Optimal Endocrine Therapy in Premenopausal Women: Duration of Endocrine Therapy & Modality of Patient Selection

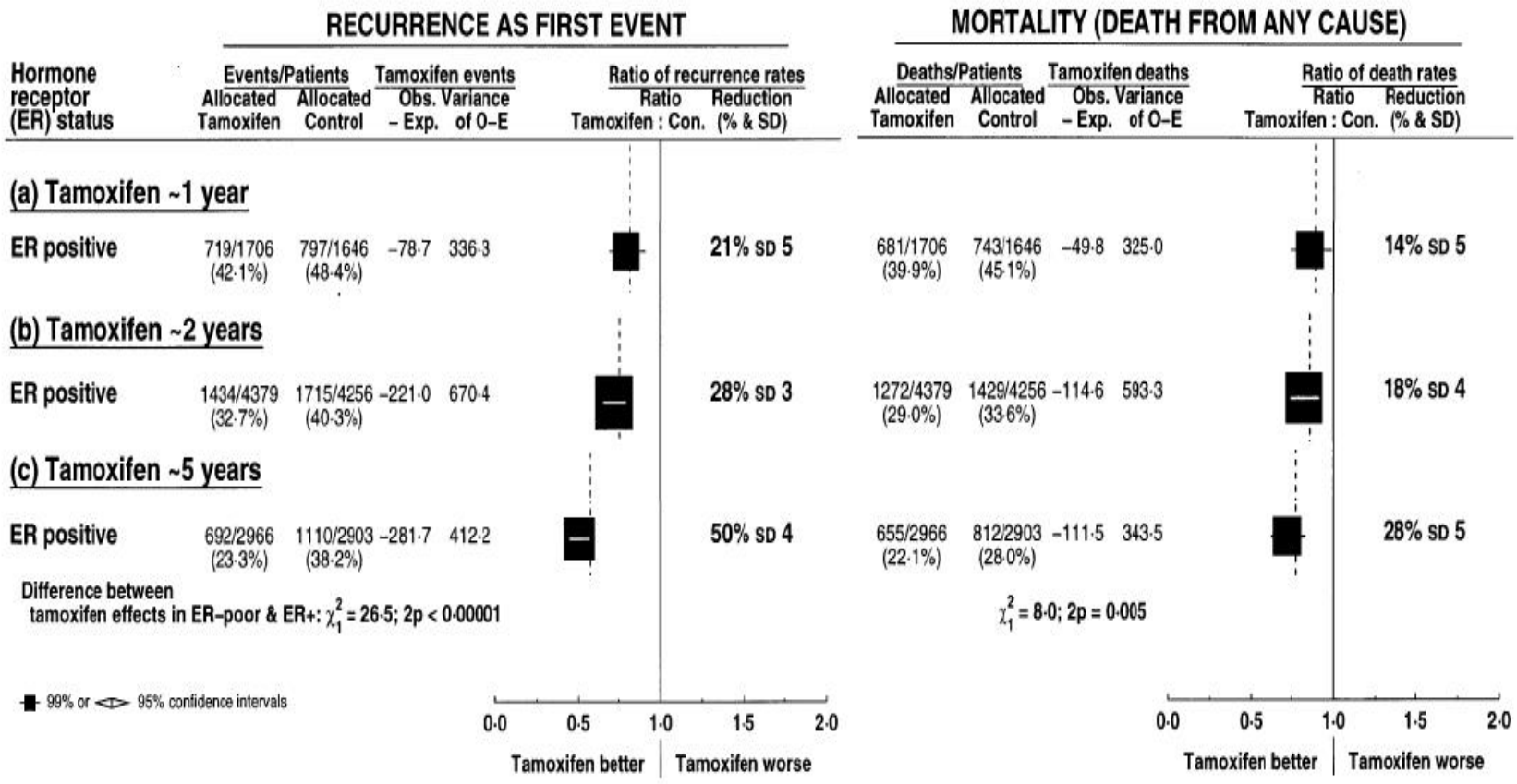
Sung-Bae Kim
Professor, Dept of Oncology
Asan Medical Center
University of Ulsan College of Medicine
Seoul, Korea

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Disclosure slide

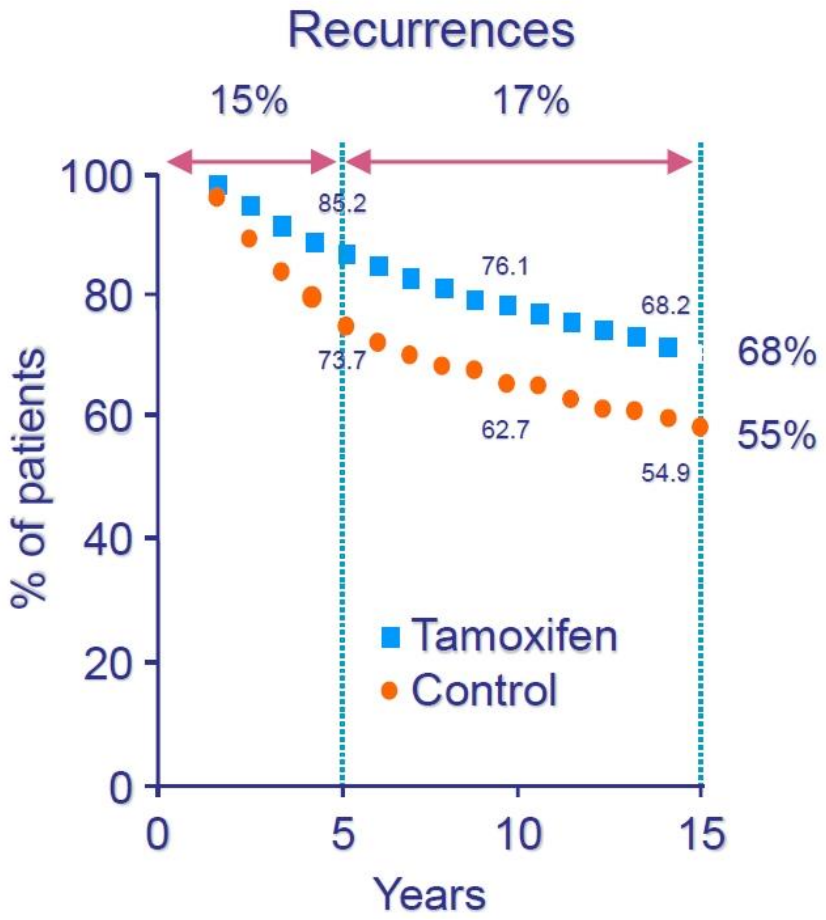
- Nothing to declare

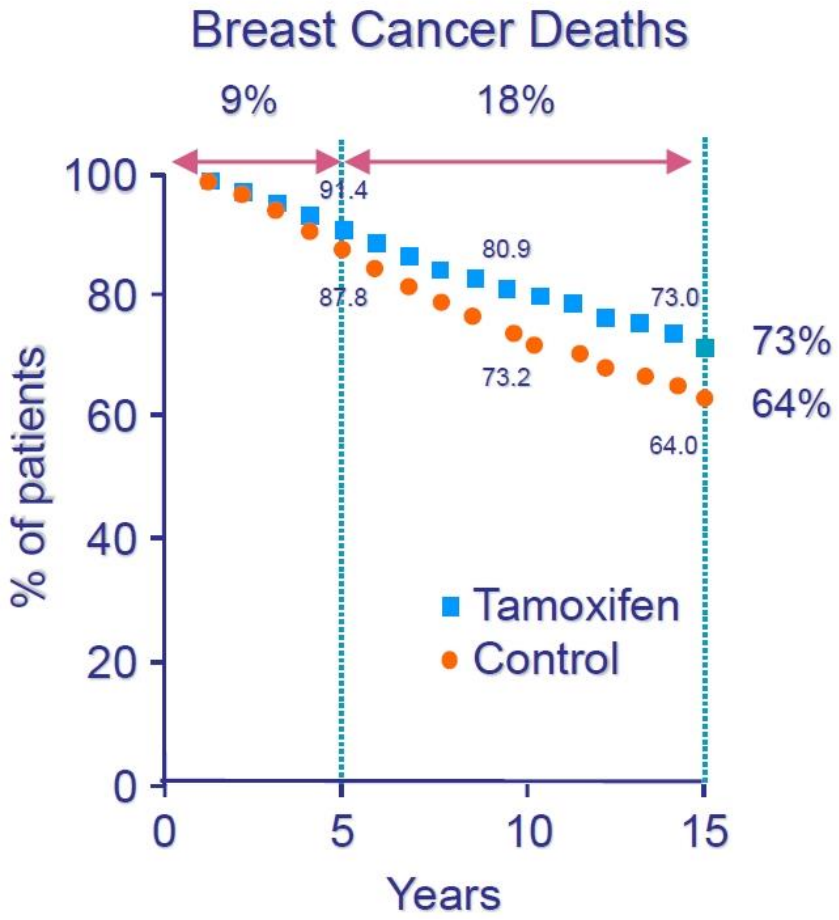
Proportional risk reductions by tamoxifen duration



EBCTG, Lancet 2011

EBCTCG-Meta Analysis

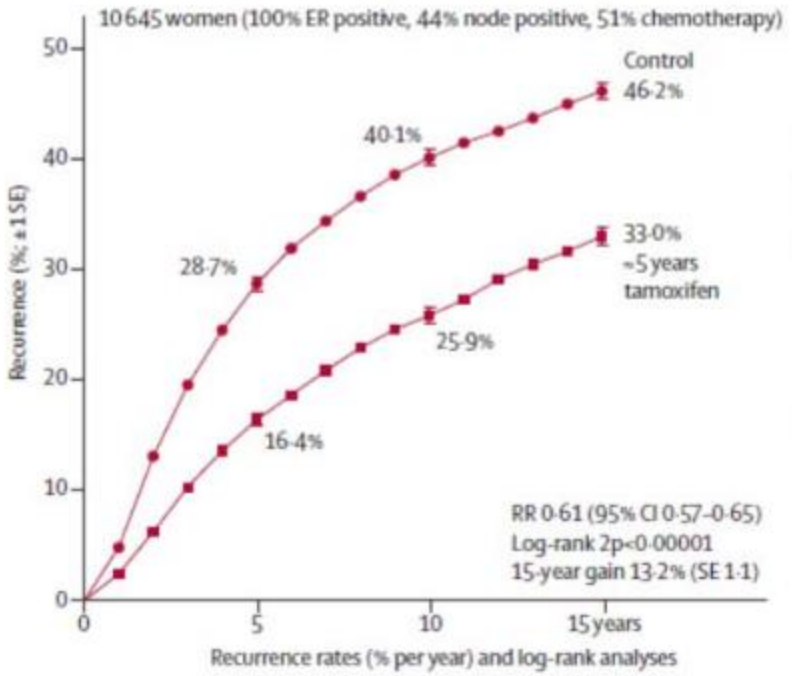




EBCTCG, Lancet 2005

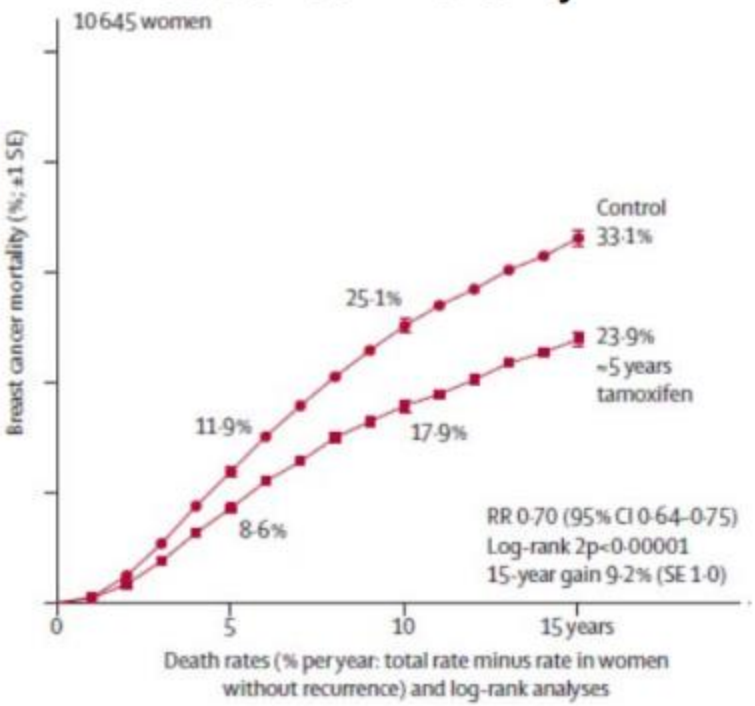
Benefits of Tamoxifen x 5 Years

Recurrence



	5y	10y	15y
Δ	12.3%	14.2%	14.2%

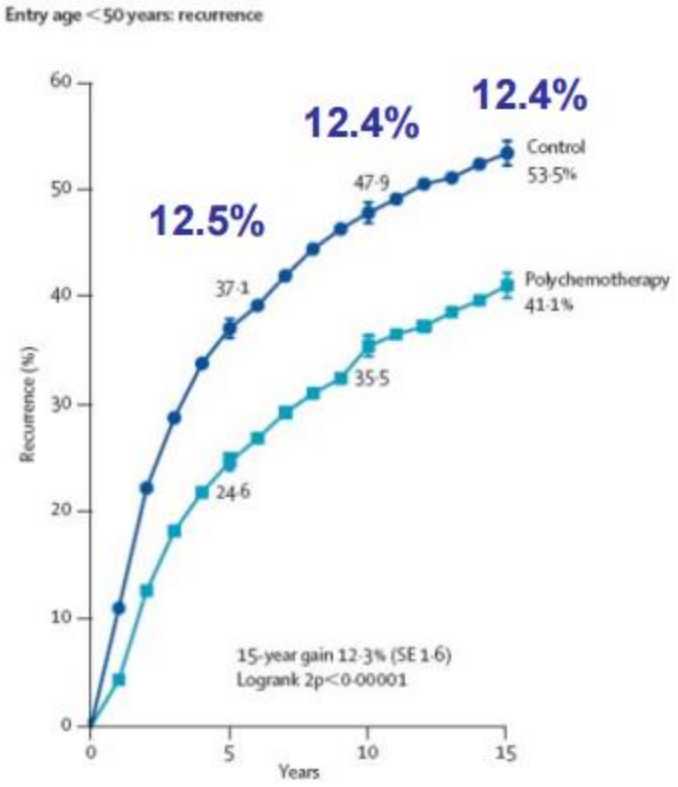
Breast Cancer Mortality

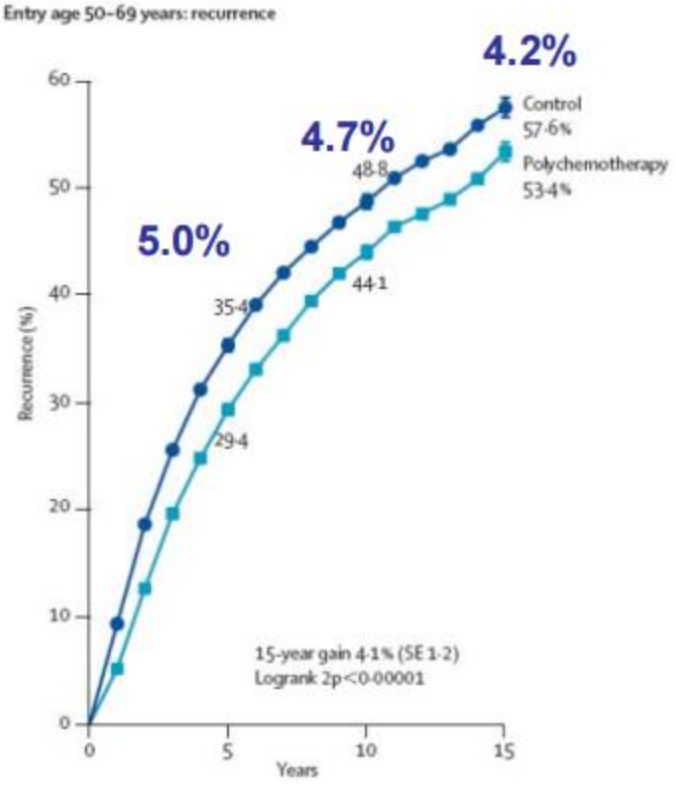


	5y	10y	15y
Δ	3.3%	7.2%	9.2%

EBCTCG, Lancet 2011

The impact of chemotherapy on recurrence is seen in years 0-5 only

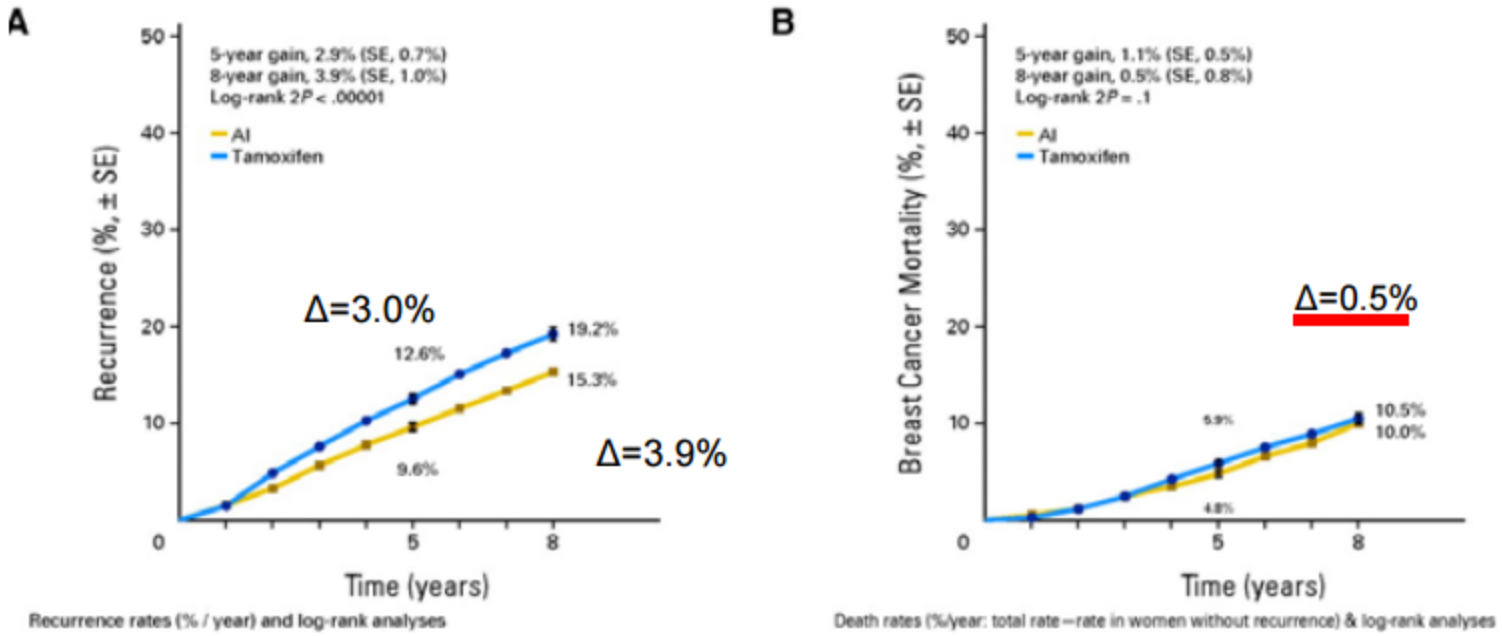




EBCTCG. Lancet 2005

5 yrs Adjuvant Tamoxifen vs. AI

Meta-analysis of ATAC (anastrazole) and BIG 1-98 (letrozole) trials, n = 9,856 mean FU 5.8 yrs



Recurrence rates (% / year) and log-rank analyses

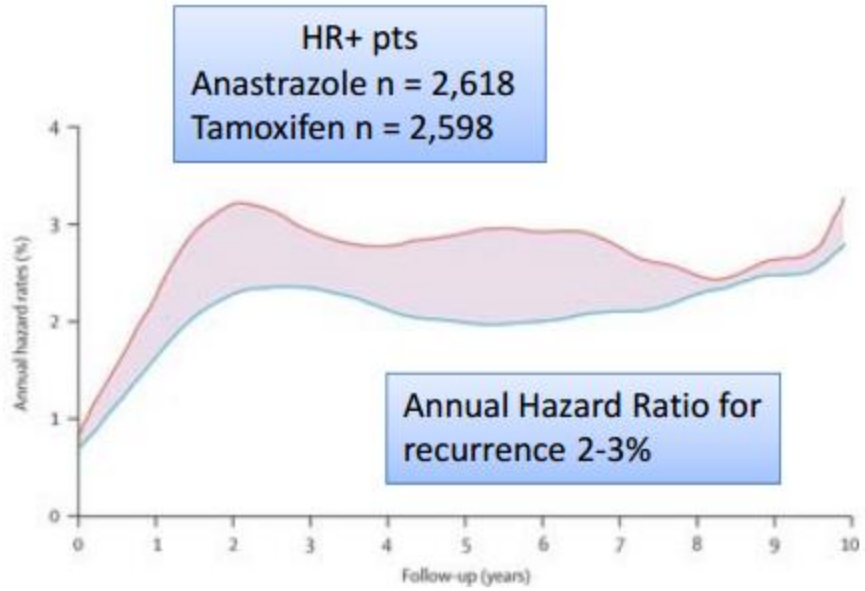
Death rates (%/year: total rate – rate in women without recurrence) & log-rank analyses

Primary benefit of AI over Tam is in recurrence rates, no statistically significant survival benefit

Dowsett *et al*. JCO 2010

Late Recurrence Remains a Challenge as Early Treatment Improves

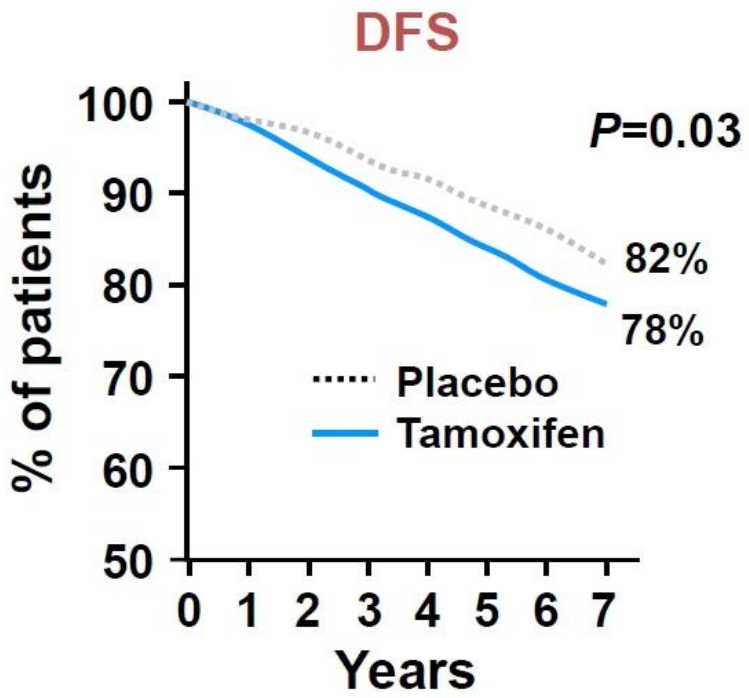
ATAC trial 10 year analysis

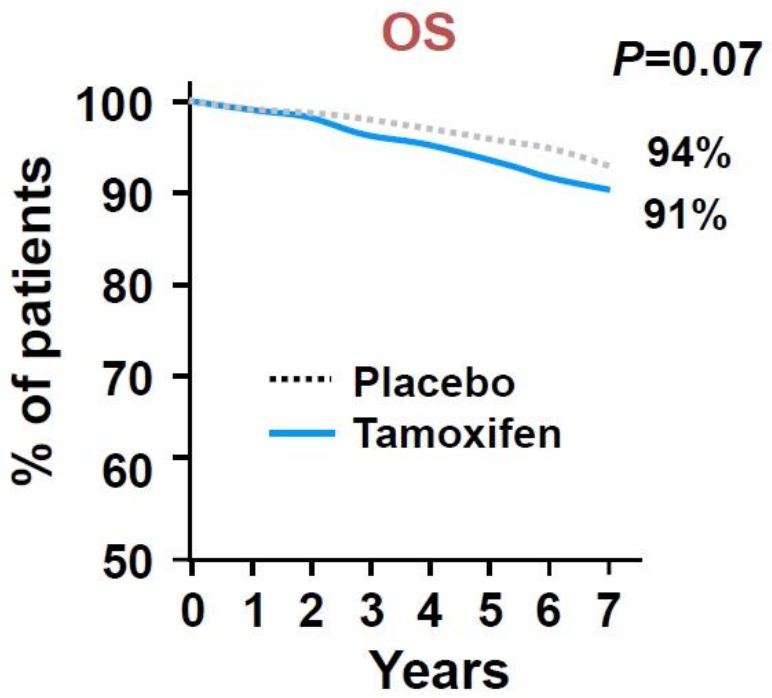


Even with recent advances, including aromatase inhibitors and trastuzumab, there appears to be persistent risk of late recurrence

Cuzick *et al*. Lancet Onc 2010

NSABP B-14: after 5 yrs TAM
>5 yrs vs placebo
1152 ER+ve LN- pts randomized





Tamoxifen demonstrated higher rates of endometrial cancer, ischemic heart disease and cerebrovascular disease.

Fisher et al. H Nat'l Cancer Inst 93:684, 2001

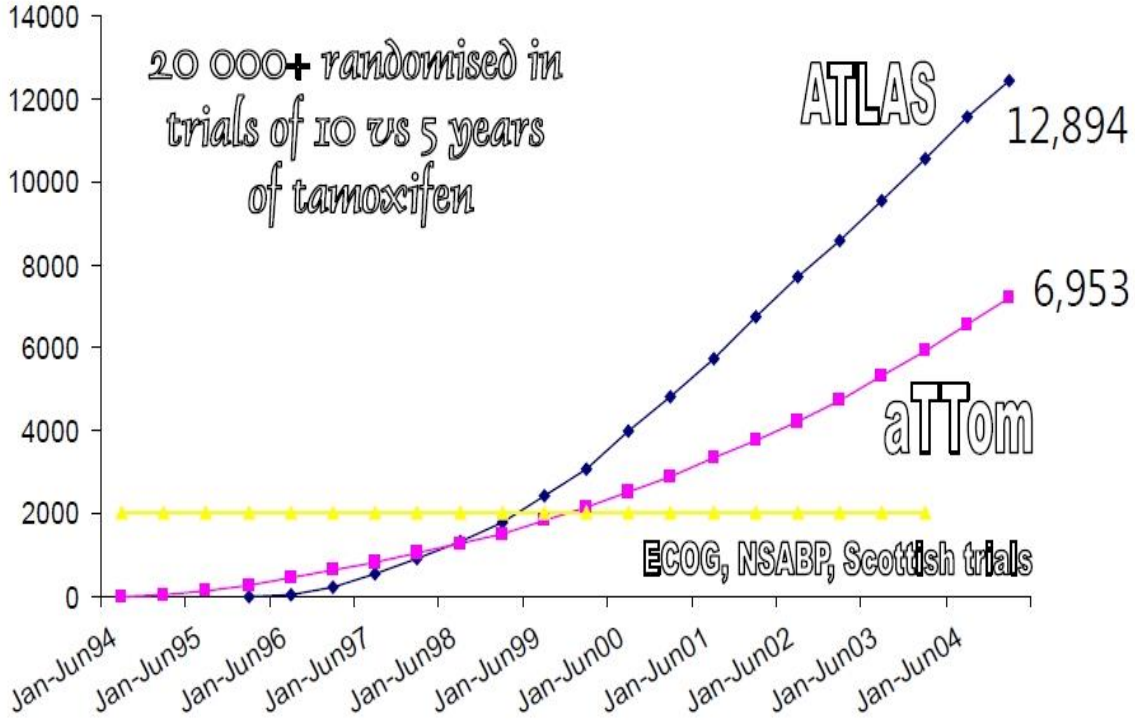
Early trials beyond 5 yrs of TAM

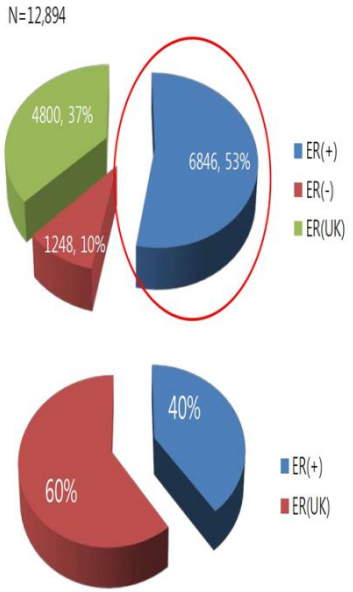
Study	Group	No.	OS	BC specific mortality	DFS	RR
ECOG[1]	Cont. Stop	100 93	86% 89% P=0.52	NR NR	85% 73% P=.01	NR NR
NSABP-B14[2]	Cont. Stop	583 569	91% 94% P=0.07	NR NR	78% 82% P=0.03	8.1% 6.0% P=0.13
Scottish[3]	Cont. Stop	173 169	59.5% 68%	23% 15%	54% 61% P=0.15	5.2% 7.1%

Summary of early, relatively small trials[4]
-inconclusive
-combined analysis (n=1,588 pts) failed to show any significant benefit of 10 yrs over 5 yrs of TAM

[1]Tormey DC, et al. JNCI 88:1828, 1996
[2]Fisher B, et al. JNCI 93: 684, 2001
[3]Stewart HJ et al . British J of cancer 74:1996
[4]2014 ASCO Educational book

ATLAS (adjuvant TAM longer against shorter)/aTTom (adjuvant TAM to offer more)

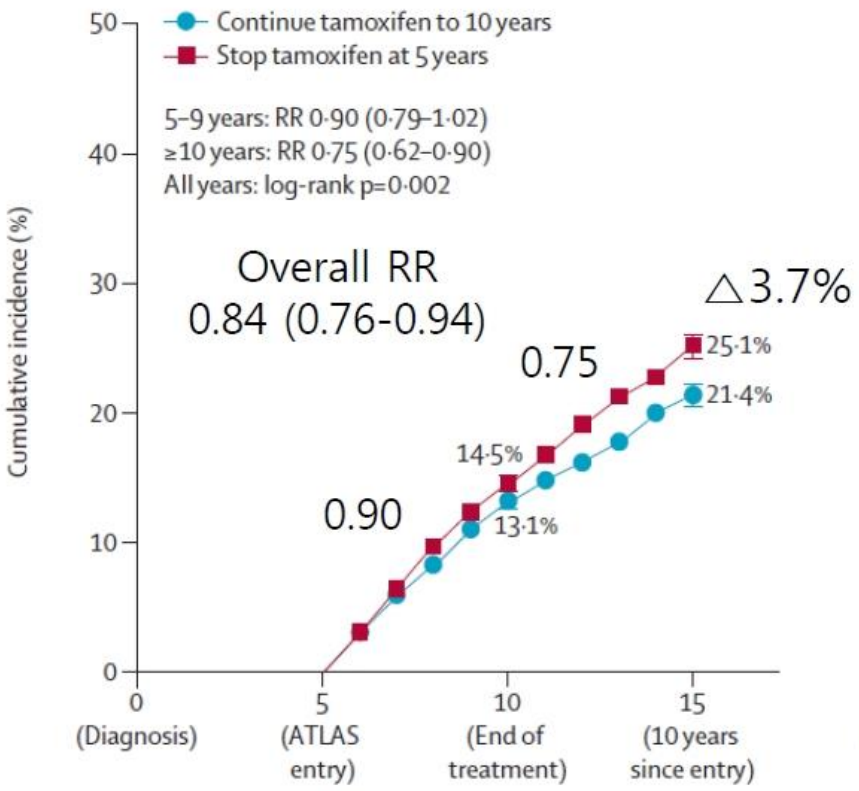




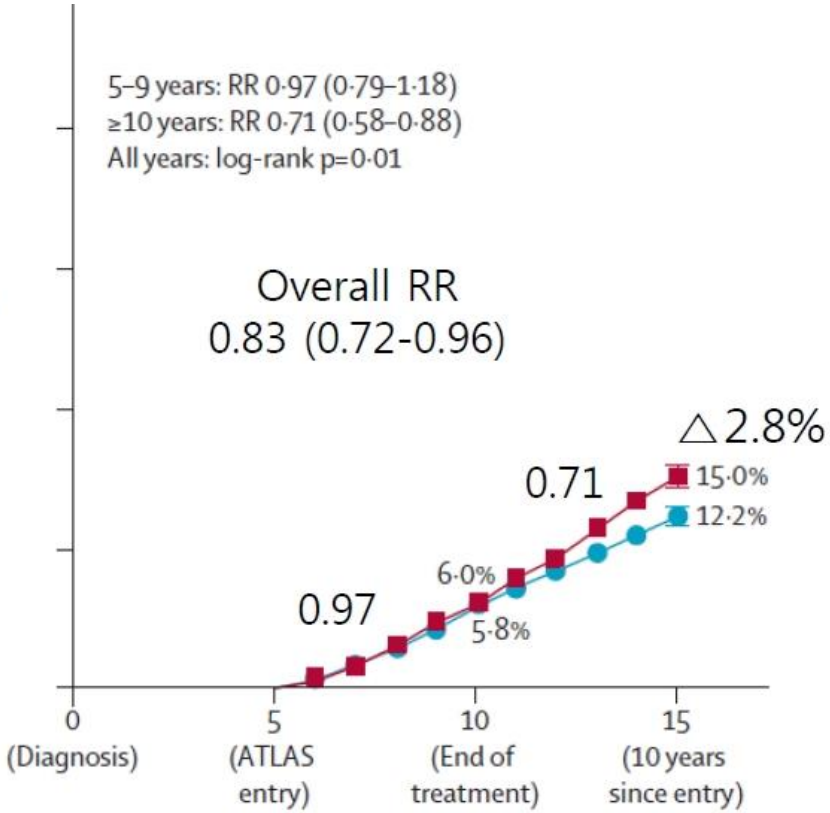
ASCO 2013, abstract #5

ATLAS

Recurrence



Breast cancer mortality



Davies et al, Lancet 2012

Pooled analysis ATLAS+aTTom: breast cancer mortality

10 vs 5 yrs BC mortality RR by period in ER+ve (or unknown) patients	*ATLAS* *ER+ve n =10543** HR (95% CI)	*aTTom* *ER+ve n= 6934 in UK* HR (95% CI)	*Combined* *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+

Gray RG et al ASCO 2013, abstract #5

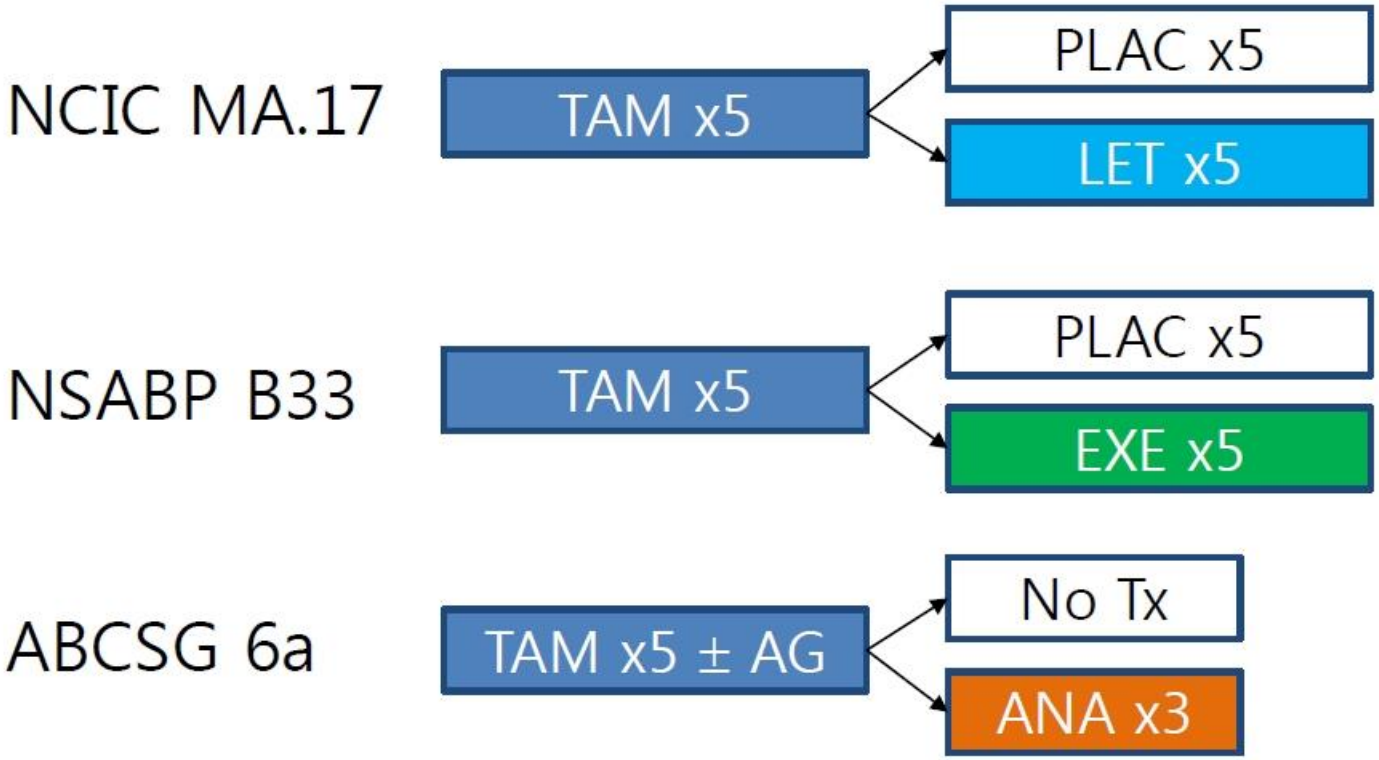
Adverse effects of extended tamoxifen

AE	10Y TAM	5Y TAM	RR (95% CI)	P-value
Endometrial ca	116	63	1.74(1.30-2.34)	0.0002
Pulmonary embolism	41	21	1.87(1.13-3.07)	0.01
Ischemic heart disease	127	163	0.76 (0.60-0.95)	0.02
Cataract	72	63	1.11 (0.79-1.56)	0.54
Bone fracture	62	70	0.86 (0.61-1,21)	0.39

- No significant difference between extension group and stopping group in death without recurrence (e.g. pulmonary embolism or endometrial cancer)
- Secondary cancer (e.g. endometrial cancer) or non-neoplastic disease were more frequently observed in extension group.

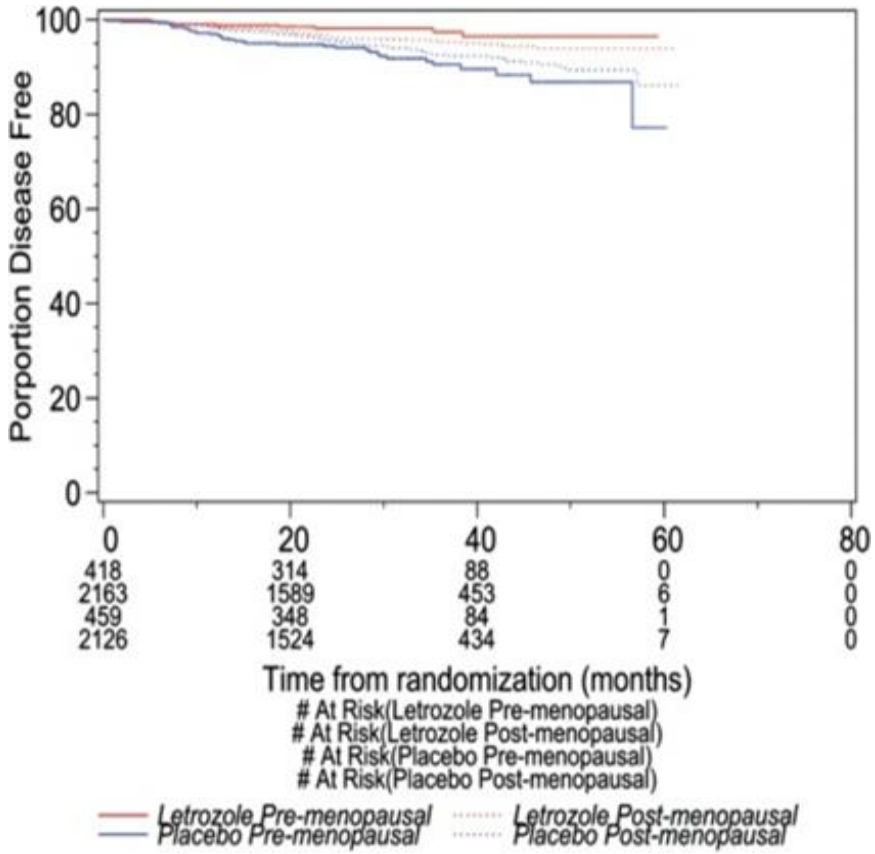
Davies et al. Lancet 2013

Extended adjuvant trials



Women who became postmenopausal in first 5 years had greatest benefit in MA-17

Pre menopausal at initial Dx (n=889)	Post menopausal (n=4,277)
10.1% (75% risk reduction) HR=0.25; p<0.0001	3.3% (31% risk reduction) HR=0.69; P=0.0008



absolute difference in 4-yr DFS : 4%(Letrozole vs Placebo)

Goss PE et al. SABCS 2009; abst#12
Goss PE et al. Ann Oncol 24:355,2013

Meta-analysis of LHRA agonists as adjuvant therapy for premenopausal women with HER+ breast cancer

- 9,022 women with HR+ disease, 6.8 Yr Med FU
- Tam+/- LHRH agonist

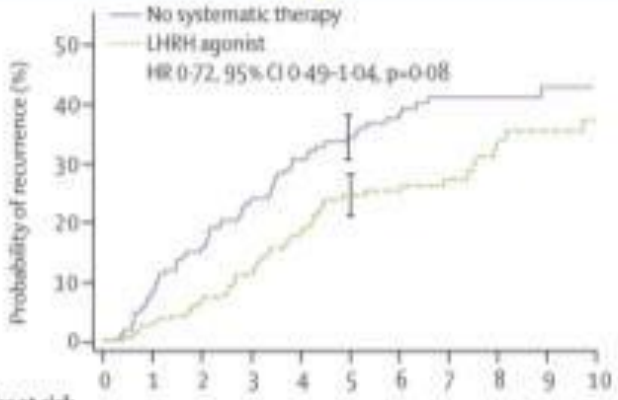
  - no significant decrease in risk of recurrence (HR 0.85) or death after recurrence HR(0.84)

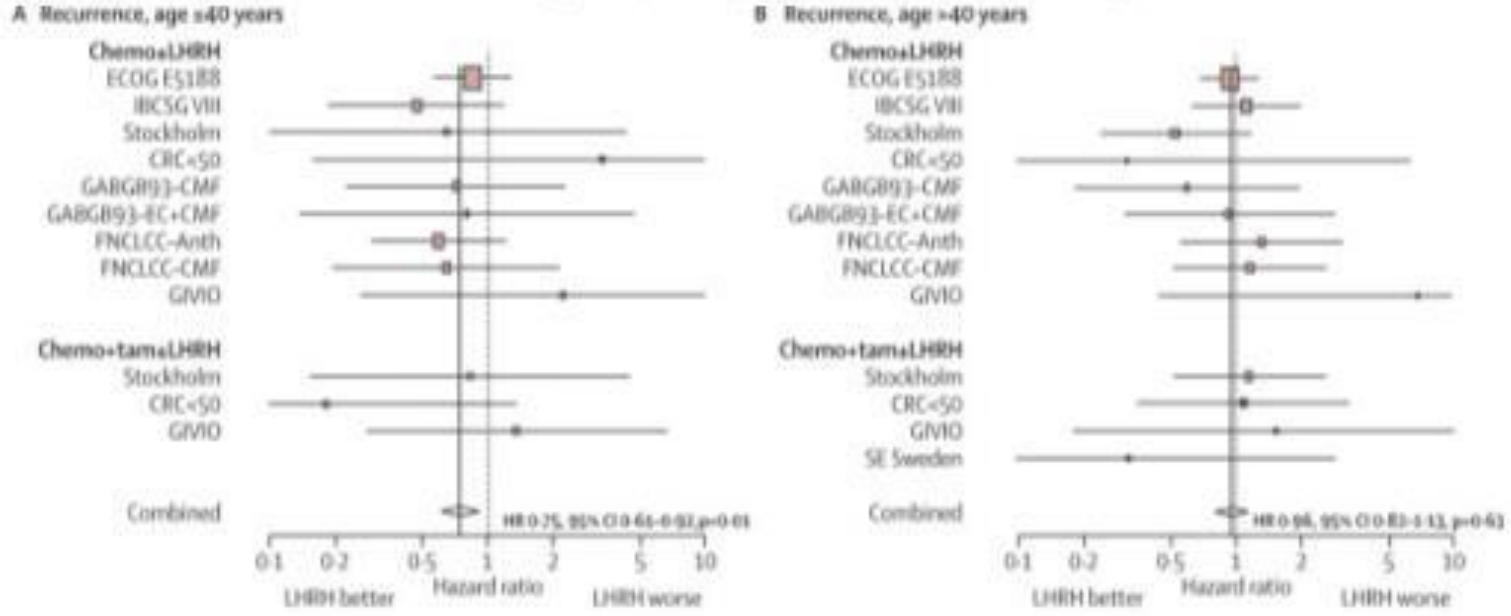
- Chemotherapy+/- tamoxifen: addition of LHRH agonist provides modest benefit

  - reduction in risk of recurrence : 12.2% (HR0.88)
  - reduction in risk of death after recurrence: 15.1% (HR0.85)

Cuzick et al: LHRH meta analysis group
Lancet 2007; 369:1714

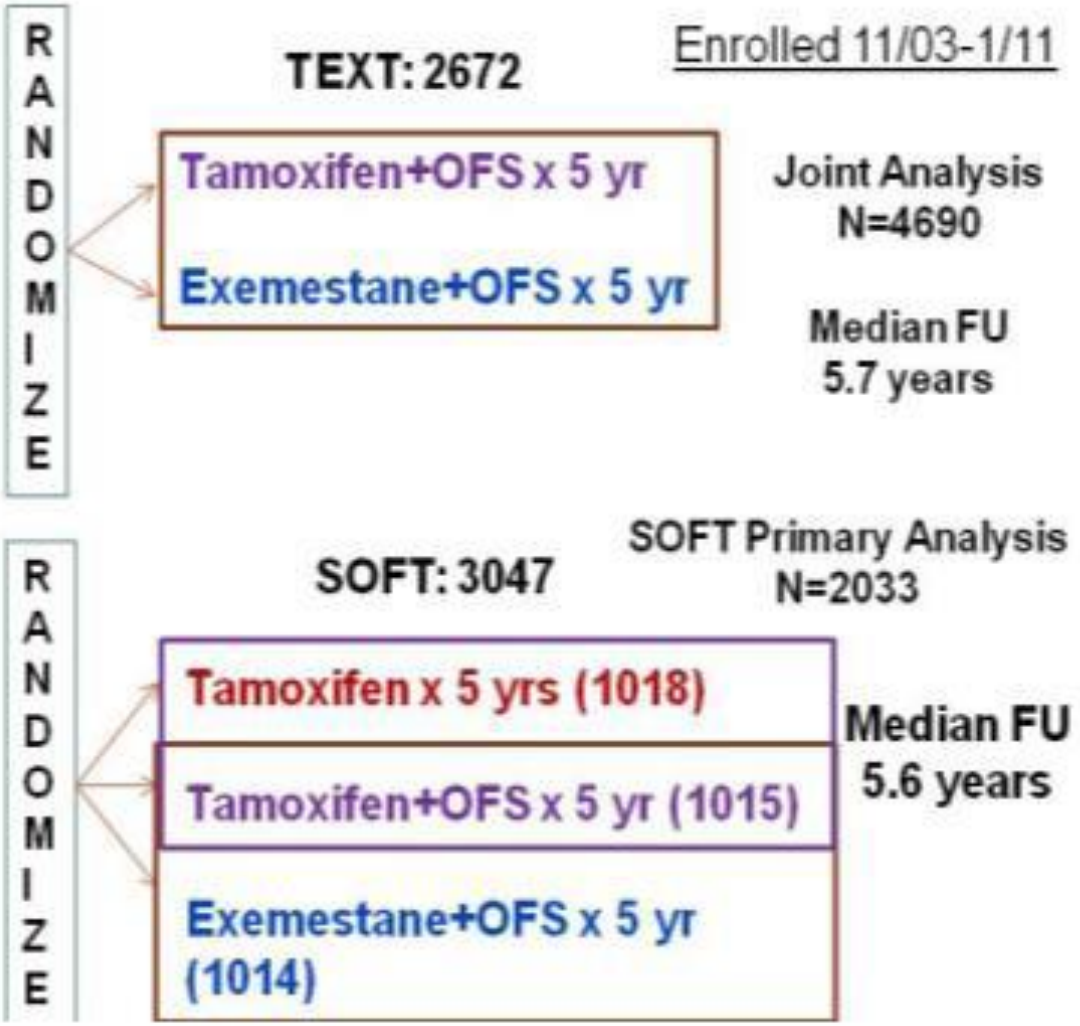
LHRH Agonists: Importance of Age





Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2007

SOFT and TEXT

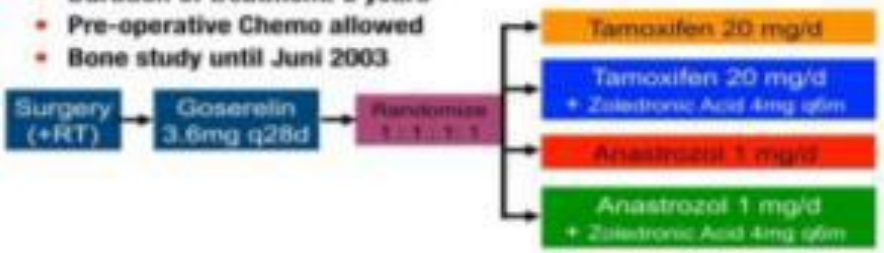


Pagani et al. NEJM 2014; Francis et al. NEJM 2014

ABCSG 12: Tamoxifen, AI's and LHRH agonists

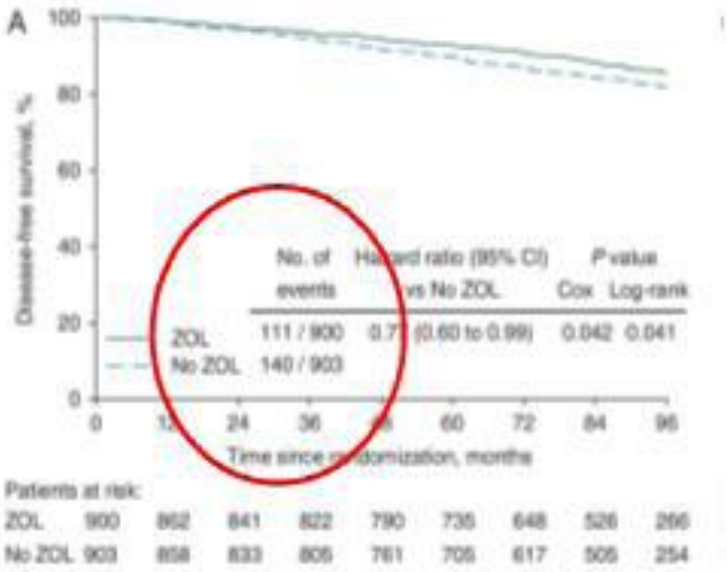
ABCSG-12 Trial Design

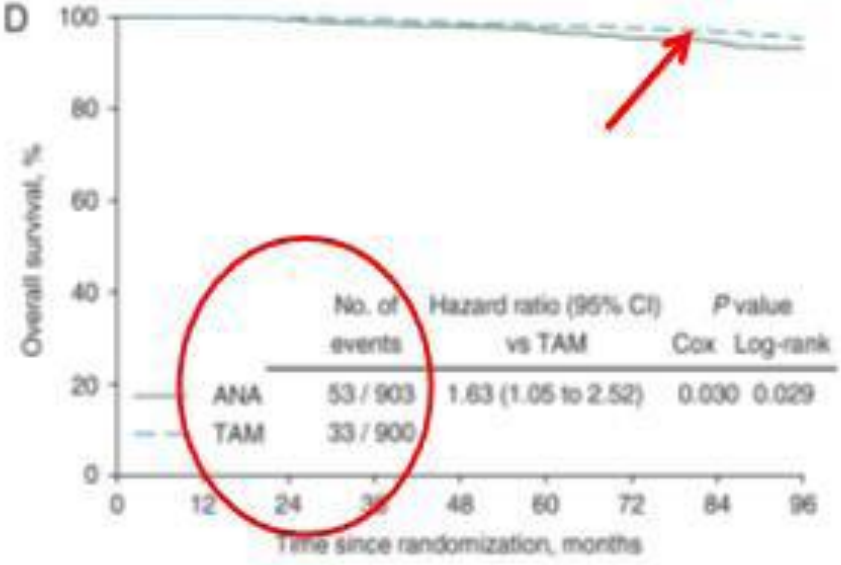
- Recruitment 1999-2006
- 1.803 premenopausal patients
- Stage I&II, <10pos nodes, ER+ and/or PgR+
- Duration of treatment: 3 years
- Pre-operative Chemo allowed
- Bone study until Juni 2003



Major Findings:

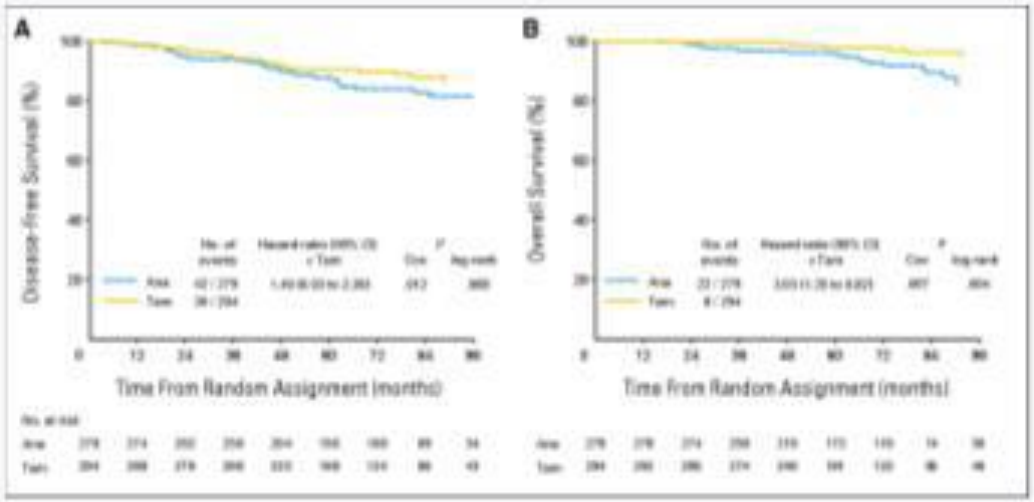
- Significant improvement in DFS with addition of Zoledronic acid No difference in DFS comparing TAM and Anastrozole
- OS difference related to inadequate OFS?

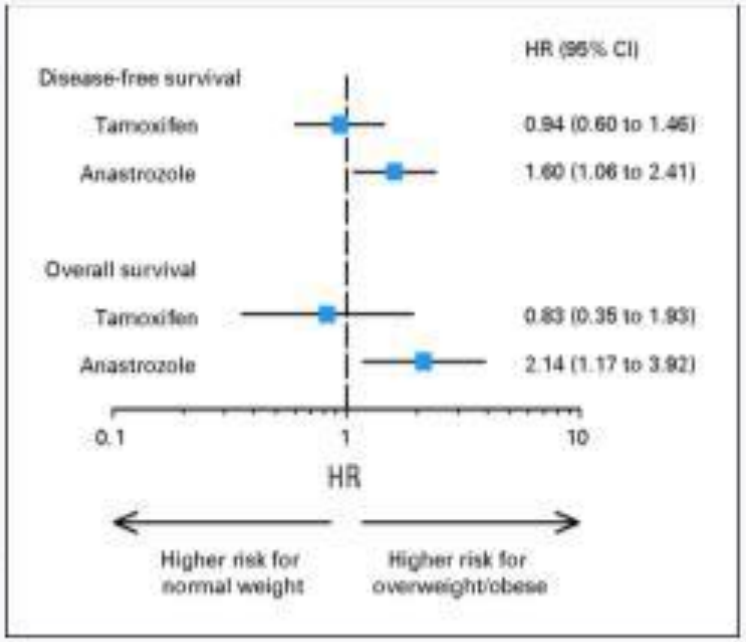




M. Gnant et al. Ann Oncol 2015;26:313-320

ABCSG 12: Outcomes According to Treatment Arm (Anastrozole vs Tamoxifen) based on BMI





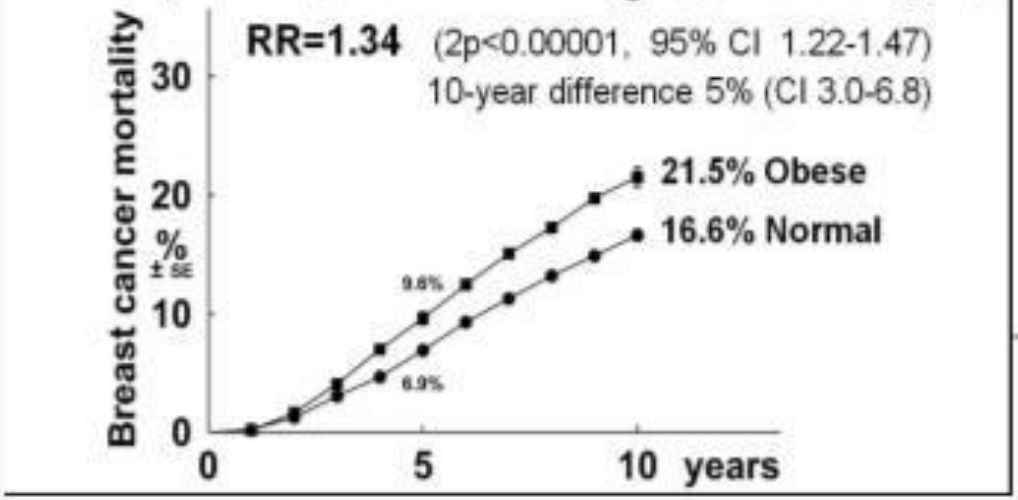
Event	Normal Weight Patients				Overweight and Obese Patients			
	Tamoxifen(n =542)		Anastrozole(n =569)		Tamoxifen(n =294)		Anastrozole(n =279)	
	No.	%	No.	%	No.	%	No.	%
All events	56	10.3	51	9.0	30	10.2	42	15.1
Distant	26	4.8	29	5.1	15	5.1	25	9.0
Deaths	16	3.0	20	3.5	8	2.7	22	7.9

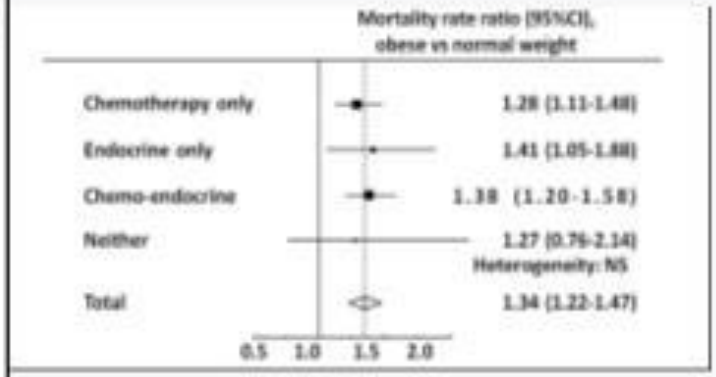
Pfeiler et al. JCO 2011;29:2653-2659

BMI and ER+ Premenopausal Breast Cancer

Pre-menopausal ER+ disease: 20,000 women

Obese (BMI ≥ 30) **vs normal weight** (BMI 20-25 kg/m^2)



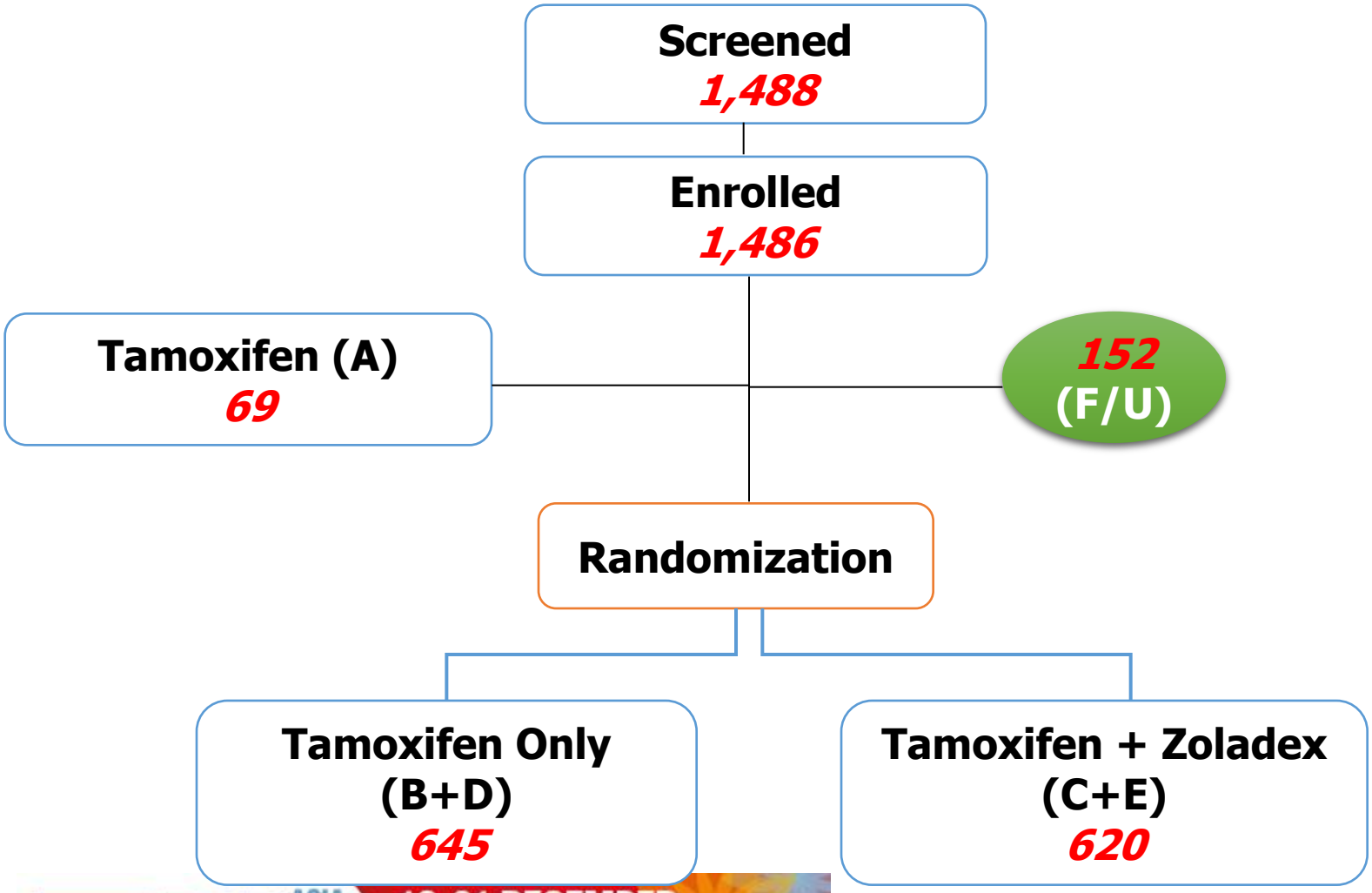


Pan, H et al. 2014 ASCO Annual Meeting

Pre-menopausal endocrine therapy

- aTTom: 10 years> 5 years of Tamoxifen
  - 25% reduced recurrence risk — 2.6% absolute Δ
  - 23% reduced breast cancer death — 1.4% absolute Δ
- ATLAS: 10 years> 5 years of Tamoxifen
  - 25% reduced recurrence risk — 3.7% absolute Δ
  - 29% reduced breast cancer death — 2.8% absolute Δ
- SOFT/TEXT: OS+AI> OS+ Tamoxifen
  - 34% reduced recurrence risk — 4 % absolute Δ
  - No change in overall survival

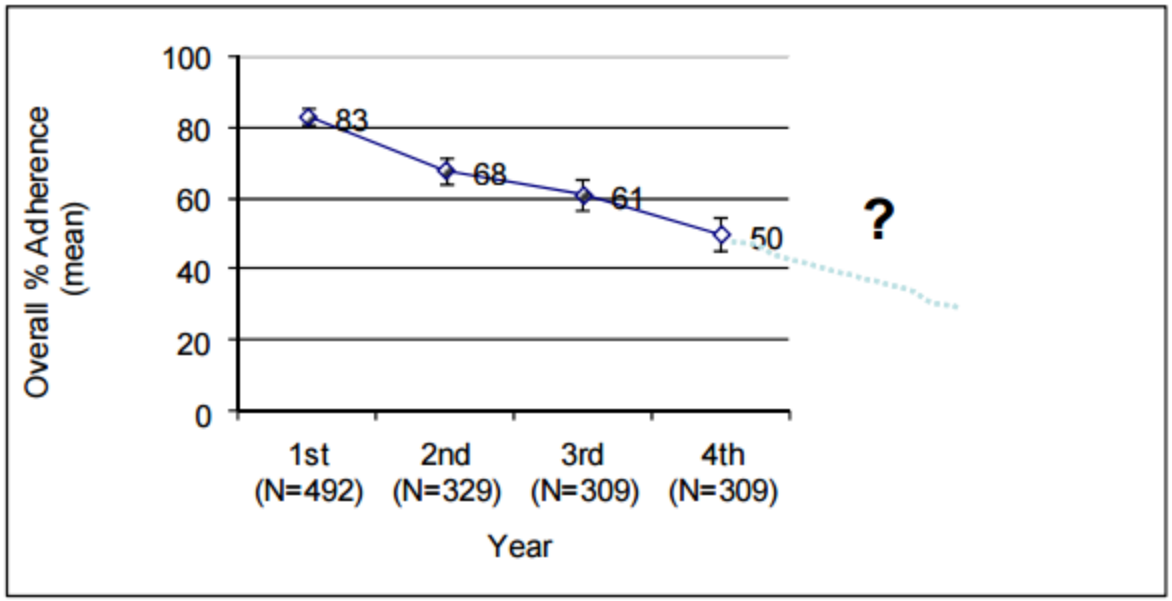
A randomised phase III study for evaluating the role of the Addition of ovarian Suppression (OFS) to Tamoxifen in young women (≤45 years) with hormone-sensitive breast cancer who Remain in premenopause or Regain menstruation After chemotherapy (ASTRRA)



Options after 5 years of TAM

Who remain premenopausal	Who are postmenopausal
• Extended TAM is a new option • Discuss side effects and personal cost • Ovarian suppression	• Switching from TAM to an AI as extended adjuvant endocrine Tx [MA 17, NSABP B33, ABCSG-6a] • Use of additional TAM if contraindication, intolerance to AI • No data to support an AI for longer than 5yrs [MA17R, NSABP B42, IDEAL, ABCSG-16]

Adherence to Adjuvant Hormonal Therapy Wanes Over Time

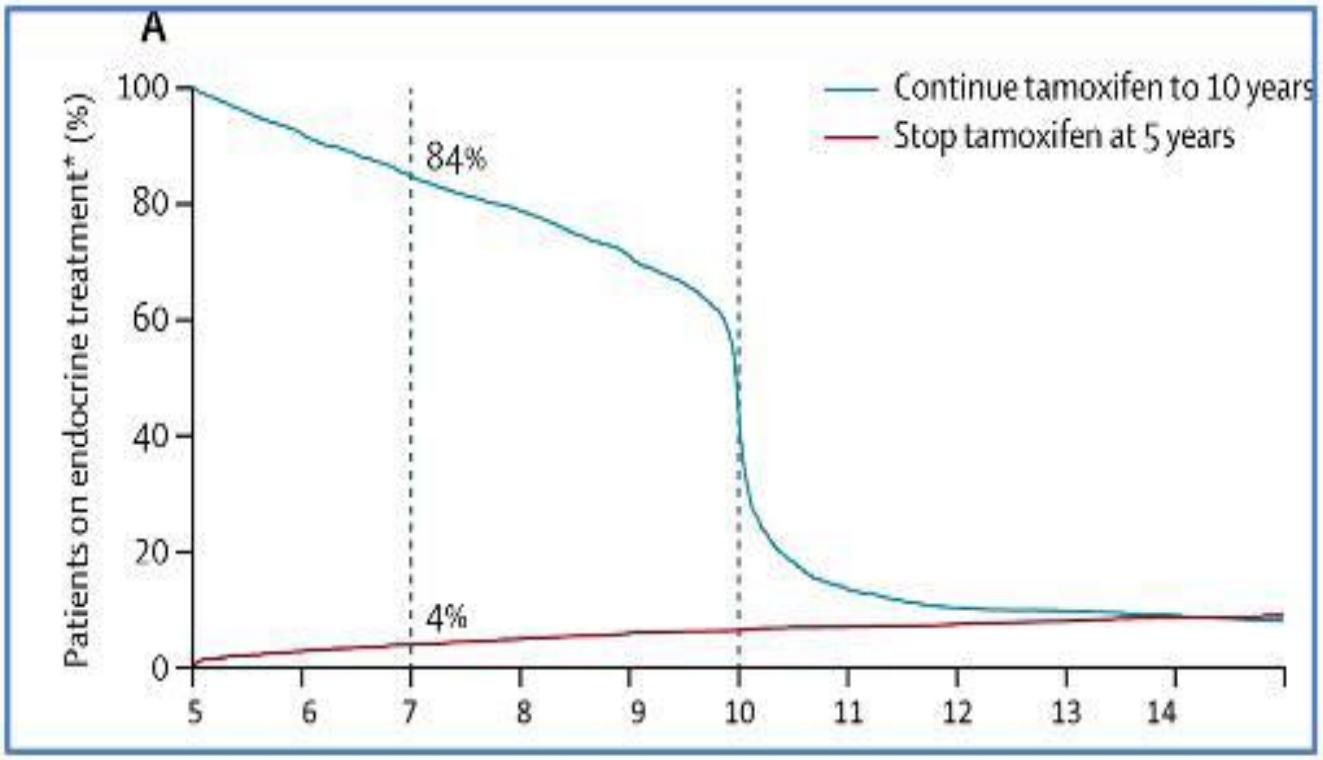


Average Adherence in New Jersey Medicare/Medicaid Population in Years 1-4 of Tamoxifen

Partridge *et al*. JCO 2003

Poor tamoxifen compliance in ATLAS

San Antonio Breast Cancer Symposium
December 8-12, 2015



Davies, Lancet 2013

Critical questions: patient selection

- Can we identify women at high risk of recurrence?
- Within that group, can we predict who will truly benefit from additional endocrine therapy?

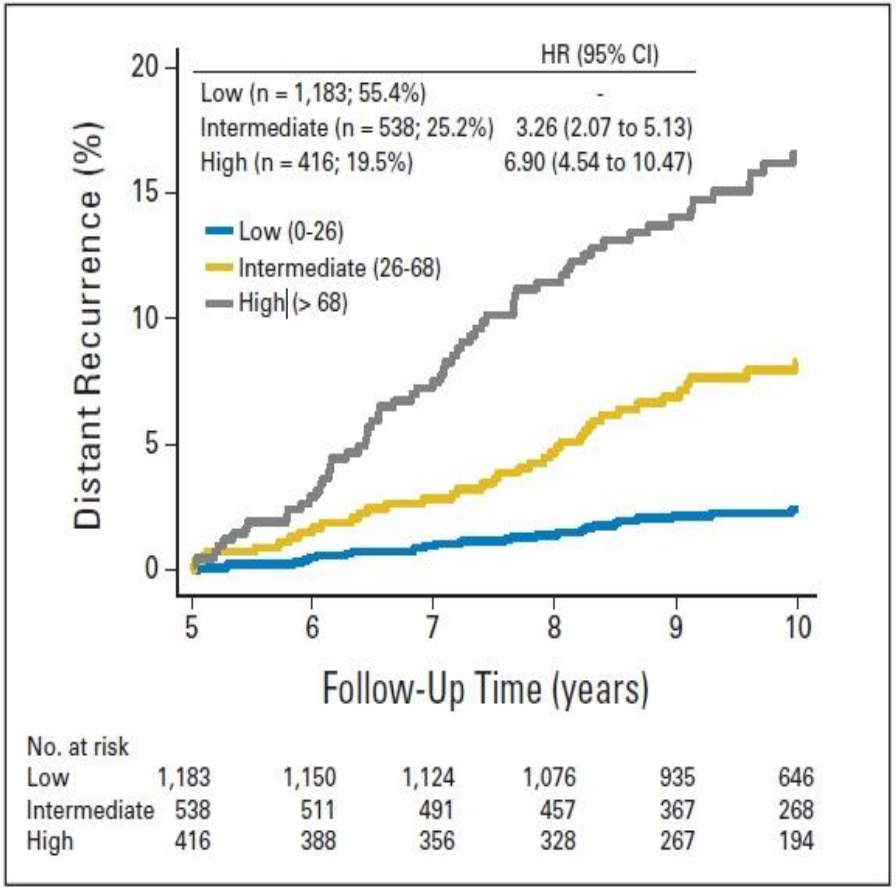
Potential molecular tests for late recurrence

Test	Abbreviation	Description
Clinical treatment score	CTS	T, N, grade, age, treatment
Immunohistochemical Score 4	IHC4	IHC for ER, PR, Ki67, HER2
Oncotype Dx	RS	21 gene assay
Prosigna risk of recurrence	ROR	PAM 50
Breast cancer index	BCI	HOXB13/IL17BR
EndoPredict	EPClin	12 gene assay

Sestak et al, J Clin Oncol, 2014

PAM 50 risk of recurrence (ROR) score for late distant recurrence

N=2137 women from TrasATAC & ABCSG 8 trials who were recurrence-free 5 yrs after diagnosis



Sestak et al, J Clin Oncol, 2014

Oncotype recurrence score in node negative patients who received tamoxifen

N=668 treated with Tamoxifen x 5 yrs in NSABP B-14

Average 10 yr distant recurrence	
Low <18	6.8% (4.0-9.6)
Intermediate 18-30	14.3% (8.3-20.3)
High >30	30.5% (23.6-37.4)

Paik e al, NEJM 2004

What we know

Type	Factor	Early recurrence	Late recurrence
Stage	Tumor size	+	+
	Nodal status	+	+
Histopathology	Grade	+	+
	Ki-67	+	+
	ER/PR expression	+	+
	IHC4	+	+
Signatures	Recurrence score	+	+
	Intrinsic subtype	+	+
	ROR	+	+
	BCI	+	+
	Endopredict	+	+

Mayer et al Breast 2015

General suggestions

- Take into account the *a priori* risk of the patient
- To which treatment will she remain adherent?
- Ovarian suppression is slightly less toxic for women who have completed chemotherapy

Clinical recommendations in pre-menopausal women

- Consider OFS+AI therapy
  - age<35
  - breast cancer that required chemotherapy
  - positive lymph nodes
- **Consider 10yrs of tamoxifen therapy for**
  - high risk biology
  - remains pre-menopausal after 5 years of tamoxifen

What we don’t know

- Who will have an early vs. late recurrence?
- Who will benefit from a longer period of endocrine therapy?
- Who will benefit from ovarian suppression+AI over tamoxifen?

Annals of Oncology 26: 1533–1546, 20
doi:10.1093/annonc/mdv22
Published online 4 May 20

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

A. S. Coates[1], E. P. Winer[2], A. Goldhirsch[3*], R. D. Gelber[4], M. Gnant[5], M. Piccart-Gebhart[6], B. Thürlimann[7], H.-J. Senn[8] & Panel Members[†]

[1]International Breast Cancer Study Group, University of Sydney, Sydney, Australia; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [3]International Breast Cancer Study Group, Program of Breast Health (Senology), European Institute of Oncology, Milan, Italy; [4]International Breast Cancer Study Group Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [5]Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [6]Internal Medicine/Oncology, Institut Jules Bordet, Brussels, Belgium; [7]Breast Center, Kantonsspital St Gallen, St Gallen; [8]Tumor and Breast Center ZeTuP, St Gallen, Switzerland

Endocrine therapy-premenoopausal

- Factors arguing for including ovarian function suppression (OFS) are: (% yes)

Involvement of 4 or more LN	90%
Age≤ 35 years	81%
Adverse result of multi-gene test	60%
Grade 3	56%

Coates AS et al Ann Oncol 2015

Endocrine therapy-premenopausal

- Factors arguing for use of OFS+AI rather than OFS+ TAM are : (% yes)

Involvement of 4 or more LN	**93%**
Age≤ 35 years	66%
Adverse result of multi-gene test	59%
Grade 3	57%

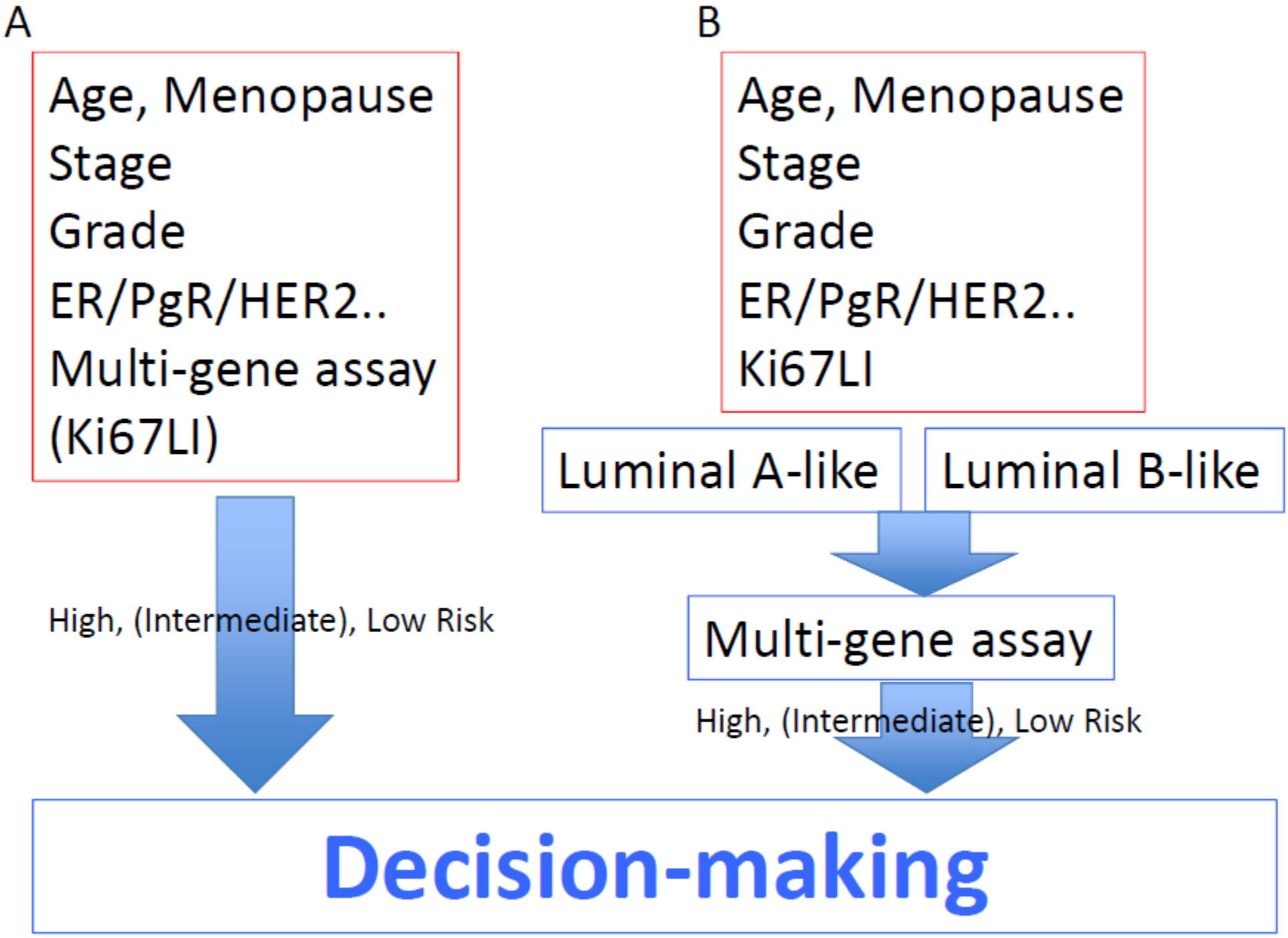
Coates AS et al Ann Oncol 2015

Multigene assay:chemotherapy-luminal B

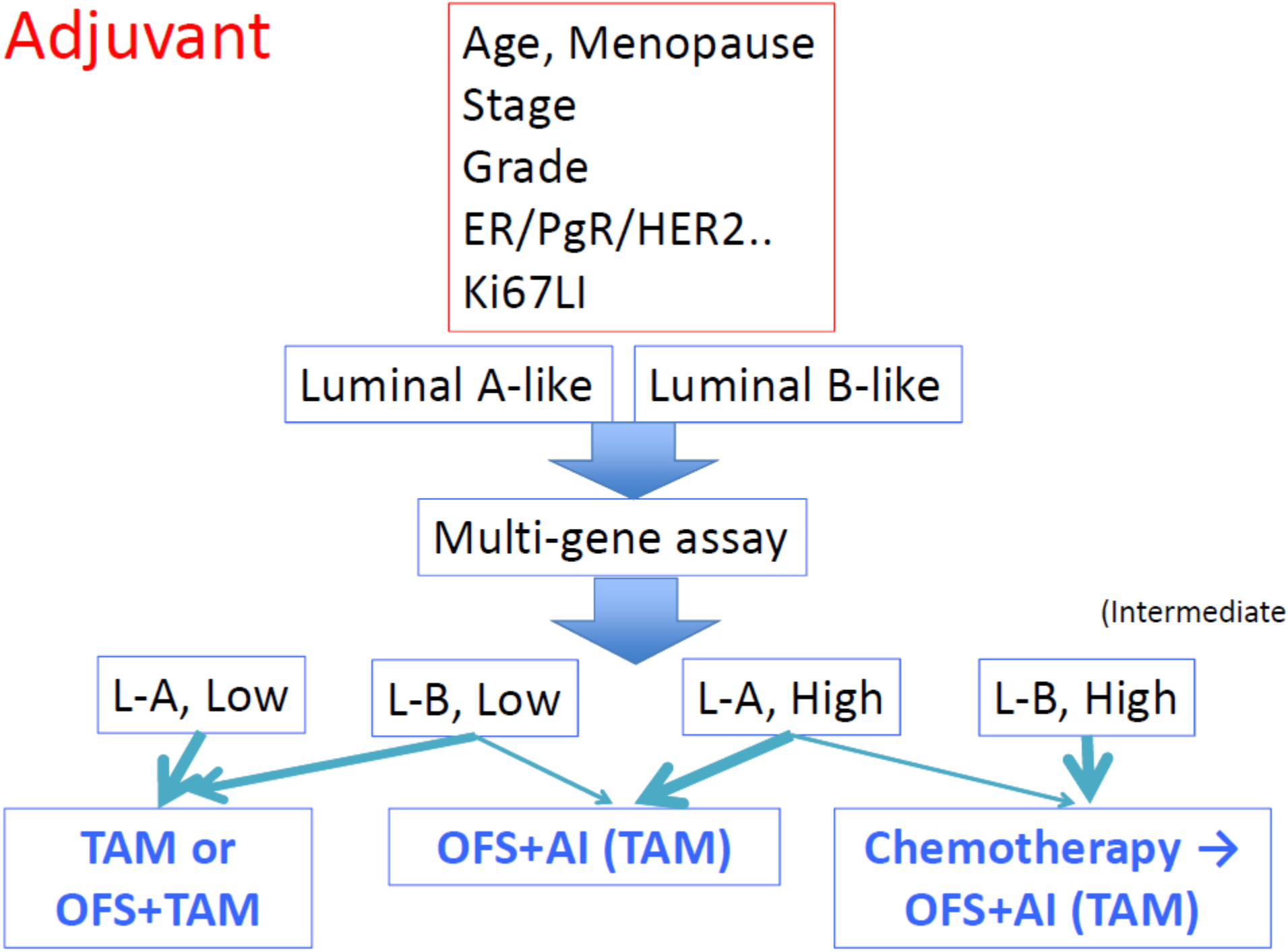
- Chemotherapy may be omitted for patients with luminal B-like disease: (% yes)

Oncotype DX RS low	95%
RS intermediate	36%
Mammaprint low risk	72%
PAM 50 ROR low	83%
Endopredict low risk	70%

Coates AS et al Ann Oncol 2015


A
Age, Menopause
Stage
Grade
ER/PgR/HER2..
Multi-gene assay
(Ki67LI)
High, (Intermediate), Low Risk
B
Age, Menopause
Stage
Grade
ER/PgR/HER2..
Ki67LI
Luminal A-like
Luminal B-like
Multi-gene assay
High, (Intermediate), Low Risk
Decision-making

Adjuvant


Age, Menopause
Stage
Grade
ER/PgR/HER2..
Ki67LI
Luminal A-like
Luminal B-like
Multi-gene assay
(Intermediate
L-A, Low
L-B, Low
L-A, High
L-B, High
TAM or
OFS+TAM
OFS+AI (TAM)
Chemotherapy →
OFS+AI (TAM)

Many unanswered questions

- Should BMI be used to select for a specific agent (Tamoxifen vs AI)
- In AI+OFS treated patients, is there a critical estradiol threshold that should be achieved?
- What are the long term implications of profound estrogen deprivation in young women?

Conclusions

- Optimal duration is a moving target and highly dependent on patient factors.
- The benefits of extended endocrine therapy options or complete estrogen deprivation must be carefully weighed with potential long term side effects.
- We need to continue to work on ways to better support our patients to make these decisions not only at diagnosis but also in long term survivor ship.
- Prediction/prevention of late recurrence should be a research priority.

Acknowledgement

- 2014 SABCS Review in Korea

  -Kim TY
- 2014 GBCC

  -Noh WC
- 2015 TIBCS

  -Partridge A

  -Francis P

  -Toi M
- 2015 SABCS

  - Goetz MP

  - Niravath P