UNIKLINIK KÖLN | Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe | Brustzentrum Köln/Frechen

CIO Centrum für Integrierte Onkologie Köln Bonn

Case #3: Multifocal Invasive Endocrine-Responsive Breast Cancer: Locoregional Approach and Choice of Systemic Therapy

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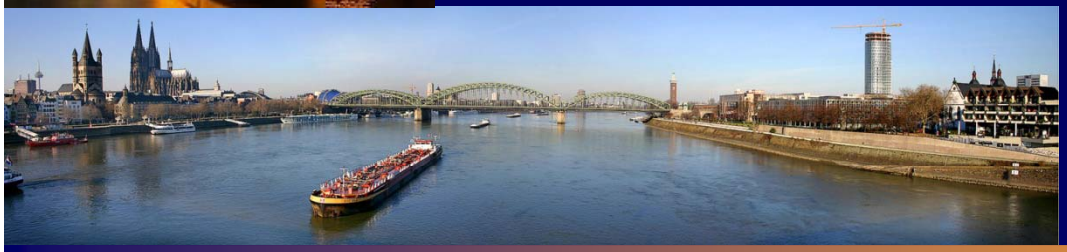

BRUSTZENTRUM KÖLN/FRECHEN

prIME oncology

Patient Case

- 59-year old postmenopausal woman
- Palpable breast mass in left lower quadrant
- Negative mammography, US 2.5-cm mass
- Core biopsy: Poorly differentiated infiltrating lobular carcinoma (ILC), ER 60%, PR 40%, HER2 negative
- History: Hormone replacement therapy with estrogen/progesterone for 4 years (age 54-58 years)
- Laboratories and chest x-ray normal
- ECOG PS: 0

Which of the Following Options Would You Recommend as a First Step?

1. Conservative surgery and sentinel node biopsy (SNB)
2. Mastectomy and SNB
3. Magnetic resonance imaging (MRI) of the left breast
4. MRI of both breasts
5. Positron emission tomography/computed tomography (PET/CT)
6. Mirror image biopsy of contralateral breast

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Preoperative Diagnosis

	Oxford / AGO LoE	GR	
➢ Palpation	5	D	++
➢ Mammography	1a	A	++
- Magnification view of microcalcifications	4	C	+
➢ Ultrasound (breast and axilla)	2b	B	++
➢ routinely pre-operative MRI	3b	B	+/-
- Lobular invasive BrCa, hereditary BrCa	4	C	+
- Unclear mammography and ultrasound	4	C	+/-
- Histologically proven invasive breast cancer or DCIS	5	D	+/-
➢ Preoperative (image directed) core-needle or (vacuum-) biopsy	2a	B	++
➢ Diagnosis by open biopsy (if alternative available)	2b	B	-

Further information

References

Further Diagnostic Work-Up

Because of ILC histology, breast MRI was performed to evaluate the full extent of disease in the left breast and to screen the contralateral side. Results showed multiple enhancing masses in all quadrants of the left breast; right breast was unremarkable.

Which of the Following Treatment Options Would You Recommend for This Patient With Multifocal ILC?

1. Left mastectomy and SNB followed by immediate reconstruction
2. Left mastectomy and SNB ± delayed reconstruction
3. Bilateral mastectomy with SNB on the left side followed by reconstruction
4. Neoadjuvant chemotherapy followed by surgery

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BCT versus Mastectomy

	Oxford / AGO LoE	GR	
➢ Survival rates after lumpectomy + XRT are equivalent to those after (modified) radical mastectomy	1a	A	++
➢ Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy	2b	B	++
➢ Conservation of the NAC (after a tumor-free frozen section of retroareolar tissue) is an adequate surgical procedure in tumors of the periphery of the gland	4b	C	+
➢ Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy	1b	A	++

Further information

References

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Sentinel Lymph Node Excision (SNE): Indications

	Oxford / AGO LoE / GR		
➢ Clinically (cN0) / sonographically neg. axilla	1b	A	++
➢ T 1	1b	A	++
➢ T 2	2b	B	+
➢ Multifocal / multicentric lesions	2b	B	+
➢ DCIS ≥ 5 cm (see DCIS) or if mastectomy is required	2b	B	+
➢ Before primary chemotherapy	3b	C	+*
➢ After primary systemic therapy	2b	B	+/-*
➢ Male breast cancer	2b	B	+
➢ In the elderly	2b	B	+

Further information

References

* Study participation recommended

Surgery and Histopathology

Surgery: Left mastectomy and axillary dissection following a positive frozen section of the SLN were performed. Only SNB was positive (1/20 examined axillary nodes).

Pathology: Multifocal ILC with additional foci of lobular carcinoma *in situ*. The largest focus of ILC was 2.5 cm, grade III, ER 60%, PR 40%, Ki-67 15%, HER2 negative; the histology of all others were similar.

Patient did not opt for immediate reconstruction of the breast.

Would You Recommend Chemotherapy to This Patient?

1. Yes
2. No

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Adjuvant Chemotherapy Without Concurrent Trastuzumab: Overview

	Oxford LoE	AGO GR	
➢ Anthracyclines (instead of CMF)	1a	A	++
➢ Taxanes (node-positive disease)	1a	A	++
➢ Taxanes (node-negative disease)	2b	B	+/-*
➢ Taxanes may be beneficial in N0-patients at high risk of recurrence			
➢ Dose-dense (node-positive disease)	1b	B	+*
➢ CMF (instead of no therapy)	1a	A	++

Further information

References

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LEHREN
HEILEN

* Study participation recommended

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Taxanes
Optimal Combination and Dosage

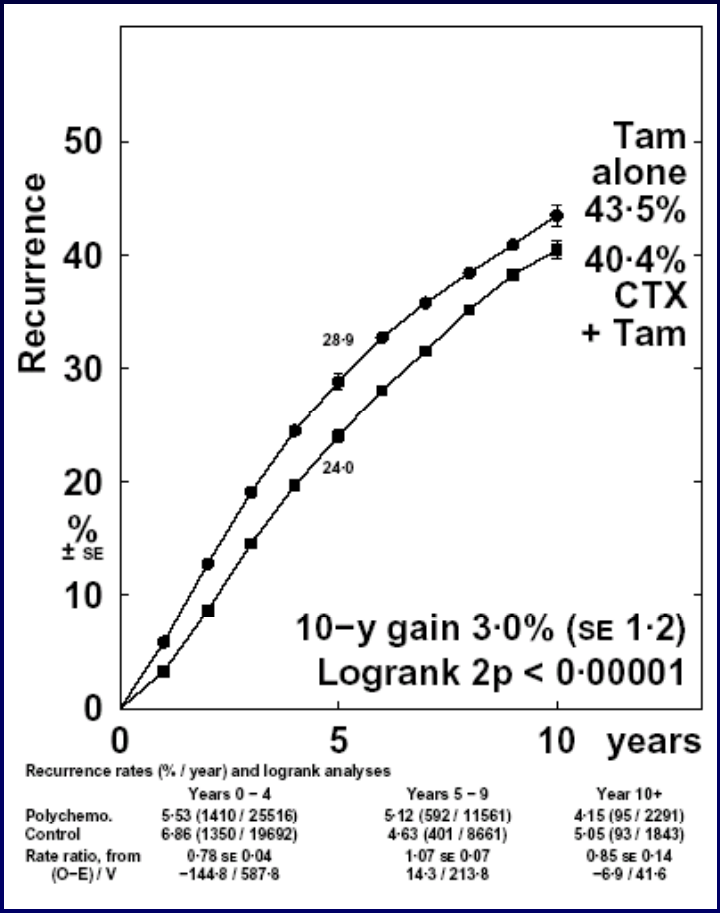
Regimen		Oxford / AGO LoE	GR	
➢ DAC	$D_{75}A_{50}C$ q3w x 6	1b	B	++
➢ FEC → D	$FE_{100}C$ q3w x 3 → D_{100} q3w x 3	1b	B	++
➢ AC → Pw	$A_{60}C$ q3w x 4 → P_{80} qw1 x 12	1b	B	++
➢ AC → D	$A_{60}C$ q3w x 4 → D_{100} qw3 x 4	1b[a]	B	++
➢ EC → D	$E_{90}C$ q3w x 4 → D_{100} qw3 x 4	1b[a]	B	++

Further information

References

Influence of Age and ER on Chemotherapy Benefits

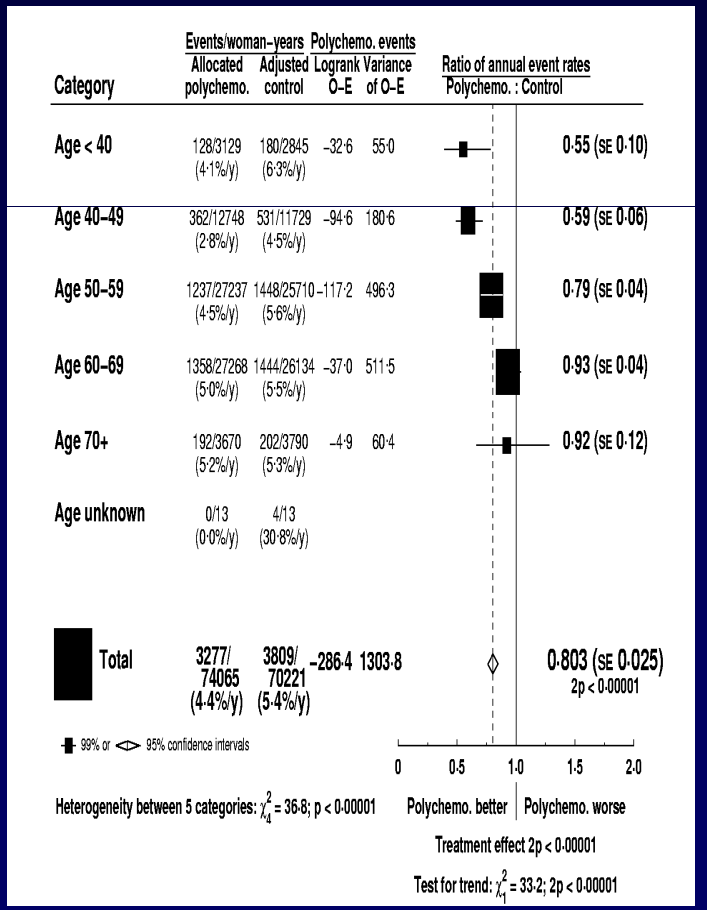
Chemotherapy: RECURRENCE
Age 50 – 69 years
ER +/? All with TAM
11333 women, 73% N + 88% ER+



Recurrence rates (% / year) and logrank analyses

	Years 0 – 4	Years 5 – 9	Year 10+
Polychemo.	5·53 (1410 / 25516)	5·12 (592 / 11561)	4·15 (95 / 2291)
Control	6·86 (1350 / 19692)	4·63 (401 / 8661)	5·05 (93 / 1843)
Rate ratio, from (O−E) / V	0·78 SE 0·04 −144·8 / 587·8	1·07 SE 0·07 14·3 / 213·8	0·85 SE 0·14 −6·9 / 41·6

Polychemotherapy vs Not: RECURRENCE
All Years
ER-Positive



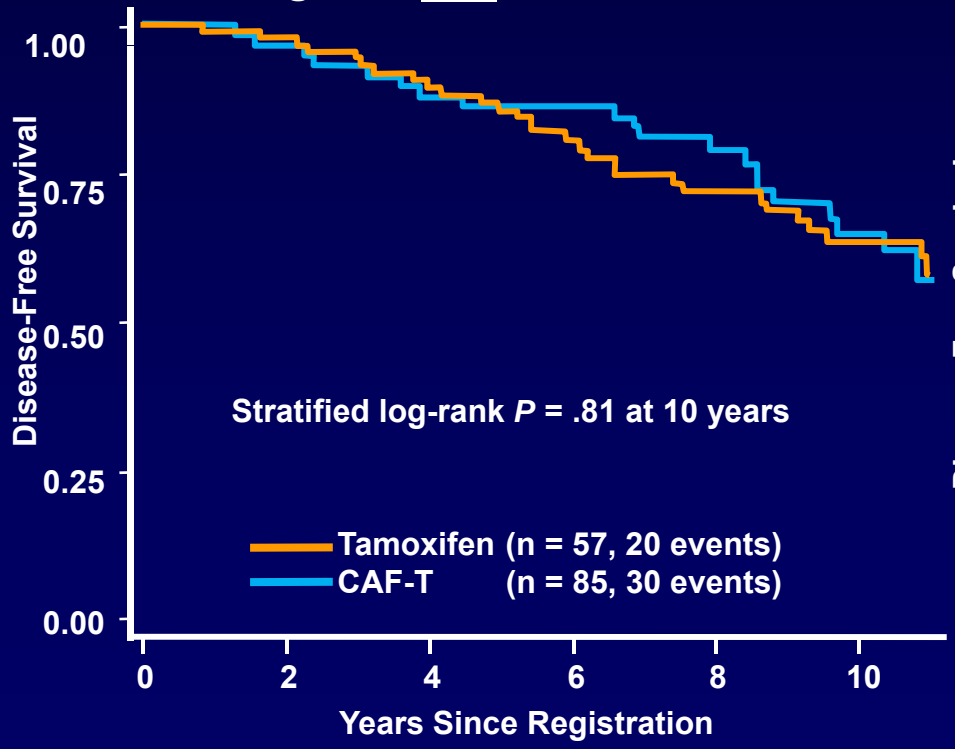
Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 2005:365(9472):1687-1717.

SWOG 8814, INT 0100

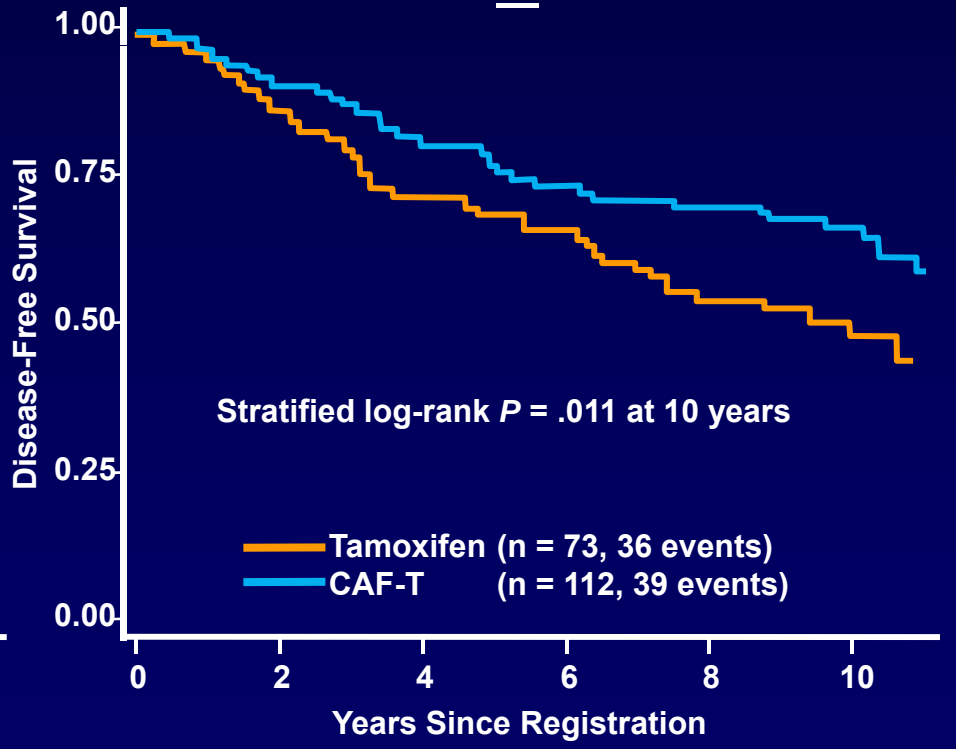
Postmenopausal women with N+ HR+ disease (n = 1470)

- TAM
- CAF-T
- CAFT

HER2 Negative and ER Allred 7-8

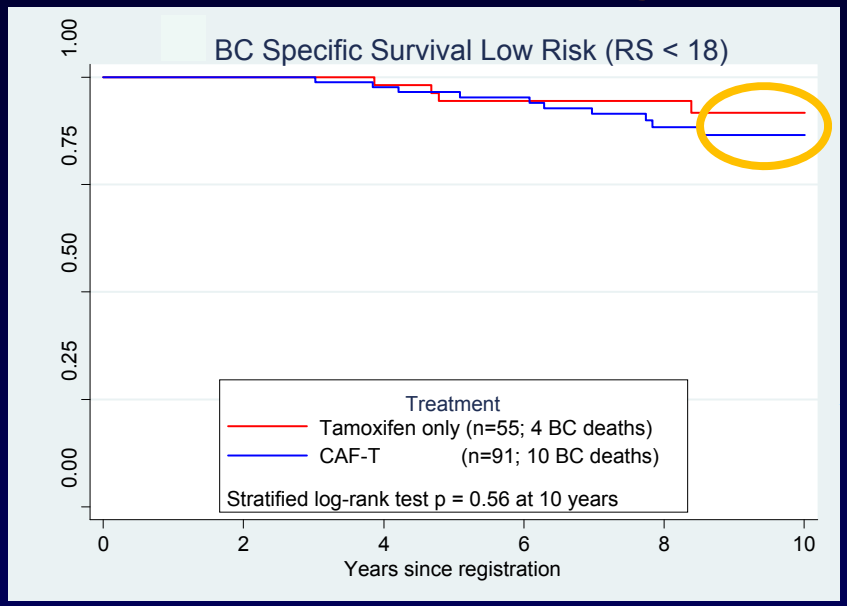


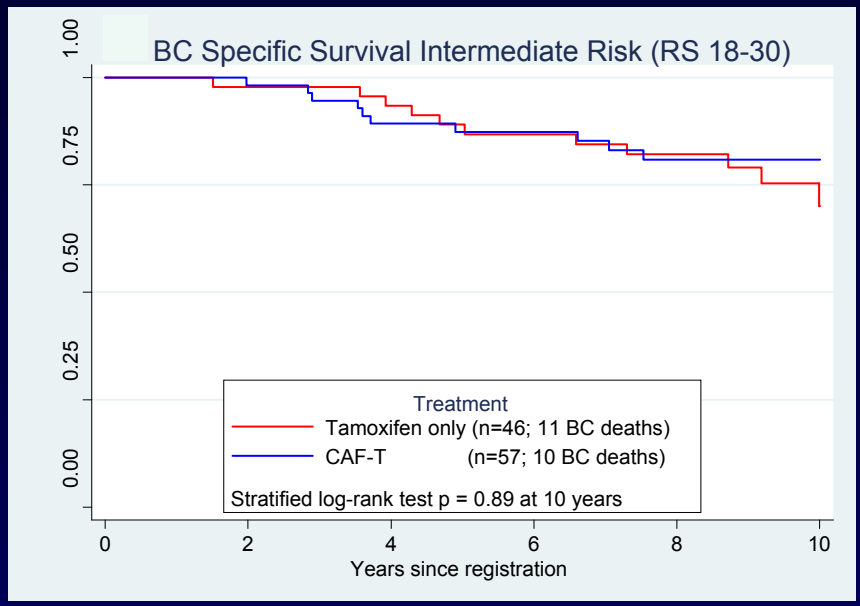
HER2 Positive or ER Allred <7

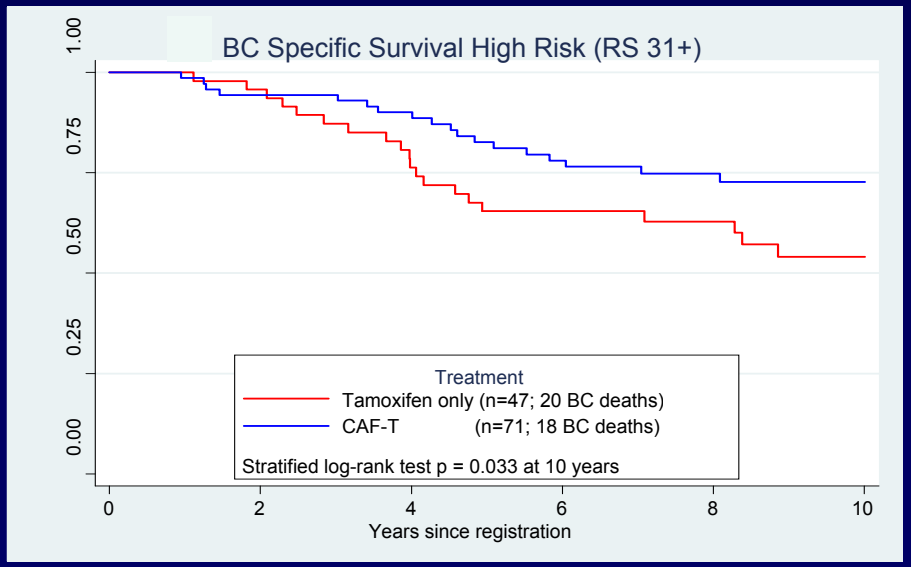


Albain K, et al. *Breast Cancer Res.* 2004;88(Suppl 1): Abstract 37.

SWOG 8814: Impact of Adding Chemotherapy to Tamoxifen for Postmenopausal Women With ER-positive Node-Positive Breast Cancer According to 21-Gene Recurrence Score



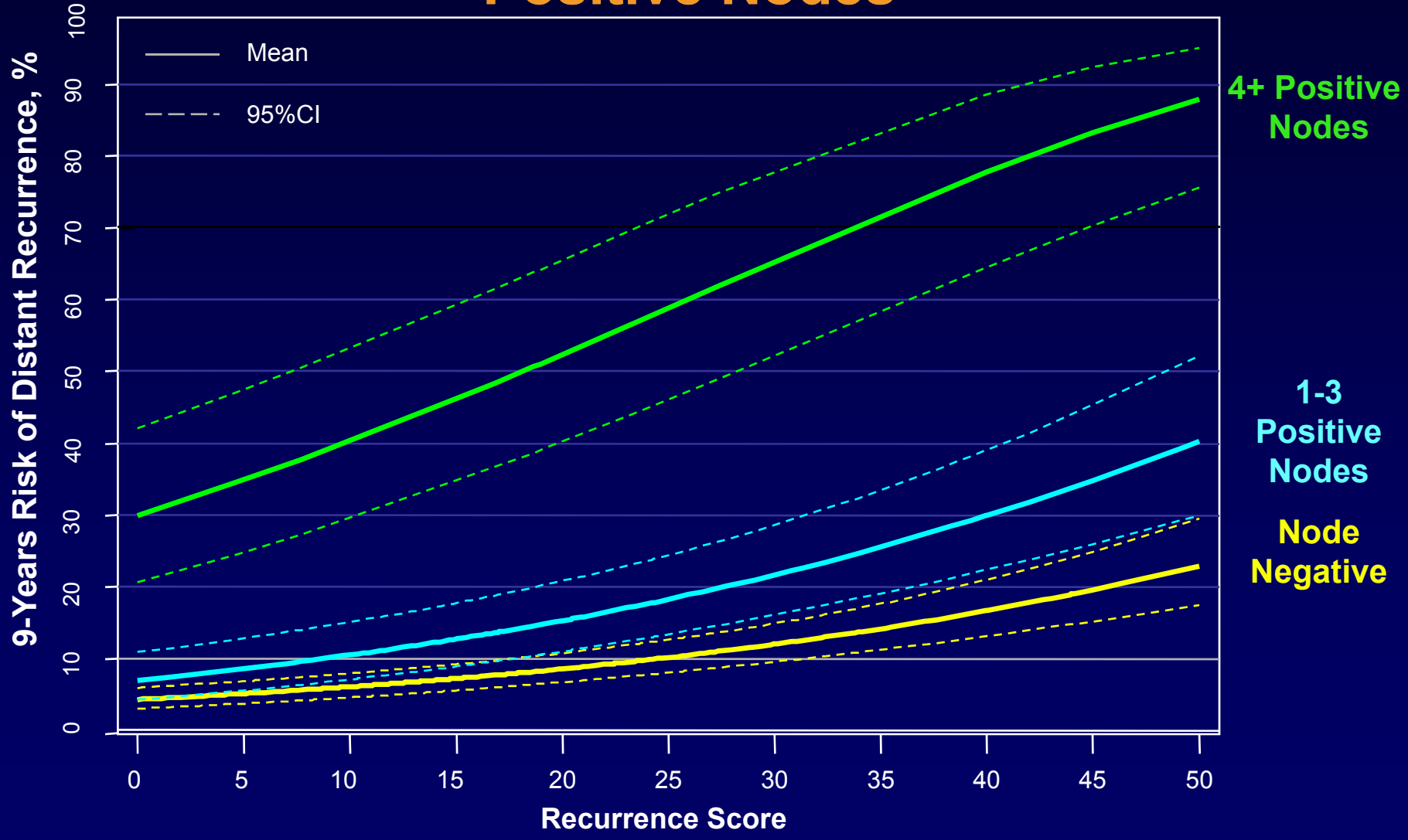




Interaction *P* = .021

Albain K, et al. *Lancet.* 2009. In press.

TransATAC: **For Any Recurrence Score the Rate of Distant Recurrence Increases with the Number of Positive Nodes**

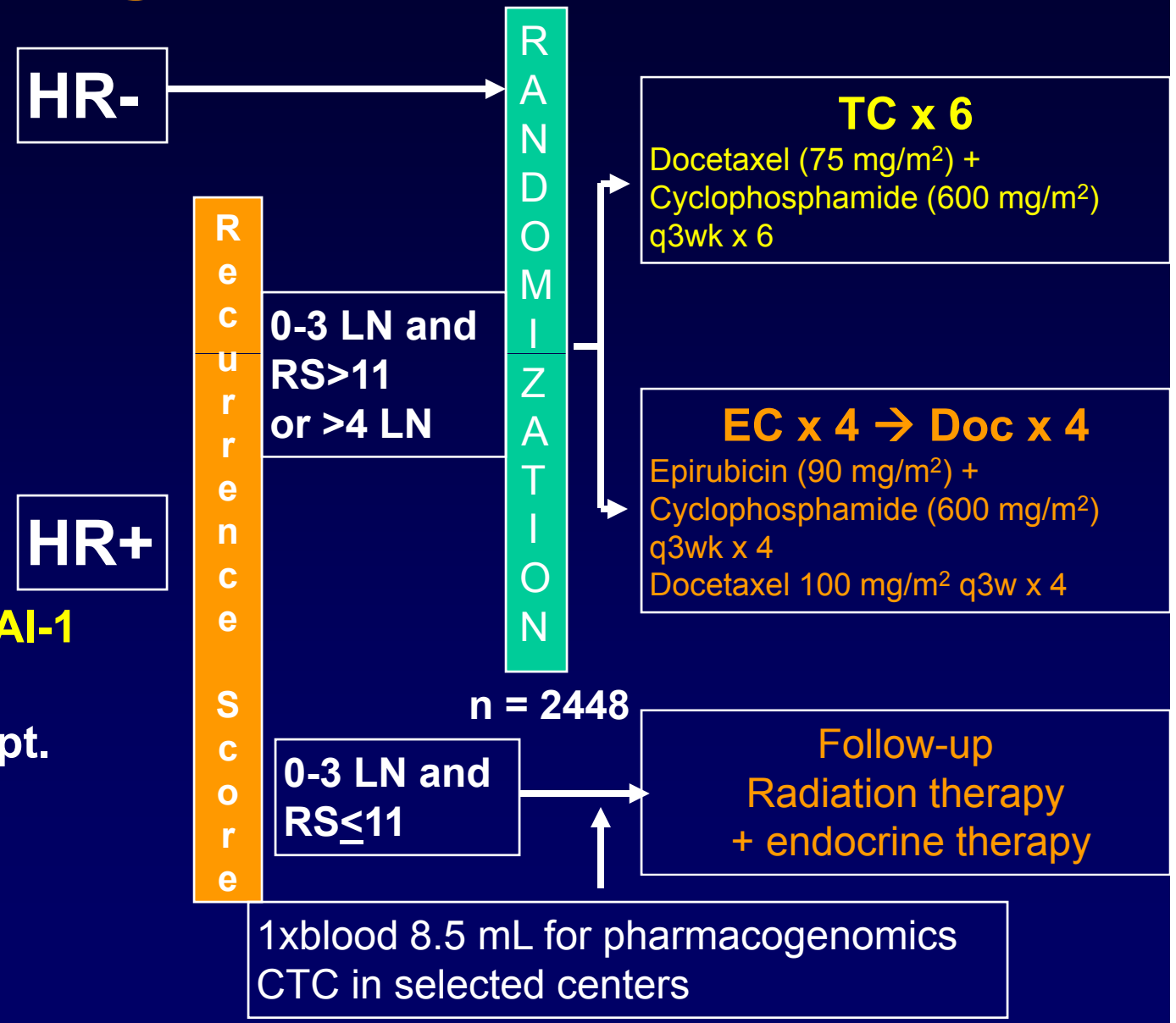


Dowsett M, et al. *Cancer Res.* 2009;69(Suppl 2): Abstract 53.

Ongoing WSG Trial Plan B

- HER2-negative breast cancer
- M0
- T1-4
- R0
- N+*
- N- high risk
  - pT>2cm
  - G2-3
  - uPA and / or PAI-1 high*
  - Hormone recept. negative
  - Age <35

*NNBC-4plus



Patient Was Treated With Anthracycline and Taxane-Based Chemotherapy.

Which of the Following Endocrine Treatment Strategies Would You Recommend?

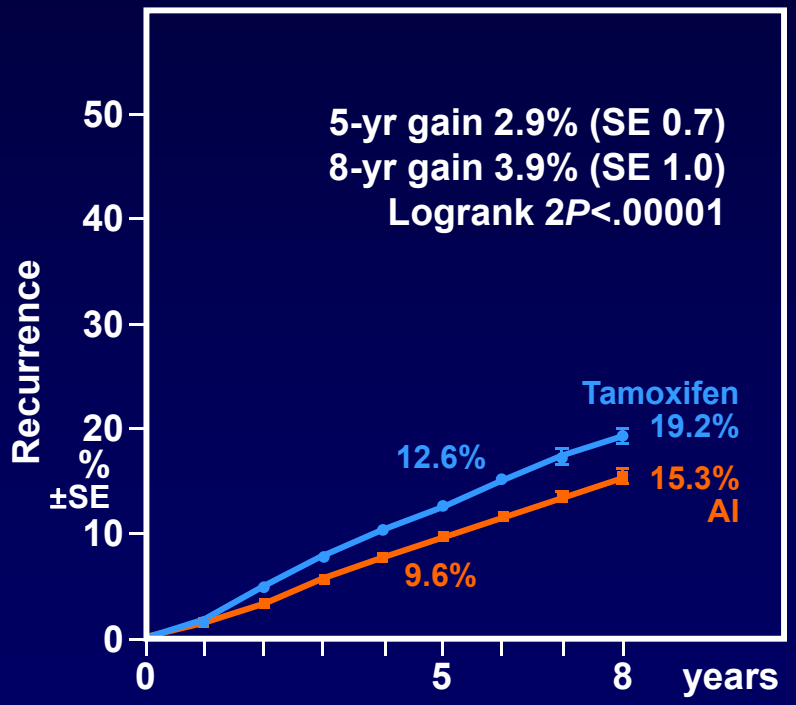
1. Aromatase inhibitor (AI) upfront for 5 years
2. Tamoxifen for 2-3 years followed by AI up to 5 years
3. Letrozole for 2 years followed by tamoxifen for 5 years
4. Tamoxifen alone for 5 years
5. Tamoxifen for 5 years followed by AI for 5 years

AIs vs Tamoxifen: Meta-Analyses of Randomized Trials of Monotherapy and Switching Strategies

Recurrence

Cohort 1: Monotherapy

23% proportional reduction

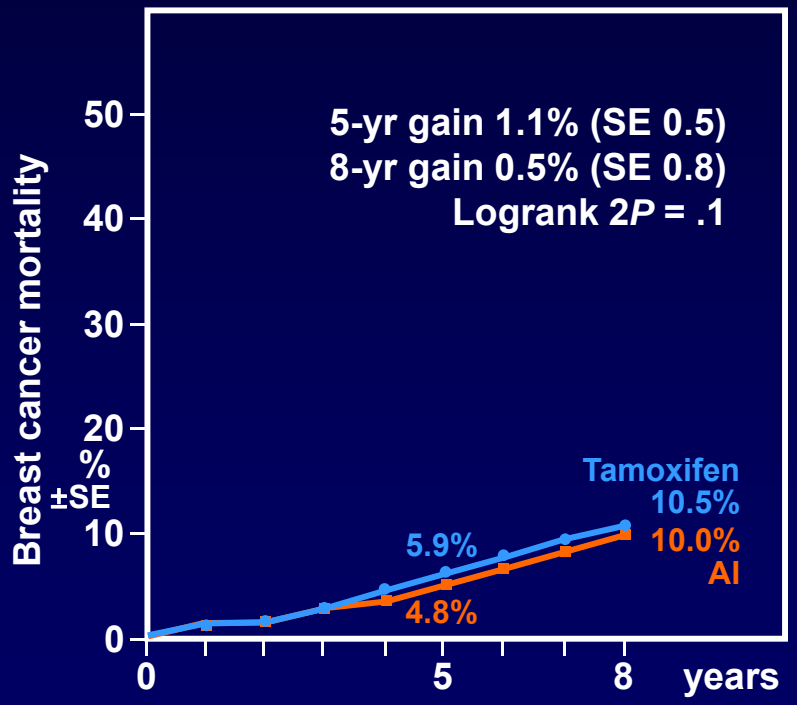


AI patients had statistically significant improvement in recurrence-free survival

BC Mortality

Cohort 1: Monotherapy

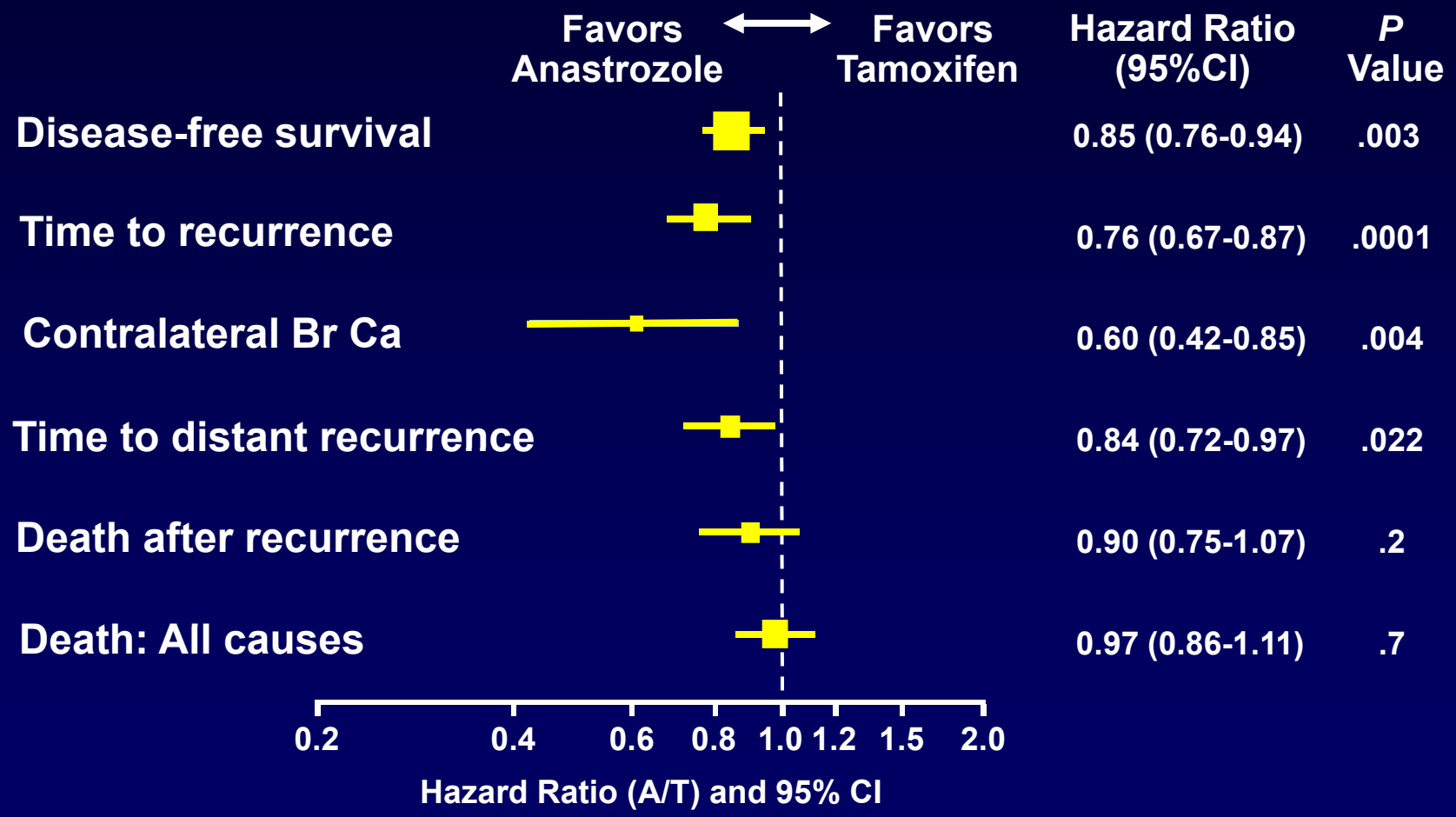
No significant difference*



***Further follow-up may be needed, given experience with tamoxifen**

Ingle JN, et al; on behalf of AIOG. *Cancer Res.* 2009;69(Suppl 2): Abstract 12.

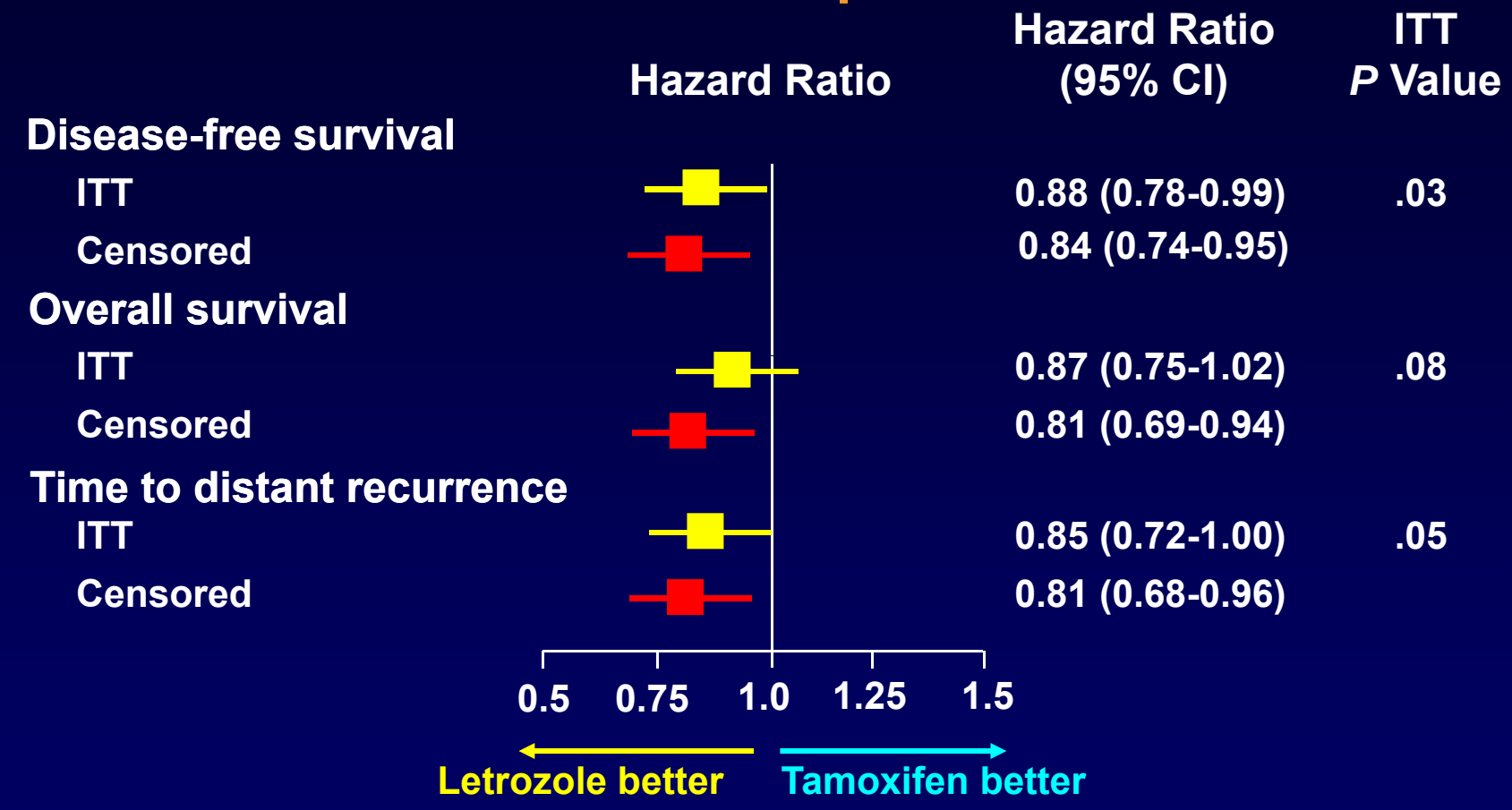
ATAC: Endpoints HR+ Patients



Br Ca = breast cancer; CI = confidence interval

Forbes JF, et al. *Lancet Oncol.* 2008;9(1):45-53.

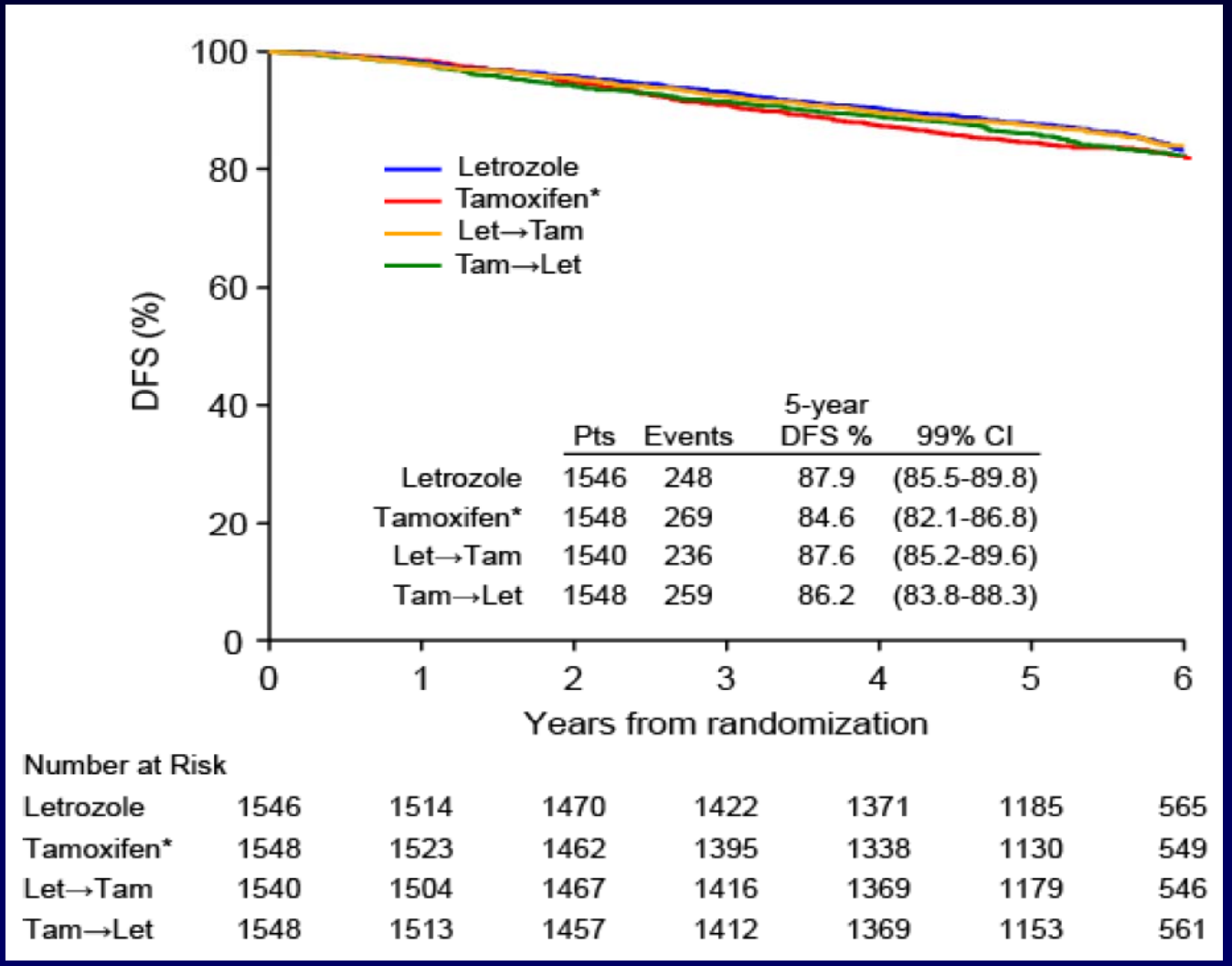
BIG 1-98 Monotherapy Update
Median Follow-Up 76 Months



Letrozole:Tamoxifen
- Breast cancer events, 321:363
- Second (nonbreast) malignancy, 101:115
- Deaths without prior cancer event, 87:87

Mouridsen H, et al. *N Engl J Med.* 2009;361(8):766-776.

BIG 1-98 Sequential Therapy
DFS from the Time of Randomization



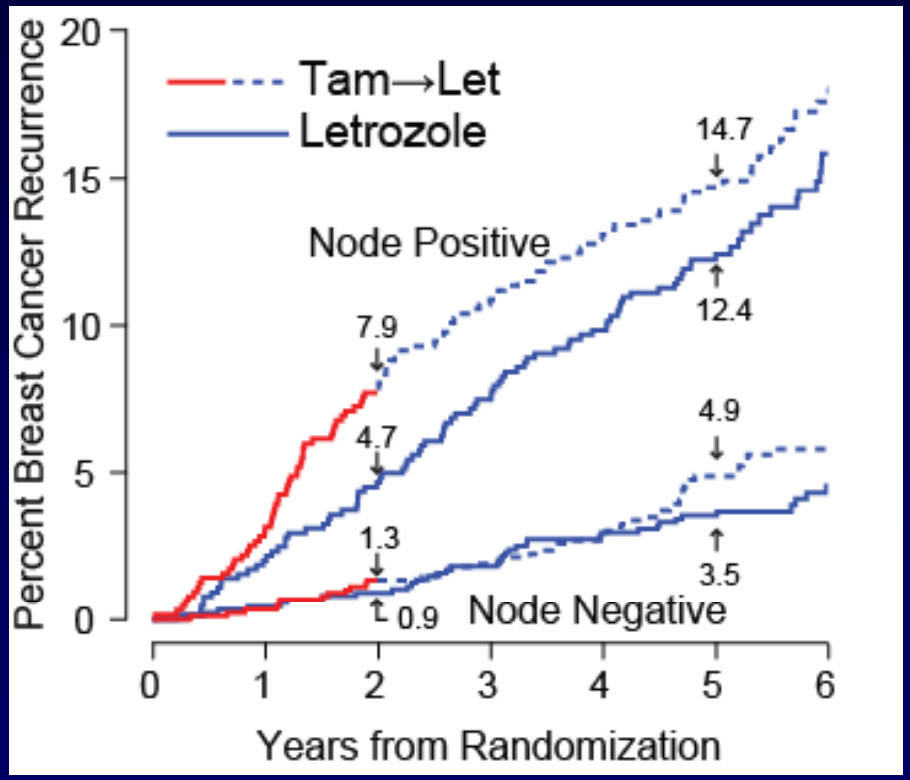
	Pts	Events	5-year DFS %	99% CI
Letrozole	1546	248	87.9	(85.5-89.8)
Tamoxifen*	1548	269	84.6	(82.1-86.8)
Let→Tam	1540	236	87.6	(85.2-89.6)
Tam→Let	1548	259	86.2	(83.8-88.3)

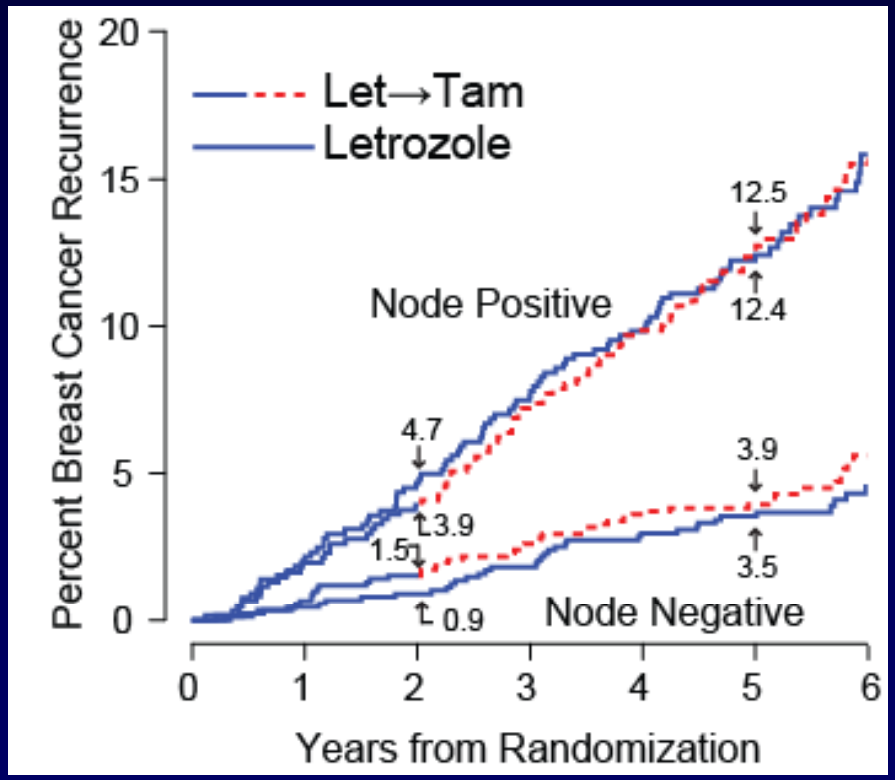
Number at Risk							
Letrozole	1546	1514	1470	1422	1371	1185	565
Tamoxifen*	1548	1523	1462	1395	1338	1130	549
Let→Tam	1540	1504	1467	1416	1369	1179	546
Tam→Let	1548	1513	1457	1412	1369	1153	561

* Includes 612 patients who crossed over to letrozole

Mouridsen H, et al. *N Engl J Med.* 2009;361(8):766-776 (Appendix page 14).

Breast Cancer Events by Nodal Status





***42% of the population is node positive; 58% node negative**

Mouridsen H, et al. *N Engl J Med.* 2009;361(8):766-776.

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Tamoxifen / Aromatase Inhibitors (AI)

	Oxford / AGO LoE / GR	
➢ **AI for 5 yrs.**	1a[a] A	++
➢ **Sequential therapy for 5 yrs.**		++
➢ **Tam followed by AI**	1a[a] A	
➢ **Letrozole followed by Tam**	1b[a] B	

Upfront and sequential AI consistently show superior DFS compared to 5y TAM !!

So far, no conclusive data to favour either upfront or sequential AI !

➢ **Tamoxifen 20 mg/d for 5 yrs.**	1a A	++
➢ **Tamoxifen in combination with AI**	1b B	- -

Further information

References

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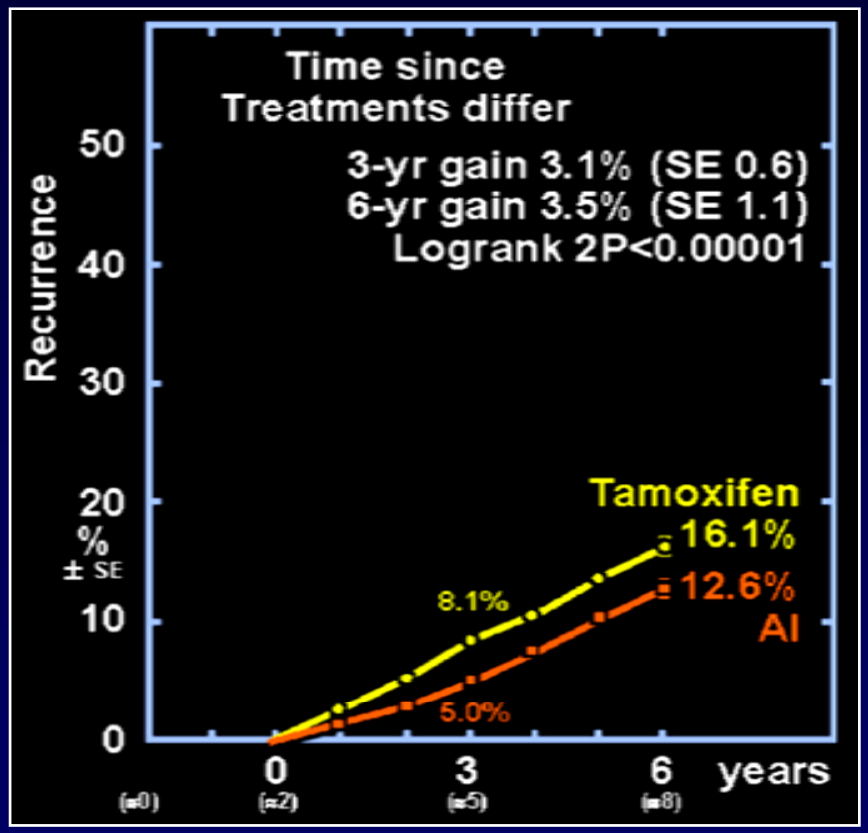
AIs vs Tamoxifen: Meta-Analyses of Randomized Trials of Monotherapy and Switching Strategies

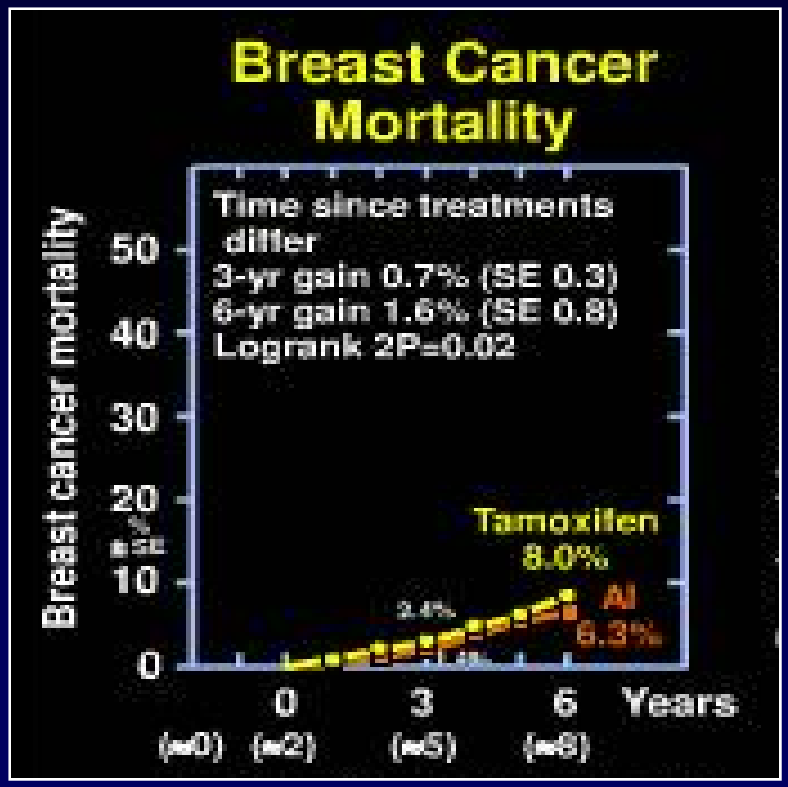
Recurrence

Cohort 2: Switching therapy



BC Mortality

Cohort 2: Switching therapy

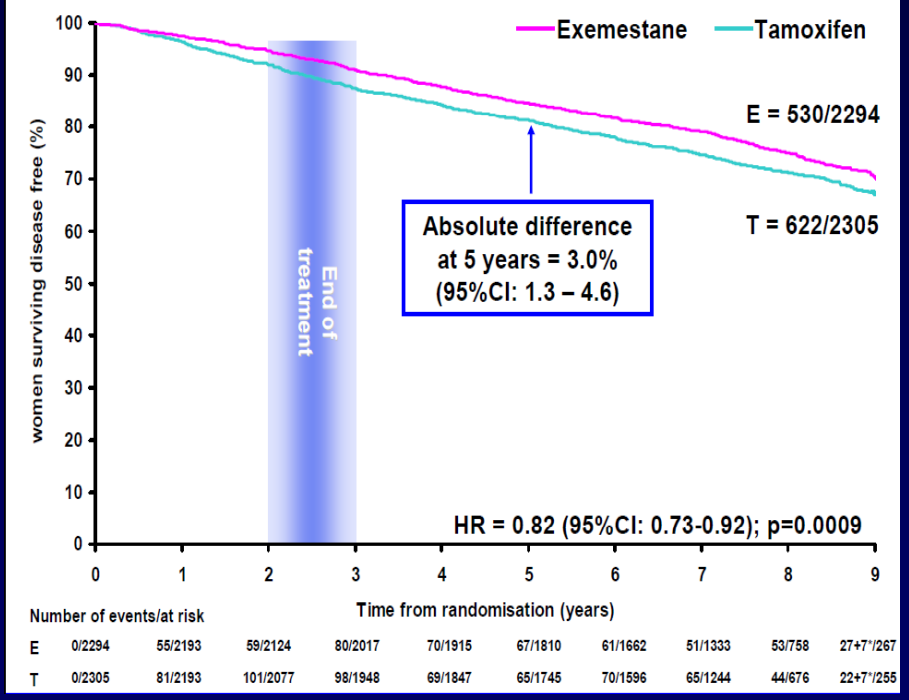


Data from Cohort 1 and Cohort 2 cannot answer the question if "switching" is better than "upfront".

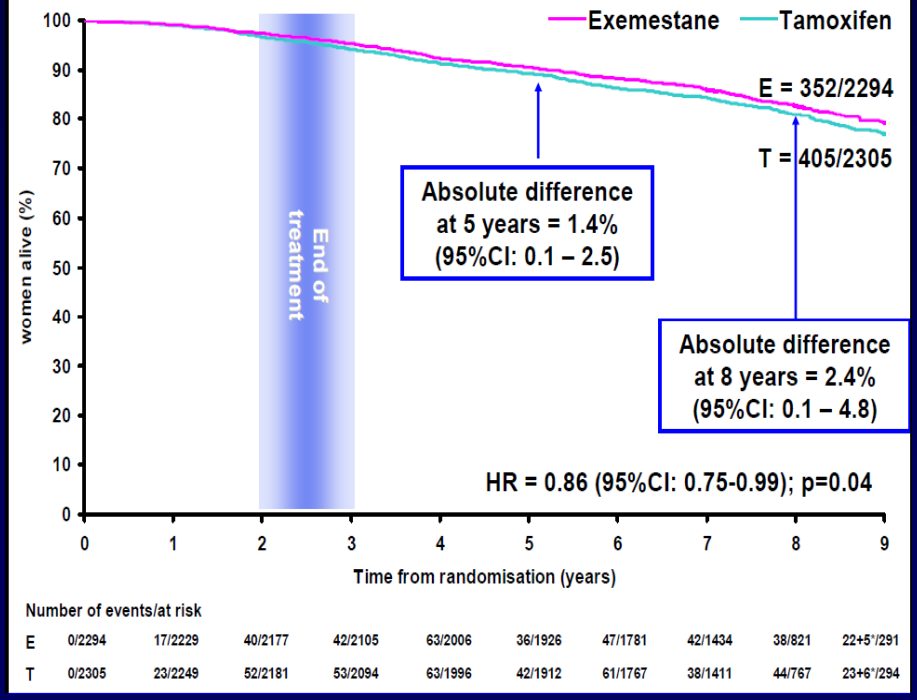
Ingle JN, et al. *Cancer Res.* 2009;69(Suppl 2): Abstract 12.

IES Update
Median Follow-Up 91 Months

Disease Free Survival – ER+/unknown



Overall survival – ER+/unknown



Coombes RC, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 5010.

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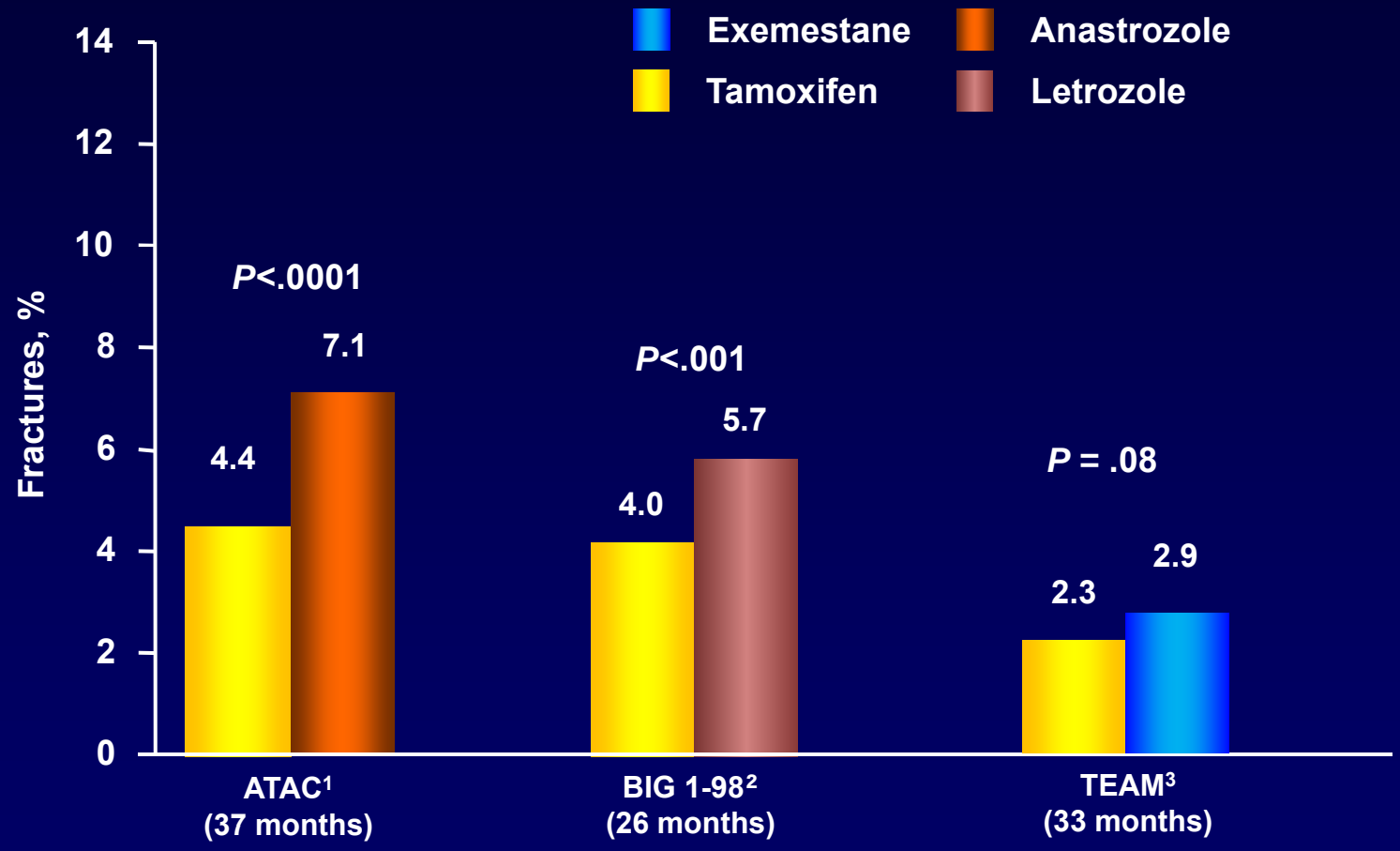
Endocrine Therapy after Tamoxifen

	Oxford / AGO LoE / GR		
After 5 yrs. tamoxifen			
➢ AI up to 3 to 5 yrs.	1b	A	+
➢ Node-positive disease	2b	B	++
➢ Long tamoxifen-free interval	2b	B	+
➢ Continuation of TAM up to 5 yrs.	2b[a]	C	+/-
After 2-3 yrs. tamoxifen			
➢ Duration of AI 3 to 2 yrs.	1b	B	++
➢ Duration of AI up to 5 yrs.	5	D	+/-

Further information

References

Fracture Rates with AIs



1. Howell A, et al. *Eur J Cancer Suppl*. 2003;1(5):Abstract 676. 2. Thürlimann B. *N Engl J Med*. 2005;353(26):2747-2757.
3. van de Velde C, et al. *Eur J Cancer Suppl*. 2009;7(2): Abstract 2BA.

In Addition, Would You Consider Adjuvant Bisphosphonates for This Patient?

1. Yes
2. No
3. Only, if indicated by deterioration in bone health

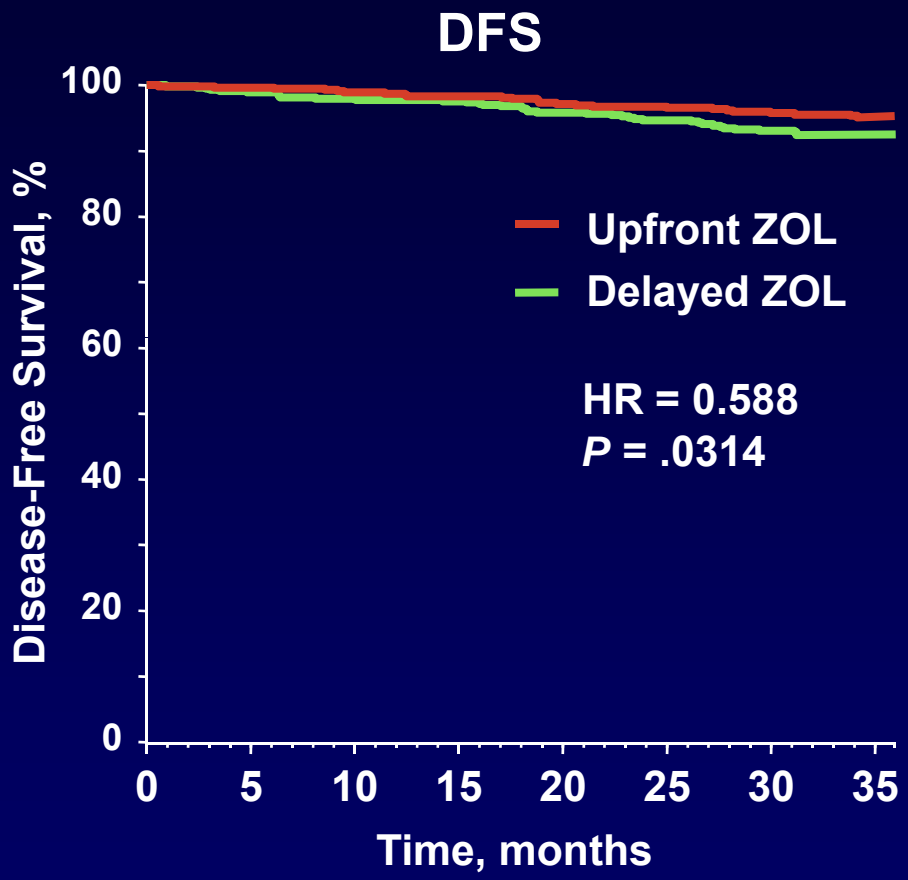
Adjuvant Clodronate Trials in Breast Cancer: Mixed Results

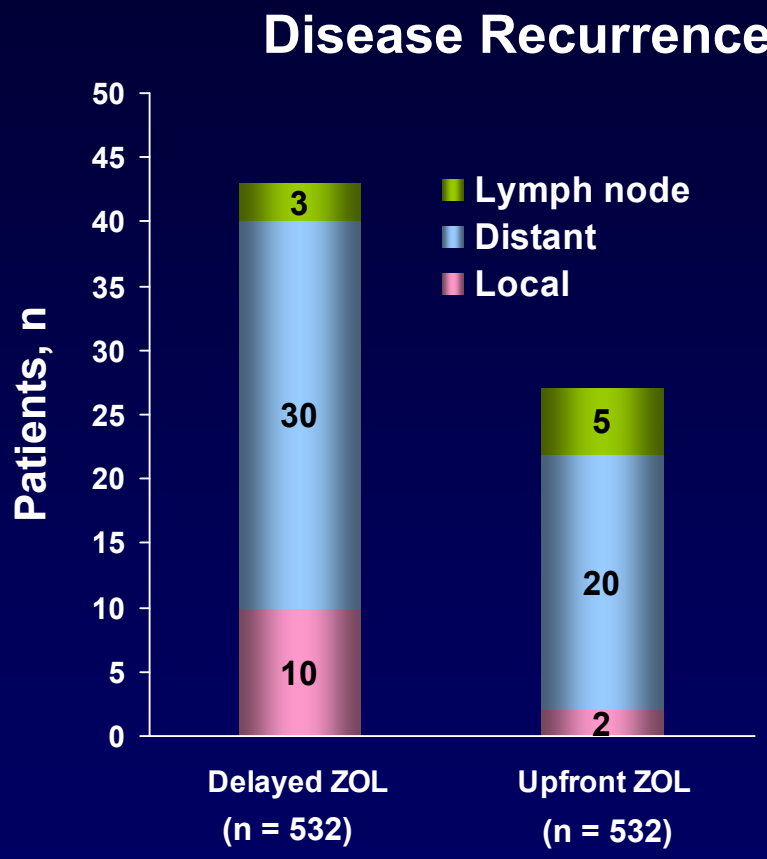
	Diel/Jaschke[1,2]	Powles[3]	Saarto[4]	Paterson[5]
No. of patients	290	1,069	299	173
Selection	BM + *	Stage I-III	LN +	BM +
Treatment length, yr	2	2	3	3
Follow-up time, yr	8.5	5/10	10	3
Skeletal effect	NS	+	NS	+
Extraskeletal effect	NS	NS	-	NS
Disease-free survival	NS	NS	- (ER -)	NS
Overall survival	+	+	NS	NS

BM = bone metastasis; LN = lymph node; NS = not significant; ER = estrogen receptor; + = better than competitor; - = worse than competitor.
*Primary breast cancer patients (T1 to T4 and N0 to N2) with micrometastases in the bone marrow.

1. Diel IJ, et al. *N Engl J Med*. 1998;339(6):357-363. 2. Jaschke A, et al. *J Clin Oncol*. 2004;22(14S): Abstract 529.
3. Powles TJ, et al. *Breast Cancer Res.* 2006;8(2):R13. 4. Saarto T, et al. *Acta Oncol.* 2004;43(7):650-656.
5. Paterson AHG, et al. *J Clin Oncol*. 1993;11(1):59-65.

ZO-FAST 36 mo: Upfront ZOL significantly reduces the risk of DFS events by 41%



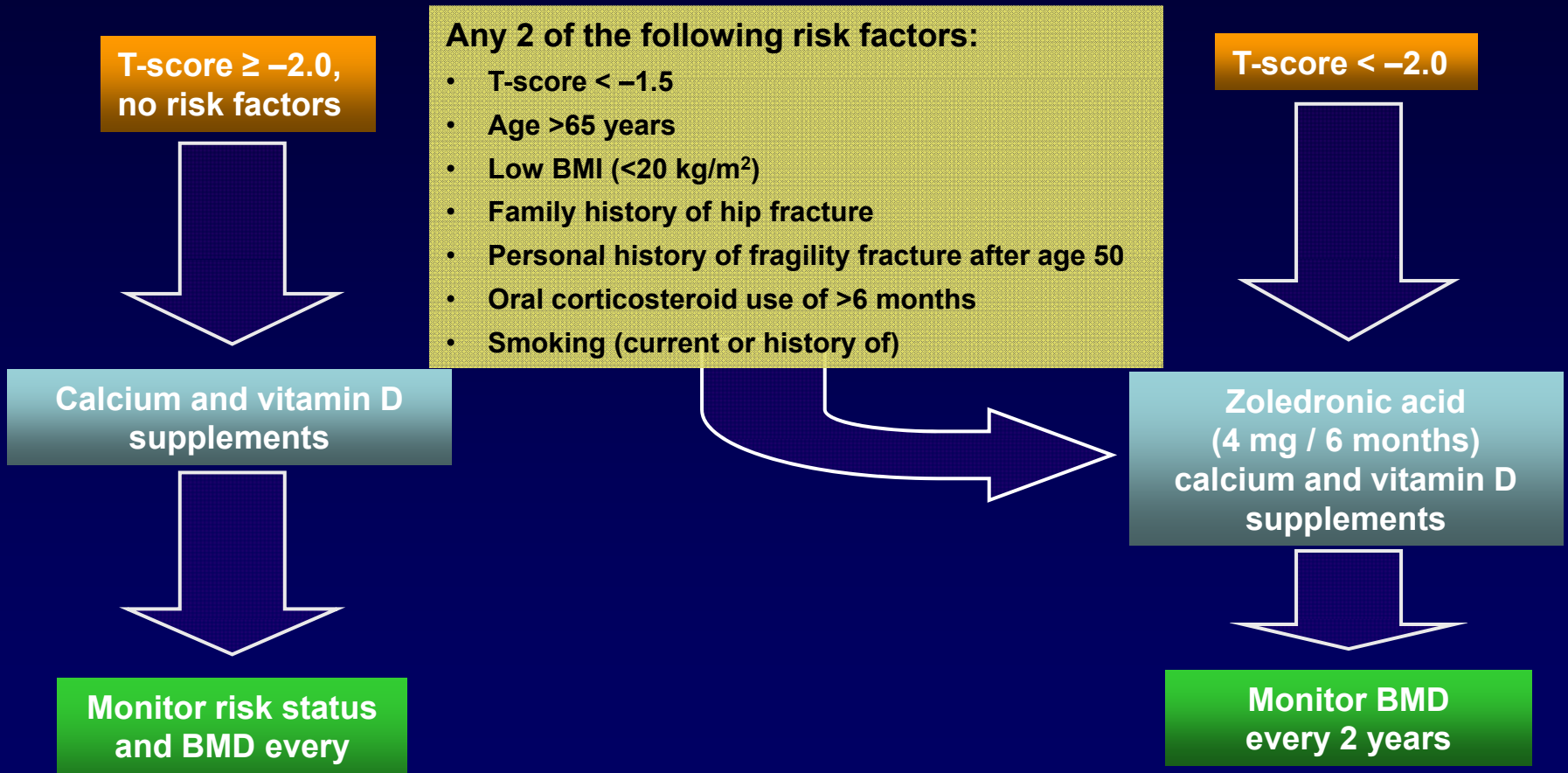


ZOL, zoledronic acid; HR, hazard ratio (Cox regression); DFS, disease-free survival.

[a] Multiple sites of metastases may be reported for the same patient.
Sites of distant metastases include: bone, brain, liver, lung, skin, lymph node, and other.

Eidtmann H, et al. *Cancer Res*. 2009;69(Suppl 2): Abstract 44.

European Recommendations for Women Initiating Aromatase Inhibitor Therapy



- Data for oral bisphosphonates are emerging
- Evidence from 4 clinical trials indicates that zoledronic acid prevents AI-associated bone loss

[a]≥ 5% drop in BMD should trigger zoledronic acid treatment (4 mg / 6 mo). Use lowest T-score from 3 sites.
BMI = body mass index

Hadji P, et al. *Ann Oncol.* 2008;19(8):1407-1416.

Adjuvant Bisphosphonate Treatment in Primary Breast Cancer

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	Oxford / AGO LoE / GR
➢ **Improvement of DFS in individual studies also for OS**	1b C +
➢ **Clodronate (1600 mg PO/d for 2y)**	1b B +
➢ **Zoledronate (4 mg IV every 6 months for 3y)**	
➢ **Postmenopausal patients**	3b[a] C +
➢ **Premenopausal patients***	2b[a] C +

*In the underlying trials, adjuvant therapy did not correspond to current standards.

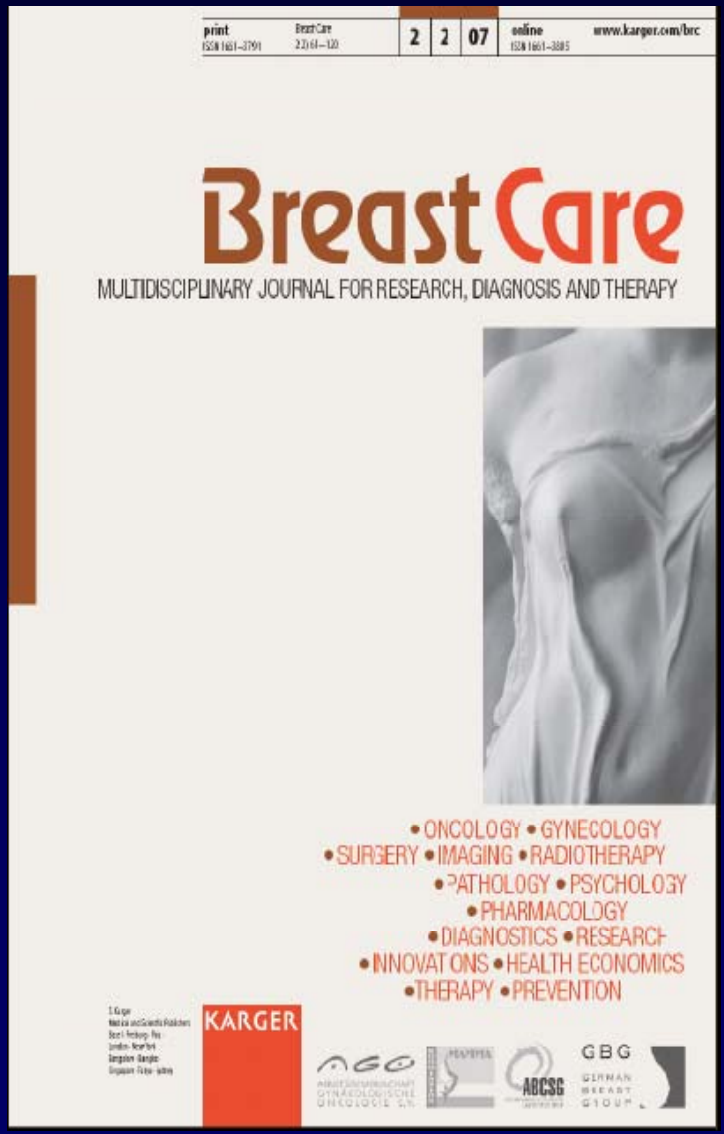
Further information

References

In Addition to History and Physical Exam, Which of the Following Imaging Studies Would You Recommend for the Follow Up of the Right Breast?

1. Yearly mammography of the right breast
2. Yearly MRI of the right breast
3. Yearly mammography and ultrasound of the right breast
4. Yearly mammography and MRI of the right breast
5. Yearly mammography and ultrasound of the right breast and MRI every 2-3 years

Evidence-Based Breast Cancer Therapy



ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE E.V.

KOMMISSION MAMMA

AGO (DKG, DGGG)

www.ago-online.org

www.karger.com/brc