Meme Kanserinde Adjuvant Endokrin Tedavide Güncel Durum

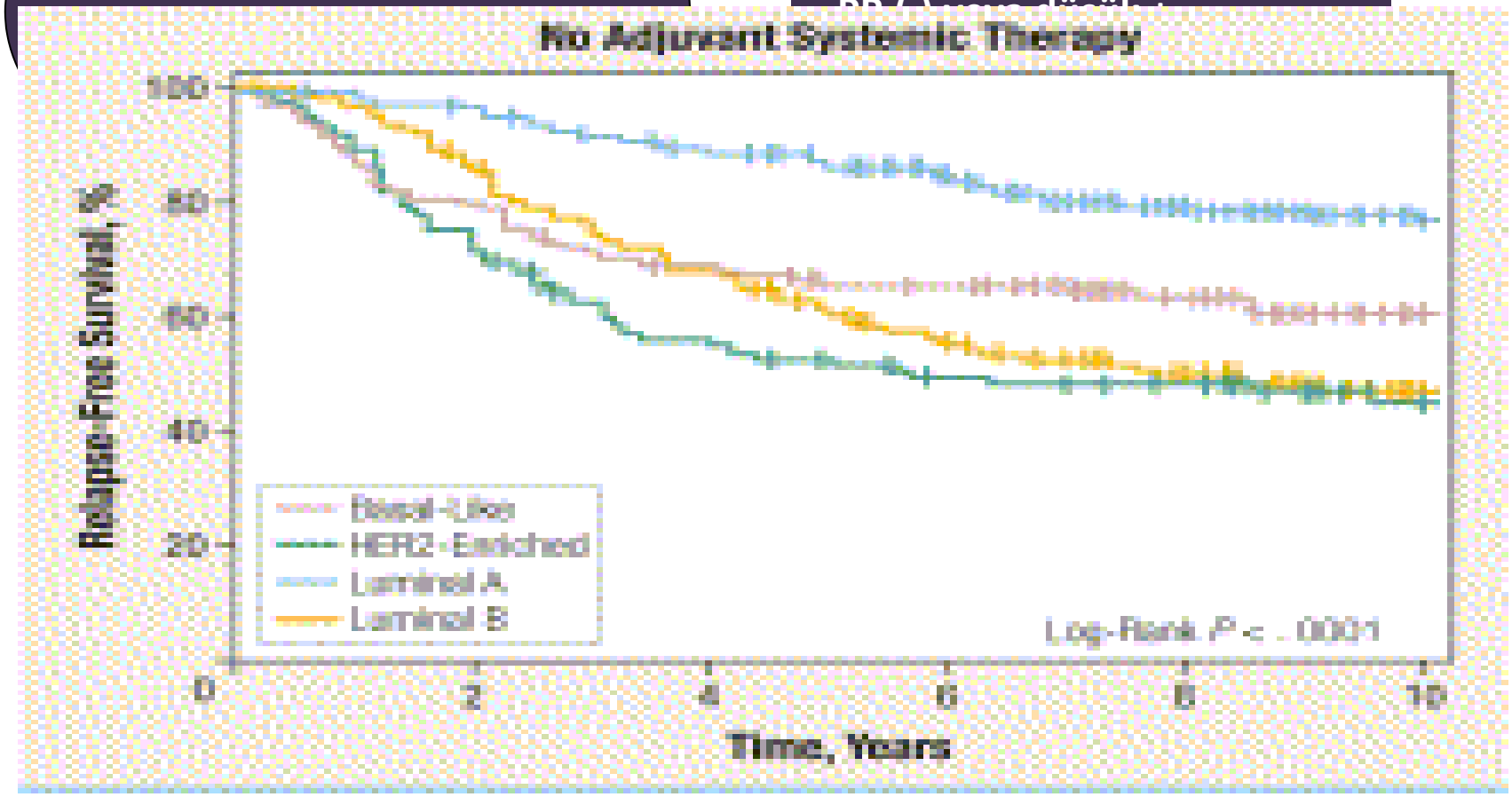
E. Prof. Dr. Dilek DİNÇOL

Şubat-2014

Luminal A-like
ER ve PR +
HER2 (-)
Ki-67 düşük

Luminal B-like (HER2 -)
ER +, HER2 (-) ve en az biri:
Ki-67 yüksek

Luminal A ve B



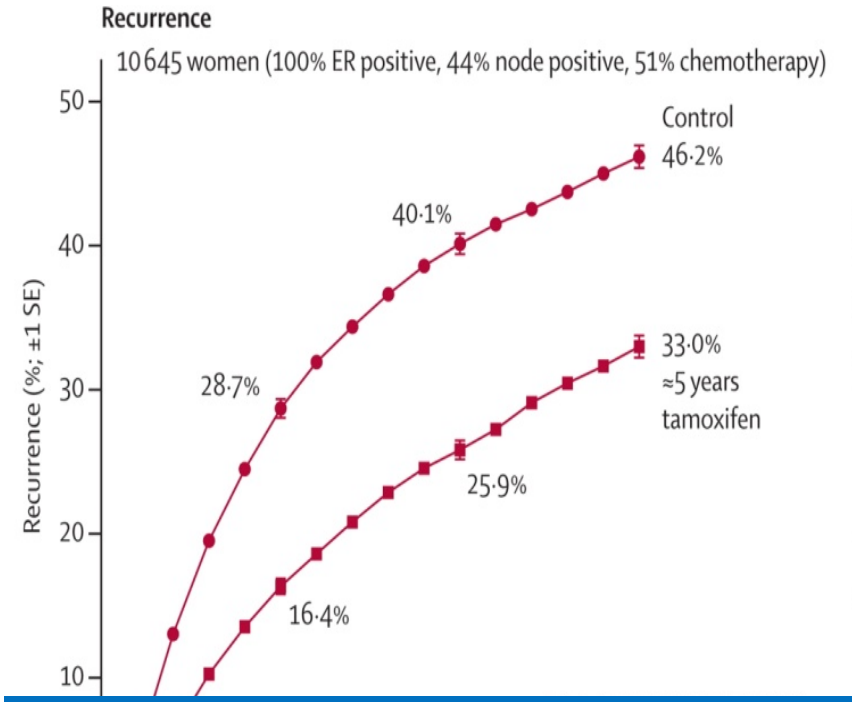
Meme Kanserinde Endokrin Tedavi (ER+ Hastalar)

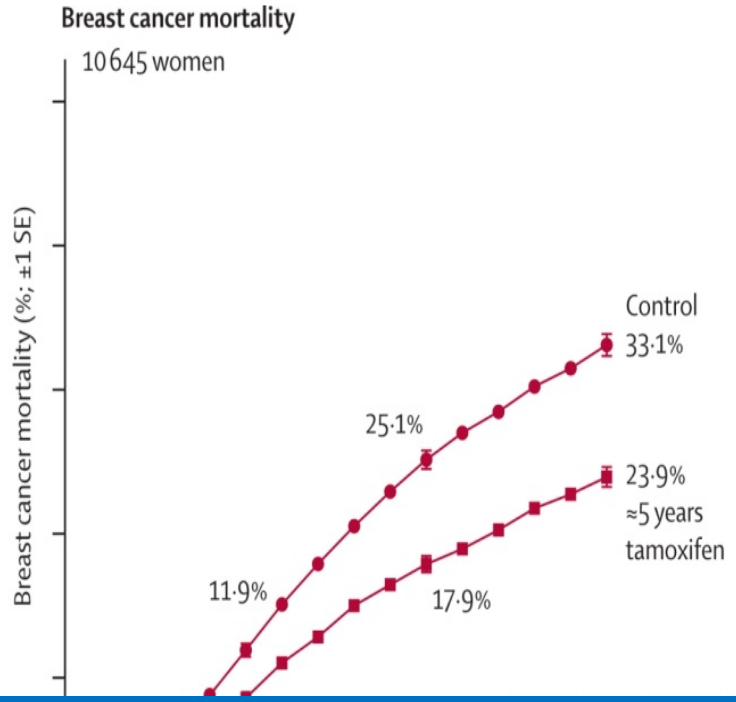
- Over ablasyonu → supresyonu
- Tamoksifen
- Aromataz inhibitörleri
  - Anastrazol
  - Letrozol
  - Exemestan

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

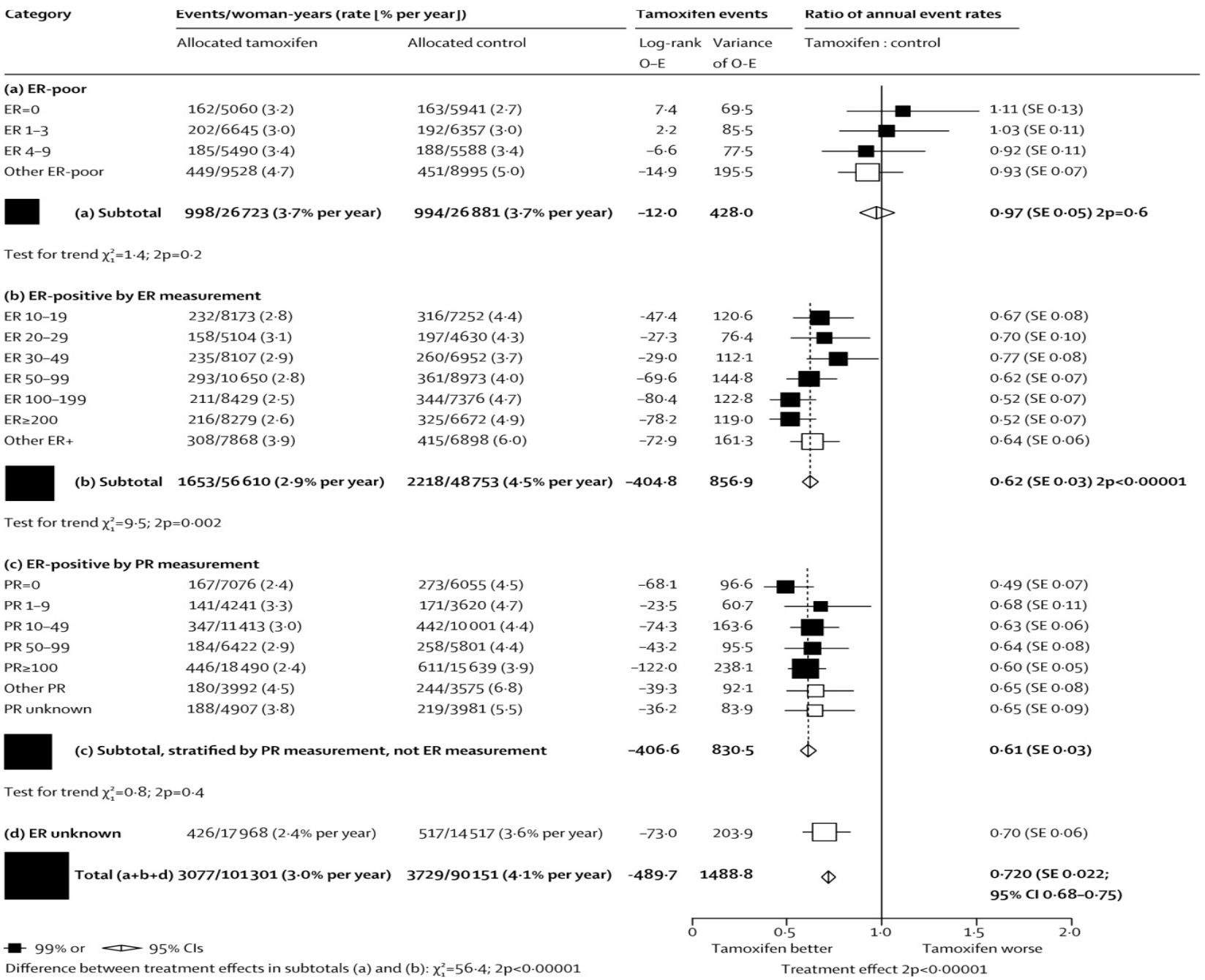
The Lancet
Volume 378, Issue 9793, Pages 771-784 (August 2011)
DOI: 10.1016/S0140-6736(11)60993-8



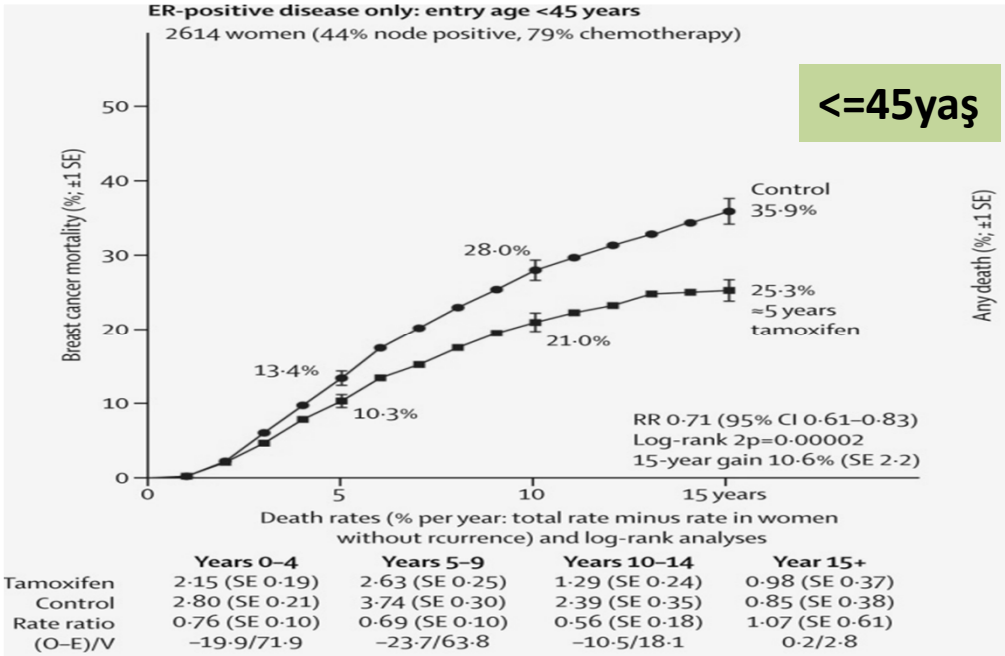


	0-4y	5-9y	10-14y
Nüks RR	0.53	0.68	0.97
P	<.00001	<.00001	
Mort. RR	0.71	0.66	0.68
P	.05	.05	.08

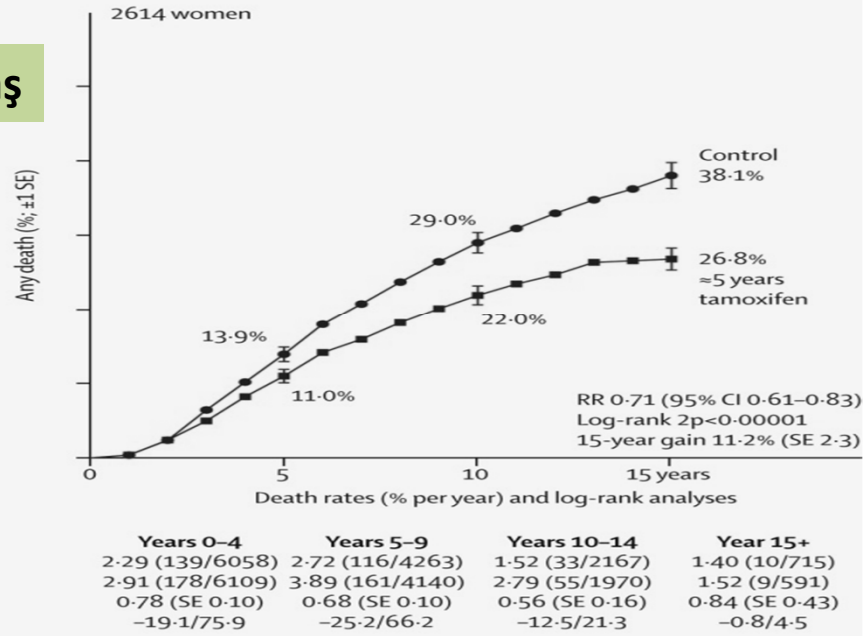
EBCTCG, LANCET2011



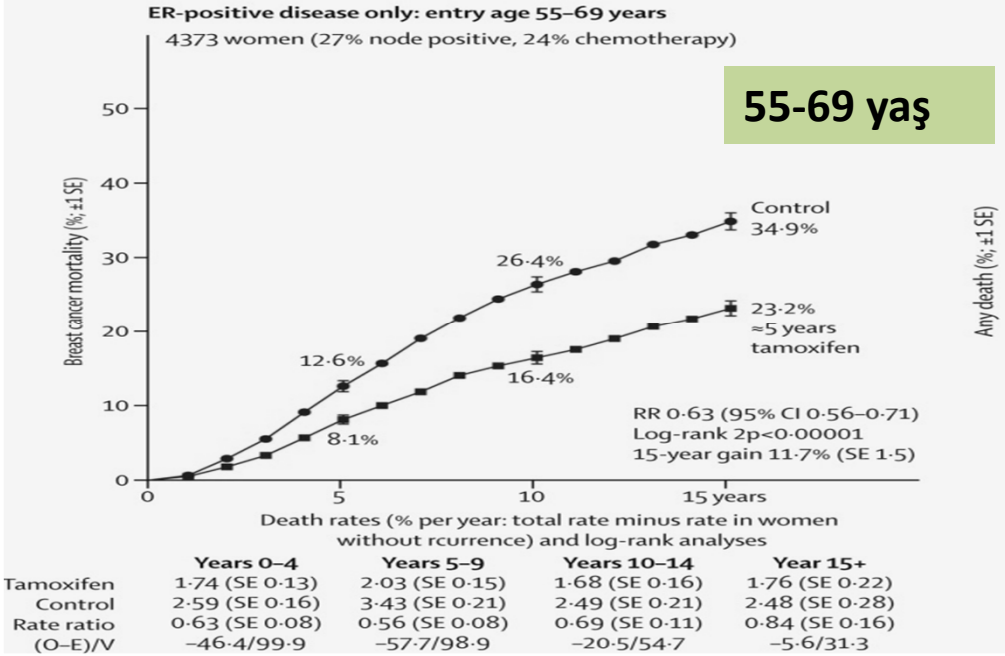
EBCTCG, LANCET2011



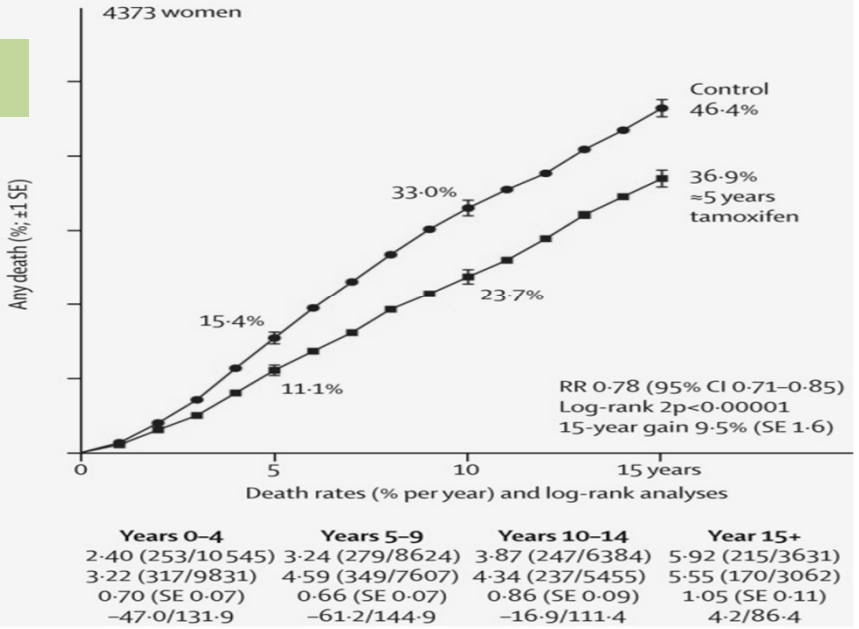
	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	2·15 (SE 0·19)	2·63 (SE 0·25)	1·29 (SE 0·24)	0·98 (SE 0·37)
Control	2·80 (SE 0·21)	3·74 (SE 0·30)	2·39 (SE 0·35)	0·85 (SE 0·38)
Rate ratio	0·76 (SE 0·10)	0·69 (SE 0·10)	0·56 (SE 0·18)	1·07 (SE 0·61)
(O–E)/V	−19·9/71·9	−23·7/63·8	−10·5/18·1	0·2/2·8



	Years 0–4	Years 5–9	Years 10–14	Year 15+
	2·29 (139/6058)	2·72 (116/4263)	1·52 (33/2167)	1·40 (10/715)
	2·91 (178/6109)	3·89 (161/4140)	2·79 (55/1970)	1·52 (9/591)
	0·78 (SE 0·10)	0·68 (SE 0·10)	0·56 (SE 0·16)	0·84 (SE 0·43)
	−19·1/75·9	−25·2/66·2	−12·5/21·3	−0·8/4·5

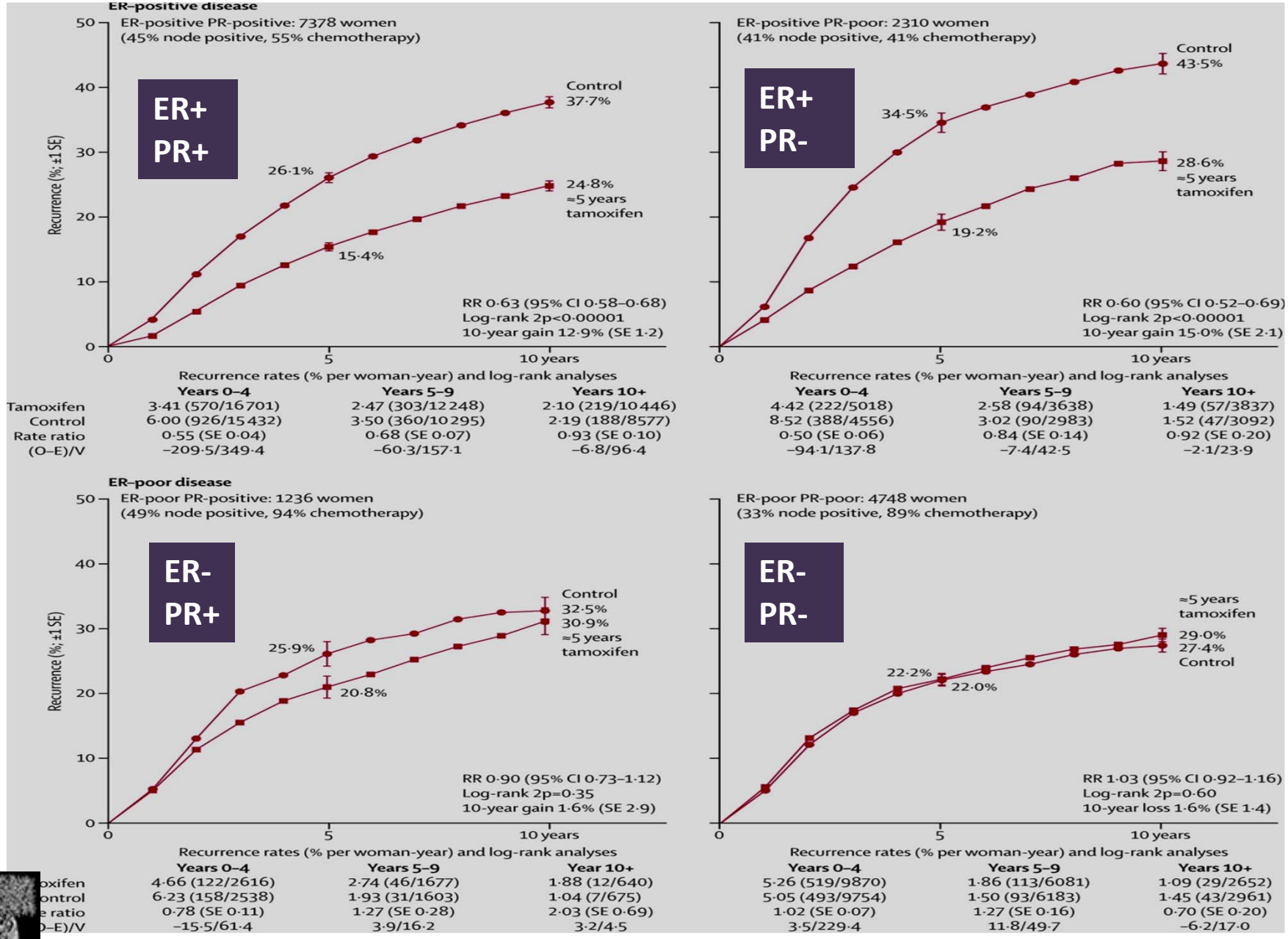


	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	1·74 (SE 0·13)	2·03 (SE 0·15)	1·68 (SE 0·16)	1·76 (SE 0·22)
Control	2·59 (SE 0·16)	3·43 (SE 0·21)	2·49 (SE 0·21)	2·48 (SE 0·28)
Rate ratio	0·63 (SE 0·08)	0·56 (SE 0·08)	0·69 (SE 0·11)	0·84 (SE 0·16)
(O–E)/V	−46·4/99·9	−57·7/98·9	−20·5/54·7	−5·6/31·3



	Years 0–4	Years 5–9	Years 10–14	Year 15+
	2·40 (253/10 545)	3·24 (279/8624)	3·87 (247/6384)	5·92 (215/3631)
	3·22 (317/9831)	4·59 (349/7607)	4·34 (237/5455)	5·55 (170/3062)
	0·70 (SE 0·07)	0·66 (SE 0·07)	0·86 (SE 0·09)	1·05 (SE 0·11)
	−47·0/131·9	−61·2/144·9	−16·9/111·4	4·2/86·4

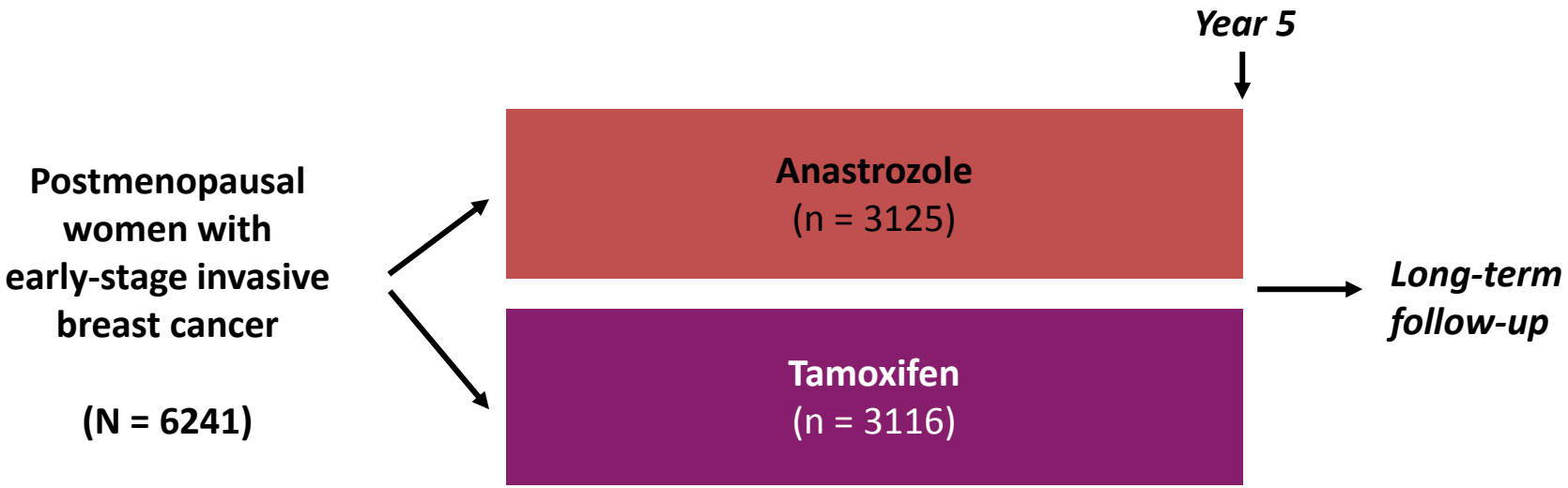
EBCTCG, LANCET2011



The Lancet 2011; 378:771-784

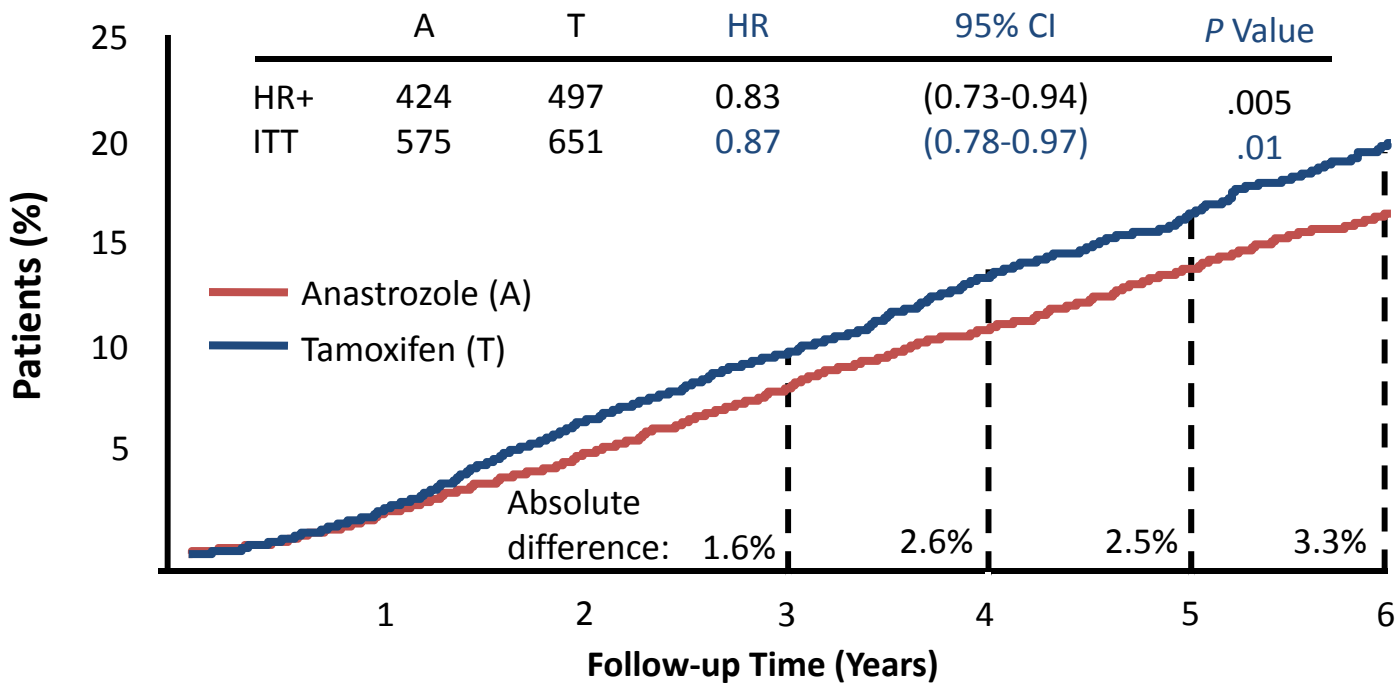
ATAC: A vs T in Postmenopausal Women With Localized Breast Cancer

- Previous ATAC results showed less disease recurrence in postmenopausal women with localized disease on anastrozole vs tamoxifen[1]
  - Anastrozole well tolerated but higher risk of fractures
- Current study assessed long-term efficacy and toxicity of anastrozole[2]



1. Howell A, et al. Lancet. 2005;365:60-62.
2. Forbes JF M, et al. SABCS 2007. Abstract 41.

ATAC-DFS (HR+)



DFS includes all deaths as a first event

Geç nüksler yıllık %2-3 hızla devam eder
Cuzick et al. Lancet Oncol 2010

Howell A. 2004 SABCS. Abstract 1.

ATAC: Efficacy Results

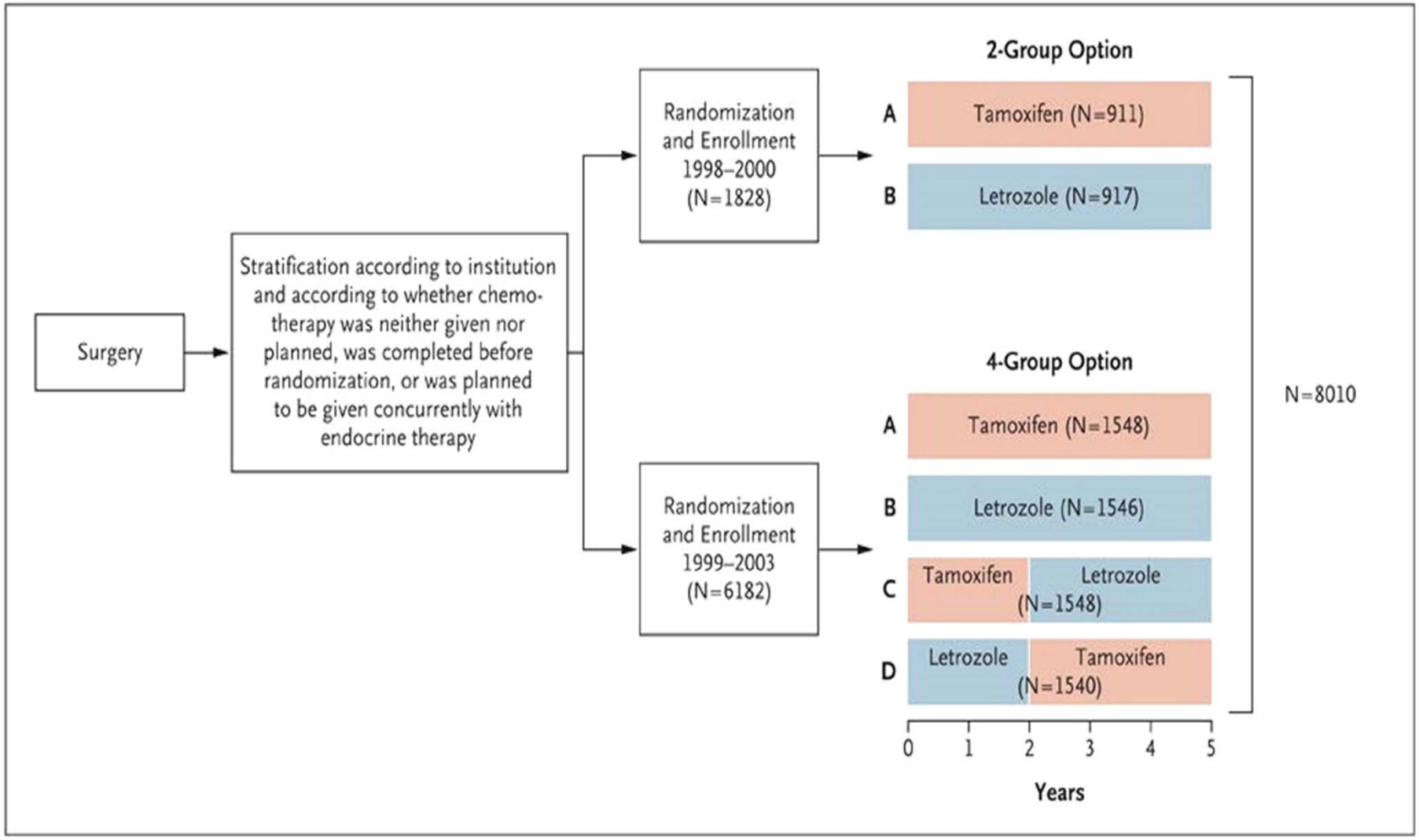
Long-term results showed that anastrozole superior to tamoxifen for DFS, TTR, TTDR, and CLBC, but not for OS and deaths after recurrence

- Similar findings observed when analyses restricted to hormone receptor–positive population

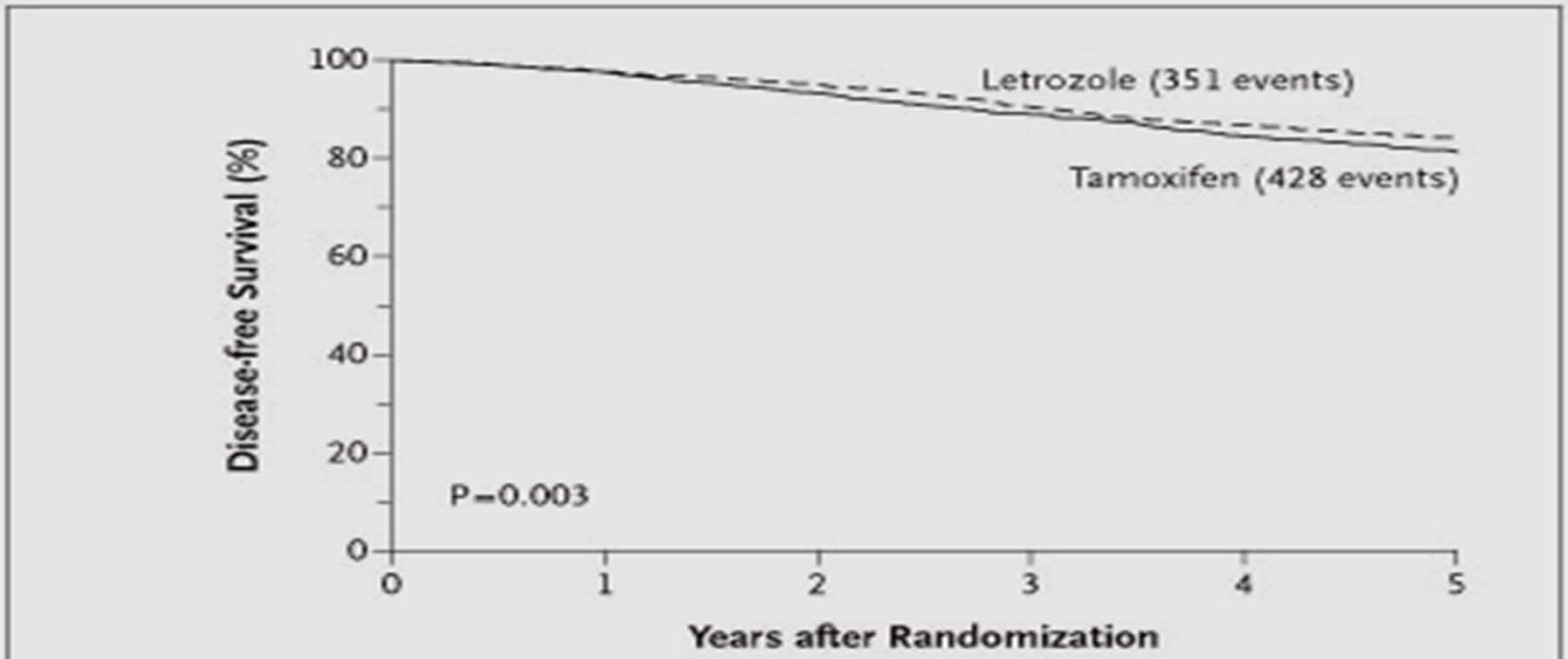
Outcome (Hormone Receptor–Positive Patients)	HR (95% CI)	*P* Value
DFS	0.85 (0.76-0.94)	.003
TTR	0.76 (0.67-0.87)	.0001
TTDR	0.84 (0.72-0.97)	.022
CLBC	0.60 (0.42-0.85)	.004
OS	0.97 (0.86-1.11)	.70
Death after recurrence	0.90 (0.75-1.07)	.20

Forbes JF, et al. SABCS 2007. Abstract 41.

Letrozole Therapy Alone or in Sequence with Tamoxifen in Women Breast Cancer
The BIG 1-98 Collaborative Group
NEJM 361;766,2009



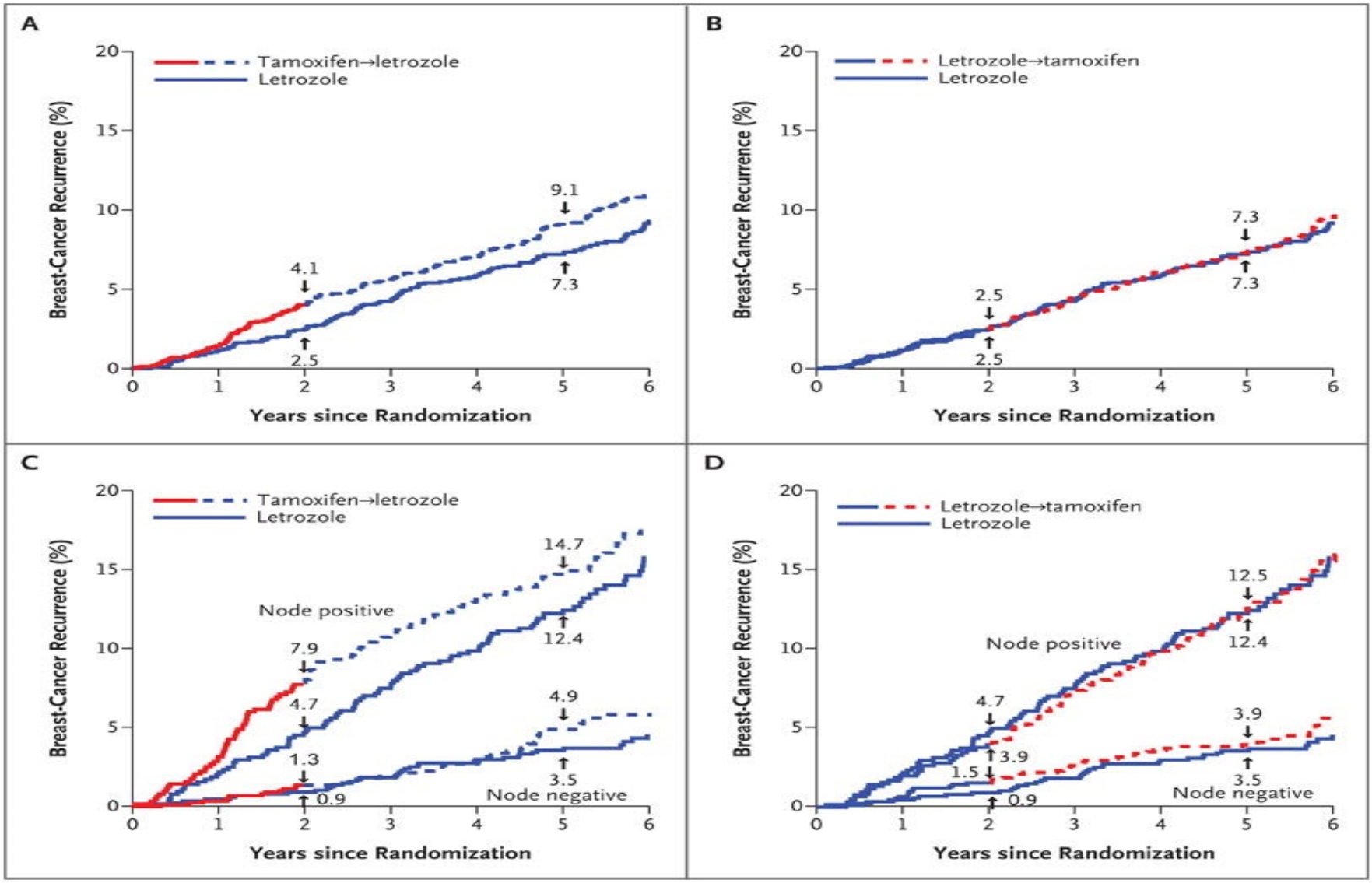
BİG 1-98, ilk analiz
Thurlimann B, et al. N **Engl J Med 2005;353:2747-57**



Letrozole						
No. at risk	4003	3892	2964	1261	892	567
Disease-free survival (%)		97.7	95.1	90.5	86.8	84.0
Tamoxifen						
No. at risk	4007	3896	2926	1238	866	544
Disease-free survival (%)		97.6	93.4	89.0	84.6	81.4

BIG 1-98 Trial

NEJM 361;766,2009



	Letrozol	Letr→Tam	Tam→Letr
DFS	% 78.6	% 77.8	% 77.3
OS	% 87.5	% 87.7	% 85.9

Regan MM, et al. Lancet Oncol 12;1101,2011
(8.1 yıl takip sonuçları)

BİG 1-98, ilk analiz
Thurlimann B, et al. N Engl J Med 2005;353:2747-57

	TAM %	LETR %	p
SVO	1	1	0.91
TromEmb	3.5	1.5	<.0001
Kardiyak			
İskemik	1.2	1.4	0.28
Kalp Yetm	0.4	0.8	0.01
Diğer KVO	0.2	0.5	0.04
Vajinal kan.	6.6	3.3	<.001
Sıcak basması	38	33.5	<.001
Gece terl.	16.2	13.9	0.004
Kırık	4.0	5.7	<.0001
Artralji	12.3	20.3	<.0001
Myalji	6.1	6.4	0.61

BIG 1-98'de Kardiyovasküler Yan Etkiler
Mouridsen H et al. JCO 25:5715,2007

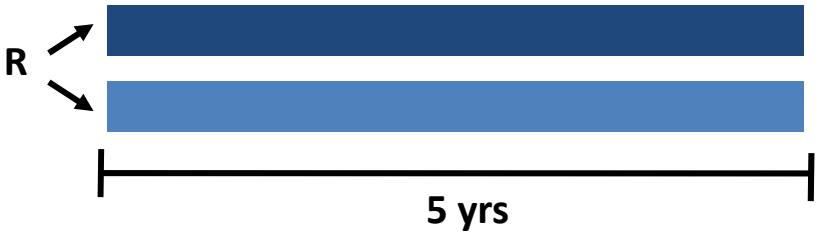
	TAM %	LETR %	p
Kardiyak Olay	4.7	4.8	
G3-5 KVO (çoğu hiperkolesteremi)	1.4	2.4	.001
TrombEmb	3.9	1.7	<.001

Meta-analysis of Randomized Trials: AIs vs Tamoxifen

Designs of Cohort 1 and Cohort 2

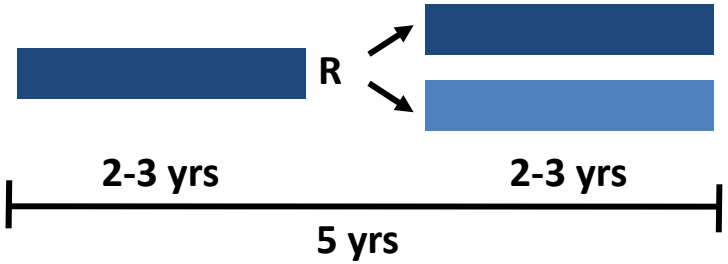
Tamoxifen AI

Cohort 1: direct comparison as monotherapy (N = 9,856)



Trials
ATAC
BIG 1-98/IBCSG 18-98

Cohort 2: comparison after 2-3 yrs of tamoxifen (N = 9,015)

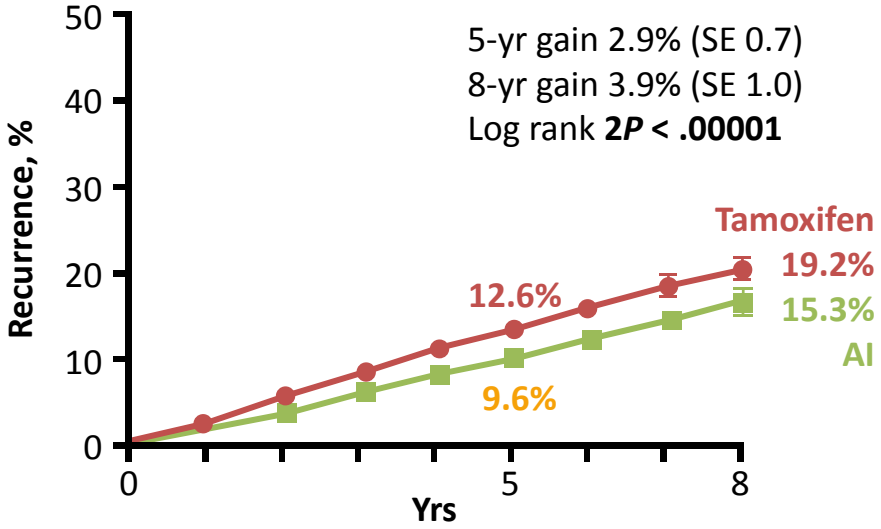


Trials
GABG/ARNO
IES/BIG 2-97
ITA
ABCSG VIII

Ingle JN, et al. SABCS 2008. Abstract 12.

Comparison of Tamoxifen vs AI: Cohort 1 Recurrence Rates

- Cohort 1 ≈ 5 yrs of AI vs tamoxifen
- ER positive
- N = 9,856

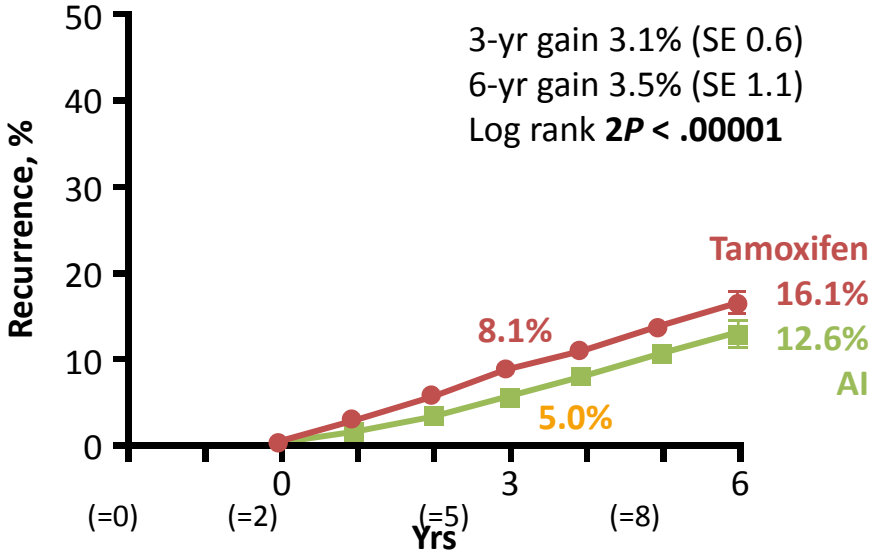


Recurrence Rates (% yr) and Log Rank Analyses			
	Yrs 0-1	Yrs 2-4	Yrs 5+
AI	1.69 (163/9647)	2.31 (261/11297)	2.33 (160/6879)
Tamoxifen	2.46 (234/9510)	2.81 (307/10938)	2.78 (180/6478)
Rate ratio, from (O-E)/V	0.67 SE 0.08 -38.4/96.6	0.81 SE 0.08 29.5/137.9	0.83 SE 0.10 -15.7/83.0

Ingle JN, et al. SABCS 2008. Abstract 12.

Comparison of Tamoxifen vs AI: Cohort 2 Recurrence Rates

- Cohort 2
  2-3 yrs of tamoxifen,
  then 2-3 yrs (AI vs tam)
- ER positive
- (N = 9,015)



Recurrence Rates (% yr) and Log Rank Analyses			
	Yrs 0-1	Yrs 2-4	Yrs 5+
AI	1.68 (187/11134)	2.81 (149/5298)	3.21 (23/716)
Tamoxifen	2.76 (303/10962)	3.00 (150/5007)	3.87 (27/697)
Rate ratio, from (O-E)/V	0.60 SE 0.07 -51.0/118.4	0.83 SE 0.11 -5.6/72.6	0.85 SE 0.27 -2.0/12.1

Ingle JN, et al. SABCS 2008. Abstract 12.

Erken Evre Meme Kanserinde Endokrin Tedavi (İlk 5 yıl)		
Premenopozal	Tamoksifen	
	+/- Over abl/sup (?)	
Postmenopozal	Tamoksifen	
	Aromataz inh.	
	Tamoksifen →	Aromataz inh.
	Aromataz inh →	Tamoksifen

Yüksek riskli postmen meme Ca'da ilk tercih Aİ olmalı.
Ardışık tedavi yan etkiler açısından yararlı olabilir

- Kardiyovasküler hast
- Endometriyal patoloji
- Osteoporoz/kırık

Over Supresyonu ile İlgili Çalışmaların Meta-Analizi
Early Breast Cancer Overview Group

- 16 randomize çalışma (1987-2001)
- N = 9022, ER veya PR + hasta
  - % 92 ER+
- Medyan FU 7.3 yıl
- Aks (-) % 51
- LHRH agonistleri genellikle 2-3 yıl, birkaç çalışmada 5 yıl kullanılmış

EBCOWG, Lancet 2007

	n	Nükste↓	p	Nüksten sonraki mortalitede ↓	p
LHRH vs takip	338	-% 28.46	.08	-% 17.8	.49
Tam+/-LHRH	1013	-% 14.5	.20	-% 15.9	.33
KT(+/-Tam) vs +/-LHRH	3307	-12.2	.04	-% 15	.04
KT vs LHRH	3184	+% 3.9	.52	-% 6.7	.40
KT vs LHRH+Tam	1577	-% 10.1	.25	-% 11.1	.37

EBCOWG, Lancet 2007

yaş	n	Nüks HR (%)	p	Nüksten sonra mortalite HR (%)	p
Sist Tx yok +/- (LHRH+Tam)					
=<40	71**	-7.9	.87	-30.5	.59
>40	336	-64.7	<.0001	-51.2	.03
Tam +/- LHRH					
=<40	203	-32	.12	-35.6	.2
>40	810	-1.5	.9	-0.1	.99
KT+/-LHRH					
=<40	714	-24.7	.01	-27.3	.02
>40	1662	-5.1	.55	-5.3	.41
(KT+Tam)+/-LHRH					
=<40	81**	-31.2	.33	-21	.66
>40	284	5.3	.82	-23.4	.41

Hormon Res+ olgularda tedavi gruplarında yaşa göre HR değişiklikleri

** hasta sayısı az

HR=hazard ratio

EBCOWG, Lancet 2007

Beş Yıldan Uzun Endokrin Tedavi

MA.17 (Letr vs Plasebo)
NSABP B-33 (Exem. vs Plasebo)
ATLAS (Tam 5-yıl vs 10-yıl)
aTTom (Tam 5-yıl vs 10-yıl)

MA 17

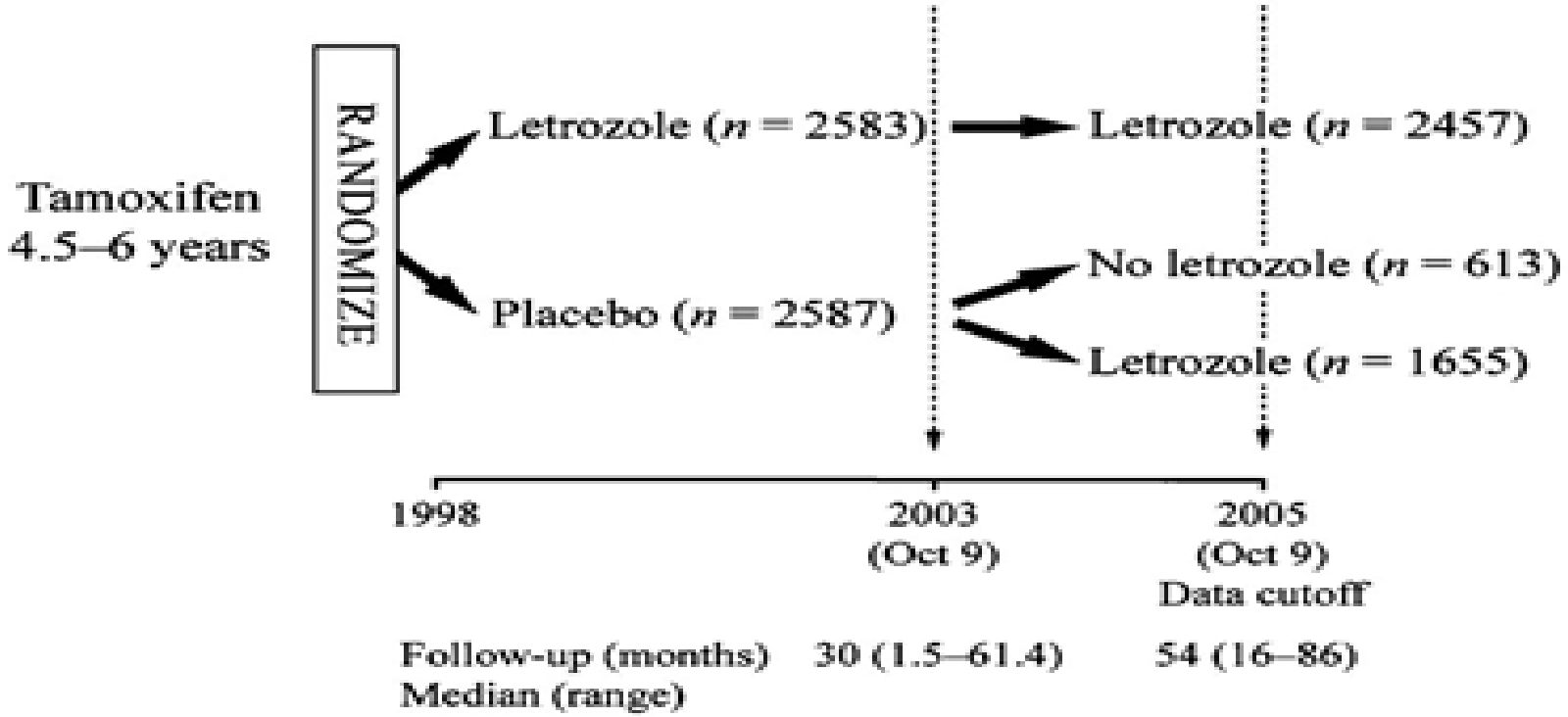


Fig. 1 Patients included in intent-to-treat analysis of the MA.17 trial, at a median follow-up of 54 months. Adapted from [26]

J Natl Cancer İnst 97:1262,2995 (30 ay takip)
Ann Oncol 19:877,2008 (64 ay takip)
Breast Cancer Res Treat 112:45,2008

FU=64 ay	4-yıl %	Univariyet analiz		Multivariyet analiz	
	4-yıl %	HR	p	HR	p
DFS			.0001		.0001
Letr	94.3	0.68		0.68	
Plasebo	91.4				
DDFS			.082		.089
Letr	96.3	0.80		0.81	
Plasebo	94.9				
OS			.853		.828
Letr	95.1	0.98		0.98	
Plasebo	95.1				

Ingle JN, et al. Ann Oncol 19;882,2008

MA.17: Nodal Duruma Göre Etkinlik Analizi 64 ay takip

	HR	p
DFS		
N+	0.51	0.0005
N-	0.74	0.01
DDFS		
N+	0.74	0.04
N-	0.90	>0.05
OS		
N+	0.84	>0.05
N-	1.24	>0.05
Kontrlat. Ca	0.61	0.033
KLCa yıllık ins. hızı : 0.28 vs 0.46		

Ingle JN et al, 19;877,2008

MA.17'de Tamoksifen Alırkenki Menopozal Duruma Göre Etkinlik

	Premenopozal → Postmen. N= 877		Postmenopozal → Postmen N=4289	
	HR	p	HR	p
DFS	0.26	.0003 İnteraction p 0.03	0.67	.006
DDFS	0.15	.02	0.45	.03

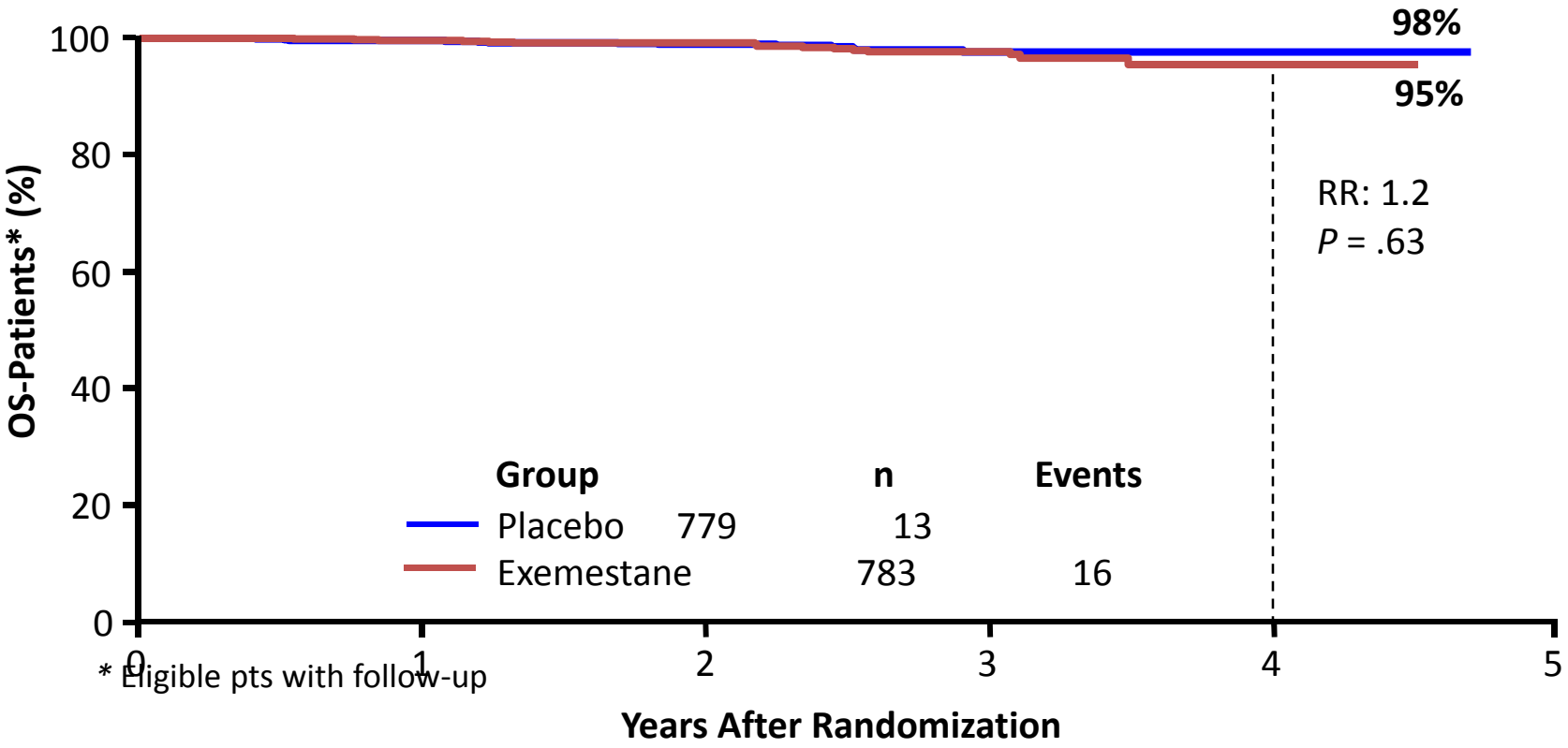
Goss et al. Ann Oncol 24;355,2013

MA. 17 Trial, Crossover Etki Dikkate Alınarak Yapılan Değerlendirme

FU 64 ay Letrozol vs Plasebo		
	HR	p
DFS	0.52	<.001
DDFS	0.61	<.001
OS	0.71	<.001

Jin H, et al. JCO 30:718,2012

Tamoksifen x 5y → Exemestan vs Plasebo
NSABP B-33



Greyd 3 toxicity: 9% vs 6% (*P* = .03)

Mamounas E, et al. SABCS 2006. Abstract 49.

MA.17: Yan Etkiler

	Letrozol	Plasebo	p
Sıcak basması	58	54	0.003
Vajinal kana.	6	8	0.005
Artrit	6	5	0.07
Artralji	25	21	<.001
Myalji	15	12	.004
Hiperkolest.	16	16	0.79
Osteoporoz (yeni tanı)	8.1	6.0	0.003
Kırık	5.3	4.6	0.25
Kvask. hastalık	5.8	5.6	0.76

Goss, Breast Cancer Res Treat 112;45,2008

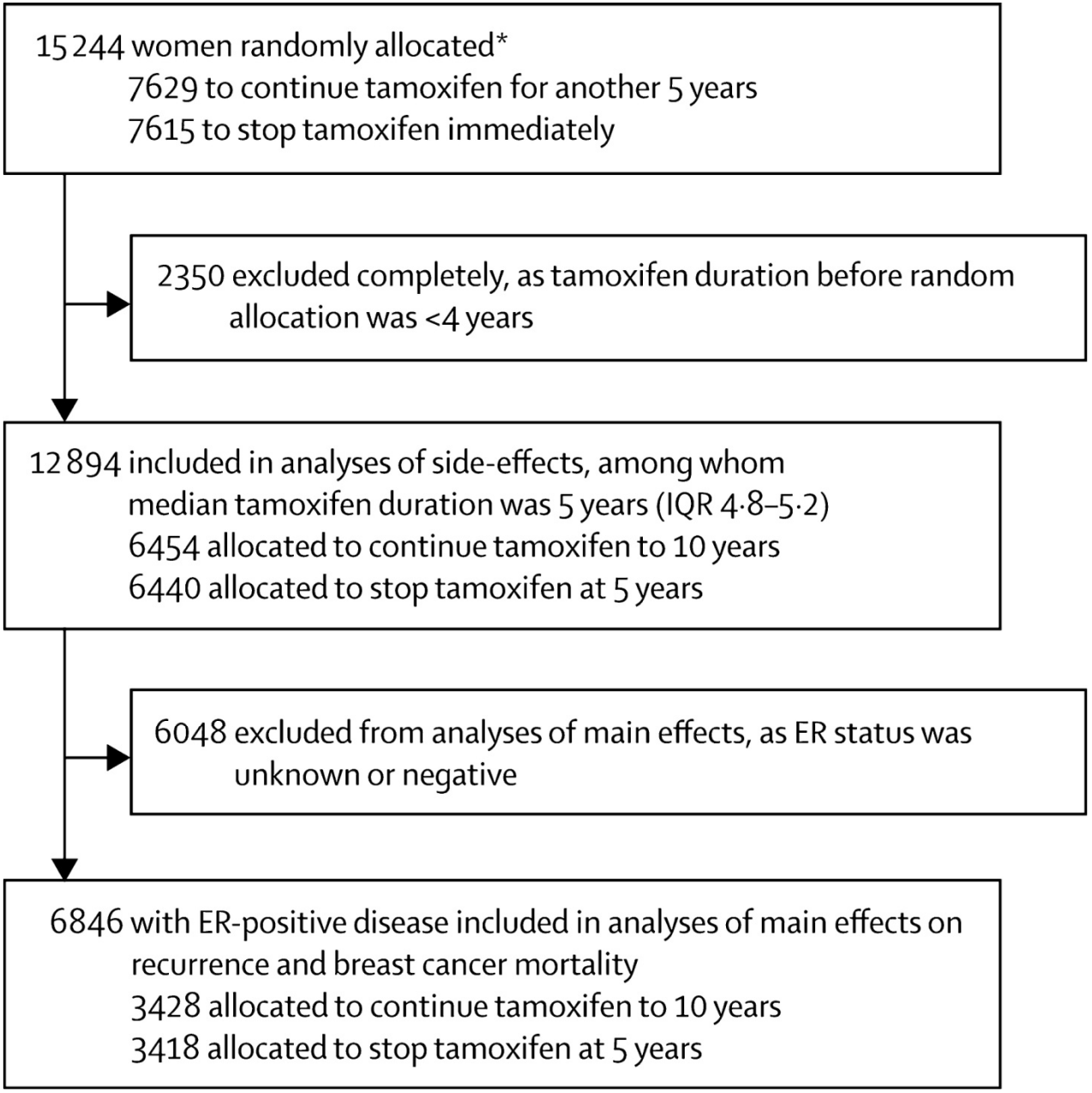
Uzamış Tamoksifen Tedavisi

- ECOG Trial, N=194
  - Tam. devam vs Tam.'i 5 yılda kes
  - Devam etmek daha iyi gibi
    - Tormey, JNCI 2001
- Scottish Adj. Trial, N= 342
  - Sürekli vs 5 yıl
  - Sürekli Tam. daha kötü
    - Stewart, JNCI 2001
- NSABP B-14, N=1152
  - 5 yıldan sonra re-rand.
  - 5 yıldan uzun Tam. daha kötü.
    - Fisher, JNCI 2001

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

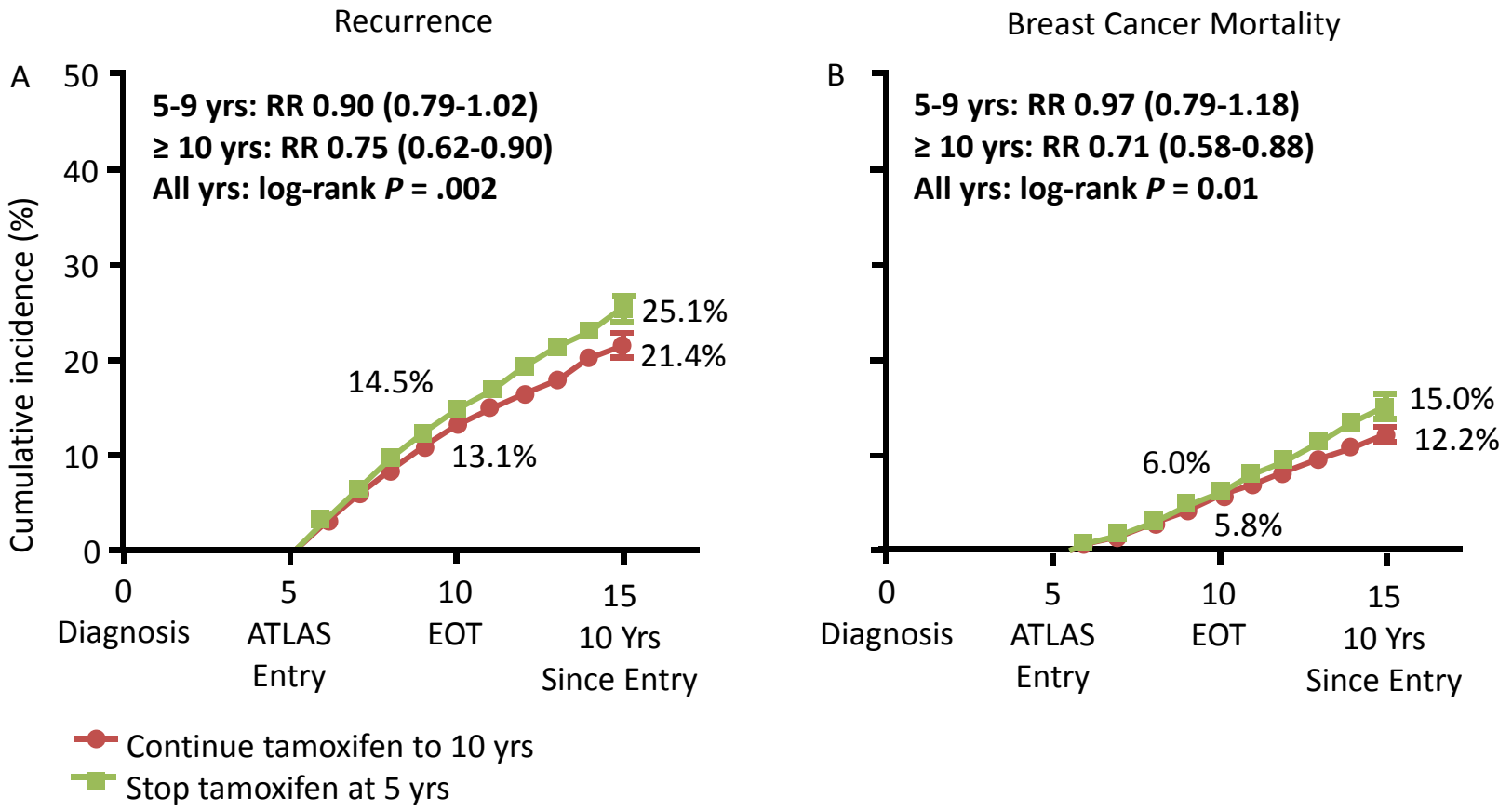
Christina Davies, MBChB, Hongchao Pan, PhD, Jon Godwin, DPhil, Richard Gray, MSc, Rodrigo Arriagada, MD, Vinod Raina, MD, Mirta Abraham, MD, Victor Hugo Medeiros Alencar, MD, Atef Badran, PhD, Xavier Bonfill, MD, Joan Bradbury, Michael Clarke, DPhil, Rory Collins, FMedSci, Susan R Davis, MBBS, Antonella Delmestri, PhD, John F Forbes, MD, Peiman Haddad, MD, Ming-Feng Hou, MD, Moshe Inbar, MD, Hussein Khaled, MD, Joanna Kielanowska, MD, Wing-Hong Kwan, MD, Beela S Mathew, MD, Indraneel Mittra, PhD, Bettina Müller, MD, Antonio Nicolucci, MD, Octavio Peralta, MD, Fany Pernas, Lubos Petruzelka, MD, Tadeusz Pienkowski, MD, Ramachandran Radhika, MD, Balakrishnan Rajan, MD, Maryna T Rubach, MD, Sera Tort, MD, Gerard Urrútia, MD, Miriam Valentini, MD, Yaochen Wang, MD, Richard Peto, FRS and for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group

The Lancet
Volume 381, Issue 9869, Pages 805-816 (March 2013)
DOI: 10.1016/S0140-6736(12)61963-1

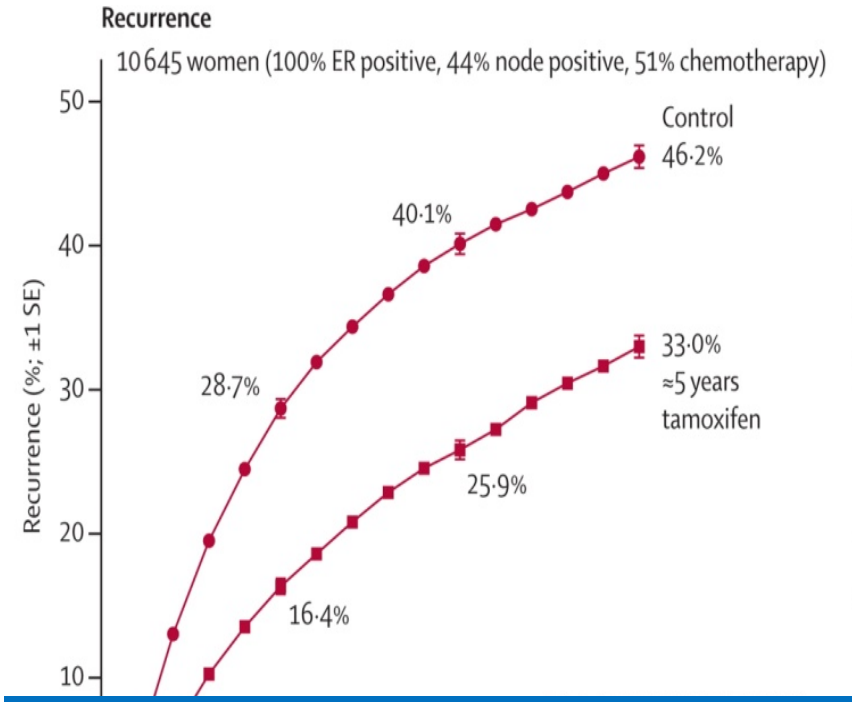


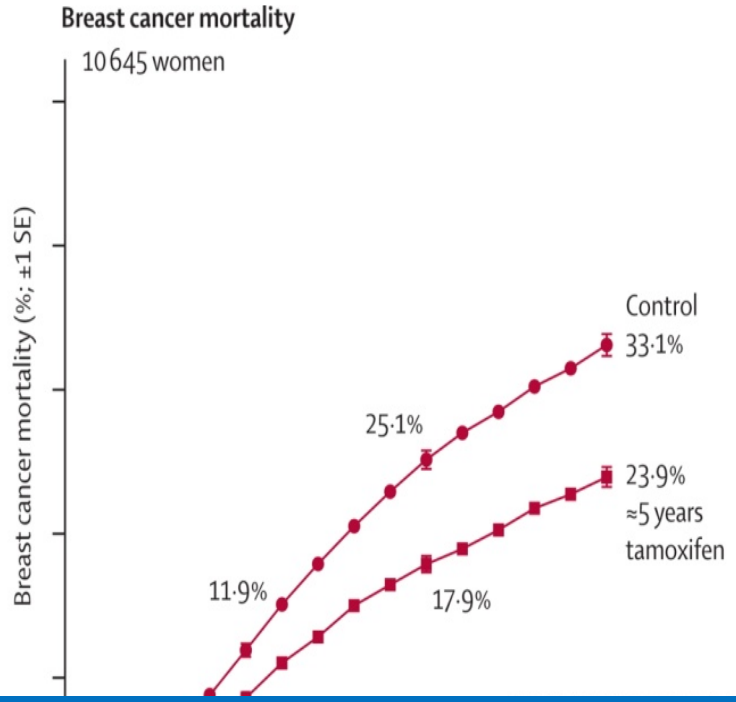
The Lancet 2013; 381:805-816

ATLAS: 5 vs 10 Yrs of Tamoxifen in ER-Positive Disease: Recurrence and Survival



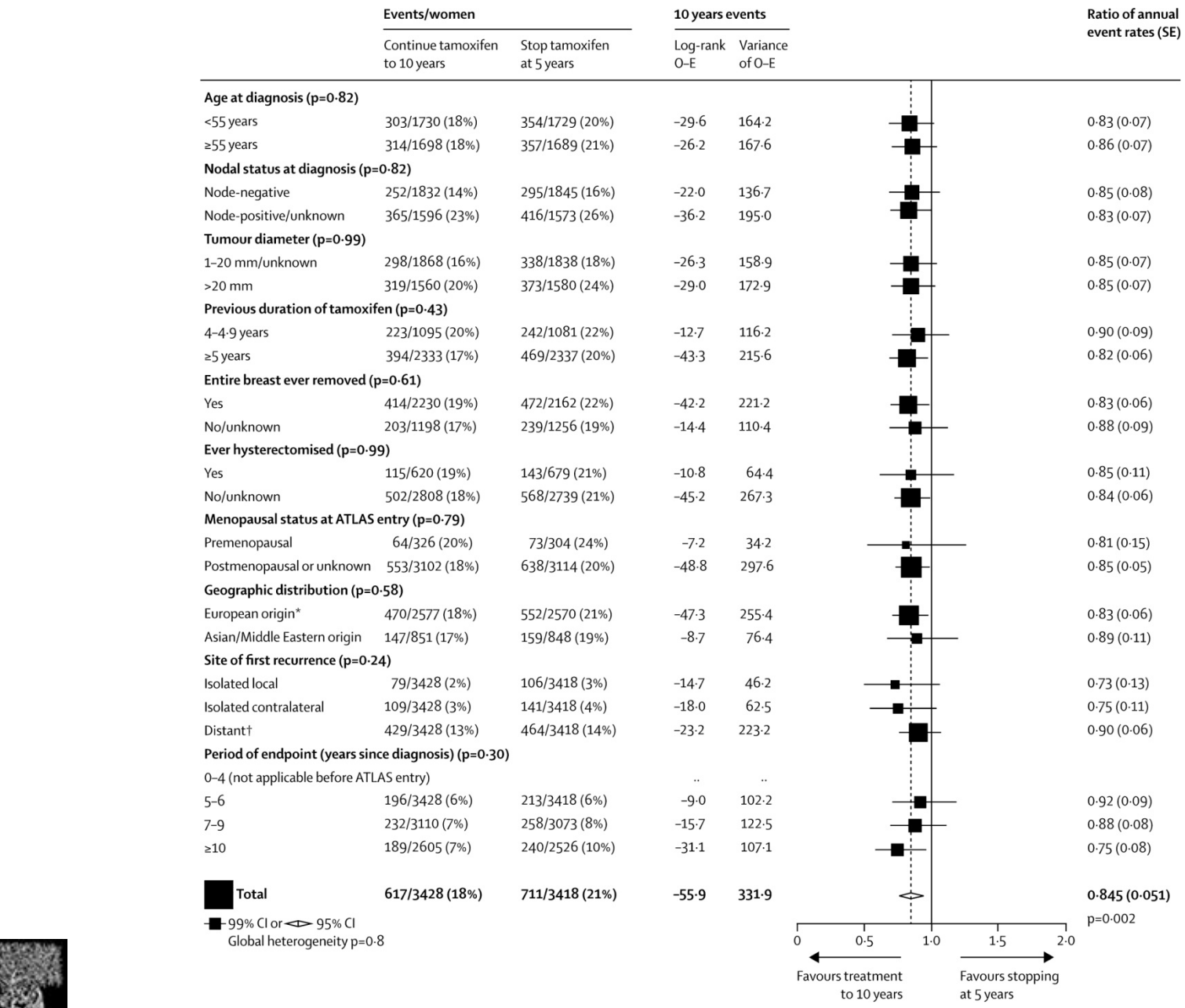
Davies C, et al. SABCS 2012. Abstract S1-2. Davies C, et al. Lancet. 2012;[Epub ahead of print]; © 2012, reprinted from the Lancet with permission from Elsevier.





	0-4y	5-9y	10-14y
Nüks RR	0.53	0.68	0.97
P	<.00001	<.00001	
Mort. RR	0.71	0.66	0.68
P	.05	.05	.08

EBCTCG, LANCET2011



The Lancet 2013; 381:805-816

ATLAS : Nükssüz Hastalar

EX	10 yıl	5 yıl	HR	p
Vasküler Olay				
Felç	62	59	1.03	0.89
PE	10	8	1.21	0.69
Kalp hast.	178	205	0.85	0.10
Kanserden ex				
Endometr.	17	11	1.49	0.29
Diğer	78	75	1.01	0.94
İkincil Ca İns.				
Karşı meme	419	467	0.88	0.05
Endometr.	116	63	1.74	0.00002
KC	3	3	0.99	0.99
Kolon	46	52	0.86	0.44
Diğer	254	251	0.99	0.91

ATLAS trial. Lancet 381;805,2013

ATLAS : Yan Etkiler(2)

Non-neoplastik Hastalıklar				
	10 yıl	5 yıl	HR	p
Felç	130	119	1.06	0.63
Pulm.emb.	41	21	1.87	0.01
ASKH	127	163	0.76	0.02
Safra taşı	75	66	1.11	0.54
Katarakt	72	63	1.11	0.54
Kırık	62	70	0.86	0.39

ATLAS tr. Lancet 381;805,2013

aTTom : 10 yıl vs 5 yıl Tamox.

Gray et al. Abs. ASCO2013

- **N= 6953**
- **Nüks (RR) = 0.85**
  - **abs. azalma % 4 (p=0.003)**
- **Meme Ca mort. RR = 0.88**
  - **abs. azalma % 2 (p=0.06)**
- **Nükssüz ölümler: benzer**
- **Tüm ölümler: benzer (henüz)**
- **10 yıla kadar fark yok**

Adjuvan Tedavide Aİ'nin 5 yıldan daha uzun kullanılması ile ilgili etkinlik veya toksisite verisi yok

Erken Evre Meme Ca End. Tedavi (İlk 5 yıl)		
Premen.	Tamoksifen (<40 yaş için) +/-	
	Over abl/sup	+/- Aİ Kanıt?
Postmen.	Tamoksifen	
	Aromataz inh.	
	Tam. →	Aİ
	Aİ →	Tam.

Erken Evre Meme Ca End. Tedavi (İkinci 5 Yıl)
PREMENOPOZAL Tamoksifen veya tedavi kesilebilir
POSTMENOPOZAL Tam. veya Aİ veya tedavi kesilebilir
Aİ veya tam. veya ted. kesilebilir
Tamoksifen (?) veya ted. kesilebilir
Aİ veya Tam.(?) veya HİÇ
Tam. veya Aİ (?) veya HİÇ

- Hastanın 5 yıldan sonra nüks riski (Adjuvant online)
- Hastanın diğer morbiditeleri (Özellikle KV hast. ve osteoporoz; end. hiperplazi/histerektomi, TE olay)
- Hastanın ilaç toleransı ve kompliyans

Teşekkür ederim

ÖRNEK OLGULAR	
AA, 34 yaş	IDK, G3, LVİ+ T1=4.5 cm T2=1.5 cm 17/17 LN+ ER %90+, PR %30+, erbB2 (-)
Adj. Online	İlk tanıda % 98.7
	5 yıl sonra % 52.3
HY, 38 yaş	IDK G3 T1 ve T2=4 cm, T3=2 cm 8/16 LN+ ER %80+, PR %90+, erbB2 (-)
Adj. Online	İlk tanıda % 84
	5 yıl sonra % 38.7
ZPÖ, 36 yaş	IDK, G2, Ki-67 % 40 T=1.6 cm LN (-) ER %95+, PR %60+, erbB2 (-)
Adj. Online	İlk tanıda % 25
	5 yıl sonra % 7.5

ÖRNEK OLGULAR	
BK, 57 yaş	**IDK, G2, T=1.6 cm, LN (-)** **ER % 95+, PR % 60+**
Adj. Online	**İlk tanıda % 25**
	5 yıl sonra % 7.5
KA, 49 yaş	**IDK, G2, T=2.1 cm, 2/22 LN+** **ER % 85+, PR %75+, erbB2 (-)** **Tam 3 yıl → Letrozol 2 yıl**
Adj. Online	**İlk tanıda % 55**
	5 yıl sonra % 20.5 **Letrozol ile devam (Aİ toplam 5 yıl)**

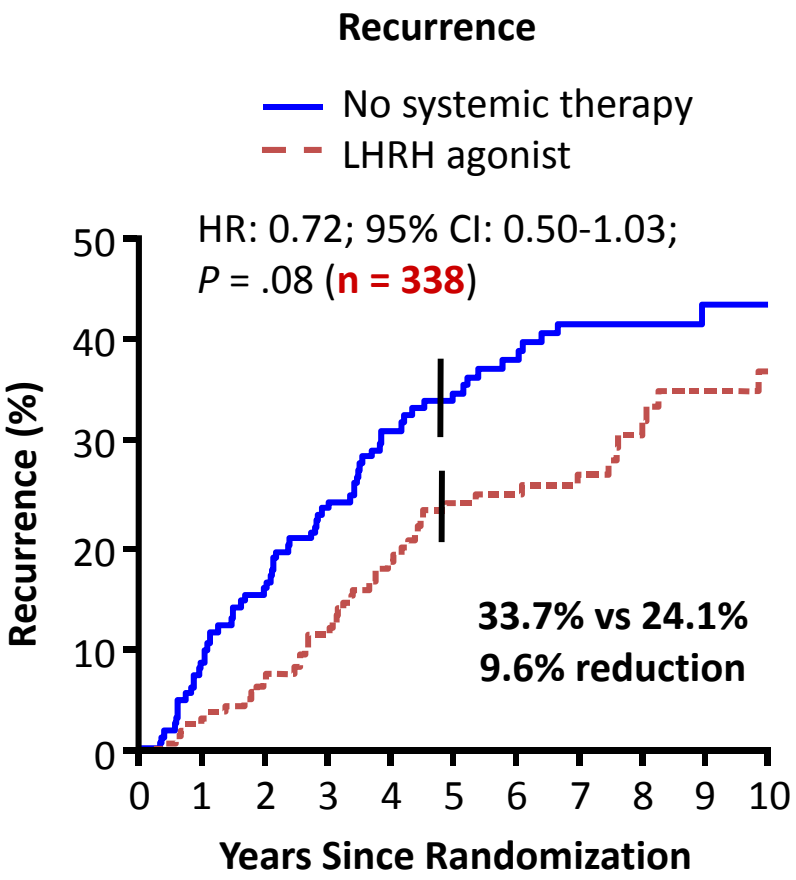
Teşekkür ederim

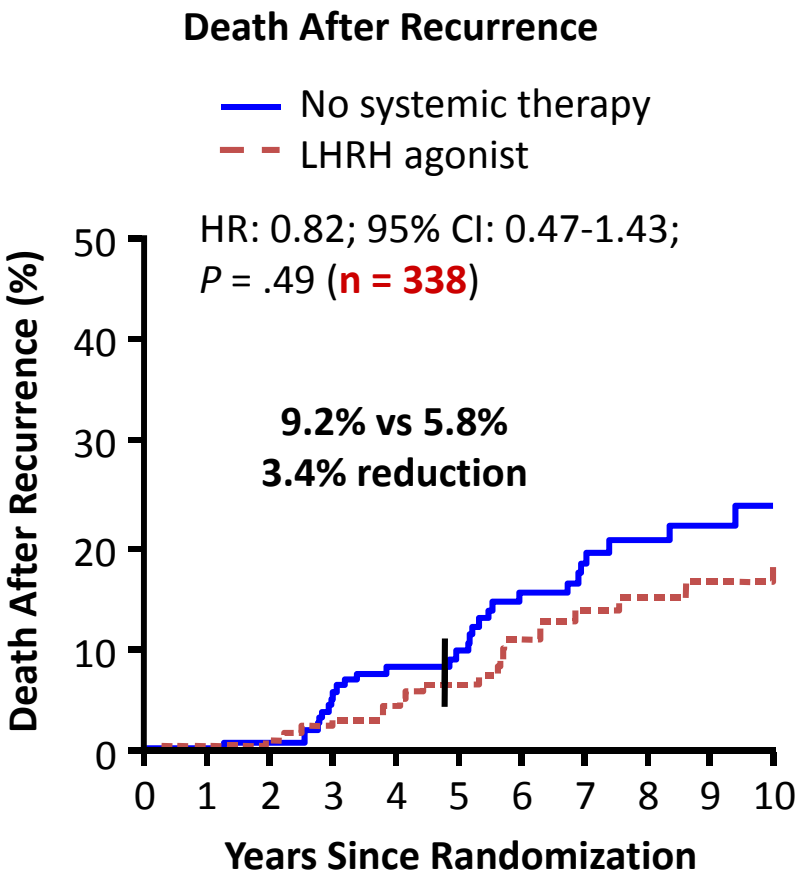
Early Breast Cancer
Overview Group: LHRH Agonist Etkisi
Meta-analysis

- 13 randomize çalışma (1987-2001)
- N = 9022

EBCOWG, Lancet 2007

LHRH agonistinin etkisi

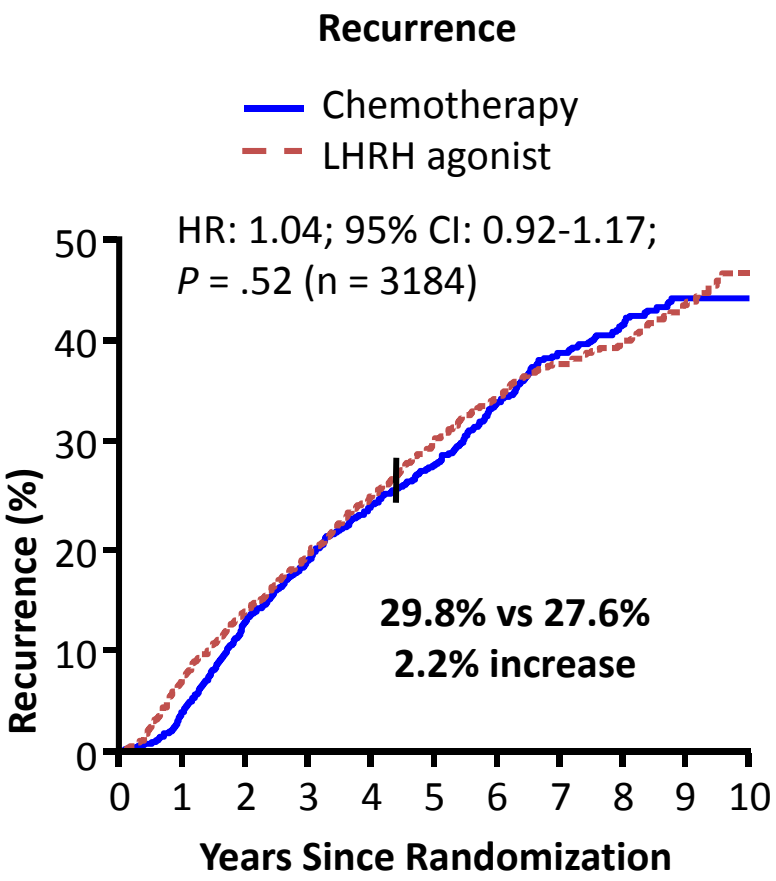


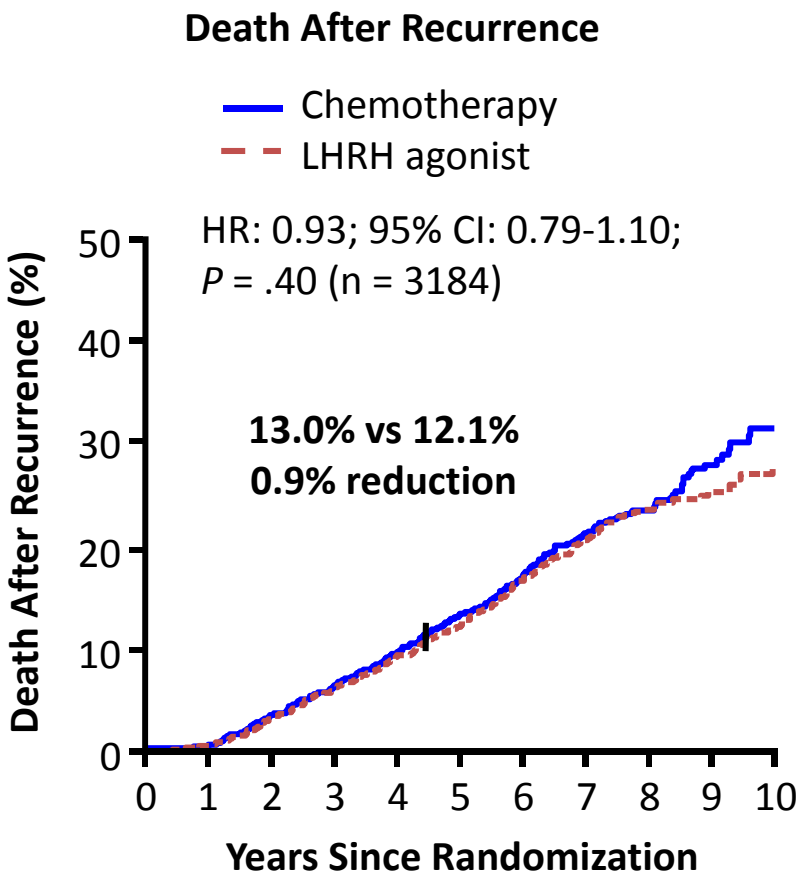


Cuzick J, et al. SABCS 2006. Abstract 15

EBCOWG, Lancet 2007

LHRH Agonistleri Kemoterapi kadar Etkili





Cuzick J, et al. SABCS 2006. Abstract 15

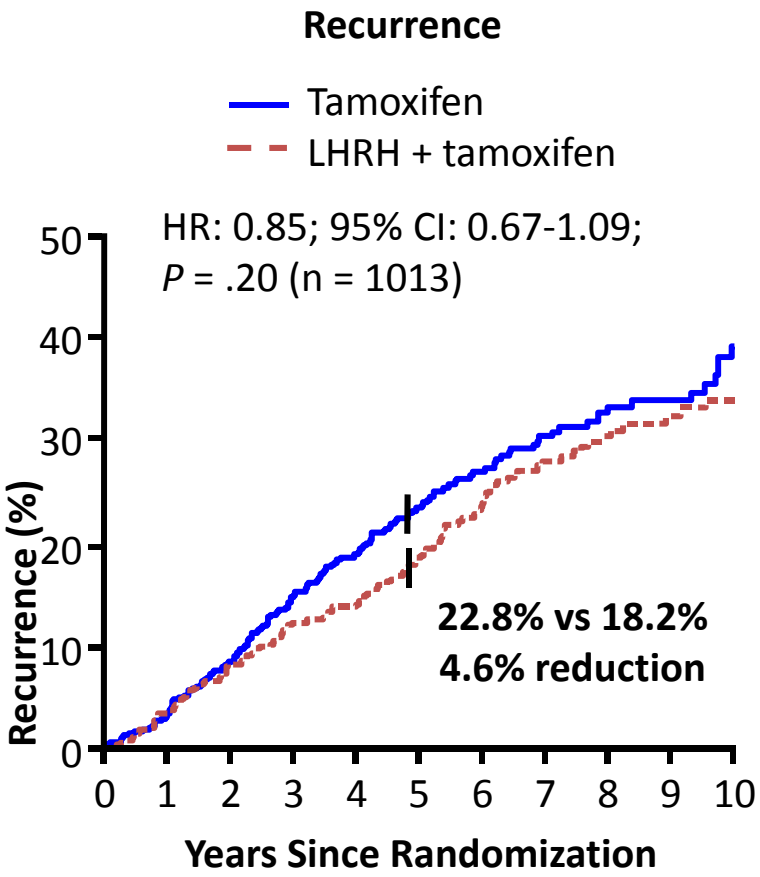
EBCOWG, Lancet 2007

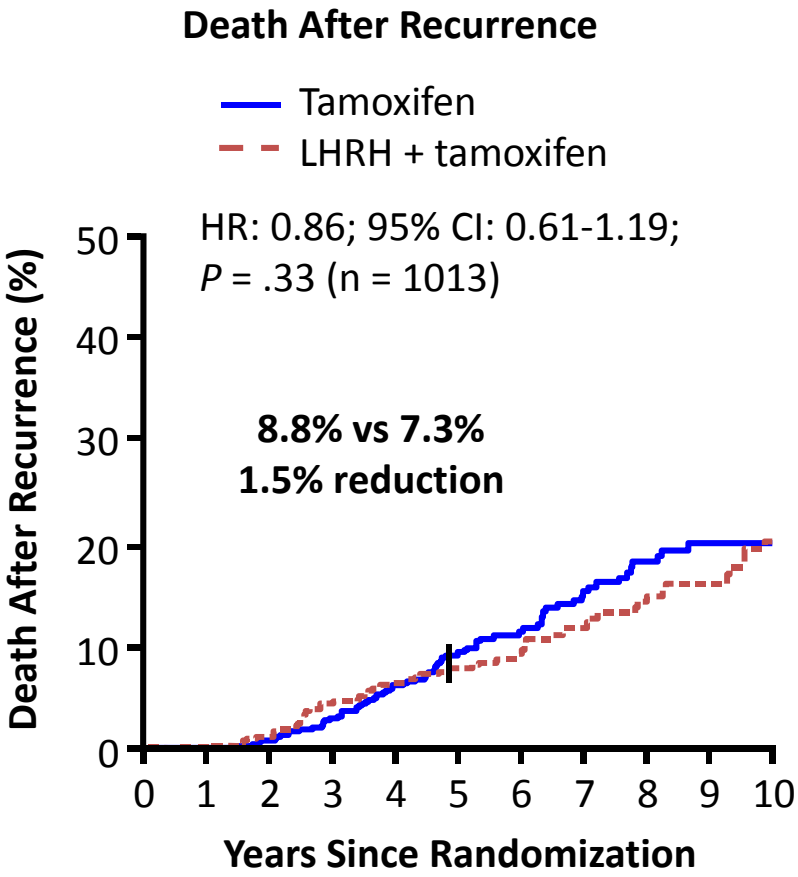
LHRH Analoğu

- **LHRH analoğu,**
  - **Tek başına kullanıldığında nüks ve ölüm olasılığını azaltmaz (?!)**
  - **Kemoterapiye eşdeğer sonuç verir (özellikle CMF)**
  - **Kemoterapi (p=.04) ve tamoksifene (p>.05) eklendiğinde etkinliği artırır**
  - **Kemoterapi ile birlikte? Ardışık?**

EBCOG, Lancet 2007

Tamoksifen vs Tamoksifen+LHRH analoğu

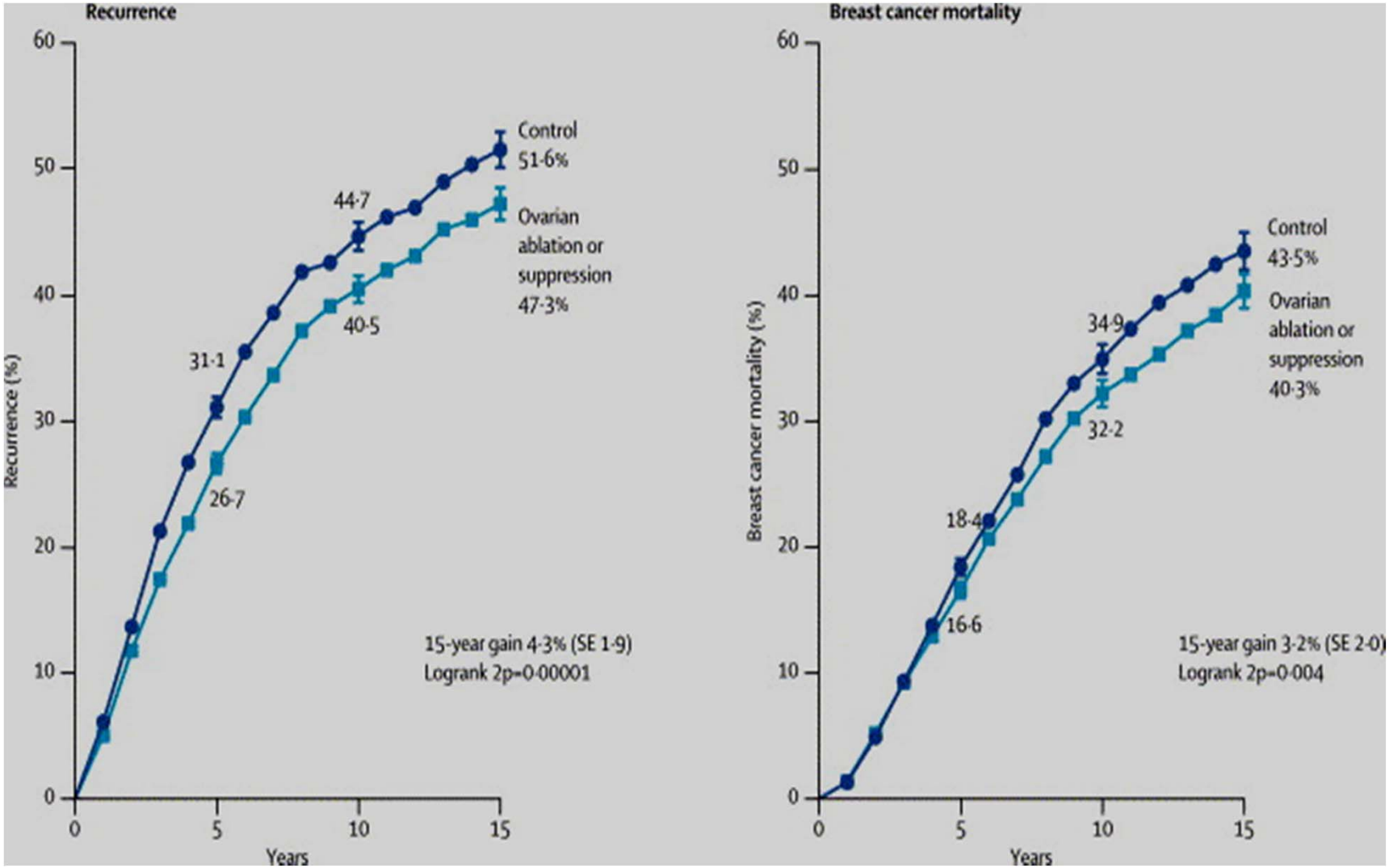




Cuzick J, et al. SABCS 2006. Abstract 15

EBCOWG, Lancet 2007

Premenopozal hastada
Over Ablasyonu veya Supresyonu



EBCTCG, Lancet 2005