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1.6.18

ER-Positive Breast Cancer

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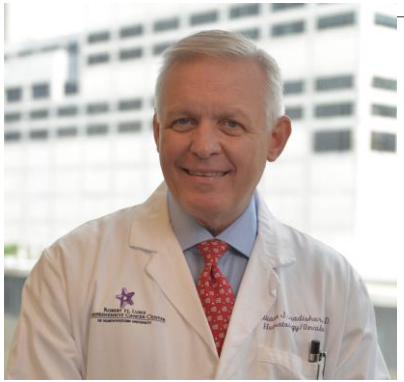

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Financial Disclosure

- None

Agenda

- Perioperative endocrine therapy- POETIC
- Metastatic Disease- MONALEESA-7, MANTA, MONARCH 2/3
- Adjuvant Endocrine Therapy- ABCSG-16, SOFT/TEXT update
- CDK4/6 Inhibitors in the elderly

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- Perioperative endocrine therapy- POETIC
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- CDK4/6 Inhibitors in the elderly

Peri-operative Aromatase Inhibitor treatment in determining or predicting long-term outcome in early breast cancer – the Poetic Trial (CRUK/07/015)

John Robertson, Mitch Dowsett, Judith Bliss, James Morden, Maggie Wilcox, Abigail Evans, Chris Holcombe, Kieran Horgan, Cliona Kirwan, Elizabeth Mallon, Mark Sibbering, Anthony Skene, Raghavan Vidya, Maggie Cheang, Jane Banerji, Lucy Kilburn, Andrew Dodson, Ian Smith

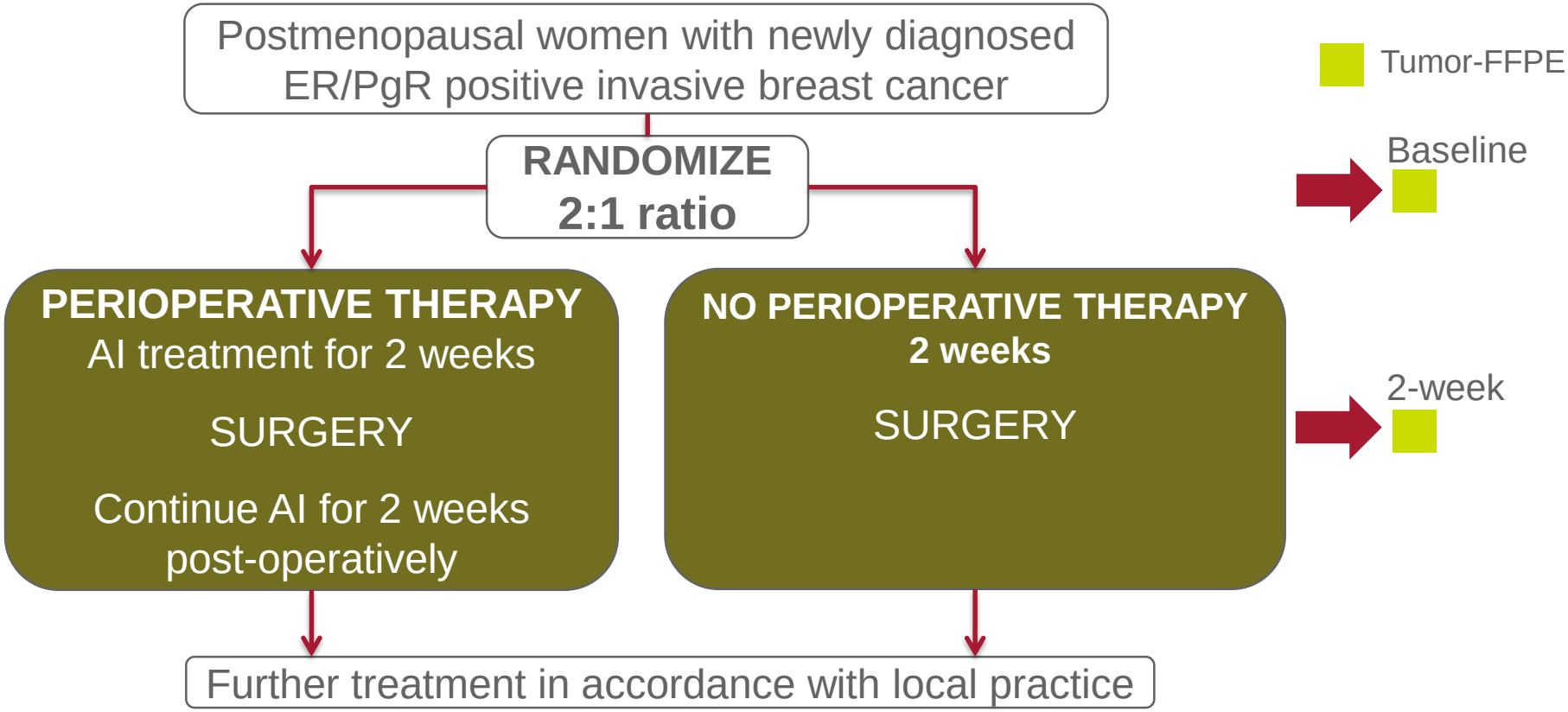
Background

- Experimental[1,2] & clinical evidence suggested peri-operative ET may improve clinical outcome in patients undergoing primary surgery for ER+ BC
- A small clinical trial (IMPACT)[3,4] suggested that tumor Ki67 levels after 2 weeks ($Ki67_{2w}$) of peri-operative AI therapy might predict outcome better than pre-treatment (Baseline) Ki67
- POETIC - phase III RCT designed to test 2 hypotheses
    1. Does peri-operative ET improve clinical outcome in patients with ER+ tumors?
    2. Does $Ki67_{2w}$ improve prediction - beyond baseline Ki67 ($Ki67_B$) - of patients with a higher risk of relapse despite receiving best current standard of care?

ET = Endocrine therapy ER = Estrogen Receptor
AI = Aromatase Inhibitor BC = Breast Cancer
POETIC = Peri-Operative Endocrine Therapy - Individualising Care

[1,2] Fisher et al Can Res1989; 49: [1] 1996-2001 & [2] 2002 - 2004
[3]Smith et al JCO 2005; [4]Dowsett et al JCO 2005

Trial design



Endpoints and statistical considerations

Primary endpoint: Time to recurrence (TTR) defined as time from randomization to local, regional, or distant tumor recurrence or breast cancer death.

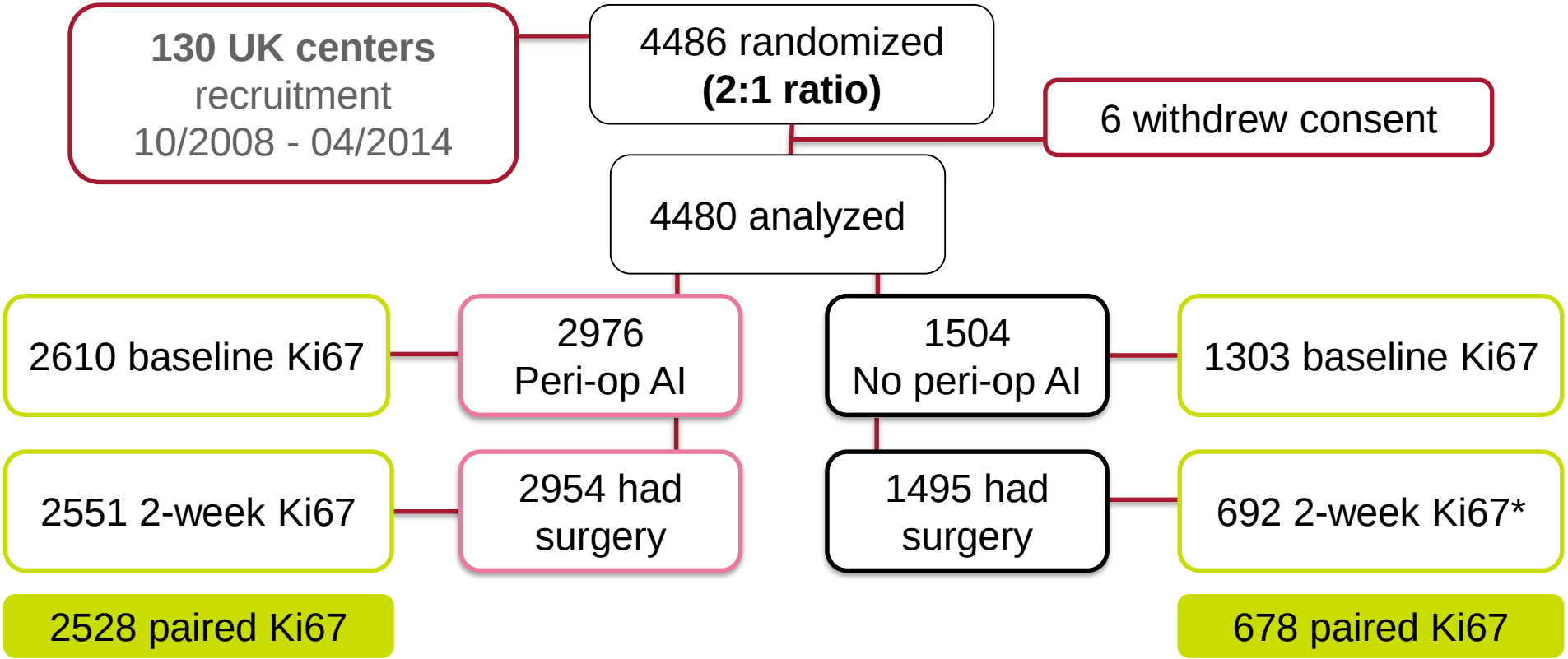
Secondary endpoints: Proliferation rate(Ki67) at baseline & Ki67 after 2 weeks of AI as predictors of outcome.

Sample size: 4350 patients to detect a 3% improvement from 10% to 7% in 5-year relapse rate with 91% power (5% alpha, two-sided) .

Analysis using survival methods including log-rank test and Cox regression models

Median follow-up = 60.7 months (IQR: 49.5 to 72.2)

Patient flow and sample availability



** Random selection of 2-week control samples*

Baseline characteristics (pre-surgery)

		Peri-op AI (N=2976)		No peri-op AI (N=1504)	
Age, median (IQR)		**67 (61, 75)**		**67 (61, 75)**	
Grade, n (%)	1	417	(**14.0**)	234	(**15.6**)
	2	1757	(**59.0**)	843	(**56.1**)
	3	521	(**17.5**)	279	(**18.6**)
	Not known*	281	(**9.4**)	148	(**9.8**)
Histological type, n (%)	Ductal	2403	(**80.7**)	1199	(**79.7**)
	Lobular	429	(**14.4**)	224	(**14.9**)
	Other/Not known	144	(**4.8**)	81	(**5.4**)
HER2 status, n (%)	Negative	2614	(**87.8**)	1319	(**87.7**)
	Positive	310	(**10.4**)	149	(**9.9**)
	Unknown	52	(**1.8**)	36	(**2.4**)

** Some centers do not routinely report grade on pre-surgery biopsy*

Pathological characteristics (post-surgery)

		Peri-op AI (N=2954*)		No peri-op AI (N=1495*)	
Tumor size, n(%)	≤2	1372	(**46.4**)	671	(**44.9**)
	2-5	1448	(**49.0**)	745	(**49.8**)
	>5	129	(**4.4**)	74	(**4.9**)
Nodal status, n(%)	N0	1814	(**61.4**)	892	(**59.7**)
	N1-3	801	(**27.1**)	434	(**29.0**)
	N4+	334	(**11.3**)	165	(**11.0**)
Vascular invasion, n(%)	Yes	813	(**27.5**)	445	(**29.8**)
	No	1990	(**67.4**)	981	(**65.6**)

**Surgery cancelled for 24 patients (17 Peri-op AI, 7 No peri-op AI). 7 patients (5 Peri-op AI, 2 No peri-op AI) withdrew consent for further follow-up prior to surgery*

7 patients were shown not to be ER+ and were therefore subsequently found to be ineligible

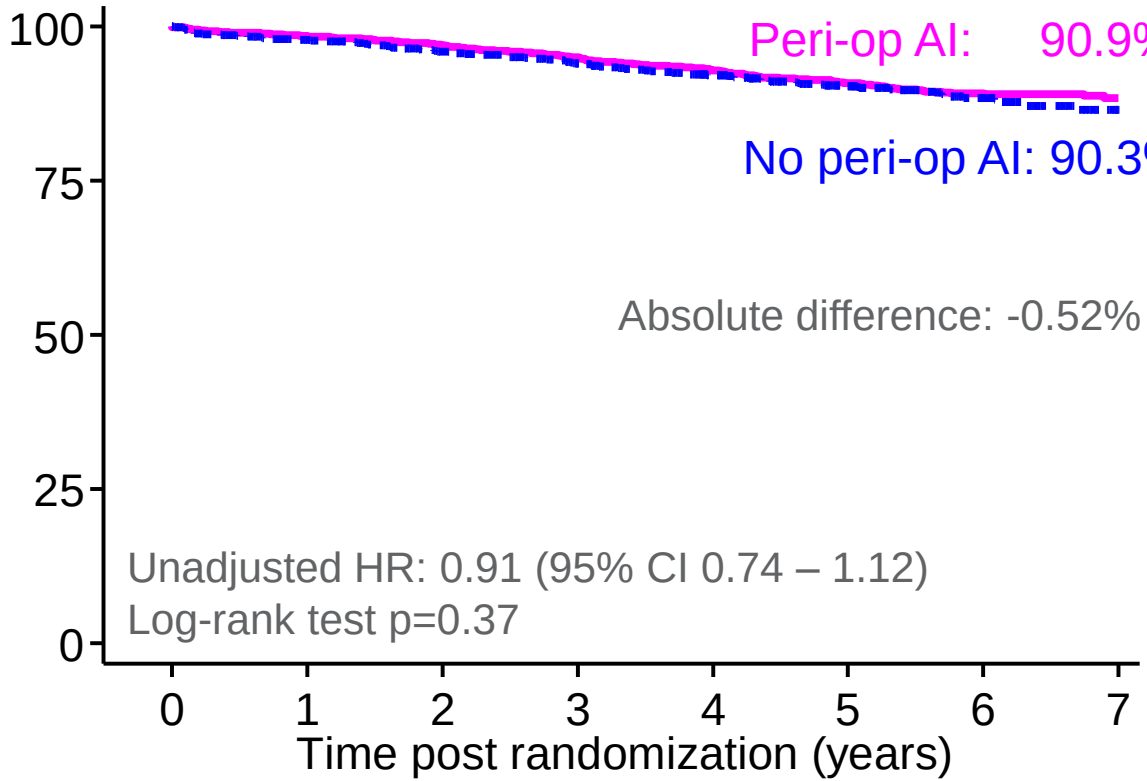
Adjuvant treatment received

		Peri-op AI		No peri-op AI	
Hormone treatment, n(%)	Yes	2908	(**98.8**)	1466	(**98.2**)
	No	35	(**1.2**)	27	(**1.8**)
Chemotherapy, n(%)	Yes	773	(**26.3**)	464	(**31.1**)
	No	2169	(**73.7**)	1030	(**68.9**)
Radiotherapy, n(%)	Yes	2235	(**76.0**)	1156	(**77.4**)
	No	707	(**24.0**)	338	(**22.6**)
Other, n(%)	Yes	223	(**7.6**)	123	(**8.2**)
	No	2711	(**92.4**)	1369	(**91.8**)

Excludes small number of unknowns

Time to recurrence

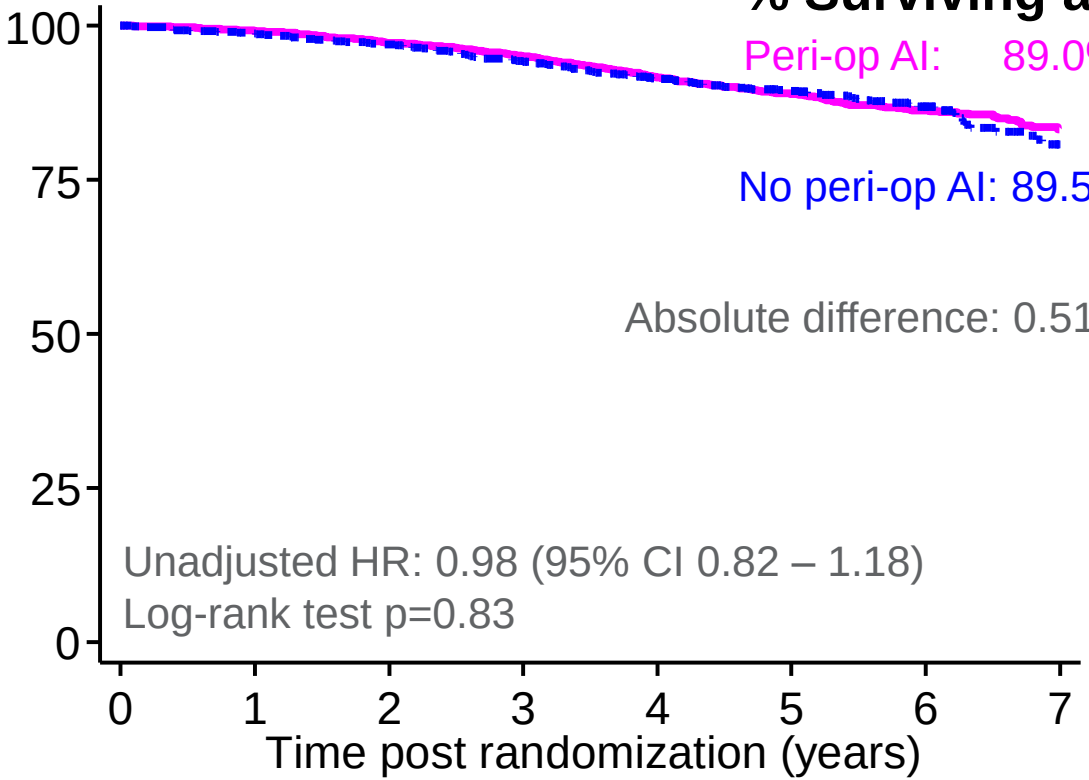
% TTR event free at 5 years



Events/N at risk

Peri-op AI:	0/2976	45/2873	43/2795	55/2645	56/2218	41/1448	17/652	3/181	Total: 263/2976 (8.8%)
No peri-op AI:	0/1504	32/1451	28/1402	27/1334	27/1111	17/733	10/337	4/81	Total: 145/1504 (9.6%)

Overall survival



Events/N at risk

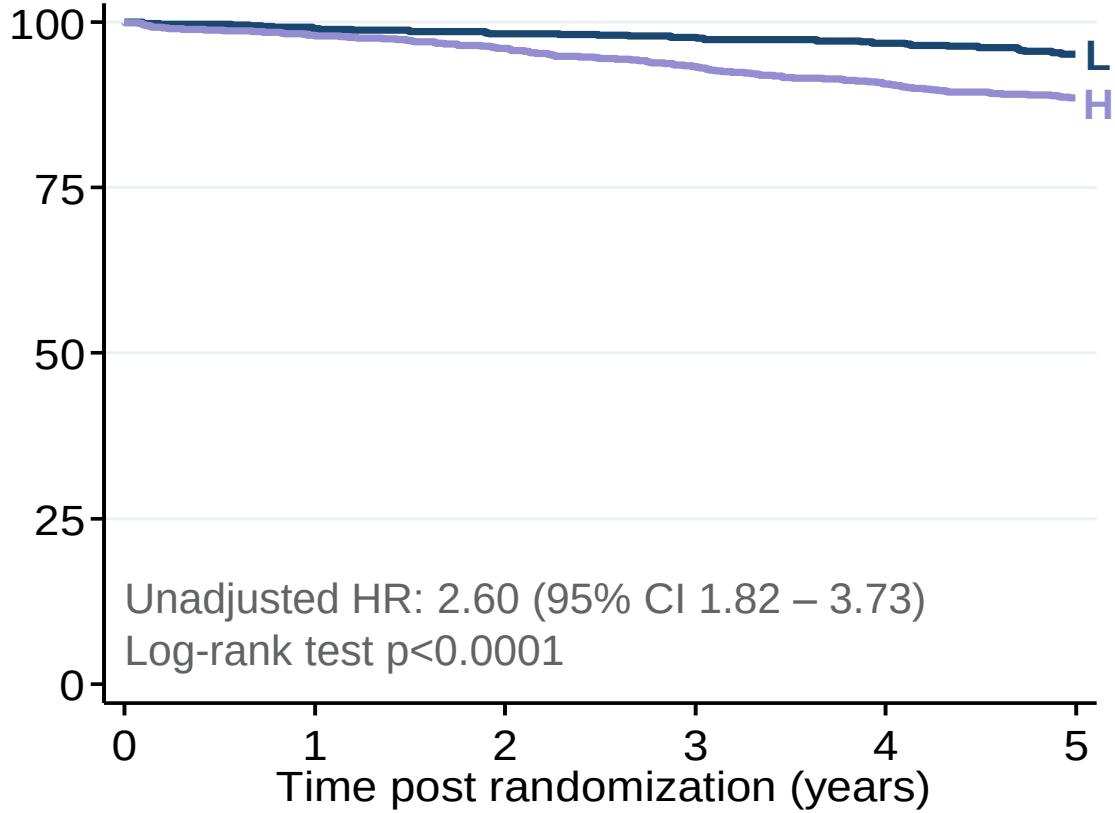
Peri-op AI:	0/2976	24/2911	56/2847	63/2716	93/2281	56/1496	30/679	12/183	Total 335/2976 (11.3%)
No peri-op AI:	0/1504	19/1475	26/1441	41/1378	39/1146	20/758	14/347	12/85	Total 172/1504 (11.4%)

Time to recurrence - event status

	Peri-op AI (N=2976)		No peri-op AI (N=1504)	
Alive and event free	2468	(**82.9**)	1216	(**80.9**)
Event contributing to TTR, n(%)	263	(**8.8**)	145	(**9.6**)
Local recurrence (isolated)*	30	(**1.0**)	14	(**0.9**)
Distant recurrence	217	(**7.3**)	123	(**8.2**)
Breast cancer death	16	(**0.5**)	8	(**0.5**)

** Includes ipsilateral SCF: 3 Peri-op AI, 2 No Peri-op AI;*

TTR by baseline Ki67 – peri-op AI patients

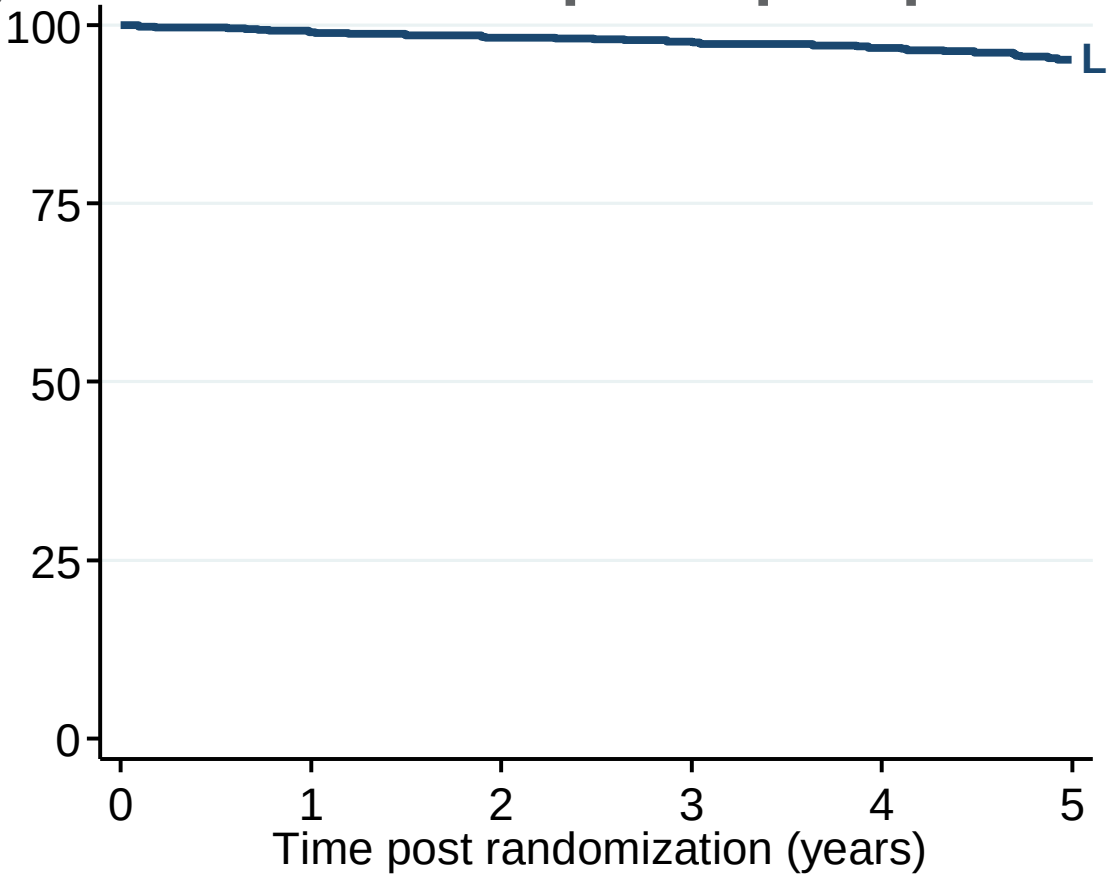


5 year absolute risk

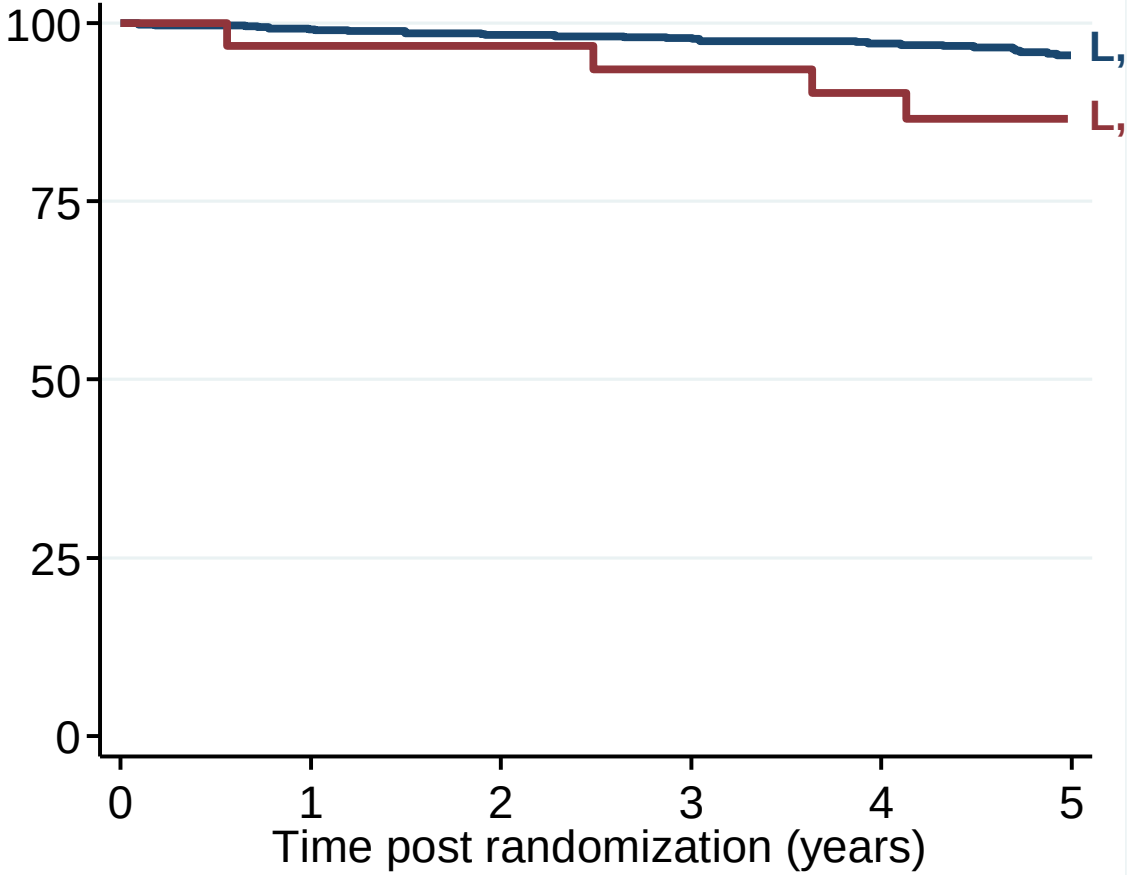
$Ki67_B$<10%: 4.9% **(95%CI: 3.5, 7.0)**

$Ki67_B$≥10%: 12.1% **(95%CI:10.5, 14.1)**

TTR by baseline Ki67 – peri-op AI patients

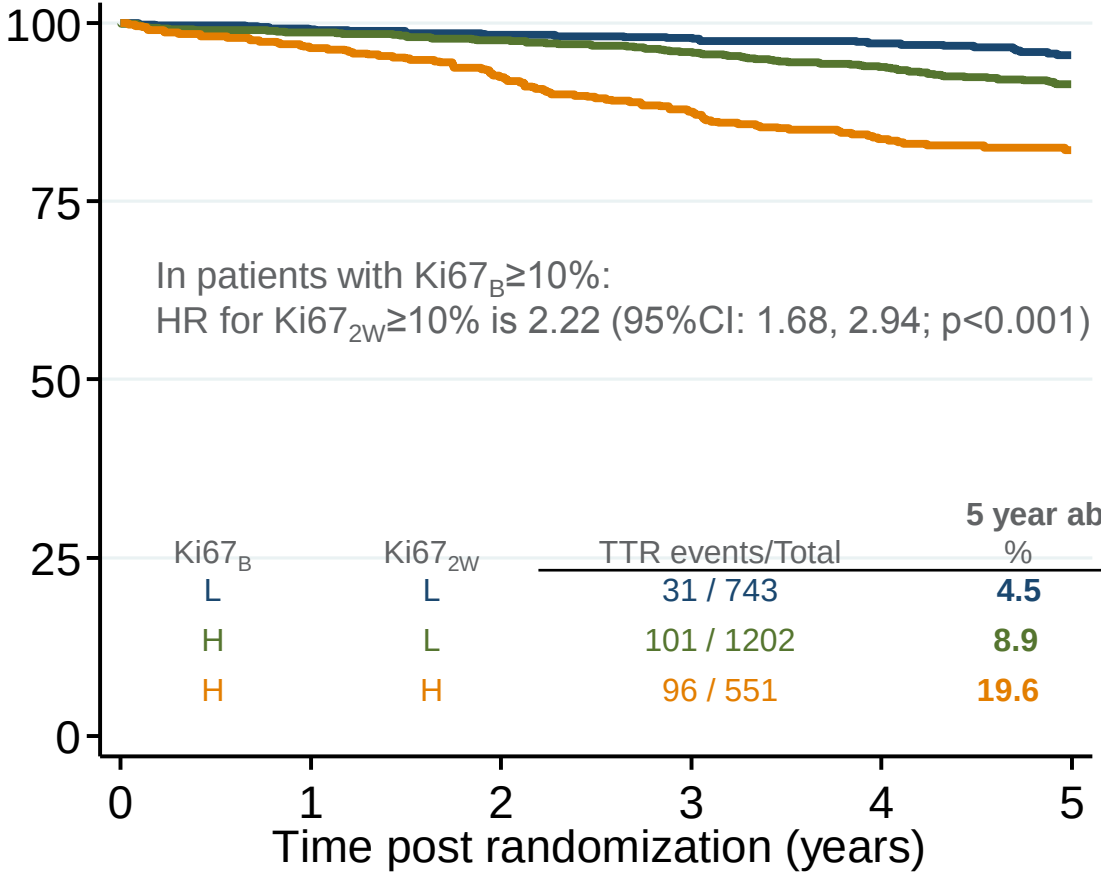


TTR by baseline and 2-week Ki67 – Peri-op AI



Only 32 patients in this group

TTR by baseline Ki67 – peri-op AI patients



$Ki67_B$	$Ki67_{2W}$	TTR events/Total	5 year absolute risk %	95% CI
L	L	31 / 743	**4.5**	(3.1, 6.6)
H	L	101 / 1202	**8.9**	(7.2, 11.0)
H	H	96 / 551	**19.6**	(15.9, 24.1)

Conclusions

- No evidence of improved clinical outcome (i.e. TTR) with peri-operative AI
- $Ki67_B$ and $Ki67_{2W}$ provide independent significant prognostic information.
- If $Ki67_B$ is low (<10%) the prognosis is good, suggesting no need for 2 weeks of AI treatment and second Ki67 measurement.
- If $Ki67_B$ is high (≥10%) then $Ki67_{2W}$ on AI treatment sub-divides patients further:
  - Low $Ki67_{2W}$ (<10%) patients will do relatively well (8.4% 5 year TTR) and may have no need for additional treatment beyond standard of care
  - High (≥10%) $Ki67_{2W}$ have a poor prognosis (19.6% 5 year TTR) and should be considered for additional chemotherapy and/or for trials of new agents

Agenda

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- CDK4/6 Inhibitors in the elderly

First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial

Debu Tripathy,[1] Joohyuk Sohn,[2] Seock-Ah Im,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Sara Hurvitz,[8] Louis Chow,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Gary Carlson,[14] Gareth Hughes,[15] Ivan Diaz-Padilla,[15] Caroline Germa,[14] Samit Hirawat,[14] Yen-Shen Lu[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Severance Hospital of Yonsei University Health System, Seoul, Republic of Korea; [3]Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Unità di Ricerca in Senologia Medica – Istituto Europeo di Oncologia, Milan, Italy; [5]Hospital de Caridade de Ijuí, CACON, Ijuí, Brazil; [6]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [7]Breast Center, University of Munich (LMU), Munich, Germany; [8]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [9]Organisation for Oncology and Translational Research, Hong Kong; [10]Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea; [11]Centro Oncológico Estatal, Instituto de Seguridad Social del Estado de México y Municipios, Toluca, Mexico; [12]Institut Català d'Oncologia, Hospital Moisès Broggi, Barcelona, Spain; [13]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [15]Novartis Pharma AG, Basel, Switzerland; [16]National Taiwan University Hospital, Taipei, Taiwan

Unmet need in premenopausal patients with HR+, HER2– ABC

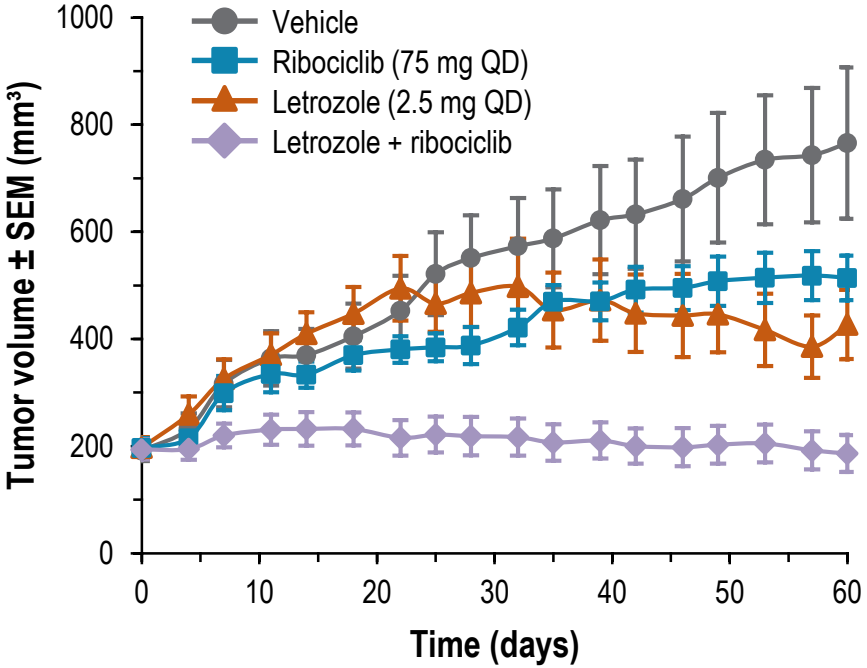
- Estimates suggest that in 2017 in the US, ~19% of invasive breast cancers will be diagnosed in women aged ≤49 years[1]
  - The proportion of patients aged <50 years may be up to 42% in the Asia-Pacific region[2]
- The last randomized trial focusing solely on premenopausal women with ABC was published in 2000[3]
- Young women with ABC have a distinct tumor biology,[4] experience more aggressive disease, and are more likely to die from their cancer than older women[5]
- Endocrine therapy with ovarian suppression is the recommended first-line treatment for premenopausal women with HR+, HER2– ABC;[6–8] however, resistance and disease progression ultimately occur
- Adding ribociclib to letrozole significantly prolonged PFS compared with letrozole alone in postmenopausal women with *de novo* and/or recurrent HR+, HER2– ABC[9]
- MONALEESA-7 is the first Phase III trial investigating CDK4/6 inhibitor-based regimens as a front-line treatment specifically for premenopausal women with ABC

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; PFS, progression-free survival.
Advanced breast cancer refers to locoregionally recurrent or metastatic disease.

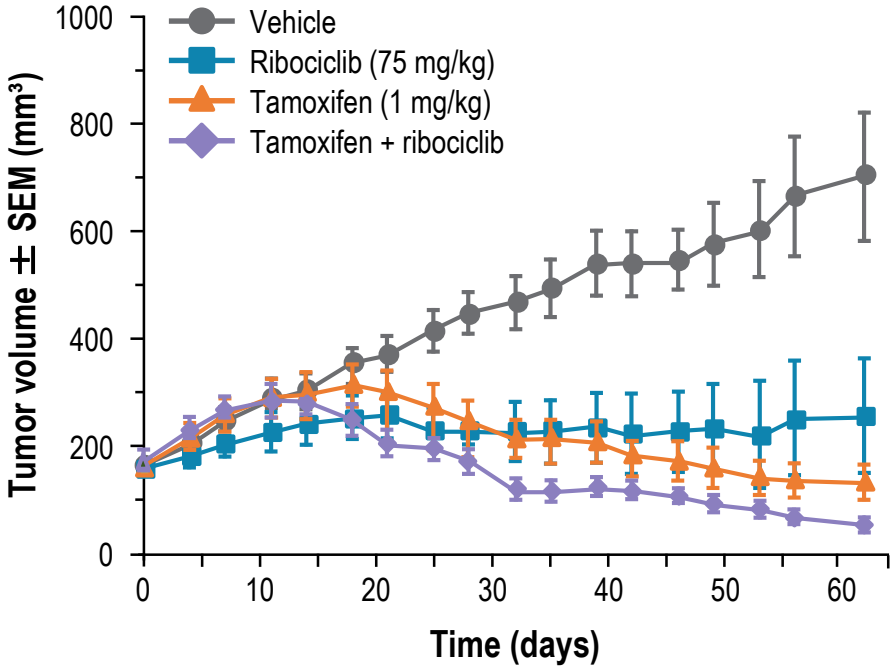
1. Desantis CE, *et al. CA Cancer J Clin* 2017;ePub ahead of print; 2. Youlden DR, *et al. Cancer Biol Med* 2014;11:101–115; 3. Klijn JGM, *et al. J Natl Cancer Inst* 2000;92:903–911; 4. Zaidi S, *et al. SABCS* 2017 (abstract P2-05-10); 5. Anders CK, *et al. Semin Oncol* 2009;36:237–249; 6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2017; 7. Rugo HS, *et al. J Clin Oncol* 2016;34:3069–3103; 8. Cardoso F, *et al. Ann Oncol* 2017;28:16–33; 9. Hortobagyi GN, *et al. N Engl J Med* 2016;375:1738–1748.

Preclinical activity of ribociclib-based combinations*

Ribociclib + letrozole[1]



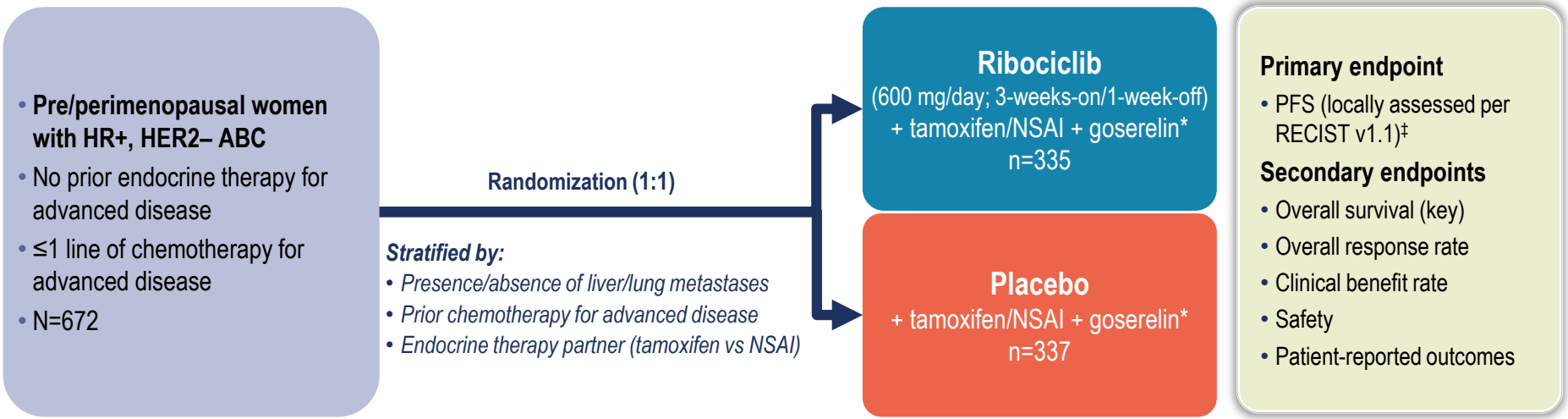
Ribociclib + tamoxifen[2]



QD, once daily; SEM, standard error of the mean.
*Patient-derived ER+ breast cancer xenograft model (HBX34) used for both analyses.

1. O'Brien NA, *et al. Cancer Res* 2014;74(suppl 19):abst 4756;
2. Caponigro G, *et al. Keystone Symposia – Kinases: Next-Generation Insights and Approaches* 2017:oral.

MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 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[1,2]), and a sample size of 660 patients

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
*Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
‡PFS by Blinded Independent Review Committee conducted to support the primary endpoint.
1. Klijn JG, *et al. J Clin Oncol* 2001;19:343–353; 2. Mourisden H, *et al. J Clin Oncol* 2001;19:2596–2606.

Key enrollment criteria

Key inclusion criteria

- Pre/perimenopausal women (per NCCN guidelines)
- ≥1 measurable lesion (RECIST 1.1) or ≥1 predominantly lytic bone lesion
- ECOG performance status of ≤1
- ≤1 line of chemotherapy for ABC
- Prior (neo)adjuvant therapy was allowed:
  - If no prior endocrine therapy OR if ≥12 months since the last dose, patient was eligible for tamoxifen or an NSAI, per investigator/patient choice
  - If last dose of tamoxifen was <12 months prior to randomization, patient was eligible for an NSAI
  - If last dose of AI/NSAI was <12 months prior to randomization, patient was eligible for tamoxifen

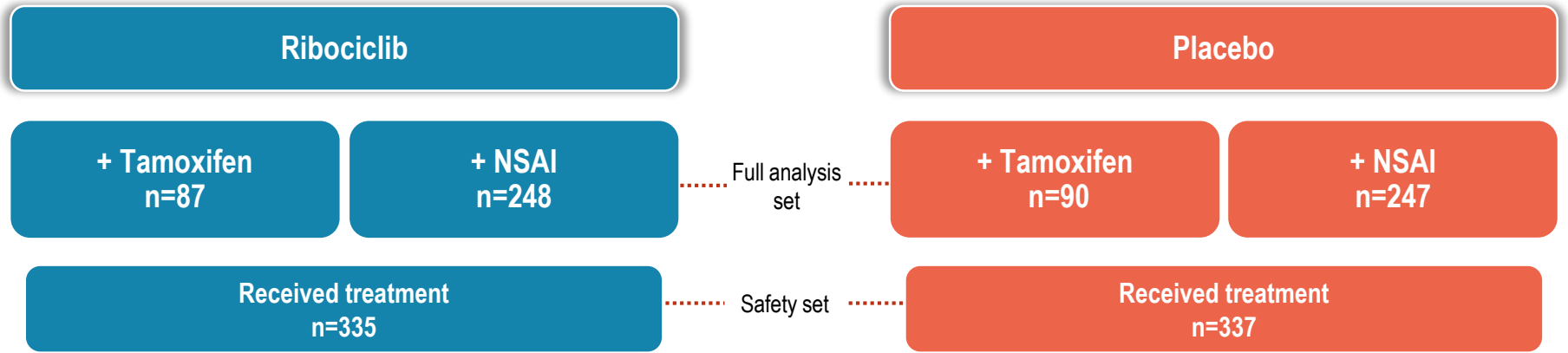
Key exclusion criteria

- Any prior endocrine therapy for ABC
- Inflammatory breast cancer
- Active cardiac disease or history of cardiac dysfunction, including QTcF >450 msec
- CNS metastases
- Symptomatic visceral disease

AI, aromatase inhibitor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network; QTcF, Fridericia's corrected QT interval.
Perimenopausal defined as neither premenopausal nor postmenopausal per NCCN guidelines.
Goserelin included in all combinations.

Accrual and analysis details

672 patients randomized between December 2014 and August 2016
Data cut-off date: August 20, 2017 (318 events)
Median time from randomization to data cut-off date: 19.2 months



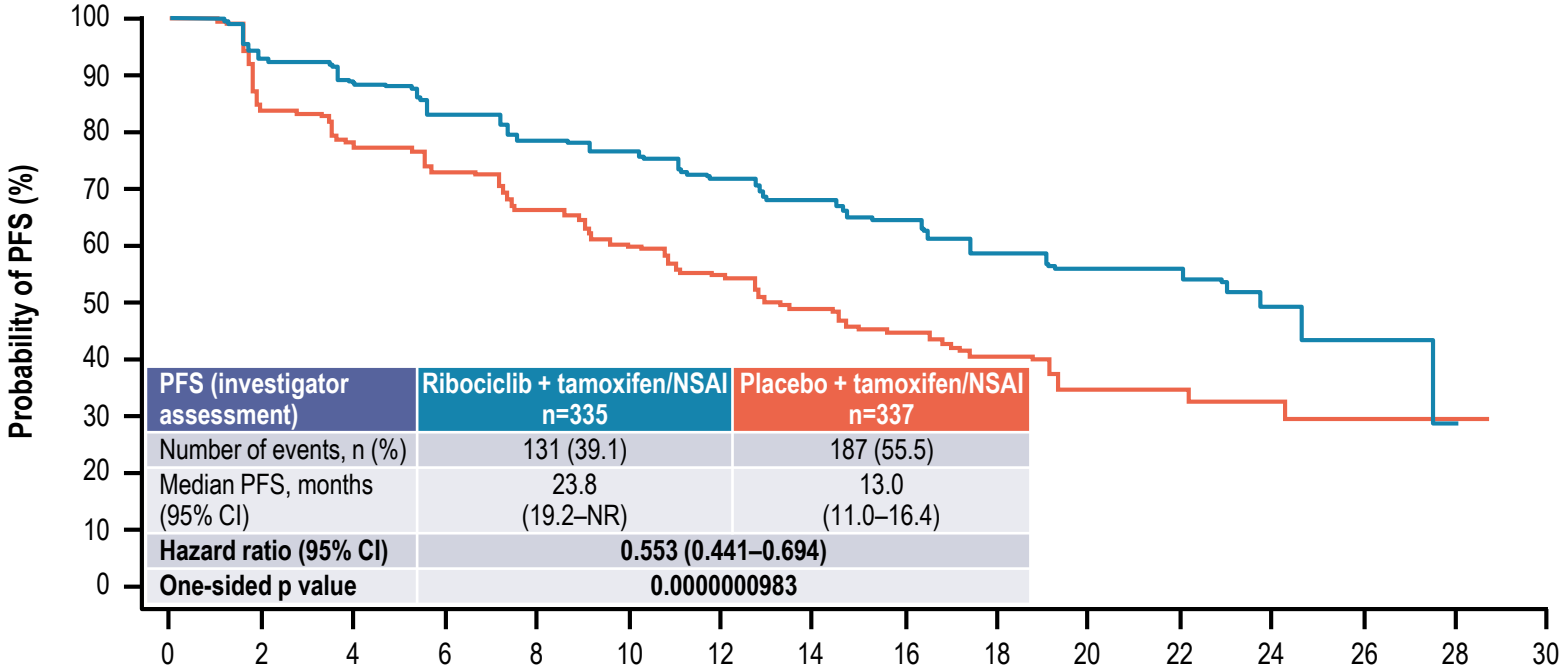
Goserelin included in all combinations.

Patient demographics and baseline characteristics

Characteristic*	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Median age, years (range)	43 (25–58)	45 (29–58)
Race		
Caucasian	187 (55.8)	201 (59.6)
Asian	99 (29.6)	99 (29.4)
Other‡	29 (8.7)	19 (5.6)
Unknown	20 (6.0)	18 (5.3)
ECOG performance status§		
0	245 (73.1)	255 (75.7)
1	87 (26.0)	78 (23.1)
Missing	3 (0.9)	3 (0.9)
Metastatic sites		
Visceral disease	193 (57.6)	188 (55.8)
Bone-only disease	81 (24.2)	78 (23.1)
***De novo* metastatic disease**	136 (40.6)	134 (39.8)
Non-*de novo* metastatic disease	199 (59.4)	203 (60.2)
Disease-free interval		
≤12 months	23 (6.9)	13 (3.9)
>12 months	176 (52.5)	190 (56.4)
Prior (neo)adjuvant endocrine therapy	127 (37.9)	141 (41.8)
Prior chemotherapy		
For advanced disease	47 (14.0)	47 (13.9)
(Neo)adjuvant only	138 (41.2)	138 (40.9)
None	150 (44.8)	152 (45.1)

*All values are n (%), unless stated otherwise; ‡'Other' includes Black, Native American, and other;
§ One patient in the placebo arm had an ECOG performance status of 2.
Goserelin included in all combinations.

Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

No. at risk

Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

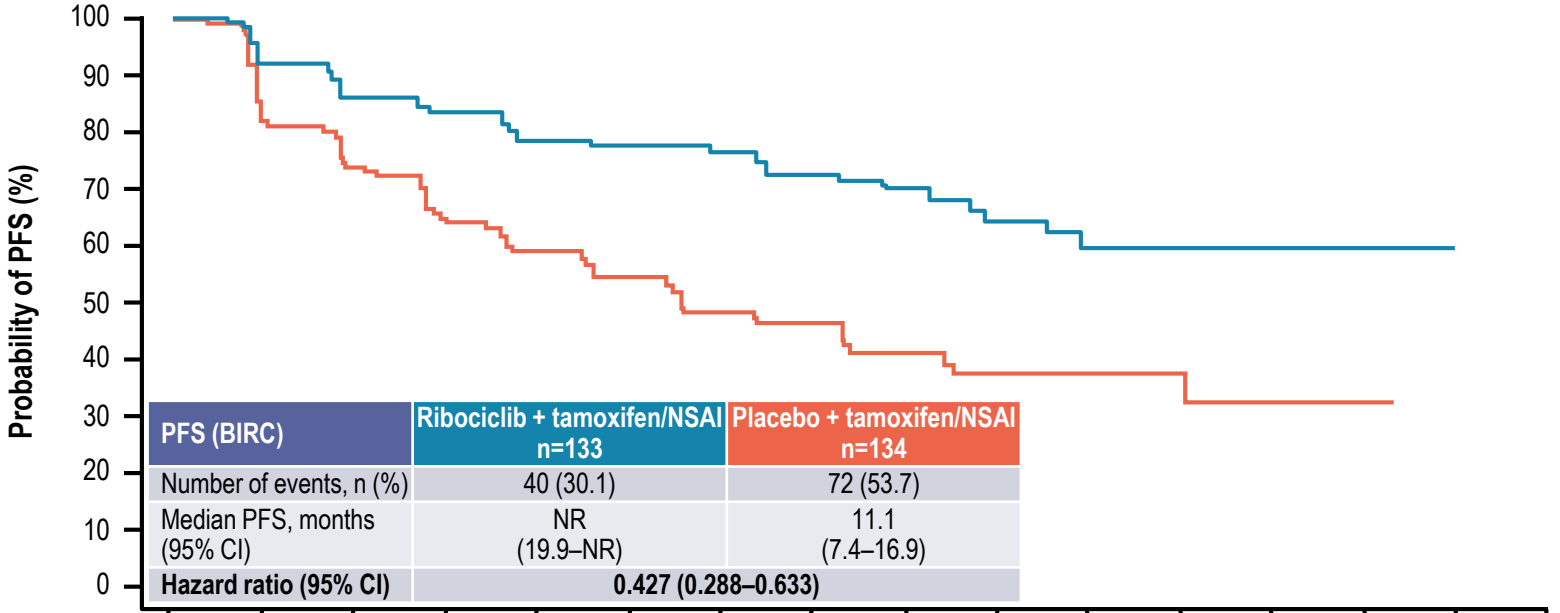
CI, confidence interval; NR, not reached.
Goserelin included in all combinations.

PFS by endocrine therapy partner (investigator-assessed)

PFS (investigator assessment)	Tamoxifen		NSAI	
	Ribociclib arm n=87	Placebo arm n=90	Ribociclib arm n=248	Placebo arm n=247
Number of events, n	39	55	92	132
Median PFS, months (95% CI)	22.1 (16.6–24.7)	11.0 (9.1–16.4)	27.5 (19.1–NR)	13.8 (12.6–17.4)
Hazard ratio (95% CI)	**0.585 (0.387–0.884)**		**0.569 (0.436–0.743)**	

Goserelin included in all combinations.

Supportive analysis: PFS (Blinded Independent Review Committee*)



PFS (BIRC)	Ribociclib + tamoxifen/NSAI n=133	Placebo + tamoxifen/NSAI n=134
Number of events, n (%)	40 (30.1)	72 (53.7)
Median PFS, months (95% CI)	NR (19.9–NR)	11.1 (7.4–16.9)
Hazard ratio (95% CI)	**0.427 (0.288–0.633)**	

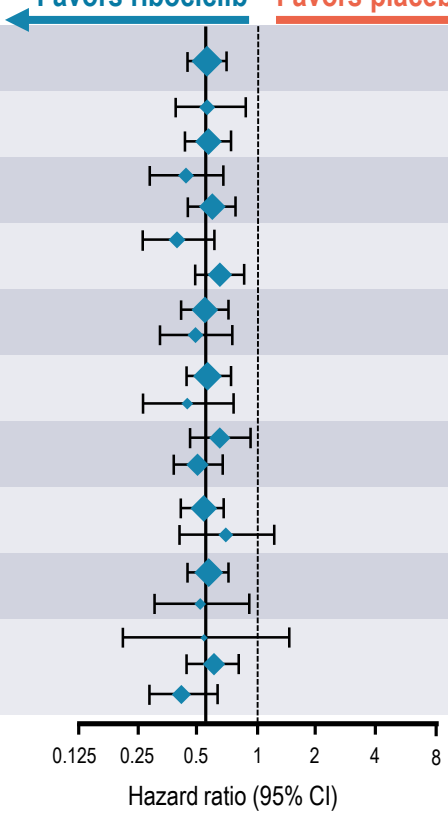
No. at risk

Ribociclib + tamoxifen/NSAI	133	115	105	100	90	87	85	64	46	32	23	16	9	2	1	0
Placebo + tamoxifen/NSAI	134	103	91	76	69	61	52	38	29	21	11	7	5	1	0	0

BIRC, Blinded Independent Review Committee.
*Audit-based review of 40% of randomized patients.
Goserelin included in all combinations.

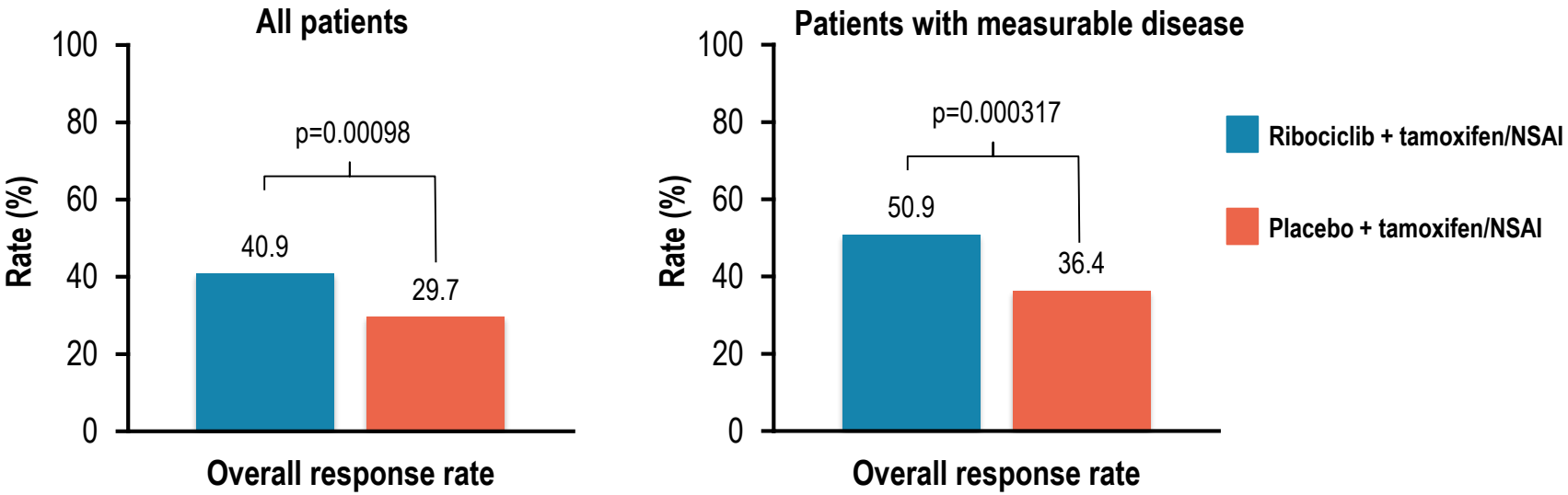
PFS subgroup analysis*

Subgroup		n (%)	Hazard ratio	95% CI
All patients		672 (100)	0.553	0.441–0.694
Endocrine therapy partner	Tamoxifen	177 (26)	0.585	0.387–0.884
	NSAI	495 (74)	0.569	0.436–0.743
Age	<40 years	186 (28)	0.443	0.293–0.671
	≥40 years	486 (72)	0.590	0.449–0.777
Race‡	Asian	198 (29)	0.401	0.258–0.625
	Non-Asian	413 (61)	0.657	0.492–0.877
ECOG performance status§	0	500 (74)	0.549	0.417–0.721
	≥1	166 (25)	0.495	0.320–0.765
ER/PgR status	ER+ and PgR+	572 (85)	0.574	0.446–0.739
	Other	100 (15)	0.444	0.258–0.765
Liver and/or lung involvement	No	329 (49)	0.642	0.454–0.907
	Yes	343 (51)	0.503	0.375–0.677
Bone-only disease	No	513 (76)	0.533	0.415–0.686
	Yes	159 (24)	0.703	0.414–1.194
Prior chemotherapy for advanced disease	No	578 (86)	0.566	0.443–0.724
	Yes	94 (14)	0.547	0.314–0.954
Disease-free interval	≤12 months	36 (5)	0.560	0.210–1.490
	>12 months	366 (54)	0.615	0.455–0.832
	De novo	270 (40)	0.428	0.287–0.640



ER, estrogen receptor; PgR, progesterone receptor.
*Locally assessed PFS; ‡Non-Asian race includes Caucasian, Black, and Native American;
§ ECOG performance status missing for n=6; 1 patient had an ECOG performance status of 2.

Secondary endpoints



- The CBR in patients with measurable disease was 79.9% for ribociclib + tamoxifen/NSAI vs 67.3% for placebo + tamoxifen/NSAI (p=0.000340)
- Overall survival data were immature at the cut-off date

CBR, clinical benefit rate.
CBR = complete response + partial response + (stable disease + non-complete response/non-progressive disease ≥24 weeks).
Goserelin included in all combinations.

Hematologic adverse events

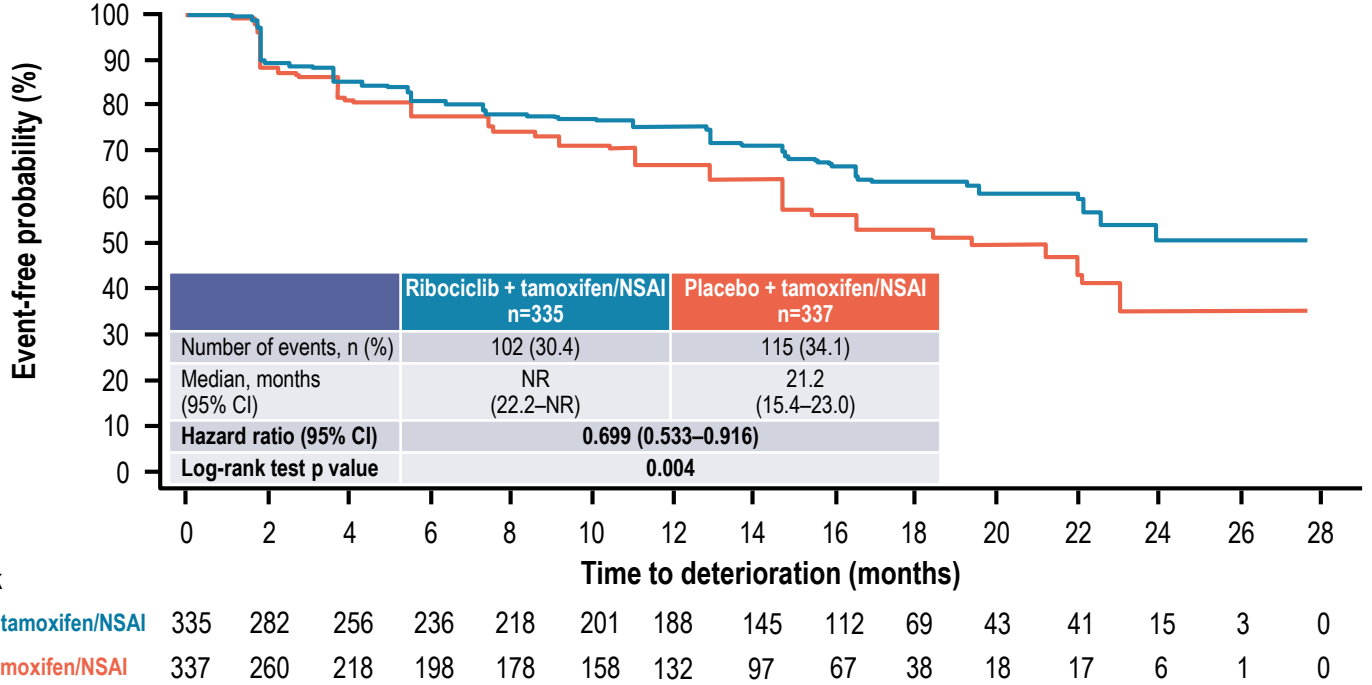
Regardless of study treatment relationship

AEs ≥5% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	75.8	50.7	9.9	7.7	3.0	0.6
Leukopenia	31.3	13.1	1.2	5.6	1.2	0
Anemia	20.9	3.0	0	10.1	2.1	0
Thrombocytopenia	8.7	0.6	0.3	2.1	0.3	0.3

- Febrile neutropenia occurred in 2.1% of patients in the ribociclib arm vs 0.6% of patients in the placebo arm

Goserelin included in all combinations.

Patient-reported outcomes (EORTC QLQ-C30 – global health status)



- There was a sustained improvement in time to definitive deterioration of at least 10% for the global health status/QoL scale in the ribociclib arm vs the placebo arm
- A clinically meaningful (>5 points) improvement from baseline in pain score was observed as early as 8 weeks in the ribociclib arm, and was sustained

QoL, quality of life.
Goserelin included in all combinations.

Conclusions

- MONALEESA-7 represents the first Phase III trial dedicated to the evaluation of a CDK4/6 inhibitor-based regimen as front-line treatment for premenopausal women with HR+, HER2– advanced breast cancer
- PFS was significantly prolonged with the addition of ribociclib to tamoxifen/NSAI + goserelin vs placebo + tamoxifen/NSAI + goserelin
  - Median PFS = 23.8 months vs 13.0 months; hazard ratio = 0.553; p=0.0000000983
- Treatment benefit was consistent across patient subgroups and regardless of endocrine partner
- Ribociclib-based combinations demonstrated a predictable and manageable safety profile
- A clinically meaningful improvement in time to deterioration of QoL and improvement in pain score were observed for patients in the ribociclib arm
- Ribociclib combined with tamoxifen/NSAI + goserelin is a potential new treatment option for premenopausal women with HR+, HER2– advanced breast cancer, regardless of disease-free interval or endocrine partner

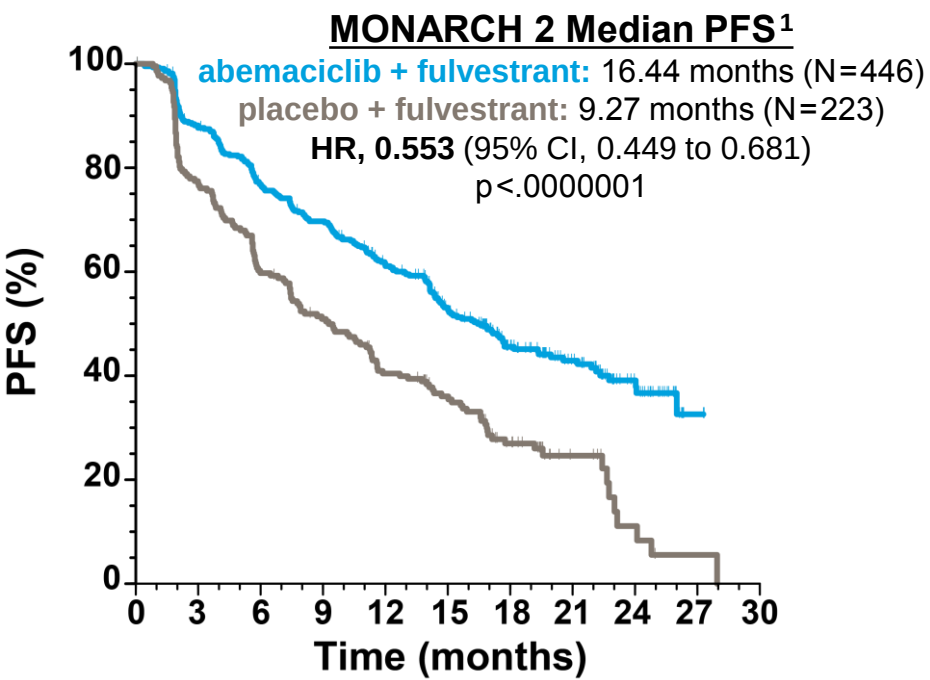
San Antonio Breast Cancer Symposium
December 5-9, 2017

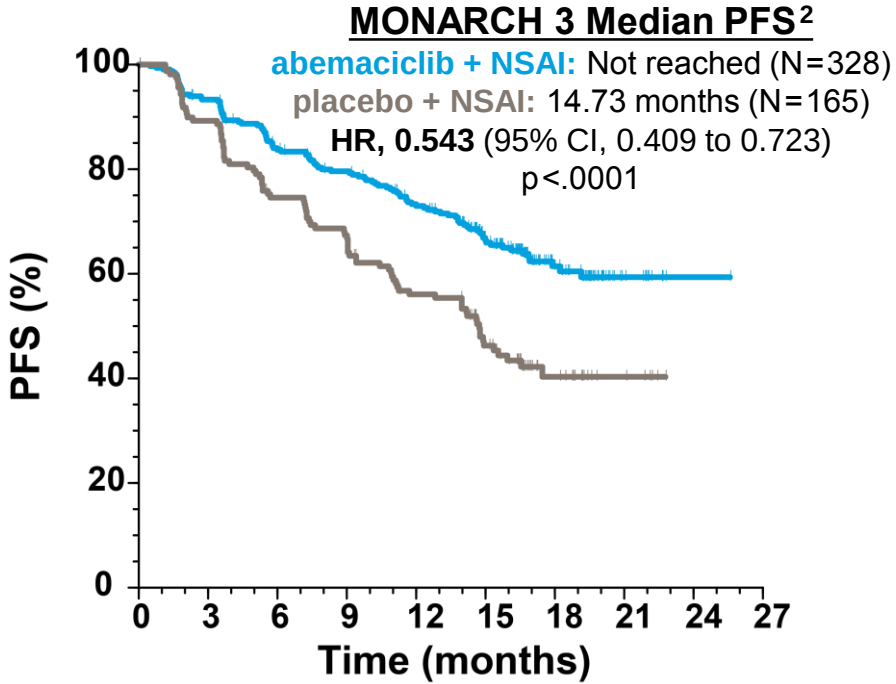
The benefit of abemaciclib in prognostic subgroups: An exploratory analysis of combined data from the MONARCH 2 and 3 studies

Matthew P. Goetz[1], Joyce O'Shaughnessy[2], George W. Sledge Jr.[3], Miguel Martin[4], Yong Lin[5], Tammy Forrester[5], Colleen Mockbee[5], Ian C. Smith[5], Angelo Di Leo[6], Stephen Johnston[7]

[1]Mayo Clinic, Rochester, MN; [2]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas TX; [3]Stanford University, Stanford, CA; [4]Instituto De Investigacion Sanitaria Gregorio Marañon, Ciberonc, Geicam; Universidad Complutense, Madrid, Spain; [5]Eli Lilly and Company, Indianapolis, IN; [6]Hospital of Prato, Istituto Toscano Tumori, Prato, Italy; [7]The Royal Marsden NHS Foundation Trust, London, UK

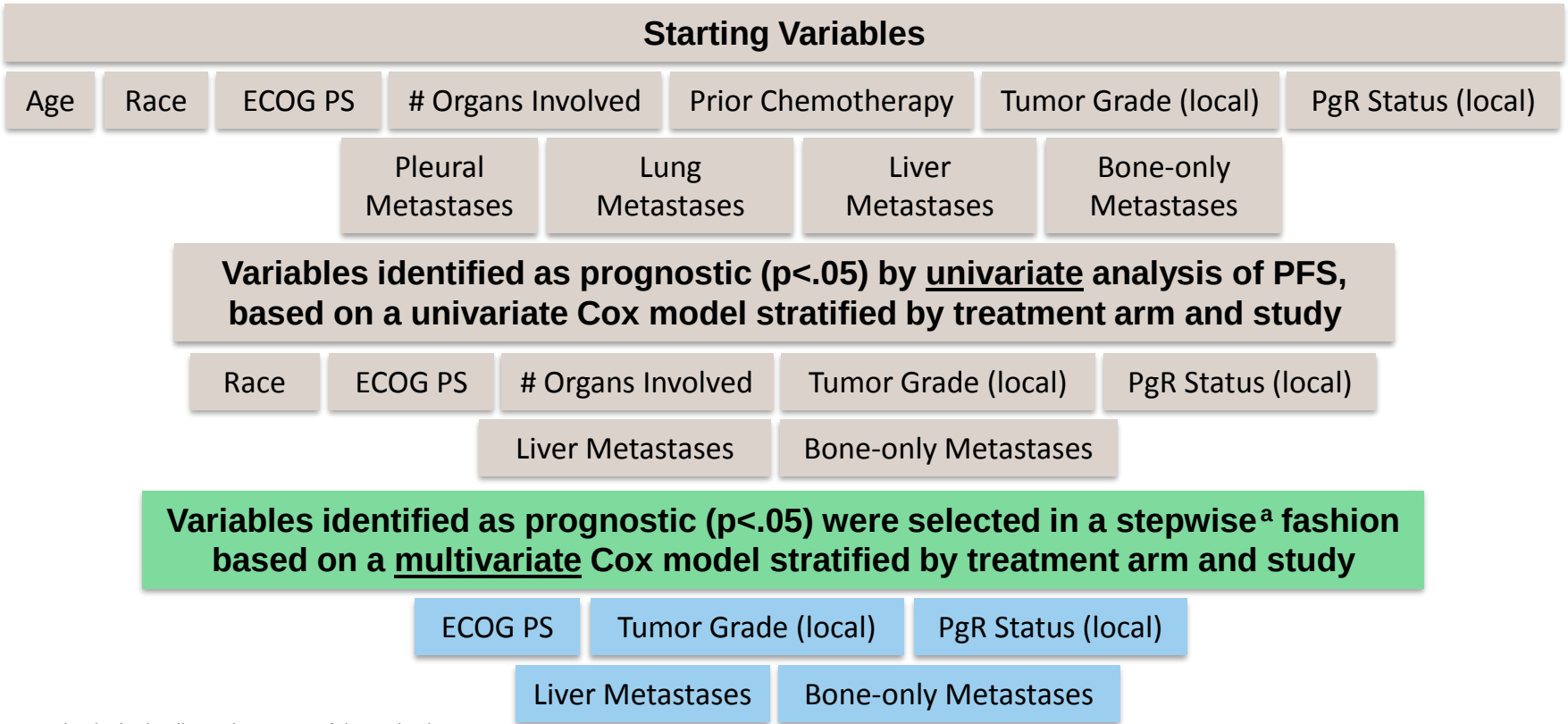
MONARCH 2 and 3 PFS (ITT)





1. Sledge GW Jr et al. *J Clin Oncol*. 2017;35(25):2875-84
2. Goetz MP et al. *J Clin Oncol*. 2017;35(32):3638-46

Prognostic Analyses – Pooled Data Across MONARCH 2 and 3

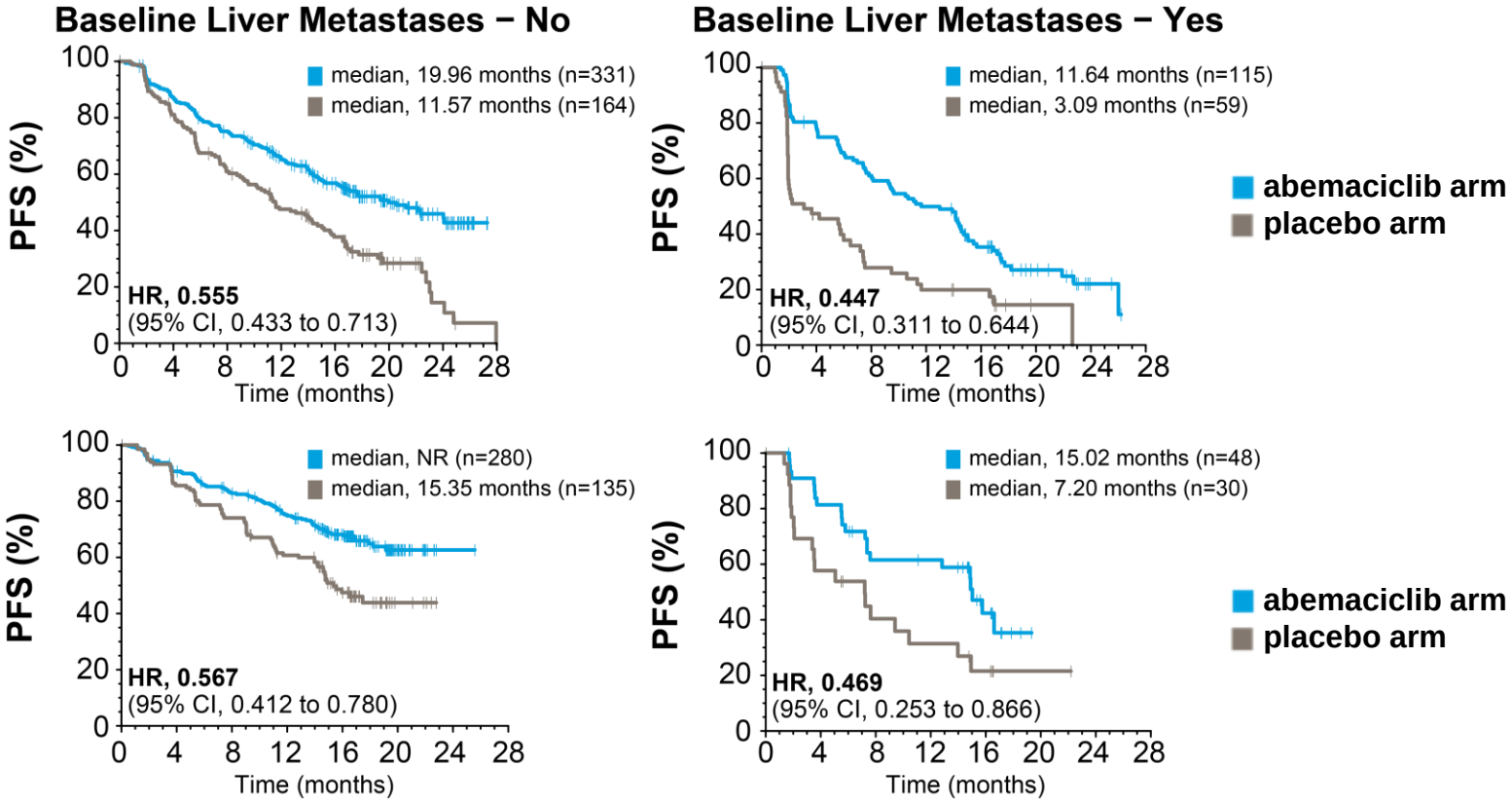


[a]*Entry p-value <.05; retaining p-value <.05*

Liver Metastases

MONARCH 2
fulvestrant +/- abemaciclib

MONARCH 3 [1,2]
NSAI +/- abemaciclib

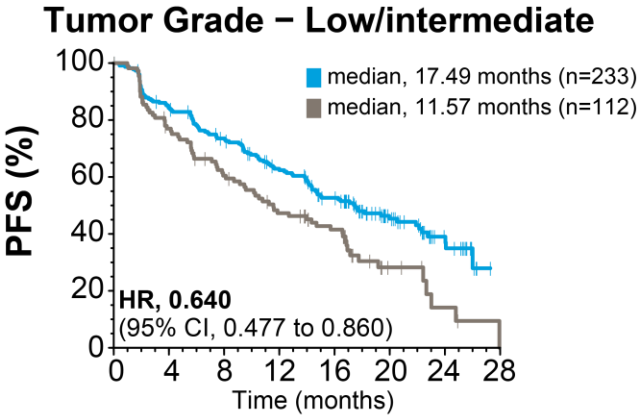


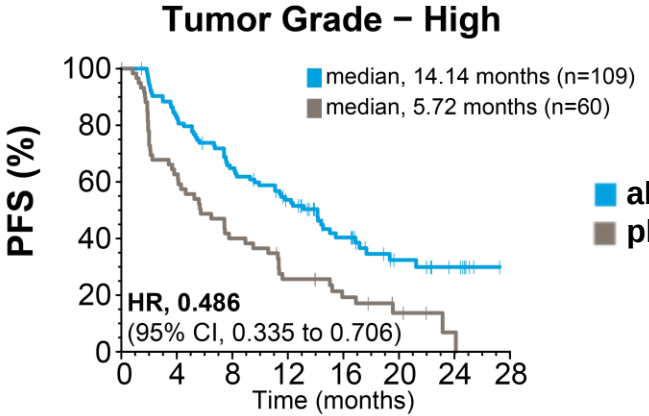
1. Goetz MP et al. *J Clin Oncol.* 2017;35(32):3638-46
2. Di Leo A et al. *Annals of Oncology.* 2017;28 (suppl_5): v605-v649

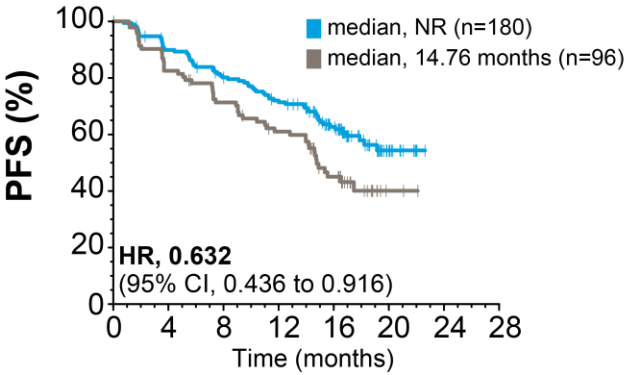
Tumor Grade

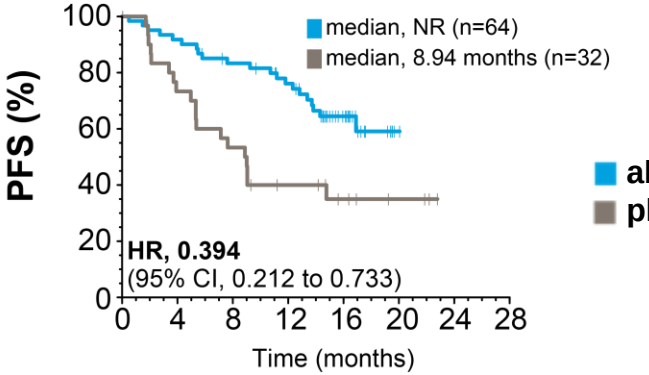
MONARCH 2
fulvestrant +/- abemaciclib

MONARCH 3
NSAI +/- abemaciclib







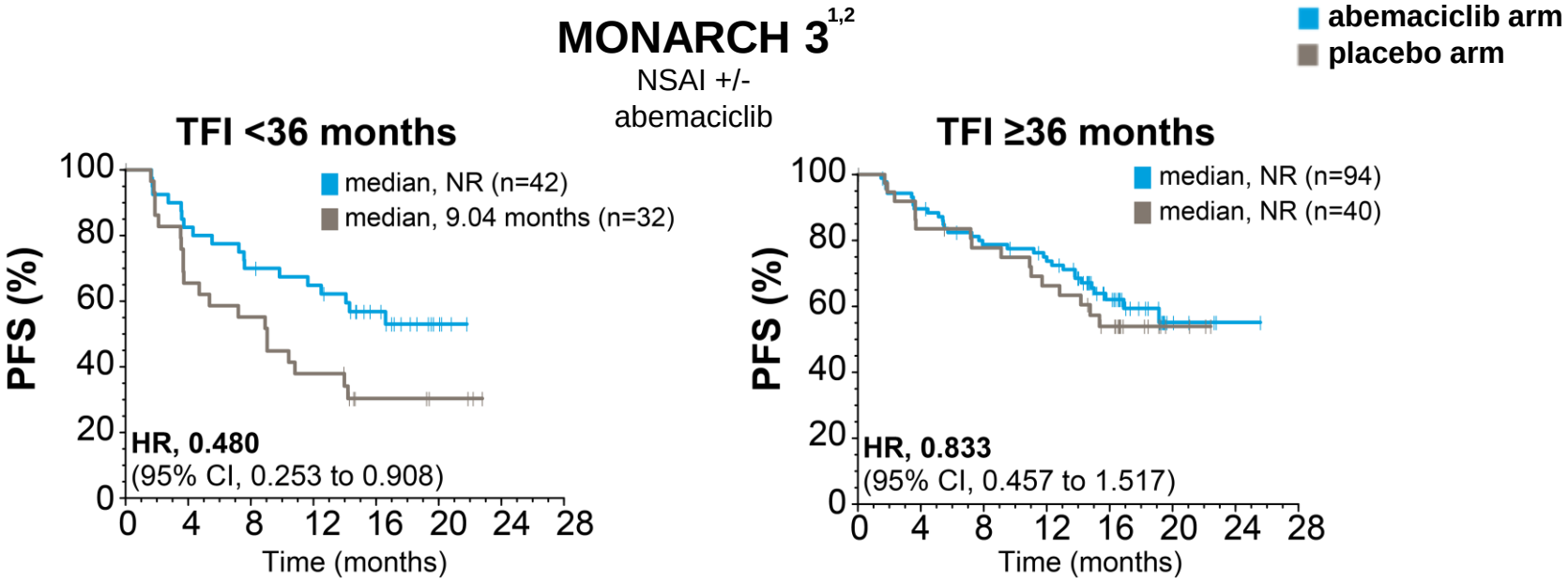


abemaciclib arm
placebo arm

Treatment-free Interval (TFI)

MONARCH 3[1,2]

NSAI +/- abemaciclib



ORR
abemaciclib arm: 43.3%
placebo arm: 22.7%

ORR
abemaciclib arm: 56.9%
placebo arm: 46.7%

***Note**: Study protocol required an interval greater than 12 months from the end of adjuvant ET until relapse. The 36-month cutoff was arbitrarily selected to be as short as possible while providing an adequate sample size.*

1. Goetz MP et al. *J Clin Oncol.* 2017;35(32):3638-46
2. Di Leo A et al. *Annals of Oncology.* 2017;28 (suppl_5): v605-v649

Conclusions

- These exploratory analyses from over 1000 patients treated in MONARCH 2 and MONARCH 3 demonstrated that all subgroups benefited from the addition of abemaciclib to endocrine therapy
- Abemaciclib in combination with endocrine therapy offered the largest benefit (PFS and ORR) in patients with clinical characteristics that make the prognosis more concerning
  - The largest improvements were in patients with liver metastases, PgR-negative tumors, or high grade tumors
- In the first-line setting, for patients with a short TFI, a substantial improvement from the addition of abemaciclib to endocrine therapy was observed
- Further data are needed to inform treatment strategies for patients with more favorable baseline prognostic factors (e.g., bone-only, long TFI)

MANTA – A randomized phase II Study of Fulvestrant in combination with the dual mTOR inhibitor AZD2014 or Everolimus or Fulvestrant alone in ER-positive advanced or metastatic breast cancer.

Peter Schmid[1], Matthias Zaiss[2], Catherine Harper-Wynne[3], Marta Ferreira[4], Sidharth Dubey[5], Stephen Chan[6], Andreas Makris[7], Gia Nemsadze[8], Adrian M. Brunt[9], Sherko Kuemmel[10], Isabel Ruiz[11], Antonia Perelló[12], Anne Kendall[13], Janet Brown[14], Hartmut Kristeleit[15], John Conibear[1], Cristina Saura[16], Julien Grenier[17], Károly Máhr[18], Michael Schenker[19], JoohyukSohn [20], Keun Seok Lee [21], Shah-Jalal Sarker[1], Aaron Prendergast[1], Carike Coetzee[1], Kelly Mousa[1], Javier Cortes[22]

[1]Barts Cancer Institute, St Bartholomew's Hospital, Queen Mary University of London, UK; [2]Praxis fuer Interdisziplinaere Onkologie, Germany; [3]Kent Oncology Centre, Maidstone and Tunbridge Wells NHS Trust, UK; [4]IPO Porto, Portugal; [5]Derriford Hospital, Plymouth Hospitals NHS Trust, UK; [6]Nottingham University Hospitals NHS Trust, UK; [7]Mount Vernon Cancer Centre, East & North Herts NHS Trust, UK; [8]Institute of Clinical Oncology, Georgia; [9]University Hospitals of North Midlands NHS Trust, UK; [10]Kliniken Essen-Mitte, Germany; [11]Hospital Universitario Sant Joan De Reus, Spain; [12]Hospital Son Espases, Spain; [13] Great Western Hospitals NHS Foundation Trust, UK; [14] Sheffield Teaching Hospitals NHS Foundation Trust, UK; [15]Queen Elizabeth Hospital, Woolwich, Lewisham and Greenwich NHS Trust, UK; [16]Vall d'Hebron University Hospital, Spain; [17]Institut Sainte Catherine, France; [18] Zala County Hospital, Hungary; [19] Sf. Nectarie Oncology Center SRL, Romania; [20] Yonsei University Health System, Republic of Korea; [21] National Cancer Center, Republic of Korea; [22]Ramon Y Cajal University Hospital, Spain

Queen Mary University of London

ECMC

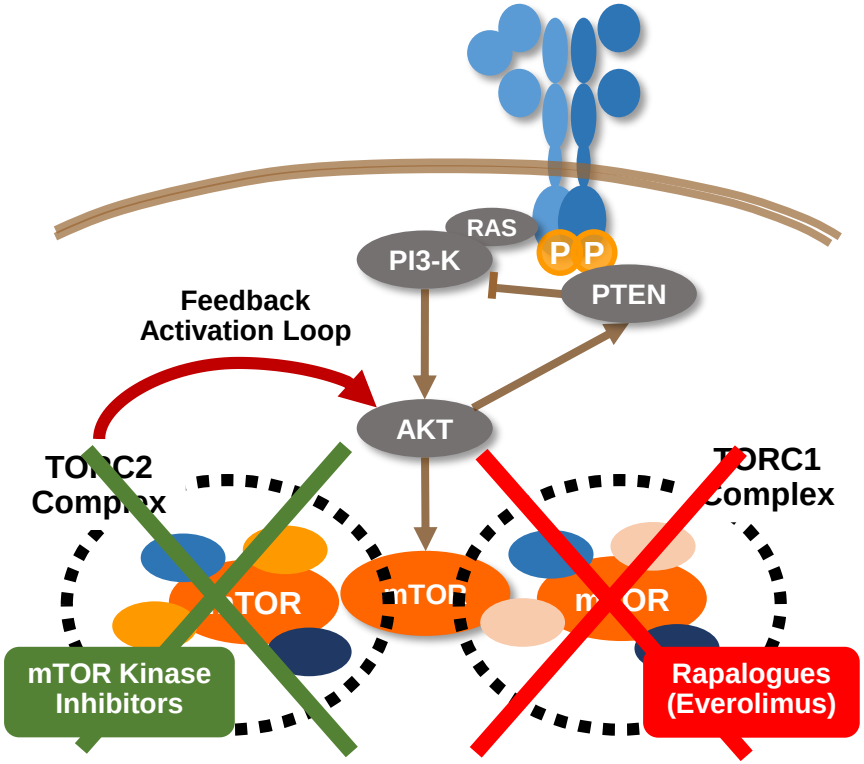
CANCER RESEARCH UK

NCRN

Barts Health NHS NHS Trust

Background

- Randomised trials have shown a substantial benefit of adding everolimus to ET
- mTORC1 inhibition alone (e.g. with everolimus) can set off a negative feedback mechanism via AKT signaling leading to resistance
- Vistusertib (AZD2014) is a dual inhibitor of both mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive)
- Vistusertib has demonstrated a broad range of activity in preclinical ER+ models, showing superior activity to Everolimus in hormone-sensitive and -resistant models

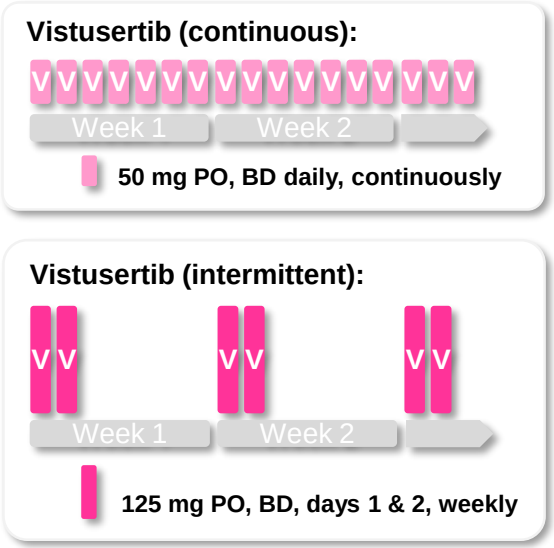


ET = endocrine therapy; ER+ = Estrogen receptor positive

Background

- Preclinical models suggest a relationship between higher exposure (AUC) of mTOR inhibitors and increased efficacy
- High-dose intermittent dosing can deliver greater pathway suppression; suppression is not continuous allowing for recovery of non-target tissues
- Vistusertib has a short half-life (mean $t_{1/2}$ = 3.3h) compared to other mTOR inhibitors; this enables high-dose intermittent schedules to be tolerated
- MANTA is the first randomised trial to compare efficacy and safety of intermittent versus continuous scheduling of a mTOR inhibitor

Treatment schedules



PO = orally; BD = twice daily; V = vistusertib

MANTA Study Design

Trial Sponsor: Queen Mary University of London

- ER+, HER2- ABC
- Postmenopausal
- Measurable or evaluable disease
- Disease resistant to AI
  - relapsed on or ≤12 months from adjuvant AI, or
  - progressed on AI in the advanced setting
- Max. 1 line of chemotherapy

R

n=90 → Fulvestrant + Vistusertib (Continuous daily schedule)

n=90 → Fulvestrant + Vistusertib (intermittent schedule; 2d on 5d off)

n=60 → Fulvestrant + Everolimus

n=60 → Fulvestrant

Stratification factors:
- Measurable Disease (vs non-measurable)
- Endocrine resistance (primary vs secondary)

Primary endpoint:
- Investigator-assessed PFS

Secondary endpoints:
- Response rates (ORR)
- Clinical benefit rate (CBR)
- Duration of response
- OS
- Safety

Secondary endocrine resistance is defined as
- **≥24 months of adjuvant ET before recurrence or**
- **CR or PR or SD for ≥24 weeks with ≥1 ET for MBC**

- **Fulvestrant: 500 mg i.m. injection on day 1, 15 & 29, and then q28 days**
- **Everolimus: 10 mg orally, once daily, continuous schedule**
- **Vistusertib (continuous): 50 mg orally, twice daily, continuous schedule**
- **Vistusertib (intermittent): 125 mg orally, twice daily, day 1&2 every week**

ET = endocrine therapy; ER = Estrogen Receptor, ABC = advanced breast cancer, AI = Aromatase inhibitor; PR/CR = Partial/Complete response, SD = stable disease, d = days; PFS = Progression-free survival

Statistical Design

- PFS by investigator assessment
  - Primary analysis: F+V_{cont} versus F
    - Median PFS from 3.7 to 11 months (HR: 0.40; 99.9% power, 1-sided α=5%)
    - Analysis at 130 PFS events
  - Secondary analysis: F+V_{cont} versus F+E
    - Median PFS from 7.4 to 11 months (HR: 0.67; 80% power, 1-sided α=10%)
    - Analysis at 120 PFS events
  - Exploratory analyses: F+V_{cont} versus F+V_{int} and F versus F+V_{int}
- Blinded independent central review (BICR)
  - Interim analysis subpopulation (73%)

Patient and Disease Characteristics

		F + V_{cont}	F + V_{int}	F	F + E
N		101	95	66	64
Endocrine Resistance, n (%)	Secondary Primary	86 (85) 15 (15)	83 (87) 12 (13)	55 (83) 11 (17)	58 (91) 6 (9)
Prior lines of therapy for ABC, n (%)	None 1 ≥2	38 (38) 30 (30) 33 (33)	41 (43) 29 (31) 25 (26)	24 (36) 25 (38) 17 (26)	24 (38) 20 (31) 20 (31)
Number of prior ET for ABC, n (%)	None 1 ≥2	44 (44) 45 (45) 12 (12)	45 (47) 36 (38) 14 (15)	29 (44) 27 (41) 10 (15)	27 (42) 25 (39) 12 (19)
Prior (neo)adjuvant chemotherapy, n (%)	Yes No	63 (62) 38 (38)	56 (59) 39 (41)	47 (71) 19 (29)	38 (59) 26 (41)
Prior metastatic chemotherapy, n (%)	Yes No	24 (24) 77 (76)	24 (25) 71 (75)	13 (20) 53 (80)	14 (22) 50 (78)

F = Fulvestrant; F+E = Everolimus; F+V(cont) = Vistusertib, continuous daily schedule; F+V(int) = Vistusertib, intermittent schedule; ABC = advanced breast cancer; ET = endocrine therapy;
Secondary endocrine resistance is defined as (i) ≥24 months of adjuvant ET before recurrence or (ii) CR or PR or SD for ≥24 weeks with ≥1 ET for MBC

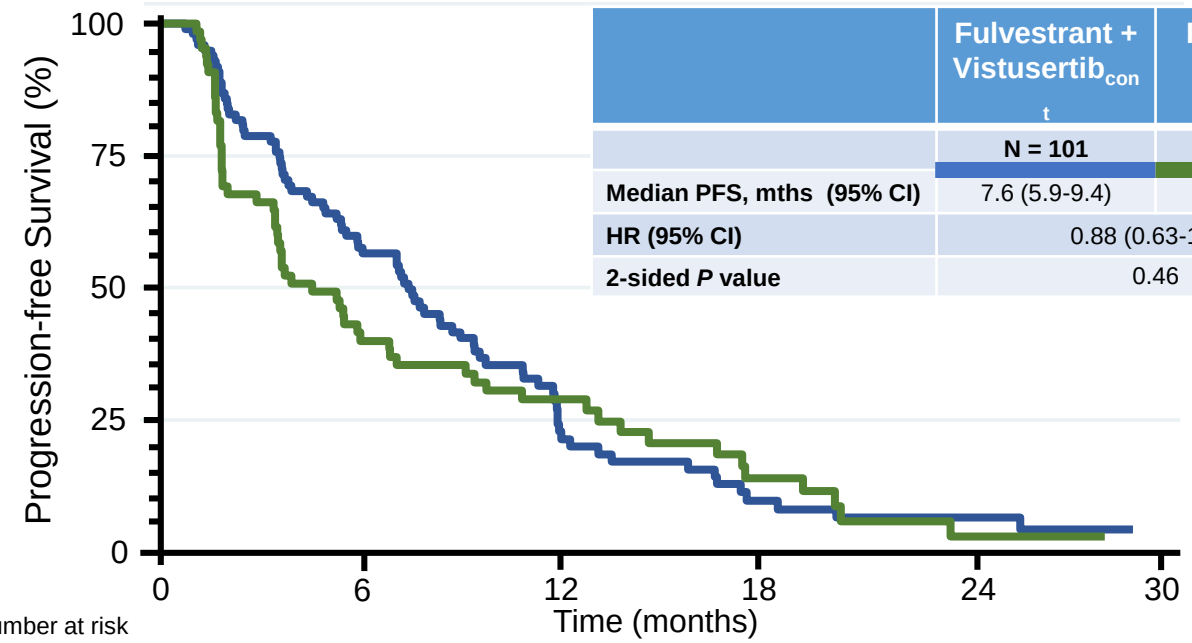
Safety (AEs occurring in ≥10%)

	F + V_{cont}		F + V_{int}		F		F + E	
	All grades	G3/4	All grades	G3/4	All grades	G3/4	All grades	G3/4
Asthenia (%)	34.8	2.2	45.7	5.4	16.1	0	53.3	3.3
Nausea (%)	31.5	0	68.5	3.3	12.5	0	26.7	0
Rash (%)	34.3	20.7	22.8	4.3	0	0	30.0	5.0
Stomatitis (%)	40.2	13.0	29.3	4.3	0	0	60.0	11.7
Diarrhoea (%)	25.0	2.2	35.9	5.4	5.4	0	31.7	1.7
Decreased appetite (%)	16.3	0	32.6	0	5.4	0	30.0	1.7
Vomiting (%)	12.0	1.1	40.2	5.4	0	0	11.7	0
Headache (%)	9.8	1.1	22.8	2.2	12.5	0	18.3	0
Pruritus (%)	23.9	2.2	12.0	3.3	1.8	0	16.7	0
Musculoskeletal pain (%)	9.8	1.1	16.3	2.2	10.7	0	13.3	0
Dry mouth (%)	13.0	0	12.0	0	3.6	0	20.0	0
Skin injury (%)	14.1	1.1	9.8	0	0	0	25.0	0
Infection (%)	15.2	5.4	10.9	1.1	3.6	0	16.7	6.7
Administration site reaction (%)	12.0	1.1	10.9	0	8.9	0	15.0	0
Oral pain (%)	10.9	3.3	12.0	0	0	0	21.7	0
Dysgeusia (%)	5.4	0	16.3	0	3.6	0	18.3	0

F = Fulvestrant; E = Everolimus; $F + V_{(cont)}$ = Vistusertib, continuous daily schedule;

Primary Endpoint: PFS (ITT Population)

Fulvestrant + Vistusertib$_{cont}$ versus Fulvestrant alone

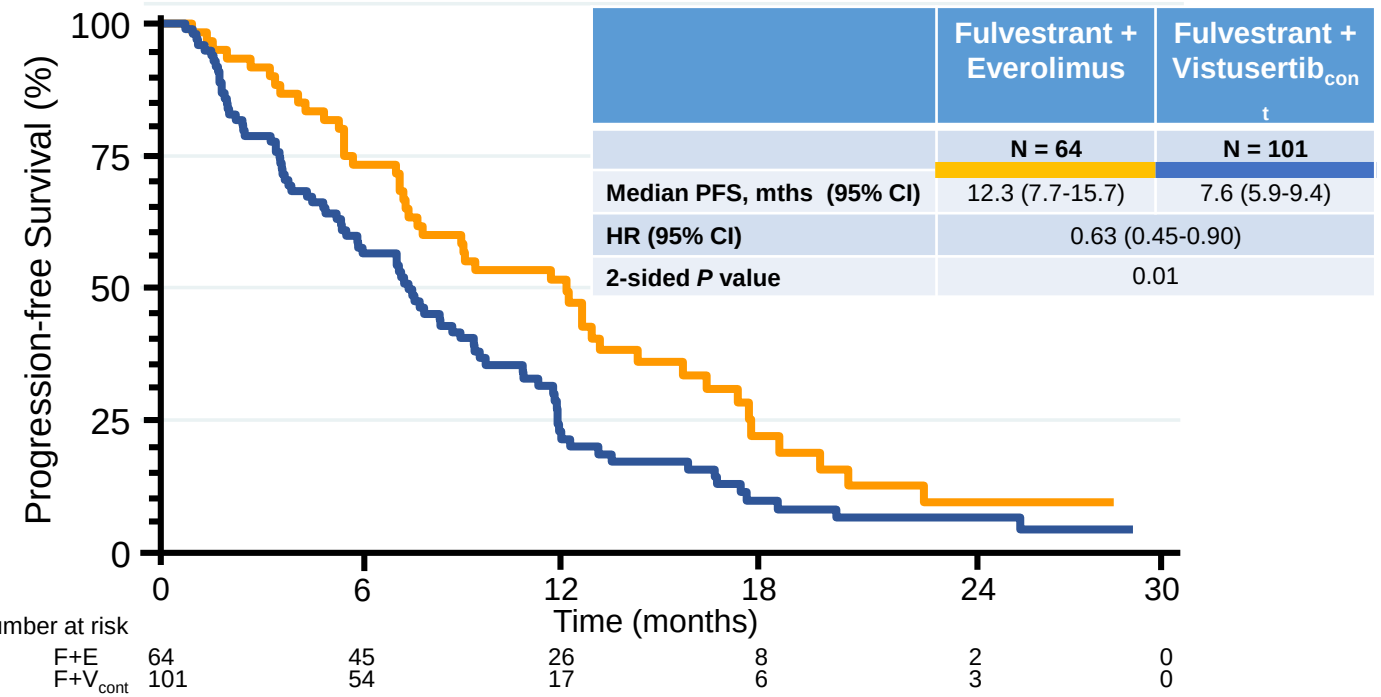


	Fulvestrant + Vistusertib$_{cont}$	Fulvestrant
	N = 101	N = 66
Median PFS, mths (95% CI)	7.6 (5.9-9.4)	5.4 (3.5-9.2)
HR (95% CI)	0.88 (0.63-1.24)	
2-sided *P* value	0.46	

F = Fulvestrant; F+V(cont) = Vistusertib, continuous daily schedule;
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; PFS = progression-free survival

Primary Endpoint: PFS (ITT Population)

Fulvestrant + Everolimus versus Fulvestrant + Vistusertib$_{cont}$

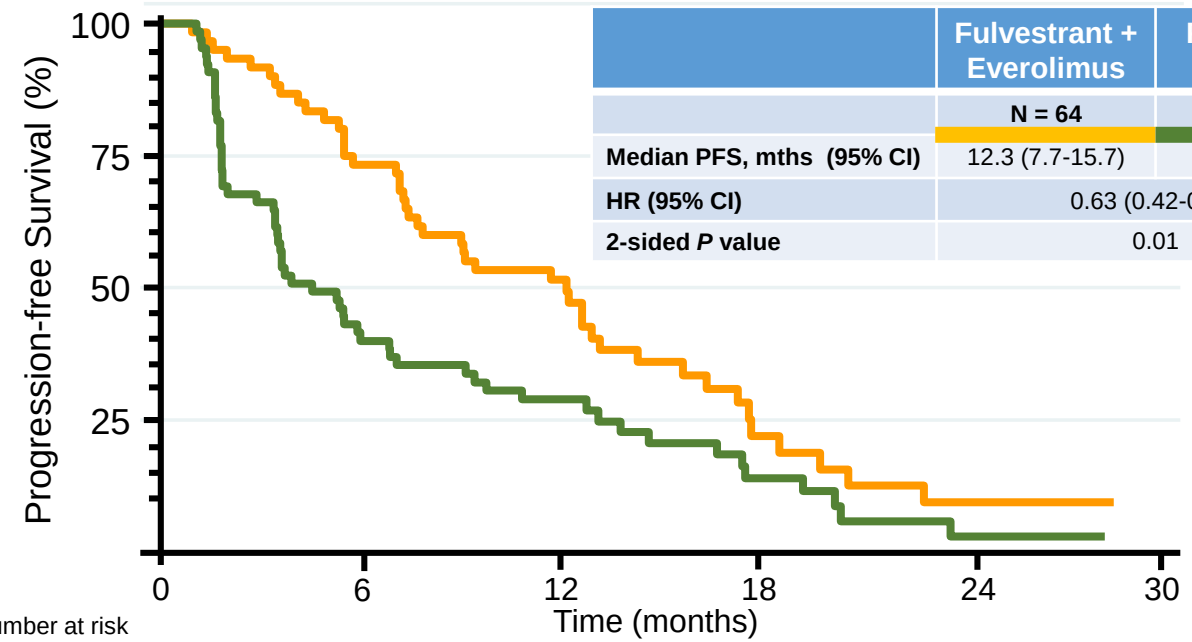


	Fulvestrant + Everolimus	Fulvestrant + Vistusertib$_{cont}$
	N = 64	N = 101
Median PFS, mths (95% CI)	12.3 (7.7-15.7)	7.6 (5.9-9.4)
HR (95% CI)	0.63 (0.45-0.90)	
2-sided *P* value	0.01	

F+E = Everolimus; F+V(cont) = Vistusertib, continuous daily schedule;
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; PFS = progression-free survival

Primary Endpoint: PFS (ITT Population)

Fulvestrant + Everolimus versus Fulvestrant

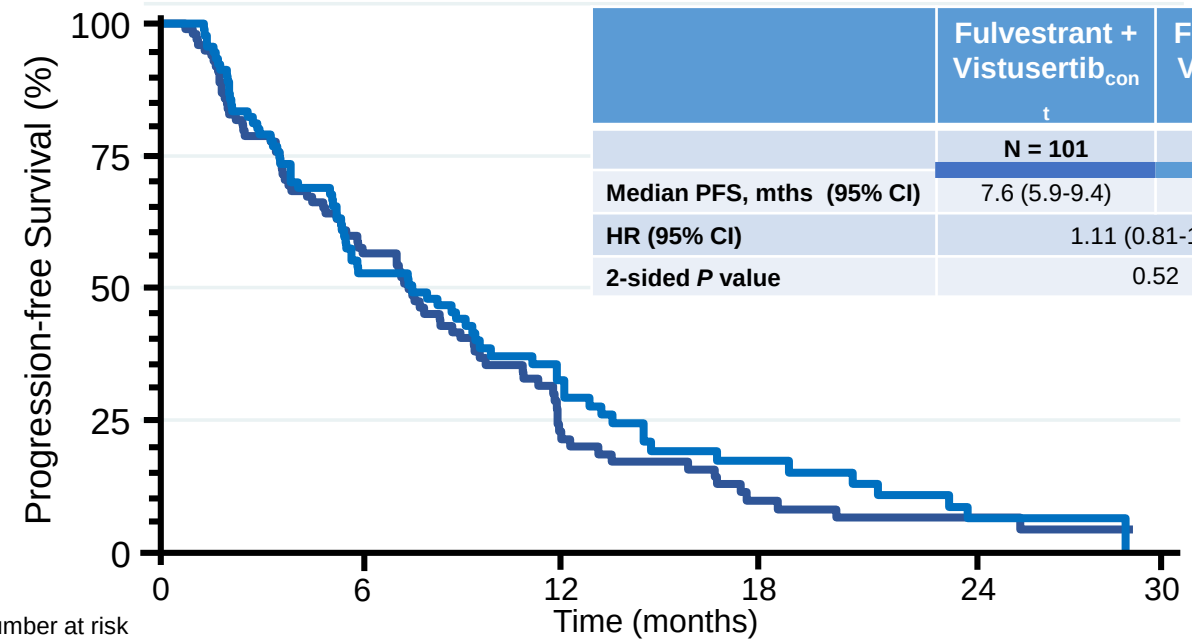


	Fulvestrant + Everolimus	Fulvestrant
	N = 64	N = 66
Median PFS, mths (95% CI)	12.3 (7.7-15.7)	5.4 (3.5-9.2)
HR (95% CI)	0.63 (0.42-0.92)	
2-sided *P* value	0.01	

F = Fulvestrant; F+E = Everolimus;
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; PFS = progression-free survival

Primary Endpoint: PFS (ITT Population)

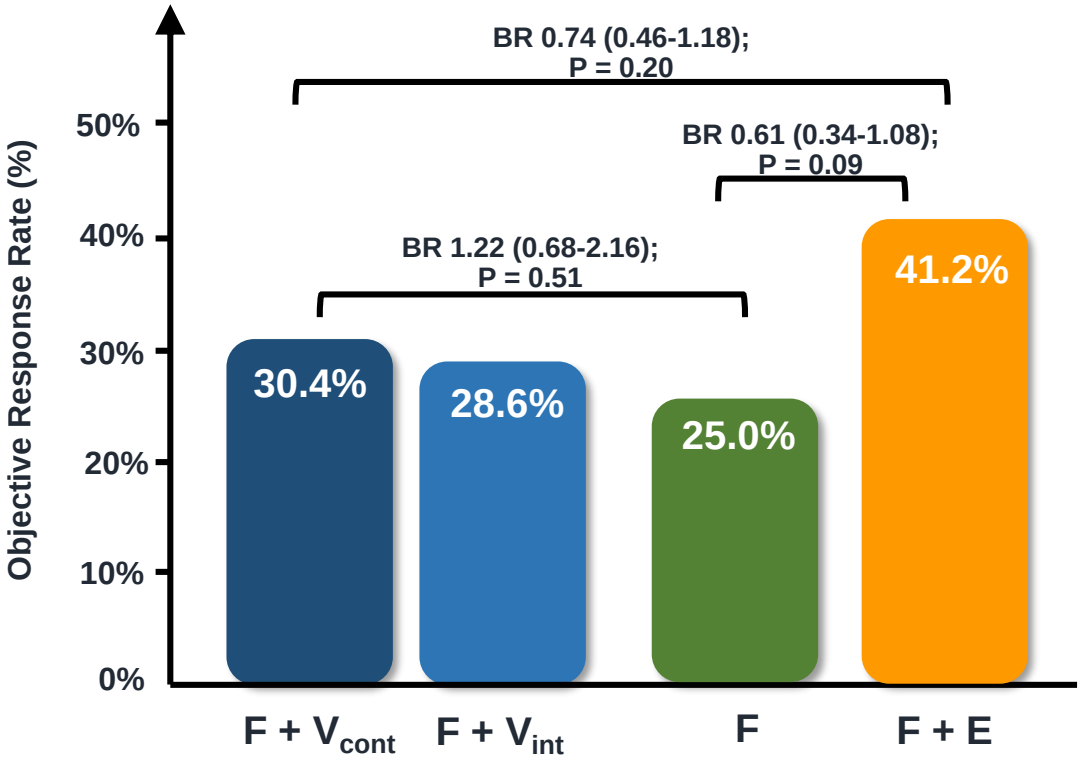
Fulvestrant + Vistusertib$_{cont}$ versus Fulvestrant + Vistusertib$_{int}$



	Fulvestrant + Vistusertib$_{cont}$	Fulvestrant + Vistusertib$_{int}$
	N = 101	N = 95
Median PFS, mths (95% CI)	7.6 (5.9-9.4)	8.0 (5.6-9.9)
HR (95% CI)	1.11 (0.81-1.52)	
2-sided *P* value	0.52	

F+V(cont) = Vistusertib, continuous daily schedule; F+V(int) = Vistusertib, intermittent schedule (2 days on, 5 days off);
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; mths = months; PFS = progression-free survival

Objective Response Rates



F = Fulvestrant; F+E = Everolimus; F+V(cont) = Vistusertib, continuous daily schedule; F+V(int) = Vistusertib, intermittent schedule (2 days on, 5 days off); BR = benefit ratio; P=2-sided p-value; PP = per-protocol

Summary and Conclusions

- The combination of Everolimus + Fulvestrant demonstrated improved PFS compared to Vistusertib + Fulvestrant (median PFS 12.3 vs 7.6 mths, HR 0.63) and to Fulvestrant (median PFS 12.3 vs 5.4 mths, HR 0.63)
- In the ITT population, the addition of Vistusertib to Fulvestrant failed to show a significant PFS improvement (median PFS 7.6 vs 5.4 mths, HR 0.88)
- Continuous daily and intermittent high-dose scheduling of Vistusertib resulted in similar anti-tumour activity
- Intermittent scheduling of Vistusertib associated with lower rate of rash or stomatitis but higher rate of nausea/vomiting

Agenda

- Perioperative endocrine therapy- POETIC
- Metastatic Disease- MONALEESA-7, MANTA, MONARCH 2/3
- Adjuvant Endocrine Therapy- ABCSG-16, SOFT/TEXT update
- CDK4/6 Inhibitors in the elderly

A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial

Professor Michael Gnant, MD, FACS
Medical University of Vienna, Vienna, Austria

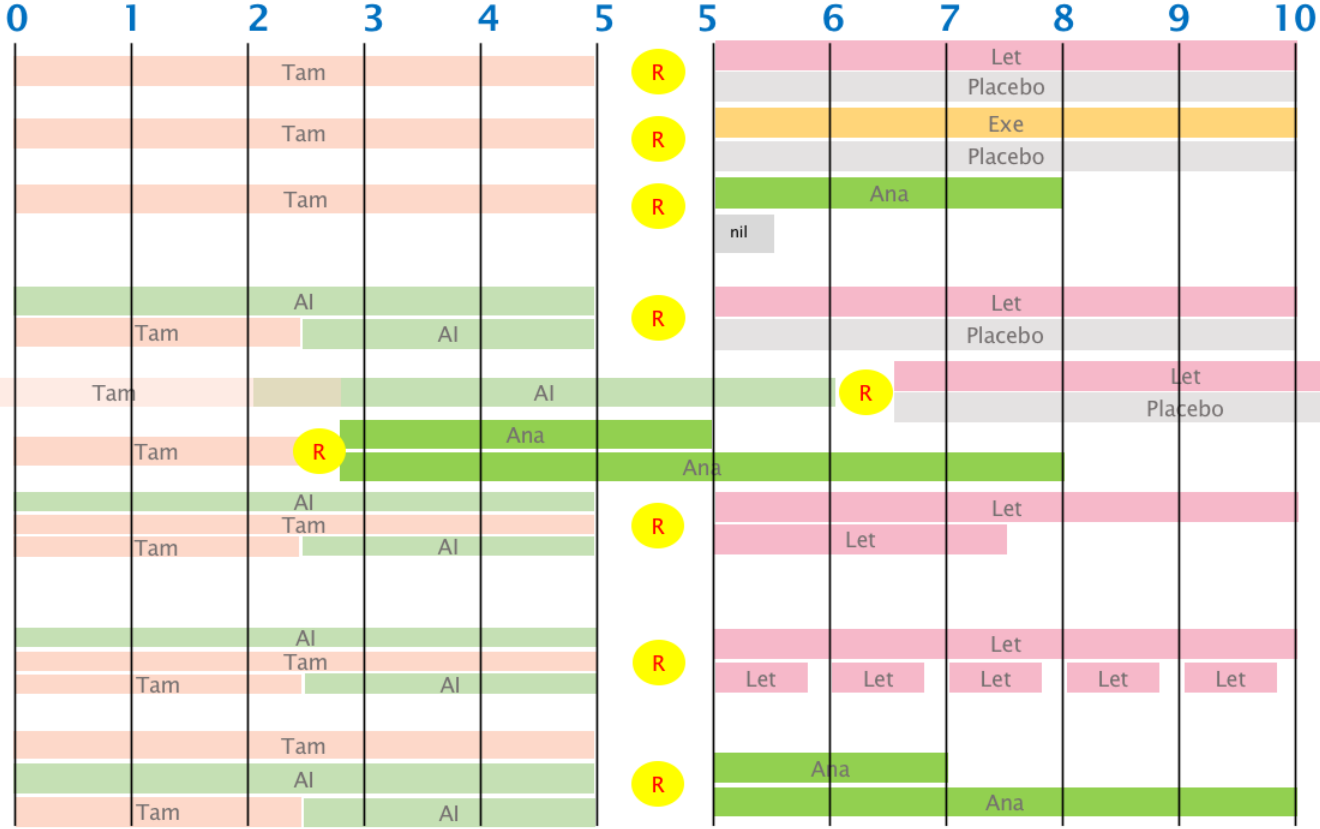
Michael Gnant, Guenther Steger, Richard Greil, Florian Fitzal, Brigitte Mlineritsch, Diether Manfreda, Christoph Tausch, Marija Balic, Peter Dubsky, Martin Moik, Josef Thaler, Daniel Egle, Vesna Bjelic-Radisic, Ursula Selim, Ruth Exner, Christian Singer, Elisabeth Melbinger-Zeinitzer, Ferdinand Haslbauer, Herbert Stoeger, Ruth Helfgott, Paul Sevelda, Harald Trapl, Viktor Wette, Lidija Soelkner, Raimund Jakesz, on behalf of the Austrian Breast and Colorectal Cancer Study Group

ABCSG-16 Background:

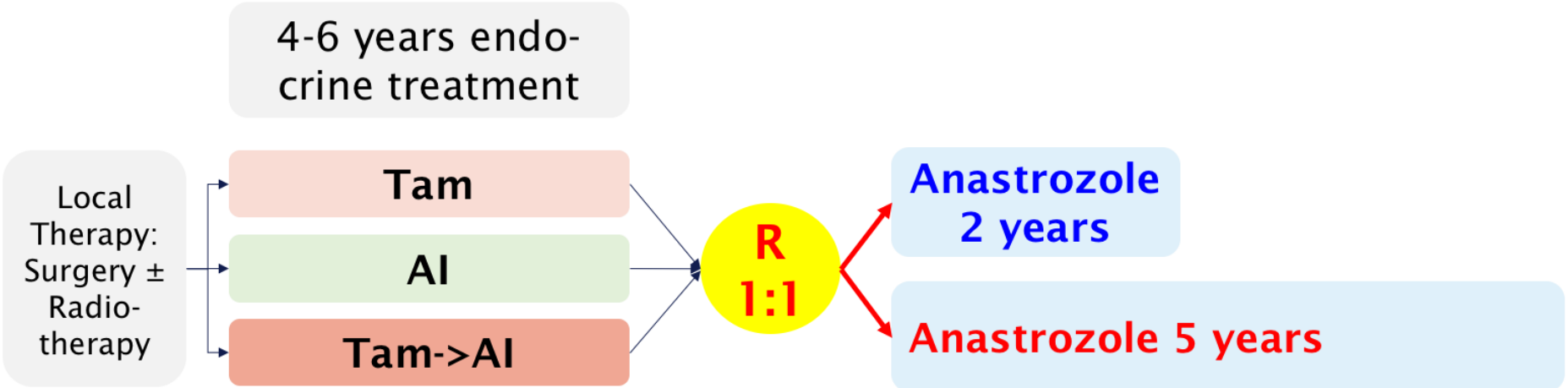
- HR+ Breast Cancer shows significant long-term risk of relapse:
  - >50 % of disease relapses occur after the first 5 years of follow-up
  - Since the risk of recurrence persists, extending adjuvant therapy is appealing
- On average...:
  - Aromatase inhibitors for 5 years are better than Tamoxifen for 5 years, but sequencing Tam and AI is an alternative to 5 years of AI
  - Prolonging Tamoxifen (after Tam) is beneficial in premenopause
  - In postmenopausal women, adding additional AI after early Tamoxifen is beneficial
    - Significant benefits after 5 years of Tamoxifen (MA17, NSABP-B33, ABCSG-6a)
    - Borderline/no benefit after previous 2-5 years of AI (MA17R, NSABP-B42, DATA, IDEAL)
  - Extended intermittent Letrozole is not worse than continuous Letrozole (SOLE)
- What is the optimal duration of extended adjuvant AI?

Pan H et al. N Engl J Med 2017; 377:1836-1846. EBCTCG. Lancet 2015; 386:1341-52 Davies C, et al. Lancet 2013: 381:805-16. Goss PE et al. JNCI 2005; 97:1262-71 Jakesz R et al. Lancet 2005; 366:455-62. Goss PE et al. N Engl J Med. 2016; 375: 209-19. Blok EJ, et al. J Natl Cancer Inst 2018 January 1 (Epub ahead of print). Tjan-Heijnen VCG, et al. Lancet Oncol 2017 October 11 Mamounas EP et al, Cancer Res 2017. Regan M, et al. Lancet Oncology 2017; online Nov 17

Extending Adjuvant AIs



ABCSG-16 Trial Design



N=3,484

Postmenopausal, HR+, T1-3, N0/N+, M0

Recruitment in 75 centers in Austria, 2004-2010

Median Follow-Up: 106.2 months (102.7-107.7)

Michael Gnant, MD, FACS

ABCSG-16 Study Objectives and End Points

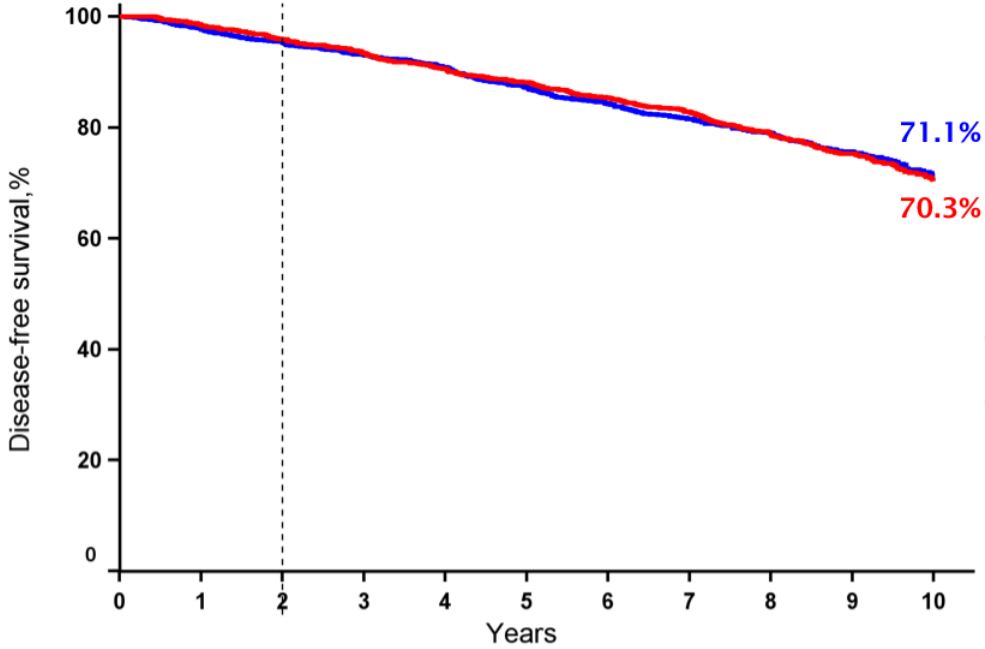
- **Study Objective**
  - Assessing the outcome effects of **additional 2 years *versus* additional 5 years of Anastrozole** after 5 years of adjuvant endocrine therapy
- **Primary endpoint**
  - **Disease free survival (DFS)** - defined as time to any evidence of local or distant metastases, contralateral breast cancer, secondary carcinoma, or death from any cause

    Two types of analyses: starting at randomization and starting two years after randomization (when treatment arms differ)
- **Secondary endpoints**
  - Overall survival (OS) - defined as time to death from any cause (from randomization and 2 years after)
  - Time to contralateral breast cancer – starting at randomization
  - Time to second primary cancer – starting at randomization
  - Time to first clinical fracture – starting two years after randomization

Michael Gnant, MD, FACS

ABCSG-16 Disease-Free Survival

Time from randomization to first DFS event

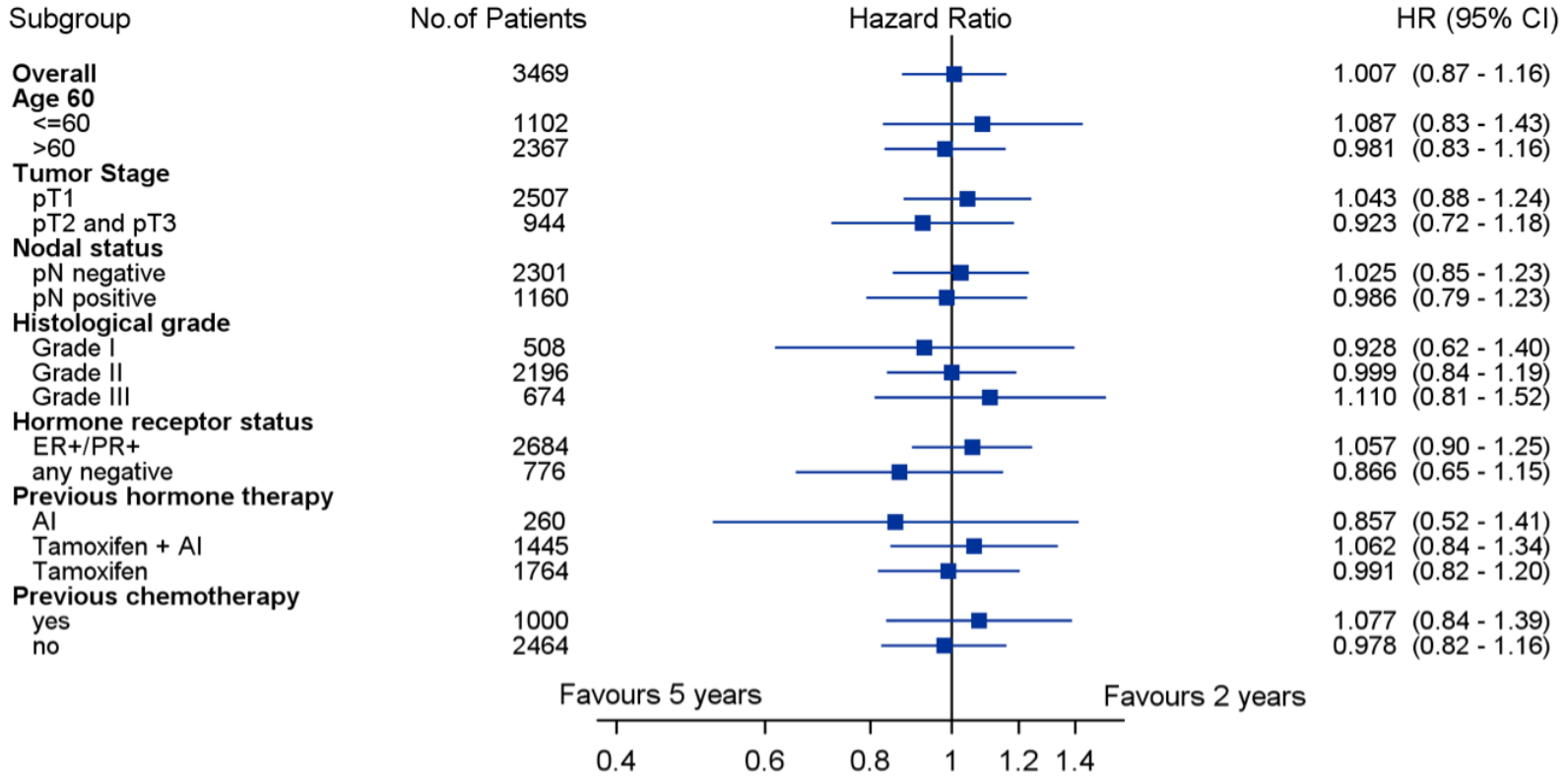


Patients at risk:

2 years	1731	1651	1601	1538	1477	1368	1206	990	741	540	214
5 years	1738	1667	1605	1551	1485	1399	1233	1026	779	554	209

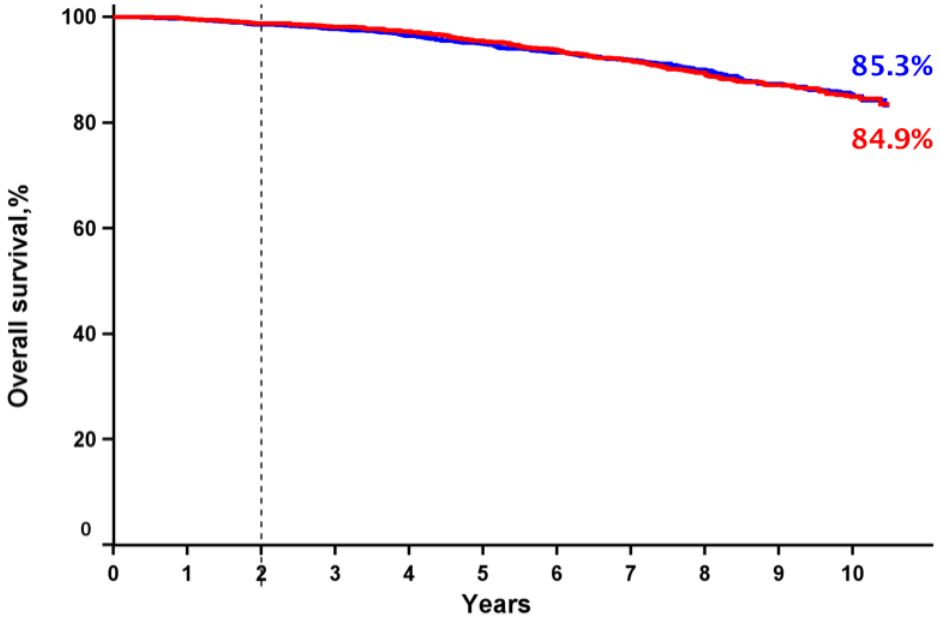
	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	378/1,731	1.007 (0.87, 1.16)	0.925
5 years	384/1,738		

ABCSG-16 DFS Subgroups



ABCSG-16 Secondary End Point: Overall Survival

Time from randomization to death from any cause



Patients at risk:

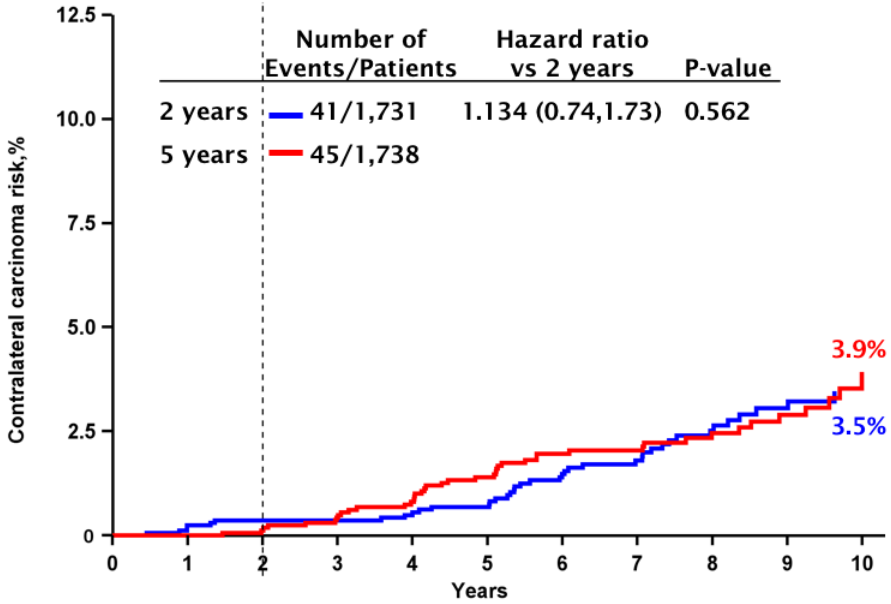
2 years	1731	1689	1661	1626	1594	1518	1352	1125	901	701	381
5 years	1738	1694	1659	1637	1606	1533	1362	1156	920	710	361

	Number of Events/Patients	Hazard ratio vs 2 years	P-value
2 years	192/1,731	1.007 (0.82,1.23)	0.947
5 years	194/1,738		

Michael Gnant, MD, FACS

ABCSG-16 Secondary End Points

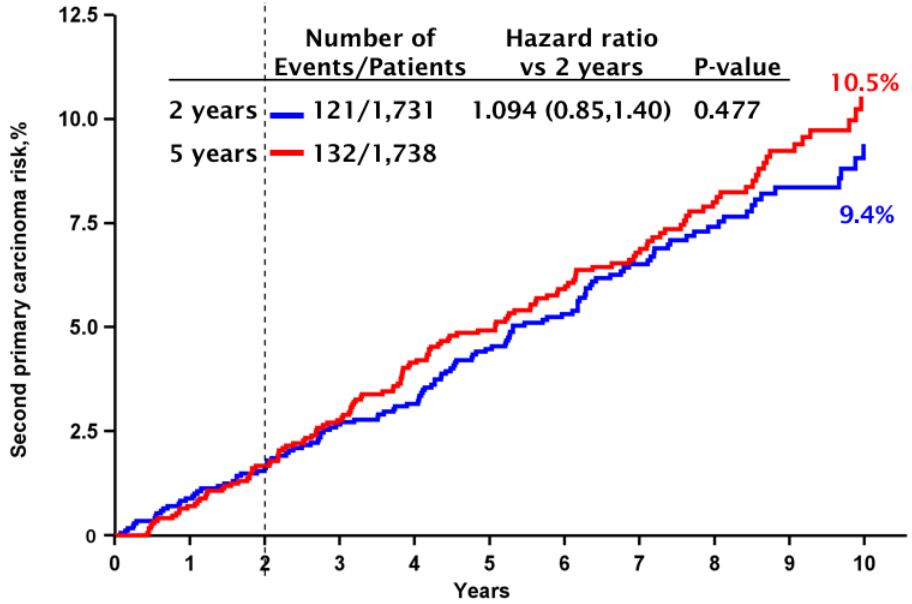
Contralateral Breast Cancer



Patients at risk:

2 years	1731	1662	1629	1585	1528	1448	1282	1058	794	588	252
5 years	1738	1676	1639	1602	1539	1454	1279	1065	821	599	235

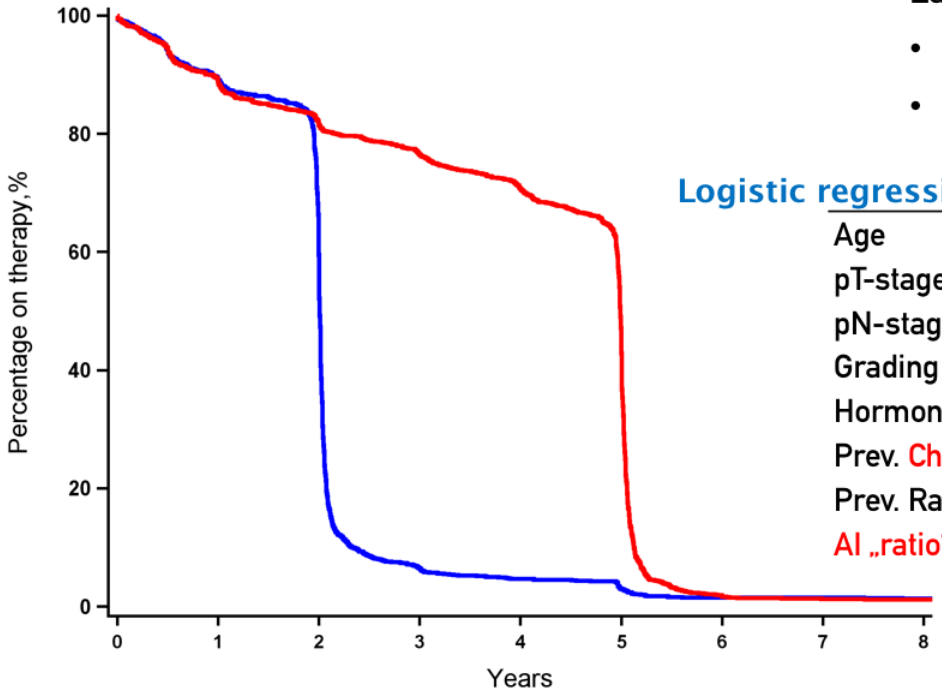
Secondary Primary Cancer



Patients at risk:

2 years	1731	1656	1616	1559	1502	1417	1261	1040	785	583	245
5 years	1738	1668	1618	1571	1502	1424	1253	1043	800	583	229

ABCSG-16 Treatment Adherence

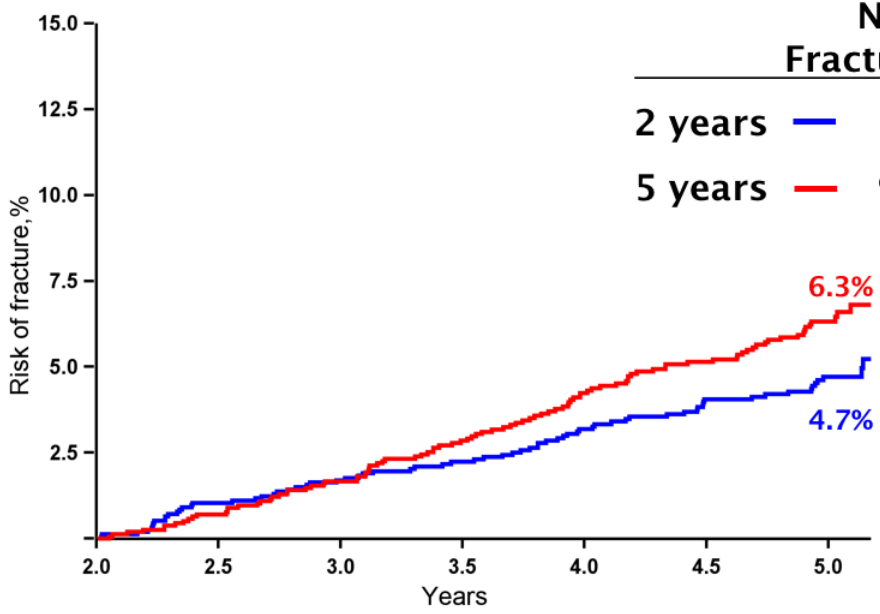


	2 years	5 years
Early/late EOT	421 (24.3%)	706 (40.6%)
• without event	356 (20.6%)	567 (32.6%)
• for DFS event	65 (3.8%)	139 (8.0%)

Logistic regression: Non-Adherent *vs* Adherent		Odds Ratio (95% CI)	P-value
Age	>60 vs ≤60	1.07 (0.89, 1.29)	0.4454
pT-stage	pT2/pT3 *vs* pT1/pTX	1.01 (0.83, 1.22)	0.9560
pN-stage	positive *vs* negative	0.93 (0.77, 1.12)	0.4187
Grading	G3 *vs* G1/G2/GX	1.21 (0.98, 1.51)	0.0806
Hormone Receptor	ER+/PR+ vs any neg.	0.91 (0.75, 1.10)	0.3190
Prev. Chemotherapy	yes *vs* no	0.79 (0.63, 0.98)	0.0303
Prev. Radiotherapy	yes *vs* no	1.10 (0.90, 1.35)	0.3660
AI „ratio“	continuous	0.65 (0.49, 0.86)	0.0030

Adherent patients:
all patients on treatment for 5 (±0.5) years in 5-years arm
all patients on treatment for 2 (±0.5) years in 2-years arm
all patients with DFS event during their treatment phase

ABCSG-16 Fractures



	Number of Fractures/Patients	Hazard ratio vs 2 years	P-value
2 years	71/1,556	1.353 (1.00,1.84)	0.053
5 years	98/1,571		

Patients at risk:

2 years	1556	1515	1480	1439	1386	1313	843
5 years	1571	1549	1514	1477	1416	1347	857

ABCSG-16 Summary

- In postmenopausal hormone-receptor positive breast cancer patients receiving 5 years of standard adjuvant endocrine therapy (Tamoxifen, Aromatase Inhibitor, sequence), additional 5 years of Anastrozole **did not improve disease-free survival** as compared to additional 2 years of Anastrozole.
- ABCSG-16 did not show a difference between additional 2 years versus additional 5 years of Anastrozole in terms of secondary end points
  - Overall survival (OS)
  - Time to contralateral breast cancer
  - Time to second primary cancer
- There were **more fractures** in the study arm of 5 additional years of Anastrozole.

Conclusion and Perspectives

- After 5 years of standard endocrine therapy, 2 additional years of Anastrozole are sufficient – there is no benefit of continuing/escalating endocrine treatment beyond 7 years.
- This is also true for those patients who are adherent to extended therapy (presumably a tolerability-“priviledged“ subgroup).
- Extension of Anastrozole treatment to 5 additional years leads to increased side effects including fractures, and should be avoided.
- In the future, translational research may identify molecular characteristics that indicate benefit of prolonged extended therapy.

Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with HR+ Early Breast Cancer: Update Of The Combined TEXT and SOFT Trials

Prudence Francis

on behalf of Olivia Pagani, MD

TEXT and SOFT Investigators and

International Breast Cancer Study Group (IBCSG)

TEXT and SOFT Designs

TEXT

TAMOXIFEN AND EXEMESTANE TRIAL
(N=2672)

Enrolled: Nov03-Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo
  OR planned chemo

RANDOMIZE

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

SOFT

SUPPRESSION OF OVARIAN FUNCTION TRIAL
(N=3066)

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo

OR

- Remain premenopausal ≤ 8 mos after chemo

RANDOMIZE

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Joint Analysis (N=4690)

Tamoxifen+OFS x 5y

Exemestane+OFS x 5y

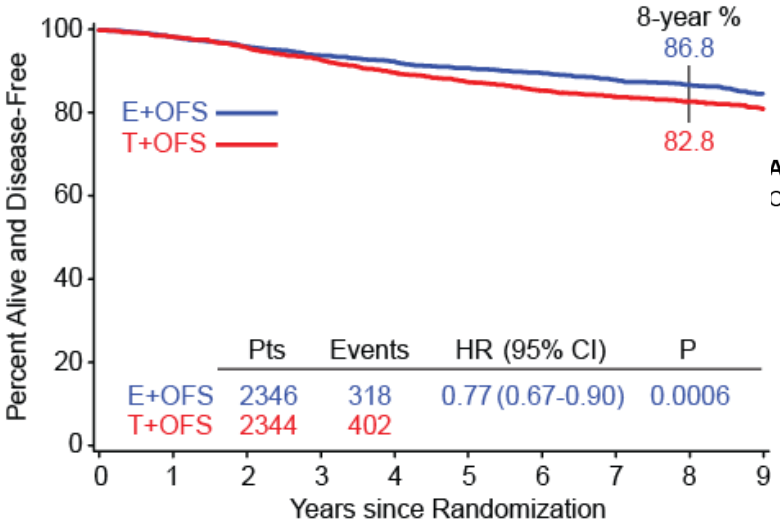
Median follow-up 9 years

OFS=ovarian function suppression

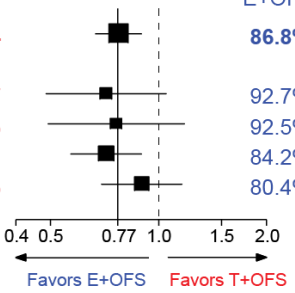
Patient Characteristics

	No chemo TEXT (N=1053)	No chemo SOFT (N=943)	Chemo TEXT (N=1607)	Prior chemo SOFT (N=1087)	Overall (N=4690)
Age <40 yr	16%	9%	30%	49%	27%
LN +	21%	8%	66%	57%	42%
T-size >2cm	19%	15%	53%	47%	36%
HER2 +	5%	3%	17%	20%	12%
Surgery to random. (median)	1.5 mo	1.8 mo	1.2 mo	8.0 mo	1.6 mo

Sustained Improvement in DFS



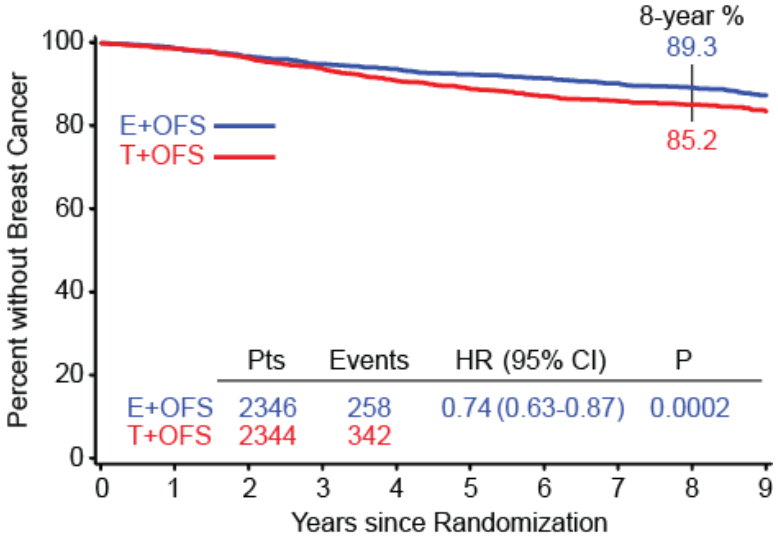
	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	Hazard Ratio	8-Year DFS E+OFS	8-Year DFS T+OFS	Difference
All Patients	**318**	**2346**	**402**	**2344**		**86.8%**	**82.8%**	**+ 4.0%**
Cohort								
No Chemotherapy TEXT	44	526	62	527		92.7%	89.1%	+ 3.6%
No Chemotherapy SOFT	35	470	47	473		92.5%	90.6%	+ 1.9%
Chemotherapy TEXT	131	806	173	801		84.2%	78.2%	+ 6.0%
Prior Chemotherapy SOFT	108	544	120	543		80.4%	76.7%	+ 3.7%



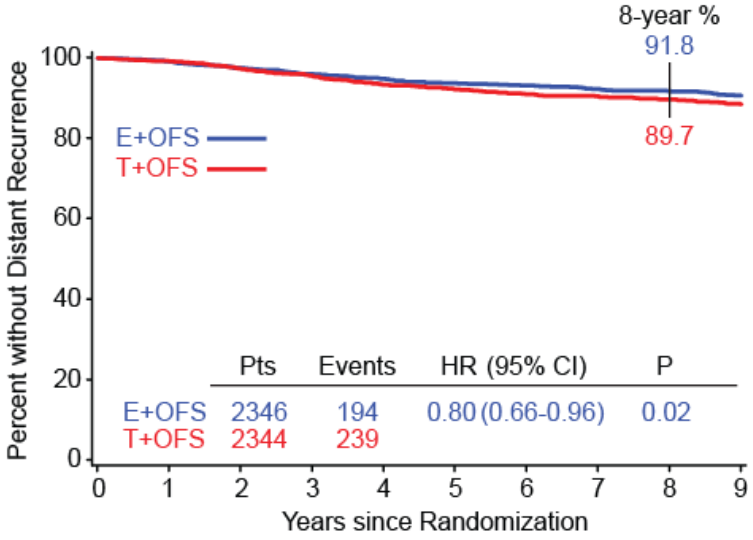
4.0% absolute improvement in 8-yr DFS for E+OFS after 9 years median follow-up

Significant Reductions in Recurrence

Breast Cancer-Free Interval



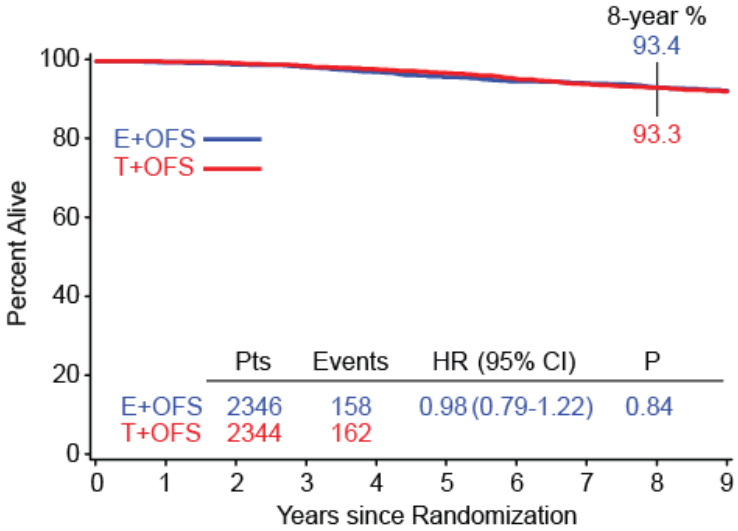
Distant Recurrence-Free Interval



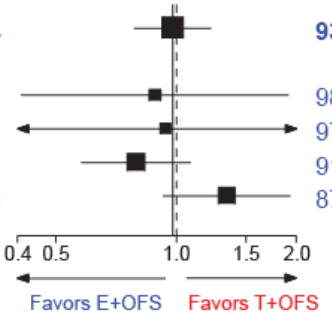
4.1% absolute improvement in 8-yr freedom from breast cancer for E+OFS

2.1% absolute improvement in 8-yr freedom from distant recurrence for E+OFS

Overall Survival



	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year OS E+OFS	8-Year OS T+OFS
All Patients	**158**	**2346**	**162**	**2344**	**93.4%**	**93.3%**
Cohort						
No Chemotherapy TEXT	12	526	14	527	98.4%	98.1%
No Chemotherapy SOFT	9	470	10	473	97.7%	97.9%
Chemotherapy TEXT	70	806	87	801	91.7%	90.1%
Prior Chemotherapy SOFT	67	544	51	543	87.2%	89.4%



E+OFS did <u>not</u> improve Overall Survival vs T+OFS, after 9 years median follow-up

HER2 Status

- HER2-negative and HER2-positive cancers are now considered clinically relevant subgroups for treatment decision-making

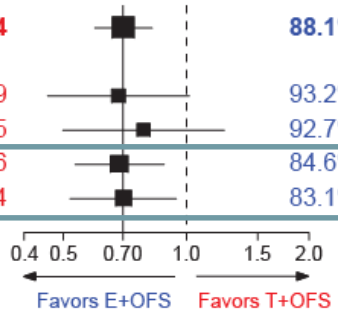
- The HER2-negative subgroup was the large majority of the trials' population: 4035 patients (86%)

- Results for the HER2-positive subgroup require further investigation:
  - Trials enrolled both before and after use of adjuvant trastuzumab

HER2-negative Patients (N=4035)

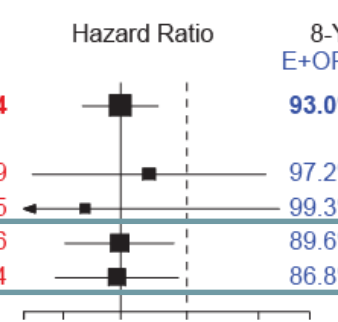
DFS

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DFS E+OFS	8-Year DFS T+OFS	Difference
All Patients	**250**	**2011**	**350**	**2024**	**88.1%**	**82.7%**	**+ 5.4%**
Cohort							
No Chemotherapy TEXT	40	492	59	499	93.2%	89.1%	+ 4.1%
No Chemotherapy SOFT	33	447	42	445	92.7%	91.3%	+ 1.4%
Chemotherapy TEXT	105	661	144	656	84.6%	77.7%	+ 6.9%
Prior Chemotherapy SOFT	72	411	105	424	83.1%	73.9%	+ 9.2%



DRFI

	E+OFS Events	E+OFS Pts	T+OFS Events	T+OFS Pts	8-Year DRFI E+OFS	8-Year DRFI T+OFS	Difference
All Patients	**144**	**2011**	**209**	**2024**	**93.0%**	**89.6%**	**+ 3.4%**
Cohort							
No Chemotherapy TEXT	16	492	20	499	97.2%	96.5%	+ 0.7%
No Chemotherapy SOFT	5	447	9	445	99.3%	98.3%	+ 1.0%
Chemotherapy TEXT	70	661	98	656	89.6%	84.6%	+ 5.0%
Prior Chemotherapy SOFT	53	411	82	424	86.8%	79.8%	+ 7.0%



- Consistent relative treatment effects in all cohorts
- Larger absolute benefits of E+OFS in chemo cohorts
- Overall Survival HR=0.86 (0.68-1.10)

Selected Adverse Events (all patients)

	E + OFS (N=2317)	T + OFS (N=2326)
Endometrial cancer	**n=4**	**n=9**
Musculoskeletal symptoms (G3-4)	**11%**	**6%**
Osteoporosis (G2-4; T score< -2.5)	**15%**	**7%**
Fractures (G3-4)	**1.6%**	**1.0%**
Hot Flashes (G3)	10%	12%
Libido decrease (G2)	15%	12%
Vaginal dryness (G2)	27%	22%
Depression (G3-4)	4.1%	4.6%
Thrombosis/embolism (G2-4)	**1.2%**	**2.3%**

Adverse Events and Treatment Adherence

- Incidence of grade 3-4 targeted AEs was similar in the two groups (32% and 31%)

- Overall, 15% of patients stopped all protocol-assigned treatment early

  More patients on E+OFS stopped assigned oral ET early

  - 14% vs 6% by 1 year
  - 25% vs 19% by 4 years

  No difference in the rate of triptorelin cessation

  - 18% vs 19% by 4 years

Conclusions

- After longer follow-up (median 9 years), results confirm statistically significant improvements in disease outcomes with E+OFS
- Adjuvant E+OFS, compared with T+OFS, shows a sustained absolute improvement in DFS (4%) and reduction in distant recurrence (2.1%)
- In patients with HER2-negative tumors (86% of the population) E+OFS improved disease outcomes in all treatment cohorts
- For HER2-negative deemed at sufficient risk to receive chemotherapy, clinically meaningful benefits are observed with E+OFS, with absolute improvements in DFS of 7% - 9%, and absolute improvements in DRFI of 5% - 7%, across TEXT and SOFT respectively

Randomized Comparison of Adjuvant Tamoxifen plus Ovarian Function Suppression vs Tamoxifen in Premenopausal Women with HR+ Early Breast Cancer: Update of the SOFT Trial

Gini Fleming, MD

on behalf of SOFT Investigators and

International Breast Cancer Study Group (IBCSG)

SOFT: Suppression of Ovarian Function Trial

Enrolled: Dec 2003-Jan 2011

Stratification

Receipt of (neo)adjuvant chemotherapy

-No chemo, enrolled within 12 weeks of surgery (47%)
-Prior chemo, premenopausal E2 level within 8 months (53%)

Nodal status

-Positive (34.5%)

OFS method intended

-Triptorelin (91%)

RANDOMIZE

Median follow-up 8 years

Tamoxifen x 5y (n=1018)

Tamoxifen+OFS x 5y (n=1015)

Exemestane+OFS x 5y (n=1014)

OFS=Ovarian Function Suppression

Patient Characteristics

	No Chemotherapy N=1419	Prior Chemotherapy N=1628	All N=3047
Age (median)	46 yr	40 yr	43 yr
<35 years	**1.5%**	**20.2%**	11.5%
Nodal status			
positive	**8.8%**	**56.9%**	34.5%
negative	91.2%	43.1%	65.5%
Grade			
1	39.7%	13.8%	25.9%
2	52.8%	49.5%	51.0%
3	**6.5%**	**33.7%**	21.0%
HER2+	**3.7%**	**19.2%**	12.0%

Endpoints

Primary:

- **Disease-free survival (DFS)**
  - Invasive recurrence (local, regional, distant)
  - Invasive contralateral breast cancer
  - Second (non-breast) invasive malignancy
  - Death without prior cancer event

Secondary:

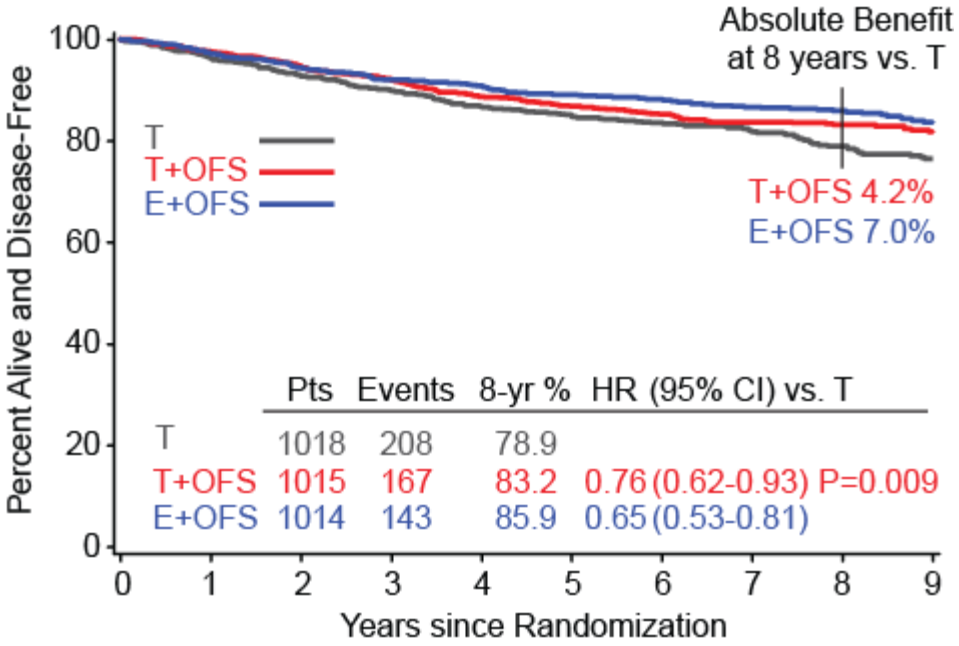
- **Breast cancer-free interval (BCFI)**
  - Invasive recurrence or contralateral breast cancer
- **Distant recurrence-free interval (DRFI)**
  - Distant recurrence
- **Overall survival (OS)**
  - Death from any cause

SOFT Primary Results

- After 5.6 years median follow-up, the primary results of SOFT found adding OFS to T did not provide a significant benefit in the overall study population of premenopausal women with HR+ BC *(NEJM 2015)*
- For those women at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of OFS improved disease outcomes
- Follow-up was immature for overall survival
- We report a planned update after 8 years median follow-up

SOFT DFS

8 years median follow-up



T+OFS significantly improves DFS vs T-alone in the overall population

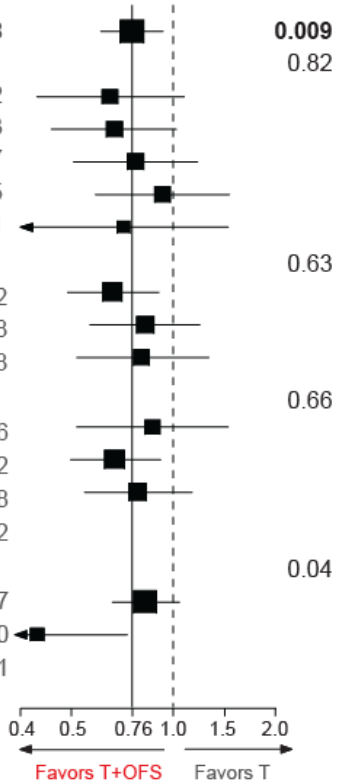
SOFT DFS

8 years median follow-up

	8-yr DFS T	8-yr DFS T + OFS	HR: T + OFS vs T	8-yr DFS E + OFS	HR: E + OFS vs T
All	**78.9%**	**83.2%**	0.76 (0.62-0.93)	**85.9%**	0.65 (0.53-0.81)
No chemo	**87.4%**	**90.6%**	0.76 (0.52-1.12)	**92.5%**	0.58 (0.38-0.88)
Prior chemo	**71.4%**	**76.7%**	0.76 (0.60-0.97)	**80.4%**	0.68 (0.53-0.88)
<35 years (n=350)	**64.3%**	**73.0%**	0.66 (0.41-1.07)	**77.4%**	0.52 (0.31-0.87)

SOFT DFS: According to Subgroups

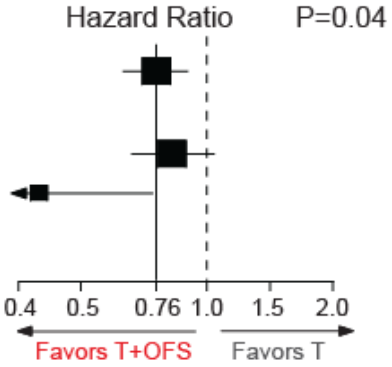
	T+OFS Events	T+OFS Pts	T Events	T Pts	P-Value
All Patients	**167**	**1015**	**208**	**1018**	**0.009**
Age at Randomization					0.82
< 35	30	121	37	112	
35 - 39	40	184	56	203	
40 - 44	43	311	54	307	
45 - 49	40	301	42	305	
50+	14	98	19	91	
Lymph Node Status					0.63
pN0	73	662	103	112	
pN+ 1-3	53	257	64	258	
pN+ 4+	41	96	41	98	
Tumor Grade					0.66
1	29	266	34	276	
2	78	518	101	492	
3	57	212	69	228	
Unknown	3	19	4	22	
HER2 Status					0.04
Negative	147	868	168	117	
Positive	16	119	31	860	
Unknown	4	28	9	41	



SOFT DFS: Effect of HER2 Status

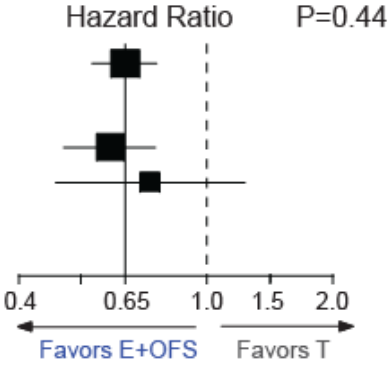
T + OFS vs T

	T+OFS Events	T+OFS Pts	T Events	T Pts
All Patients	167	1015	208	1018
HER2 Status				
Negative	147	868	168	860
Positive	16	119	31	117
Unknown	4	28	9	41



E + OFS vs T

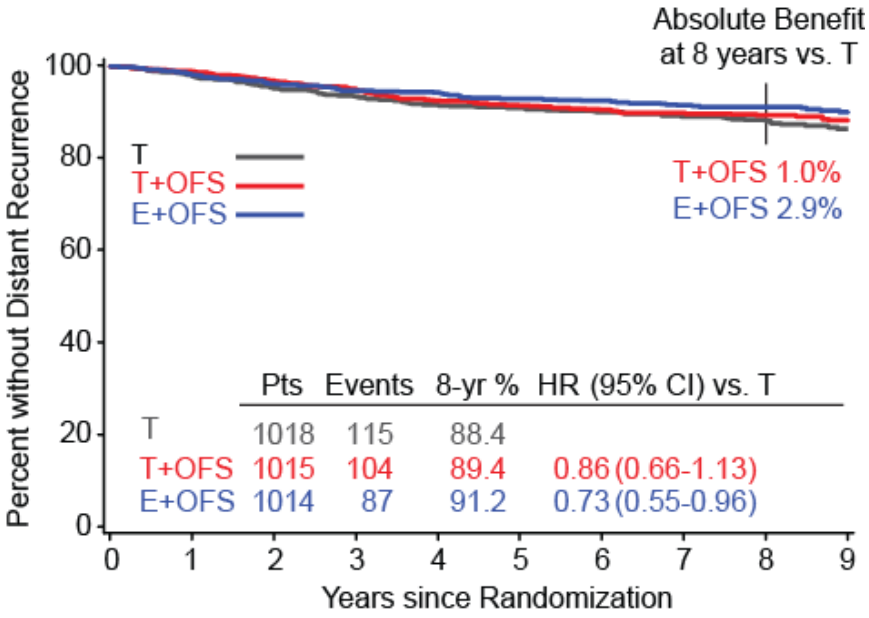
	E+OFS Events	E+OFS Pts	T Events	T Pts
All Patients	143	1014	208	1018
HER2 Status				
Negative	105	858	168	860
Positive	31	130	31	117
Unknown	7	26	9	41



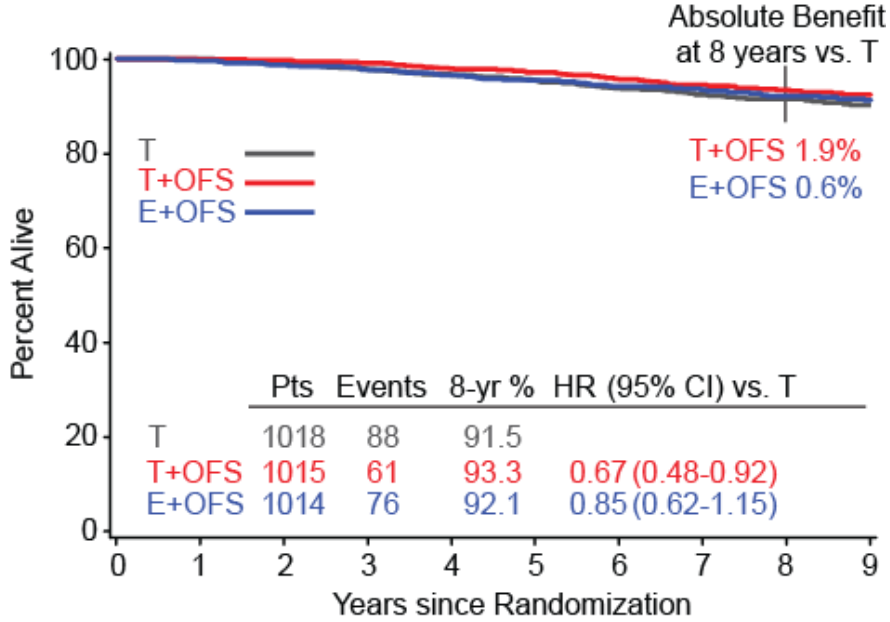
61% of HER2+ received trastuzumab

SOFT Secondary Endpoints

Distant Recurrence-Free Interval



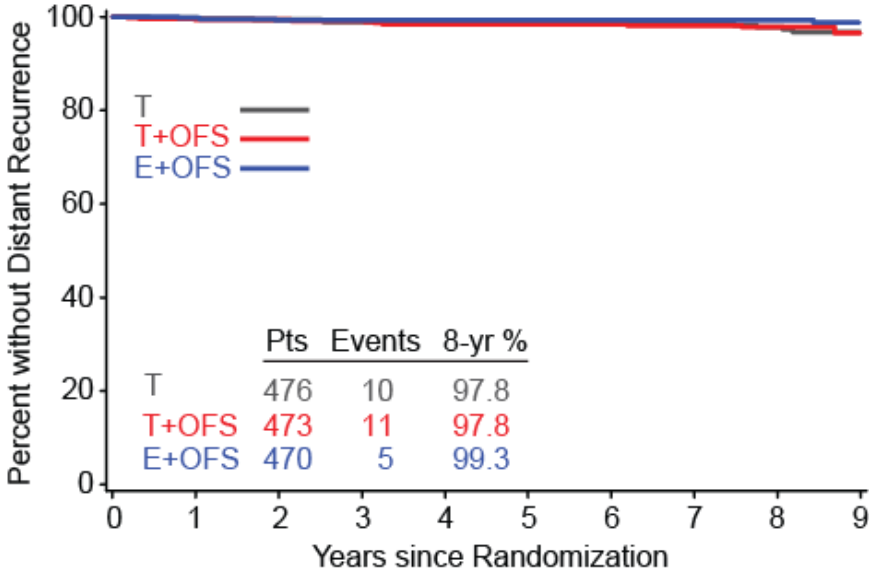
Overall Survival



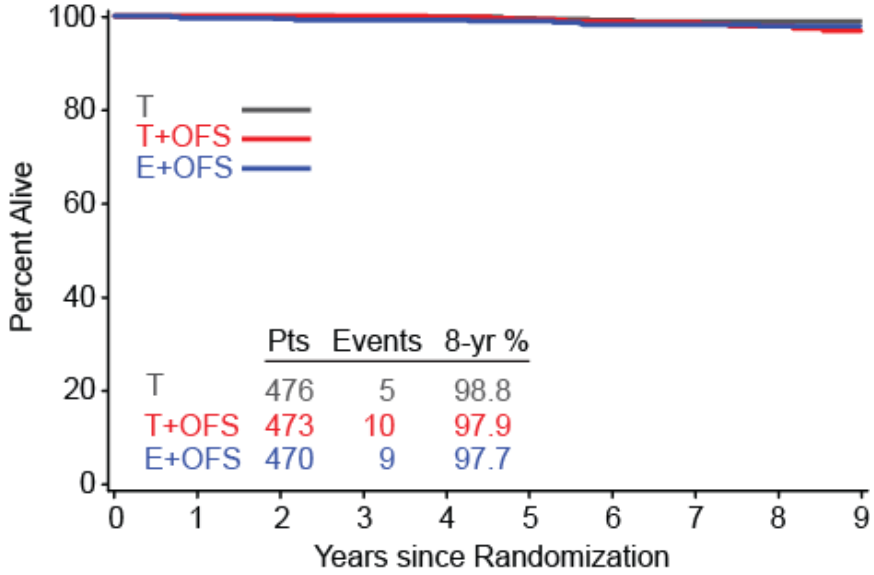
A small overall survival benefit is seen with T+OFS vs T, at 8 yrs median follow-up

SOFT Secondary Endpoints: No Chemo

Distant Recurrence-Free Interval



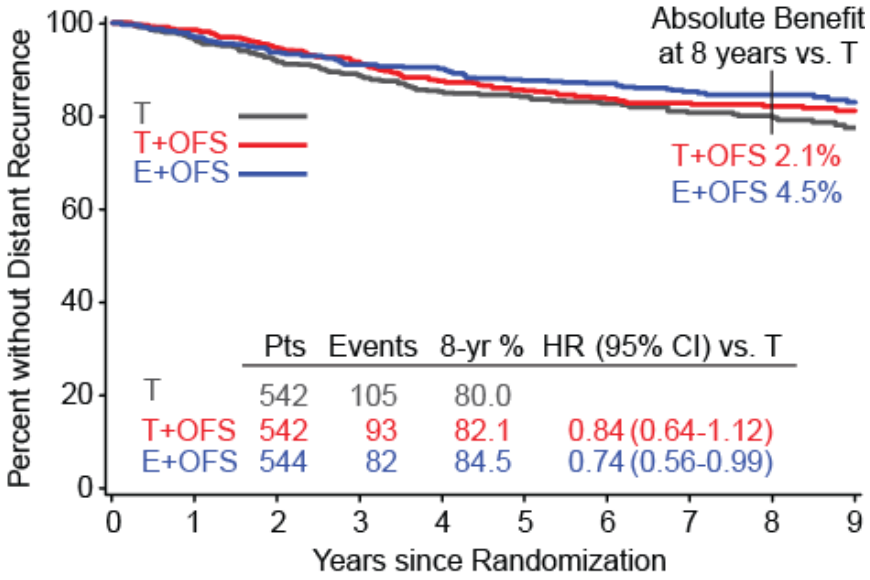
Overall Survival



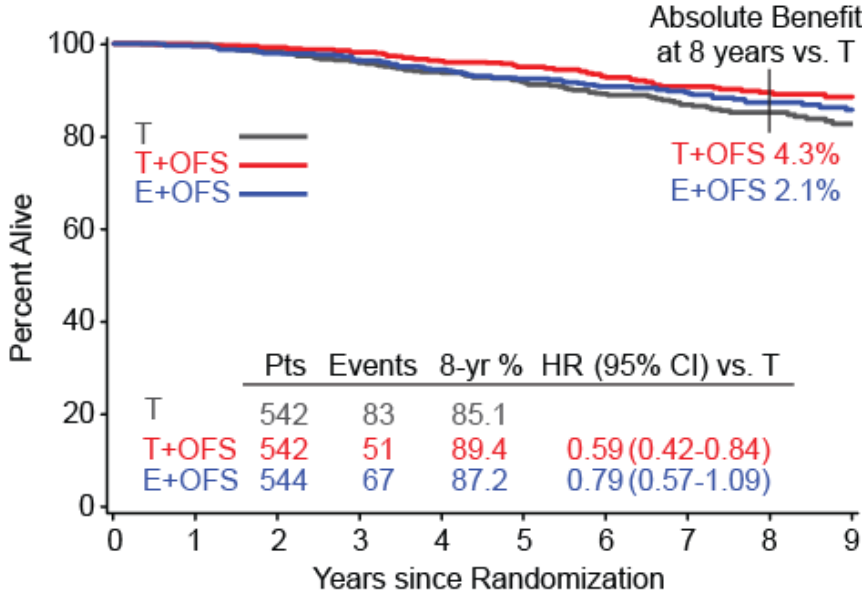
No Chemo cohort remains at low risk of distant recurrence with T alone; 12 of 24 deaths were in setting of no distant recurrence

SOFT Secondary Endpoints: Prior Chemo

Distant Recurrence-Free Interval



Overall Survival



Prior Chemo cohort has small absolute OS improvements in OFS arms at 8 yrs

Selected Adverse Events

	T (N=1005)	T + OFS (N=1006)	E + OFS (N=1000)
Endometrial cancer (n)	**N=7**	**N=4**	N=3
Thrombosis/embolism (G2-4)	**2.2%**	**2.2%**	0.9%
Hot flashes (G3)	7.8%	**13.2%**	**10.7%**
Libido decrease (G2)	11.5%	**15.9%**	**17.5%**
Musculoskeletal symptoms (G3-4)	6.7%	5.9%	**12.0%**
Osteoporosis (G2-4; T score<-2.5)	3.9%	6.1%	**11.9%**
Depression (G3-4)	4.1%	4.5%	3.9%

Conclusions

- Addition of OFS to tamoxifen significantly improves DFS at 8 yrs median follow-up
  - HR=0.66 (8.7% absolute benefit) in DFS for women under age 35
  - DFS outcomes further improved by use of exemestane plus OFS
- Small OS benefit is seen at 8 yrs
  - Evident in women with prior chemotherapy
  - Consistent with time course of events in ER+ disease
- Population not receiving chemotherapy has a low risk of distant metastases at 8 yrs with tamoxifen alone
- Follow-up continues

Agenda

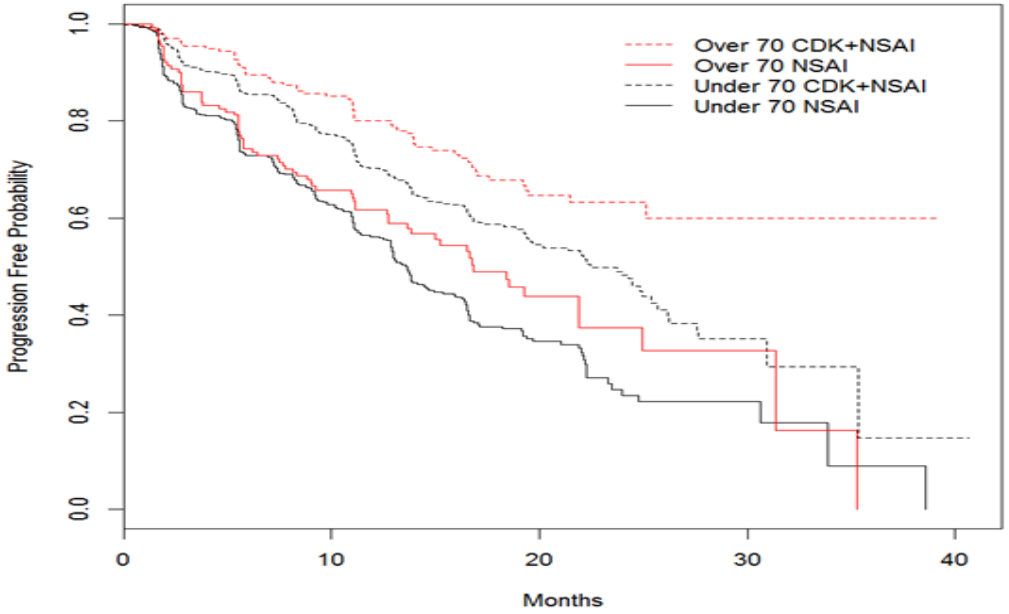
- Perioperative endocrine therapy- POETIC
- Metastatic Disease- MONALEESA-7, MANTA, MONARCH 2/3
- Adjuvant Endocrine Therapy- ABCSG-16, SOFT/TEXT update
- CDK4/6 Inhibitors in the elderly

U.S. Food and Drug Administration pooled analysis of outcomes of older women with hormone-receptor positive metastatic breast cancer treated with a CDK4/6 inhibitor as initial endocrine based therapy

Harpreet Singh, Lynn Howie, Erik Bloomquist, Suparna Wedam, Laleh Amiri-Kordestani, Shenghui Tang, Rajeshwari Sridhara, Amna Ibrahim, Kirsten Goldberg, Amy McKee, Julia A. Beaver, Richard Pazdur

Office of Hematology and Oncology Products
U.S. Food and Drug Administration

Efficacy of CDK4/6 Inhibitors in Patients ≥ 70



	Median PFS (95% CI)
Age≥70 CDK4/6 (n=280)	NR (25.1 months, NR)
Age <70 CDK4/6 (n=826)	23.75 months (21.9, 25.4)
Age ≥70 AI only	16.8 months (13.7, 21.9)
Age <70 AI only	13.8 months (12.9, 14.7)

HR 0.54 95% CI (0.47, 0.62)

No treatment difference across age subgroups.
Similar results with alternate age cut offs (>65, >75, etc)

Safety and Tolerability

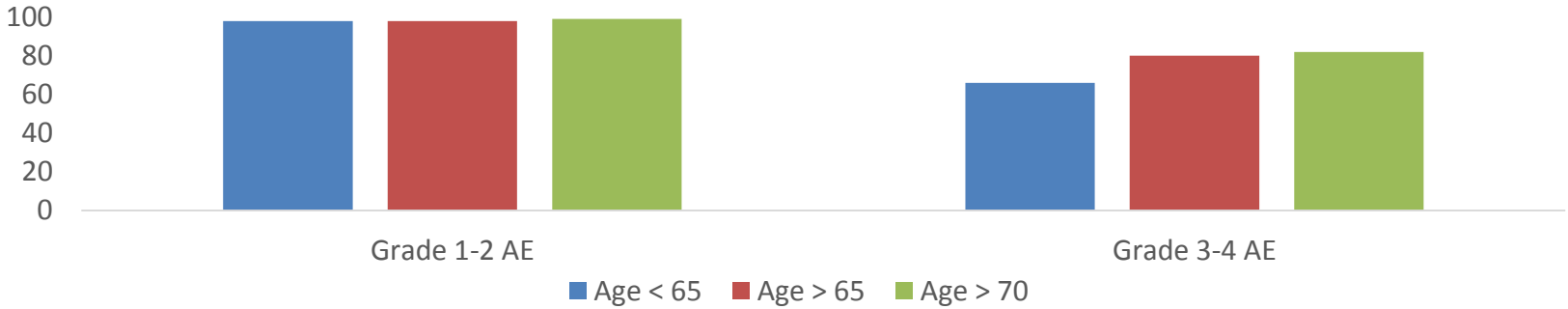
- Safety Population: Received at least one dose of CDK 4/6 inhibitor

	Age<65	Age ≥ 65	Age ≥ 70	Age ≥ 75	Age ≥ 80	Age ≥ 85
OVERALL (n=1106)	627 (57)	479 (43)	280 (25)	125 (11)	48 (4)	13 (1)

- AE's occurred up to 30 days after last dose
  - Severity (AE Toxicity Grade 1-5)
  - Serious Adverse Events
  - AE's leading to Dose Interruption, Reduction, Discontinuation
  - Selected Adverse Events (neutropenia, infection, hepatoxicity, fatigue, diarrhea)

Pooled Adverse Events: Severity

	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479(%)	Age ≥ 70 years N = 280 (%)
Grade 1-2 Adverse Events	610 (98)	470 (98)	277 (99)
Grade 3-4 Adverse Events	417 (66)	385 (80)	229 (82)
Grade 5 Adverse Events	7 (1)	11 (2)	8 (3)



Pooled Adverse Events: Tolerability

	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479 (%)	Age ≥ 70 years N = 280 (%)
AE leading to dose reduction and/or interruption	411 (66)	360 (75)	216 (77)
AE leading to discontinuation	50 (8)	76 (16)	48 (17)
Serious Adverse Events	103 (16)	147 (31)	93 (33)

Conclusions

- Older patients with breast cancer benefit from treatment with CDK4/6 inhibitors as initial endocrine based therapy for HR positive, HER2 negative, metastatic breast cancer
- Severity of adverse events and rates of dose modifications and interruptions higher in ≥65, ≥70
- Rates of selected adverse events similar across pooled trials