Adjuvant endocrine therapy:

What and how long?

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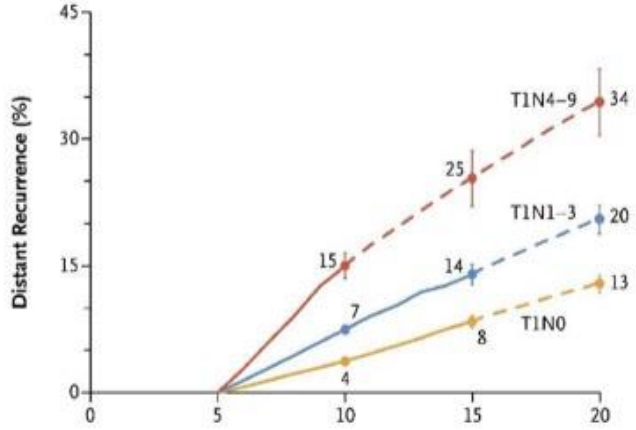
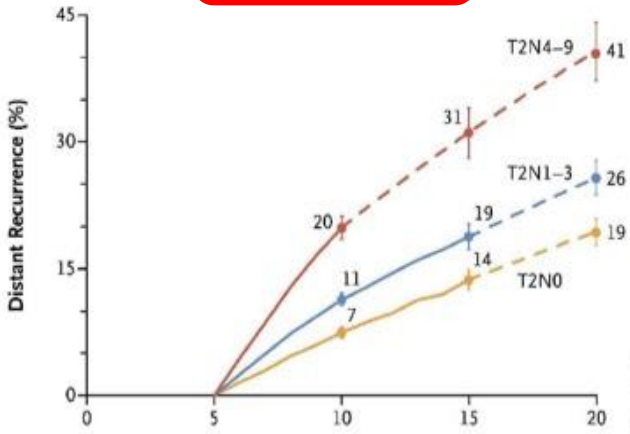
Adjuvant endocrine therapy (ET) in ER+ disease

- In women given 5 years adjuvant ET, appreciable risks continue during years 5-20, even for T1N0
- After 5 years of ET for N0 disease, the risks of distant recurrence during years 5-20 were reported to be T1N0: 13% & T2N0: 19%

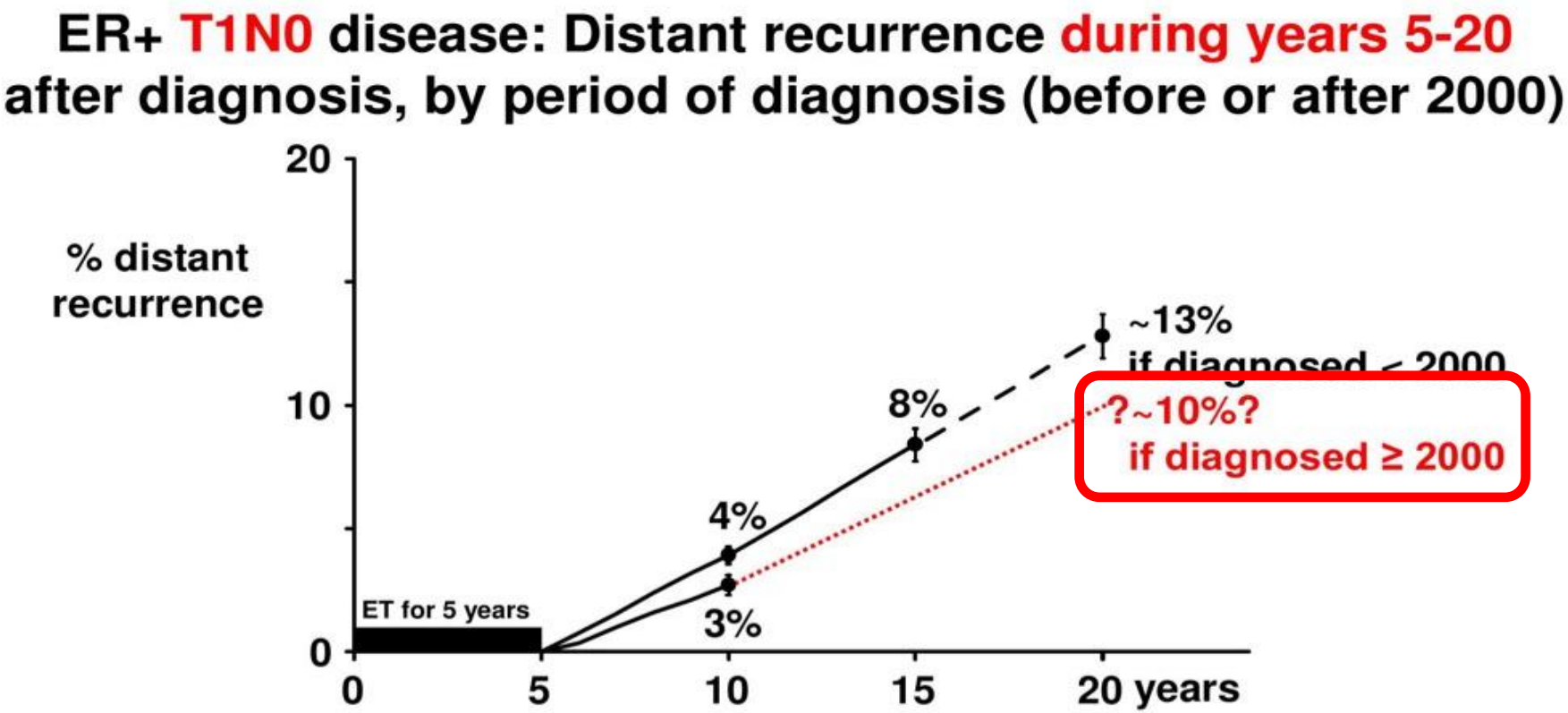




(EBCTCG *NEJM* 2017; 377: 1836)

EBCTCG. NEJM 2017

Clinical implication of late recurrence in HR positive breast cancer



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**

General Principles in Adjuvant Endocrine Therapy AGO ++

- Adjuvant endocrine therapy is divided into initial therapy (years 0-5) and extended adjuvant therapy (EAT, years 6-15).
- Standard treatment duration is 5 years.
- Extended treatment should be considered based on individual benefits and risks.
- Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability and risk of recurrence.
- Switch to another better tolerated endocrine treatment (Tam or AI) is better than to stop.
- AI should be used as first treatment in postmenopausal patients especially in cases of lobular cancers and high risk of recurrence.
- To date, there is no sufficiently validated biomarker that identifies patients for early versus late recurrence.

Overview of studies regarding EAT

Premenopausal → Premenopausal	Premenopausal → Postmenopausal	Postmenopausal
5 yrs tamoxifen	5 yrs tamoxifen	5 yrs tamoxifen 5 yrs tamoxifen → AI 5 yrs AI
↓	↓	↓
tamoxifen	**Aromatase inhibitors**	**Aromatase inhibitors**
aTTom	MA17	SALSA (2004-2010)
ATLAS		GIM 4 (2005-2015)
		NSABP B-42 (2006-2010)
		DATA (2006-2009)
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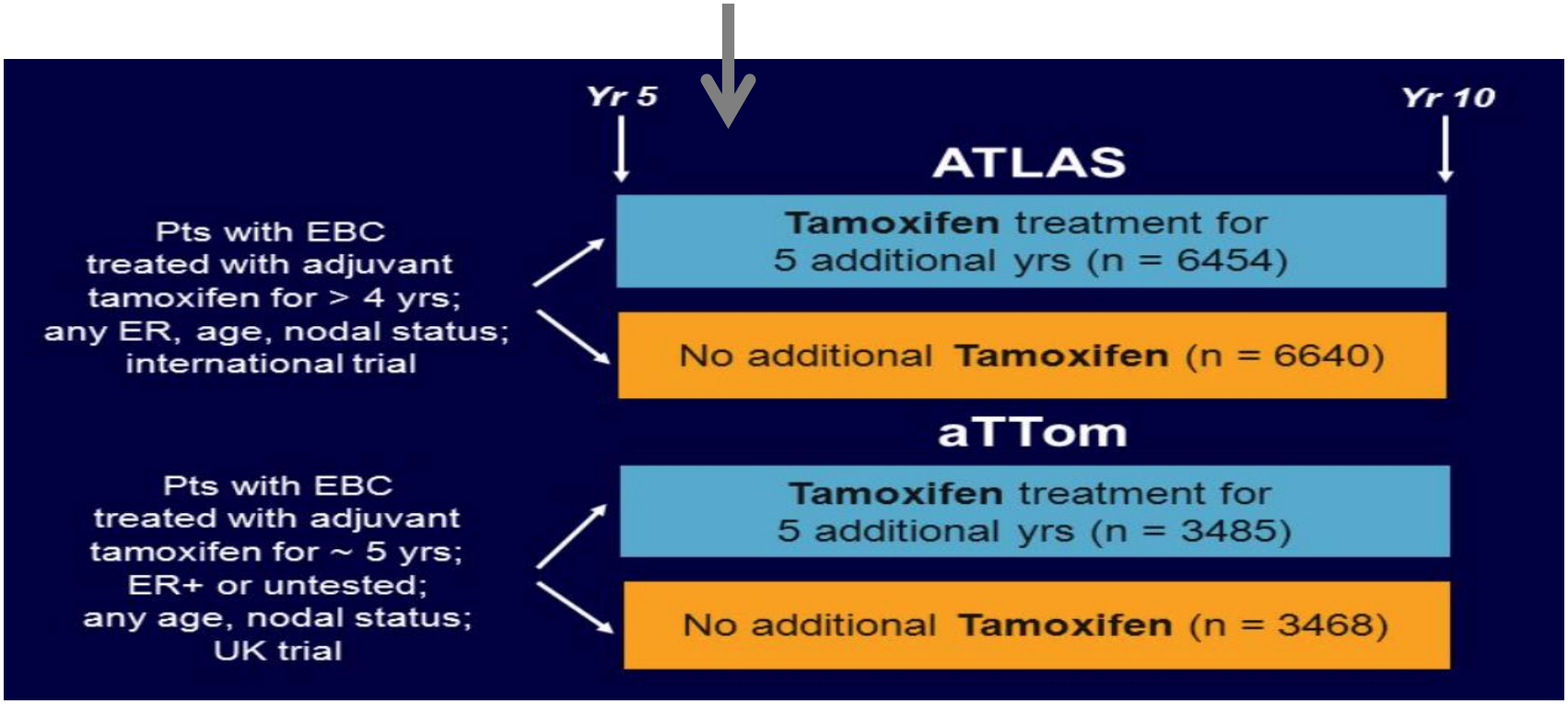
		MA.17R (2009-2015)

Design of ATLAS and aTTom



Pooled analysis ATLAS + aTTom: Breast Cancer Mortality

10 vs 5 yrs BC mortality RR by period in ER+ve (or unknown) patients	ATLAS[1] Er+ve n=10543* HR (95% CI)	aTTom[2] 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

Also significant improvements in **Overall Survival**

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

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

Gray RG et al. ASCO 2013 (Abstract 5); [1]ATLAS: Smith ASCO 2014; [2]aTTom: Gray ASCO 2013

EBCTCG. NEJM 2017

Side-effects in ATLAS

Select Adverse Events (Any ER Status)

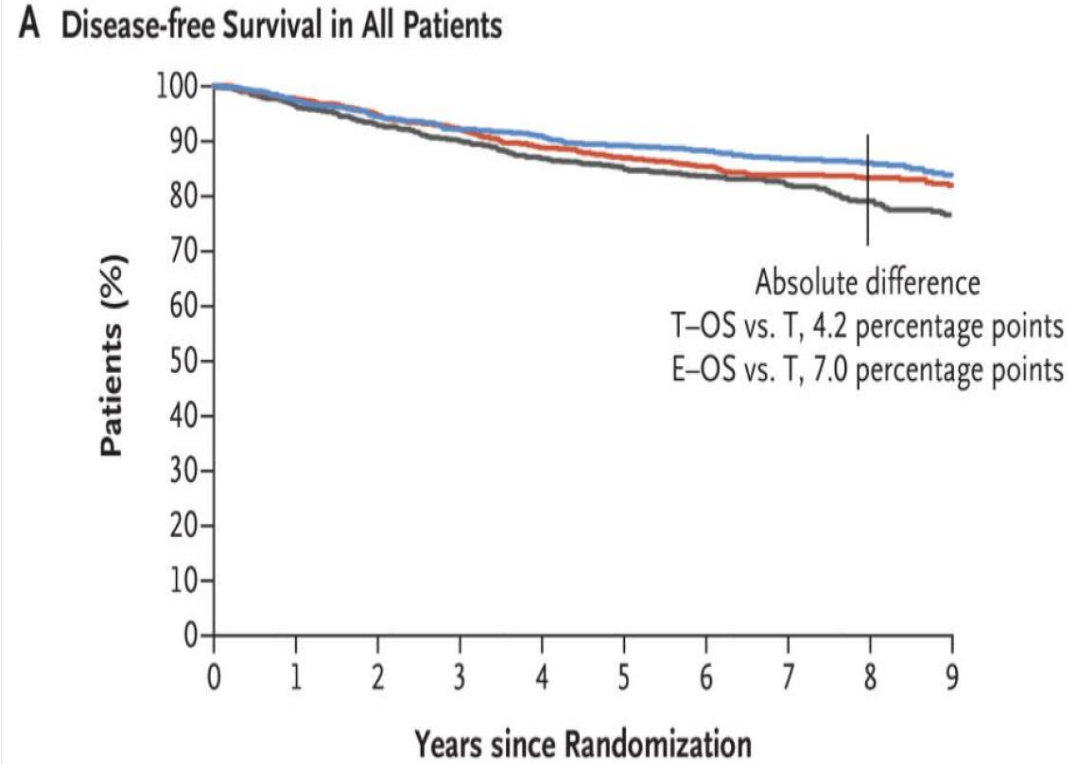
Event	Continue TAM to 10 y (no.)	Stop TAM at 5 y (no.)	Event RR (2*p*-value)
Second cancer incidence			
Contralateral BC	419	467	0.88 (0.05)
Endometrial cancer*	116	63	1.74 (0.0002)
Nonneoplastic disease†			
Stroke	130	119	1.06 (0.63)
Pulmonary embolus	41	21	1.87 (0.01)
Ischemic heart disease	127	63	0.76 (0.02)

* Mainly endometrial adenocarcinoma but includes all other uterine tumors except cervical cancer; uterine tumors exclude those with recorded hysterectomy at study entry

† Ever hospitalized or died

Davies et al., Lancet 2012

Escalation of ET in premenopausal women through GnRH (SOFT)

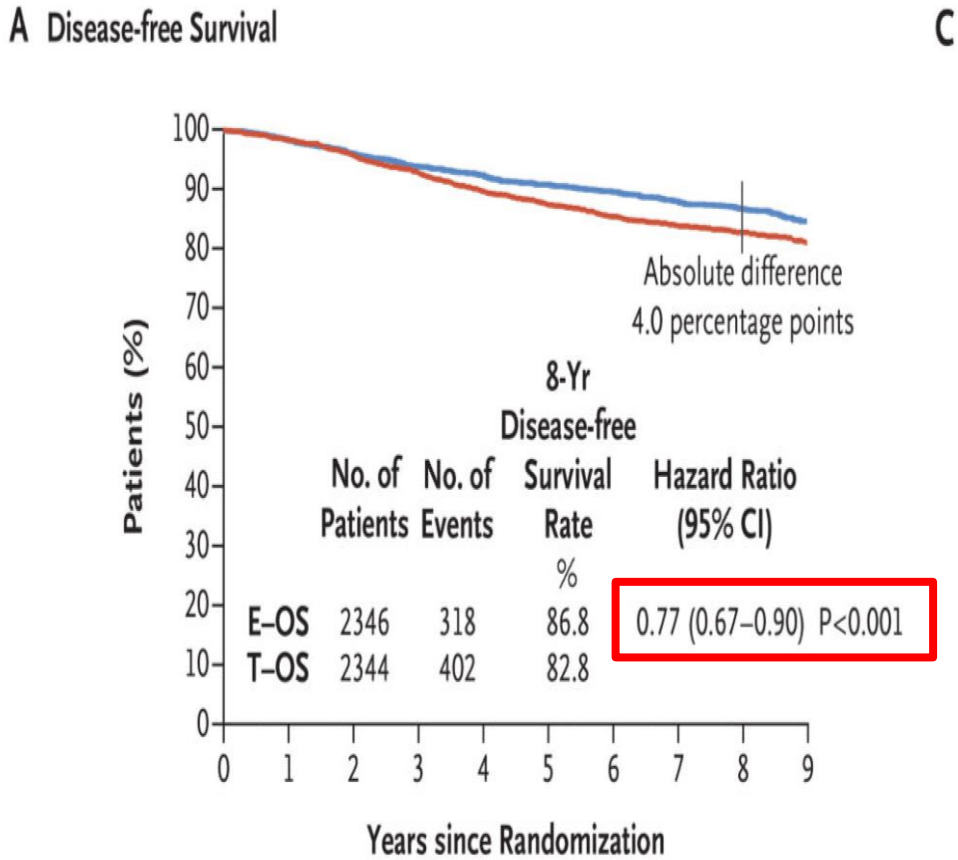


No. at Risk					
T	957	858	771	522	221
T–OS	968	888	795	558	252
E–OS	956	875	805	562	246

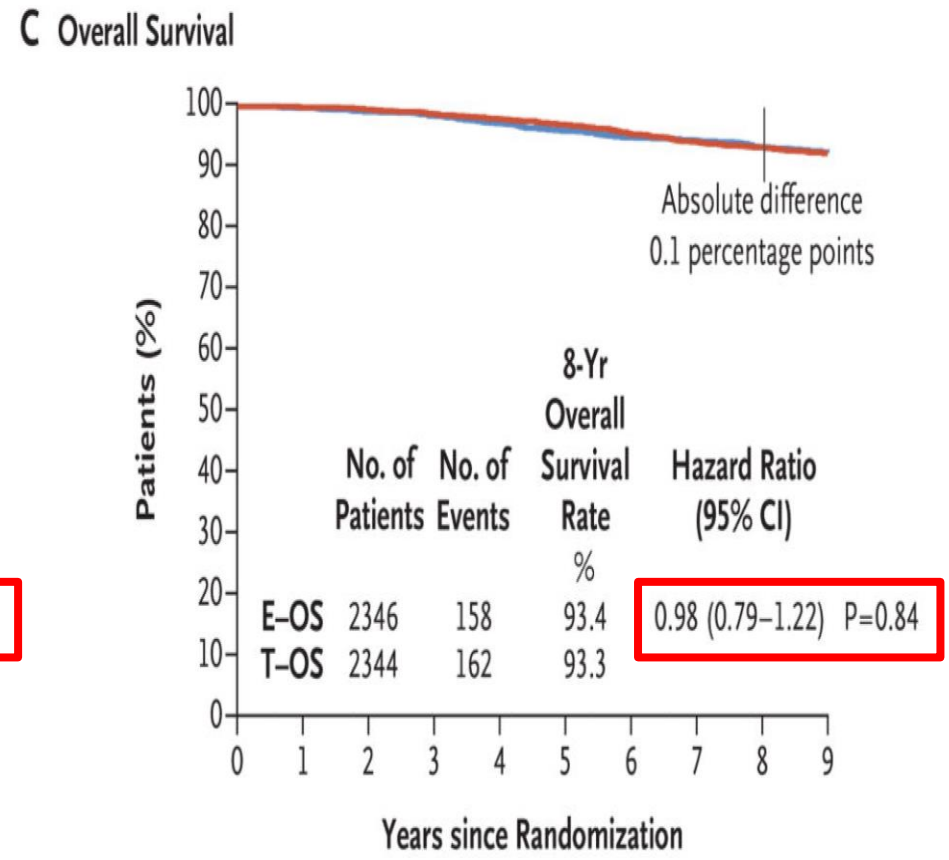
	No. of Patients	No. of Events	8-Yr Disease-free Survival Rate %	Hazard Ratio (95% CI) vs. T
T	1018	208	78.9	
T–OS	1015	167	83.2	0.76 (0.62–0.93)
E–OS	1014	143	85.9	0.65 (0.53–0.81)

Francis et al., NEJM 2019

Escalation of ET in premenopausal women through GnRH (SOFT / TEXT)



No. at Risk					
E–OS	2232	2073	1931	1391	861
T–OS	2257	2066	1866	1337	834



No. at Risk					
E–OS	2289	2224	2101	1551	988
T–OS	2308	2238	2123	1547	988

Francis et al., NEJM 2019

Side-effects of escalated endocrine therapy in premenopausal women (SOFT / TEXT)

Adverse Event	Tamoxifen (N = 1005)		Tamoxifen plus Ovarian Suppression (N = 2326)		Exemestane plus Ovarian Suppression (N = 2317)	
	Any Event	Grade 3 or 4 Event	Any Event	Grade 3 or 4 Event	Any Event	Grade 3 or 4 Event
	number of patients (percent)					
Any targeted adverse event	962 (95.7)	247 (24.6)	2295 (98.7)	721 (31.0)	2288 (98.7)	748 (32.3)
Allergic reaction or hypersensitivity	35 (3.5)	2 (0.2)	110 (4.7)	9 (0.4)	122 (5.3)	12 (0.5)
Injection-site reaction	4 (0.4)	0	189 (8.1)	1 (<0.1)	174 (7.5)	1 (<0.1)
Hot flushes	808 (80.4)	78 (7.8)	2175 (93.5)	284 (12.2)	2141 (92.4)	234 (10.1)
Depression	476 (47.4)	41 (4.1)	1195 (51.4)	108 (4.6)	1197 (51.7)	95 (4.1)
Sweating	492 (49.0)	NA	1391 (59.8)	NA	1286 (55.5)	NA
Insomnia	470 (46.8)	30 (3.0)	1383 (59.5)	105 (4.5)	1375 (59.3)	89 (3.8)
Fatigue	612 (60.9)	34 (3.4)	1496 (64.3)	70 (3.0)	1450 (62.6)	75 (3.2)
Hypertension	181 (18.0)	57 (5.7)	550 (23.6)	188 (8.1)	564 (24.3)	168 (7.3)
Cardiac ischemia or infarction†	5 (0.5)	4 (0.4)	10 (0.4)	6 (0.3)	17 (0.7)	7 (0.3)
Thrombosis or embolism	22 (2.2)	17 (1.7)	53 (2.3)	47 (2.0)	27 (1.2)	20 (0.9)
Nausea	241 (24.0)	0	692 (29.8)	14 (0.6)	747 (32.2)	17 (0.7)
Musculoskeletal symptom	703 (70.0)	67 (6.7)	1809 (77.8)	132 (5.7)	2082 (89.9)	263 (11.4)
Osteoporosis	138 (13.7)	1 (0.1)	648 (27.9)	7 (0.3)	977 (42.2)	10 (0.4)
Fracture	53 (5.3)	8 (0.8)	140 (6.0)	23 (1.0)	179 (7.7)	37 (1.6)
Vaginal dryness	426 (42.4)	NA	1144 (49.2)	NA	1245 (53.7)	NA
Decreased libido	434 (43.2)	NA	981 (42.2)	NA	1056 (45.6)	NA
Dyspareunia	242 (24.1)	16 (1.6)	636 (27.3)	35 (1.5)	733 (31.6)	56 (2.4)
Urinary incontinence	166 (16.5)	6 (0.6)	433 (18.6)	9 (0.4)	317 (13.7)	9 (0.4)
CNS cerebrovascular ischemia	6 (0.6)	4 (0.4)	10 (0.4)	7 (0.3)	6 (0.3)	5 (0.2)
CNS hemorrhage	15 (1.5)	0	26 (1.1)	2 (0.1)	19 (0.8)	1 (<0.1)
Glucose intolerance‡	18 (1.8)	4 (0.4)	68 (2.9)	23 (1.0)	63 (2.7)	15 (0.6)
Hyperglycemia‡	20 (2.0)	1 (0.1)	92 (4.0)	20 (0.9)	71 (3.1)	14 (0.6)

Francis et al., NEJM 2019

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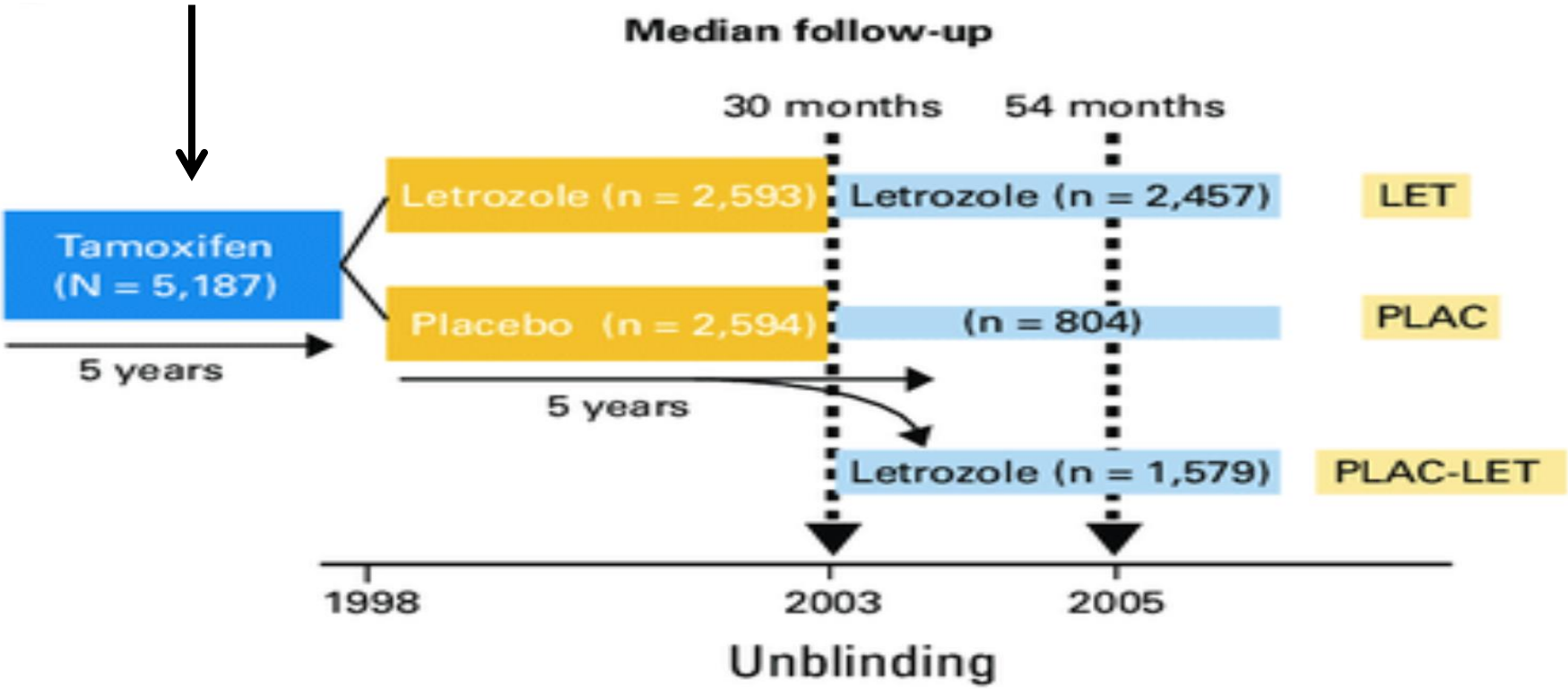
		MA.17R (2009-2015)

Design of MA.17 (postmenopausal women)

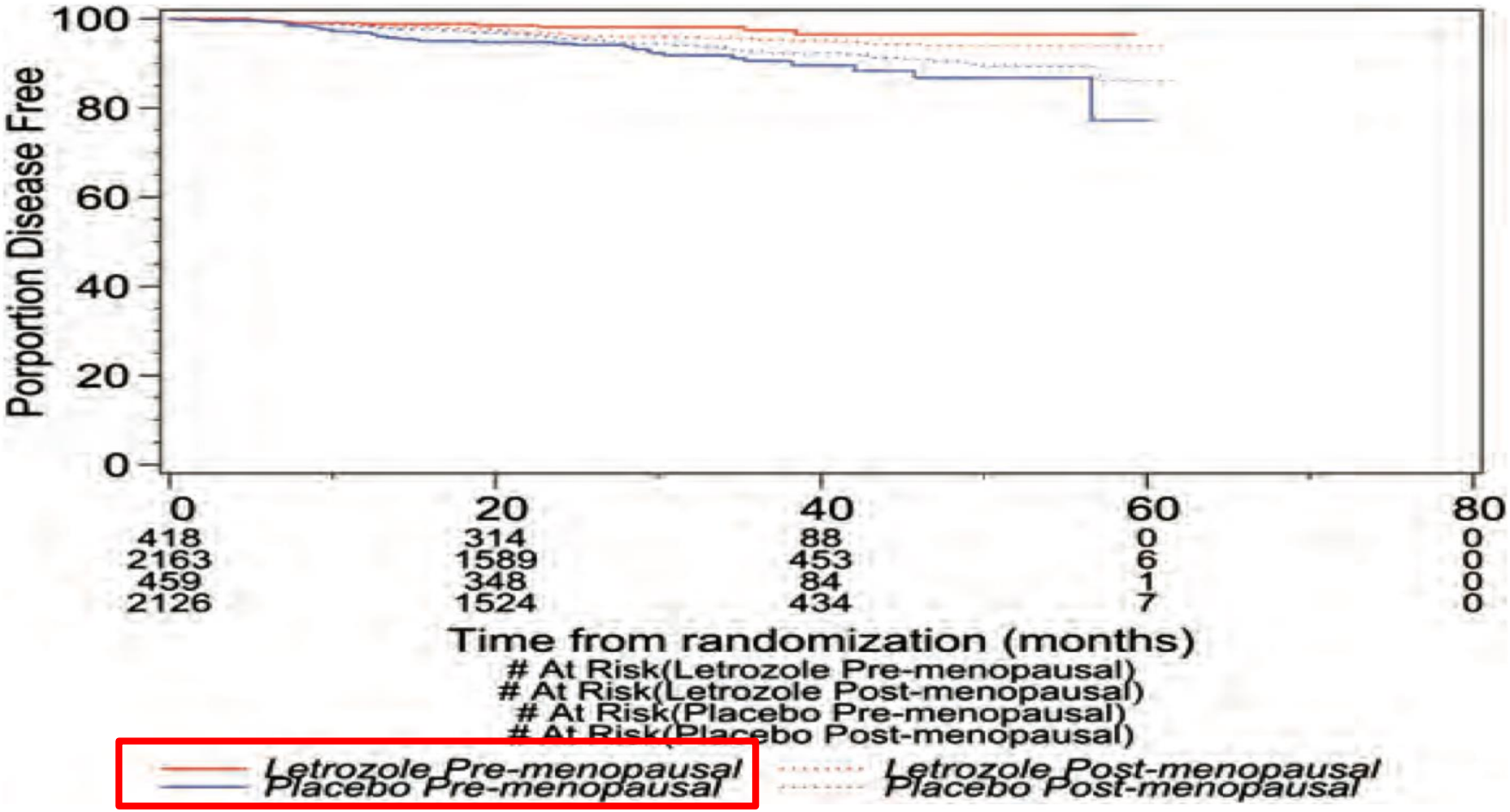
Menopausal status prior to initiation of tamoxifen:

- **Premenopausal (n = 889)**
- **Postmenopausal (n = 4277)**



Goss P et al., J Natl Cancer Inst 2005

Results of MA.17 (effect of prior menopausal status)



Goss P et al., Ann Onc 2012

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Premenopausal Patients Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford LoE	Oxford GR	AGO
In case of high risk of recurrence			
▪ 5 years Tamoxifen after 5 years Tamoxifen)	1a	A	++
▪ 2–5 years AI after 5 years Tamoxifen in initially premenopausal patients with validated postmenopausal status in the course of therapy	1b	B	+
▪ 5 years Tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

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Decision criteria for extended therapy

Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and /or T2/T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

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Clinical trials of EAT

Trial	Sample size	Median FU (yrs)	Treatment arm	Yrs 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	DFS HR (95%CI)	OS HR (95%CI)
MA.17[34]	5187	5.3	I																0.68 (0.56-0.83)	0.99 (0.79-1.24)
			C																	
NSABP B-33[33]	1598	2.5	I																0.68 (0.45-1.03)	NR
			C																	
ABCSG 6a[32]	856	5.2	I																0.62 (0.40-0.96)*	0.89 (0.53-1.34)
			C																	
ATLAS[26]	6846	7.6	I																0.84 (0.76-.93)*	0.87 (0.78-0.97)
			C																	
aTTom[28,27]	6953	~9.0	I																0.86 (0.77-0.96)*	0.94 (0.86-1.03)
			C																	
MA.17R[6]	1918	6.3	I																0.80 (0.63-1.01)	0.97 (0.73-1.28)
			C																	
DATA[3]	1660	4.4	I																0.79 (0.62-1.02)	0.91 (0.65-1.29)
			C																	
IDEAL[4]	1824	6.6	I																0.92 (0.74-1.16)	1.04 (0.78-1.38)
			C																	
NSABP B-42[5]	3966	6.9	I																0.85 (0.73-0.99)	1.15 (0.92-1.44)
			C																	
SOLE[36]	4884	5.0	I						Intermittent 9 months per year										1.08 (0.93-1.26)	0.85 (0.68-1.06)
			C						Continuous											

Red: tamoxifen. Gray: aromatase inhibitor. Diagonal lines: either tamoxifen or an aromatase inhibitor.

FU follow-up, *I* intervention arm, *C* control arm, *yrs.* years, *DFS* disease-free survival, *HR* hazard ratio, *CI* confidence interval, *OS* overall survival

*No data on DFS available, data on RFS reported

Hellemond et al., Curr Treat Options in Oncol 2018

Metaanalysis regarding EAT with AI

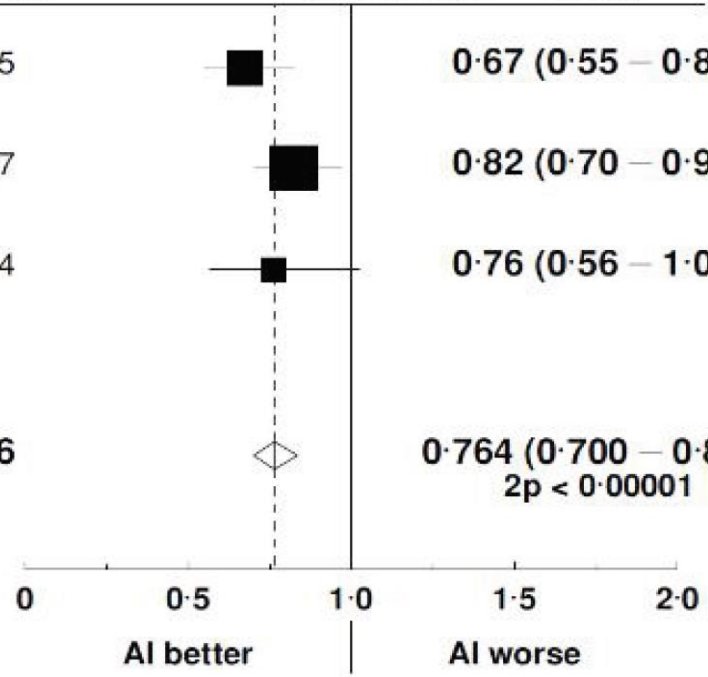
Any third generation AI (Exemestane, Anastrozole, Letrozole)
Vs.
No further adjuvant endocrine therapy

Trial (recruitment period)	(a) Tamoxifen alone	(b) Tamoxifen then AI	(c) AI alone
ABCSG VIa (1990–1995)	442	393	-
MA.17 (1998–2002)	4959	-	-
NSABP B-33 (2001–2003)	1550	-	-
ATENA (2001–2005)	358	-	-
SALSA (2004–2010)	-	3392	-
GIM 4 (2005–2015)	-	2031	-
NSABP B-42 (2006–2010)	-	1532	2387
DATA (2006–2009)	-	1827	-
LATER (2007–2012)	174	138	39
IDEAL (2007–2011)	-	1263	510
AERAS (2007–2012)	-	(≈255)	(≈1442)
MA.17R (2009–2015)	-	1473	386
All trials (% with data)	**7,483 (100%)**	**12,304 (98%)**	**4764 (70%)**
Median follow-up (yrs)	**4.9**	**6.1**	**6.5**

Gray et al. SABCS 2018

Effect on recurrence by prior endocrine therapy

Prior therapy	Events/Women Allocated AI	Events/Women Allocated control	AI events Logrank O–E	AI events Variance of O–E	Ratio of annual event rates Ratio AI : Control (& CI)
(a) Tamoxifen alone	272/3718 (7·3%)	383/3765 (10·2%)	–61·7	155·5	0·67 (0·55 – 0·83)
(b) Tamoxifen then AI	510/5664 (9·0%)	606/5723 (10·6%)	–51·6	267·7	0·82 (0·70 – 0·97)
(c) AI alone	134/1661 (8·1%)	174/1661 (10·5%)	–20·4	74·4	0·76 (0·56 – 1·02)
Total	**916/11043 (8·3%)**	**1163/11149 (10·4%)**	**–133·7**	**497·6**	**0·764 (0·700 – 0·835) 2p < 0·00001**



99% or 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2_2 = 4{\cdot}1$; $p > 0{\cdot}1$; NS

Treatment effect 2p < 0·00001

Results of AERAS

Postmenopausal women with primary breast cancer who had received 4 years 9 months to 5 years 2 months of adjuvant therapy with Anastrozole

Amendment: postmenopausal women who had received Tamoxifen and then received Anastrozole for more than 2 years, a total of 5 years of adjuvant therapy, were also allowed.

R

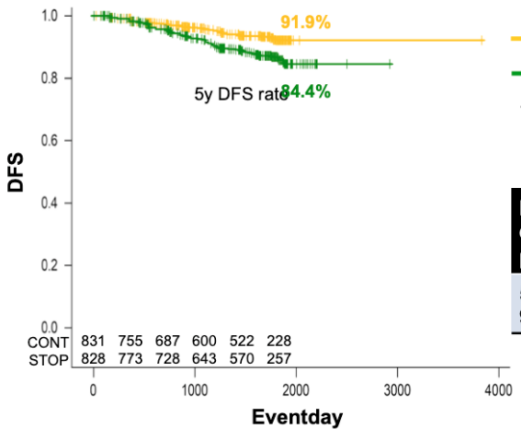
1:1
1697 Patients randomized in ITT, Nov 2007–Nov 2012

CONTINUAL GROUP
Extended use of Anastrozole for an additional **5** years

STOP GROUP
No extended use of Anastrozole

FOLLO W UP (median follow up period: 4.9Y)

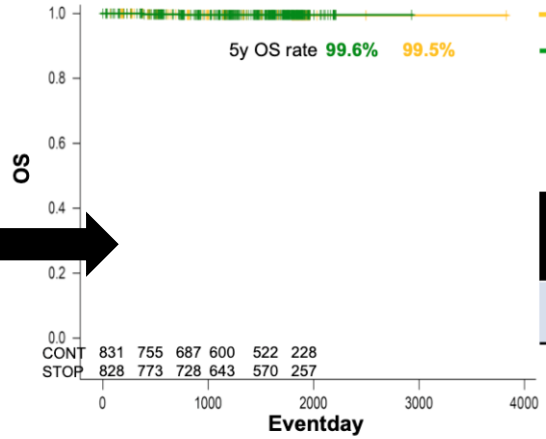
Time from randomization to first DFS event



CONT
STOP
+ Censored

T1	51,8%
N1/2	20,8%

Number of events/ patients	Hazard ratio	p-value
51/831 98/828	0.548	p=0.0004

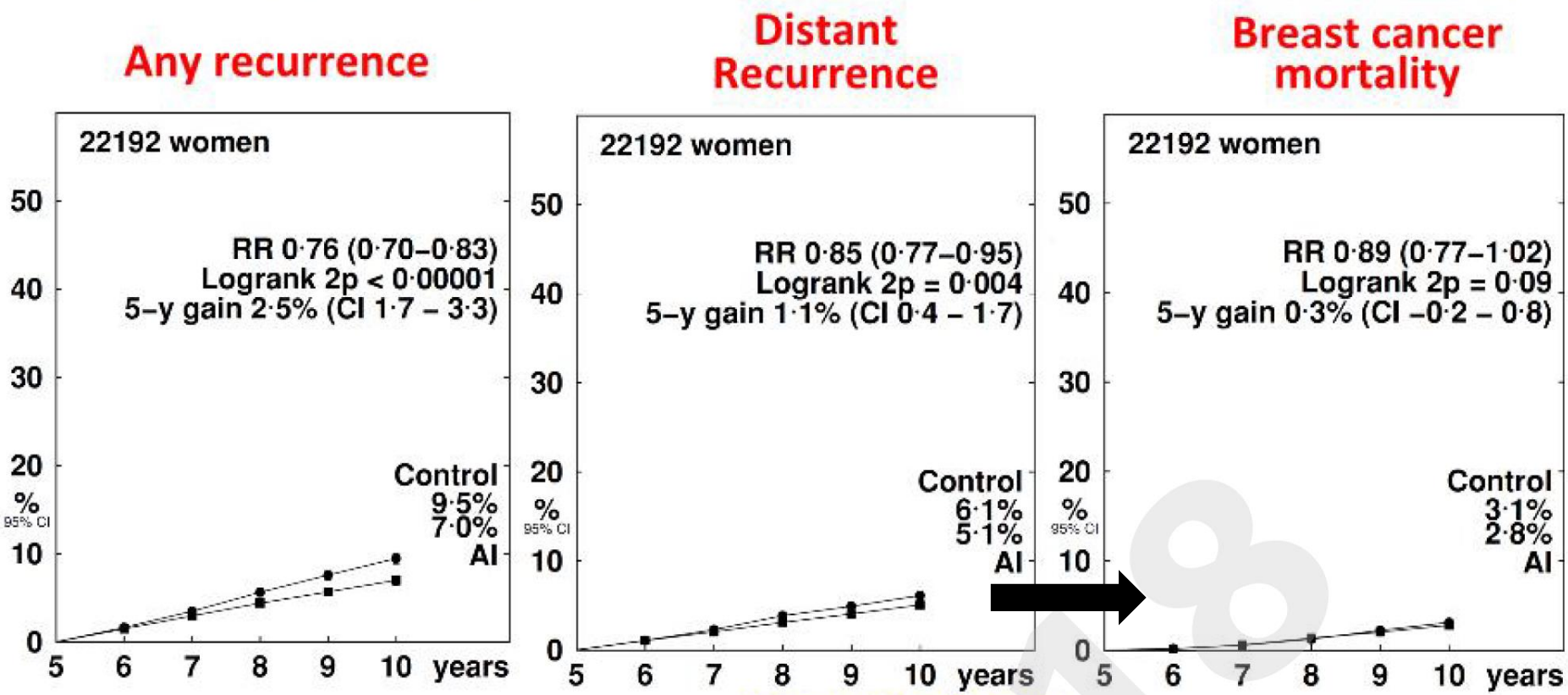


CONT
STOP
+ Censored

Number of events/ patients	Hazard ratio	p-value
4/831 3/828	1.389	p=0.665

Ohtani S et al. SABCS 2018

(b) Effect on several endpoints



MA 17.R: Reduction of contralateral recurrence risk (secundary prevention)

Stratification by lymph node status at diagnosis, prior adjuvant chemotherapy, interval between last AI dose and randomization, duration of prior tamoxifen

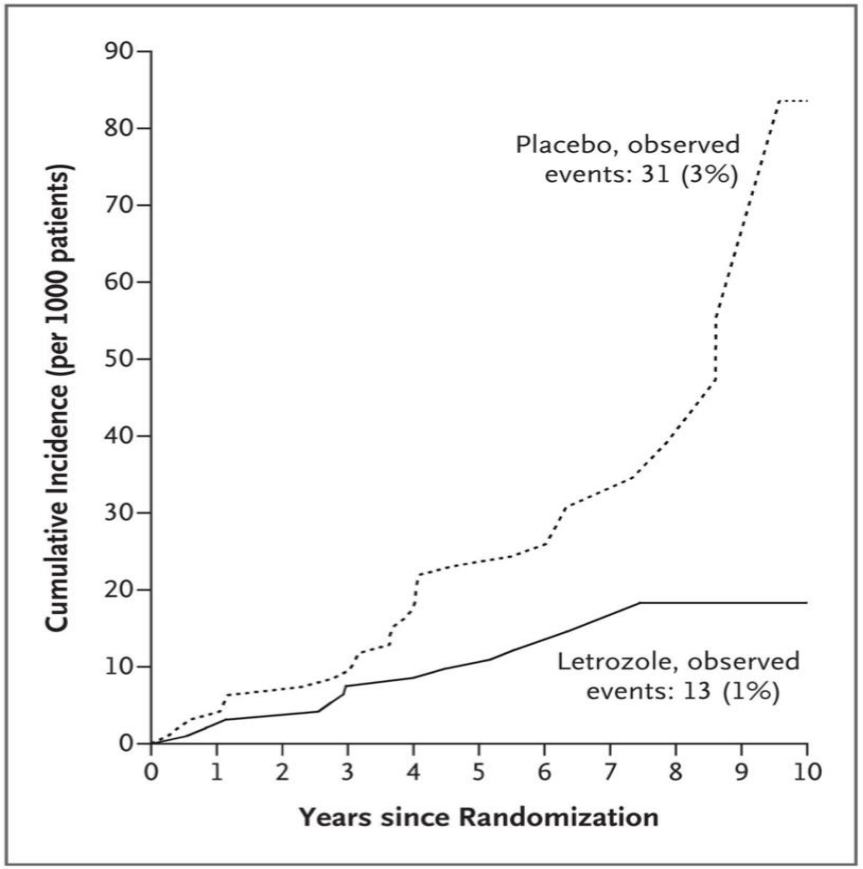
Postmenopausal pts with ER+ and/or PgR+ breast cancer who completed 4.5-6 yrs of letrozole 2.5 mg PO QD ± prior tamoxifen (N = 1918)

Letrozole 2.5 mg PO QD for 5 yrs (n = 959) → ***Follow-up***

Placebo for 5 yrs (n = 959) → ***Follow-up***

Median follow-up: 6.3 yrs

- Primary endpoint: DFS (from randomization)
- Secondary endpoints: OS, CBC, safety, QoL



Goss et al., NEJM 2017

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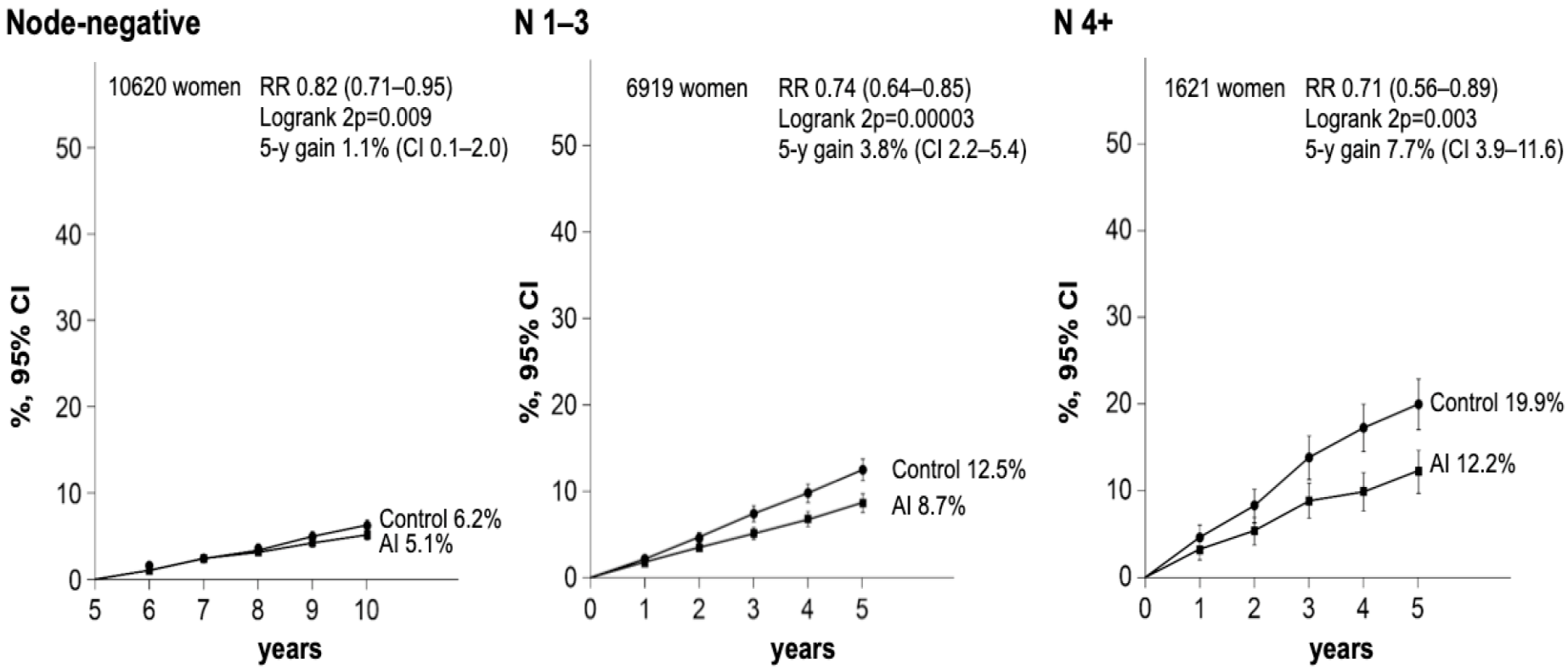
Influence of nodal status on efficacy of EAT (EAT metaanalysis)



Gray et al. SABCS 2018

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Postmenopausal Patients Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford LoE	Oxford GR	AGO
In case of high risk of recurrence			
▪ 5 years Tamoxifen after 5 years Tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years Tamoxifen	1a	A	++
▪ After initial AI containing therapy (upfront or switch) prolongation of endocrine therapy with AI for 2–5 years*			
▪ high risk and good tolerabilty of the AI	1a	A	+
▪ low risk, poor tolerabilty of the AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT	1b	B	+/-

* Up to date, no impact on OS

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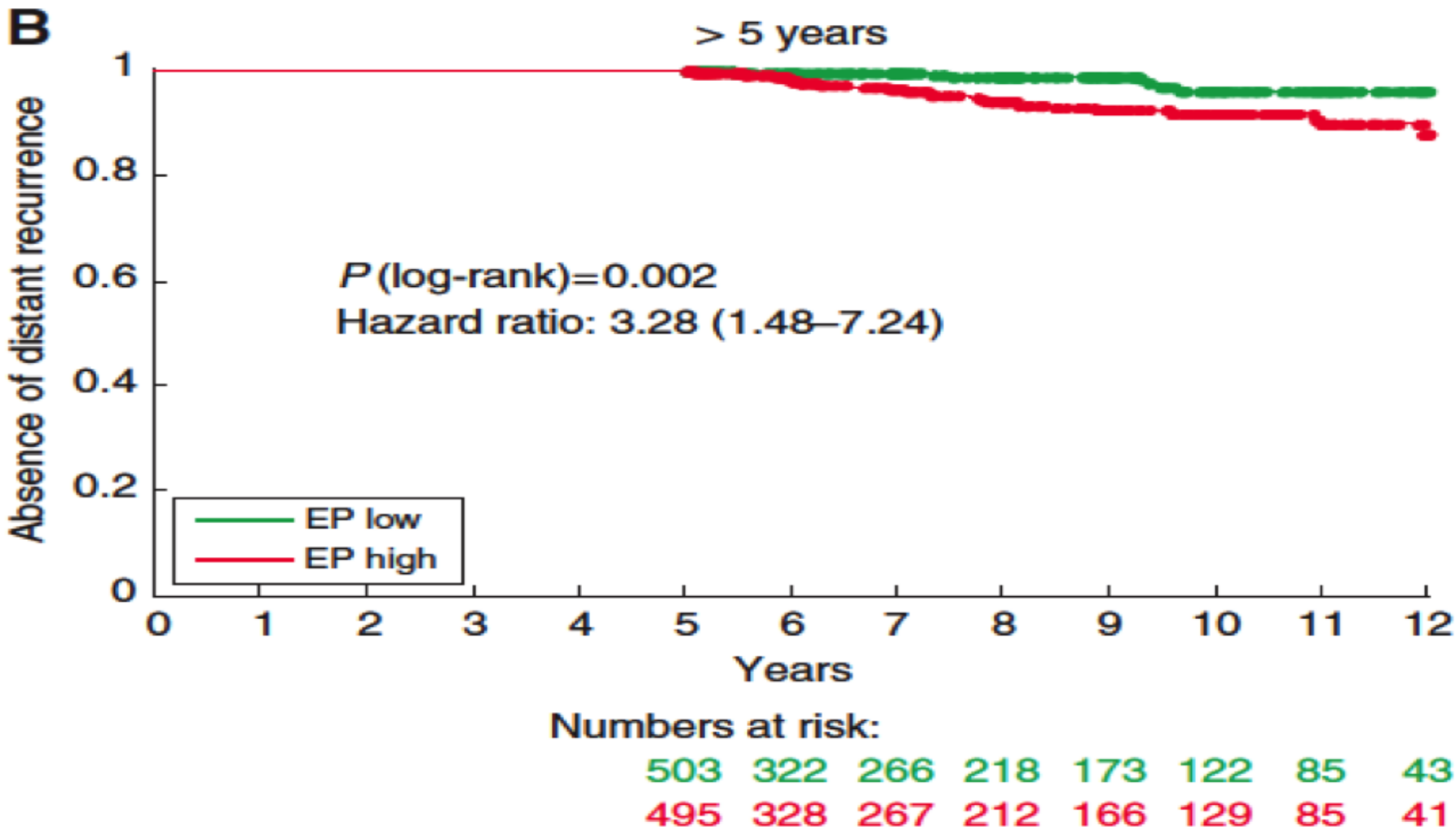
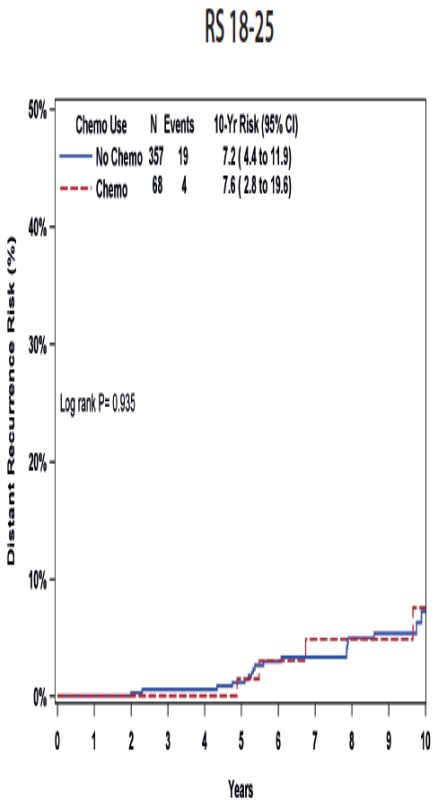
- adherence

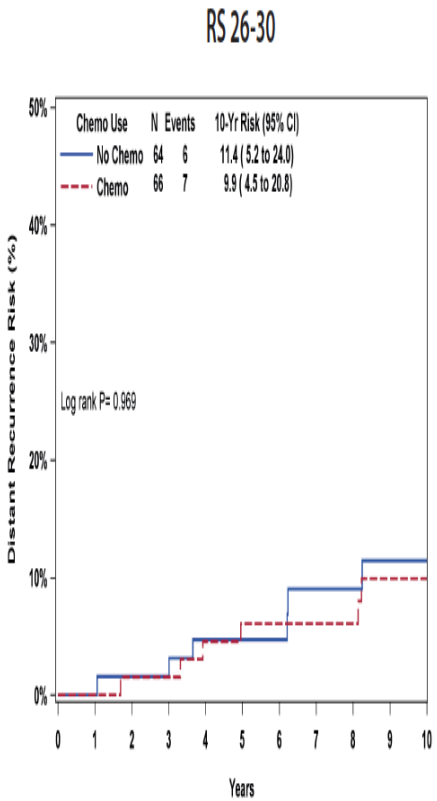
Identification of patients at risk for late recurrence (Endopredict)

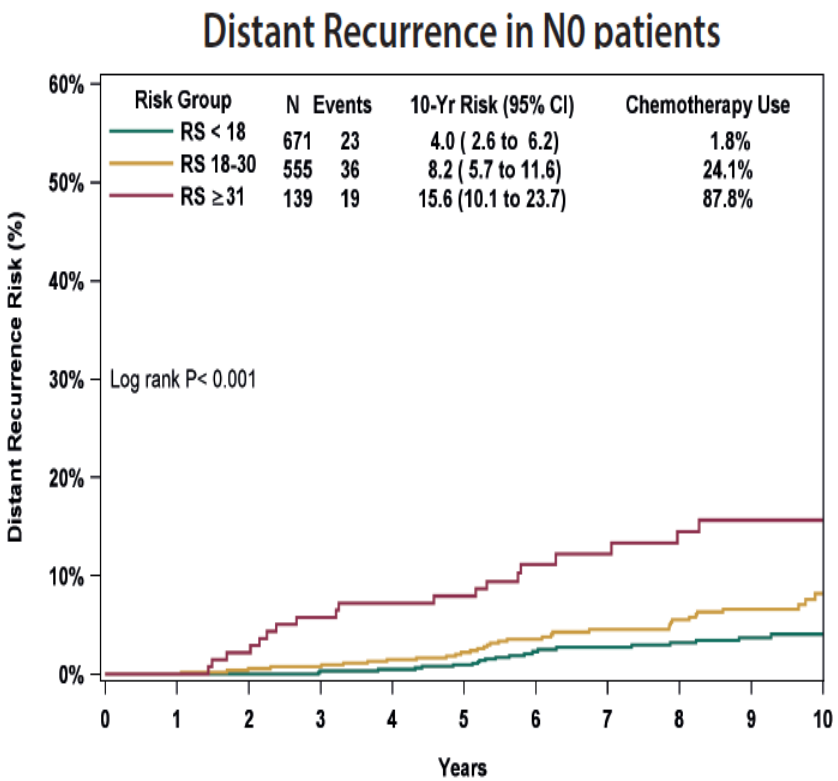


Dubsky et al., BJC 2013

Identification of patients at risk for late recurrence (Oncotype)

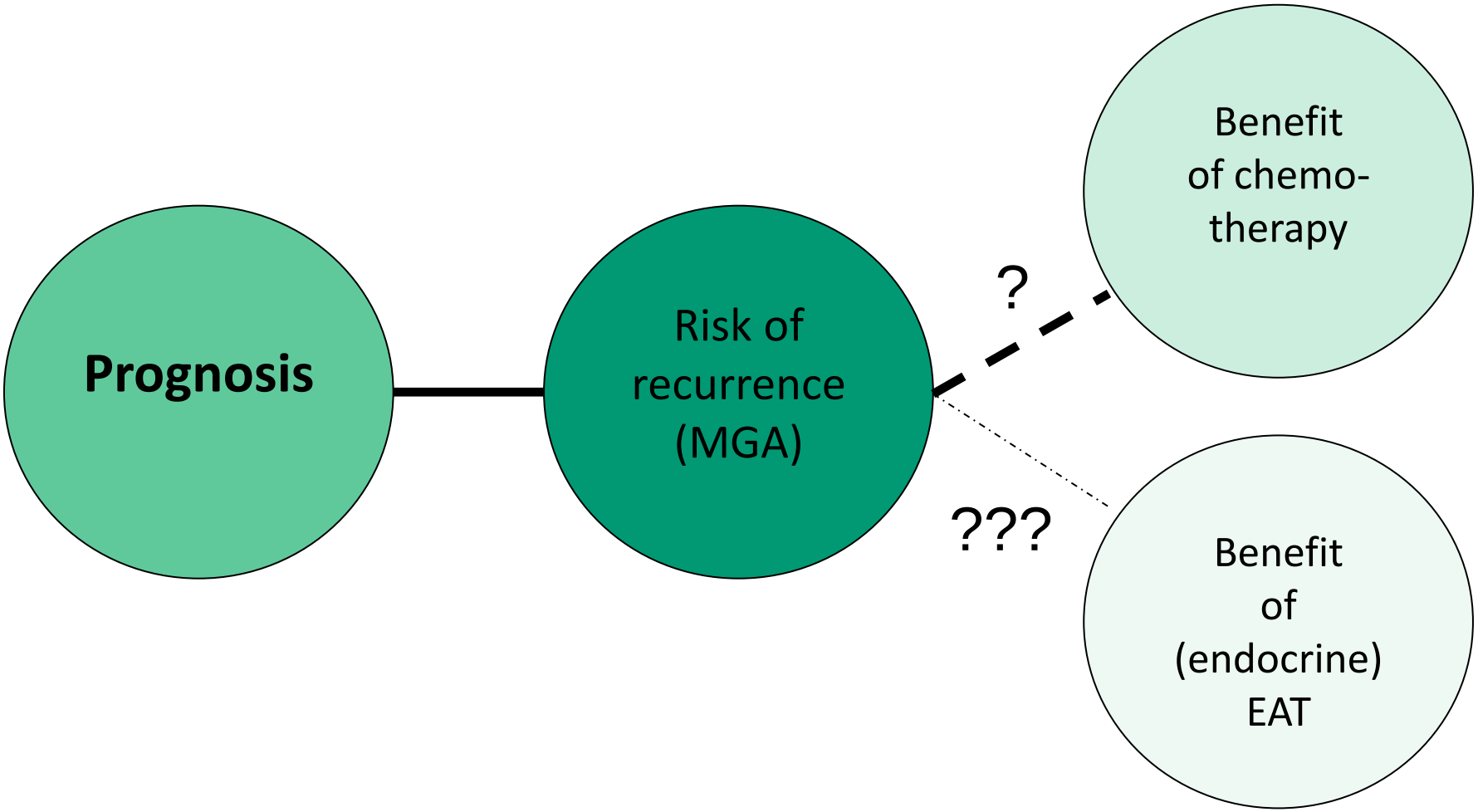




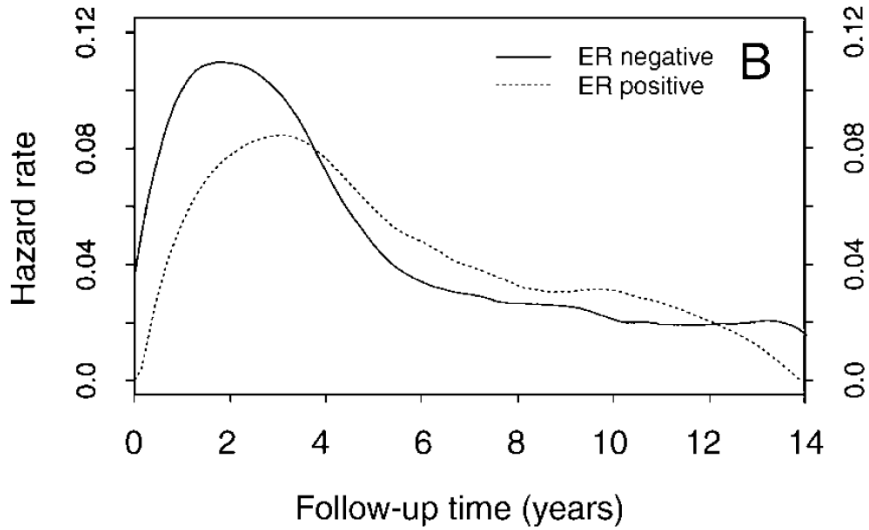


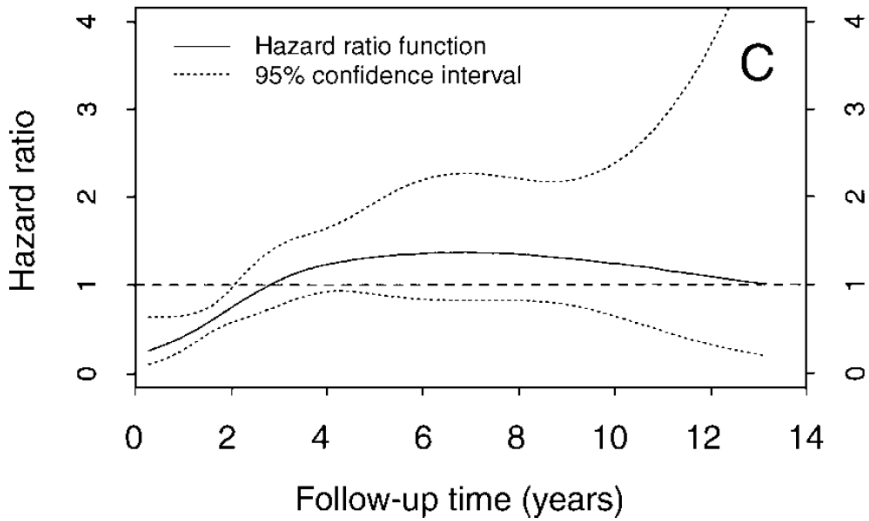
Stemmer et al., SABCS 2017

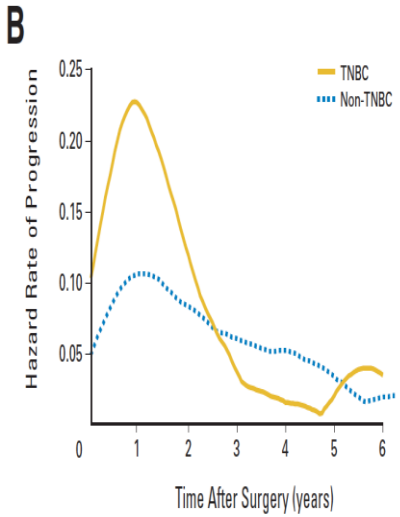
Implication of MGAs

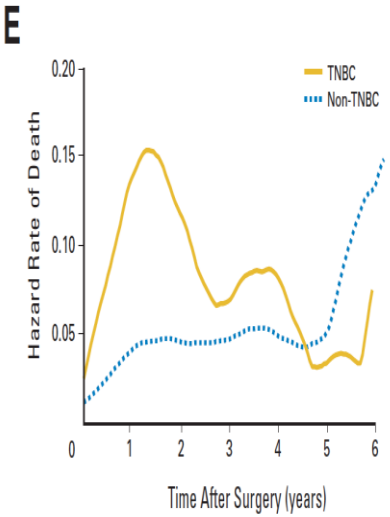


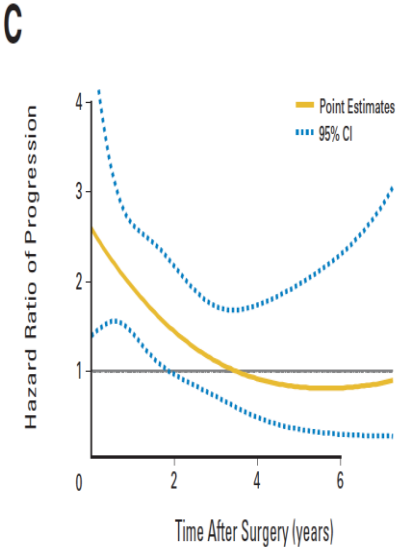
Recurrences over time depending on HR / TNBC status

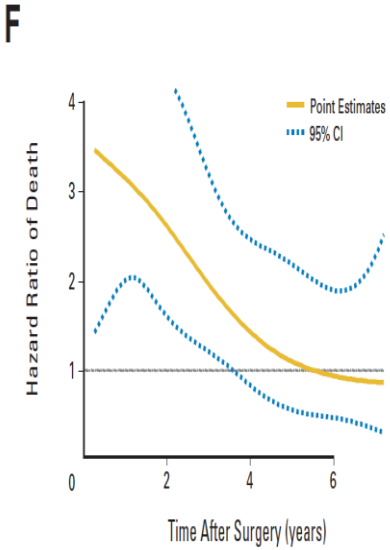






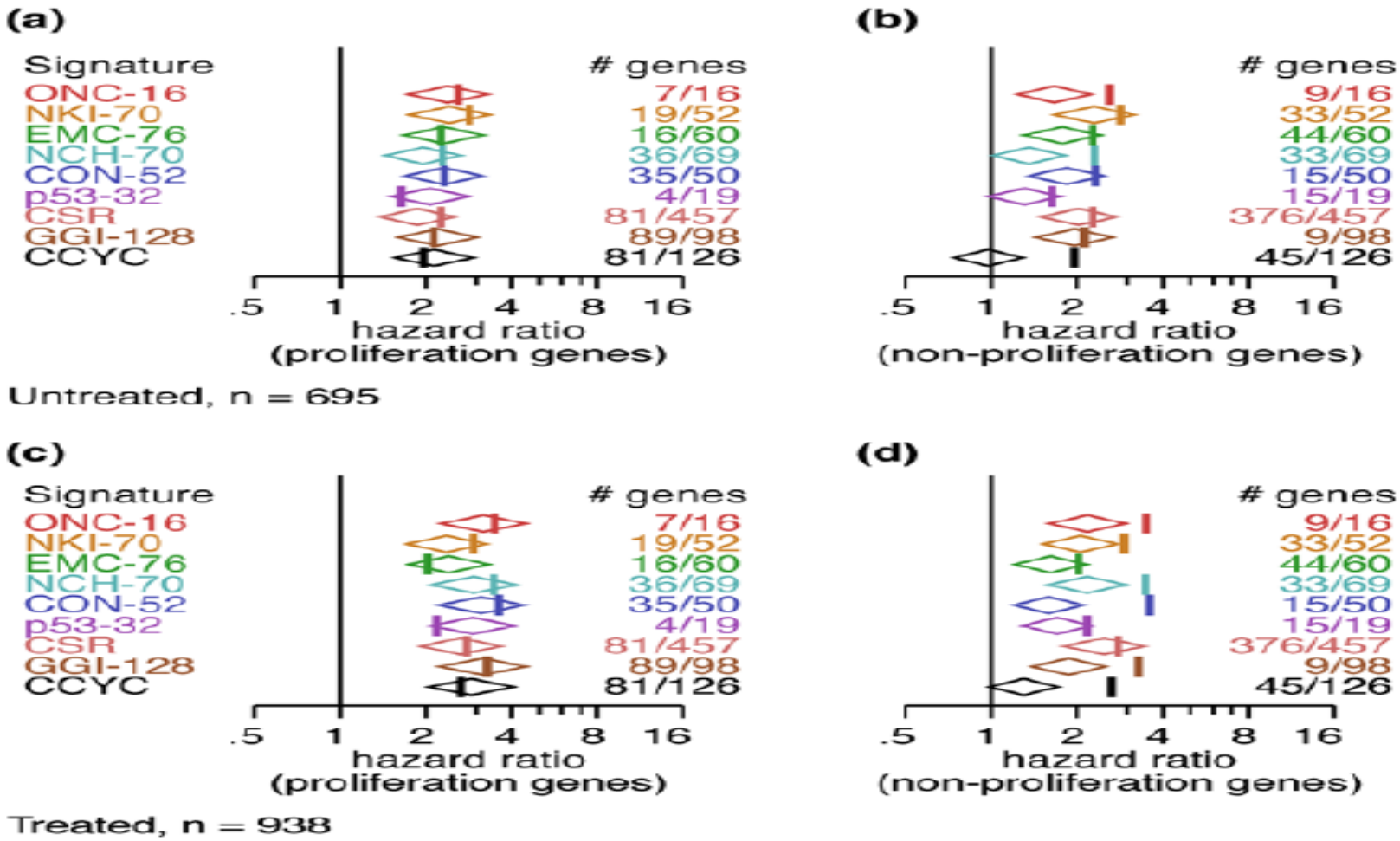






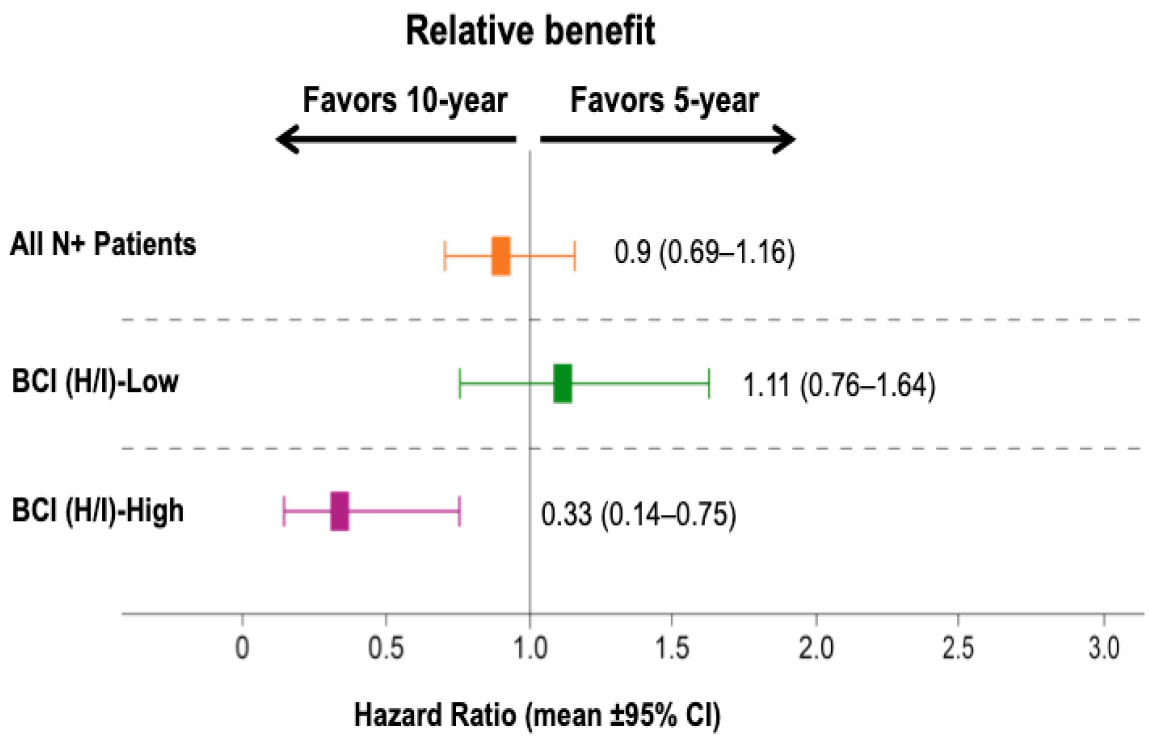
Hess et al., BCRT 2003; Liedtke et al., J Clin Oncol 2008

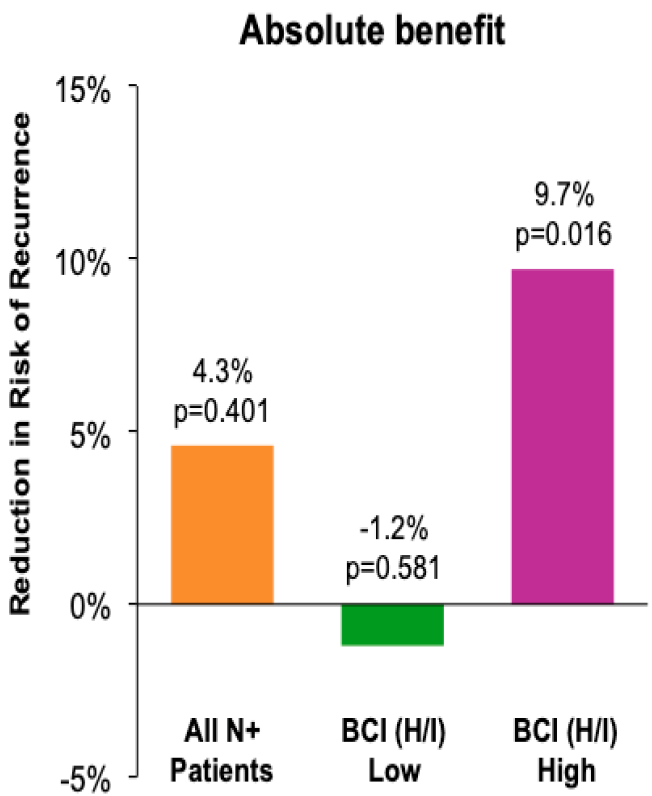
Impact of tumor cell proliferation on prognosis



Wirapati et al., BCR 2008

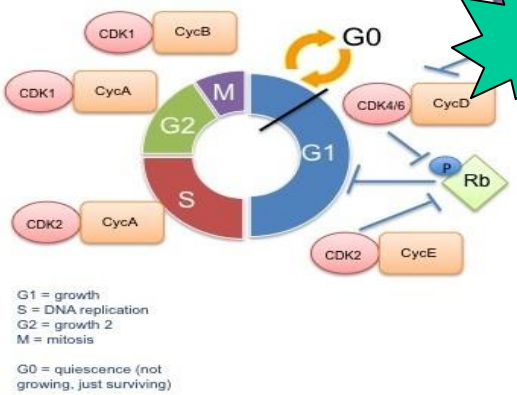
Breast Cancer Index predicts benefit from extended endocrine therapy in HR+ breast cancer

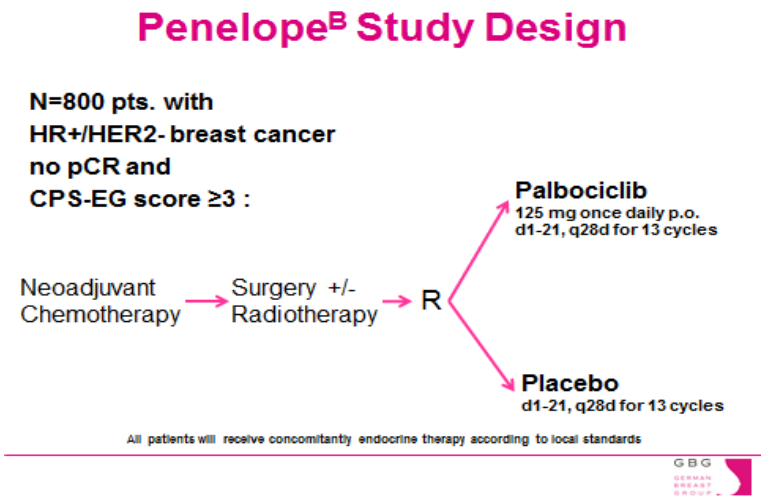




Bartlett et al., SABCS 2019

Trials regarding adjuvant endocrine therapy in BC





Study acronym Trial ID number Phase country	Sample size (*n*)	Purpose	Inclusion criteria	Endocrine therapy before randomization (years)	Treatment arms	Outcome measures	First results expected
EarLEE-2 NCT03081234 Phase III USA	4000	Evaluate efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment of intermediate risk early BC	Pre- and postmenopausal women with HR+ BC Her2– AJCC prognostic stage group II	None	Any endocrine therapy combined with 1) 2 years ribociclib 2) 2 years placebo	IDFS RFS OS Qol	2025
MonarchE	3580	Evaluate efficacy of abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone	Pre- and postmenopausal women with HR+ BC Her2 – N+ status and 1 of the following indicating a higher risk of relapse: - 4 or more N+ - Tumor size ≥ 5 cm - Grade 3 histology - Ki67 index of ≥ 20%	None	Standard 5-year adjuvant endocrine treatment with 1) 2 years palbociclib 2) none	IDFS DRFS OS Toxicity	2022
PALLAS NCT02513394 Phase III USA	4600	Evaluate efficacy of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone	Pre- and postmenopausal women with HR+ BC stage II or III Her2-	None	Standard 5 year adjuvant endocrine treatment with 1) 2 years palbociclib 2) none	IDFS DRFS OS LRRFS	2020

A anastrozole, *AI* aromatase Inhibitor, *BC* breast cancer, *BCFI* breast cancer-free interval, *DFS* disease-free survival, *DDFS* distant disease-free survival, *DMFS* distant metastases-free survival, *E* exemestane, *EFS* event free survival, *HR* hormone receptor, *IDFS* invasive disease-free survival, *L* letrozole, *LRRFS* local recurrences-free survival, *P* placebo, *OS* overall survival, *QOL* quality of life, *T* tamoxifen

Guidelines Breast
Version 2019.1

Decision criteria for extended therapy

Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and /or T2/T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

What to do?

	Type of initial endocrine therapy	Reasons to consider particular therapy	Reasons to consider extended endocrine therapy	Type of extended endocrine therapy
Preferred	AI x 5 years	1) Higher risk of early relapse [2] 2) History or risk of thromboembolic event 3) History of depression	Currently no evidence for extended endocrine therapy [4,5]	
	OR			
Preferred	Sequential therapy T 2-3 years - AI 2-3 years (total 5 years)	1) Significant osteopenia/osteoporosis 2) Musculoskeletal and/or joint discomfort 3) Significant cardiovascular disease	1) N+ disease [3,4,35] 2) ER and PR positive disease [3,35] 3) Treatment is well tolerated	AI 2-3 years [3]
Less Preferred	T x 5 years	1) AI contraindicated 2) Intolerant for AI 3) Postmenopausal due to chemotherapy	1) N+ disease 2) ER and PR positive disease 3) No contraindications for AI anymore 4) Treatment is well tolerated	AI up to 5 years [34]
			1) N+ disease 2) ER and PR positive disease 3) Contraindication for AI 4) Treatment is well tolerated	T up to 5 years [26,28]

Hellemond et al., Curr Treat Options in Oncol 2018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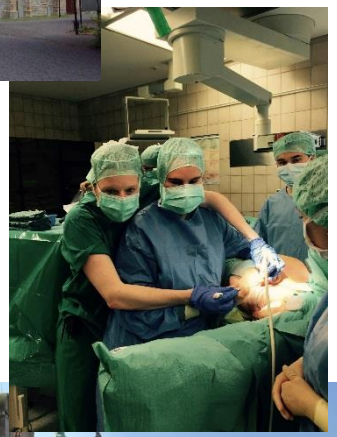

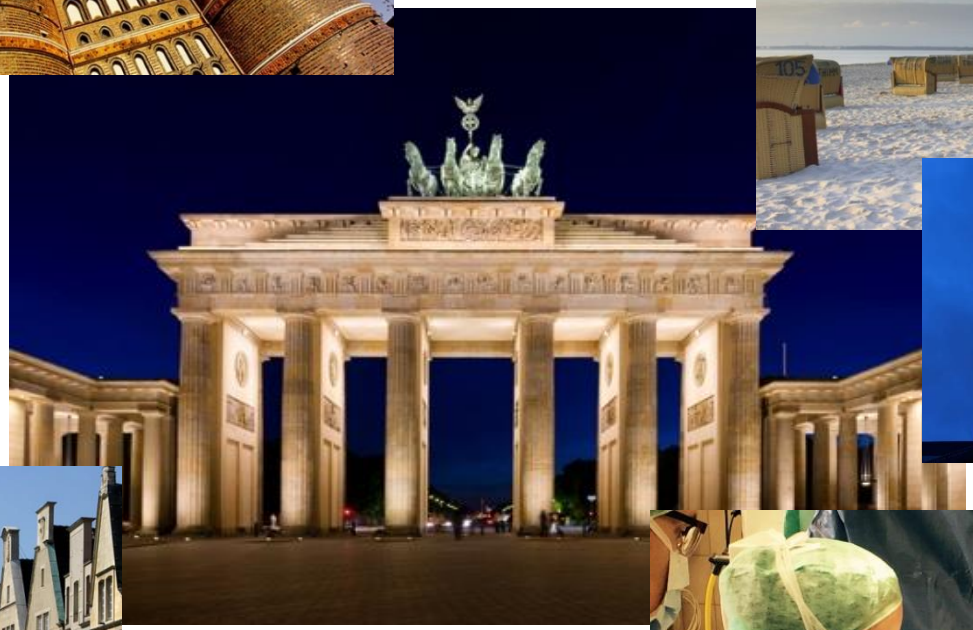

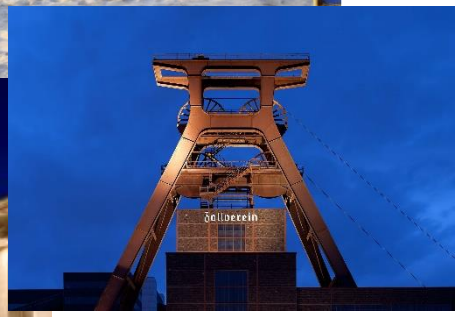
Zollverein