Updates in Hormone-receptor Positive Breast Cancer

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Objectives

- Cyclin kinase inhibitors in pre/perimenopausal women
- Targeting the PI3K/AKT/PTEN pathway
- Update on optimal endocrine therapy in premenopausal women

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Phase III MONALEESA-7 Trial of Premenopausal Patients With HR+/HER2– Advanced Breast Cancer Treated With Endocrine Therapy ± Ribociclib: Overall Survival Results

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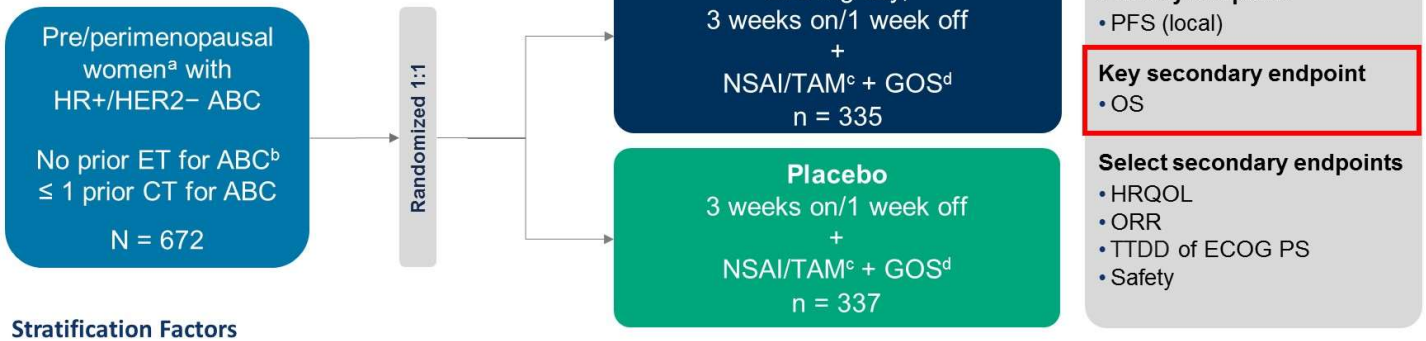
Presented By Sara Hurvitz at 2019 ASCO Annual Meeting

MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients



Stratification Factors

- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.

[a] Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg. and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection.

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Key Patient Baseline Characteristics

	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)
Age (range), years	43 (25-58)	45 (29-58)
Race, n (%)		
White	187 (56)	201 (60)
Asian	99 (30)	99 (29)
Black	10 (3)	9 (3)
Other/unknown	39 (12)	28 (8)
ECOG PS, n (%)[a]		
0	245 (73)	255 (76)
1	87 (26)	78 (23)
2	0	1 (< 1)
Previous neoadjuvant or adjuvant ET, n (%)		
No	208 (62)	196 (58)
Yes	127 (38)	141 (42)
Previous chemotherapy for advanced disease, n (%)	47 (14)	47 (14)

[a] Data were missing for 3 patients in each arm.

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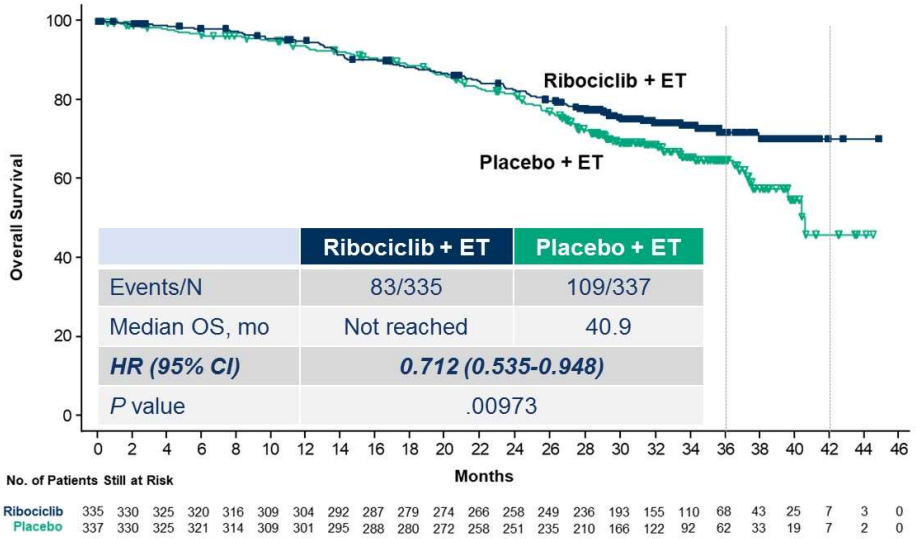
Overall Survival



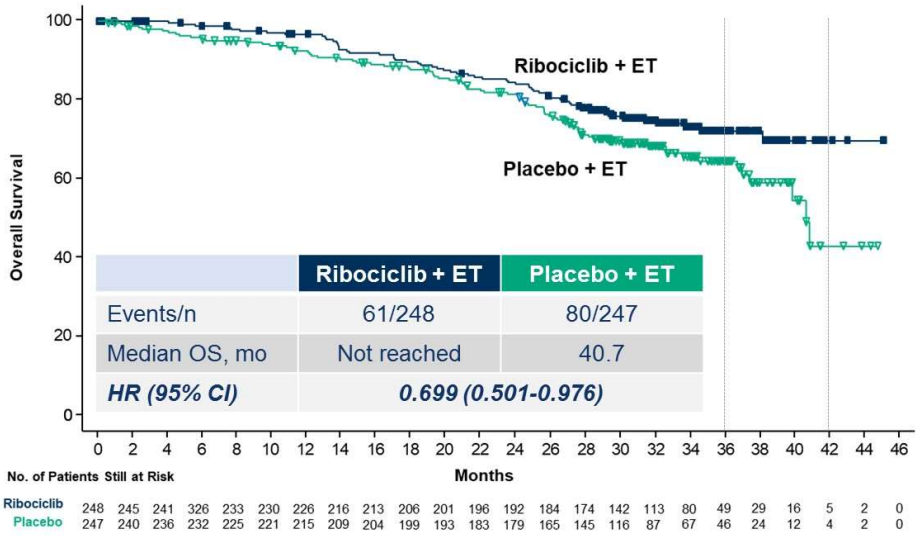
	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

Overall Survival in the NSAI Subgroup

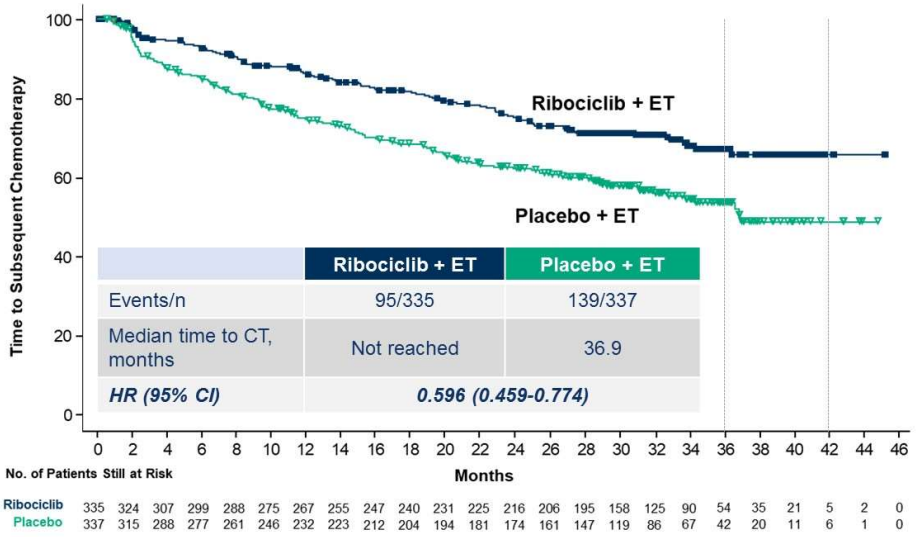


- ≈ 30% relative reduction in risk of death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	72.2%	64.6%
42 months	69.7%	43.0%

Time to First Subsequent Chemotherapy

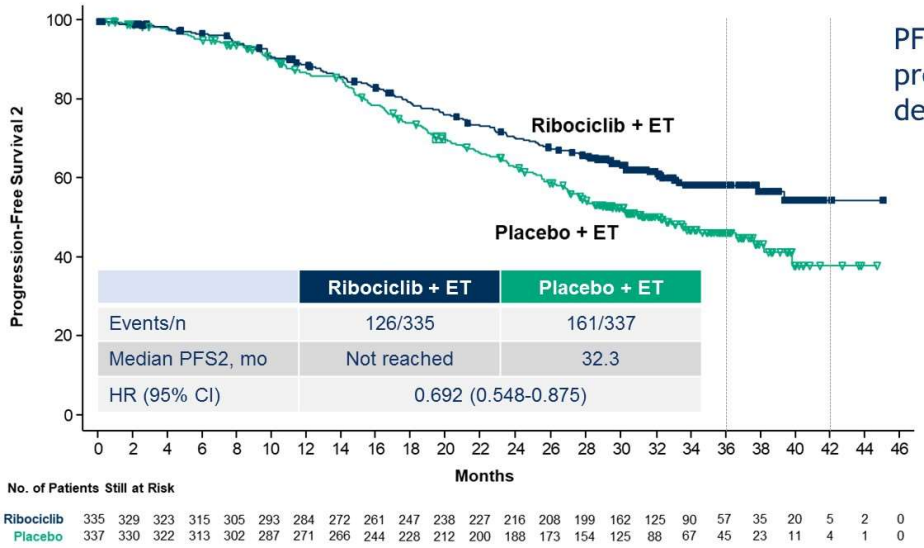


	Ribociclib + ET	Placebo + ET
Events/n	95/335	139/337
Median time to CT, months	Not reached	36.9
HR (95% CI)	***0.596 (0.459-0.774)***	

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	67.2%	53.8%
42 months	65.8%	49.0%

Progression-Free Survival 2



	Ribociclib + ET	Placebo + ET
Events/n	126/335	161/337
Median PFS2, mo	Not reached	32.3
HR (95% CI)	0.692 (0.548-0.875)	

PFS 2: time from randomization to progression on the next line of therapy or death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	58.4%	46.2%
42 months	54.6%	37.8%

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Safety

- The median treatment duration was approximately 2 years in the ribociclib arm and approximately 1 year in the placebo arm
- After 15 months of additional follow-up, the adverse event profile for the ribociclib arm remained consistent with the known safety profile
- The rates of grade 3 or 4 adverse events of special interest in the ribociclib and placebo arms, respectively, were:
  - Neutropenia, 63.5% and 4.5%
  - Hepatobiliary toxicity, 11% and 6.8%
  - Prolonged QT interval, 1.8% and 1.2%

Reference: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.

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How does this change clinical practice?

Study	PALOMA 2 (palbociclib)	MONALEESA 2 (ribociclib)	MONALEESA 7 (ribociclib)	MONARCH 3 (abemaciclib)
Population	postmenopausal	postmenopausal	Pre/perimenopausal	postmenopausal
N	666	668	672	493
Prior chemotherapy for ABC?	No	No	≤ 1	No
Median PFS (mos)	24.8 v 14.5	25.3 vs 16	23.8 vs 13	28.2 v 14.7
OS	Not reported	Not reported	Not reached v 40.9 mos	Not reported
References	Finn, et al, NEJM 2016	Hortabagyi, et al, NEJM 2016; Ann Onc 2018	Tripathy, et al, Lancet Onc 2018	Sledge, et al JCO 2017; Johnson et al, npjBreast Can 2019

Future directions

- The use of cyclin kinase inhibitors in the upfront or 2nd-line setting in combination with endocrine therapy is standard of care

- Studies are on-going/completed with cyclin kinase inhibitors in the adjuvant setting

- Other agents, including oral estrogen receptor down regulators, are in phase III trials

Objectives

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Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER positive breast cancer (FAKTION): A randomised, double-blind, placebo-controlled, phase II trial

Robert H Jones, Margherita Carucci, Angela Casbard, Rachel Butler, Fouad Alchami, Catherine Bale, Pavel Bezecny, Johnathan Joffe, Sarah Moon, Chris Twelves, Ramachadran Venkitaraman, Simon Waters, and Sacha J Howell

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PI3K/AKT/PTEN pathway in ER positive Breast Cancer

- The PI3K/AKT/PTEN pathway is activated in approximately 50% of ER positive metastatic breast cancer[1-4]
  - PIK3CA activating mutation (30-45%)
  - PTEN loss/inactivation (3-8%)
  - AKT1 activating mutation (2-6%)

- Pre-clinically:
  - pathway activation leads to ligand independent activation of ER[5,6]
  - pathway inhibition leads to compensatory increase in ER-dependant transcription[7-9]

- There is a strong rationale for simultaneous targeting of the PI3K/AKT/PTEN and ER pathways

[1]TCGA. Nature 2012; 490: 61–70. [2]Stemke-Hale K et al. Cancer Res. 2008; 68:6084-91. [3]Hortobagyi et al. J Clin Oncol. 2016;34:419-26. [4]Baselga J et al. Lancet Oncol. 2017;18:904–916 [5]deGraffenried LA et al. Clin Cancer Res 2004; 10:8059–67. [6]Miller TW et al. J Clin Oncol 2011; 29:4452-61. [7]Bosch A et al. Sci Transl Med. 2015;7:283ra51, [8] Ribas R et al. Mol Cancer Ther. 2015;14:2035-48 [9]Toska E et al. Science. 2017;355:1324-1330.

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Capivasertib (AZD5363) in ER positive breast cancer

- Capivasertib is a potent and selective inhibitor of Akt 1-3 isoforms[1]
- Synergistic activity seen with fulvestrant pre-clinically in endocrine sensitive and resistant models[1,2]
- Modest clinical activity seen with monotherapy in tumours with AKT1 (E17K) mutations[3] but minimal activity in tumours with PIK3CA mutations[4] ER+ MBC
- No effect in combination with paclitaxel chemotherapy in PIK3CA mutant ER+ MBC (BEECH)[5]
  - Co-treatment with endocrine therapy was not permitted

[1]Davies BR et al. Mol Cancer Ther 2012;11:873–87. [2] Ribas R et al. Mol Cancer Ther. 2015;14:2035-48. [3]Hyman DM et al J Clin Oncol. 2017;35:2251-2259.
[4]Banerji U et al. Clin Cancer Res. 2018;24:2050-2059 [5]Turner NC et al Ann Oncol. 2019,

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FAKTION Trial design

Phase 1b

3+3 design - fulvestrant 500mg q 4weeks + loading dose (LD) C1D15: Starting dose capivasertib 400mg bd 4 days on / 3 days off
N=9 SRC recommended not to dose escalate to established single agent dose 480mg bd 4 days on / 3 days off

Phase 2

Eligibility

- Post-menopausal women
- ER+/Her2- Metastatic or unresectable LABC
- Progression on AI for MBC/LABC **or** relapse on adjuvant AI
- Maximum 1 line chemotherapy for MBC
- Maximum 3 lines ET for MBC
- Measurable or non-measurable disease
- Controlled type II diabetes allowed

Exclusion

- Prior fulvestrant or PI3K/AKT/mTOR inhibitor therapy

N = 140

R

1:1

Fulvestrant 500mg q4weeks + LD Capivasertib 400mg bd 4 days on / 3 days off from C1D15
N=69

Fulvestrant 500mg q4weeks + LD Placebo bd 4 days on / 3 days off from C1D15
N=71

Primary endpoint:
Investigator assessed PFS in the intent to treat (ITT) population

Secondary endpoints:

- Safety and toxicity
- Objective Response rate (ORR), Clinical Benefit Rate (CBR) and Overall Survival (OS) in ITT population
- PFS/ORR/CBR in PI3K/AKT/PTEN pathway activated vs non-activated tumours

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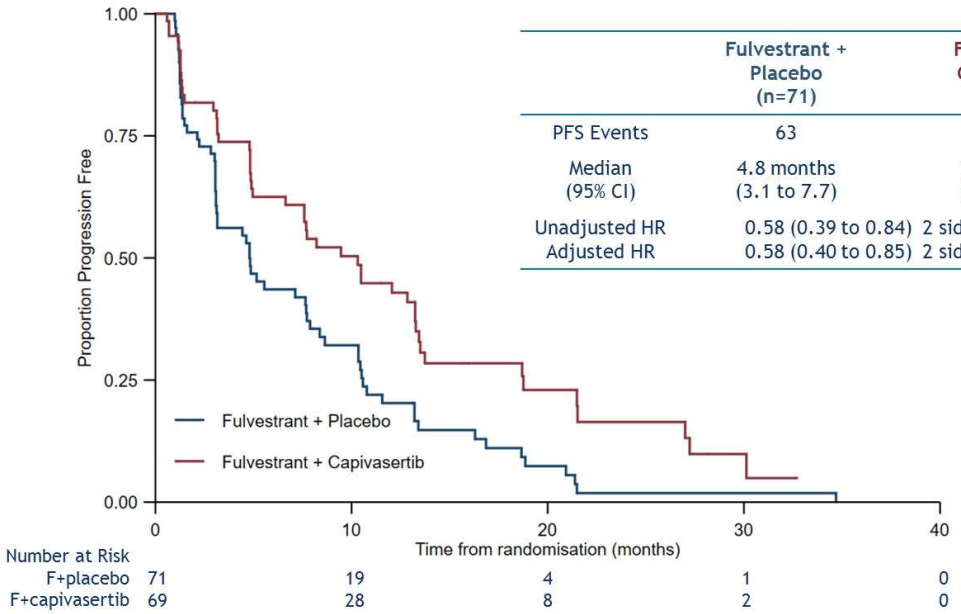
Baseline Characteristics

	Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
Median age (range), years	61 (40-82)	62 (42-81)
ECOG PS 0/1	66 (93%)	67 (97%)
IDC	58 (82%)	57 (83%)
Measurable disease	50 (70%)	49 (71%)
Visceral disease	47 (66%)	49 (71%)
Bone-only disease	8 (11%)	10 (14%)
Secondary AI resistance	45 (63%)	44 (64%)
Prior lines of endocrine therapy for MBC: 0	6 (9%)	9 (13%)
1	45 (63%)	39 (57%)
≥2	20 (28%)	20 (29%)
Chemotherapy for MBC	20 (28%)	17 (25%)
PI3K/AKT/PTEN pathway activated:	28 (39%)	31 (45%)
PIK3CA exon 9/20 mutations	24 (34%)	27 (39%)
PTEN null by IHC	4 (6%)	4 (6%)

Bold type = minimisation factors

Progression Free Survival in the ITT population



	Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
PFS Events	63	49
Median (95% CI)	4.8 months (3.1 to 7.7)	10.3 months (5.0 to 13.2)
Unadjusted HR	0.58 (0.39 to 0.84) 2 sided p = 0.004	
Adjusted HR	0.58 (0.40 to 0.85) 2 sided p = 0.005	

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Treatment exposure

		Fulvestrant + Placebo (n=71)	Fulvestrant + Capivasertib (n=69)
Median Duration of capivasertib/placebo, months (IQR)		4.9 (2.3 - 10.6)	7.7 (1.5 - 13.5)
Median Duration of fulvestrant, months (IQR)		4.6 (2.8 - 10.5)	9.2 (3.0 - 14.1)
Dose reductions - capivasertib or placebo:		3 (4%)	27 (39%)
Number of dose reductions:	1	3 (4%)	17 (24.5%)
	2	0	8 (11.5%)
	3	0	2 (3%)
Toxicity leading to capivasertib dose reduction*:	Rash	-	14 (20%)
	Diarrhoea	-	8 (12%)
	Nausea	-	3 (4%)
	Vomiting	-	2 (3%)
Discontinuation due to toxicity		0	8 (12%)

* Some participants had more than one toxicity leading to dose reduction

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Notable adverse events affecting >10% of the study population

	Fulvestrant + Placebo (n=71)		Fulvestrant + Capivasertib (n=69)	
	All grades	CTCAE G3-5	All grades	CTCAE G3-5*
Any adverse event	67 (94%)	21 (30%)	69 (100%)	40 (58%)
Diarrhoea	25 (35%)	3 (4%)	56 (81%)	10 (14%)
Rash	13 (18%)	0	35 (51%)	14 (20%)
Hyperglycaemia	11 (16%)	0	29 (42%)	3 (4%)
Vomiting	15 (21%)	0	27 (39%)	2 (3%)
Nausea	36 (51%)	0	38 (55%)	0
Infections (composite term**)	13 (18%)	2 (3%)	26 (38%)	4 (6%)
Oral mucositis	5 (7%)	0	10 (14%)	0
Fatigue	41 (58%)	3 (4%)	40 (58%)	1 (1%)
Dizziness	1 (1%)	0	7 (10%)	0
Back pain	11 (16%)	0	17 (25%)	0

*2 patients died without progression on the Capivasertib arm: 1 with atypical chest infection and 1 with haemorrhage
** preferred terms falling under the Systems Organ Classification: infections and infestations

Other toxicities affecting >10%, but with similar distributions in each arm (or worse in placebo): abdominal pain; anorexia; arthralgia; non-cardiac chest pain; constipation; cough; dry mouth; dyspnea; extremity pain; flu symptoms; headache; injection site reactions; pain; pruritus; hot flashes.

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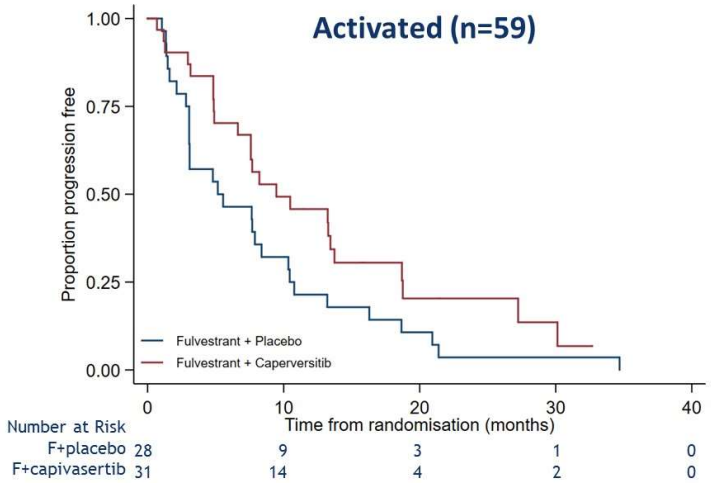
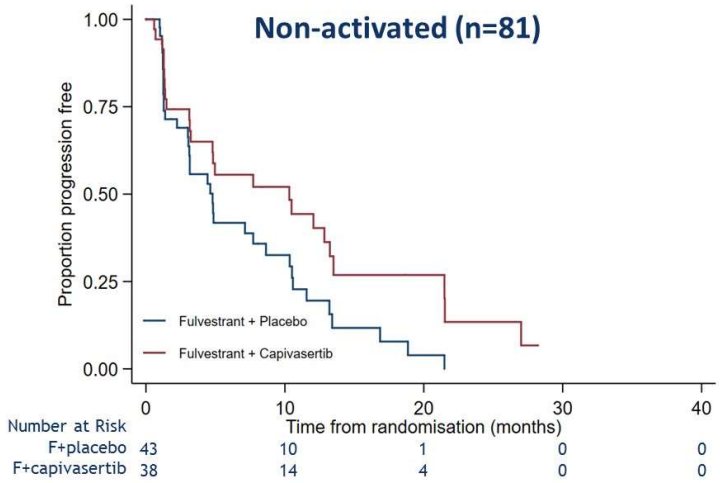
Progression Free Survival by PI3K/AKT/PTEN pathway activation status



	Fulvestrant + Placebo (n=28)	Fulvestrant + Capivasertib (n=31)
Median (95% CI)	5.2 months (3.1 to 8.4)	9.5 months (6.6 to 13.7)
Hazard Ratio	0.59 (0.34 to 1.03)	2-sided p=0.064



	Fulvestrant + Placebo (n=43)	Fulvestrant + Capivasertib (n=38)
Median (95% CI)	4.8 months (3.0 to 8.6)	10.3 months (3.2 to 13.2)
Hazard Ratio	0.56 (0.33 to 0.96)	2-sided p=0.035

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How does this change clinical practice?

- On May 24, 2019, the FDA granted approval for alpelisib in combination with fulvestrant for hormone receptor positive, HER2 negative, PIK3CA mutated metastatic breast cancer based on the SOLAR-I trial.

Original Article

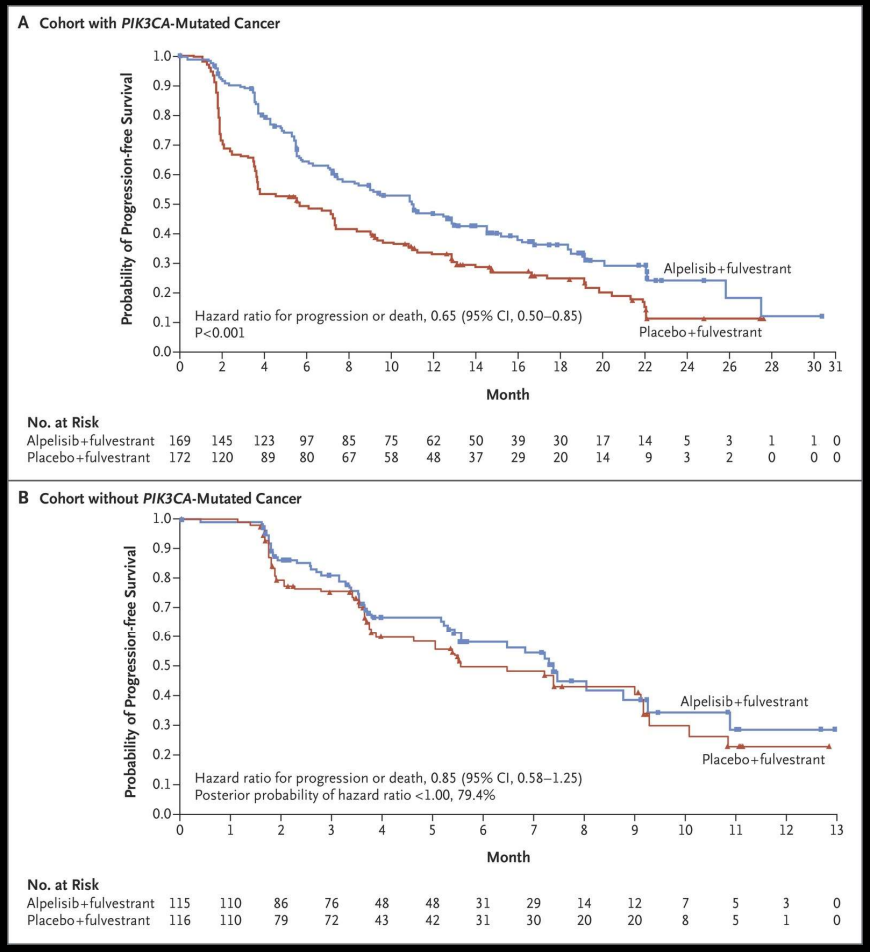
Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

Fabrice André, M.D., Eva Ciruelos, M.D., Gabor Rubovszky, M.D., Mario Campone, M.D., Sibylle Loibl, M.D., Hope S. Rugo, M.D., Hiroji Iwata, M.D., Pierfranco Conte, M.D., Ingrid A. Mayer, M.D., Bella Kaufman, M.D., Toshinari Yamashita, M.D., Yen-Shen Lu, M.D., Kenichi Inoue, M.D., Masato Takahashi, M.D., Zsuzsanna Pápai, M.D., Anne-Sophie Longin, M.Sc., David Mills, M.Sc., Celine Wilke, M.D., Samit Hirawat, M.D., Dejan Juric, M.D., for the SOLAR-1 Study Group

N Engl J Med
Volume 380(20):1929-1940
May 16, 2019

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Analysis of Progression-free Survival.



André F et al. N Engl J Med 2019;380:1929-1940

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Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.

Table 3. Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.*

Adverse Event	Alpelisib–Fulvestrant Group (N=284)			Placebo–Fulvestrant Group (N=287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia†	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea‡	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea‡	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash§	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting‡	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Weight loss	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0
Alopecia	56 (19.7)	0	0	7 (2.4)	0	0
Mucosal inflammation	52 (18.3)	6 (2.1)	0	3 (1.0)	0	0
Pruritus	51 (18.0)	2 (0.7)	0	16 (5.6)	0	0
Headache	50 (17.6)	2 (0.7)	0	38 (13.2)	0	0
Dysgeusia	47 (16.5)	0	0	10 (3.5)	0	0
Arthralgia	32 (11.3)	1 (0.4)	0	47 (16.4)	3 (1.0)	0

André F et al. N Engl J Med 2019;380:1929-1940

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How does this change clinical practice?

- On May 24, 2019, the FDA granted approval for alpelisib in combination with fulvestrant for hormone receptor positive, HER2 negative, PIK3CA mutated metastatic breast cancer based on the SOLAR-I trial.

- Capivaseritib remains investigational with a phase III trial planned.

Objectives

- Cyclin kinase inhibitors in pre/perimenopausal women
- Targeting the PI3K/AKT/PTEN pathway
- Update on optimal endocrine therapy in premenopausal women

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Original Article

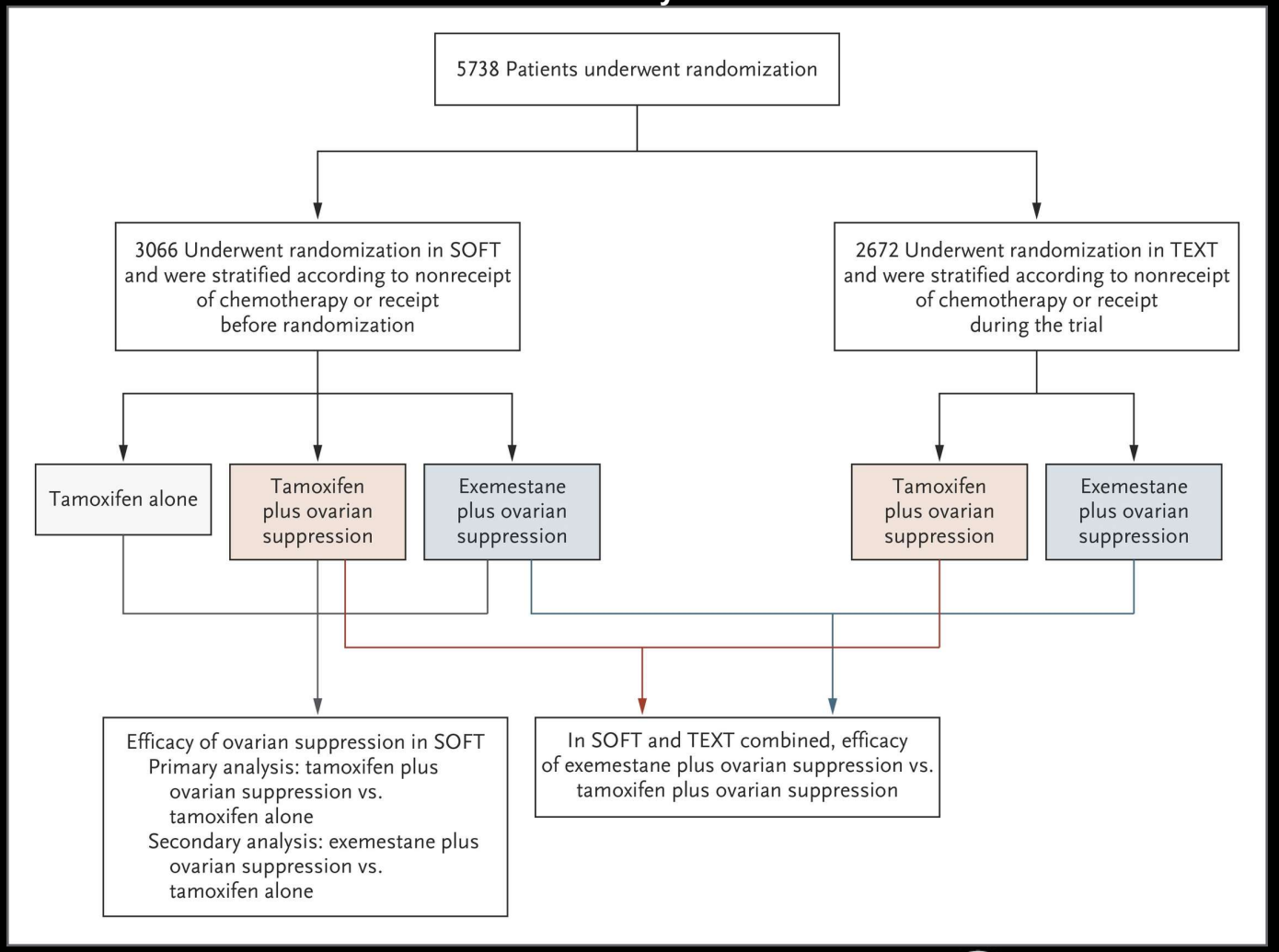
Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

Prudence A. Francis, M.D., Olivia Pagani, M.D., Gini F. Fleming, M.D., Barbara A. Walley, M.D., Marco Colleoni, M.D., István Láng, M.D., Ph.D., Henry L. Gómez, M.D., Ph.D., Carlo Tondini, M.D., Eva Ciruelos, M.D., Harold J. Burstein, M.D., Ph.D., Hervé R. Bonnefoi, M.D., Meritxell Bellet, M.D., Silvana Martino, D.O., Charles E. Geyer, Jr., M.D., Matthew P. Goetz, M.D., Vered Stearns, M.D., Graziella Pinotti, M.D., Fabio Puglisi, M.D., Ph.D., Simon Spazzapan, M.D., Miguel A. Climent, M.D., Lorenzo Pavesi, M.D., Thomas Ruhstaller, M.D., Nancy E. Davidson, M.D., Robert Coleman, M.D., M.B., B.S., Marc Debled, M.D., Stefan Buchholz, M.D., James N. Ingle, M.D., Eric P. Winer, M.D., Rudolf Maibach, Ph.D., Manuela Rabaglio-Poretti, M.D., Barbara Ruepp, Pharm.D., Angelo Di Leo, M.D., Ph.D., Alan S. Coates, M.D., Richard D. Gelber, Ph.D., Aron Goldhirsch, M.D., Meredith M. Regan, Sc.D., for the SOFT and TEXT Investigators and the International Breast Cancer Study Group

N Engl J Med
Volume 379(2):122-137
July 12, 2018

The NEW ENGLAND JOURNAL of MEDICINE

Randomization and Analyses in SOFT and TEXT.



Francis PA et al. N Engl J Med 2018;379:122-137

Characteristics of the Patients in SOFT and TEXT at Baseline, According to Chemotherapy Status.

Table 1. Characteristics of the Patients in SOFT and TEXT at Baseline, According to Chemotherapy Status.*

Characteristic	SOFT		TEXT	
	No Chemotherapy (N=1419)	Chemotherapy (N=1628)†	No Chemotherapy (N=1053)	Chemotherapy (N=1607)†
Median age — yr	46	40	45	43
Age group — no. (%)				
<35 yr	21 (1.5)	329 (20.2)	41 (3.9)	191 (11.9)
35–39 yr	110 (7.8)	473 (29.1)	123 (11.7)	289 (18.0)
40–49 yr	1045 (73.6)	772 (47.4)	768 (72.9)	1047 (65.2)
≥50 yr	243 (17.1)	54 (3.3)	121 (11.5)	80 (5.0)
Lymph-node status — no. (%)				
Negative	1294 (91.2)	701 (43.1)	835 (79.3)	542 (33.7)
Positive	125 (8.8)	927 (56.9)	218 (20.7)	1065 (66.3)
Tumor size — no. (%)				
≤2 cm	1213 (85.5)	800 (49.1)	846 (80.3)	738 (45.9)
>2 cm	199 (14.0)	764 (46.9)	204 (19.3)	846 (52.6)
Unknown	7 (0.5)	64 (3.9)	3 (0.3)	23 (1.4)
HER2 status — no. (%)‡				
Negative	1329 (93.7)	1257 (77.2)	991 (94.1)	1317 (82.0)
Positive	53 (3.7)	313 (19.2)	53 (5.0)	276 (17.2)
Unknown or not assessed	37 (2.6)	58 (3.6)	9 (0.9)	14 (0.9)
Median interval from surgery to randomization (IQR) — mo	1.8 (1.2–2.4)	8.0 (5.7–10.3)	1.5 (1.1–1.9)	1.2 (0.9–1.6)

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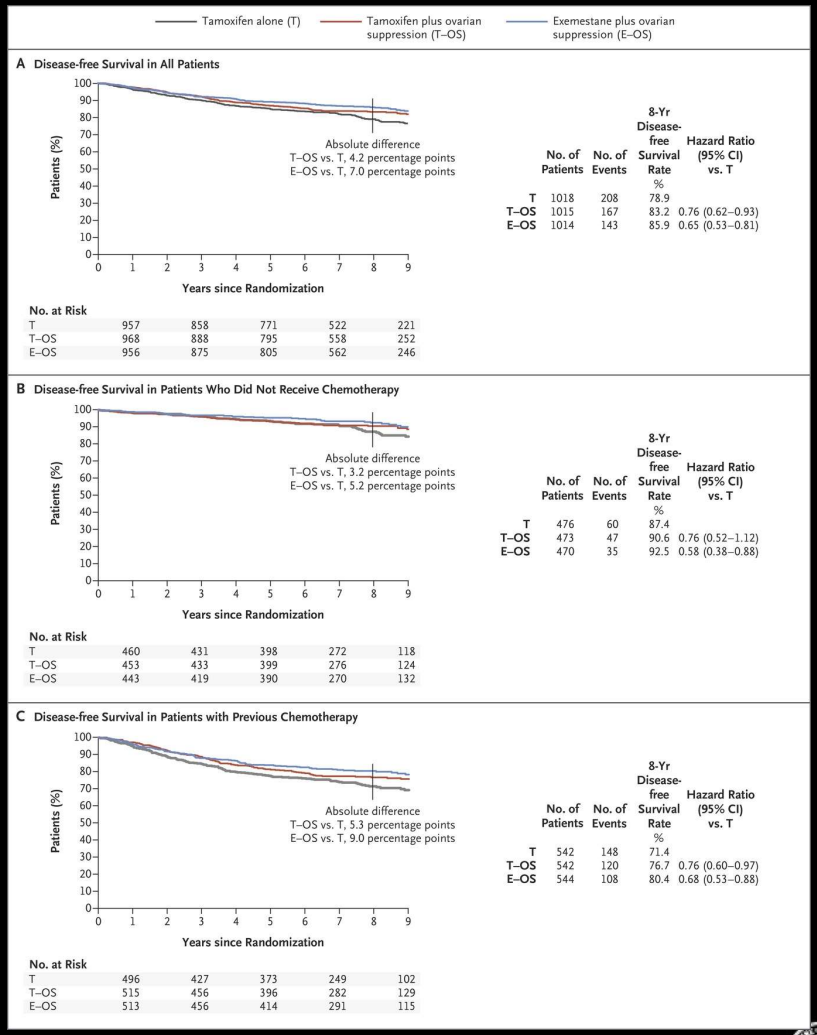
Kaplan–Meier Estimates of Disease-free Survival after a Median Follow-up of 8 Years in SOFT.



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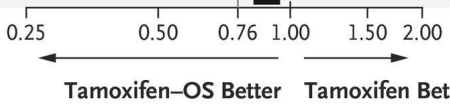
Disease-free Survival among All Patients and According to HER2 and Chemotherapy Status in SOFT.

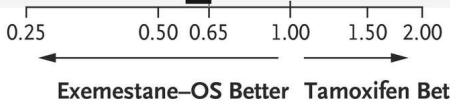
A Tamoxifen plus Ovarian Suppression vs. Tamoxifen Alone

Subgroup	Tamoxifen–OS	Tamoxifen	Hazard Ratio (95% CI)	8-Yr Disease-free Survival, Tamoxifen–OS	8-Yr Disease-free Survival, Tamoxifen
	no. of events/no. of patients			%	
All patients	167/1015	208/1018	0.76 (0.62–0.93)	83.2	78.9
HER2 status					
Positive	16/119	31/117	0.41 (0.22–0.75)	85.4	68.3
Negative	147/868	168/860	0.83 (0.67–1.04)	82.8	79.9
Chemotherapy					
None	42/445	55/437	0.72 (0.48–1.07)	91.3	87.7
Previous	105/423	113/423	0.88 (0.68–1.15)	73.9	71.9



B Exemestane plus Ovarian Suppression vs. Tamoxifen Alone

Subgroup	Exemestane–OS	Tamoxifen	Hazard Ratio (95% CI)	8-Yr Disease-free Survival, Exemestane–OS	8-Yr Disease-free Survival, Tamoxifen
	no. of events/no. of patients			%	
All patients	143/1014	208/1018	0.65 (0.53–0.81)	85.9	78.9
HER2 status					
Positive	31/130	31/117	0.74 (0.45–1.22)	75.2	68.3
Negative	105/858	168/860	0.60 (0.47–0.76)	88.0	79.9
Chemotherapy					
None	33/447	55/437	0.56 (0.36–0.86)	92.7	87.7
Previous	72/411	113/423	0.62 (0.46–0.83)	83.1	71.9



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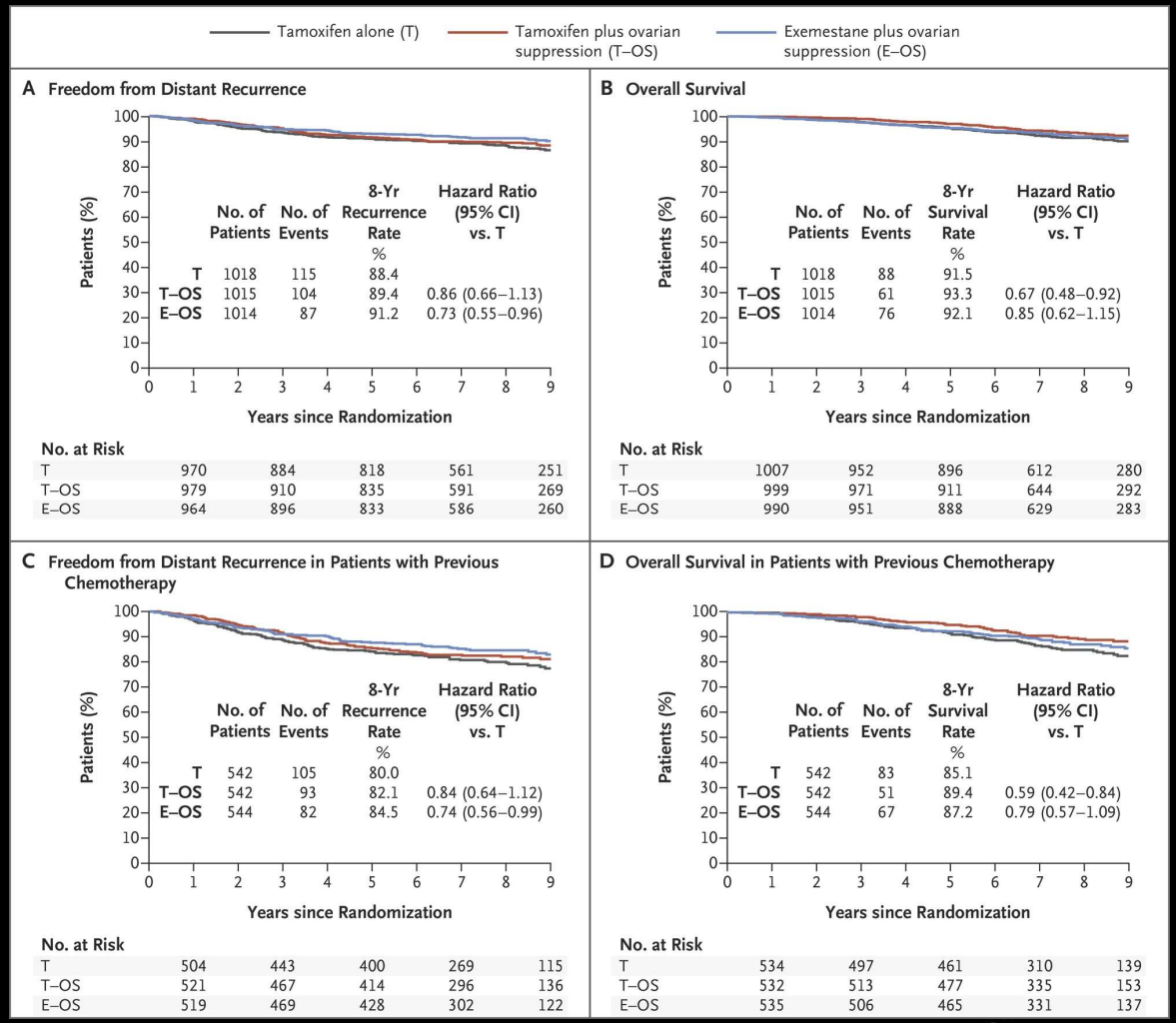
Kaplan–Meier Estimates of Freedom from Distant Recurrence and of Overall Survival in SOFT.



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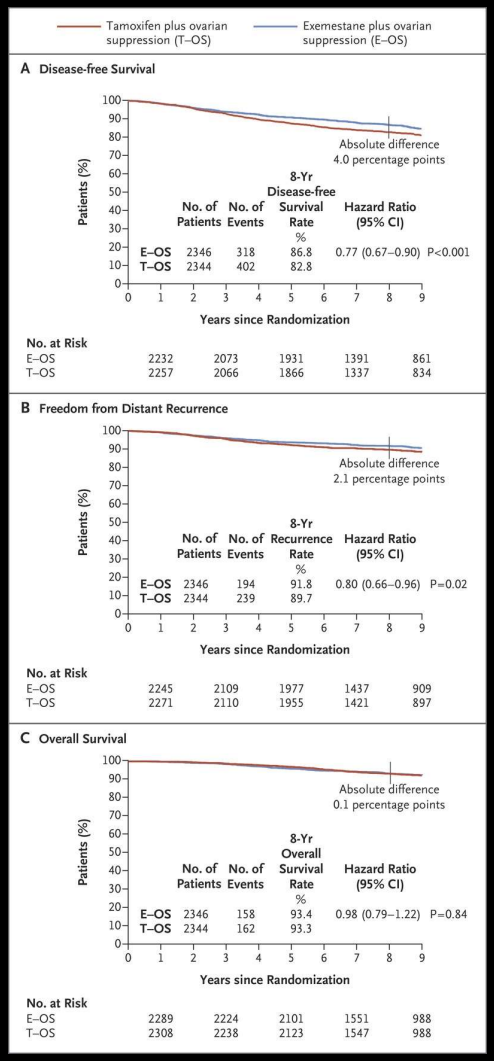
Kaplan–Meier Estimates of Disease-free Survival, Freedom from Distant Recurrence, and Overall Survival in the Combined SOFT and TEXT Population.



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Targeted Adverse Events during Treatment.

Table 2. Targeted Adverse Events during Treatment.*

Adverse Event	Tamoxifen (N=1005)		Tamoxifen plus Ovarian Suppression (N=2326)		Exemestane plus Ovarian Suppression (N=2317)	
	Any Event	Grade 3 or 4 Event	Any Event	Grade 3 or 4 Event	Any Event	Grade 3 or 4 Event
	number of patients (percent)					
Any targeted adverse event	962 (95.7)	247 (24.6)	2295 (98.7)	721 (31.0)	2288 (98.7)	748 (32.3)
Allergic reaction or hypersensitivity	35 (3.5)	2 (0.2)	110 (4.7)	9 (0.4)	122 (5.3)	12 (0.5)
Injection-site reaction	4 (0.4)	0	189 (8.1)	1 (<0.1)	174 (7.5)	1 (<0.1)
Hot flushes	808 (80.4)	78 (7.8)	2175 (93.5)	284 (12.2)	2141 (92.4)	234 (10.1)
Depression	476 (47.4)	41 (4.1)	1195 (51.4)	108 (4.6)	1197 (51.7)	95 (4.1)
Sweating	492 (49.0)	NA	1391 (59.8)	NA	1286 (55.5)	NA
Insomnia	470 (46.8)	30 (3.0)	1383 (59.5)	105 (4.5)	1375 (59.3)	89 (3.8)
Fatigue	612 (60.9)	34 (3.4)	1496 (64.3)	70 (3.0)	1450 (62.6)	75 (3.2)
Hypertension	181 (18.0)	57 (5.7)	550 (23.6)	188 (8.1)	564 (24.3)	168 (7.3)
Cardiac ischemia or infarction†	5 (0.5)	4 (0.4)	10 (0.4)	6 (0.3)	17 (0.7)	7 (0.3)
Thrombosis or embolism	22 (2.2)	17 (1.7)	53 (2.3)	47 (2.0)	27 (1.2)	20 (0.9)
Nausea	241 (24.0)	0	692 (29.8)	14 (0.6)	747 (32.2)	17 (0.7)
Musculoskeletal symptom	703 (70.0)	67 (6.7)	1809 (77.8)	132 (5.7)	2082 (89.9)	263 (11.4)
Osteoporosis	138 (13.7)	1 (0.1)	648 (27.9)	7 (0.3)	977 (42.2)	10 (0.4)
Fracture	53 (5.3)	8 (0.8)	140 (6.0)	23 (1.0)	179 (7.7)	37 (1.6)
Vaginal dryness	426 (42.4)	NA	1144 (49.2)	NA	1245 (53.7)	NA
Decreased libido	434 (43.2)	NA	981 (42.2)	NA	1056 (45.6)	NA
Dyspareunia	242 (24.1)	16 (1.6)	636 (27.3)	35 (1.5)	733 (31.6)	56 (2.4)
Urinary incontinence	166 (16.5)	6 (0.6)	433 (18.6)	9 (0.4)	317 (13.7)	9 (0.4)
CNS cerebrovascular ischemia	6 (0.6)	4 (0.4)	10 (0.4)	7 (0.3)	6 (0.3)	5 (0.2)
CNS hemorrhage	15 (1.5)	0	26 (1.1)	2 (0.1)	19 (0.8)	1 (<0.1)
Glucose intolerance‡	18 (1.8)	4 (0.4)	68 (2.9)	23 (1.0)	63 (2.7)	15 (0.6)
Hyperglycemia‡	20 (2.0)	1 (0.1)	92 (4.0)	20 (0.9)	71 (3.1)	14 (0.6)

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How does this change clinical practice?

- OS should be considered in combination with tamoxifen or an aromatase inhibitor, versus tamoxifen alone
- No direct comparison with extended tamoxifen therapy or sequential AI after tamoxifen
- How to incorporate results of gene expression assays?
- OS and AI increase side effects and challenge compliance

Questions?