Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2022.1E

Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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- **Versions 2002–2021:**
  Bauerfeind / Dall / Diel / Fasching / Fersis / Fehm / Friedrichs / Gerber / Göring / Hanf/ Harbeck / Huober / Jackisch / Lisboa / Loibl / Lück / Lux / Maass / von Minckwitz / Möbus / Müller / Nitz / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen

- **Version 2022:**
  Friedrich / Untch

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Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1 GR: A AGO: ++

Endocrine responsive – hormone receptor positive
Immunhistology (ER and/or PgR)

0%	**pos. cells:**	**endocrine resistant**
1–10%	**pos. cells:**	**possibly endocrine sensitive**
> 10%	**pos. cells:**	**endocrine sensitive**
Unknown hormone receptor status:		**endocrine sensitive**

If ER negative / PR positive (> 10% positive cells): reassess IHC status

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

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	Oxford		
	LoE	GR	AGO
Assessment of menopausal status:			
▪ **Menstruation history**			++
▪ **FSH, E2**			++

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Adjuvant Endocrine Therapy

	Oxford		
	LoE	GR	AGO
Endocrine therapy:			
▪ Endocrine responsive	1a	A	++
▪ endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to T-DM1 / anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Non-responsive: No endocrine therapy	1a	A	++

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General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5) and extended adjuvant therapy (EAT, years 6-10+).**
- **Standard treatment duration is 5 years.**
- **Extended therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, especially in case of lobular cancers and / or high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker for identification of patients at risk for early versus late recurrence.**

Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford		
	LoE	GR	AGO
▪ **Low recurrence risk:**			
▪ **Tamoxifen for 5 years**	1a	A	++
▪ **Increased recurrence risk:**			
▪ **OFS 2-5 years* + tamoxifen for 5 years**	1a	A	++
▪ **OFS# + AI for 5 years**	1a	A	++
▪ **GnRHa monotherapie** (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie)	1a	B	+

OFS: ovarian function suppression;
* as long as tolerated and the patient is clearly premenopausal
after chemotherapy if ovarian function resumes within 24 months
The application of chemotherapy in the trials served as surrogate for high recurrence risk
\# in premopausal women AI only in combination with OFS

TEXT / SOFT Joint Analysis

TEXT
Premenopausal
Patients with HR+ BC
≤ 12 wks after surgery
(N = 2672)

SOFT
Premenopausal patients with HR+ BC
≤ 12 wks after surgery
(if no chemo) *or*
≤ 8 mos after chemo
(N = 3066)

5 yrs

Tamoxifen 20 mg/day
+ OFS* (n = 1328)

Exemestane 25 mg/day
+ OFS* (n = 1332)

Tamoxifen 20 mg/day
+ OFS* (n = 1016)

Exemestane 25 mg/day
+ OFS* (n = 1014)

Tamoxifen 20 mg/day

Median follow-up: 5.7 yrs

Joint Analysis

Tamoxifen + OFS*
(n = 2344)

Exemestane + OFS*
(n = 2346)

*OFS
- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

Nach Pagani O, et al. N Eng J Med, 371(2) 2014

Adjuvante Endocrine Therapy in Premenopausal Patients

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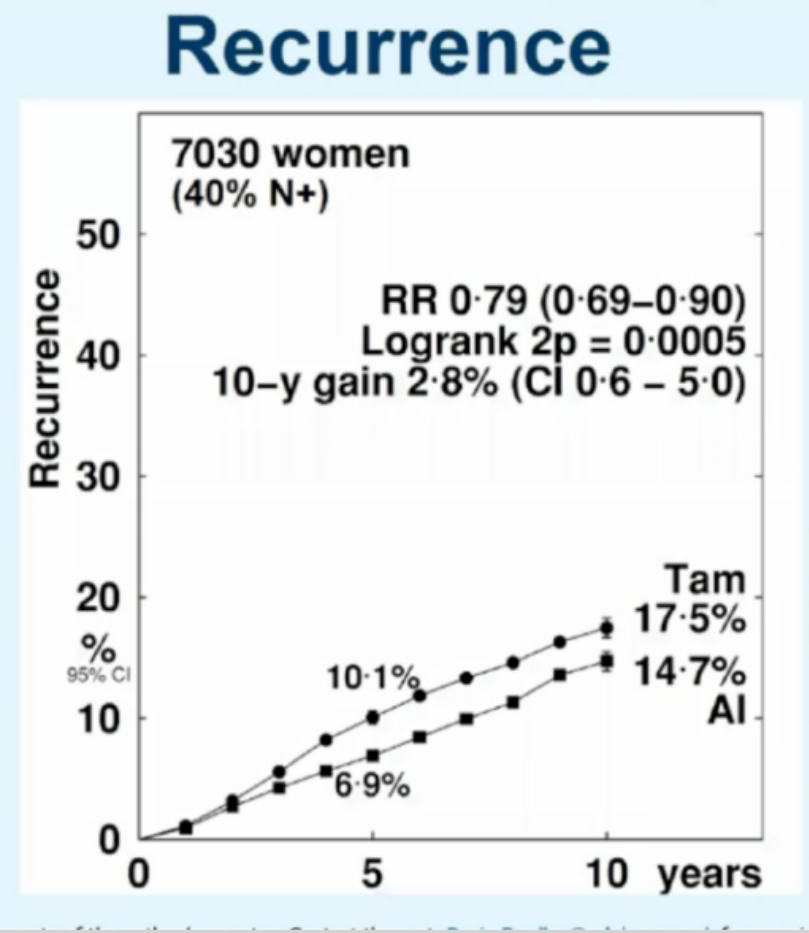

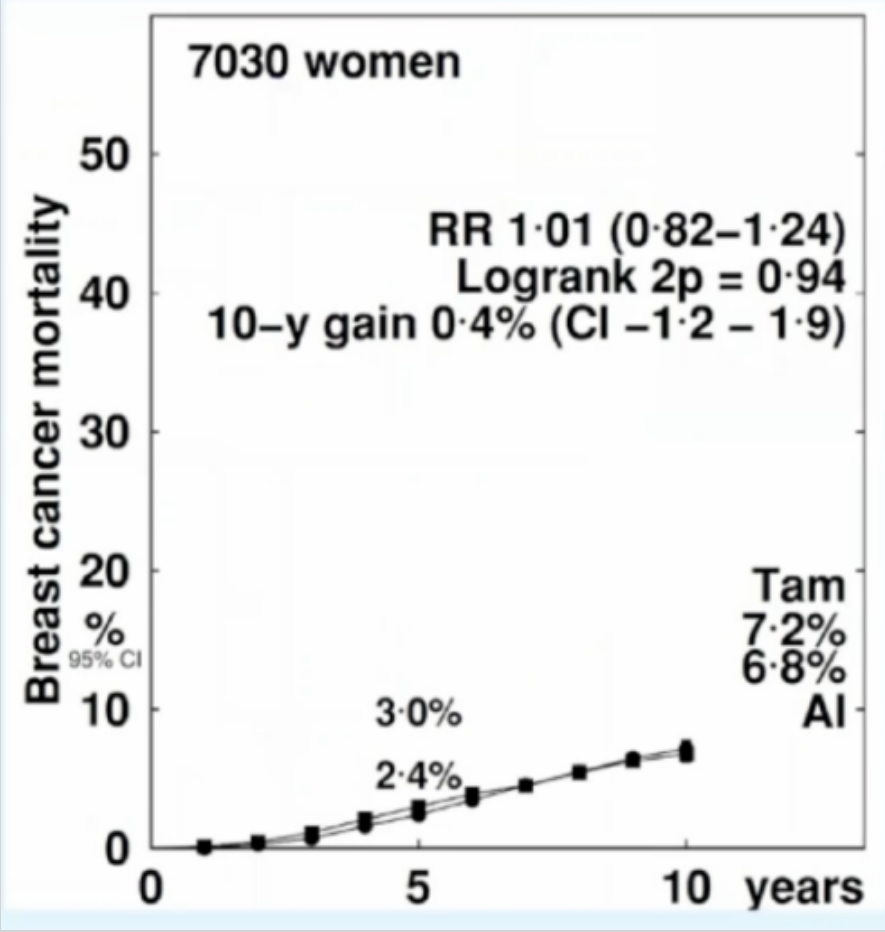

Adjuvante Endocrine Therapy in Premenopausal Patients

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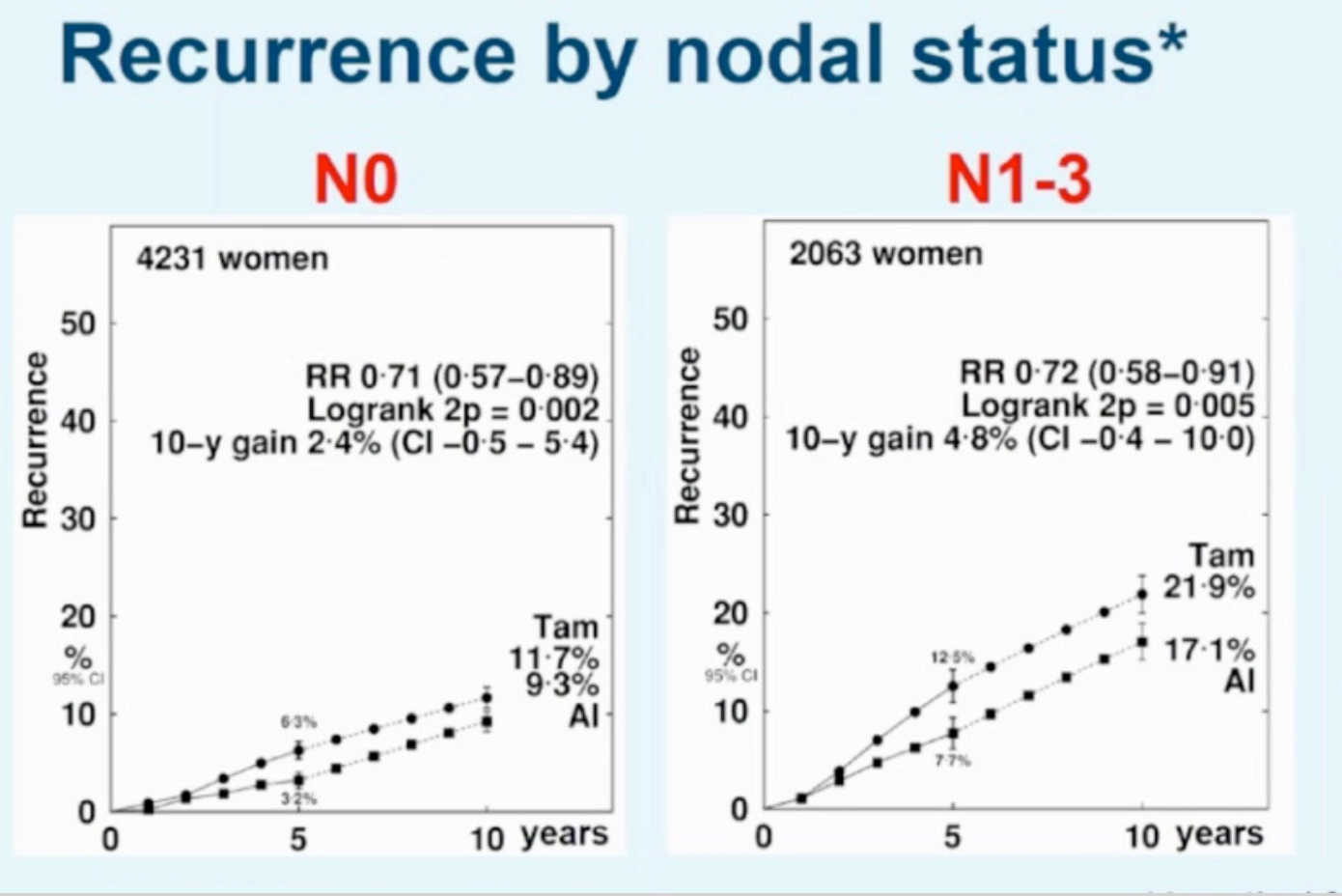

Adjuvante Endocrine Therapy in Premenopausal Patients

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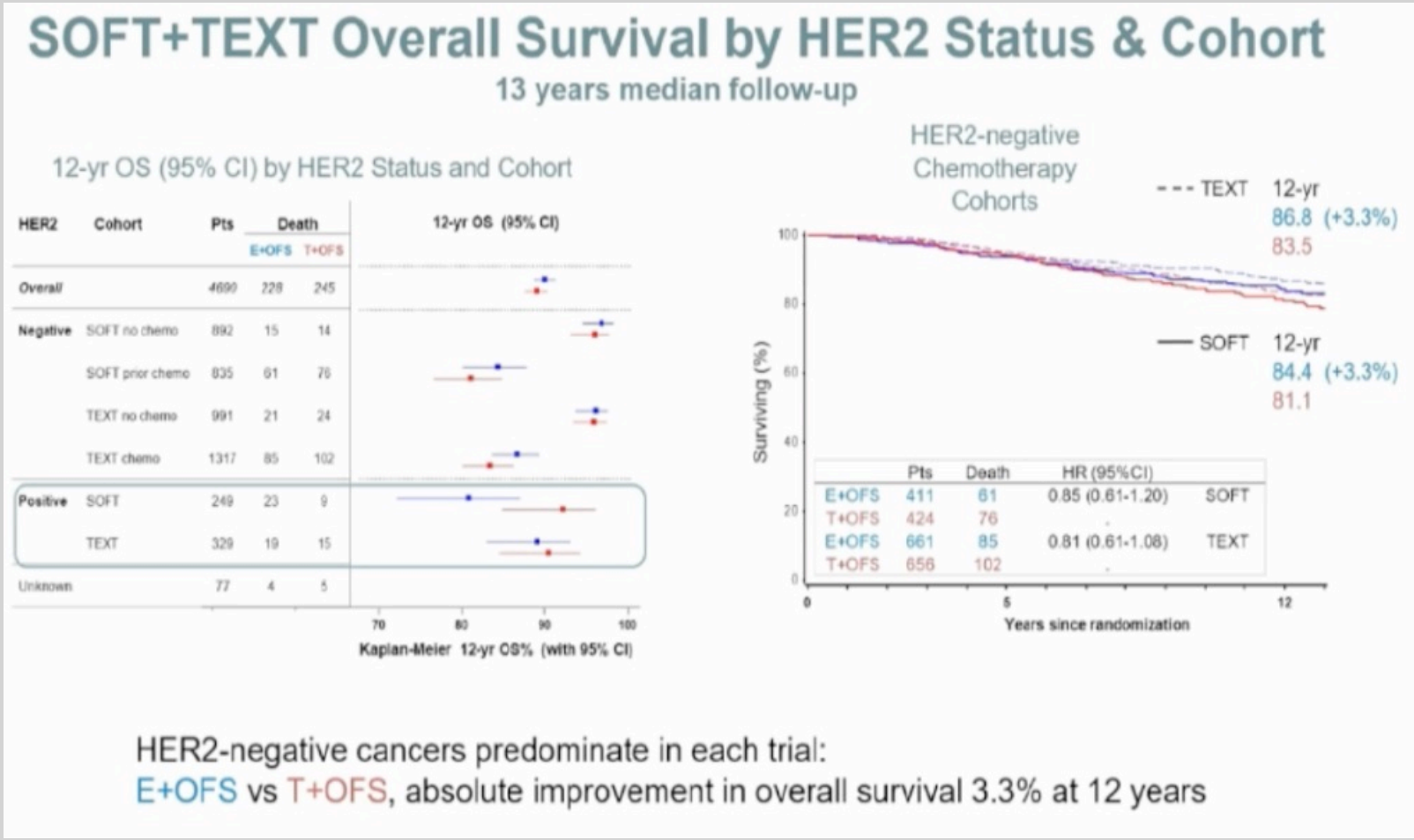

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Adjuvante Endocrine Therapy in Premenopausal Patients

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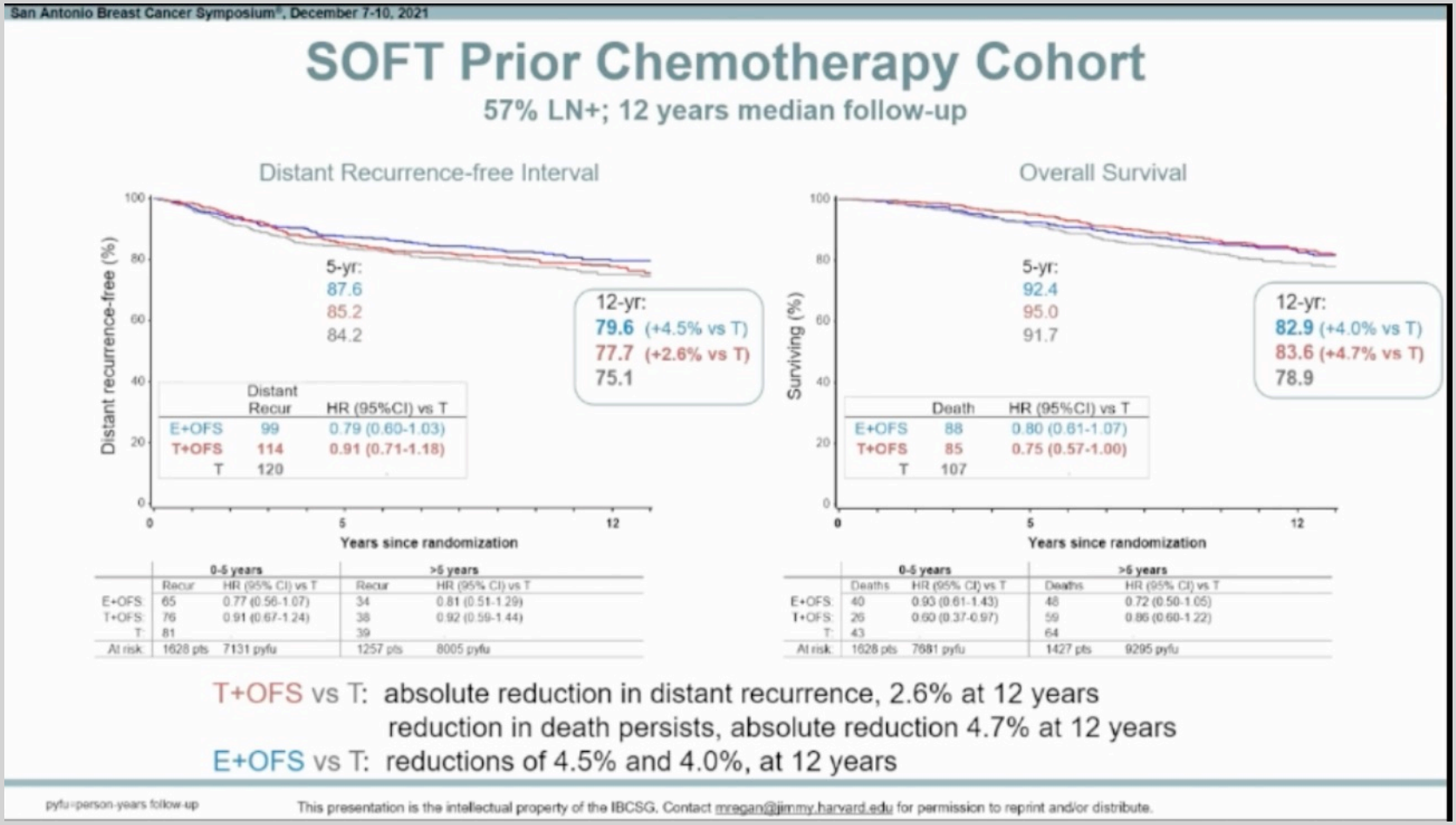

Adjuvante Endocrine Therapy in Premenopausal Patients

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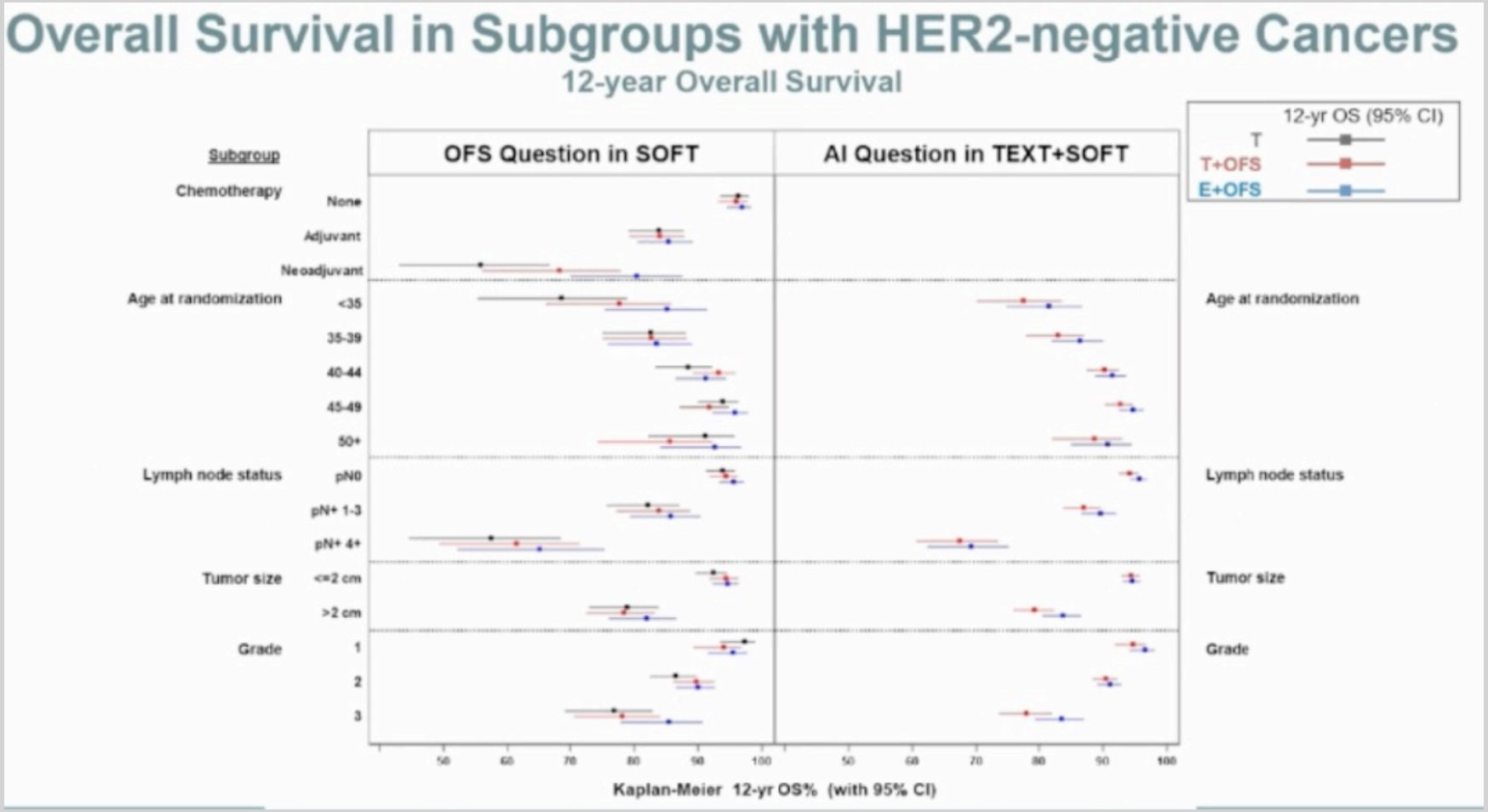

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GnRH Analogue every 3 Months

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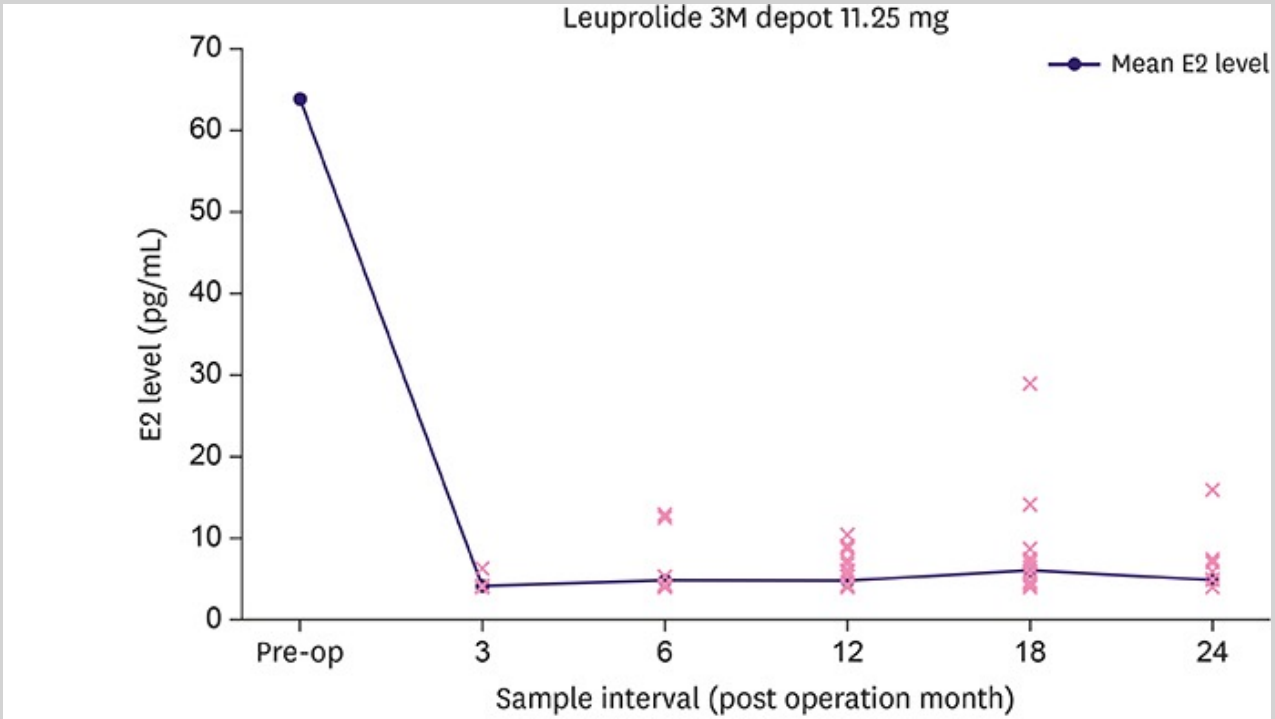

Mean pg/mL (SD)	63.7 (93.8)	4.1 (0.5)	4.8 (2.5)	4.8 (1.7)	6.1 (5.1)	4.9 (2.3)
Number	318	19	23	35	27	30

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Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 1-5)

	Oxford		
	LoE	GR	AGO
▪ Aromatase inhibitor (AI) for first 5 years	1a	A	++
▪ Non steroidal-AI in lobular cancer	2b	B	+
▪ High risk of recurrence	2b	B	+
▪ Sequential therapy for first 5 years *	1a	A	++
▪ Tam (2-3 yrs.) followed by AI to complete 5 years	1a	A	++
▪ AI (2-3 yrs.) followed by tamoxifen to complete 5 years	1b	C	++
▪ Tamoxifen 20 mg/d for 5 years**	1a	A	+

* in postmenopausal patients, AI should be integrated in the first five years

** Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present

Aromatase Inhibitor vs. Tamoxifen vs. Sequentieller Therapie - 5 Jahre Upfront Therapie

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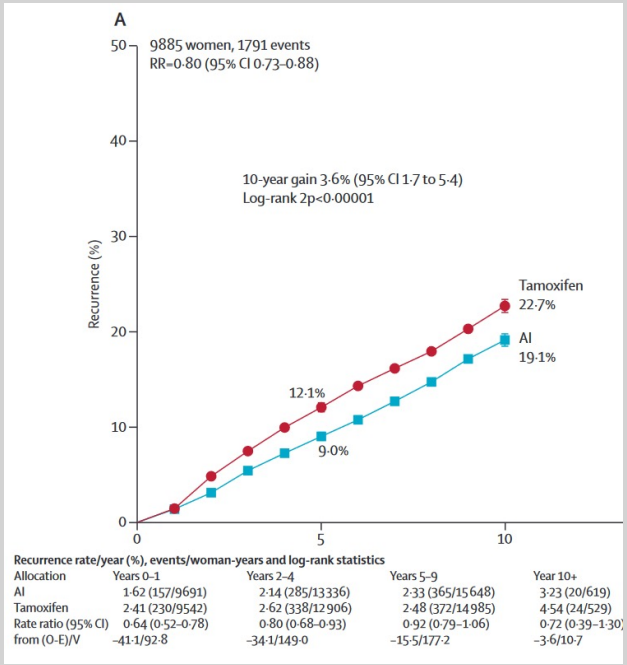
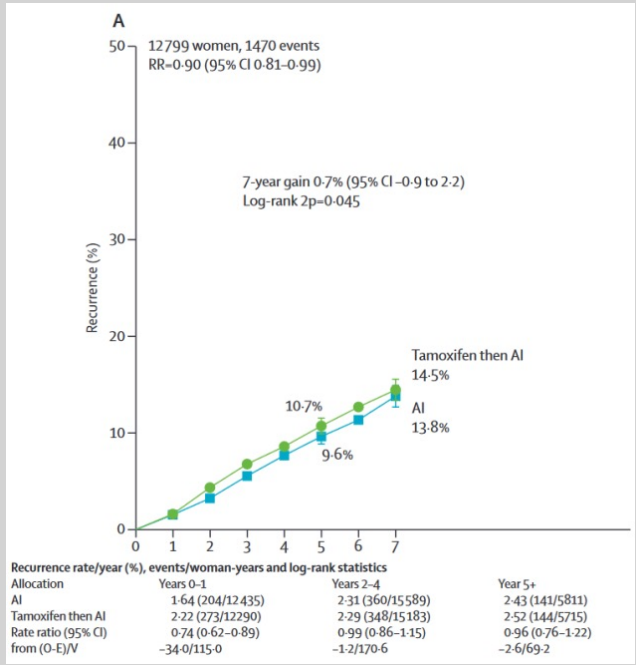


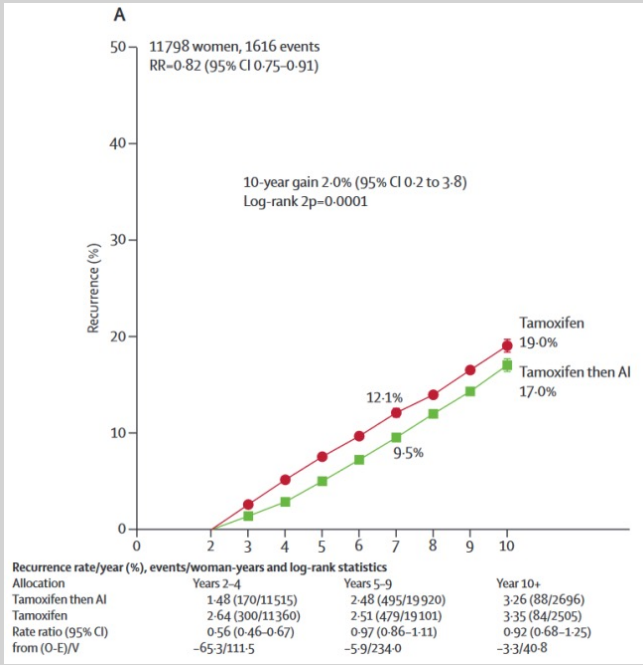
Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13336)	2·33 (365/15648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12906)	2·48 (372/14985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	−41·1/92·8	−34·1/149·0	−15·5/177·2	−3·6/10·7



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

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12435)	2·31 (360/15589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12290)	2·29 (348/15183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	−34·0/115·0	−1·2/170·6	−2·6/69·2



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

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	−65·3/111·5	−5·9/234·0	−3·3/40·8

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Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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Adjuvante Endocrine-Based Therapy with CDK4/6 Inhibitors and PARP Inhibitors

	Oxford		
	LoE	GR	AGO
In patients with increased risk of recurrence and characteristics corresponding to study criteria			
▪ **Abemaciclib for 2 years***	1b	B	+
▪ **Olaparib for 1 year in patients with *gBRCA1/2* mutations****	1b	B	+
▪ **Palbociclib for 1-2 years**	1b	B	-

* corresponding to MonarchE-Study
** corresponding to OlympiA-Study

How to calculate CPS+EG Score?

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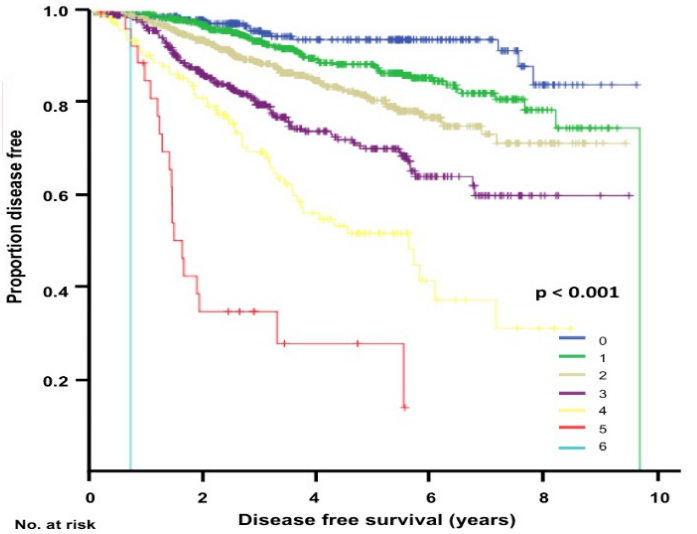
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;
Marmé F, et al. Eur J Cancer 2016

PARP-Inhibitors in Addition to Standard Endocrine Therapy in the Adjuvant / Post-Neoadjuvant Situation

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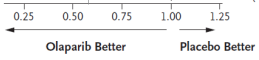
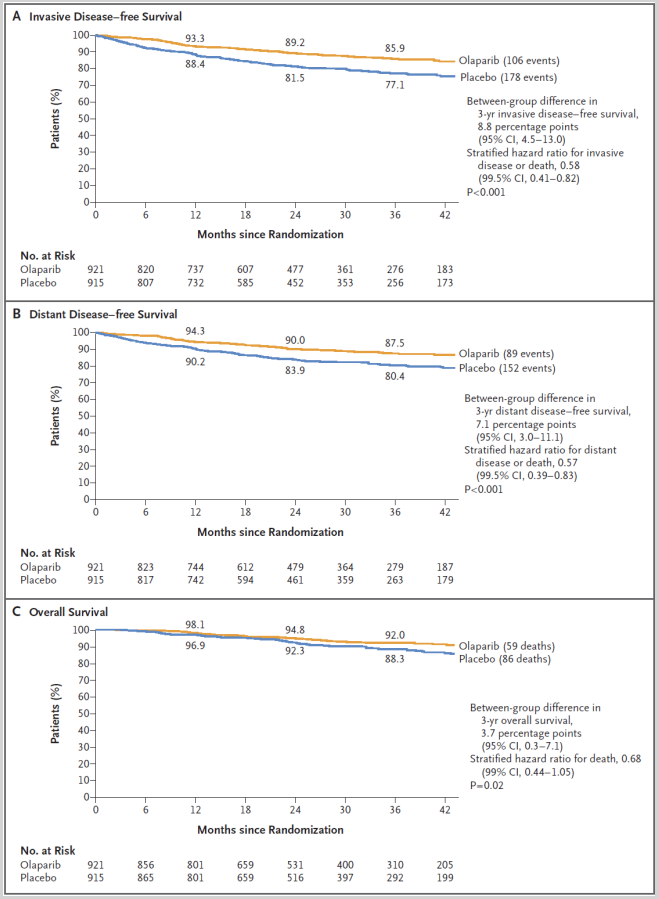
Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)





CDK4/6 Inhibitors in Addition to Standard Endocrine Therapy in the Adjuvant / Post-Neoadjuvant Situation

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	monarchE	PALLAS	PENELOPE[B]
N	5,637	5,600	1,250
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib
% of pts. with NACT	37%	n.r.	100%
Duration of CDK4/6i treatment	24 mths	24 mths	12 mths
Follow-up	27.1 mths	24 mths	43 mths
Discontinuation rate	28%	42%	20%
Discontinuation rate due to AE_{CDKi}	17%	27%	5%
IDFS-HR (95%-CI)	0.70 (0.58-0.82) p<0.0001	0.96 (0.81-1.14) p=0.65	0.93 (0.74-1.16) p=0.525
2-yrs IDFS	92.7% vs. 90.0%	n.r.	88% vs. 78%
3-yrs IDFS	88.8% vs. 83.4%	88% vs. 89%	81% vs. 78%
4-yrs IDFS	n.r.	84.2% vs. 84.5%	73% vs. 72%

IDFS: invasive disease-free survival

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Premenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	++
▪ 2–5 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

Postmenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years tamoxifen after 5 years tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI for 2–5 years*			
▪ High-risk and good tolerabilty of AI	1a	A	+
▪ Low-risk, poor tolerabilty of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-

* Up to date, no impact on OS

Extended Aromatase Inhibitor Treatment following 5 or more Years of Endocrine Therapy: A Metaanalysis of 22192 Women in 11 Randomised Trials (EBCTCG)

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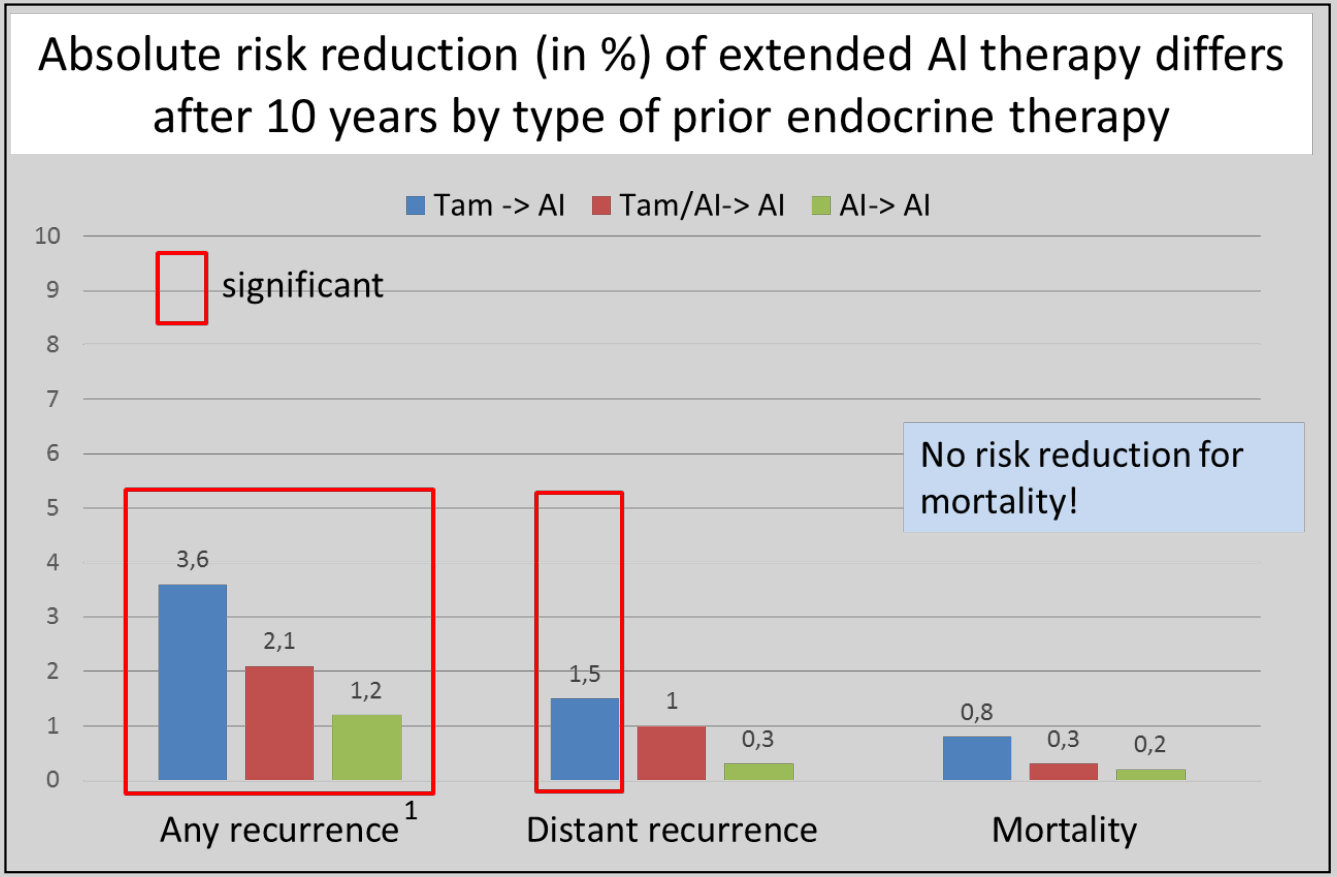
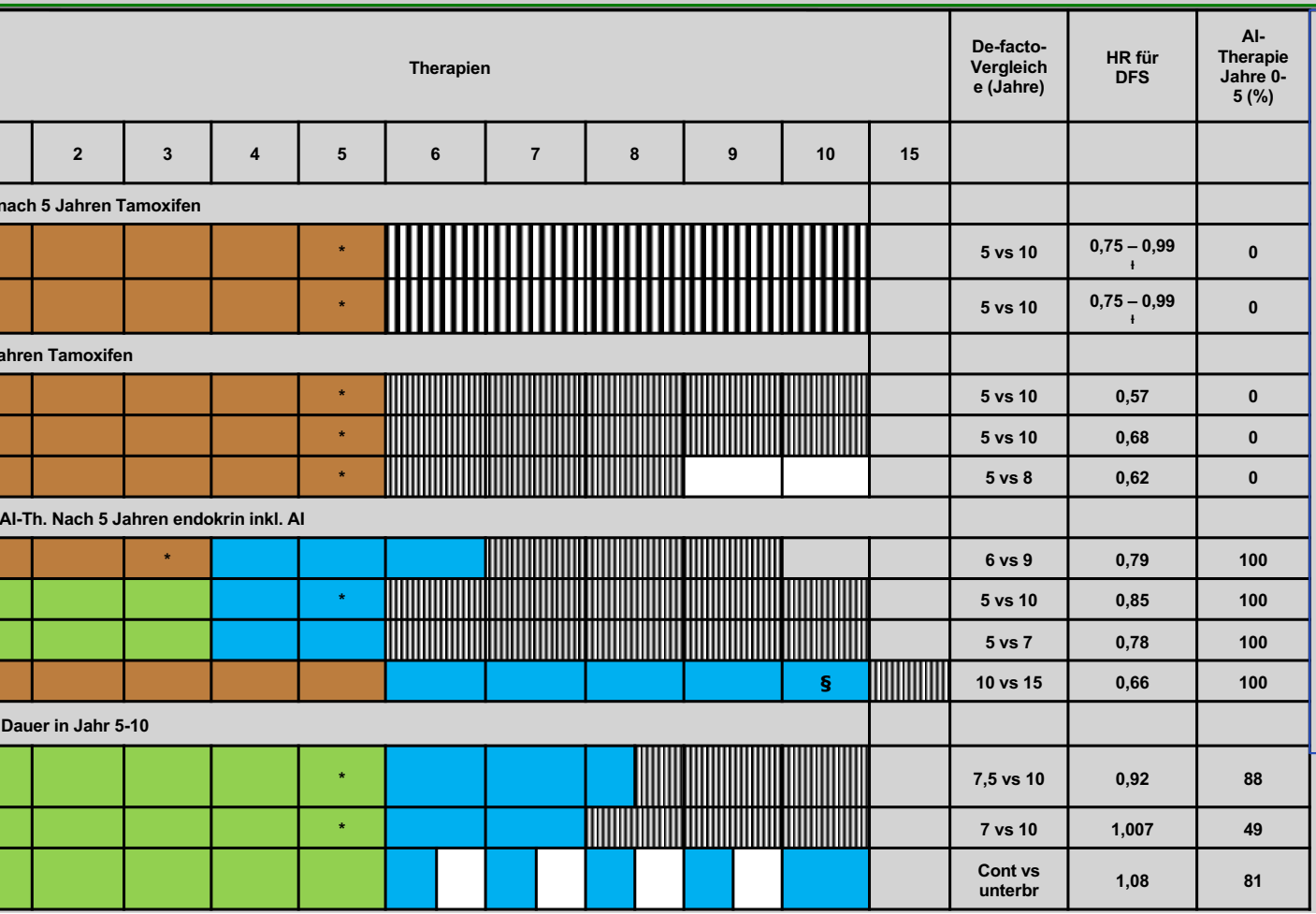


[1] *(new primary breast cancer, local and distant recurrence)*

Gray R et al. SABCS 2018 (GS3-03)

Extended Adjuvant Treatment, Overiew



Braun: Tamoxifen

Grün: Tamoxifen oder AI

Blau: AI

Gestreift: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo

*: Rando-misierungs-zeitpunkt

§ : MA17R nach 5 Jahren AI mit /ohne Tam zuvor

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Decision Criteria for Extended Adjuvant Therapy

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Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and / or T2 / T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score
- BCI (H/I) (Breast Cancer Index)

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

	Oxford		
	LoE	GR	AGO
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information *https://fertiprotekt.com/english*)**			++
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-

Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient–Level Data

N = 837 patients from 5 trial, median follow-up time 5.0 years (IQR, 3.0-6.3 years)

	Control	GnRH	HR (95%-CI)	P-value
POI[1,2]	30.9%	14.1%	0.38; 0.26 to 0.57	< 0.001

1 *premature ovarian insufficiency*
2 *different definitions and time points were used*
3 *i n most trials POI and not pregnancy was defined as the primary endpoint*

No significant differences in disease-free survival and overall survival were observed between groups.

Lambertini M et al. J Clin Oncol 2018