



Definindo a melhor duração de terapia endócrina adjuvante para câncer de mama

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LACOG Breast Cancer Steering Committee

Potenciais Conflitos de Interesse

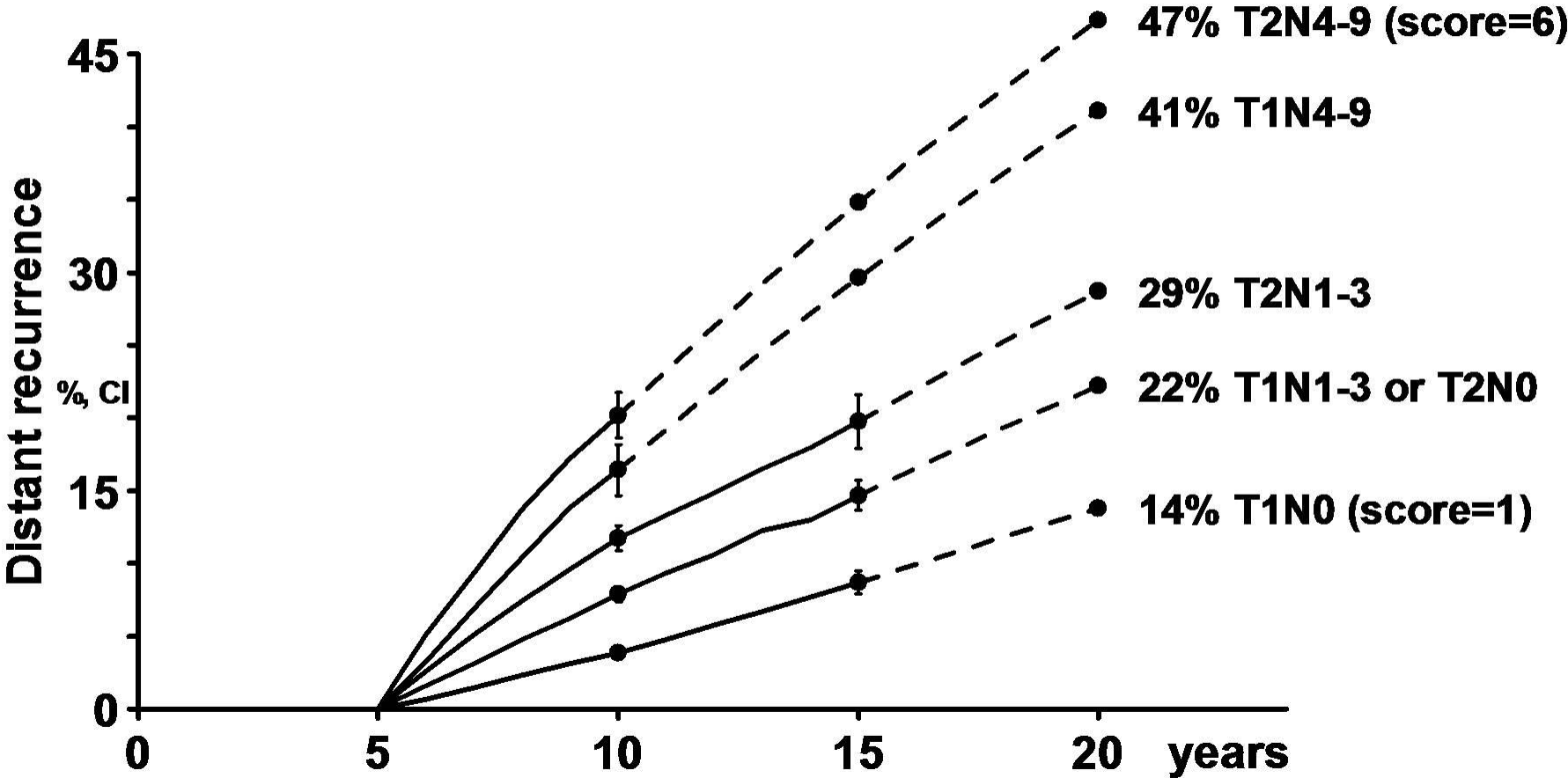
- Participação em protocolos de pesquisa – ROCHE, Astra-Zeneca, Pfizer, MSD, BMS, Novartis
- Patrocínio Congressos/Eventos - ROCHE, Pfizer
- Participação em Expert Panel - Zodiac

Qual a Duração Ideal da HT
adjuvante?

Long Term Recurrence Risk after use of Endocrine Therapy for Only 5 years

Effect of additive “T+N score” (range 1-6)

Score: 1/ 2 for T1/ T2, plus 0/ 1/ 4 for N0/ N1-3/ N4-9



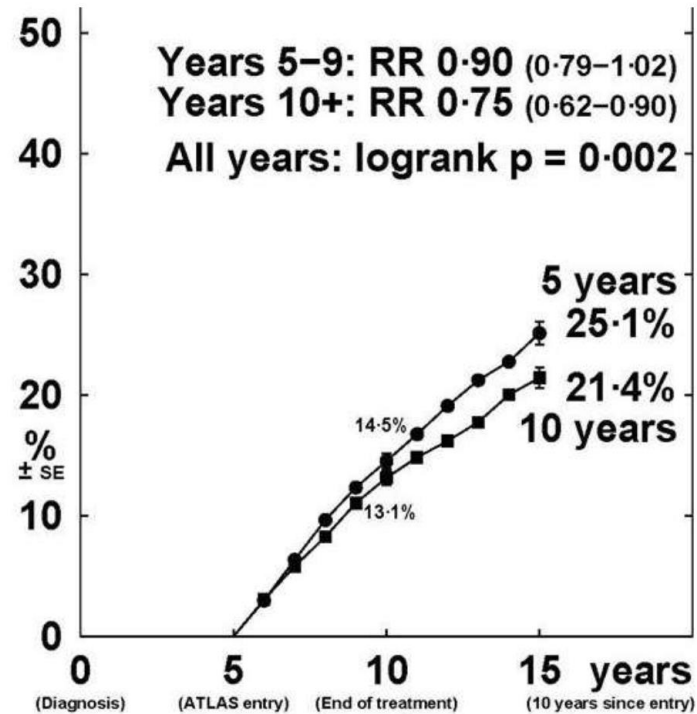
Studies of 5 vs. 10 years of Tamoxifen

Trial and Year	Number Randomized	Recruitment Period	Follow Up (years)
ECOG 1996	194	1982-1987	5.6
NSABP B-14 2001	1172	1987-1994	6.8
Scottish 2001	242	1985-1989	15
ATLAS 2012	6846	1996-2005	7.6
aTTOm 2013	6953	1991-2005	15

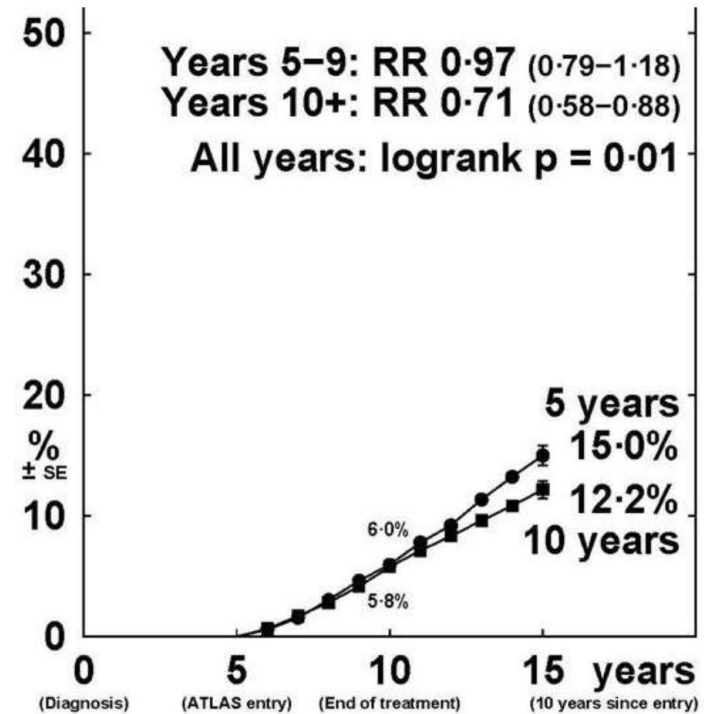
ATLAS: Tamoxifeno 10 anos

ATLAS: 6846 women, ER+, 10 vs 5 years tamoxifen

RECURRENCE



BREAST CANCER MORTALITY

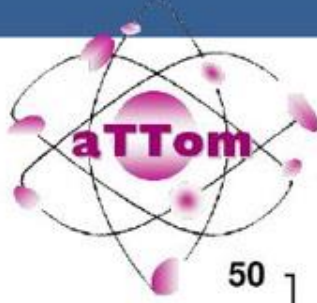


Recurrence rates (% / year) and logrank analyses

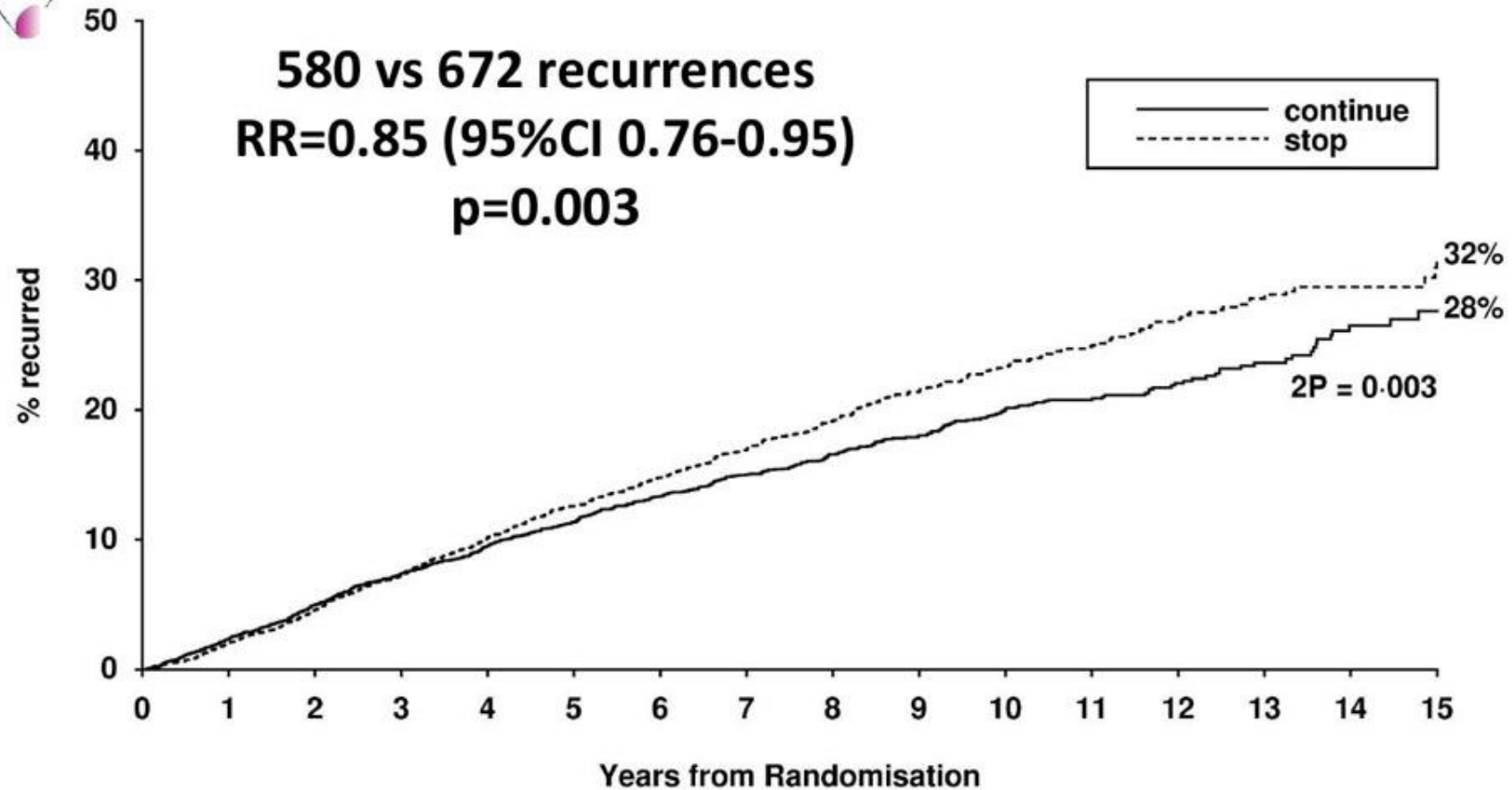
Tamoxifen allocation	Years 5 - 9	Years 10 - 14	Year 15+
Continue to 10 years	2.83 (428 / 15115)	1.96 (165 / 8439)	2.54 (24 / 945)
Stop at 5 years	3.16 (471 / 14889)	2.66 (214 / 8038)	3.03 (26 / 859)
Rate ratio, from (O-E) / V	0.90 SE 0.06 -24.8 / 224.7	0.74 SE 0.09 -29.1 / 94.7	0.85 SE 0.26 -2.1 / 12.5

Death rates (% / year: total rate - rate in women without recurrence) & logrank analyses

Tamoxifen allocation	Years 5 - 9	Years 10 - 14	Year 15+
Continue to 10 years	1.17 SE 0.09	1.38 SE 0.12	1.64 SE 0.39
Stop at 5 years	1.21 SE 0.09	2.01 SE 0.15	2.29 SE 0.47
Rate ratio, from (O-E) / V	0.97 SE 0.10 -3.2 / 94.0	0.70 SE 0.10 -27.2 / 77.5	0.79 SE 0.27 -2.5 / 10.6

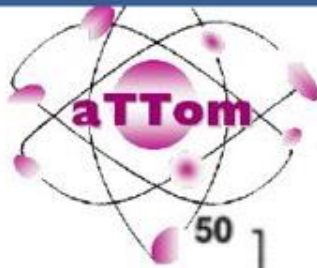


10 vs 5 years of Tam: Recurrence by Treatment

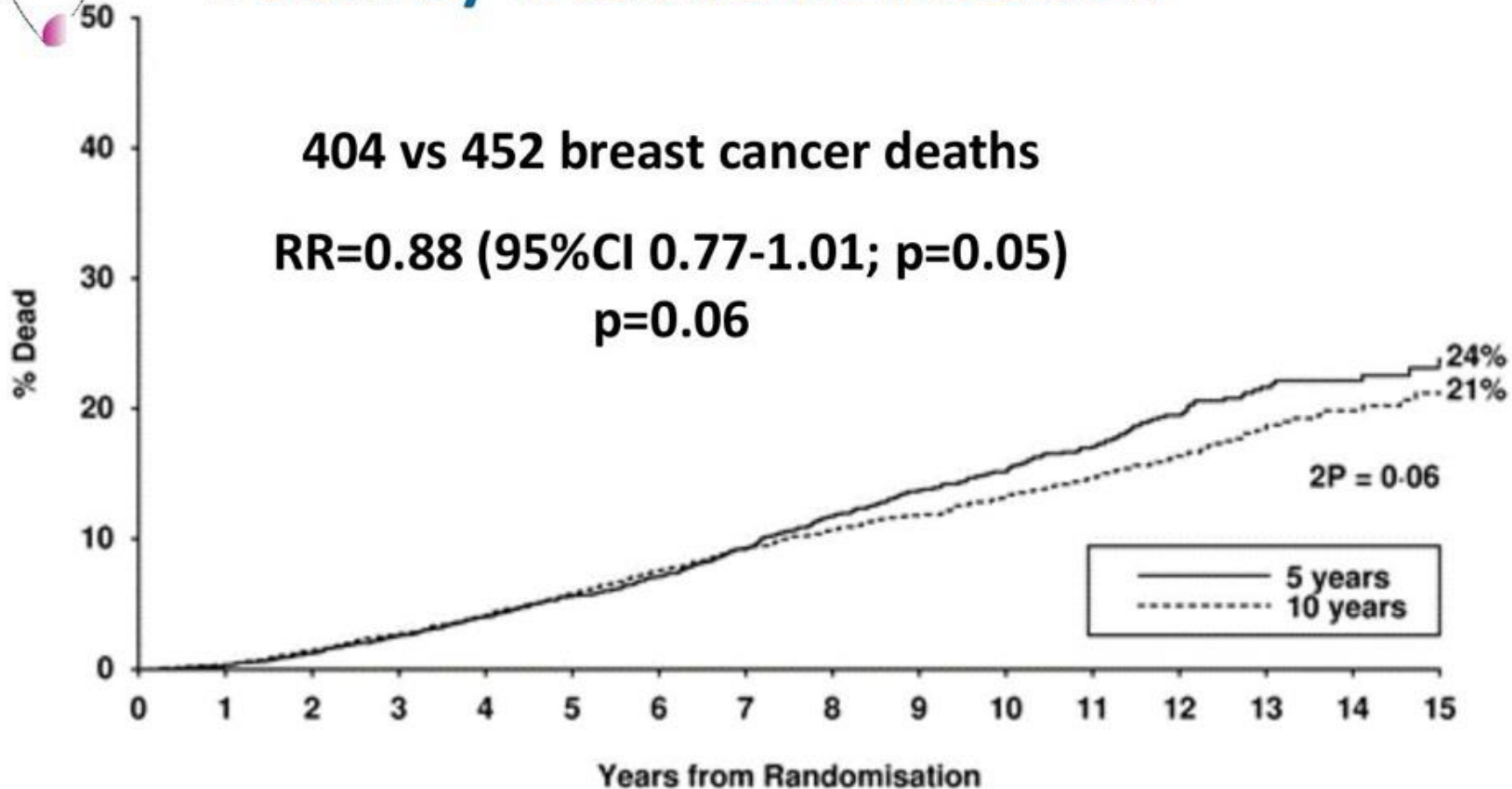


At risk:

continue	3468	3283	3113	2933	2754	2513	2210	1959	1576	1239	924	682	463	314	190	101
stop	3485	3305	3139	2928	2714	2453	2180	1908	1527	1143	843	618	429	275	164	87



10 vs 5 years of Tam: Breast Cancer Death by Treatment Allocation



At risk:

5 years	3485	3399	3293	3145	2981	2748	2482	2206	1785	1347	1013	743	520	334	207	116
10 years	3468	3384	3275	3143	2972	2753	2474	2207	1804	1419	1066	794	551	369	226	130

ASCO 2013

Pooled analysis ATLAS + aTTom: Breast Cancer Mortality

10 vs 5 yrs BC mortality RR by period in ER+ve (or unknown) patients	<i>ATLAS</i> ER+ve n = 10543* HR (95% CI)	<i>aTTom</i> ER+ve n = 6934 in UK HR (95% CI)	<i>Combined</i> ER+ve n = 17477 HR (95% CI)
Years 5-9	0.92 (0.77-1.09)	1.08 (0.85-1.38)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) P=.002	0.75 (0.63-0.90) P=.007	0.75 (0.65-0.86) P=.00004
All years	0.83 (0.73-0.94), P=.004	0.88 (0.74-1.03) P=.1	0.85 (0.77-0.94) P=.001

* IPCW (Inverse probability of censoring weighted) estimate of the effect in ER+

Also significant improvements in **Overall Survival**

5-9yrs HR 0.99 (0.89-1.10)
 10-14yrs HR 0.84 (0.77-0.93) (p=0.0007)
 All yrs HR 0.91 (0.84-0.97) (p=0.008)

Gray RG et al. ASCO 2013 (Abstract 5)

ATLAS: Effects of Allocation on Second Cancer Incidence

	<u>Number of events</u>		Log-rank O-E	Variance of O-E	Event rate ratio (95% CI)	p value*
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years				
Second cancer incidence						
Contralateral breast cancer	419	467	-28.9	221.5	0.88 (0.77-1.00)	0.05
Endometrial cancer	116	63	24.8	44.8	1.74 (1.30-2.34)	0.0002
Primary liver cancer	3	3	-0.0	1.5	0.99 (0.20-4.90)	0.99
Colorectal cancer	46	52	-3.8	24.5	0.86 (0.58-1.27)	0.44
Unspecified site	254	251	-1.3	126.2	0.99 (0.83-1.18)	0.91

(O-E=observed minus expected)

ATLAS: Effects of Allocation on non-neoplastic Disease

	<u>Number of events</u>		Log-rank O-E	Variance of O-E	Event rate ratio (95% CI)	p value*
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years				
Non-neoplastic disease (ever hospitalized or died)						
Stroke	130	119	3.8	62.2	1.06 (0.83-1.36)	0.63
Pulmonary embolus	41	21	9.7	15.5	1.87 (1.13-3.07)	0.01
Ischemic heart disease	127	63	-20.2	72.5	0.76 (0.60-0.95)	0.02
Gallstones	75	66	3.7	35.2	1.11 (0.80-1.54)	0.54
Cataract	72	63	3.5	126.2	1.11 (0.79-1.56)	0.54
Bone fracture	62	70	-4.9	33.0	0.86 (0.61-1.21)	0.39

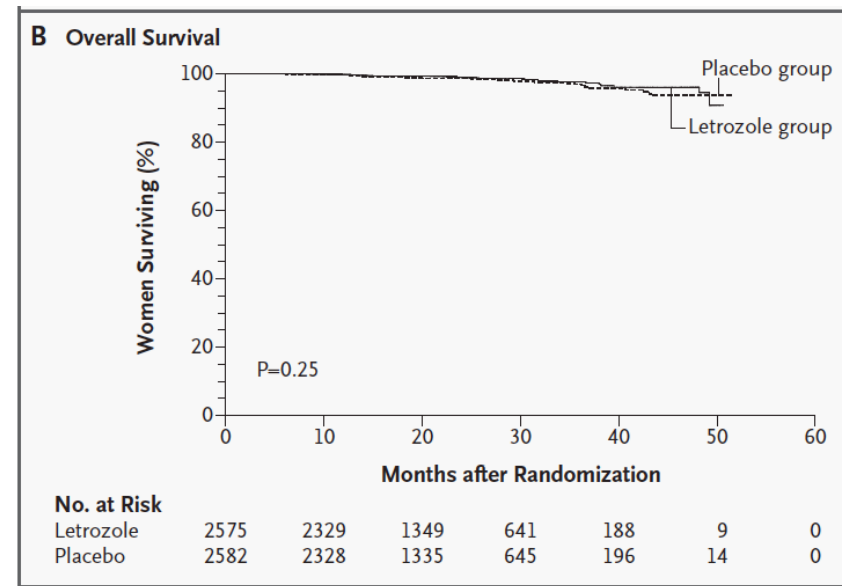
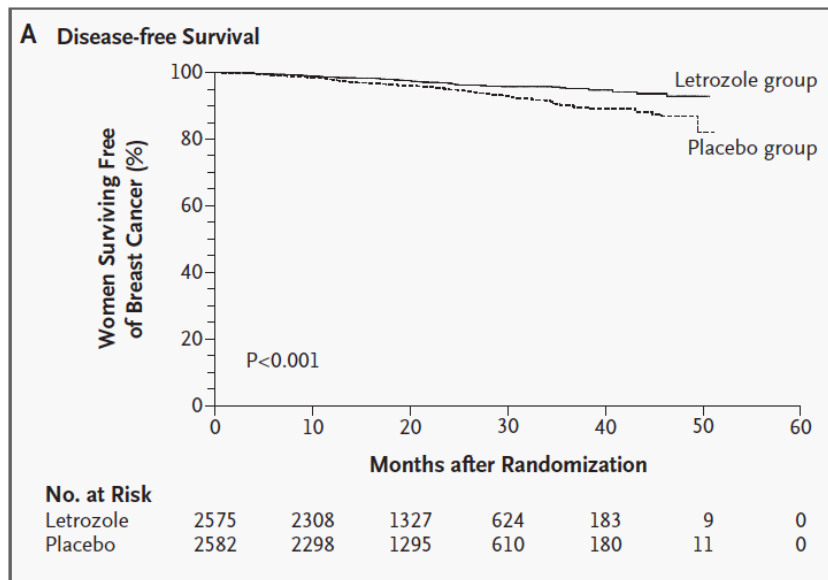
(O-E=observed minus expected)

10 Anos de Tamoxifeno vs 5 anos

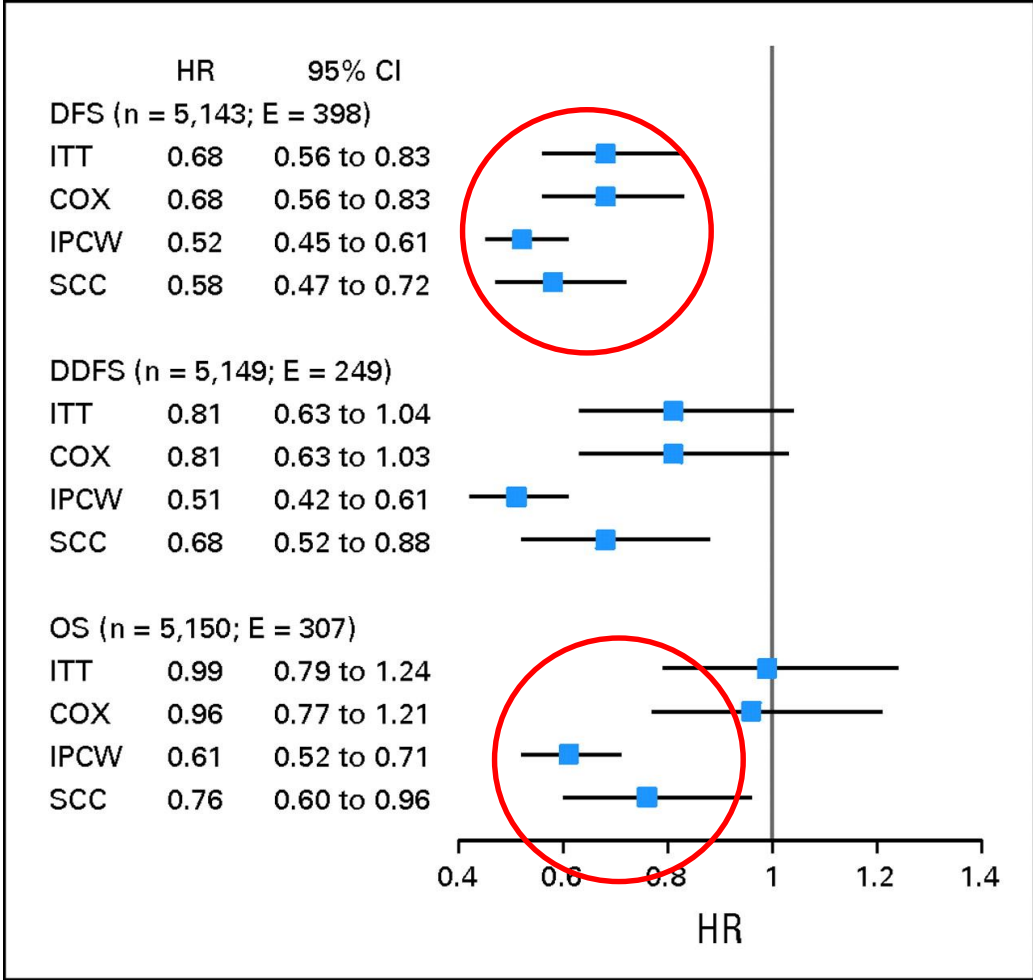
- Reduz recorrência do Câncer de Mama
- Aumenta sobrevida Câncer Específica e Mortalidade Geral
 - Benefício somente surge após os 10 anos de uso
- Reduz Câncer de Mama Contralateral
- Aumenta risco de Câncer de Endométrio
- Aumenta risco de TEP

Terapia Hormonal Extendida: MA 17

Tamoxifeno 5 anos → Letrozol 5 anos



MA17 Trial



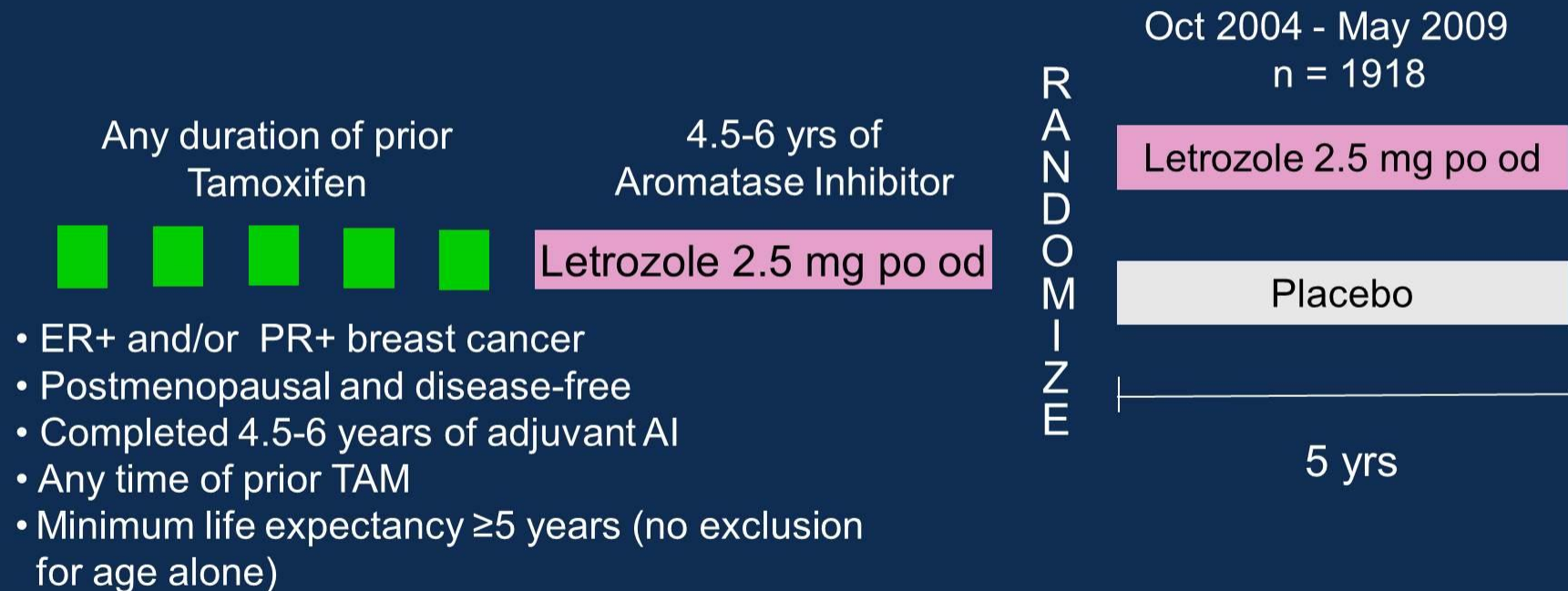
Jin H et al. JCO 2012;30:718-721

Estudos de IA além de 5 anos

- MA-17R
- NSABP B42
- IDEAL
- DATA
- ABCSG-16
- SOLE

MA.17R Trial Schema and Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

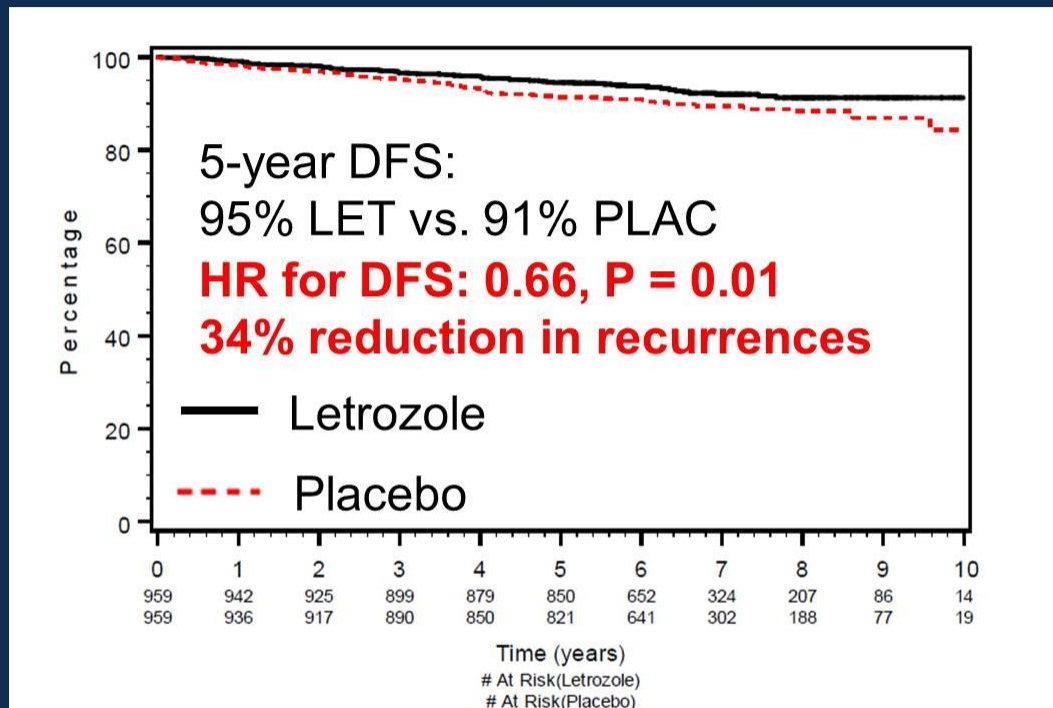


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MA.17R Primary Endpoint: DFS at med F/U of 6.3 yrs



	LET	PLAC
DFS events	67 (7.0)	98 (10.2)
Distant recurrences	42	53
Loco-regional recurrences	19	30
Bone recurrences	28	37
New Contralateral breast cancers [§] CBC	13 (1.4)	31 (3.2)

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NSABP B-42: **Schema**

- 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

AI X 5 yrs

or

TAM X ≤ 3 yrs ~~to~~ AI to Complete 5 yrs

Stratification:

Pathological nodal status (Negative, Positive)

Prior adjuvant TAM (Yes, No)

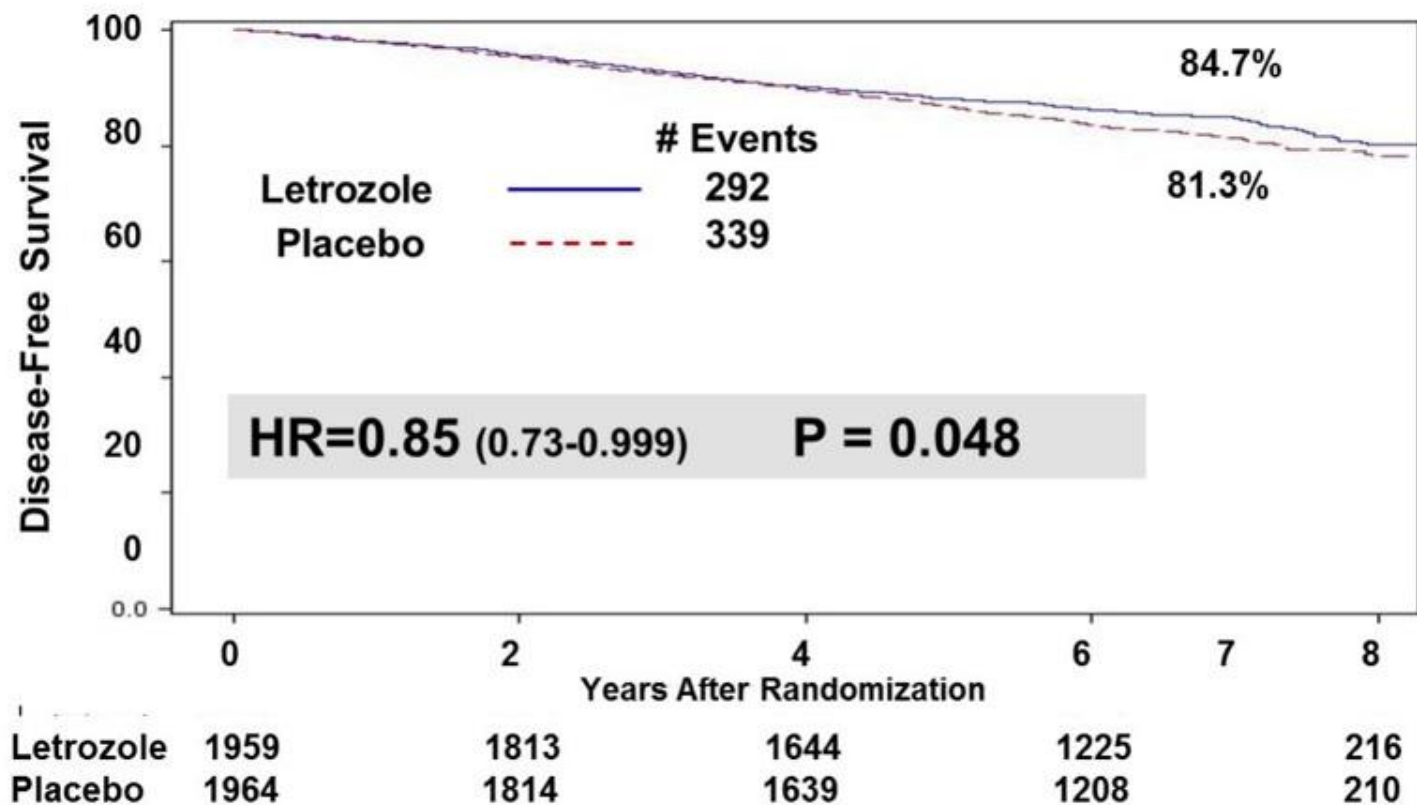
Lowest BMD T score: spine, hip, femur (> -2.0 , ≤ -2.0 SD)

R

Letrozole X 5 yrs

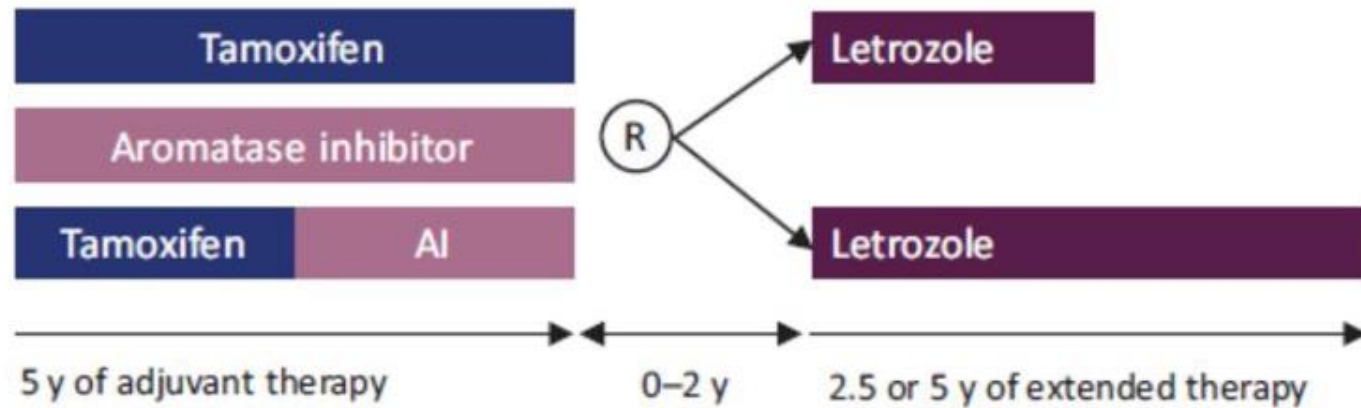
Placebo X 5 yrs

NSABP B-42: Disease-free Survival



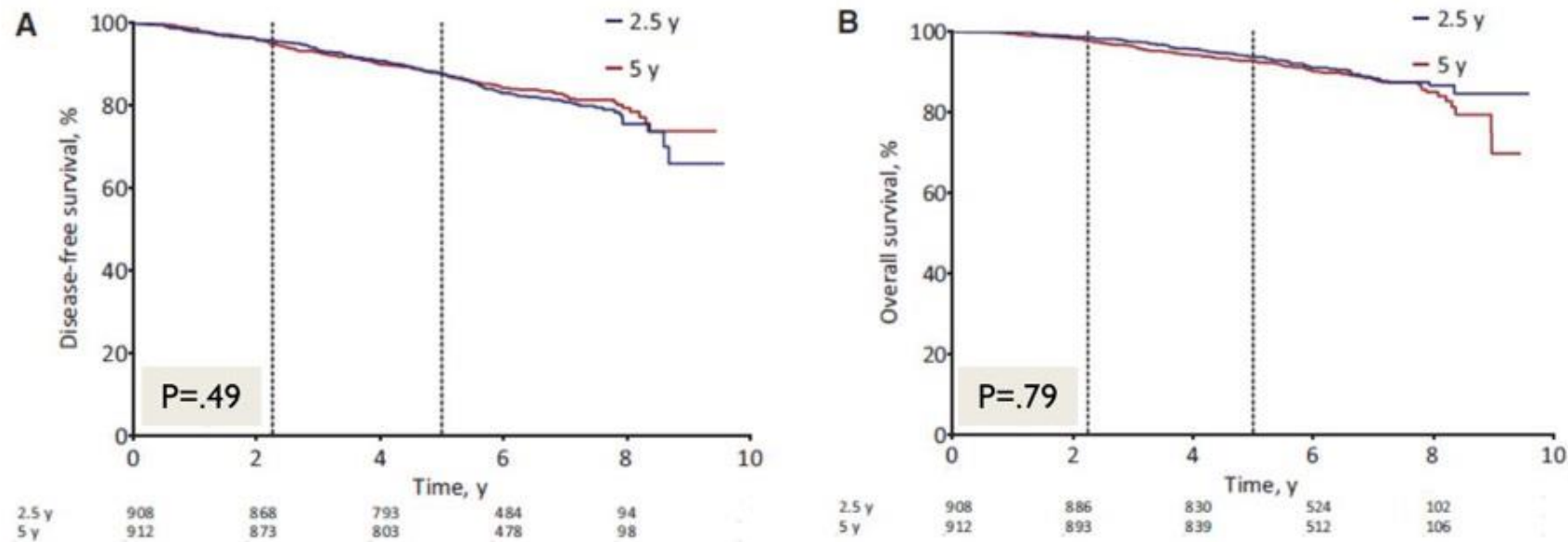
***P-value did not reach statistical significance level of 0.0418**

IDEAL Trial (BOOG 2006-05)



*7.5-10 years of endocrine therapy
2.5-10 years of AI*

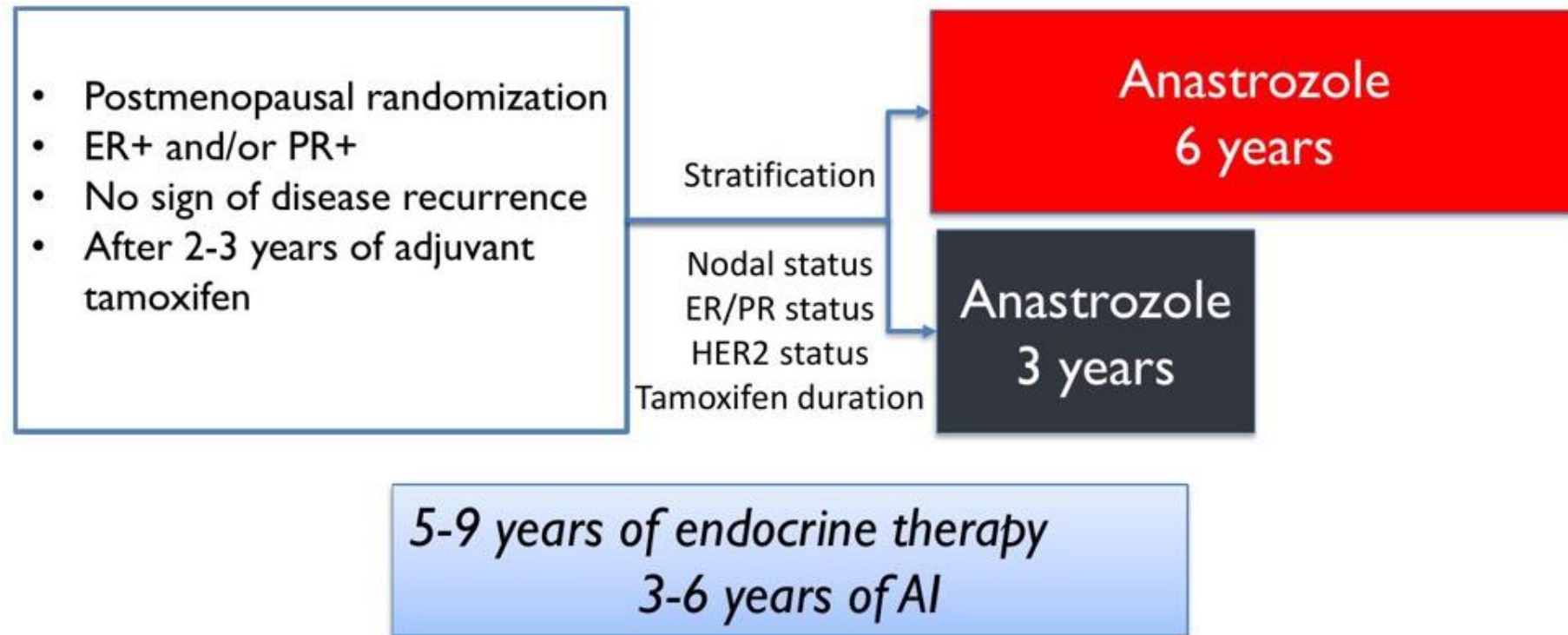
IDEAL: Kaplan-Meier analysis: (A) Disease-free and, (B) Overall Survival



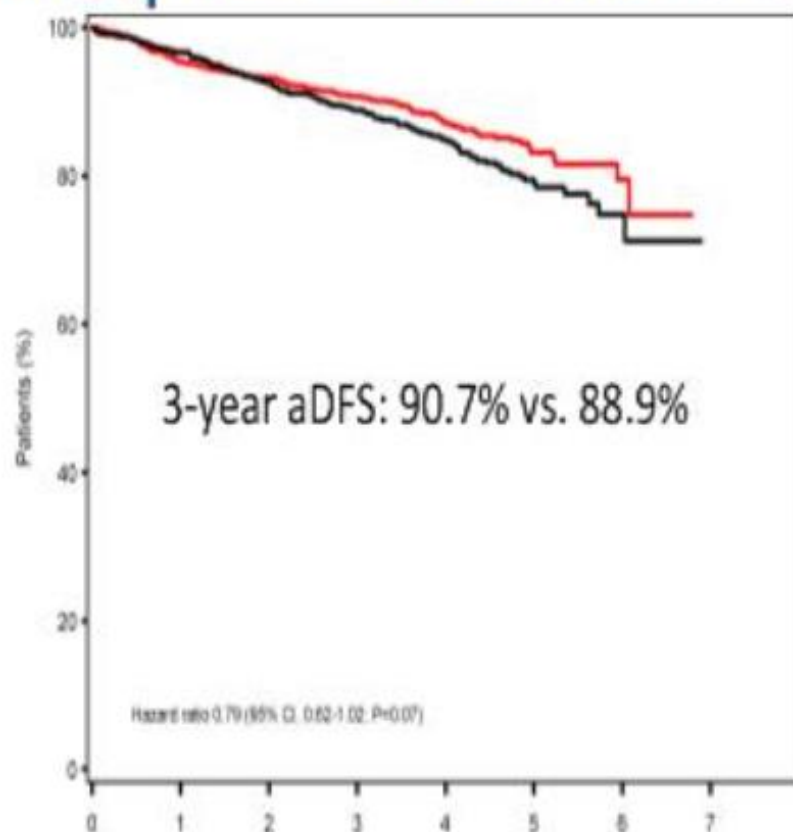
Blok et al, *JNCI* 2018

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Extended Adjuvant AI After Sequential Endocrine Therapy (DATA)



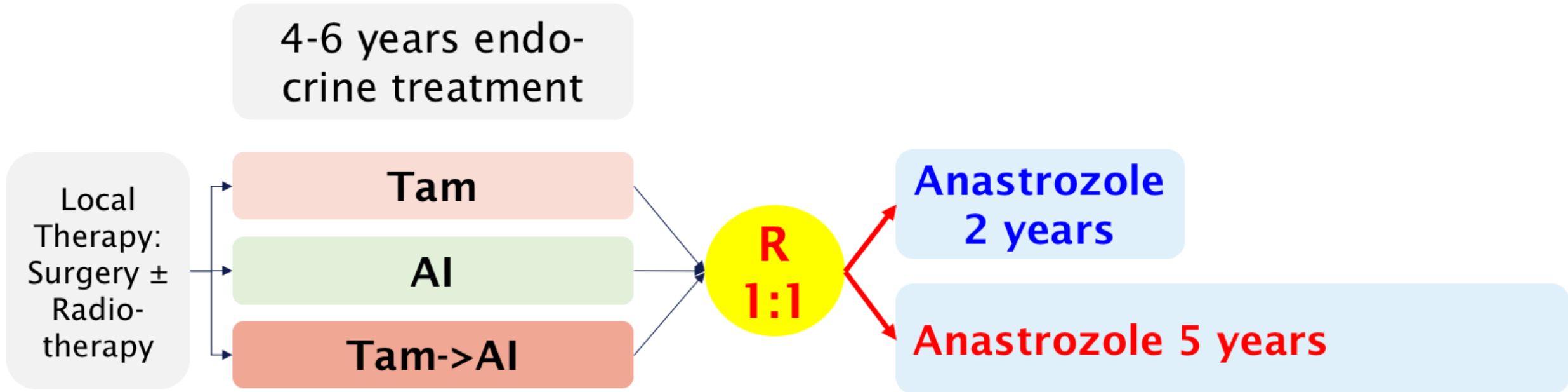
adapted Disease-Free Survival (aDFS)



N=1660	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
5-year aDFS (%)	83.1	79.4
HR (95% CI)	0.79 (0.62 – 1.02)	
P-value	0.07	

Number at Risk	Follow-up starting 3 years after randomization (years)							
	0	1	2	3	4	5	6	7
6-year	827	789	769	698	445	162	24	0
3-year	833	801	762	692	453	173	28	0

ABCSCG-16 Trial Design



N=3,484

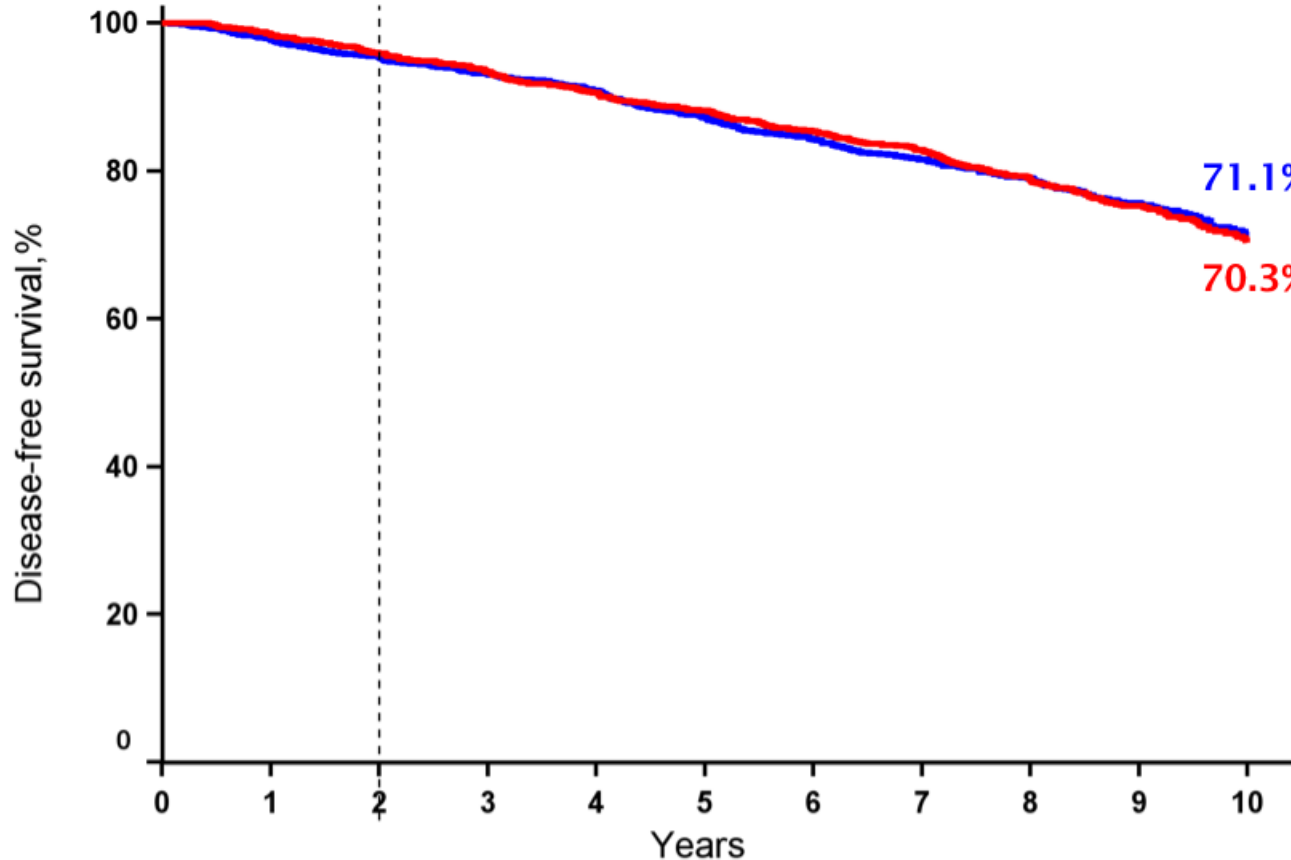
Postmenopausal, HR+, T1-3, N0/N+, M0

Recruitment in 75 centers in Austria, 2004-2010

Median Follow-Up: 106.2 months (102.7-107.7)

ABCSCG-16 Disease-Free Survival

Time from randomization to first DFS event



	Number of Events/Patients	Hazard ratio vs 2 years	P-value
— 2 years	378/1,731	1.007 (0.87, 1.16)	0.925
— 5 years	384/1,738		

Patients at risk:

	0	1	2	3	4	5	6	7	8	9	10
2 years	1731	1651	1601	1538	1477	1368	1206	990	741	540	214
5 years	1738	1667	1605	1551	1485	1399	1233	1026	779	554	209

SOLE: Study of Letrozole Extension

After 4 to 6 years of Prior Adjuvant Endocrine Therapy

Postmenopausal, HR-positive, Node-positive



4884 Patients Randomized in ITT, Nov 2007 - July 2012

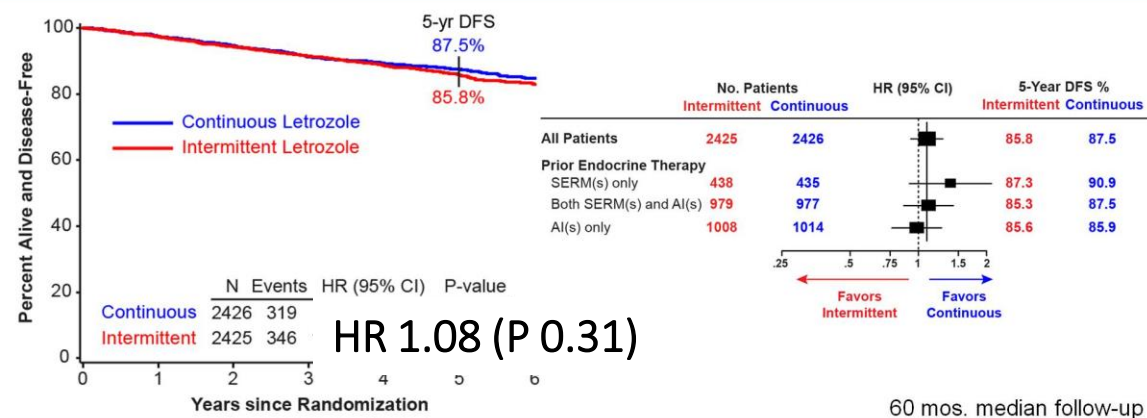
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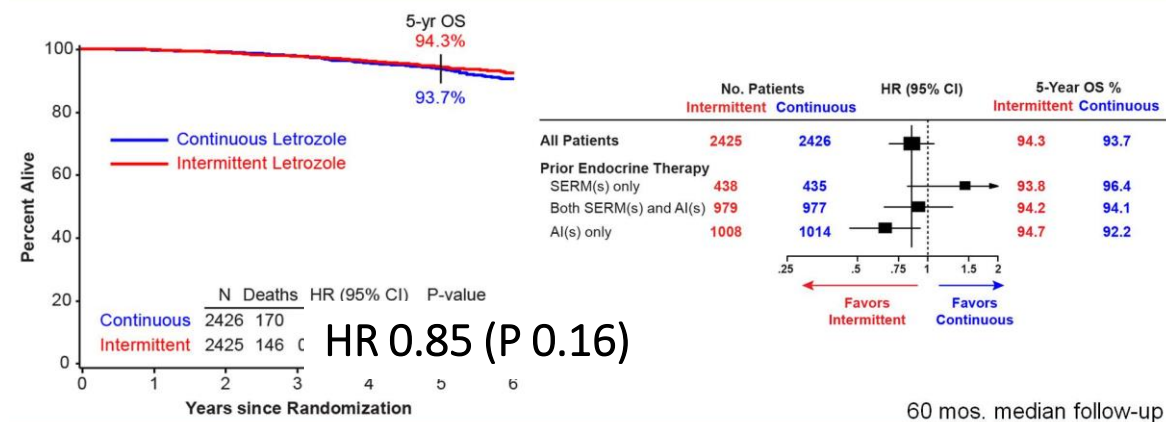
Presented by: Marco Colleoni, MD

SOLE

Primary Endpoint: Disease-Free Survival



Overall Survival



Extending AI Duration Beyond 5 years

	Number (% Node+)	Duration ET/AI	DFS benefit	OS benefit	New BC benefit
MA-17R	1918 (53%)	10-15 5-10	Yes	No	Yes
NSABP B42	3966 (42%)	5-10 2-10	No	No	Yes
IDEAL	1824 (74%)	7.5-10 2.5-10	No	No	Yes
DATA	1912 (67%)	5-9 3-6	No	No	No
SOLE	4884 (99%)	5-10 5-10 cont/int	No	No	?
ABCSG 16	3469 (31%)	7-10 5-10	No	No	No

Extending AI Duration Beyond 5 years: Percent Experiencing Adverse Events by Arm

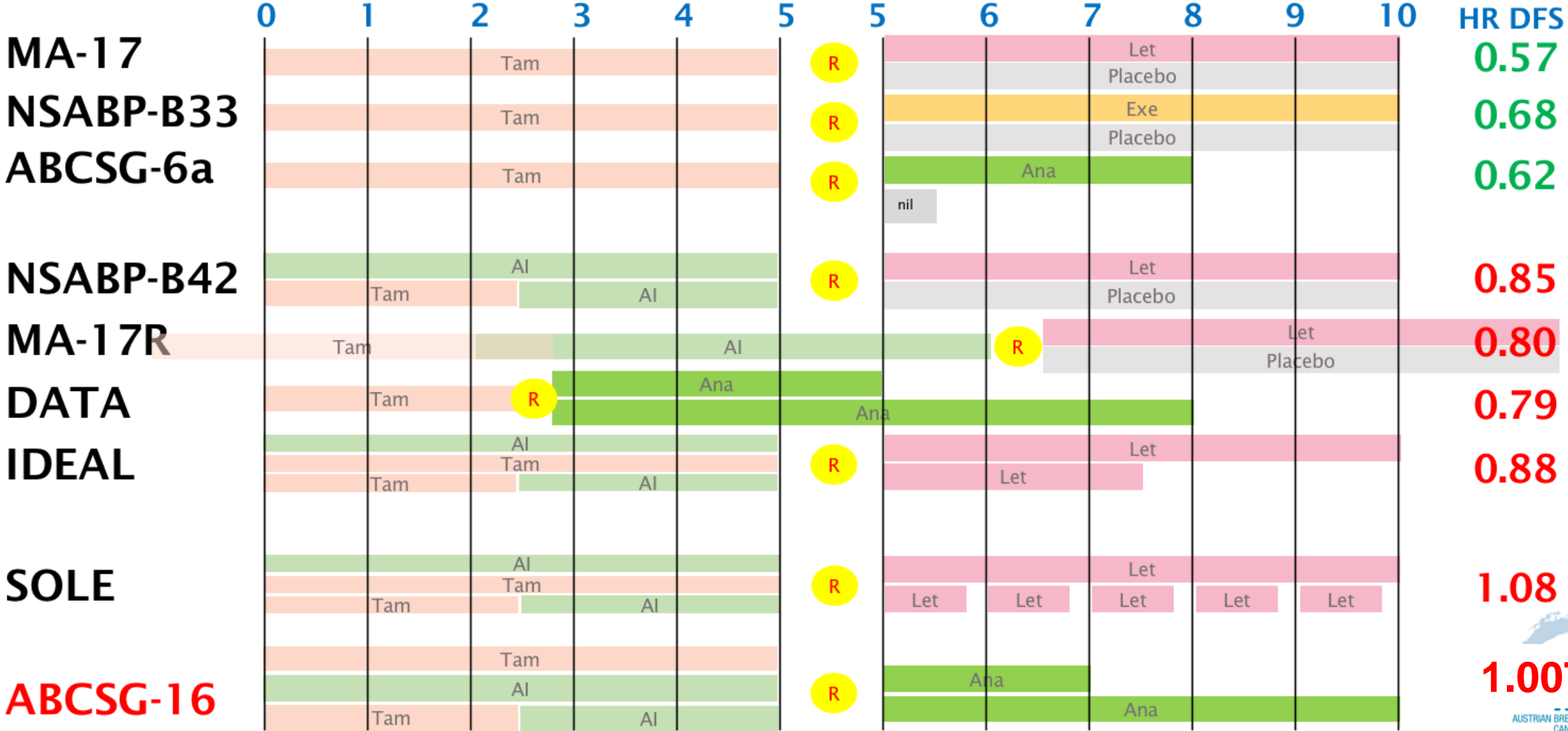
	MA-17R		NSABP B42		IDEAL		DATA (years 0-6)		SOLE		ABCSG 16	
	AI	Plc	AI	Plc	AI 5 ys	AI 2.5 ys	AI 6 ys	AI 3 ys	AI Cont.	AI Int.	AI 5ys	AI 2 ys
Arthralgia	53	50			14.7	13.2	60	54	68	66		
Hot Flashes	38	37			13.1	10.5			54	52		
Vaginal Dryness	11	10										
Cardio-vascular	12	10					15	14				
Fracture	14	9	5.4	4.8	5	2.8	10	8	10	9	6,3	4.7

AI- aromatase inhibitor, Cont- continuous, Int- intermittent, Plc- placebo, ys-years

Adherence/Compliance

	AI/Long	Placebo/Short
MA-I7R	62.5%	62.3%
NSABP B42	60.3%	62.5%
IDEAL	57.5%	73.5%
DATA	66%	84%
SOLE	85-90%	85-90%
ABCSG 16	59.4%	75.7%

Extending Adjuvant AIs



TAKE HOME

- Tumores HR+ apresentam recidivas > 20 a pós Dx e risco se correlaciona com T, N+ e G
- A utilização de HT por mais de 5 anos reduz de uma forma geral as taxas de recidiva
- 10 anos de TAM
 - Reduz ~ 4% a taxa de recorrência e ~2% a mortalidade por câncer de mama vs. 5 anos, mas o benefício somente aparece na segunda década pós diagnóstico
 - Aumenta risco de Ca Endometrial e Eventos Tromboembólicos
- A utilização de IA após 5 anos de TAM
 - Reduz recorrência e provavelmente melhora SG

TAKE HOME

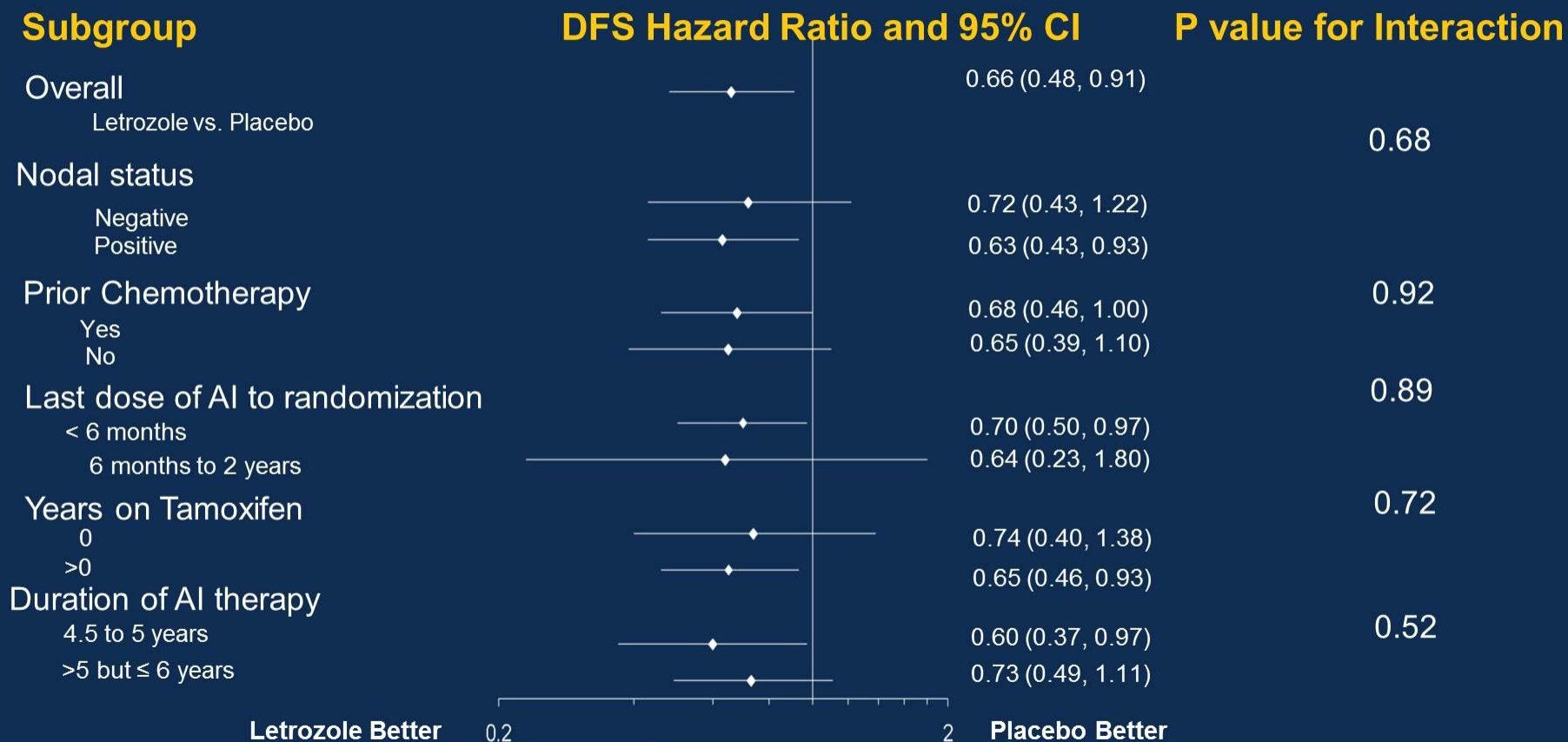
- Uso de IA por Mais de 5 anos:
 - Aumenta discretamente SLP (~2%)
 - Reduz Recorrência Contralateral
 - Não traz impacto em Sobrevida Global
 - A Duração Ideal não está clara, mas provavelmente não há benefício importante com mais de 7 anos de uso (ABCSG 16)
 - Aumenta risco de eventos osteoporóticos (FRATURA)
 - Terapia Intermitente vs. Contínua tem EFICACIA SIMILAR, mas há melhora em alguns parâmetros de QoL
 - Aderência ~ 60%

OBRIGADO!

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BACKUP

MA.17R - DFS by pre-specified subgroups

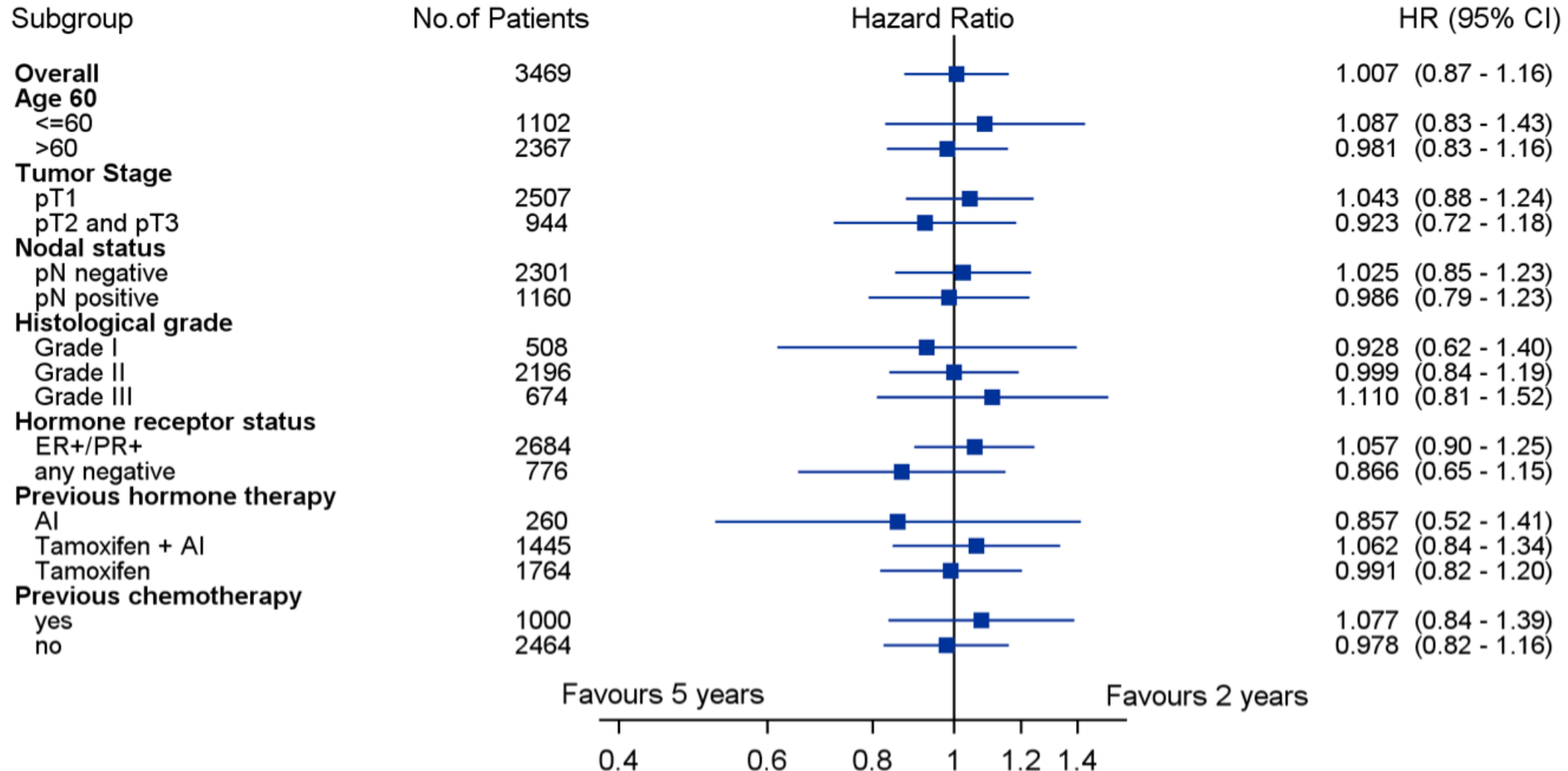


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ABCSCG-16 DFS Subgroups



MA.17R – Quality of Life

Measurements:

MENQOL and SF-36 at baseline and at 12, 24, 36, 48, 60 months
Compliance >85% at each time point

Results:

No between-group differences for:

- SF-36 summary score

- Most SF-36 subscales

- No difference in any of the four MENQOL subscales

There was a difference in favor of placebo for **SF-36 role-function-physical** subscale, but difference (3.2 pts) smaller than minimum difference for clinical significance (5 pts)

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