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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **Versions 2002–2017:**
  Bauerfeind / Dall / Diel / Fersis / Friedrichs / Gerber / Göring / Hanf / Harbeck / Huober / Jackisch / Lisboa / Lück / Lux Maass / von Minckwitz / Möbus / Müller / Oberhoff / Schaller / Scharl / Schneeweiss /Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2018:**
  Jackisch / Lück

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Assessment of Steroid Hormone Receptor Status

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

Endocrine responsiveness: formerly known as receptor negativ

Immunohistochemistry (ER and / or PgR)

0%	**pos. cells:**	**endocrine non responsive**
1-9%	**pos. cells:**	**endocrine doubtfully responsive**
≥ 10%	**pos. cells:**	**endocrine responsive**
Hormon Receptor Status unknown:		**endocrine responsive**

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Adjuvant Endocrine Therapy
Assessment of Menopausal Status

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

Adjuvant Endocrine Therapy

Standard therapy for responsive / doubtfull endocrine responsive tumors:

	Oxford		
	LoE	GR	AGO
▪ **Endocrine therapy**	1a	A	++
▪ **Chemotherapy followed by endocrine therapy** (dependent on individual risk and tumor biology)	1a	A	++

Adjuvant Endocrine Therapy

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	Oxford		
	LoE	GR	AGO
▪ Endocrine responsive & doubtfull responsive Endocrine therapy	1a	A	++
▪ Endocrine therapy Sequentially after CT	2b	C	++
▪ 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 0-5) and extended adjuvant therapy (EAT, years 6-15).**
- **Standard treatment duration is 5 years.**
- **Extended treatment should be considered based on individual benefits and risks.**
- **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 to stop.**
- **AI should be used as first treatment in postmenopausal patients especially in cases of lobular cancers and high risk of recurrence.**
- **To date, there is no validated biomarker that identifies patients for early versus late recurrence.**

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Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 0-5)

	Oxford LoE	Oxford GR	Oxford AGO
Tamoxifen* 5 -10 years	1a	A	++
GnRH alone **(only, if relevant contraindication for Tam)**	1a	B	+
Without indication for neo-/adjuvant chemotherapy and preserved ovarian function			
Tamoxifen	1b	B	++
Tamoxifen + OFS**	1b	B	+/-
AI + OFS**	1b	B	+/-
Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)			
Tamoxifen + OFS 5 years**	1b	B	+
➔ in patients < 35 years	1b	B	++
AI + OFS**	1b	B	+/-
➔ in patients < 35 years	1b	B	+

OFS: ovarian Function-Suppression; EOC: end of chemotherapy treatment as long as tolerable and the pat. is clearly premenopausal
**** only limited data on OS available**

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Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 0-5)

	Oxford		
	LoE	GR	AGO
▪ **Aromatase Inhibitor (AI) for first 5 years**	1a	A	++
▪ Lobular cancer			
▪ High risk of recurrence			
▪ **Sequential therapy for first 5 years ***			++
▪ 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 at some point
** Tamoxifen might be offered to very old patients or in patients with very low rik of recurrence or if contraindications for AI ar present

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Pre- and Postmenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT)
(Years 6-10)

	Oxford LoE	GR	AGO
Premenopause:			
▪ 2.5 - 5 years AI after 5 years Tamoxifen premenopausal in patients with validated postmenopausal status in the course of therapy	1b	B	+
▪ 5 years Tamoxifen after 5 years Tamoxifen (in case of high risk of recurrence)	1a	A	++
Postmenopause:			
▪ After 2 - 5 years Tamoxifen AI for 2.5 - 5 years	1a	B	++
▪ After initial therapy with AI further prolongation of endocrine therapy with AI*			
▪ high risk and good tolerabilty of the AI	1b	B	+
▪ low risk, poor tolerabilty of the AI	1b	B	-

* Up to date, no impact on OS

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

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	Oxford		
	LoE	GR	AGO
▪ CT + GnRHa (preserve ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status)	1a	B	+
▪ CHT + GnRHa (preserve fertility)	2a	B	+/-
▪ Fertility preservation counselling	4	C	++
▪ Fertility preservation using assisted reproduction therapy (ART) (further information www.fertiprotect.de)	4	C	+

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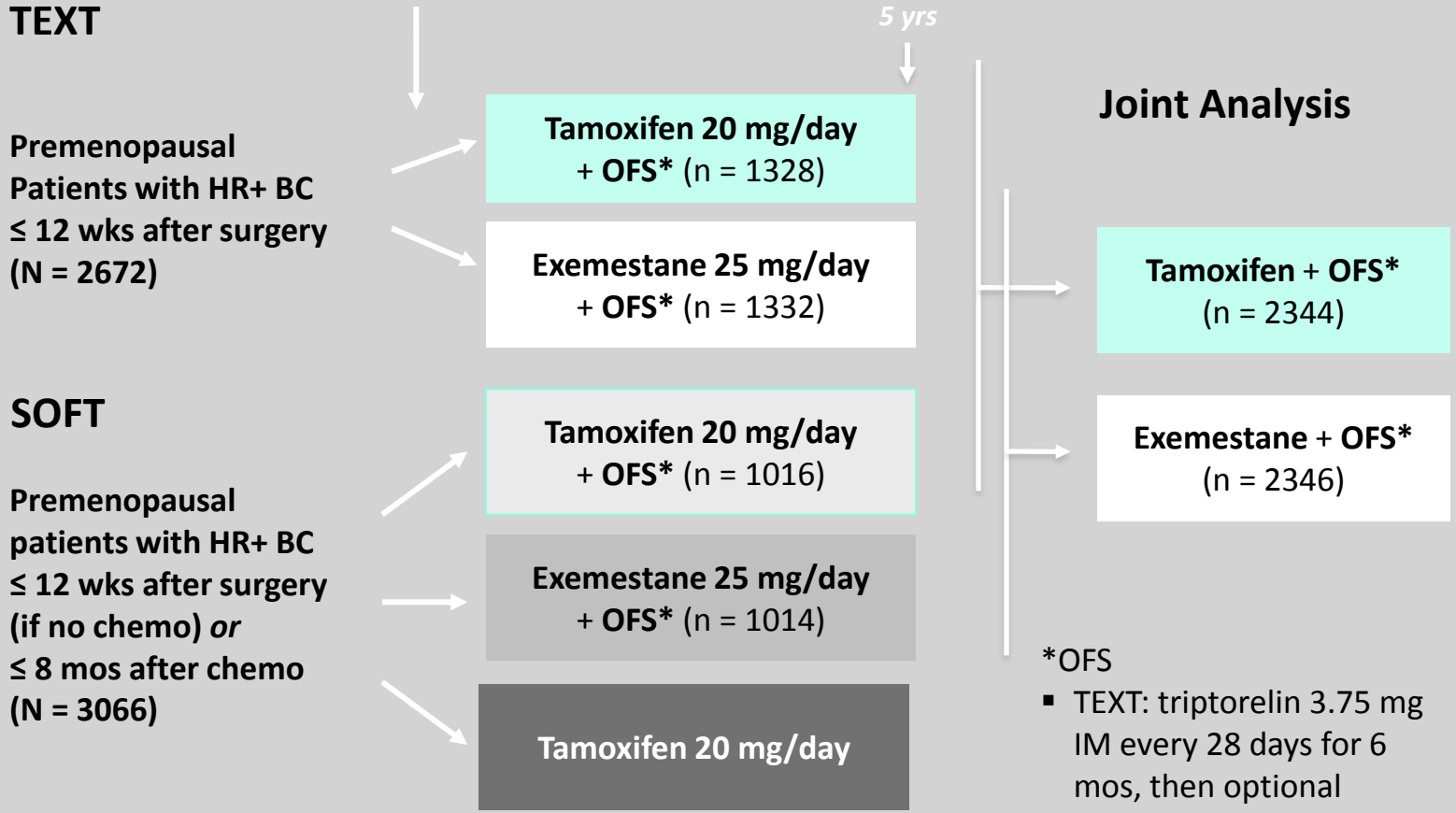
TEXT /SOFT Joint Analysis



Median follow-up: 5.7 yrs

*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

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**

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

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	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

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

Aromatase Inhibitor vs. Tamoxifen vs. Sequentiell Therapy – 5 Years Upfront Therapie

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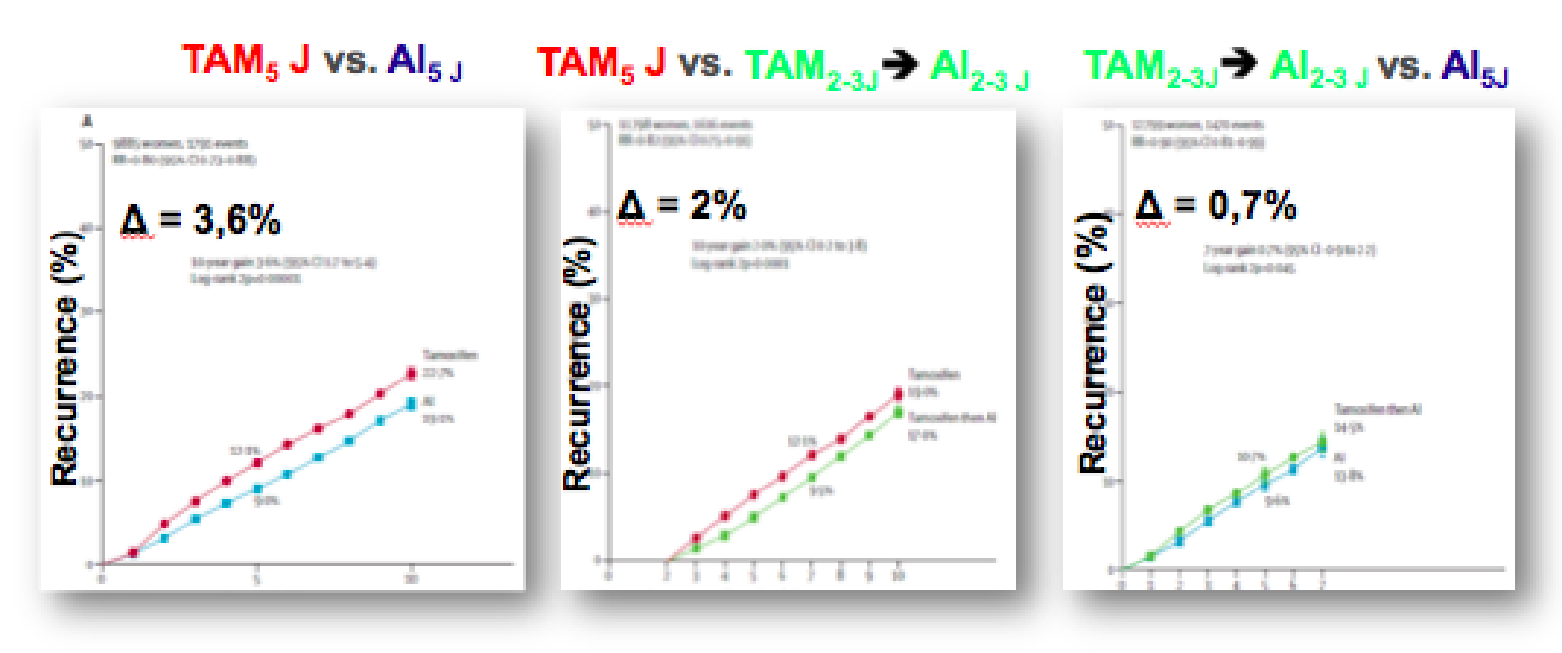

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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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.

Extended Endocrine Therapies

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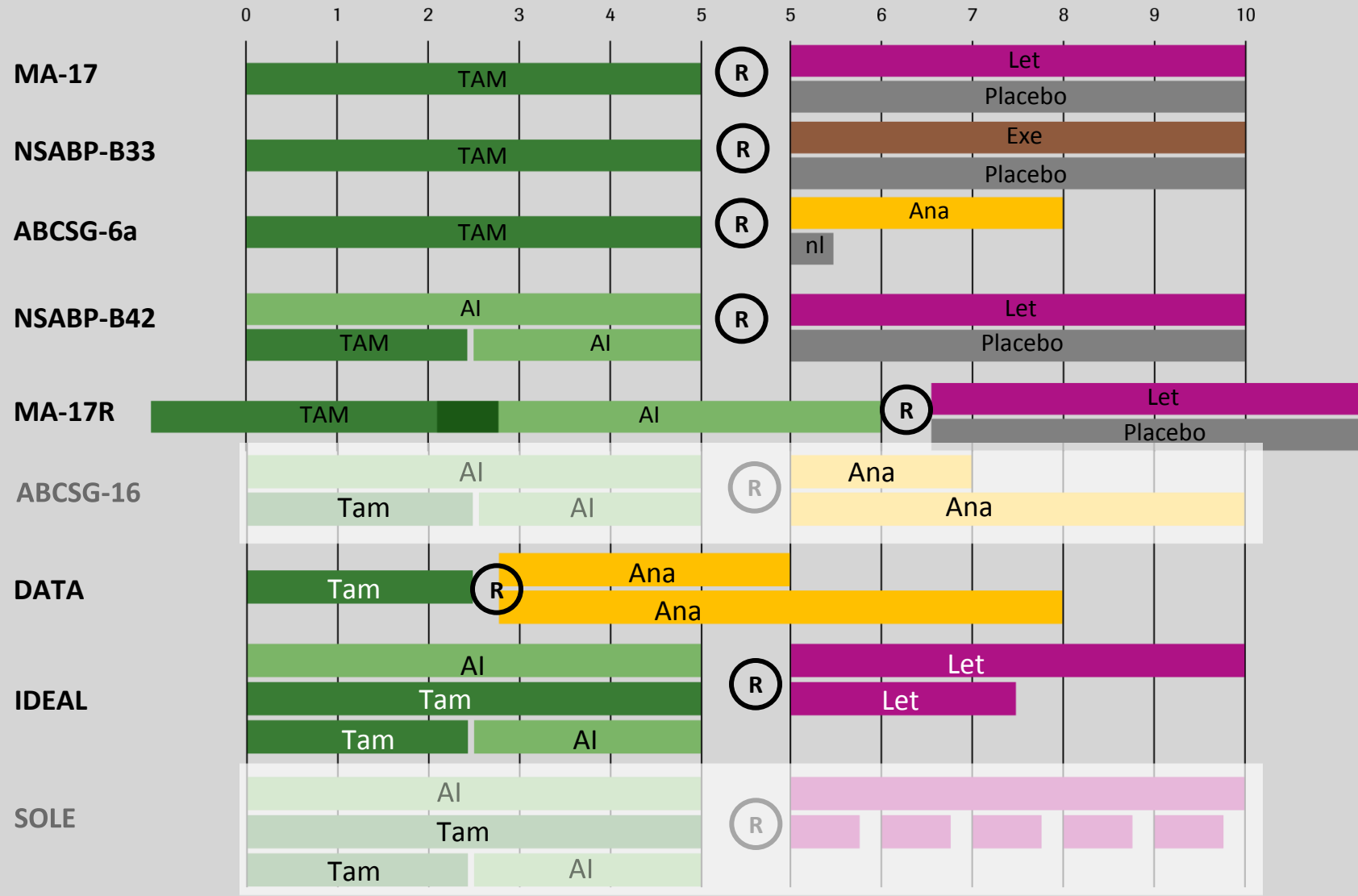

Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

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

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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

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

Conclusion for Possible Therapy Decision Extended Endocrine Therapy

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- **After 2 - 5 years tamoxifen**
  → add aromatase inhibitor for 2,5 to 5 years.

- **After initial aromatase inhibitor therapy consider carefully:**
  - **further AI therapy:**
    - **up to now well tolerated AI therapy,**
    - **good bone health,**
    - **younger age,**
    - **high risk by clinopathological factors,**
    - **node positive disease.**

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

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