

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Guidelines Breast
Version 2010.1.1D

Adjuvante endokrine Therapie prämenopausaler Patientinnen

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➤ **Version 2002:**
Scharl

➤ **Version 2003 - 2008:**
**Jackisch / Harbeck / Huober / Lisboa /
Maass / von Minckwitz / Schaller / Scharl /
Schneeweiss / Solomeyer / Untch**

➤ **Version 2010:**
Gerber / Göhring

Adjuvante endokrine Therapie prämenopausaler Patientinnen

Bestimmung des Menopausenstatus:

AGO

➤ **Menstruationsanamnese**

+

➤ **FSH, E2**

++

Standardtherapie für prämenopausale Patientinnen mit rezeptorpositiven Tumoren

Oxford / AGO
LoE / GR

Standardtherapie für rezeptorpositive Tumoren:

- **Endokrine Therapie** **1a A** **++**
- **Chemo-endokrine Therapie** **1a A** **++**
(abhängig vom individuellen Risiko und dem Grad der ER/PgR Expression)

Bestimmung des Steroid-Hormonrezeptorstatus

Oxford LoE: 1

GR: A

AGO: ++

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„Endocrine responsiveness“

(früher rezeptorpositiv):

Immunhistochemie (ER und / oder PgR)

0% pos. Zellen: endokrin nicht sensitiv

≥ 1% pos. Zellen : endokrin sensitiv

Status unbekannt: endokrin sensitiv

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**GnRH-Analoga (GnRHa) =
Ovarektomie = Radiotherapie**

Oxford LoE: 4

(Chemo-)Endokrine Therapie prämenopausaler Patientinnen mit endokrin sensitiven Tumoren

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➤ Hohes oder mittleres Risiko

- | | | | |
|-----------------------|----|---|------|
| ➤ Chemo → TAM | 1a | A | ++ |
| ➤ Chemo → TAM + GnRHa | 1a | B | +/-* |
| ➤ < 40 Jahre | 2a | C | +* |

➤ Niedriges oder mittleres Risiko

- | | | | |
|--|----|---|-----|
| ➤ TAM allein | 1a | A | ++ |
| ➤ TAM + GnRHa | 1a | B | +* |
| ➤ GnRHa allein (bei Kontra-
indikationen gegen TAM) | 1a | B | +/- |

* Studienteilnahme empfohlen

Aromatasehemmer bei prämenopausalen Patientinnen mit endokrin sensitiven Tumoren



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	Oxford / AGO LoE / GR		
➤ GnRHa + Anastrozol	1b	B	-*
➤ falls relevante Kontraindik. gegen TAM	1b	B	-
➤ AI allein	1c	A	--
➤ AI nach GnRHa (induzierte Amenorrhoe)	5	D	--
➤ “Upfront“-AI bei Patientinnen mit chemotherapieinduzierter Amenorrhoe (CIA, TIA)	4	C	--

* Studienteilnahme empfohlen

Dauer der Behandlung

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Tamoxifen	5 Jahre	1a	A	++
Tamoxifen	5 – 10 Jahre	2b^a	C	+/-
GnRH-Analoga	2 – 5 Jahre	1b	A	++
Amenorrhoeinduktion nach CT durch GnRH-Analoga		2b	D	+/-

Prognose der Erkrankung nach GnRHa-Therapie (≥ 2 Jahre) ist unabhängig von der Ovarialfunktion (funktionell / nicht funktionell)

LoE 2b

Ovarschutz und Fertilitätserhaltung bei prämenopausalen Patientinnen mit adjuvanter Chemotherapie (CT)



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LoE / GR

CT + GnRHa

(GnRHa Applikation > 2 Wochen vor Chemotherapie)

- **HR+** 3b C -
- **HR-** 1b B -
- **BRCA-1- und/oder -2-Mutation** 5 D -

Beeinflussung des Chemoeffektes nicht ausgeschlossen!

- **Beratung über Fertilitätserhaltung** 5 D +

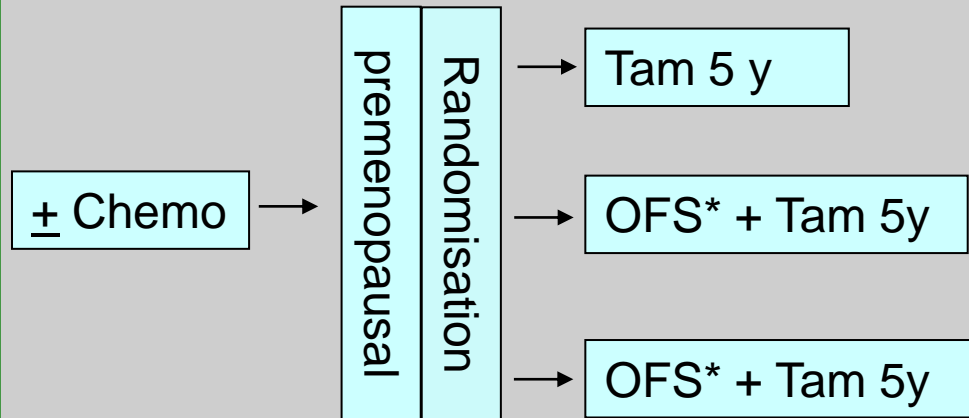
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Ongoing RCTs

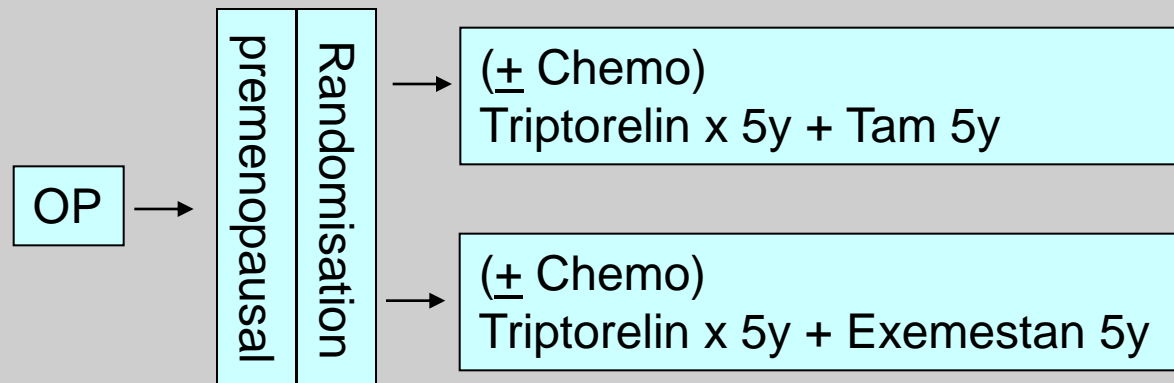
<http://www.germanbreastgroup.de>

SOFT- (Suppression of Ovarian Function) trial



OFS = Ovarian Function Supression = Triptorelin 5y or BSO or radiomenolysis

TEXT- (Tamoxifen Exemestan) trial





Use of Luteinising-Hormone-Releasing Hormone Agonists as Adjuvant Treatment in Premenopausal Patients with Hormone-Receptor-Positive Breast Cancer: A Meta-Analysis of Individual Patient Data from Randomised Adjuvant Trials

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Chemo ± LHRH	n	RRR*	95% CI	
Age ≤ 40 years	714	-24.7	(-39.5 to 6.2),	p = 0.01
Age > 40 years	1662	- 5.1	(-20.1 to 12.7),	p = 0.55

Chemo + tam ± LHRH	n	RRR*	95% CI	
Age ≤ 40 years	81	-31.2	(-67.5 to 46.0),	p = 0.33
Age > 40 years	284	5.3	(-33.3 to 66.3),	p = 0.82

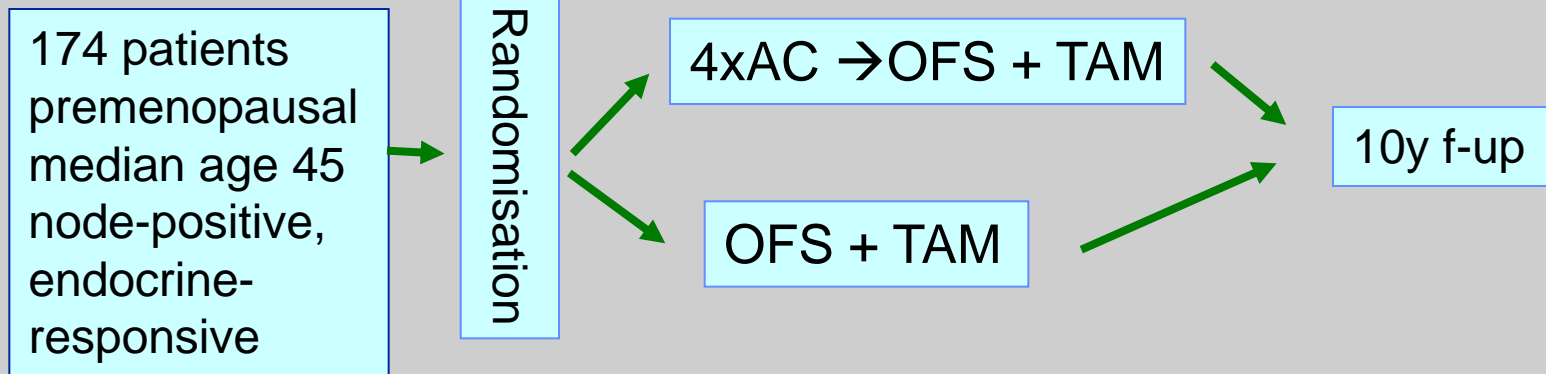
(Chemo ± tam) ± LHRH (Combination of previous comparisons: chemo ± LHRH and chemo + tam ± LHRH!)

Age ≤ 40 years	795	-25.2	(-39.4 to -7.7),	p = 0.01
Age > 40 years	284	- 3.9	(-18.1 to 12.9),	p = 0.63

* relative risk reduction

Cuzick J et al., Lancet 2007; 369:1711-23

Chemo + Castration + TAM vs. Castration + TAM



DFS hazard ratio = 1.02 (0.57-1.83); P = 0.94

OS hazard ratio = 0.97 (0.44-2.16); P = 0.94

- Trial was closed prematurely due to low accrual rate.
- No evidence that AC chemotherapy provides additional disease control for premenopausal patients with lower-risk node-positive endocrine-responsive breast cancer who receive adequate adjuvant endocrine therapy.

Thürliman B et al: 10-year update of IBCSG 11-93
Breast Cancer Res Treat. 2009; 113:137-44

Cochrane

- Meta-analyses of 14 randomized trials that involved over 13 000 patients assessing the effect of GnRHa \pm Tamoxifen \pm Chemotherapy concluded
- (A) GnRHa monotherapy: results suggest that adjuvant GnRHa monotherapy is similar to older chemotherapy protocols (eg. CMF) in terms of recurrence-free and overall survival in ER+ patients. There are insufficient data to compare GnRHa monotherapy to tamoxifen alone, but available results suggest that these treatments are comparable in terms of recurrence-free survival.

(B) GnRHa + anti-oestrogen therapy: there are insufficient data to compare the combination of an GnRHa plus tamoxifen to tamoxifen alone. Results suggest that the GnRHa plus tamoxifen combination may be superior to an GnRHa alone or to chemotherapy alone, but the chemotherapy protocols tested are outdated. The data comparing GnRHa plus aromatase inhibitors to GnRHa plus tamoxifen are currently inconclusive.

(C) GnRHa + chemotherapy: there are insufficient data to compare the GnRHa + chemotherapy combination to an GnRHa alone, although results from a single study suggest comparable efficacy in ER+ patients. There is a trend towards improved recurrence-free and overall survival in patients who received an GnRHa plus chemotherapy combination in comparison to chemotherapy alone.

(D) GnRHa + chemotherapy + tamoxifen: there is a trend towards improved recurrence-free and overall survival in patients who received an GnRHa plus tamoxifen plus chemotherapy in comparison to chemotherapy alone.

GnRHa: Observation Studies

	Recchia 2006	Fox 2003	Del Mastro 2006	Urrutico- echea 2008
N	100	24	29	60
Pts.-charact.				
pT	2-3,	1-2	1-3,	-
N+	58 %	50 %	55 %	-
Horm. rec. pos.	52 %	-	86 %	72 %
Age (med., years)	43	35	38	34
Med. F/U [mths]	75	34	72	43
GnRH-a application	during Chemo up to 1 year	during Chemo		
Chemotherapy	FAC, CMF, E₁₂₀- CMF, Taxane, high-dose Chemo	AC, AC-T, FAC, AT- CMF	FEC, AC-T	FEC, FEC-T, AC, EC-T
Regular menstr. ≤1 year after Chemo	100% (<40 y.) 56% (>40 y.)	96% -	94% (<40y) 42% (>40y)	86% -
Pregnancies/ Births	3% / 2%	21% / 8%	-	20% / 16%

GnRHa: RCTs

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	Badawy (2009)		Ismail-Khan (2008)		ZOR0 (2009)	
	Chemo+ GnRH-a	Chemo	Chemo+ GnRH-a	Chemo	Chemo+ GnRH-a	Chemo
N	39	39	25	24	30	30
Pts.-character.						
pT	-	-	-	-	1-4	1-4
N+	-	-	50 %	50 %	35%	42%
Horm. rec. pos.	-	-	-	-	0%	0%
Age (med., years)	30	29	39	39	35	38
Med. F/U [mths]	8	8	18	18	24	24
GnRH-a appl.	During Chemo		During Chemo		During Chemo	
Chemotherapy	6x FA₅₀₀C d1q6-8w		6x FAC, AC-T, TAC		6x FEC, AC-T, TAC	
Regular menstr.						
≤1 year	90%	33%	83%	79%	83%	80%
- end of F/U	-	-	88%	84%	93%	97%
Pregn. / Births	-	-	0	8%	3% / 3%	3% / 0