ESMO Preceptorship on Breast Cancer

ESMO PRECEPTORSHIP ON BREAST CANCER

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ABC3

Navigating the conundrum of endocrine therapy in ABC

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European School of Oncology
Learning to care

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ER POSITIVE / HER-2 NEGATIVE MBC

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. (LoE: 1 A) (93%)

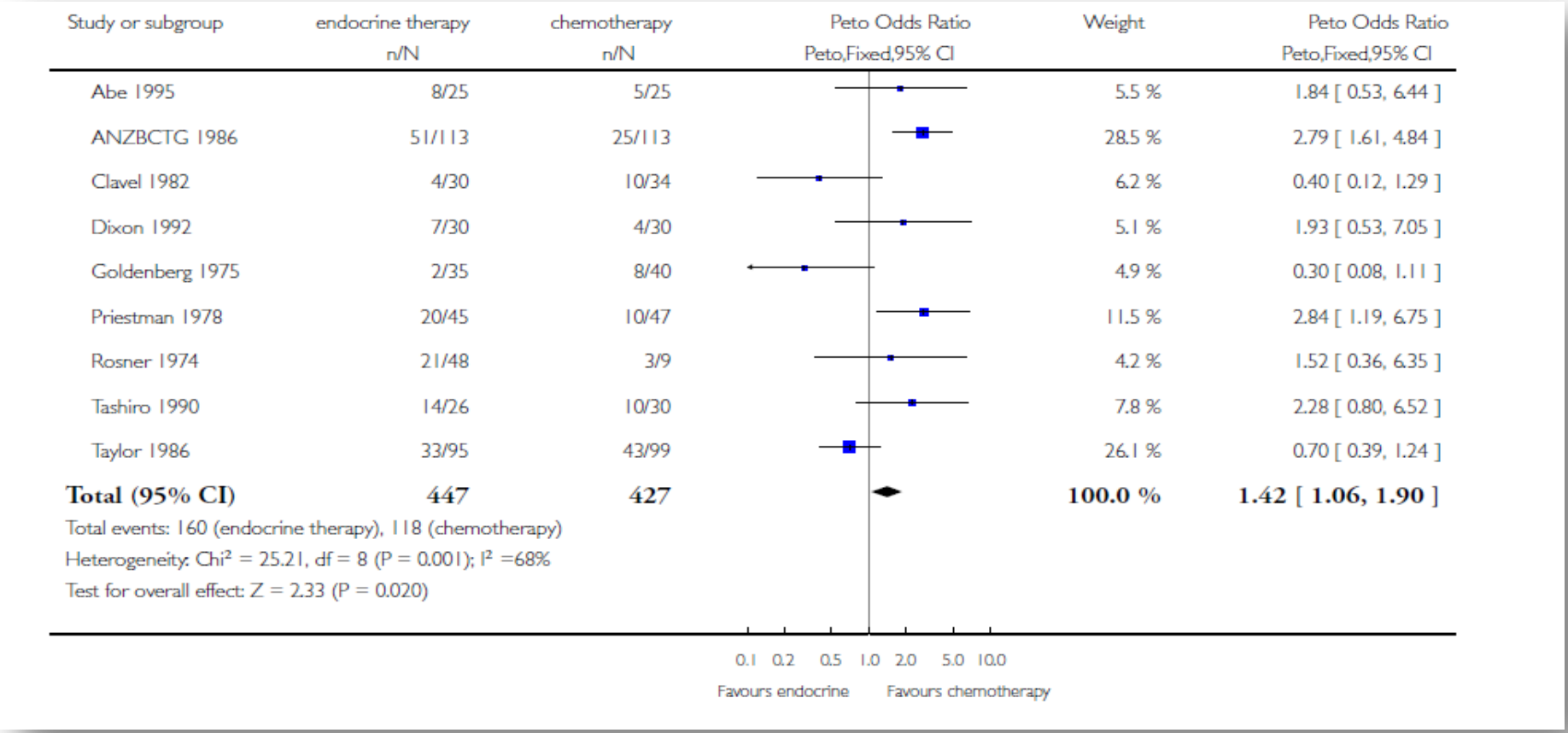
VISCERAL CRISIS is defined as **severe organ dysfunction** as assessed by signs and symptoms, laboratory studies, and **rapid progression of disease.**

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.

(LoE: Expert opinion) (95%)

Treatment of HR+ ABC

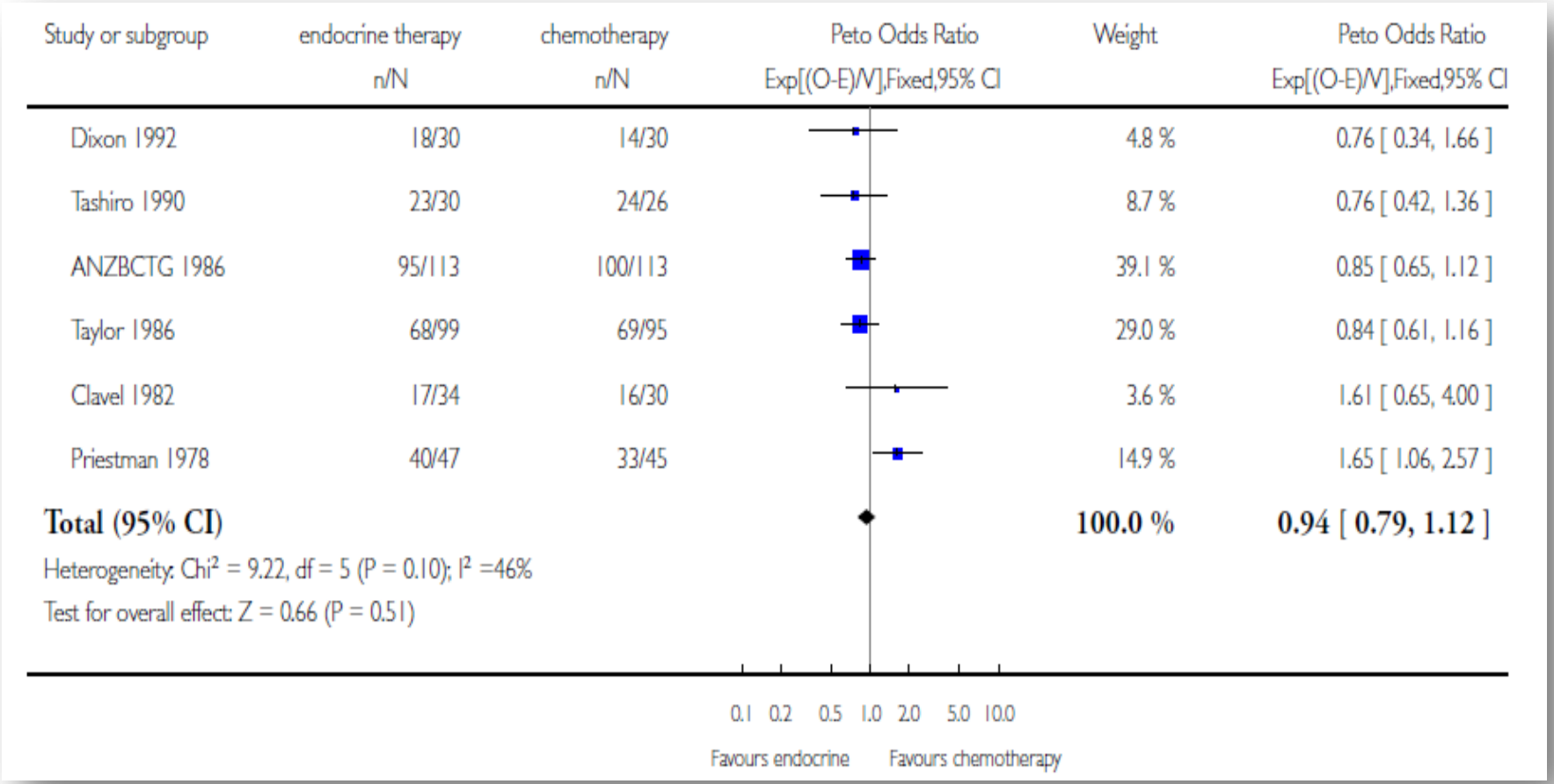
⇒ Direct comparisons: chemotherapy has a higher response rate



Wilcken et al., Cochrane Database Syst Rev , 2009.

Treatment of HR+ ABC

⇒ Direct comparisons: No significant differences in overall survival



Wilcken et al., Cochrane Database Syst Rev , 2009.

Meta-analysis: Chemotherapy vs Endocrine Therapy in MBC

Methods

- Randomized trials of chemotherapy alone vs endocrine therapy alone

Results

- No significant difference for OS in 6 trials (N = 692):
  HR: 0.94 (95% CI: 0.79-1.12; *P* = .5)
- Significant difference favoring chemotherapy for ORR in 8 trials (N = 817):
  HR: 1.25 (95% CI: 1.01-1.54; *P* = .04)
  - However, the 2 largest trials demonstrated trends in opposite directions
- Toxicity: Little information available on adverse events and QoL
  - Increased toxicity with chemotherapy (nausea, vomiting, alopecia)
  - 3 of 7 trials noted QoL aspects with differing results

Authors' Conclusions

- *"In women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease."*

Wilcken N, et al. Cochrane Database Syst Rev. 2003;(suppl 2):CD002747. Slide credit: clinicaloptions.com

In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium

D. J. A. Lobbezoo[1,2], R. J. W. van Kampen[1], A. C. Voogd[1,3], M. W. Dercksen[2], F. van den Berkmortel[4], T. J. Smilde[5], A. J. van de Wouw[6], F. P. J. Peters[7], J. M. G. H. van Riel[8], N. A. J. B. Peters[9], M. de Boer[1], P. G. M. Peer[10] & V. C. G. Tjan-Heijnen[1*]

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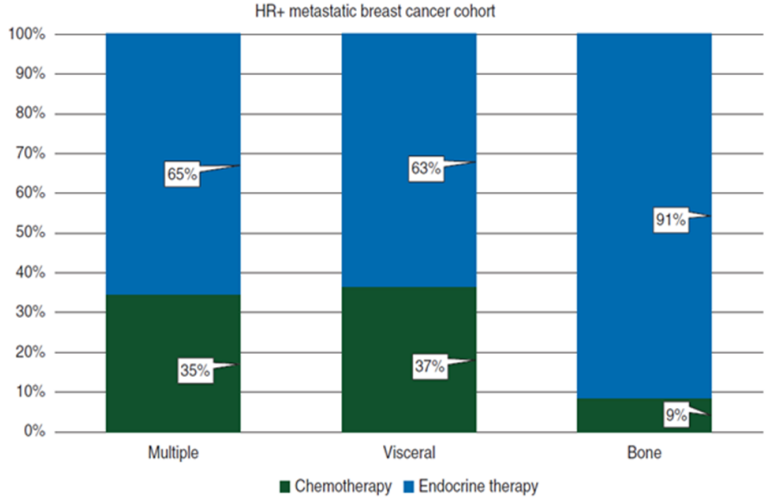
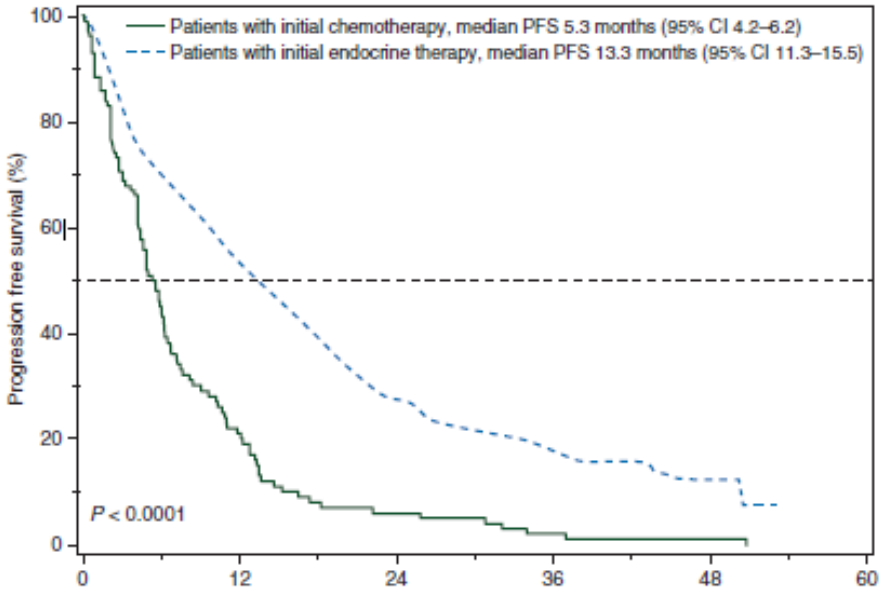
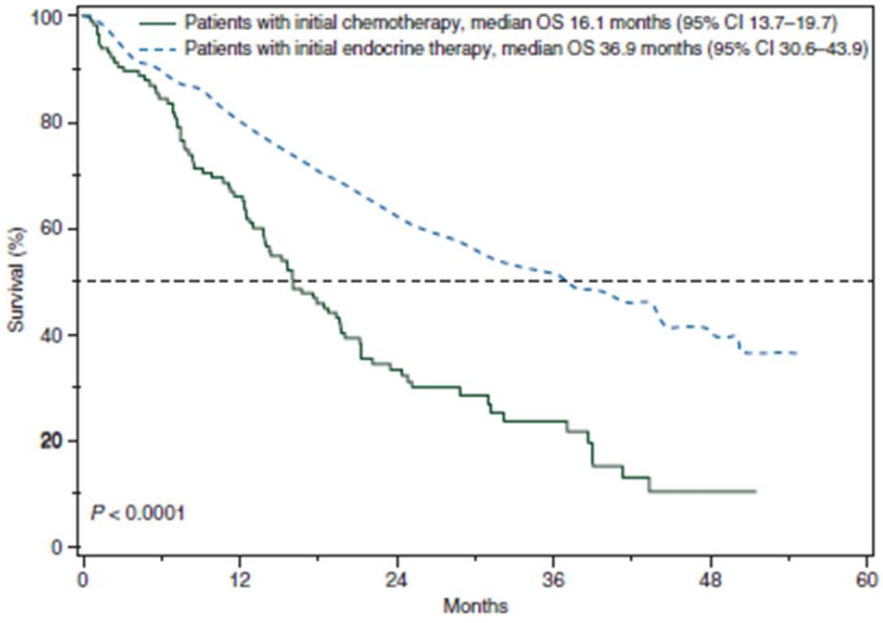


Starting with ET vs. Starting with CT

PFS



OS



ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

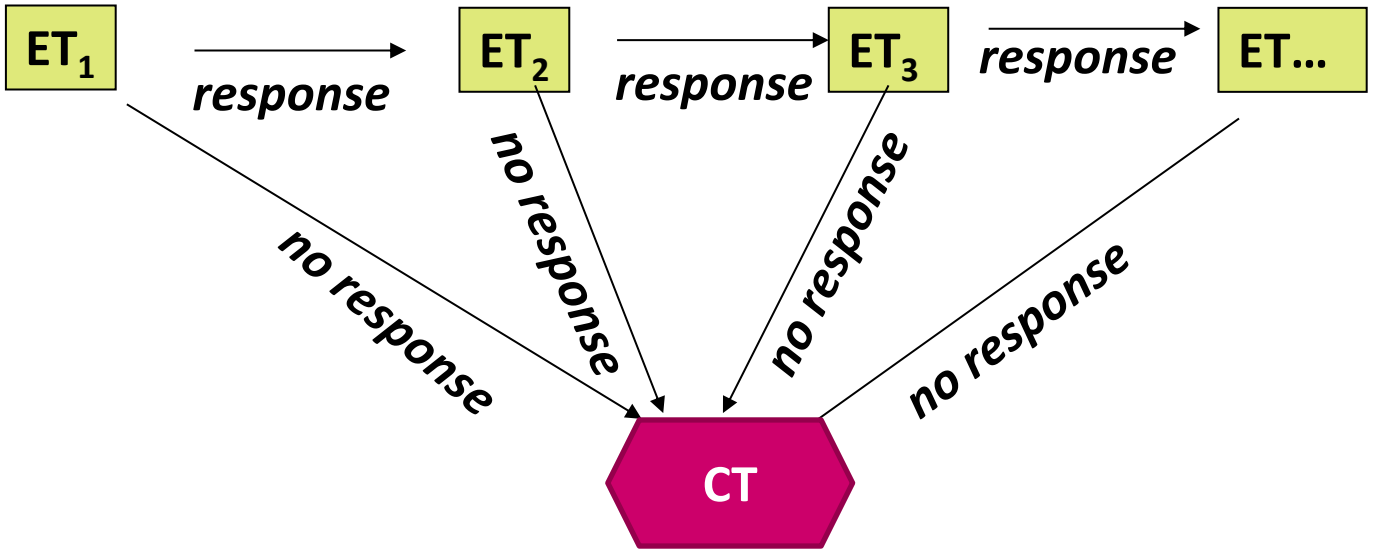


Image adapted from Senkus & Cardoso F, et al. *Ann Oncol*. 2013, ESMO GUIDELINES

Endocrine-Based Therapies for Breast Cancer

Year	Agent	Mechanism
1977	**SERMs** Tamoxifen Toremifene	Antagonizes ER in breast tissue
1990s	**AIs** Anastrozole Exemestane Letrozole	Inhibit estrogen production in postmenopausal women
2000s	**ERD** Fulvestrant	Impairs ER dimerization, increases ER degradation, and disrupts nuclear localization of ER
2010s	**Combinations** Exemestane/everolimus Letrozole/palbociclib Fulvestrant/palbociclib	Blockade of estrogen signaling and prosurvival or cell cycle pathways

Lim E, et al. Oncology (Williston Park). 2012;26:688-694.
Croxtall JD, et al. Drugs. 2011;71:363-380.
Vidula N, et al. Clin Breast Cancer. 2016;16:8-17.
Mustonen MV, et al. World J Clin Oncol. 2014;5:393-405.

Slide credit: clinicaloptions.com

ER POSITIVE / HER-2 NEGATIVE MBC

For pre-menopausal women, for whom ET was decided, ovarian suppression/ablation combined with additional endocrine therapy is the preferred choice. (LoE: 1 B) (93%)

For pre-menopausal women, the additional endocrine agent can be AI or tamoxifen, according to type and duration of prior adjuvant endocrine therapy but AI absolutely mandates the use of ovarian suppression/ablation. (LoE: 1 B) (95%)

Fulvestrant is also a valuable option, but for the moment also mandates the use of ovarian suppression/ablation. (LoE: 1 C) (95%)

ER POSITIVE / HER-2 NEGATIVE MBC

The preferred 1st line ET for postmenopausal patients depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant. (LoE: 1 A) (84%)

Initial Treatment of Hormone Receptor–Positive Advanced Breast Cancer

- Premenopausal SOC: ovarian suppression or ablation plus endocrine therapy as recommended for postmenopausal women[1]
- Postmenopausal SOC: AIs due to improved efficacy vs tamoxifen[1]

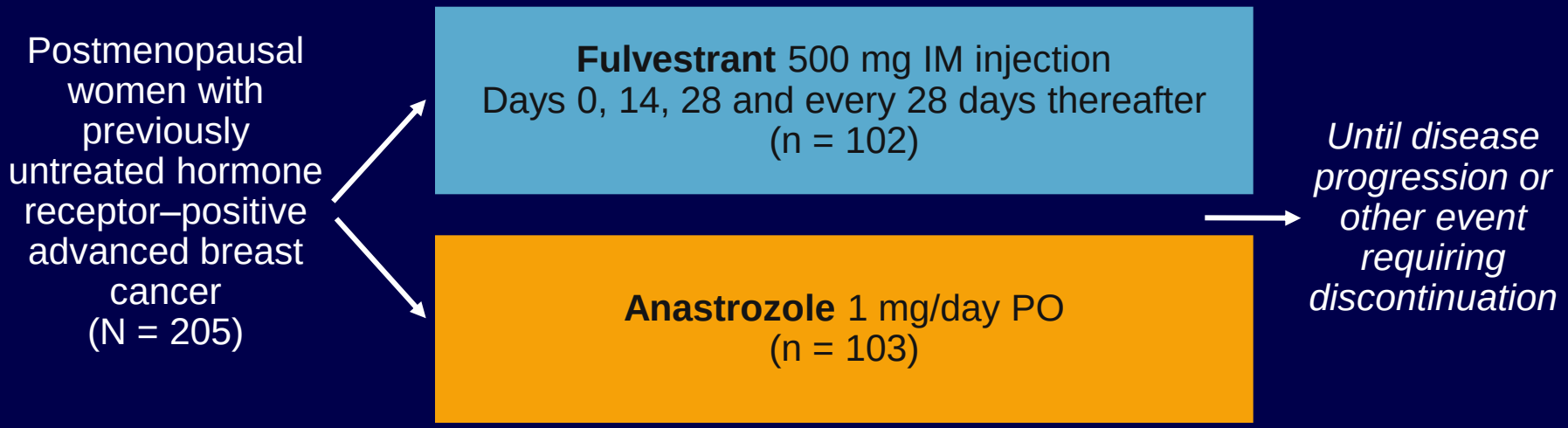
AI	Parameter	AI vs Tamoxifen, Mos
Anastrozole[2]	TTP	10.7 vs 6.4
Letrozole[3]		
Exemestan		

BUT: These patients were treated with Tam alone in the adjuvant setting! Different from nowadays

- Fulves
- Prelim ved efficacy vs anastrozole[6,7]
  - TTP, fulvestrant vs anastrozole: 23.4 vs 13.1 mos[6]

1. NCCN Guidelines. Breast Cancer. v2.2016.
2. Bonneterre J, et al. Cancer. 2001;92:2247-2258.
3. Mouridsen H, et al. J Clin Oncol. 2003;21:2101-2109.
4. Paridaens RJ, et al. J Clin Oncol. 2008;26:4883-4890.
5. Howell A, et al. J Clin Oncol. 2004;22:1605-1613.
6. Robertson FJ, et al. Breast Cancer Res Treat. 2012;136:503-511.
7. Ellis MJ, et al. J Clin Oncol. 2015;33:3781-3787.

Phase II FIRST: First-line Fulvestrant vs Anastrozole for Advanced Breast Cancer



- Primary endpoint: clinical benefit rate

Ellis MJ, et al. J Clin Oncol. 2015;33:3781-3787.

Slide credit: clinicaloptions.com

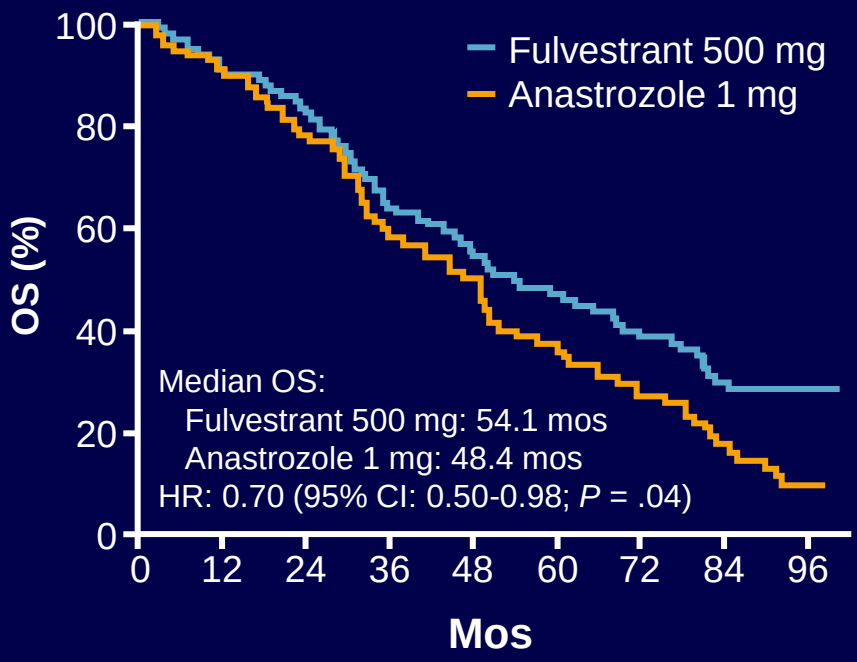
FIRST: Results

- Clinical benefit rate and time to progression analyses

Outcome	Fulvestrant 500 mg (n = 102)	Anastrozole 1 mg (n = 103)
CBR, %	72.5	67.0
mTTP, mos	23.4*	13.1

*P = .01

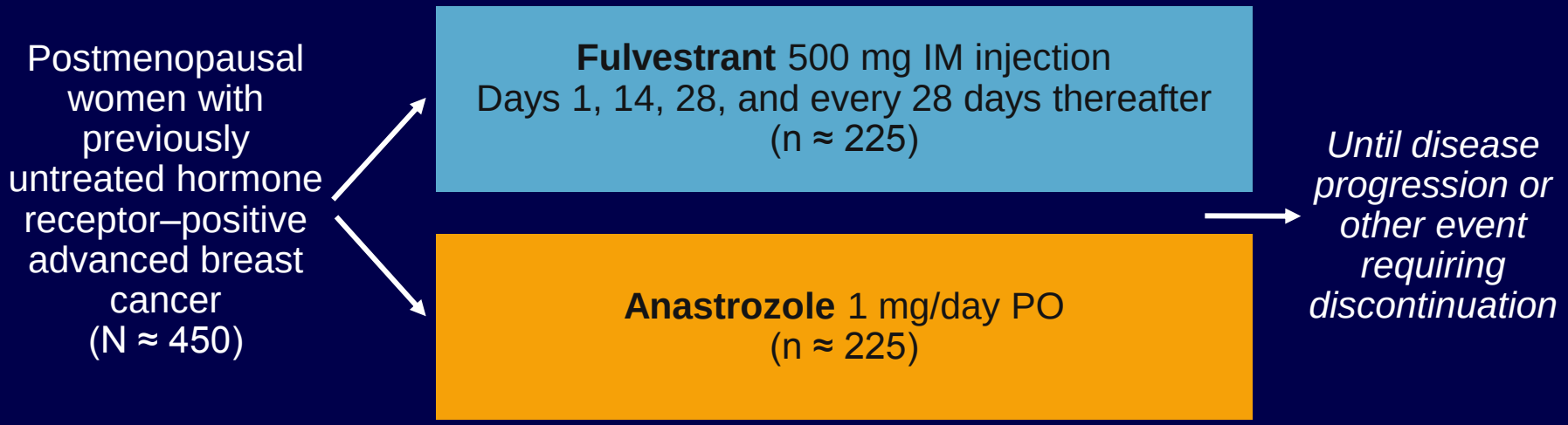
- OS analysis
  - Not a defined endpoint in original protocol



Ellis MJ, et al. J Clin Oncol. 2015;33:3781-3787.

Slide credit: clinicaloptions.com

Phase III FALCON: First-line Fulvestrant vs Anastrozole for Advanced Breast Cancer



- Primary endpoint: PFS
- Secondary endpoints including: OS, ORR, DoR, CBR, and safety

ClinicalTrials.gov. NCT01602380.

Slide credit: clinicaloptions.com

Optimal post-aromatase inhibitor treatment is uncertain.

Available options include, but are not limited to, tamoxifen, another AI (with a different mechanism of action), fulvestrant HD, megestrol acetate and everolimus + AI. (LoE: 1 A) (97%)

and HT + Palbociclib, where available

ER POSITIVE / HER-2 NEGATIVE MBC

The combination of a nonsteroidal AI and fulvestrant as first-line therapy for post-menopausal patients resulted in significant improvement in both PFS and OS compared to AI alone in one phase III trial and no benefit in a second trial with a similar design.

Subset analysis suggested that the benefit was limited to patients without prior exposure to adjuvant ET (tamoxifen). Based on these data, combination ET may be offered to some patients with MBC without prior exposure to adjuvant ET.

(LoE: 2 B) (33% Yes, 53% No, 14% Abstain)

Mechanisms of *De Novo* & Acquired Endocrine Resistance

De Novo **ET Resistance** **Acquired ET Resistance**

- **The lost/inactivation of ER/ER pathway**
- **Activation of PI3K/AKT/mTOR pathway**
- **Activation of the growth factor or HER pathway activation**

1. Osborne CK, et al. *Ann Rev Med*. 2011;62:233-247; 2. Arpino G, et al. *Endocr Rev*. 2008;29:217-233; 3. Shou J, et al. *J Natl Cancer Inst.* 2004;96(12):926-935; 4. Chung YL, et al. *Int J Cancer.* 2002;97:306-312; 5. Meng S, et al. *Proc Natl Acad Sci USA*. 2004;101:9393-9398; 6. Nicholson RI, et al. *Endocr Relat Cancer*. 2004;11:623-641; 7. Gee JM, et al. *Endocrinology.* 2003;144:5105-5117; 8. Knowlden JM, et al. *Endocrinology*. 2005;146:4609-4618; 9. Miller W, et al. AARC Special Conference: Targeting PI3K/mTOR Signaling in Cancer; 2011. Abstract A09.

PRIMARY ENDOCRINE RESISTANCE is defined as:

Relapse while on the first 2 years of adjuvant ET, or

PD within first 6 months of 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

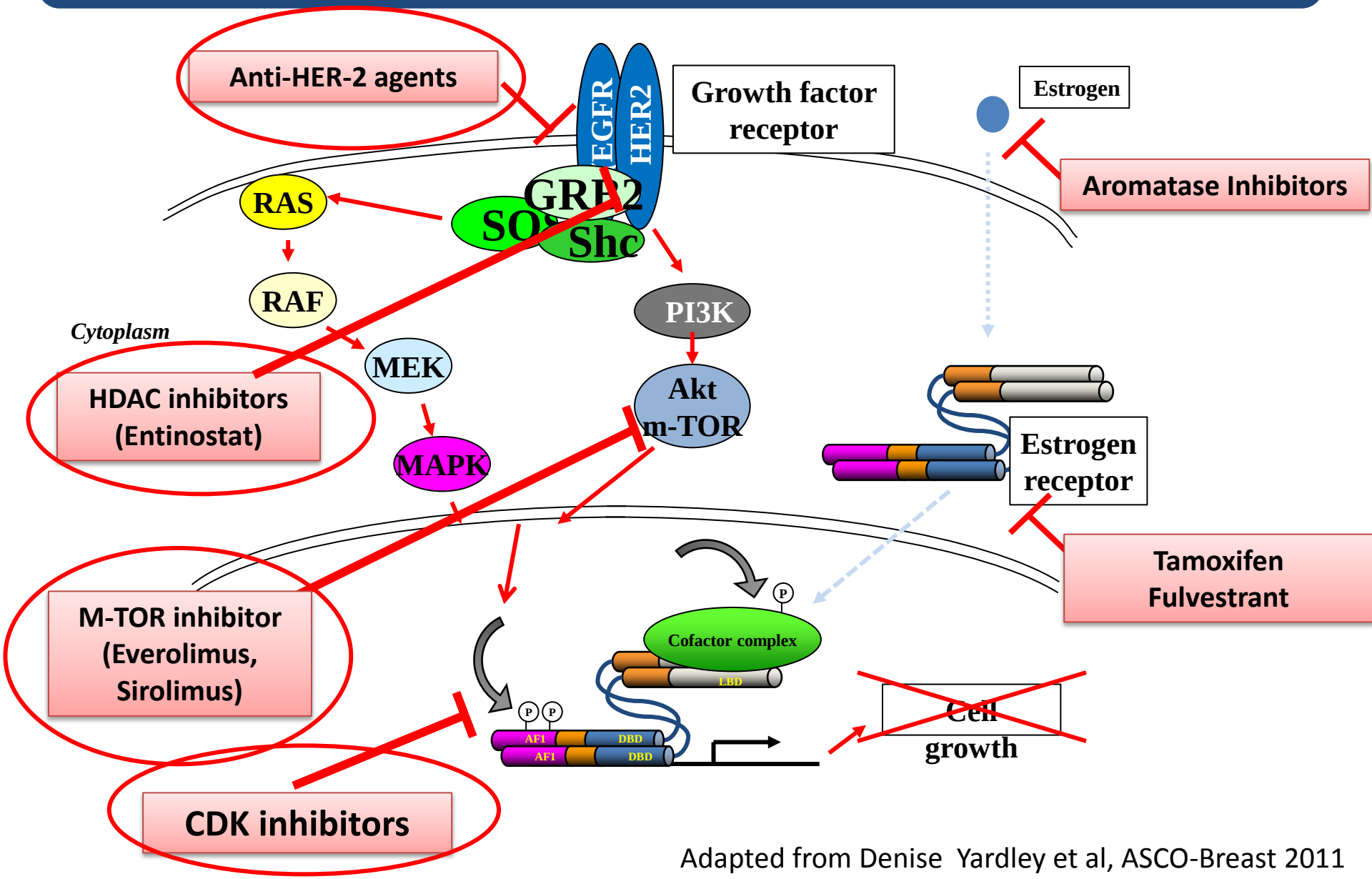
Relapse within 12 months of completing adjuvant ET, or

PD ≥ 6 months after initiating ET for MBC, while on ET

(LoE: Expert opinion) (67%)

Note: resistance is a continuum and these definitions help mainly clinical trials and not necessarily clinical practice

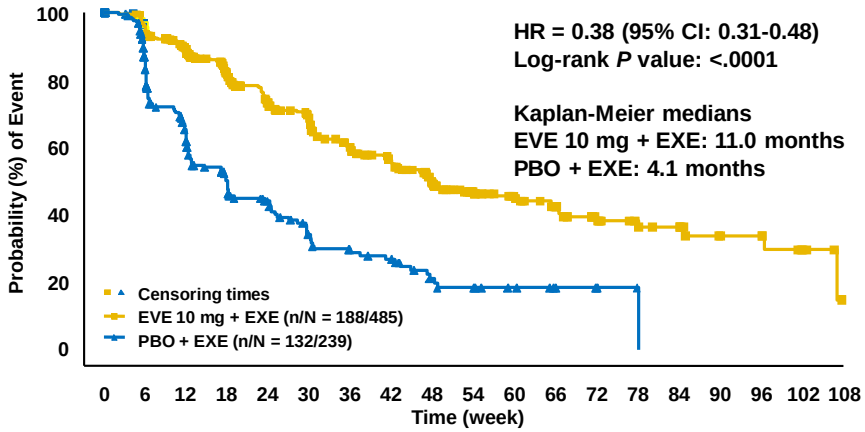
ER & GROWTH FACTOR PATHWAYS & ENDOCRINE RESISTANCE



Adapted from Denise Yardley et al, ASCO-Breast 2011

BOLERO-2 (18-ms FU): PFS Central

BOLERO-2



Number of patients still at risk

EVE 10 mg + EXE	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
PBO + EXE	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

2

Piccart M, et al. ASCO 2012. Abstract 559.

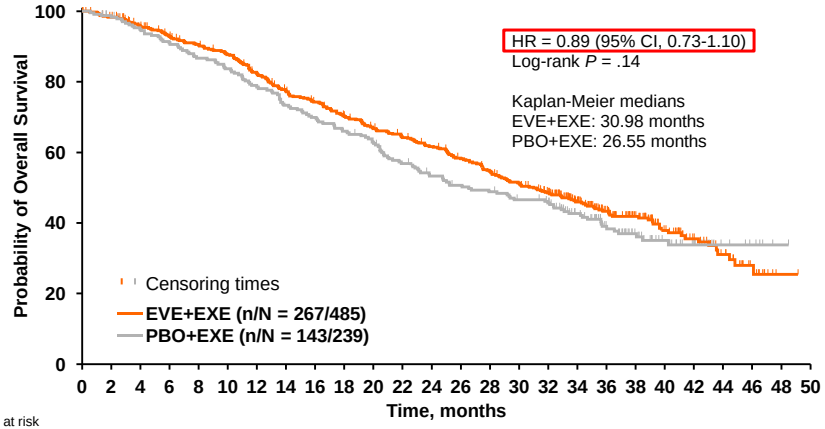
BOLERO-2

Everolimus + AI

4.6 to 6.9 ms benefit PFS

No statistical significant benefit in OS

BOLERO-2 (39-mo): Final OS Analysis



No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39 months median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013): 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

Piccart M, et al, EBCC 2014,LBA

EVEROLIMUS: Adverse Events

Most Common Adverse Events (AEs)

- **Fatigue**
- **Stomatitis**
- **Rash**
- **Anorexia**
- **Diarrhea**

Less frequent but clinically relevant:

- **Hyperglycemia**
- ***Pneumonitis: Rare but potentially fatal***

Significant % (about 20%) of EVE–treated patients required a dose reduction

Clinical Management Strategy

- **Focus on patient awareness and early intervention**
- **Importance of well defined management & dose reduction/delay or drug discontinuation guidelines (they exist for stomatitis, pneumonitis, hyperglycemia)**

ER POSITIVE / HER-2 NEGATIVE MBC

The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a non-steroidal AI, since it significantly prolongs PFS, albeit without OS benefit.
The decision to treat must take into account the individual relevant toxicities associated with this combination and should be made on a case by case basis. (LoE: 1 B) (85%)
Tamoxifen can also be combined with everolimus. (LoE: 2 B) (85%)

Notes: a) At present, no predictive biomarker exists to identify those patients who will benefit from this approach. b) some studies have shown an excess in mortality with this combination in patients >70 years-old.

Palbociclib (PD 0332991; CDK4/6 inhibitor)

- **Background:**

✓ PD 0332991, is a selective inhibitor of CDK4/6

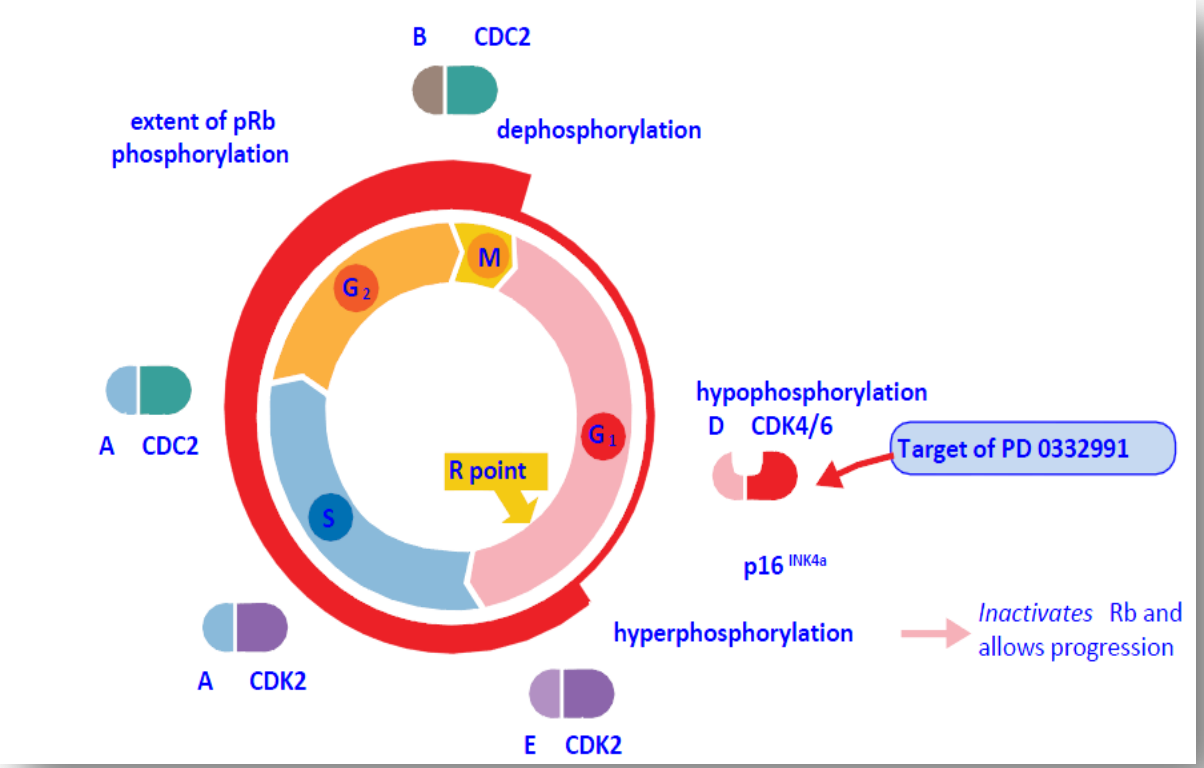
✓ Prevents cellular DNA synthesis

✓ Luminal ER subtype,

✓ ↑ expression of cyclin D1&Rbprotein

✓ ↓ p16 expression

Sensitivity to PD0332991



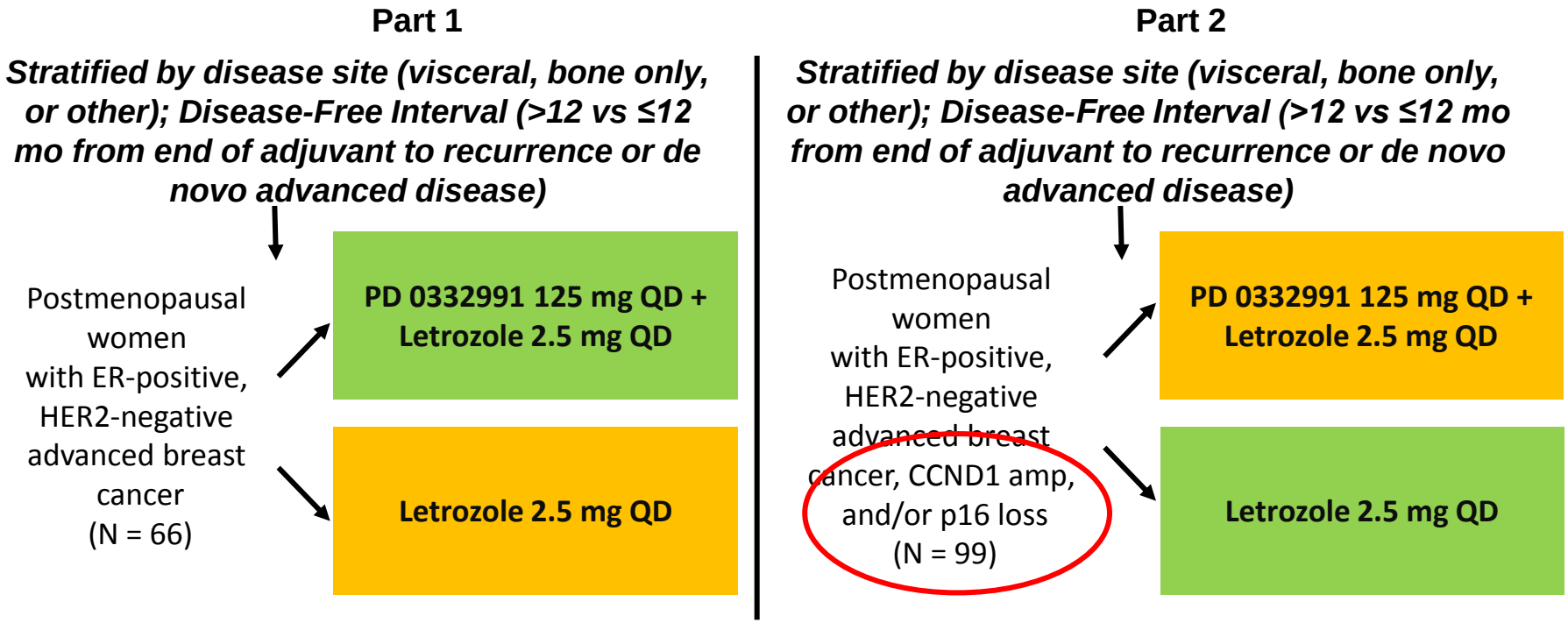
Finn RS, et al. SABCS 2012. Abstract S1-6

Palbociclib + Letrozole vs. Letrozole Study

Primary endpoint: PFS

Secondary endpoints: RR, OS, safety, correlative biomarker studies

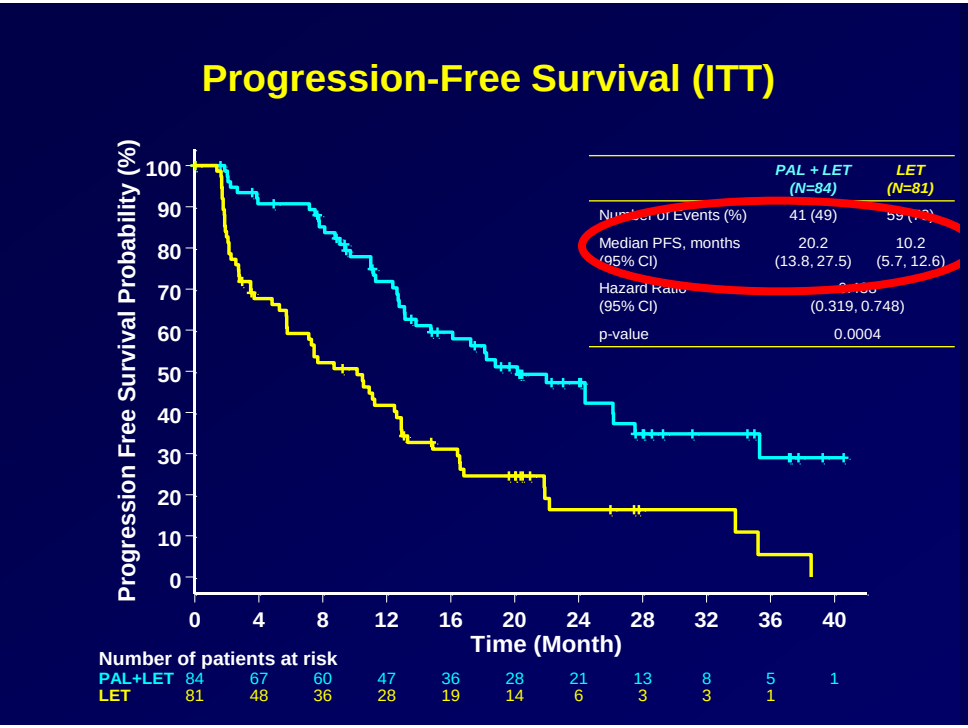
- 2-part, randomized phase II study

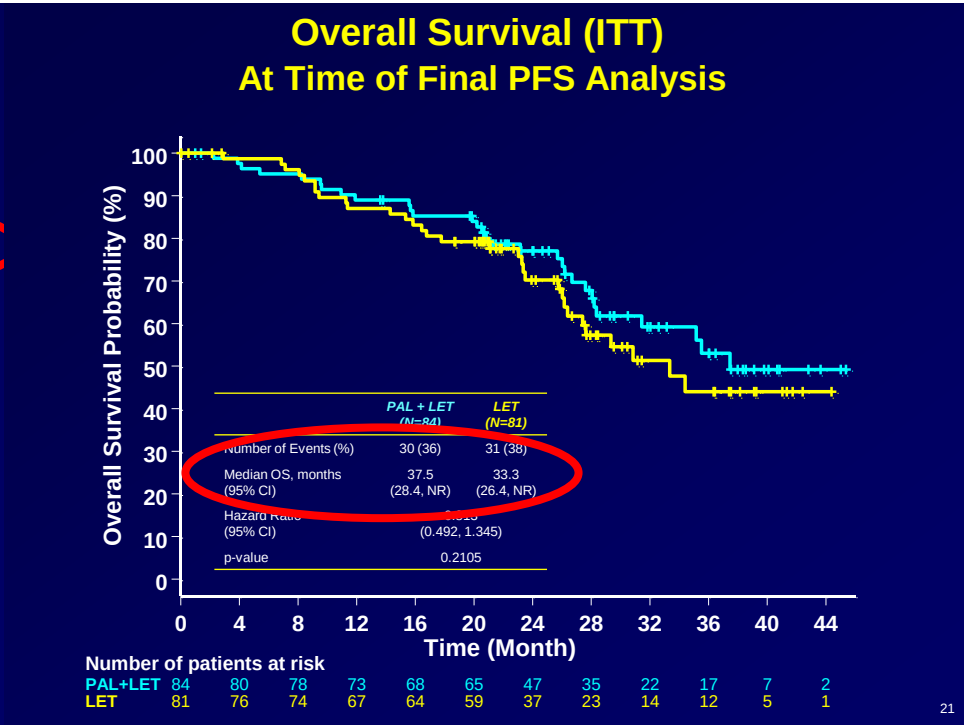


All patients continued assigned treatment until disease progression, withdrawal of consent, or unacceptable toxicity with follow-up tumor assessment every 2 mos

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

Palbociclib + Letrozole vs Letrozole: PFS (Final results)



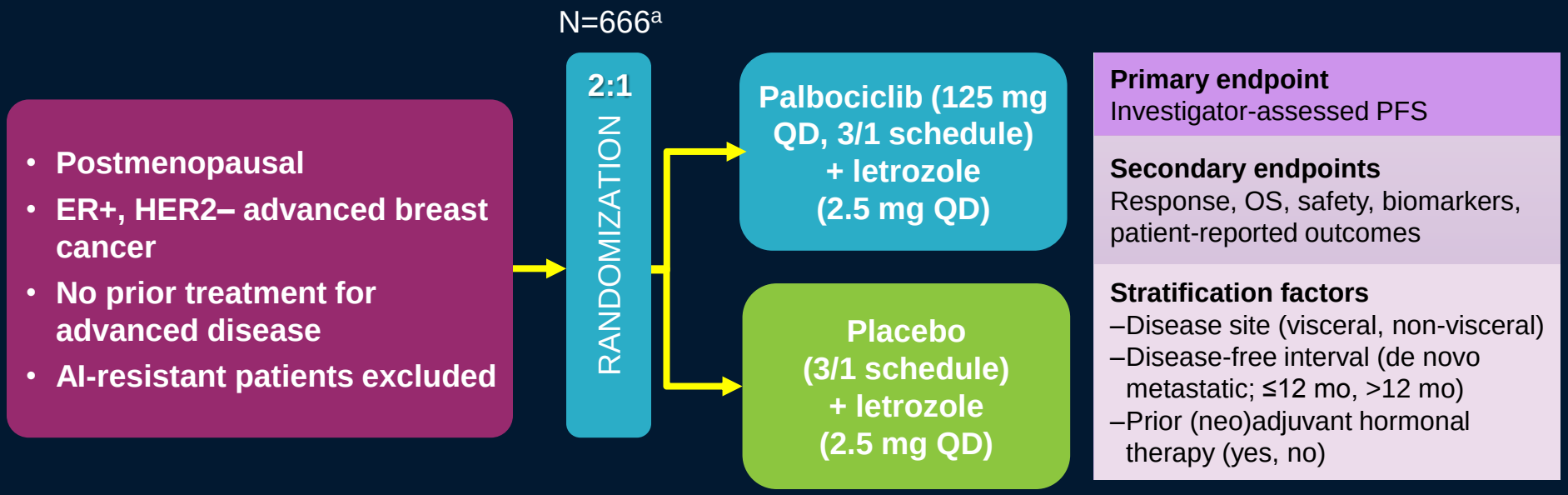


	PAL + LET (N=84)	*LET (N=81)*
All randomized patients, n	84	81
Objective Response Rate, % (95% CI)	43 (32, 54)	33 (23, 45)
Complete Response, n (%)	1 (1%)	1 (1%)
Partial Response, n (%)	35 (42%)	26 (32%)
Clinical Benefit Rate, % (95% CI)*	81 (71, 89)	58 (47, 69)
Stable Disease ≥24 weeks, n (%)	32 (38%)	20 (25%)

Few dropouts due to toxicity. Main side effect: neutropenia (but no infection)

Finn RS, et al. AACR 2014, Abstract CT101

PALOMA-2: Study Design (1008)[1]



- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided α=0.025

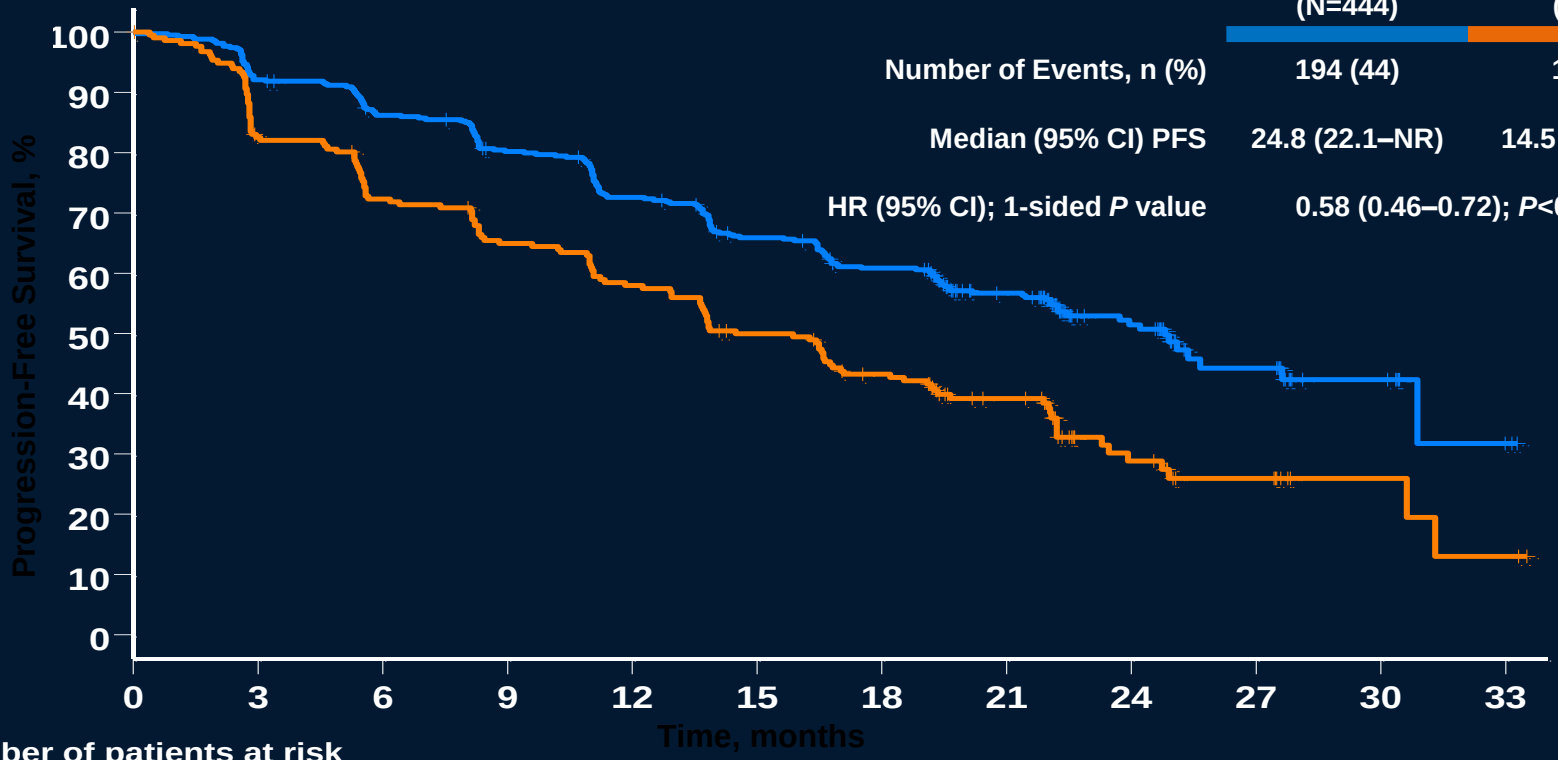
  Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos
- Blinded independent central review of efficacy endpoints performed as supportive analysis

[a]Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

1.clinicaltrials.gov NCT01740427

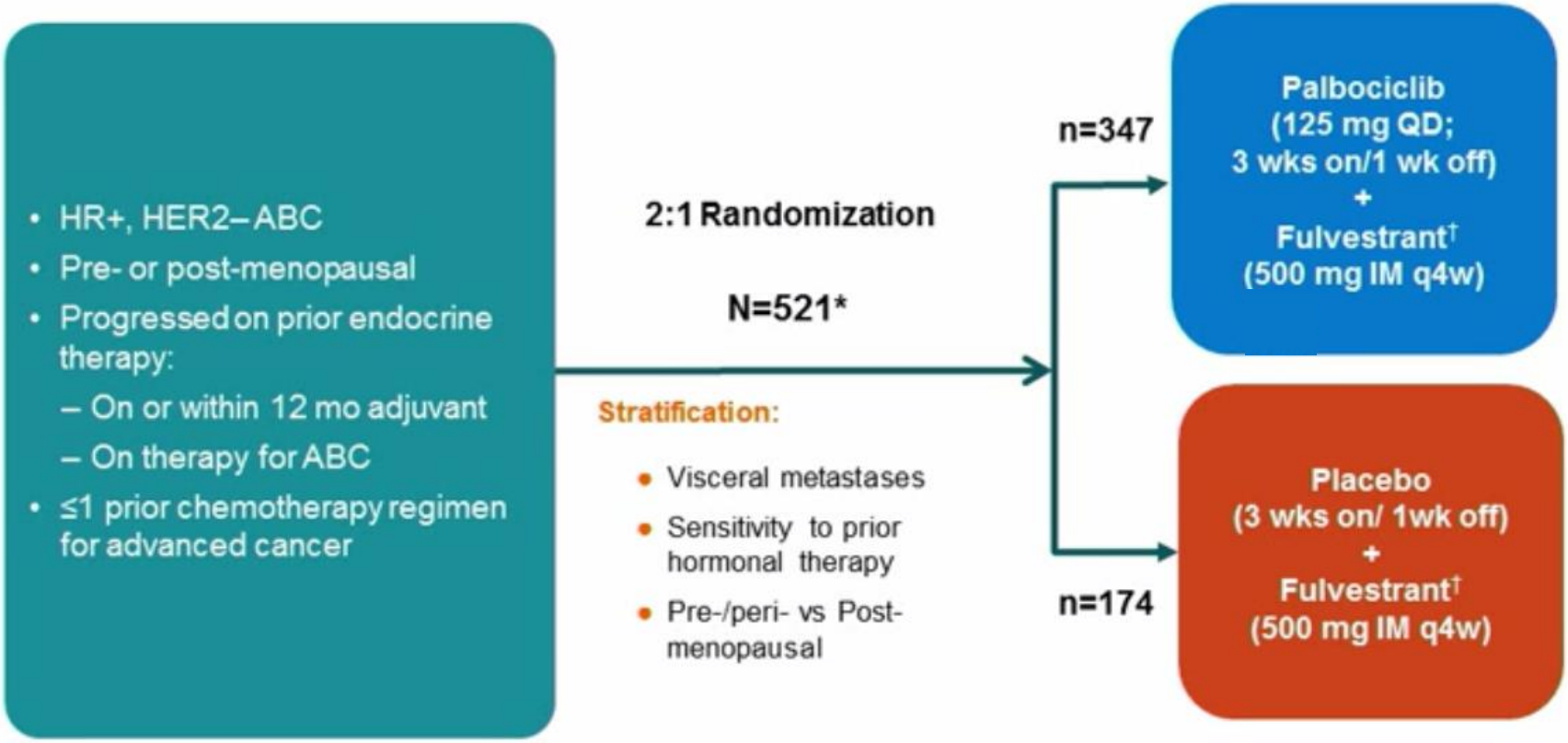
PALOMA-2

PFS: Investigator-Assessed - (ITT Population)



ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

PALOMA3 Study Design

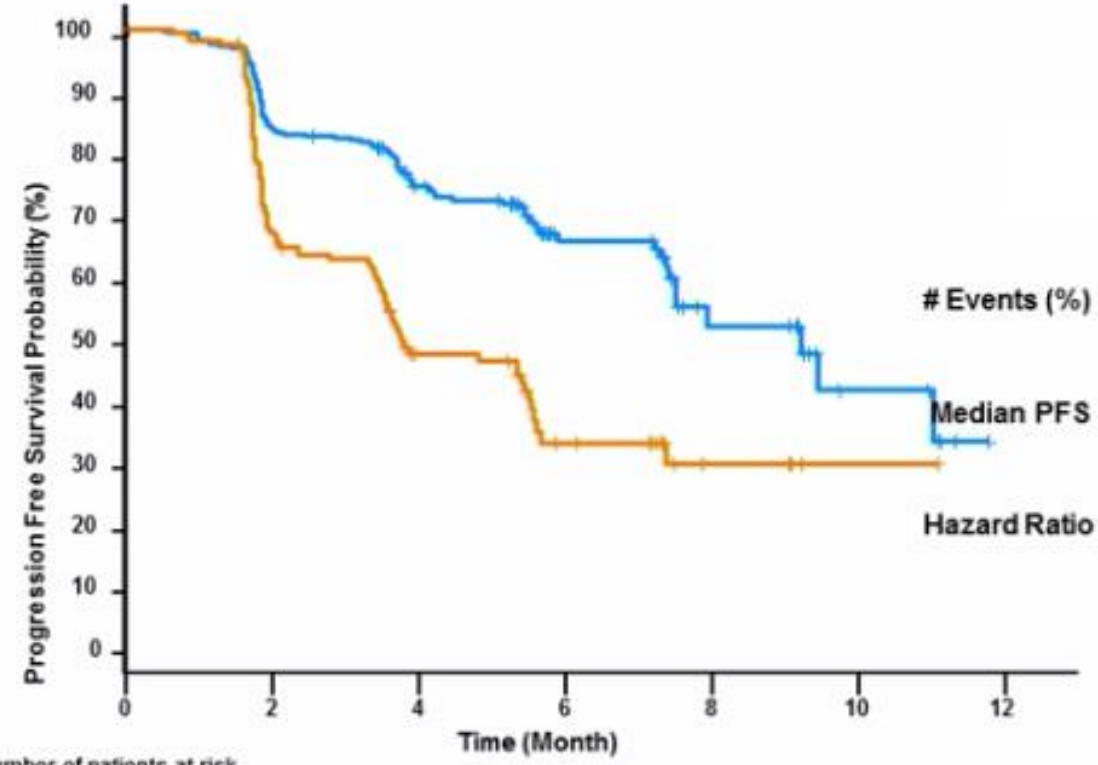


- ***Pre- and peri-menopausal women received concurrent ovarian function suppression with goserelin[1].***
- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

Adverse Events—All Cause

AE, %	Palbociclib + Fulvestrant (n=345) Any Grade	Grade 3	Grade 4	Placebo + Fulvestrant (n=172) 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
Fatigue	38	2	0	27	1	0
Nausea	29	0	0	26	1	0
Anemia	26	3	0	10	2	0
Headache	21	<1	0	17	0	0
Thrombocytopenia	19	2	1	0	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

Primary Endpoint: PFS (Investigator-Assessed) ITT Population



Number of patients at risk

PAL+FUL	347	279	132	59	16	6
FUL	174	109	42	16	6	

	Placebo + Fulvestrant n=174	Palbociclib + Fulvestrant n=347
# Events (%)	93 (53.4)	102 (29.4)
Median PFS	3.8 (3.5, 5.5)	9.2 (7.5, NE)
Hazard Ratio	0.422 (0.318, 0.560)	
	<0.000001	

Similar benefit seen in all subgroups examined

CI=confidence interval; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

Clinical Implications

- Confirms findings from front-line randomized phase II that led to accelerated approval
- Provides support for combination of fulvestrant + palbociclib in second line setting
- In practice, palbociclib can be used in either the first-line or second-line setting, and can be used with either AI or fulvestrant

NO OS SURVIVAL RESULTS YET!

But due to improved QoL: ESMO MCBS score 4

ER POSITIVE / HER-2 NEGATIVE MBC

The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients (except patients relapsing < 12 months from the end of adjuvant AI), provided a significant improvement in PFS (10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options, where available. OS results are still awaited.

LoE: 1A

Statement revised after SABCS & ASCO

ER POSITIVE / HER-2 NEGATIVE MBC

The addition of CDK4/6 inhibitor palbociclib to Fulvestrant, beyond 1st line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited. For pre/peri-menopausal pts, an LHRH-agonist must also be used. (LoE: 1 B) (86%)

At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these type of agents and research efforts must continue.

CDK4/6 Inhibitors in Hormone Receptor–Positive Metastatic Breast Cancer

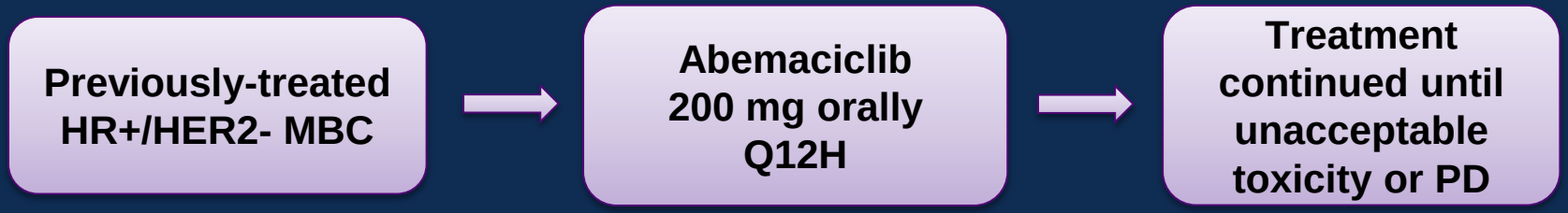
Agent	Target (IC_{50}, nM)	Phase III Trials	Phase I Dose-Limiting Toxicities
Palbociclib (PD0332991)	CDK4 (11) CDK6 (15)	First-line combo: ▪ Letrozole* Second-line combo: ▪ Exemestane ▪ Fulvestrant*	Neutropenia, thrombocytopenia‡
Abemaciclib (LY2835219)	CDK4 (2) CDK6 (10)	First-line combo: ▪ Anastrozole or letrozole ▪ Fulvestrant	Fatigue
Ribociclib (LEE011)	CDK4 (10) CDK6 (39)	First-line combo: ▪ Letrozole ▪ Fulvestrant ▪ Tamoxifen or NSAI† Second-line combo: ▪ Fulvestrant	Neutropenia, mucositis, pulmonary embolism, asymptomatic thrombocytopenia, hyponatremia, QTcF prolongation (> 500 ms), increased creatinine

* Approved. †Premenopausal women; NSAI in combination with goserelin. ‡Phase II grade 3/4.

Hamilton E, et al. Cancer Treat Rev. 2016;45:129-138.

Slide credit: clinicaloptions.com

MONARCH 1: Phase 2 Study Design



Primary objective

To evaluate abemaciclib with respect to confirmed objective response rate based on investigator assessment (per RECIST v1.1)

Secondary objectives

Duration of response, progression-free survival, overall survival, clinical benefit rate, safety

Statistical design

A sample size of 128 patients provides 82% power, assuming a true response rate of 25%, to exclude an ORR of ≤15% on the lower bound of the 95% CI at 12 months follow-up

Presented by: Maura N. Dickler, MD

MONARCH 1: Most Common Adverse Events

Investigator Assessed TEAEs[a] >20% (N=132)	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %	All Grades %
Diarrhea	41.7	28.8	19.7	0	90.2
Fatigue	21.2	31.1	12.9	0	65.2
Nausea	39.4	20.5	4.5	0	64.4
Decreased appetite	28.0	14.4	3.0	0	45.5
Abdominal pain	22.0	14.4	2.3	0	38.6
Vomiting	22.7	10.6	1.5	0	34.8
Headache	13.6	6.8	0	0	20.5
Lab abnormalities[b]					
Creatinine increased[c]	46.9	50.8	0.8	0	98.5
White blood cell decreased	18.5	44.6	27.7	0	90.8
Neutrophil count decreased	17.7	43.1	22.3	4.6	87.7[d]
Anemia	30.0	38.5	0	0	68.5
Platelet count decreased	28.9	10.2	2.3	0	41.4

[a]CTCAE Version 4.03, [b]N = 130 for lab abnormalities listed, except platelet count decreased (N=128), [c]Abemaciclib is a competitive inhibitor of OCT2, MATE1, and MATE2-K, efflux transporters of creatinine; cystatin C calculated GFR was not raised, [d]One patient who received cytotoxic chemotherapy within the 30 day follow up window experienced febrile neutropenia

Presented by: Maura N. Dickler, MD

Presented by: Maura N. Dickler, MD

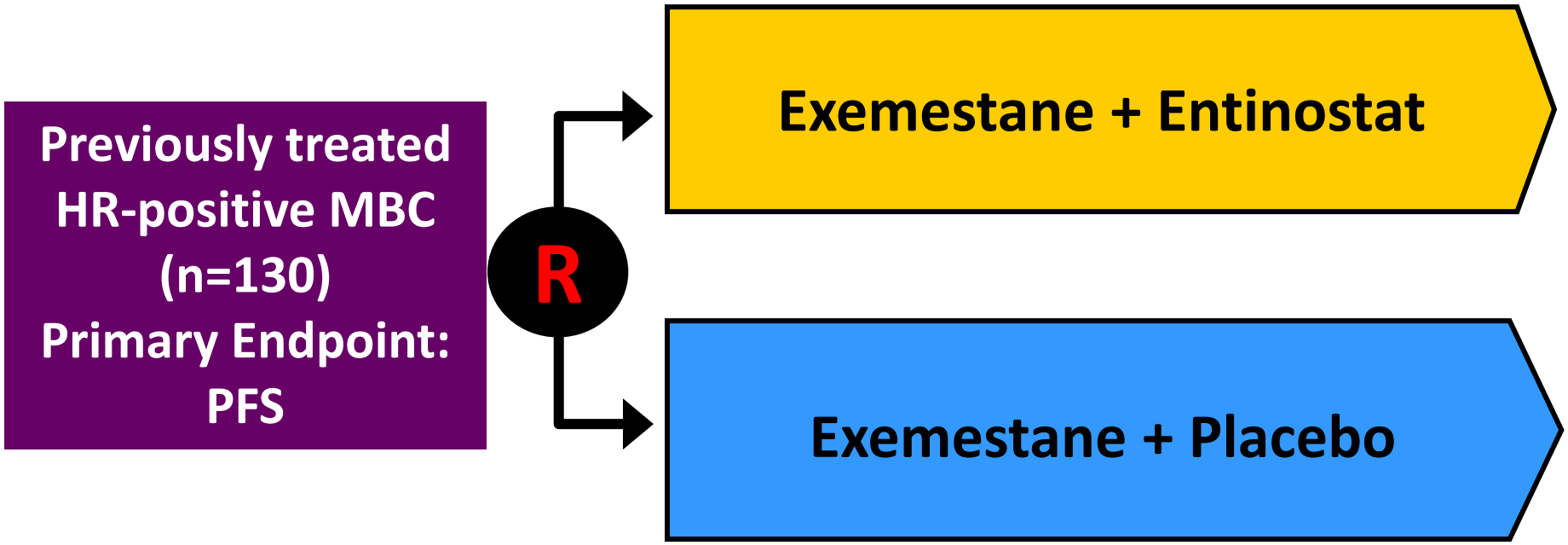
Conclusions – MONARCH 1

- Abemaciclib, a CDK4 & 6 inhibitor, demonstrates single agent activity in heavily pretreated patients with HR+/HER2- MBC
  - ORR of 19.7% (95% CI: 13.3, 27.5; 15% not excluded)
  - Median DoR of 8.6 mos
  - CBR of 42.4%, median PFS of 6.0 mos, median OS of 17.7 mos
- Safety and toxicity profile of twice daily continuous administration was consistent with previous experience
  - Few patients (7.6%) discontinued treatment due to adverse events
- Phase III studies of abemaciclib in combination with endocrine therapies are ongoing
  - MONARCH 2: abemaciclib plus fulvestrant in endocrine pre-treated MBC
  - MONARCH 3: abemaciclib plus an NSAI as initial treatment for MBC

Presented by: Maura N. Dickler, MD

Presented by: Maura N. Dickler, MD

Phase II Randomized Trial of Exemestane with or without Entinostat, a Novel HDAC Inhibitor

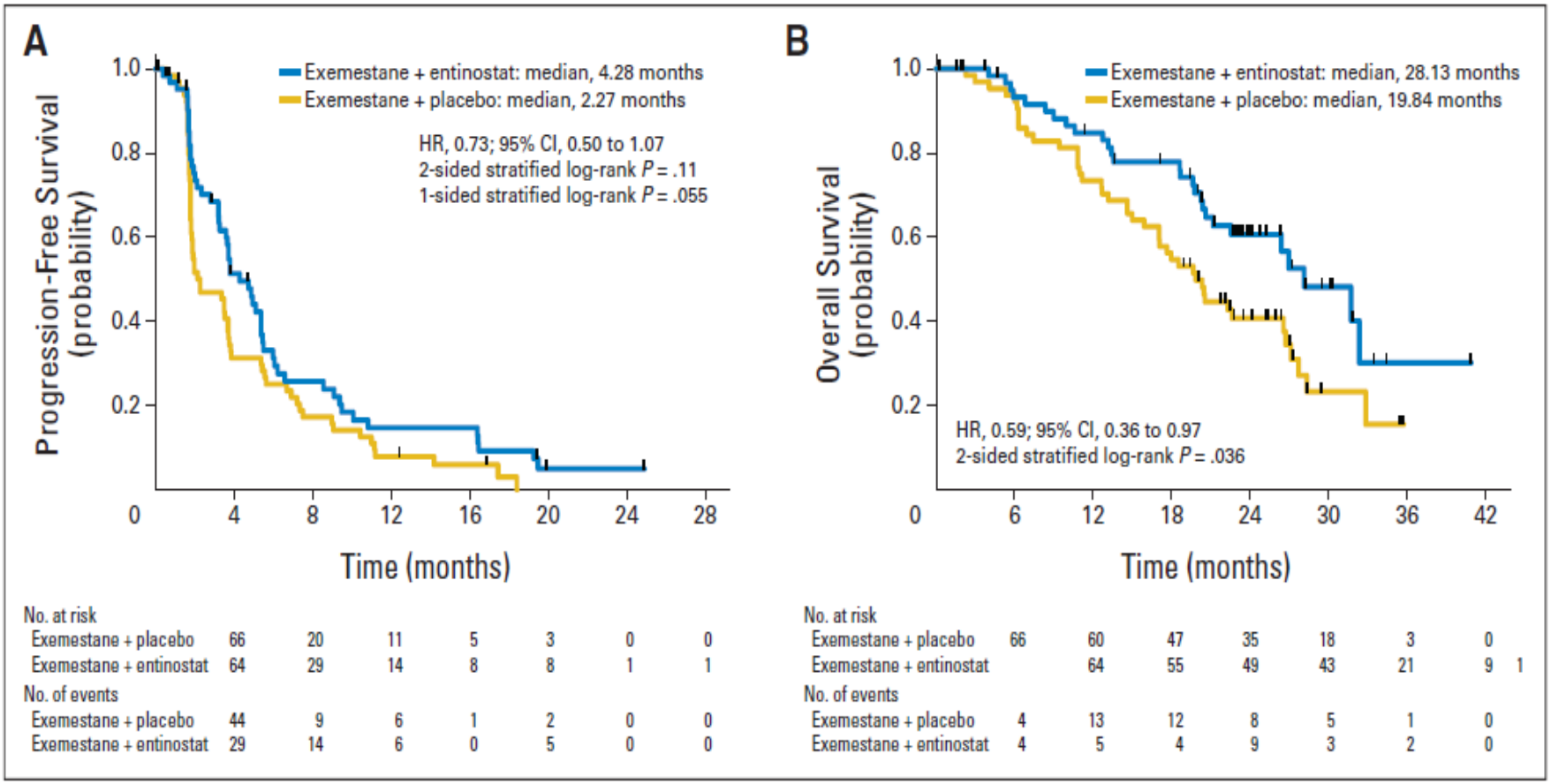


HR, hormone receptor; MBC, metastatic breast cancer; R, randomisation

Yardley D, et al. J Clin Oncol 2013

Exemestane +/- HDAC inhibitor Entinostat

PFS **OS**



No. at risk							
Exemestane + placebo	66	20	11	5	3	0	0
Exemestane + entinostat	64	29	14	8	8	1	1
No. of events							
Exemestane + placebo	44	9	6	1	2	0	0
Exemestane + entinostat	29	14	6	0	5	0	0

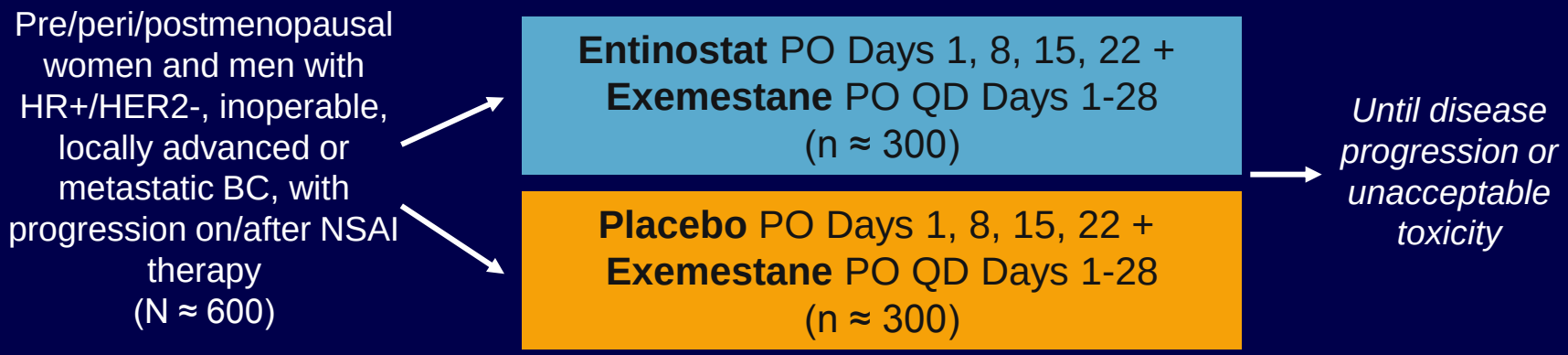
No. at risk							
Exemestane + placebo	66	60	47	35	18	3	0
Exemestane + entinostat	64	55	49	43	21	9	1
No. of events							
Exemestane + placebo	4	13	12	8	5	1	0
Exemestane + entinostat	4	5	4	9	3	2	0

Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS). (A) Vertical tick marks represent the PFS time of patients without progressive disease. (B) Vertical tick marks represent the survival time of patients alive or lost to follow-up as of the last contact.

Yardley D, et al. J Clin Oncol 2013

Phase III E2112: Exemestane ± Entinostat in Advanced Breast Cancer

- Entinostat: oral, histone deacetylase inhibitor



*Pre/perimenopausal female and all male pts receive goserelin acetate SC Day 1.

- Primary endpoints: OS, PFS
- Secondary endpoints: ORR (CR or PR), TTD, toxicity
- Other outcomes: adherence, QoL, protein lysine acetylation

ClinicalTrials.gov. NCT02115282.

Slide credit: clinicaloptions.com

ER POSITIVE / HER-2 NEGATIVE MBC

The optimal sequence of endocrine agents after 1st line ET is uncertain. It depends on which agents were used in the (neo)adjuvant and 1st line ABC settings.

Available options include AI, tamoxifen, fulvestrant + palbociclib, AI + everolimus, tamoxifen + everolimus, fulvestrant, megestrol acetate and estradiol.
(LoE: 1 A) (93%)

It is currently unknown how the different combinations of endocrine + biological agents compare with each other, and with single agent CT. Several trials are ongoing.

WHEN CHEMOTHERAPY IS NEEDED . . .

CHEMOTHERAPY (general)

Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for MBC.

Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

(LoE: 1 B). (96%)

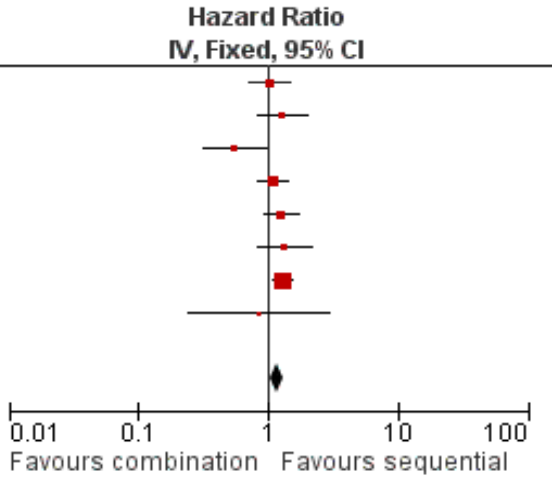
Please see also Cardoso et al, JNCI 2009; 101: 1174–1181

Cochrane meta-analysis of Combination vs. Sequential monoCT for ABC

Progression-free survival (all trials)

Study or Subgroup	log[Hazard Ratio]	SE	Combination Total	Sequential Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Alba 2004	0.0296	0.1827	69	75	10.7%	1.03 [0.72, 1.47]
Baker 1974	0.239	0.2295	46	30	6.8%	1.27 [0.81, 1.99]
Beslija 2006	-0.6033	0.2865	50	50	4.3%	0.55 [0.31, 0.96]
Conte 2004	0.0862	0.139	106	92	18.5%	1.09 [0.83, 1.43]
Fountzilas 2001	0.2151	0.1579	90	93	14.3%	1.24 [0.91, 1.69]
Park 2010	0.2776	0.2429	41	40	6.0%	1.32 [0.82, 2.12]
Sledge 2003	0.2469	0.0962	230	453	38.5%	1.28 [1.06, 1.55]
Tomova 2010	-0.1625	0.6415	46	53	0.9%	0.85 [0.24, 2.99]
Total (95% CI)			**678**	**886**	**100.0%**	**1.16 [1.03, 1.31]**

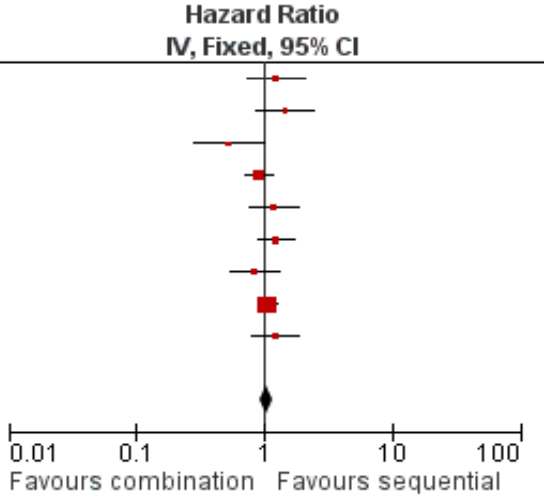
Heterogeneity: Chi² = 9.41, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 2.52 (P = 0.01)



Overall survival (all trials)

Study or Subgroup	log[Hazard Ratio]	SE	Combination Total	Sequential Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Alba 2004	0.2151	0.2634	69	75	4.5%	1.24 [0.74, 2.08]
Baker 1974	0.3716	0.2606	46	30	4.6%	1.45 [0.87, 2.42]
Beslija 2006	-0.6387	0.3182	50	50	3.1%	0.53 [0.28, 0.99]
Chlebowski 1989	-0.1054	0.1282	129	93	19.2%	0.90 [0.70, 1.16]
Conte 2004	0.174	0.2355	106	92	5.7%	1.19 [0.75, 1.89]
Fountzilas 2001	0.1989	0.1667	90	93	11.3%	1.22 [0.88, 1.69]
Park 2010	-0.1744	0.235	41	40	5.7%	0.84 [0.53, 1.33]
Sledge 2003	0.0488	0.0901	230	453	38.8%	1.05 [0.88, 1.25]
Tomova 2010	0.1989	0.211	46	53	7.1%	1.22 [0.81, 1.84]
Total (95% CI)			**807**	**979**	**100.0%**	**1.04 [0.93, 1.16]**

Heterogeneity: Chi² = 10.54, df = 8 (P = 0.23); I² = 24%
Test for overall effect: Z = 0.76 (P = 0.45)



Dear RF et al. Combination vs. sequential single agent CT for MBC (Review) 2013

HER-2 NEGATIVE MBC

In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not need combination CT, single agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines.

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

(LoE: 1 B) (77%)

HER-2 NEGATIVE MBC

In the absence of medical contraindications or patient concerns, anthracycline or taxane based regimens, preferably as single agents, would usually be considered as first line CT for HER-2 negative MBC, in those patients who have not received these regimens as (neo)adjuvant treatment and for whom chemotherapy is appropriate. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient (LoE: 1 A) (71%).

HER-2 NEGATIVE MBC

In patients with taxane-naive and anthracycline-resistant MBC or with anthracycline cumulative dose or toxicity (i.e. cardiac) who are being considered for further CT, taxane-based therapy, preferably as single agents, would usually be considered as treatment of choice. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

(LoE: 1 A) (59%).

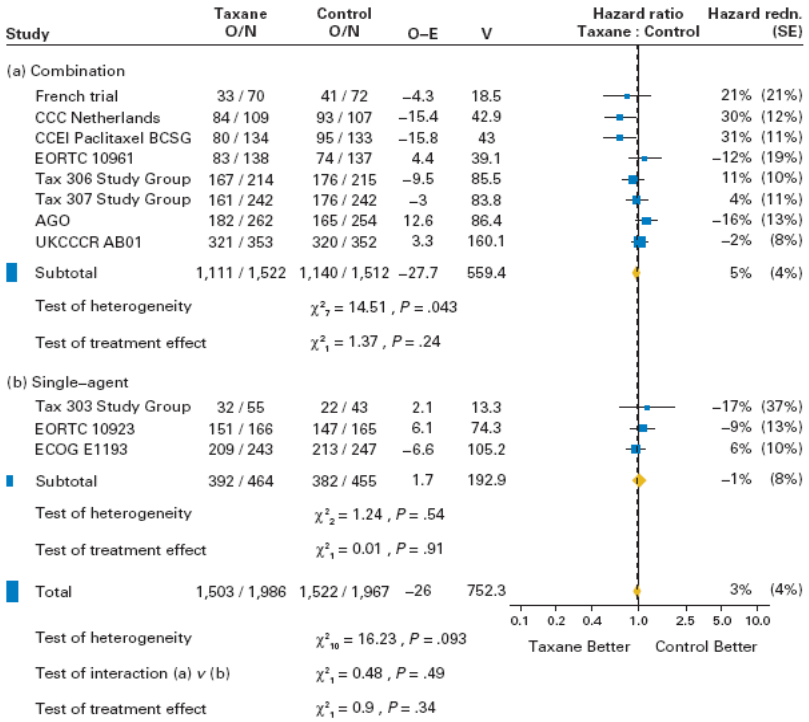
VOLUME 26 · NUMBER 12 · APRIL 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Taxanes Alone or in Combination With Anthracyclines As First-Line Therapy of Patients With Metastatic Breast Cancer

Martine J. Piccart-Gebhart, Tomasz Burzykowski, Marc Buyse, George Sledge, James Carmichael, Hans-Joachim Lück, John R. Mackey, Jean-Marc Nabholtz, Robert Paridaens, Laura Biganzoli, Jacek Jassem, Marijke Bontenbal, Jacques Bonneterre, Stephen Chan, Gul Atalay Basaran, and Patrick Therasse

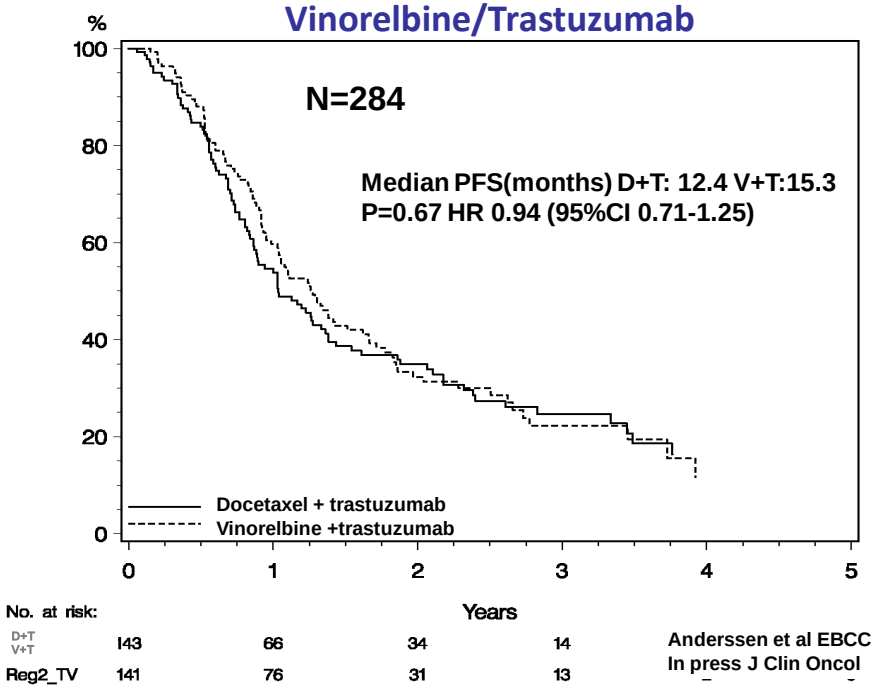


Study	Taxane O/N	Control O/N	O–E	V	Hazard ratio Taxane : Control	Hazard redn. (SE)
(a) Combination						
French trial	33 / 70	41 / 72	–4.3	18.5		21% (21%)
CCC Netherlands	84 / 109	93 / 107	–15.4	42.9		30% (12%)
CCEI Paclitaxel BCSG	80 / 134	95 / 133	–15.8	43		31% (11%)
EORTC 10961	83 / 138	74 / 137	4.4	39.1		–12% (19%)
Tax 306 Study Group	167 / 214	176 / 215	–9.5	85.5		11% (10%)
Tax 307 Study Group	161 / 242	176 / 242	–3	83.8		4% (11%)
AGO	182 / 262	165 / 254	12.6	86.4		–16% (13%)
UKCCCR AB01	321 / 353	320 / 352	3.3	160.1		–2% (8%)
Subtotal	1,111 / 1,522	1,140 / 1,512	–27.7	559.4		5% (4%)
Test of heterogeneity		$\chi^2_7 = 14.51$, $P = .043$				
Test of treatment effect		$\chi^2_1 = 1.37$, $P = .24$				
(b) Single–agent						
Tax 303 Study Group	32 / 55	22 / 43	2.1	13.3		–17% (37%)
EORTC 10923	151 / 166	147 / 165	6.1	74.3		–9% (13%)
ECOG E1193	209 / 243	213 / 247	–6.6	105.2		6% (10%)
Subtotal	392 / 464	382 / 455	1.7	192.9		–1% (8%)
Test of heterogeneity		$\chi^2_2 = 1.24$, $P = .54$				
Test of treatment effect		$\chi^2_1 = 0.01$, $P = .91$				
Total	1,503 / 1,986	1,522 / 1,967	–26	752.3		3% (4%)
Test of heterogeneity		$\chi^2_{10} = 16.23$, $P = .093$				
Test of interaction (a) *v* (b)		$\chi^2_1 = 0.48$, $P = .49$				
Test of treatment effect		$\chi^2_1 = 0.9$, $P = .34$				

PATIENTS IN THESE TRIALS WERE TAXANE-NAÏVE (Dogma even less valid for today's 1st line population)

- **Single-agent T significantly worse than single-agent A in PFS but not in RR nor OS.**
- **T-based significantly better than A-based combinations in RR and PFS, but not in OS.**

HERNATA Trial of Docetaxel/Trastuzumab vs Vinorelbine/Trastuzumab



Anderssen et al EBCC 2010
In press J Clin Oncol

Extrapolating from HER-2+ disease:
Vinorelbine seems at least as good as taxane and significantly less toxic

Vinorelbine & Capecitabine: Consistent efficacy results & NO ALOPECIA

TRAVIOTA:
Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab

First-line MBC
No prior trastuzumab
Measurable Disease
N=81

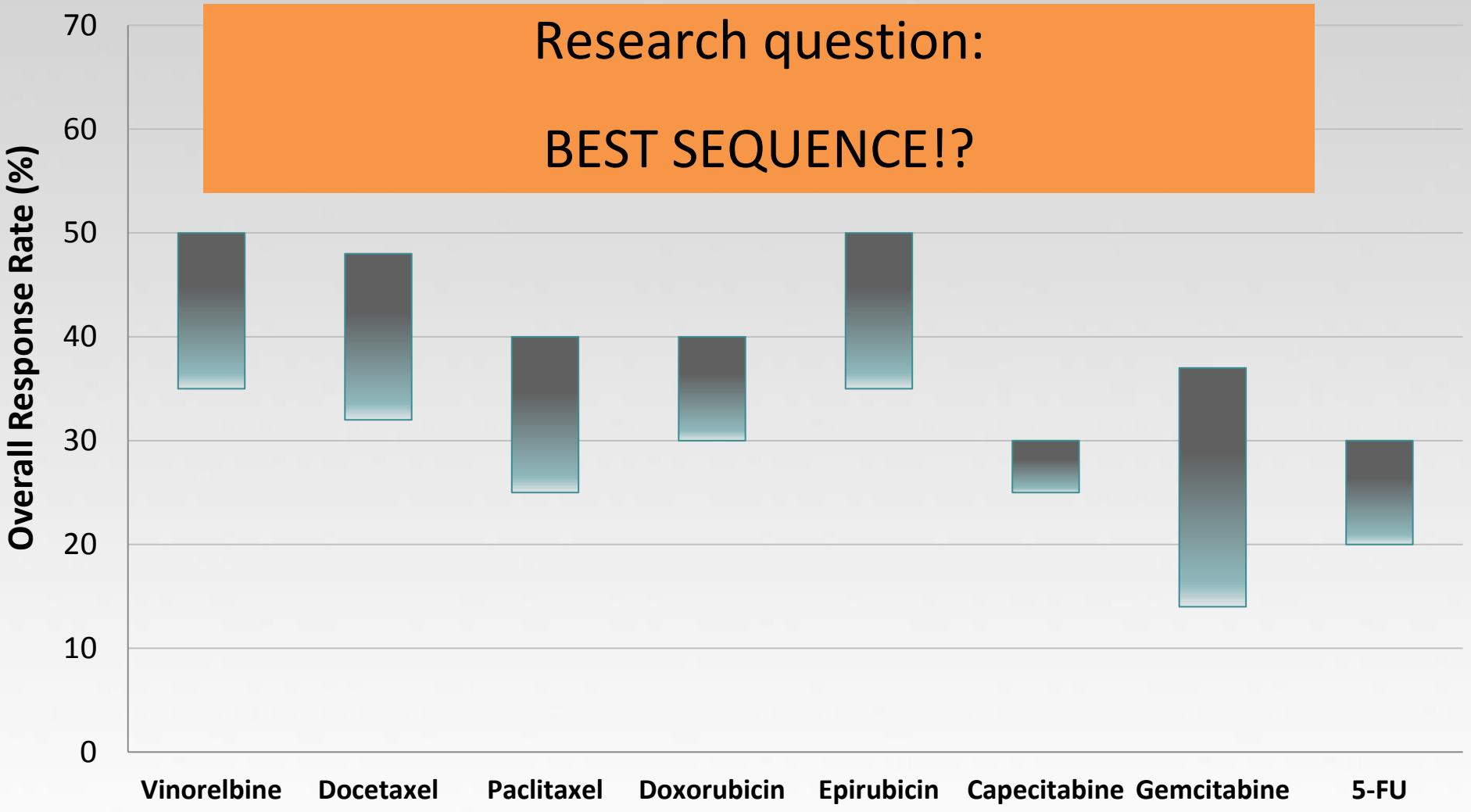
- Paclitaxel or Docetaxel + Trastuzumab
- Vinorelbine + Trastuzumab

	RR	TTP
Taxane Arm	58%	6.0 months
Vinorelbine Arm	66%	8.5 months

p=0.09

Burstein HJ, et al. *Cancer.* 2007;110:965-972.

Clinical Efficacy of Cytotoxic Agents



From: Hamilton A. *J Clin Oncol*. 2005; 23:1760-1775; Swart R. *Medscape Reference.* March 28, 2011, http://emedicine.medscape.com/article/1946040-overview.

Medscape EDUCATION

A Phase III, Open-label, Randomized, Multicenter Study Of Eribulin Mesylate Versus Capecitabine In Patients With Locally Advanced Or Metastatic Breast Cancer Previously Treated With Anthracyclines And Taxanes

Peter A. Kaufman,[1] Ahmad Awada,[2] Christopher Twelves,[3] Louise Yelle,[4] Edith A. Perez,[5] Jantien Wanders,[6] Martin S. Olivo,[7] Yi He,[7] Corina E. Dutcus,[7] Javier Cortes[8]

[1]Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [2]Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium; [3]Leeds Institute of Molecular Medicine and St James's Institute of Oncology, Leeds, UK; [4]Department of Medicine, University of Montreal, Montreal, Canada; [5]Mayo Medical Clinic, Jacksonville, FL, USA; [6]Eisai Ltd, Hatfield, UK; [7]Eisai Inc., Woodcliff Lake, NJ, USA; [8]Vall D'Hebron University Hospital, Barcelona, Spain

Study Design

- Global, randomized, open-label Phase III trial (Study 301)

Patients (N=1102)

Locally advanced or MBC

- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin mesylate
1.4 mg/m^2† 2- to 5-min IV
Day 1 & 8 q21 days

Randomization 1:1

Capecitabine
1250 mg/m^2 BID orally
Days 1-14, q21 days

Co-primary endpoint

- OS and PFS

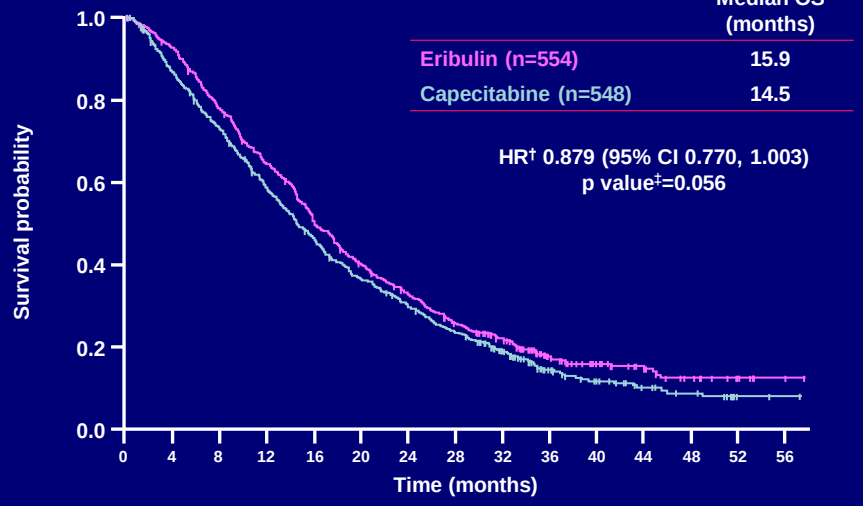
Secondary endpoints

- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

- Stratification:
  - Geographical region, HER2 status

†Equivalent to 1.23 mg/m^2 eribulin

Overall Survival



	Median OS (months)
Eribulin (n=554)	15.9
Capecitabine (n=548)	14.5

HR† 0.879 (95% CI 0.770, 1.003)
p value‡=0.056

ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

- No major differences in outcomes
- 1st drug to "as good as capecitabine" in 1st/2nd line

- Different toxicity profile
- A new good treatment option

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 4-8, 2012

Progression-free Survival

Independent Review

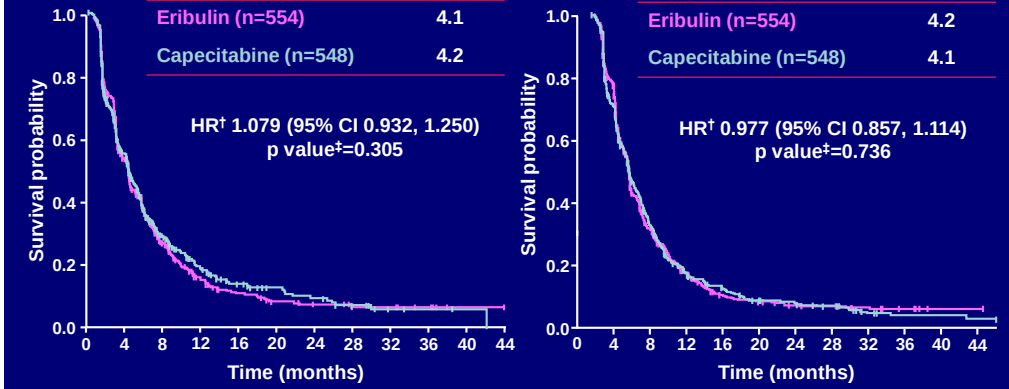
	Median (months)
Eribulin (n=554)	4.1
Capecitabine (n=548)	4.2

HR† 1.079 (95% CI 0.932, 1.250)
p value‡=0.305

Investigator Review

	Median (months)
Eribulin (n=554)	4.2
Capecitabine (n=548)	4.1

HR† 0.977 (95% CI 0.857, 1.114)
p value‡=0.736



ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

HER-2 NEGATIVE MBC

Even if given in the adjuvant setting, provided that cumulative dose has not been achieved and that there are no cardiac contra-indications, anthracyclines can be re-used in MBC, particularly if there has been at least one year of disease-free survival.

(LoE: 1 C) (93%)

CHEMOTHERAPY (general)

Duration of each regimen and number of regimens should be tailored to each individual patient (LoE: Expert opinion). (96%)

Usually each regimen should be given until progression of disease or unacceptable toxicity (unacceptable should be defined together with the patient) (LoE: 1B). (72%)

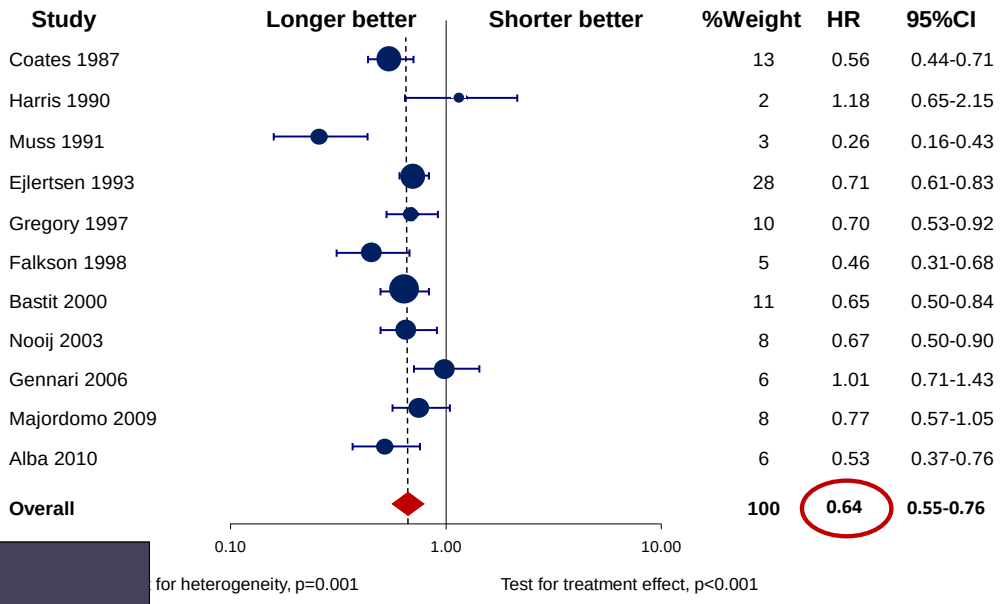
✓ **A meta-analysis of published trials (Gennari et al) concluded that longer 1st line CT duration is associated with a marginally longer OS and a substantially longer PFS.**

Optimal Duration of Chemotherapy?

- Longer CT duration associated with :
- significant and clinically meaningful improvement in PFS (HR 0.64; 95% CI 0.55 – 0.76)
- significant improvement in OS (HR 0.91; 95% CI 0.84-0.99)

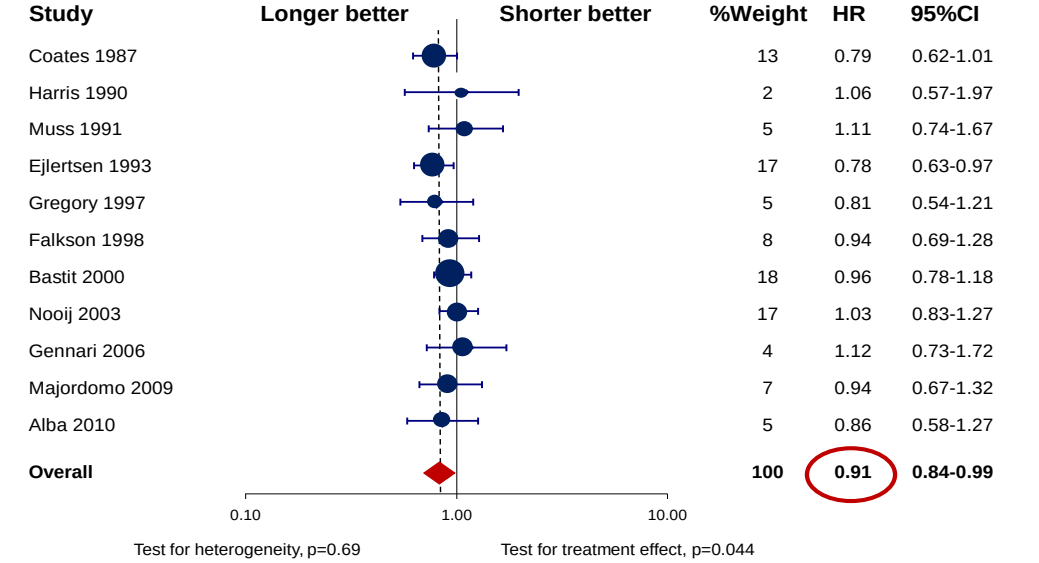
U1

Results: Progression Free Survival



U1

Results: Overall Survival



These results provide support to the clinical approach of prolonging 1st line CT in the absence of significant toxicity and disease progression (when CT is the only option…)

Role of biologics, HT, metronomic CT !?!

Gennari et al, J Clin Oncol 2011

Metronomic chemotherapy is an reasonable treatment option, for patients not requiring rapid tumor response.
(LoE: 1 B) (88%)

The better studied regimen is CM (low dose oral cyclophosphamide and methotrexate); other regimens are being evaluated (including capecitabine and vinorelbine).

Randomized trials are needed to accurately compare metronomic CT with standard dosing regimens.

Bridging the Gap

ABC4

European School of Oncology
learning to care

Advanced Breast Cancer

2-4 November 2017 • Lisbon, Portugal

Fourth International Consensus Conference

SAVE THE DATE

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