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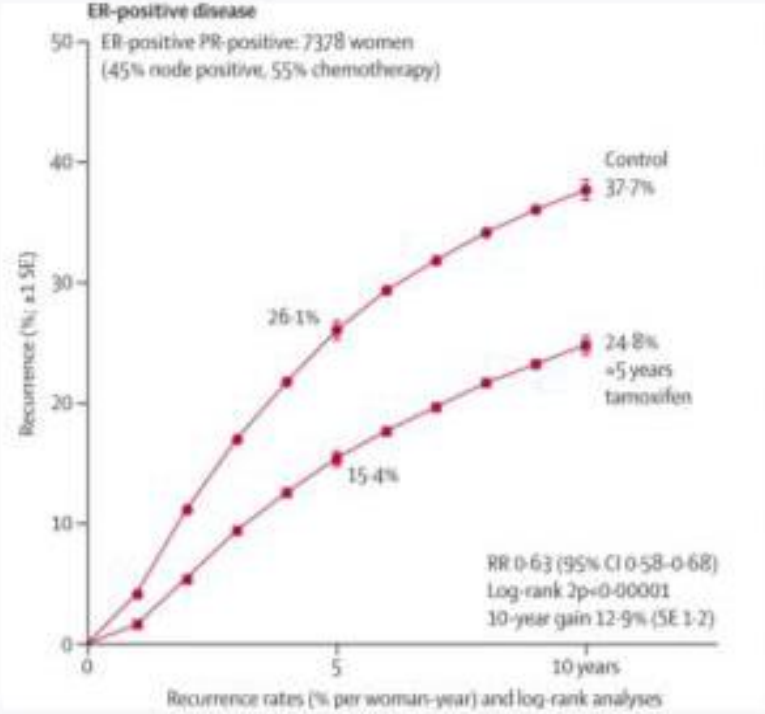
Endokrine Therapie des Mammakarzinoms

Oleg Gluz
Westdeutsche Studiengruppe/Brustzentrum Niederrhein
Uniklinik Köln

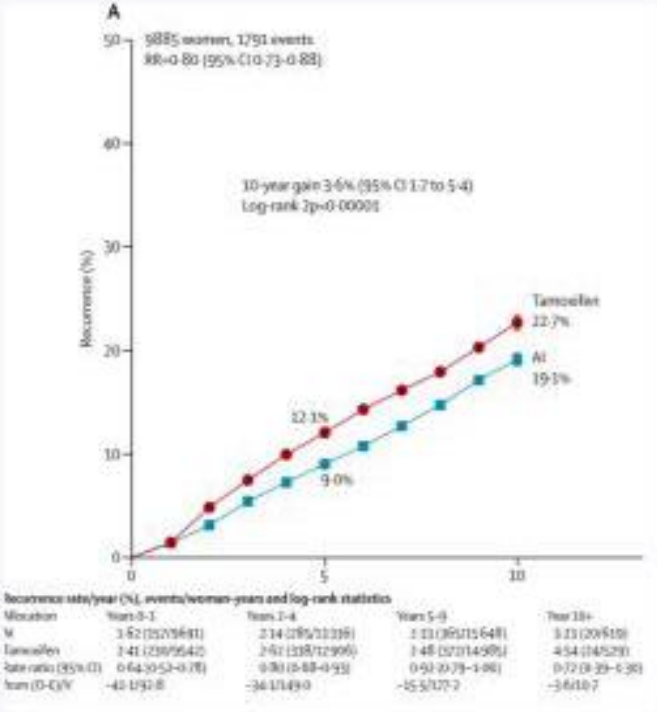
Einleitung

Tamoxifen and Aromatase Inhibitors: Adjuvant Treatment of Postmenopausal ER+ Breast Cancer

Tamoxifen vs Control



AI's vs Tamoxifen



Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2011 and 2015

.eben

Adjuvante endokrine Therapie in der Prämenopause: SOFT-/TEXT-Studie – Studiendesign

Studienaufnahme: Nov 2003 – Apr 2011

- Prämenopausal
- ≤ 12 Wo nach OP
- Geplante OS
- Keine geplante Chemo ODER geplante Chemo

Randomisierung

Tamoxifen and EXemestan Trial (n = 2672)

Tamoxifen + OS x 5 J.

Exemestan + OS x 5 J.

- Prämenopausal
- ≤ 12 Wo nach OP
- Keine Chemo

ODER

- Verbleiben prämenopausal
- ≤ 8 Mo nach Chemo

Randomisierung

Suppression of Ovarian Function Trial (n = 3066)

Tamoxifen x 5 J.

Tamoxifen + OS x 5 J.

Exemestan + OS x 5 J.

Gemeinsame Analyse
(n = 4690)

Tamoxifen + OS x 5 J.

Exemestan + OS x 5 J.

Medianer Follow-up 9 Jahre

t

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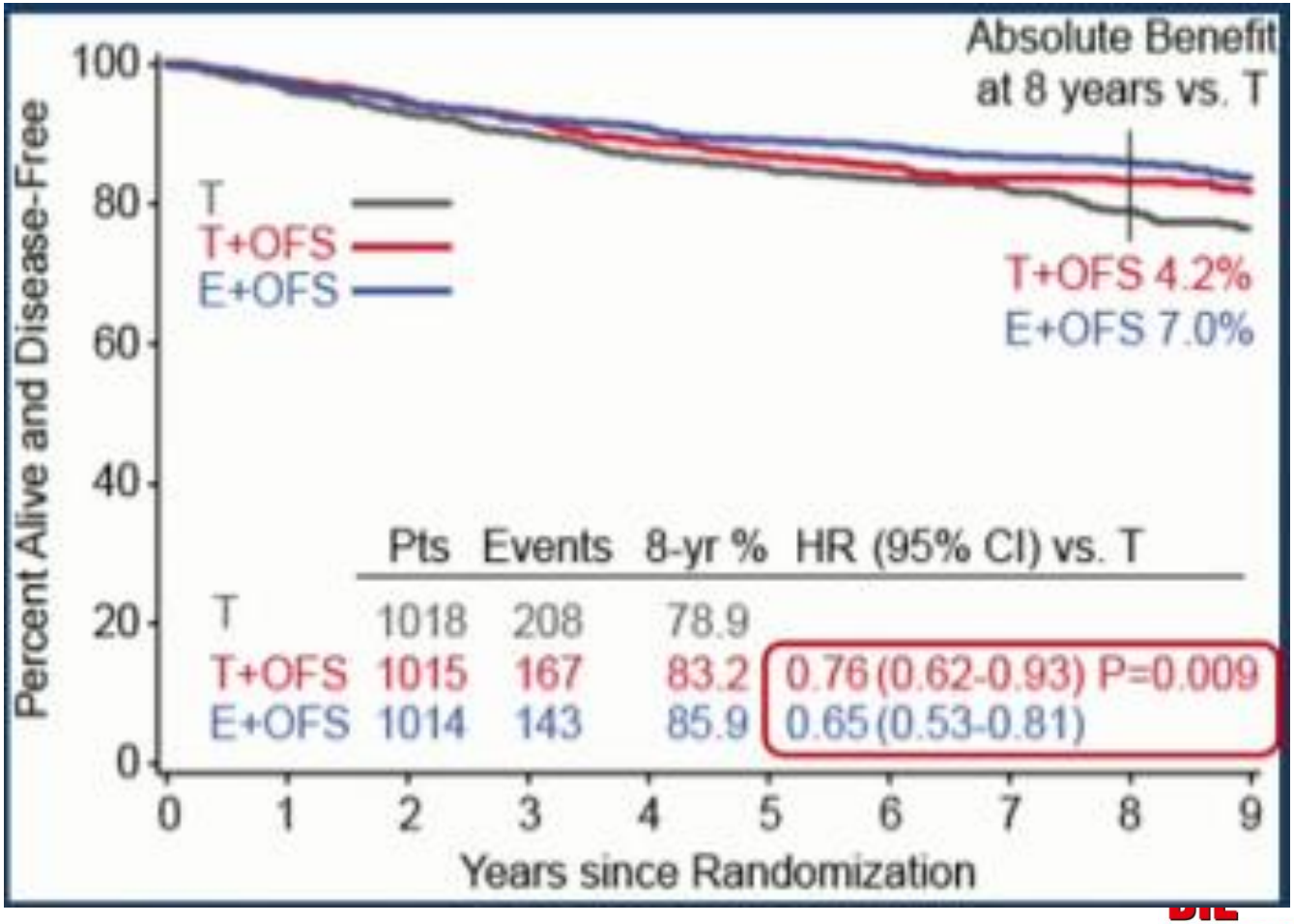
SOFT
8 Jahres Daten



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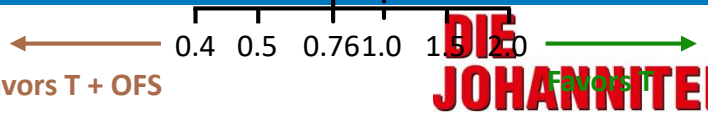
SOFT – DFS: According to Subgroups

	T + OFS		T		Hazard Ratio	p-Value
	Events	Pts	Events	Pts		
All Patients	167	1015	208	1018		**0.009**
Age of Randomization						0.82
<35	30	121	37	112		
35-39	40	184	56	203		
40-44	43	311	54	307		
45-49	40	301	42	305		
50+	14	98	19	91		
Lymph Node Status						0.63
pNO	73	662	103	112		
pN+ 1-3	53	257	64	258		
pN+ 4+	41	96	41	98		
Tumor Grade						0.66
1	29	266	34	276		
2	78	518	101	492		
3	57	212	69	228		
Unknown	3	19	4	22		
HER2 Status						0.04
Negative	147	868	168	117		
Positive	16	119	31	860		
Unknown	4	28	9	41		



Mod. Fleming G et al. SABCS 2017, Oral Session – General Session 4, Estimated No. GSM-03

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 20, 2019 VOL. 380 NO. 25

Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer

J.A. Sparano, R.J. Gray, P.M. Ravdin, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, M.M. Keane, H.L.G. Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

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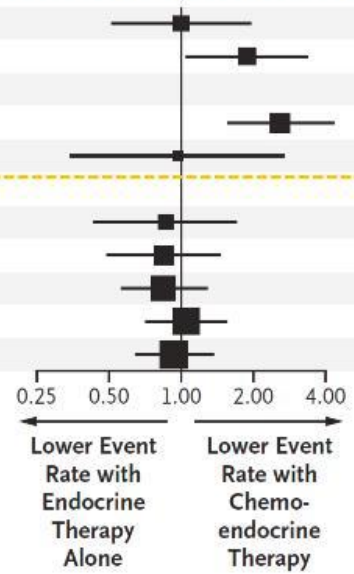
Effect of Age and Menopausal Status on Chemotherapy Benefit

RS: 16-25

Subgroup	No. of Patients	No. of Events
≤40 Yr of age	203	35
41–45 Yr of age	441	51
46–50 Yr of age		
Before menopause	630	69
After menopause	141	15
51–55 Yr of age		
Before menopause	287	34
After menopause	472	54
56–60 Yr of age	826	94
61–65 Yr of age	710	109
>65 Yr of age	628	117



n engl j med 380;25 nejm.org June 20, 2019

San Antonio Breast Cancer Symposium®, December 10 -14, 2019

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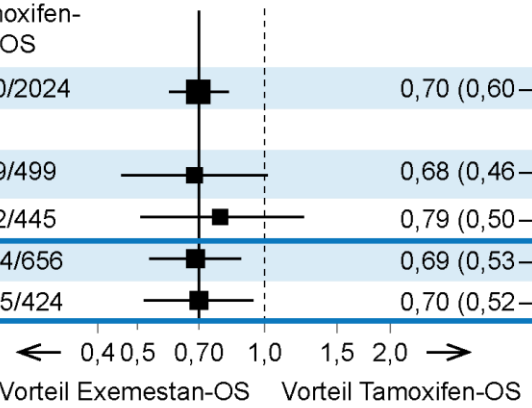
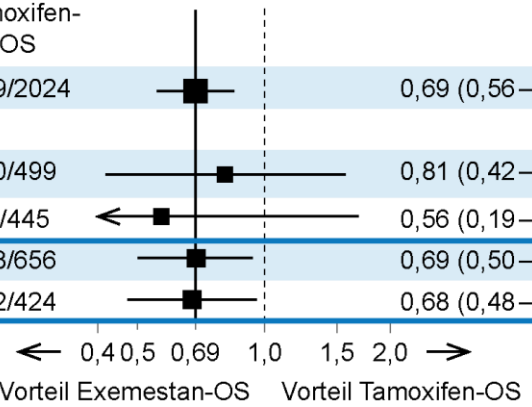
SOFT- und TEXT-Studie – Endpunkte der finalen Analyse (Chemotherapie-Kohorte, AI + GnRH vs. TAM + GnRH)

DFS	n Ereignisse/Patienten		Hazard Ratio (95%-KI)	8-Jahres-DFS (%)		Differenz
	Exemestan-OS	Tamoxifen-OS		Exemestan-OS	Tamoxifen-OS	
Alle HER2- Patienten	250/2011	350/2024	0,70 (0,60–0,83)	88,1%	82,7%	+5,4%
Kohorte						
Keine Chemotherapie in TEXT	40/492	59/499	0,68 (0,46–1,02)	93,2%	89,1%	+4,1%
Keine Chemotherapie in SOFT	33/447	42/445	0,79 (0,50–1,24)	92,7%	91,3%	+1,4%
Chemotherapie in TEXT	105/661	144/656	0,69 (0,53–0,88)	84,6%	77,7%	+6,9%
Vorherige Chemotherapie in SOFT	72/411	105/424	0,70 (0,52–0,95)	83,1%	73,9%	+9,2%



DRFI	n Ereignisse/Patienten		Hazard Ratio (95%-KI)	8-Jahres-DFS (%)		Differenz
	Exemestan-OS	Tamoxifen-OS		Exemestan-OS	Tamoxifen-OS	
Alle HER2- Patienten	144/2011	209/2024	0,69 (0,56–0,85)	93,0%	89,6%	+3,4%
Kohorte						
Keine Chemotherapie in TEXT	16/492	20/499	0,81 (0,42–1,56)	97,2%	96,5%	+0,7%
Keine Chemotherapie in SOFT	5/447	9/445	0,56 (0,19–1,69)	99,3%	98,3%	+1,0%
Chemotherapie in TEXT	70/661	98/656	0,69 (0,50–0,93)	89,6%	84,6%	+5,0%
Vorherige Chemotherapie in SOFT	53/411	82/424	0,68 (0,48–0,95)	86,8%	79,8%	+7,0%



- Die Addition von GnRH + Exemestan ist in der Gruppe der jungen Patientinnen mit hohem Rezidivrisiko, bei denen eine Chemotherapie indiziert ist und deren Östrogenspiegel trotz Chemotherapie prämenopausal bleibt eine sinnvolle Therapieoption.

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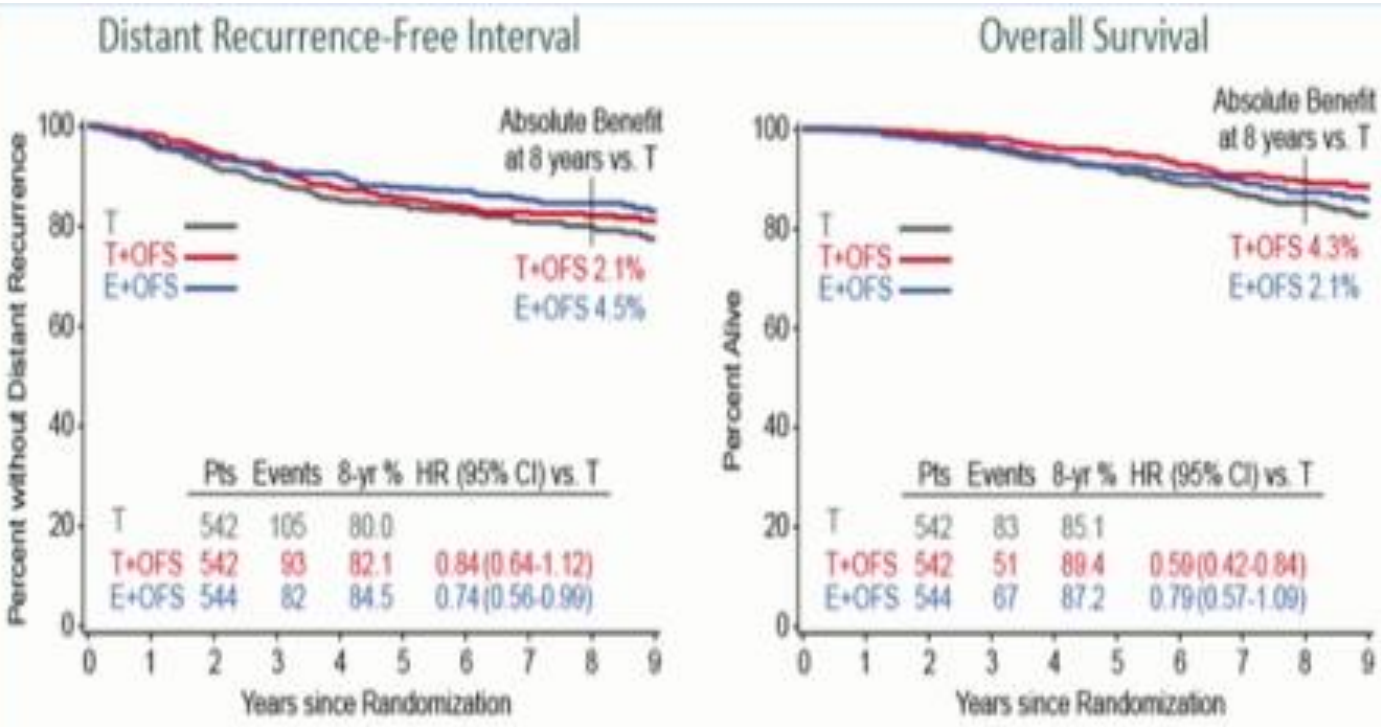
SOFT: Chemotherapie-Kohorte



Chemo Cohort: Median age 40 years

~ 47% pT2, ~ 57% pN+, ~ 35% grade 3, 18% HER2+ve

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Endokrine Therapieoptionen bei prämenopausalen Patientinnen

Adjuvante endokrine Therapie bei prämenopausalen Patientinnen (Jahr 0–5)

	Oxford LoE	Oxford GR	AGO
▪ Tamoxifen* 5–10 Jahre	1a	A	++
▪ GnRHa Monotherapie (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie)	1a	B	+
▪ Ohne Indikation zu neo-/adjuvanter Chemotherapie mit erhaltener Ovarialfunktion:			
▪ Tamoxifen	1b	B	++
▪ Tamoxifen + OFS**	1b	B	+/-
▪ AI + OFS**	1b	B	+/-
▪ Nach neo/-adjuvanter Chemotherapie mit erhaltener Ovarialfunktion (≤ 8 Monate EOC):			
▪ Tamoxifen + OFS 5 Jahre**	1b	B	+
→ Bei Patientinnen < 35 Jahre	1b	B	++
▪ AI + OFS 5 Jahre**	1b	B	+/-
→ Bei Patientinnen < 35 Jahre	1b	B	+

OFS: Ovarialfunktions-Suppression; EOC: Ende der Chemotherapie

OFS#: Vermehrte Nebenwirkungen (AI+ OFS) gegenüber (Tam + OFS) vs. (Tam) können die Compliance beeinträchtigen.

* Behandlung nur solange sie tolerabel ist und die Pat. eindeutig prämenopausal ist

** Bisher liegen nur Daten für das krankheitsfeie Überleben (DFS) vor

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Guidelines Breast
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LEHREN
HEILEN

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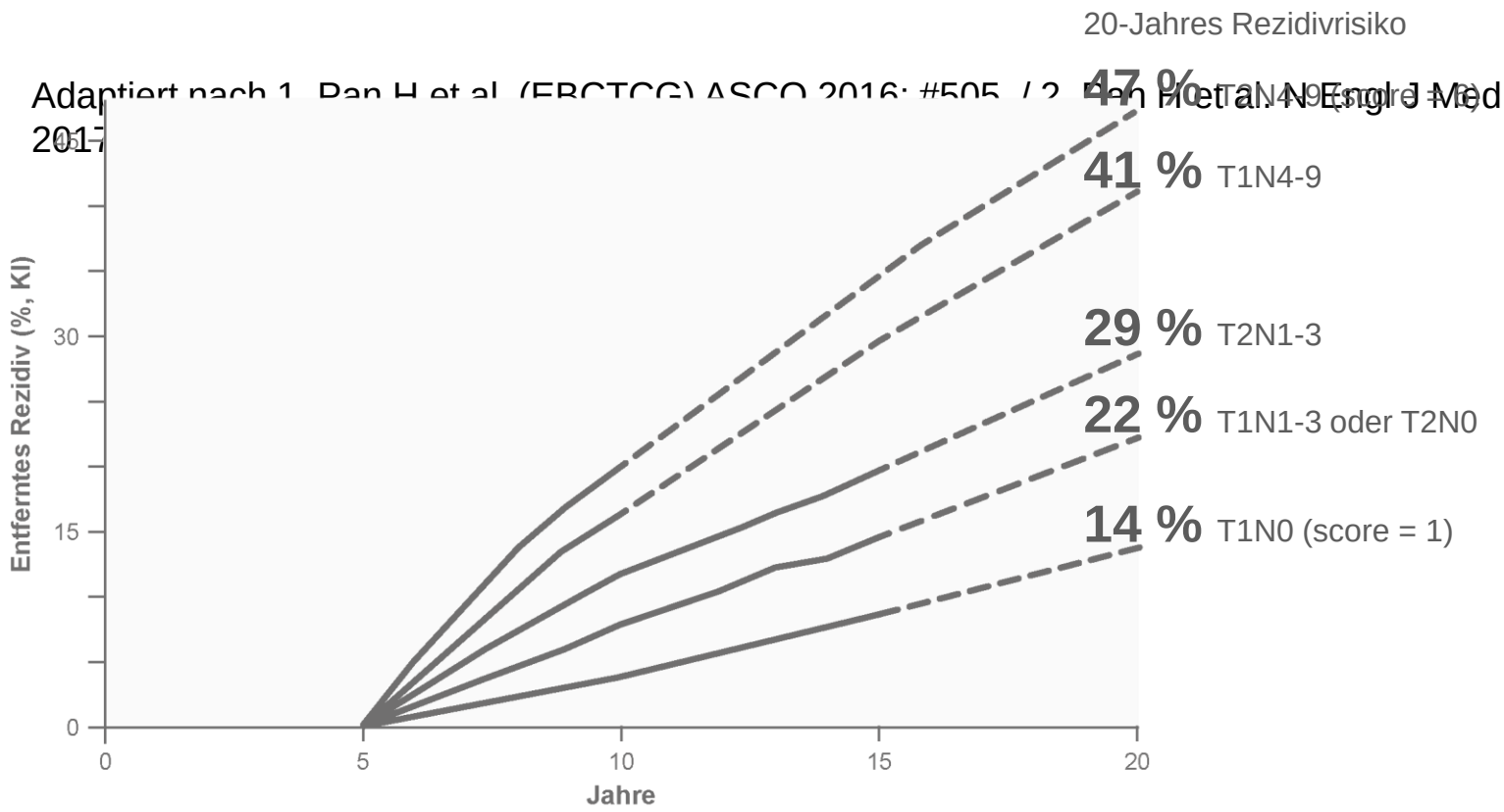
Rezidivrisiko nach 5-jähriger endokriner Therapie adjustiert an Tumorgröße und Nodalstatus

- Adaptiert nach 1. Pan H et al. (EBCTCG) ASCO 2016; #505 / 2. Pan H et al. N Engl J Med. 2017



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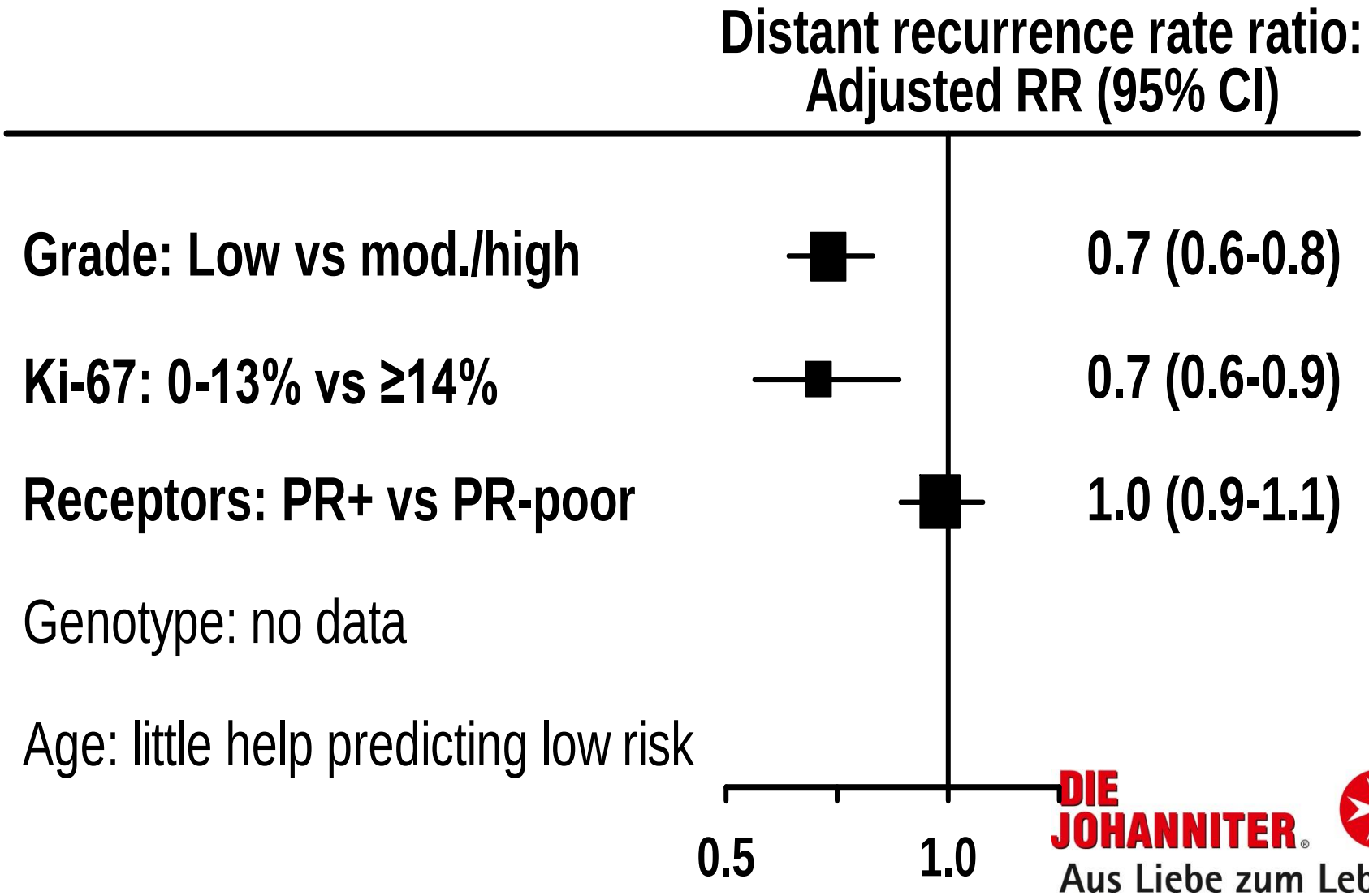

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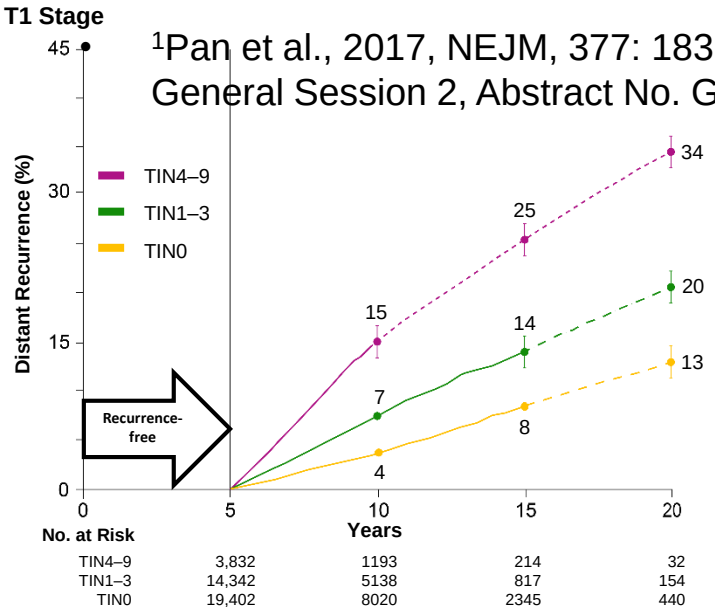
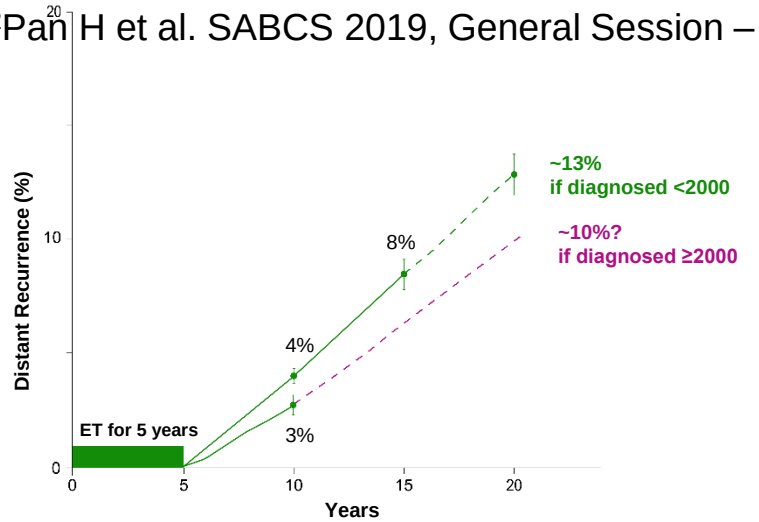
Background

[1]Pan et al., 2017, NEJM, 377: 1836–1846. [2]Pan H et al. SABCS 2019, General Session – General Session 2, Abstract No. GS2-04





Extended endocrine therapy can reduce risk of recurrence (ATLAS, aTTom, MA. 17, MA.17R, NSABP B-14/B-33/B-42, ABCSG-6a/16, DATA, IDEAL, SOLE)

→ **Identification of patients who are at high risk of late recurrence is crucial**

Integration of Clinical Variables for the Prediction of Late Distant Recurrence in Patients With Estrogen Receptor–Positive Breast Cancer Treated With 5 Years of Endocrine Therapy: CTS5

Mitch Dowsett, Ivana Sestak, Meredith M. Regan, Andrew Dodson, Giuseppe Viale, Beat Thürlimann, Marco Colleoni, and Jack Cuzick

J Clin Oncol 2018, 36, 1941-48

CTS⑤ CALCULATOR

Tumour size (mm) 15

Tumour Grade Grade 2

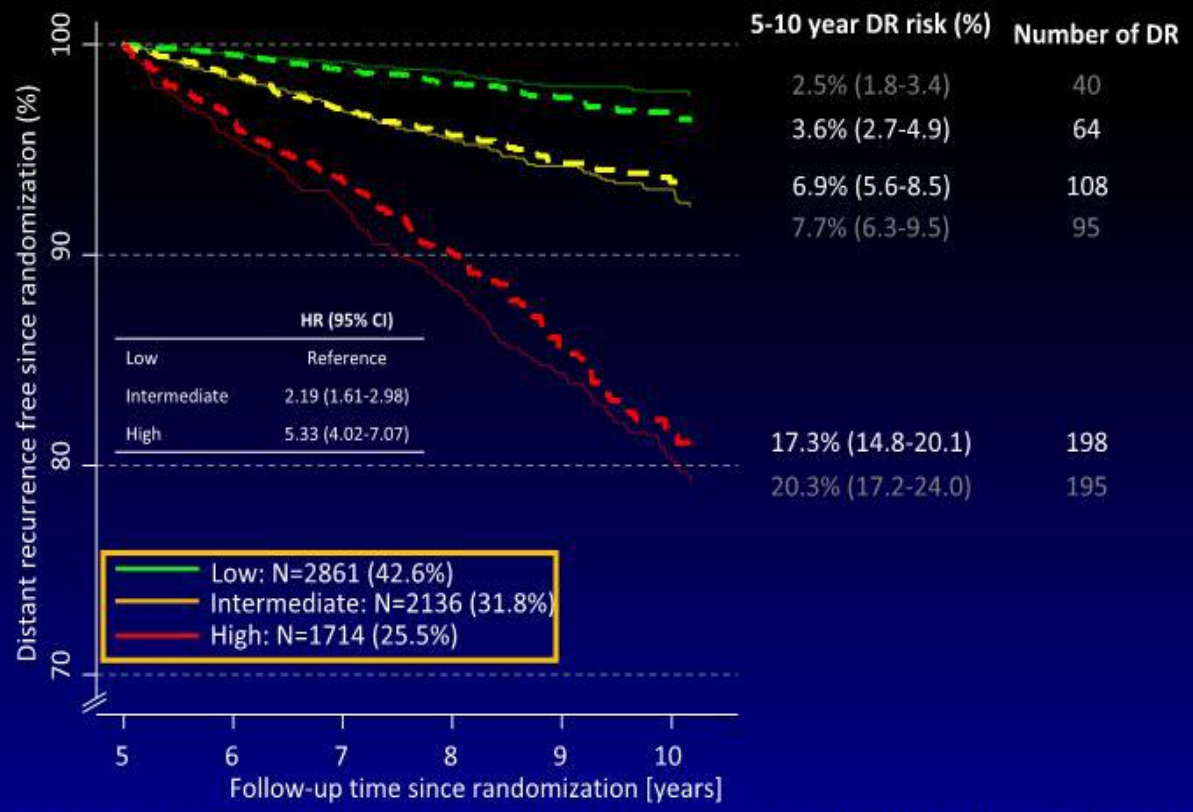
Patient age (years) 67

Number of nodes involved 1

UPDATE RESULT ⇒

San Antonio Breast Cancer Symposium®, December 4-8, 2018

DR free (%) in years 5-10 by CTS5(ATAC) in BIG 1-98



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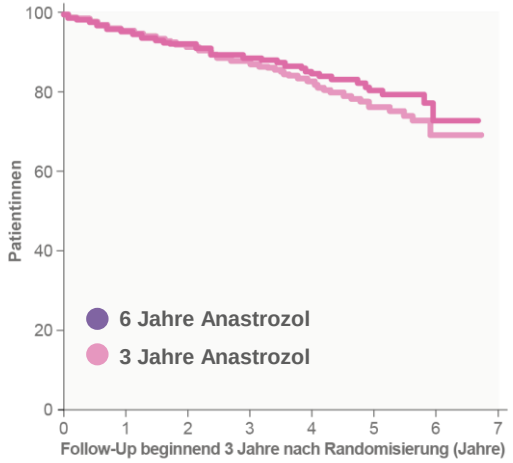
ABER: nicht alle Studien sind positiv...

DATA

Progressionsfreies Überleben

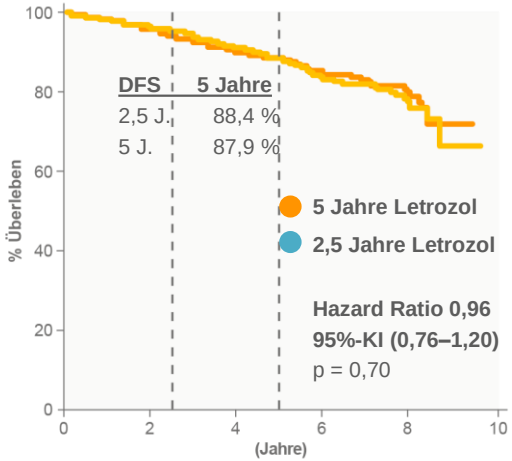


6 Jahre	827	789	769	698	445	182	24	0
3 Jahre	833	801	762	682	453	173	28	0

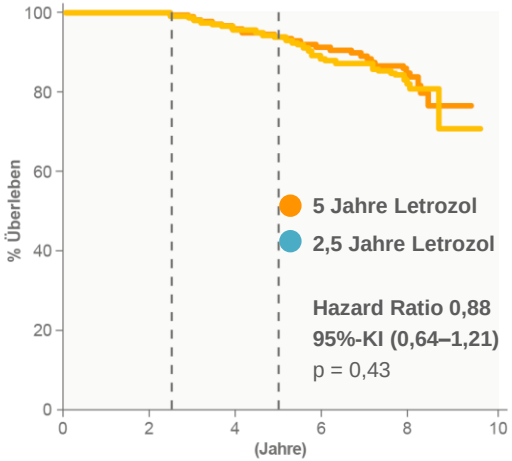
n = 1.660	6 Jahre Anastrozol (n = 827)	3 Jahre Anastrozol (n = 833)
3 Jahre aDSF (%)	90,7	88,9
HR (95%-KI)	8,75	
p-Wert	<0,001	
5 Jahre aDSF (%)	83,1	79,4
HR (95%-KI)	0,79 (0,62-1,02)	
p-Wert	0,07	

IDEAL

DFS primär

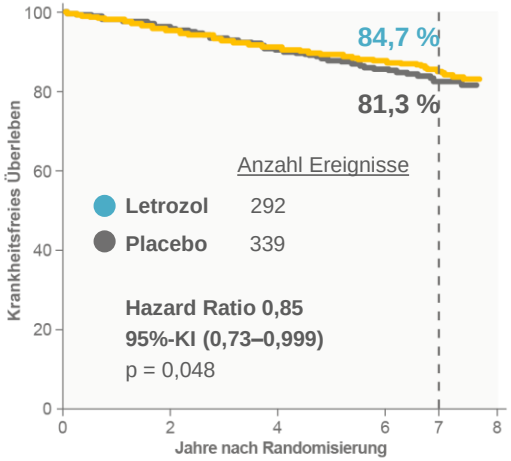


DFS sekundär



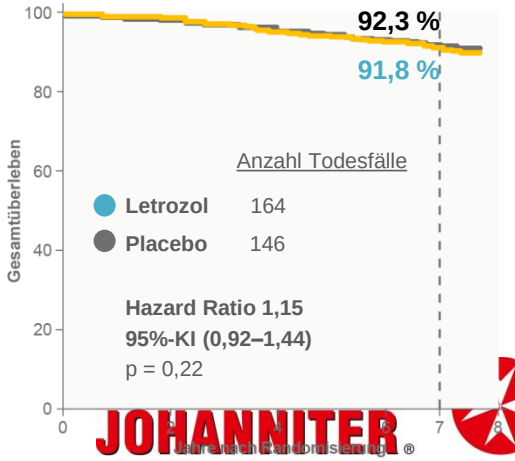
NSABP B-42

Krankheitsfreies Überleben



Letrozol	1959	1813	1644	1225	216
Placebo	1964	1814	1639	1208	210

Gesamtüberleben



Letrozol	1959	1902	1781	1499	281
Placebo	1964	[illegible]	[illegible]	1528	291

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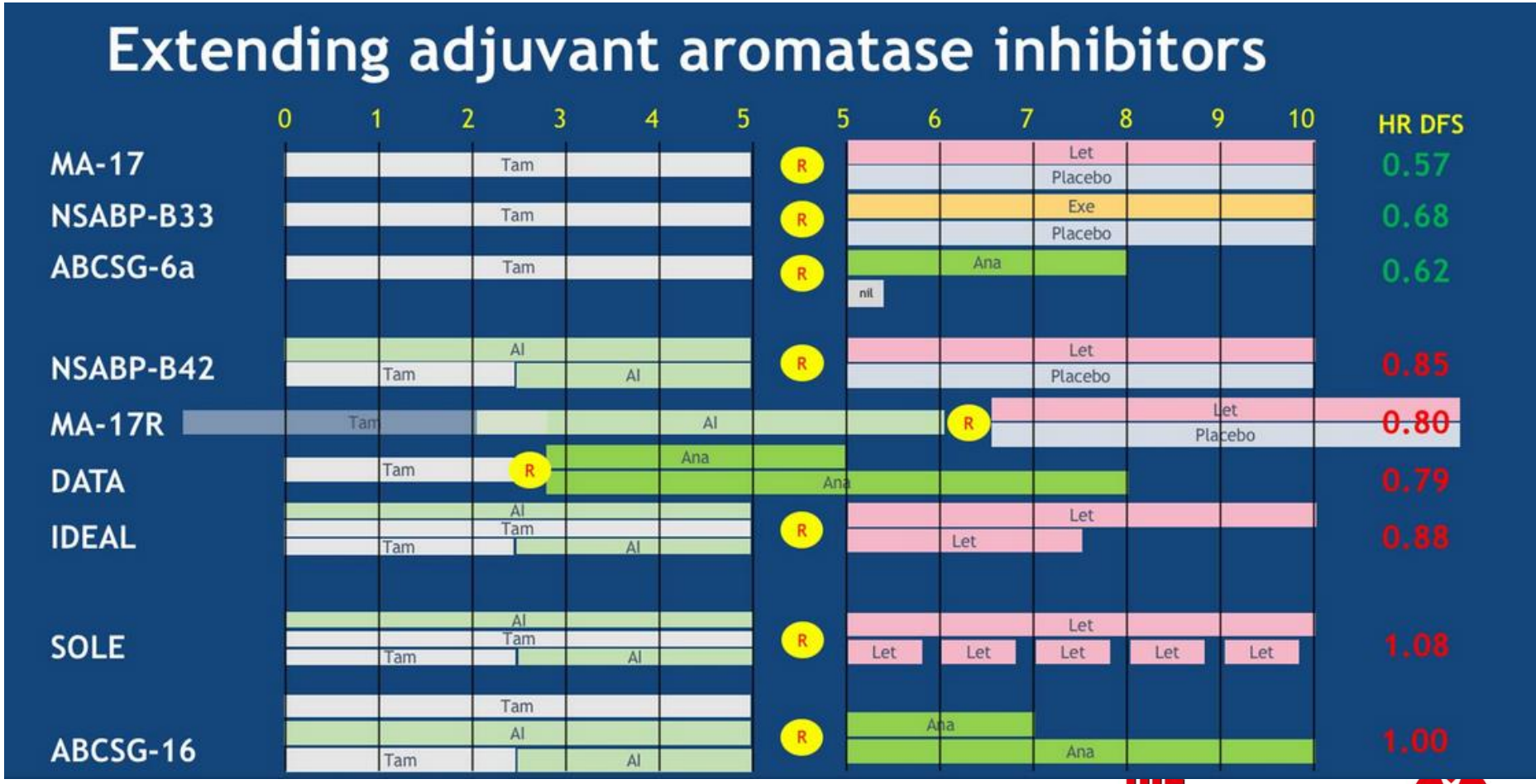
Adaptiert nach 1. Tjan-Heijnen VC et al. SABCS 2016; #S1-03. / 2. Blok EJ et al. SABCS 2016; #S1-04. / 3. Mamounas T et al. SABCS 2016; #S1-05.

Studien zur verlängerten endokrinen Therapie



Gnant ASCO 2018

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GIM4 Study Design

Postmenopausal at randomization
ER+ and/or PR+
T1-3; N0-N+
No sign of disease recurrence
Tam for 2-3 yrs

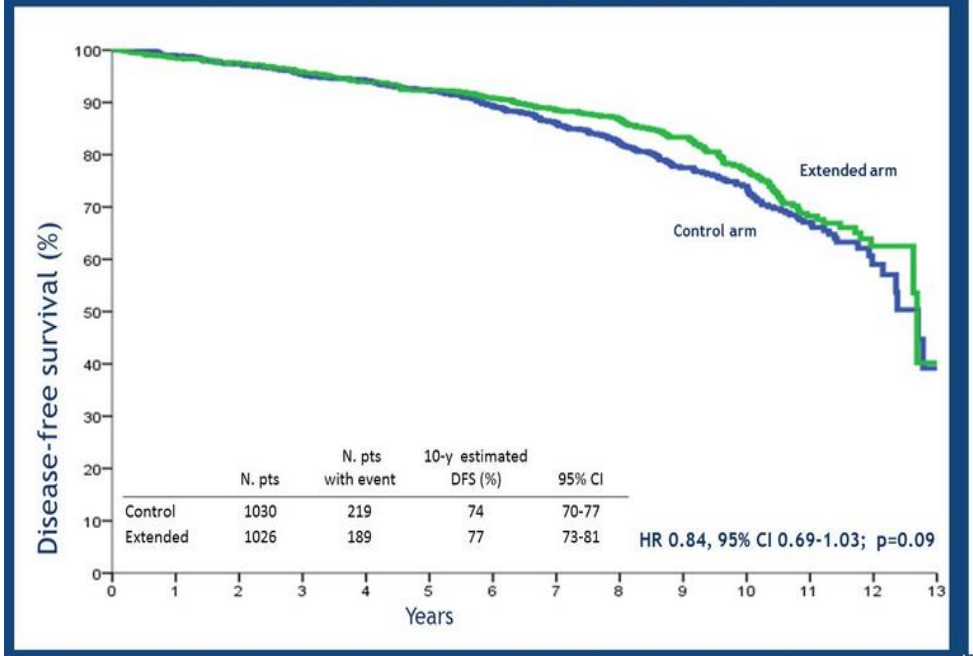
R

Control arm
3-2 yrs Letrozole
(up to 5 yrs of ET)

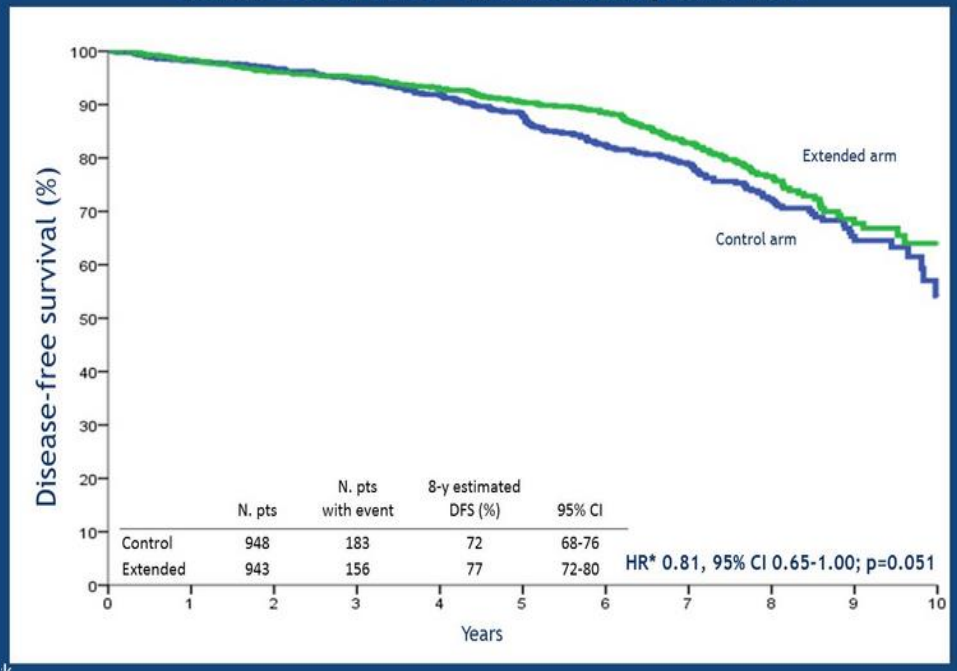
Extended arm
5 yrs Letrozole
(up to 7-8 yrs of ET)

N=2056
Recruitment in 64 centres in Italy (GIM group), 2005-2010
Median follow-up: 10.4 years (IQR 8.8-11.4)

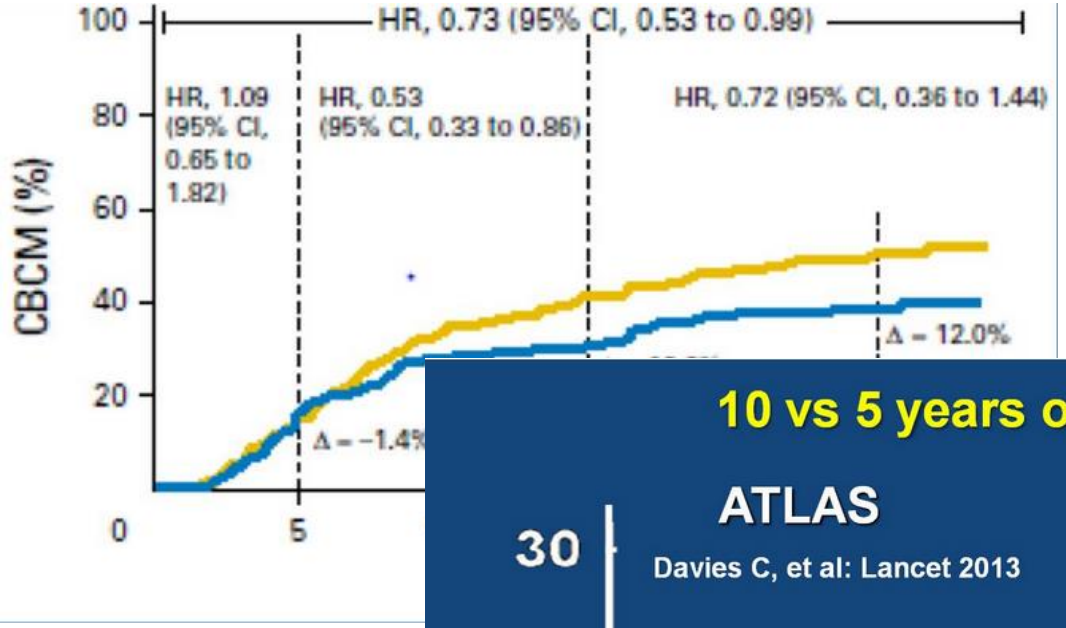
Disease-Free Survival - ITT population. N=2056

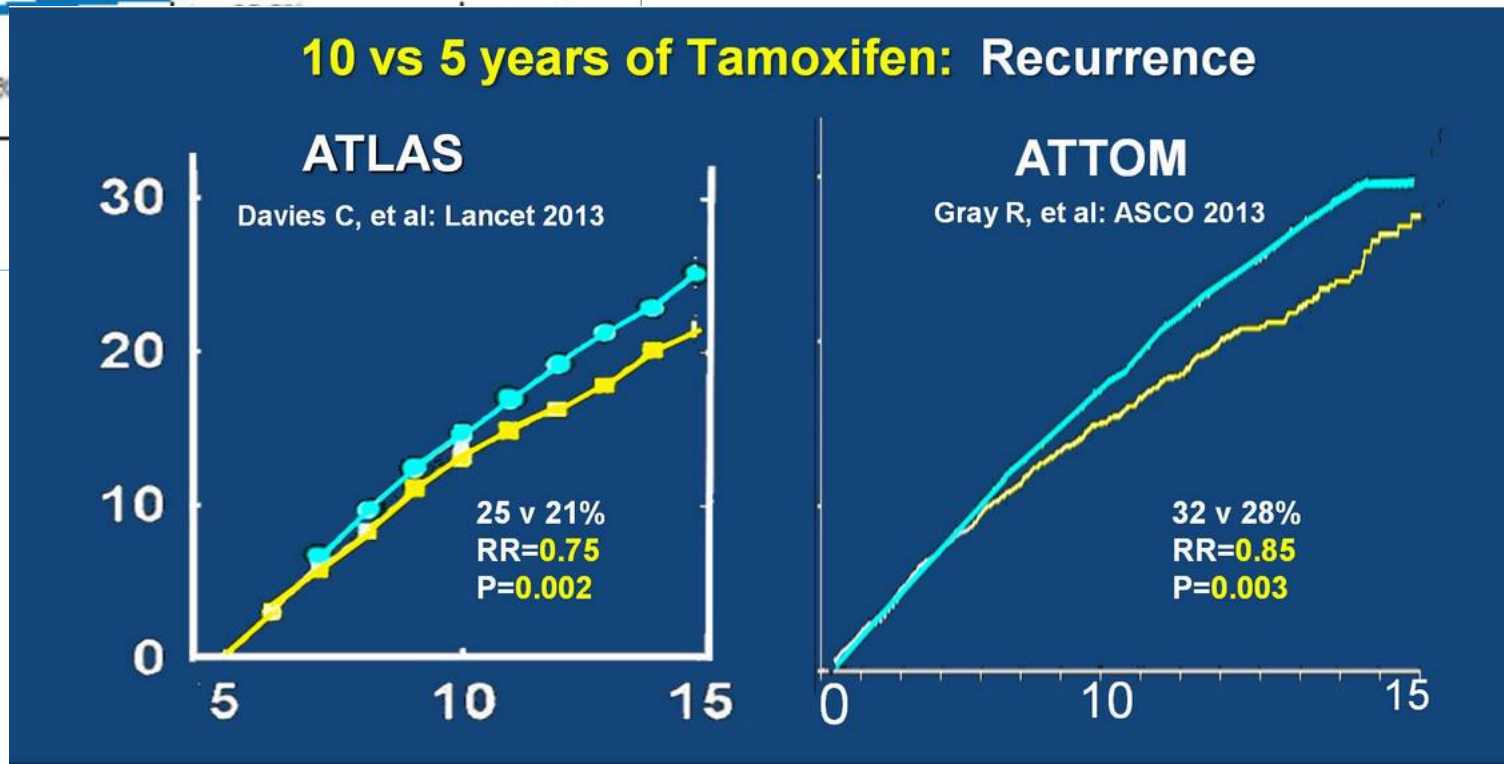


Disease-free Survival - Landmark analysis. N=1891



Effekte der verlängerten Tamoxifen-Therapie erst spät sichtbar



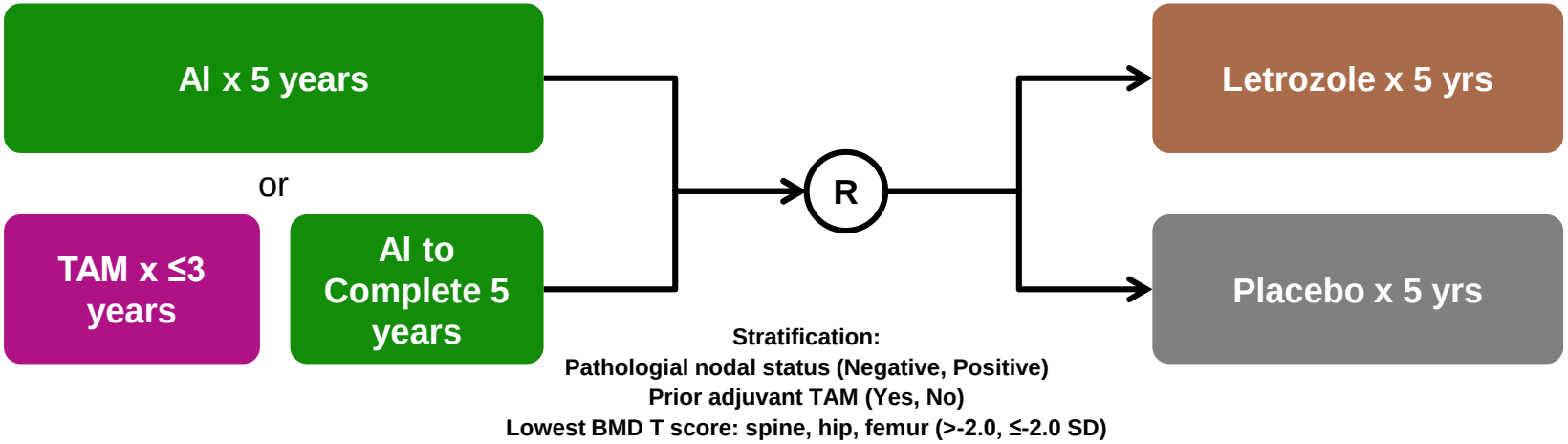


Eckholm et al
Gray et al.

NSABP B-42 – Study Design

- Extended adjuvant Therapy (EAT)

- Postmenopausal pts with ER+ or PR+ breast cancer
- Stage I, II or IIIa invasive BC at diagnosis
- Disease-free after 5 years of endocrine therapy



Mod. Mamounas EP et al. SABCS 2019, General Session — General Session 1, Abstract NCT01254-01

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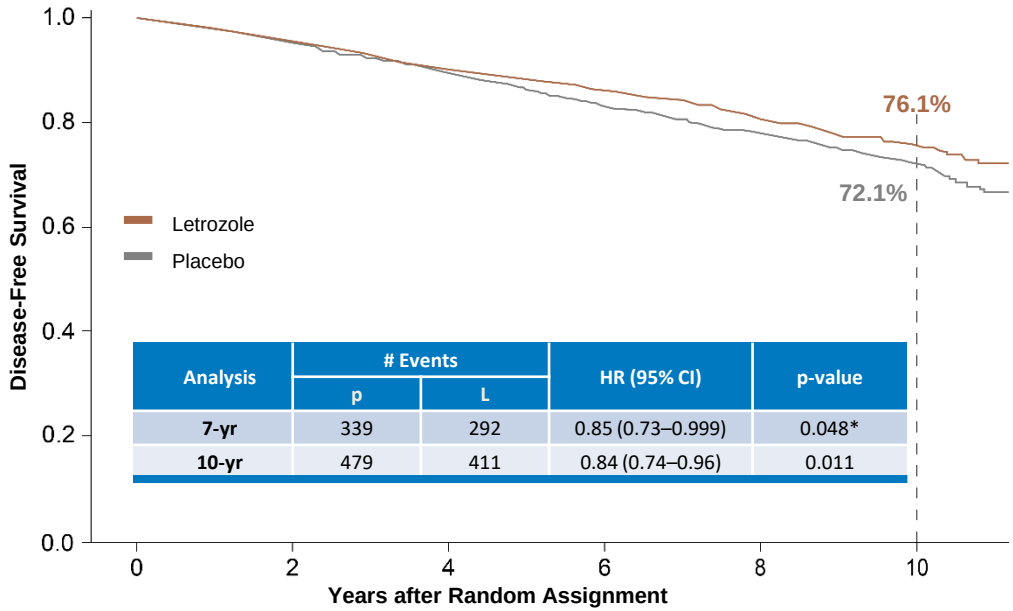
NSABP B-42 – Disease-Free Survival

Extended adjuvant Therapy (EAT)



Analysis	# Events		HR (95% CI)	p-value
	p	L		
7-yr	339	292	0.85 (0.73–0.999)	0.048*
10-yr	479	411	0.84 (0.74–0.96)	0.011

Placebo	1953	1815	1645	1417	1180	394
Letrozole	1950	1820	1662	1467	1225	394

Mod. Mamounas EP et al. SABCS 2019, General Session — General Session 4, Abstract No. GS4-01

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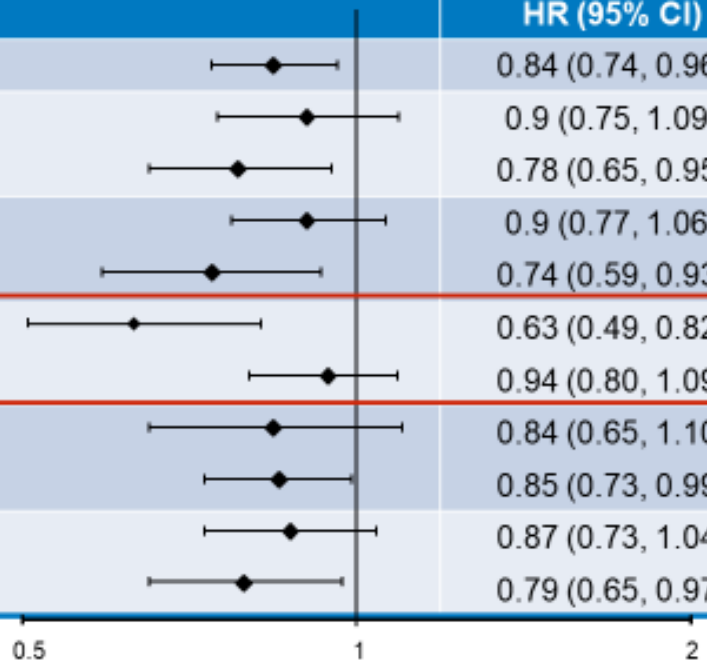
NSABP B-42 – Letrozole Effect on DFS in Subgroups

Extended adjuvant Therapy (EAT)

		HR (95% CI)	p-interaction
All Patients		0.84 (0.74, 0.96)	
Nodal Status	Negative	0.9 (0.75, 1.09)	0.3
	Positive	0.78 (0.65, 0.95)	
Prior TAM	No	0.9 (0.77, 1.06)	0.16
	Yes	0.74 (0.59, 0.93)	
T-score	≤-2.0	0.63 (0.49, 0.82)	0.01
	>-2.0	0.94 (0.80, 1.09)	
Age	<60	0.84 (0.65, 1.10)	0.9
	≥60	0.85 (0.73, 0.99)	
Surgery	Lumpectomy	0.87 (0.73, 1.04)	0.55
	Mastectomy	0.79 (0.65, 0.97)	



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Mod. Mamounas EP et al. SABCS 2019, General Session — General Session 4, Abstract No. GS4-01

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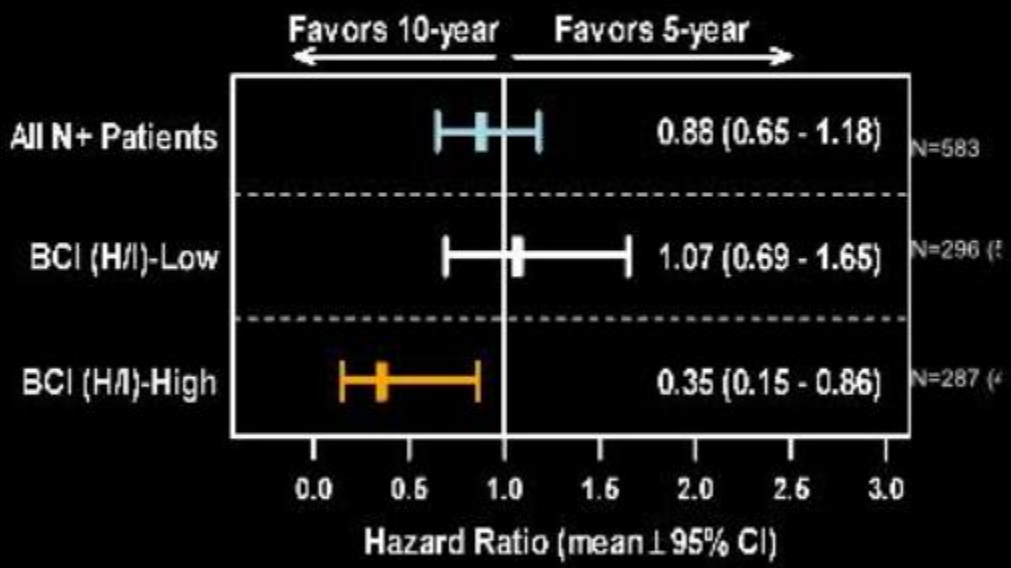
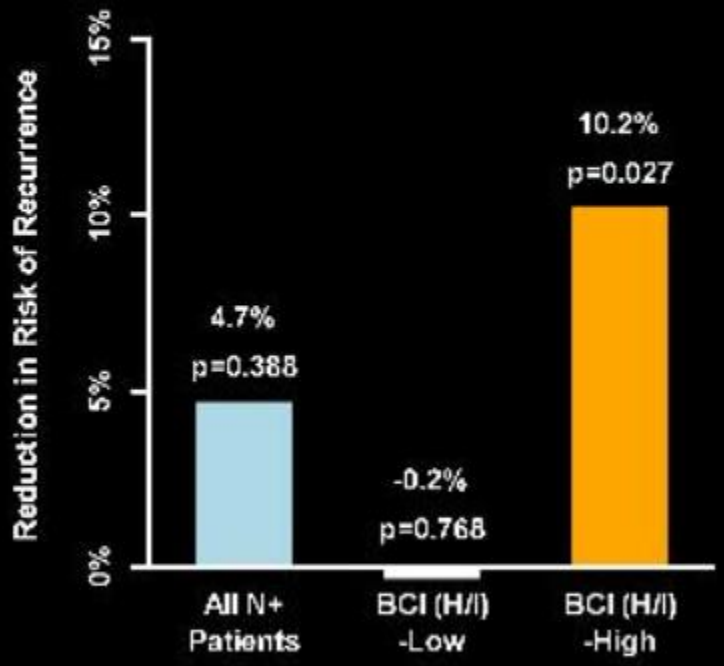
Mod. Mamounas EP et al. SABCS 2019, General Session — General Session 4, Abstract No. GS4-01

Relative Benefit of Extended Tamoxifen by BCI (H/I) Status: Trans-aTTom N+ cases





Bartlett ASCO 2019

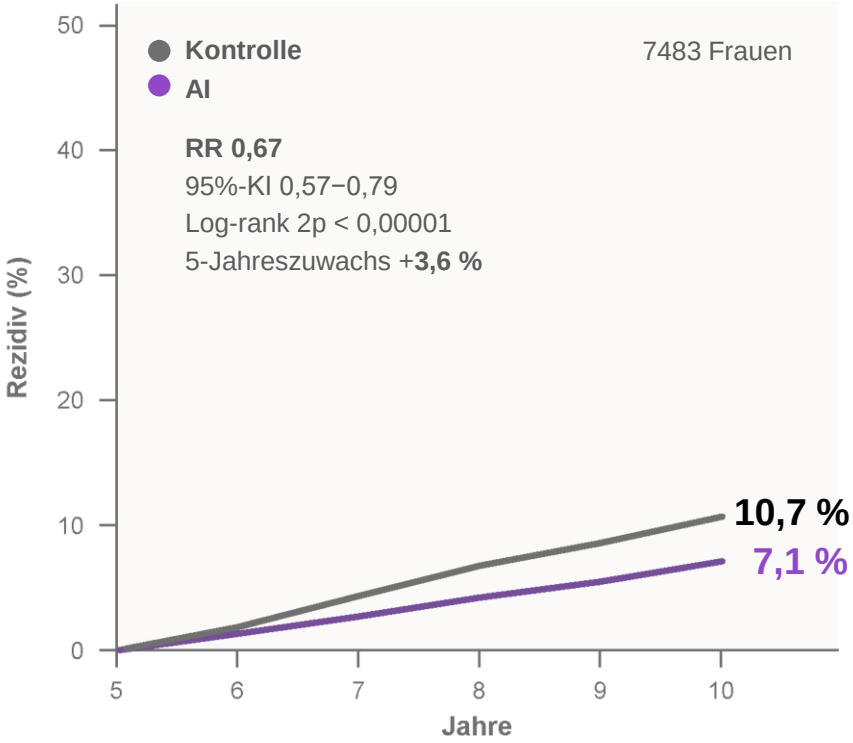
DIE JOHANNITER®
Aus Liebe zum Leben

Metaanalyse zur verlängerten AI-Therapie im Anschluss an eine ET von ≥ 5 Jahren

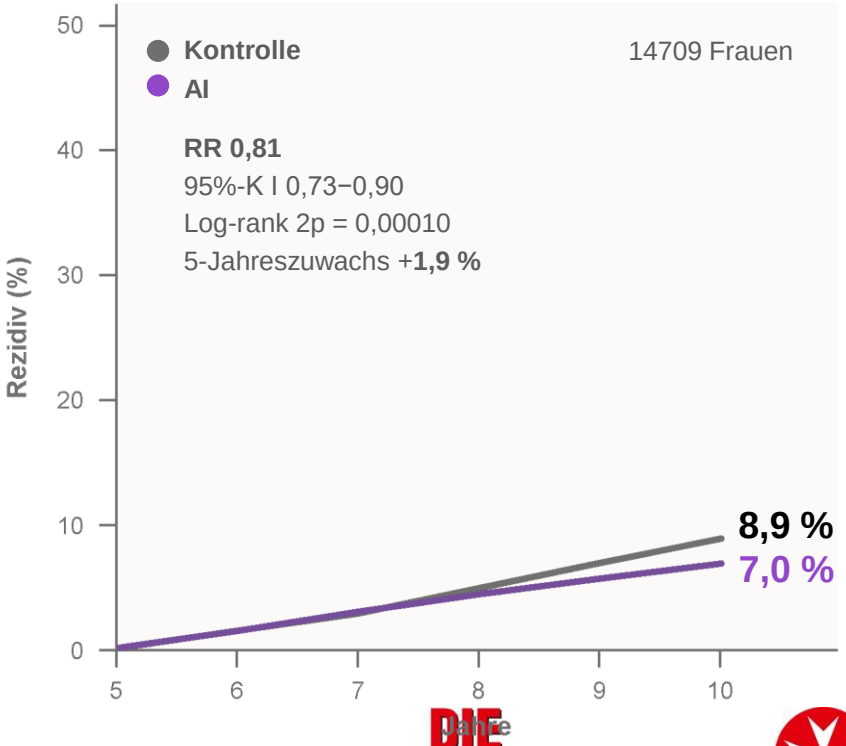
Effekt einer verlängerten AI-Therapie nach 5–10 Jahre auf das Auftreten eines Rezidivs nach Art der vorherigen ET

- Adaptiert nach Gray R et al. SABCS 2018; Oral Session – Abstract No. GS3-03.

Vorheriges Tamoxifen



Vorherige AI



DIE JOHANNITER®
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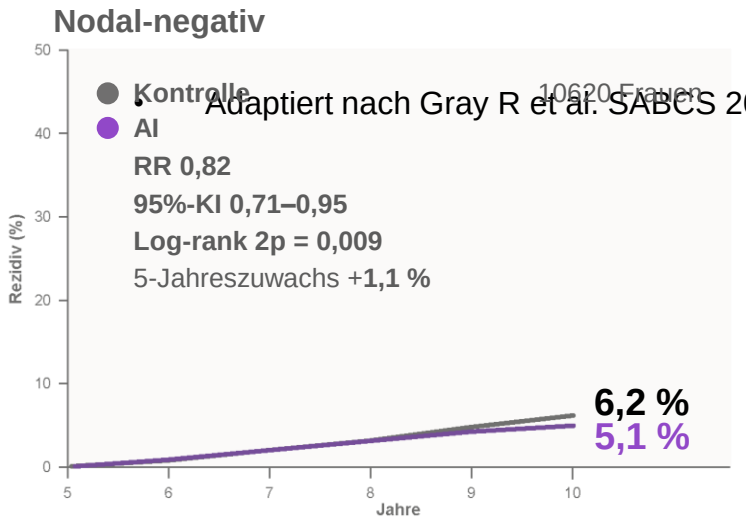
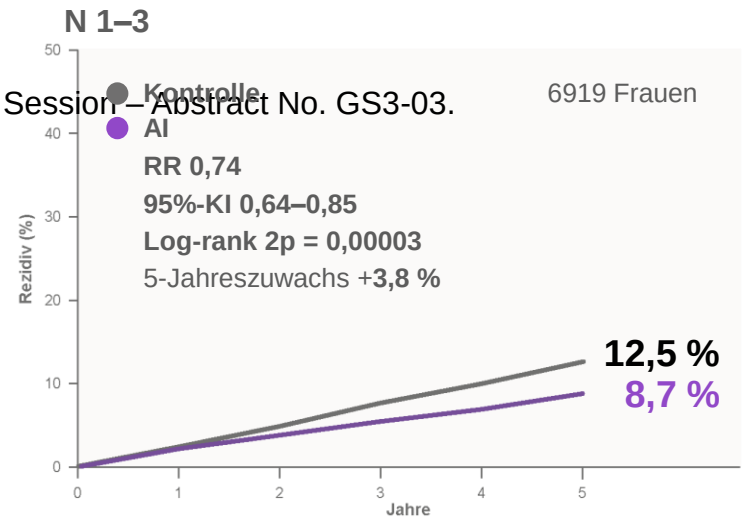
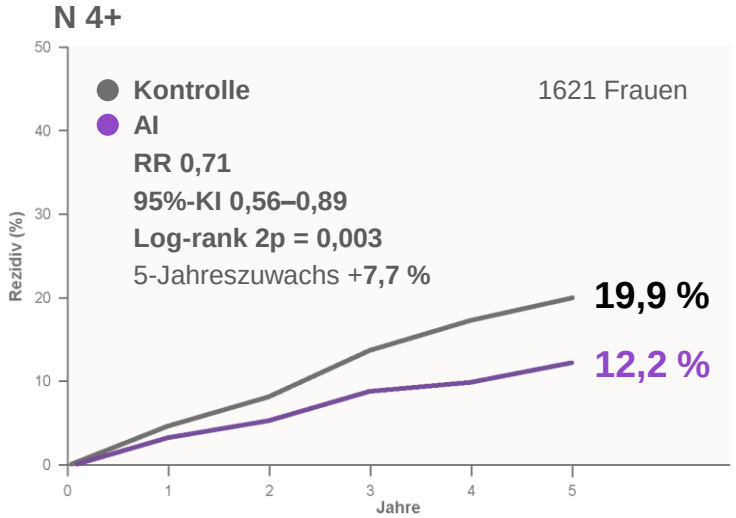
Metaanalyse zur verlängerten AI-Therapie im Anschluss an eine ET von ≥ 5 Jahren: Auftreten eines Rezidivs

Adaptiert nach Gray R et al. SABCS 2018; Oral Session – Abstract No. GS3-03.







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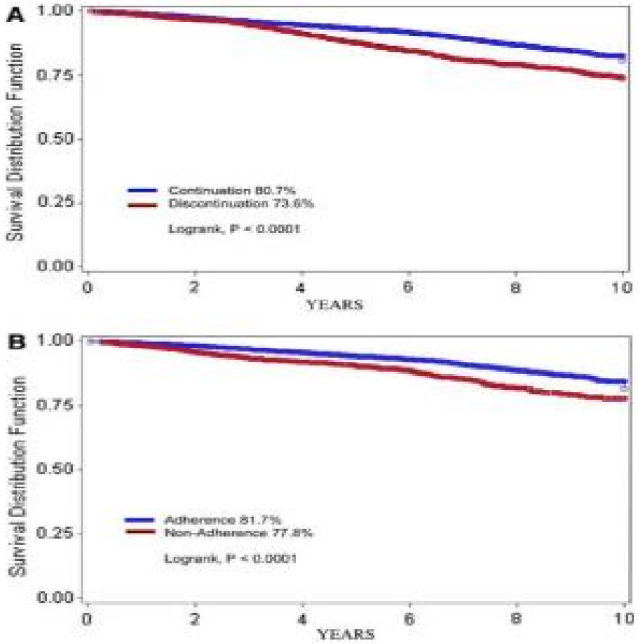
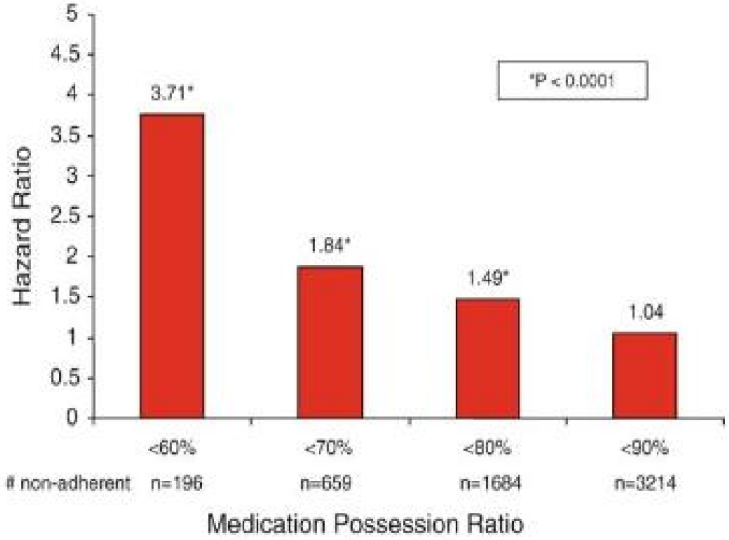
Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer





Hershman, DL et al *BCRT* 2010

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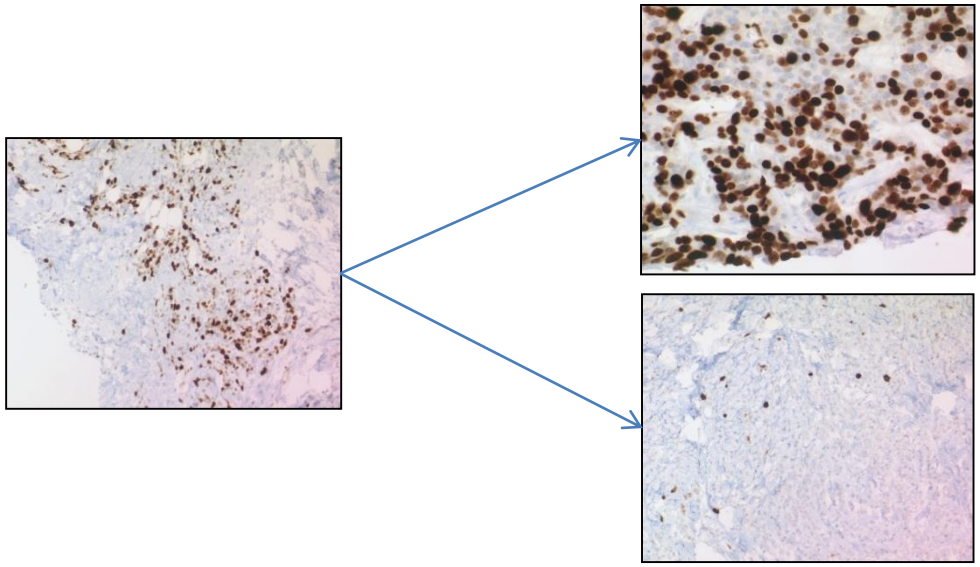
Welche Antihormontherapie-Wann?
Subjektives Kochrezept 2020

- **Prämenopausal low risk (z.B. pT1, pN0, G1):**
  - **Tamoxifen 5 Jahre**
- **Prämenopausal Mittelrisiko:**
  - **Tamoxifen 10 Jahre**
- **Prämenopausal (v.a. junge Pat < 40-45 Jahre alt) Hochrisiko (v.a. prämenopausal nach der CHT):**
  - **GnRH Analoga für 2-5 Jahre+Tamoxifen (oder AI in der Kombination mit GnRH) für 5 Jahre→5 Jahre Tamoxifen (?)**
- **Perimenopausal:**
  - **Großzügig 5 Jahre Tam→5 Jahre AI**
- **Postmenopausal**
  - **invasiv duktal: 2 Jahre AI→3 Jahre Tam oder 2 Jahre Tam→3 Jahre AI oder 5 Jahre AI, Invasiv lobulär 5 Jahre AI (Anastrozol/Letrozol)**
- **Falls ER/PR>50% und N+ oder T2-3 oder G3 oder höheres genomisches Risiko….**
  - **Verlängerte adjuvante endokrine Therapie: AI-Tam oder AI für 7-10 Jahre**

DIE JOHANNITER
Ausbiebe zum Leben

Wie kann die Effektivität der endokrinen Therapie früh abgeschätzt werden? Präoperative Gabe→Ki-67 Abfall



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JNCI JOURNAL OF THE NATIONAL CANCER INSTI

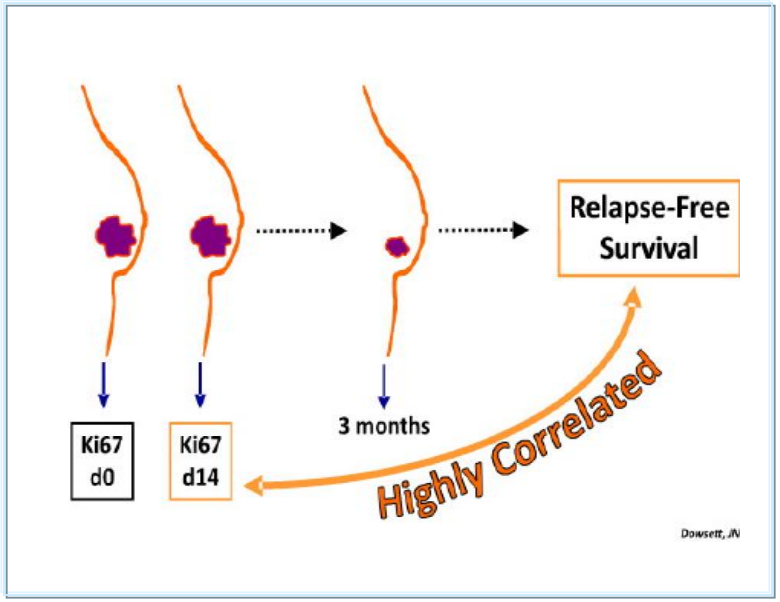
ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRE

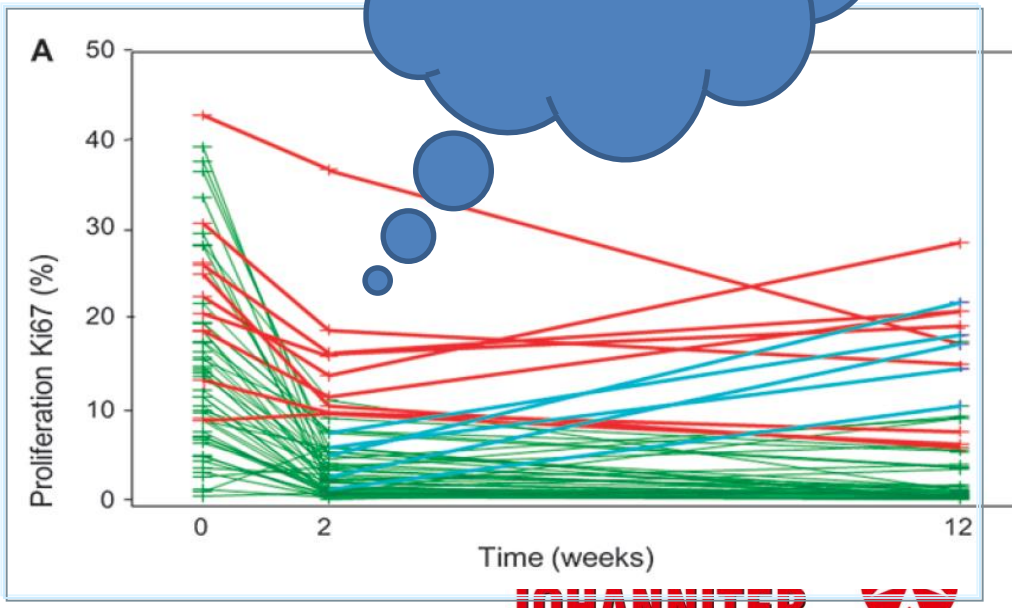
Oxford Journals › Medicine › JNCI J Natl Cancer Inst › Volume 99, Issue 2 › Pp. 167-170. 2007

Prognostic Value of Ki67 Expression After Short-Term Presurgical Endocrine Therapy for Primary Breast Cancer

Mitch Dowsett, Ian E. Smith, Stephen R. Ebbs, J. Michael Dixon, Anthony Skene, Roger A'Hern, Janine Salter, Simone Detre, Margaret Hills, Geraldine Walsh and On behalf of the IMPACT Trialists Group

Was zu tun?





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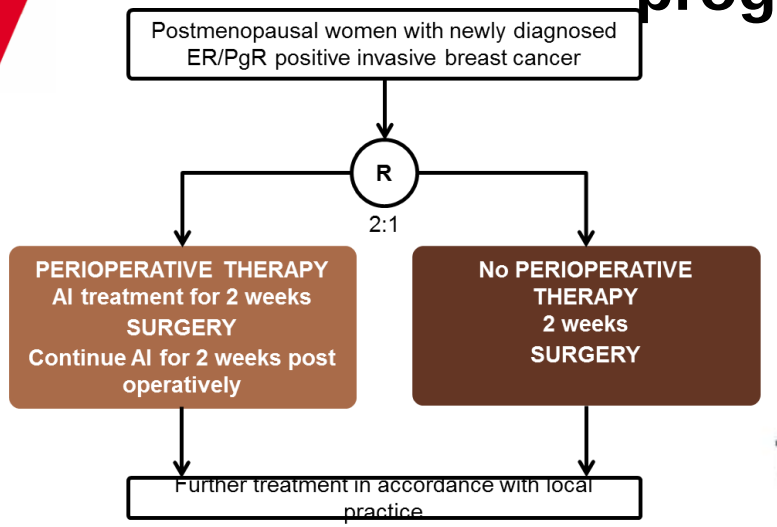
Poetic: Dynamischer Ki-67 ist ein sehr guter prognostischer Marker

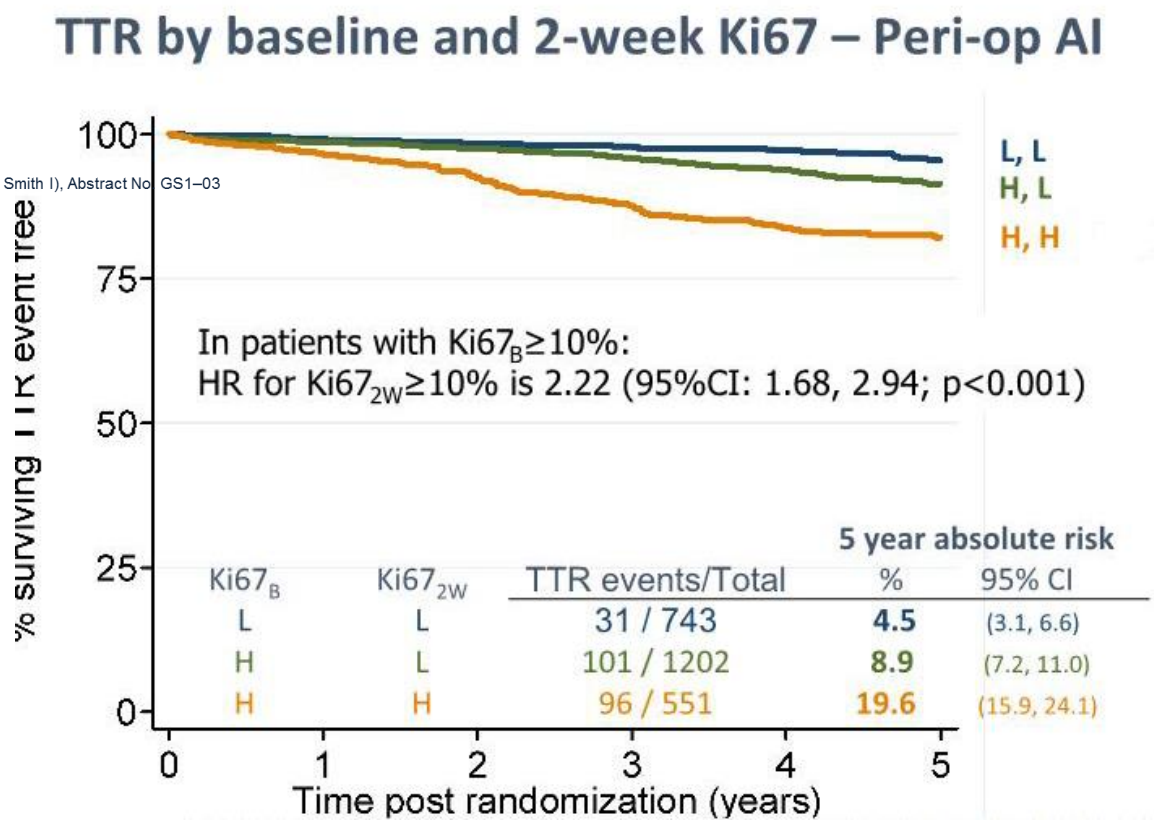


Tumor-FFPE

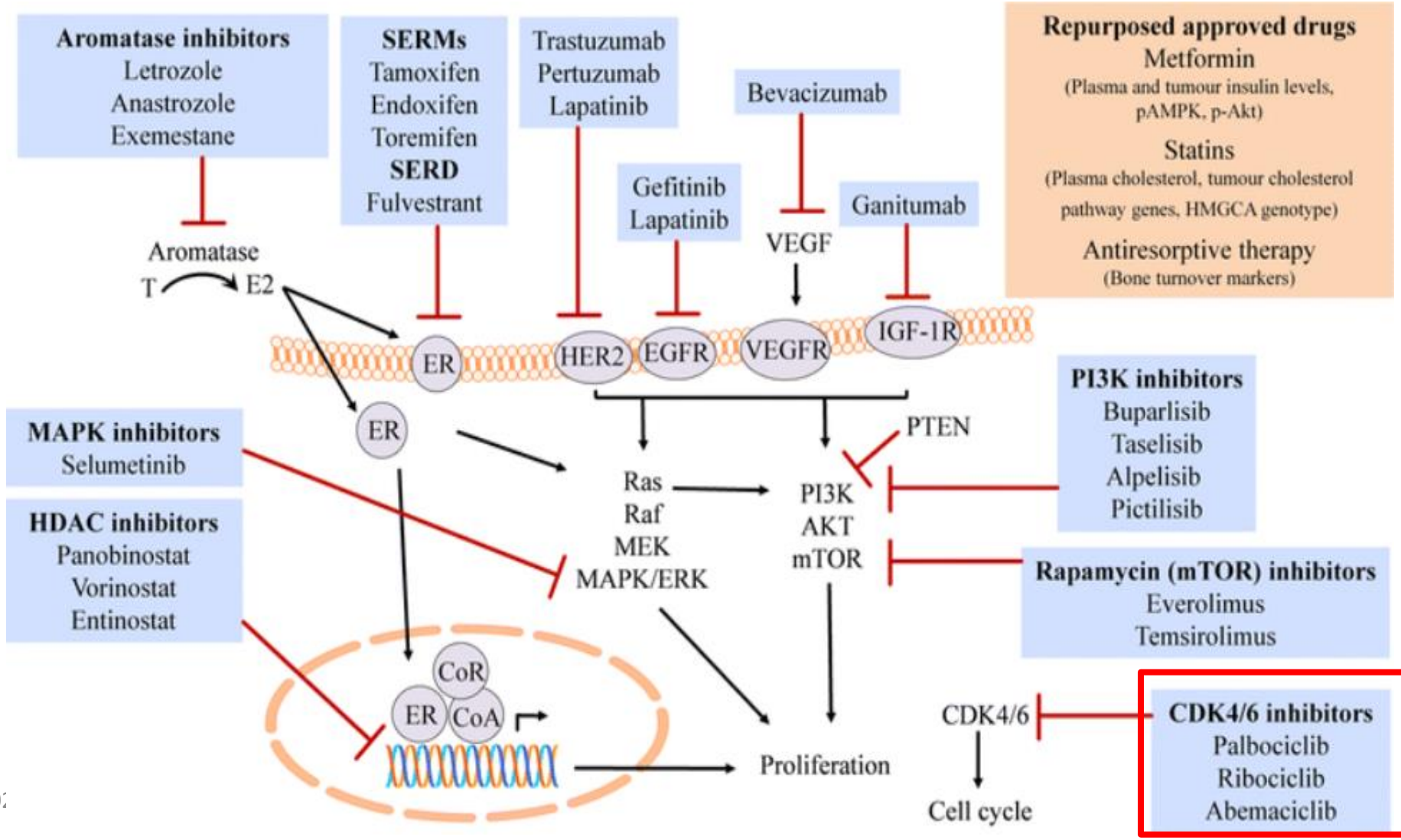
Baseline

2-week

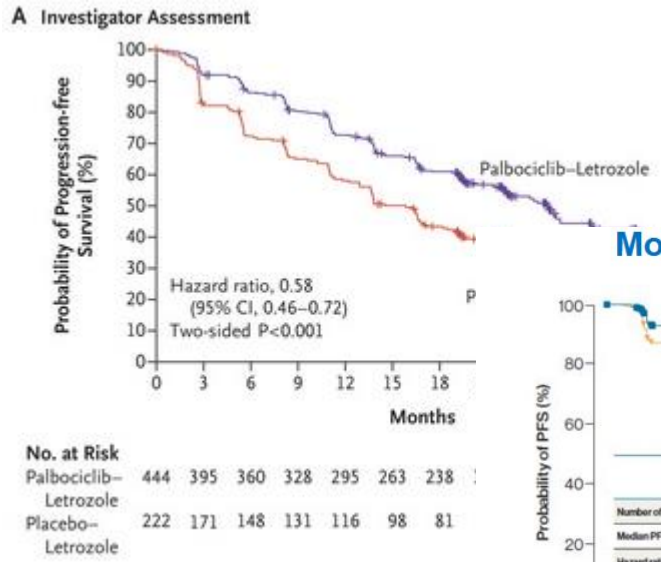
Mod. Robertson JFR et al. SABCS 2017, Oral Session – General Session 1 (presenter: Smith I), Abstract No. GS1–03



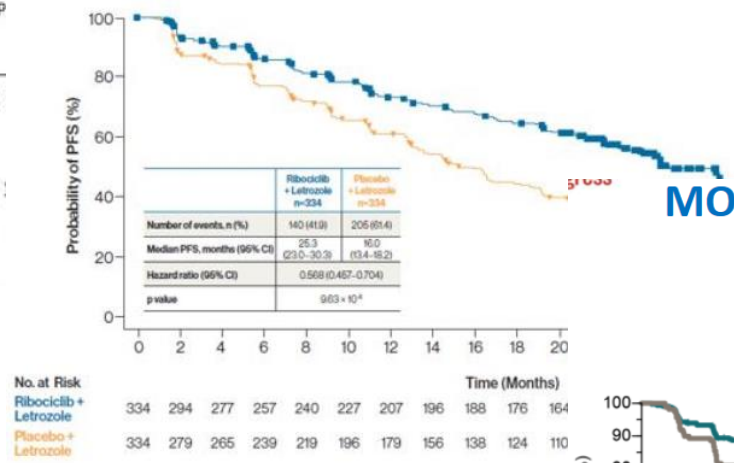
Womit kann die Resistenz überwunden werden?



Endokrine Therapie +/- CDK 4/6 Inhibitoren: Palbociclib, Ribociclib, Abemaciclib bei HR+/HER2- M1 Mammakarzinom



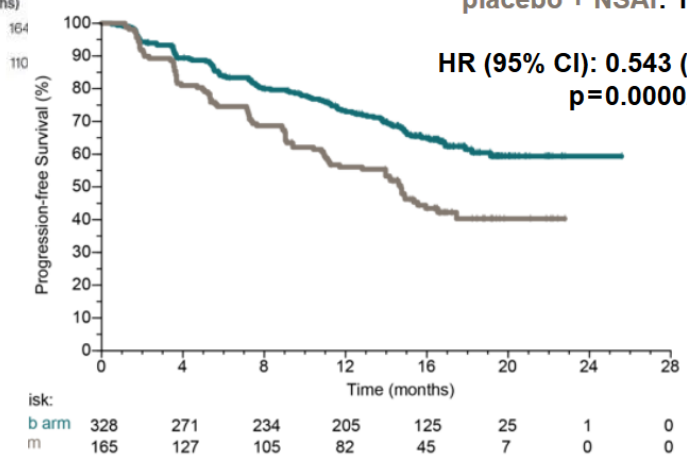
Monaleesa 2 - Updated results ASCO 2017



MONARCH 3: Primary Endpoint: PFS (ITT

Median PFS
abemaciclib + NSAI: **not reached**
placebo + NSAI: **14.7 months**

HR (95% CI): 0.543 (0.409, 0.723)
p=0.000021



Hortobagyj et al. Goetz et al. Finn et al.

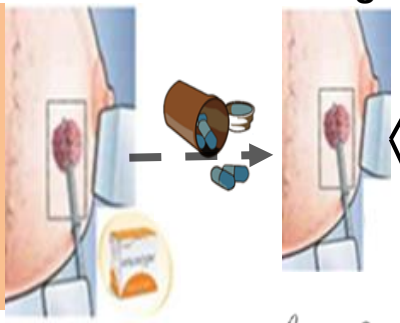
ADAPT CYCLE

Prognosis Estimation

Efficacy Estimation

Candidates for (neo)adjuvant chemotherapy

Biopsy



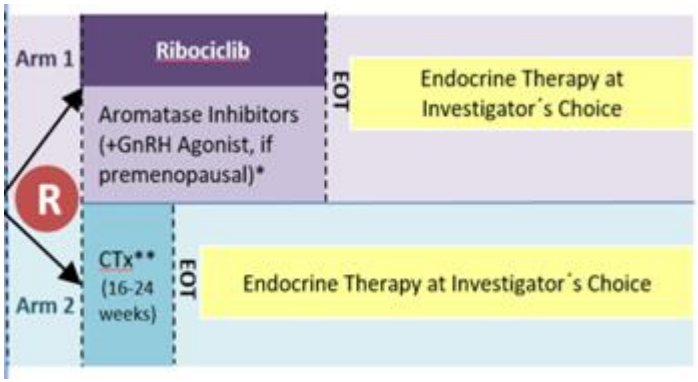
Ki-67
RS (OncotypeDx)

3 weeks (+/- 1 week)

Biopsy or surgery

Ki-67

- **N2-3** → **RS** ▪ **<25** → **Ki-67post** ▪**<10%***
- **N0** ▪ **N1** → **RS** ▪ **>25** → **Ki-67post** ▪**<10%***
- **N0** ▪ **N1** → **RS** ▪ **<25** → **Ki-67post** ▪**≥10%****



- High risk
- Intermediate risk
- Low risk

LKP Prof. Harbeck, Prof. Kümmel, study development
PD O. Gluz

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