Optimizing therapy selection in ER[+] HER2[-] Advanced Breast Cancer

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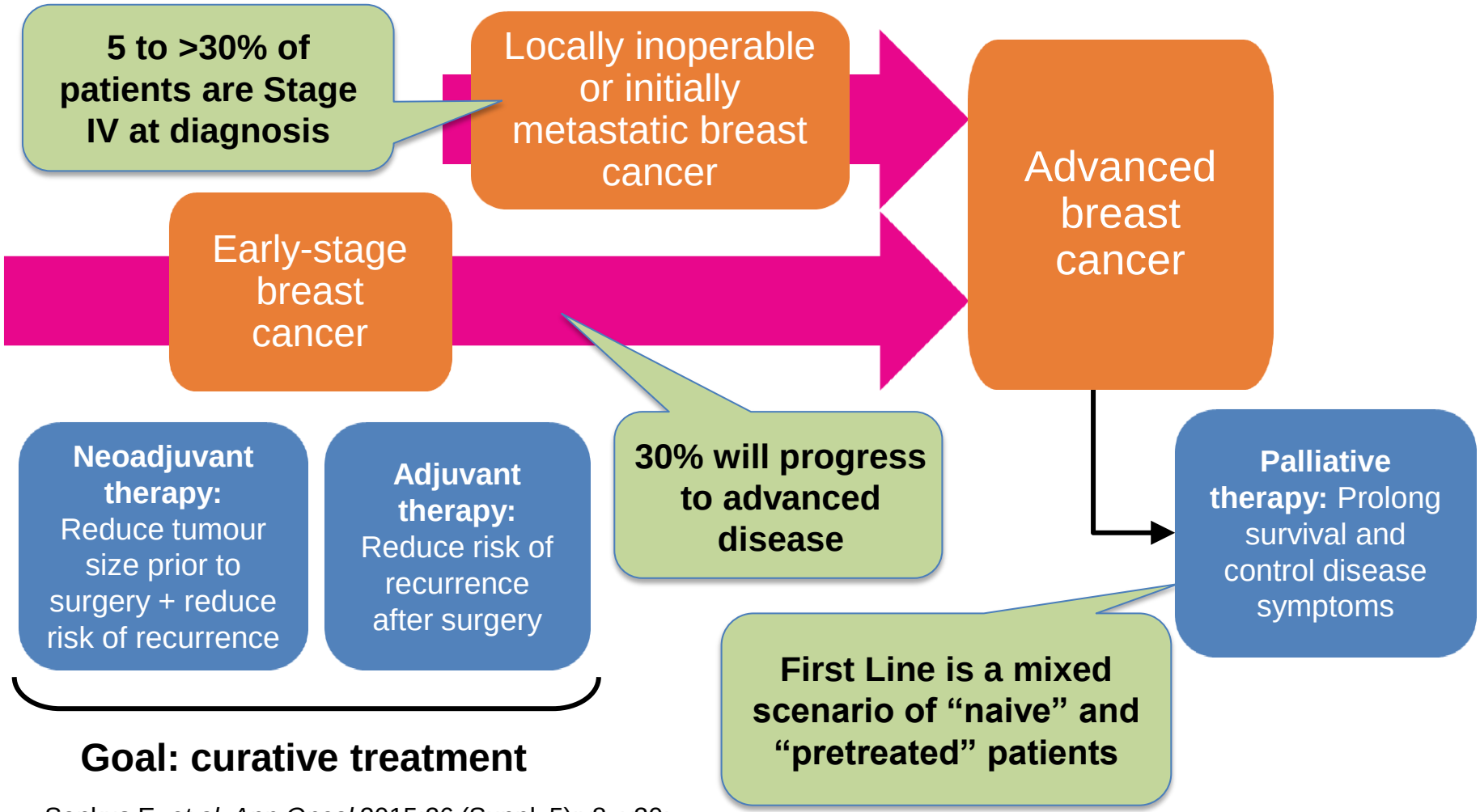
P2016-0585[20180426]-V1.0C

Evolution of Breast Cancer Treatment



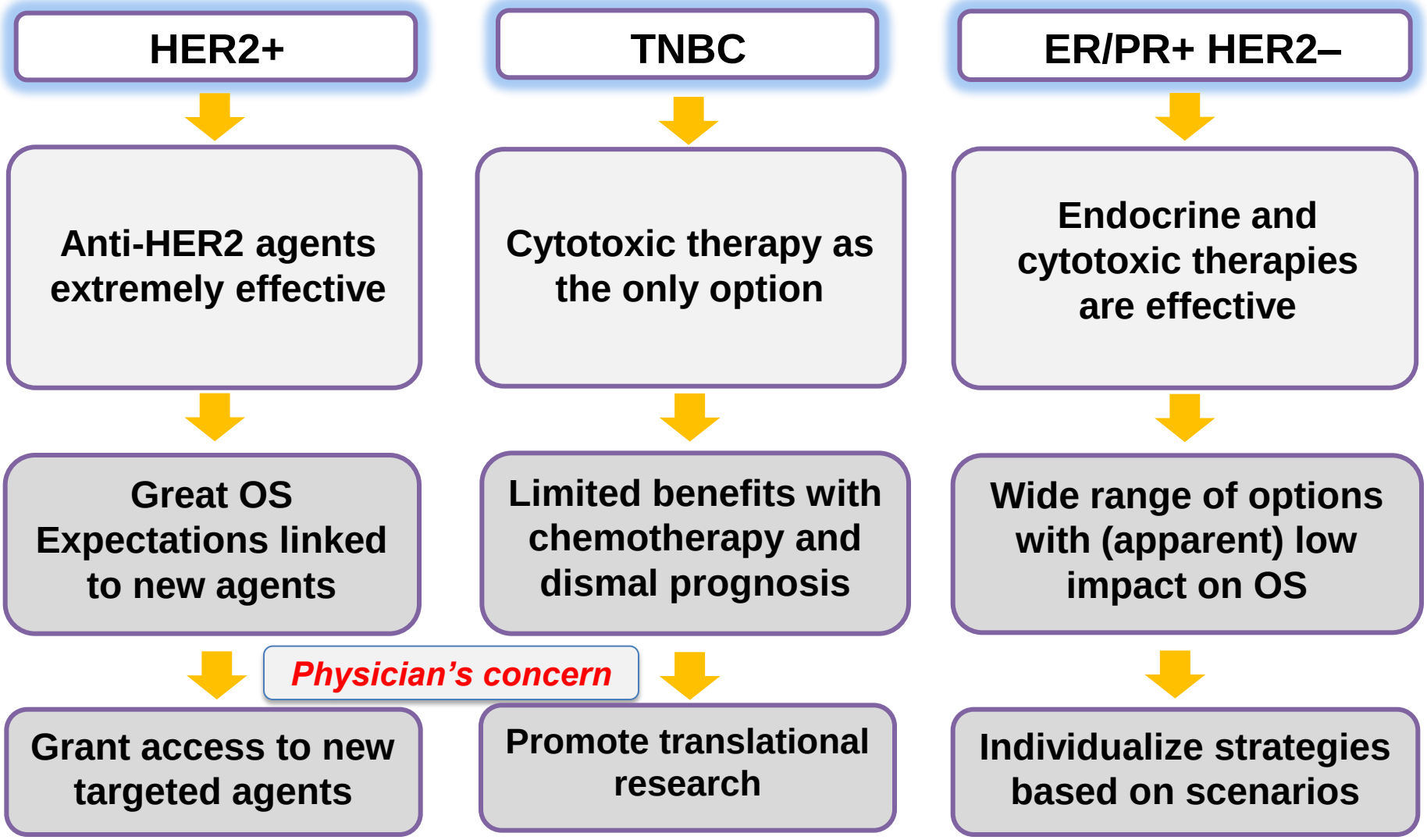
Senkus E, *et al. Ann Oncol* 2015;26 (Suppl. 5):v8–v30;
O'Shaughnessy J. *Oncologist* 2005;10 Suppl. 3:20–29;
Cardoso F, *et al. The Breast* 2014;23:489–502.

Goals in the Treatment of MBC ESMO/NCCN Guidelines

- Metastatic breast cancer is incurable yet treatable
- Treatment aims:
  - Maintain or improve quality of life
  - Delay disease progression
  - Control disease symptoms
- Treatment decision guided by tumour phenotype
- A large number of active agents – combinations, but standard management still debatable
- Appropriate management supports goal of improving survival

Cardoso F, *et al. The Breast* 2014;23:489–502;
NCCN Guidelines: Breast Cancer. Version 3.2015.

In 2015 Molecular Phenotypes Drive Treatment Algorithms for ABC



International Treatment Guidelines Emphasise Endocrine Therapy for HR+/HER2– ABC

ASCO recommendations[1]

Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for patients with hormone receptor–positive advanced/metastatic breast cancer, except for immediately life threatening disease or if there is concern regarding endocrine resistance.

- ***The <u>main benefit is less toxicity and better quality of life</u> for the patient associated with endocrine therapy compared with ch*** is no

E

ES ***EH*** disease or

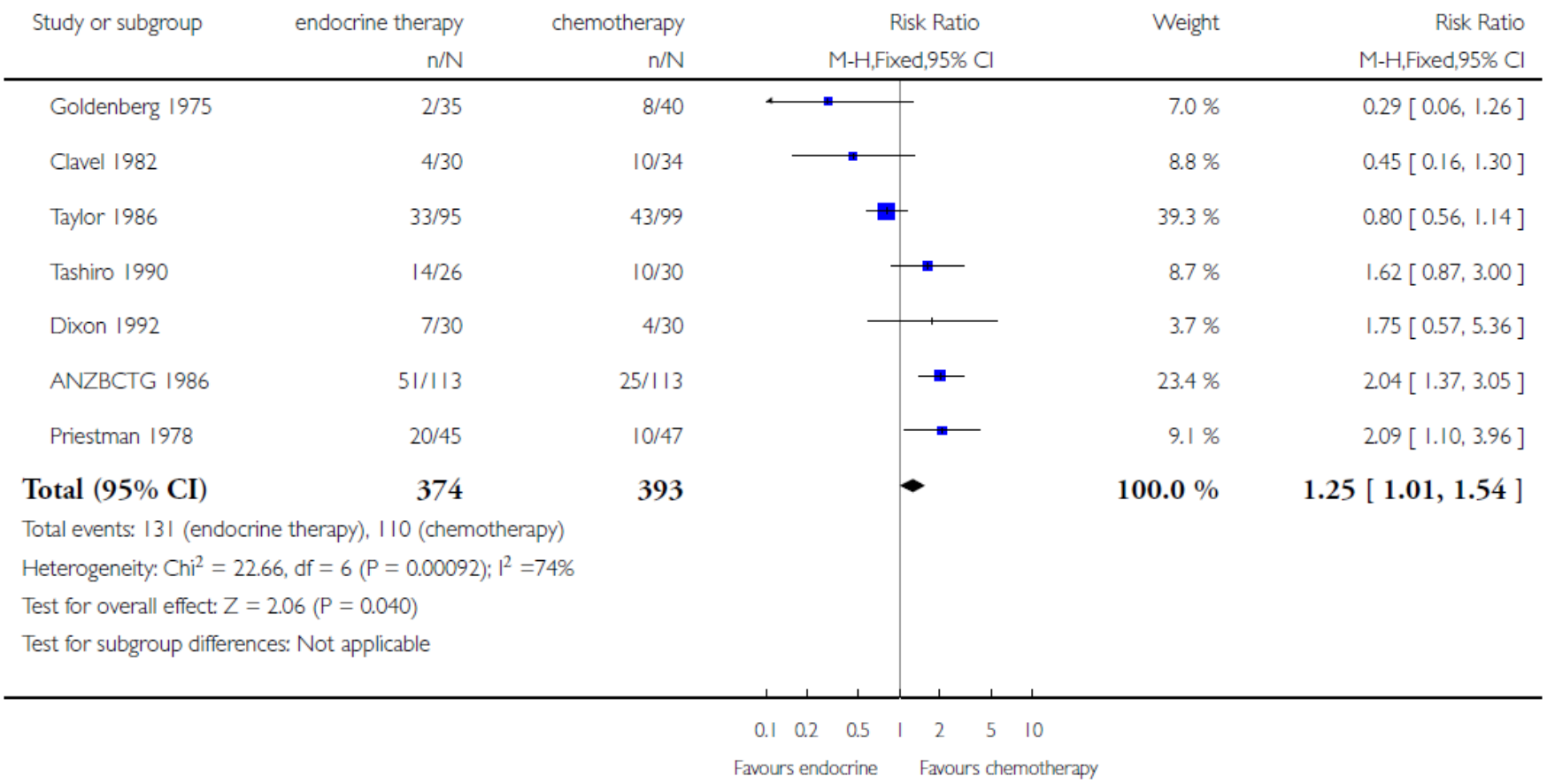
NC

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy.

No mention to the potential superiority of endocrine therapy in terms of activity

1. Partridge AH, *et al. J Clin Oncol* 2014;32:3307–3329;
2. Cardoso F, *et al. The Breast* 2014;23:489–502; 3. NCCN Guidelines: Breast Cancer. Version 3.2015.

Chemotherapy vs Endocrine Therapy Trials: Objective Response Rate



Study or subgroup	endocrine therapy n/N	chemotherapy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Goldenberg 1975	2/35	8/40		7.0 %	0.29 [0.06, 1.26]
Clavel 1982	4/30	10/34		8.8 %	0.45 [0.16, 1.30]
Taylor 1986	33/95	43/99		39.3 %	0.80 [0.56, 1.14]
Tashiro 1990	14/26	10/30		8.7 %	1.62 [0.87, 3.00]
Dixon 1992	7/30	4/30		3.7 %	1.75 [0.57, 5.36]
ANZBCTG 1986	51/113	25/113		23.4 %	2.04 [1.37, 3.05]
Priestman 1978	20/45	10/47		9.1 %	2.09 [1.10, 3.96]
Total (95% CI)	**374**	**393**		**100.0 %**	**1.25 [1.01, 1.54]**

Total events: 131 (endocrine therapy), 110 (chemotherapy)

Heterogeneity: $Chi^2 = 22.66$, df = 6 (P = 0.00092); $I^2 = 74\%$

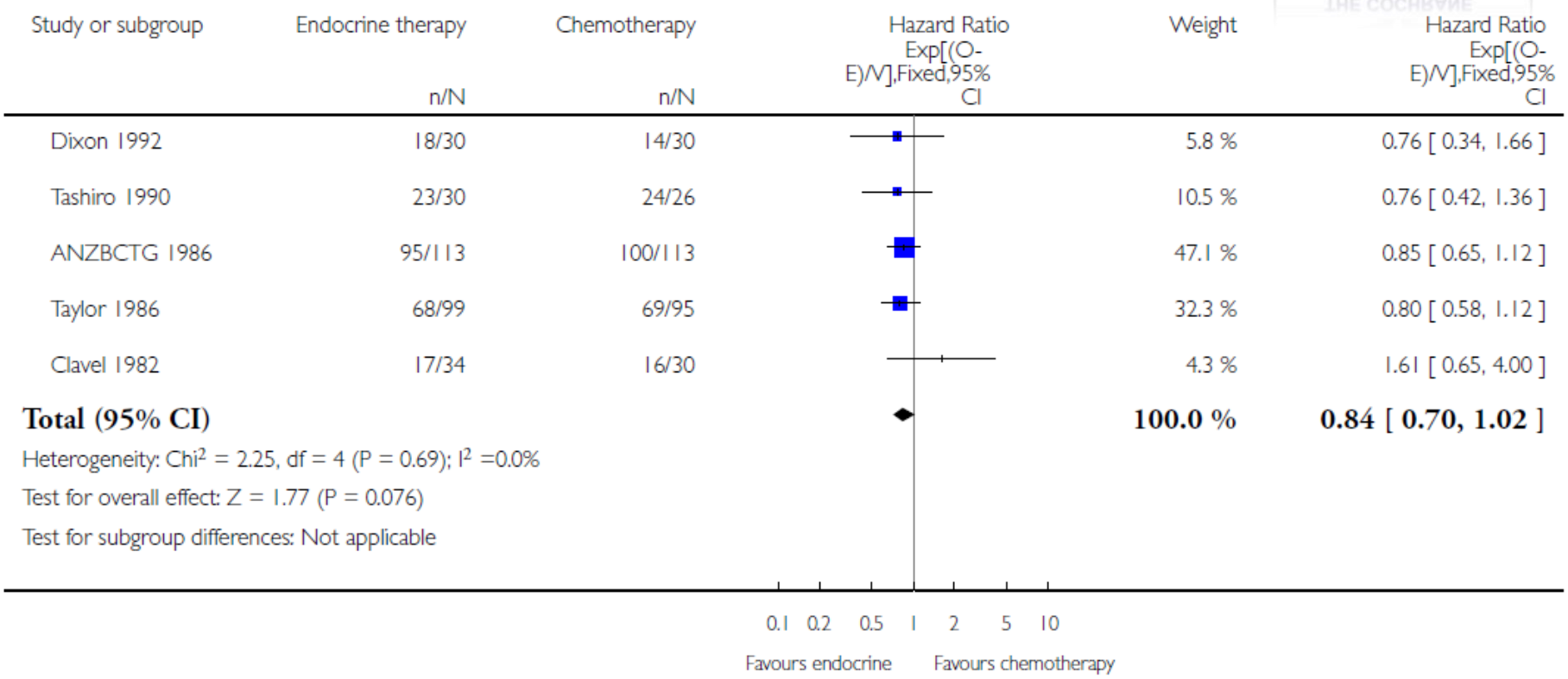
Test for overall effect: Z = 2.06 (P = 0.040)

Test for subgroup differences: Not applicable

Receptor status was mostly unknown in all studies

Wilcken N, et al. *Cochrane Database Syst Rev*. 2003;(2):CD002747.

Chemotherapy vs Endocrine Therapy Trials: Overall Survival



Receptor status was mostly unknown in all studies

Wilcken N, et al. Cochrane Database Syst Rev. 2003

Treatment of “Rapidly Progressive Disease” ABC Recommendations

ER POSITIVE MBC[1]

- **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 (LoE: 1 A).

VISCERAL CRISIS[2]

- is defined as **severe organ dysfunction** as assessed by signs and symptoms, laboratory studies, **and rapid progression of disease**.

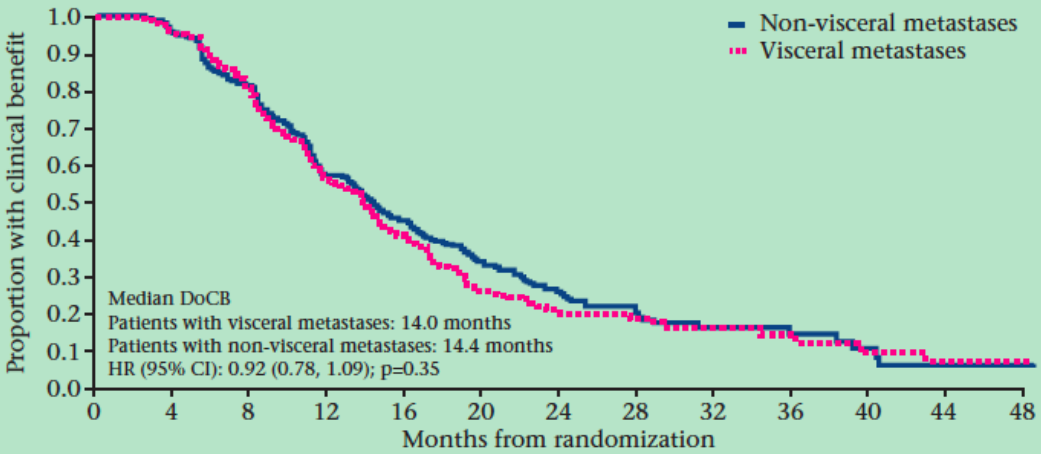
  Visceral crisis is **not the mere presence of visceral metastases** but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible. (LoE: Expert opinion).

1. Cardoso F, *et al. The Breast* 2012;21:242–252;
2. Cardoso F, *et al. The Breast* 2014;23:489–502.

Visceral Metastases from HR+ MBC are not a Criteria for Endocrine Resistance

Combined analysis of four, Phase III, randomised controlled trials of 1st-line ET for ABC in postmenopausal women with available data on visceral vs. non-visceral metastases*

Figure 3. Kaplan–Meier plot of DoCB in patients with visceral metastases versus non-visceral metastases (all endocrine therapies combined from all trials)



95% CI, 95% confidence interval; DoCB, duration of clinical benefit; HR, hazard ratio

"ET for advanced/metastatic BC is as effective in responsive patients with visceral metastases as in those with non-visceral metastases."

DoCB, duration of clinical benefit

*Similar results were observed from studies using tamoxifen only. Robertson JFR, *et al.* SABCS 2014 (Abstract P1-13-02).

First Line Therapy

HR[+] Metastatic Breast Cancer

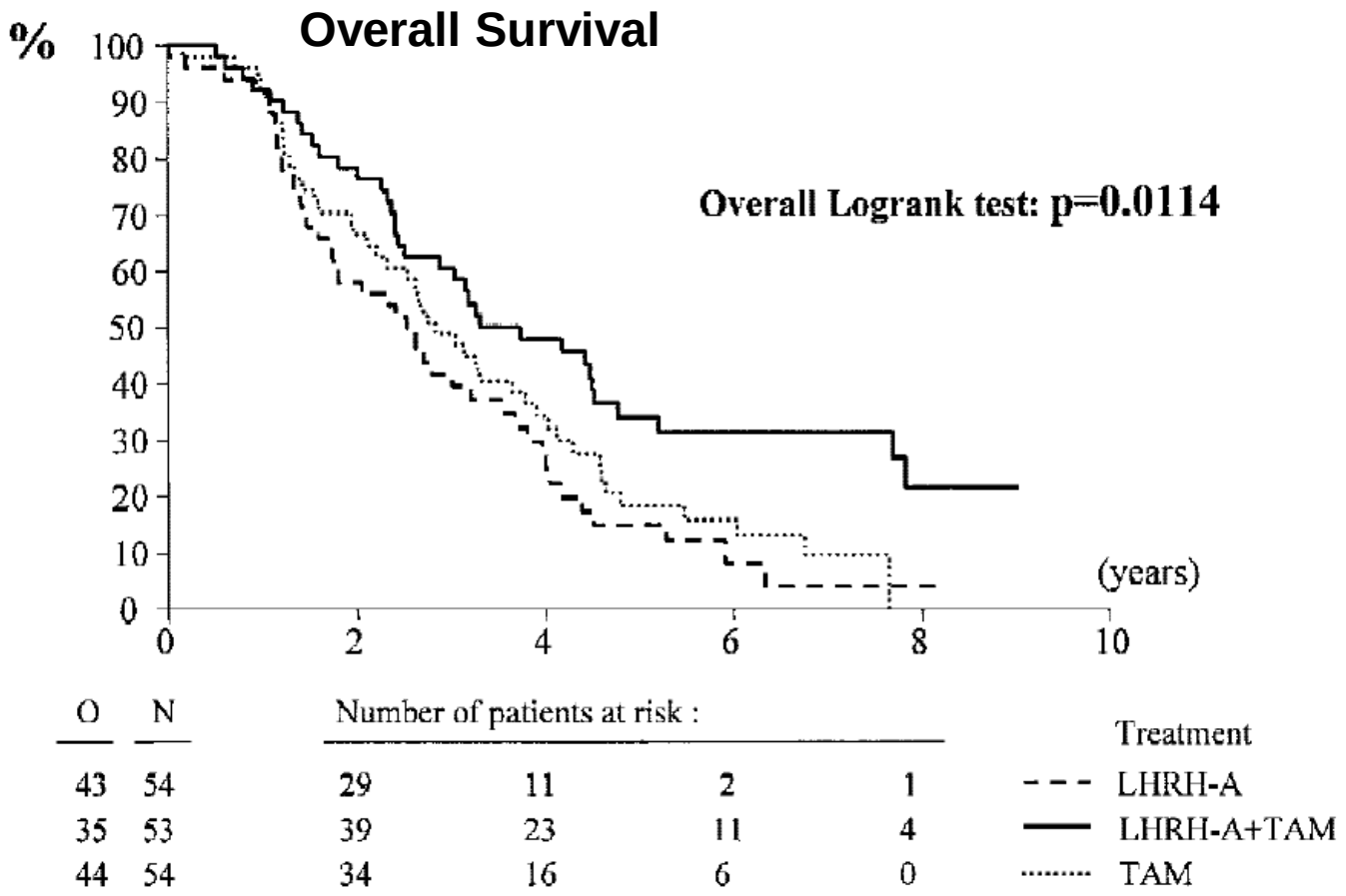
Endocrine Sensitive

“De Novo” MBC

Naïve MBC

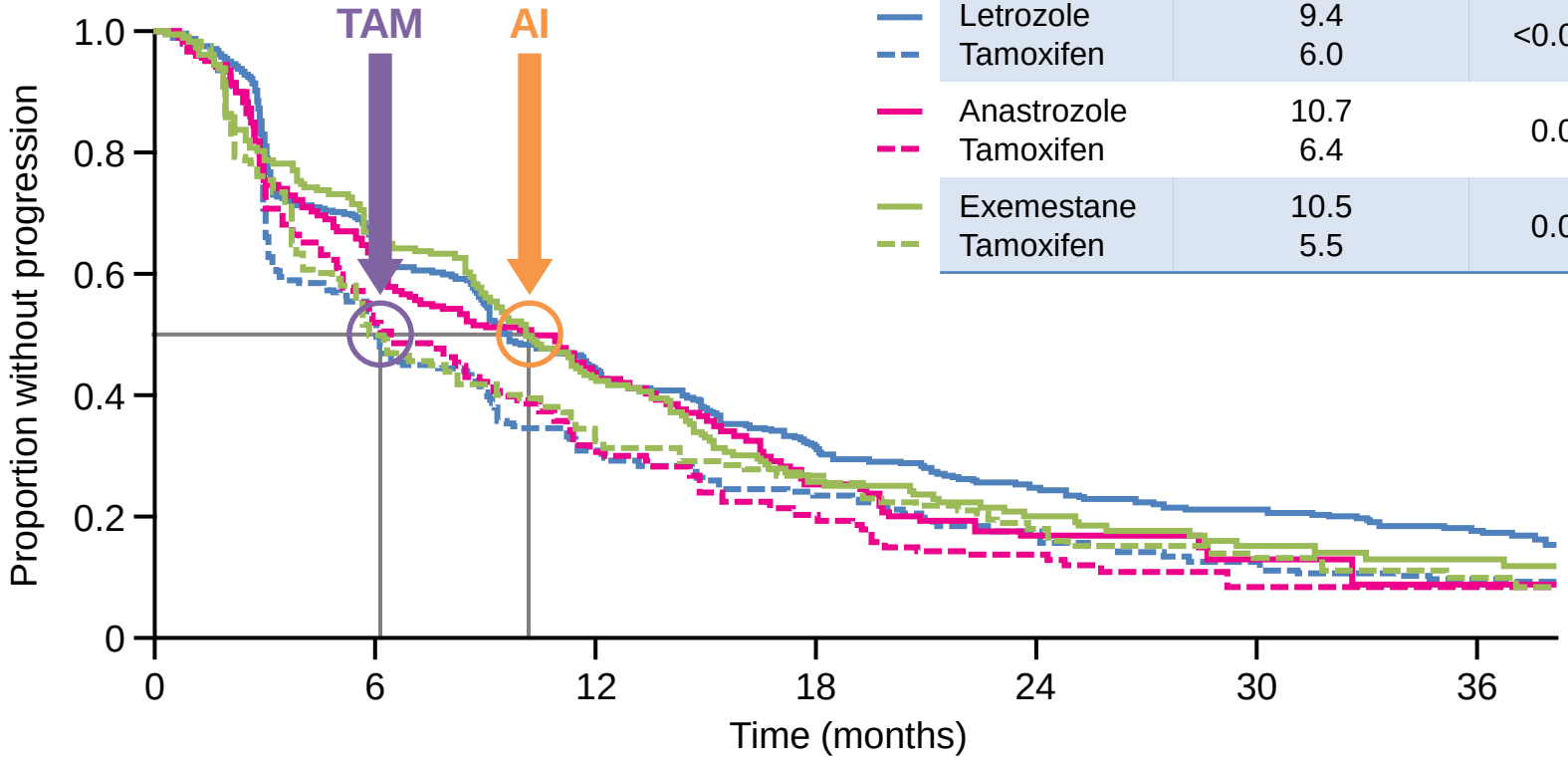
MBC > 1 year from the end of ET for EBC

EORTC Premenopausal: Survival Benefit for Ovarian Suppression and TAM



Klijn JG, et al. *J Natl Cancer Inst.* 2000;92:903-911.

First-Line Therapy: Aromatase Inhibitors Showed Consistent Superiority over Tamoxifen (Postmenop)



	TTP (months)	P
Letrozole	9.4	<0.0001
Tamoxifen	6.0	
Anastrozole	10.7	0.022
Tamoxifen	6.4	
Exemestane	10.5	0.028
Tamoxifen	5.5	

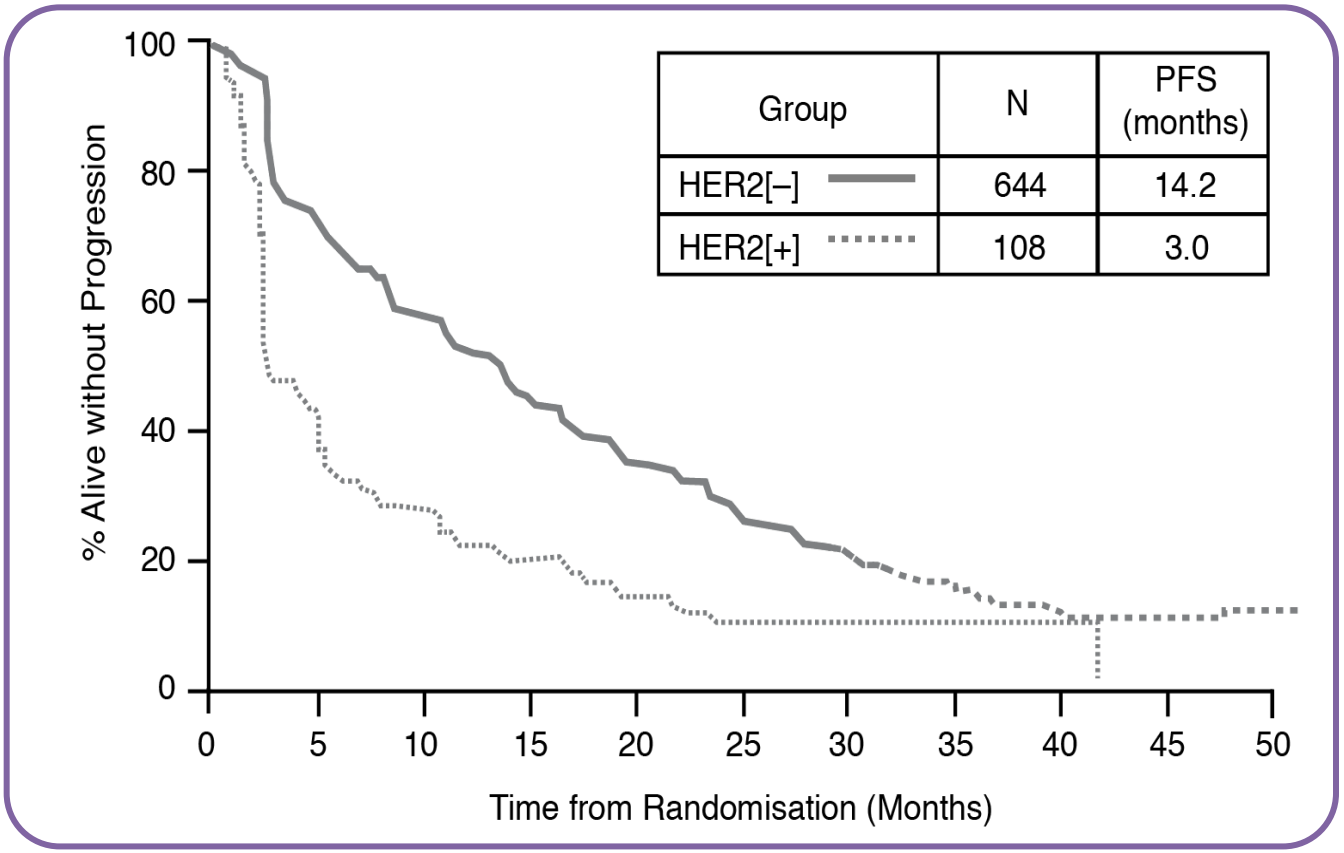
AI, aromatase inhibitor; TAM, tamoxifen.

Mouridsen, *et al. Oncologist* 2004;4:489–496;
Bonneterre, *et al. Cancer* 2001;92:2247–2258;
Paridaens, *et al. J Clin Oncol* 2008;26:4883.

HER2 Overexpression is a Strong Predictor of Endocrine Resistance Among ER+ ABC Patients

30008 Study: Letrozole arm efficacy by HER2 status

- Comparison of control arms (LET) in both groups of treatment (by HER2 status)
- Median TTP for LET alone
  - 14.2 mos (HER2–)
  - 3.0 mos (HER2+)



HER2, human epidermal growth factor receptor 2; LET, letrozole; mos, months; TTP, time-to-progression.

Adapted from Johnston S, *et al. J Clin Oncol* 2009;27:5538–5546.

Front-Line Aromatase Inhibitors Improving Efficacy Over the Last Decade

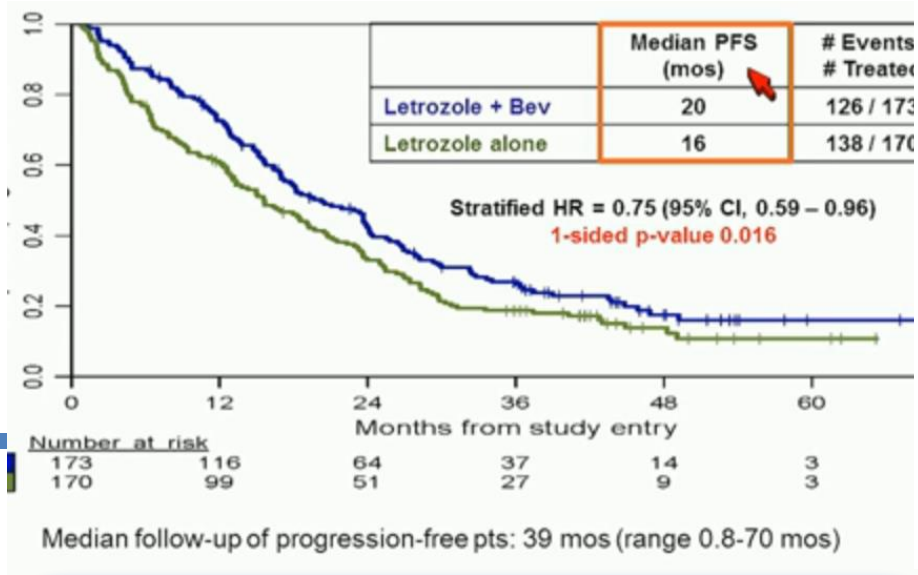
Letrozole single agent arm from recent Phase III trials for first-line ER+ MBC

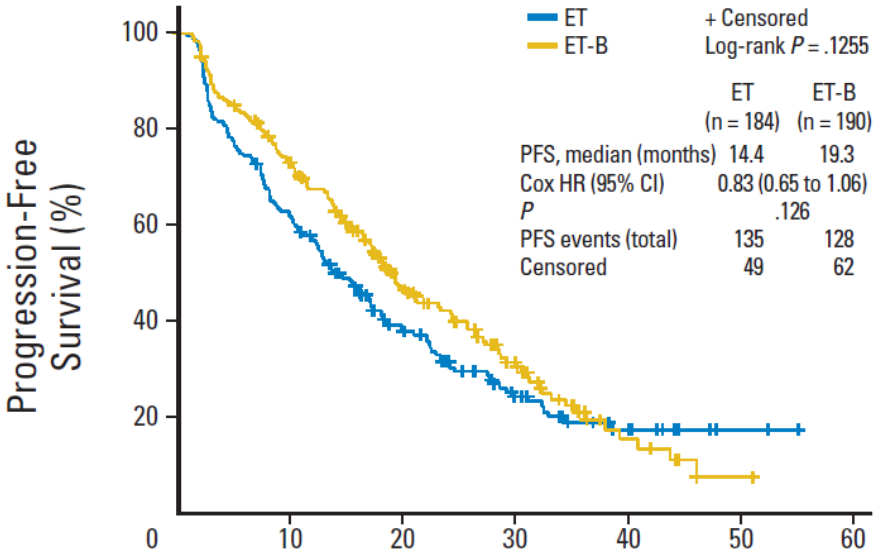
Letrozole single agent first-line trials	Year	Criteria	CBR (%)	TTP median (months)
Mouridsen	2004	**ER+**	50	**9.4**
Wolf	2012	**ER+**	–	**9.0**
Johnston	2009	**ER+/HER2–**	64	**15.0**
Martin	2015	**ER+/HER2–**	67	**14.4**
Dickler	2015	**ER+/HER2–**	62	**16.0**

CBR, clinical benefit rate

Mouridsen, 2003; Wolf 2012; Johnston *J Clin Oncol* 2009;27:5538–5546; Martin *J Clin Oncol* 2015; Dickler ASCO 2015 (Abstract 501).

New Approaches: LET + Bevacizumab CALGB-40503 and GEICAM-LEA





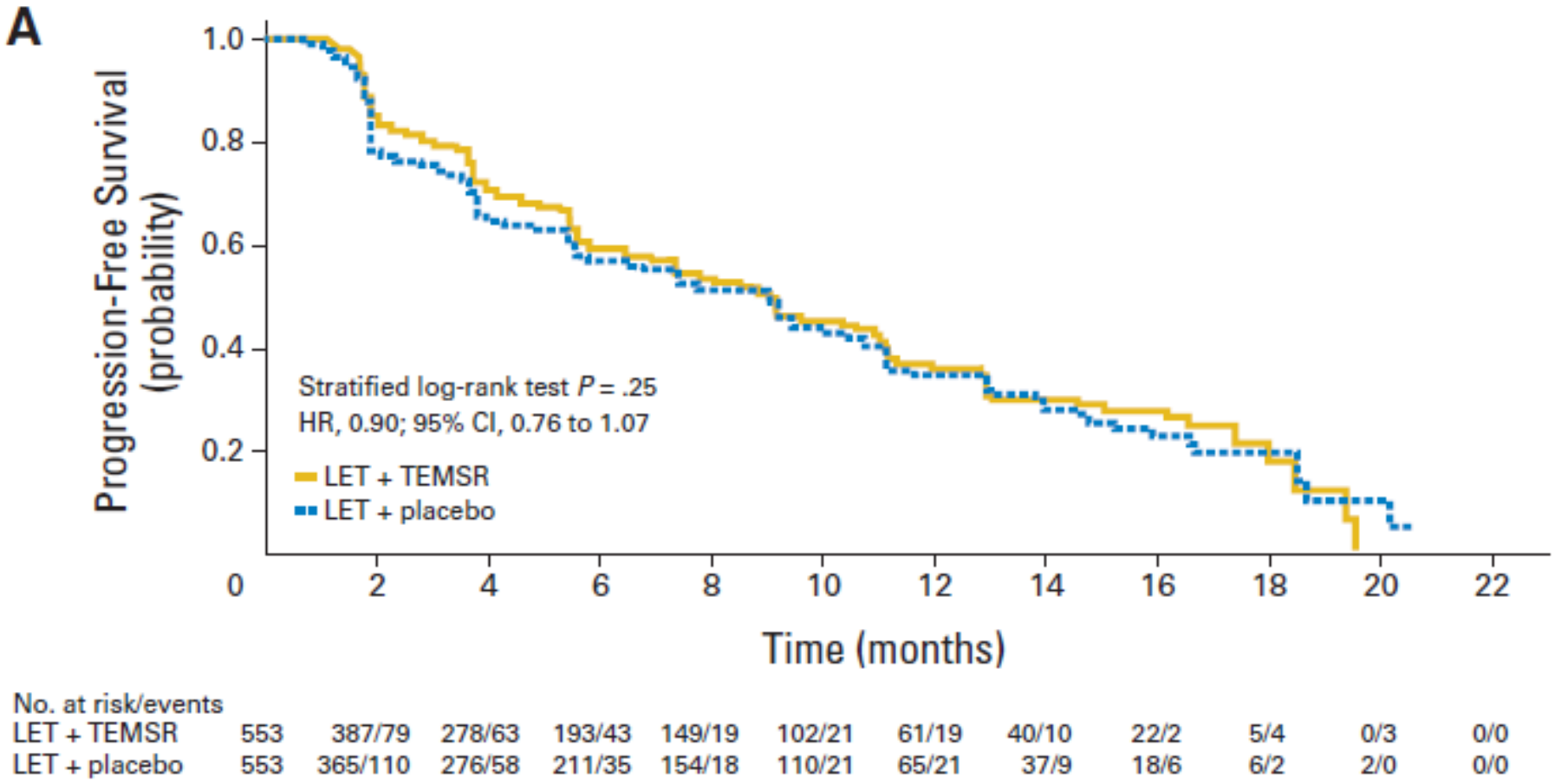
Statistically significant (*P* = 0.016), but clinically nonrelevant
Predefined benefit: HR<0.67
Median TTP increase >6 months

Nonsignificant (*P* = 0.126);
8 toxicity deaths on bevacizumab

ASO 2015

Martin M, et al. *J Clin Oncol.* 2015 [epub ahead of print];
Dickler MN, et al. ASCO 2015. Abstract 501.

Combination treatment: mTOR Inhibitors: Temsirolimus

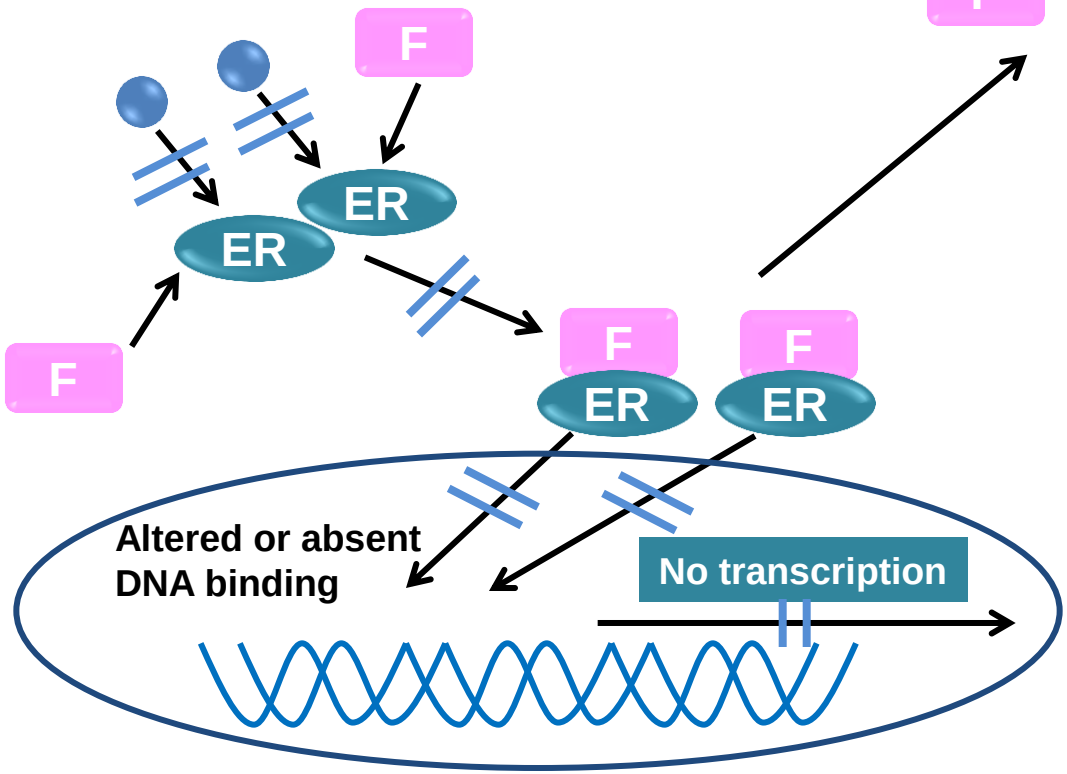


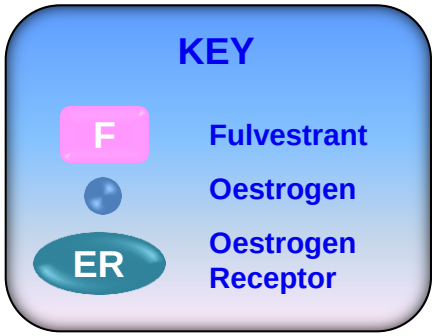
No. at risk/events												
LET + TEMSR	553	387/79	278/63	193/43	149/19	102/21	61/19	40/10	22/2	5/4	0/3	0/0
LET + placebo	553	365/110	276/58	211/35	154/18	110/21	65/21	37/9	18/6	6/2	2/0	0/0

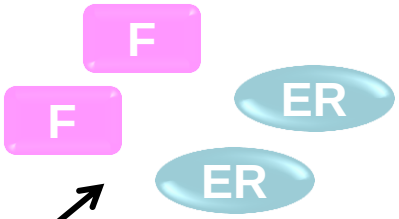
Wolf A, et al. *J Clin Oncol.* 2012;31:195-202.

Fulvestrant: The dual Mechanism of action may explain the delay (PFS gains) on resistance mechanisms

1. Fulvestrant competitively binds ER, creating a conformational change, blocking oestrogen binding[1–6]





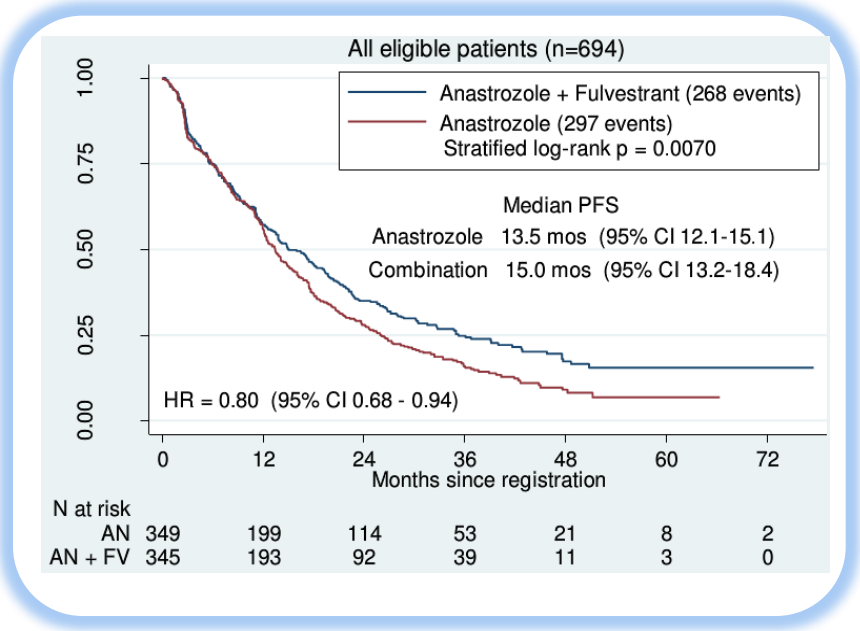


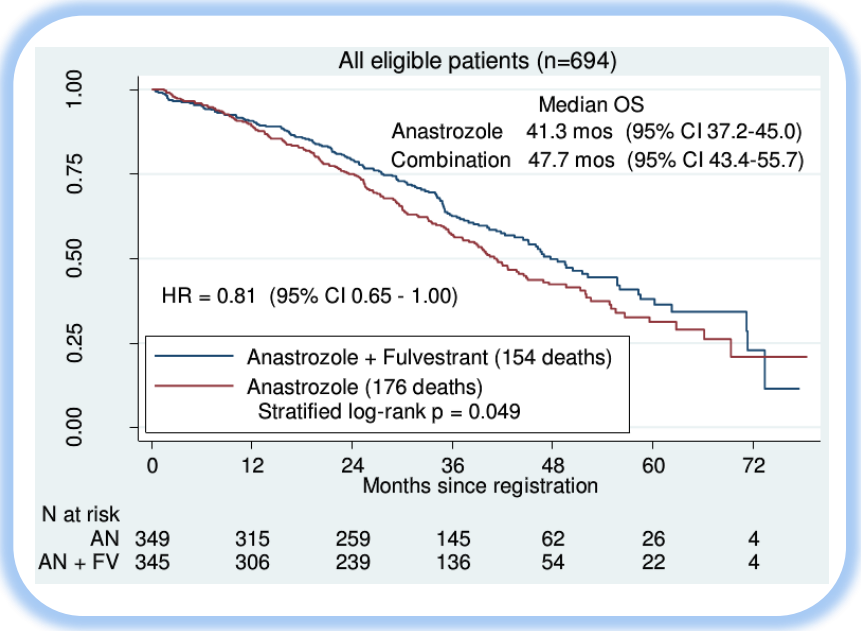
2. Fulvestrant accelerates degradation of ER, inhibiting both receptor dimerisation and translocation to the nucleus, resulting in inhibition of oestrogen-stimulated cell division[1–4]

1. Osborne et al. Br J Can 2004; 2. Howell. Int J Gynecol Cancer 2006; 3. Wakeling. Endocr Relat Cancer 2000; 4. Carlson. Clin Breast Cancer 2005; 5. Dowsett et al. Breast Cancer Res Treat 2005; 6. Parker. Breast Cancer Res Treat 1993

Combination treatment: SWOG S0226 Fulvestrant (250) and Anastrozole

- Phase III SWOG S0226 study
- Postmenopausal with inoperable IIIB or IV breast cancer ER/P+
- Measurable evaluable disease
- Primary objective: Progression-free survival (PFS)



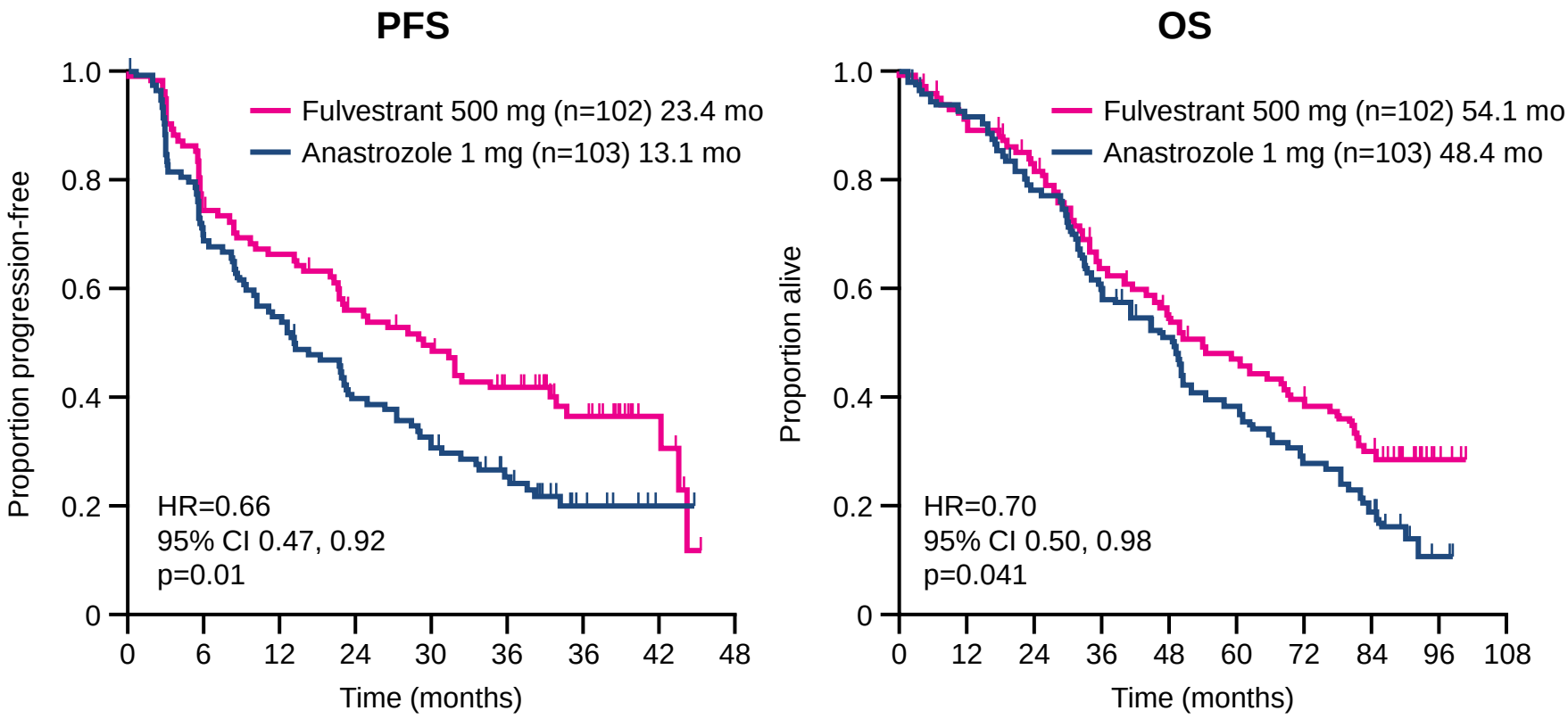


Fulvestrant is not approved in this setting. Please refer to the Summary of Product of Characteristics (SmPC) for all licensed indications. The SmPC is available from your local representative.

Mehta RS, et al. *N Engl J Med*. 2012;367:435-444.

New Approaches: Phase II - FIRST Study
Fulvestrant HD vs. Anastrozole

Postmenopausal patients with Stage IIIB or IV, ER/PR+ HER2–
Primary Objective: CB (no differences)

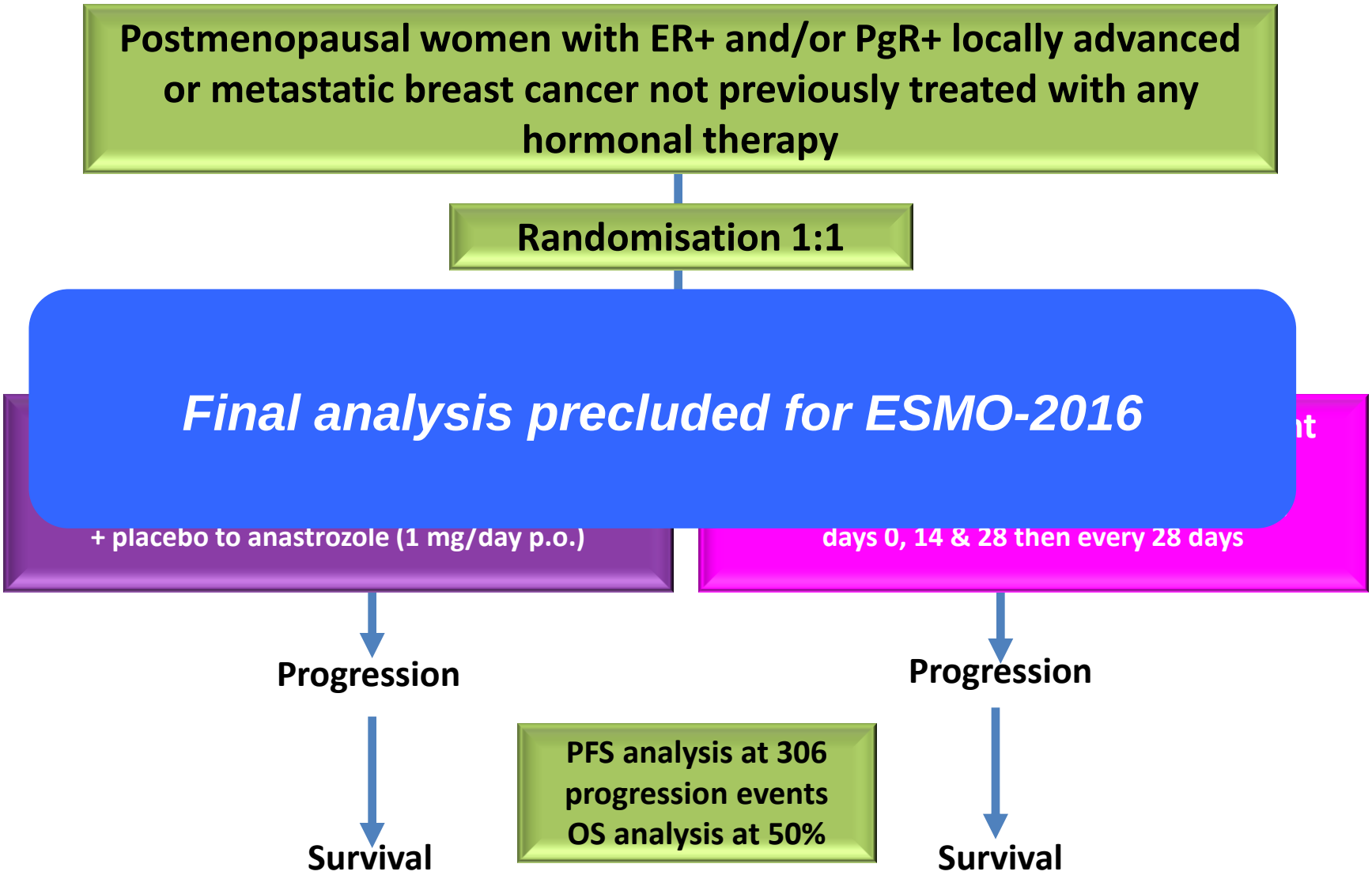


Fulvetrant is not approved in Korea

CB, clinical benefit; HD, high dose.

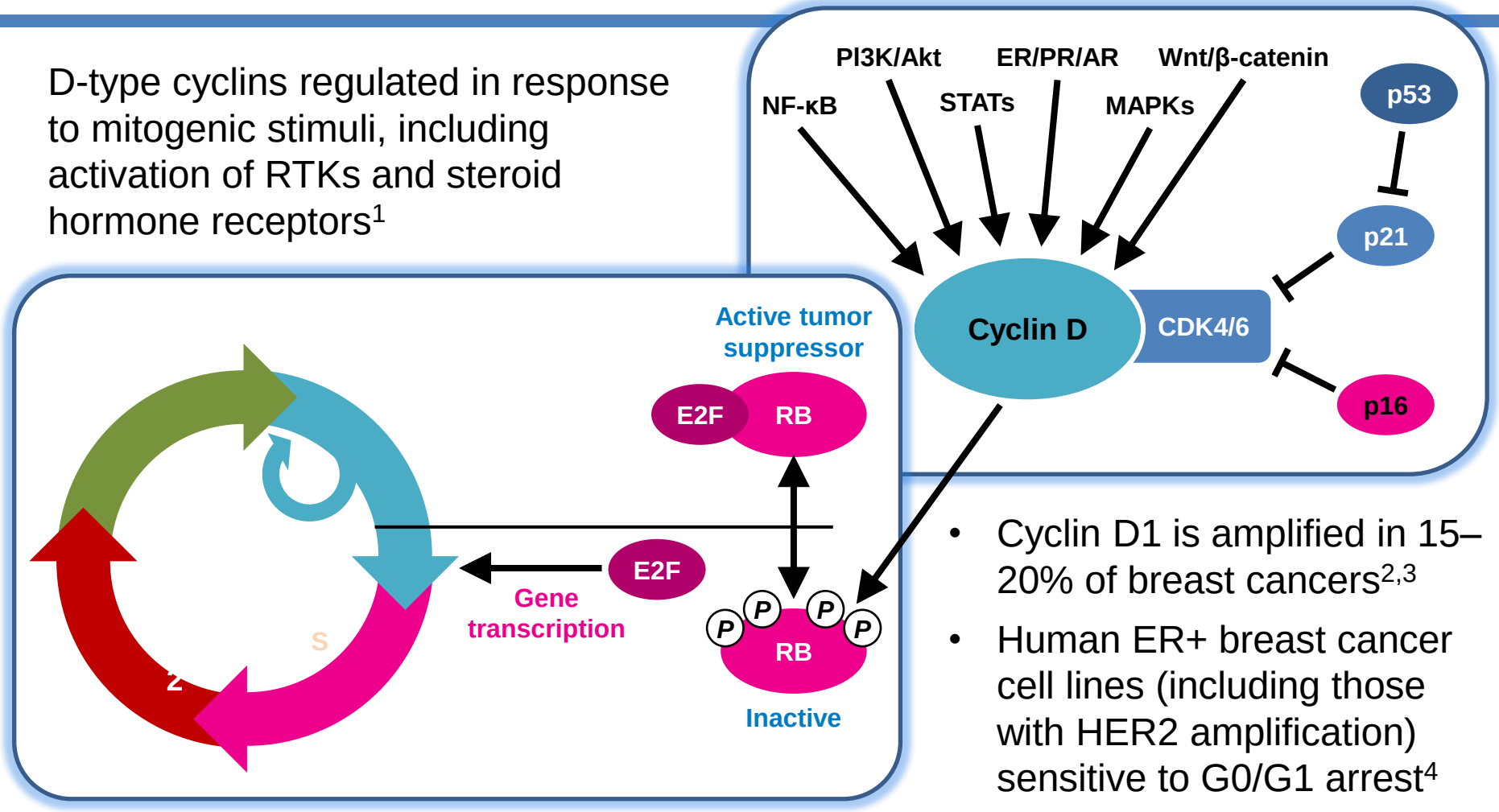
Bergh J, *et al. J Clin Oncol* 2012;30:1919–1925.

First Line Fulvestrant High Dose Phase III Registration Study



Cyclin D – Retinoblastoma cascade regulates 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]

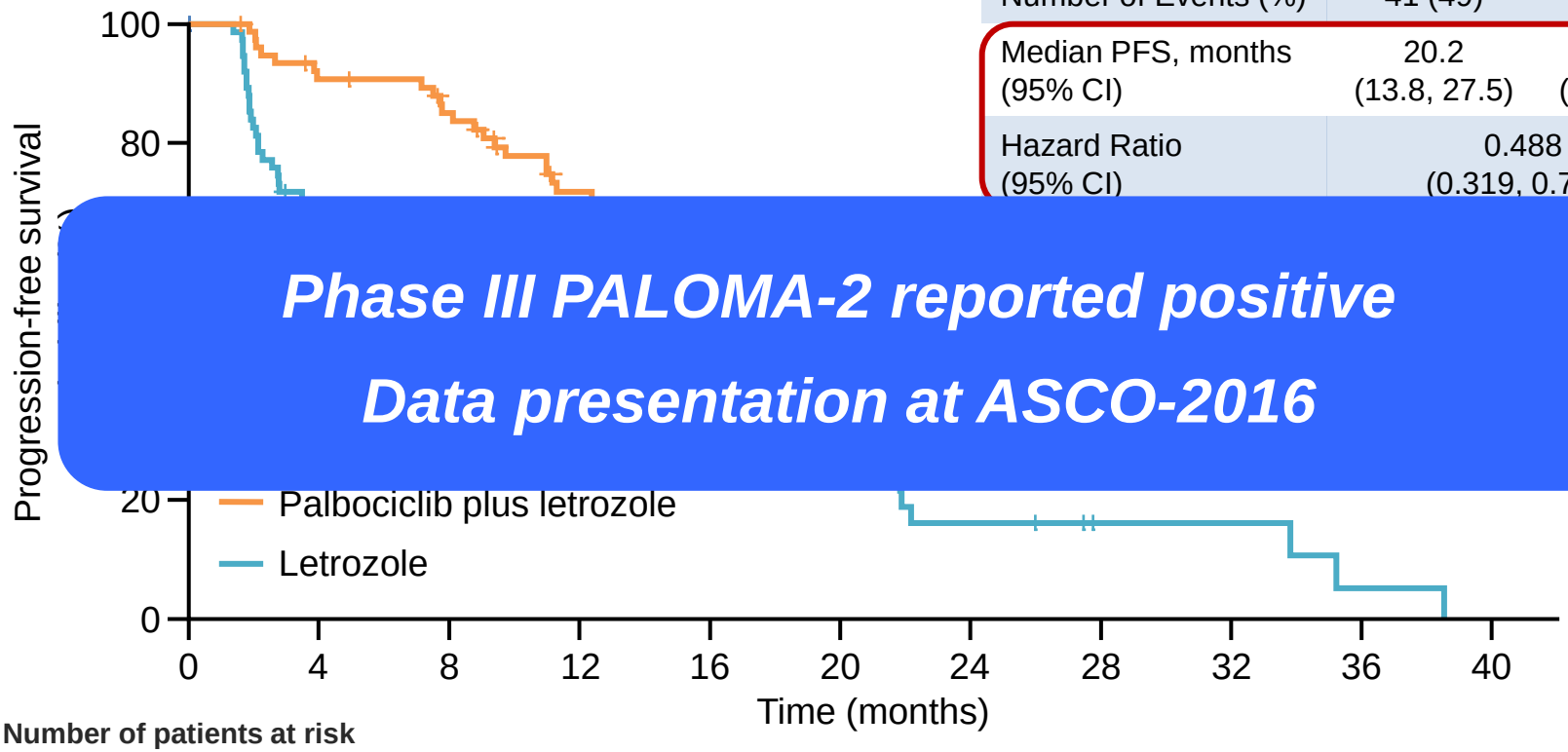
Lange et al. Endocrine-Related Cancer 2011;18:C19–C24; [1]Caldon CE, et al. J Cell Biochem 2006;97:261–274; [2]Buckley MF, et al. Oncogene 1993;8:2127–2133; [3]Dickson C, et al. Cancer Lett 1995;90:43–50; [4]Finn RS, et al. Breast Cancer Res 2009;11:R77

CDK4/6 inhibitors currently in Phase III First Line

Agent	Company	Development Status	Trials Brand Name
Palbociclib (PD0332991)	Pfizer	Phase III	**PALOMA-2**
Ribocioclib (LEE011)	Novartis	Phase III	**MONALEESA-2**
Abemaciclib (LY28335219)	Lilly	Phase III	**MONARCH-3**

New approaches: Phase II – PALOMA-1
Palbociclib Front-Line: PFS (ITT Population)

	PAL + LET (n=84)	LET (n=81)
Number of Events (%)	41 (49)	59 (73)
Median PFS, months (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)
Hazard Ratio (95% CI)	0.488 (0.319, 0.748)	



Phase III PALOMA-2 reported positive

Data presentation at ASCO-2016

Number of patients at risk

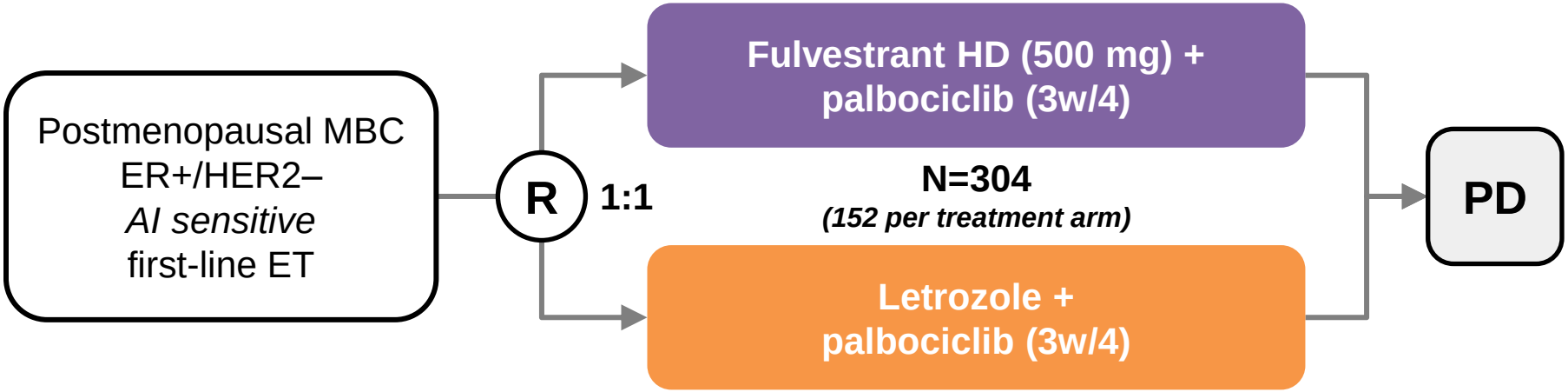
PAL + LET	84	67	60	47	36	28	21	13	8	5	1
LET	81	48	36	28	19	14	6	3	3	1	

PAL, palbociclib

Palbociclib is not approved in Korea

Finn RS, *et al. Lancet Oncol* 2015;16:25–35.

Palbociclib and Fulvestrant Front-Line: PARSIFAL Design



Stratification factors:

- Visceral disease
- Adjuvant AI

Primary Objective:

- 1-year PFS Rates
- Odds Ratio: 70% vs. 85%

PD, progressive disease; R, randomisation.

Llombart, *et al.* ASCO 2015.

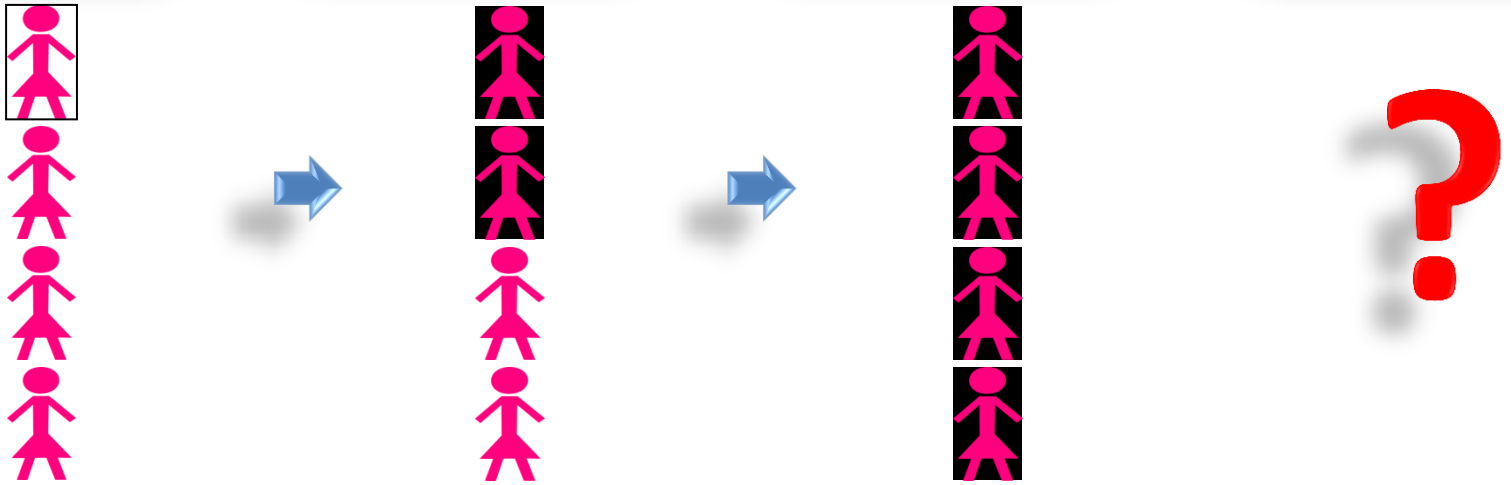
Treatment of Aromatase Inhibitor-Resistant Disease

Aromatase inhibitors are first-line endocrine therapy for postmenopausal patients

Approximately 50% of ER+ patients do NOT respond to initial treatment

Even those who do respond to initial treatment will eventually progress

"Optimal post-aromatase inhibitor treatment is uncertain"



ER+, estrogen receptor positive.

Normanno N, et al. *Endocr Rel Cancer.* 2005;12:721-747; NCCN Guidelines. Breast Cancer. Version 2012. NICE. CG81 Advanced breast cancer: Diagnosis and treatment. 2009. http://publications.nice.org.uk/advanced-breast-cancer-cg81; Cardoso F, et al. *Ann Oncol.* 2010;21(suppl 5): v15-v19; Cardoso F, et al. *Breast.* 2012;24:242-252.

Second Line Therapy – Progression to AI

HR[+] Metastatic Breast Cancer

Endocrine Resistant

“De Novo” MBC

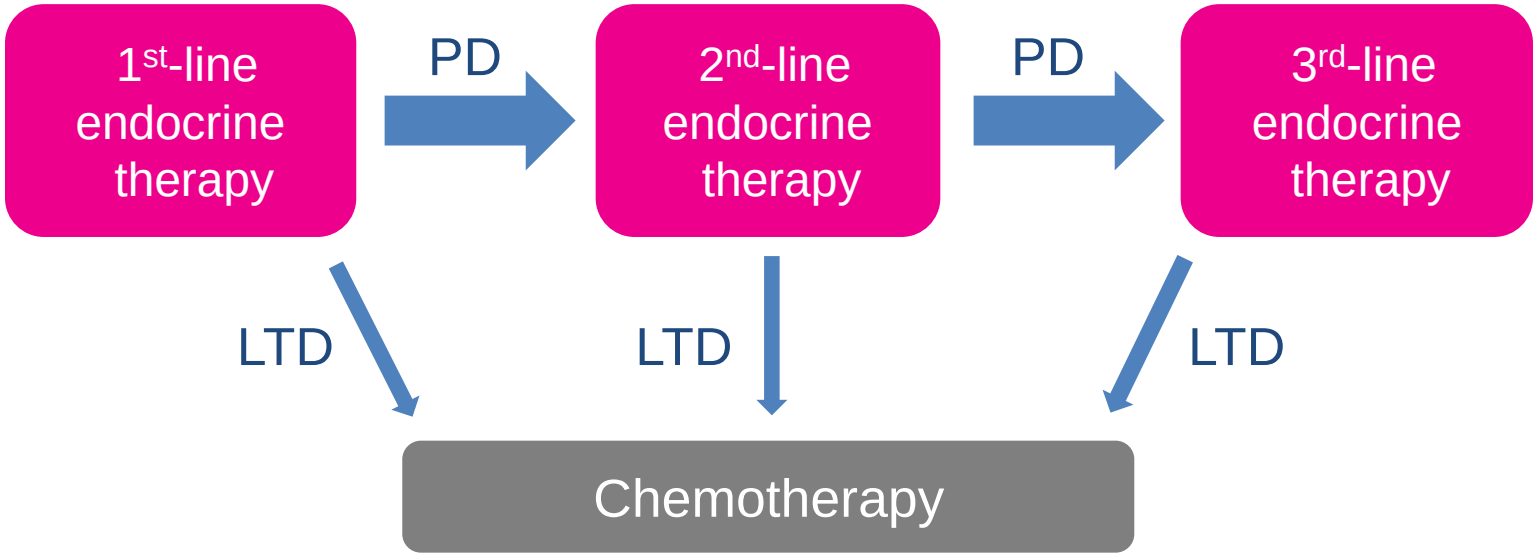
Naïve MBC

MBC > 1 year from the end of ET for EBC

When to Switch from Endocrine to Chemotherapy

*"**Chemotherapy** should be reserved for **cases of <u>rapidly progressive disease</u> or <u>proven endocrine-resistance</u>**."* – ESMO/ABC2 guidelines[1]

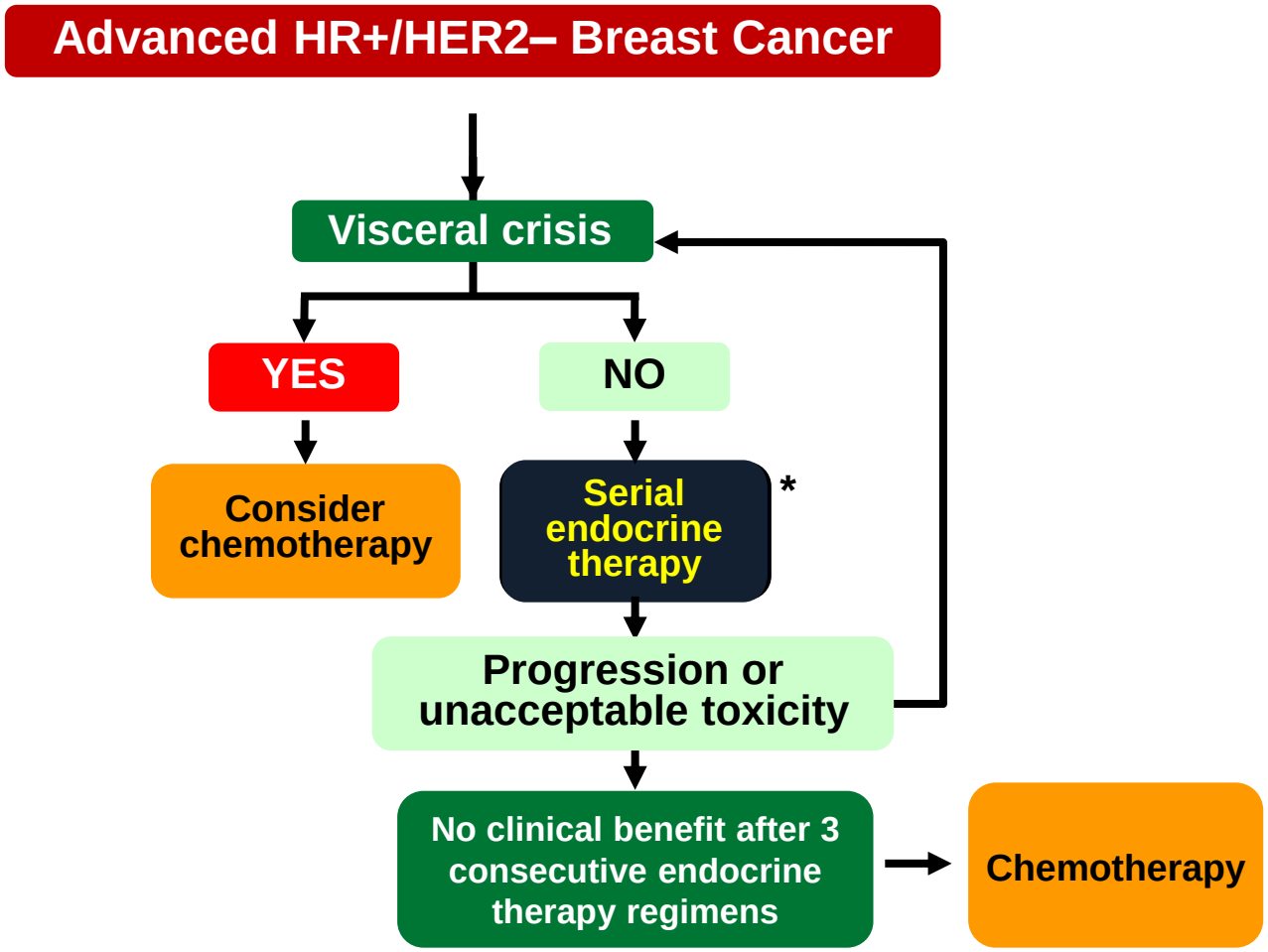
*"Endocrine therapy, rather than **chemotherapy**… except for **immediately life threatening disease or if there is concern regarding endocrine resistance**."* – ASCO guidelines[2]



LTD, life threatening disease;
PD, progressive disease.

1. Cardoso F, *et al*. *The Breast* 2014;23:489–502;
2. Partridge AH, *et al*. *J Clin Oncol* 2014;32:3307–3329.

NCCN Guidelines Recommend Serial Endocrine Therapy for HR+, HER2– ABC, Not in Visceral Crisis



HER2, human epidermal growth factor receptor 2.
*Consider the addition of everolimus to exemestane in women who fulfill the entry criteria for BOLERO-2.
National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer*. V.3.2014.

On progression to Front-Line Therapy
How is Endocrine Resistance Defined?

Primary Endocrine Resistance is defined as:[1]

- Relapse while on the first 2 years of adjuvant ET, or
- PD within first 6 mos of initiating 1st-line ET for MBC, while on ET

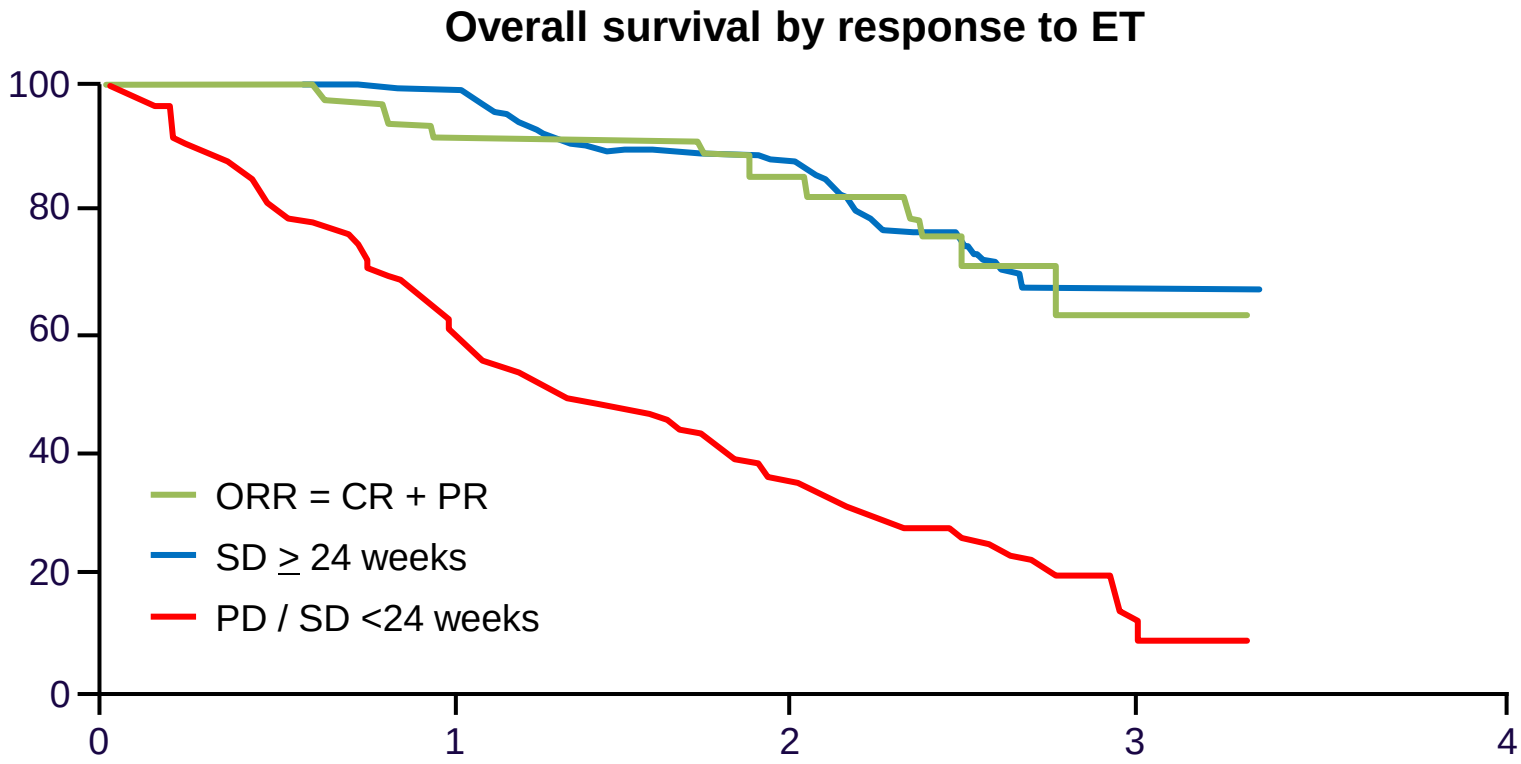
Secondary (Acquired) Endocrine Resistance is defined as:

- Relapse while on adjuvant ET but after the first 2 years, or
- Relapse within 12 months of completing adjuvant ET, or
- PD ≥6 months after initiating ET for MBC, while on ET

ET resistance is a "progressive, step-wise process, and the underlying mechanism remains unclear."[2]

1. Cardoso F, *et al. The Breast* 2014;23:489–502;
2. Fan W, *et al. Future Med Chem* 2015;12:1511–1519.

Clinical Benefit Criteria: Prognostic Marker for Endocrine Treatment



	ORR (PR + CR)		SD> 24 weeks		Disease Progression	
	N	2 years OS	N	2 years OS	N	2 years OS
Anastrozole	33	85%	78	86%	42	51%
Megestrol Ac.	31	70%	71	72%	47	48%

Robertson JFR, *Eur J Cancer* 1997.

Clinical Benefit Criteria: Prognostic and Predictive Skill for Endocrine Treatment

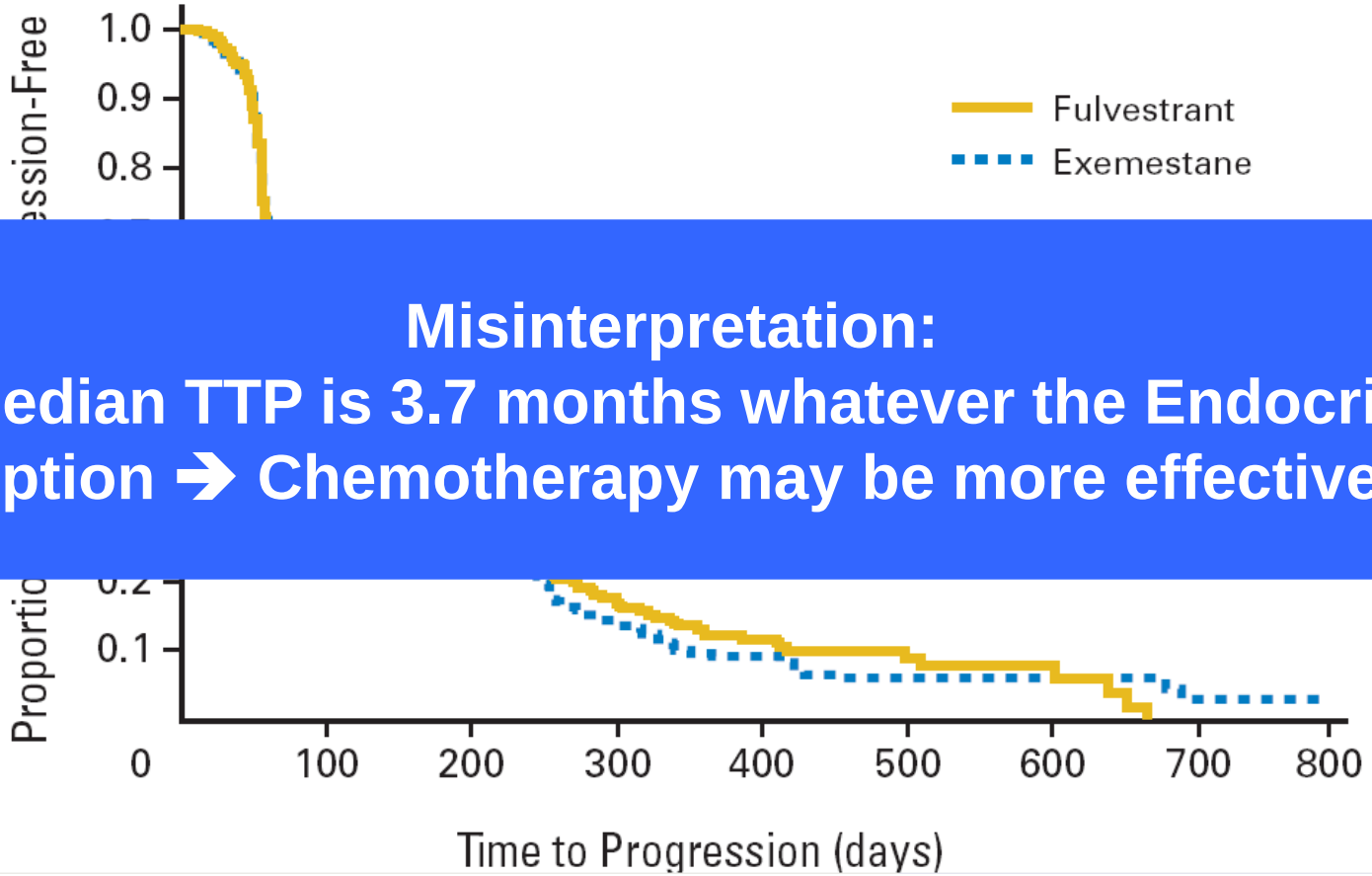
- Clinical Benefit to the previous line of endocrine therapy seems the best predictor for new benefits on subsequent endocrine lines

Clinical Benefit on Prior Line	2nd Line		3rd Line		4th Line	
	N	CB (%)	N	CB (%)	N	CB (%)
YES	68	**69%**	23	43%	5	20%
NO	17	**29%**	9	22%	4	0

- The absence of Clinical Benefit does not formally contraindicate new endocrine therapies, but closer follow-up seems reasonable

Agrawal A, *et al. World J Surg Oncol* 2006;4:40.

NSAI Resistant: EFECT Study
Fulvestrant vs. Exemestane: Low Median TTP



Misinterpretation:
If median TTP is 3.7 months whatever the Endocrine option ➔ Chemotherapy may be more effective

- Fulvestrant: 250 mg – no lowering dose
- 60% >2 prior endocrine lines

NSAI, non-steroidal aromatase inhibitor

Chia S, *et al. J Clin Oncol* 2008;26:1664–1670.

Historic Second Line Endocrine Therapy Phase III Results

Postmenopausal Patients Progressing on tamoxifen, letrozole or anastrozole

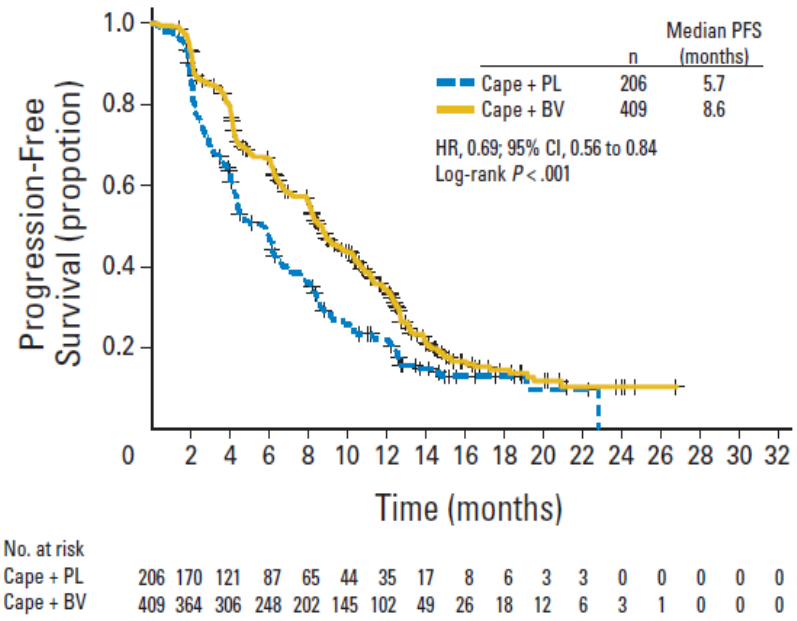
	LET	EXE	FULV 250
Control	**MEG. AC**	**MEG. AC**	**EXE**
HR PFS	1.04	0.82	0.96
p	NS	0.037	NS
Median PFS	3,8	4,8	3,7

LET, letrozole; EXE, exemestane; FULV 250, fulvestrant 250 mg; MEG AC, megestrol acetate

Dombernowsky et al. J Clin Oncol. 1998;16:453-61. Kaufmann et al. J Clin Oncol. 2000 Apr;18(7):1399-411. Chia et al. J Clin Oncol. 2008;26:1664-1670.

Efficacy of First-Line Chemotherapy in ER+/HER2–: Capecitabine (RIBBON I study)

		Capecitabine + PBO (n=206)
Median age		57.0 (23–88)
Sites of dis, %	Visceral	71.4
HR status, %	Positive	73.7



	Capecitabine + PBO (n=206)	Capecitabine + beva (n=409)
ORR, %	23.6	35.4
p value	0.0097	
CR, %	0.6	2.2
PR, %	23	33.2
CBR,%	Not assessed	Not assessed

Baseline risk factor	n	Capecitabine + PBO, median
Hormone receptor status		
Positive	458	6.2
Negative	143	4.2

Beva, bevacizumab; PBO, placebo.

Robert NJ, *et al. J Clin Oncol* 2011.

How Are Physicians Treating ER+/HER2–?

Analysis	Nº ER+/ HER2–	First-Line Treatment for ABC		Number of ET Lines Before First CT		
		CT	ET	1 Line	2 Lines	≥3 Lines
US[1]	19,120	40%	60%	44%	12%	4%
Europe[2]	355	31%	69%	62%	7%	0%

Front-line endocrine therapy is chosen for 60%–70% of ER+ ABC patients

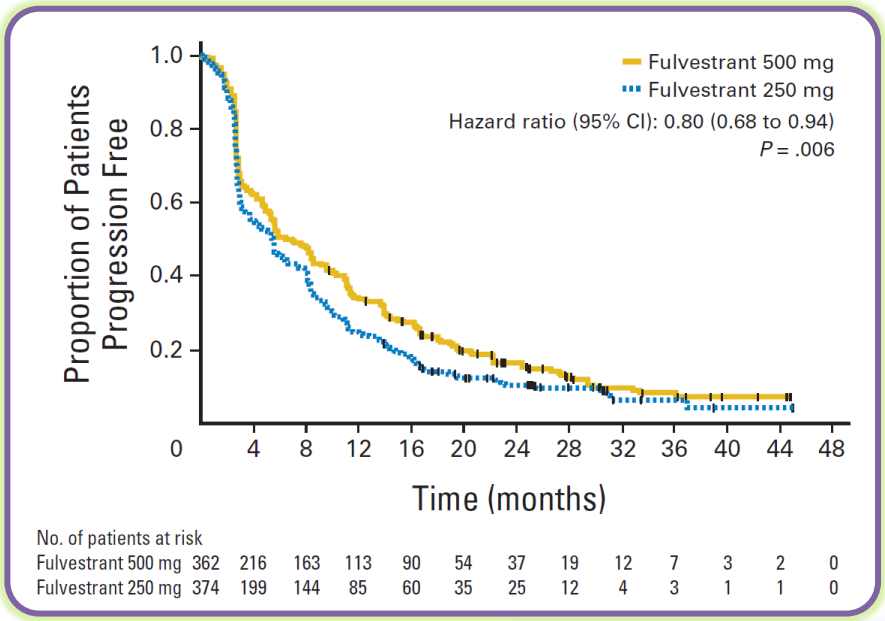
- E… d
  p… ABC
- A…
  t…

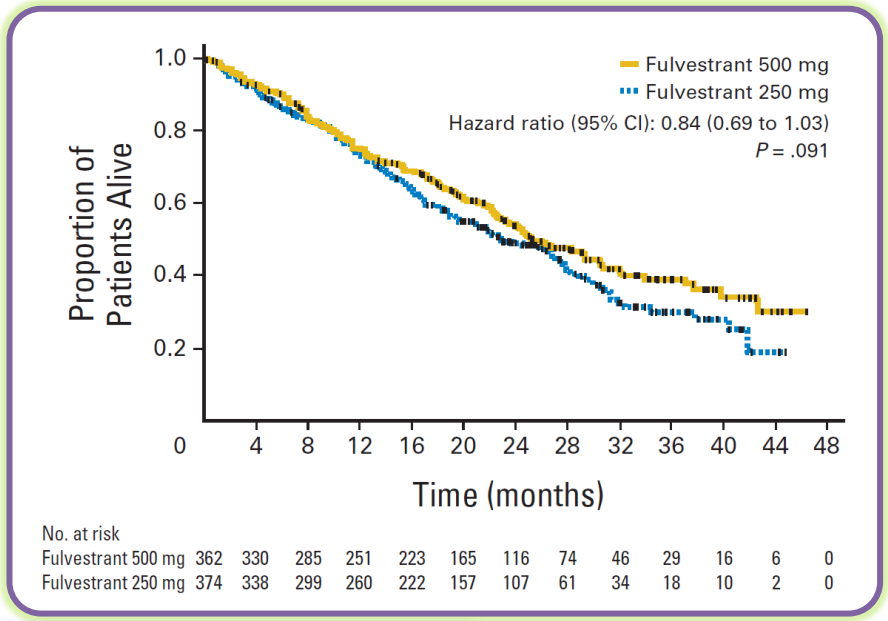
Fewer than 1 out of 4 (25%) treated with front-line ET continue on a second endocrine option. Chemotherapy is the preferred option on progression to a first-line endocrine treatment

CT, chemotherapy; HT, hormonal therapy.

1. Swallow E, *et al. Curr Med Res Opin* 2014;30:1537–1545;
2. Andre F, *et al. Curr Med Res Opin* 2014;30:1007–1016.

Second Line (AI Resistant): CONFIRM Fulvestrant HD (500) vs LD (250) – TTP (ITT)



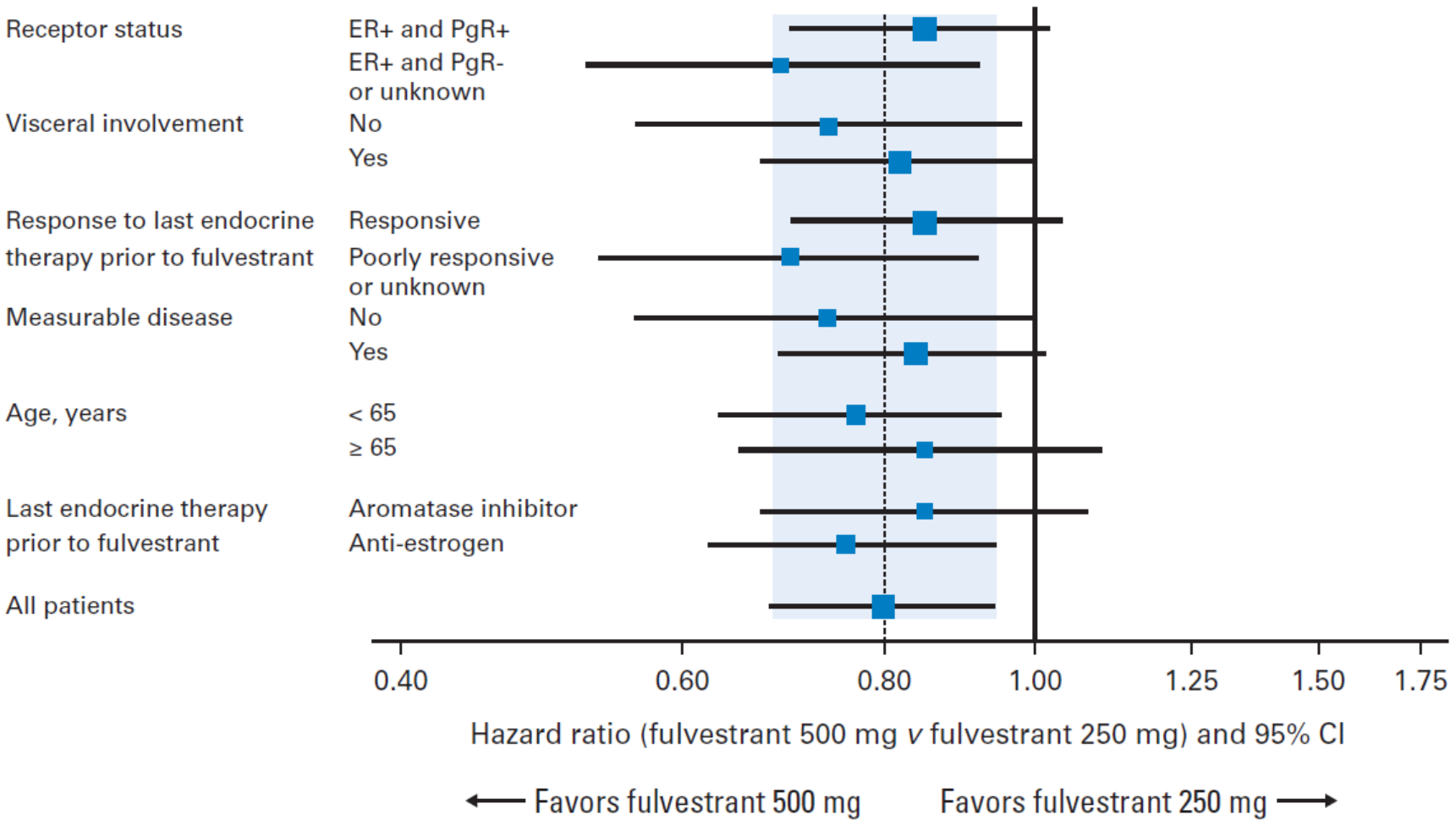


	Fulvestrant 500	Fulvestrant 250
Events (%)	82	85.8
Median TTP (mo)	6.5	5.5

- **Similar toxicity profile**

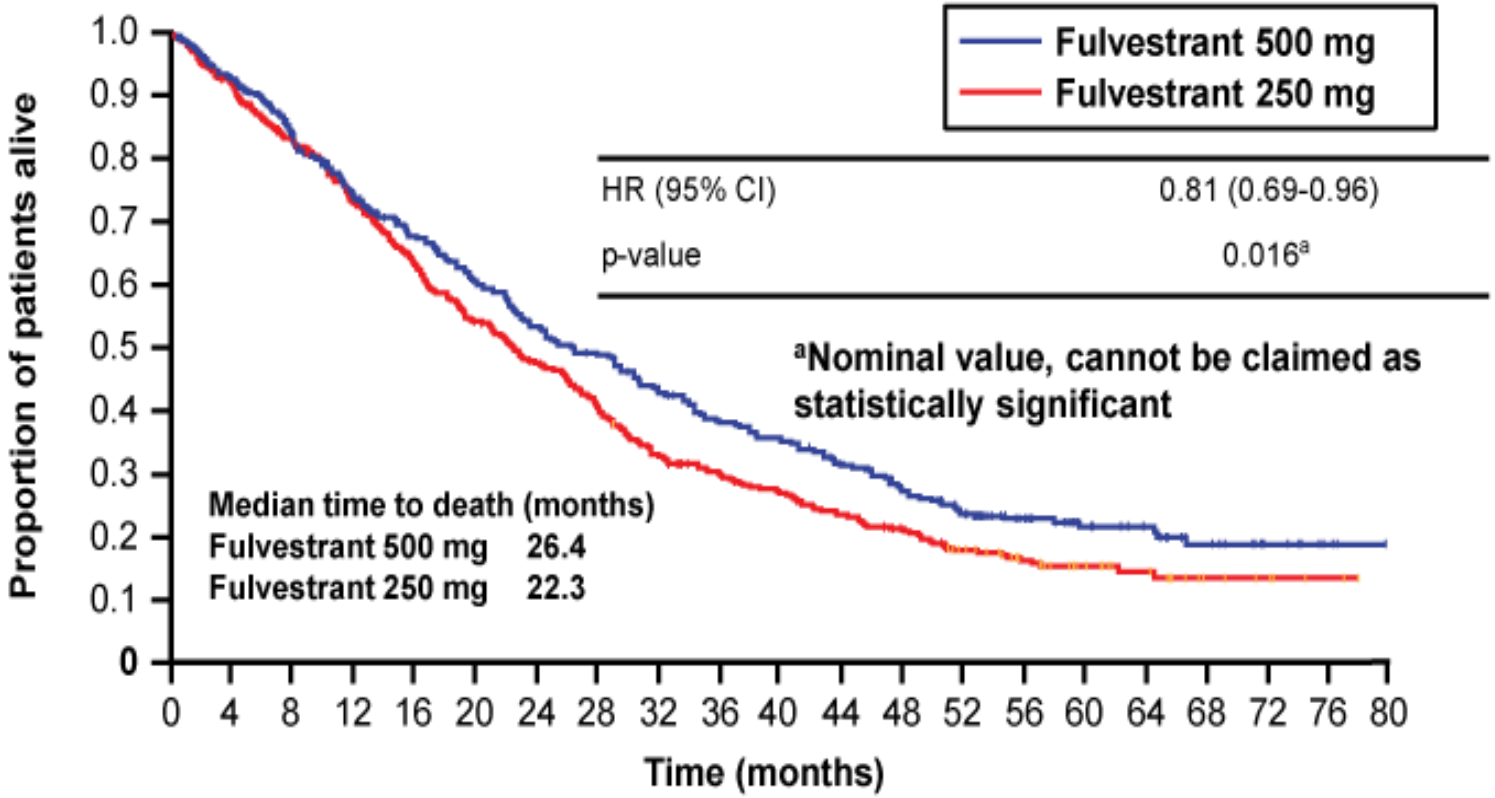
Di Leo A, et al. *J Clin Oncol*. 2010;28:4594-4600.
Erratum in: *J Clin Oncol.* 2011;29:2293.

Second Line (AI Resistant): CONFIRM PFS by Predefined Covariates



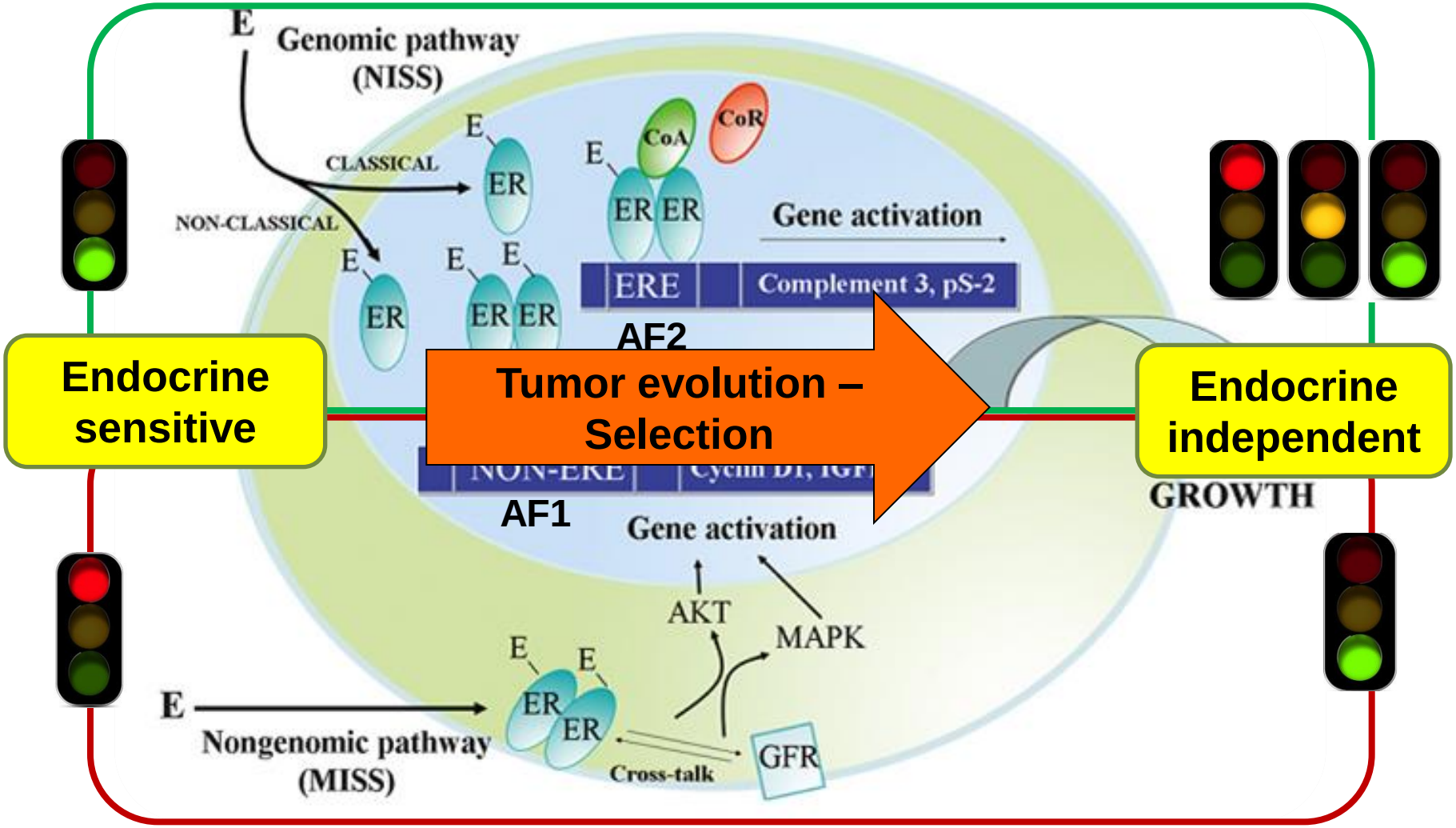
Di Leo A, et al. *J Clin Oncol*. 2010;28:4594-4600.
Erratum in: *J Clin Oncol.* 2011;29:2293.

Second Line (AI Resistant): CONFIRM Long-term Benefits in OS (ITT)



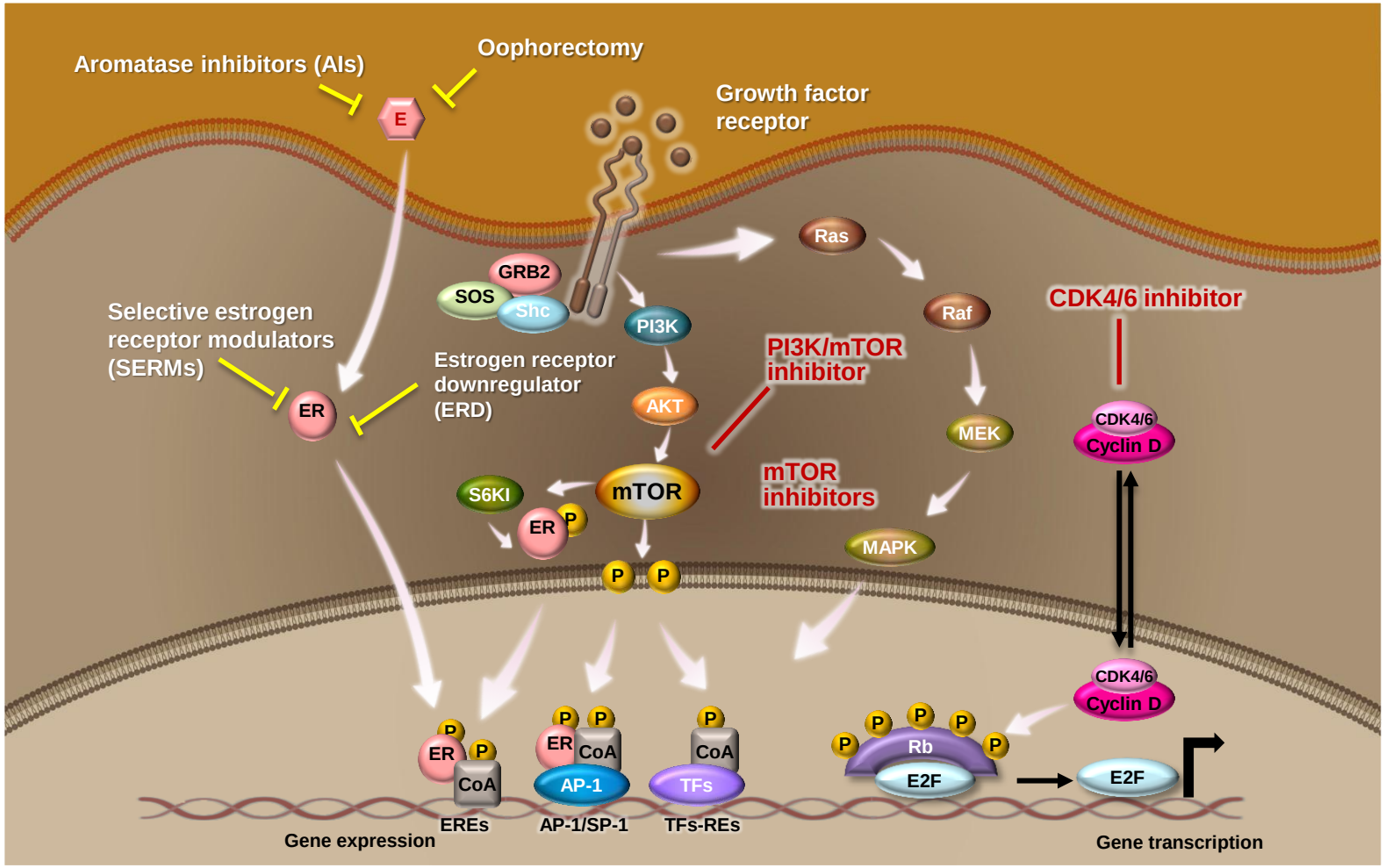
Di Leo A, et al. *J Clin Oncol*. 2010;28:4594-4600.
Erratum in: *J Clin Oncol.* 2011;29:2293.

ER Signaling Pathways: Most Prevalent Mechanisms of Resistance to AI



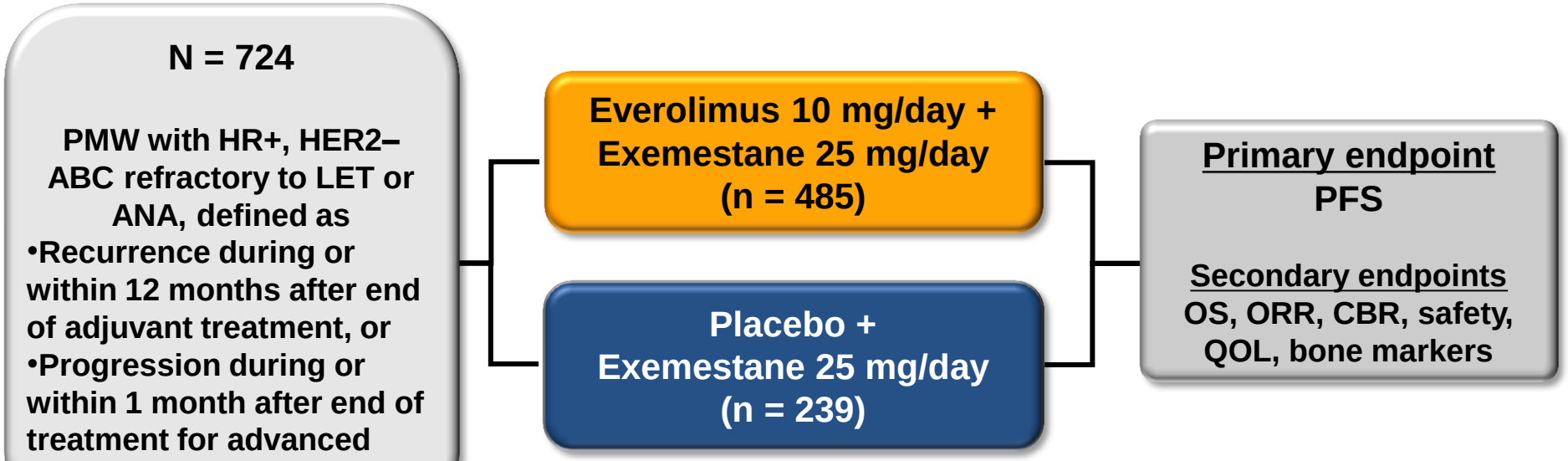
Zilli M, et al. *Biochim Biophys Acta.* 2009;1795:62-81.

Endocrine and Targeted Therapies for HR+/HER2– Advanced Breast Cancer



Adapted from Yardley DA, et al. ASCO BC 2011. Abstract 268; Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247; Yamnik RL, et al. *J Biol Chem.* 2009;284:6361-6369.

BOLERO-2: Phase III Exemestane ± Everolimus in Patients with ABC Progressing After NSAIs

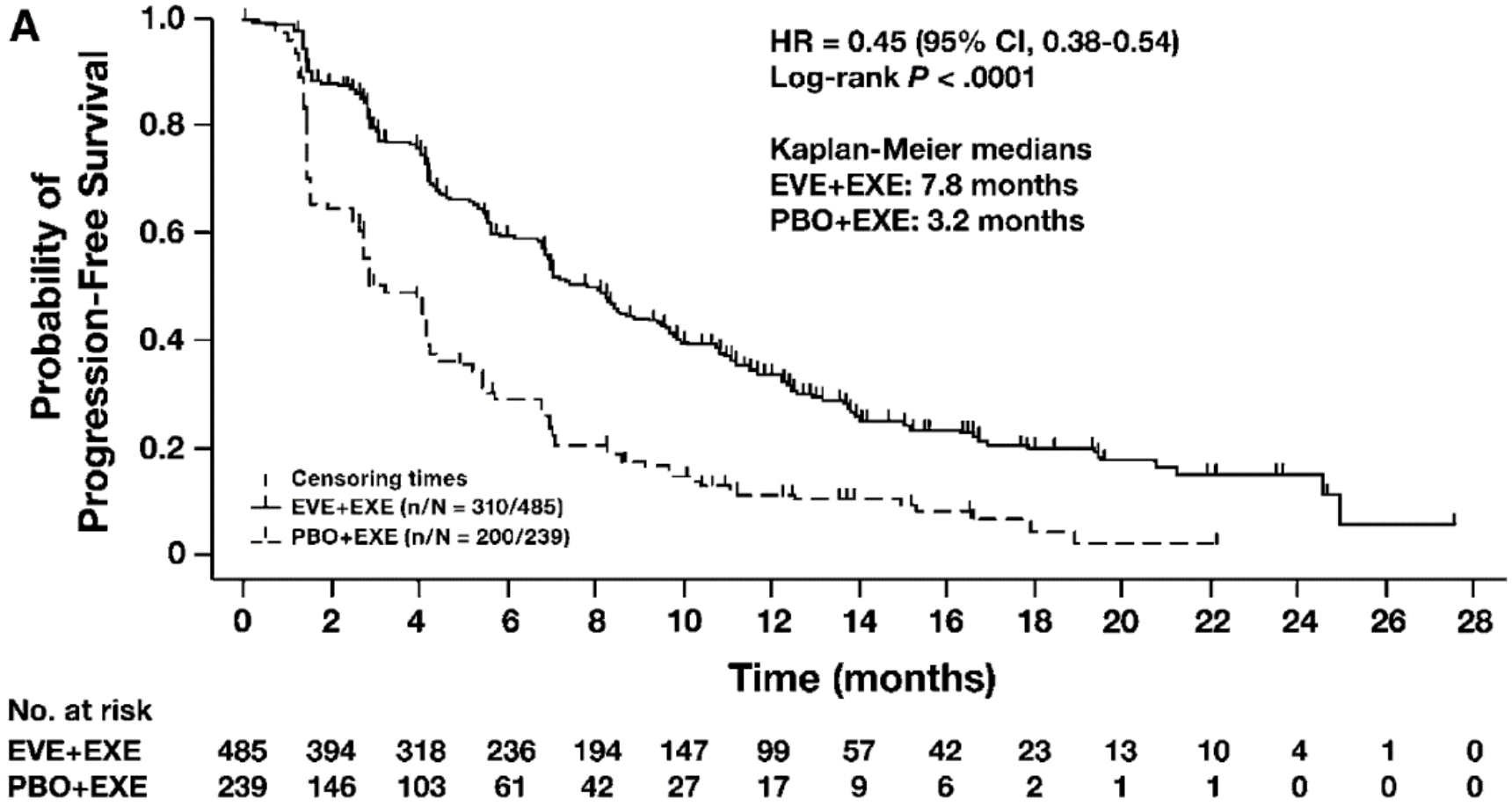


- Stratification
  1. Sensitivity to prior endocrine therapy
  2. Presence of visceral disease
- No crossover

NSAI, nonsteroidal aromatase inhibitor; LET, letrozole; ANA, anastrozole; QOL, quality of life.

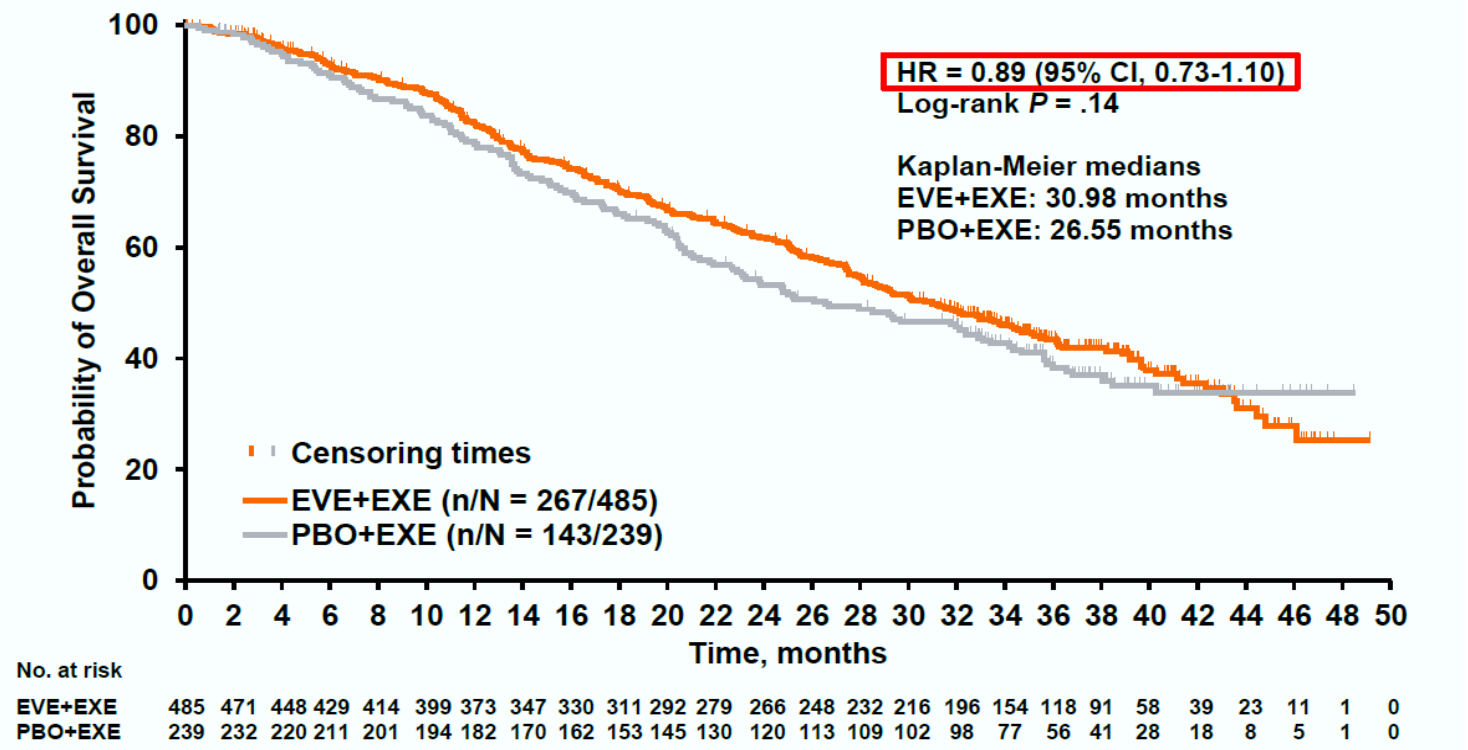
Baselga J, et al. *N Engl J Med*. 2012;366:520-529.

EVE + EXE More Than Doubled Median PFS-Final Analysis by Local Assessment



Yardley D, et al. *Adv Ther.* 2013;30(10):870-884.

EVE + EXE Demonstrated a 4.4-month Not Statistically Significant Improvement in OS at 39-month Final Analysis



- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: October 3, 2013)
- 55% of patients (n = 267) in the EVE + EXE arm
- 60% of patients (n = 143) in the PBO + EXE arm

One-sided *P* value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®.
IXRS, Interactive Voice and Web Response System.
Piccart M, et al. *Ann Oncol.* 2014;25:2357-2362.

BOLERO-2: Longer Median Time from Randomization to First Chemotherapy or Death for EVE + EXE vs PBO + EXE

Time from Randomization to First Chemotherapy or Death	Everolimus + Exemestane (n = 485)	Placebo + Exemestane (n = 239)
Number of events, n (%)	**366 (75.5)**	**192 (80.3)**
Chemotherapy	257 (53.0)	150 (62.8)
Death	109 (22.5)	42 (17.6)
Number censored, n (%)	**119 (24.5)**	**47 (19.7)**
Discontinued from study	105 (21.6)	45 (18.8)
Ongoing at data cutoff[a]	14 (2.9)	2 (0.8)
Time from randomization to first chemotherapy or death, months		
25th percentile (95% CI)	5.68 (5.03-6.57)	3.06 (2.53-3.48)
Median (95% CI)	11.86 (10.45-13.08)	5.98 (5.09-7.39)
75th percentile (95% CI)	25.10 (22.97-28.06)	14.16 (10.74-18.50)

[a]Ongoing without any chemotherapy by the cutoff date.

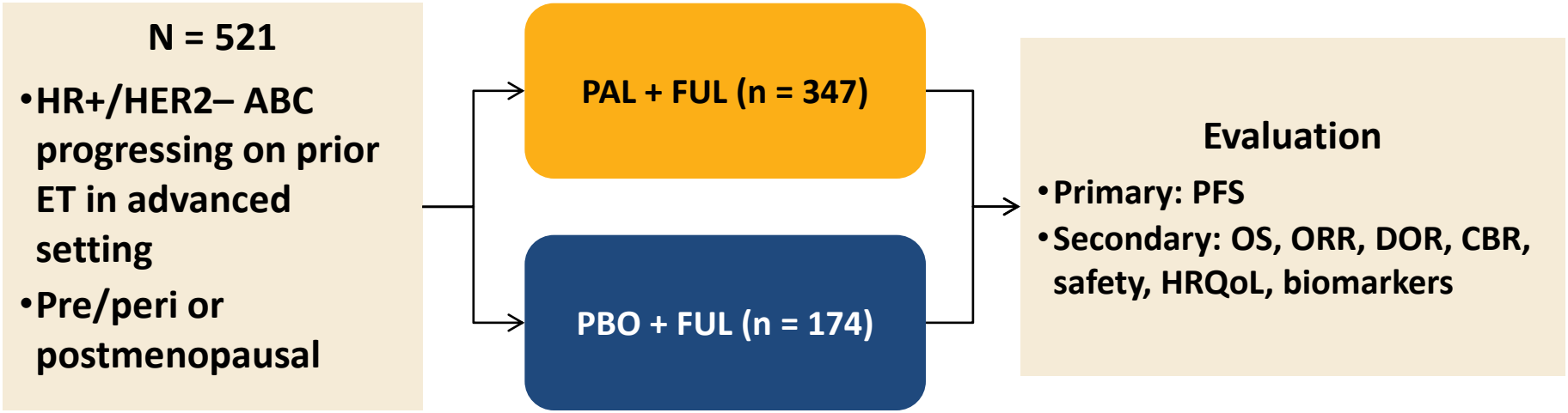
Piccart M, et al. *Ann Oncol.* 2014;25(12):2357-62.

PALOMA-3: Phase III Trial of FUL ± PAL in Women with HR+/HER2– MBC Progressing on Prior ET

Objectives

- To determine efficacy and safety of palbociclib (PAL) plus fulvestrant (FUL) in pts with HR+/HER2– mBC progressing on prior ET

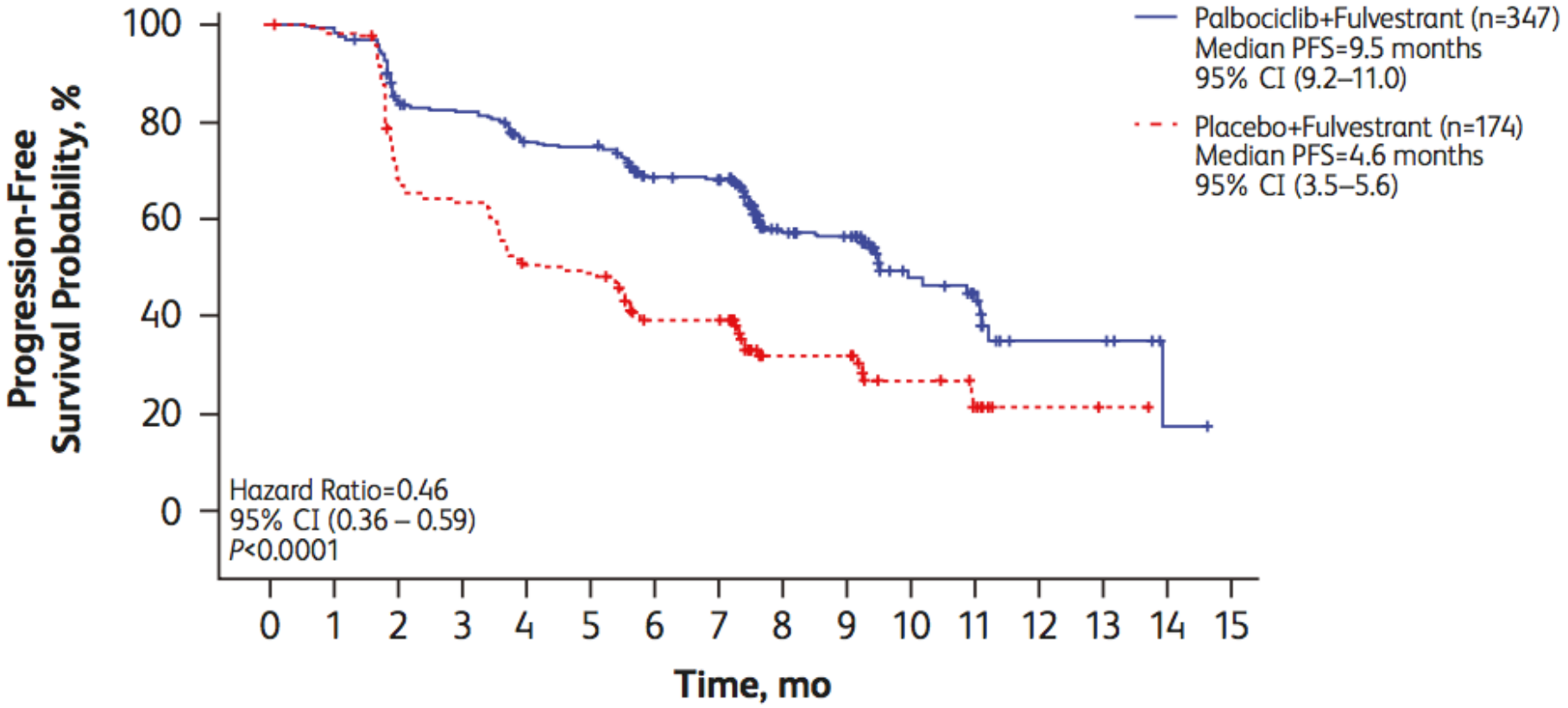
Methodology



ABC, advanced breast cancer; CBR, clinical benefit rate; DOR, duration of response; ET, endocrine therapy; FUL, fulvestrant; HRQoL, health related quality of life; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression free survival.

Turner NC, et al. ASCO 2015. Abstract #LBA502.

Paloma 3: PALBO-FULV vs. FLV 500
PFS población global (ITT)



FUL=fulvestrant; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.
*Investigator-assessed.

Palbociclib is not approved in Korea

M Cristofanili; SABCS 2015

Second Line Endocrine Therapy Phase III Results

Postmenopausal Patients Progressing on tamoxifen, letrozole or anastrozole

	LET	EXE	FV LD	FV HD	EXE + RAD	FVHD + PALBO
Control	**MEG. AC**	**MEG. AC**	**EXE**	**FV LD**	**EXE**	**FV HD**
HR PFS	1.04	0.82	0.96	0.80	0.43	0.42
p	NS	0.037	NS	0.006	<0.00001	<0.00001
Median PFS	3,8	4,8	3,7	6,5	7,8	9,2

LET, letrozole; EXE, exemestane; FVLD, fulvestrant 250 mg; FVHD, fulvestrant 500 mg; RAD, everolimus; PALBO, palbociclib; MEG AC, megestrol acetate

Dombernowsky et al. J Clin Oncol. 1998;16:453-61. Kaufmann et al. J Clin Oncol. 2000 Apr;18(7):1399-411. Chia et al. J Clin Oncol. 2008;26:1664-1670. Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600. Yardley D et al. Adv Ther. 2013; 30(10):870-884

Face-to-Face:
CONFIRM vs PALOMA-3 vs BOLERO-2

All studies had the same indication, but not the same population

Percentage	CONFIRM	PALOMA-3	BOLERO-2
Progression on AI	65	85	100
Benefit to prior line of ET	NK	79	85
Prior chemotherapy for ABC	NK	31	24
1st – 2nd ABC line of therapy	100	62	61
Dose intensity	98	91	78
Discontinuations	2,3	2,5 (SAE related)	6.5 + 6.7*
PFS HR	**0.80**	**0.42**	**0.45**

***Includes treatment discontinuations and consent withdrawal.**

CONFIRM / Fulvestrant
Toxicity profile

	N (%) patients		P-value
	Fulvestrant 500mg N=361	Fulvestrant 250mg N=374	
Endometrial dysplasia	0	0	
GI disturbances	73 (20.2)	76 (20.3)	1.000
Hot flushes	30 (8.3)	23 (6.1)	0.318
Injection site reactions	49 (13.6)	50 (13.4)	1.000
Joint disorders	68 (18.8)	70 (18.7)	1.000
Osteoporosis	1 (0.3)	0	0.492
Thromboembolic events	3 (0.8)	6 (1.6)	0.506
Urinary tract infection	8 (2.2)	8 (2.1)	1.000
Vaginitis	3 (0.8)	1 (0.3)	0.366
Weight gain	1 (0.3)	1 (0.3)	1.000

BOLERO-2 / Everolimus
Toxicity profile

	EVE + EXE (n = 482), %				
	Grade				
AE (Preferred Term)	All	1	2	3	4
Stomatitis	59	29	22	8	0
Rash	39	29	9	1	0
Fatigue	37	18	14	4	<1
Diarrhoea	34	26	6	2	<1
Nausea	31	21	9	<1	<1
Decreased appetite	31	19	10	1	0
Weight decreased	28	10	16	2	0
Cough	26	21	4	1	0
Pneumonitis*	16	7	6	3	0
Hyperglycaemia*	14	4	5	5	<1

*Incidence <25%, but AE of special interest.
Yardley D, et al. *Adv Ther.* 2013;30(10):870-884.

Yardley D, et al. *Adv Ther.* 2013;30(10):870-884.

PALOMA-3 / Palbociclib
Adverse Events—All Cause

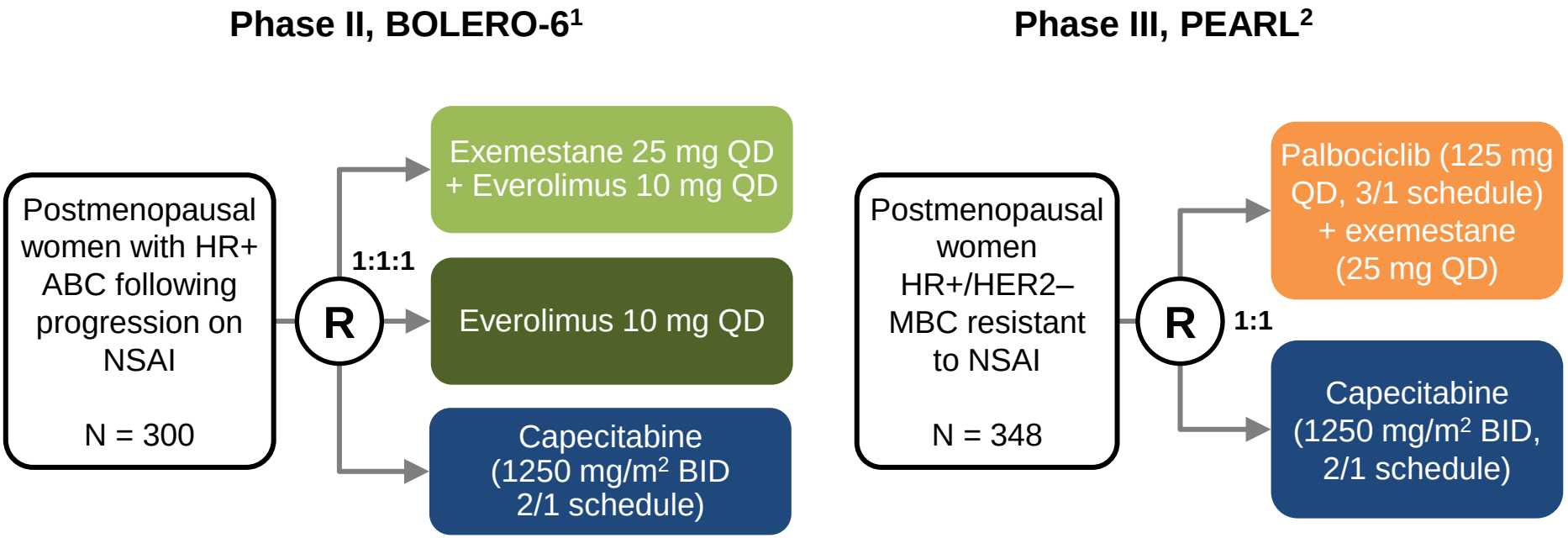
AE, %	Palbociclib + Fulvestrant (n=345)			Placebo + Fulvestrant (n=172)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	98	59	11	89	16	2
Neutropenia	79	53	9	3	0	1
Leukopenia	46	25	1	4	0	1
Anemia	26	3	0	10	2	0
Thrombocytopenia	19	2	1	0	0	0
Fatigue	38	2	0	27	1	0
Nausea	29	0	0	26	1	0
Headache	21	<1	0	17	0	0
Upper respiratory infection[a]	19	<1	0	16	0	0
Diarrhea	19	0	0	17	1	0
Constipation	17	0	0	14	0	0
Alopecia	15	0	0	6	0	0

AE=adverse event. AEs with ≥15% incidence in the palbociclib + fulvestrant group reported.

Palbociclib is not approved in India

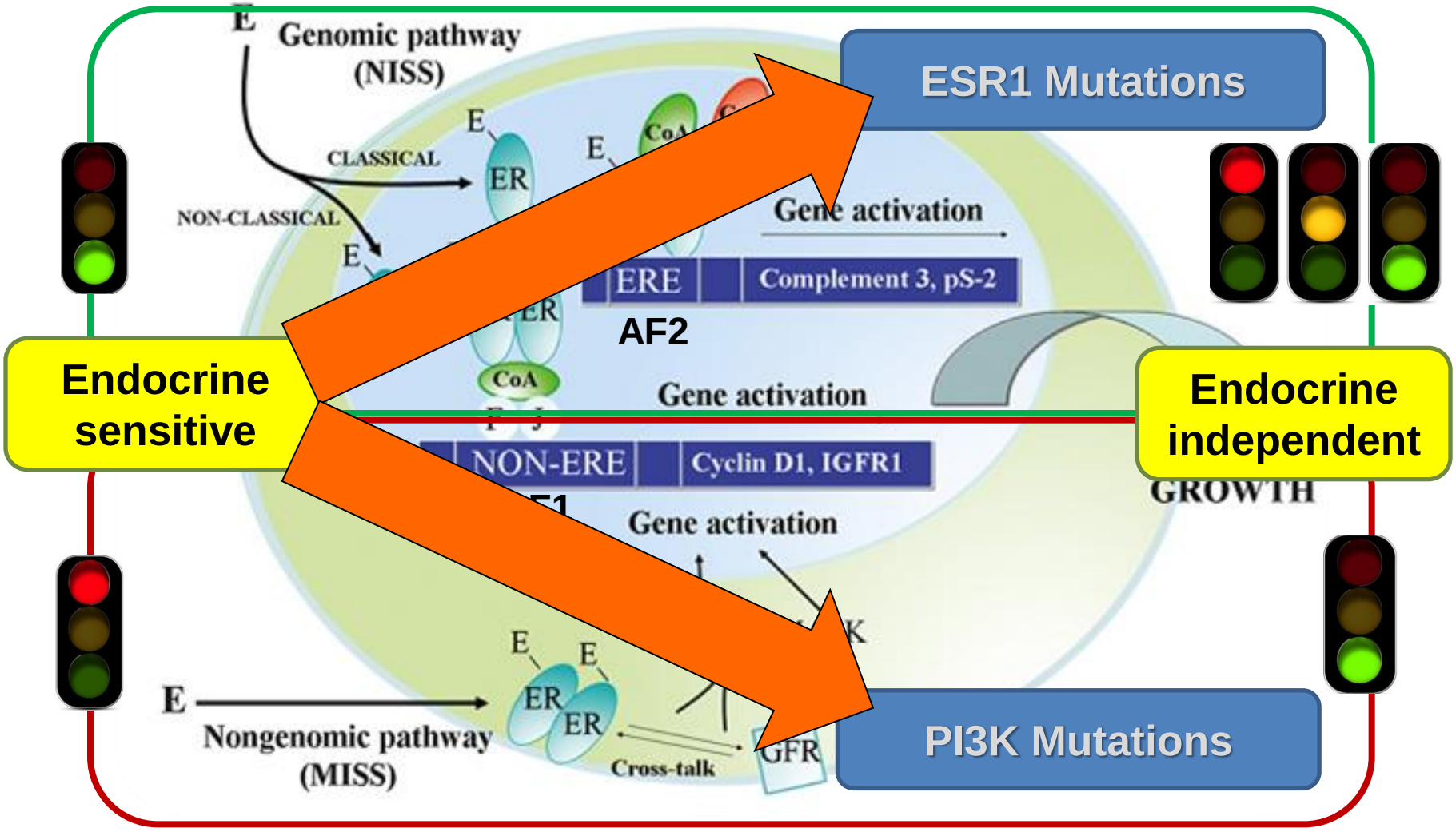
Turner NC, et al. *N Engl J Med*. 2015;373:209-219
Turner NC, et al. ASCO 2015 (Abstract LBA502)

Other Options After NSAI: Phase II–III Trials Face-to-Face – Endocrine Therapy vs Capecitabine



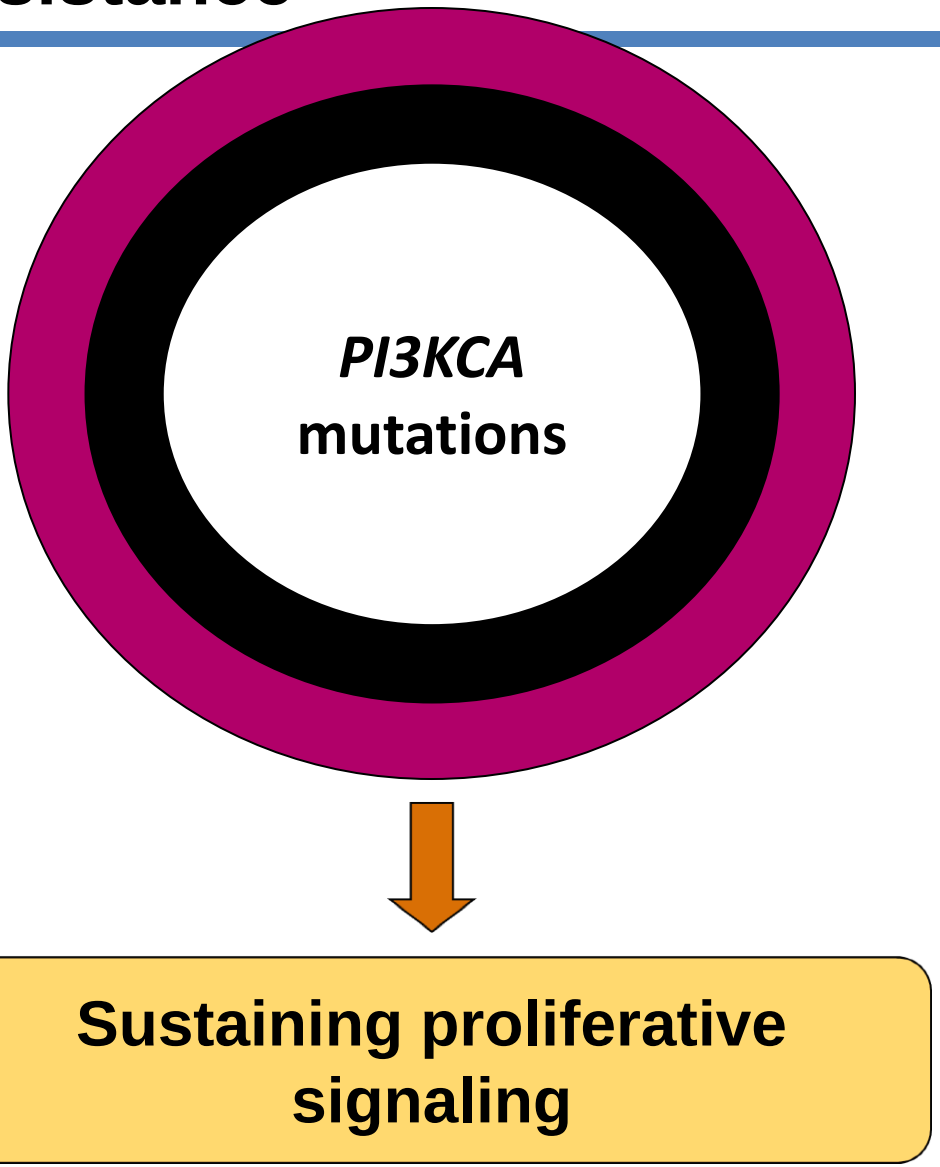
1. Clinicaltrials.gov NCT01783444;
2. Clinicaltrials.gov NCT02028507.

ER Signaling Pathways: Most Prevalent Mechanisms of Resistance to AI

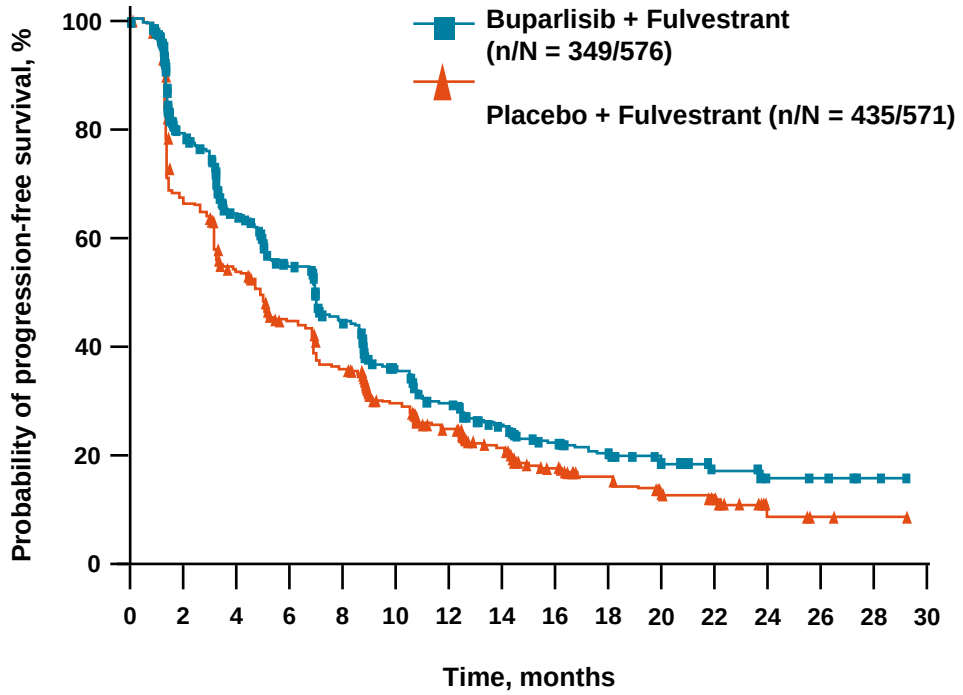


Zilli M, et al. *Biochim Biophys Acta.* 2009;1795:62-81.

Acquired Resistance



BELLE-2 Met the Primary Endpoint for PFS Improvement in the Full Population



Full Population (N = 1147)	Buparlisib + Fulvestrant n = 576	Placebo + Fulvestrant n = 571
Median PFS, months (95% CI)	6.9 (6.8–7.8)	5.0 (4.0–5.2)
HR (95% CI)	0.78 (0.67–0.89)	
One-sided *P* value	<.001	

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI, 0.68–0.94]; one-sided *P* value = .003)
- Follow-up for OS analysis is ongoing, with a prespecified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

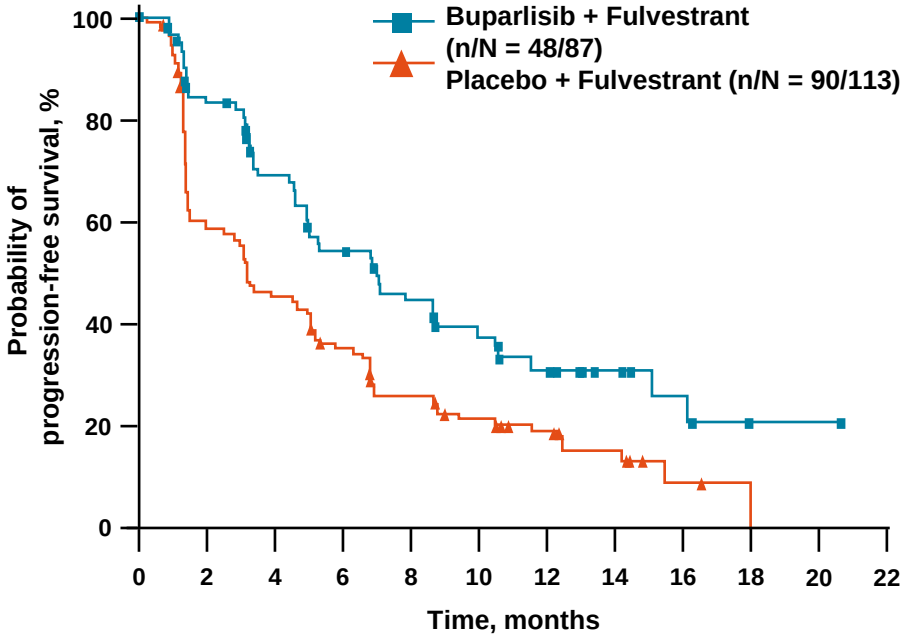
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

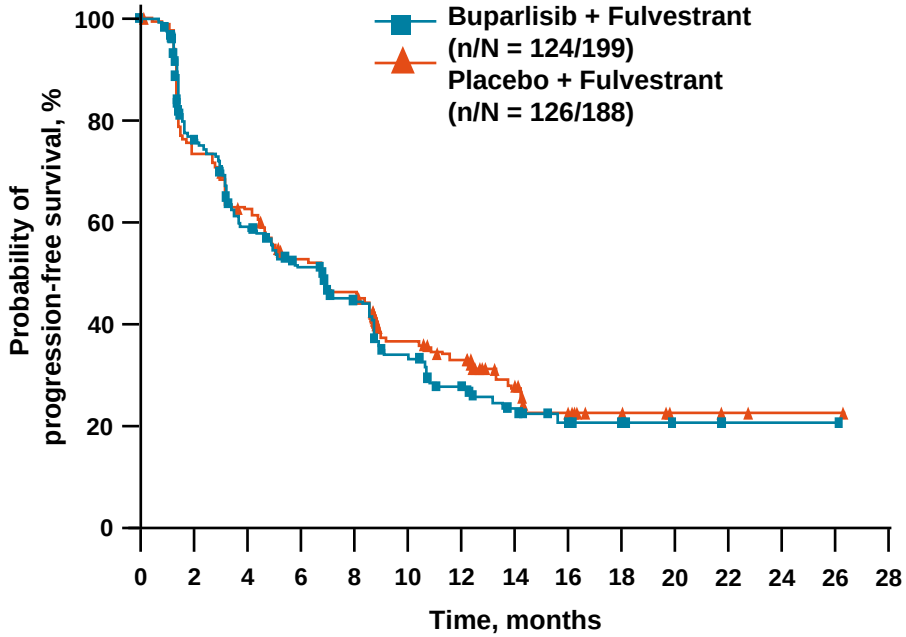
Baselga J, et al. SABCS 2015. Poster S6-01.

Buparlisib + Fulvestrant: Clinically Meaningful PFS Improvement in Patients with ctDNA *PIK3CA* Mutations

ctDNA *PIK3CA* Mutant n = 200	Buparlisib + Fulvestrant n = 87	Placebo + Fulvestrant n = 113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<.001	

ctDNA *PIK3CA* Nonmutant n = 387	Buparlisib + Fulvestrant n = 199	Placebo + Fulvestrant n = 188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	.642	





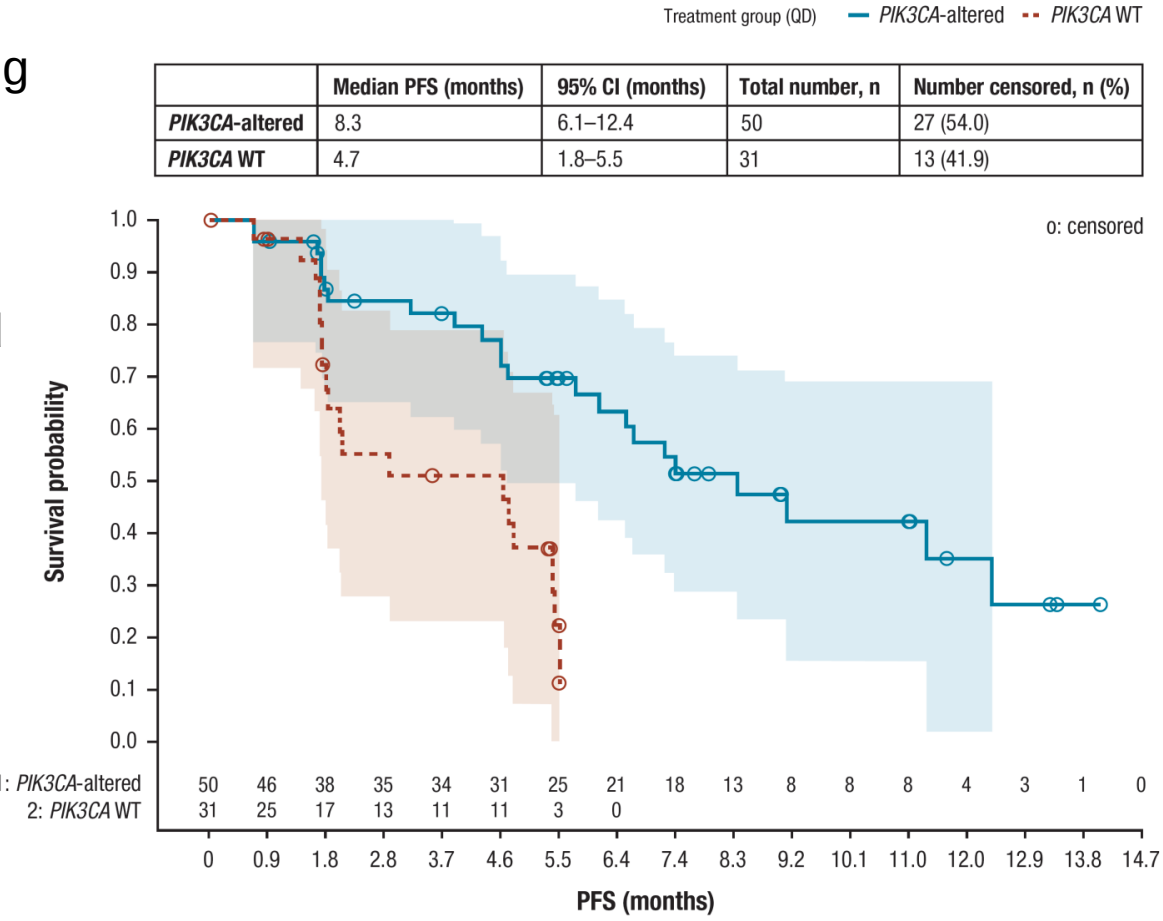
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Baselga J, et al. SABCS 2015. Poster S6-01.

Alpelisib + Fulvestrant Activity in Patients with ABC Harboring Mutant or Wildtype *PIK3CA*

- Alpelisib + Fulvestrant 500 mg demonstrated encouraging clinical activity across dose levels
- Patients with *PIK3CA*-altered tumors had better response vs WT
  - Increased ORR (not shown)
  - Longer PFS benefit

	Median PFS (months)	95% CI (months)	Total number, n	Number censored, n (%)
***PIK3CA*-altered**	8.3	6.1–12.4	50	27 (54.0)
***PIK3CA* WT**	4.7	1.8–5.5	31	13 (41.9)

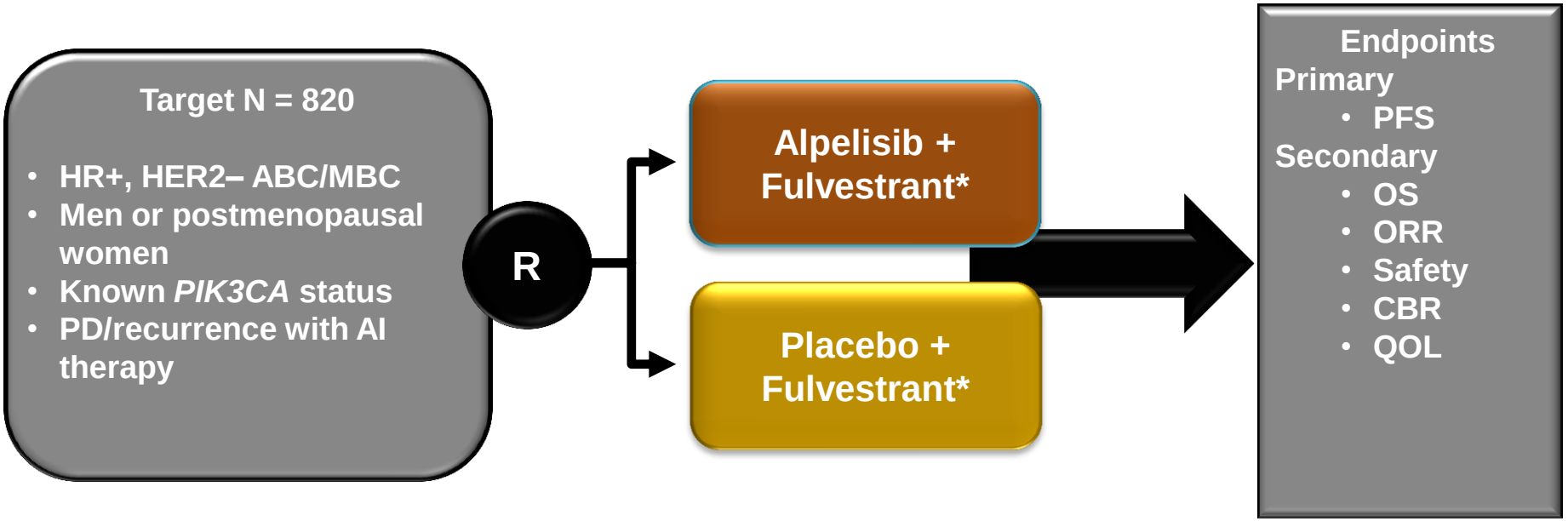


ABC, advanced breast cancer; CI, confidence interval; ORR, overall response rate; PFS, progression-free survival; PIK3CA, phosphoinositide 3-kinase, catalytic, alpha; QD, once daily; WT, wildtype.

Reprinted from Janku F, et al. SABCS 2014. Abstract PD5-5 (poster presentation); www.clinicaltrials.gov (NCT01219699).

SOLAR-1: Alpelisib + Fulvestrant Treatment in ABC Following AI Therapy

SOLAR-1 (NCT02437318)[1]: Phase III randomized, double-blind, placebo-controlled study

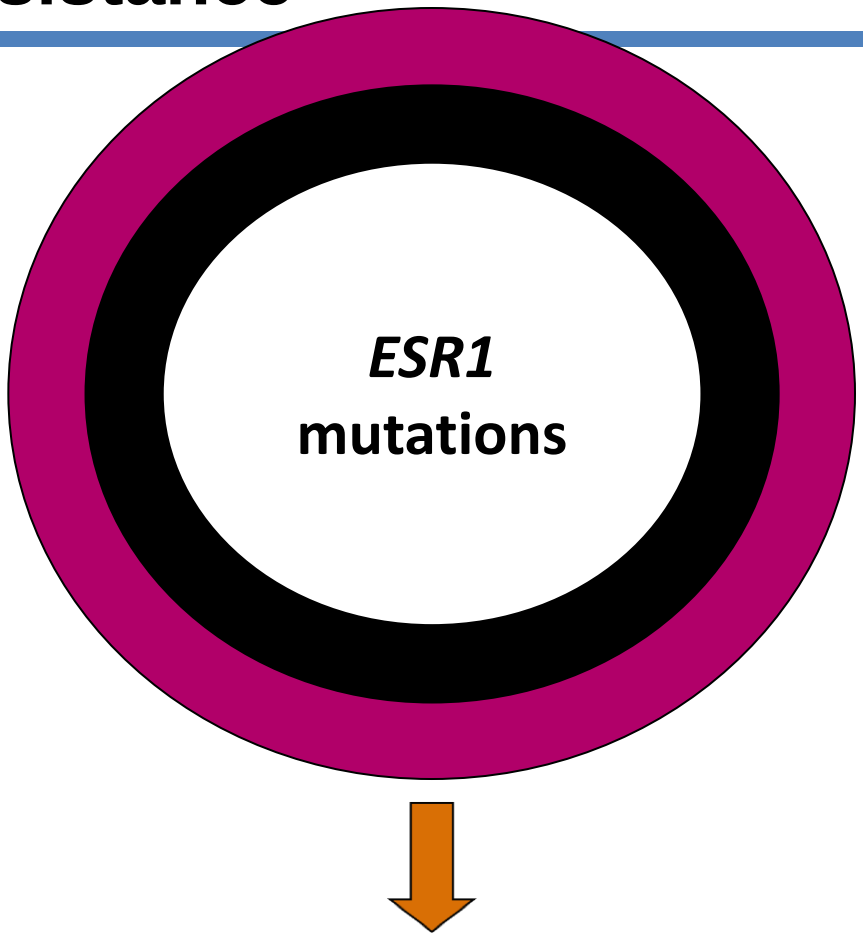


Enrollment began July 2015; study is currently enrolling

ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; IM, intramuscular; MBC, metastatic breast cancer; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PIK3CA, phosphoinositide 3-kinase, catalytic, alpha; PO, oral; QOL, quality of life.
*Alpelisib or placebo (300 mg; PO; once daily); fulvestrant (500 mg; IM; Day 1 and Day 15 of Cycle 1, then Day 1 of each subsequent 28-day cycle).

1. www.clinicaltrials.gov (NCT02437318).

Acquired Resistance



ESR1 Mutations in Metastatic Breast Cancer

Mutations of the ER gene (ESR1 mutations) have recently been identified as a causative factor for the development of endocrine resistance

ESR1 mutations are only rarely found in primary breast cancer and are only found at an appreciable frequency after the development of hormone resistance

Most of the ESR1 mutations occur in a hotspot within the ligand binding domain (LBD), and constitutively activate the ER in a ligand independent manner

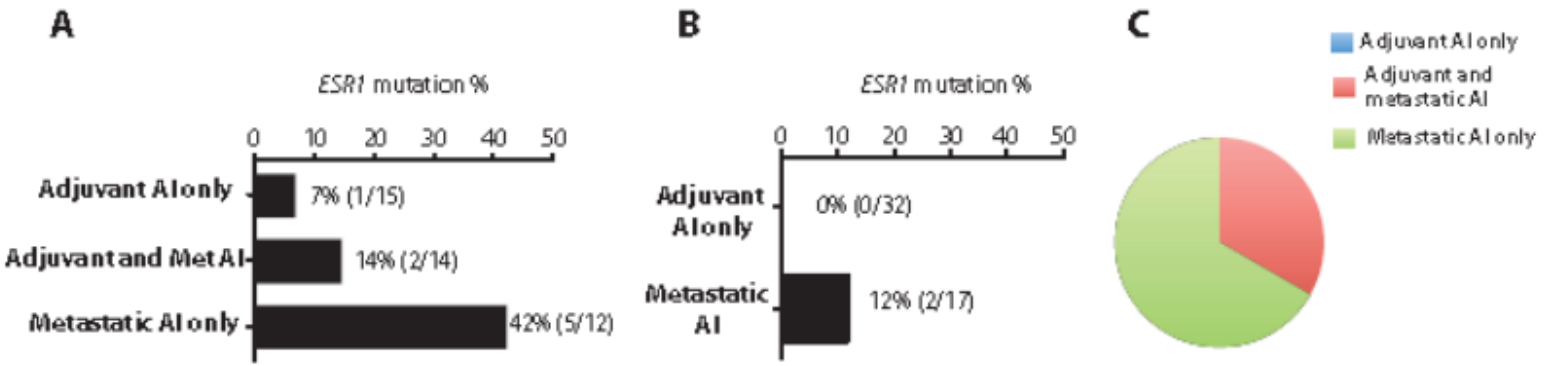
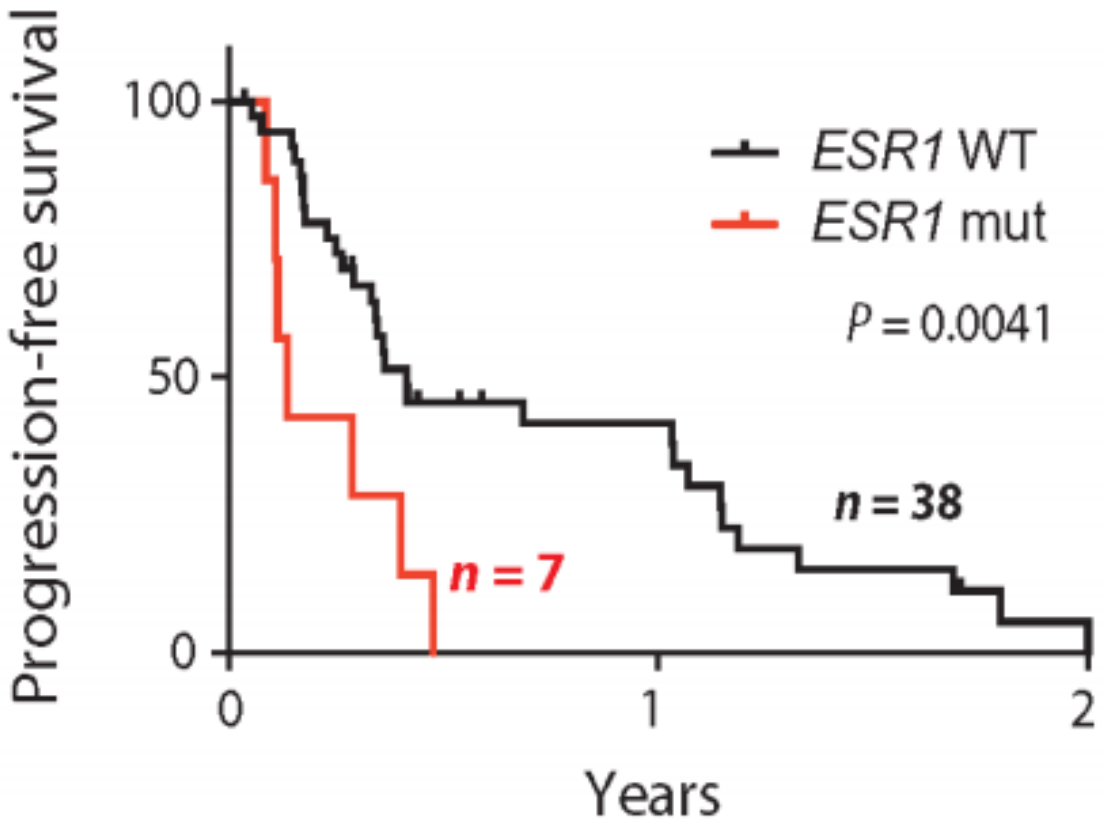


Fig. 4. Validation and independent series confirm the importance of timing of previous AI exposure for *ESR1* mutation selection. (**A**) *ESR1* mutation rate assessed only in patients with detection of a mutation other than *ESR1* in plasma DNA. $P = 0.061$, χ^2 test overall; $P = 0.035$, adjuvant AI only versus metastatic AI only. (**B**) Assessment of *ESR1* mutation rate in an independent series of 49 breast tumor biopsies that had recurred after previous AI therapy. No *ESR1* mutations were identified in breast tumor biopsies relapsing after adjuvant AI (0%; 95% CI, 0 to 10.9). (**C**) Reassessment of a second independent series of *ESR1* mutant–positive cancers, with timing of previous AI therapy (9).

Gendreau S, et al. SABCS 2015. Poster PD6-03.

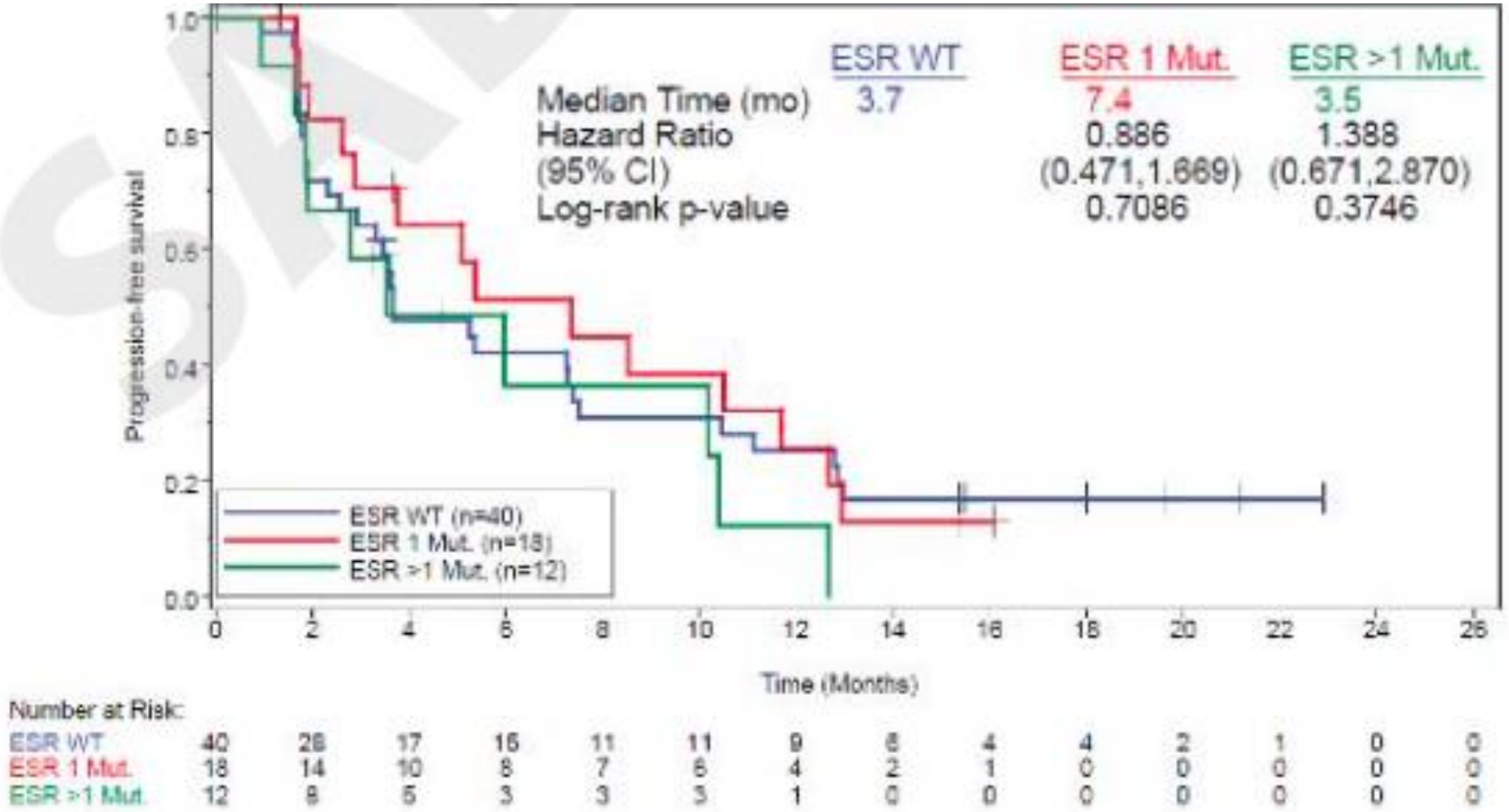
ctDNA *ESR1* Mutations: Potential Mechanism of Resistance to Aromatase Inhibitors

PFS on AI therapy after ctDNA analysis for patients with ESR1 mutant and WT ctDNA (HR, 3.1; 95% CI, 1.9 to 23.1; P = 0.0041, log-rank test).



Gendreau S, et al. SABCS 2015. Poster PD6-03.

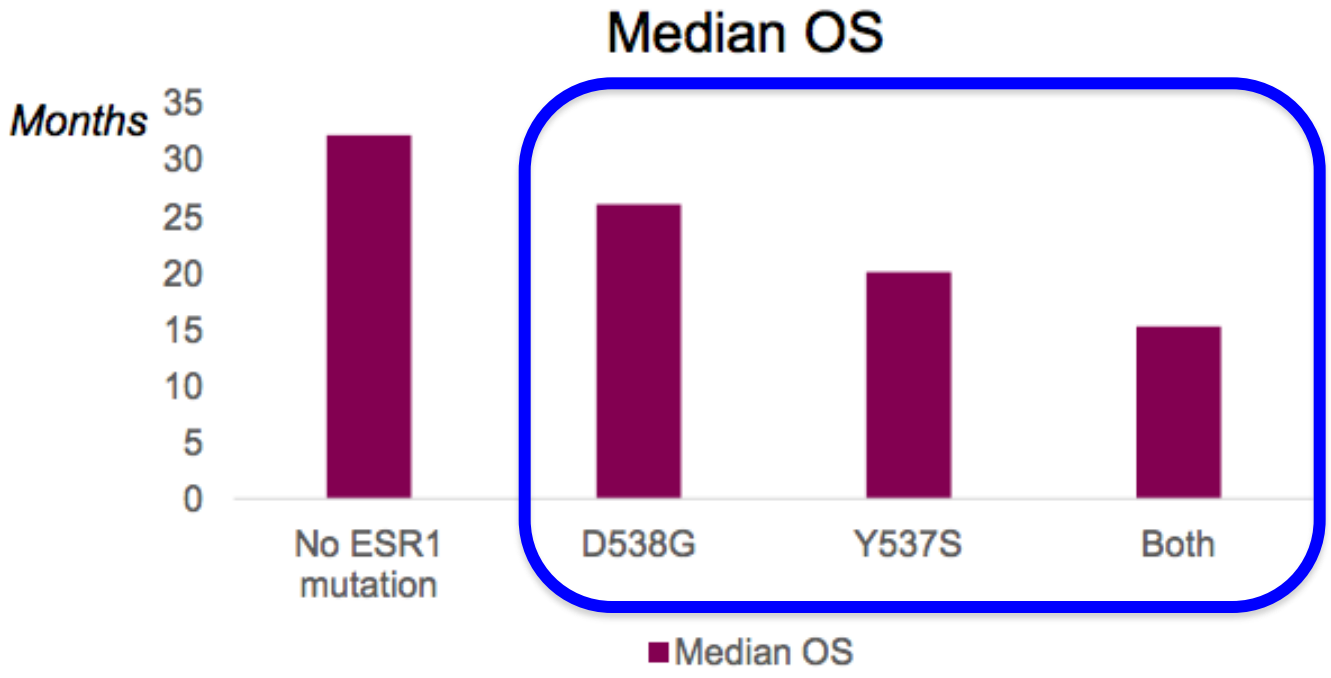
ctDNA *ESR1* Mutations: Not a Resistant Mechanism for Fulvestrant (FERGI Trial)



Gendreau S, et al. SABCS 2015. Poster PD6-03.

BOLERO-2: *ESR1* Mutations and Overall Survival

- Cell free DNA samples analysed from 541 of the 724 women in BOLERO2
- Almost 30% tested positive for ESR1 mutations (D538G and Y537S)

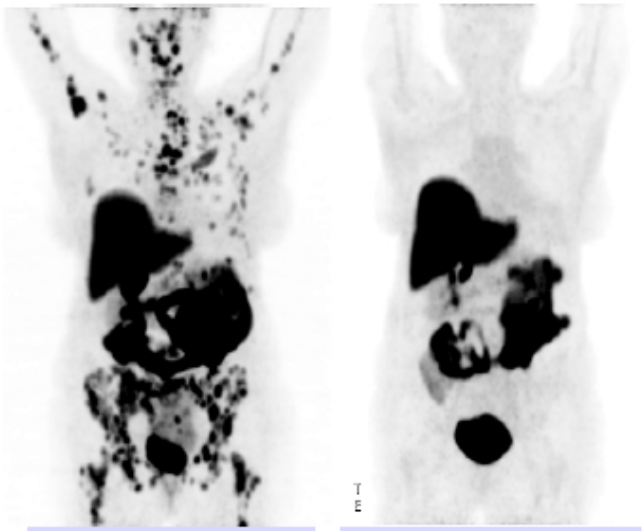


Gendreau S, et al. SABCS 2015. Poster PD6-03.

Phase I Study of ARN-810 (GDC-0810), a Novel and Potent Oral Selective Estrogen Receptor Degrader, in Postmenopausal Women with Metastatic Estrogen Receptor Positive (ER+), HER2- Breast Cancer

Aditya Bardia,[1] Maura N Dickler,[2] Ingrid A Mayer,[3] Eric Winer,[4] Umar Mahmood,[1] Gary Ulaner,[2] H Charles Manning,[3] Peter Rix,[5] Jeffrey H Hager,[5] Debasish Roychowdhury,[5] Edna Chow Maneval,[5] Carlos L Arteaga,[3] and Jose Baselga[2]

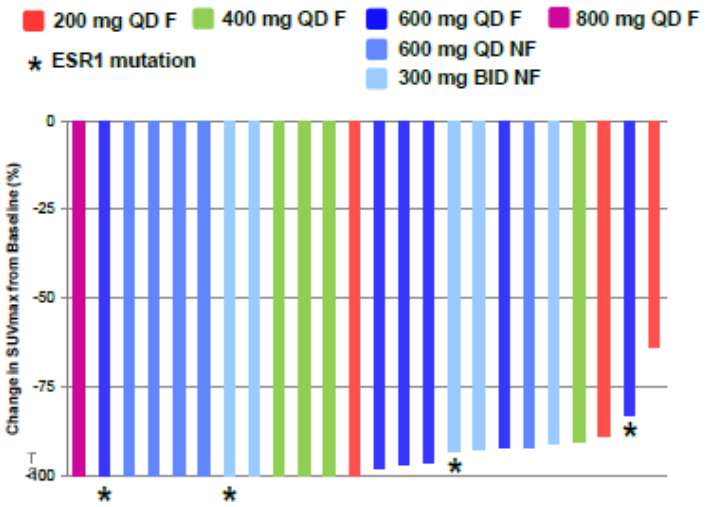
[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN; [4]Dana Farber Cancer Institute, Boston, MA; [5]Seragon Pharmaceuticals, a wholly owned subsidiary of Genentech, Inc., San Diego, CA



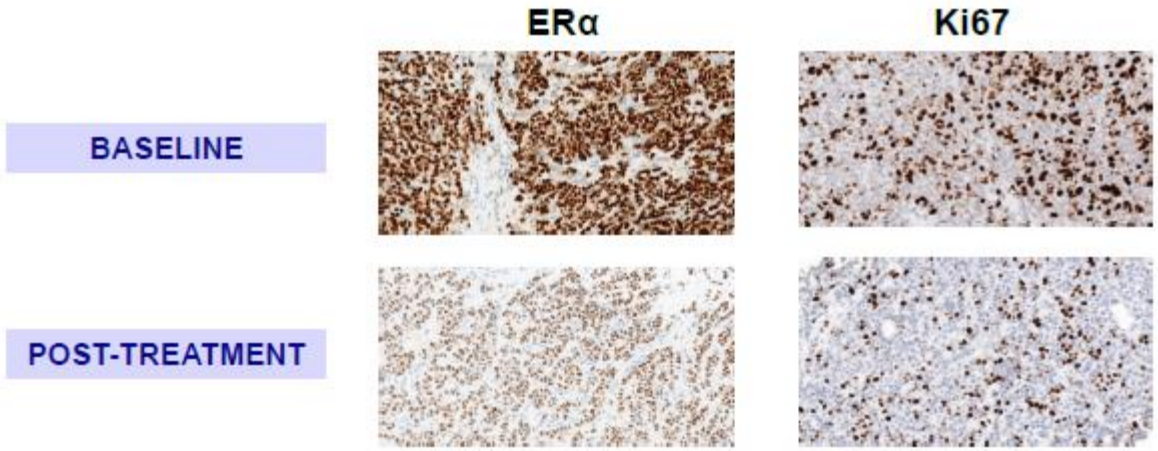
BASELINE
(ESR1 mutation patient)

CYCLE 2
(treated at 600 mg QD F)

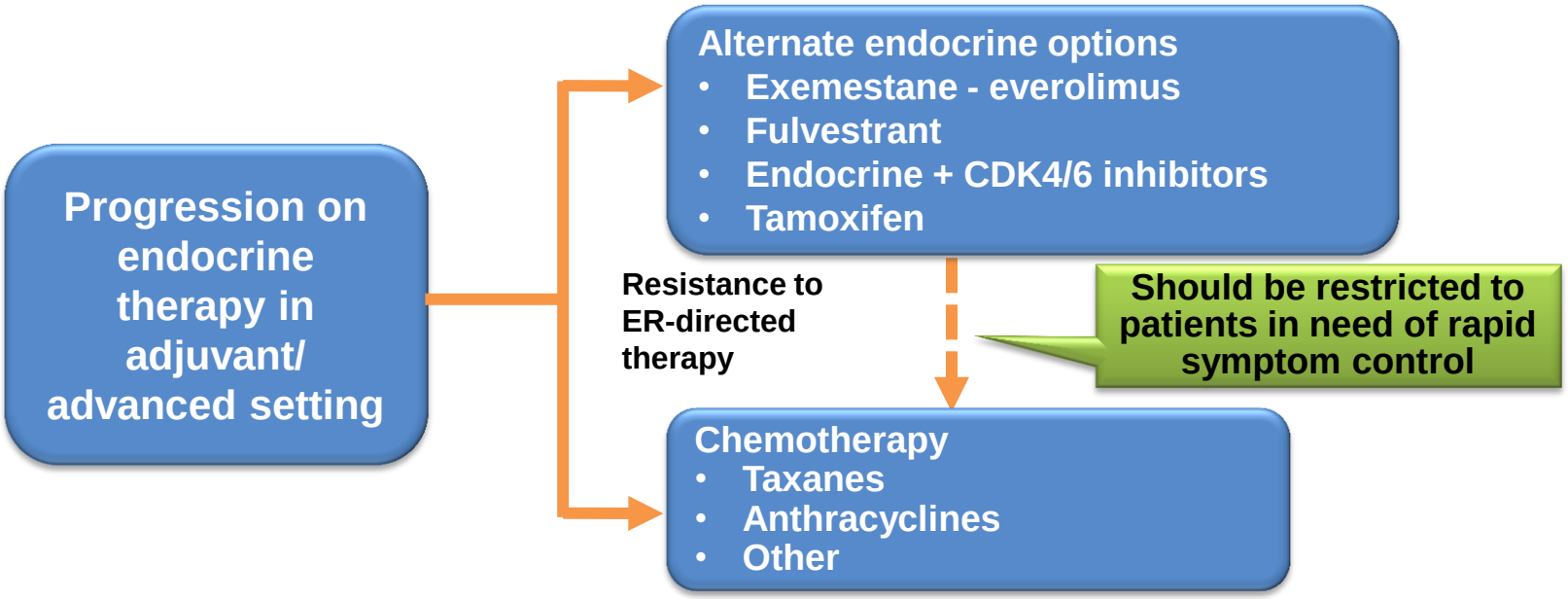
Waterfall plot showing FES-PET response rates across 6 different dose regimens



NOTE: Only 1 patient at 800 mg QD F had pre- and post-treatment images. No images were collected for the 100 mg QD dose cohort and post-treatment scans had not yet been performed for the 800 mg QD NF and 400 mg BID NF cohorts at the time of data cutoff. All patients treated at 600 and 800 mg QD had FES-PET scans performed between 18 and 24 hours post-dose.



Conclusions



NCCN[1]	ABC1[2]
Recommend 3 consecutive endocrine therapy regimens before switching to chemotherapy	No consensus following initial AI therapy; options include • Tamoxifen • Another AI • Fulvestrant • Megestrol acetate

AIs, aromatase inhibitors; ER, estrogen receptor; HR, hormone receptor; NCCN, National Comprehensive Cancer Center. Guidelines refer to postmenopausal HR+ advanced breast cancer, and recommend endocrine therapy for patients who are not in visceral crisis.

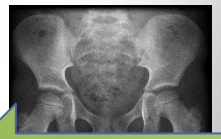
1. NCCN Guidelines. Breast Cancer. Version 2.2012; 2. Cardoso F, et al. *Breast*. 2012;21:242-252.

Endocrine-Resistant ER+/HER2– ABC: Treatment Decision Guided by Patient Scenario

PROFILE A

Good response, nonvisceral disease

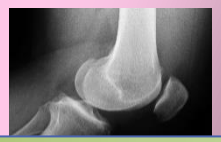
- Long DFI post-adjuvant Rx (eg, >12 mo) or long response to 1L ET Rx (eg, >12 mo)
- Predominantly bone-only mets
- Possible low-risk soft tissue mets (eg, skin/lymph)
- Asymptomatic



PROFILE B

Moderate response, nonvisceral disease

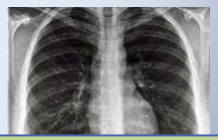
- Short DFI (eg, <12 mo) or recurrence while on adjuvant Rx or moderate response to 1L ET Rx (eg,~6 mo)
- Predominantly bone-only mets
- Possible low-risk soft tissue mets (eg, skin/lymph)
- No or minimal symptoms



PROFILE C

Low visceral burden

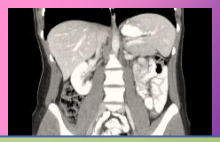
- Good or moderate response to prior endocrine therapy*
- Lower risk due to lower tumor burden (eg, discrete 1–2 met[s])
- No or minimal symptoms



PROFILE D

Moderate visceral burden

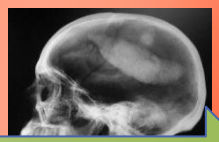
- Moderate response to prior endocrine therapy*
- Increased risk due to greater disease burden
- More extensive visceral met(s)
- Minimal/moderate symptoms



PROFILE E

Medical crisis stage

- Fast-progressing, life-threatening, aggressive disease
- Resistant to endocrine therapy
- Mets in high-risk sites requiring immediate medical intervention
- Highly symptomatic, requiring systemic treatment



Patient Factors

Fulvestrant → **EVE *(Palbo?)***

EVE *(Palbo?)* → **Fulv** / **CT**

Chemotherapy

Sequential ET