

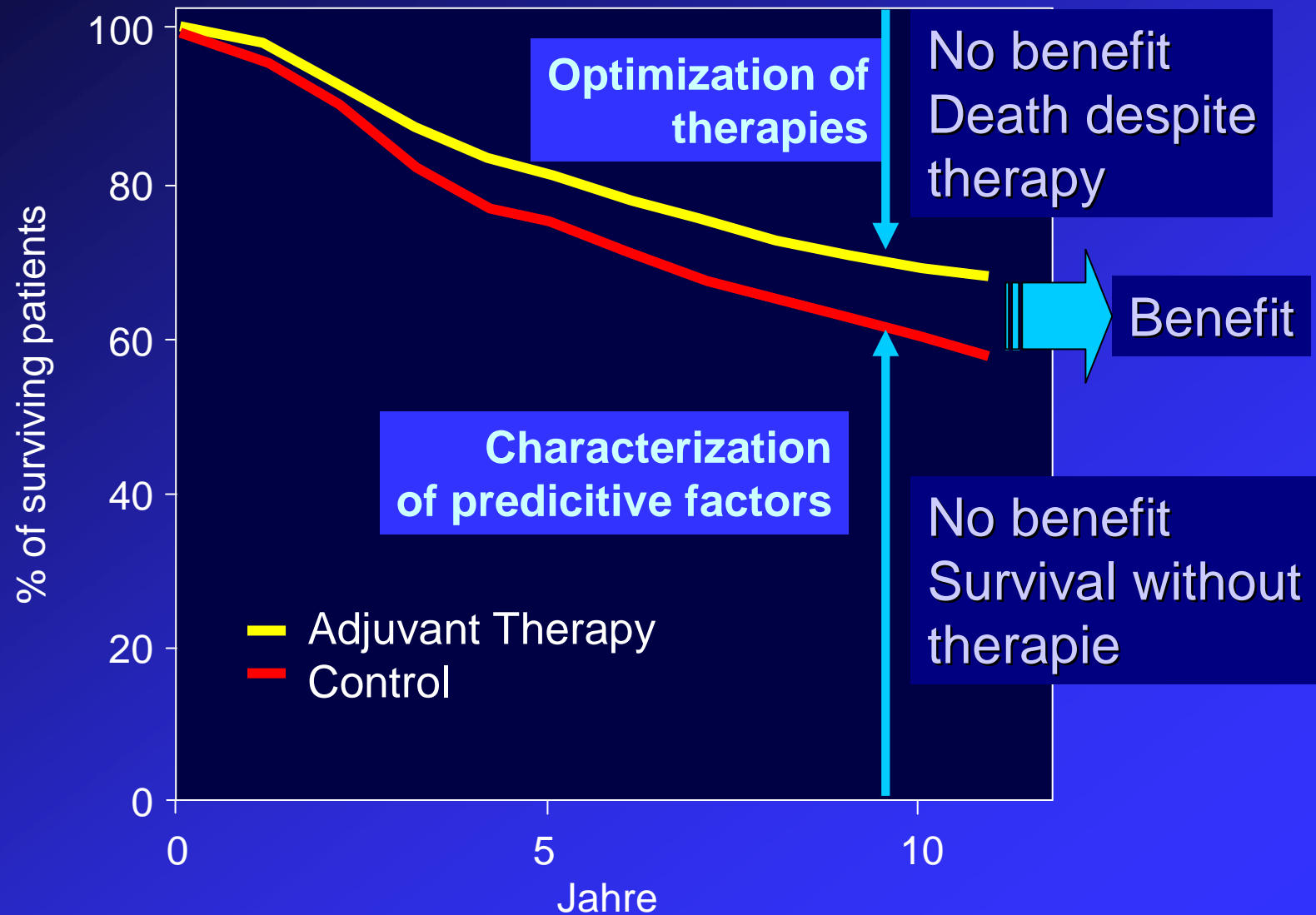
Onkologie in Klinik und Praxis
Wilhelminenspital, 08.11.2011

Adjuvante Therapie **des** **Mammakarzinoms**

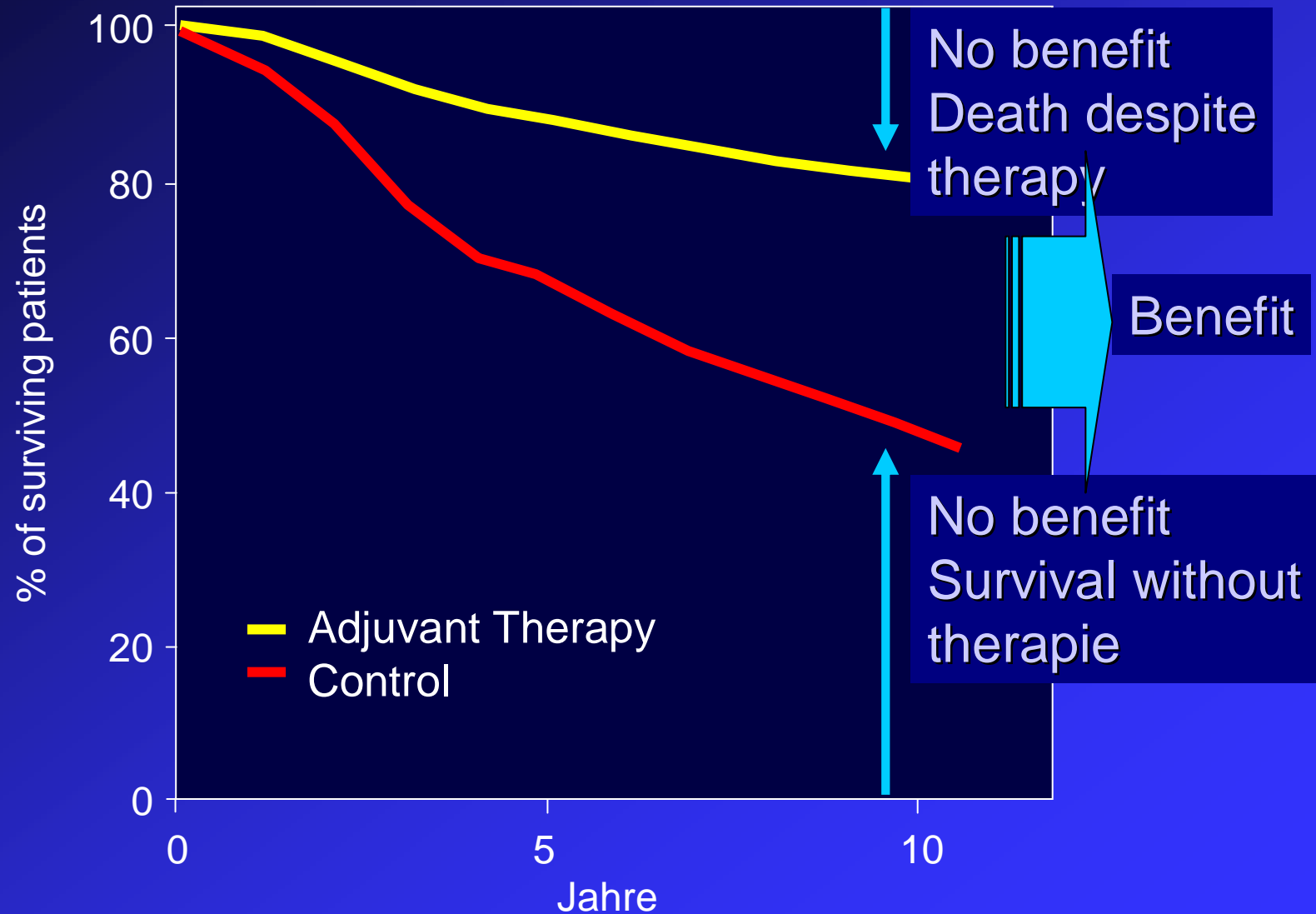
Günther Steger
Universitätsklinik für Innere Medizin I
Klinische Abteilung für Onkologie
Medizinische Universität Wien

Steger OKP2011

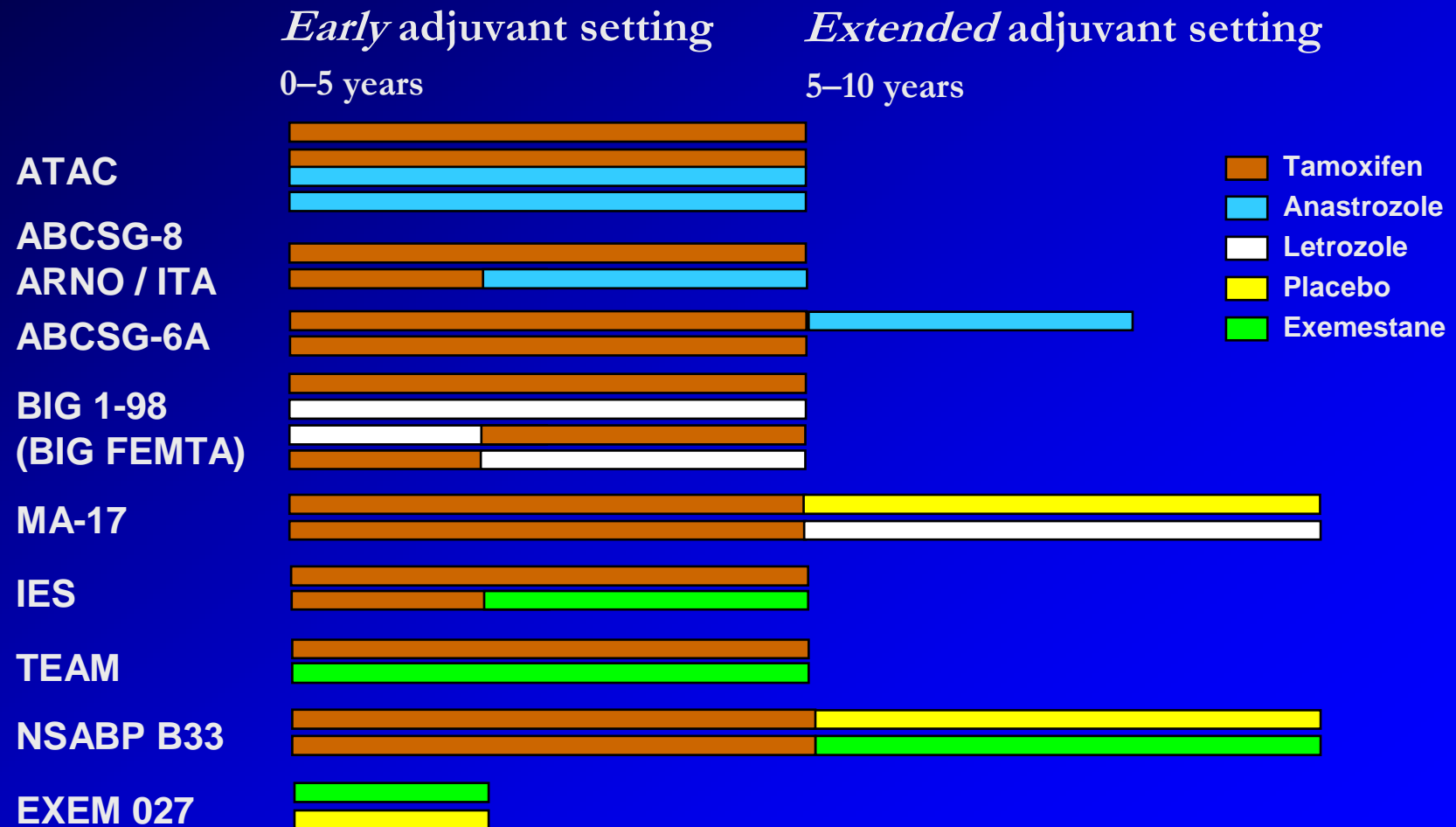
Risks and Benefits of adjuvant Treatment



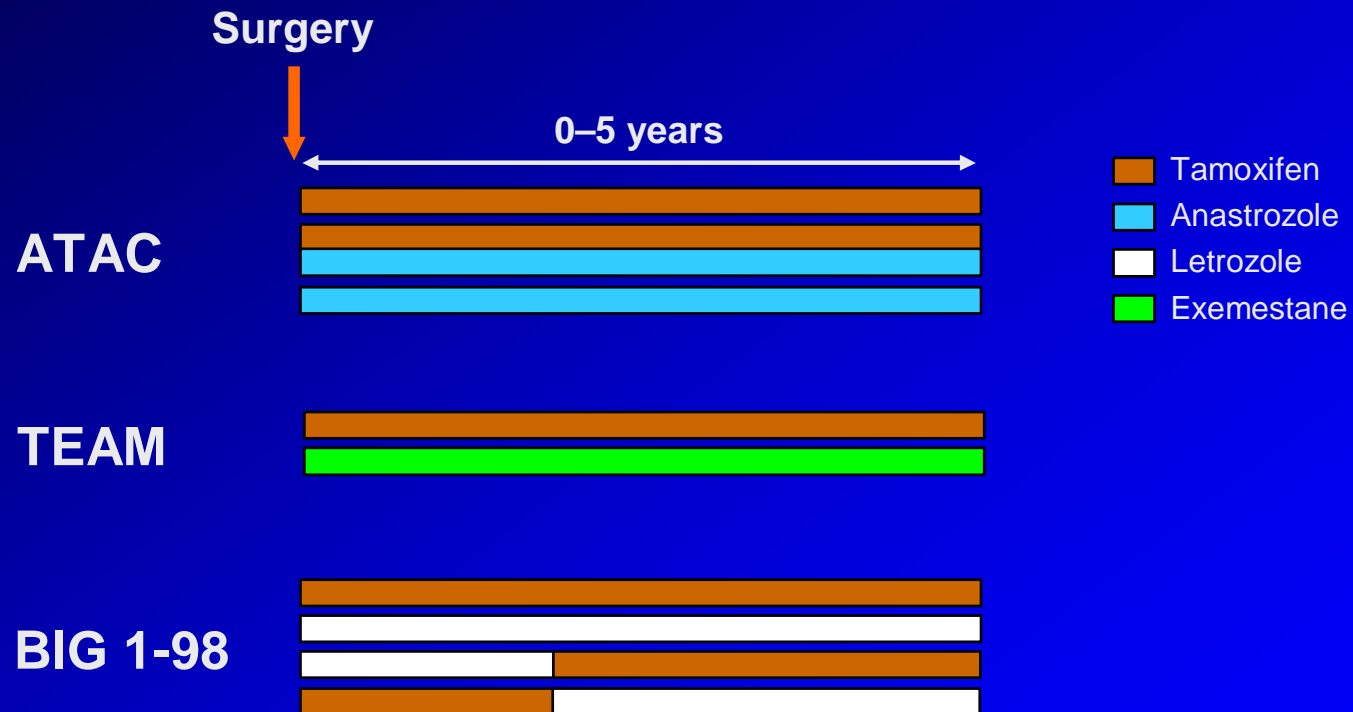
Risks and Benefits of adjuvant Treatment



Studien mit Aromatasehemmern

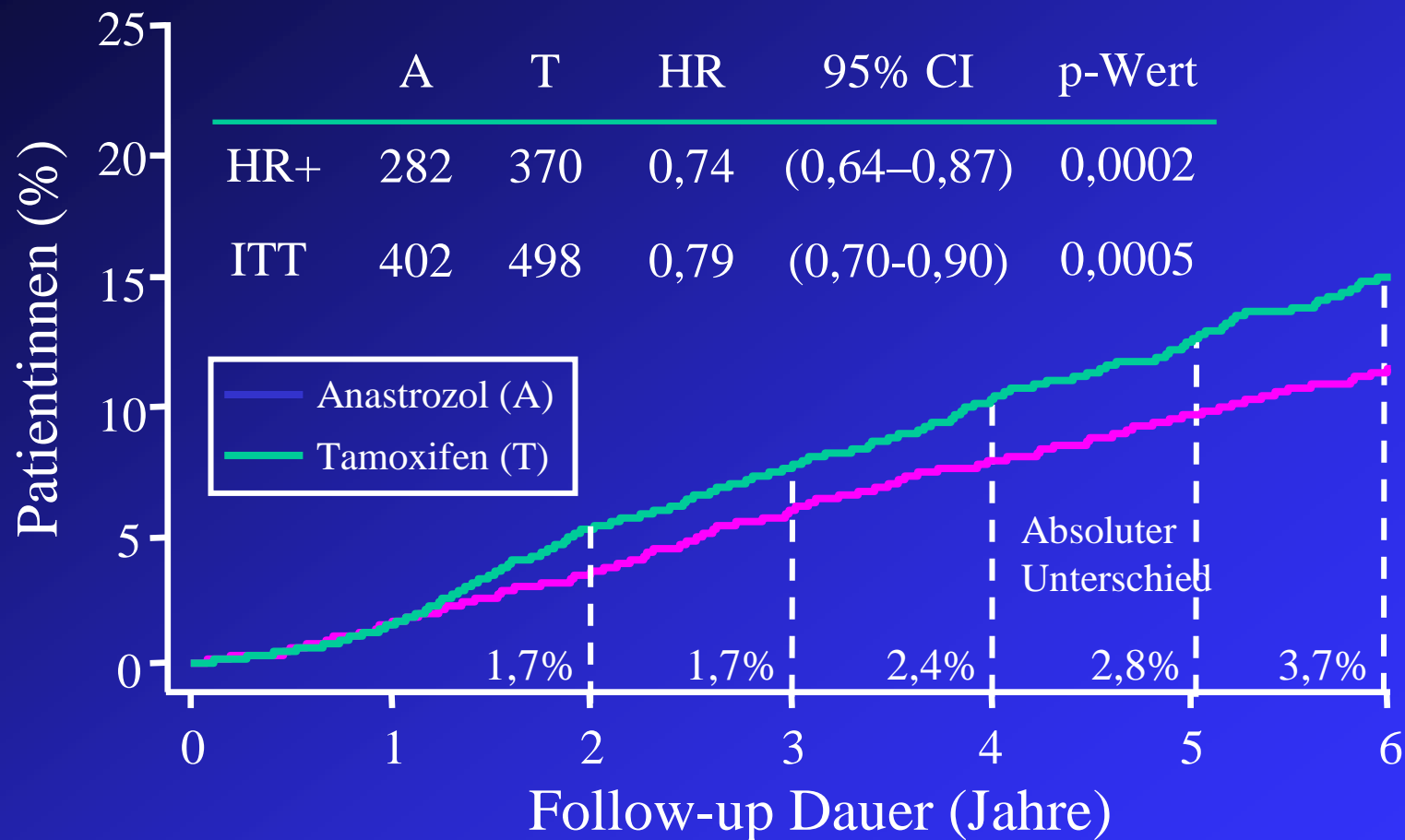


Early (upfront) trials



ATAC: Mammakarzinom-Ereignisse*

KM Kurven für HR+ Patientinnen



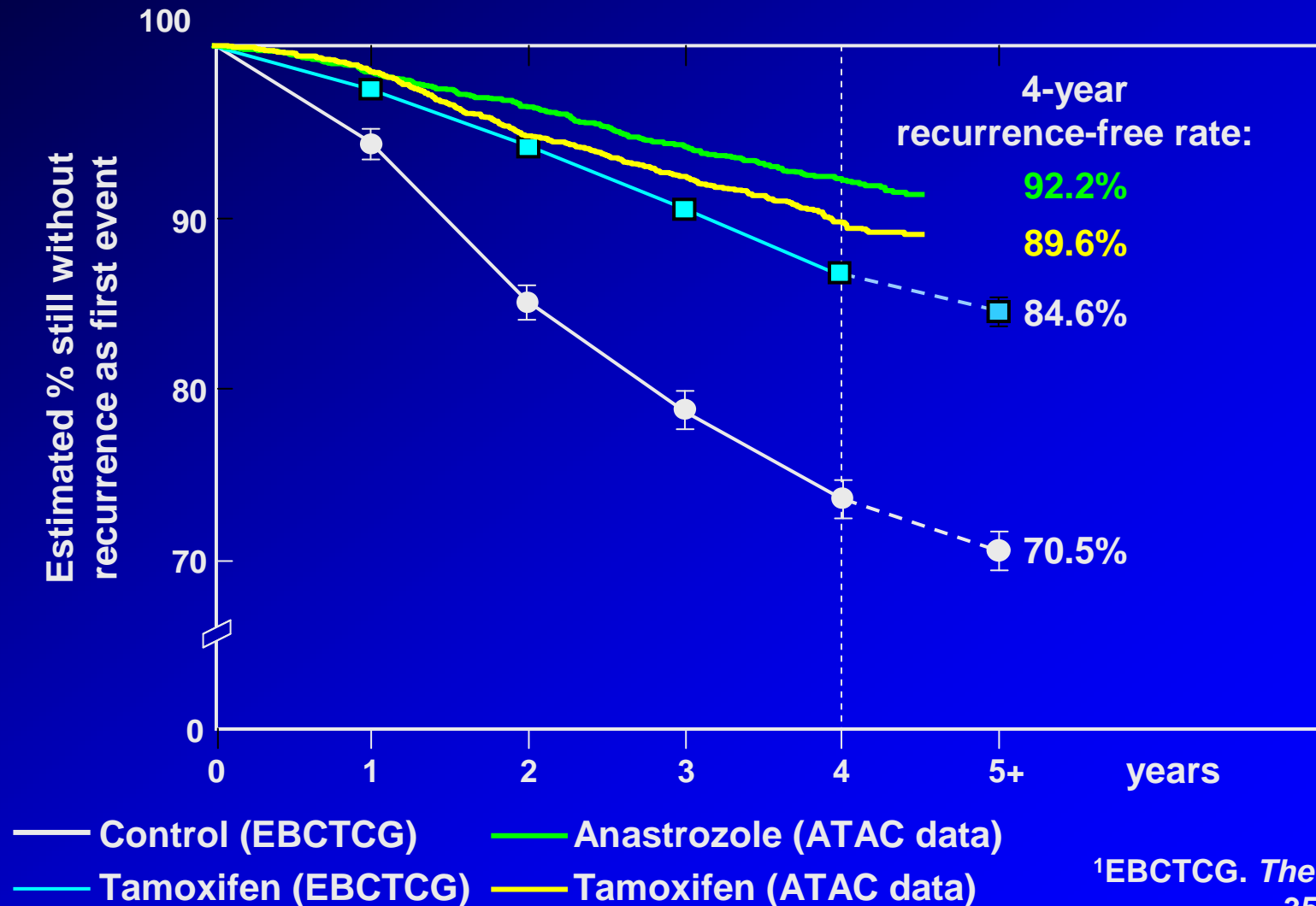
A	2618	2540	2448	2355	2268	2014	830
T	2598	2516	2398	2304	2189	1932	774

*TTR = Time to Recurrence, Todesfälle vor Krankheitsereignis nicht miteingeschlossen

Steger UKF 2011

Howell, SA 2004

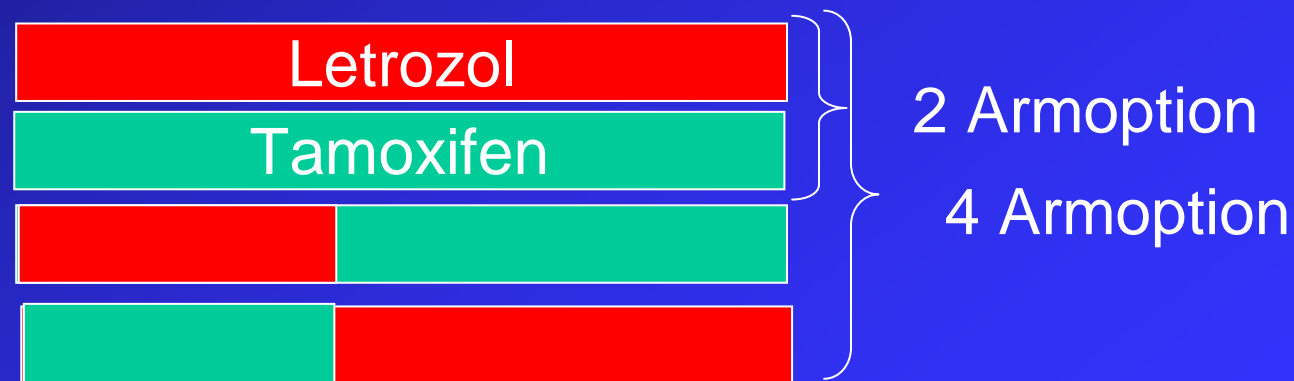
ATAC und EBCTCG 1995:¹ HR +ve Patients >50 Years



¹EBCTCG. *The Lancet* 1998;
351: 1451–1467

BIG 1-98 Studie

- Letrozol vs. Tamoxifen
- Letrozol A und C
- Tamoxifen B und D
- Ereignisse nach Switch in Arm C und D wurden nicht berücksichtigt.
- N=8.010, Follow-up 25,6 Monate



BIG 1-98 trial: Risk reduction

TTR

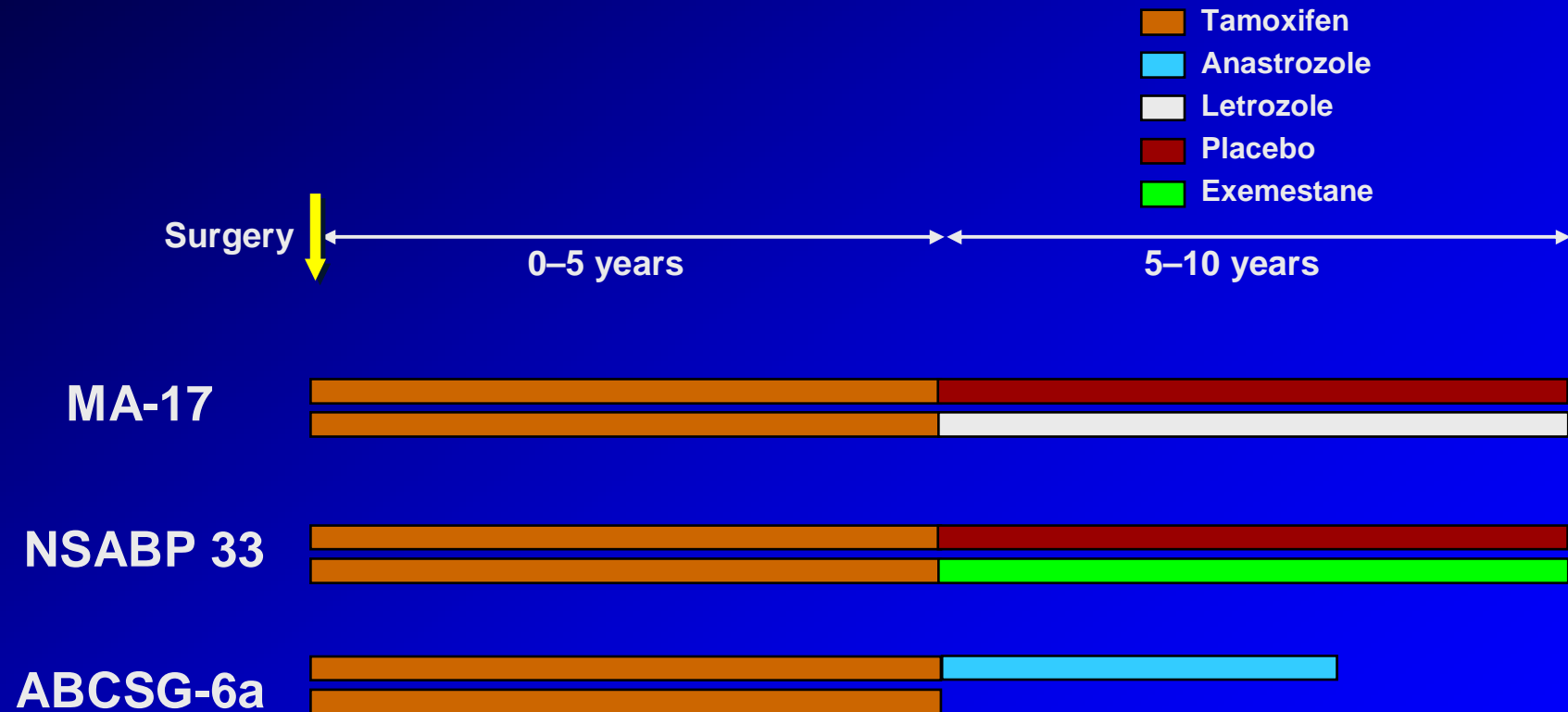
Follow-up (months)	Relative	p-value	At	Absolute
25.8	19%	0.003	5 yrs	2.6%

■ At 25.8 months

- Significant reduction in time to recurrence, 28%; **p=0.0002**
- Significant reduction in distant metastases, 24%; **p=0.006**
- Trend to mortality reduction, 14%; **p=0.16**

The ATAC Trialist's Group. *Lancet* 2002; **359**: 2131; *Cancer* 2003; **98**: 1802–10;
Lancet 2005; **365**: 60–2.

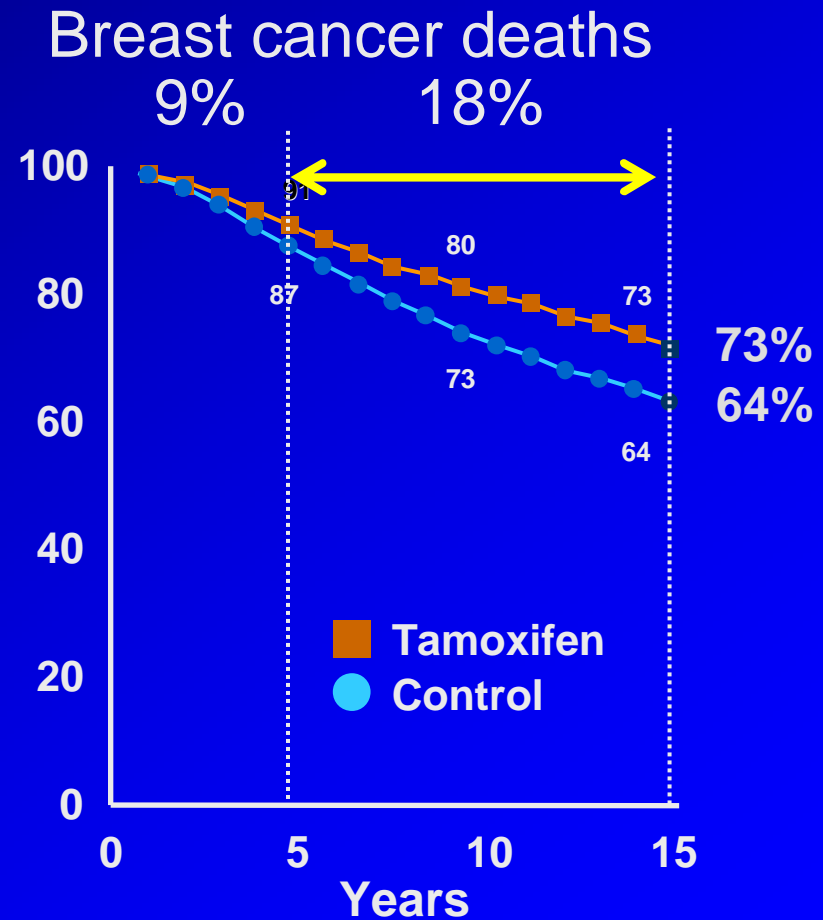
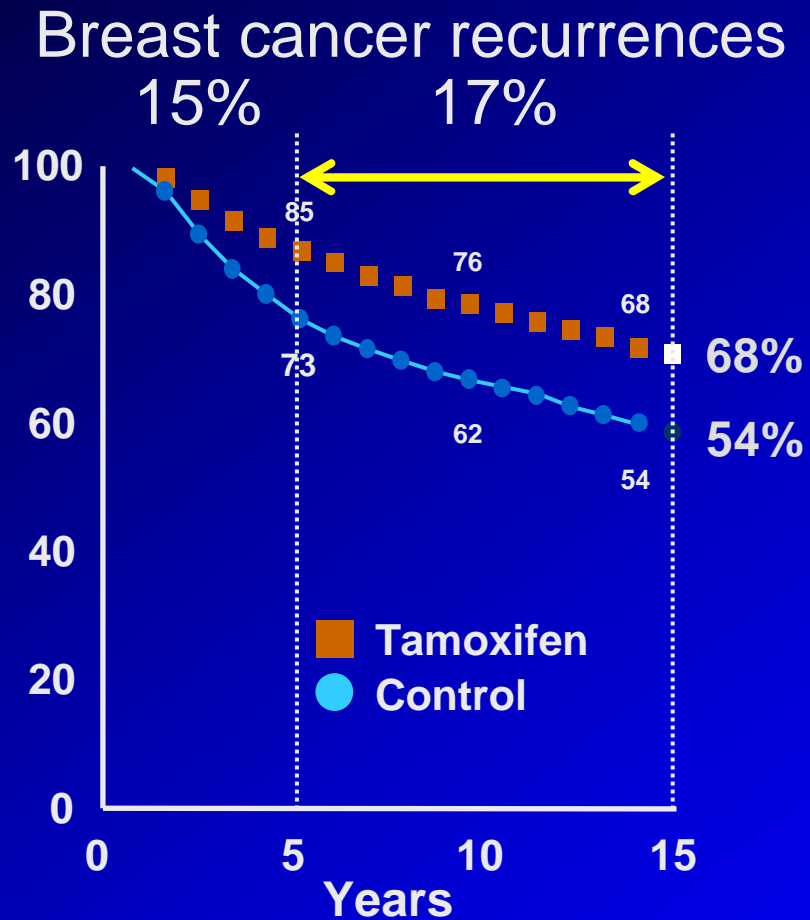
Extended trials



Warum entstehen späte Rezidive ?

- aufgrund einer weiterbestehenden genetischen Prädisposition (als new tumors).
- „spontan“, durch „erwachende“ dormants.
- als Ausdruck der Resistenzentwicklung von dormants und Mikrometastasen.

Timing of breast cancer events



MA-17

The NEW ENGLAND JOURNAL of MEDICINE

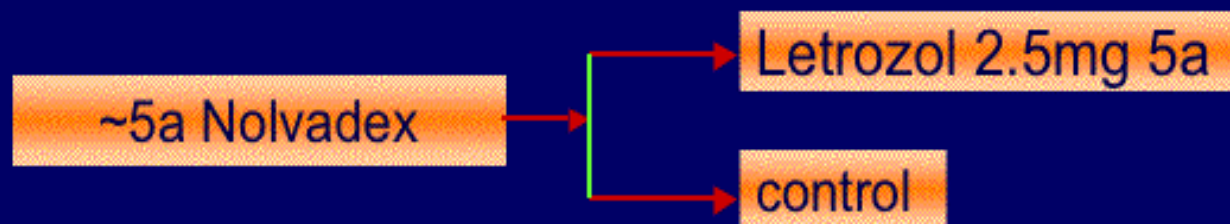
ESTABLISHED IN 1812

NOVEMBER 6, 2003

VOL. 349 NO. 19

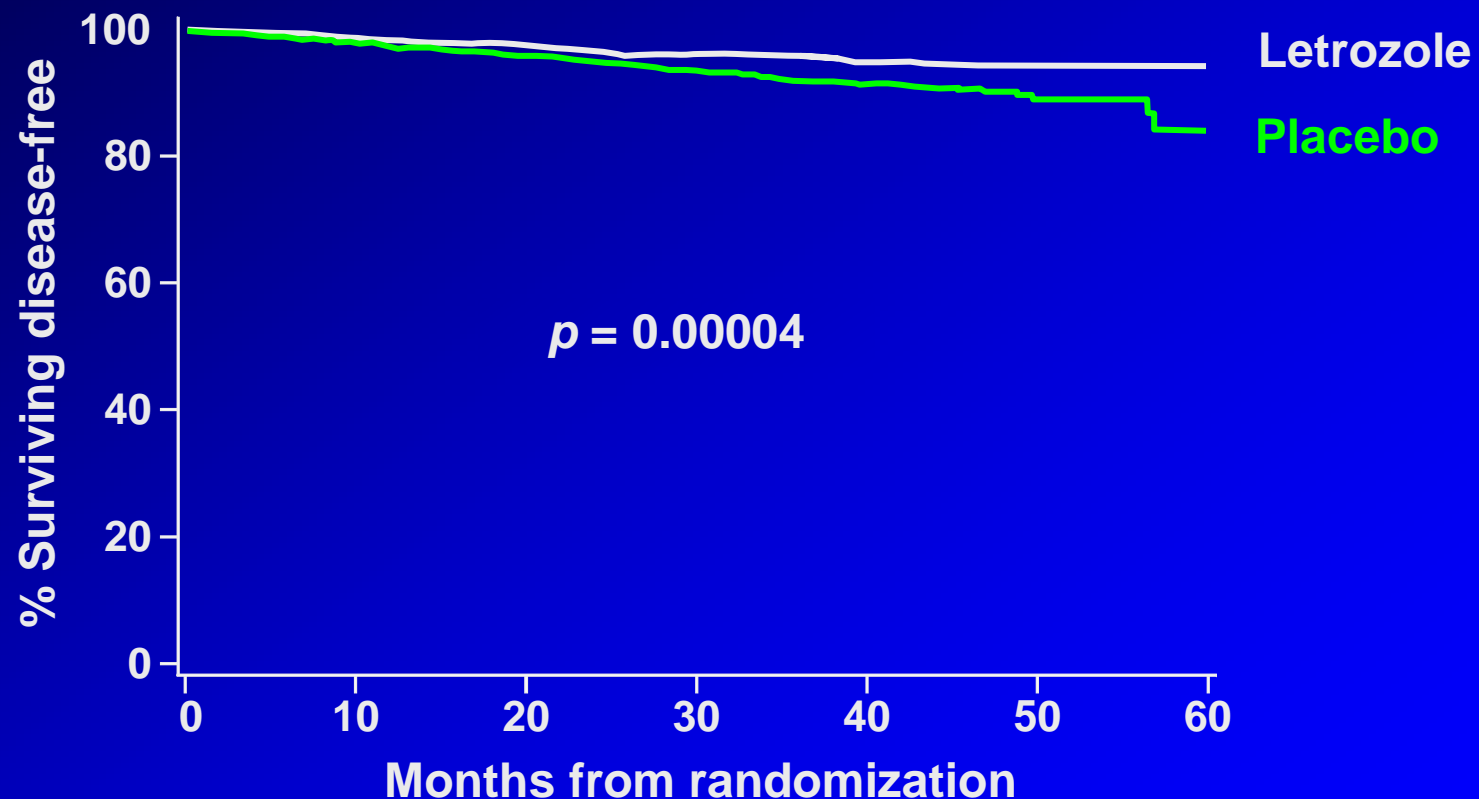
A Randomized Trial of Letrozole in Postmenopausal Women after Five Years of Tamoxifen Therapy for Early-Stage Breast Cancer

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.



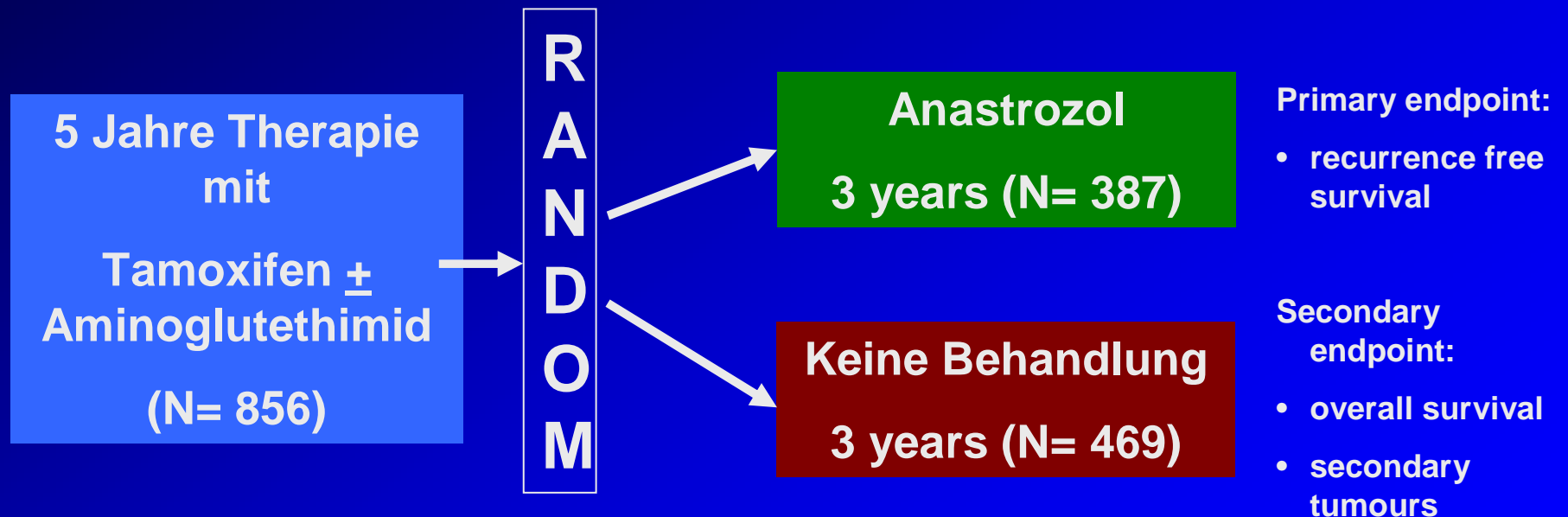
MA-17:DFS - all patients

Letrozole reduced risk of recurrence by 42%

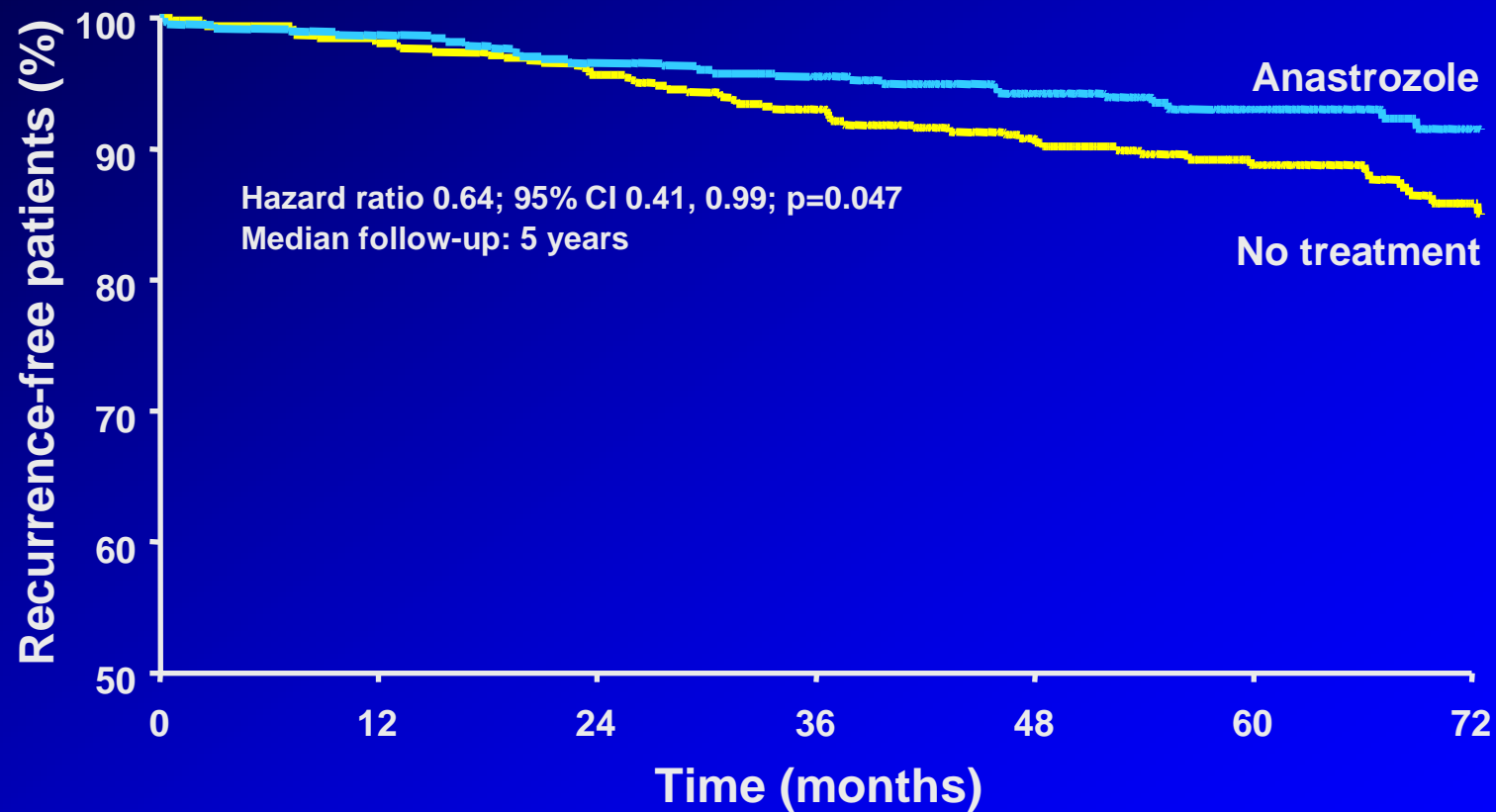


No. at risk (Letrozole)	2583	2497	1905	1110	541	176	6
No. at risk (Placebo)	2587	2489	1874	1075	519	164	8

ABCSG 6a - Studiendesign



ABCESG 6a: RFS*



* Based on incidence of local, contralateral and metastatic disease

ABCSG-16 (SALSA)

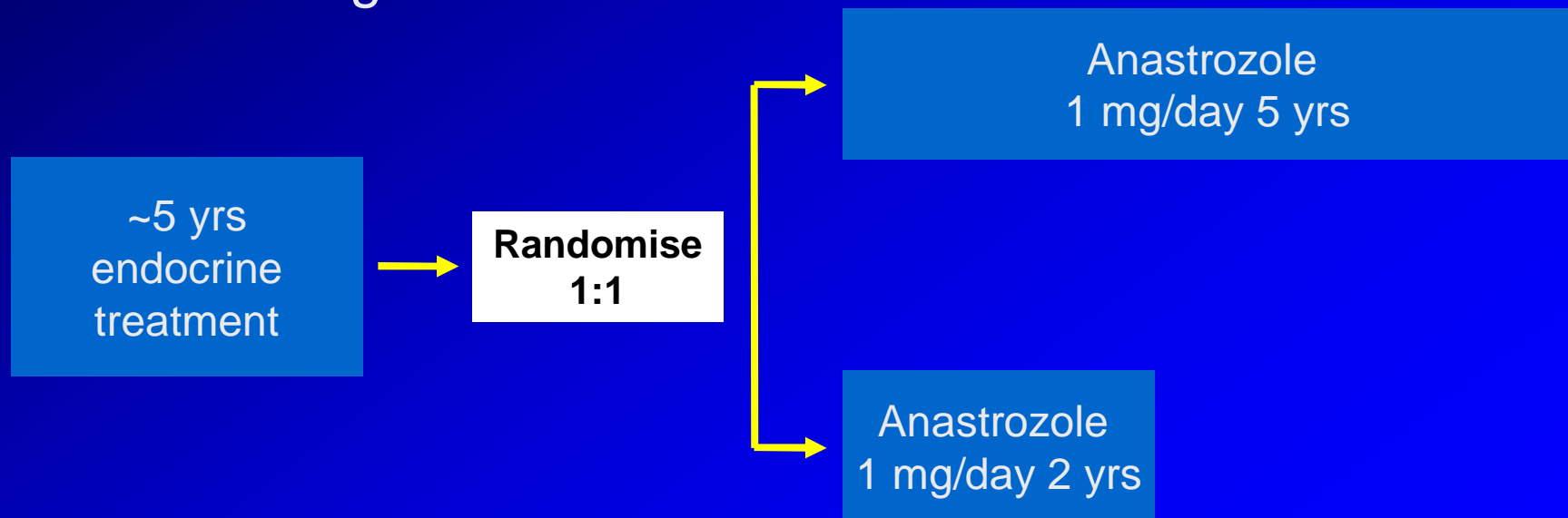
(Sekundäre Adjuvante Langzeitstudie mit Anastrozol)

Accrual 2004–2010

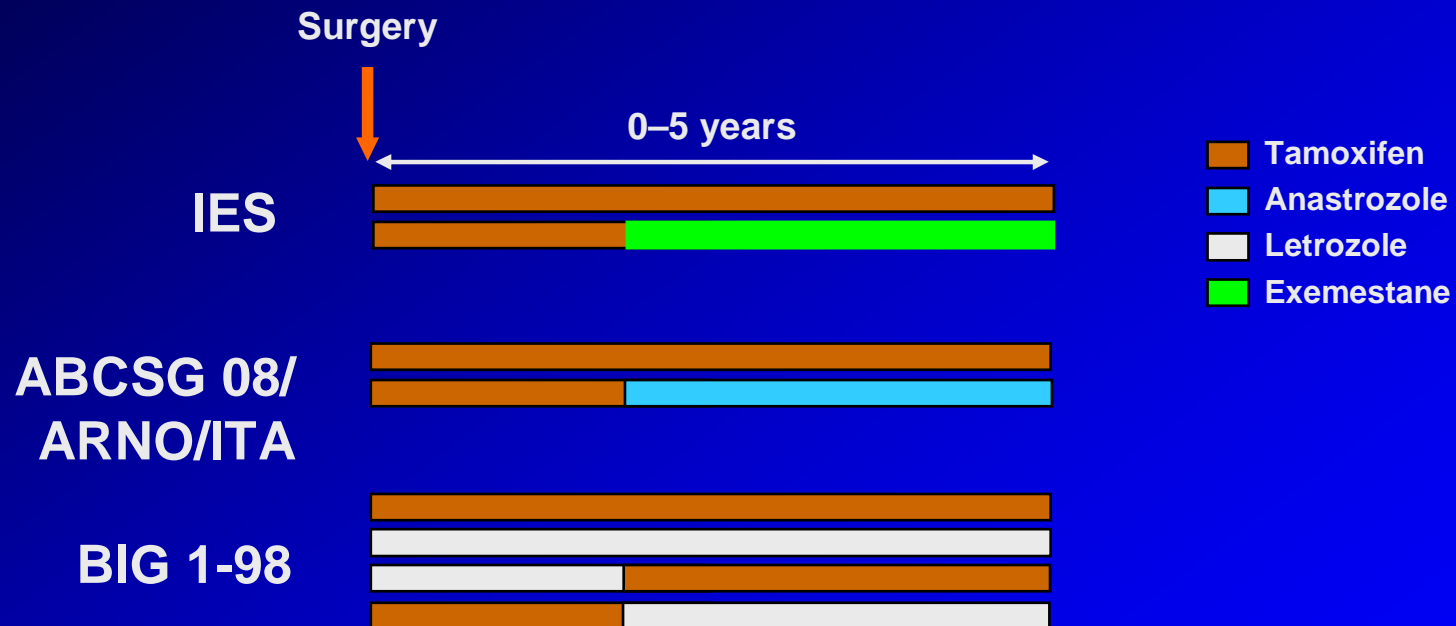
3,500 postmenopausal patients

After 5 years of endocrine treatment

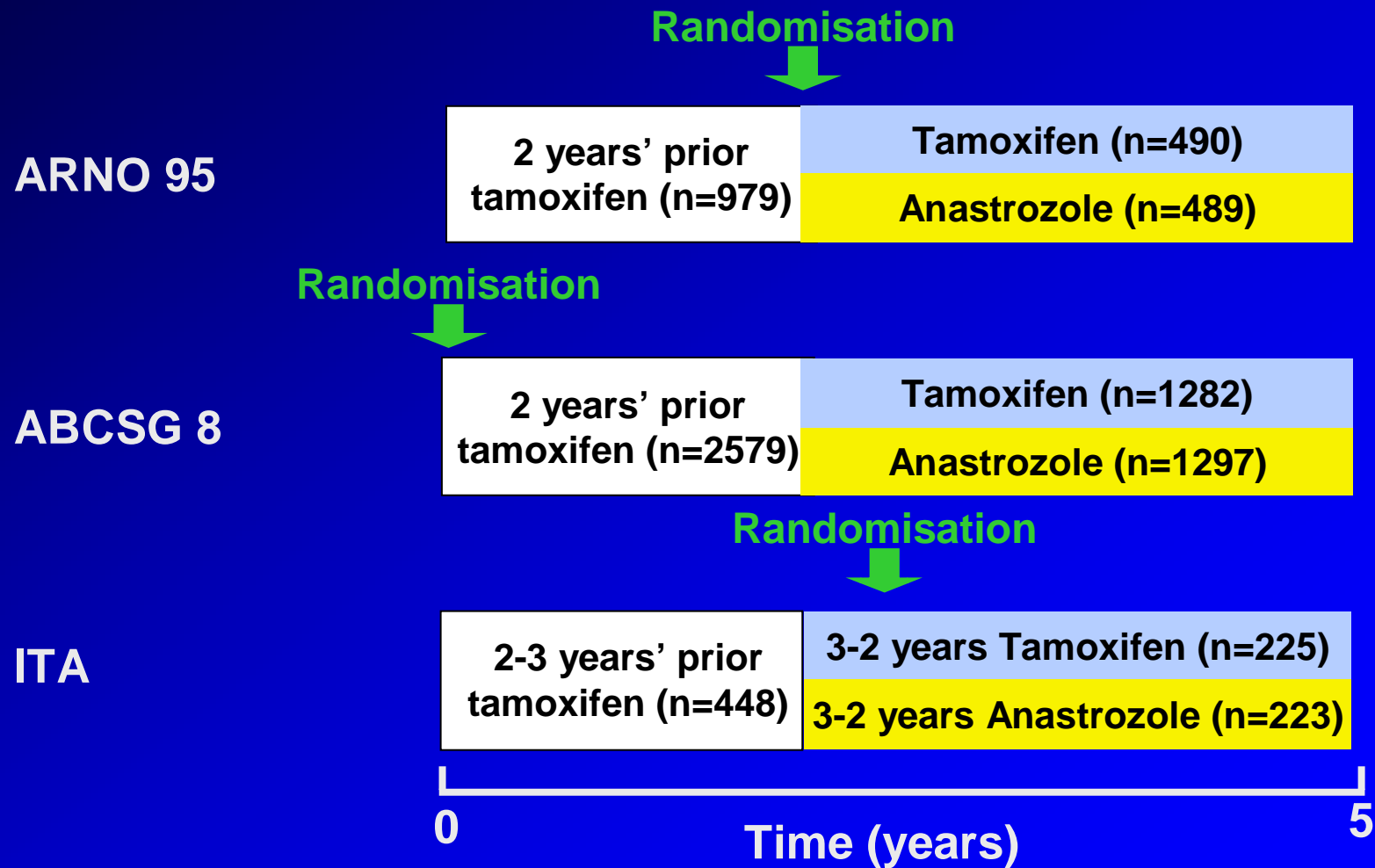
ER+ and/or PgR+



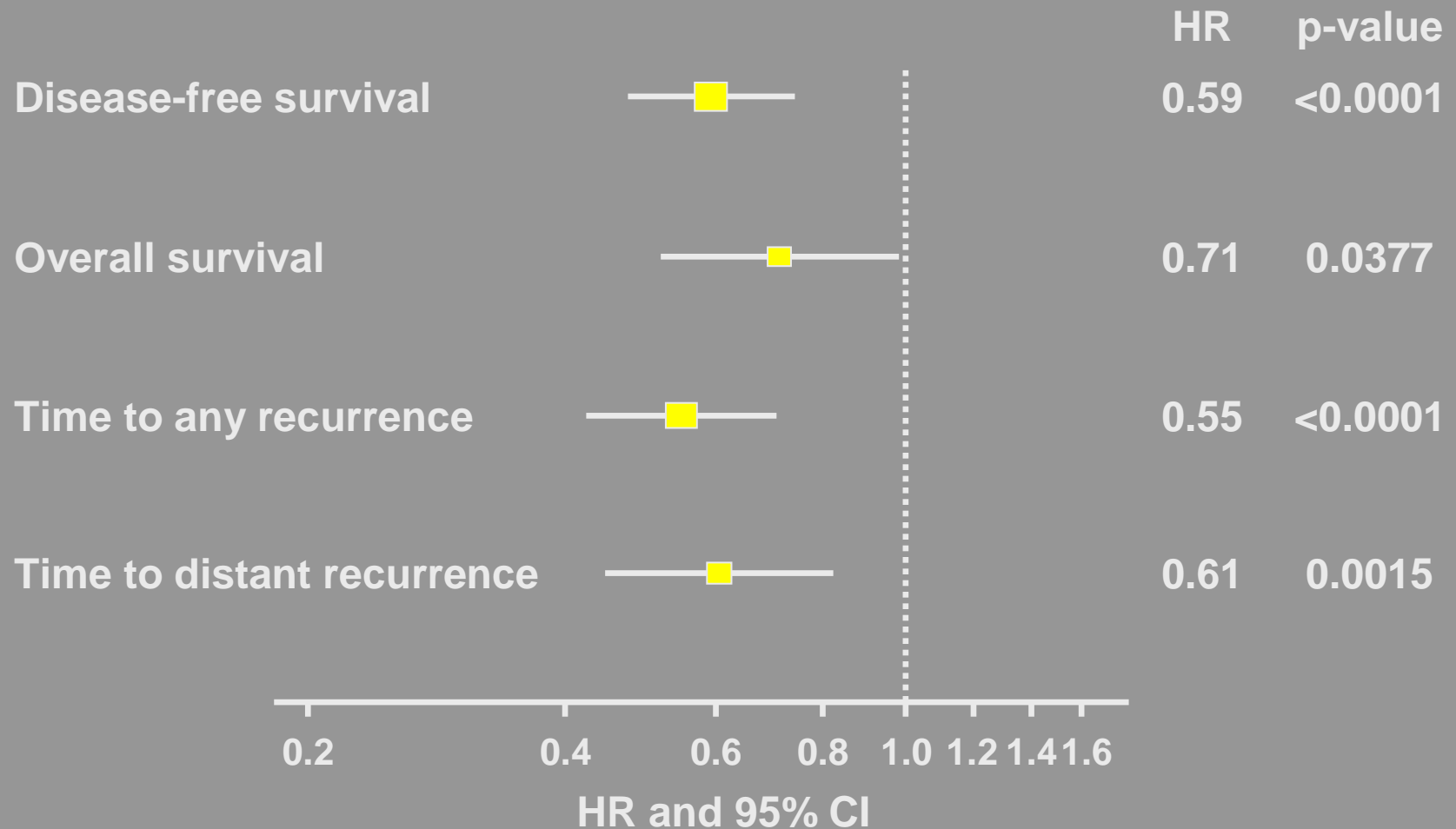
Early sequential trials



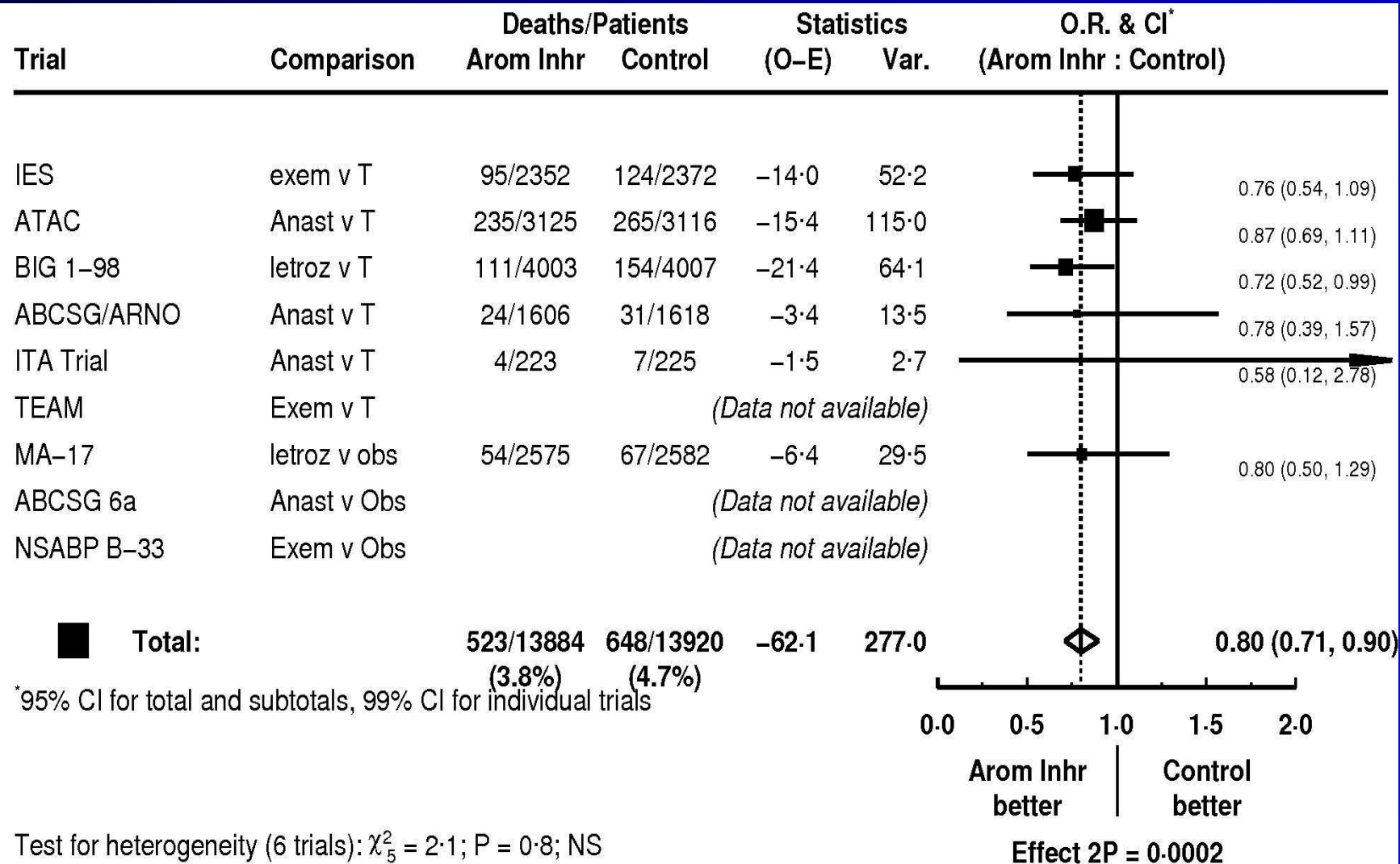
Metaanalyse: Study designs



Forest plot: summary of efficacy (ITT population)



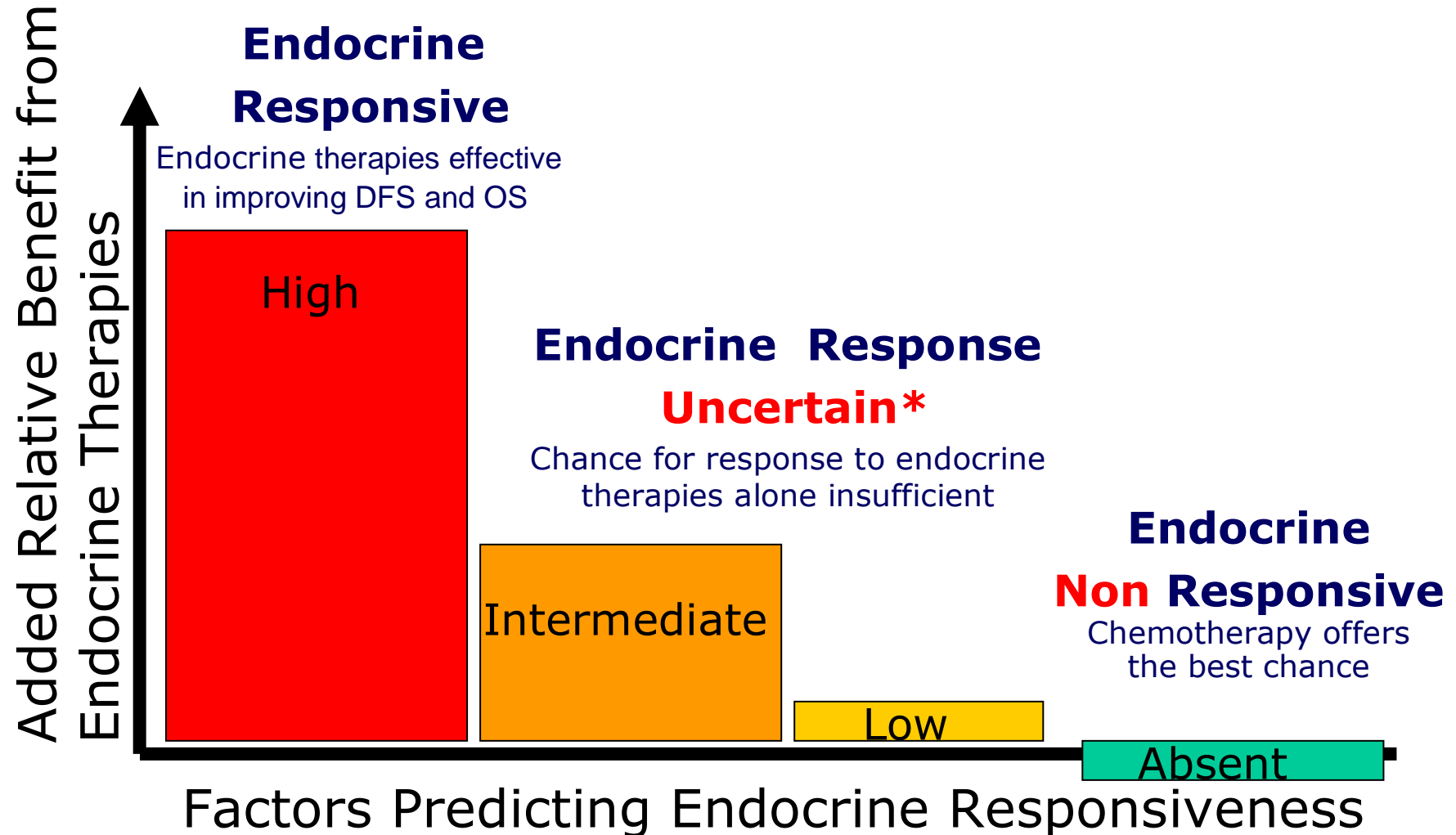
Breast Cancer DEATHS in trials of aromatase inhibitors versus tamoxifen or no treatment



ASCO Technology Assessment

Optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen.

St. Gallen 2005



* e.g., levels of ER positivity, lack of PgR expression, HER2/neu overexpression, increased proliferation markers, large micro-metastatic burden of disease ...

CONSENSUS St. Gallen 2005

Receptorstatus

	HR pos		HR uncertain		HR neg
Meno-status	Prä	Post	Prä	Post	Prä
N0 low	Tam or nil	Tam or AI or nil (Tam > AI)	Tam or nil	Tam or AI or 0 (Tam > AI)	Chemotherapy (6xAnthrac.Triplet)
N0 + risk N+ average (= N1-3)	Tam +/- OFS or CT>Tam +/-OFS or OFS	Tam or AI CT>Tam or CT>AI or CT> T>AI	CT>Tam (+/-OFS) or CT alone	CT>Tam or CT>AI or CT> Tam>AI	Chemotherapy (6 cycles/months) +/- Taxan
high risk N4+	CT>Tam +/-OFS	CT>T or CT>AI	CT (6xTriplet) + Taxan > ET		Chemotherapy (6 cycles 7 months) + Taxan

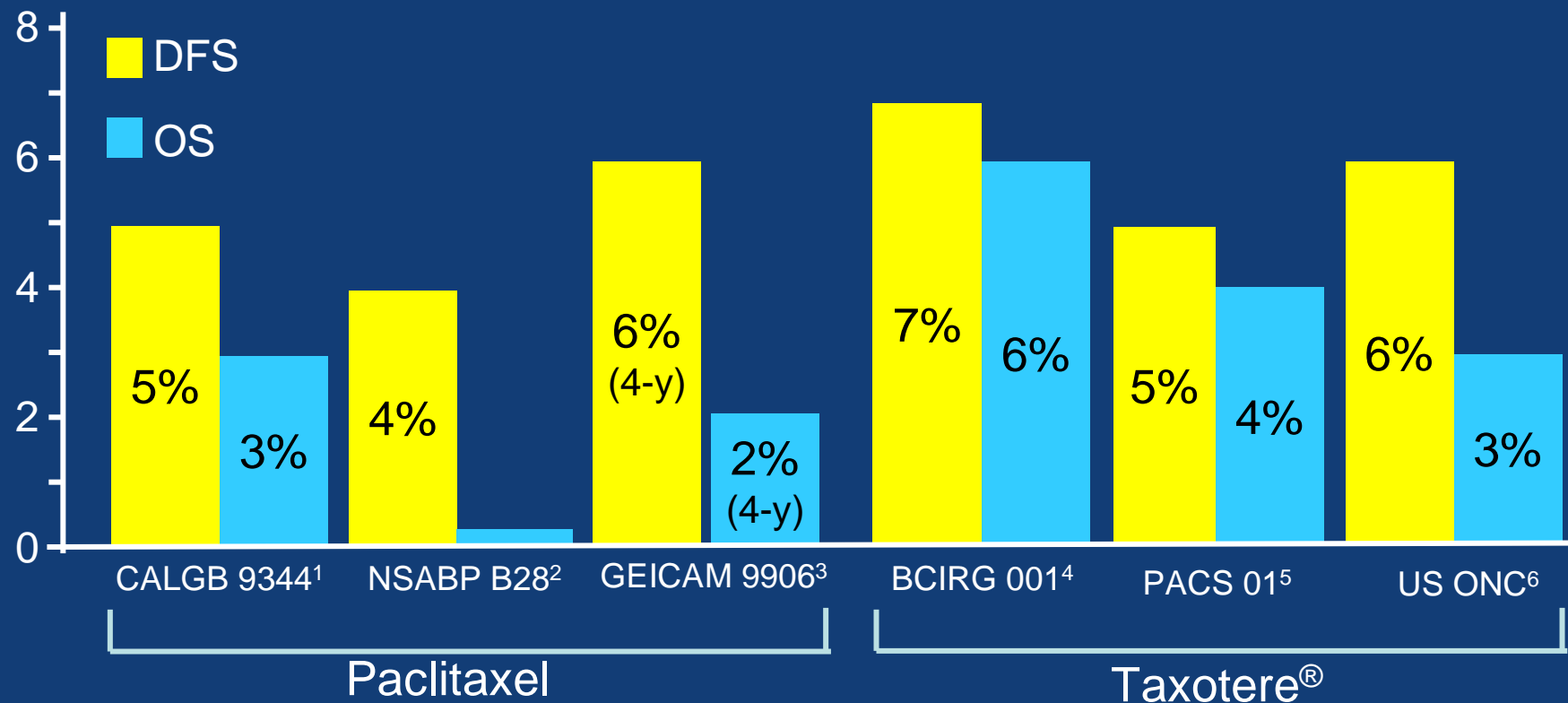
AI: Anastrozol or Letrozol
 2-3a Tamoxifen > Anastrozol or Exemestane
 5a Tamoxifen > Letrozol or Anastrozol

HR: Hormonrezeptoren; Tam: Tamoxifen; AI: Aromataseinhibitoren; OFS: ovarian function suppression; ET: endocrine treatment

CONSENSUS St. Gallen 2005

Rolle der Taxane ?

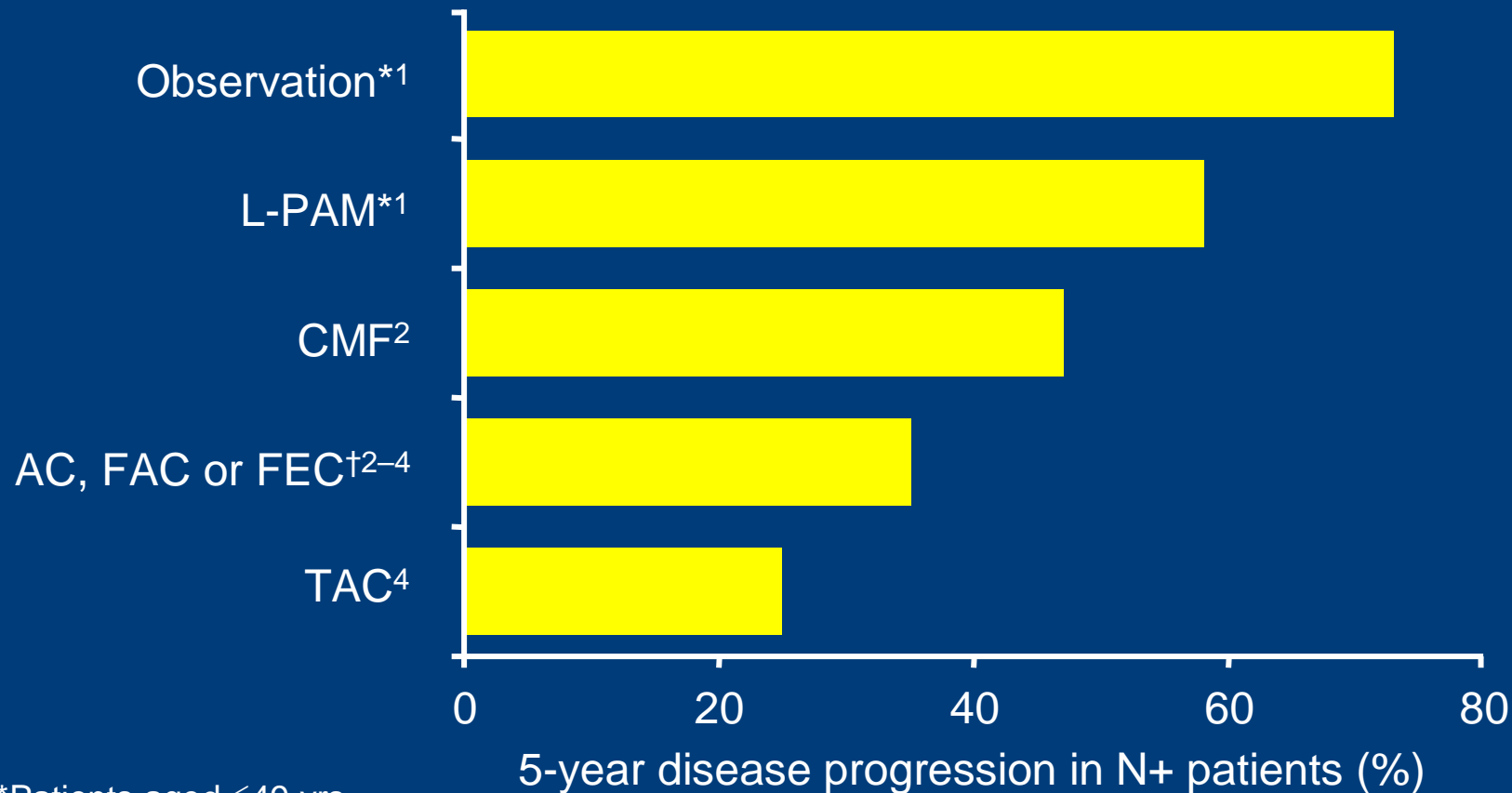
Adjuvant trials with taxanes: absolute 5-year benefit over comparator



DFS, disease-free survival;
OS, overall survival

1. Henderson IC et al. J Clin Oncol 2003;21:976-83; 2. Mamounas EP et al. ASCO 2003. Abstract 12; 3. Martin M et al. SABCS 2005. Abstract 39. 4. Martin M et al. N Engl J Med 2005;352:2302-13; 5. Roché H et al. SABCS 2004; Abstract 27; 6. Jones S et al. J Clin Oncol 2006;24:5381-7

Improvements in chemotherapy outcomes in high-risk breast cancer



*Patients aged ≤ 49 yrs

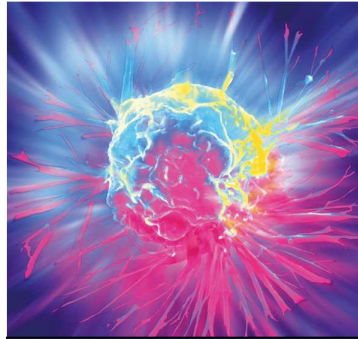
[†]Average value

N, node

1. Fisher B et al. J Clin Oncol 1986;4:929–41; 2. Levine M et al. J Clin Oncol 1998;16:2651–8;
3. Bang S et al. Cancer 2000;89:2521–6; 4. Martin M et al. N Engl J Med 2005;352:2302–13

CONSENSUS St. Gallen 2005 - Rolle der Taxane

Meno-status	Receptorstatus					
	HR pos		HR uncertain		HR neg	
	Prä	Post	Prä	Post	Prä	Post
N0 low	Tam or nil	Tam <u>or</u> AI or nil (Tam > AI)	Tam or nil	Tam <u>or</u> AI <u>or</u> 0 (Tam > AI)	Chemotherapy (6xTriplet)	
N0 + risk N+ average (= N1-3)	Tam +/- OFS or CT>Tam +/-OFS or OFS	Tam or AI CT>Tam or CT>AI or CT> T>AI	CT>Tam (+/-OFS) or CT alone	CT>Tam or CT>AI or CT> Tam>AI	Chemotherapy (6 months) +/- Taxan	
high risk N4+	CT>Tam +/-OFS	CT>T <u>or</u> CT>AI Ari <u>or</u> Exe Ari>2/3a T Let >5aT	CT (6xTriplet) + Taxan > ET		Chemotherapy (6 months) + Taxan	



ADJUVANTE THERAPIE DES MAMMAKARZINOMS ASCO 2005



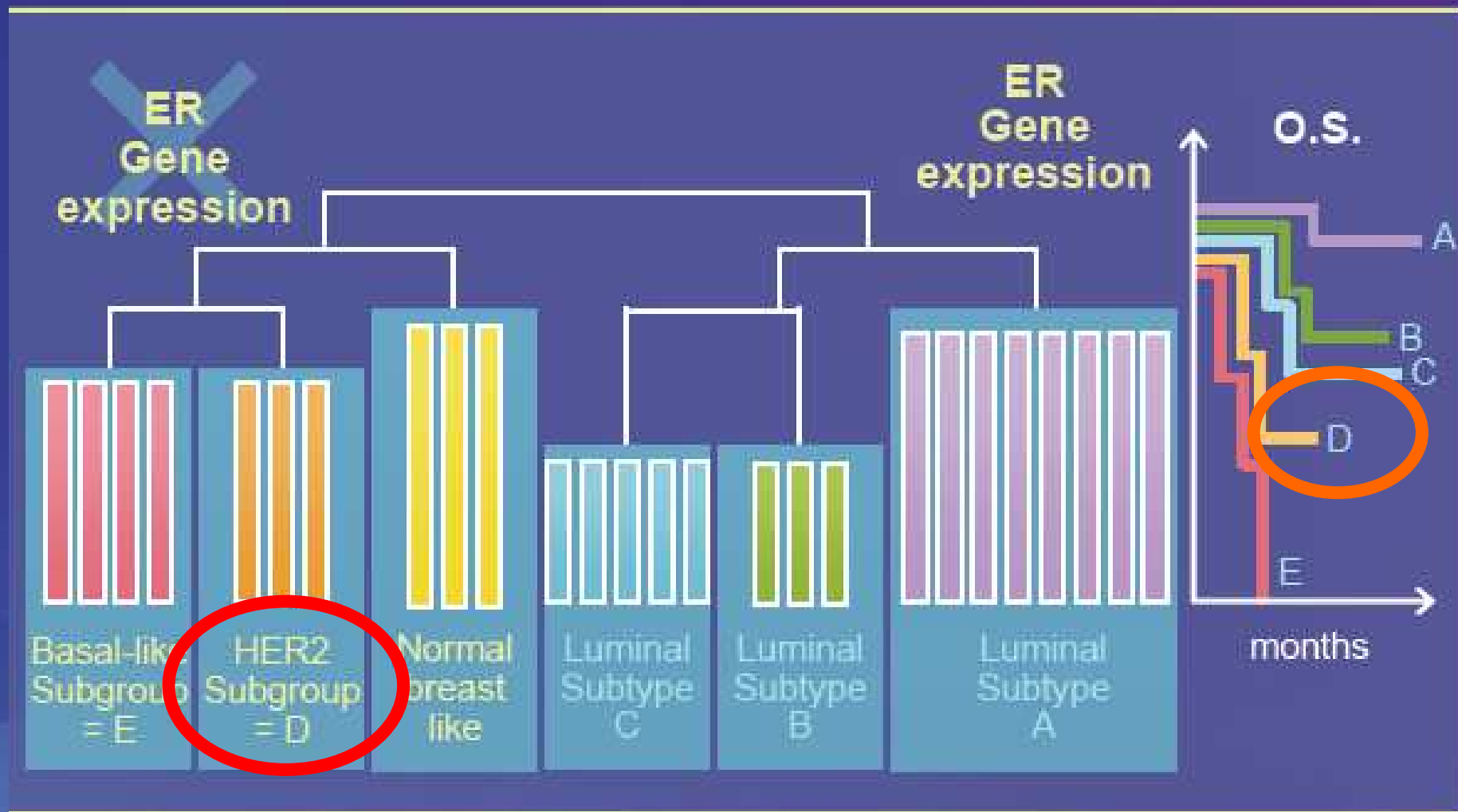
OXFORD STYLE
DEBATES

IST HERCEPTIN[®] EIN NEUER STANDARD FÜR HER2-positiven MAMMAKARZINOME ?

G. Steger

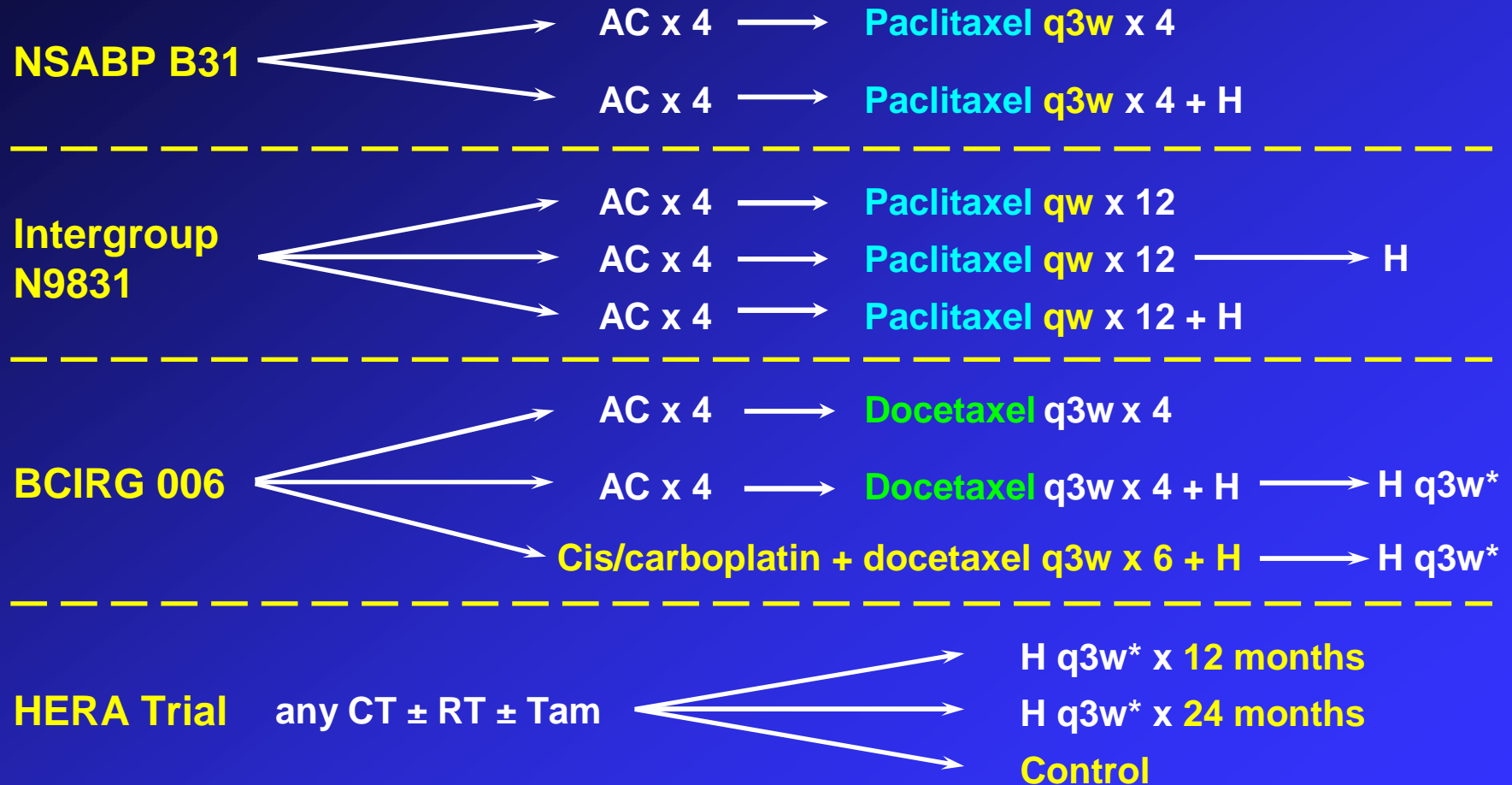
Medizinische Universität Wien

Gene Expression Patterns of Breast Carcinomas Predict Survival



HERCEPTIN® - Adjuvant Studies

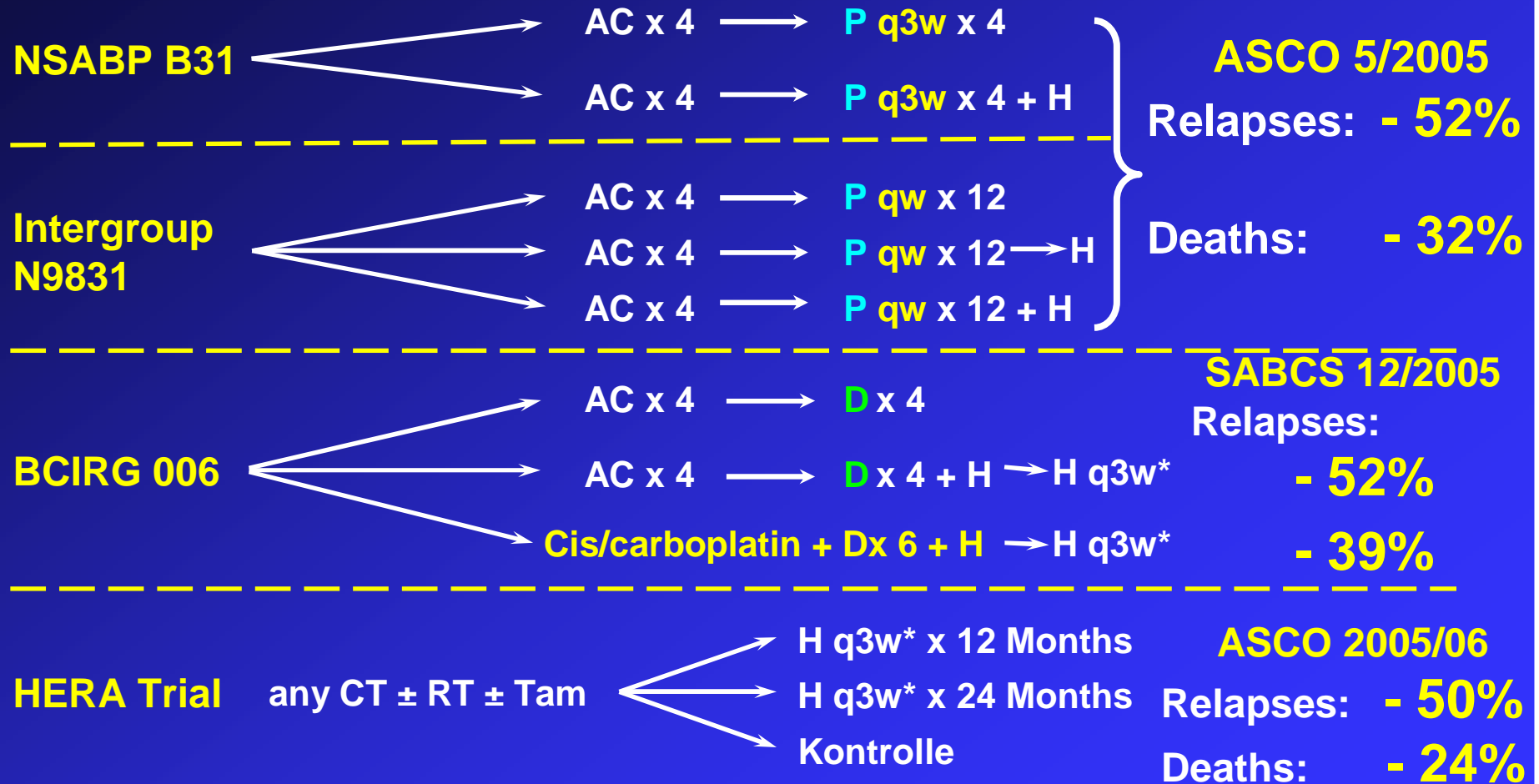
Summary of the 4 Main Studies



*q3w with 6mg/kg
H = Herceptin®

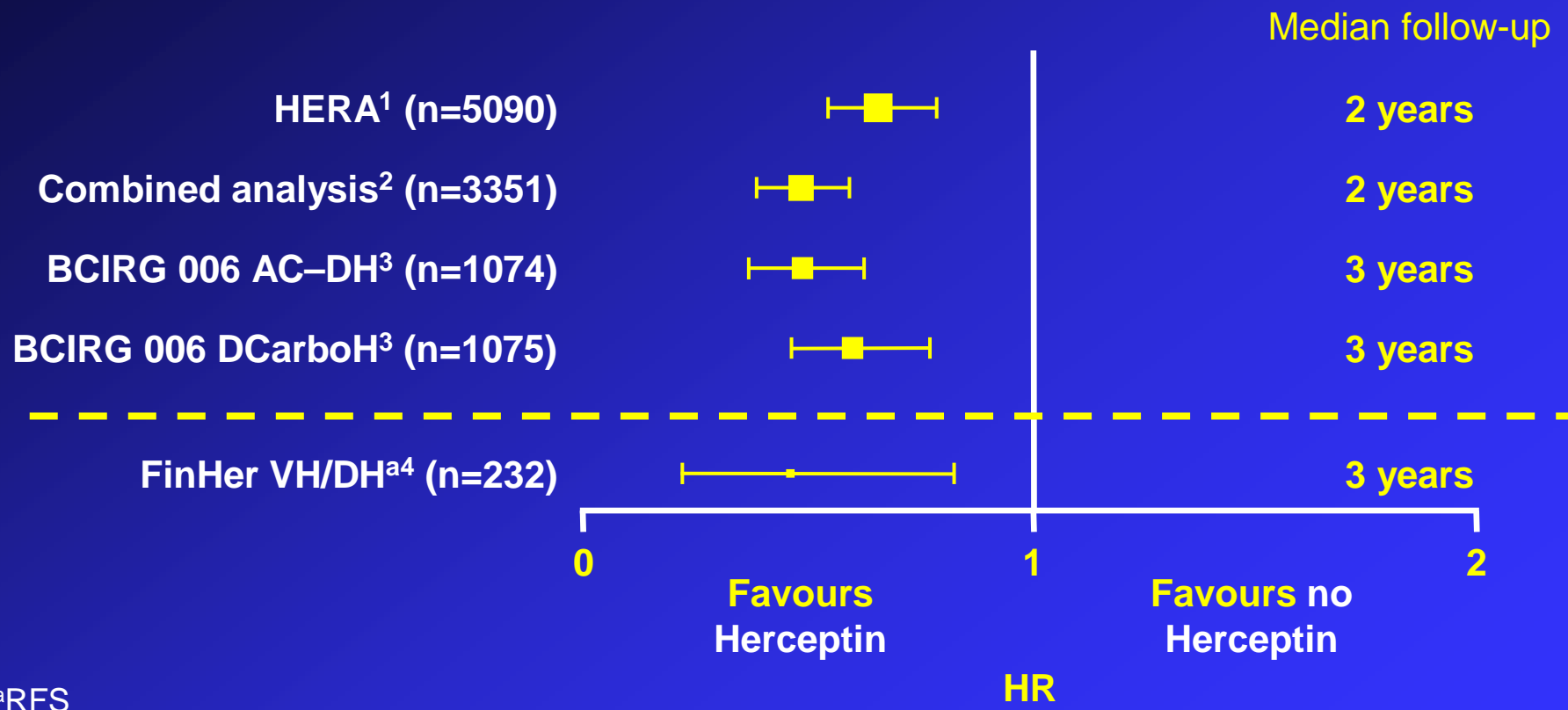
HERCEPTIN® - Adjuvant Studies

Summary of the 4 Main Studies



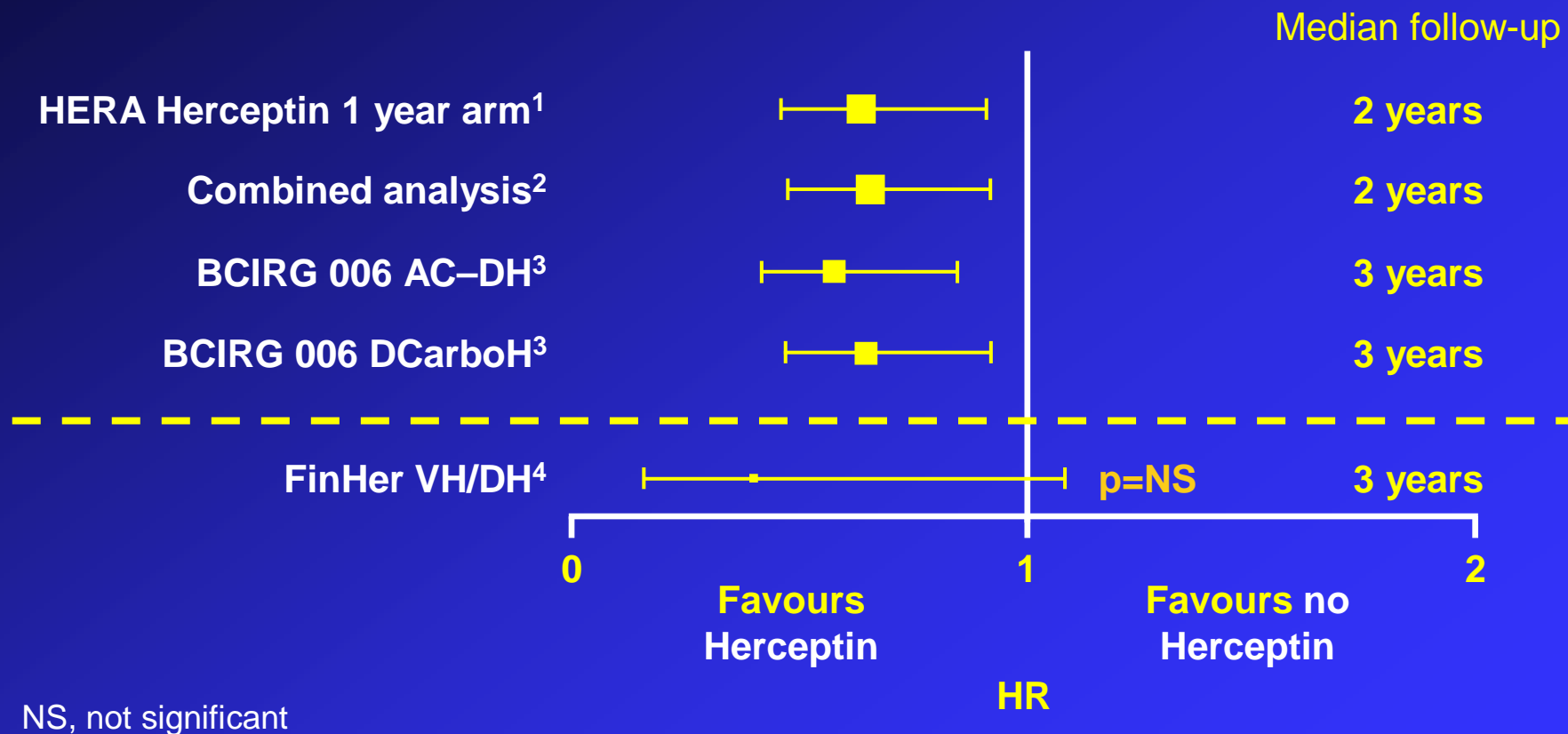
*q3w with 6mg/kg
H = Herceptin®

Adjuvant Trastuzumab Trials: Summary of DFS data to date



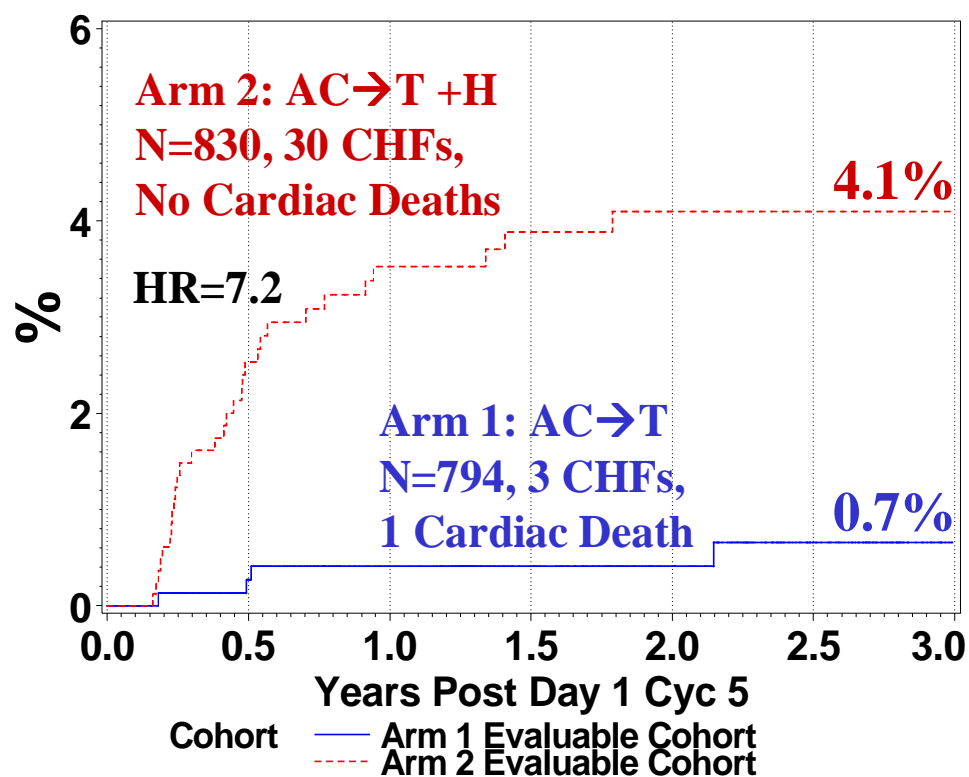
1. Smith I et al. Lancet 2007;369:29–36; 2. Romond EH et al. N Engl J Med 2005;353(16):1673–84;
3. Slamon D et al. SABCs 2006;Abstract 52; 4. Joensuu H et al. N Engl J Med. 2006;354:809-20

Adjuvant trastuzumab trials: summary of OS data to date

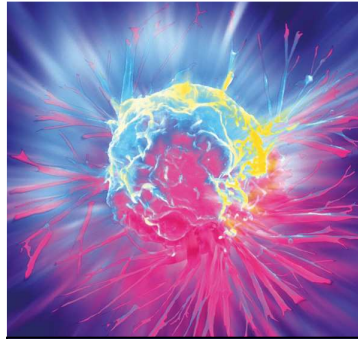


1. Smith I et al. Lancet 2007;369:29–36; 2. Romond EH et al. N Engl J Med 2005;353(16):1673–84; 3. Slamon D et al. SABCs 2006;Abstract 52; 4. Joensuu H et al. N Engl J Med. 2006;354:809-20

B-31: Cumulative Incidence of Cardiac Events in the Evaluable Cohort



Yrs Post Day 1 Cyc 5	Cum Inc Arm 1 (%)	Cum Inc Arm2 (%)	No. At Risk
0.5	0.3	2.5	1412
1.0	0.4	3.5	1168
1.5	0.4	3.9	924
2.0	0.4	4.1	719
2.5	0.7	4.1	532
3.0	0.7	4.1	357



ADJUVANTE THERAPIE DES MAMMAKARZINOMS ASCO 2005



OXFORD STYLE
DEBATES

**IST HERCEPTIN^R EIN
NEUER STANDARD FÜR
HER2-positiven
MAMMAKARZINOME ?**

JA !

*G. Steger
Medizinische Universität Wien*

St. Gallen 2009

Goldhirsch A et al: **TRESHOLDS FOR THERAPIES: St Gallen 2009**

Ann Oncol 20: 1319-1329, 2009

Therapiemodalität	Indikationsparameter	Kommentar
Endokrine Therapie	Jede positive IHC auf ER oder PgR (in Österreich >10% der Zellen positiv)	PgR+ mit ER- sollten neuerliche evaluiert werden- hohe Artefaktwahrscheinlichkeit ⁴
Anti-Her2 Therapie	Lt. ASCO/CAP Her2+	=30% IHC oder >2.2 FISH; jedoch auch die weniger stringenten Kriterien von z.B. HERA zulässig
Chemotherapie bei Her2+	Keine publizierte Evidenz für Her2 Therapie ohne Chemotherapie !	Tumore mit <1cm und ohne weitere Risikofaktoren (s. Tabelle 3) können auch ohne adjuvante Chemo/Immuntherapie behandelt werden.
bei triple negativ	Fast alle Patientinnen	Ausgenommen sind sehr kleiner Tumore, medulläre, apokrine, adenoid zystische Tumore ohne weitere Risikofaktoren (s. Tabelle 2)
bei ER+, Her2-	Risikoabschätzung	Details in Tabelle 2



UNIV. KLINIK FÜR INNERE MEDIZIN I
Medizinische Universität Wien

Adjuvante Therapie
des Mammakarzinoms

*Primary Therapy of Early Breast Cancer
10th International Conference*

St. Gallen 2011

***DATEN - FAKTEN:
KONSEQUENZEN?***

*30. März 2011
Palais Ferstel
Wien*

Pathology: Subtypes

- Choice of therapy depends on tumour subtype as defined by multi-gene array analysis? Yes 18,5 No 75,6 A 5,9
- For practical purposes tumour subtype can be ascertained by non-genetic tests for ER, PgR, Her2 and Ki67? Yes 82,9 No 12,2 A 4,9
- Yes/no Choice of cytotoxic therapy should be influenced by tumour subtype Yes 74,4 No 18,6 A 7,0

Endocrine Therapy: Establishing Standards for Postmenopausal

- Should **all** receive an **AI**?
Yes **50,0** No **50,0** A **0**
- Should ~~only~~ **N-positive** receive an **AI**?
Yes **79,1** No **20,9** A **0**
- Should **any** receive **Tam alone**?
Yes **89,1** No **10,9** A **0**
- If an **AI**, need it be started **up front**?
Yes **41,3** No **52,2** A **0**
- Consider **switch to tam** in patients intolerant to AIs
(especially in low risk patients)
Yes **97,8** No **0** A **2,2**

Chemotherapy

Basic Questions

Factors arguing **for inclusion of ChT** are:

- Histological grade 3 tumor ?
Yes **95,5** No **2,3** A **2,3**
- Ki-67 > 14%? „high“ Yes **68,8** No **14,6** A **16,6**
- Low hormone receptor status (< 50%) „low“
Yes **68,1** No **31,9** A **0**
- Positive HER2 status? Yes **95,7** No **4,3** A **0**
- Triple negative status? Yes **97,7** No **2,3** A **0**

IDC

Targeted Therapy

- Is **trastuzumab** for 1 year, with concurrent ChT (usually a taxane) or following ChT, a standard adjuvant treatment for HER2-positive phenotype?

Yes 100,0	No 0,0	A 0,0
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- ... also for tumors between 5 mm and < 1cm? **NO**

Yes 78,7	No 14,9	A 6,4
----------	---------	-------

- ... shorter than 1 year'

rich countries

Yes 25,6	No 62,8	A 11,6
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poor countries

- ... longer than 1 year?

Yes 71,1	No 13,3	A 15,6
----------	---------	--------

Yes 4,7	No 83,7	A 11,6
---------	---------	--------

Neo Adjuvant Systemic Therapy

- Should neoadjuvant regimens for HER2-positive disease **always** contain anti-HER2 drug?

Yes **87,2** No **8,5** A 4,3

- Is **dual** HER2-targeting a reasonable option for the preoperative setting for HER2-disease?

Yes **21,7** No **67,4** A 10,9