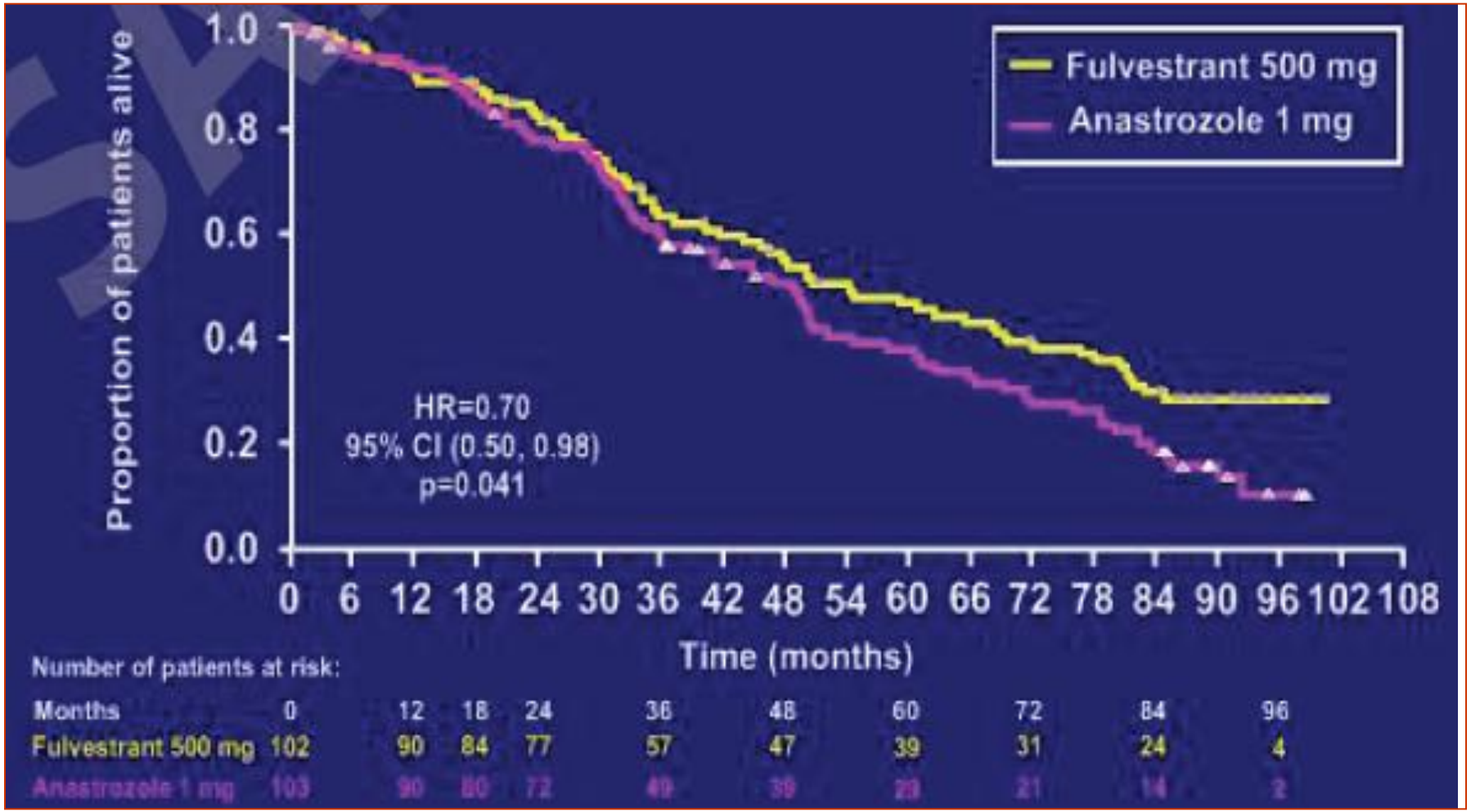
Overall survival analysis



OS data available only in 84% of Fulv-treated pts and in 82% of Ana-treated pts

Robertson, SABCS 2014

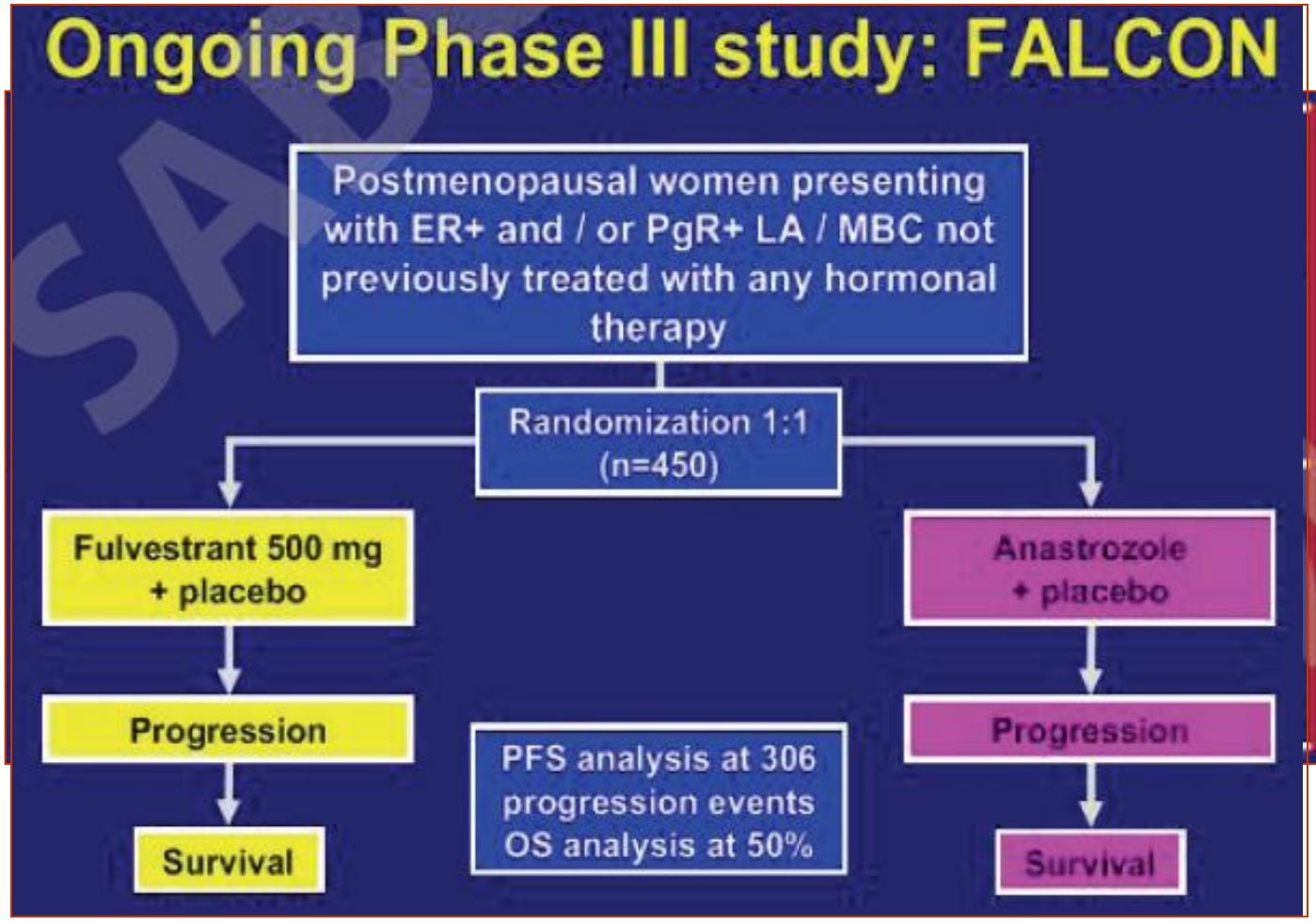
FIRST – overall survival



Robertson, SABCS 2014

Fulvestrant or NSAI?

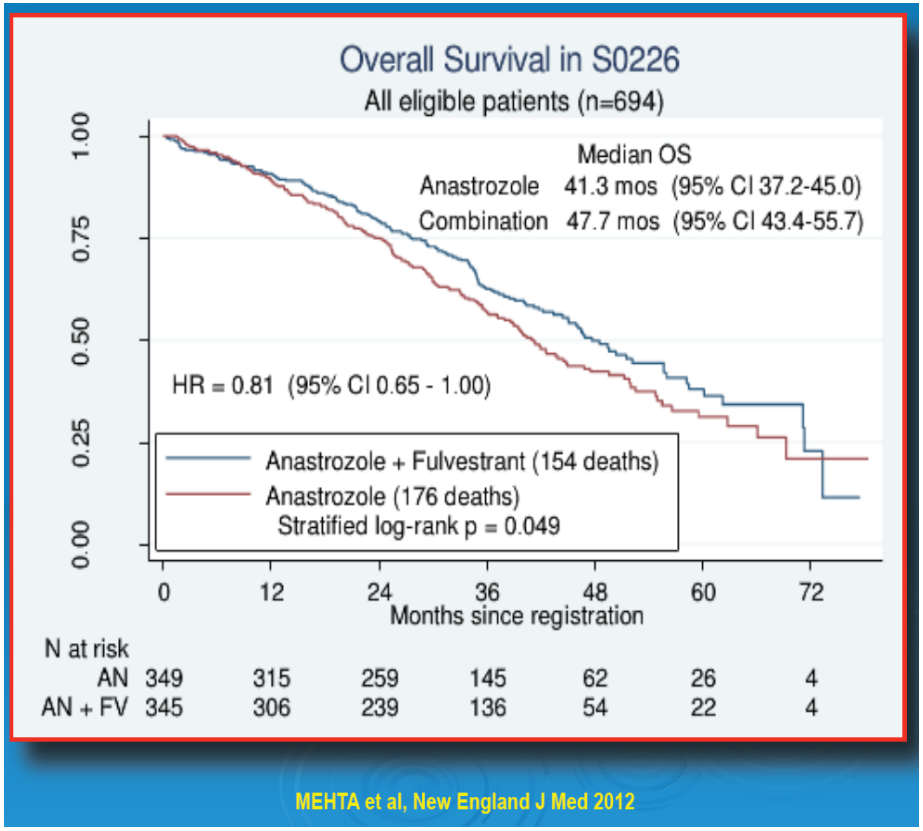
Trial cross-comparison

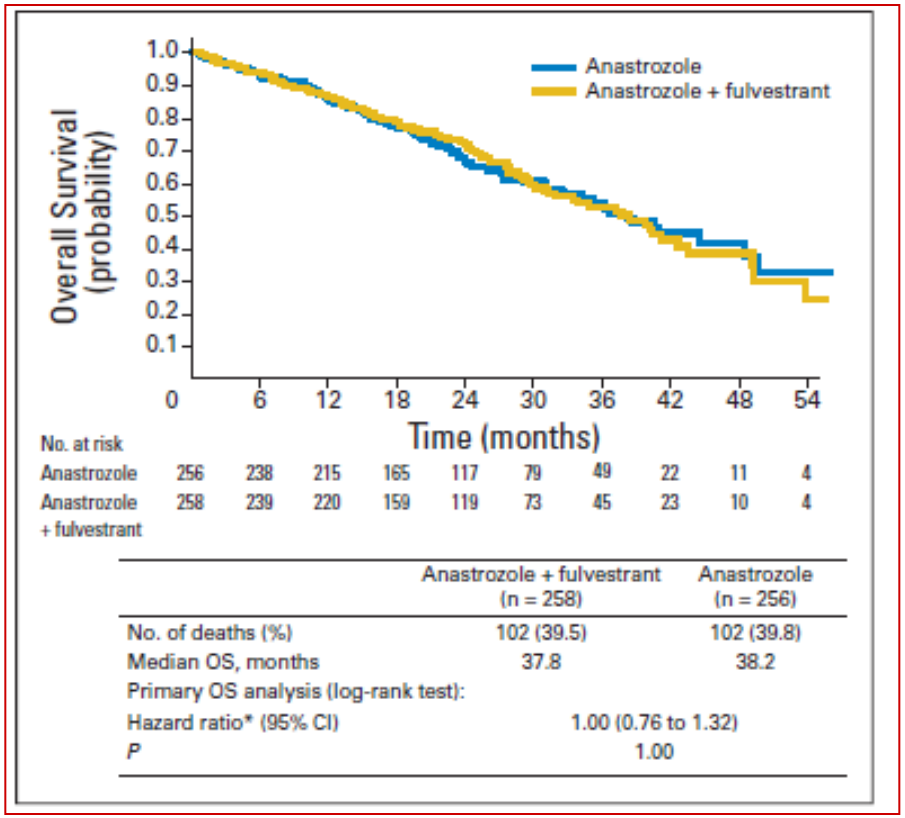


Robertson, SABCS 2014

Improving endocrine responsiveness

Complete suppression of estrogen signal





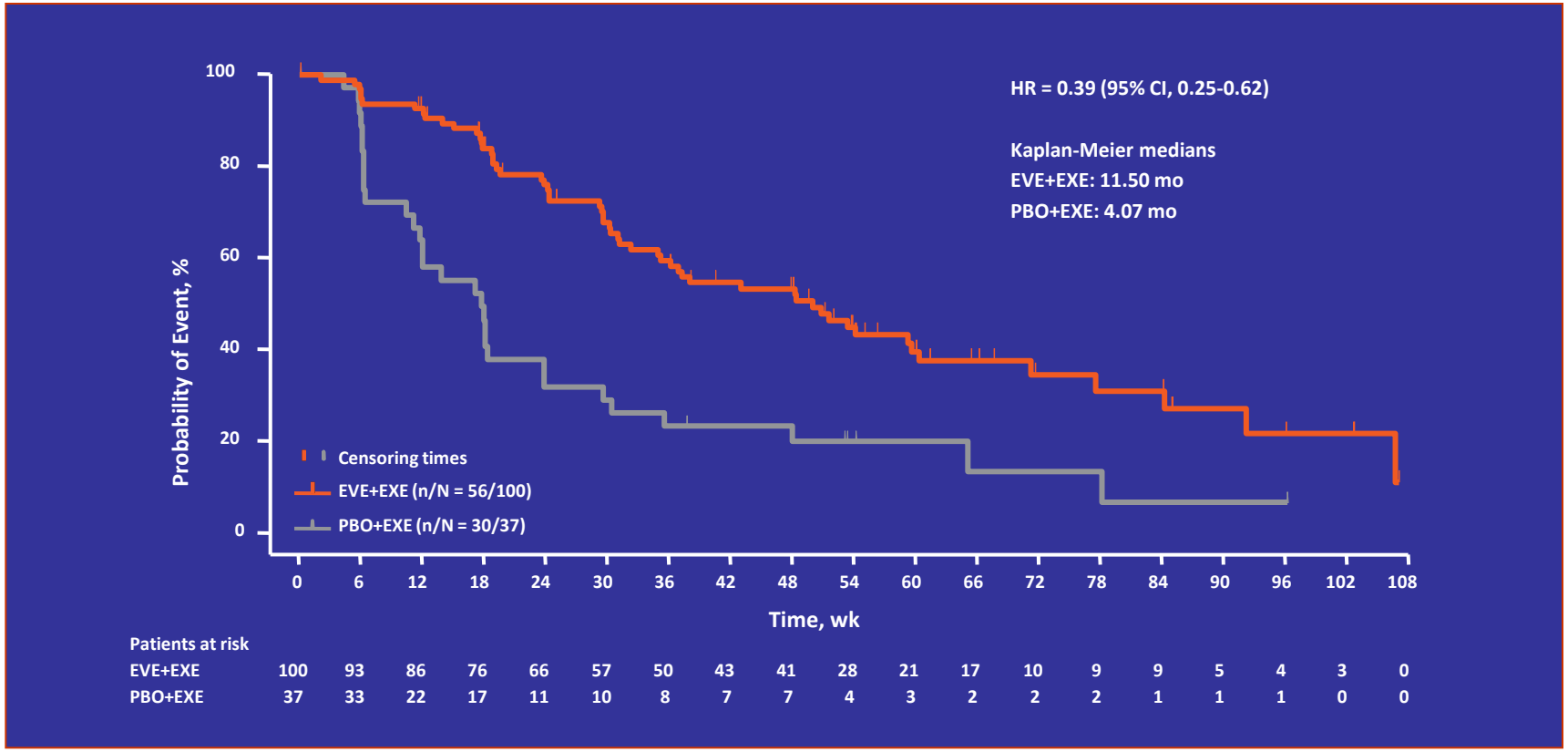
	Anastrozole + fulvestrant (n = 258)	Anastrozole (n = 256)
No. of deaths (%)	102 (39.5)	102 (39.8)
Median OS, months	37.8	38.2
Primary OS analysis (log-rank test):		
Hazard ratio* (95% CI)	1.00 (0.76 to 1.32)	
P	1.00	

SWOG: 66% Tam-naive pts

FACT: 70% Tam-pretreated pts

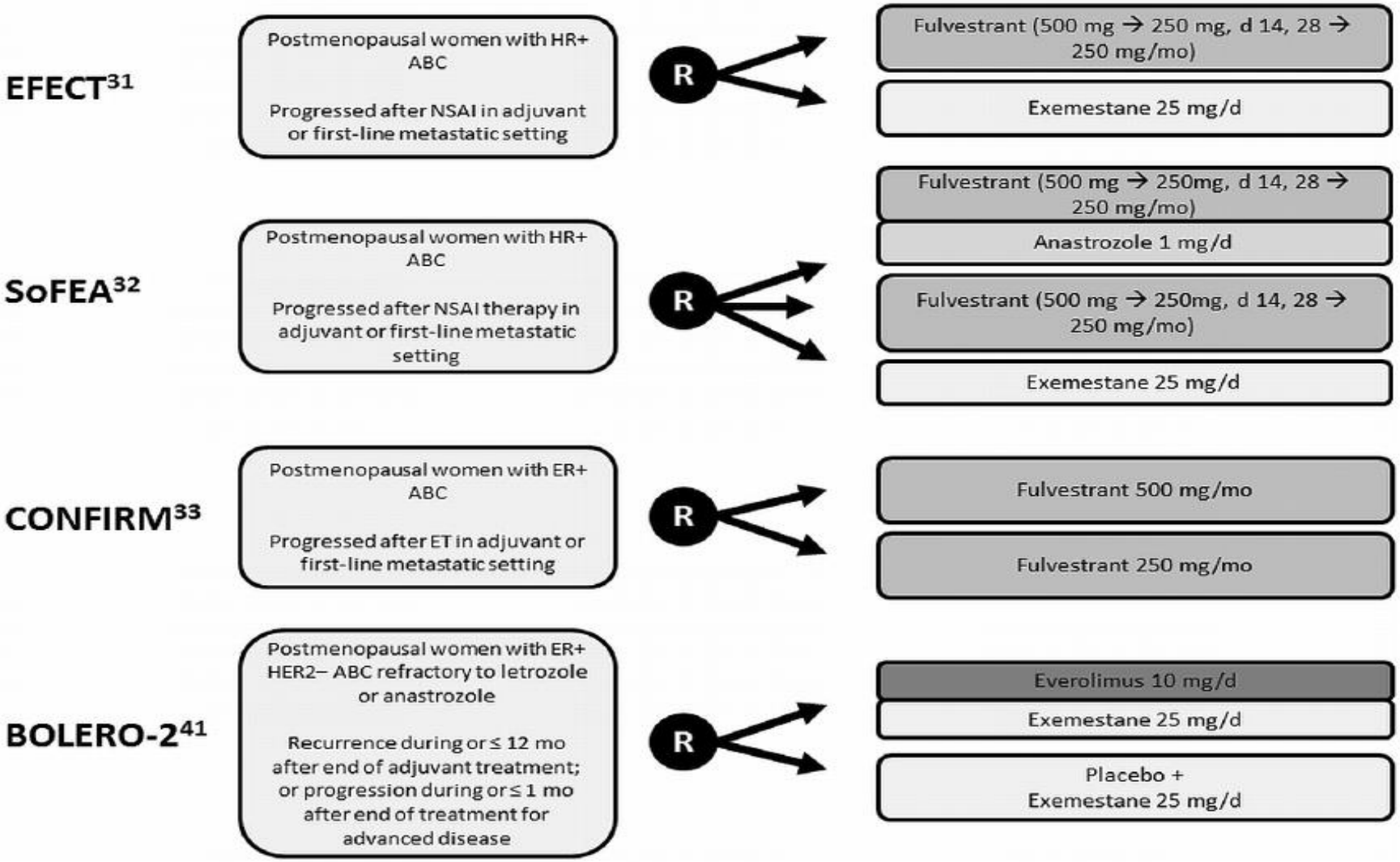
Overcoming endocrine resistance to AI

First line treatment



Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
[a] Includes patients who also had prior neoadjuvant therapy.
Piccart M, et al. SABCS 2012; poster P6-04-02.

Overcoming endocrine resistance
Second line



Pritchard 2013

Endocrine therapy after progression to NSAI

Cross comparison

Table 1. Design of the trial available on endocrine therapy in postmenopausal women with breast cancer who progressed on a prior endocrine therapy.

	EFECT [7]	SoFEA [10]	BOLERO-2 [9,11]
Study design	Fulvestrant vs exemestane	Fulvestrant 250 mg + anastrozole vs fulvestrant + placebo vs exmestane	Exemestane + everolimus vs exemestane + placebo
Inclusion criteria	Progression ≤6 months of NSAI treatment ECOG 0–2 No more than 1 CT line for mBC No CNS metastasis or visceral crisis	Progression on NSAI (≥12 months of adjuvant therapy or ≥6 months for mBC) ECOG 0–2 No visceral metastasis	NSAI resistance (recurrence ≤12 months after end of adjuvant treatment or progression ≤1 month after the end of treatment for mBC) No CNS metastasis or visceral crisis
Setting	Relapse or progression on AI	Relapse or progression on AI	Relapse or progression on AI
Primary end point	TTP	PFS	PFS
n	693	723	724
Prior HT (%)	100 in both arms	100 in all arms	100 in both arms
Prior HT for mBC (%)	89 vs 86	83 vs 78 vs 83	79 vs 84
Prior TAM	None	70 vs 74 vs 67	47 vs 49
Prior AI (%)	100 in both arms	100 in all arms	100 in both arms
Median follow-up (months)	NR	37.9	18

AI: Aromatase inhibitor; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; HT: Hormone therapy; mBC: Metastatic breast cancer; NR: Not reported; NSAI: Nonsteroidal aromatase inhibitor; PFS: Progression-free survival; TAM: Tamoxifen; TTP: Time to progression.

Pronzato, Future Oncol 2015

Endocrine therapy after progression to NSAI

Cross comparison

Table 3. Efficacy outcomes with different endocrine-based strategies in postmenopausal women with breast cancer who progressed on a prior endocrine therapy.

	PFS (months)	Clinical benefit (%)	Response rate (%)	Ref.
Exemestane	3.7	31.5	6.7	[7]
Fulvestrant	4.8	32	10.2	[10]
Fulvestrant + anastrozole	4.4	34	7	[10]
Exemestane + everolimus	11.0	51.3	12.6	[11]

Only the longest PFS for each treatment strategy are reported.
PFS: Progression-free survival.

Pronzato, Future Oncol 2015

Effects on Overall Survival from phase 3 clinical studies exploring combination regimens

Trial ID	Treatment arms	Study size, *N*	Setting	Overall survival outcomes
SWOG [16] NCT00075764	ANA + FUL versus ANA	695	First-line	• Median OS: 47.7 months (95% CI 43.4–55.7 months) versus 41.3 months (95% CI 37.2–45.0 months); HR 0.81 (95% CI 0.65–1.00); $p = 0.049$ • Result driven by TAM-naive (effectively, endocrine therapy-naive) subset: HR 0.74 (95% CI 0.56–0.98); $p = 0.04$ • No difference between arms for OS in TAM-pretreated patients: HR 0.91 (95% CI 0.65–1.28); $p = 0.59$
FACT [17]	ANA + FUL versus FUL	514	Second-line	• Median OS: 37.8 months versus 38.2 months • HR 1.00 (95% CI 0.76–1.32); $p = 1.00$
SoFEA [18] NCT00253422 and NCT00944918	ANA + FUL versus FUL versus EXE	723	First-line/ second-line	• Median OS: 20.2 months versus 19.4 months versus 21.6 months • No significant difference between any pairwise comparisons
LEA [19] NCT00545077	LET/FUL versus LET/ FUL + Bev	374	First-line	• Median OS: 51.8 months versus 52.1 months • HR 0.87 (95% CI 0.58–1.32); $p = 0.518$
HORIZON [20] NCT00083993	TEM + LET versus PBO + LET	1112	First-line	• Median OS: NE versus NE • HR 0.89 (95% CI 0.65–1.23); $p = 0.50$
BOLERO-2 [29] NCT00863655	EVE + EXE versus PBO + EXE	724	First-line/ second-line	• Median OS: 30.98 months versus 26.55 months • HR 0.89 (95% CI, 0.73–1.10); $p = 0.14$

ANA, anastrozole; Bev, bevacizumab; CI, confidence interval; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; HR, hazard ratio; HR^+, hormone-receptor-positive; LET, letrozole; NE, not estimable; OS, overall survival; PBO, placebo; TAM, tamoxifen.

Jerusalem, Canc Treat Rev 2015

CONFIRM

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

Fulvestrant (HD)* (*n*=362)

Fulvestrant (AD) (*n*=374)**

Progression

Regular Follow-up

Progression

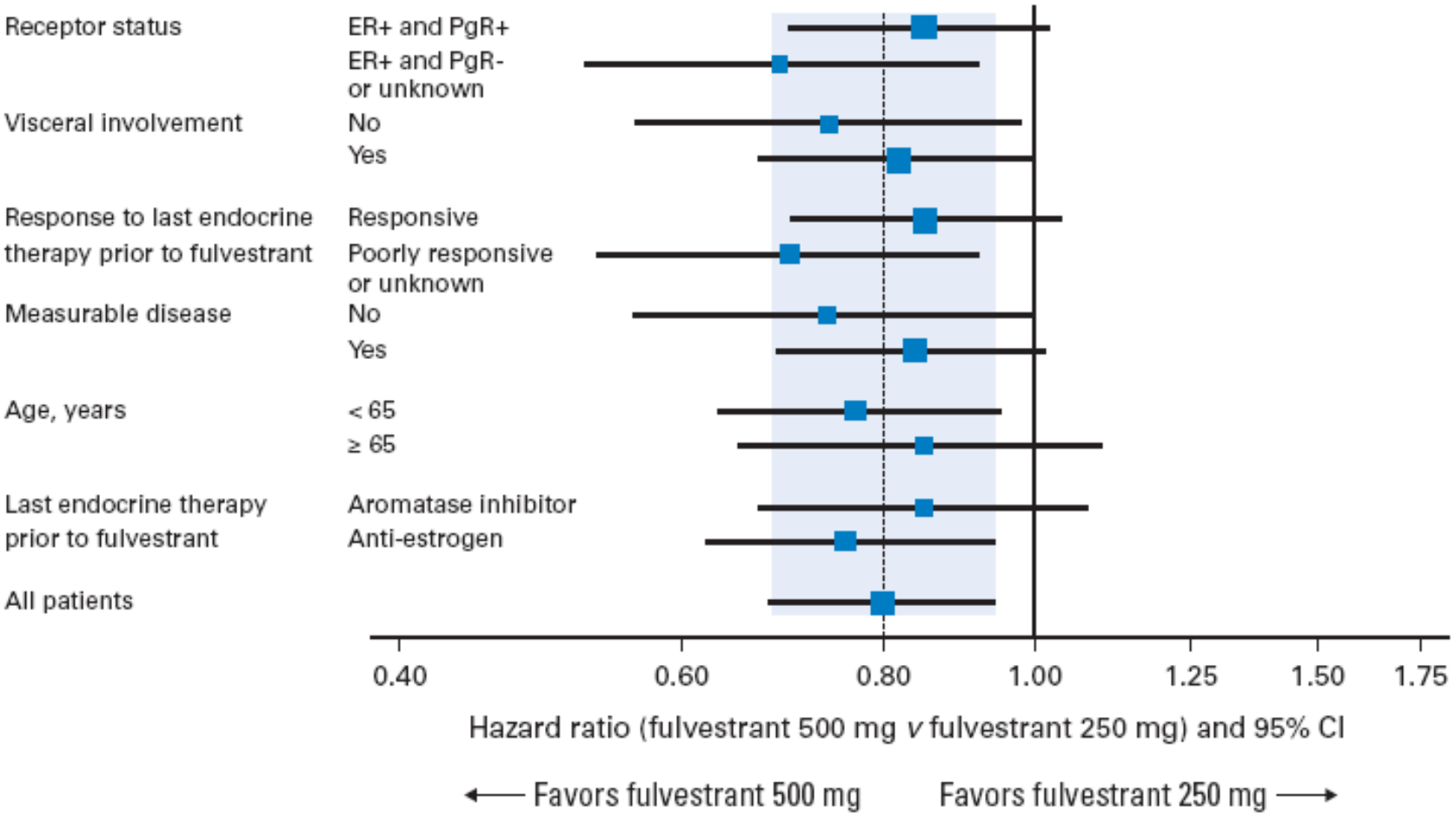
° last endocrine therapy: **AI 42%; antiestrogen 58%;** endocrine-sensitive: 63-66%

* **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

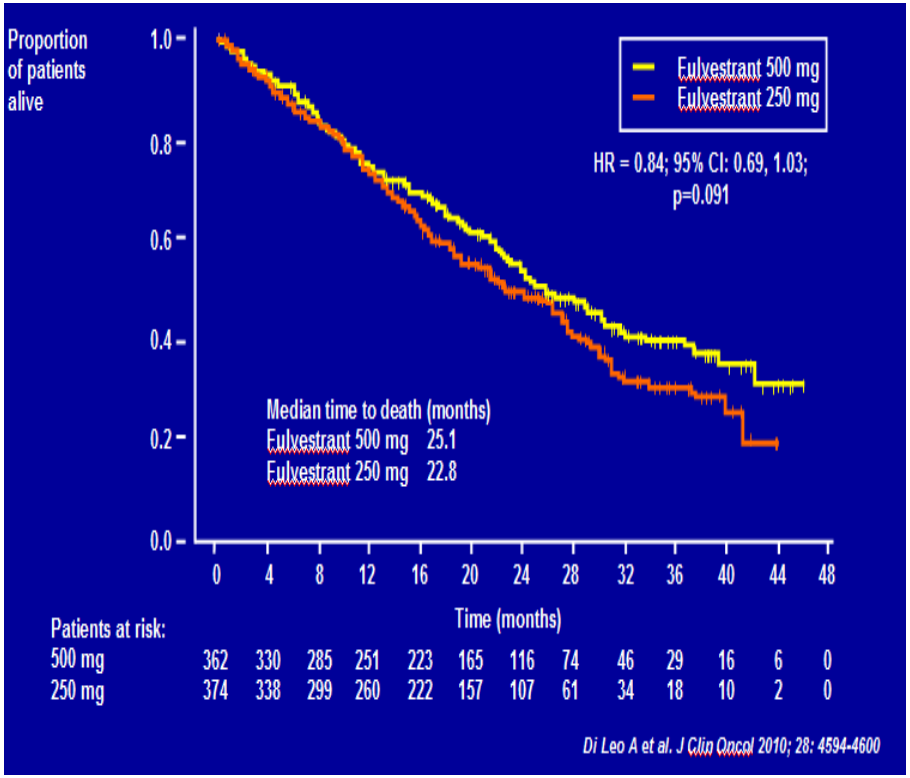
Effect on PFS of HD-Fulvestrant in pre-specified subgroups



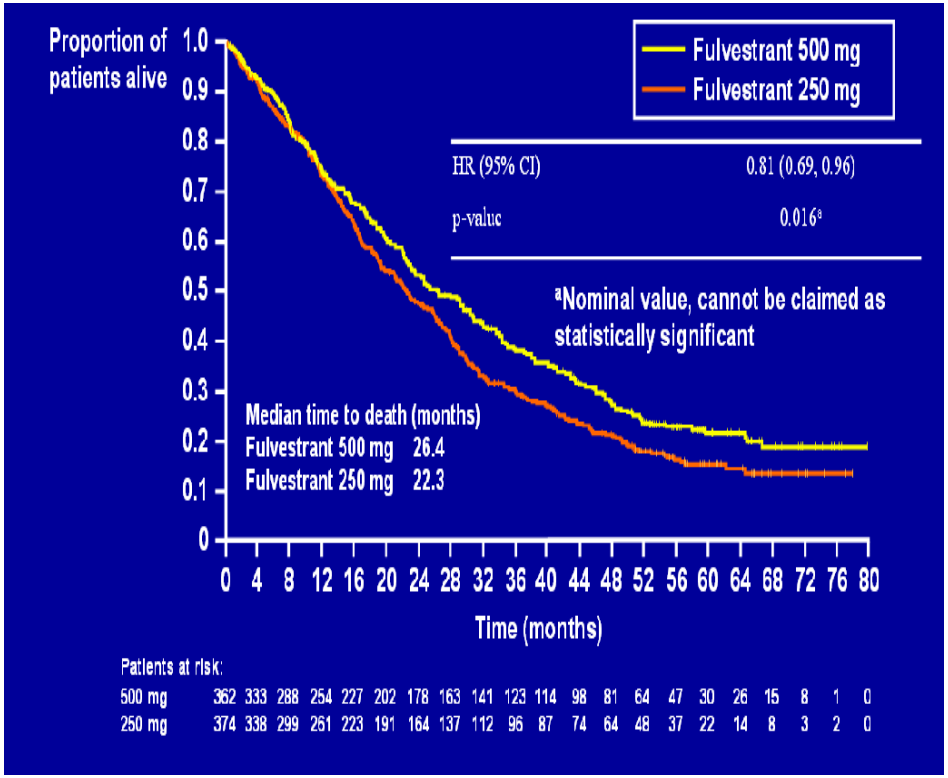
DiLeo, JCO 2010

Effect of higher Fulvestrant dose on OS first and final analyses

50% events



75% events



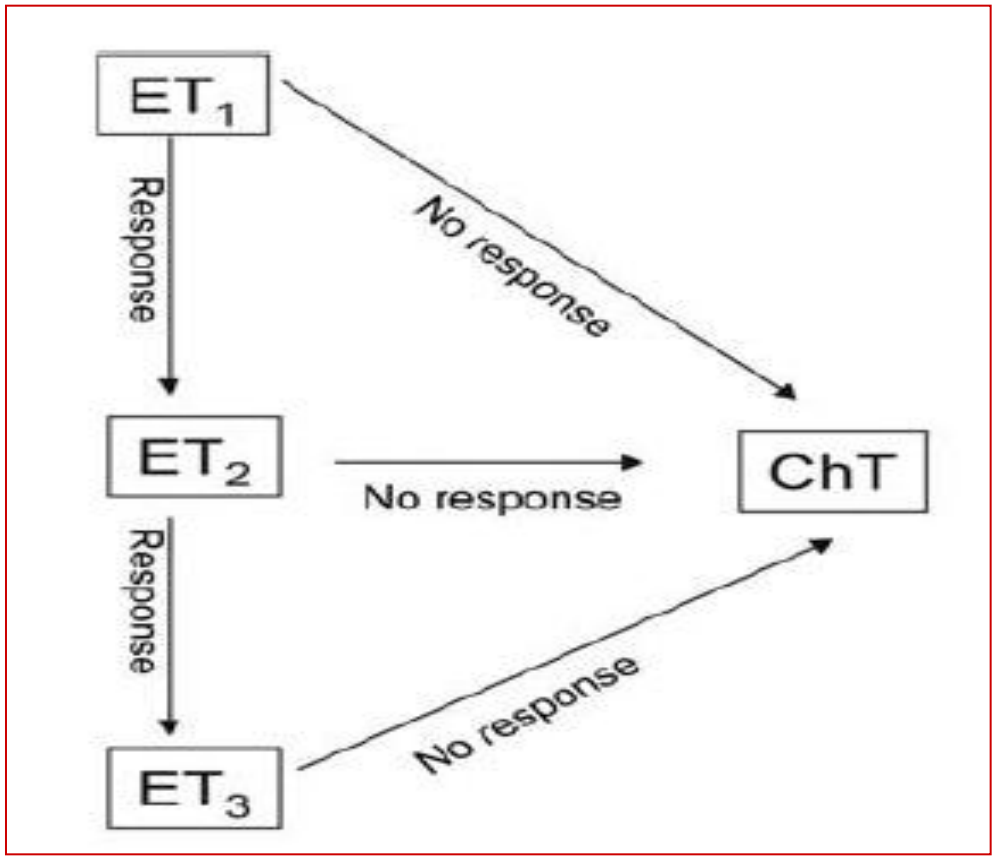
Di Leo, SABCS 2012

Main trial characteristics versus Bolero-2

	CONFIRM - FULV 500	BOLERO2 - EVE-EXA
Hormone-sensitive*	63%	84%
Last therapy with AI	42%	75%
First line	52%	16%
Second –third line	48%	84%
Visceral disease	66%	56%
Median PFS (mos)	6.5	7.4
Median PFS control arm	5.5	3.2
PFS HR vs control	0.80	0.44

* recurrence after the first 2 years on adjuvant endocrine therapy or SD > 24 weeks or RP as best response to first-line ET for advanced disease.
** recurrence > 12 months after the end of adjuvant treatment or PD > 1 month after the end of treatment for advanced disease.

Is there an optimal sequence of hormonal drugs?



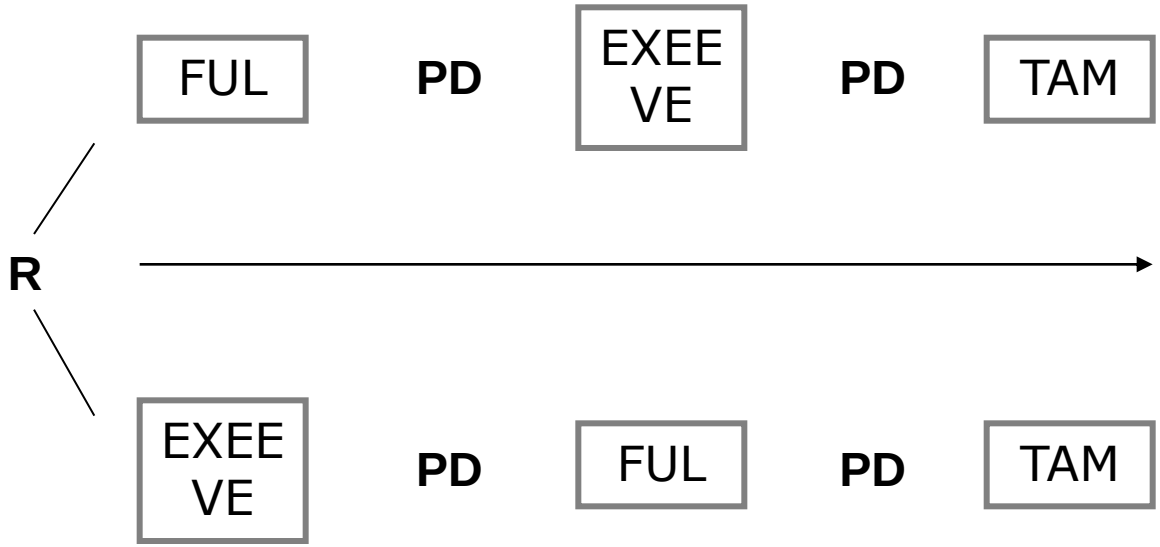
40% → 30% → 20% → 15%

First line | Second line | Third line | Fourth line

EudraCT N. 2012-001028-36

Sequenza ottimale di ormonoterapia in pazienti con carcinoma mammario metastatico ricadute dopo terapia adiuvante con inibitori delle aromatasi: studio randomizzato tra due diverse sequenze di terapia endocrina.

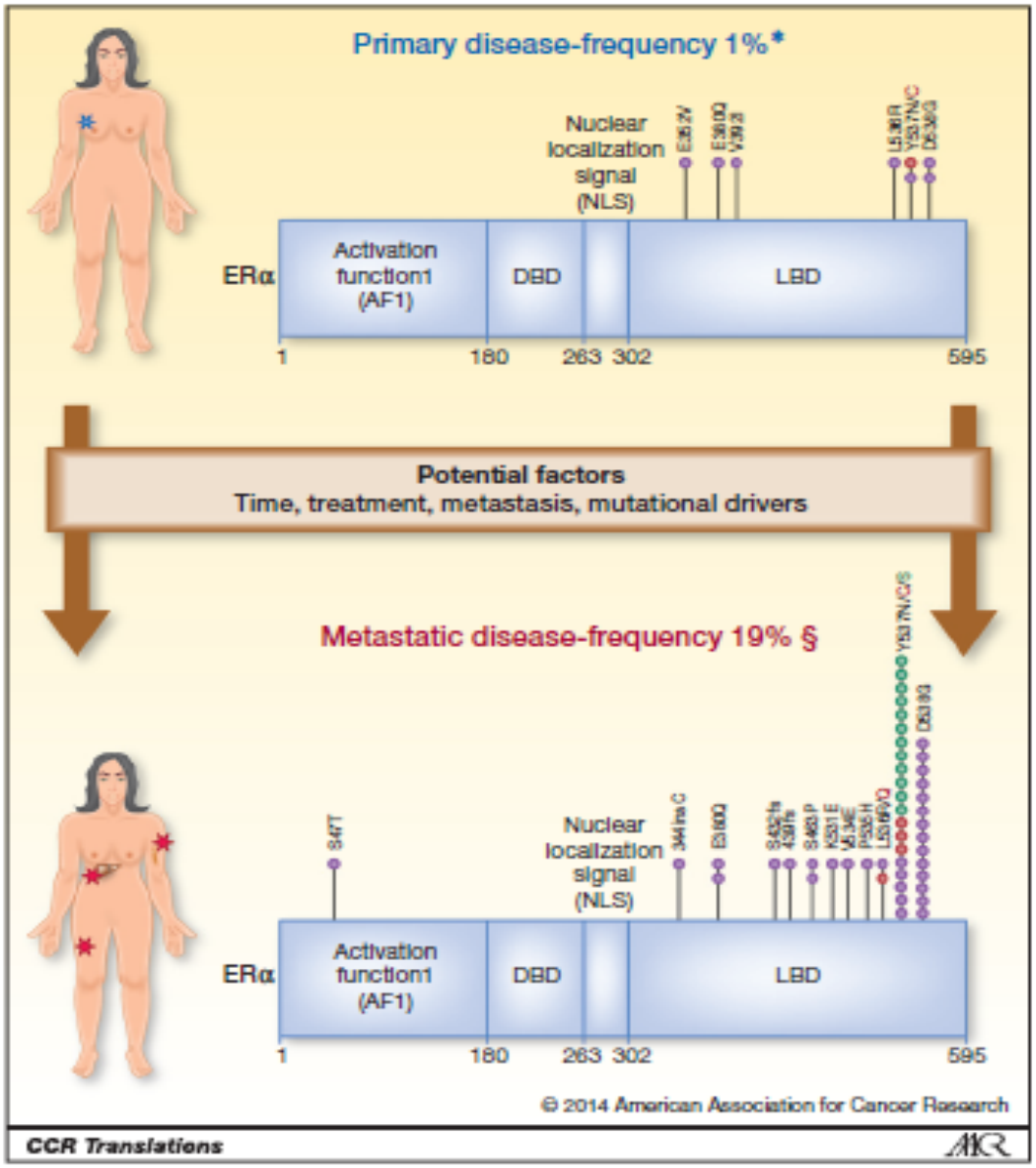
Donne in postmenopausa, affette da carcinoma della mammella metastatico ormonoresponsivo, ricadute dopo terapia adiuvante con inibitori dell'aromatasi



Endpoint primario: sopravvivenza globale libera da progressione (PFS) delle due sequenze ormonali

Endpoint secondari PFS di ciascun farmaco, tempo mediano alla progressione all'interno di ogni sequenza e per ogni agente ormonale somministrato, OS, TTC, profilo di sicurezza delle due sequenze, costo delle due sequenze

Estrogen receptor mutations



Segal, CCR 2014

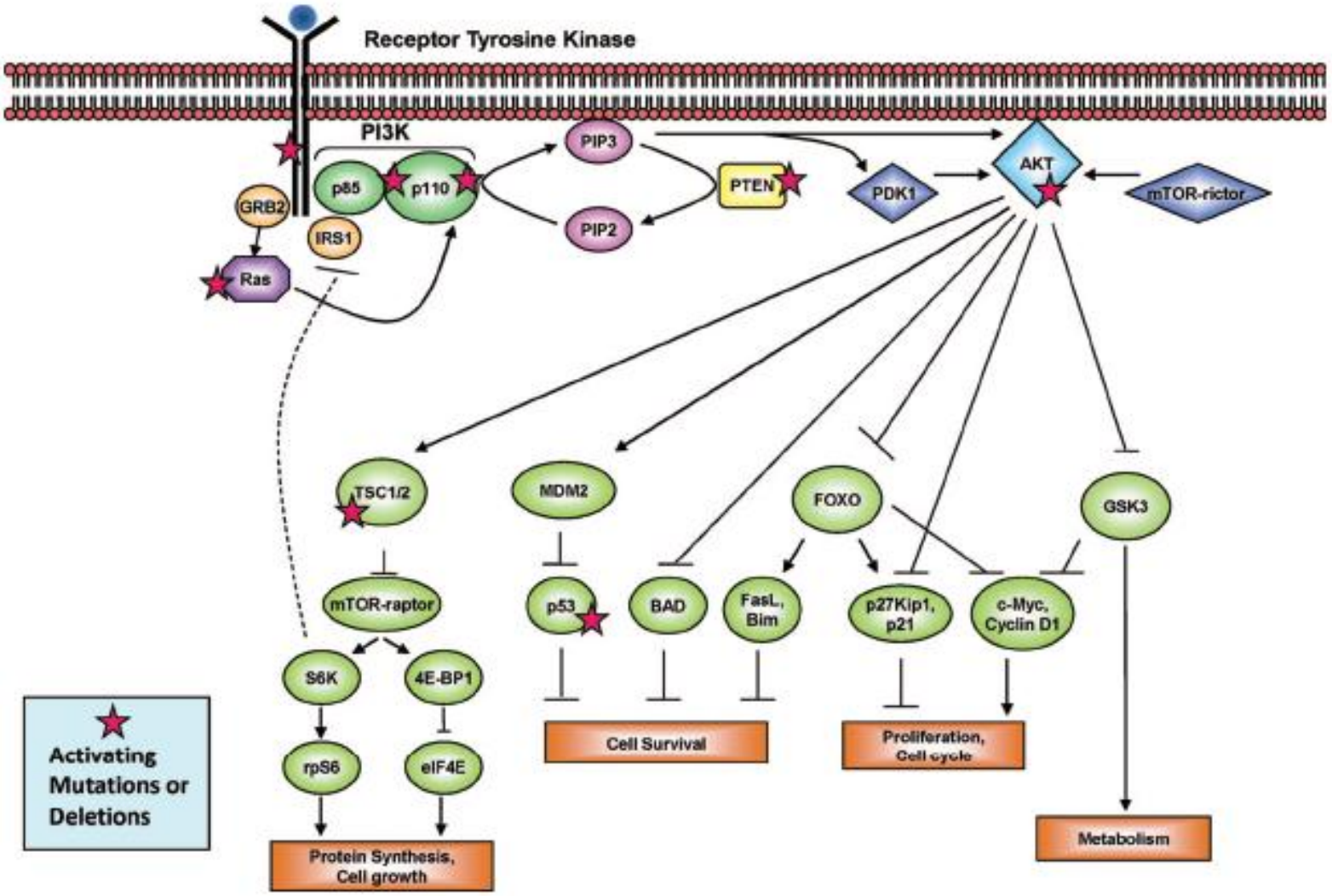
Possible therapeutic fallout of ESR1 gene alteration identication

- Ligand-binding domain mutation may be treated with higher doses of fulvestrant or alternative anti-estrogens with higher potencies, but not with estrogen deprivation (AIs)
- Gene-traslocation cannot be treated with classical endocrine therapies and require alternative therapies
- Gene-amplification could be treated with both estradiol and anti-estrogens, but not estrogen deprivation (AIs)

Shao, SABCS 2013

New strategies to overcome endocrine-resistance

PI3K pathway as a new target to overcome hormone resistance



Ongoing studies exploring combination of hormones with PIK3Ca inhibitor

BELLE-2

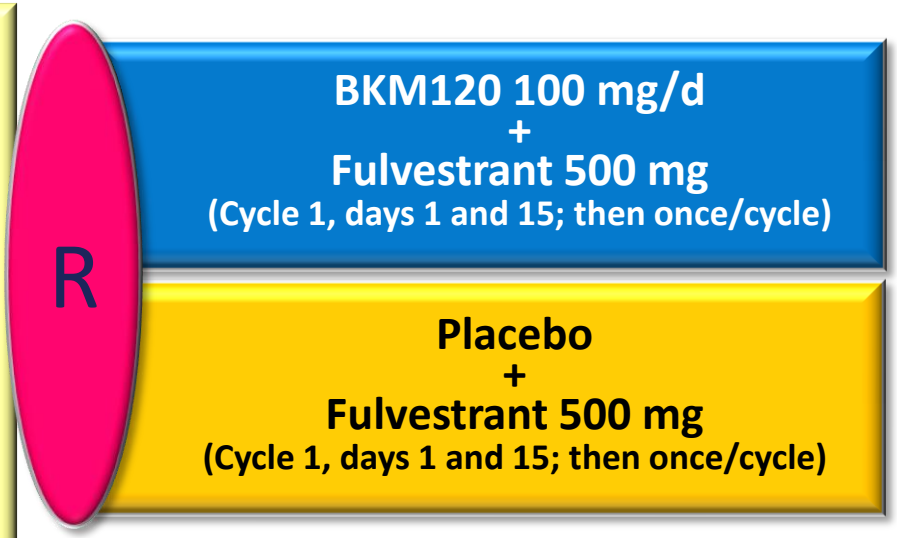
Recruiting
(N to 842)

Breast cancer
- **LA/MBC**
- **Progression on/after AIs**
- **HR$^+$**
- **HER2$^-$**
- **No brain mets**
- **No CV disease**

BELLE-3

Recruiting
(N to 615)

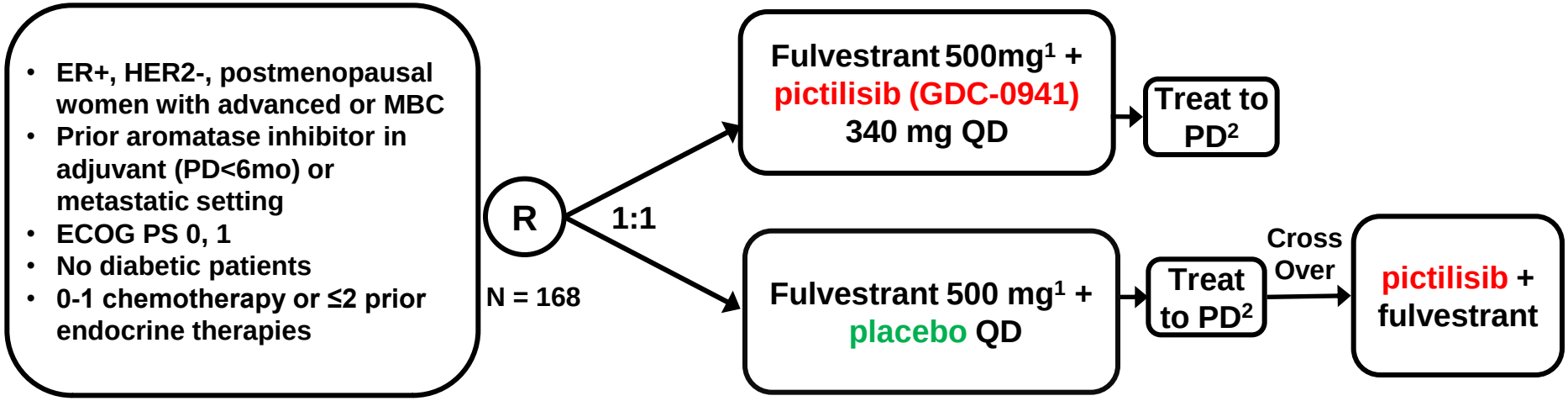
Breast cancer
- **LA/MBC**
- **Progression on/after mTORi**
- **HR$^+$**
- **HER2$^-$**
- **No brain mets**
- **No CV disease**



Key endpoints:
- Primary: PFS at 5.5 mo
- Secondary: ORR, OS, CBR, safety, biomarkers, HRQoL

FERGI Phase II Study of PI3K Inhibitor

Pictilisib plus Fulvestrant vs Fulvestrant



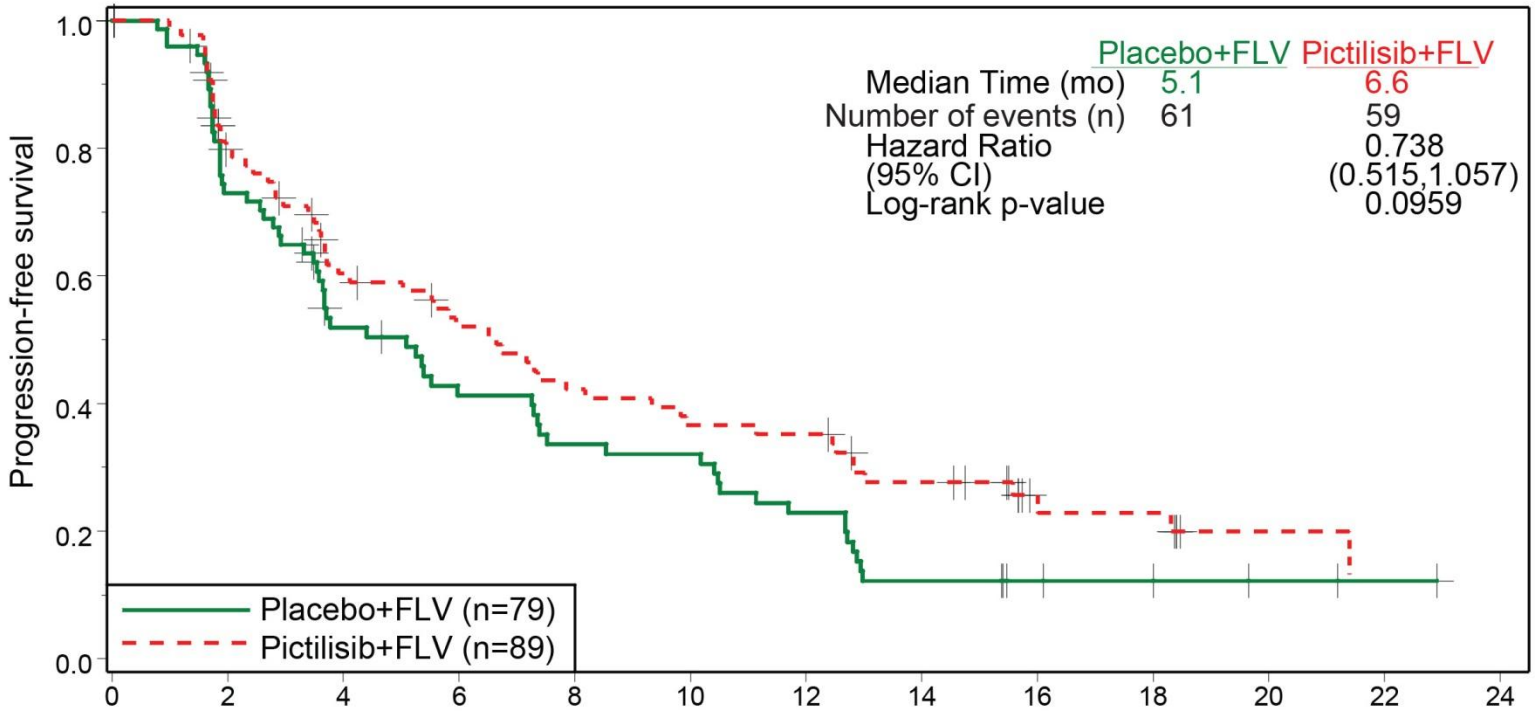
Stratification factors	1° objective	2° objectives
• *PIK3CA*-MT and *PTEN* loss[3] • Measurable disease • 1º vs. 2º resistance[4]	• PFS in the ITT • PFS in *PIK3CA*-MT pts • Safety	• Objective response rate • Duration of objective response • PK

[1] Administered on D1 of each 28 day cycle and C1D15; [2] Tumor assessments performed every 8 weeks; [3]Exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 were detected by RT-PCR; [4] Disease relapse during or within 6 months of completing AI treatment in the adjuvant setting, or disease progression within 6 months of starting AI treatment in the metastatic setting. [5] Data presented is with an additional year of follow up per-protocol primary analysis

- **Median duration of follow up 17.5 months**
- **About 40% PIK3Ca mutated**
- **50% secondary resistance**

Krop, SABCS 2014

Progression-Free Survival in the ITT Population



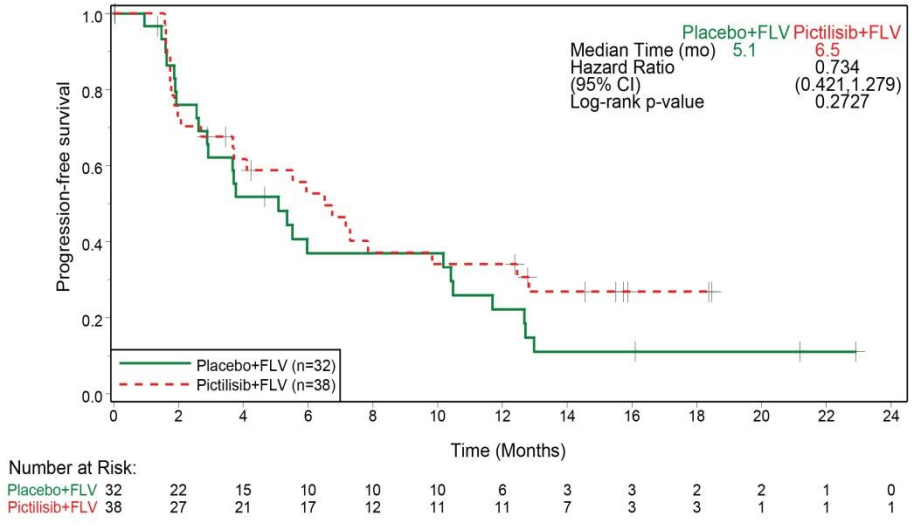
Number at Risk:

Placebo+FLV	79	54	35	27	22	21	15	8	5	4	2	1	0
Pictilisib+FLV	89	63	45	37	30	26	25	18	9	8	3	2	2

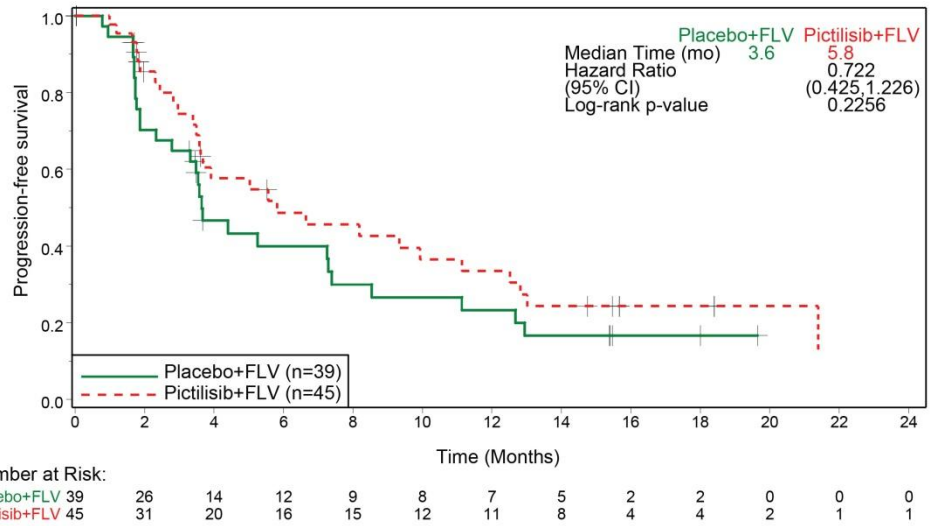
Krop, SABCS 2014

Progression-Free Survival Based on Tumor *PIK3CA* Mutation Status

***PIK3CA*-Mutant Population**



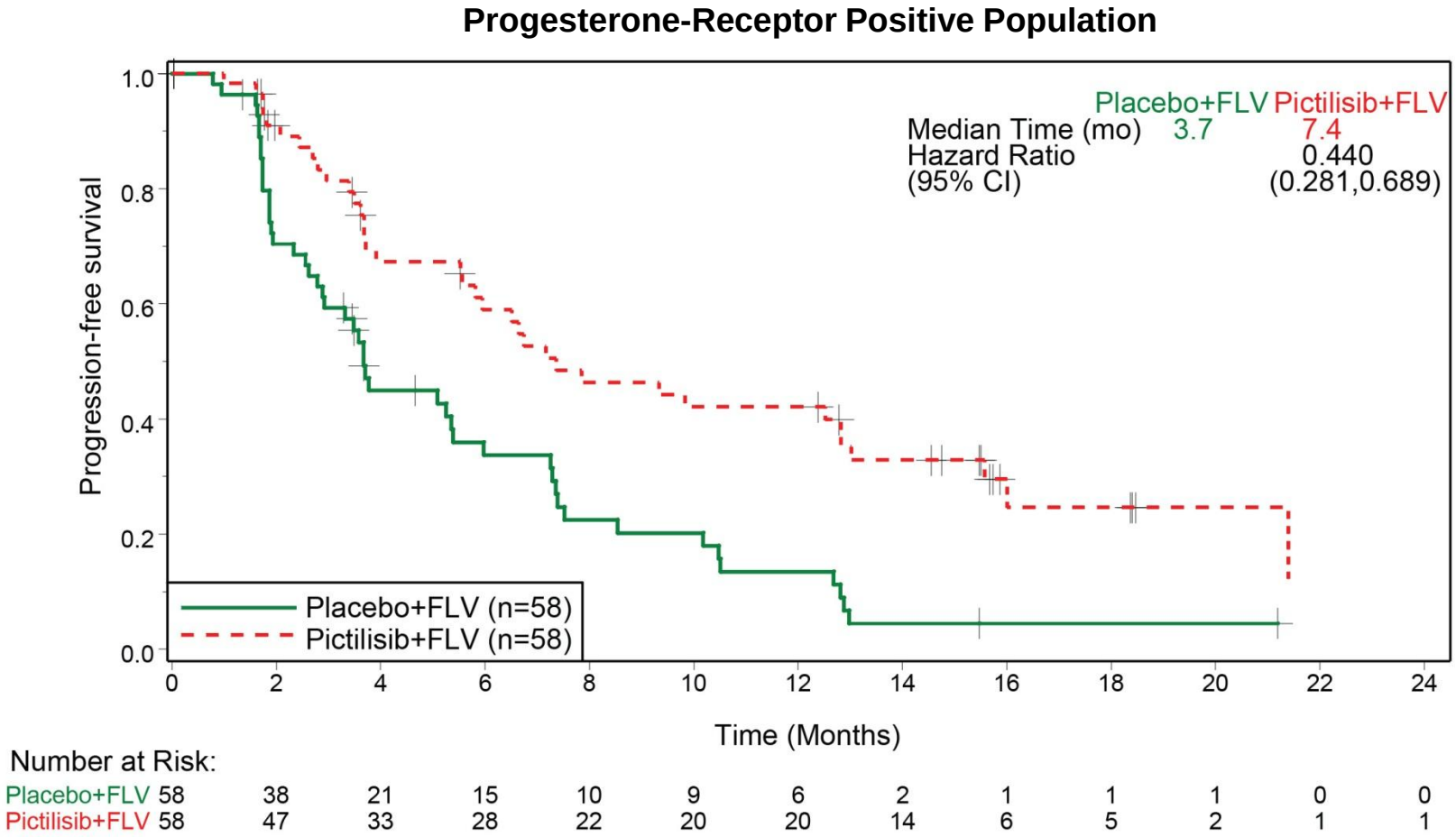
***PIK3CA* "Wild-Type" Population**



- **PIK3CA mutation status does not predict benefit of the addition of pictilisib to fulvestrant, even if numerically higher responses observed in PIK3CA mut with pictilisib**

Krop, SABCS 2014

Progression-Free Survival in Patients with ER and PR Positive Disease

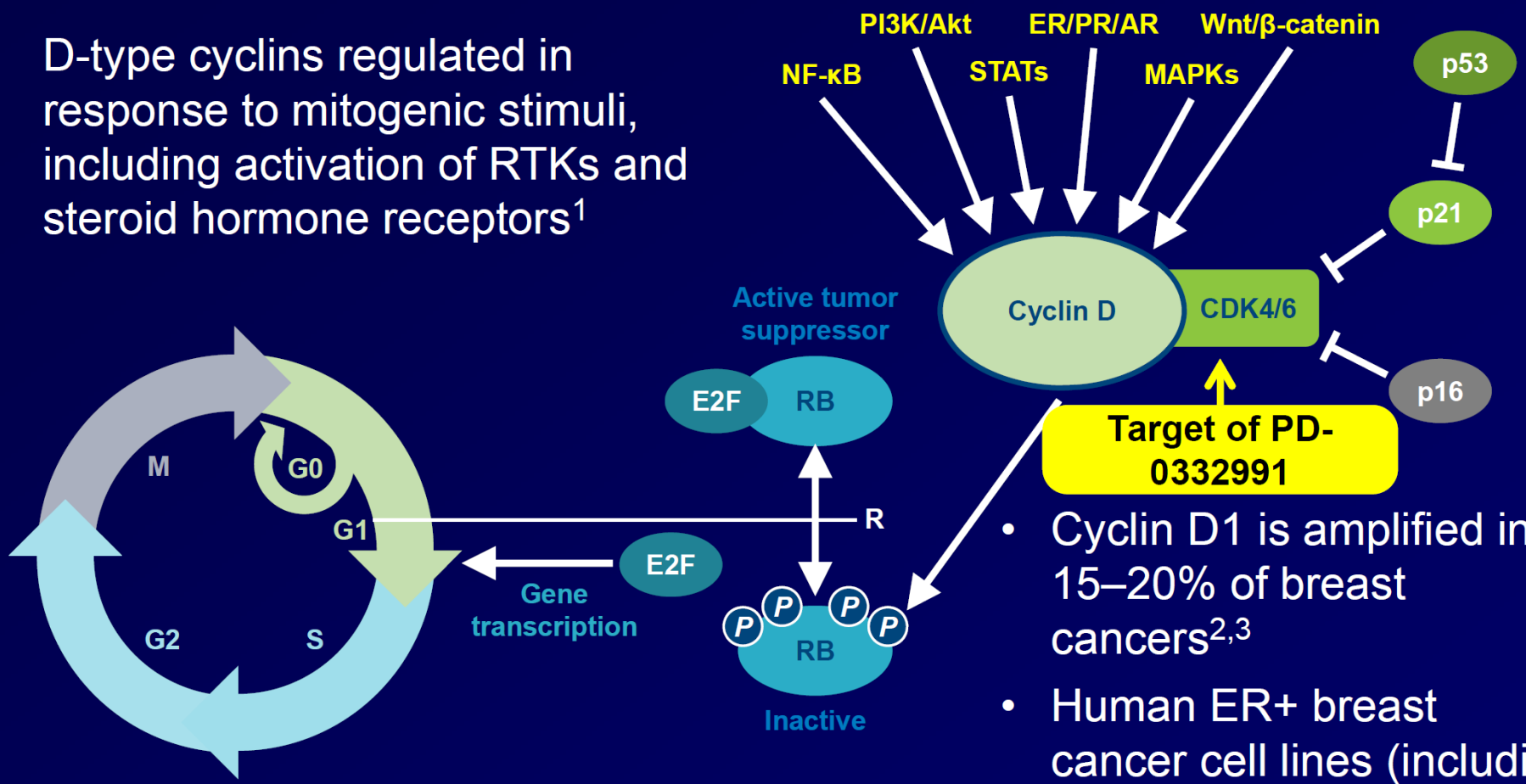


No difference according to the PIK3CA status

Krop, SABCS 2014

Regulation of the G1/S Checkpoint in Breast Cancer

D-type cyclins regulated in response to mitogenic stimuli, including activation of RTKs and steroid hormone receptors[1]

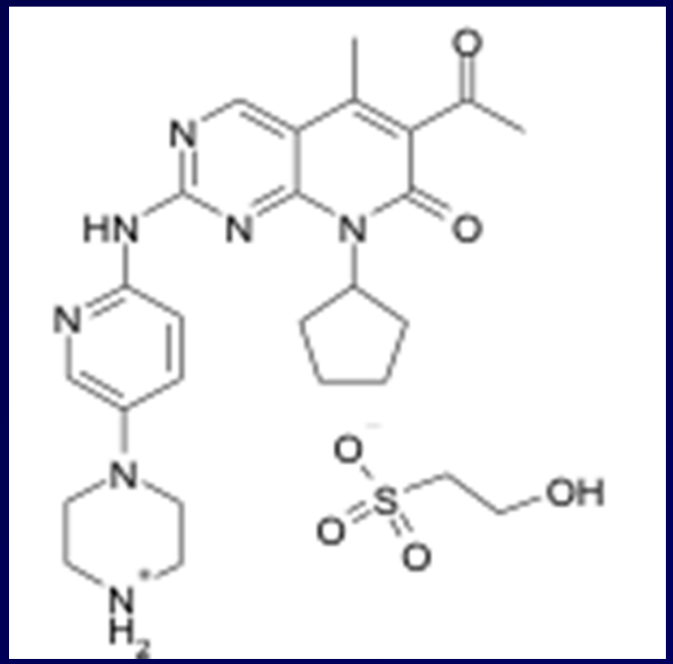


- Cyclin D1 is amplified in 15–20% of breast cancers[2,3]
- Human ER+ breast cancer cell lines (including those with HER2 amplification) sensitive to G0/G1 arrest[4]

Lange et al. Endocrine-Related Cancer 2011;18:C19–C24; [1]Caldon CE, et al. J Cell Biochem 2006;97:261–274; [2]Buckley MF, et al. Oncogene 1993;8:2127–2133; [3]Dickson C, et al. Cancer Lett 1995;90:43–50; [4]Finn RS, et al. Breast Cancer Res 2009;11:R77

PD-0332991 (Palbociclib): a CDK 4/6 Inhibitor

- Oral, highly selective inhibitor of Cdk4/6
- Prevents cell-cycle progression from G1 to S phase
  - Inhibiting cell proliferation and cellular DNA synthesis
- *In vitro* activity in Rb-positive tumor cell lines and primary tumors

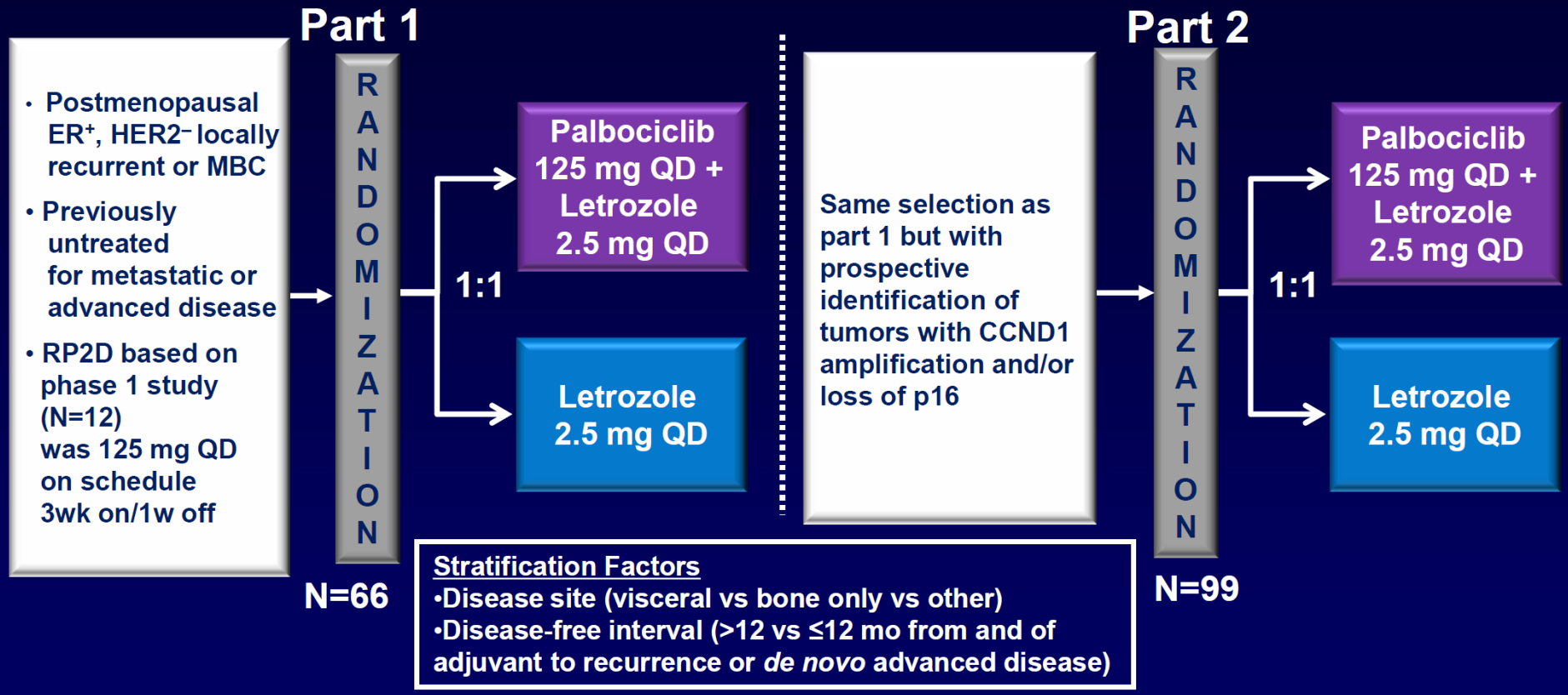


PD-0332991

- Low nanomolar concentrations block Rb phosphorylation, inducing G1 arrest in sensitive cell lines
- Inhibits proliferation in cultured and xenografted leukemia, myeloma, breast cancer, colon cancer, and lung cancer cells

Fry DW, et al. Mol Cancer Ther 2004;3:1427
Menu E, et al. Cancer Res 2008;68:5519
Sutherland RL, Musgrove EA. Breast Cancer Res 2009;11:112

PALOMA-1/TRIO-18 (Phase 2): Palbociclib (PD0332991) + LET vs LET, 1st-line ER$^+$, HER2$^-$ ABC



Endpoints
Primary: Progression-free survival
Secondary: Antitumor activity, OS, PRO of pain, biomarkers, safety

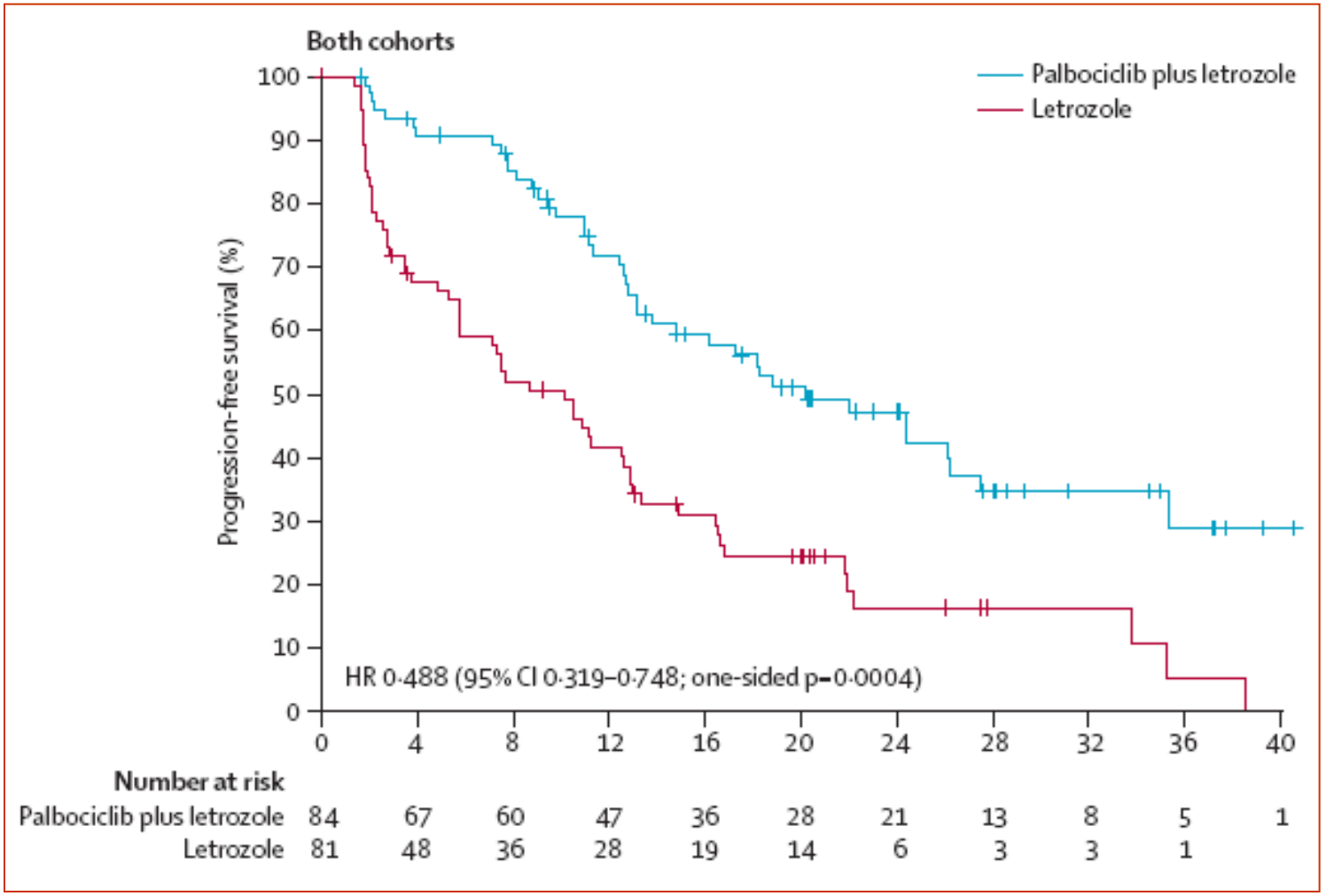
Finn RS, et al. SABCS 2012; Abstract S1-6.

Patient characteristics

	Both cohorts		Cohort 1		Cohort 2	
	Palbociclib plus letrozole (n=84)	Letrozole (n=81)	Palbociclib plus letrozole (n=34)	Letrozole (n=32)	Palbociclib plus letrozole (n=50)	Letrozole (n=49)
Median age (years)	63 (54–71)	64 (56–70)	66 (56–72)	64 (57–70)	62 (54–70)	63 (56–71)
ECOG performance status						
0	46 (55%)	45 (56%)	23 (68%)	20 (63%)	23 (46%)	25 (51%)
1	38 (45%)	36 (44%)	11 (32%)	12 (38%)	27 (54%)	24 (49%)
Disease stage						
III	2 (2%)	1 (1%)	2 (6%)	0	0	1 (2%)
IV	82 (98%)	80 (99%)	32 (94%)	32 (100%)	50 (100%)	48 (98%)
Disease site*						
Visceral	37 (44%)	43 (53%)	10 (29%)	11 (34%)	27 (54%)	32 (65%)
Bone only	17 (20%)	12 (15%)	7 (21%)	6 (19%)	10 (20%)	6 (12%)
Other (non-visceral)	30 (36%)	26 (32%)	17 (50%)	15 (47%)	13 (26%)	11 (23%)
Disease-free interval*						
>12 months from adjuvant treatment to recurrence	25 (30%)	30 (37%)	10 (29%)	10 (31%)	15 (30%)	20 (41%)
≤12 months from adjuvant treatment to recurrence or de-novo advanced disease	59 (70%)	51 (63%)	24 (71%)	22 (69%)	35 (70%)	29 (59%)
De-novo advanced disease only	44 (52%)	37 (46%)	19 (56%)	17 (53%)	25 (50%)	20 (41%)
Previous systemic treatment						
None	44 (52%)	37 (46%)	19 (56%)	17 (53%)	25 (50%)	20 (41%)
Chemotherapy	34 (40%)	37 (46%)	11 (32%)	14 (44%)	23 (46%)	23 (47%)
Hormonal	27 (32%)	28 (35%)	11 (32%)	11 (34%)	16 (32%)	17 (35%)
Tamoxifen	24 (29%)	24 (30%)	8 (24%)	8 (25%)	16 (32%)	16 (33%)
Anastrozole	8 (10%)	11 (14%)	4 (12%)	5 (16%)	4 (8%)	6 (12%)
Letrozole	2 (2%)	1 (1%)	0	0	2 (4%)	1 (2%)
Exemestane	4 (5%)	2 (2%)	3 (9%)	1 (3%)	1 (2%)	1 (2%)

Finn RS, Lancet Oncol 2015

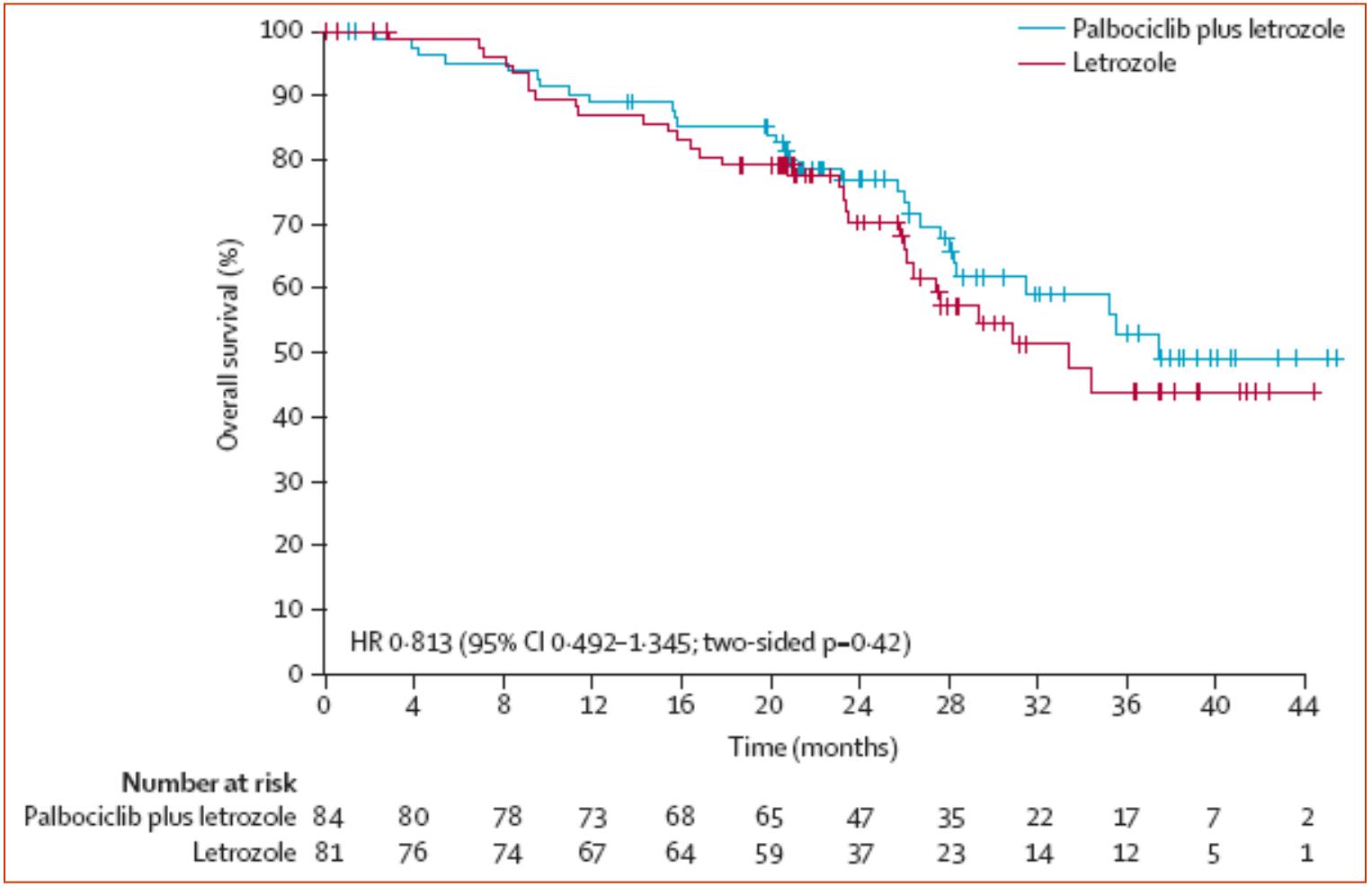
Palbociclib increased PFS



Median PFS was 20·2 months for the palbociclib plus letrozole group and 10·2 months for letrozole

Finn RS, Lancet Oncol 2015

Palbociclib did not increase OS



Median OS was 37·5 months in the palbociclib plus letrozole group and 33·3 months in the letrozole group

Finn RS, Lancet Oncol 2015

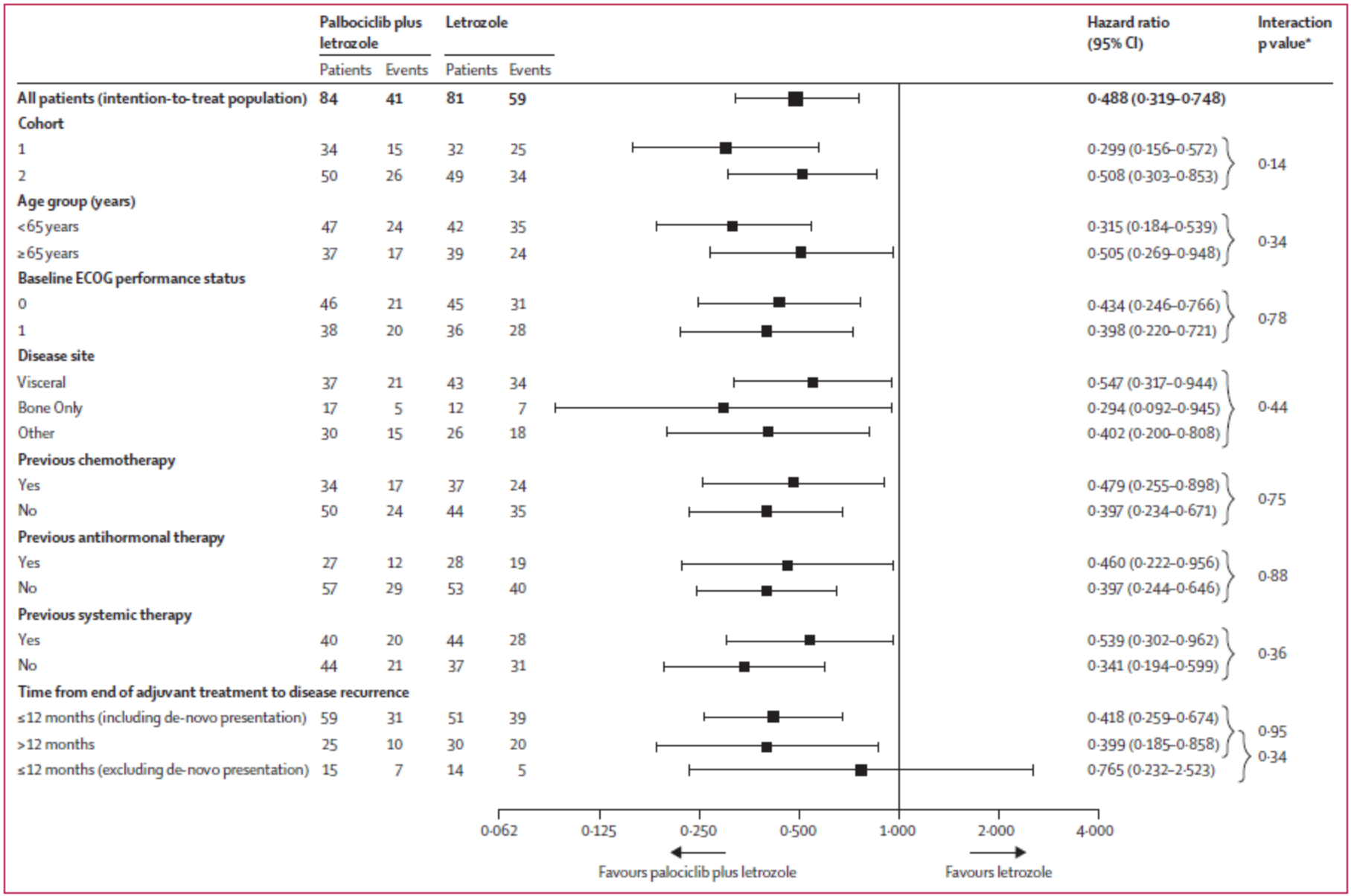


Figure 3: **Subgroup analysis for progression-free survival**
ECOG=Eastern Cooperative Oncology Group. *Two-sided p value.

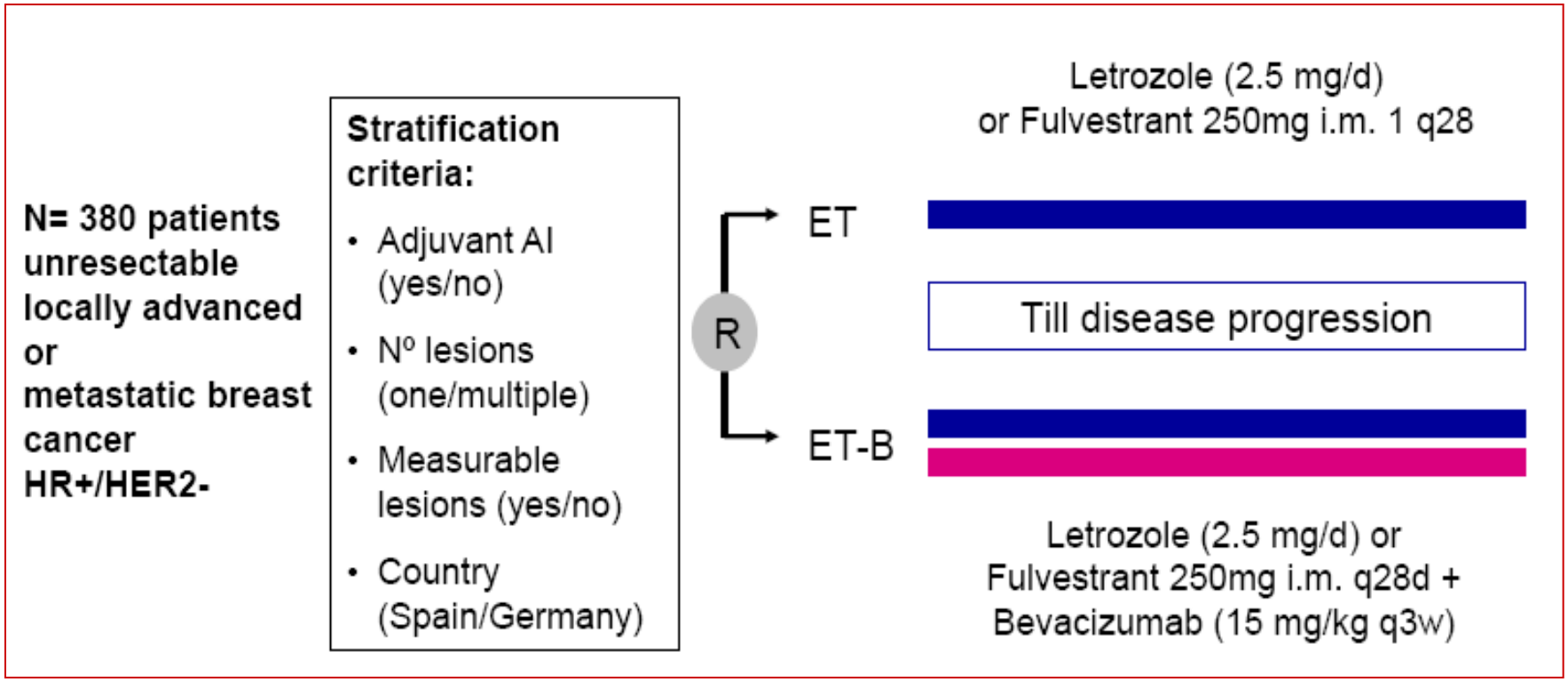
Safety profile of palbociclib

	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0
Fatigue	30 (36%)	2 (2%)	2 (2%)	17 (22%)	1 (1%)	0
Anaemia	24 (29%)	4 (5%)	1 (1%)	4 (5%)	1 (1%)	0
Nausea	19 (23%)	2 (2%)	0	9 (12%)	1 (1%)	0
Arthralgia	18 (22%)	1 (1%)	0	10 (13%)	2 (3%)	0
Alopecia	18 (22%)	NA	NA	2 (3%)	NA	NA
Diarrhoea	14 (17%)	3 (4%)	0	8 (10%)	0	0
Hot flush	17 (21%)	0	NA	9 (12%)	0	NA
Thrombocytopenia	12 (14%)	2 (2%)	0	1 (1%)	0	0
Decreased appetite	12 (14%)	1 (1%)	0	5 (6%)	0	0
Dyspnoea	11 (13%)	2 (2%)	0	5 (6%)	1 (1%)	0
Nasopharyngitis	13 (16%)	0	0	8 (10%)	0	0
Back pain	11 (13%)	0	1 (1%)	11 (14%)	1 (1%)	0
Headache	12 (14%)	0	0	8 (10%)	0	0
Vomiting	12 (14%)	0	0	2 (3%)	1 (1%)	0
Asthenia	9 (11%)	2 (2%)	0	3 (4%)	0	0
Bone pain	8 (10%)	1 (1%)	1 (1%)	3 (4%)	0	0
Constipation	10 (12%)	0	0	7 (9%)	0	0
Cough	10 (12%)	0	0	8 (10%)	0	0
Stomatitis	10 (12%)	0	0	2 (3%)	0	0
Epistaxis	9 (11%)	0	0	1 (1%)	0	0
Influenza	8 (10%)	1 (1%)	0	1 (1%)	0	0
Musculoskeletal pain	8 (10%)	1 (1%)	0	5 (6%)	0	0
Upper respiratory tract infection	8 (10%)	1 (1%)	0	2 (3%)	0	0
Dizziness	8 (10%)	0	0	3 (4%)	0	0
Peripheral neuropathy	8 (10%)	0	0	4 (5%)	0	0
Oropharyngeal pain	8 (10%)	0	0	1 (1%)	0	0
Pain in extremity	8 (10%)	0	0	6 (8%)	0	0

Hormonal therapy for ER+/HER2- ABC Summary

- **Should we treat ER+/HER2- ABC with hormones as first option?**
  - YES, provided that response is not a compelling endpoint
- **Could we use fulvestrant as first line instead of AI?**
  - YES, it can be an option in case of long (>1yr) DFI after AI or TAM, or in untreated pts (but not licensed for this pts)
- **Could we use exemestane-everolimus as first line?**
  - YES, but it can be an option only in patients treated with AI and relapsing within 12 months
- **Should we use exemestane-everolimus or HD-Fulvestrant as second line after NSAI?**
  - Both strategies can be used, considering patient charcteristics and benefit & harms of therapies (but we lack direct comparison)

Hormone plus bevacizumab



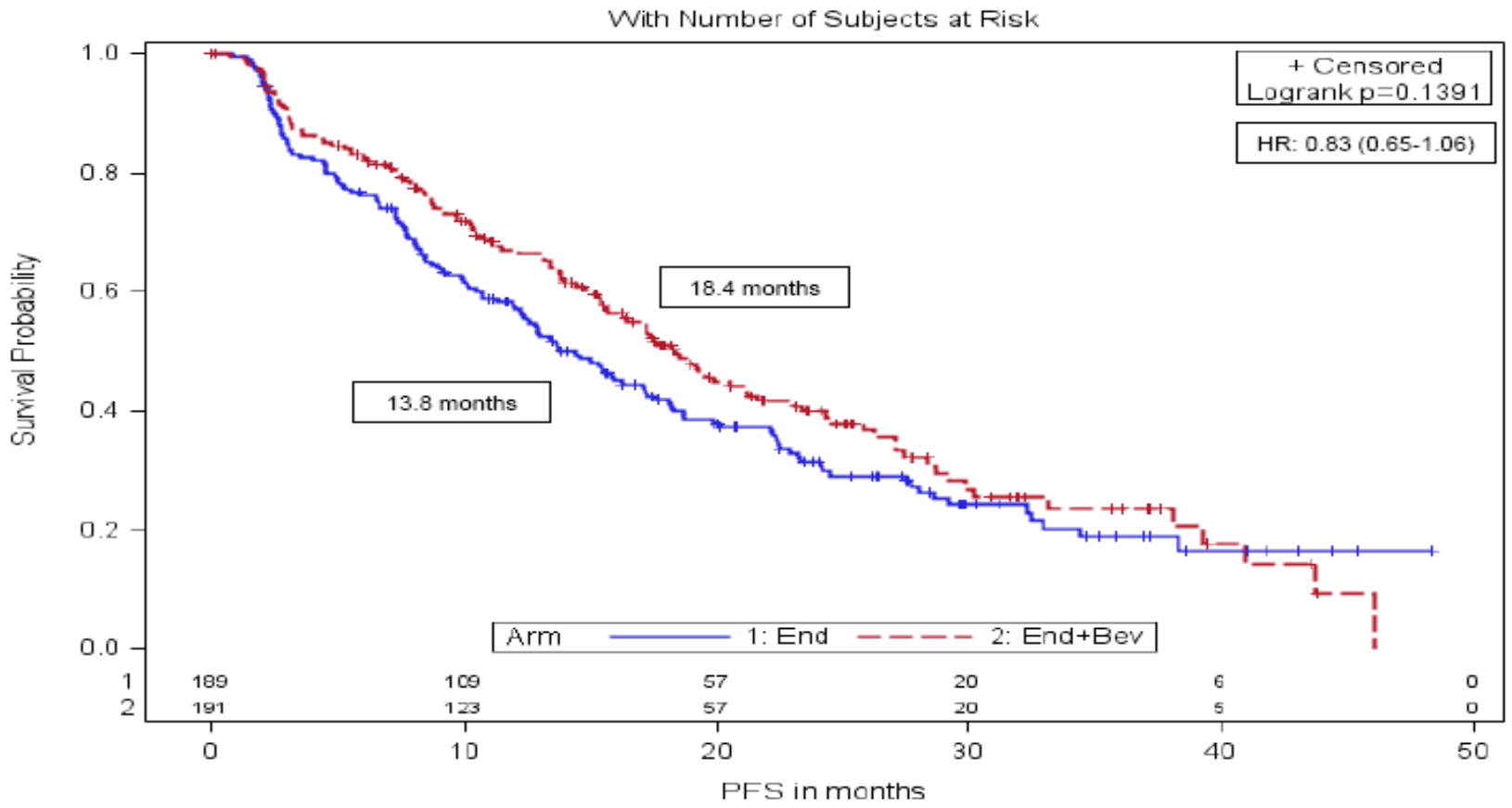
Primary Endpoint: **PFS**

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

Letrozole 90%, Fulvestrant 10%)

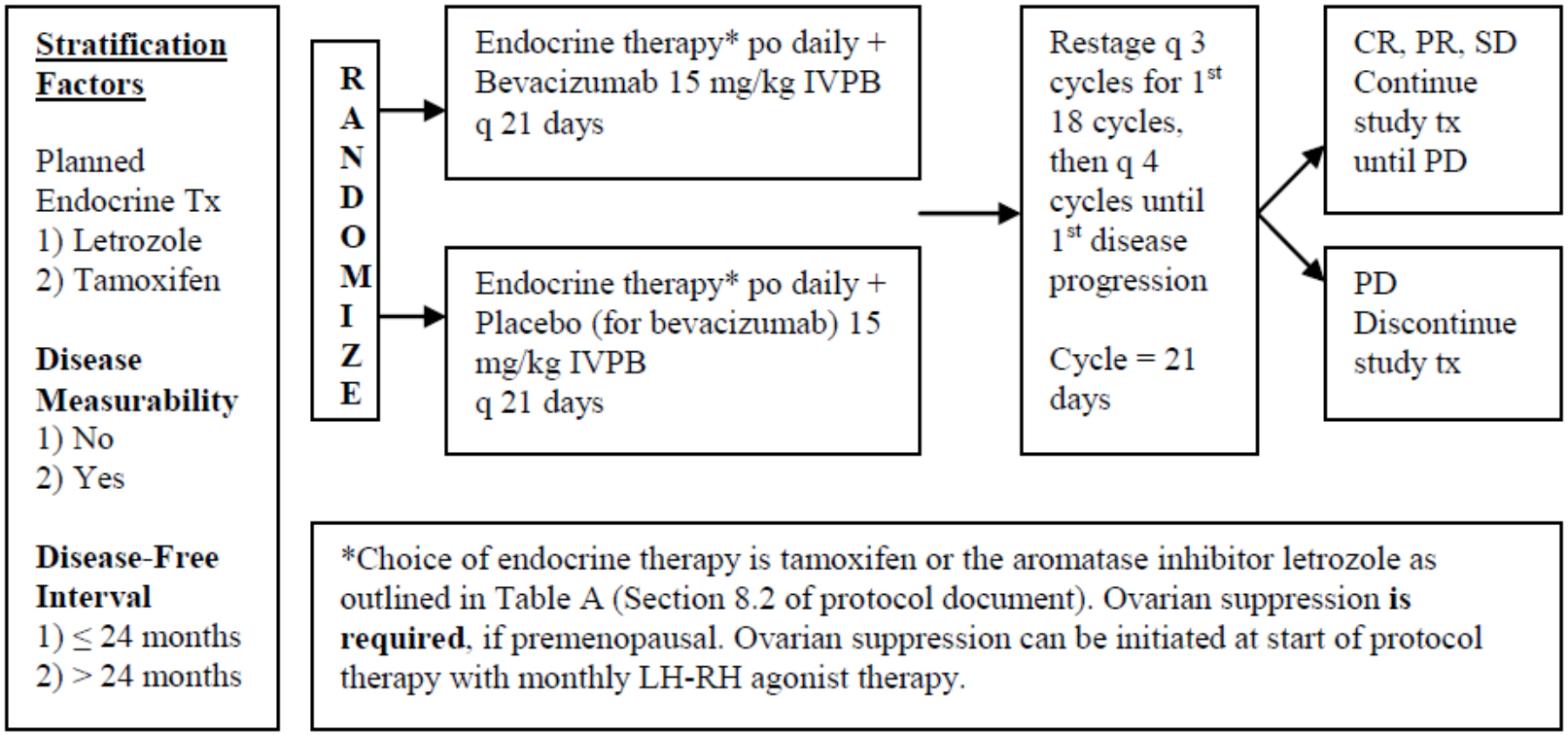
Martin, SABCS 2012

Progression Free Survival



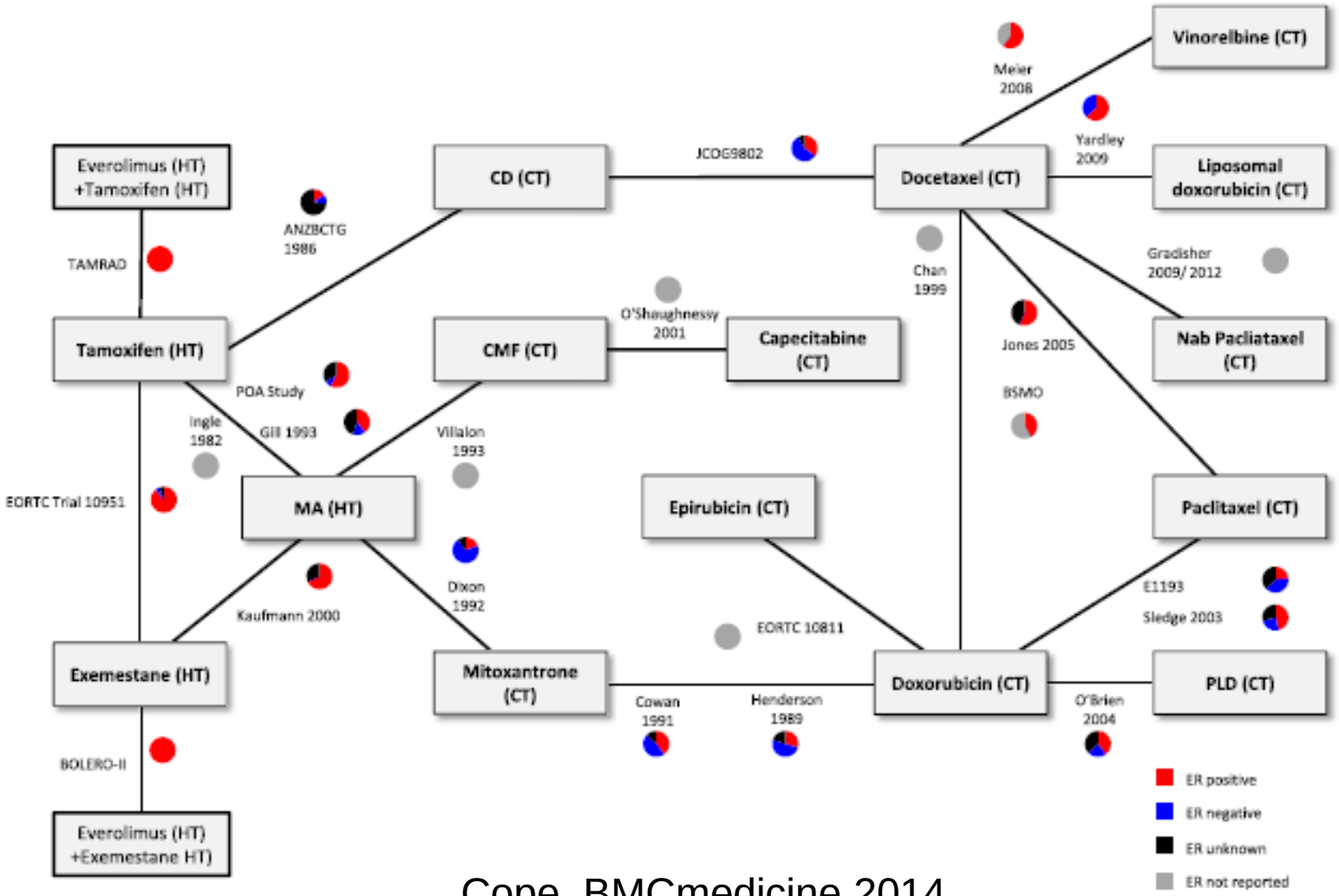
Median Overall Survival: 42 vs 41 mos. HR:1.18

Phase III CALGB 40503 trial
Endocrine therapy ± Bevacizumab



ACTIVATED May 15, 2008
ENROLLMENT 502 patients
CLOSED

Examestane-everolimus or Chemotherapy ?



Cope, BMCmedicine 2014