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Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

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- **Versionen 2002–2016:**

  Bauerfeind / Dall / Diel / Fersis / Friedrichs / Gerber / Göring / Harbeck / Huober / Jackisch / Lisboa / Lück / Maass / von Minckwitz / Möbus / Müller / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2017:**

  Hanf / Lux

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Bestimmung des Steroid-Hormonrezeptorstatus

Oxford LoE: 1 **GR: A** **AGO: ++**

„Endokrines Ansprechen“ (früher rezeptorpositiv):

Immunhistologie (ER und / oder PgR)

0%	**pos. Zellen:**	**endokrin nicht sensitiv**
1-9%	**pos. Zellen**	**endokrin fraglich sensitiv**
≥ 10%	**pos. Zellen :**	**endokrin sensitiv**

Status unbekannt: **endokrin sensitiv**

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Bestimmung des Menopausenstatus

Oxford / AGO LoE / GR

Bestimmung des Menopausenstatus:

- **Menstruationsanamnese** **+**
- **FSH, E2** **++**

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Adjuvante endokrine Therapie

Standardtherapie für endokrin sensitive / fragl. sensitive Tumoren:

	Oxford / AGO LoE / GR		
➢ **Endokrine Therapie**	1a	A	++
➢ **Chemo-endokrine Therapie** (abhängig vom individuellen Risiko und Tumorbiologie)	1a	A	++

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Adjuvante endokrine Therapie

	Oxford / AGO LoE / GR		
➢ **Endokrin sensitiv & fraglich sensitiv: endokrine Therapie**	1a	A	++
➢ **Endokrine Therapie sequentiell nach einer Chemotherapie**	2b	C	++
➢ **Nicht endokrin sensitiv: keine endokrine Therapie**	1a	A	++

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Generelle Prinzipien der adjuvanten endokrinen Therapie
AGO ++

- **Die adjuvante endokrine Therapie wird in die initiale Therapie (Jahre 0-5) und die erweiterte adjuvante Therapie (EAT, Jahre 6-15) eingeteilt.**
- **Standard ist die Therapiedauer von 5 Jahren.**
- **Erweiterte Therapiedauer nach individueller Nutzen-Risiko-Abwägung.**
- **Dauer, Wahl & Sequenz von AI oder Tam hängen v.a. von Menopausenstatus, Verträglichkeit und Risiko ab.**
- **Der Wechsel auf eine andere endokrine Therapie (Tam oder AI) ist besser als zu stoppen.**
- **Beginn mit AI bei postmenopausalen Pat. insbesondere bei Hochrisiko- und lobulären Karzinomen.**
- **Es existiert kein validierter Biomarker für einen frühen versus einen späten Rückfall.**

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Adjuvante endokrine Therapie bei prämenopausalen Patientinnen

	Oxford LoE	/ AGO GR	
➢ **Tamoxifen* 5-10 Jahre**	**1a**	**A**	**++**
➢ **GnRHa Monotherapie** (nur bei relevanten Kontraindikationen für Tam)	**1a**	**B**	**+**
➢ **Bei Pat. mit Ovarialfunktion (innerhalb von 8 Monaten) nach adjuvanter Chemotherapie:**			
➢ **#OFS (Ovarialfunktionssuppression) 5 Jahre + TAM 5 Jahre**	**1b**	**B**	**+/-**
➢ **Bei Patientinnen < 35 Jahre**	**1b**	**B**	**+**
➢ **#OFS 5 Jahre + AI 5 Jahre**	**1b**	**B**	**+/-**

*** Behandlung so lange tolerabel und prämenopausal**

 # Gesteigerte Nebenwirkungen können Compliance beeinträchtigen. Höhere Compliance bei TAM ist effektiver als Kombination mit GnRH oder Behandlung mit GnRH+AI mit eingeschränkter Compliance.

Initiale adjuvante endokrine Therapie bei postmenopausalen Patientinnen (Jahre 0-5)

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	Oxford / AGO LoE / GR		
➢ **AI für die ersten 5 Jahre**	1a	A	++
➢ **Insbesondere beim lobulären Karzinom**			
➢ **Hohes Rezidivrisiko**			
➢ **Sequentielle Therapie für die ersten 5 Jahre**			++
➢ **Tam (2-3 Jahre) gefolgt von AI bis zur Gesamtdauer von 5 Jahren**	1a	A	
➢ **AI (2-3 Jahre) gefolgt von Tamoxifen bis zur Gesamtdauer von 5 Jahren**	1b	C	
➢ **Tamoxifen 20 mg/d für 5 Jahre**	1a	A	+

Erweiterte adjuvante endokrine Therapie (EAT) bei postmenopausalen Patientinnen (Jahre 6-10)

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	Oxford / AGO LoE	GR	
➢ **2,5 - 5 Jahre AI nach 5 Jahren Tamoxifen prä-menopausal bei im Verlauf eindeutig nach-gewiesener postmenopausaler Situation**	1b	B	+
➢ **5 Jahre Tamoxifen nach 5 Jahren Tamoxifen (bei erhöhtem Risiko)**	1a	A	++
➢ **Nach 2 - 5 Jahren Tamoxifen AI für 2,5 bis 5 Jahre**	1a	B	++
➢ **Nach initialer AI-Therapie Verlängerung der endokrinen Therapie mit AI***			
➢ **höheres Risiko und bei guter Verträglichkeit des AIs**	1b	B	+
➢ **niedriges Risiko, schlechte Verträglichkeit des AIs**	1b	B	-

* **Bislang ohne Einfluss auf das Gesamtüberleben (OS)**

Prophylaxe des ovariellen Funktionsausfalls und Fertilitätserhaltung bei prämenopausalen Patientinnen mit (neo-)adjuvanter Chemotherapie (CT)

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	Oxford / AGO LoE / GR		
➢ **CHT + GnRHa** (zur Prophylaxe des ovariellen Funktionsausfalls) (GnRHa Applikation > 2 Wochen vor Chemotherapie unabhängig vom Hormonrezeptorstatus)	1a	B	+
➢ **Angebot zur Beratung über Fertilitätserhaltung**	4	C	++
➢ **Fertilitätserhalt mit assist. reprod. Therapie (Information: www.fertiprotect.de)**	4	C	+

TEXT /SOFT Joint Analysis

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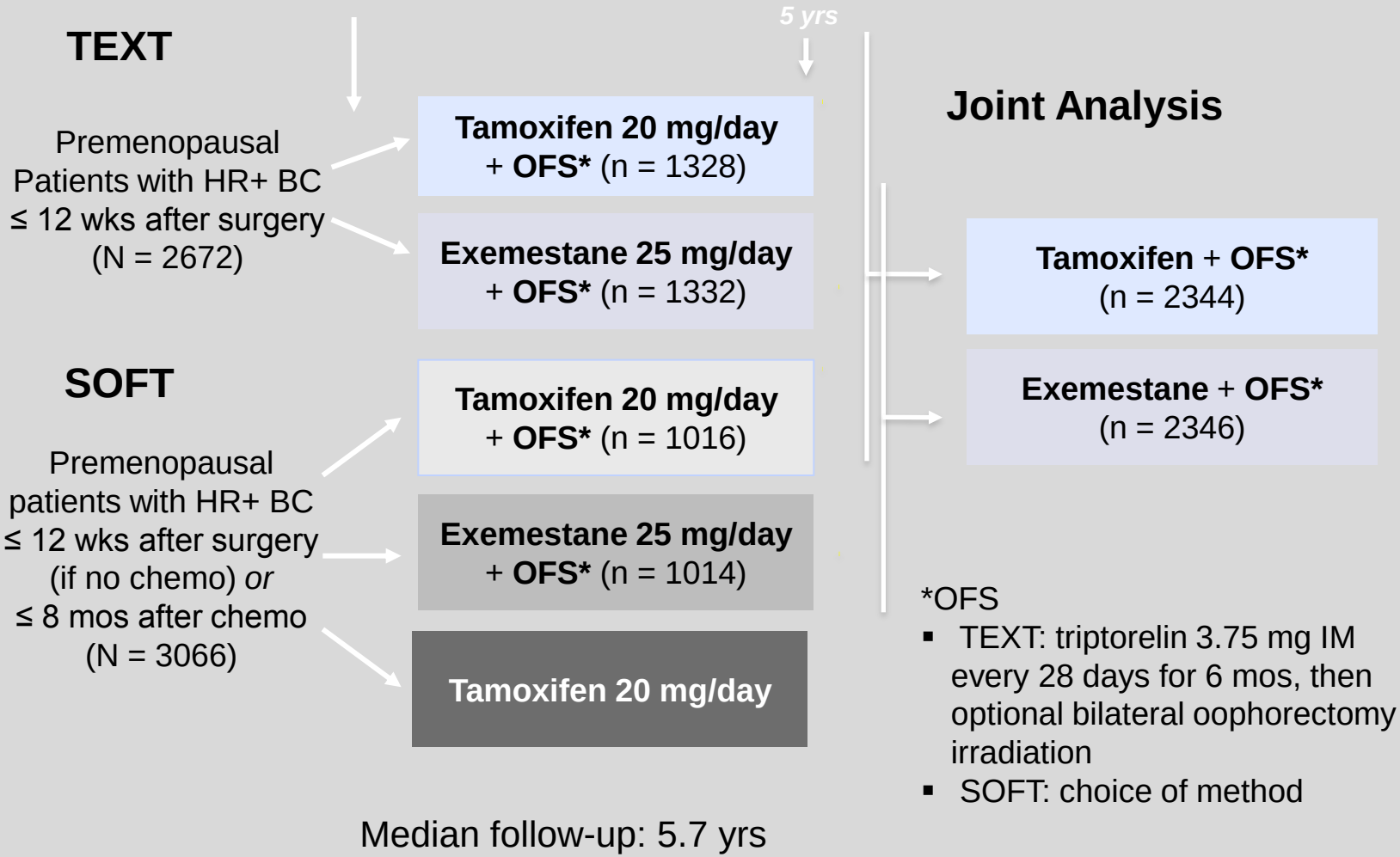

*OFS
- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

Median follow-up: 5.7 yrs

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

Incomplete Ovarian Suppression within SOFT – Study (SOFT-EST-Substudy)

- **In Soft-EST: Exe + OFS: E2, E1, E1-Sulfate - levels were significantly lower than in pats. with Tam + OS**
- **66% of premenopausal pats. on Exe + OFS had profound persistent suppression of E2 etc. for 12 months.**
- **However, 34% had an E2 level greater than menopausal threshold at least once, 17% at all time-points:**
  - **These patients were more likely younger than 35 y; chemo-naïve; had higher BMI**
  - **Importantly:** Combining ABCSG-12, SOFT, and TEXT studies, **showed 65 fewer DFS events** (HR 0.89, 95% CI 0.57–1.39) **but 30 more deaths** for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.31, 95% CI 0.93–1.84, P = 0.12, s = 0.03, heterogeneity, P = 0.18).
- **Hence the question arises, whether incomplete ovarian suppression led to this discrepancy**

Ovarian Suppression in Combination Endocrine Adjuvant Therapy in Premenopausal Women with Early Breast Cancer

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Chlebowski RT, Pan K, Col NF, Breast Cancer Res Treat
DOI 10.1007/s10549-016-4024-4

“Conclusion: Given the discordance between DFS and OS and inconsistent estrogen suppression with ov. suppr. plus AI, adding AI to ov. suppr. as adjuvant therapy in premenopausal women is premature.“

10 yrs versus 5 yrs Breast Cancer Mortality in ER+
Rate ratio per period in aTTom and ATLAS
5 yrs. vs. 10 yrs Tamoxifen

	10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)	10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)	10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)
Years 5-9	**1.08 (0.85-1.38)**	**0.92 (0.77-1.09)**	**0.97 (0.84-1.15)**
Years 10+	**0.75 (0.63-0.90) p = 0.07**	**0.75 (0.63-0.90) p = 0.002**	**0.75 (0.65-0.86) p = 0.00004**
All years	**0.88 (0.74-1.03) p = 0.1**	**0.83 (0.73-0.86) p = 0.004**	**0.85 (0.77-0.94) P= 0.001**

nach Grey et al ASCO 2013
J Clin Oncol 31, 2013 (suppl. Abstr 5)

Upfront Therapies
Overview

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Initial Therapy (years 1-5)

Trial	Source	AI	Indication	Pts	F/U mo	DFS/BCFS/TTR/ TTDR/CBC	OS	Side Effects	Remarks
ATAC	ATAC Trialists´ Group 2010	A	upfront vs T	6241	120	HR + patients: DFS HR 0·86, p=0·003 TTR ·0,79, p=0·0002 TTDR 0·85, p=0·02	HR 0.87 p=0·4	SAE T>A gyn AE T>A VE T>A SE A>T	only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR-=ER+PR+ (Cuzick 2010) QoL→ (Cella 2006)
BIG 1-98	BIG 1-98 Collaborative Group 2011	L	upfront[2] vs T	4922	97	DFS = 0·86 P = 0,007	P = 0,048	SAE T=L gyn AE T>L TE T>L CE L>T SE L>T	L>T in particular in case of N+
NCIC CTG MA.27	Goss 2010	E	upfront vs A	7576	49	EFS HR 1,02 DDFS HR 0,95	ns	Osteoporosis A>E El. liver enzymes E>A Hyperlypidaemia A>E	Randomization for Celecoxib cancelled
Meta-analysis EBCTCG	EBCTCG 2015		5 y. AI vs. 2-3 y. tam → AI to y. 5 vs. 5 y. Tam	31920		10 y. gain recurrence rate 5 y. AI vs. 5 y. Tam 3,6%, p<0,00001	10 y. gain OS 5 y. AI vs. 5 y. Tam 2,1%, p<0,009		
						10 y. gain recurrence rate 5 y. AI vs. 2-3 y. Tam → AI to y. 5 0,7%, p<0,045	10 y. gain OS 5 y. AI vs. 2-3 y. Tam → AI to y. 5 1,1%, p<0,11		
						10 y. gain recurrence rate 2-3 y. Tam → AI to y. 5 vs. 5 y. Tam 2,0% p<0,0001	10 y. gain OS 2-3 y. Tam → AI to y. 5 vs. 5 y. Tam 1,5% , p<0,01		

A anstrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; CVE, cardiovascular events; Cx, chemotherapy; DFS, disease-free survival; RFS relapse-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; Qol, quality of life; Rx, radiotherapy; SAE, serious advesrse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; VE, vascular event; (?) according to retrospective analysis. * only HR positive population

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5 Years of Aromatase Inhibitor versus 5 Years of Tamoxifen

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Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R.
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.
Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1.
Epub 2015 Jul 23.

5 Years of Aromatase Inhibitor versus Tamoxifen to Years 2-3 Followed by AI to year 5

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Version 2017.1D

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R.
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Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1.
Epub 2015 Jul 23.

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Tamoxifen to Years 2-3 Followed by AI to Year 5 versus 5 Years of Tamoxifen

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R.
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.
Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1.
Epub 2015 Jul 23.

Upfront Monotherapy: Meta-analyses of DFS and OS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

Upfront Sequential Therapy: Meta-analyses of DFS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

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Upfront Sequential Therapy: Meta-analyses of OS

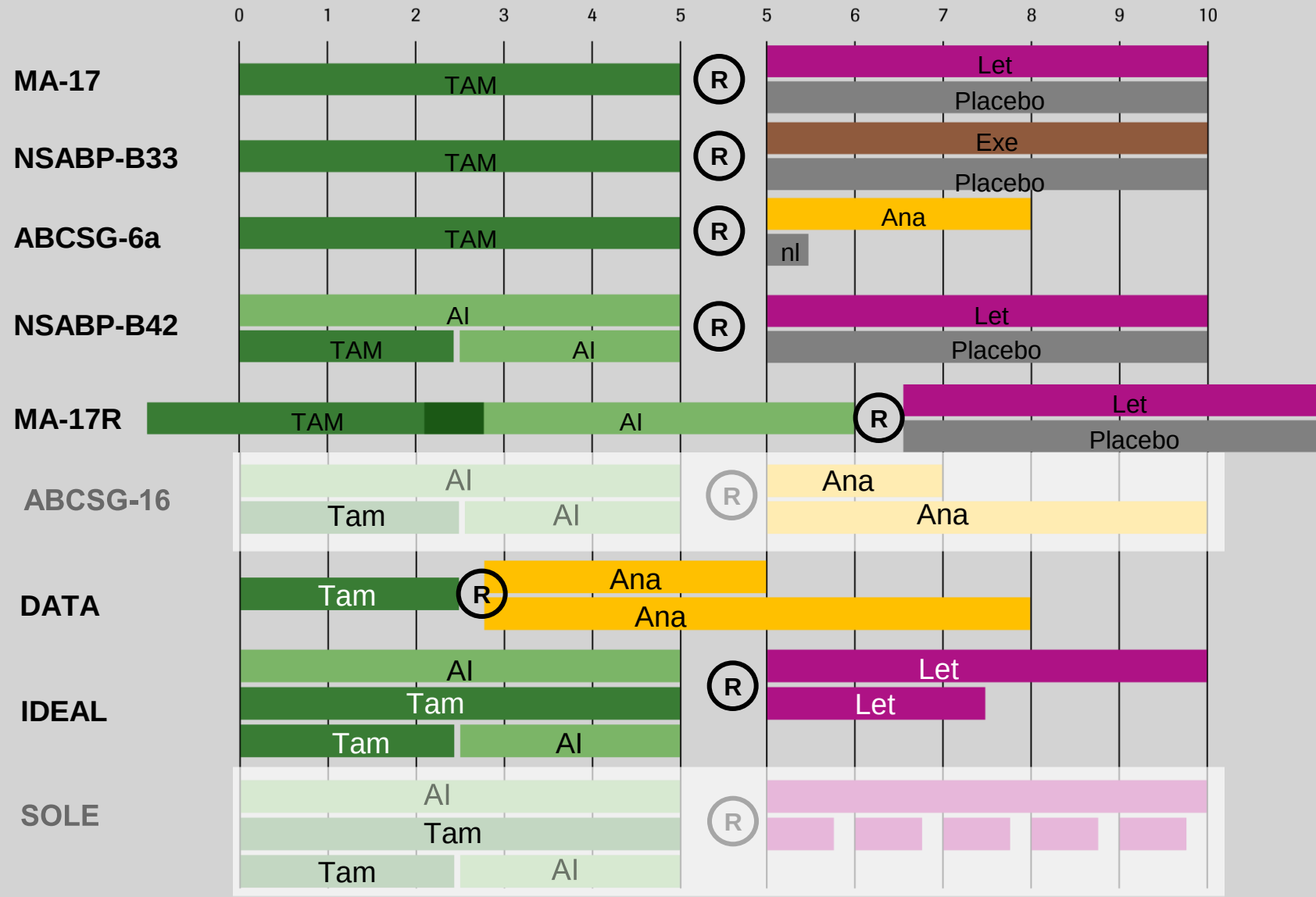
Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

Upfront sequential therapy: Meta-analyses of DFS and OS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

Extended Endocrine Therapies

Gnant M. et al., SABCS, 2016 (S1-06, Discussion)



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Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy I

Trial	Source	Patient number	Population	Upfront therapy	Trial Arms	Reported outcomes
ECOG	Tomey 1996	193	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	RFS: 85% vs. 73% (p=0.10) OS: 86% vs. 89% (p=0.52)
Scottish	Stewart 1996	342	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	Events: 60 vs. 49 EFS HR: 1.27 (0.87-1.85)
NSABP B-14	Fisher 2001	1142	Prem./postm.	Tamoxifen	Tamoxifen vs. placebo	DFS: 78% vs. 82% (p=0,03) OS: 91% vs. 94% (p=0,07)
ATLAS	Davies 2013	6846	Prem./postm.	Tamoxifen	Tamoxifen vs. placebo	Recurrence: 617 vs. 711 (p=0,01) OM: 639 vs. 722 (p=0,01)
aTTOM	Gray 2013	6953	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	Recurrence: 580 vs. 672 (p=0.003) OM: 849 vs. 910 (p=0.1)
MA.17	Goss 2005	5187	Postm.	Tamoxifen	Letrozole vs. placebo	DFS: HR 0.68 (0.55-0.83; p=0.001) OS: HR 0.98 (0.78-1.22; p=0.85)
NSABP B-33	Mamounas 2008	1598	Postm.	Tamoxifen	Exemestane vs. placebo	DFS: 91% vs. 89% (p=0.07) RFS: 96% vs. 94% (p=0.004)
ABCSG-6a	Jakesz 2007	856	Postm.	Tamoxifen	Anastrozole vs. placebo	Recurrence: 30 vs. 56, HR 0.64 (0.41-0.99: p=0.047)
Meta-analysis	Petrelli 2013	29138	Prem./postm.	Tamoxifen	Fixed duration (5 years) with an extended course of endocrine therapy vs. no therapy	RFS OR: 0.72 (0.56-0.92; p=0.01) BCSS OR: 0.78 (0.69-0.9; p=0.0003) OS OR: 0.89 (0.80-0.99; p=0.03)

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival; EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival; prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival

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Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy II

Trial	Source	Patient number	Population	Upfront therapy	Trial Arms	Reported outcomes
LATER	Zdenkowski 2016	360	Postm.	≥ 4 years of endocrine therapy (11.7% AI, 50.3% Tam, 38.0% other)	5 y. letrozole vs. observation	Breast cancer recurrence difference: 8.4% (3.8%-13.0%), p=0.0004
MA17R	Goss 2016	1918	Postm.	5 years of any other AI with or without prior tamoxifen	Letrozole vs. placebo	DFS: 95% vs. 91% (HR for disease recurrence or occurrence of contralateral breast cancer: 0.66; p=0.01) OS: 93% vs. 94% (HR: 0.97; p=0.83)
IDEAL	Blok 2016	1824	Postm.	5 years of tamoxifen, AI or tamoxifen → AI	Letrozole 2.5 vs. 5 years	DFS HR: 0.88 (0.64-1.21; p=0.43) 5-year DFS: 88.4 vs. 87.9% OS HR: 1.09 (0.70-1.70)
DATA	Tjan-Heijnen 2016	1912	Postm.	Tamoxifen 2-3 years	Anastrozole 6 vs. 3 years	DFS HR: 0.79 (0.62-1.02; p=0.07) 5-year DFS: 83.1 vs. 79.4 OS HR: 0.91 (0.65-1.29)
NSABP B-42	Mamounas 2016	3923	Postm.	AI or tamoxifen → AI 5 years	Letrozole vs. placebo	DFS HR: 0.85 (0.73-0.999; p=0.048*) * did not reach statistical significance level of 0.0418

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival; EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival; prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival

Vorschlag für eine mögliche Entscheidungs-findung für die erweiterte Adjuvanz

- **Nach 2 bis 5 Jahren Tamoxifen → Hinzunahme von Aromatasehemmer für 2,5 bis 5 Jahren,**
- **Nach initialer Aromatasehemmertherapie sorgfältige Überlegung und Abwägung:**
  - **weitere Therapie mit AI:**
    - **bisherige gute Verträglichkeit der AI-Therapie,**
    - **gute Knochengesundheit,**
    - **jüngeres Alter,**
    - **hohes Risiko nach immunhistochemischen Eigenschaften,**
    - **positiver Nodalstatus.**

nach Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

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Mögliche Wege