



## Tomás Reinert

- Oncologista Clínico do Hospital do Câncer Mãe de Deus

31 MAIO  
A 2 JUN  
2018

XIX CONGRESSO SUL-BRASILEIRO  
DE GINECOLOGIA E OBSTETRÍCIA  
IV JORNADA SUL-BRASILEIRA  
DE MASTOLOGIA



# Quem deve receber hormonioterapia por 10 anos?

## Tomás Reinert

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# Dr George Beatson – 1896

104 THE LANCET.] DR. BEATSON: INOPERABLE CASES OF CARCINOMA OF THE MAMMA. [JULY 11, 1896.

another thirty years it would then have entirely disappeared. The first great drop in its rate took place in the decade 1840-50, about the time that serious attention began to be given to sanitary reforms and especially to land drainage. It then remained scarcely reduced for about seventeen years; but from 1867 to 1894 it has been steadily on the decline. It is in this period that most of the great sanitary works have been carried out in this country. Can we doubt that it is to them that we owe so substantial a diminution of the disease? And need we despair of carrying it on to its fitting close? Let it be remembered that this improvement has taken place in spite of the increasing aggregation of the population in towns and without any special measures of repression

## ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.<sup>1</sup>

BY GEORGE THOMAS BEATSON, M.D. EDIN.,  
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON,  
GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY  
TO THE UNIVERSITY OF EDINBURGH.



Beatson GW. Lancet 1896

# AN ANALYSIS OF NINETY-NINE CASES OF INOPERABLE CARCINOMA OF THE BREAST TREATED BY OOPHORECTOMY

BY

HUGH LETT, M.B.VICT., F.R.C.S.,

ASSISTANT SURGEON BELGRAVE HOSPITAL FOR CHILDREN; LATE SURGICAL  
REGISTRAR LONDON HOSPITAL, ETC.

Received December 6th, 1904—Read January 24th, 1905

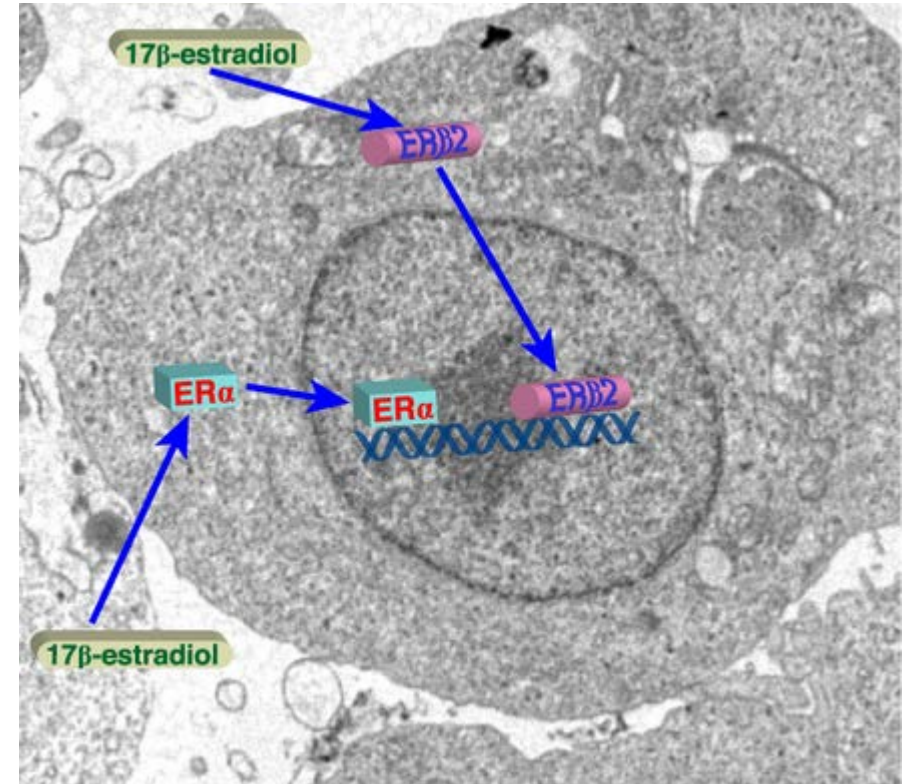
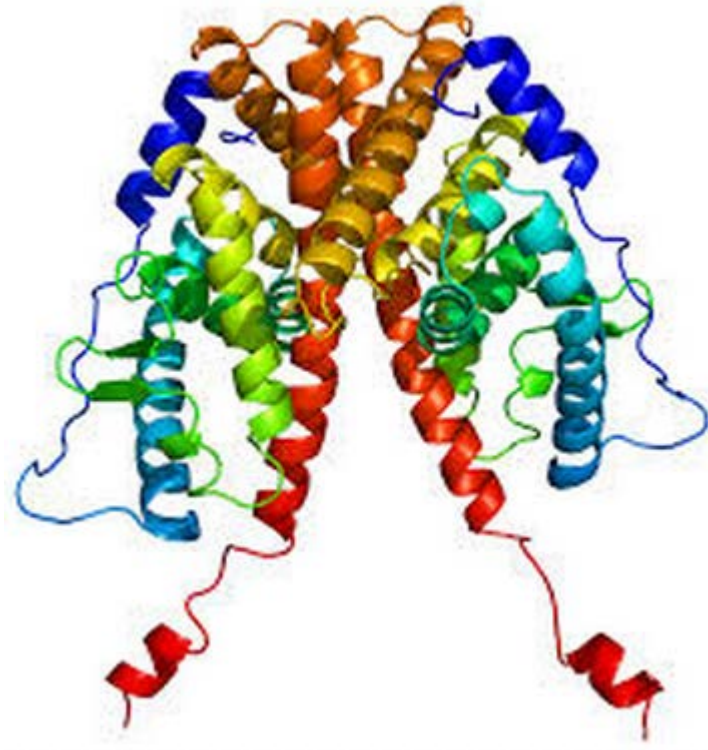
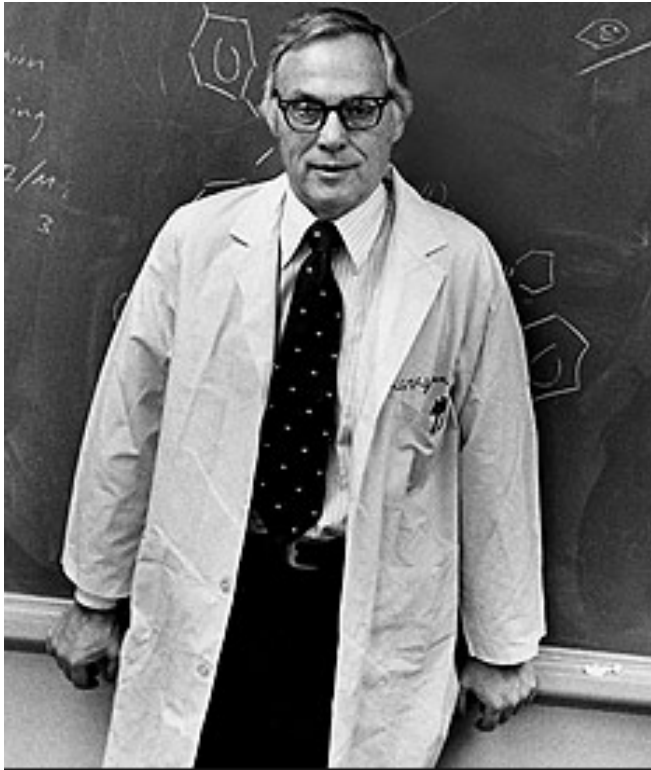
In six months most of nodules disappeared Rapid disappearance of recurrence. Marked gain in strength and weight	17 months 14 months	Local recurrence. Growths in viscera. Died July, 1898. Relapse of growth. Cancer of liver. Died October, 1901.
Ulcer healed, and there was no distinct lump in the left breast three months after operation. Ten months after operation had gained 2 st. 7½ lbs. Eighteen months' good health	29 months	Recurrence of ulceration 18 months after operation. Died December, 1900.
Relief of pain	12 months	Died 1896; secondary growths in liver.
Very slight	5 months	Died October, 1897; growths in lung and liver.
None	5 weeks	Died September, 1899.
December 2nd, 1903: two or three small glands in left axilla; very small hard gland in left supra-clavicular region, no pain, and no recurrence in scar. September 28th, 1904: small nodule in the scar; considerable increase in size in the gland in left supra-clavicular region	40 months, still alive	



# Estrogen Receptors in Human Breast Cancer

WILLIAM L. MCGUIRE

*From the Department of Physiology and Medicine, University of Texas Medical School at San Antonio, San Antonio, Texas 78229*



# Câncer de mama receptor hormonal positivo (RH+)

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- Mais comum
- Principal causa de mortalidade
- Doença “luminal” → incertezas mais frequentes

Oncologistas buscam evitar tanto sub-tratamento quanto tratamento excessivo

# Câncer de mama receptor hormonal positivo (RH+)

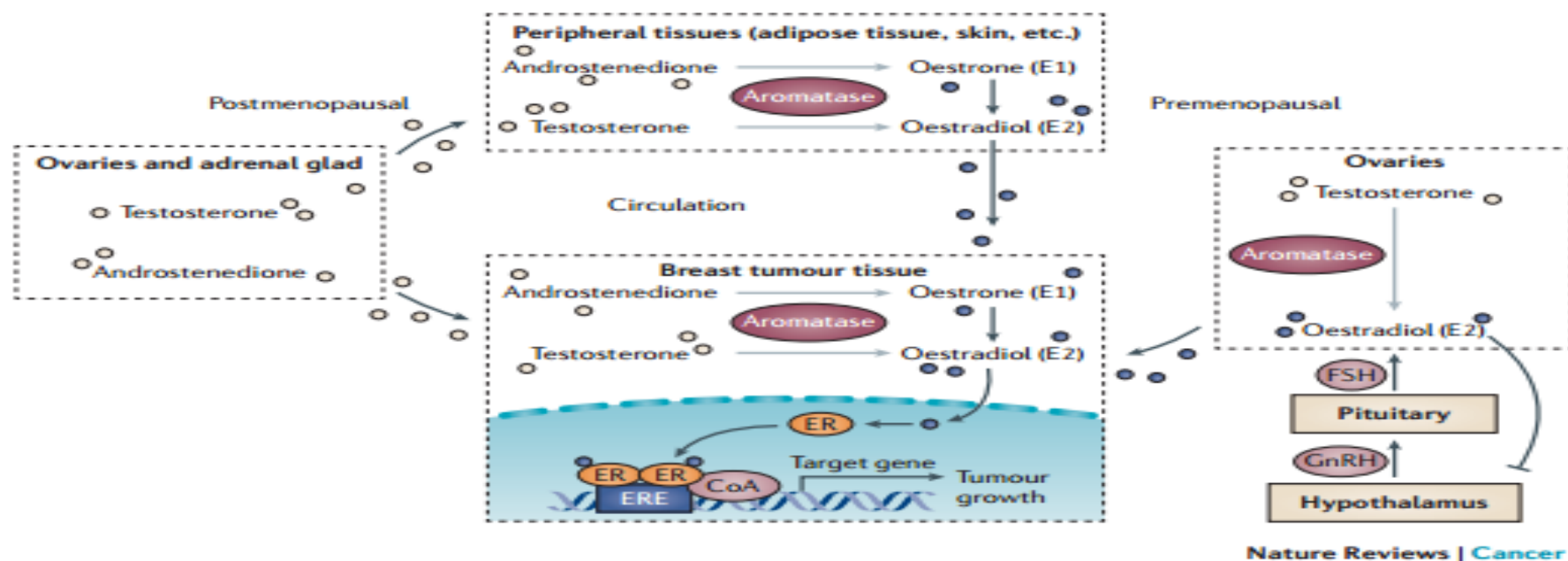
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- Terapia endócrina é o pilar principal do tratamento
- Terapia endócrina pode ser considerada o tratamento oncológico com maior impacto global, dada a incidência de tumores de mama no mundo e os benefícios significativos da hormonioterapia
- Aproximadamente 25-30% dos tumores RH+ em estágio inicial terão recidiva, na maioria dos casos após cinco anos do diagnóstico apesar do tratamento locorregional e sistêmico
- Na doença metastática, resposta em ~30% das pacientes e benefício clínico na ampla maioria
- Entretanto, resistência e progressão de doença invariavelmente acontecem

# Mecanismo de ação da terapia endócrina

Terapia-alvo dirigida à via do receptor de estrogênio (RE)

- Deprivação estrogênica → Inibidores de aromatase e supressão da função ovariana
- Modulação/degradação do RE → tamoxifeno e fulvestranto





# Primeiros estudos de hormonioterapia adjuvante

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The Lancet • Saturday 5 February 1983

**CONTROLLED TRIAL OF TAMOXIFEN AS  
ADJUVANT AGENT IN MANAGEMENT OF  
EARLY BREAST CANCER**

**Interim Analysis at Four Years by Nolvadex Adjuvant  
Trial Organisation\***

- 1 ou 2 anos de tamoxifeno
- Redução significativa das recidivas
- Maioria das recorrências após o período de tratamento
- Hipótese de que tratamentos mais longos melhorariam desfechos

# Primeiros estudos de hormonioterapia adjuvante

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J Natl Cancer Inst. 1996 Nov 6;88(21):1543-9.

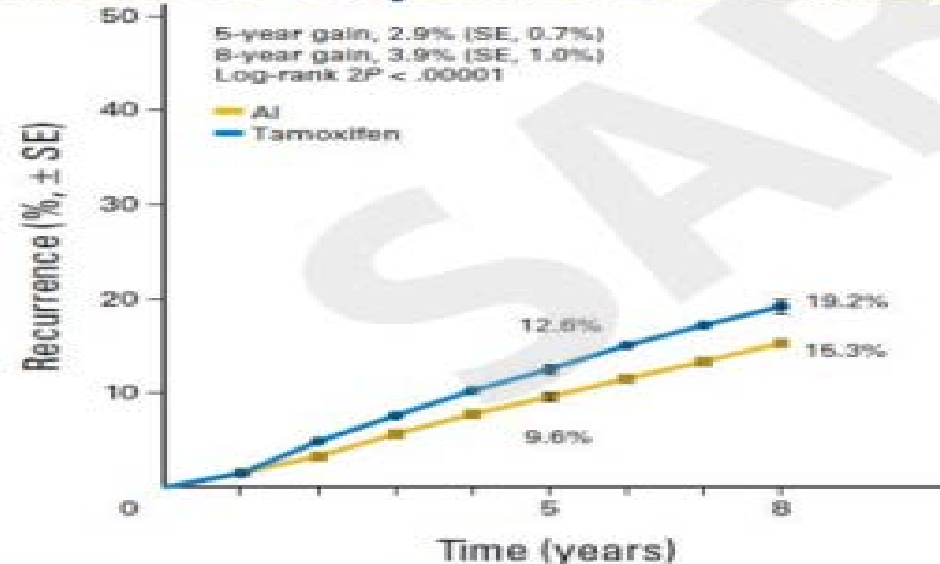
**Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. Swedish Breast Cancer Cooperative Group.**

- ECR 2 vs 5 anos de tamoxifeno adjuvante
- Melhora da SLP e sobrevida global com HR 0.82
- SG 10 anos 80 vs 74%

## Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)\*

### Adjuvant AI in Postmenopausal Women is Superior to Tamoxifen



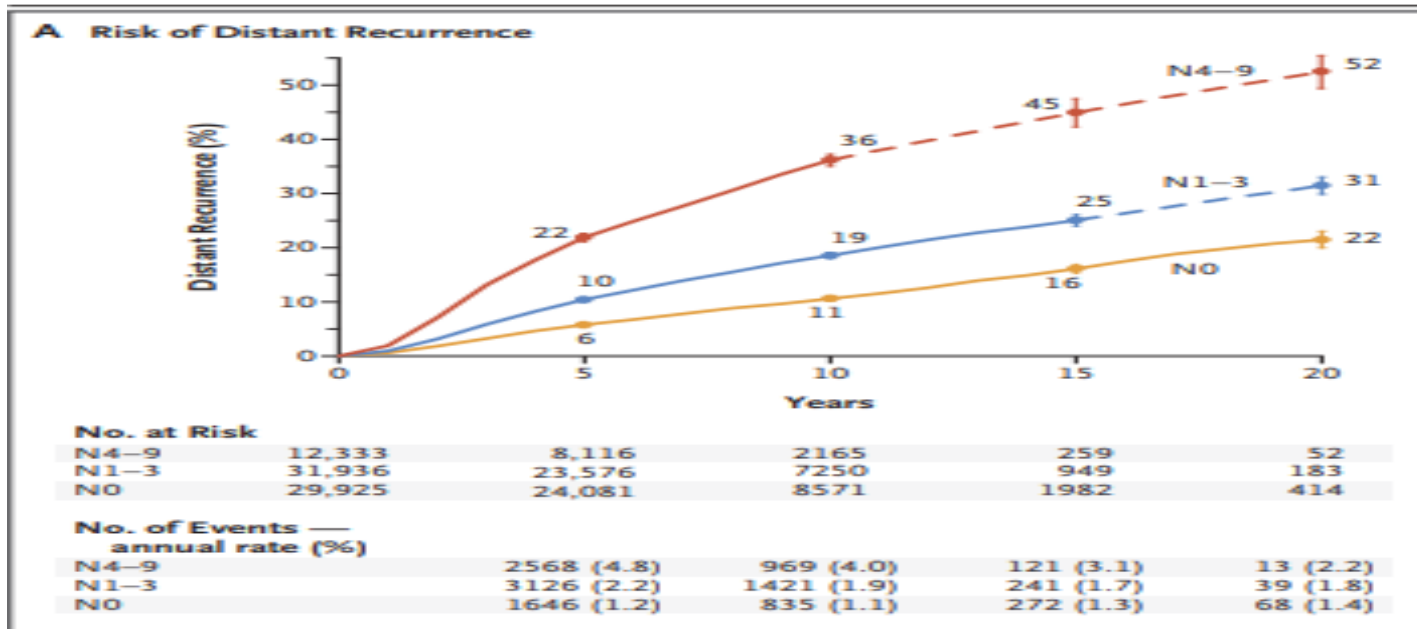
Dowsett et al, JCO 2009

# Risco de recidiva após 5 anos de hormonioterapia adjuvante

## ORIGINAL ARTICLE

### 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

Hongchao Pan, Ph.D., Richard Gray, M.Sc., Jeremy Braybrooke, B.M., Ph.D., Christina Davies, B.M., B.Ch., Carolyn Taylor, B.M., B.Ch., Ph.D., Paul McGale, Ph.D., Richard Peto, F.R.S., Kathleen I. Pritchard, M.D., Jonas Bergh, M.D., Ph.D., Mitch Dowsett, Ph.D., and Daniel F. Hayes, M.D., for the EBCTCG\*



# Adjuvância extendida: 5 anos de IA após 5 anos de tamoxifeno

## The NEW ENGLAND JOURNAL of MEDICINE

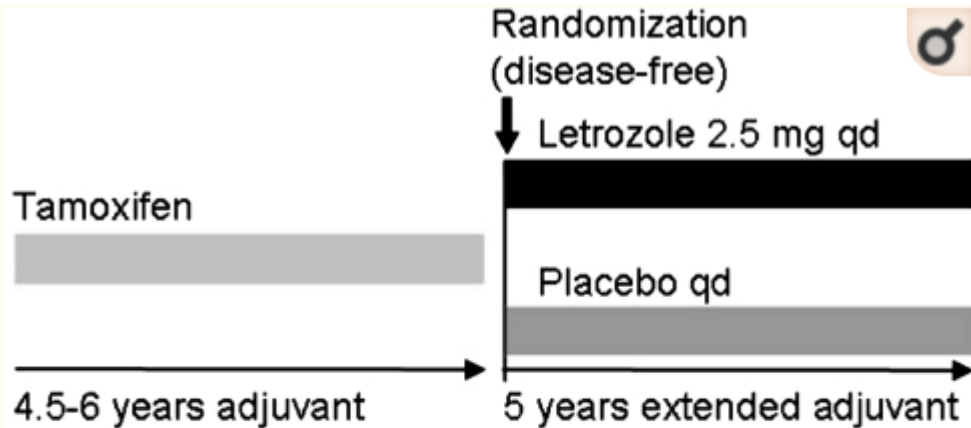
ESTABLISHED IN 1812

NOVEMBER 6, 2003

VOL. 349 NO. 19

### A Randomized Trial of Letrozole in Postmenopausal Women after Five Years of Tamoxifen Therapy for Early-Stage Breast Cancer

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., Silvana Martino, D.O., Nicholas J. Robert, M.D., Hyman B. Muss, M.D., Martine J. Piccart, M.D., Ph.D., Monica Castiglione, M.D., Dongsheng Tu, Ph.D., Lois E. Shepherd, M.D., Kathleen I. Pritchard, M.D., Robert B. Livingston, M.D., Nancy E. Davidson, M.D., Larry Norton, M.D., Edith A. Perez, M.D., Jeffrey S. Abrams, M.D., Patrick Therasse, M.D., Michael J. Palmer, M.Sc., and Joseph L. Pater, M.D.

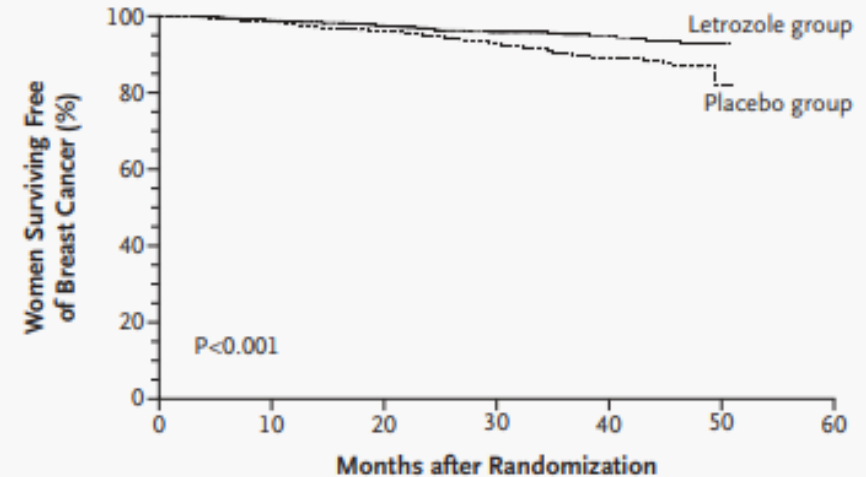


Primary end point: disease-free survival

Secondary end points: overall survival/safety

Substudies: quality of life, bone mineral density, bone markers,

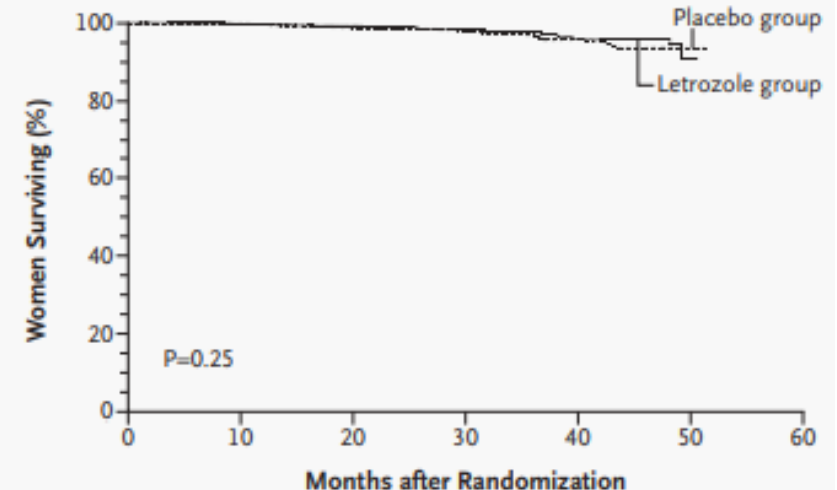
#### A Disease-free Survival



#### No. at Risk

Letrozole	2575	2308	1327	624	183	9	0
Placebo	2582	2298	1295	610	180	11	0

#### B Overall Survival

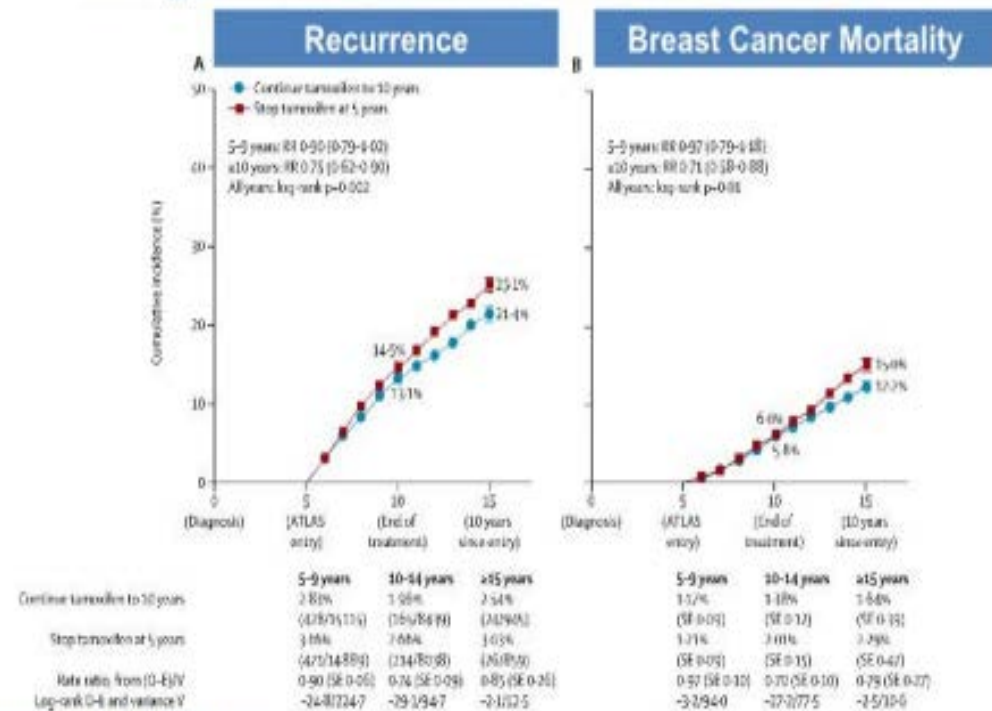


#### No. at Risk

Letrozole	2575	2329	1349	641	188	9	0
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# Adjuvância extendida: 10 anos de tamoxifeno

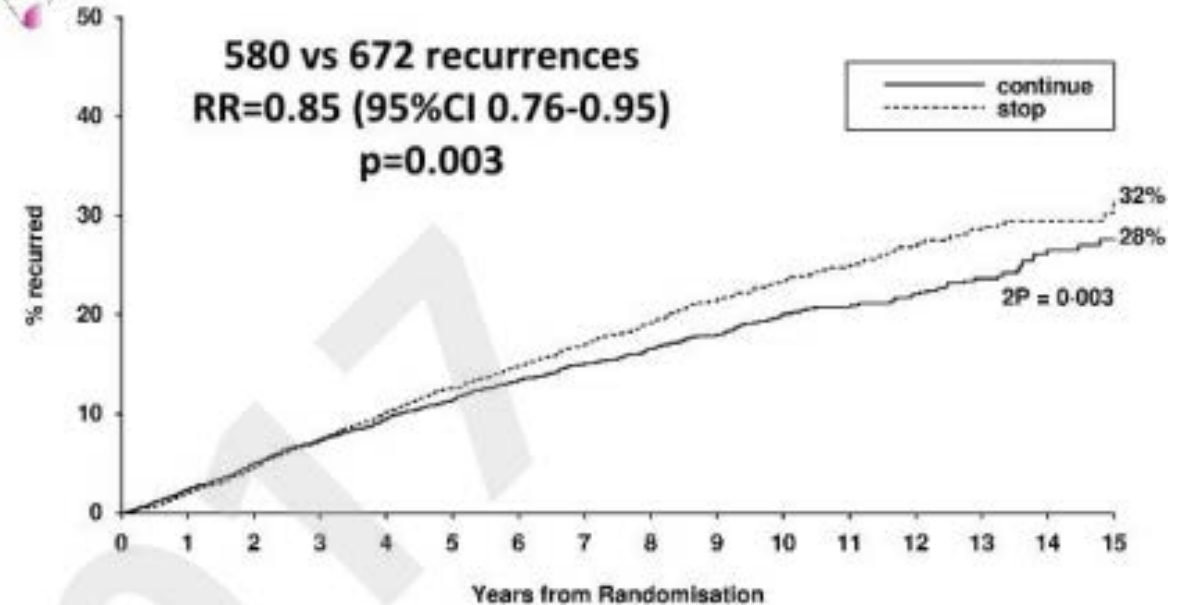
## ATLAS: Tamoxifen to 10 ys vs. Stopping at 5 ys in Women with ER+ Disease



Davies C, et al, *Lancet* 2012



## 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

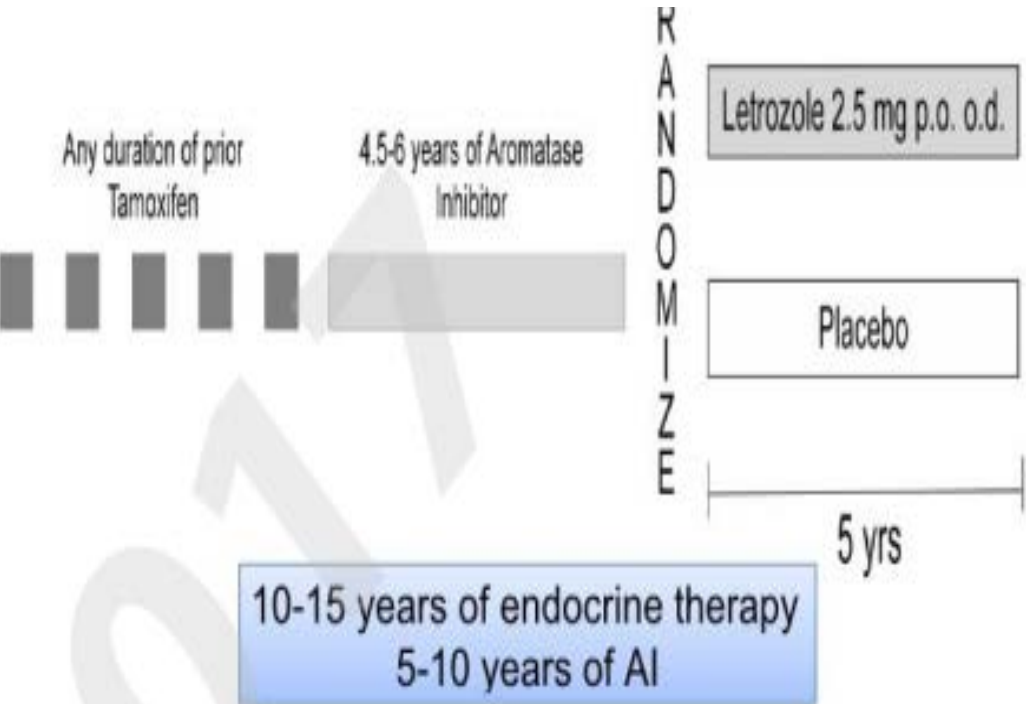


# Adjuvância extendida: 10 anos de IA

ORIGINAL ARTICLE

## Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

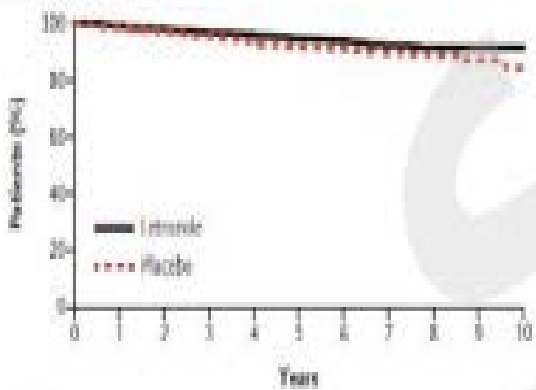
P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, and W.R. Parulekar



## MA17R: Kaplan-Meier Analysis: (A) Disease-free and, (B) Overall Survival

HR letrozole vs placebo:  
0.66 (95% CI, 0.48 to 0.91; P = 0.01)      0.97 (95% CI, 0.73 to 1.28; P = 0.83)

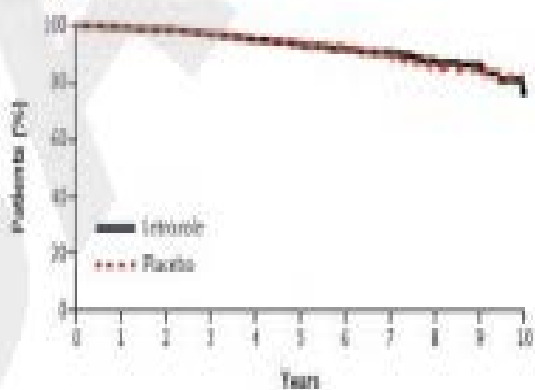
A Disease-free Survival



No. at Risk

Letrozole	119	942	823	699	579	459	332	224	107	86	14
Placebo	109	936	817	690	559	421	302	188	77	19	

B Overall Survival



No. at Risk

Letrozole	939	832	741	621	503	389	280	143	221	93	14
Placebo	1059	953	843	723	595	474	360	227	204	84	20

# Adjuvância extendida: 10 anos de IA

ORIGINAL ARTICLE

## Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, and W.R. Parulekar

Diminuição recorrência: 7.0 vs 10.2%

(RRA = 3.2%) (NNT= 31) (56.730 comprimidos de IA)

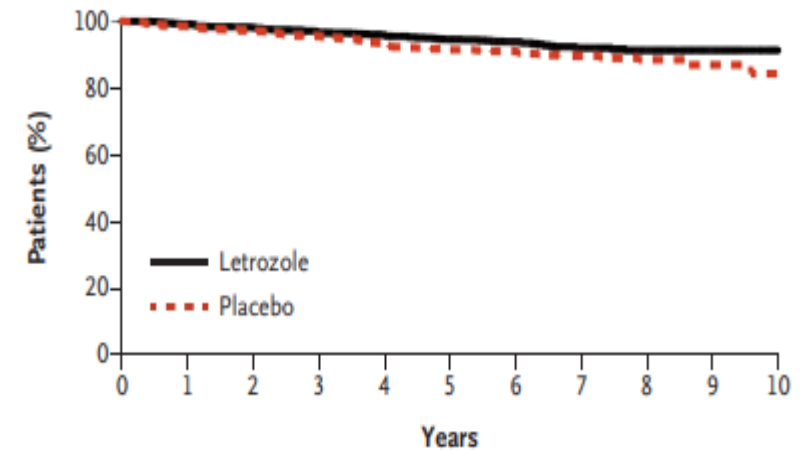
Diminuição recidiva sistêmica: 4.4% vs 5.5%

(RRA=1.1%) (NNT= 90) (164.250 comprimidos de IA)

Diminuição tumores contra-laterais: 1.4% vs 3.2%

(RRA = 1.8%) (NNT= 55) (100.375 comprimidos de IA)

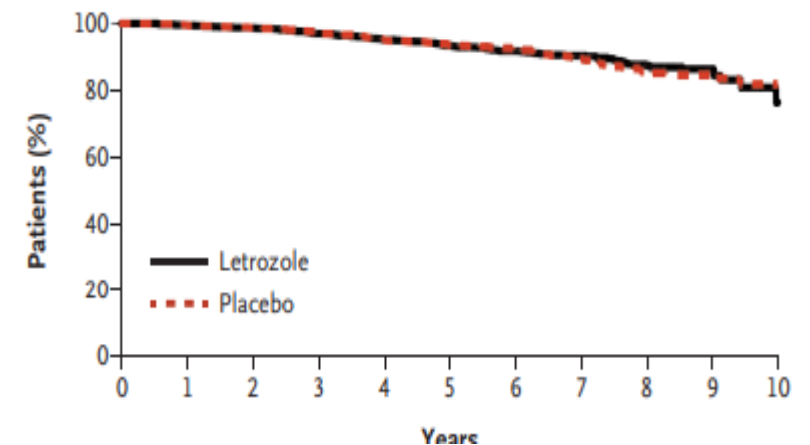
A Disease-free Survival



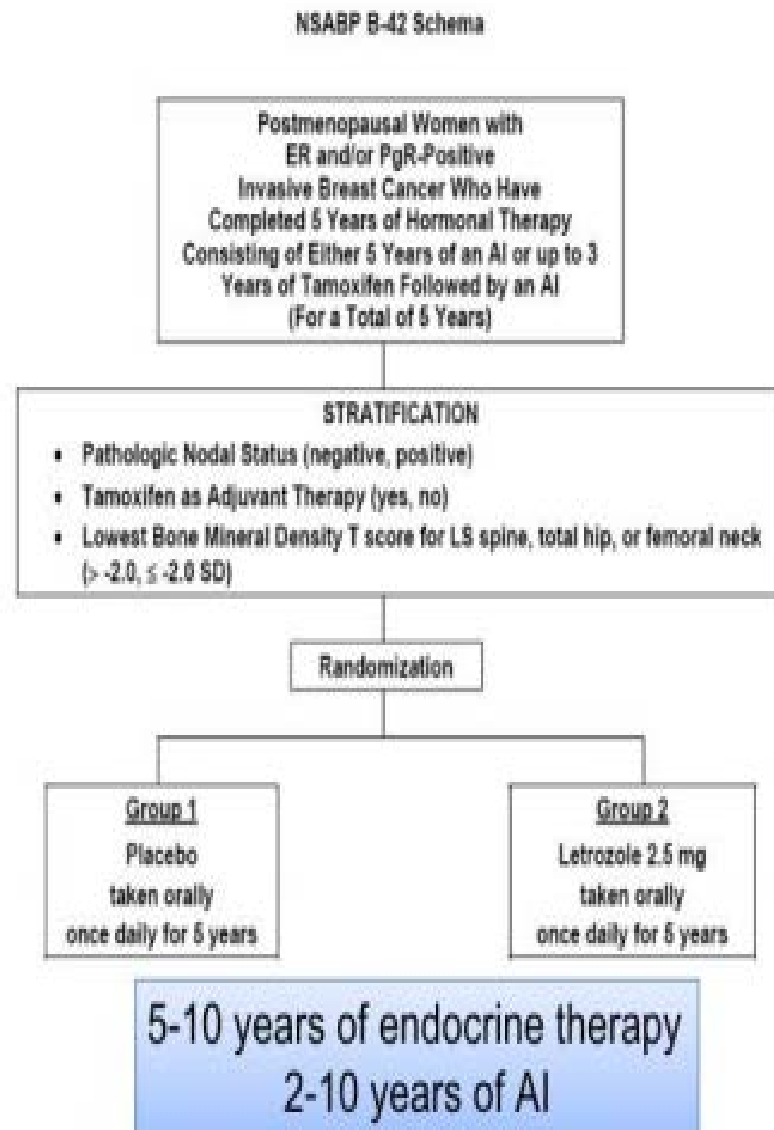
No. at Risk

Letrozole	959	942	925	899	879	850	652	324	207	86	14
Placebo	959	936	917	890	850	821	641	302	188	77	19

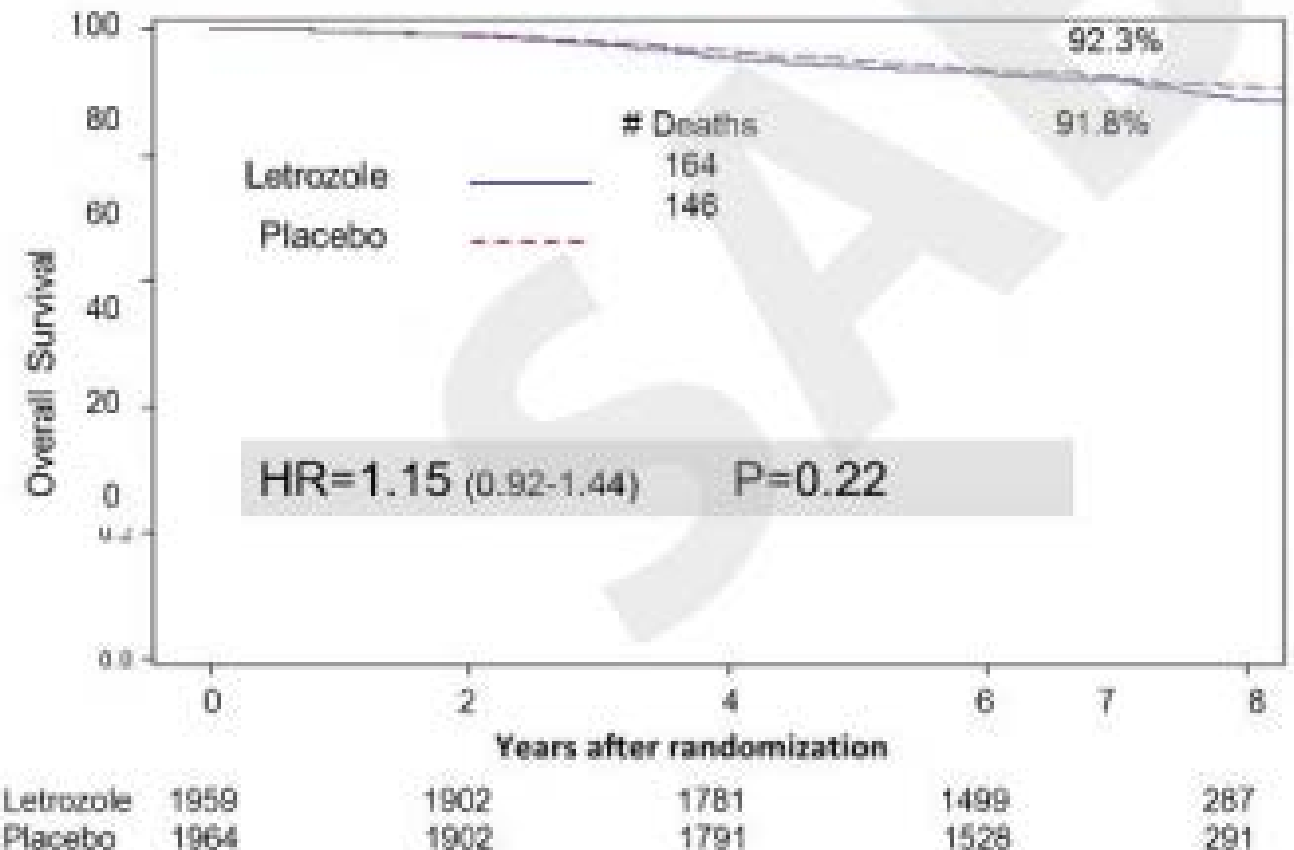
B Overall Survival



# Adjuvância extendida: 10 anos de IA

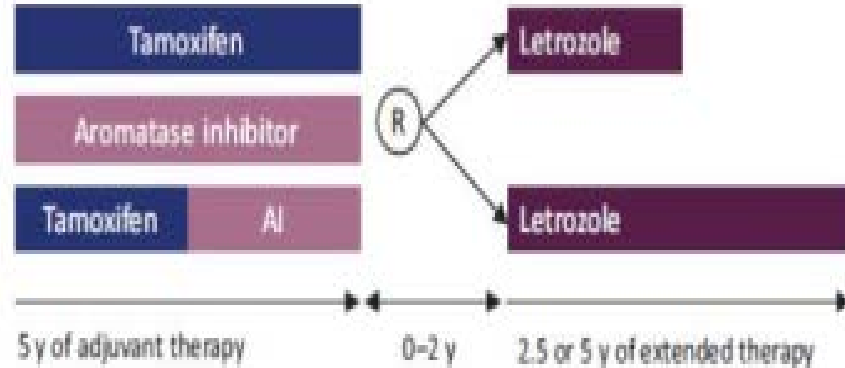


## NSABP B-42: Overall Survival



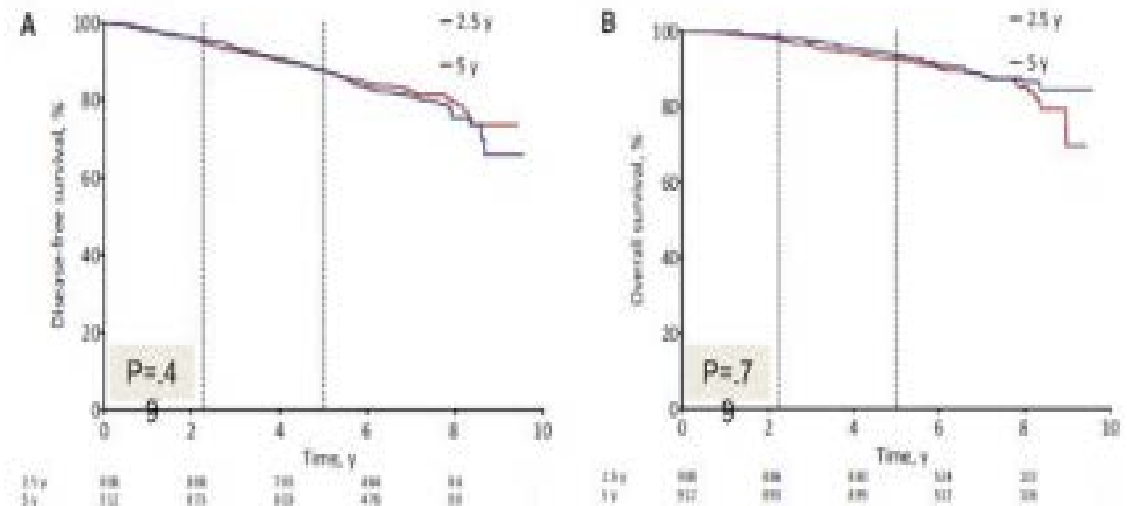
# Adjuvância extendida: 10 anos de IA

## IDEAL Trial (BOOG 2006-05)



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

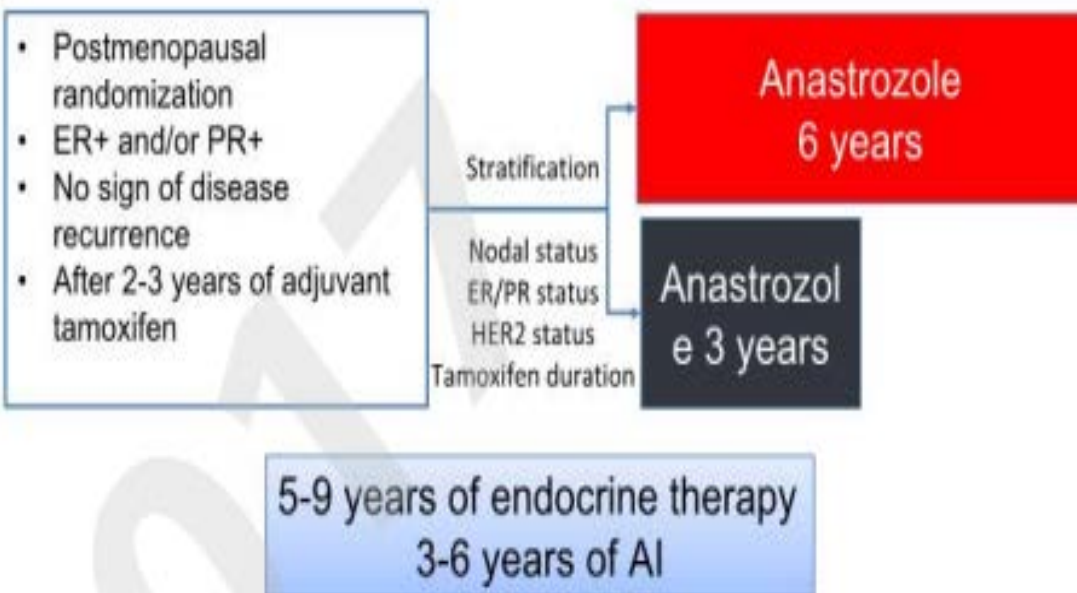
## IDEAL: Kaplan-Meier analysis: (A) Disease-free and, (B) Overall Survival



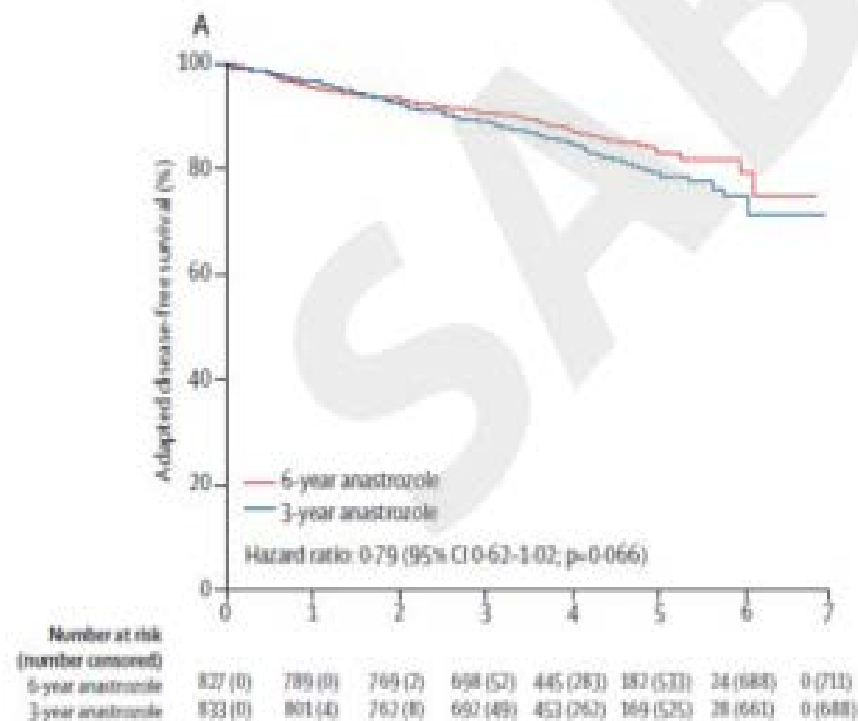
Blok et al, JNCI 2018

# Adjuvância extendida: 10 anos de IA

## Extended Adjuvant AI After Sequential Endocrine Therapy (DATA)



## DATA: Kaplan-Meier Estimates, Adapted Disease-free Survival



## Extending AI Duration Beyond 5 years

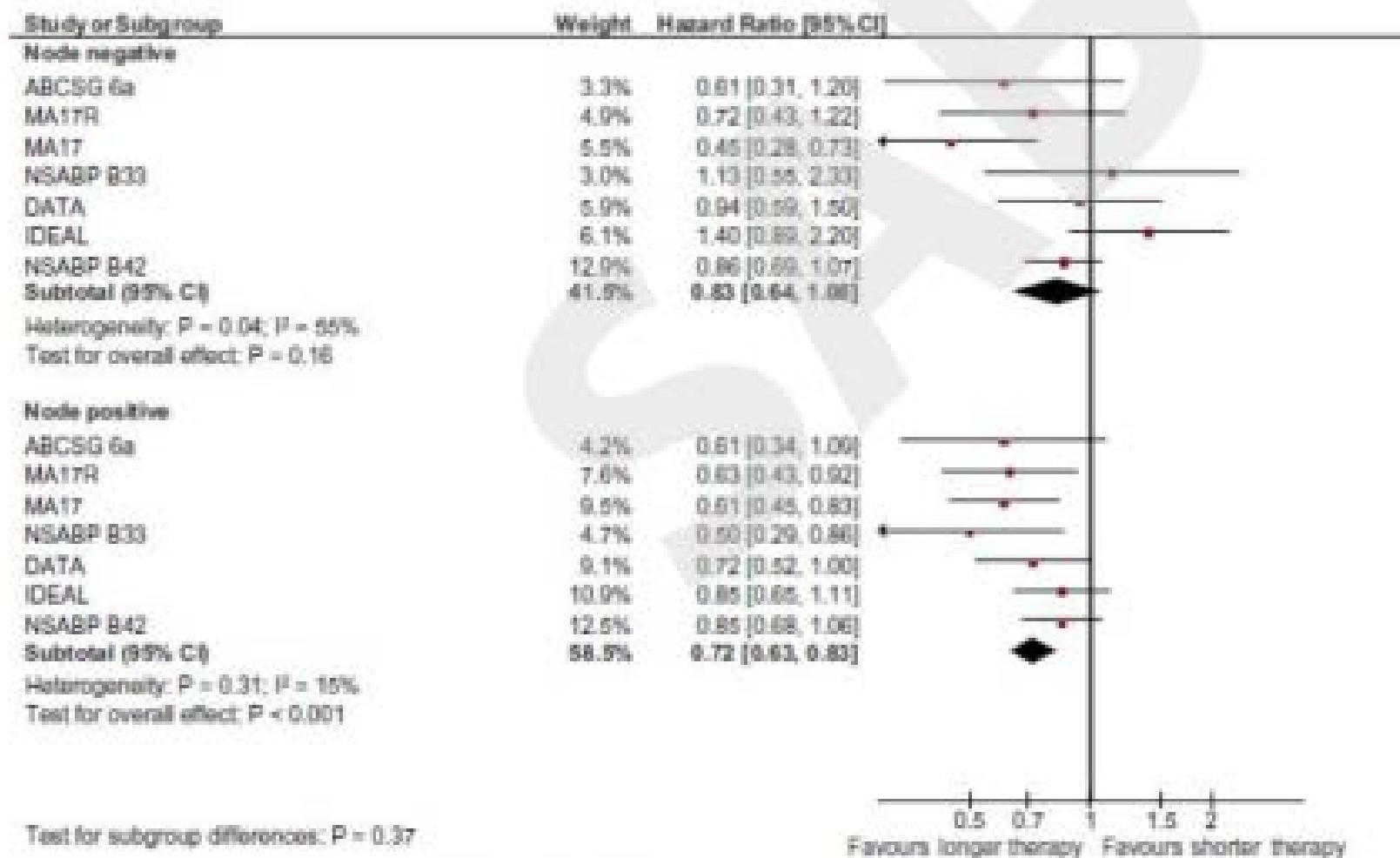
	Number (% Node+)	Duration ET/AI	DFS benefit	OS benefit	New BC benefit
MA-17R	1918 (53%)	10-15 5-10	Yes	No	Yes
NSABP B42	3966 (42%)	5-10 2-10	No	No	Yes
IDEAL	1824 (74%)	7.5-10 2.5-10	No	No	Yes
DATA	1912 (67%)	5-9 3-6	No	No	No
SOLE	4884 (99%)	5-10 5-10 cont/int	No	No	?

ET- endocrine therapy, Int- intermittent, AI- aromatase inhibitor, Cont- continuous,



# Meta-analysis: Extended AI Therapy

## Forest Plot for Disease-free Survival According to Nodal involvement



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

	MA-17R		NSABP B42		IDEAL		DATA (years 0-6)		SOLE	
	<i>AI</i>	<i>Plc</i>	<i>AI</i>	<i>Plc</i>	<i>AI</i> 5 ys	<i>AI</i> 2.5 ys	<i>AI</i> 6 ys	<i>AI</i> 3 ys	<i>AI</i> Cont.	<i>AI</i> Int.
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

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

# Conclusões: hormonioterapia adjuvante estendida

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- Modesto aumento de SLP/SG com 10 anos de tamoxifeno
- Aumento mínimo/ausente em SLP com extensão da terapia com IA
- NUNCA foi demonstrado aumento da sobrevida com mais de cinco anos de IA
- Discreta diminuição na taxa de tumores contra-laterais
- Aumento no perfil de efeitos adversos (MA17 Number need to harm fracture: 20)

# Conclusões: Quem precisa de 10 anos de hormonioterapia?

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DE UMA MANEIRA GERAL, 5 ANOS DE HORMONIOTERAPIA ADJUVANTE É O TRATAMENTO PADRÃO

CANDIDATAS A ADJUVÂNCIA EXTENDIDA:

PACIENTE COM BOA TOLERÂNCIA E TUMORES COM ALTO RISCO DE RECIDIVA TARDIA

APÓS 5 ANOS DE TAMOXIFENO:

CONSIDERAR 5 ANOS DE TAMOXIFENO ADICIONAL (ATLAS/ATTOM)

CONSIDERAR 5 ANOS DE IA (MA17)

APÓS 5 ANOS DE IA:

DISCUTIR RISCO X BENEFÍCIO

CONSIDERAR:

SOMENTE pacientes que vem tendo boa tolerância

SOMENTE pacientes com tumores de alto risco (N+)

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Obrigado pela atenção!

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