Who Are the Candidates for Ovarian Suppression & Extended Endocrine Therapy

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GBCC 2019

DOI

Personal financial interests

- Honoraria -20,000E for 5 years; Taiho, Chugai, Takeda, Shimadzu, Eisai, Daiichi Sankyo, Yakult, Kyowa-Hakko-Kirin, Konica-Minolta, Pfizer, Eli Lilly, MSD, Genomic Health, AstraZeneca. Novartis, Bayer, Sanofi, C&C Res Lab

Institutional financial interests

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Non-financial interests

- Member of Board of Directors: Board of Directors: Jpn Society Clinical Oncology, Jpn Surgical Society, Jpn Breast Cancer Society, Jpn Society Molecular Targeting Therapy, Jpn Breast Cancer Research Group organization, Jpn Breast Cancer Research Group association, Ogranisation for Oncology and Translational Research, Kyoto Breast Cancer Research Network

Who Are the Best Candidates for

- Ovarian Ablation
- Extended Hormonal Therapy

OA/OFS

- **OA/ OFS vs No treatment**
- **OFS + TAM vs TAM**
- **OFS + AI vs TAM**
- **With or Without Zoledronic acid**

- OA/ OFS > No treatment
- OFS + TAM > TAM
- OFS + AI > TAM
- With ZA > Without ZA

Affecting Factors:

Chemotherapy: Given or Not

Age: -35 / 35-

Stage: n- / 1-3/ 4-

Biology: HR levels

Grade/ Ki67LI

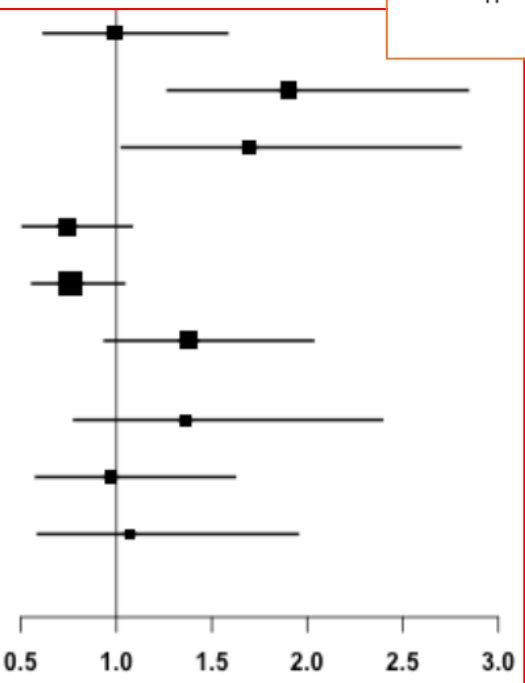
Multigene Relapse Risk

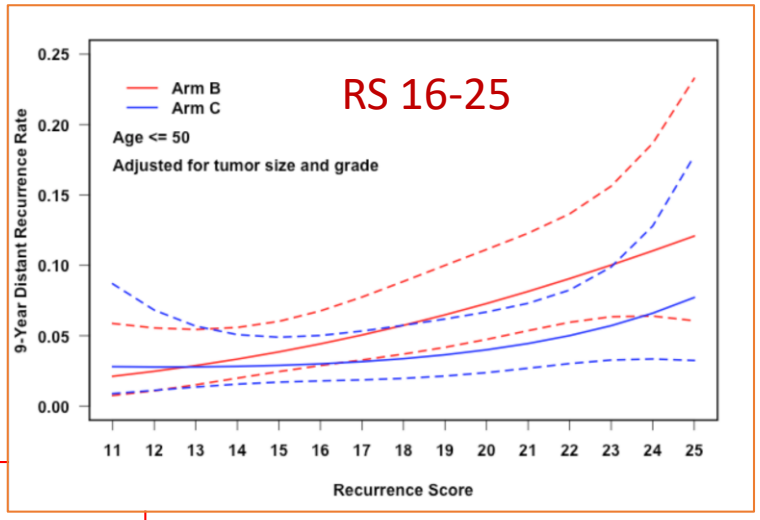
Tailor-x: Node-negative, +/-Chemotherapy

J.A. Sparano, et al. N Engl J Med 2018;379:111-21.

DFS Hazard Ratios for Subsets, Arm B vs. Arm C

Group	n	Ratio	95% Conf Int
Overall	6711	1.08	(0.94, 1.24)
RS 11-15	2373	0.95	(0.75, 1.22)
RS 16-20	2712	1.04	(0.84, 1.29)
RS 21-25	1626	1.32	(1.01, 1.71)
Age <=50, RS 11-15	801	0.99	(0.62, 1.58)
Age <=50, RS 16-20	923	1.90	(1.27, 2.84)
Age <=50, RS 21-25	492	1.70	(1.03, 2.80)
Age 51-65, RS 11-15	1250	0.74	(0.51, 1.08)
Age 51-65, RS 16-20	1425	0.76	(0.56, 1.04)
Age 51-65, RS 21-25	870	1.38	(0.94, 2.03)
Age >65, RS 11-15	322	1.36	(0.78, 2.39)
Age >65, RS 16-20	364	0.97	(0.58, 1.62)
Age >65, RS 21-25	264	1.07	(0.59, 1.95)





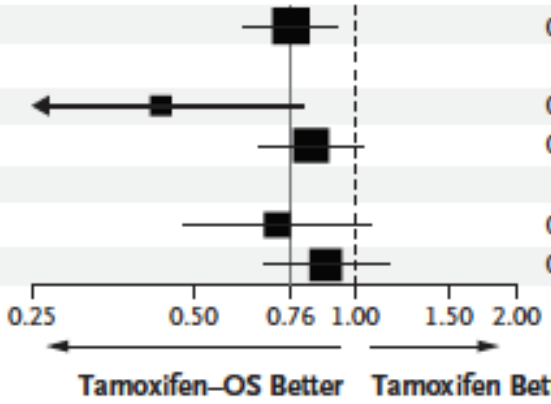
Tailor-x: Node-negative

RS	Hormone therapy	Chemotherapy
10	**TAM 5y**	-
15	Premenopausal: TAM or TAM→AI (78%) OFS (13%)	-
20		Premenopausal?
25	Postmenopausal AI (91%)	Premenopausal
		Pre- and Post-Menopausal (TC, A..)

IBCSG: TAM vs TAM/ AI + OFS (SOFT)

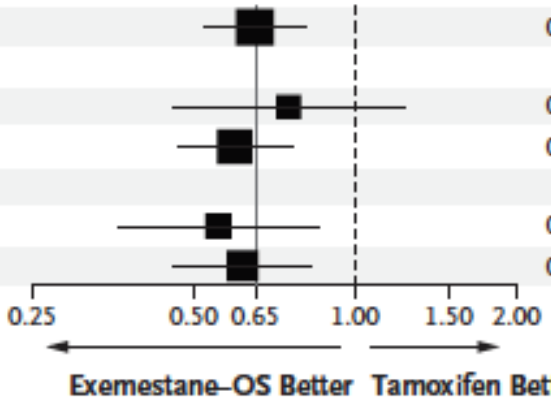
A Tamoxifen plus Ovarian Suppression vs. Tamoxifen Alone

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

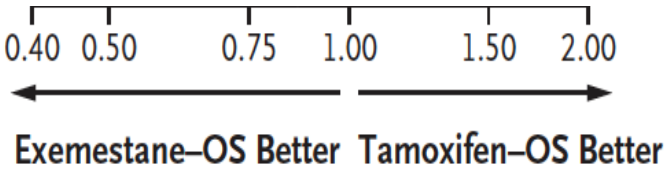


P.A. Francis et al. N Engl J Med 2018;379:122-37.

IBCSG: TAM + OFS vs AI + OFS

P.A. Francis et al. N Engl J Med 2018;379:122-37.

Disease-free survival					
All HER2-negative	250/2011	350/2024	0.70 (0.60–0.83)	88.1	82.7
Cohort					
No chemotherapy in TEXT	40/492	59/499	0.68 (0.46–1.02)	93.2	89.1
No chemotherapy in SOFT	33/447	42/445	0.79 (0.50–1.24)	92.7	91.3
Chemotherapy in TEXT	105/661	144/656	0.69 (0.53–0.88)	84.6	77.7
Previous chemotherapy in SOFT	72/411	105/424	0.70 (0.52–0.95)	83.1	73.9

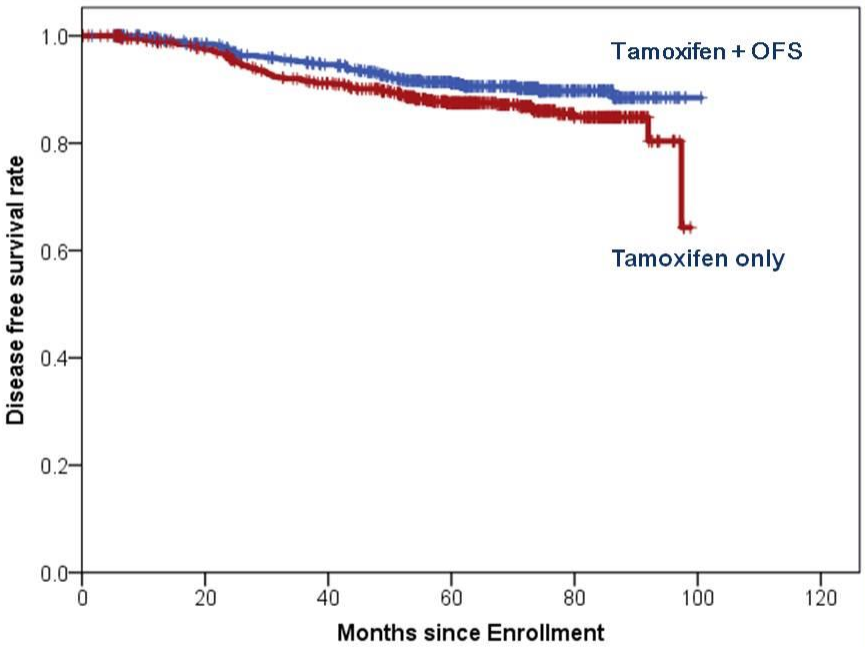


Role of adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy: the ASTRRA study

Woo Chul Noh, Jong Won Lee, Seok Jin Nam, Seho Park, Seock-Ah Im, Eun Sook Lee, Yong Sik Jung, Jung Han Yoon, Sung Soo Kang, Soo-Jung Lee, Kyong Hwa Park, Joon Jeong, Se-Heon Cho, Sung Yong Kim, Hee-Jung Kim, Hyun-Ah Kim, Chanheun Park, Se-Hwan Han, Wonshik Han, Min Hee Hur

Presented By Woo Chul Noh at 2018 ASCO Annual Meeting

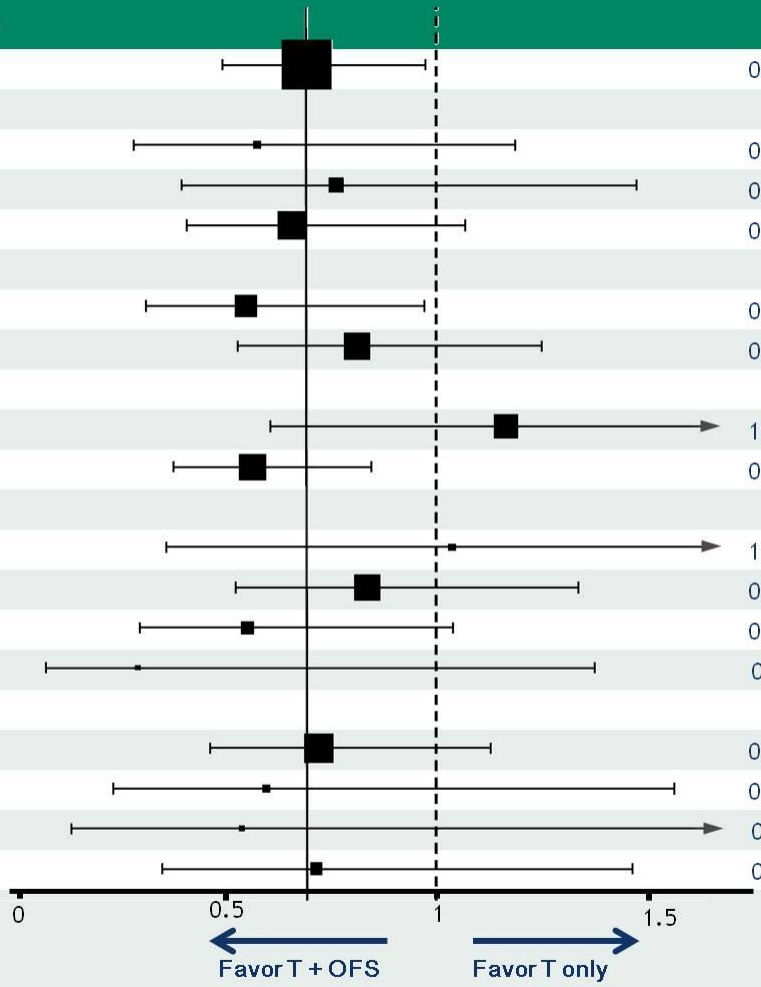
Disease free survival (Primary Endpoint)



	Pts	Events	5-yr %	HR	95% CI		P-value
					Lower	Upper	
Tamoxifen only	647	80	87.5				
Tamoxifen +OFS	635	52	91.1	0.686	0.483	0.972	0.033

- Definition
  - Local/ regional recurrence
  - Distant recurrence
  - Contralateral breast cancer
  - Secondary malignancy
  - Death, any reason

	No. of Patients		No. of Event		5-Yr DFS (%)		Hazard Ratio	P-value
	T+OFS	T only	T+OFS	T only	T+OFS	T only	(95% CI)	
All patients	635	647	52	80	91.1	87.5	0.69 (0.48-0.97)	0.033
Age at Enrollment								
<35	89	83	12	17	83.7	76.9	0.56 (0.27-1.19)	0.133
35-39	173	194	14	22	91.3	88.9	0.76 (0.39-1.48)	0.416
40-45	373	370	26	41	93.3	88.8	0.65 (0.40-1.07)	0.089
Lymph Node Status								
Negative	288	285	17	33	93.7	88.2	0.54 (0.30-0.97)	0.039
Positive	347	358	35	47	89.1	87.0	0.81 (0.52-1.25)	0.340
Tumor Size								
<2cm	307	310	18	17	93.6	95.1	1.17 (0.60-2.26)	0.651
≥2cm	328	337	34	63	88.9	80.4	0.56 (0.37-0.84)	0.006
Tumor Grade								
1	117	89	7	6	94.3	95.3	1.04 (0.35-3.09)	0.948
2	314	349	29	41	89.8	88.3	0.83 (0.52-1.34)	0.451
3	148	157	14	27	89.8	81.6	0.54 (0.29-1.04)	0.065
Unknown	56	52	2	6	95.7	87.0	0.28 (0.06-1.38)	0.118
HER2 Status								
Negative	360	362	31	46	91.1	88.6	0.72 (0.45-1.13)	0.151
Positive	84	92	6	12	91.9	86.1	0.59 (0.22-1.57)	0.291
Equivocal	30	24	3	4	89.7	81.3	0.53 (0.12-2.39)	0.411
Unknown	161	169	12	18	91.2	86.8	0.71 (0.34-1.47)	0.354



OA/OFS (IHC risk)

	Low Risk	Chemotherapy None	Int. Risk	Chemotherapy Given Risk: Int.-High
- 35 y.o.				
35 y.o. -				
Stage 1				
Stage 2/3				

IHC: Immunohistochemistry

OA/OFS

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	YES/	No/	Abstain
•Those given chemotherapy	68 /	26 /	6
•Age <= 35 years	72 /	23 /	4
•Intermediate risk no chemo	45 /	42 /	13

•Node Involvement of:	1	2-3	4-
	38 /	13 /	18

OA/OFS

	Low Risk (IHC)	Chemotherapy None	Intermediate Risk	Chemotherapy Given Risk: Int-High
- 35 y.o.	YES	YES	YES	YES
35 y.o.-	No	C by C	C by C	YES
Stage 1	No	No	C by C	YES
Stage 2/3	C by C	C by C	YES	YES

C by C: Case by Case IHC: Immunohistochemistry

OA/ OFS (Multigene risk)

	M-G Low Risk	Chemotherapy None	M-G Intermediate Risk	Chemotherapy Given
- 35 y.o.	No?	YES?	YES	YES
35- 50	No	C by C	YES?	YES
Stage 1	No	No	C by C	YES
Stage 2/3	C by C	C by C	YES	YES

C by C: Case by Case

M-G: Multigene assay

Summary-OA/OFS

- Indication of OA/OFS is personalized using Age, Stage, Biology and precise predictions of recurrence risks and therapeutic impact.
- Still many issues remain unresolved.
- Further investigations in Asian females are also needed.

EBCTCG 2018 SABCS

Gray R et al.

SABCS, December 4 -8, 2018

Extended Aromatase Inhibitor treatment following 5 or more years of endocrine therapy: a meta-analysis of 22,192 women in 11 randomised trials

Early Breast Cancer Trialists' Collaborative Group

All authors declare no relevant conflict of interest

Extended AI treatment after 5+ years of prior endocrine therapy: methods

Meta-analysis of individual patient data on postmenopausal women with ER-positive (99%) or ER-unknown (1%) tumours in trials of:

Any third-generation AI (exemestane, anastrozole, letrozole) vs no further adjuvant therapy **following**:

a) ≈ 5 years of tamoxifen alone (n=7,500)

b) ≈ 5-10 years of tamoxifen then AI (n=12,600)

c) ≈ 5 years of AI alone (n=4,800)

10-year Survival Outcomes

	Any Recurrence	Distant Recurrence	BC Mortality
TAM 5y **TAM 5y → AI**	**10.7% vs 7.1%** **RR 0.67** **P<0.00001**	**6.7% vs 5.2%** **RR 0.77** **P: 0.008**	**3.6% vs 2.7%** **RR 0.77** **P: 0.05**
TAM **TAM 5-10y → AI**	**9.2% vs 7.1%** **RR 0.82** **P: 0.002**	6.2% vs 5.3% RR 0.92 P: 0.29	3.1% vs 2.9% RR 0.93 P: 0.45
AI 5y **AI 5y → AI**	**7.9% vs 6.6%** **RR 0.76** **P: 0.02**	**4.7% vs 4.4%** **RR 0.78** **P: 0.09**	2.7% vs 2.4% RR 0.99 P: 0.97

10-year Survival Outcomes-2

	Node Negative	Node Positive 1-3	Node Positive 4-
Recurrence Control vs AI All Trials	6.2% vs 5.1% RR 0.82 P: 0.009	12.5% vs 8.7% RR 0.74 P: 0.00003	19.9% vs 12.2% RR 0.71 P: 0.003

	5y DFS
5y AI	84.4%
AI beyond 5y AI	91.9%

HR 0.548

P 0.0004

Summary-2
Extended Hormonal Therapy with AI

- Extended 10y Adjuvant Endocrine Therapy (ET) with AI may be useful for reducing recurrence rate in all 3 sequential schemes.
- AI 10y, may be better than AI 5y, although further follow-up is needed.

De-escalation of Hormonal Therapy

	Stage 1	Stage 2-
Chemotherapy None	TAM 5y AI 5y	LHRHa + TAM 5y LHRHa + AI 5y AI 5y?
Chemotherapy Given	LHRHa + TAM (35y-, Int. Risk?) LHRHa + AI ET 10y	

Prediction of late recurrence, particularly over 10 years, is difficult at present time.

Escalation of Therapy for HR+/HER2-

	Stage 1	Stage 2-
Chemotherapy None	TAM 10y? AI 5y	ET 10 y (with AI 5y)
Chemotherapy Given	ET 10y (with AI 5y or more) + Oral FU + CDK4/6 inhibitors + PARP inhibitors (BRCA variants) …..	

THANK YOU ♪

Duration (Postmenopausal) beyond 5 years

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	YES/	No/	Abstain
Stage 1/ n0, after 5 years tamoxifen?	26 /	**72** /	2
Stage 1/ n0, after 5 years of an AI?	20 /	**78** /	2
Stage 2, node-negative, after 5 years of tamoxifen?	**68** /	28 /	4
Stage 2, node-negative, **after 5 years of an AI**?	35 /	**59** /	6
Stage 2, node-positive, after 5 years of an TAM?	**98** /	2	
Stage 2, node-positive, after 5 years of an AI?	**81** /	13 /	6

OA/OFS

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- **Premenopausal/ and RS 21-25**

TAM/	OFS +ET/	Chemo +ET/	Chemo +OFS +ET	Abstain
17	3	42	10	6