

Recent advances in hormone therapy

Suzette DELALOGUE
Gustave Roussy, Villejuif, France

Conflicts of interest

	Consulting/ expert	Conferences / formations	Research grants /clinical trials	Stock options	Patent
Abott			x		
Amgen		x	x		
Astra Zeneca		x	x		
Eisei		x			
GE	x	x	x		
Genomic Health	x	x	x		
GSK	x	x	x		
Iris/Servier			x		
Novartis	x	x	x		
Pfizer	x	x	x		
Puma	x		x		
Roche	x	x	x		
Sanofi		x	x		





Outline

- Prevention
- Adjuvant setting
- Advanced disease

Outline

- Prevention
- Adjuvant setting
- Advanced disease

SERMs for BC prevention: TAM

	N	pop	FU ans	Nb K placebo	Nb K Tam	HR
 Fisher NSABPP1 JNCI 2005	13388	Gail \geq 1.66% at 5 yrs	7	347	205	0.57
 Veronesi Italy JNCI 2007	5408	Hysterec tomy	11	74	62	0.84 NS
 Powles Marsden JNCI 2007	2471	Familial risk	13	104 (inf)	82 (inf)	0.78 NS
 Cuzick IBIS1 JNCI 2007	7145	High risk	8	195	142	0.73

SERMs for BC prevention: meta-analysis 2013

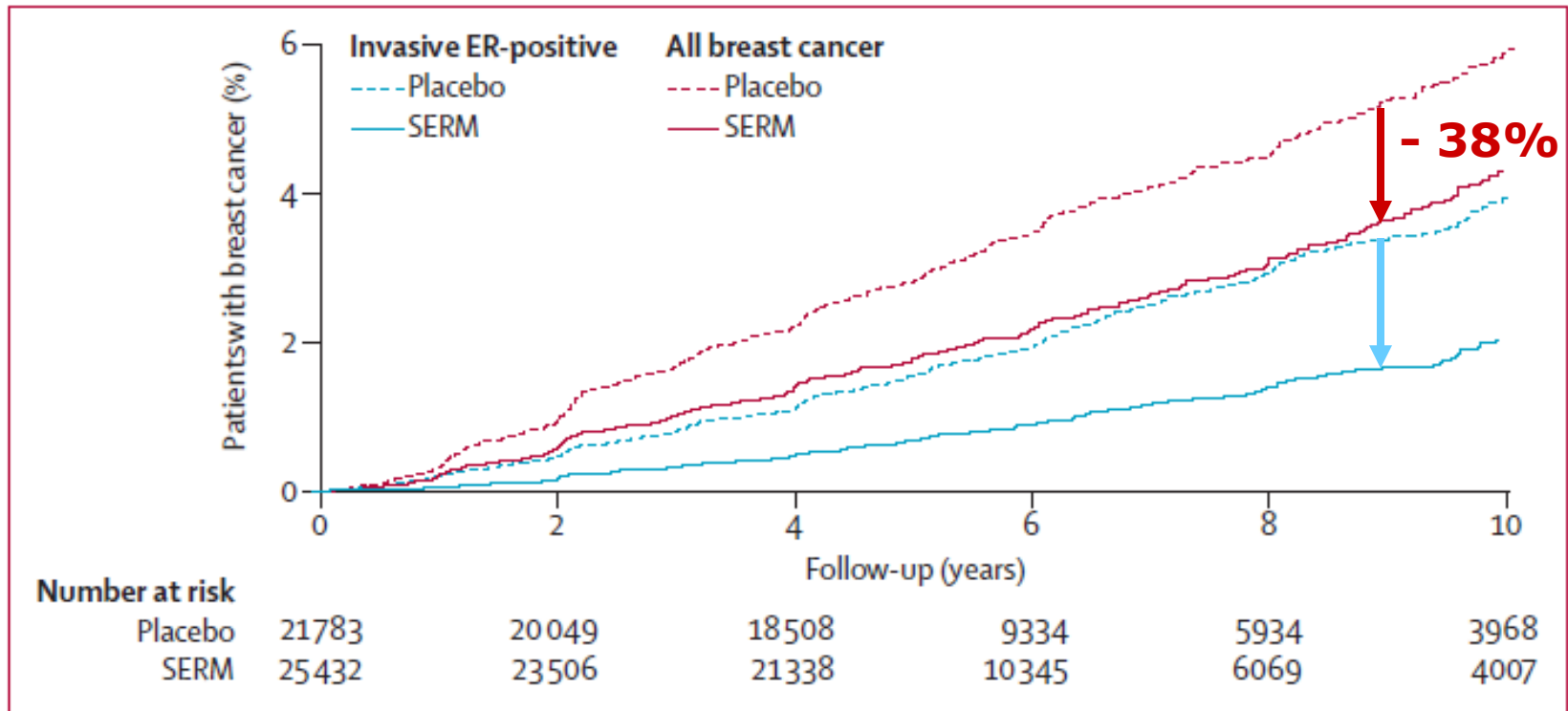


Figure 1: Cumulative incidence for all breast cancer (including ductal carcinoma in situ) and all ER-positive invasive cancers in years 0-10 according to treatment allocation
SERM=selective oestrogen receptor modulator. ER=oestrogen receptor.

42 women treated to avoid 1 BC

SERMs for BC prevention: meta-analysis 2013

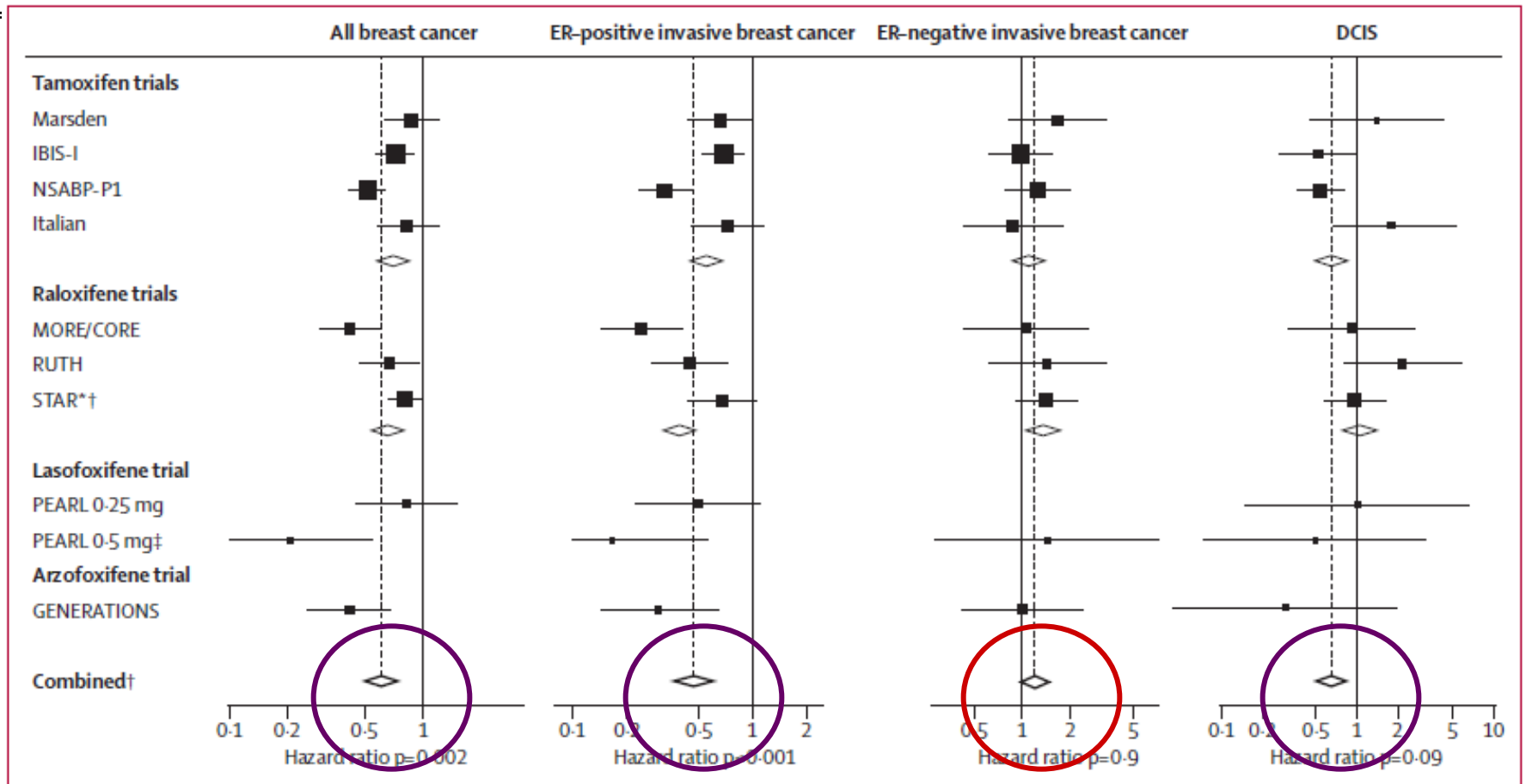


Figure 3: All breast cancers, invasive breast cancer, and DCIS in years 0-10

ER=oestrogen receptor. DCIS=ductal carcinoma in situ. *Adjusted by overall tamoxifen effect to give raloxifene versus placebo comparisons. †STAR data not included in comparisons. ‡Data for ER-invasive cancer are pooled.

SERMs for BC prevention: meta-analysis 2013

	Endometrial cancer	All other cancer*	Any death	Breast cancer death
Marsden	12 vs 5	55 vs 60	54 vs 54	12 vs 9
IBIS-I	19 vs 11	110 vs 113	65 vs 55	10 vs 12
NSABP-P-1	36 vs 15	101 vs 103	59 vs 71	4 vs 6
Italian	..	106 vs 91	36 vs 38	2 vs 2
MORE/CORE	6 vs 8	112 vs 132	81 vs 84	..
RUTH	21 vs 17	204 vs 203	548 vs 585	2 vs 0
STAR§ (raloxifene vs tamoxifen)	37 vs 65	354 vs 323	202 vs 236	4 vs 11
PEARL (0.5 mg vs 0.25 mg vs placebo)	2 vs 2 vs 3	25 vs 20 vs 22	92 vs 73 vs 65	..
GENERATIONS	9 vs 4	74 vs 75	103 vs 98	..
All events	105 vs 63	787 vs 799	1038 vs 1050	30 vs 29
HR or OR (95% CI)	HR 1.56 (1.13-2.14)	HR 0.98 (0.89-1.08)	HR 0.98 (0.90-1.06)	HR 1.03 (0.55-1.92)

Data are number of patients for selective oestrogen receptor modulator versus vs placebo, unless otherwise in pulmonary embolism, retinal thrombosis; excluding superficial thrombosis. §Including myocardial infarction,

Table 3: Major non-breast cancer events in the prevention trials

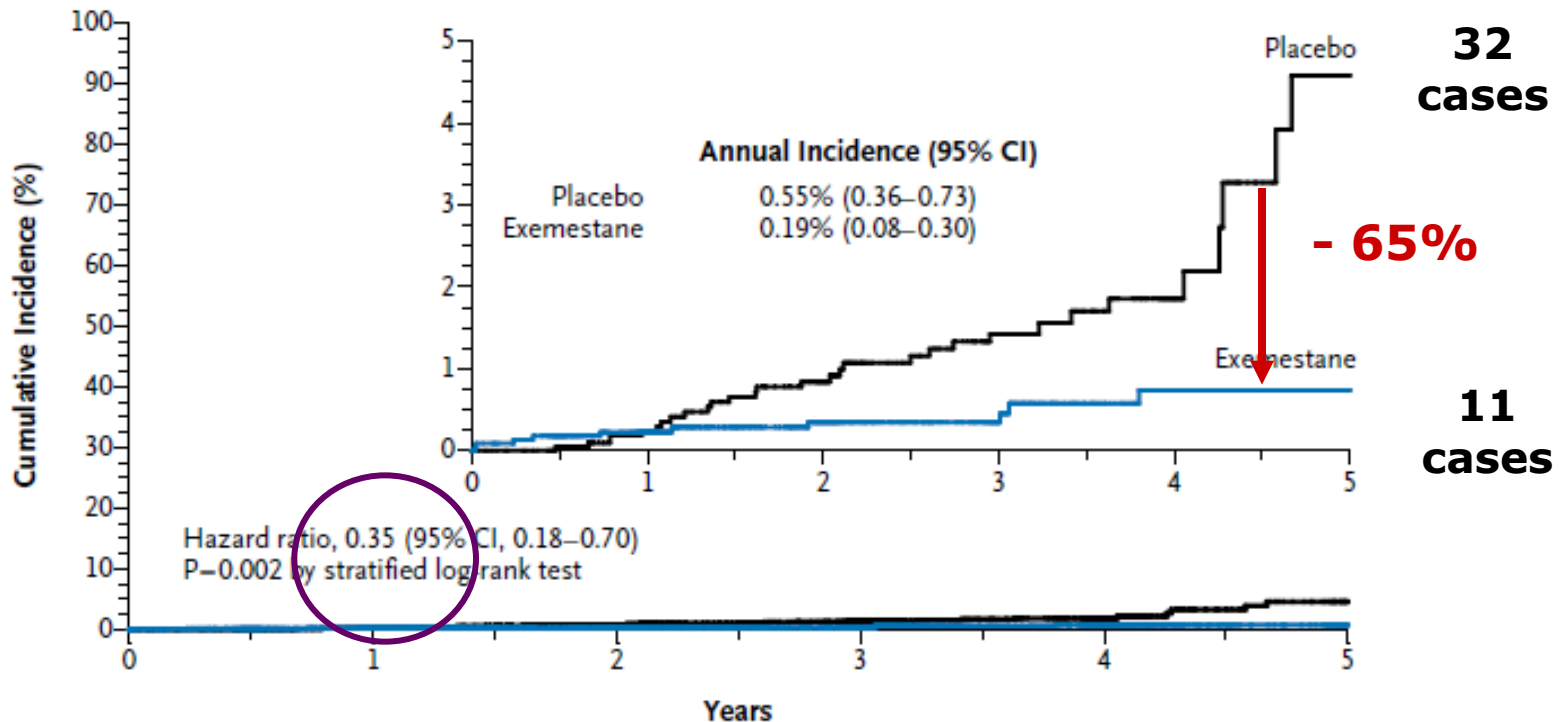
SERMs for BC prevention: meta-analysis 2013

Venous thrombotic events†	Cardio-vascular events‡	All fractures	Non-vertebral fractures	Vertebral fractures	Cataracts
..
65 vs 43	40 vs 38	229 vs 252	221 vs 244	8 vs 8	76 vs 70
55 vs 29	90 vs 82	502 vs 539	480 vs 509	22 vs 30	578 vs 513
11 vs 10	14 vs 10
47 vs 25	82 vs 78	353 vs 450	214 vs 225	139 vs 225	275 vs 280
106 vs 73	487 vs 481	529 vs 591	470 vs 499	59 vs 92	570 vs 561
154 vs 202	233 vs 220	1272 vs 1364	1195 vs 1299	65 vs 77	603 vs 739
48 vs 37 vs 18	47 vs 54 vs 76	359 vs 422 vs 508	203 vs 233 vs 246	156 vs 189 vs 262	320 vs 317 vs 330
43 vs 17	71 vs 64	426 vs 508	316 vs 327	110 vs 181	382 vs 400
375 vs 215	831 vs 829	2298 vs 2848	1904 vs 2050	494 vs 798	2201 vs 2154
OR 1.73 (1.47-2.05)	OR 0.99 (0.91-1.09)	OR 0.85 (0.80-0.89)	OR 0.93 (0.87-0.99)	OR 0.66 (0.59-0.73)	OR 1.01 (0.95-1.06)

†Indicated. ‡HR=hazard ratio. OR=odds ratio. *Excluding endometrial cancer. †Including deep vein thrombosis, cerebrovascular accident, and transient ischaemic accident. ‡STAR data not included for overall effect.

AI for prevention: exemestane

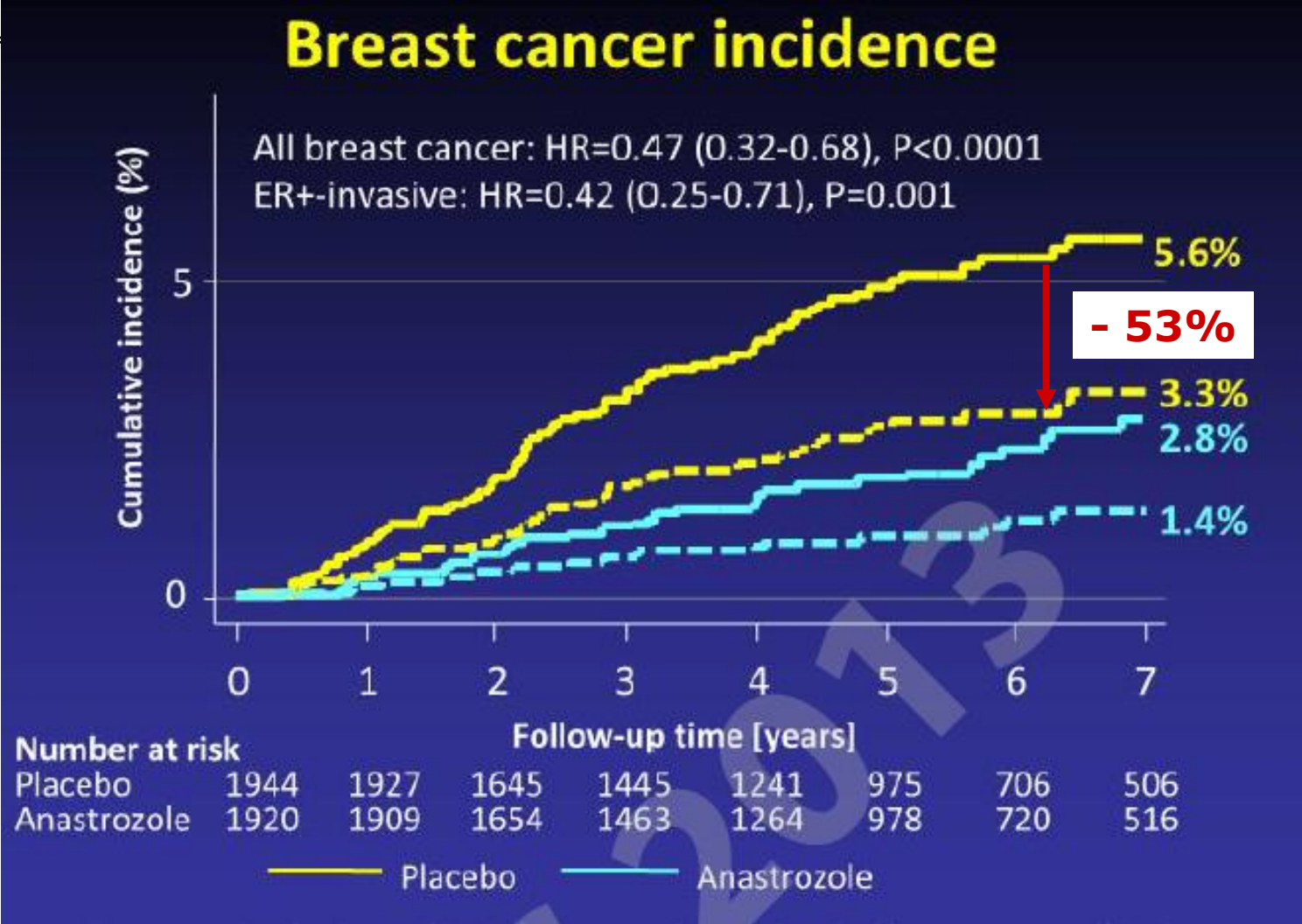
FU 35 months



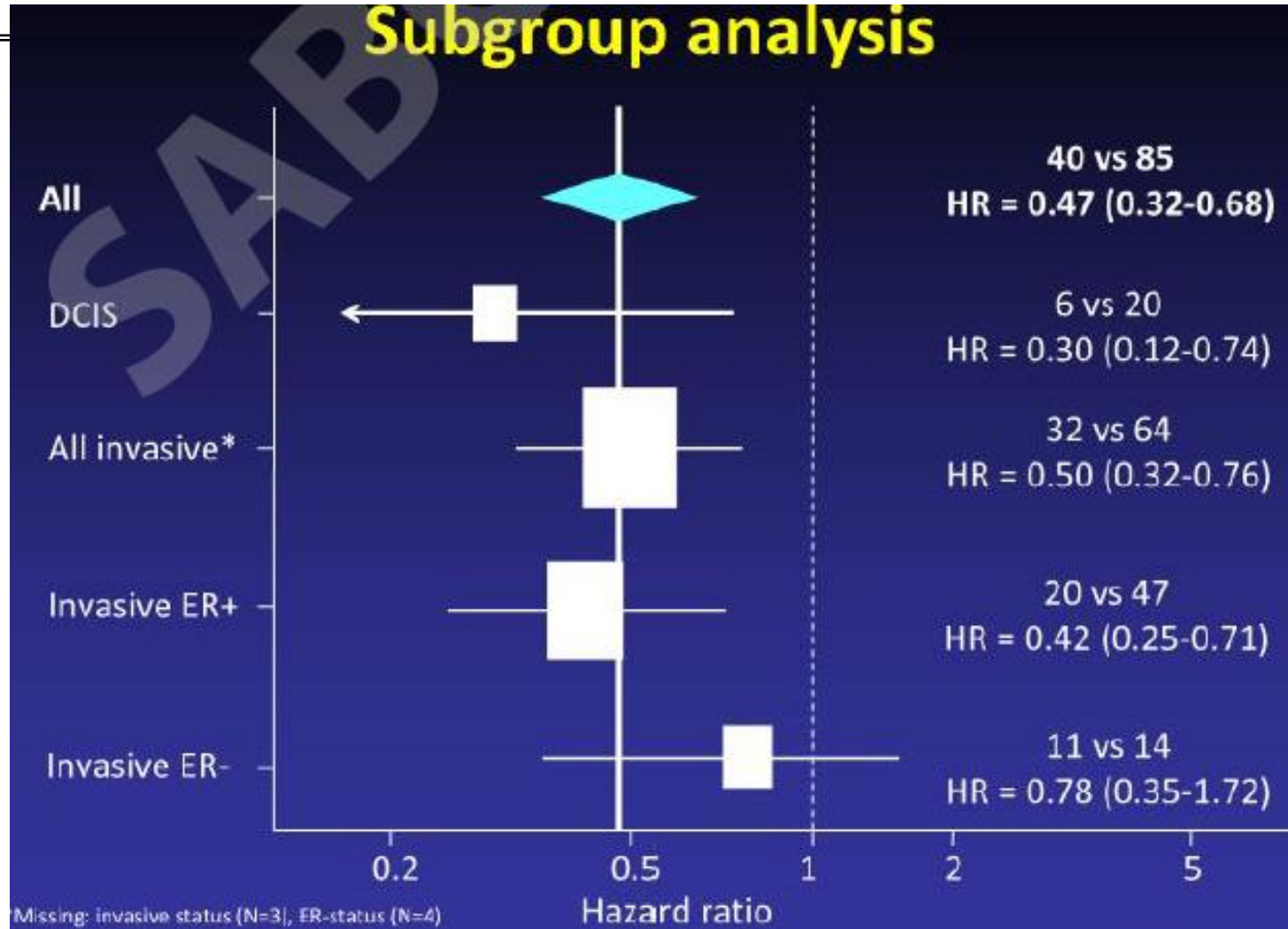
No. at Risk

Placebo	2275	1905	1468	986	477	82
Exemestane	2285	1902	1468	980	464	77

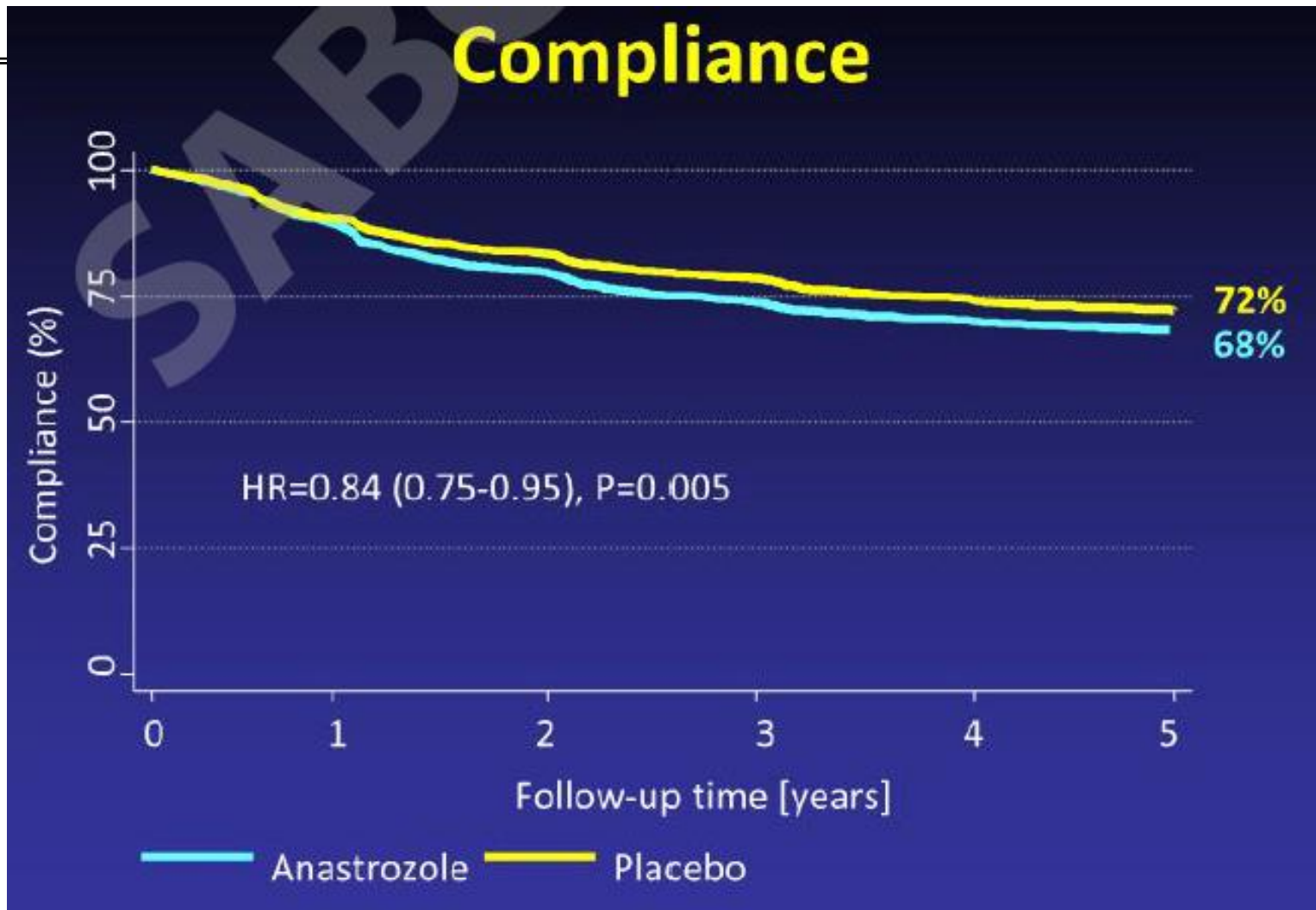
AI for prevention: anastrozole



AI for prevention: anastrozole



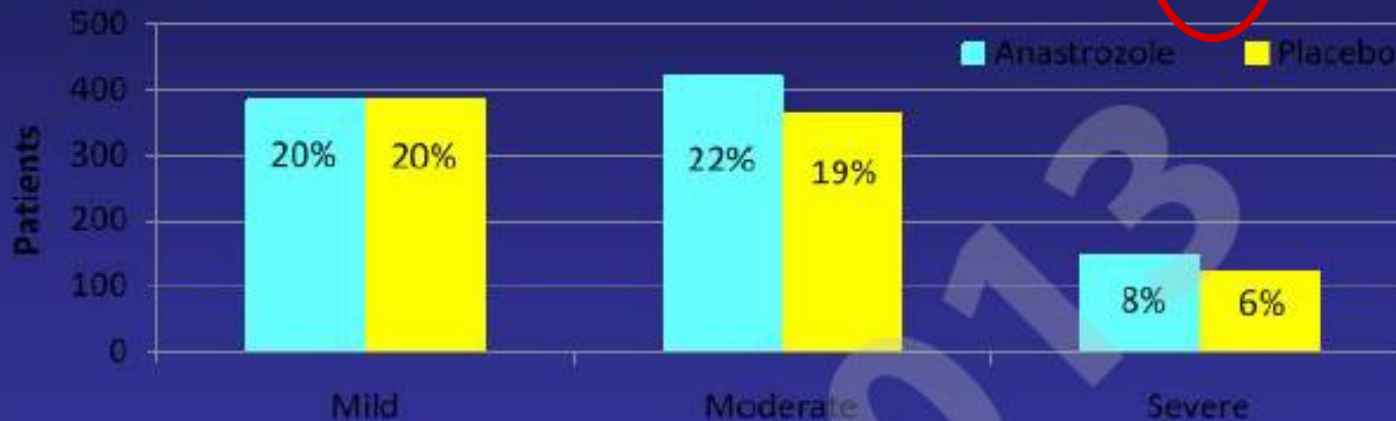
AI for prevention: anastrozole



AI for prevention: anastrozole

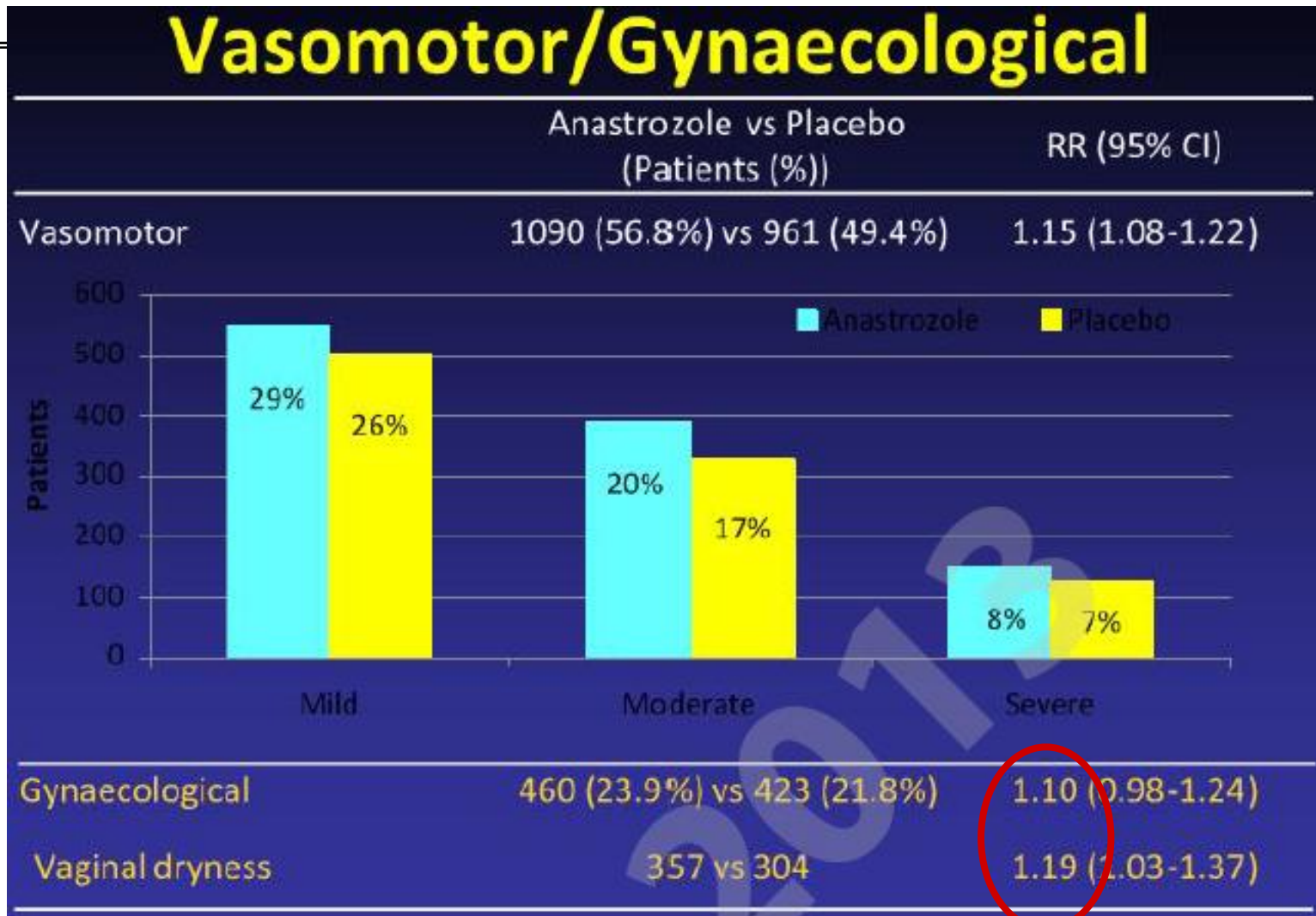
Fractures/Musculoskeletal

	Anastrozole vs Placebo (Patients %)	RR (95% CI)
Fractures	164 (8.5%) vs 149 (7.7%)	1.11 (0.90-1.38)
Musculoskeletal	1226 (63.9%) vs 1124 (57.8%)	1.10 (1.05-1.16)
Arthralgia	972 vs 894	1.10 (1.03-1.18)



Joint stiffness	143 vs 96	1.51 (1.17-1.94)
Carpal tunnel/Nerve compression	67 vs 43	1.58 (1.08-2.30)

AI for prevention: anastrozole



International recommendations

Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline

ASCO 2013

Kala Visvanathan, Patricia Hurley, Elissa Bantug, Powel Brown, Nananda F. Col, Jack Cuzick, Nancy E. Davidson, Andrea DeCensi, Carol Fabian, Leslie Ford, Judy Garber, Maria Katapodi, Barnett Kramer, Monica Morrow, Barbara Parker, Carolyn Runowicz, Victor G. Vogel III, James L. Wade, and Scott M. Lippman

Key Recommendations

- Tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in premenopausal or postmenopausal women age ≥ 35 years at increased risk of breast cancer or with lobular carcinoma in situ (LCIS). Tamoxifen is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack; during prolonged immobilization; or in women who are pregnant, may become pregnant, or are nursing mothers. Tamoxifen is not recommended in combination with hormone therapy.
- Raloxifene (60 mg per day orally for 5 years) should be discussed as an option to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 years at increased risk of breast cancer or with LCIS. It should not be used for breast cancer risk reduction in premenopausal women. Raloxifene is not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilization.
- Exemestane (25 mg per day orally for 5 years) should be discussed as an alternative to tamoxifen or raloxifene to reduce the risk of invasive breast cancer, specifically ER-positive breast cancer, in postmenopausal women age ≥ 35 years at increased risk of breast cancer or with LCIS or atypical hyperplasia. Exemestane should not be used for breast cancer risk reduction in premenopausal women.

Outline

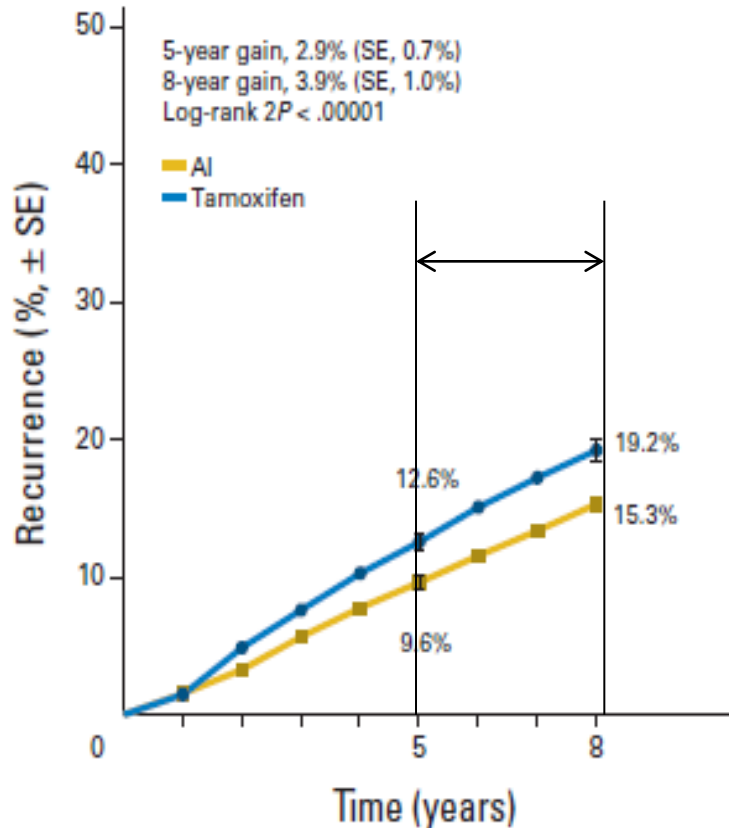
- Prevention
- Adjuvant setting
- Advanced disease

Current questions – adjuvant HT

- Treatment duration?
- How to anticipate resistance?
- Can we decrease treatments? Not for now...

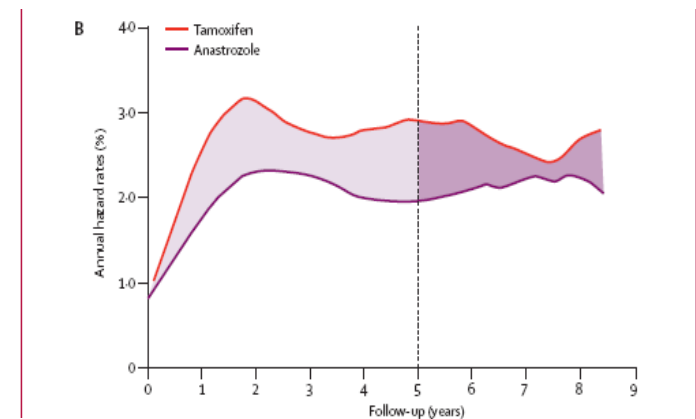
HR+: long term risk of relapse is a major issue

Recurrences



Annual risk of relapse appears stable after 5 years (1-2% per year)

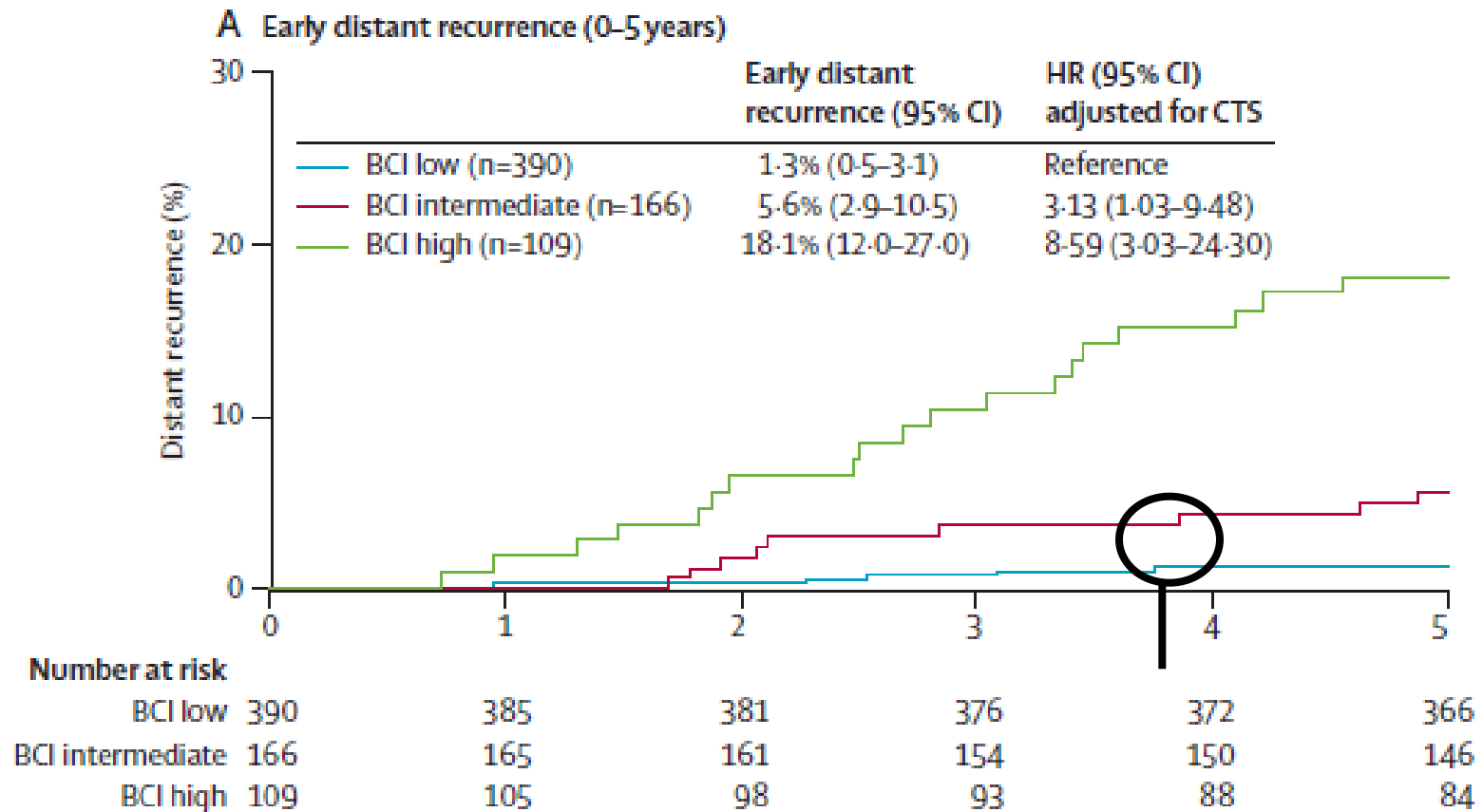
Dowsett meta analysis
AI jan 2010, J Clin
Oncol



ATAC 2008, The Lancet

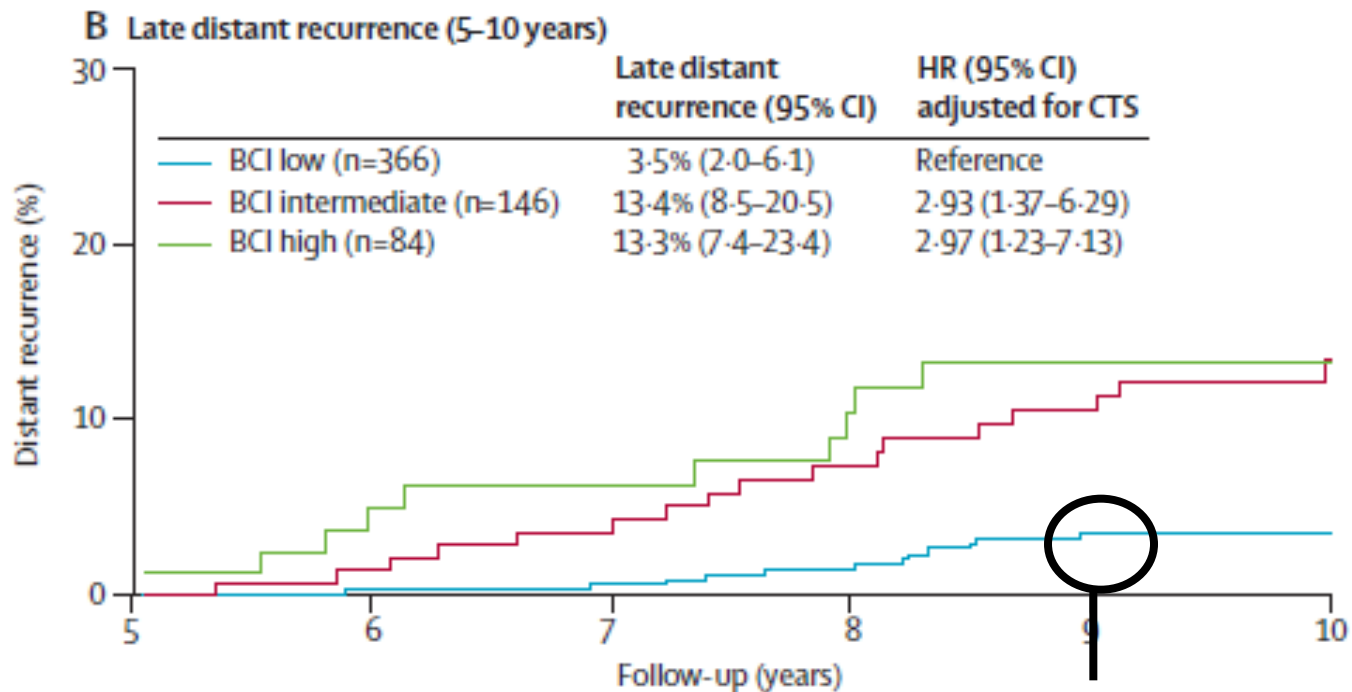
Can we predict for late relapse?

Breast cancer Index: **early relapse** (TransATAC)



Can we predict for late relapse?

Breast cancer Index: late relapse (TransATAC)



Number at risk		5	6	7	8	9	10
BCI low	366	357	347	332	310	190	
BCI intermediate	146	140	129	119	109	67	
BCI high	84	74	70	62	57	34	

Benefits of prolonged HT?

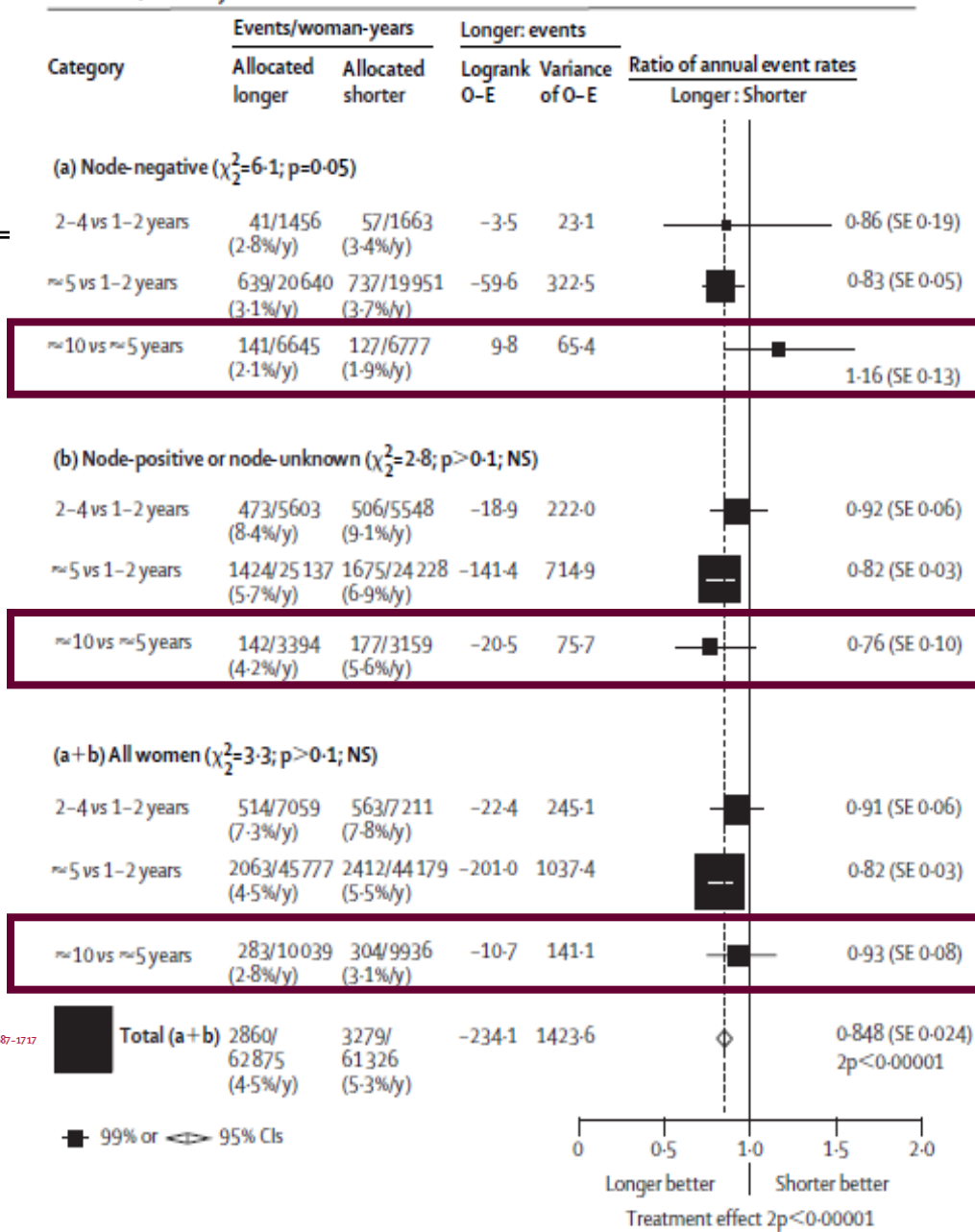
Meta-analysis recurrences

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Lancet 2005; 365: 1687-1717

Recurrence/woman-years



Heterogeneity between proportional effects in (a) and in (b): $\chi^2_1=1.0$; 2p>0.1; NS

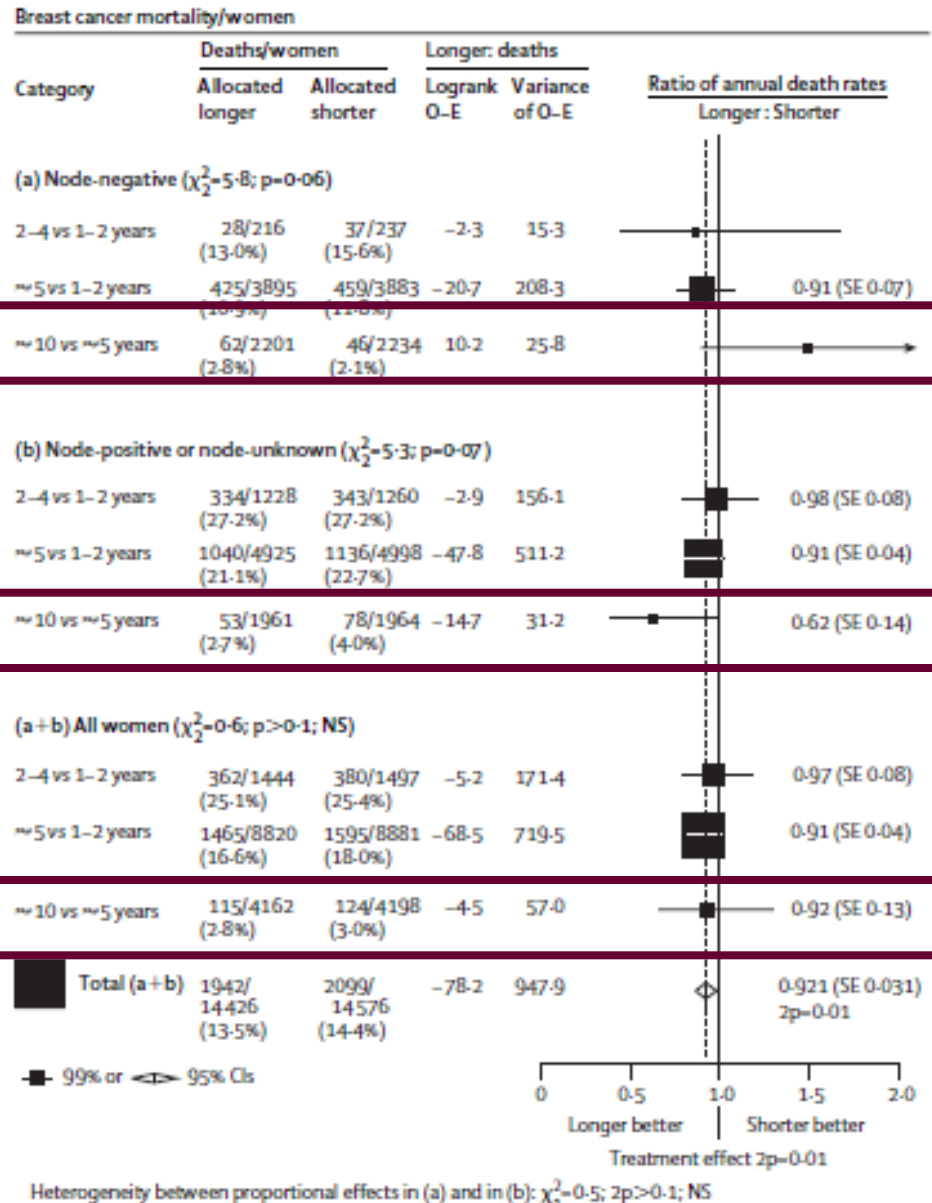
Benefits of prolonged HT?

Meta-analysis Mortality

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Lancet 2005; 365: 1687-1717



Lancet 2005; 365: 1687-1717

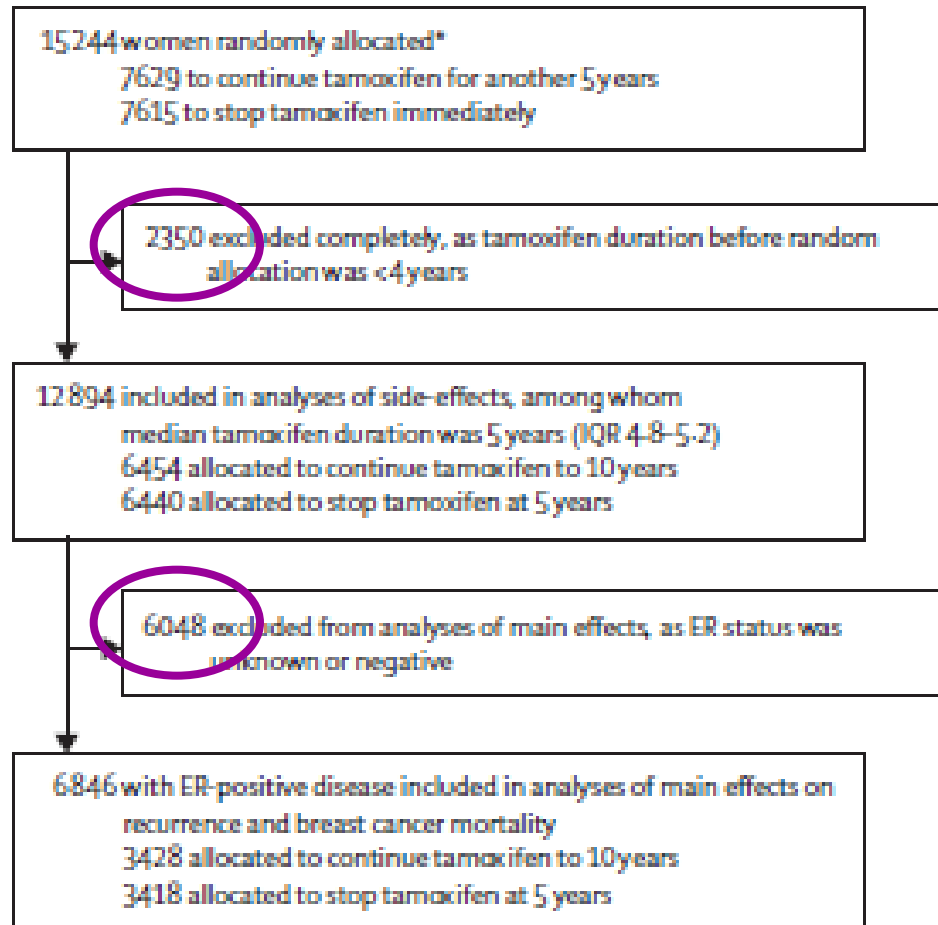
Treatment duration: recent data

Atlas trial

1995-2005

Open design

TAM 10 yrs vs 5 yrs
(rando at 5 yrs)

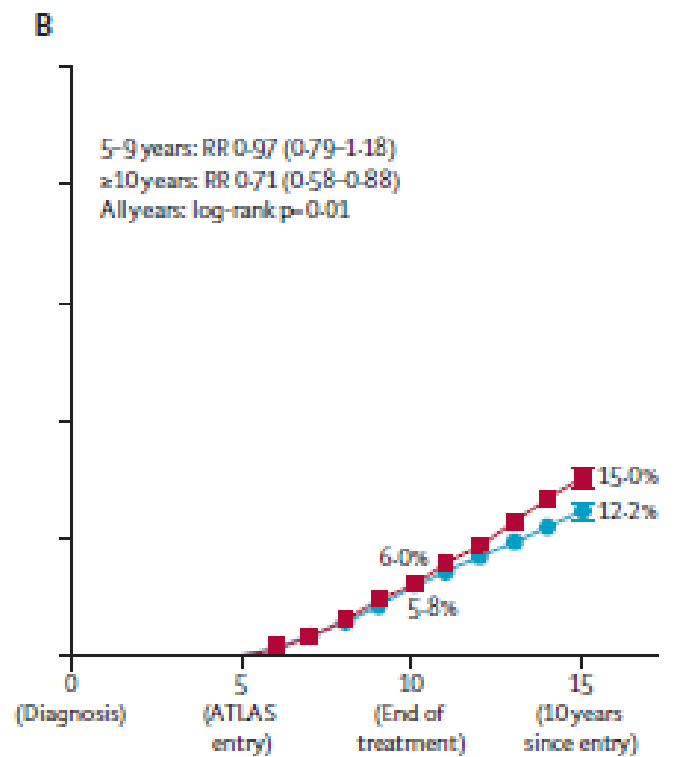
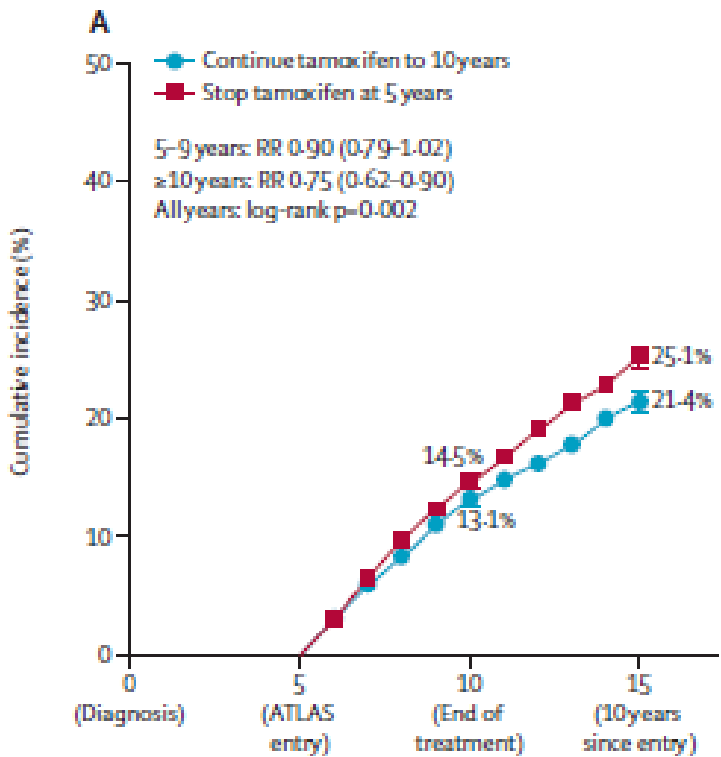


Treatment duration: recent data

Atlas

Relapse

Breast cancer mortality



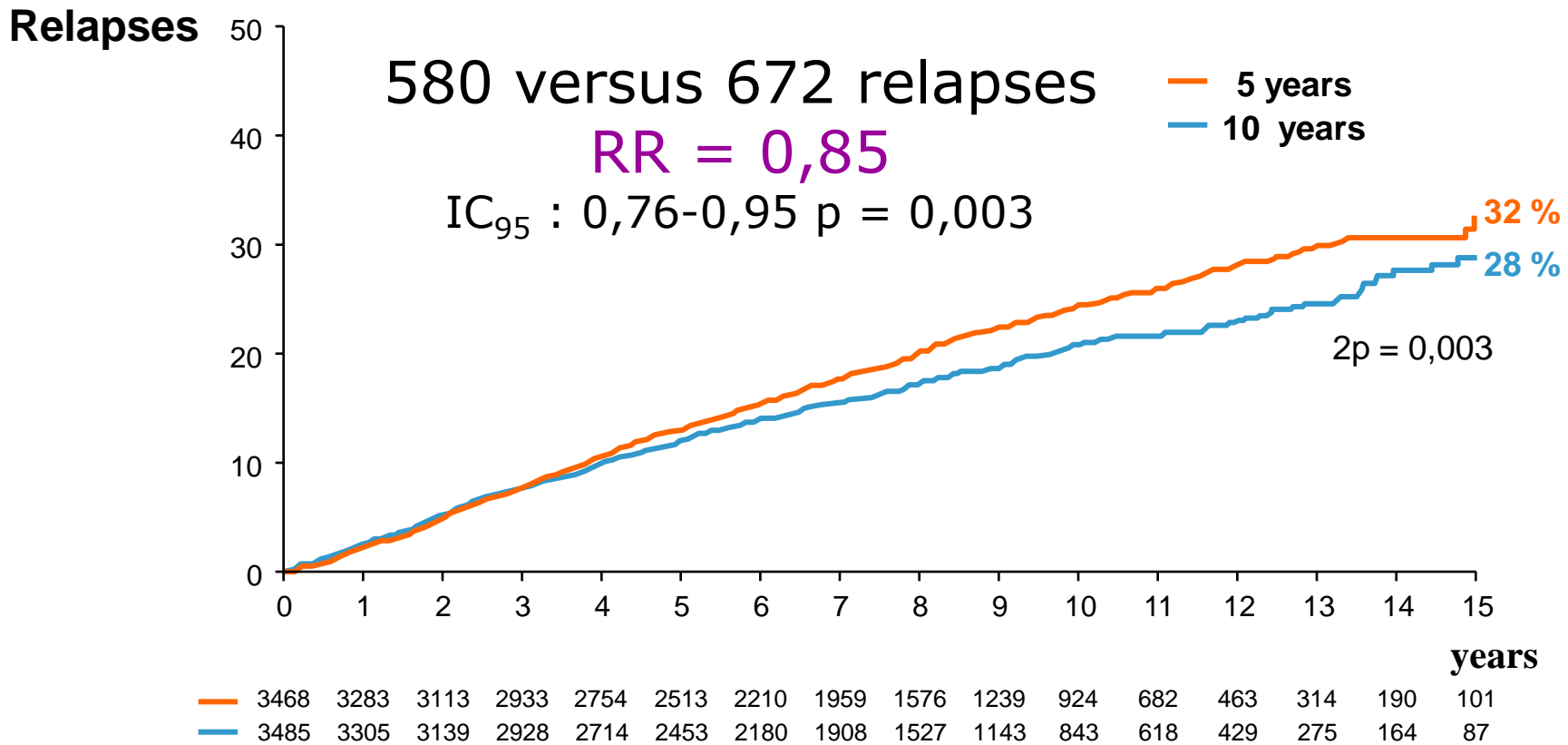
Treatment duration: recent data

Atlas

- **RR pulm embolism 1.87**
- **RR Endometrial cancer 3.1**
- **Overmortality endometrial cancer 0.2%**

Treatment duration: recent data

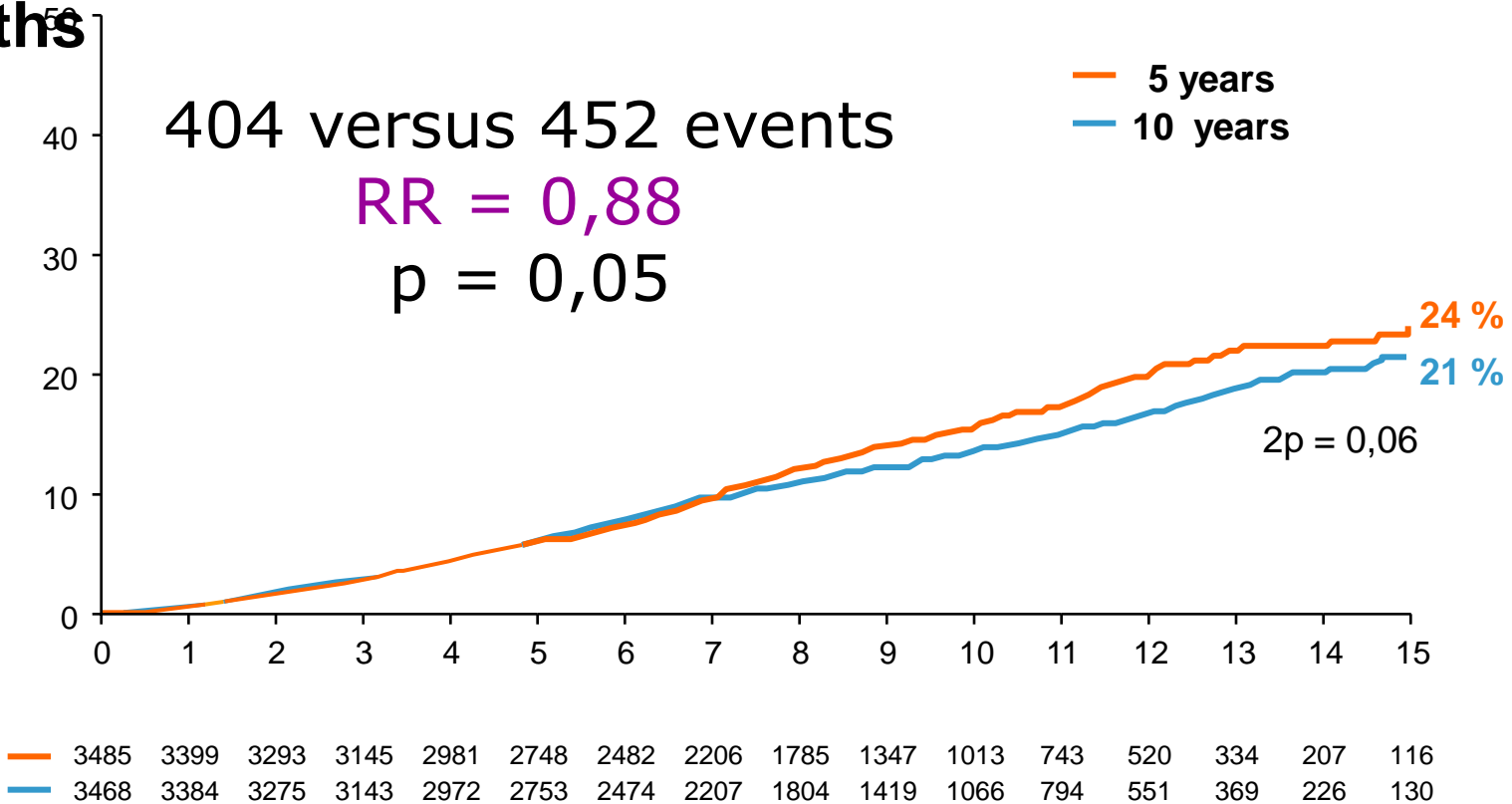
At-TOM: same design



Treatment duration: recent data

At-TOM

BC deaths

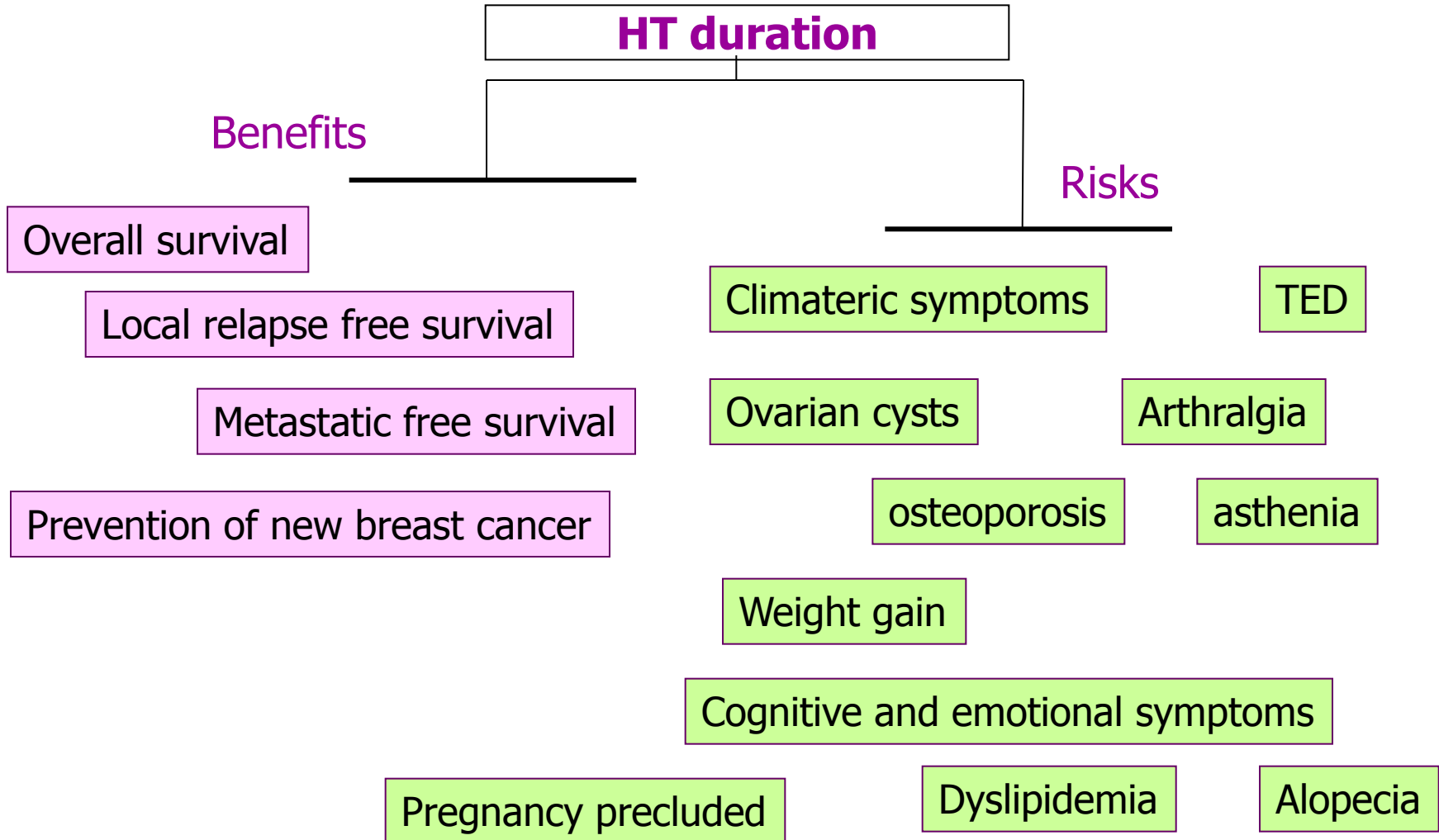


Treatment duration: recent data

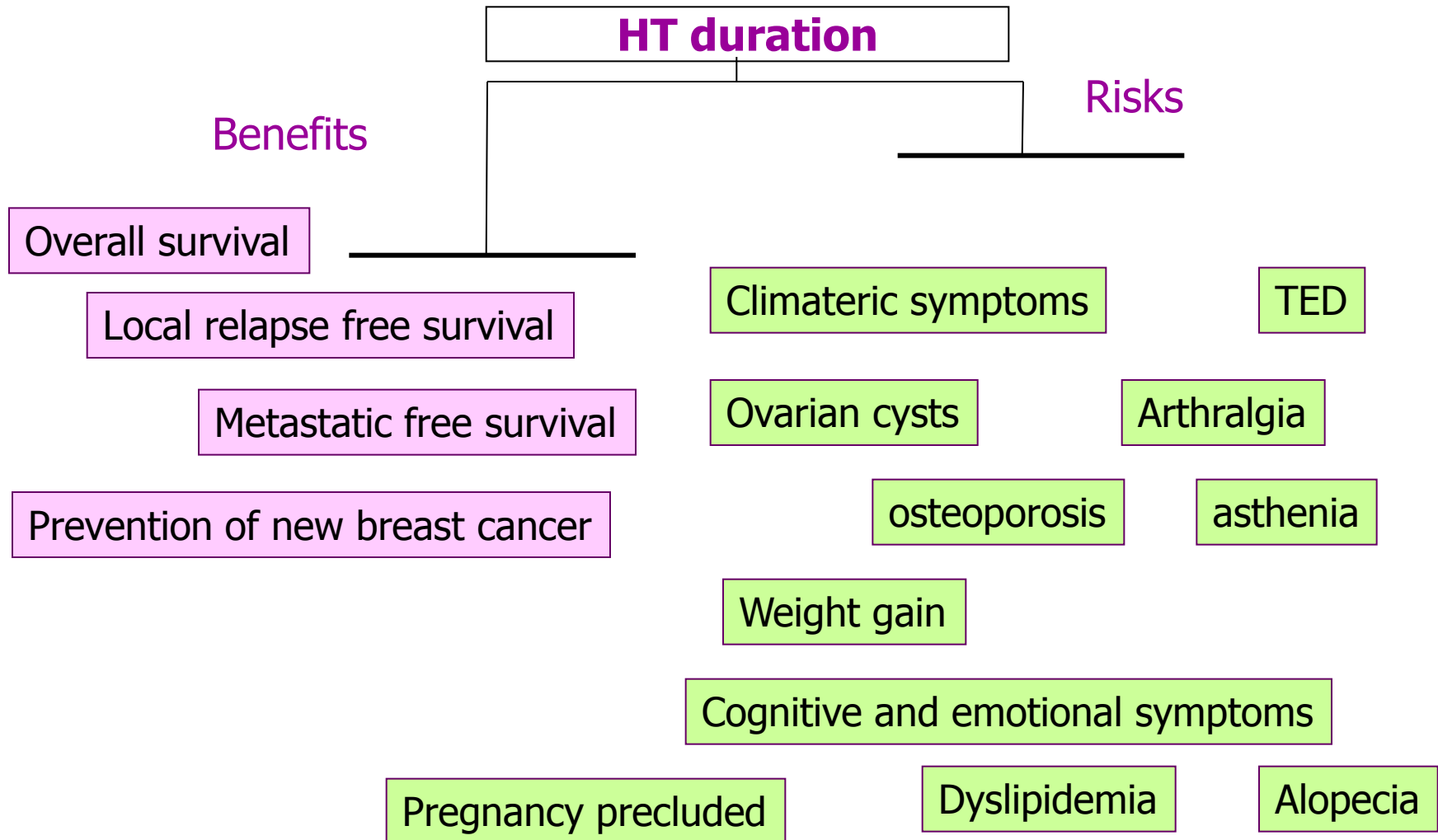
At-TOM

	10 years n (%)	5 years n (%)	RR (IC ₉₅)	p
Endometrial cancer	102 (2,9)	45 (1,3)	2,20 (1,31- 2,84)	< 0,0001
Death from endometrial cancer	37 (1,1)	20 (0,6)	1,83 (1,09- 3,09)	0,02

Treatment duration: no definitive proof of concept + a risk-benefit balance...



Treatment duration: no definitive proof of concept + a risk-benefit balance...

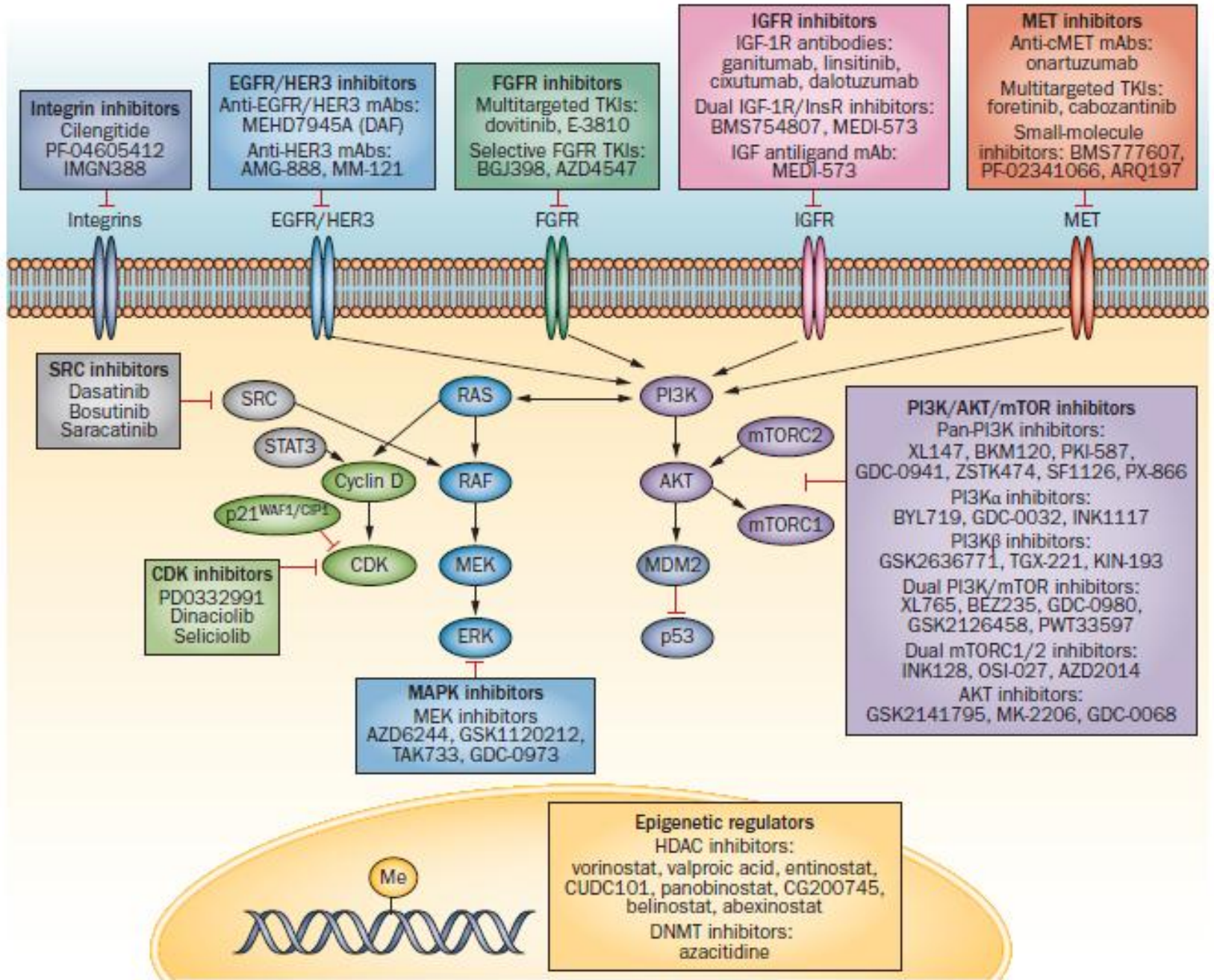


Outline

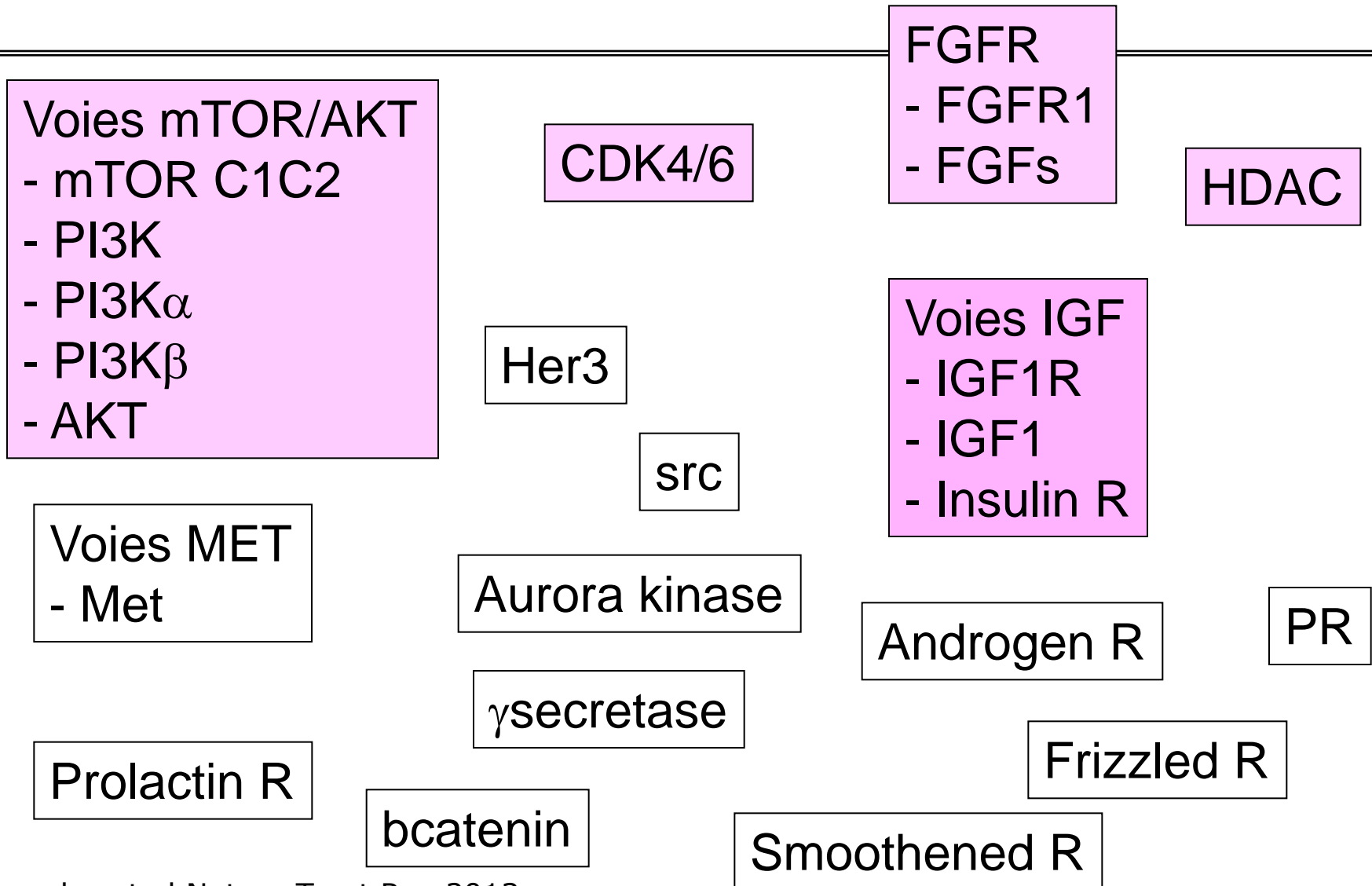
- Prevention
- Adjuvant setting
- Advanced disease

Challenge towards 2020

- Individually identify and prevent/treat hormone resistance

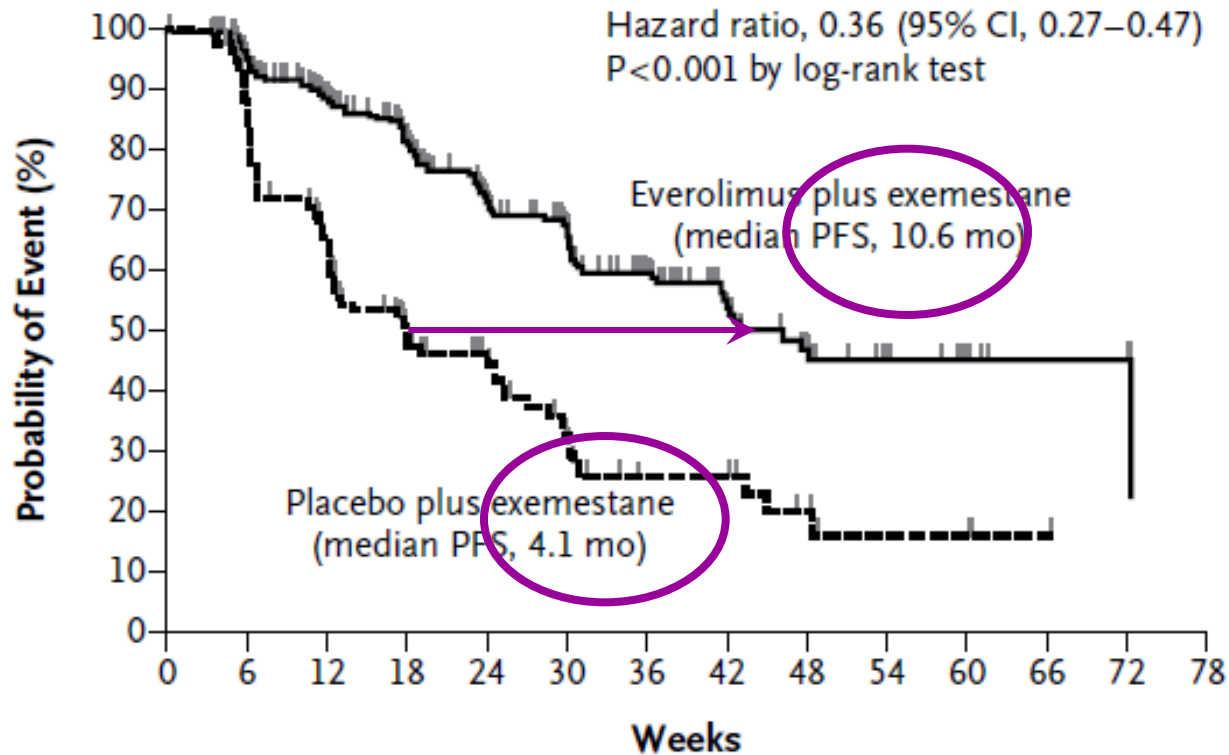


Current targeted developments towards hormone resistance reversion/prevention



Initial proof of concept: mTOR inhibitor can reverse HT resistance (everolimus: Affinitor®)

B Central Assessment



No. at Risk

Everolimus	458	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Anti CDK4/6: ex palbociclib randomised phase II



LET +
palbo

LET alone

Thanks a lot

**GUSTAVE
ROUSSY**
CANCER CAMPUS
GRAND PARIS

