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ER/PR Breast Disease: Early Stage, Locally Advanced and Metastatic Breast Cancer

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Outline

- Advanced stage
  - Overview
  - M-THOR inhibitors
  - CDK4/6 inhibitors

- Early stage
  - Update in adjuvant endocrine treatment
  - Genomic signatures: Mammaprint and Oncotype-DX

Current Treatment of Advanced Hormone Receptor Positive (HR+) HER2- Breast Cancer

- Nearly 75% of patients have invasive breast cancers are hormone receptor positive (HR^+)

- Endocrine therapy is the standard of care for patients with HR^+ breast cancer, recommended by national and international guidelines

- Several developments in the past years offer promising treatment options and better care for patients with HR^+, $HER2^-$ early and advanced breast cancer

New Trials of Hormone Therapy Alone in First-Line Advanced Breast Cancer

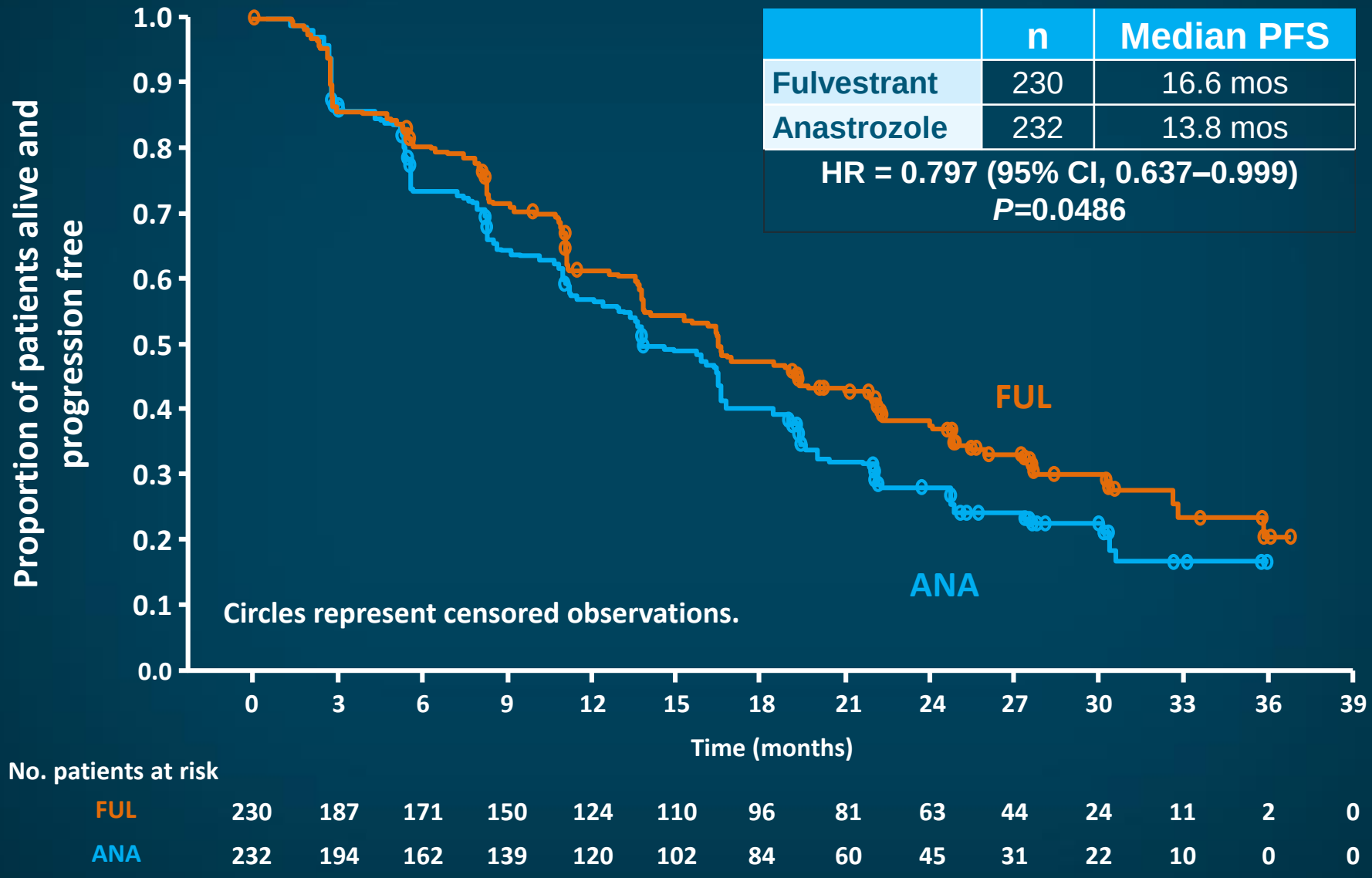
FALCON: (*F*ulvestrant and *A*nastrozo*L*e *CO*mpared in Hormonal Therapy-*N*aïve Advanced BC)

- Randomized, double-blind, parallel-group, international, multicenter study
- Randomization of 450 patients was planned to achieve 306 progression events; if true PFS HR was 0.69 this would provide 90% power for statistical significance at the 5% two-sided level (log-rank test).

BC = breast cancer; PgR = progesterone receptor; HER = human epidermal growth receptor; PO = by mouth; ORR = objective (or overall) response rate; CBR = clinical benefit rate; DoR = duration of response; EDoR = expected DoR; DoCB = duration of clinical benefit; EDoCB = expected DoCB; HRQoL = health-related quality of life; FACT-B = Functional Assessment of Cancer Therapy for BC; TOI = Trial Outcome Index.

Robertson JFR et al. *Lancet*. 2016;388:2997-3005.

FALCON: Primary Endpoint, PFS



	n	Median PFS
Fulvestrant	230	16.6 mos
Anastrozole	232	13.8 mos

HR = 0.797 (95% CI, 0.637–0.999)
P=0.0486

No. patients at risk

FUL	230	187	171	150	124	110	96	81	63	44	24	11	2	0
ANA	232	194	162	139	120	102	84	60	45	31	22	10	0	0

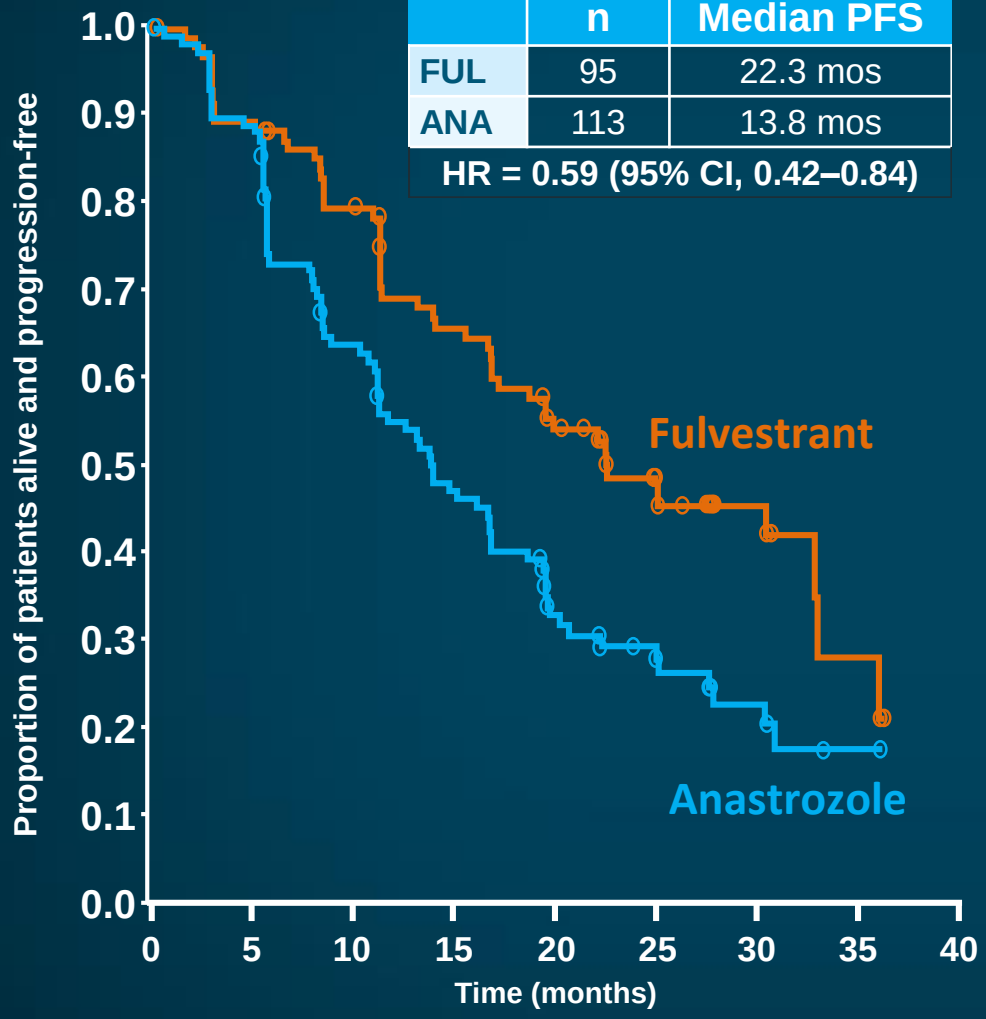
Robertson JFR et al. *Lancet*. 2016;388:2997-3005.

FALCON: PFS in Patients ± Visceral Disease

Without visceral disease

	n	Median PFS
FUL	95	22.3 mos
ANA	113	13.8 mos

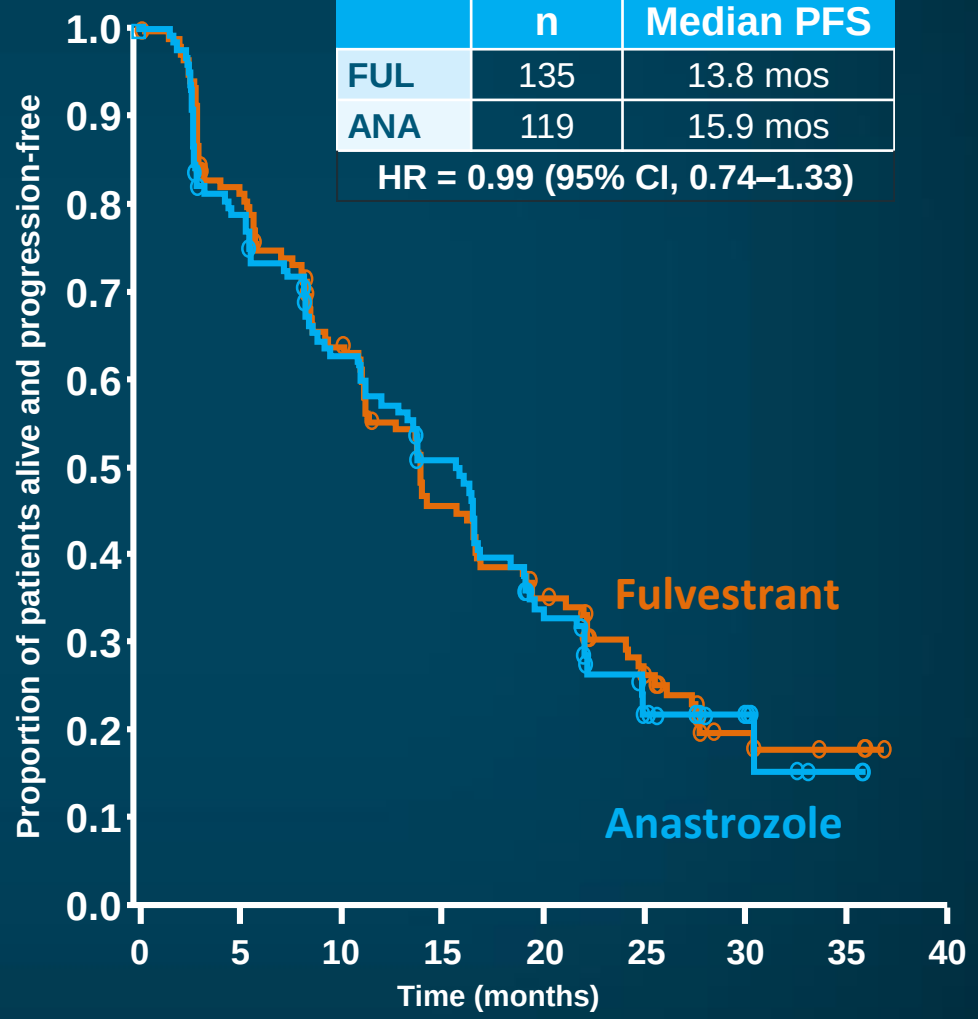
HR = 0.59 (95% CI, 0.42–0.84)



With visceral disease

	n	Median PFS
FUL	135	13.8 mos
ANA	119	15.9 mos

HR = 0.99 (95% CI, 0.74–1.33)



Post hoc interaction test $P<0.01$. Circles represent censored observations.

Robertson JFR et al. *Lancet*. 2016;388:2997–3005.

Major Challenge in Endocrine Resistance

- Approximately 30-50% of patients with HR^+ advanced breast cancer do not respond to initial endocrine therapy.
- The majority (if not all) of patients with HR^+ advanced breast cancer will ultimately progress despite endocrine therapy.

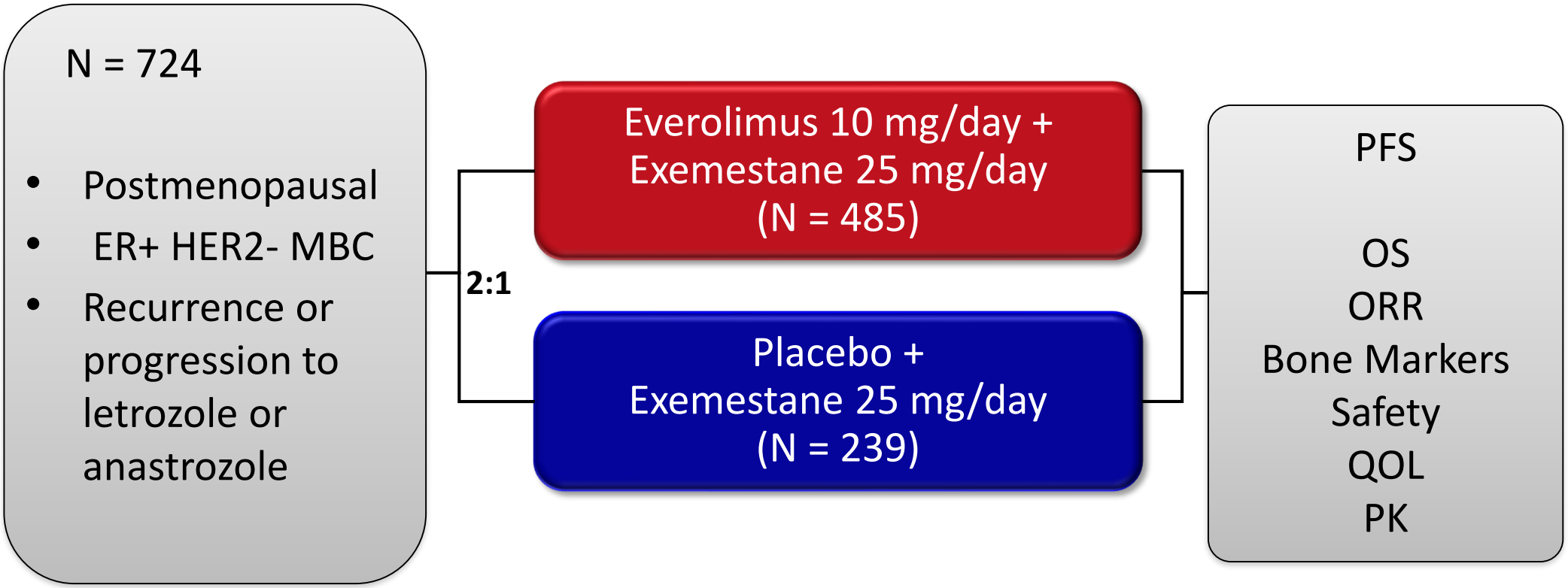
Bedard PL, et al. *Breast Cancer Res Treat*. 2008;108(3):307-317.

Approaches to Overcoming Resistance to Endocrine Therapy

- Alterations of downstream signaling pathways such as PI3K, (mTOR and PI3K inhibitors)

- Alterations of the cell cycle machinery (CDK inhibitors)

BOLERO-2 Schema

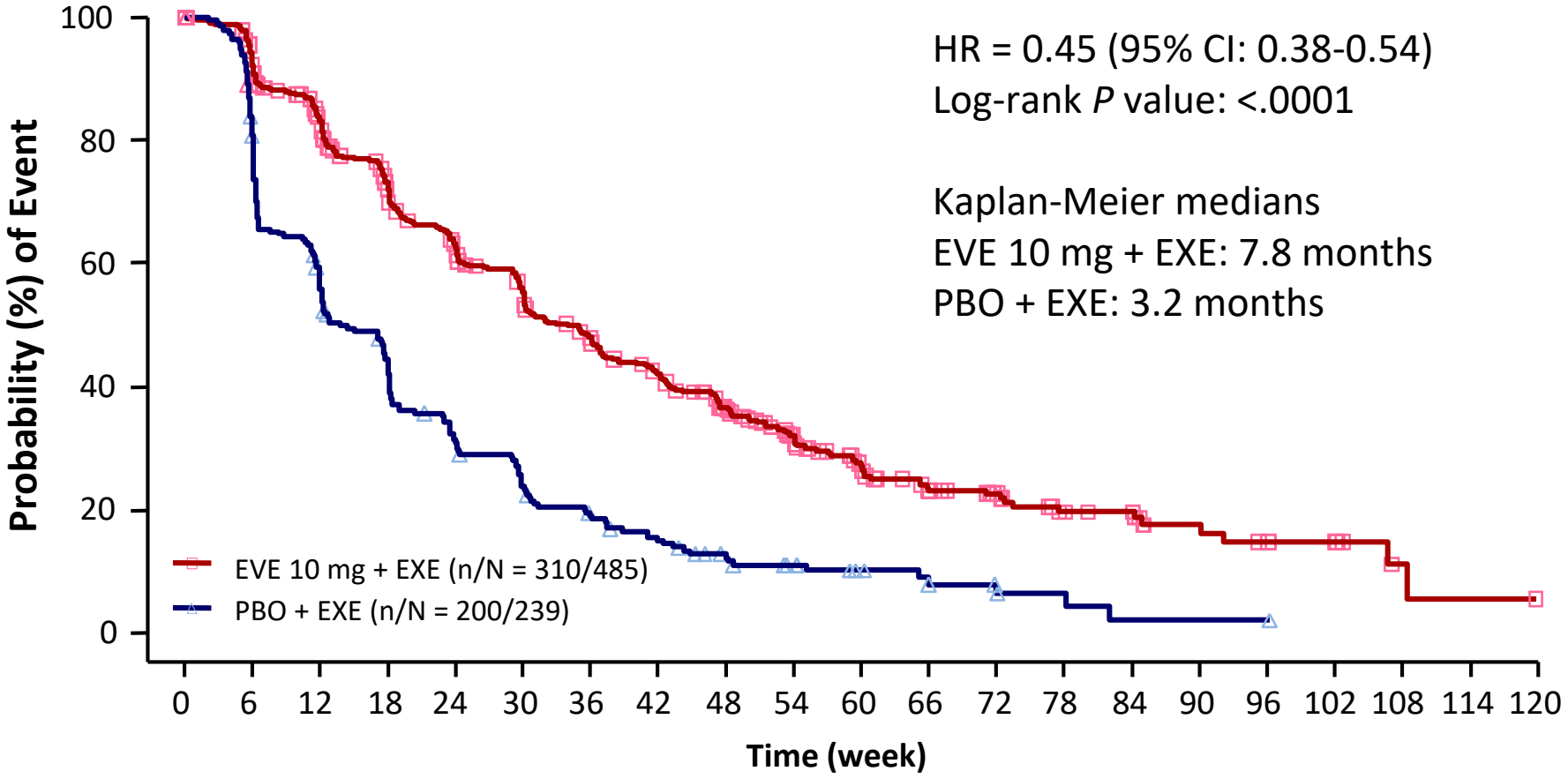


- Stratification:
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease

No cross-over

, Baselga et al NEJM 2012.

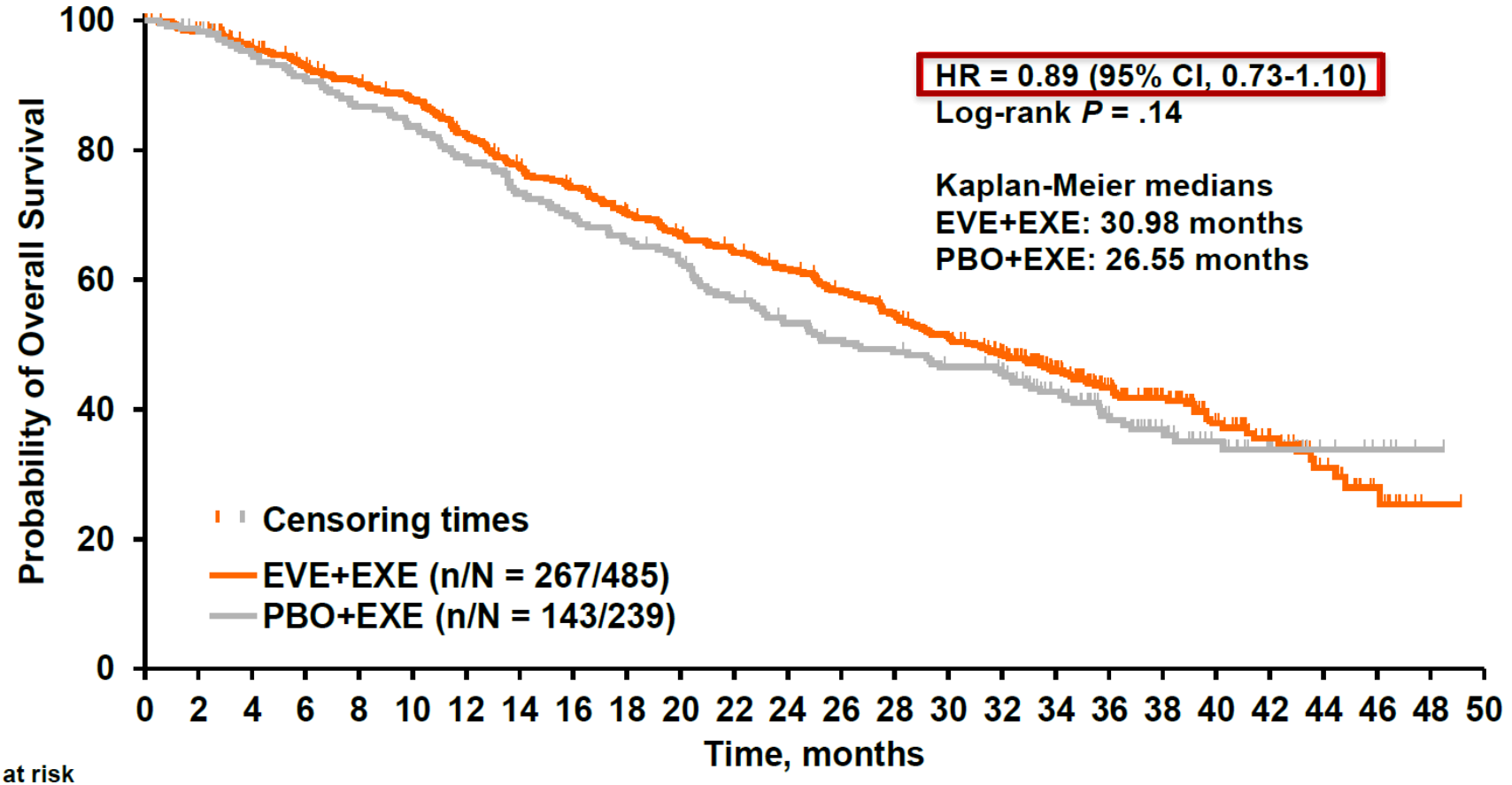
BOLERO-2: Primary Endpoint, PFS (18-Month Follow-Up, Local)



Consistent results with central analysis:
HR = 0.38 (95% CI: 0.31-0.48); log-rank *P* value: <.0001
Kaplan-Meier medians: EVE 10 mg + EXE: 11.01 months vs PBO + EXE: 4.14 months

Baselga J, et al. N Engl J Med 2012;366(6):520-9.

BOLERO-2 (39 months): Final OS Analysis



No. at risk

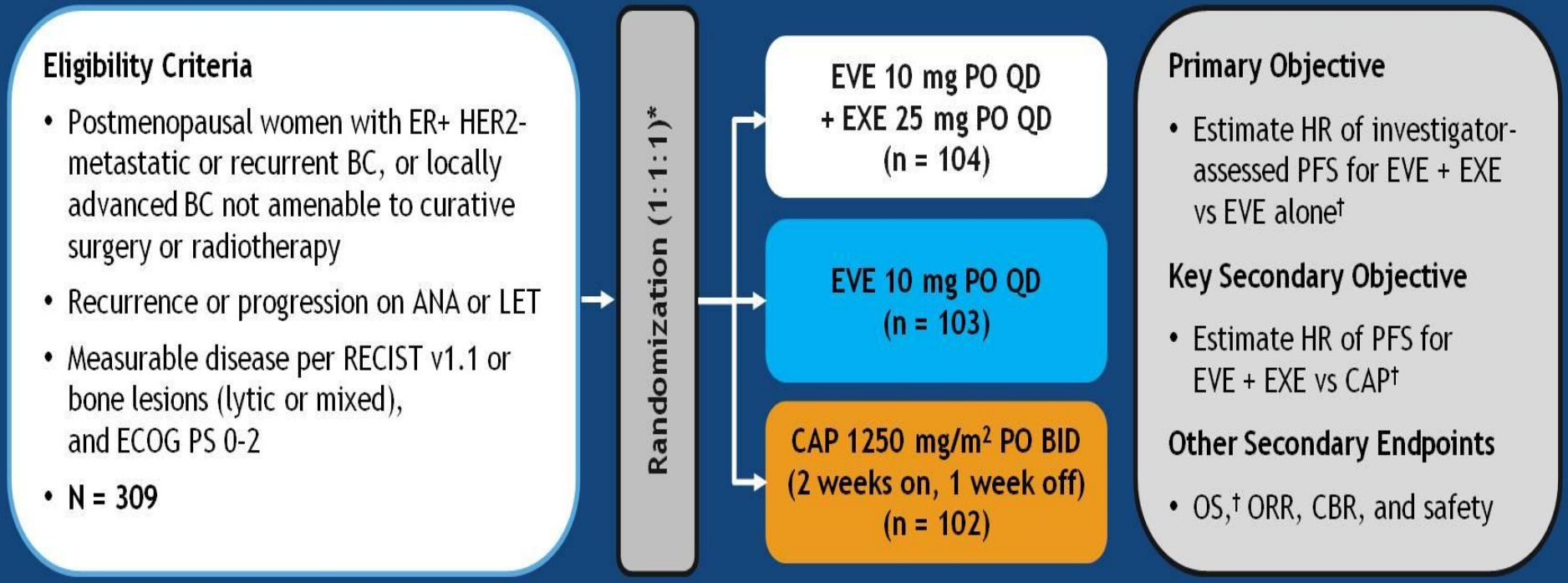
EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- 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

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®.
Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; IXRS®, Interactive Voice and Web Response System; PBO, placebo.

Randomized, Open-Label, Phase II Study

- BOLERO-6 randomized 309 patients to receive EVE + EXE (n = 104), EVE alone (n = 103), or CAP (n = 102)



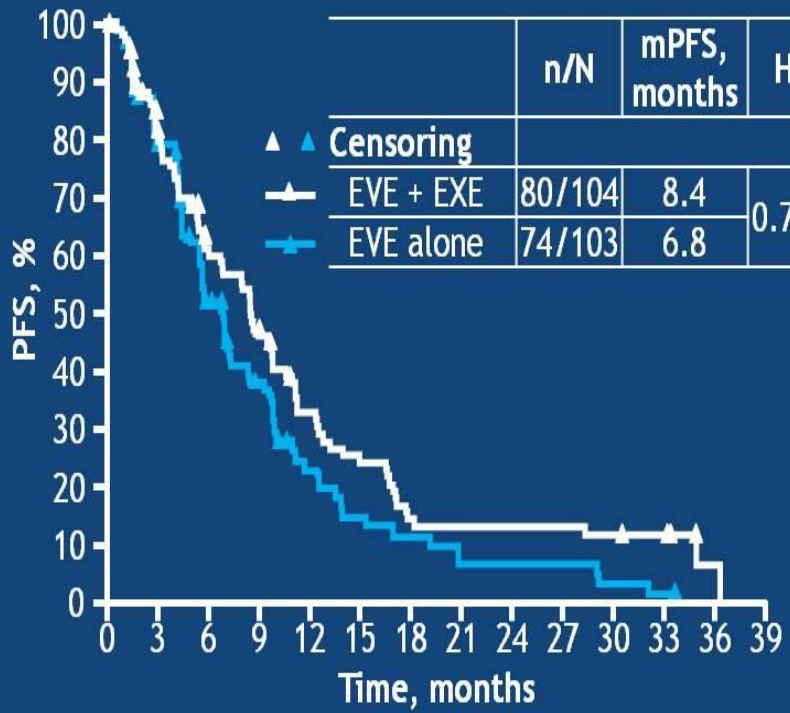
- BOLERO-6 was not powered to perform statistical comparisons between arms

*Stratified by presence or absence of visceral disease (lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion, or malignant ascites; †Stratified multivariate Cox regression models were adjusted on treatment and the following prognostic and baseline covariates where imbalances between arms were observed: bone-only lesions (yes vs no); prior chemotherapy (yes vs no); ECOG PS (0 vs 1-2); organs involved (2 vs 1, and ≥3 vs 1); race (Caucasian vs non-Caucasian); age (<65 vs ≥65 years).
ANA, anastrozole; BID, twice daily; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PO, oral administration; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Primary Objective
Estimated HR of PFS for EVE + EXE vs EVE alone

EVE + EXE offers a PFS benefit vs EVE alone



	n/N	mPFS, months	HR* (90% CI)
Censoring			
EVE + EXE	80/104	8.4	0.74 (0.57-0.97)
EVE alone	74/103	6.8	

Patients still at risk

EVE + EXE	104	73	52	39	26	19	11	10	10	10	9	5	1	0
EVE alone	103	66	40	26	14	9	7	4	4	4	2	1	0	0

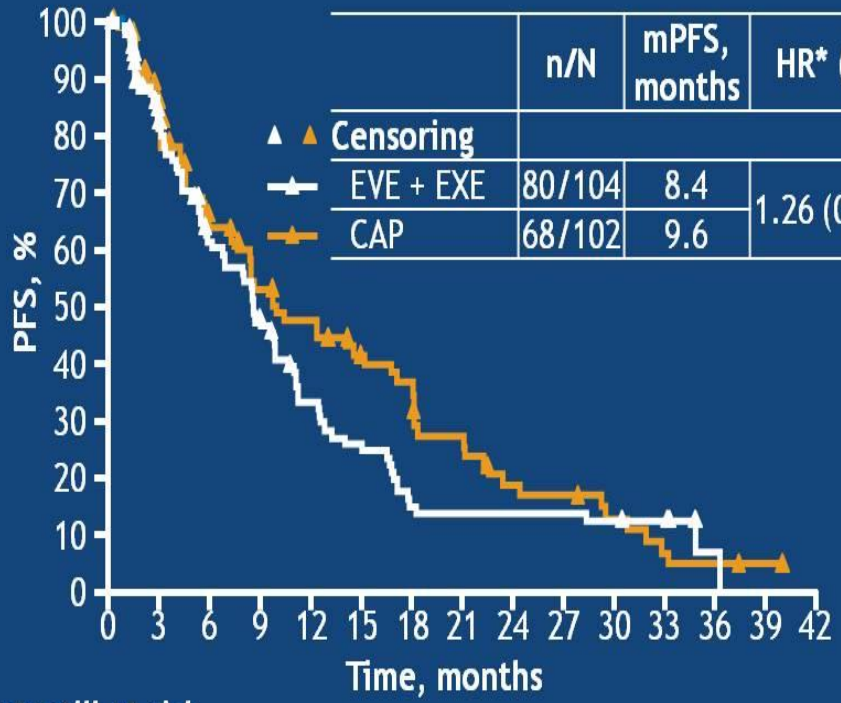
- Estimated HR of PFS for EVE + EXE vs EVE alone was 0.74 (90% CI 0.57-0.97)
- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - EVE alone arm, 18%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave **a consistent HR (0.73; 90% CI 0.56-0.97)** for EVE + EXE vs EVE alone

*EVE + EXE vs EVE alone (obtained from a stratified Cox model).
mPFS, median progression-free survival.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Key Secondary Objective
Estimated HR of PFS for EVE + EXE vs CAP

CAP may have been favored by baseline imbalances and potential informative censoring



	n/N	mPFS, months	HR* (90% CI)
EVE + EXE	80/104	8.4	1.26 (0.96-1.66)
CAP	68/102	9.6	

Patients still at risk

EVE + EXE	104	73	52	39	26	19	11	10	10	10	9	5	1	0	0
CAP	102	68	48	38	33	26	19	14	10	9	6	3	2	1	0

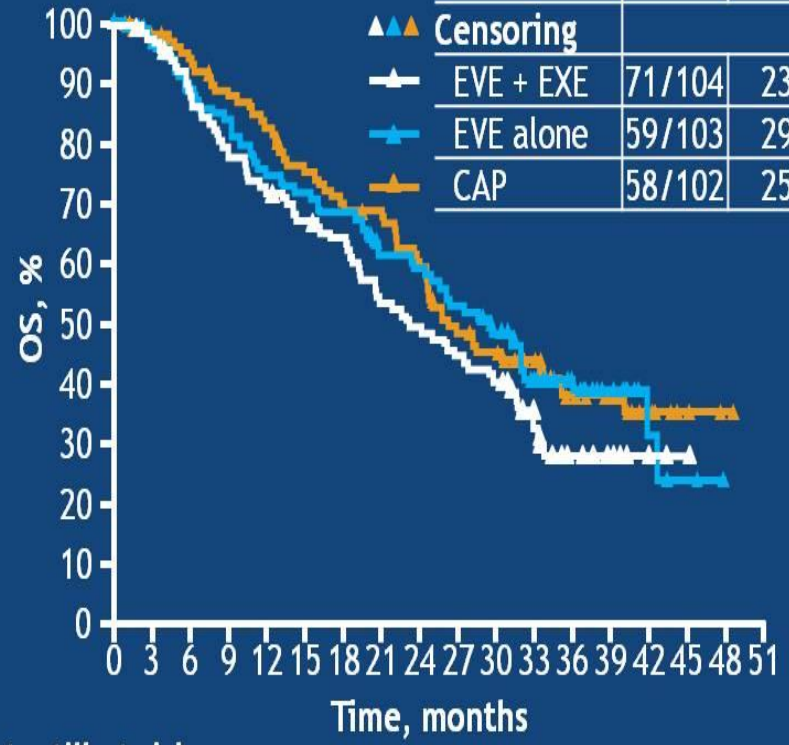
- Estimated HR of PFS for EVE + EXE vs CAP was 1.26 (90% CI 0.96-1.66)
- Censored for initiating new antineoplastic therapies:
  - EVE + EXE arm, 9%
  - CAP arm, 20%
- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors gave **a HR of 1.15 (90% CI 0.86-1.52)** for EVE + EXE vs CAP

*EVE + EXE vs CAP (obtained from a stratified Cox model).

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Overall Survival
EVE + EXE vs EVE alone or CAP

	n/N	mOS, months	HR* (90% CI)
Censoring			
EVE + EXE	71/104	23.1	
EVE alone	59/103	29.3	1.27 (0.95-1.70)
CAP	58/102	25.6	1.33 (0.99-1.79)



Patients still at risk																	
EVE + EXE	104	101	92	81	74	67	63	53	48	43	39	22	13	8	3	1	0	0
EVE alone	103	96	86	81	72	69	66	57	55	49	43	27	21	11	4	2	0	0
CAP	102	94	88	83	78	70	64	61	54	43	38	31	21	16	7	3	1	0

- New antineoplastic therapies initiated at EOT:
  - EVE + EXE arm, 78%
  - EVE alone arm, 81%
  - CAP arm, 79%

- A stratified multivariate Cox regression model accounting for baseline imbalances and known prognostic factors **gave a HR of 1.27 (90% CI 0.94-1.70)** for EVE + EXE vs EVE alone and **a HR of 1.19 (90% CI 0.88-1.62)** for EVE + EXE vs CAP

*EVE + EXE vs EVE alone or CAP (obtained from a stratified Cox model).
EOT, end of treatment; mOS, overall survival.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Adverse Events

AE,* %	EVE + EXE (n = 104)		EVE alone (n = 103)		CAP (n = 102)	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
Total	100	70	98	59	100	74
Stomatitis†	49	9	46	5	25	7
Fatigue	38	8	31	3	35	8
Diarrhea	35	5	33	3	54	8
Anemia	32	13	25	10	22	7
Elevated GGT	15	9	16	12	2	2
Elevated AST	15	7	14	8	9	1
Hypertension	14	6	8	2	5	3
Hyperglycemia	13	4	17	8	8	1
Pneumonia	11	7	9	3	3	2
Neutropenia	4	0	4	2	15	6
PPE syndrome	3	1	3	0	61	27

- Most frequent all-grade AEs:
  - Stomatitis in EVE-containing arms
  - PPE syndrome and diarrhea in CAP arm
- Grade 3-4 AEs more frequent in EVE + EXE arm vs EVE alone arm, and comparable between EVE + EXE and CAP arms

*≥5% grade 3-4 events in any arm; †BOLERO-6 was not designed to use the SWISH[1] protocol for stomatitis prevention.
AE, adverse event; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia.

1. Rugo HS et al. *Lancet Oncol* 2017;18:654-662.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Conclusions

- Median PFS with EVE + EXE (8.4 months) consistent with BOLERO-2 (7.8 months),[1] and vs EVE alone here (6.8 months) corresponded to estimated 26% reduction of risk of disease progression or death (HR 0.74)
  - Median PFS with EVE alone numerically longer than previously reported in a small phase II study (3.5 months)[2]
  - No new safety signals observed with EVE + EXE

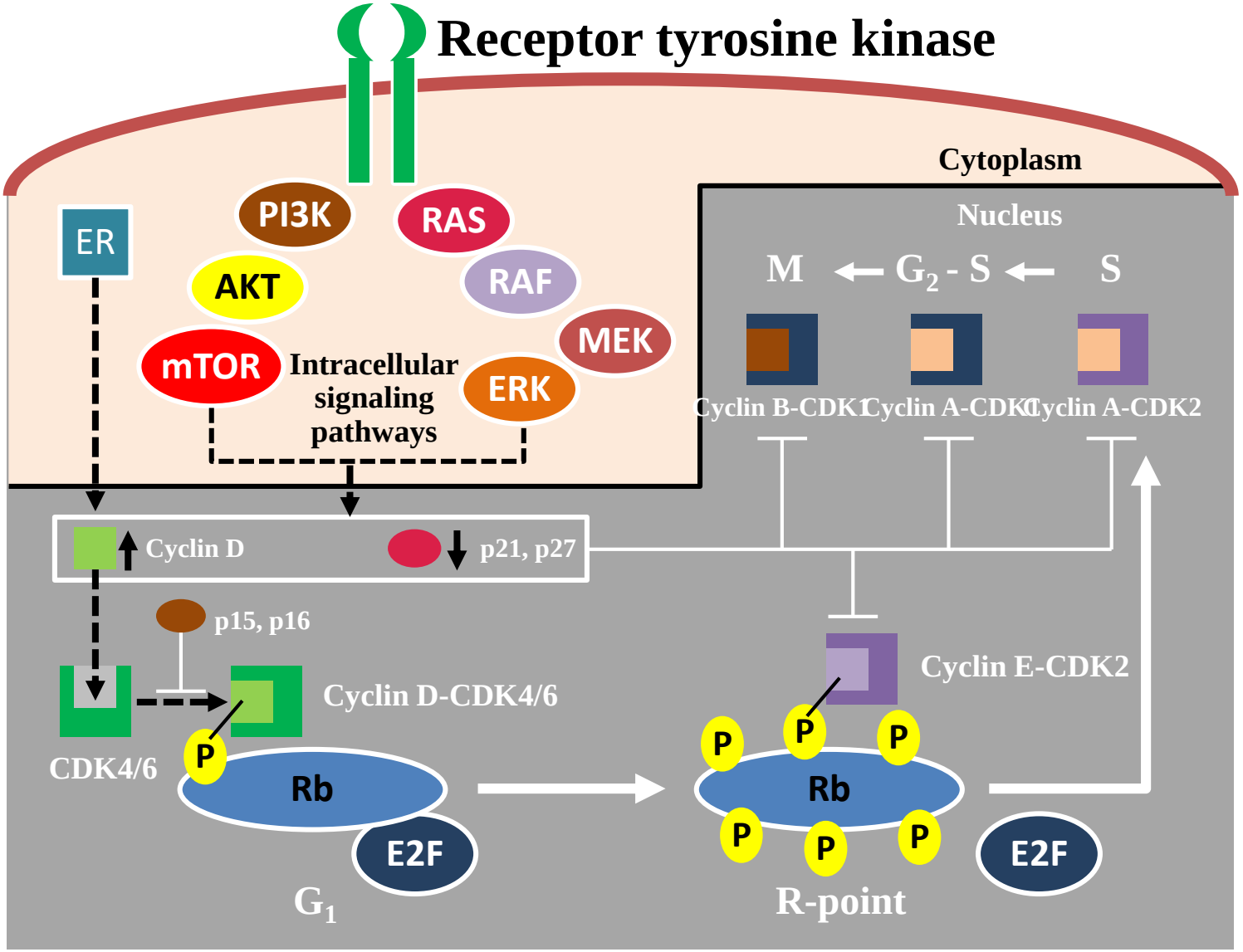
- A numerical median PFS difference was observed for CAP over EVE + EXE (9.6 vs 8.4 months), which may be attributed to various baseline characteristics favoring CAP and potential informative censoring
  - Median PFS with CAP also inconsistent with previous studies (4.1-7.9 months)[3-7]

1. Yardley DA, et al. *Adv Ther*. 2013;30:870-884; 2. Ellard SL, et al. *J Clin Oncol*. 2009;27:4536-4541 [NCI Canada]; 3. Robert NJ, et al. *J Clin Oncol*. 2011;29:1252-1260; 4. O'Shaughnessy JA, et al. *Oncologist*. 2012;17:476-484; 5. Stockler MR, et al. *J Clin Oncol*. 2011;29:4498-4504; 6. Kaufmann M, et al. *Eur J Cancer*. 2010;46:3184-3191; 7. Harbeck N, et al. *Breast Cancer Res Treat*. 2017;161:63-72.

http://jamanetwork.com/journals/jamaoncology/fullarticle/10.1001/jamaoncol.2018.2262

Cell Cycle Control in Breast Cancer and CDK Inhibition

Regulation of G1/S Checkpoint in Breast Cancer



ERK = extracellular signal-regulated kinase; MEK = mitogen-activated protein kinase kinase; mTOR = mammalian target of rapamycin; Rb = retinoblastoma; P = phosphate; PI3K = phosphatidylinositol 3-kinase; CDK = cyclin-dependent kinase.

Ingham M, Schwartz GK. *J Clin Oncol.* 2017;35:2949-2959.

In Breast Cancer, Frequent Alterations in Cyclin D/CDK4/6

- Amplification of cyclin D1 (11q13) in ER+ breast cancer
  - Noncatalytic effects of cyclin D1 on transcription, DNA repair, etc.
- Cyclin dependent kinase 4 (CDK4) amplification/overexpression
- Rb loss uncommon ER+ disease
- Loss of negative regulators (p16, p27)
- Association of above with response to antiestrogens and prognosis
- Growth factor signaling (steroid and peptide) and cell cycle progression

Arnold A, Papanikolaou A. *J Clin Oncol*. 2005;23:4215-4224.

Summary of 1st and 2nd line CDK4/6i Trials

Table 1. Select Randomized Clinical Studies of Endocrine Therapy Plus CDK4/6-Directed Therapy in Estrogen Receptor–Positive Metastatic Breast Cancer

Study	Regimen	Phase	No.	PFS, Endocrine Alone (months)	PFS, + CDK 4/6 Inhibitor (months)	Hazard Ratio (95% CI)
First line						
PALOMA-1	Letrozole with or without palbociclib	II	165	10.2	20.2	0.488 (0.319 to 0.748)
PALOMA-2	Letrozole with or without palbociclib	III	666	14.5	24.8	0.58 (0.46 to 0.72)
MONALEESA-2	Letrozole with or without ribociclib	III	668	14.7	25.3	0.56 (0.43 to 0.72)
MONARCH-3	NSAI with or without abemaciclib	III	493		NCT02246621*	
Second line						
PALOMA-3	Fulvestrant with or without palbociclib	III	521	4.6	9.5	0.46 (0.36 to 0.59)
MONARCH-2	Fulvestrant with or without abemaciclib	III	669	9.3	16.4	0.553 (0.449 to 0.681)
MONALEESA-3	Fulvestrant with or without ribociclib	III	725		NCT02422615	

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; PFS, progression-free survival; NSAI, nonsteroidal aromatase inhibitor.
*Interim analysis reportedly met primary end point of improved PFS in the combination arm.[8]

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

Side effects of CDK4/6 inhibitors

Table 2. Dosing and Toxicity for Cyclin-Dependent Kinase 4/6 Inhibitors

	Palbociclib (125 mg per day [3 weeks on, 1 week off])		Ribociclib (600 mg per day [3 weeks on, 1 week off])		Abemaciclib (200 mg twice per day [continuous])	
Common Adverse Event*	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
Neutropenia	74-81	54-67	74	59	46	27
Thrombocytopenia	16-22	2-3	NR	NR	16	3
Fatigue	37-40	2-4	37	2	40	3
Diarrhea	21-26	1-4	35	1	86	13
Nausea	25-35	0-2	52	2	45	3
QTc prolongation	NR	NR	3	NR	NR	NR

NOTE. Data are given as percent.
Abbreviation: NR, not reported; QTc, corrected QT interval.
*Common adverse events in phase III trials in the metastatic setting.

Wander S, Mayer EL, Burstein HJ. J Clin Oncol 2017

MONALEESA-3: Phase III placebo-controlled study of ribociclib + fulvestrant

- **Postmenopausal women and men with HR+/HER2- ABC**
- No or ≤1 line of prior endocrine therapy for advanced disease
- N=726

Randomization (2:1)

Stratified by:
- *Presence/absence of liver/lung metastases*
- *Prior endocrine therapy*

Ribociclib
(600 mg/day orally; 3-weeks-on/1-week-off)
+
fulvestrant
(500 mg)*
n=484

Placebo
+
fulvestrant
(500 mg)*
n=242

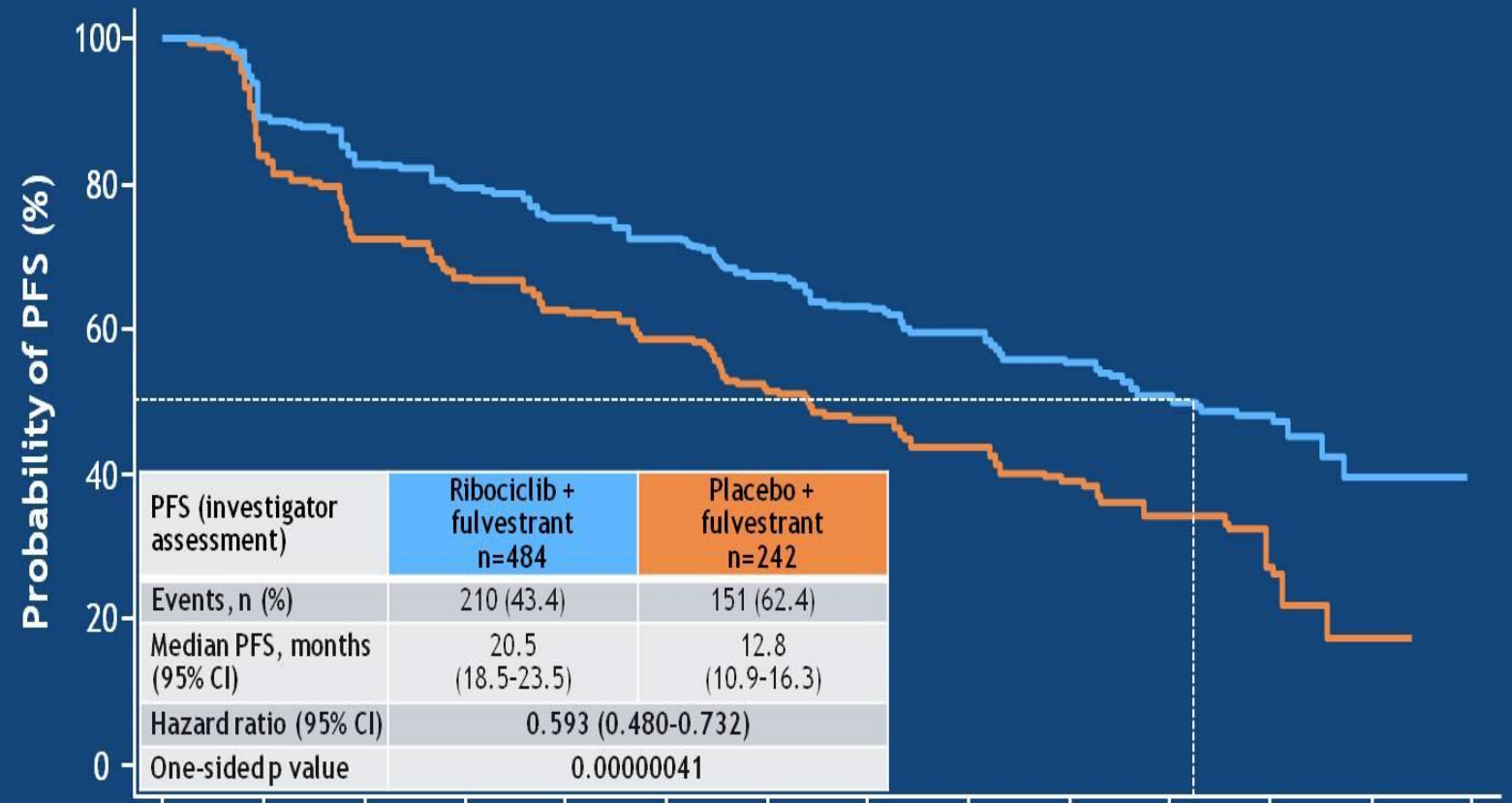
Primary endpoint
- PFS (locally assessed per RECIST v1.1)

Secondary endpoints
- Overall survival
- Overall response rate
- Clinical benefit rate
- Time to response
- Duration of response
- Time to definitive deterioration of ECOG PS
- Patient-reported outcomes
- Safety
- Pharmacokinetics

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~364 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm), and a sample size of 660 patients

ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria In Solid Tumors.
*Fulvestrant administered intramuscularly on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of every 28-day cycle thereafter.

Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + fulvestrant n=484	Placebo + fulvestrant n=242
Events, n (%)	210 (43.4)	151 (62.4)
Median PFS, months (95% CI)	20.5 (18.5-23.5)	12.8 (10.9-16.3)
Hazard ratio (95% CI)	0.593 (0.480-0.732)	
One-sided p value	0.00000041	

No. at risk

Ribociclib + fulvestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
Placebo + fulvestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

- The hazard ratio of 0.593 corresponds to a 41% reduction in risk of progression in the ribociclib vs placebo arm

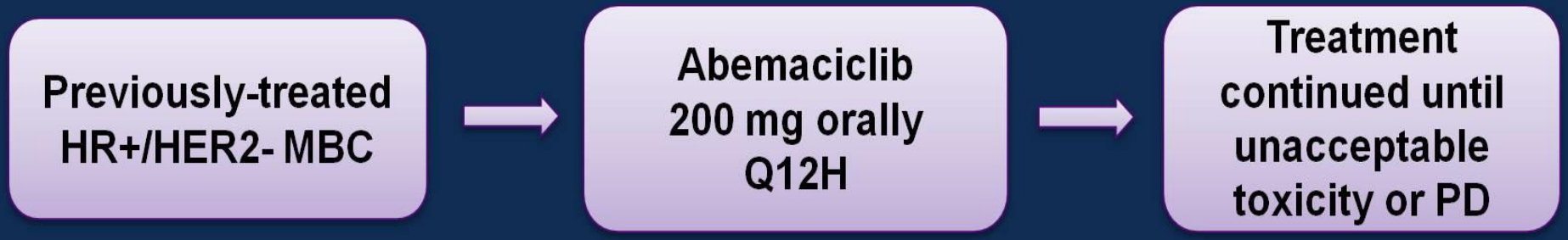
CI, confidence interval.

Conclusions

- Patients receiving ribociclib + fulvestrant had a statistically significant and clinically meaningful improvement in PFS vs placebo + fulvestrant
  - Hazard ratio: 0.593; p=0.00000041; 41% reduction in risk of disease progression vs placebo
- Ribociclib treatment benefit was consistent across patient subgroups
- Prolonged PFS was observed with first-line ribociclib + fulvestrant (hazard ratio: 0.577; 95% CI: 0.415-0.802)
  - Benefit was also observed in patients who received treatment in the second-line setting (hazard ratio: 0.565; 95% CI: 0.428-0.744)
- Ribociclib + fulvestrant demonstrated a manageable safety profile, consistent with previous Phase III ribociclib studies
- Ribociclib combined with fulvestrant may be a new first- or second-line treatment option for postmenopausal women with HR+/HER2- ABC
- This is the first study to show that CDK4/6 inhibitor + fulvestrant combinations are efficacious in patients with *de novo* ABC and patients with disease that relapsed >12 months after completion of prior (neo)adjuvant endocrine therapy

CDK 4/6 Single Agent Therapy in ER+ HER-2 normal Refractory Metastatic Breast Cancer

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)

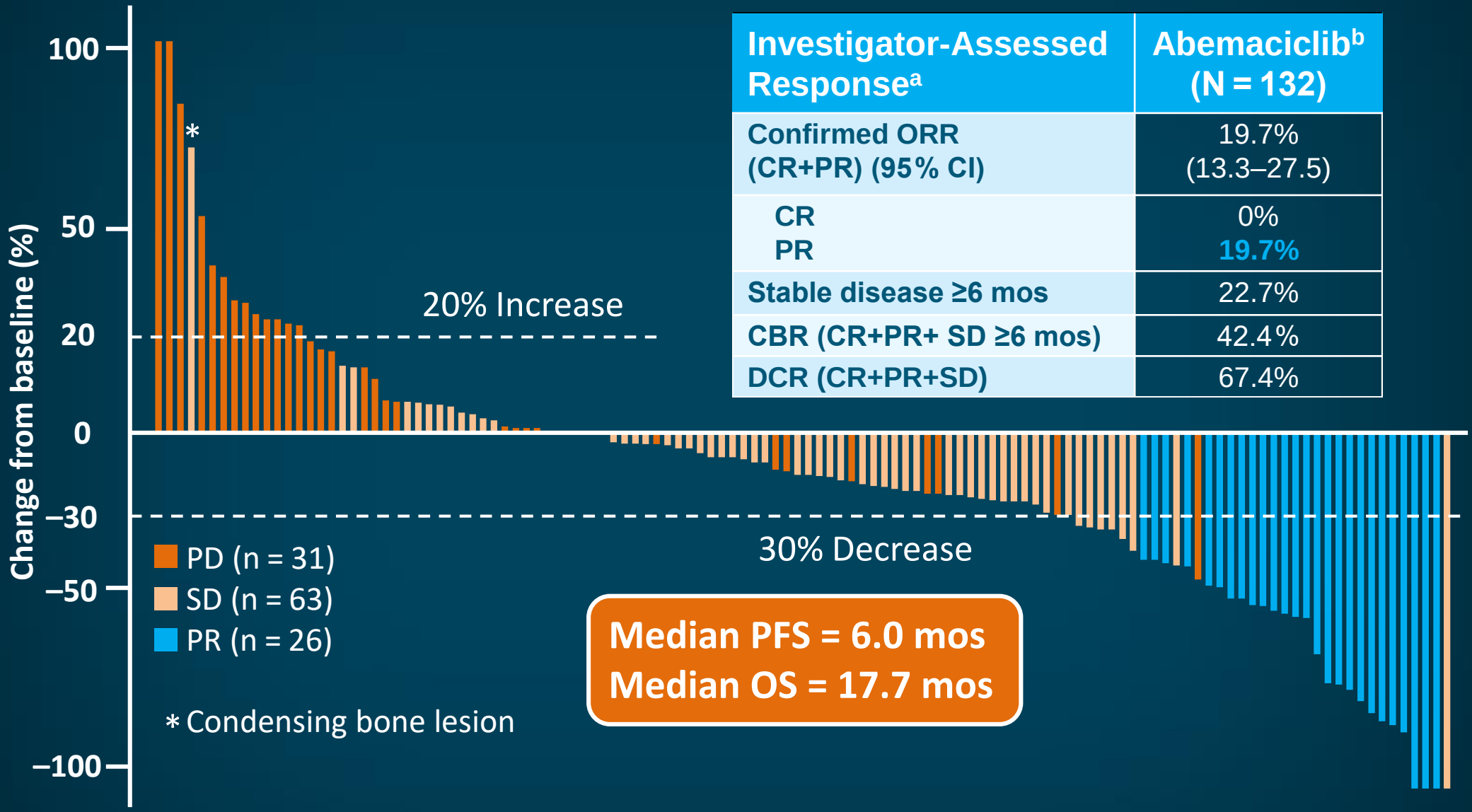
Secondary objectives

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

MONARCH 1: Late-Line Abemaciclib ER+ MBC



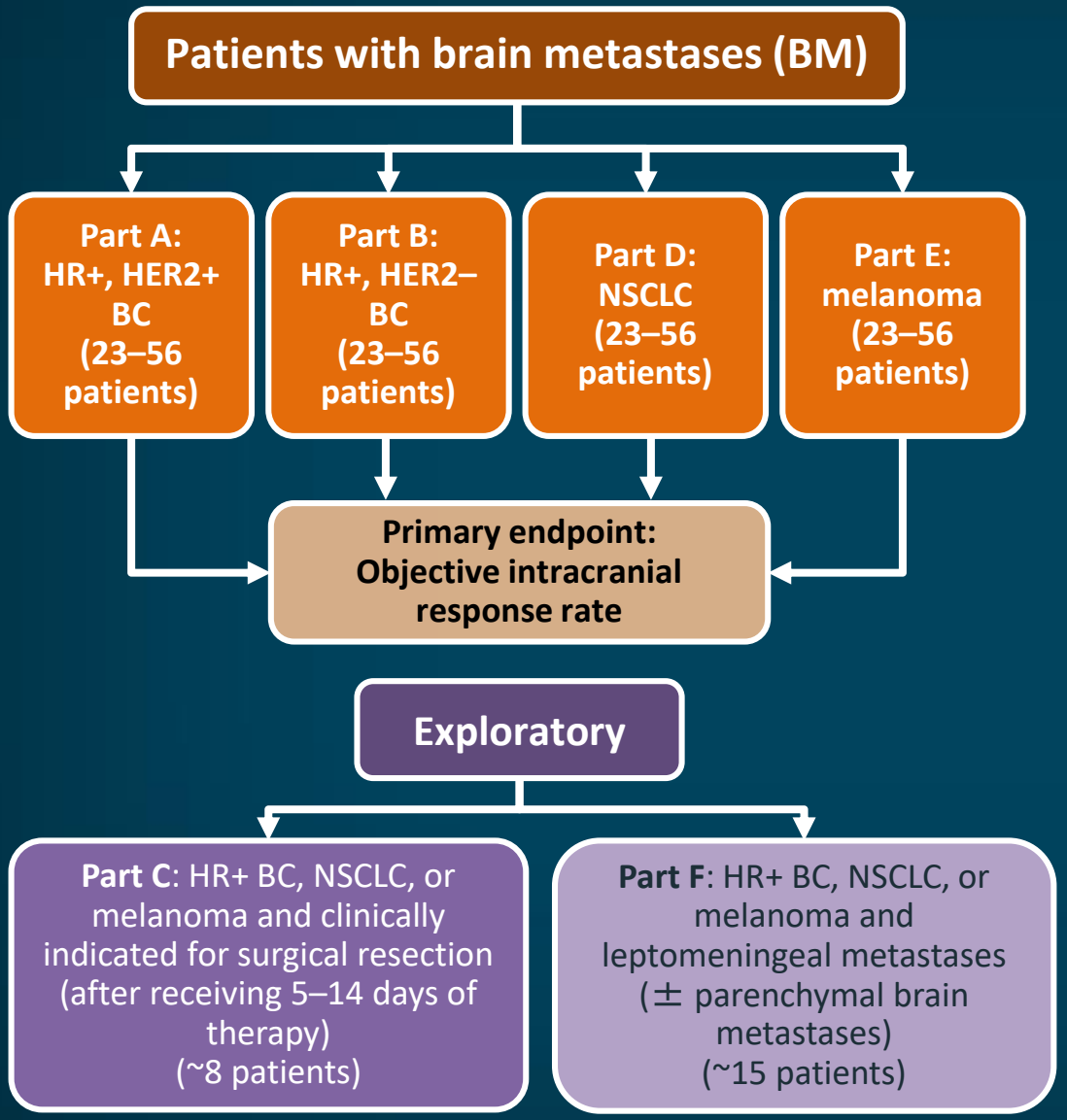
Investigator-Assessed Response[a]	Abemaciclib[b] (N = 132)
Confirmed ORR (CR+PR) (95% CI)	19.7% (13.3–27.5)
CR	0%
PR	19.7%
Stable disease ≥6 mos	22.7%
CBR (CR+PR+ SD ≥6 mos)	42.4%
DCR (CR+PR+SD)	67.4%

[a]Assessments based on independent review were comparable. [b]200 mg monotherapy dose.

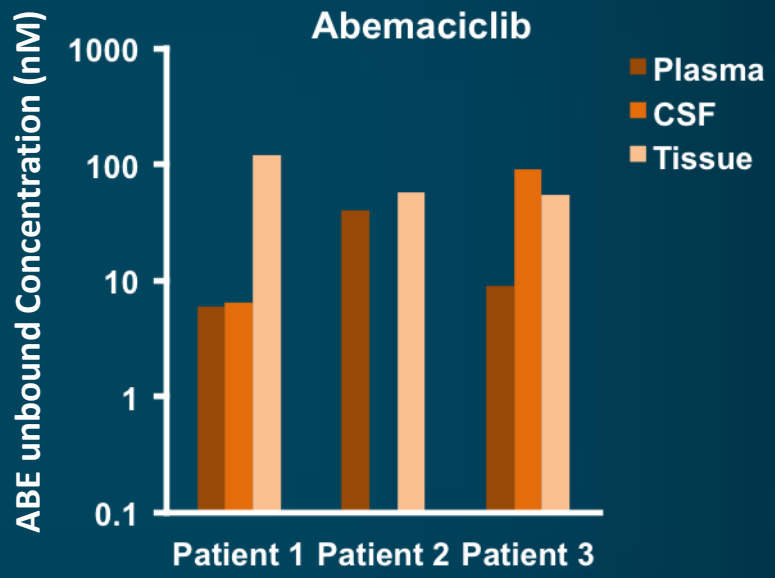
CR = complete response; PR = partial response; DCR = disease control rate; SD = stable disease.

Dickler MN et al. *Clin Cancer Res.* 2017;23:5218-5224.

Abemaciclib for Brain Metastases*



Plasma, CSF, and resected tumor tissue unbound concentrations of ABE



8.7% ORR; 17% CBR
Heavily-pretreated BM metastatic BC

NSCLC = non-small-cell lung cancer; CSF = cerebrospinal fluid. * Abemaciclib is not FDA-approved for this indication.

NCI02308020. Sahebjam S et al. *J Clin Oncol*. 2016;34(suppl): abstract 526. Tolaney SM et al. *J Clin Oncol.* 2017;35(suppl): abstract 1019.

Summary: CDK4/6 Inhibitors in ER+ MBC

- The 3 CDK4/6 inhibitors seem to be consistent and comparable in prolonging PFS in combination with endocrine therapy in the metastatic setting with acceptable toxicity.
- We have no overall survival data yet in phase III trials.
- Selection of agent, sequence, and number of drugs should be patient-specific; most patients are receiving CDK4/6i + AI in US.
- Given activity in advanced setting, now moving to adjuvant setting
- Resistance is universal
  - Next generation of trials is looking at switching ET or CDKI with addition of other drugs to inhibit resistance pathways.

Take home points in HT in ER+ HER-2- MBC

- Endocrine therapy is the cornesrtone of the treatment of HR+ MBC.

- Resistance to endocrine therapy is a challenge.

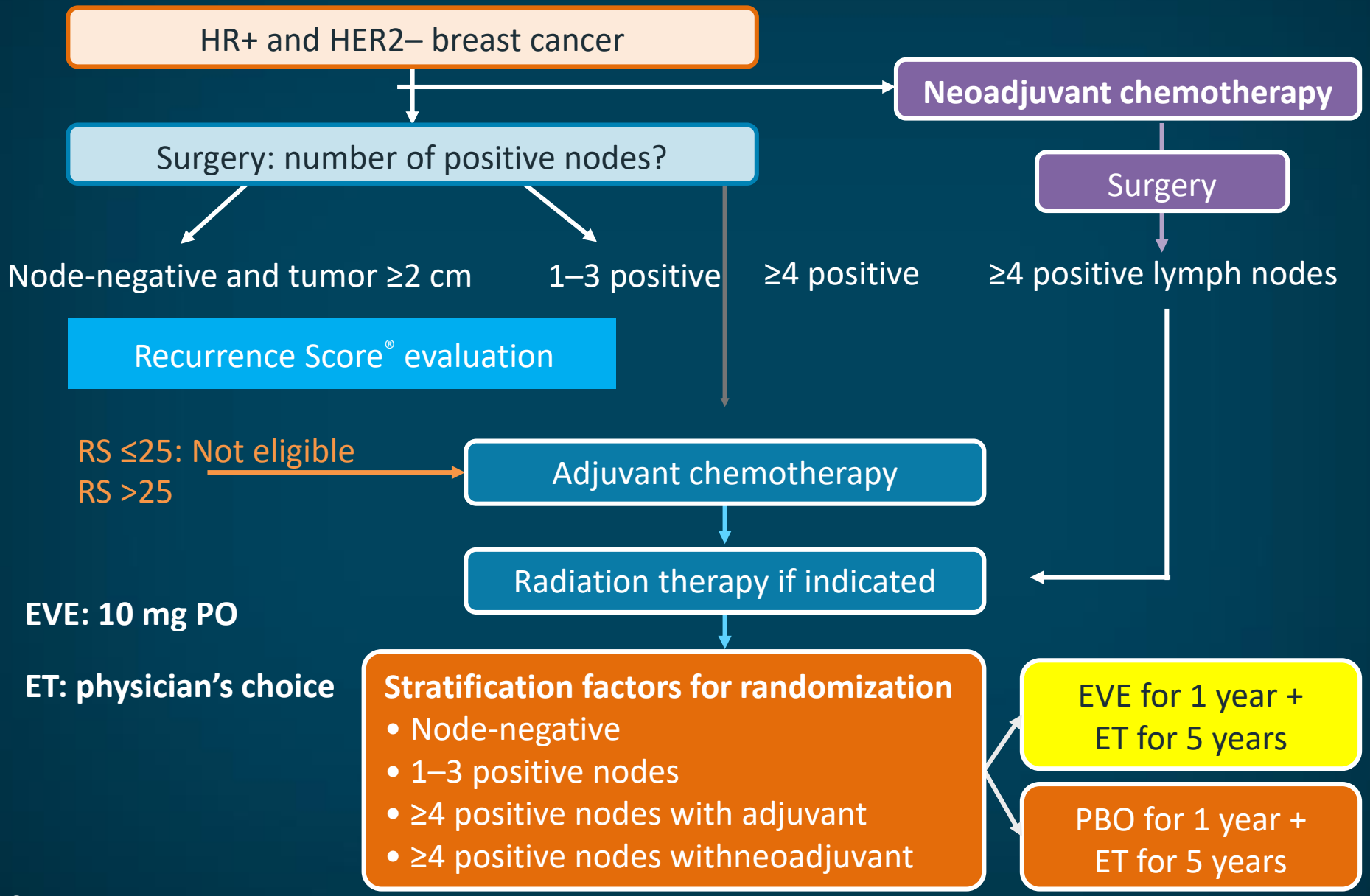
- Mutations of the PI3K pathway are frequent in breast cancer.
- Aberrations in PI3K – Common mechanism of endocrine resistance.

- CDK inhibitors –-basad therapy is the standard of care in first or second line setting. All agents with nearly identical activity but have different side effect profiles. Optimal use" remains unclear and survival data is still evolving

- Everolimus – clinical benefit when used in combination with endocrine therapy.
  - Reverse endocrine resistance
  - Represents an option in the treatment of patients with MBC.
  - Challenges: Toxicities and patient selection

MTHOR and CDK Inhibition in Early Breast Cancer

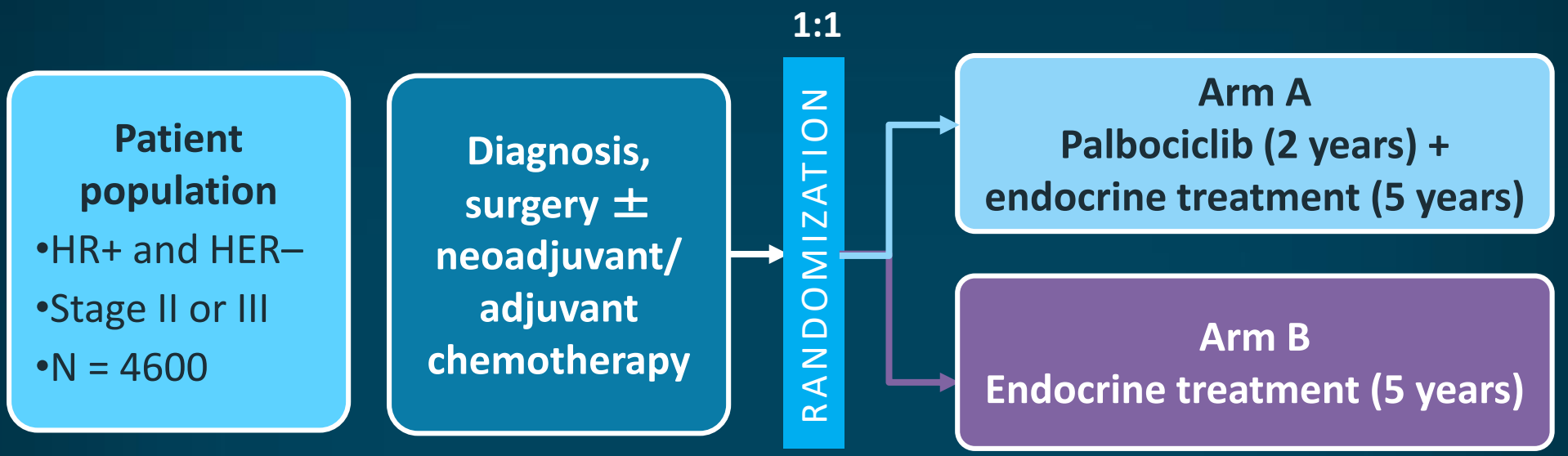
Phase III SWOG-S1207 Trial Design



RS = recurrence score.

NCT01674140. Chavez-MacGregor M et al. SABCS 2012: abstract OT2-2-04.

PALLAS Study Schema



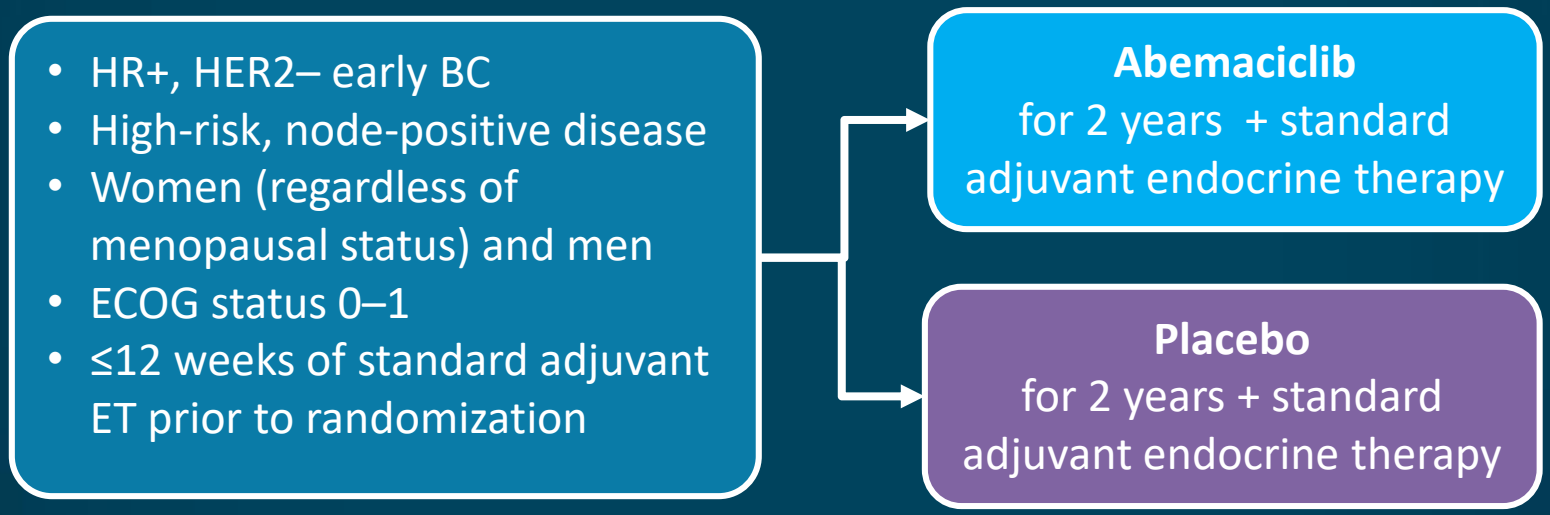
Trial design: PALLAS is an international open-label, phase III trial randomizing patients to 2 years of palbociclib combined with at least 5 years of provider-choice endocrine therapy versus endocrine therapy alone.
Arm A: palbociclib 125 mg once daily, day 1–21 in a 28-day cycle for total duration of 2 years, in addition to standard adjuvant endocrine therapy.
Arm B: standard adjuvant endocrine therapy (AI, tamoxifen, LHRH agonist).

LHRH = luteinizing hormone-releasing hormone.

NCT02513394.

MONARCH E Study Schema

- MONARCH E is a randomized, open-label phase 3 study of abemaciclib + standard adjuvant endocrine therapy versus standard adjuvant therapy alone in patients with high-risk, early stage, node-positive, HR+, HER2– breast cancer.
- Target N = 3580



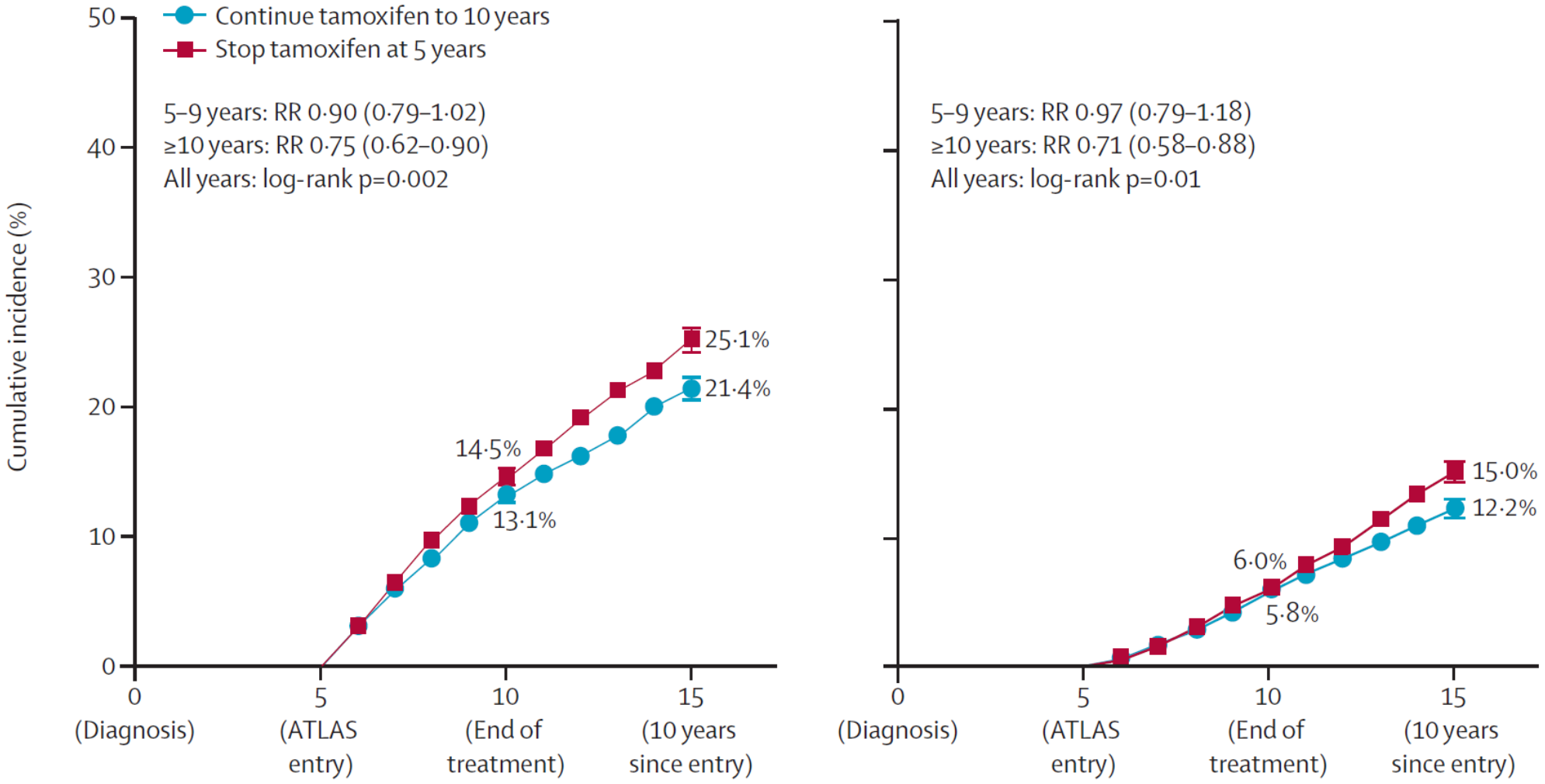
Primary outcome measure: invasive disease-free survival (IDFS)
Secondary Outcome Measures: IDFS for patients with Ki67 Index ≥20%; DRFS; OS; change from baseline on FACT-B, FACT-ES, FACIT-F, EQ-5D-5L; and pharmacokinetics

NCT03155997.

Adjuvant Hormonal Therapy

Premenopausal HR+ Early Breast Cancer

ATLAS: Adjuvant Tamoxifen 5 vs. 10 years



Davis C et al. Lancet 2013

Absolute Improvements in Freedom from Distant Recurrence with Adjuvant Endocrine Therapies for Premenopausal Women with HR+ HER2-negative Breast Cancer: Results from TEXT and SOFT

Meredith M. Regan, Prudence A. Francis, Olivia Pagani, Gini F. Fleming, Barbara A. Walley, Giuseppe Viale, Marco Colleoni, István Láng, Henry L. Gómez, Carlo Tondini, Graziella Pinotti, Angelo Di Leo, Alan S. Coates, Aron Goldhirsch, Richard D. Gelber, for the SOFT and TEXT Investigators and International Breast Cancer Study Group

2018 ASCO ANNUAL MEETING

#ASCO18

IBCSG

INTERNATIONAL BREAST CANCER STUDY GROUP

Presented By Meredith Regan

SOFT and TEXT Designs

Enrolled: Nov03 - Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

RANDOMIZE

TEXT (n=2672)

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Current Follow-up

Median follow-up 9 years

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (47%)

OR

- Remain premenopausal
  ≤ 8 mos after chemo (53%)

RANDOMIZE

SOFT (n=3066)

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Median follow-up 8 years

OFS=ovarian function suppression

Analysis Approach

- 4891 (86%) of 5707 SOFT and TEXT patients with HER2-negative cancers
  - excluded HER2+ by local or central lab, and/or absent HRs by central lab
- Endpoint: distant recurrence-free interval (DRFI)
  - From randomization until distant recurrence (censored at last follow-up or death without recurrence)
  - 8-yr freedom from distant recurrence, by Kaplan-Meier estimate
- Assessed magnitude of absolute improvement across a continuum of *risk of recurrence*
- Examined 4 cohorts of patients, defined by trial and chemotherapy use

Characteristics by Cohort (HR+/HER2-)

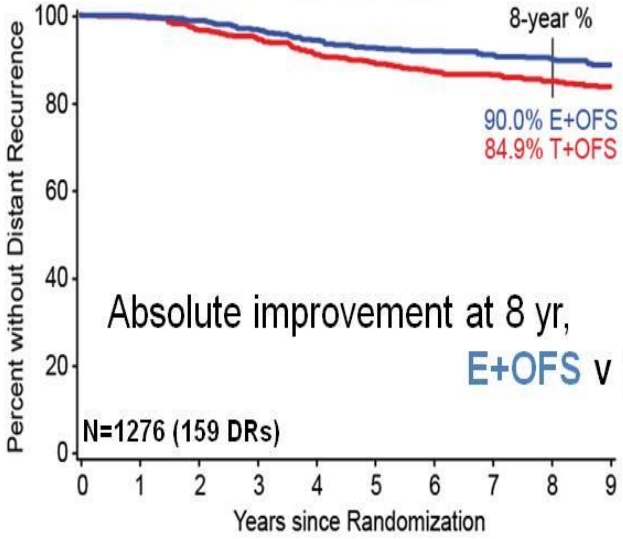
		TEXT		SOFT	
Chemo-therapy	N=1276	Age<40	30%	N=1271	Age<40	49%
		LN+	69%		LN+	58%
		T-size>2cm	52%		T-size>2cm	46%
		PgR<50%	23%		PgR<50%	38%
		Grade 3	30%		Grade 3	28%
		Ki-67≥20%	42%		Ki-67≥20%	35%
No Chemo-therapy	N=991	Age<40	16%	N=1353	Age<40	9%
		LN+	21%		LN+	9%
		T-size>2cm	20%		T-size>2cm	13%
		PgR<50%	13%		PgR<50%	9%
		Grade 3	15%		Grade 3	9%
		Ki-67≥20%	27%		Ki-67≥20%	19%

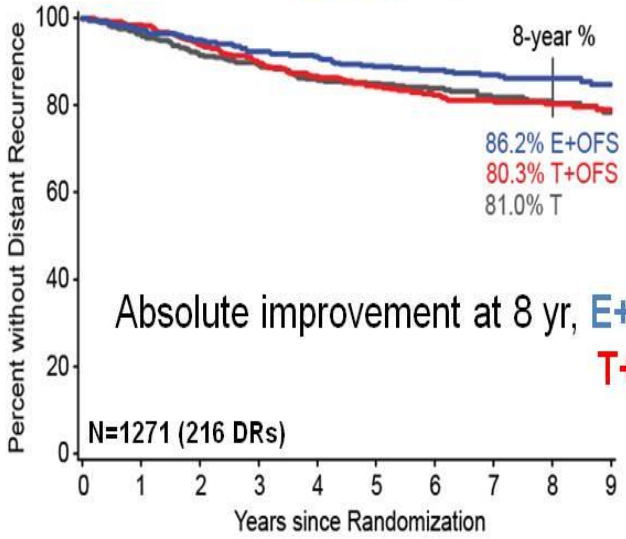
Distant Recurrence-free Interval by Cohort (HR+/HER2-)

TEXT

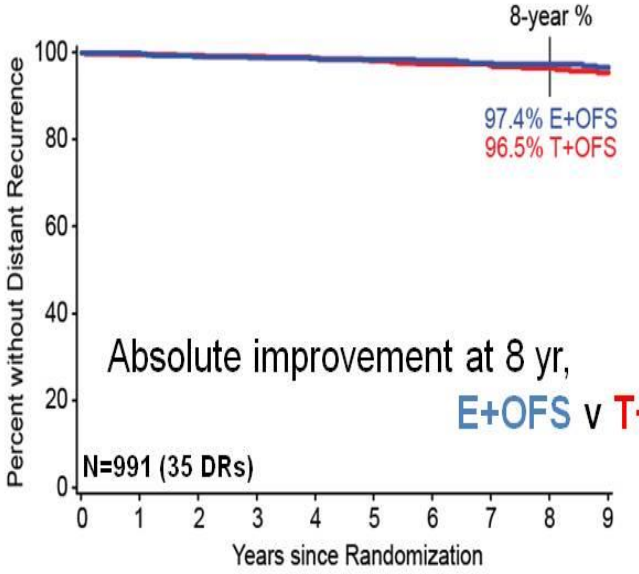
SOFT

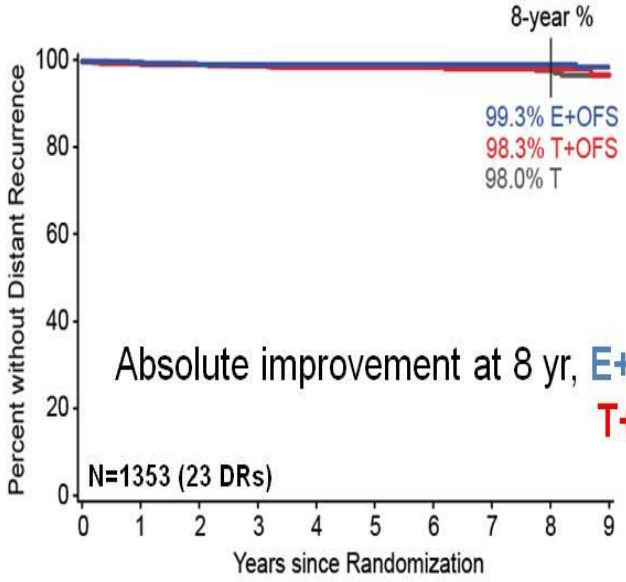
Chemo-therapy





No Chemo-therapy





Presented By Meredith Regan

Conclusions

Among premenopausal women in SOFT & TEXT with HR+/HER2- cancers, magnitude of absolute improvement in 8-yr freedom from distant recurrence varied widely according to *risk of recurrence*:

- Those at higher risk may experience 10-15% improvement with E+OFS vs T+OFS or T alone
- Improvement with E+OFS may be 4-5% for patients at intermediate risk, most of whom also received chemotherapy
- For those at low risk, potential benefit of escalating endocrine therapy from T-alone may be minimal, as >97% of these women were without distant recurrence at 8 years

Presented By Meredith Regan at 2018 ASCO Annual Meeting

Adjuvant Hormonal Therapy Premenopausal Early Breast Cancer 2018

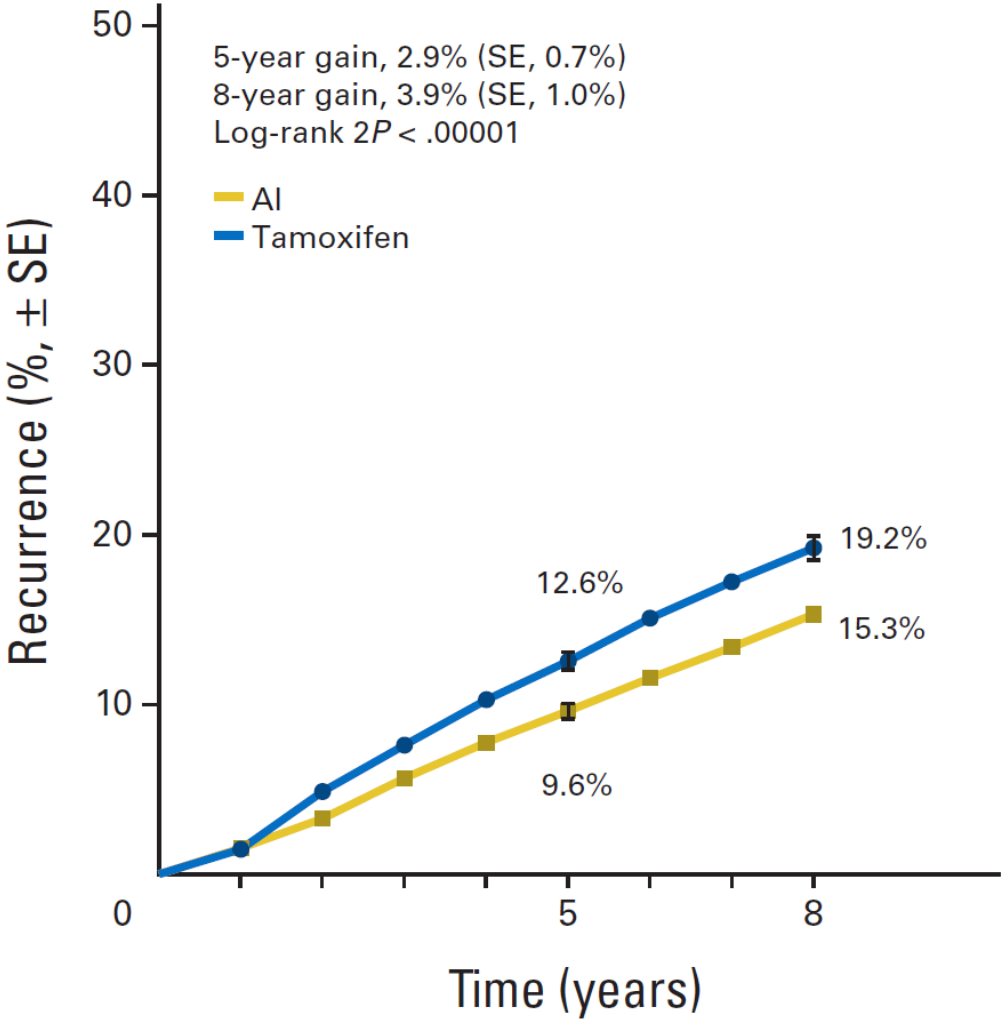
- Low risk: Tamoxifen 5 years
- High risk: Ovarian ablation or suppression plus aromatase inhibitor x 5 years
- High risk: Ovarian ablation or suppression plus aromatase inhibitor x aromatase inhibitor x 2-3 years follow by tamoxifen 2-3 years
- High risk: If poor tolerance to aromatase inhibitor, tamoxifen x 5 to 10 years
- Be aware of transitory chemotherapy-induced ovarian function failure

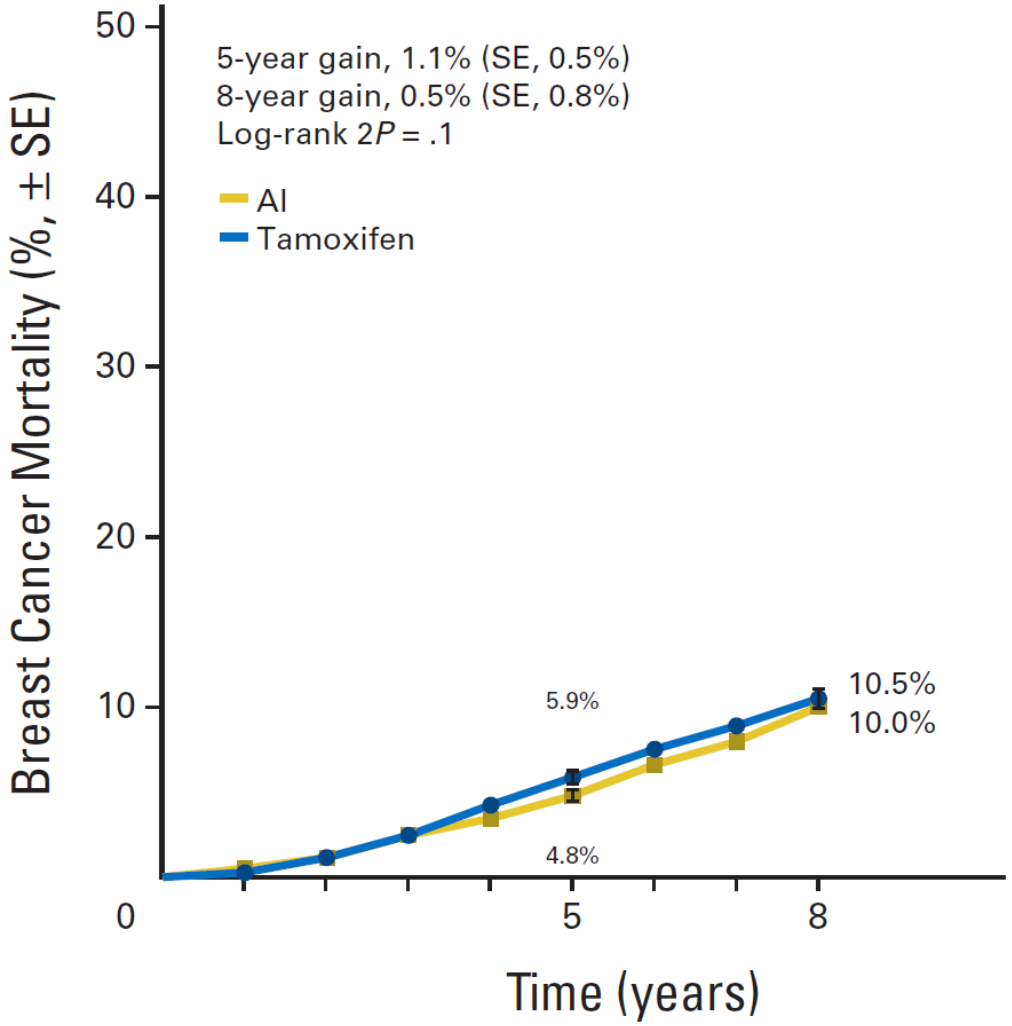
Adjuvant Hormonal Therapy

Postmenopausal HR+ Early Breast Cancer

Meta-Analysis of Adjuvant Tamoxifen vs. Aromatase Inhibitor Trials

N ≈ 19,000 Patients

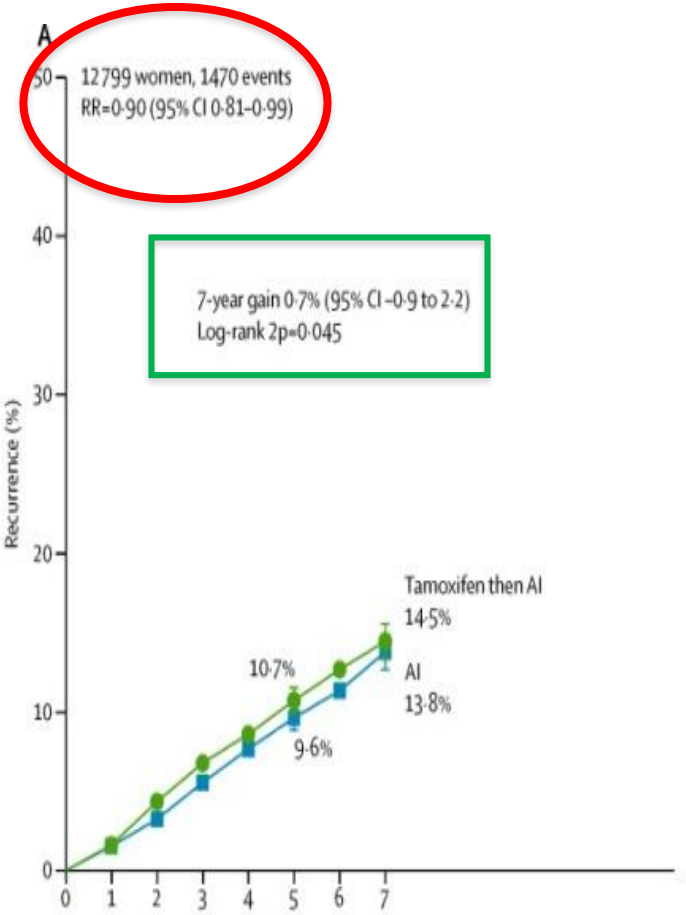




Dowsett M, et al J Clin Oncol 2010

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

AI $_{5}$ vs TAM $_{2-3}$ → AI $_{2-3}$



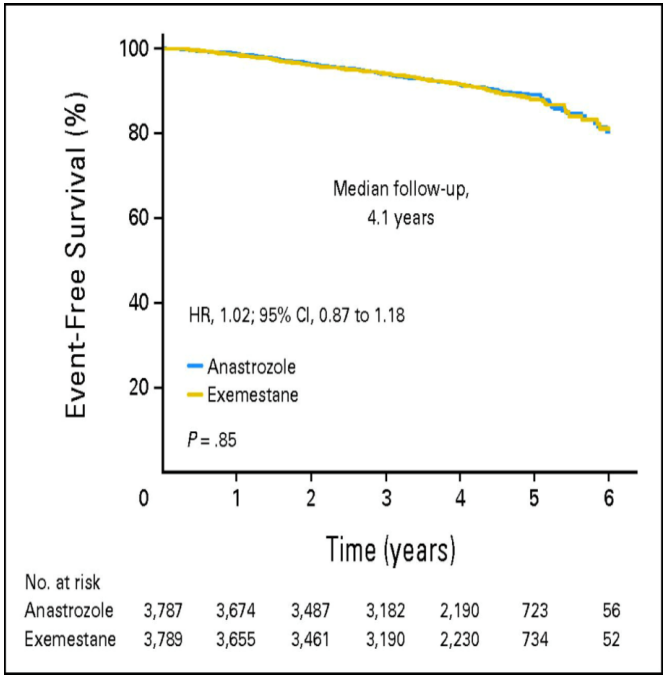
Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12 435)	2·31 (360/15 589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12 290)	2·29 (348/15 183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	−34·0/115·0	−1·2/170·6	−2·6/69·2

EBCTCG. Lancet 2015;386:1341-52.

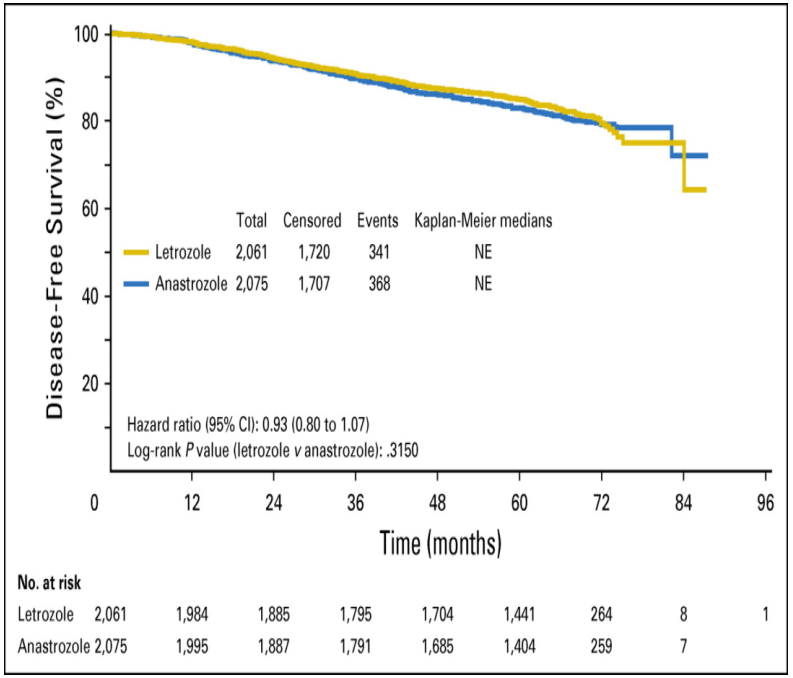
AIs are equally effective*

MA 27: ANA vs EXE



Goss PE, et al
JCO 2012;31:1398-1404

FACE: LET vs ANA



Smith I, et al.
JCO 2017; DOI: 10.1200/JCO.2016.69.2871

Adjuvant Hormonal Therapy Postmenopausal Early Breast Cancer 2018

- Aromatase inhibitor x 5 years
- Aromatase inhibitor x 2-3 years follow by tamoxifen 2-3 years then aromatase inhibitor x 5 years
- If poor tolerance to aromatase inhibitor, tamoxifen x 5 to 10 years
- Consider aromatase Inhibitors x 10 years in high risk patients
- All new generation aromatase inhibitors have similar clinical efficacy
- Be aware of transitory chemotherapy-induced amenorrhea

Do all patients with ER+ HER-2 normal early breast cancer benefit equally from current treatments, hormonal therapy and systemic chemotherapy?

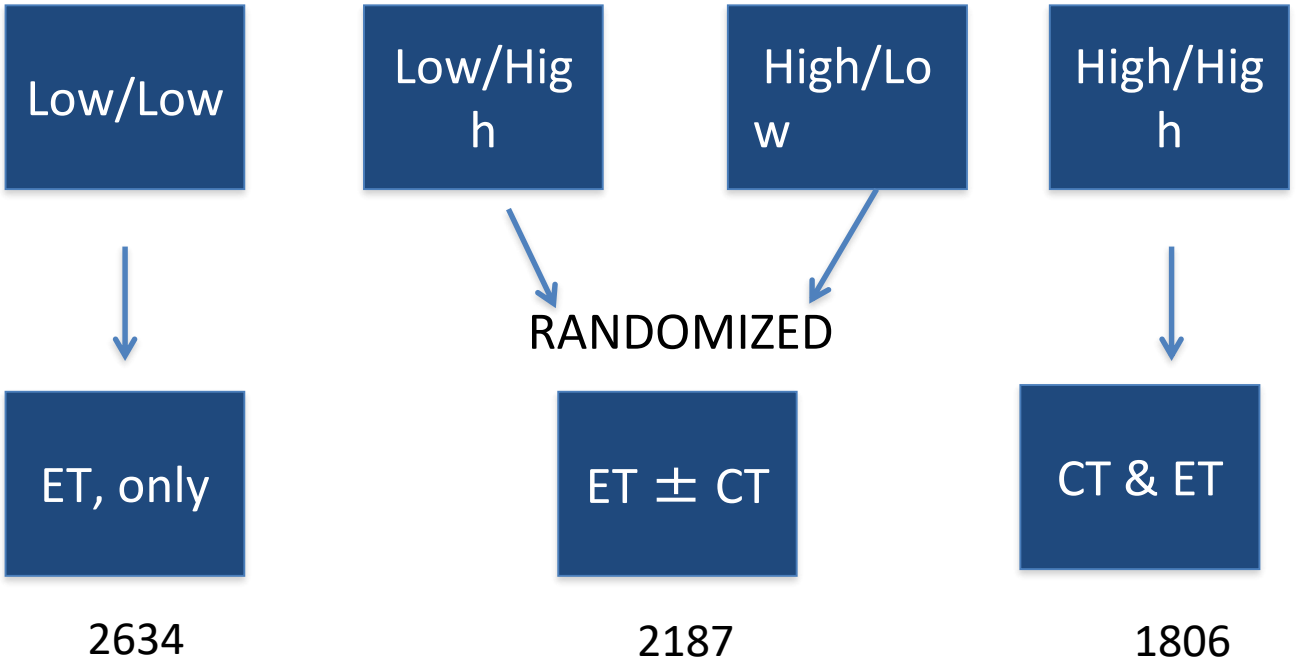
Do we have new clinical or ancillary tools to do “Precision Medicine” in 2018

Genonic Signatures

- To identify patients a low risk at baseline
- To select patients for adjuvant hormonal therapy alone
- To select patients for adjuvant chemotherapy
- To identify patients at high residual risk after 5 years of adjuvant hormonal therapy
- To select patients for extended hormonal therapy

MINDACT

Early stage breast cancer
Stratify by clinical and genomic risk



NEJM 2016;375:717-29

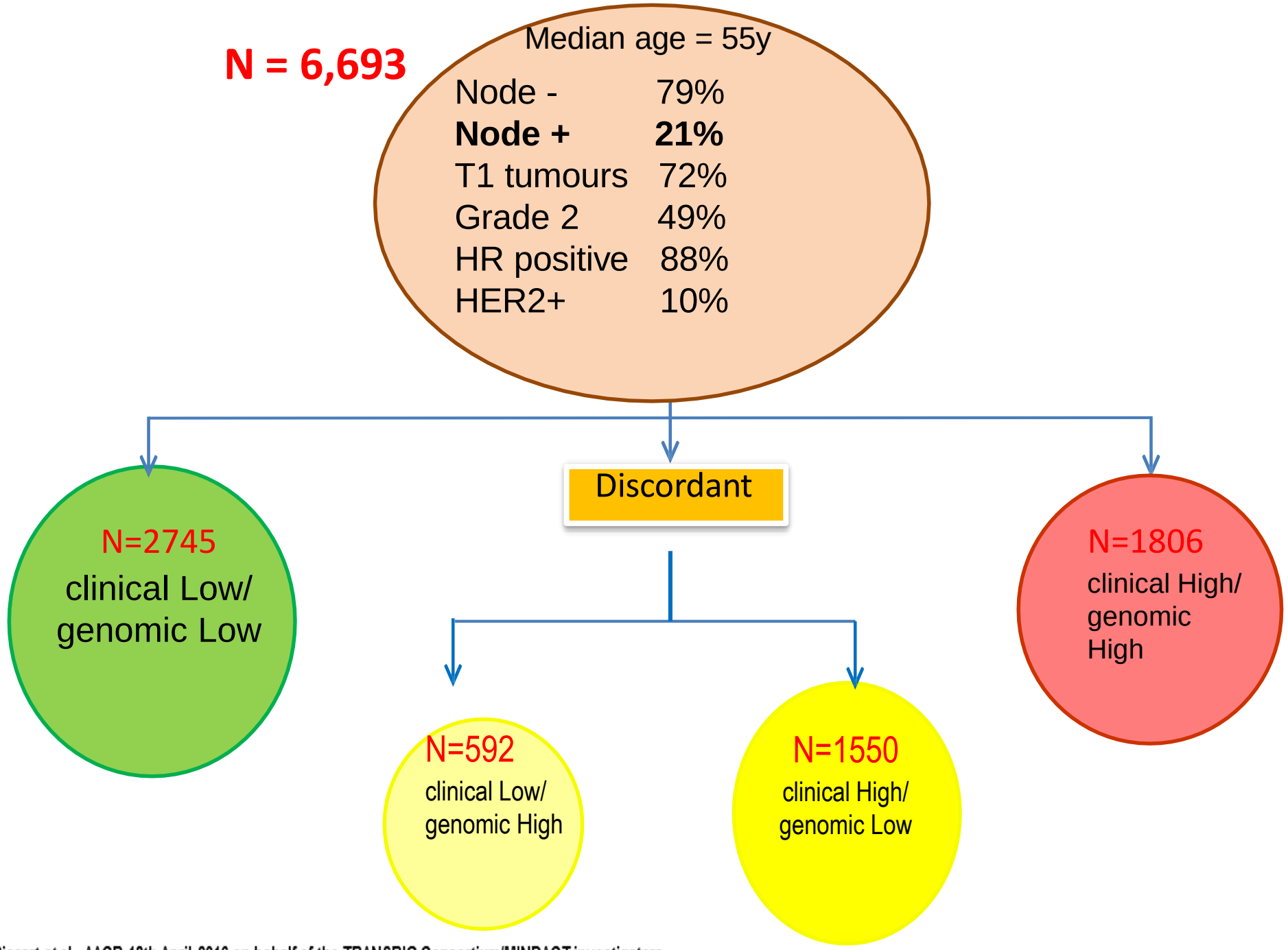
Definition of High Risk Clinical Assessment in MINDACT:
(Patients assessed as clinically High Risk†)

- Hormone Receptor POSITIVE, Lymph Node NEGATIVE (HR+/LN0) and:
  - T ≥ 1cm & Grade 3
  - T ≥ 2cm & Grade 2 or 3
  - T > 3cm & Any Grade
- Any Lymph Node POSITIVE (LN+ 1-3) ‡
- Triple NEGATIVE
- HER2 POSITIVE

† Clinical High Risk was defined in MINDACT as the level of risk of recurrence for which most clinical guidelines advise adjuvant systemic chemotherapy. Clinical Low Risk was defined as the level of risk for which there would be little or no meaningful clinical benefit from adjuvant systemic chemotherapy. Clinical Low Risk was defined using Adjuvant!Online (modified version 8.0, including HER2) as greater than 92% breast cancer specific survival at 10-years for ER- patients without adjuvant systemic chemotherapy. For ER+ patients, Clinical Low Risk was defined as 88% breast cancer specific survival at 10-years, without any systemic therapy, and 92% with endocrine therapy, to account for the 4% average absolute benefit of adjuvant endocrine therapy for ER+ patients.

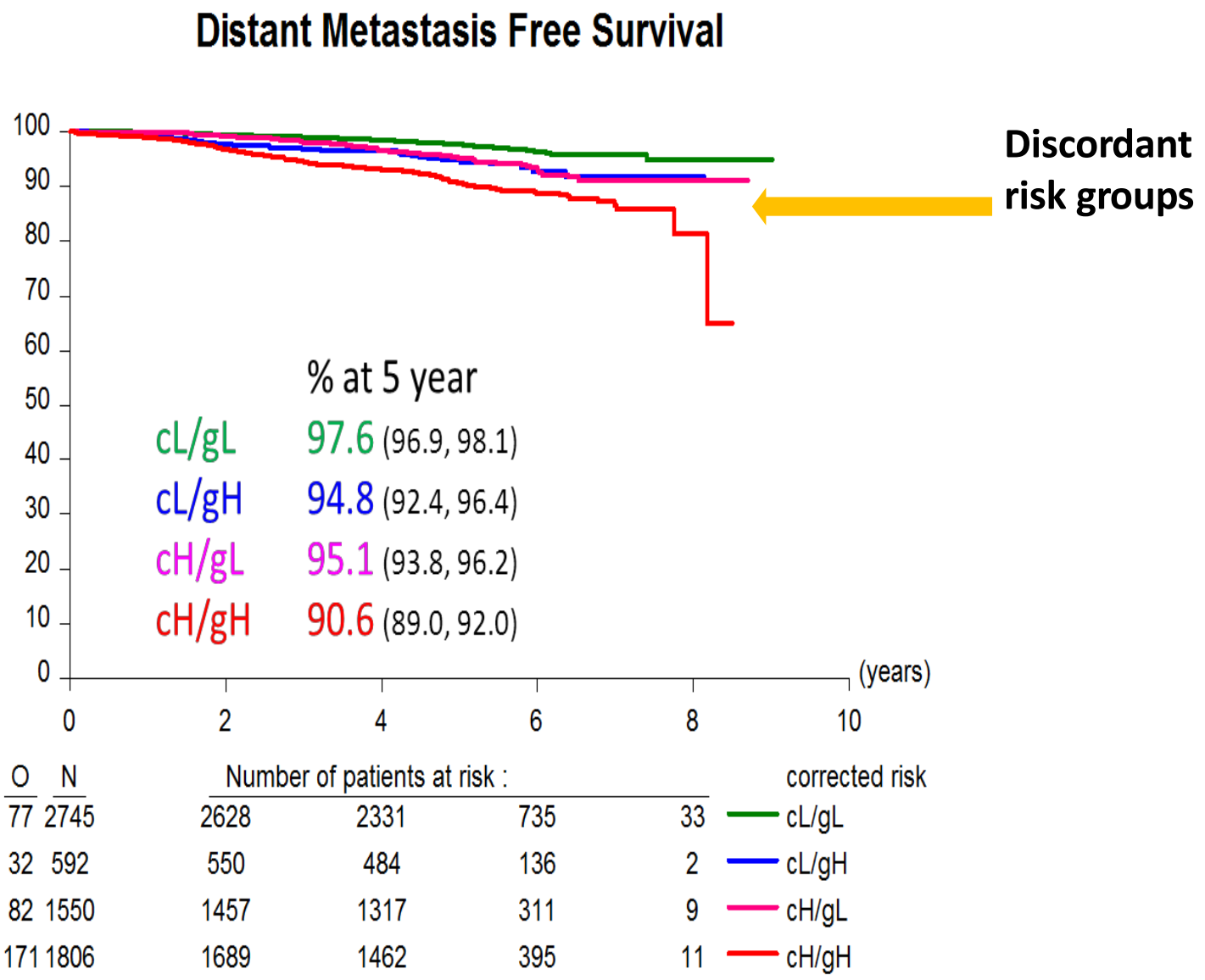
‡ Patients that were LN+, Grade I and tumors ≤ 2cm were classified as clinical low risk in MINDACT

The MINDACT study: Patientd emographics



from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators

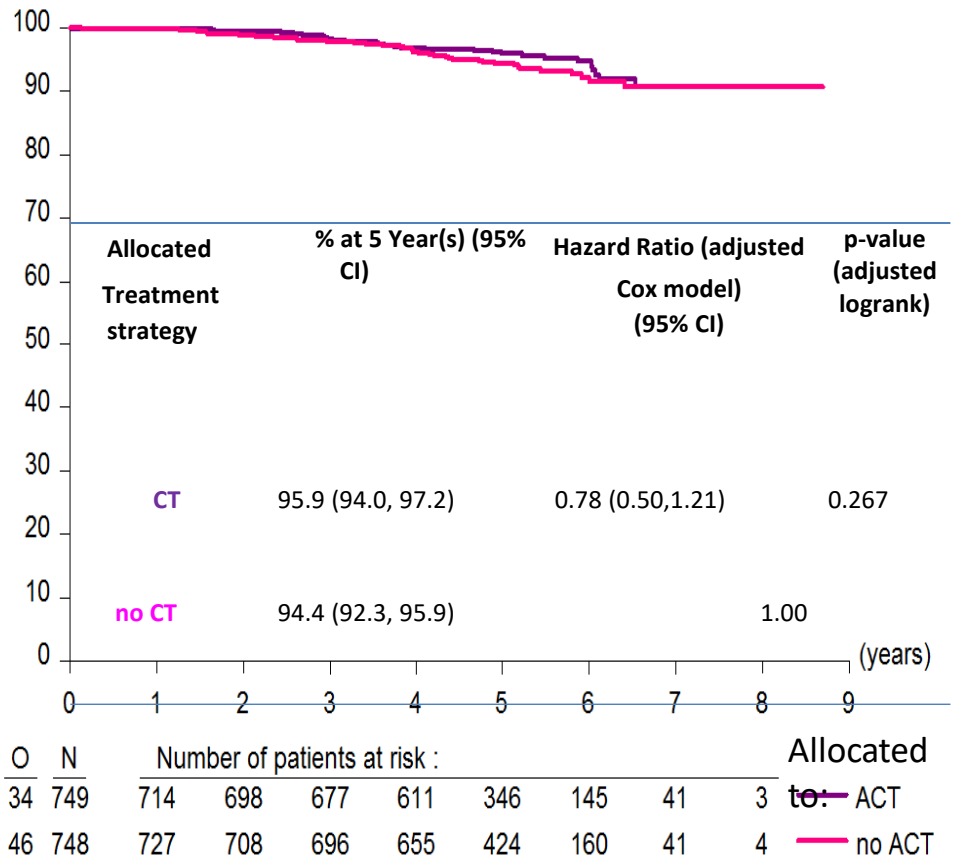
DMFS MINDACT population at 5-year median follow-up



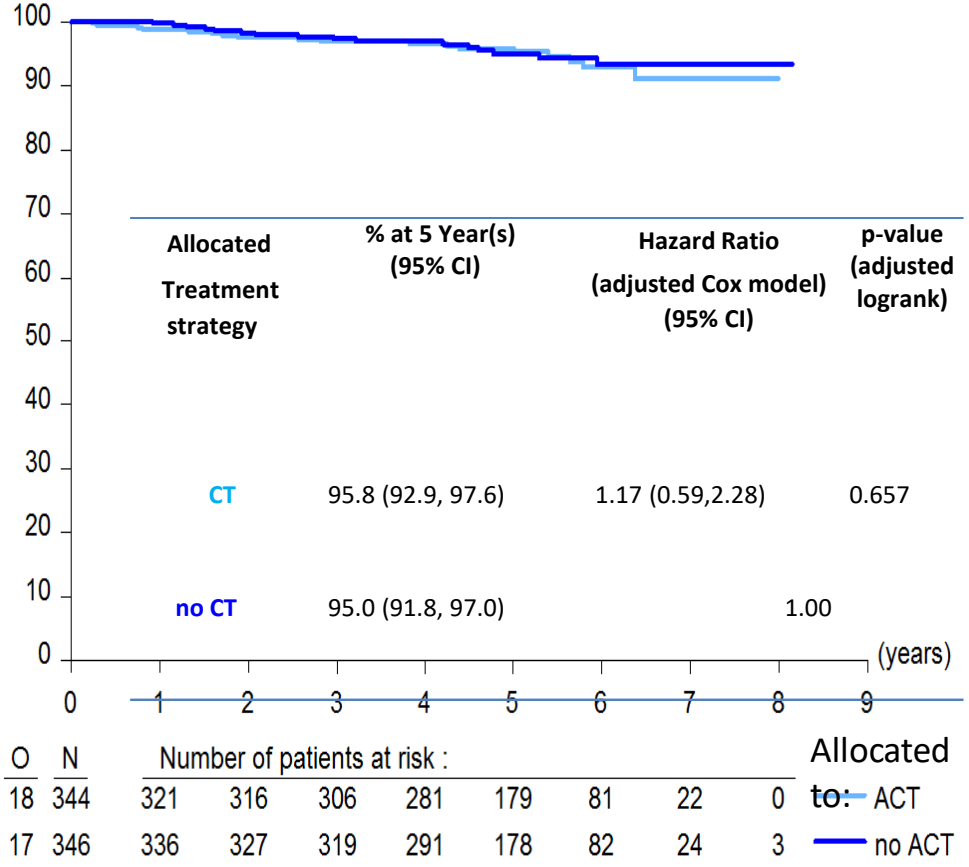
Efficacy: CT vs no CT in discordant risk

Intent-to-treat analysis

Distant Metastasis Free Survival
c-High/g-Low



Distant Metastasis Free Survival
c-Low/g-High



from Piccart et al., AACR 18th April 2016 on behalf of the TRANSBIG Consortium/MINDACT investigators

Conclusions

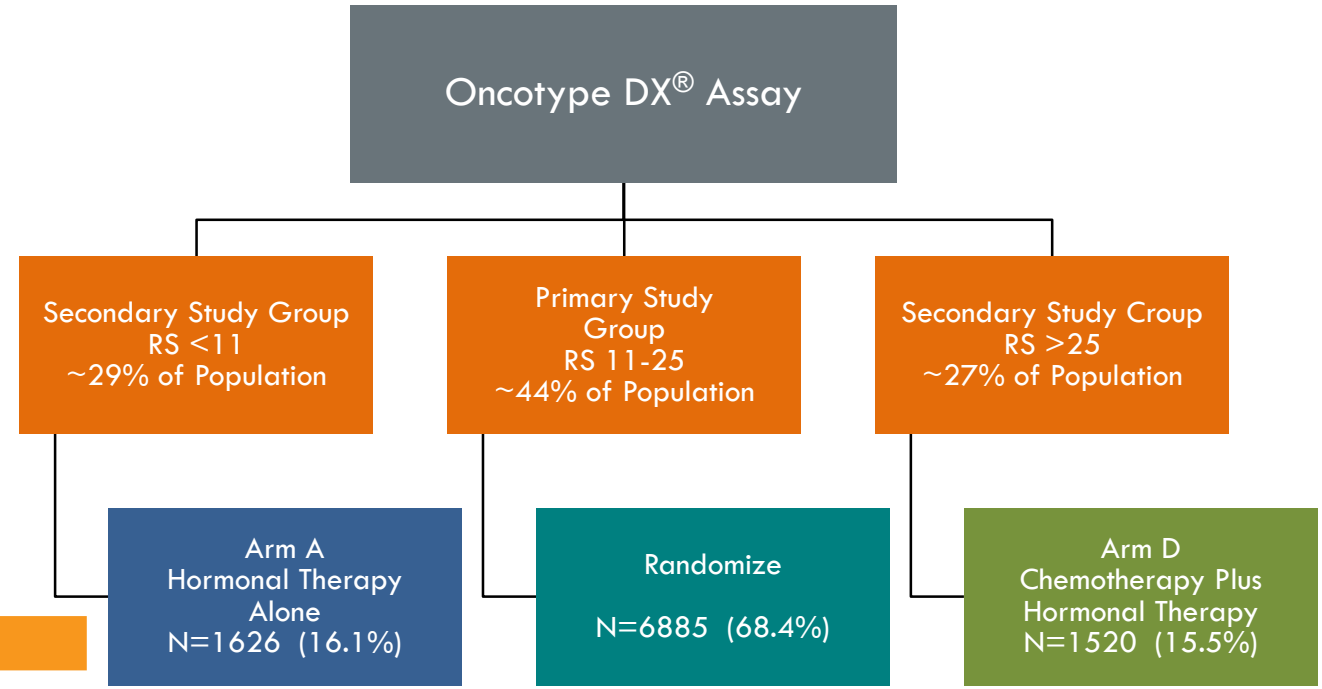
- In the first prospective, randomized data for lymph node positive patients (1-3+ LN), MammaPrint Low Risk patients show **no statistically significant or clinically meaningful benefit** of adding chemotherapy

- **46%** of patients identified as high risk for recurrence according to clinical-pathological factors as described in the publication, and who therefore would be usual candidates for adjuvant chemotherapy, were reclassified as Low Risk by MammaPrint® and MINDACT shows no statistically significant or clinically meaningful benefit of chemotherapy

- In the HR+/HER2-/LN0 group, following MammaPrint results to optimize treatment decisions can result in a
  - **97.8%** DMFI in MammaPrint Low Risk patients without chemotherapy
  - **94.6%** DMFI for MammaPrint High Risk patients with chemotherapy

TAILORx: A Clinical Trial Assigning Individualized Options for Treatment (Rx)

Eligible 10,253 pts prospectively enrolled (2006-2010)



Published in NEJM 2015

Patients in Arm A were predominantly treated with AI (59%) and tamoxifen (34%)

Study Arms for Primary Analysis
To be reported at a later date

RS: Recurrence Score® result

TAILORx Methods: Key Eligibility Criteria

Met NCCN Guidelines for Recommending or Considering Adjuvant Chemotherapy

- Women with invasive breast cancer
- Age 18-75 years
- Node-negative
- ER and/or PR-positive in local lab (before ASCO-CAP guidelines)
- HER2-negative in local lab
- Tumor size - 1.1-5.0 cm (or 0.6-1.0 cm and int-high grade)
- Willing to have chemotherapy treatment assigned or randomized based on RS assay results

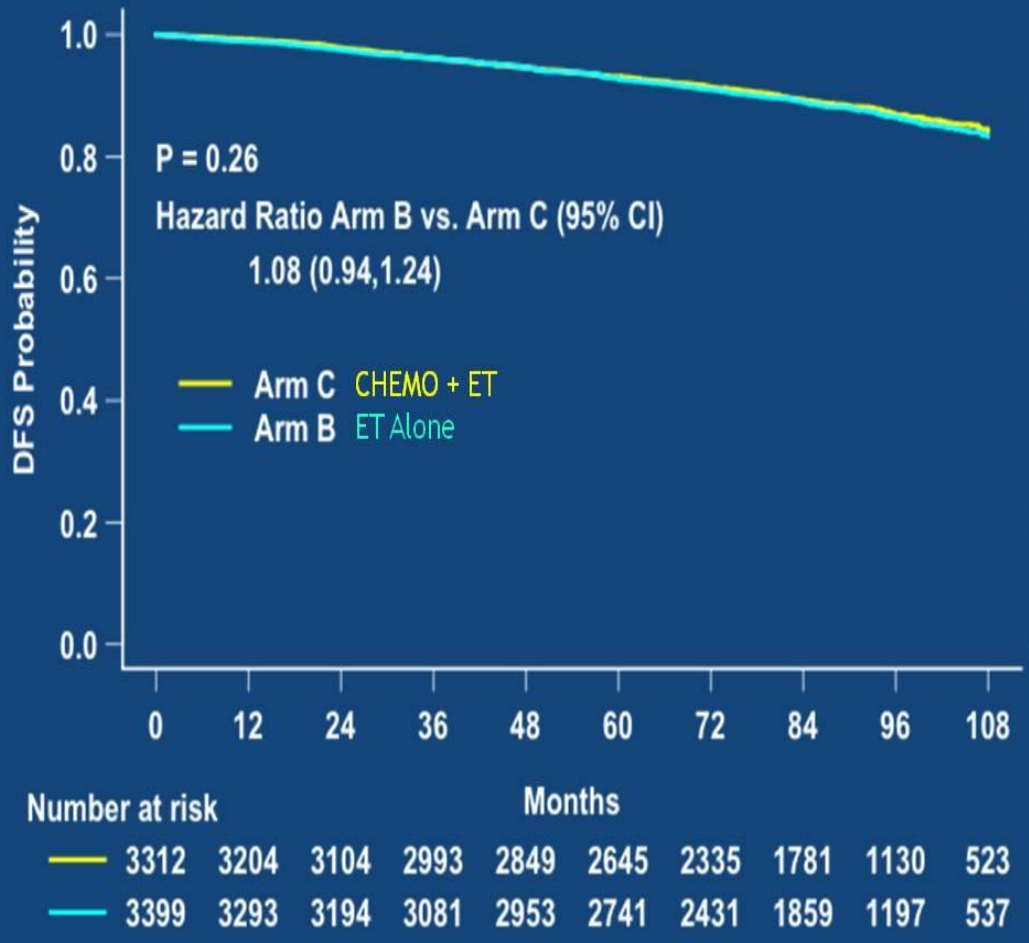
TAILORx Results - ITT Population: Demographics & Treatment in RS 11-25 Arms (N=6,711)

- **Patient characteristics**
  - Median age 55 years, and 33% were 50 or younger
  - 63% had tumor size 1-2 cm and 57% had intermediate grade histology (57%)
  - Clinical risk criteria: 74% low risk, 26% high risk
- **Systemic Treatment**
  - Endocrine therapy
    - Comparable adherence and duration in both arms
    - Postmenopausal - included AI in 90%
    - Premenopausal - included OS in 15%
  - Chemotherapy
    - Most common regimens were TC (56%) and anthracycline-containing (36%)

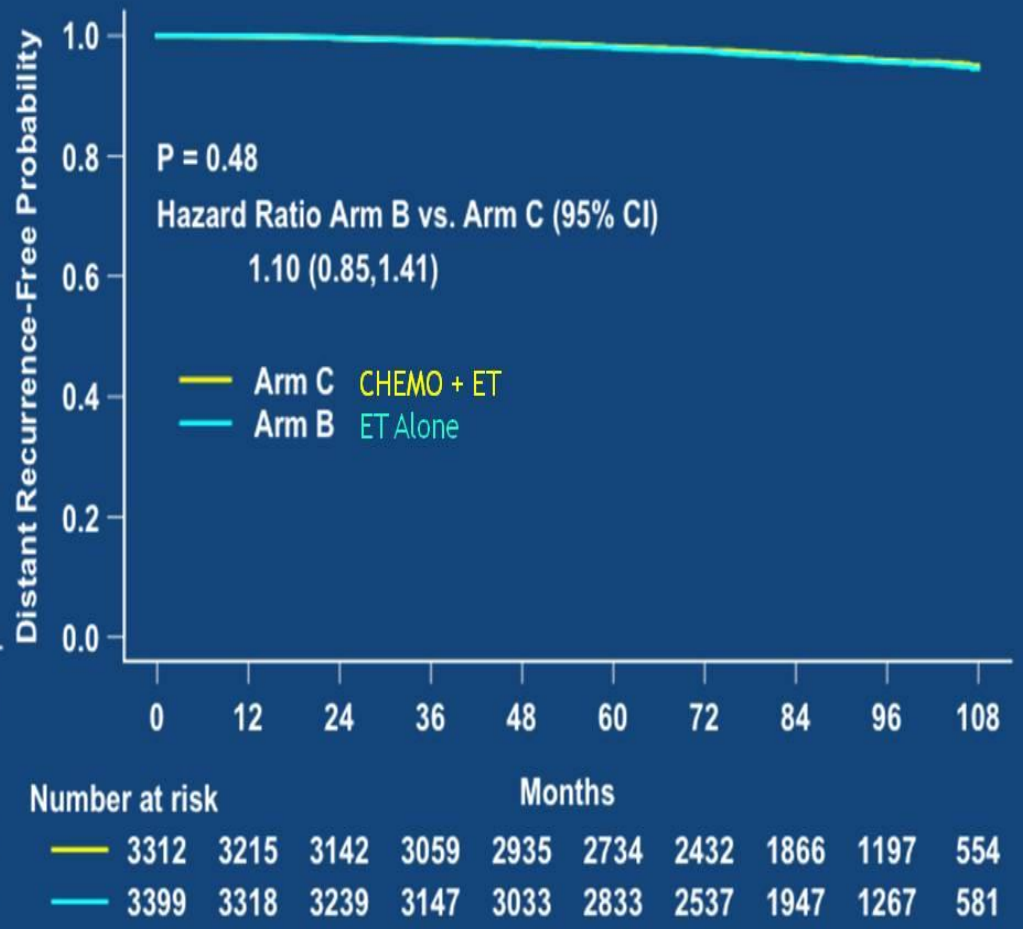
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as fist event, of which 199 (23.8%) were distant

Primary Endpoint
Invasive Disease-Free Survival



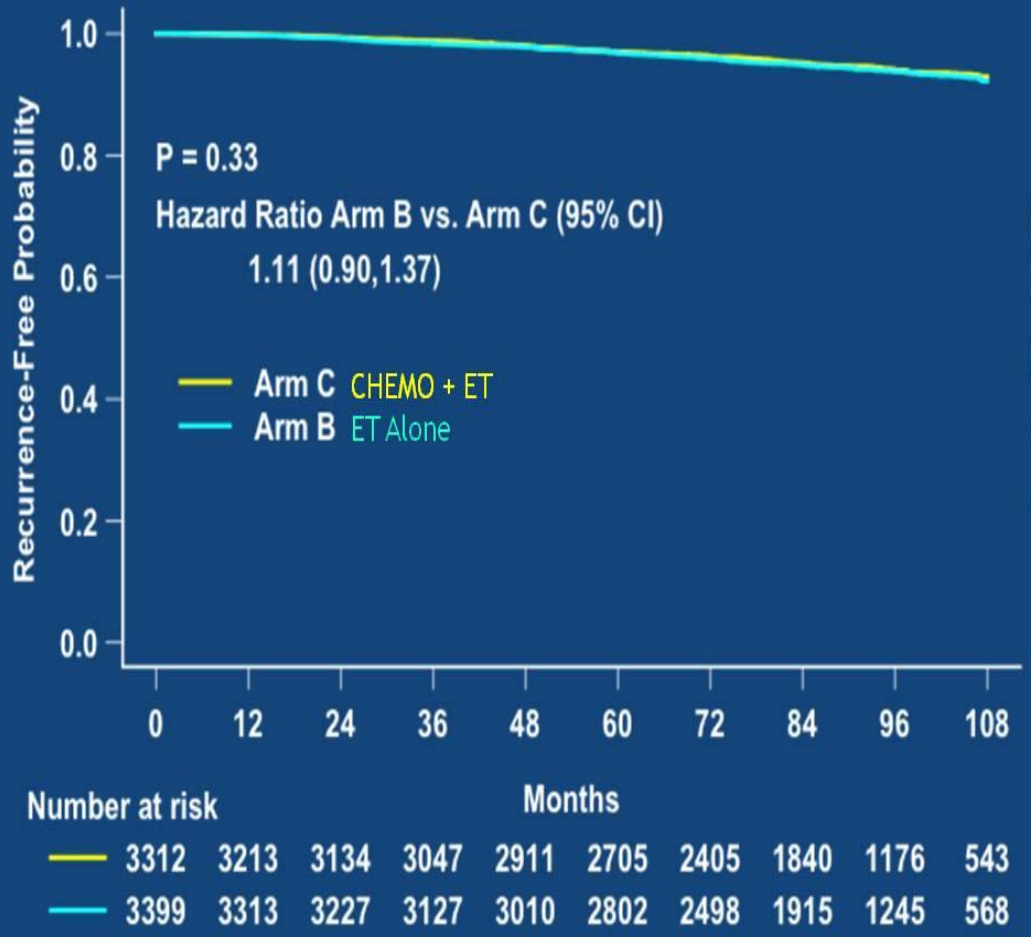
Secondary Endpoint
Distant Relapse-Free Interval



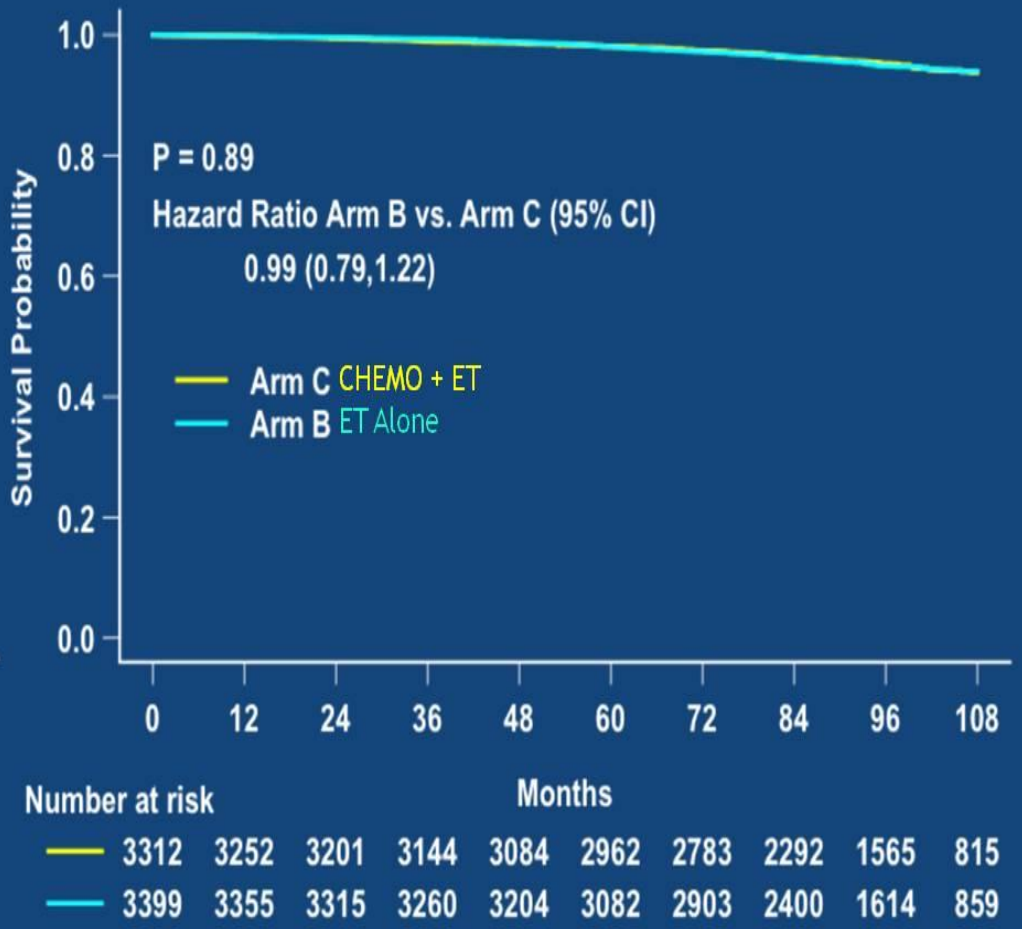
TAILORx Results – ITT Population: RS 11-25 (Arms B & C)

Other Secondary Endpoints

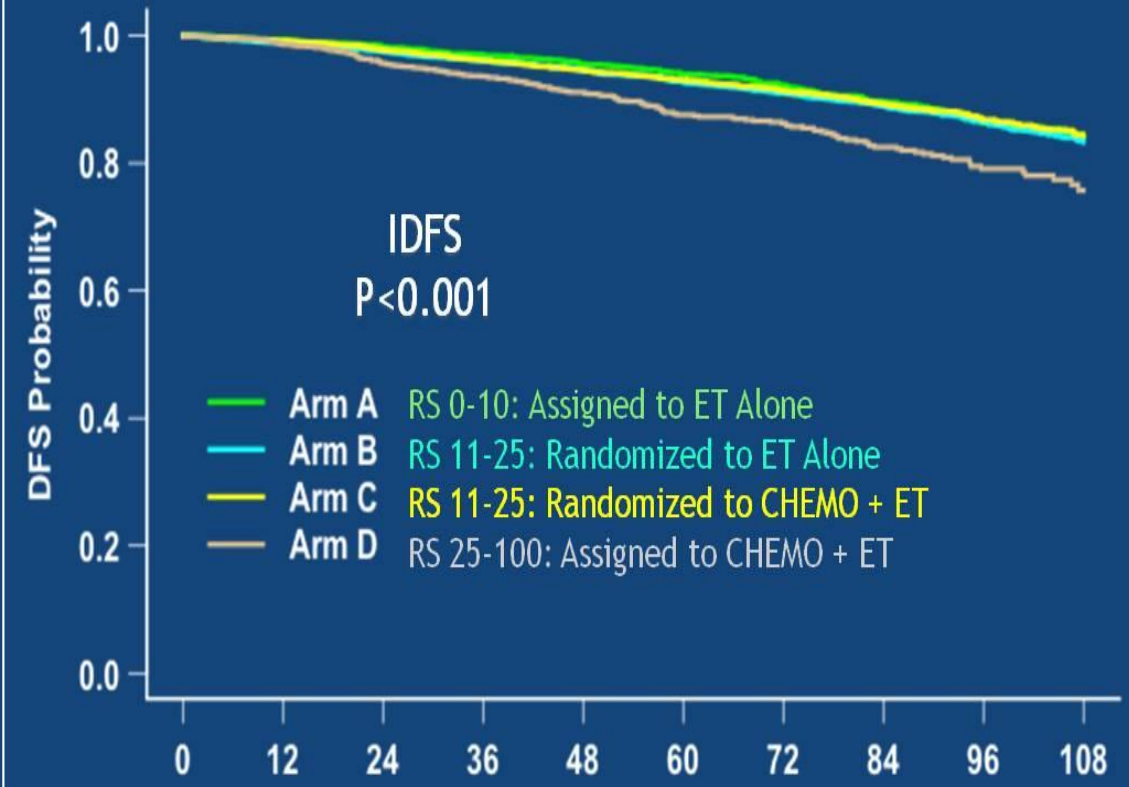
Relapse-Free Interval



Overall Survival



TAILORx Results - ITT Population: All Arms (A,B,C & D)



9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone
- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)
- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET

TAILORx Results - ITT Population: Exploratory Analysis of Chemotherapy Treatment Interactions in RS 11-25 Arms

No statistically significant chemo treatment interactions

- RS
  - 11-15 vs. 16-20 vs. 21-25
  - 11-17 vs. 18-25
- Tumor size (≤ 2 cm vs. > 2 cm)
- Grade (low vs. int. vs. high)
- Menopausal status (pre vs. post)
- Clinical risk category (high vs. low)

Statistically significant chemo treatment interactions

- Age (≤ 50, 51-65, > 65) and chemo benefit
  - IDFS (p=0.003)
  - RFI (p=0.02)
- Age (or menopause), RS (11-15, 16-20, 21-25), and chemo benefit
  - IDFS - Age-RS (p=0.004)
  - IDFS - Menopause-RS (p=0.02)

TAILORx Results - ITT Population: Potential Chemotherapy Benefit in Women ≤ 50 Years (N=2216) in RS 11-25 Arms

- **RS 16-25 - some chemo benefit**
  - RS 16-20: 9% fewer IDFS events, including 2% fewer distant recurrences
  - RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences

- **RS 0-15 - good prognosis with endocrine therapy**
  - 3% distant recurrence with ET alone
  - no evidence for chemo benefit in RS 11-15

TAILORx Results: Summary

- **Primary conclusions**
  - **RS 11-25:** ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  - **RS 0-10:** Distant recurrence rates very low (2-3%) with ET alone at 9 years
  - **RS 25-100:** Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET
- **Other observations**
  - **Age – RS – Chemo treatment interaction:**
    - Some chemo benefit in women 50 or younger with a RS 15-25
    - Greatest impact on distant recurrence with RS 21-25


The University of Texas
MD Anderson Cancer Center
Albert B. and Margaret M. Alkek Hospital
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®