

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer



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in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2009.1.0

START

Neoadjuvant (Primary) Systemic Therapy



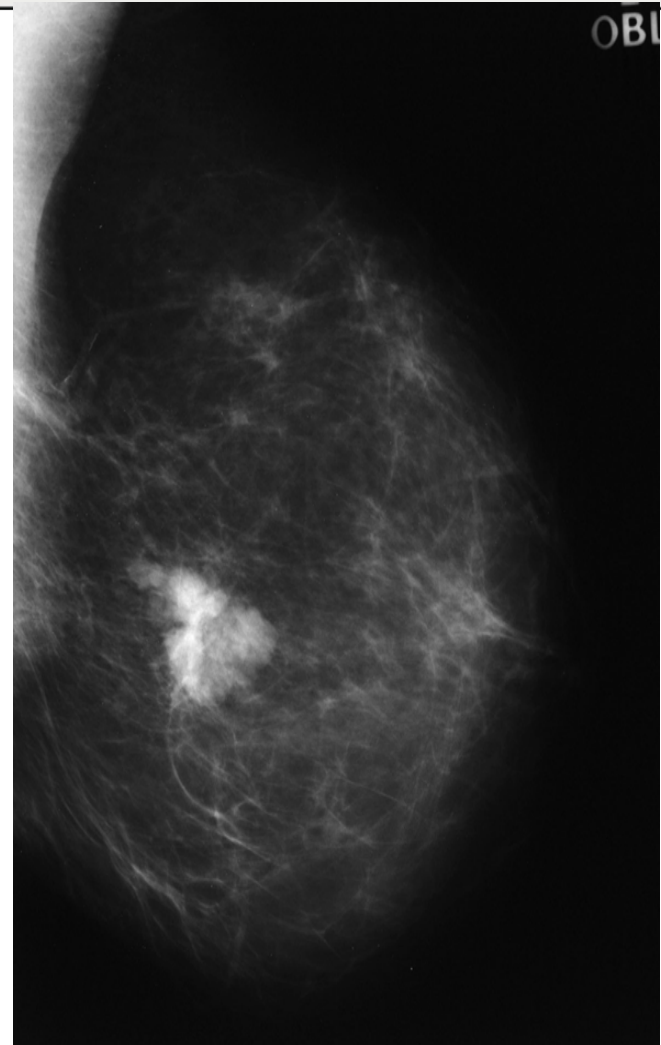
Further
information

References

FORSCHEN
LEHREN
HEILEN

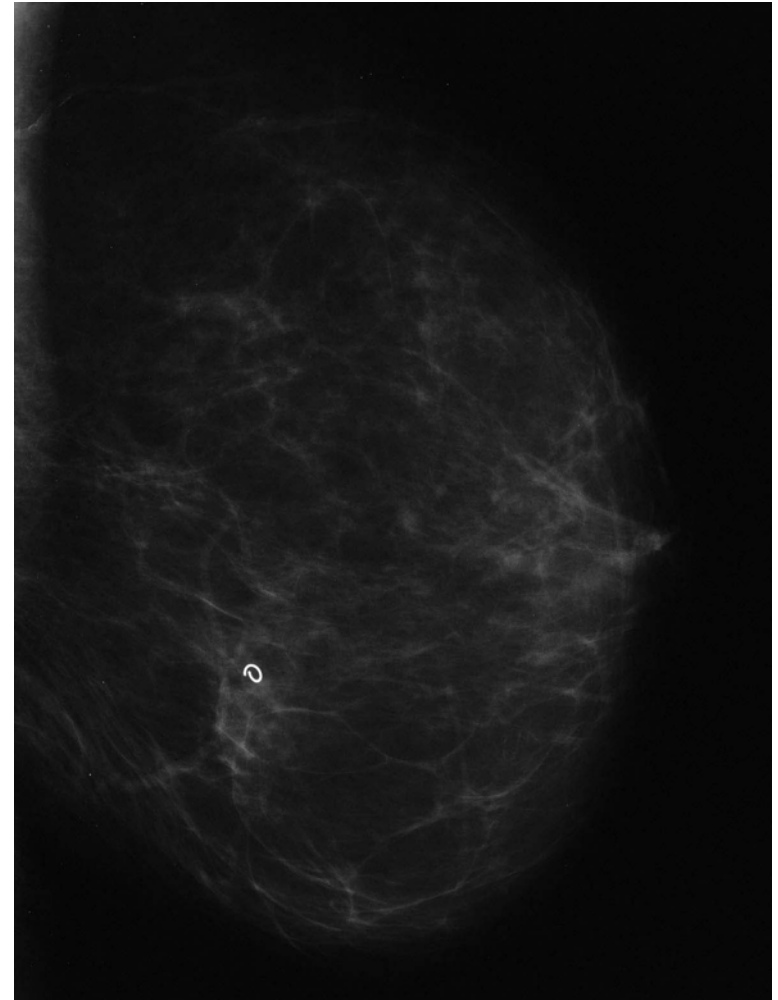
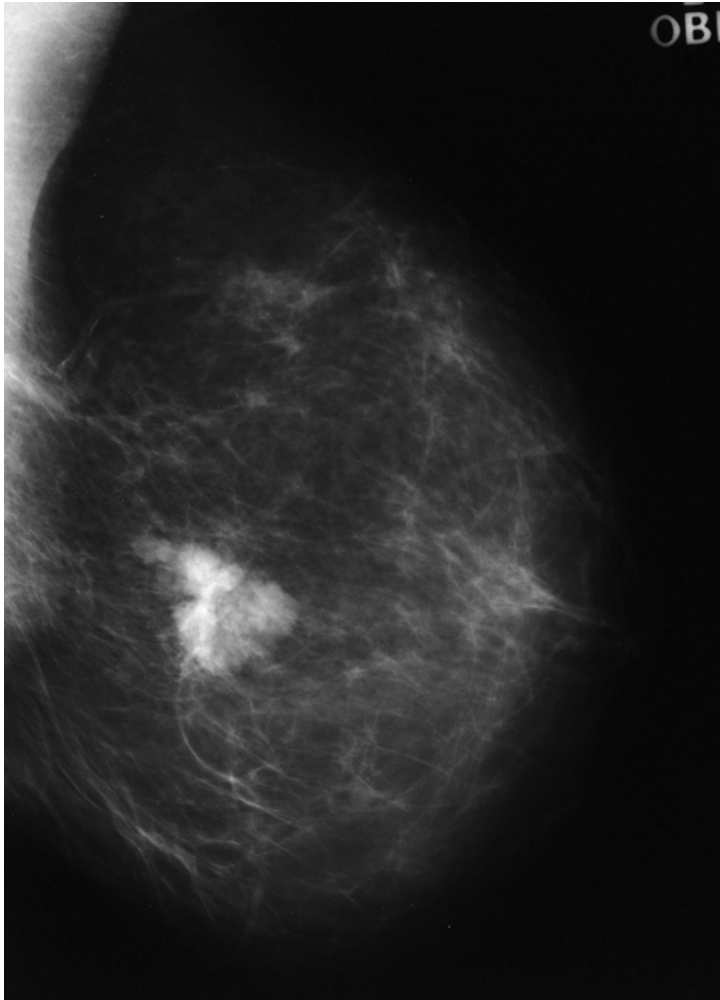


Deutsche
Krebsgesellschaft e.V.



In
Zusammenarbeit
mit der
AWMF, DKH
und der





In
Zusammenarbeit
mit der
AWMF, DKH
und der

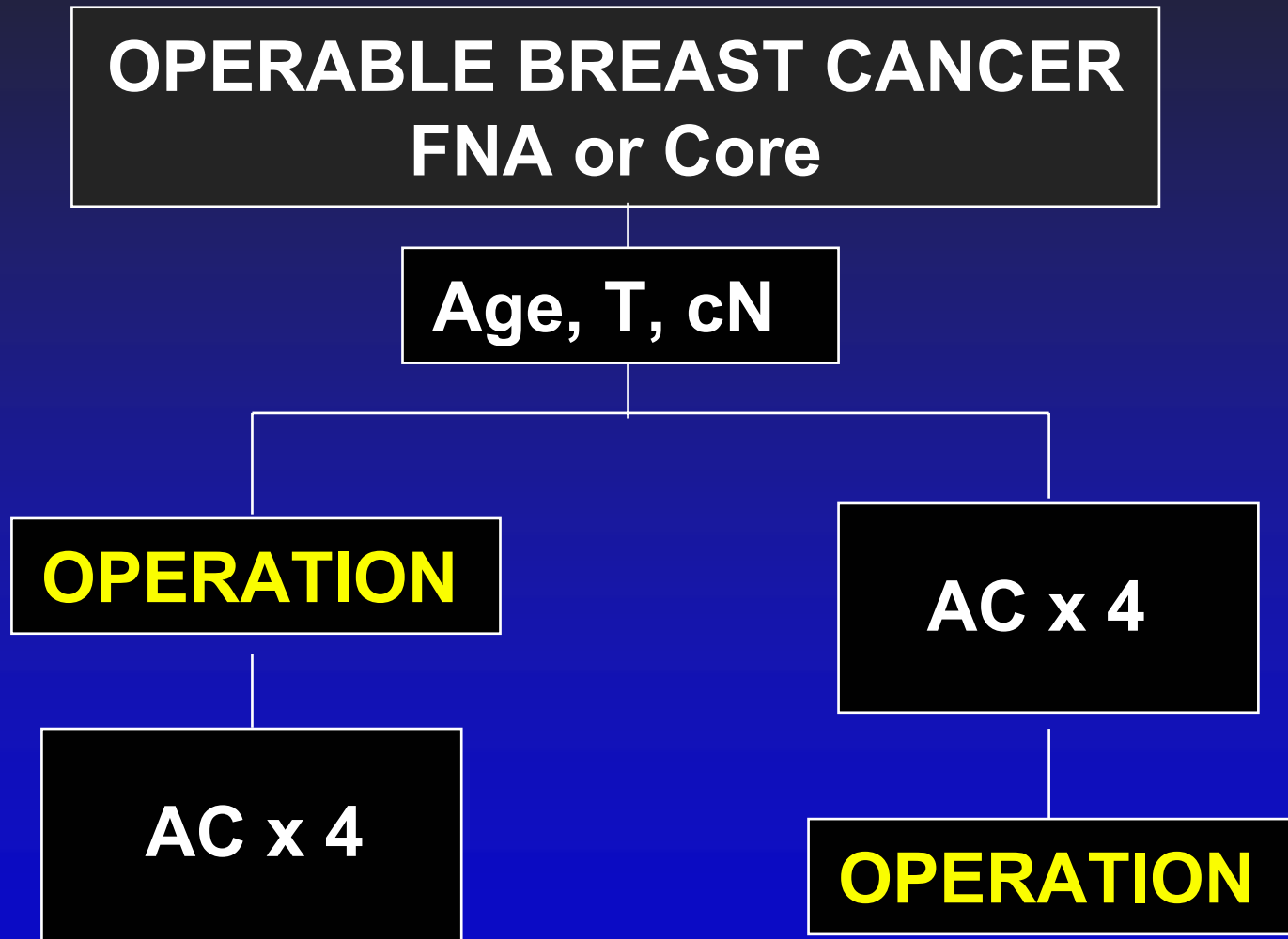








B-18



Seq tam for women ≥ 50 yrs. only

NSABP B-18

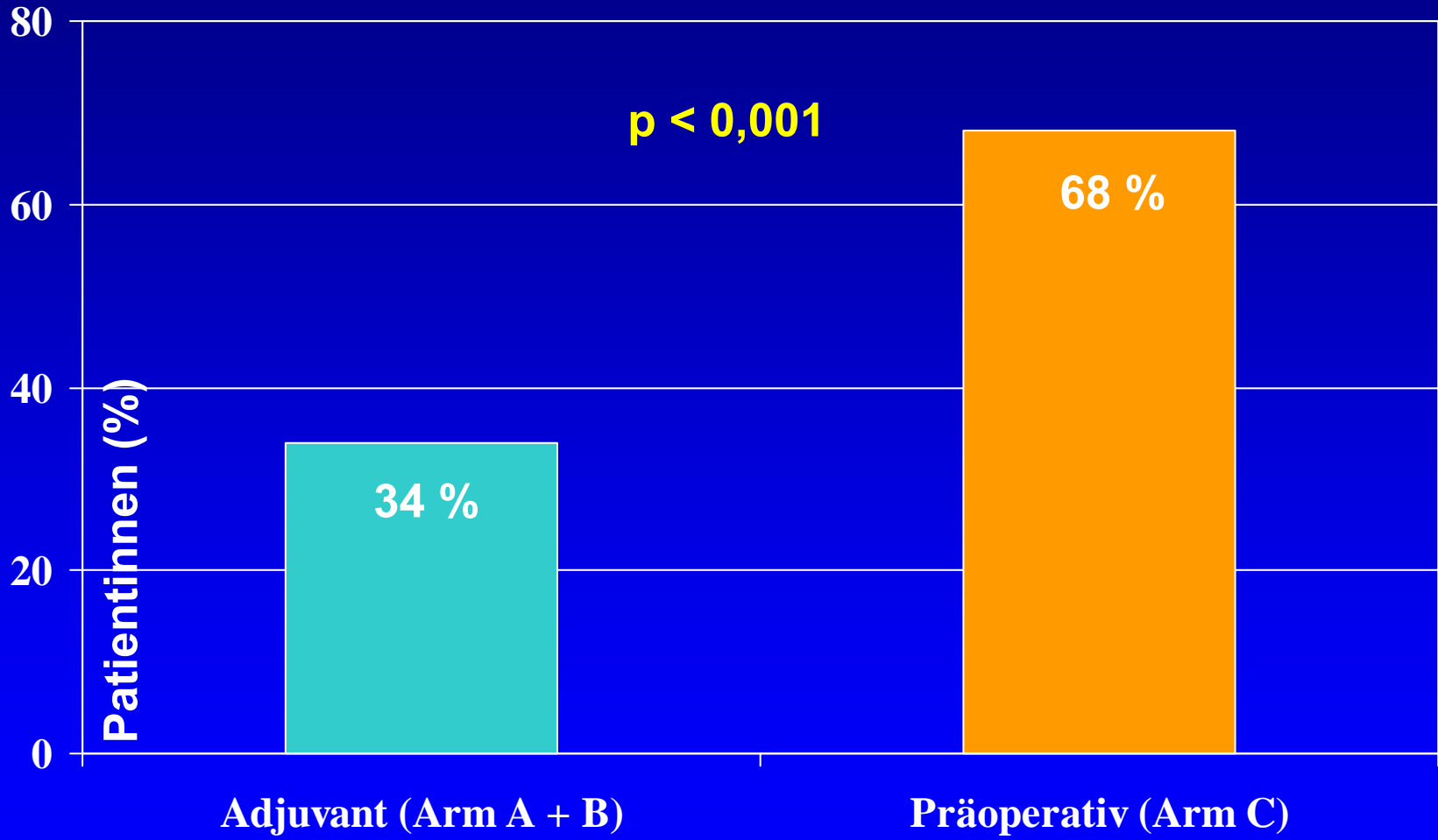
OPENED: Oct. 1988

CLOSED: Apr. 1993

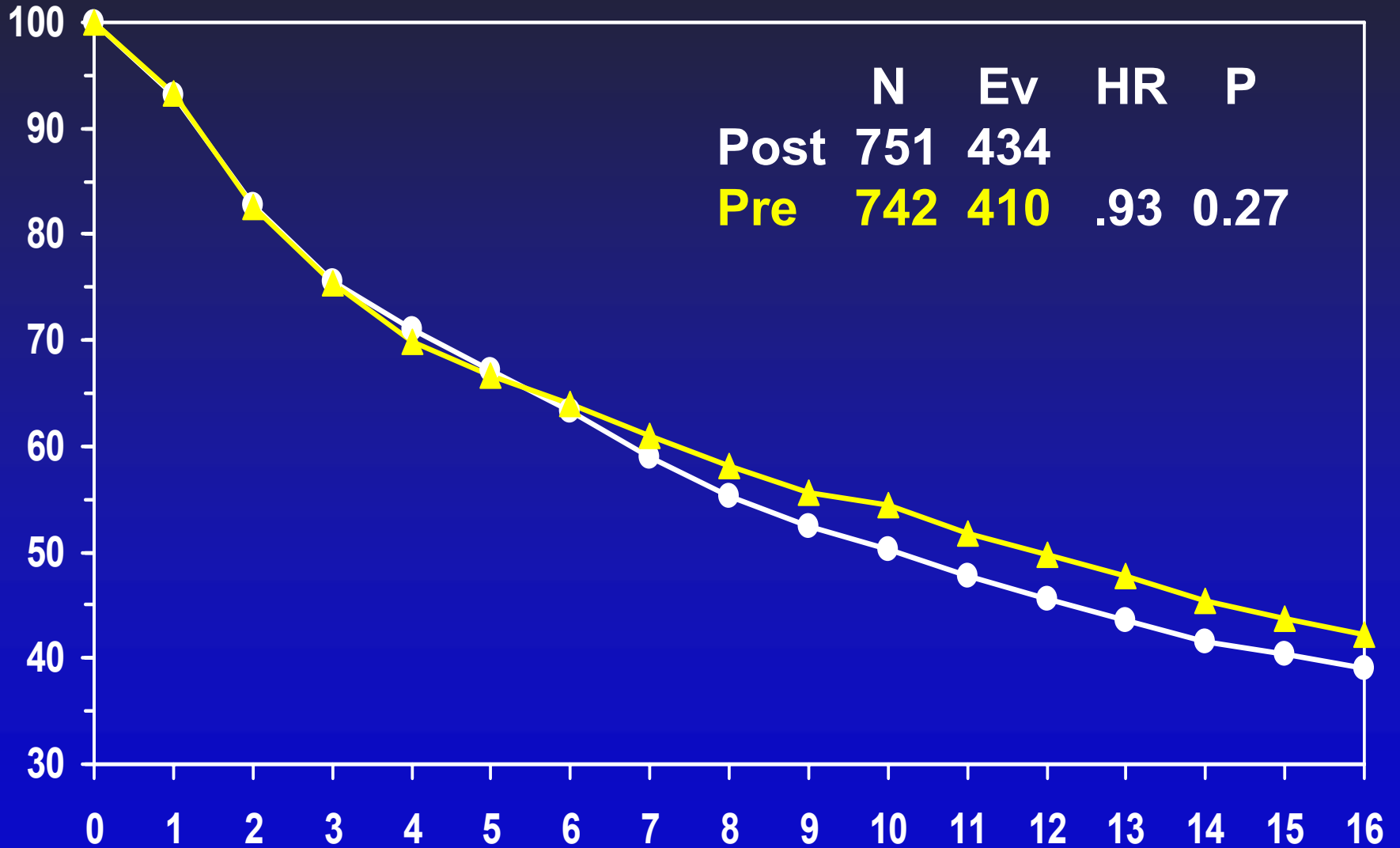
ACCRUAL: 1,523

MTS: 9.5 years (2001)
16 years (2007)

BET

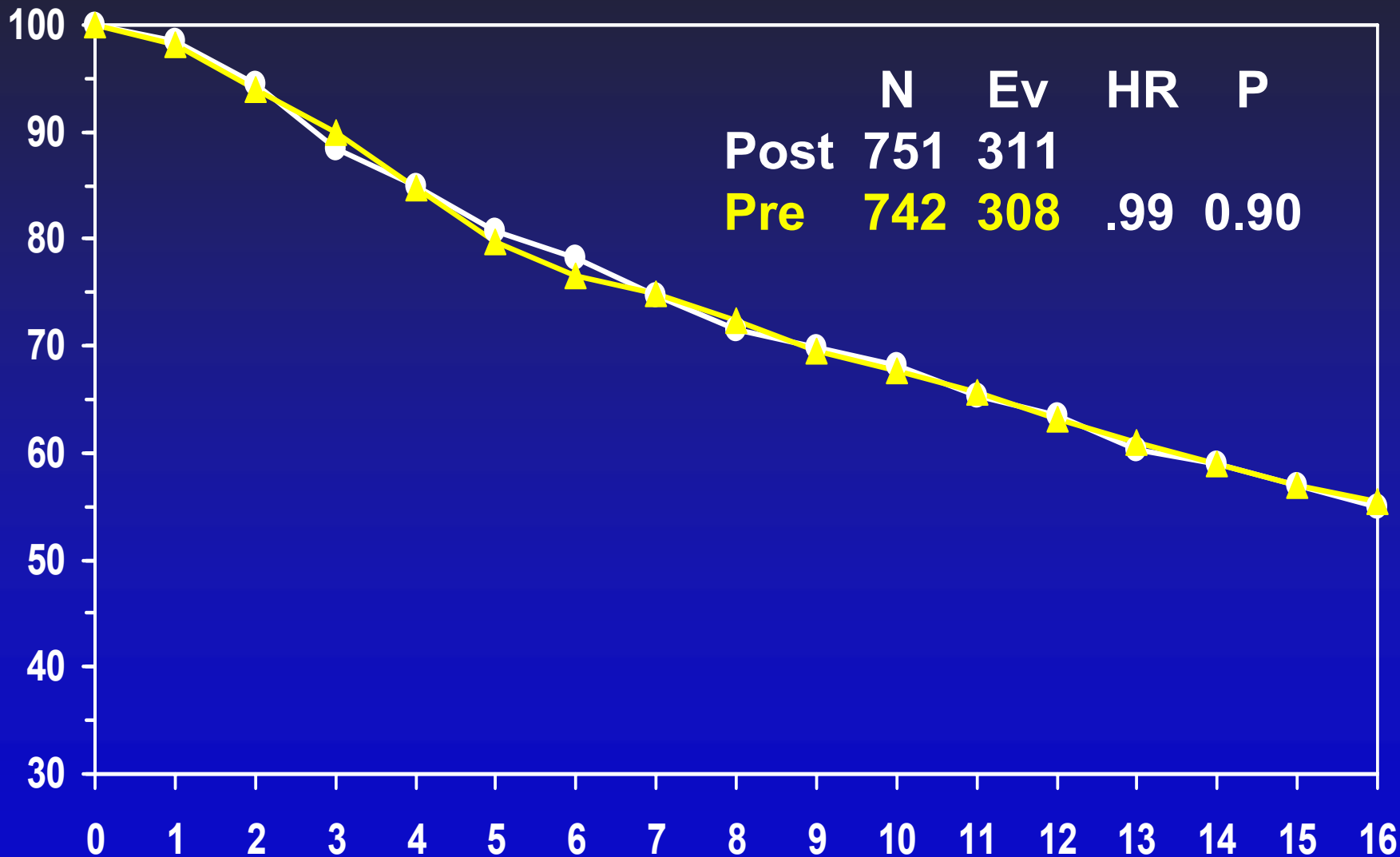


DFS

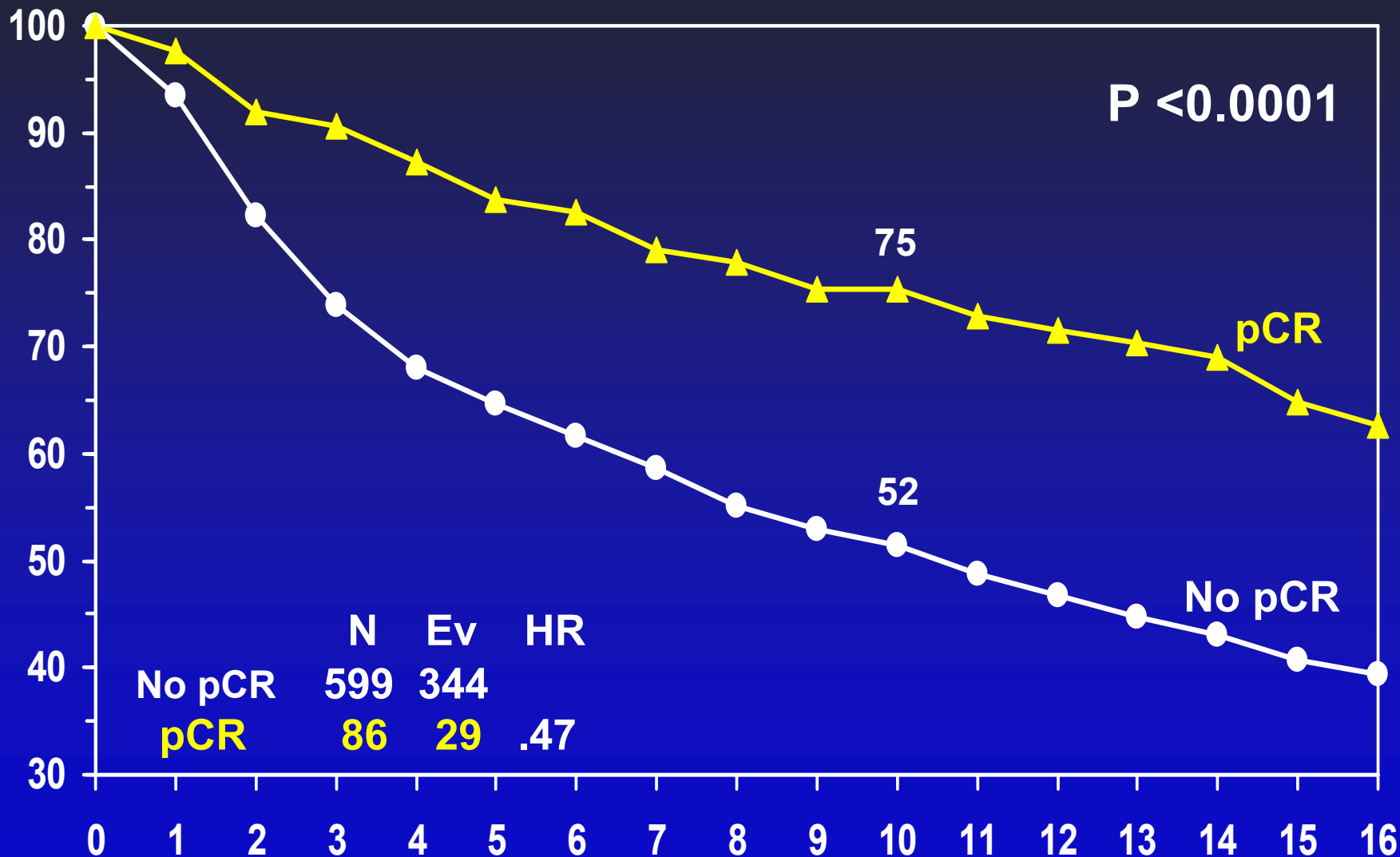


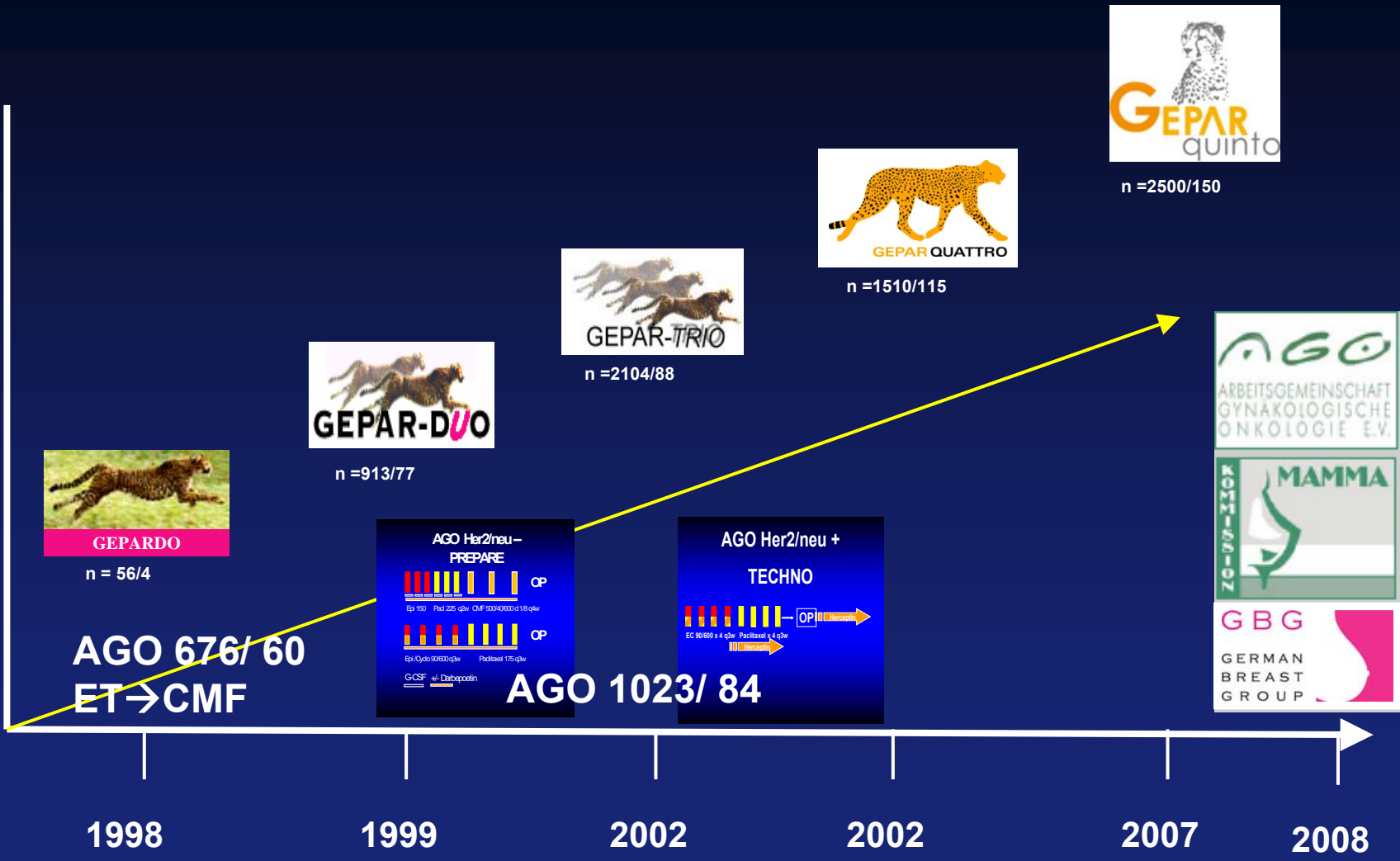
JCO 2'08

Survival



DFS and pCR





GEPARDO
n = 56/4



n = 913/77



n = 2104/88



n = 1510/115



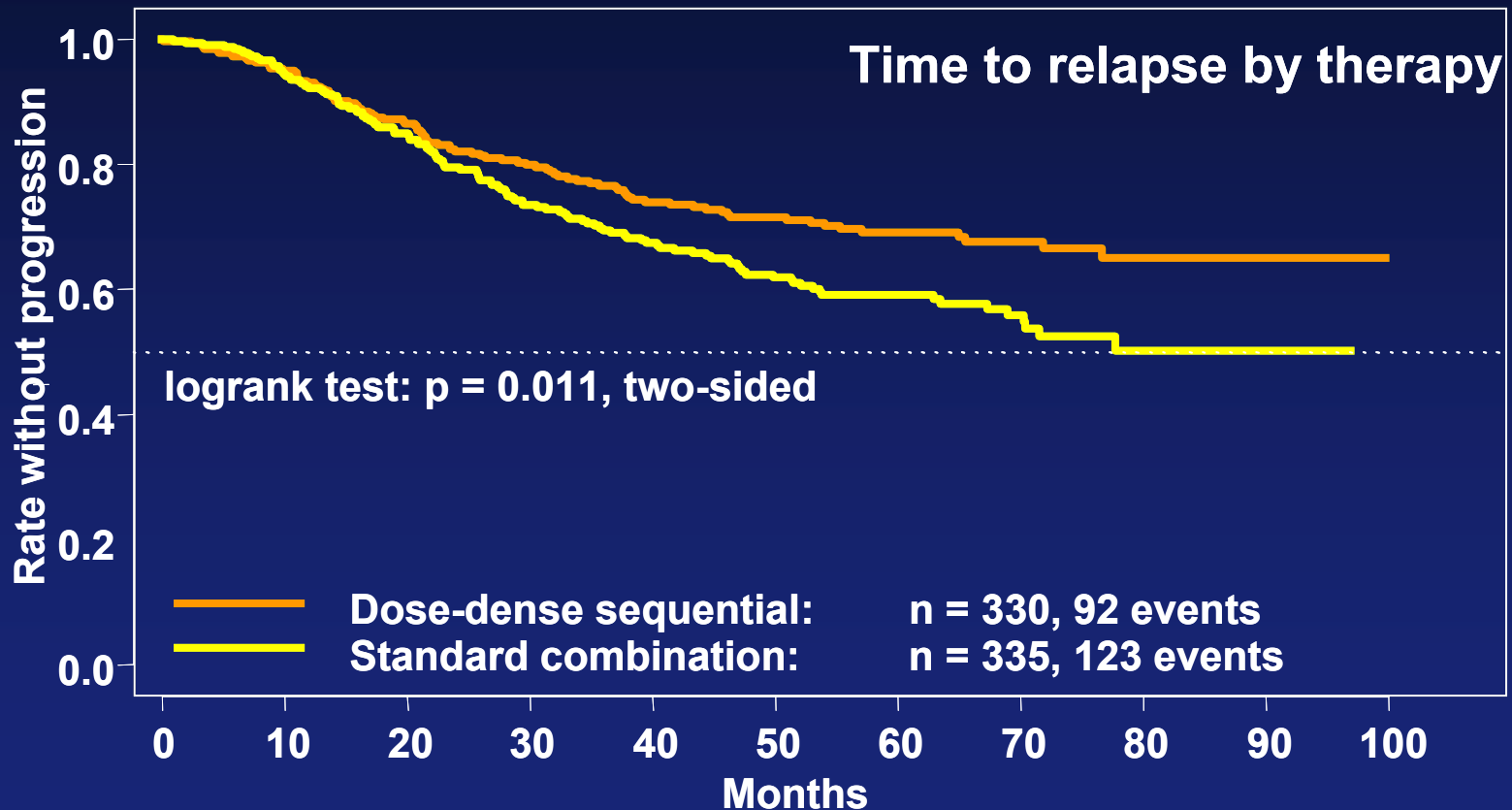
n = 2500/150



3x E → 3x T q2w
4x ET q3w

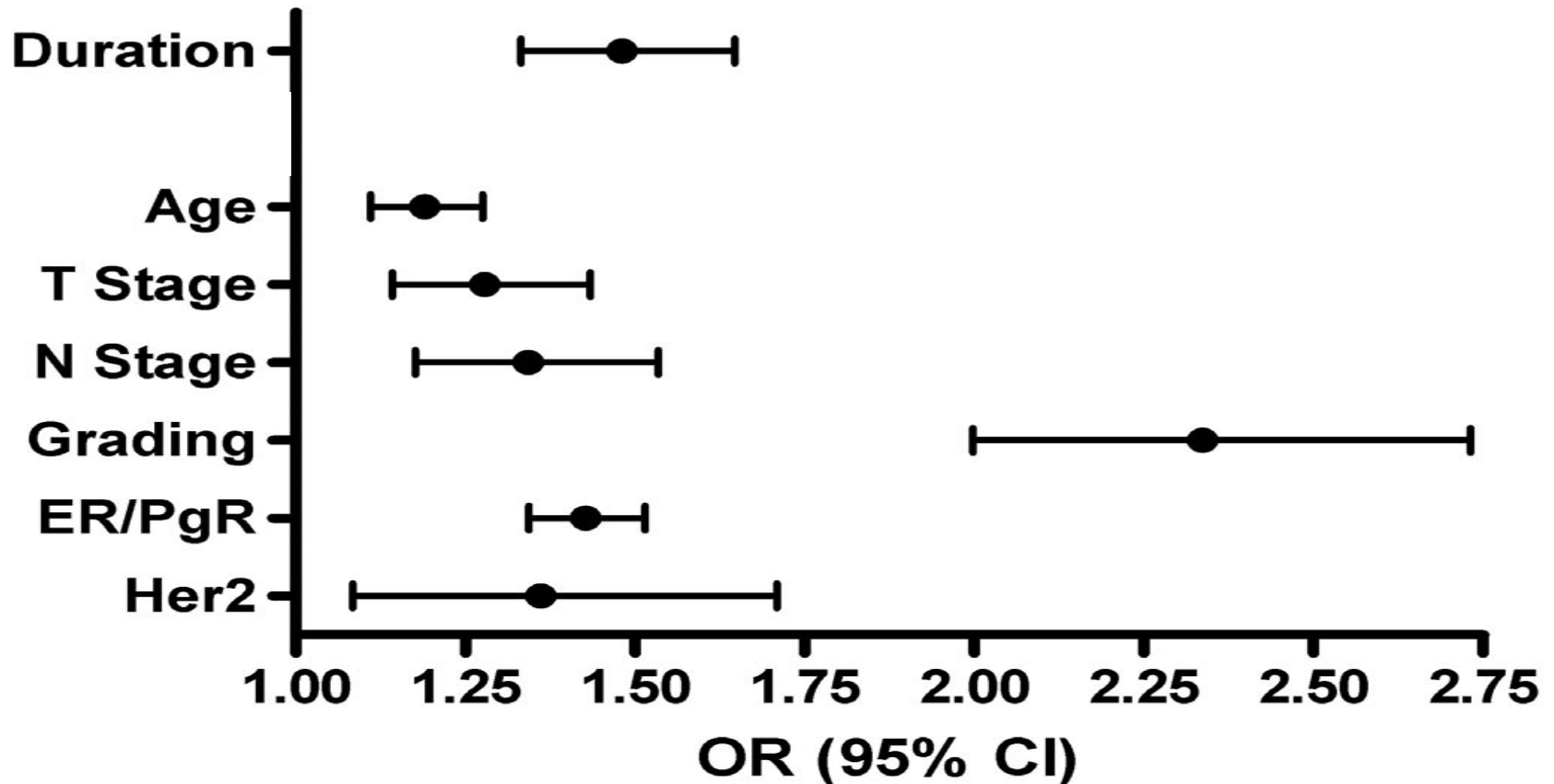
→ OP
→ OP

→ CMF
→ CMF



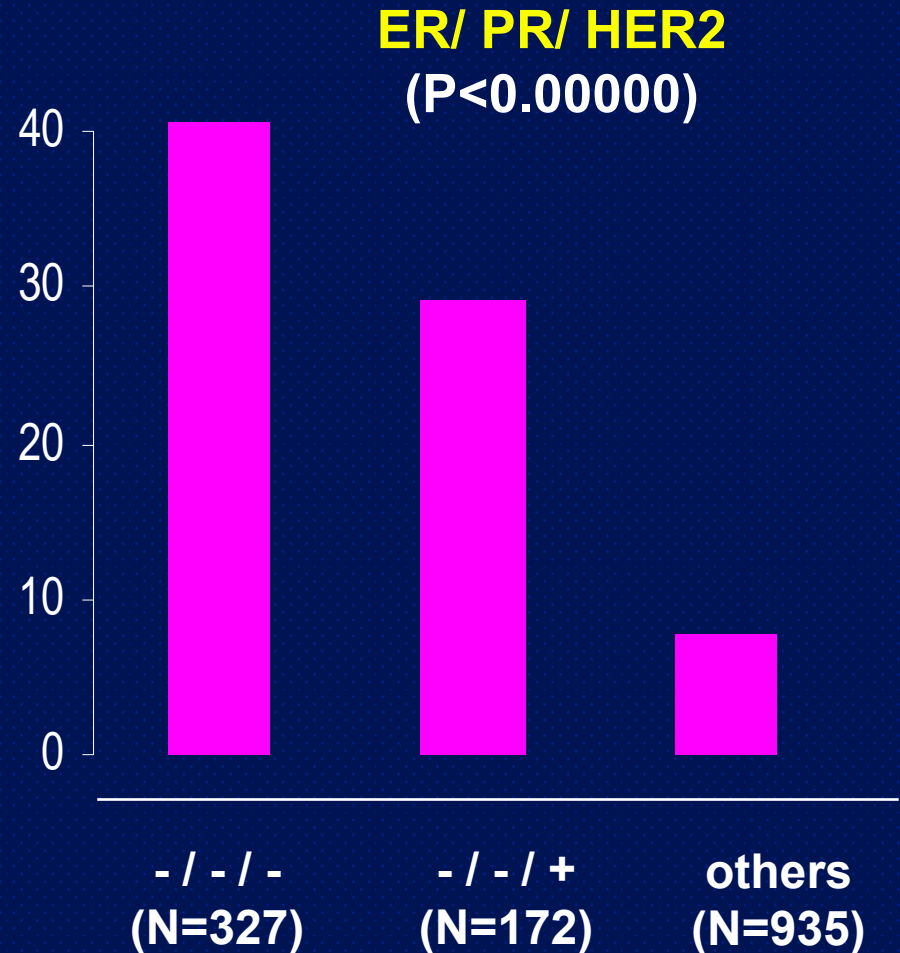
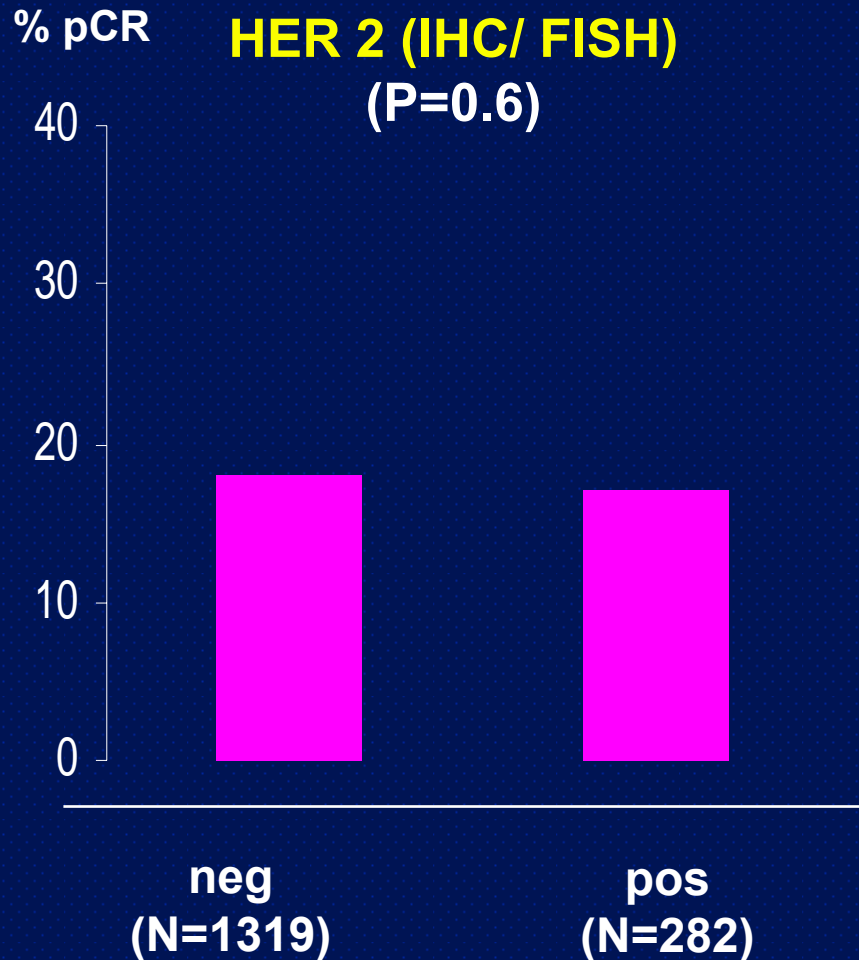
Multivariate Backward Stepwise[#] Analysis of Treatment and Baseline Factors*

(n=5172 excluding patients with missing values or trastuzumab treatment)



Path CR in Subgroups

% pCR



Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia, W. Fraser Symmans, Ana M. Gonzalez-Angulo, Bryan Hennessy, Marjorie Green, Massimo Cristofanilli, Gabriel N. Hortobagyi, and Lajos Pusztai

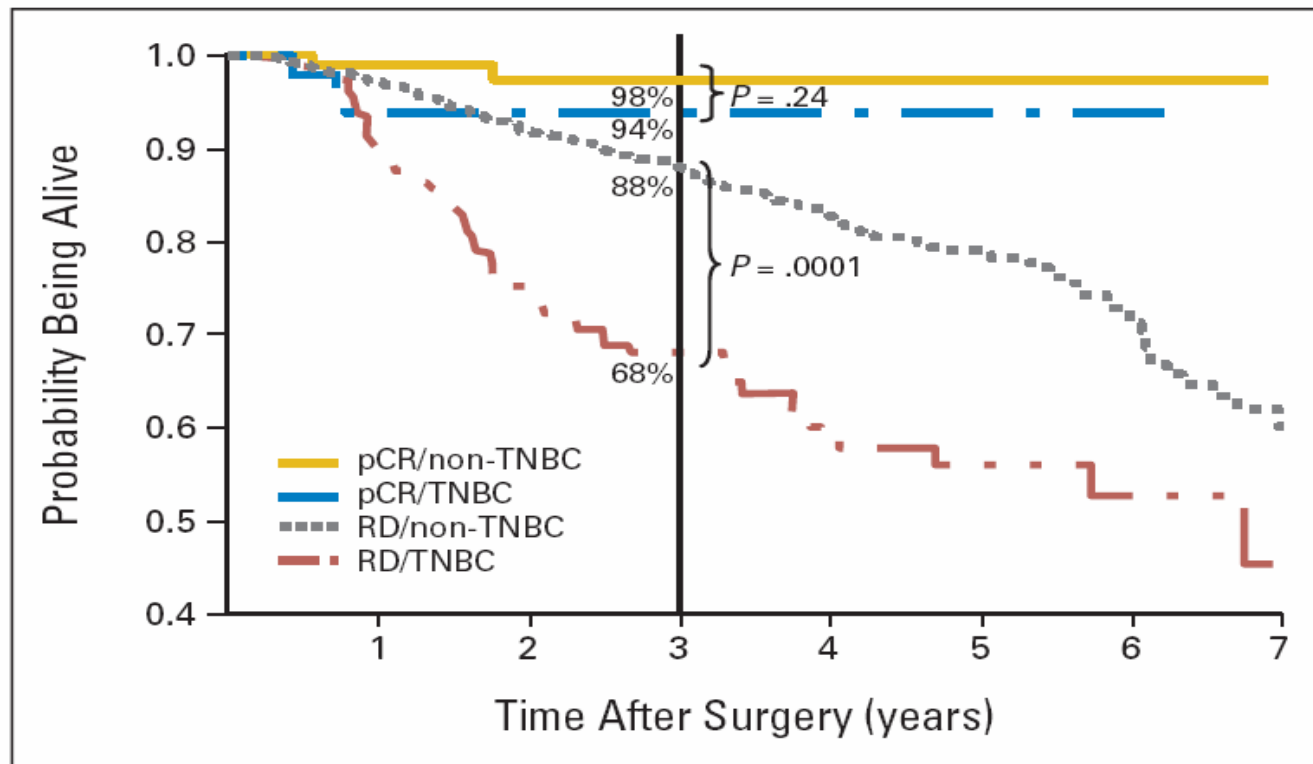


Fig 2. Overall survival as a function of response to chemotherapy (pathologic complete response [pCR] v residual disease [RD]) and triple-negative status (triple-negative breast cancer [TNBC] v non-TNBC).

German NEO-PARP-Study (Start Jan '11)

***N=300 triple neg &
N=300 HER2-/ER+***

***T4 or
T3 or
T>3cm, N+
HER2 neg***

R*

TACx6

TACx6 + BSI-201

TCyclohex6 + BSI-201

TCarbox6 + BSI-201

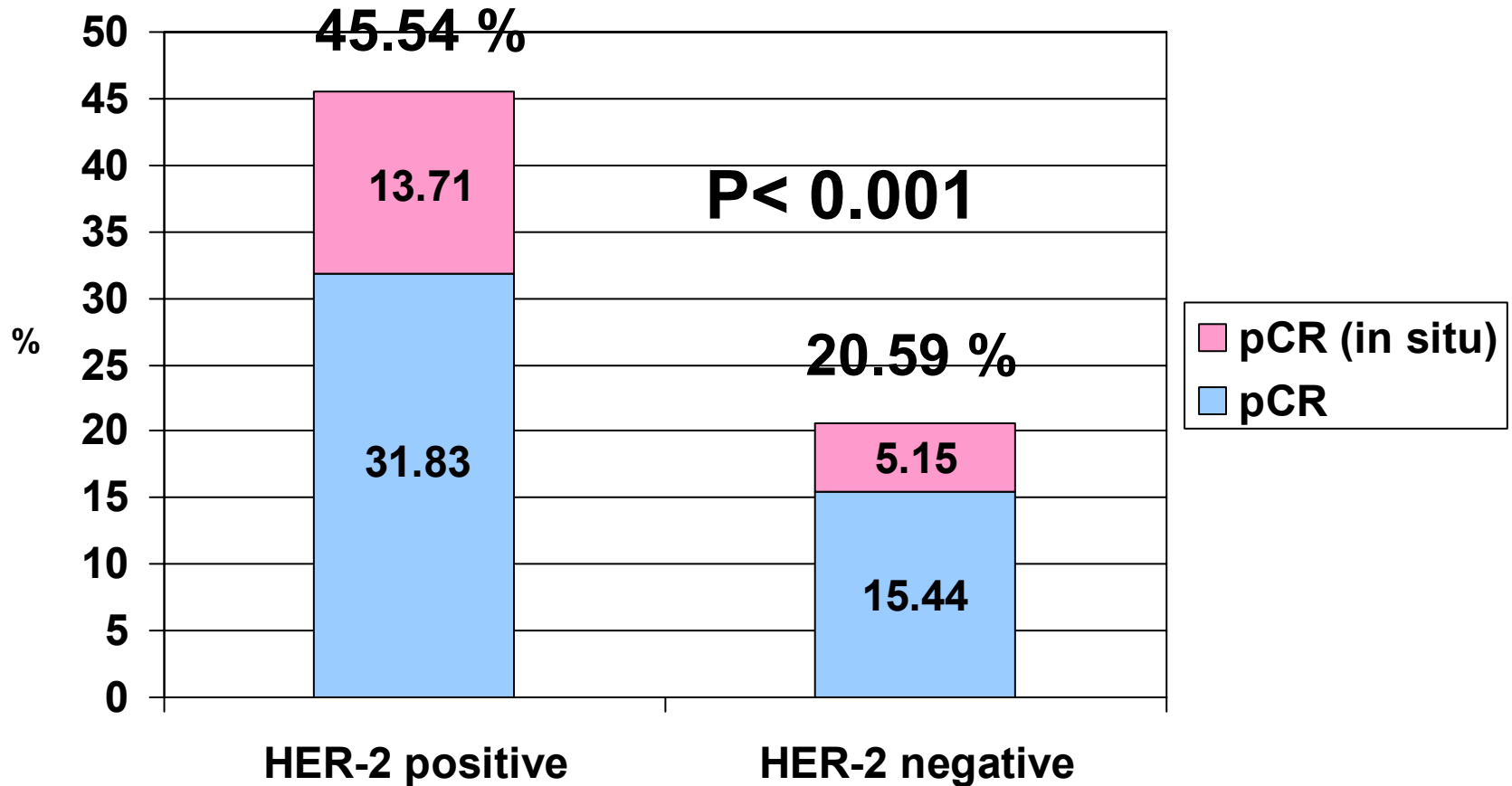
Surgery

****stratified acc. to PARP (IHC)
and ER/PgR status***

Sponsor: Sanofi-Aventis D

***Endpoints:
pCR, Safety, Biomarker***

Pathologic Complete Response



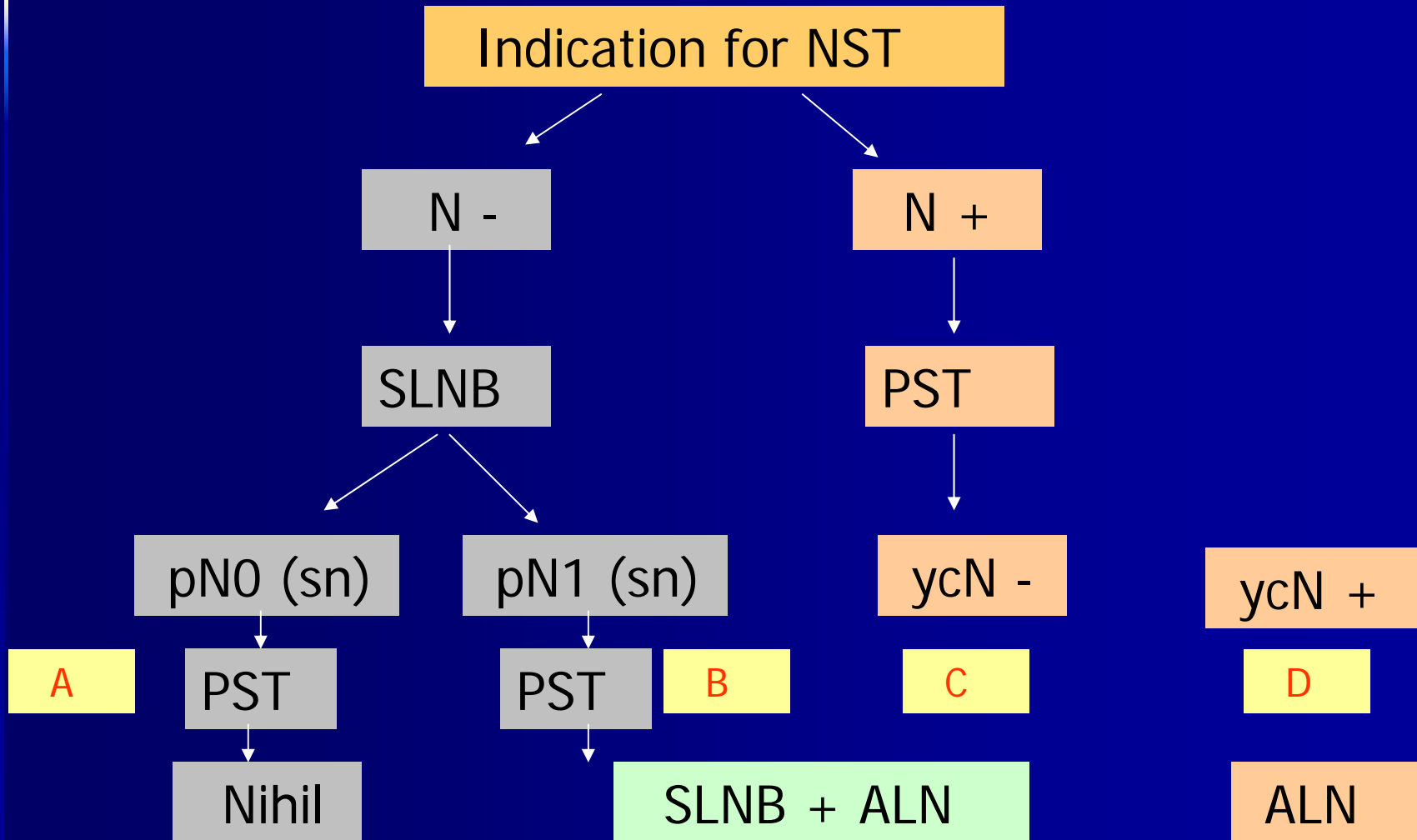


Axillary nodes after neoadjuvant therapy

	Her2		Total
	neg	pos	
Negative	645	361	1006
%	61,02	79,87	66,67
Pos 1-3 nodes	233	62	295
%	22,04	13,72	19,55
Pos 4-9 nodes	125	21	146
%	11,83	4,65	9,68
Pos >10 nodes	54	8	62
%	5,11	1,77	4,11
Total	1057	452	1509
%	100	100	100



SENTINA-Trial



Strategien – prä-Chemo

- **Untersuchung (möglichst) durch Operateur**
- **(evtl.) zusätzliche Fotodokumentation der Tumorlokalisation durch Einzeichnung auf der Haut**
- **Festlegung des wahrscheinlichen operativen Vorgehens**
- **Klinische Kontrolle des Ansprechens während der Chemotherapie**
- **Clipmarkierung im Tumorbett**

Neoadjuvant Systemic Chemotherapy Indications

Oxford / AGO LOE / GR

- | | | | |
|--|----|---|-----|
| ➤ Inflammatory breast cancer | 2b | B | ++ |
| ➤ Inoperable breast cancer | 1c | A | ++ |
| ➤ Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation | 1b | B | + |
| ➤ If similar postoperative adjuvant chemotherapy is indicated | 1b | A | + * |

Further
information

References

Primary systemic therapy

Surgical procedures

Oxford / AGO
LoE / GR

- | | | | |
|---|-----------|----------|-----------|
| ➤ Precise documentation of tumor location
before, during and at the end of PST | 5 | D | ++ |
| ➤ Surgery after PST | 2b | C | ++ |
| ➤ Microscopically clear margins | 5 | D | ++ |
| ➤ Excision within new margins | 3b | C | + |
| ➤ Sentinel node biopsy
(see chapter “Surgery”) | | | |

Primary systemic therapy

Timing of surgery and radiotherapy

Oxford / AGO
LoE / GR

Surgery

4 C ++

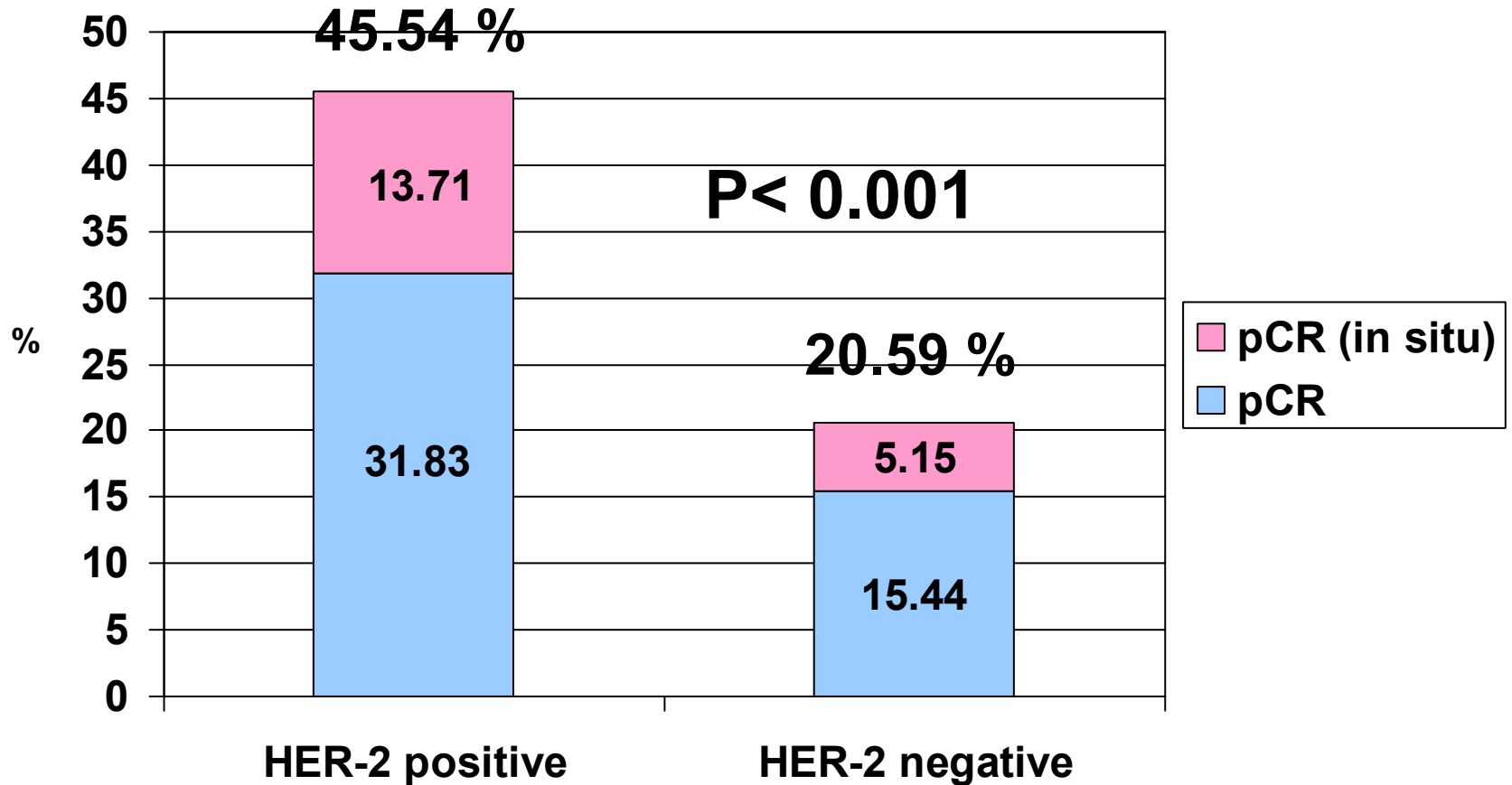
- After leucocyte nadir
(2 to 4 weeks after last course of
chemotherapy)

Radiotherapy after mastectomy

2b B ++

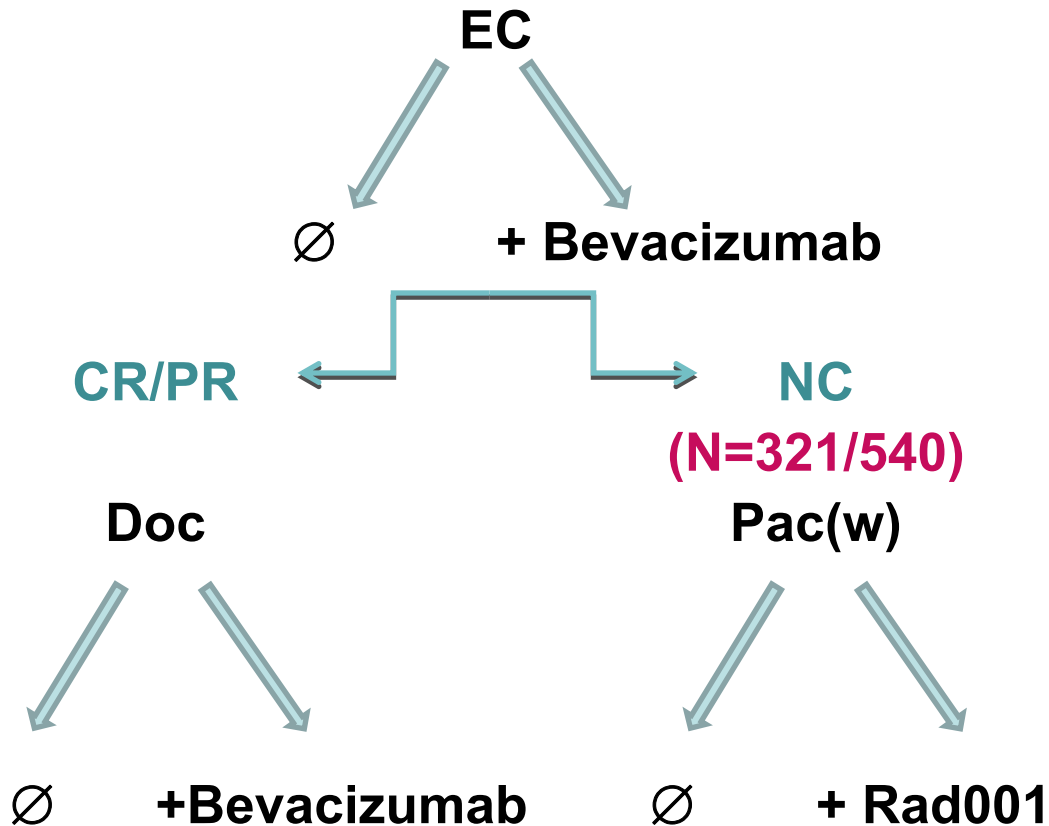
- 2-3 weeks after surgery
- Indications according to stage of
disease before PST (cN+, cT3/4a-d)

pCR nach 4 X EC +H → 4 X D + H



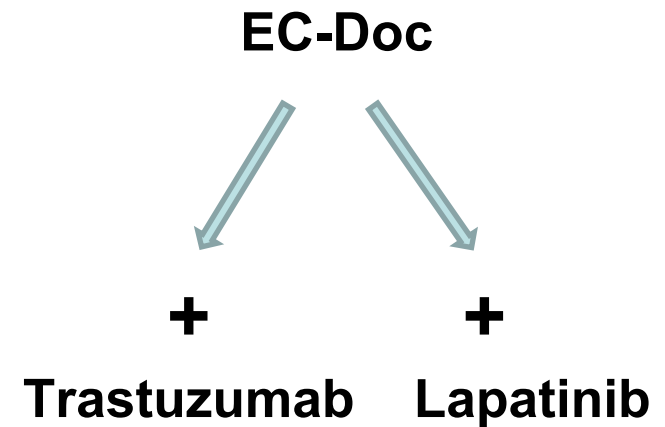
HER2-negative:

(N=1948, closed)

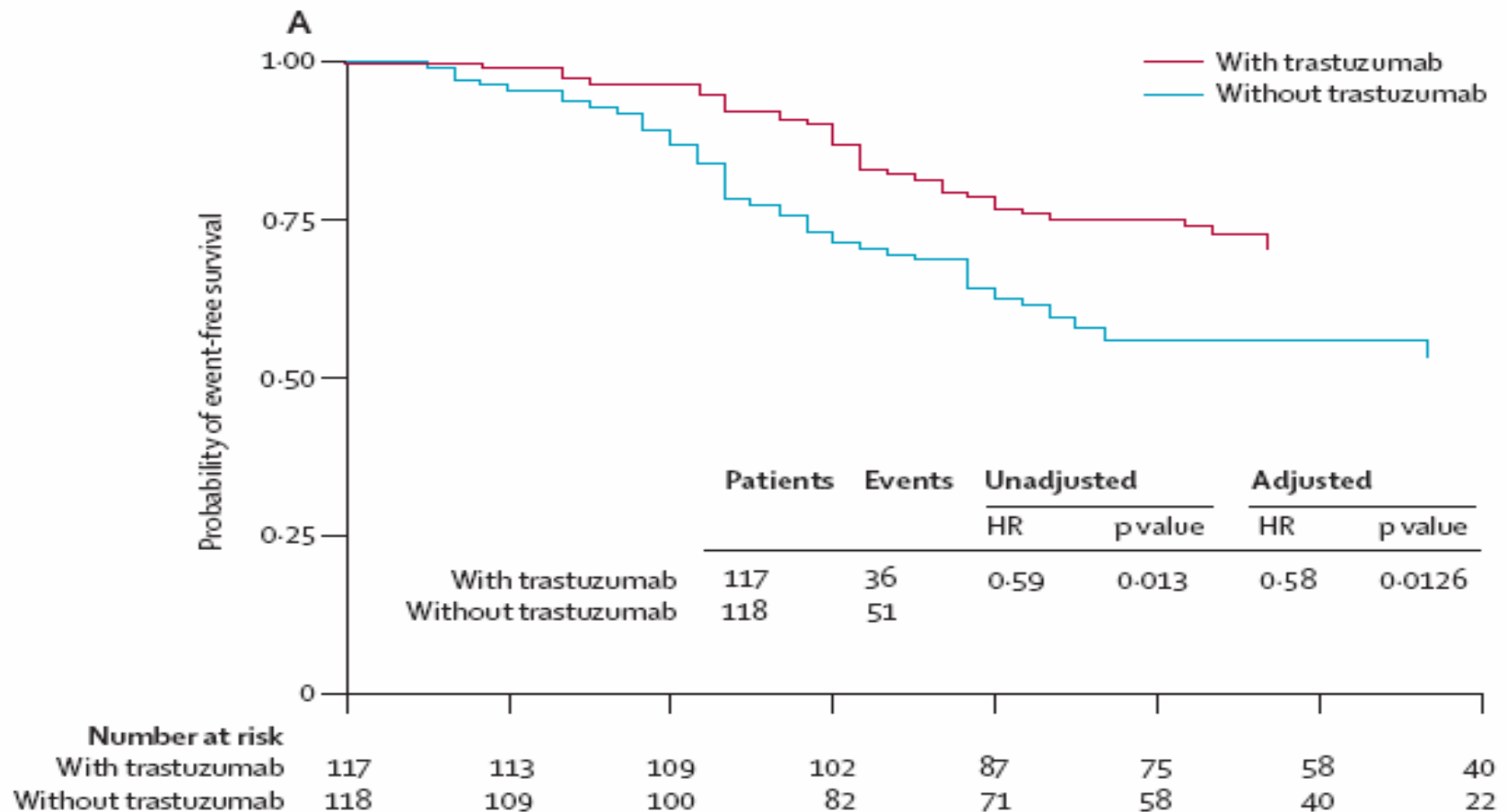


HER2-positive:

(N=620, closed)

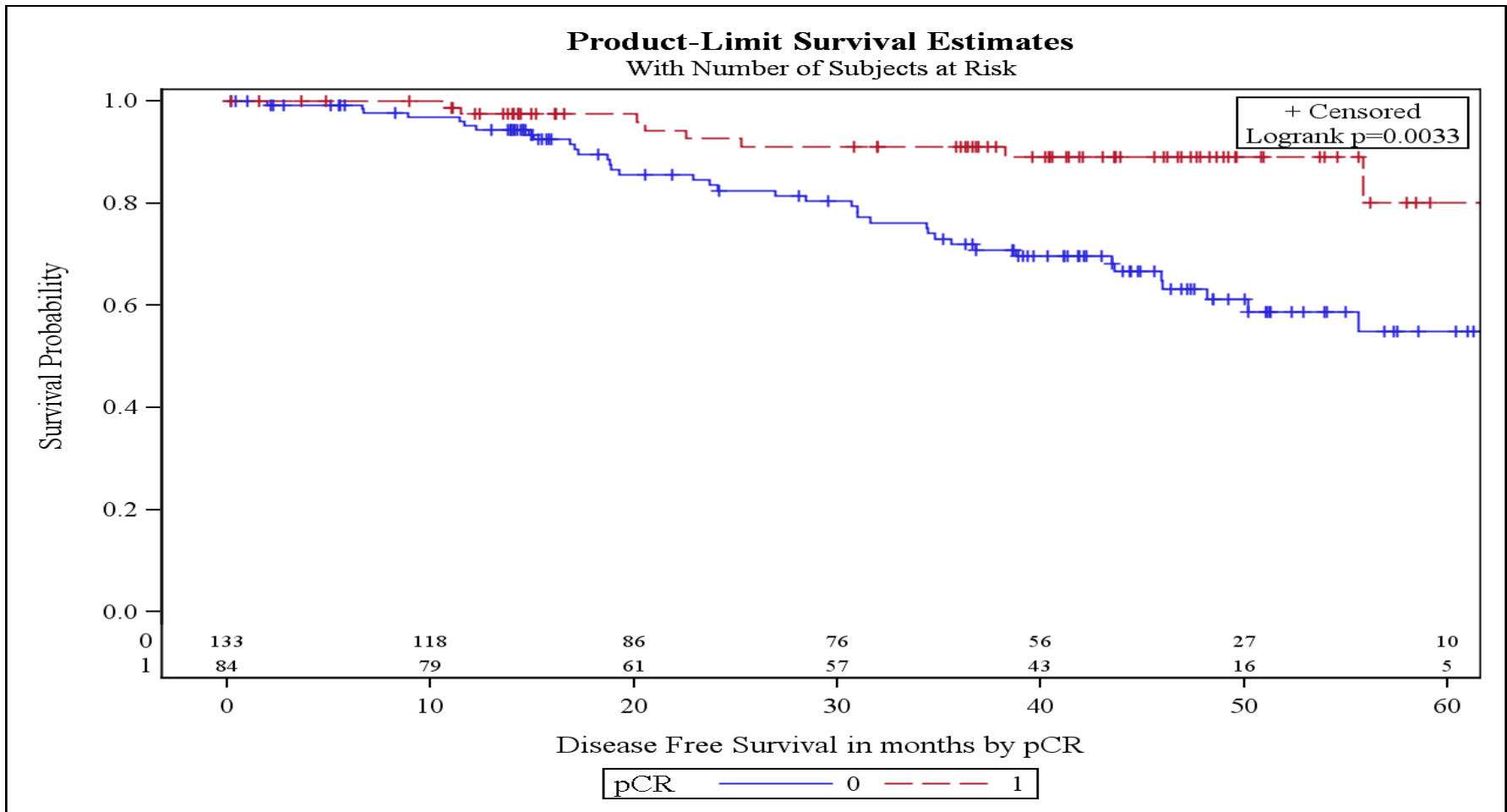


Long-term outcome in patients receiving $3 \times A_{60} T_{150} \rightarrow 3 \times T_{175} \rightarrow CMFx4 \pm Trastuzumab$



PCR predicts survival in HER2-positive disease treated with EC-P+trastuzumab

Results of the TECHNO-study



IMMER NEOADJUVANT ?

NICHT IMMER , ABER IMMER ÖFTER





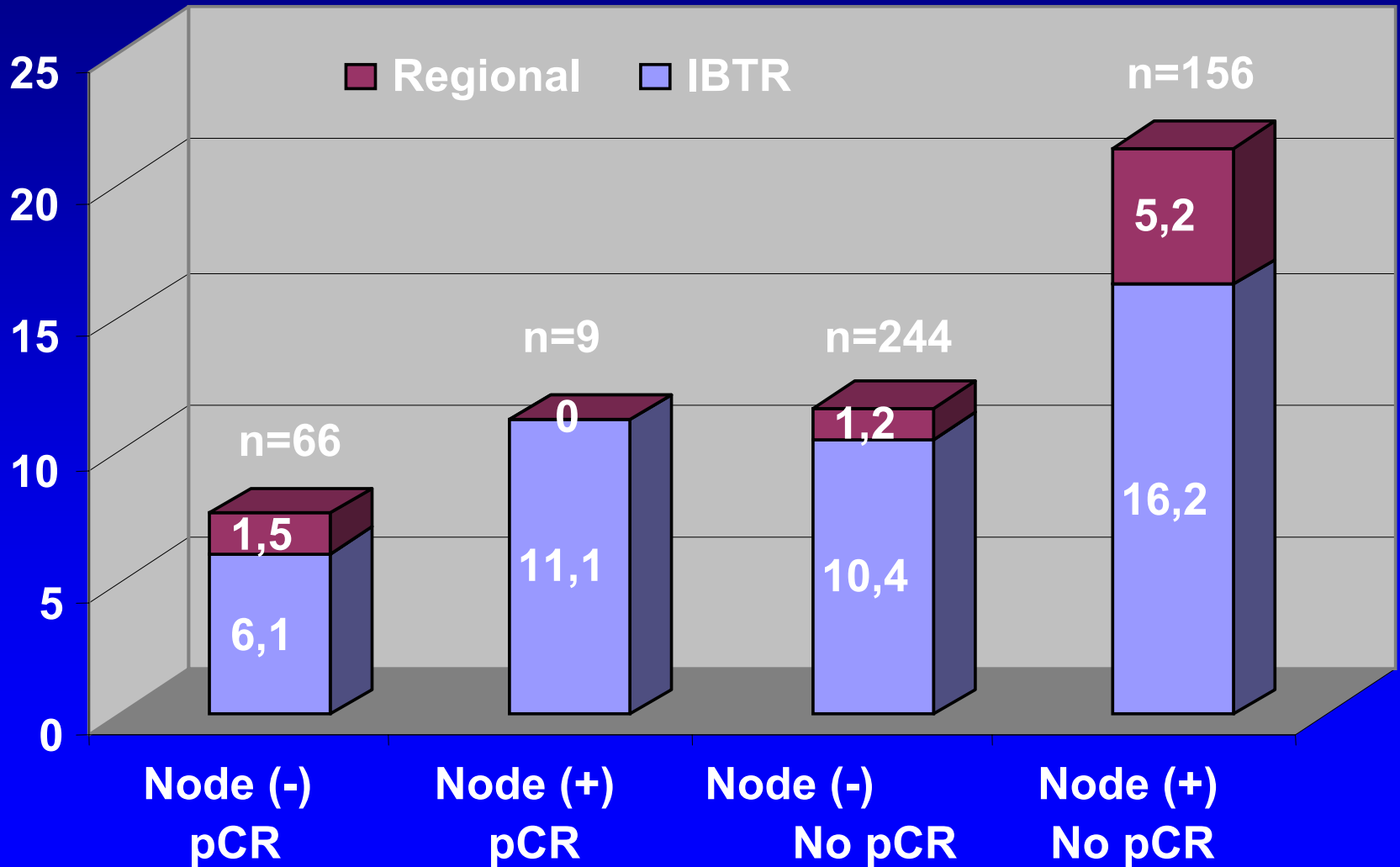
Quality control in the locoregional treatment of breast cancer **EUSOMA**

Qualitätskriterium – Lokalrezidivrate

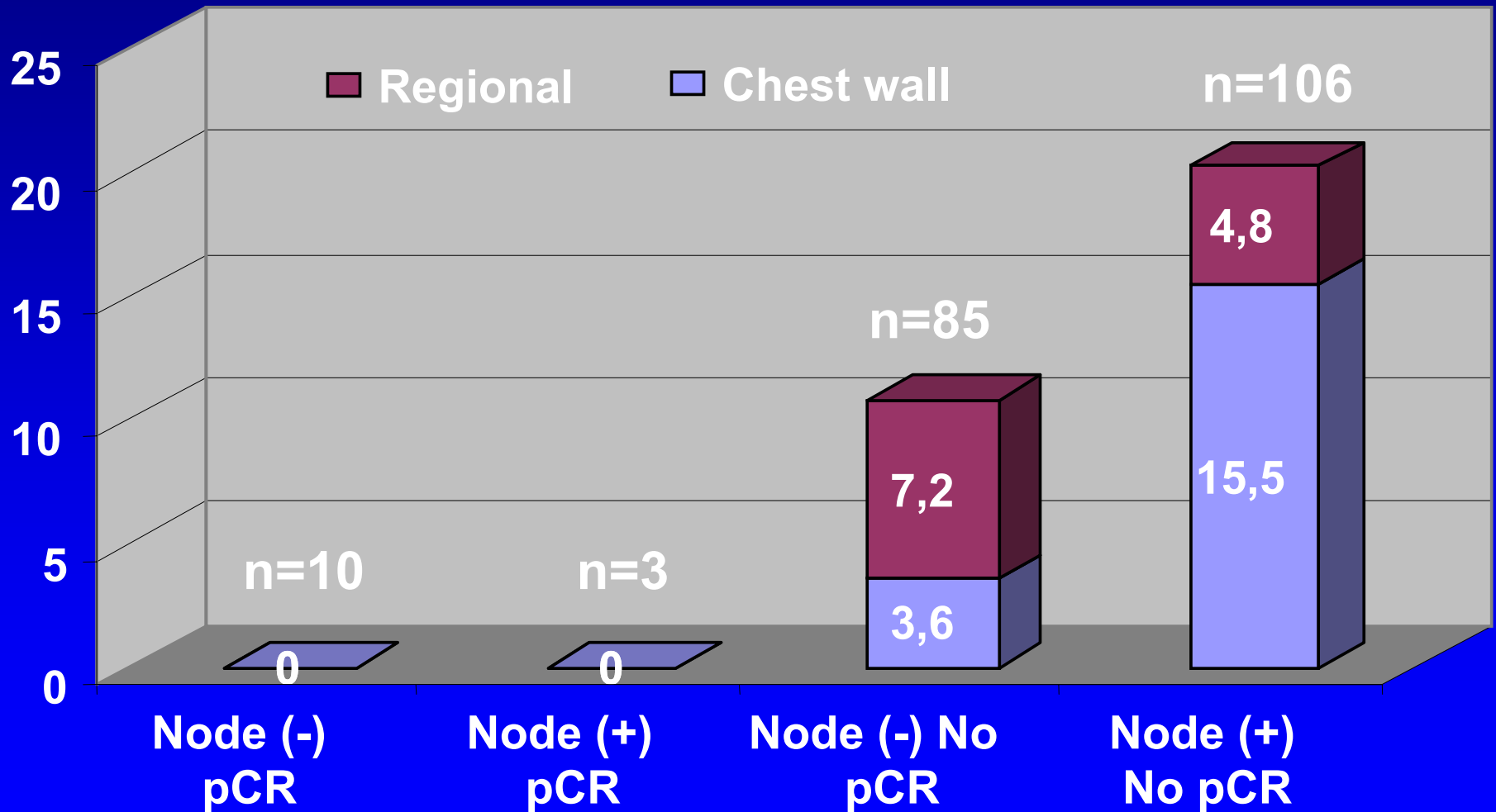
Bei BET: max. 15 % n. 10 Jahren

Bei ME: max. 10 % n. 10 Jahren

10 Jahres Lokalrezidive (%) nach PST BET (n= 475)



10 Jahres Lokalrezidive (%) nach PST Mastektomie (n = 204)



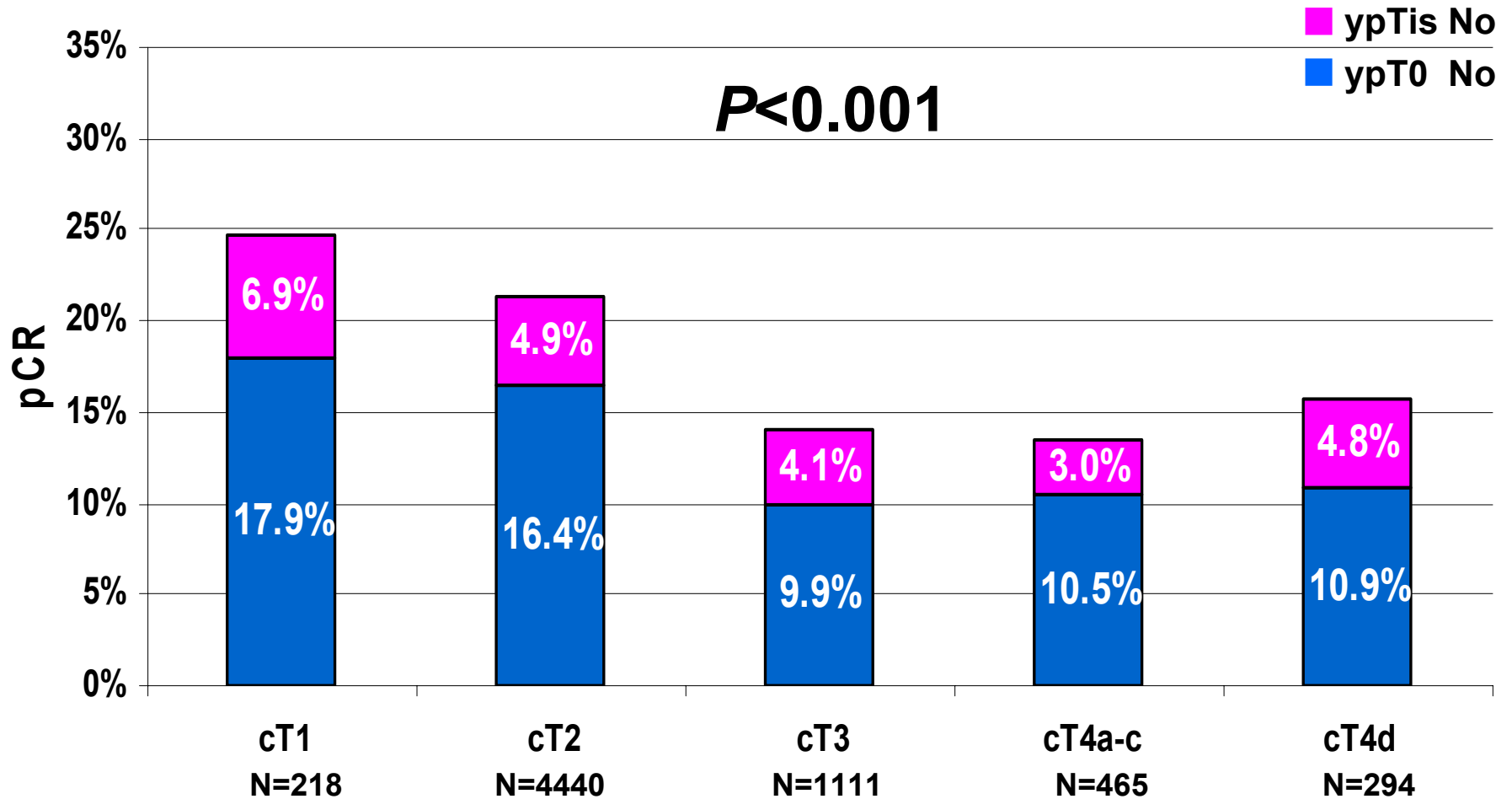
Lokalrezidive 10 Jahre NSABP B 18

Gruppe	Neoadjuvant AC			Adjuvant AC		
	N	Event	Cum. Inc. (95% CI)	N	Event	Cum. Inc. (95% CI)
Alle	742	109	14.2 (11.9, 17.0)	751	96	12.3 (10.2, 15.0)
< 50 J., kein Tam	380	66	17.0 (13.6, 21.3)	389	64	16.0 (12.7, 20.1)
≥ 50 J., Tamoxifen	362	43	11.3 (8.4, 15.1)	362	32	8.5 (6.0, 11.9)
Klinisch N-	548	77	13.3 (10.7, 16.5)	556	67	11.8 (9.3, 14.8)
Klinisch N+	194	32	16.8 (12.2, 23.1)	195	29	14.0 (9.9, 19.9)
< 2 cm	214	32	15.6 (11.4, 21.4)	205	25	11.5 (7.8, 16.9)
2 – 5 cm	429	55	11.8 (9.1, 15.3)	449	55	11.7 (9.1, 15.2)
> 5 cm	99	22	23.5 (16.2, 34.1)	97	16	16.9 (10.8, 26.4)

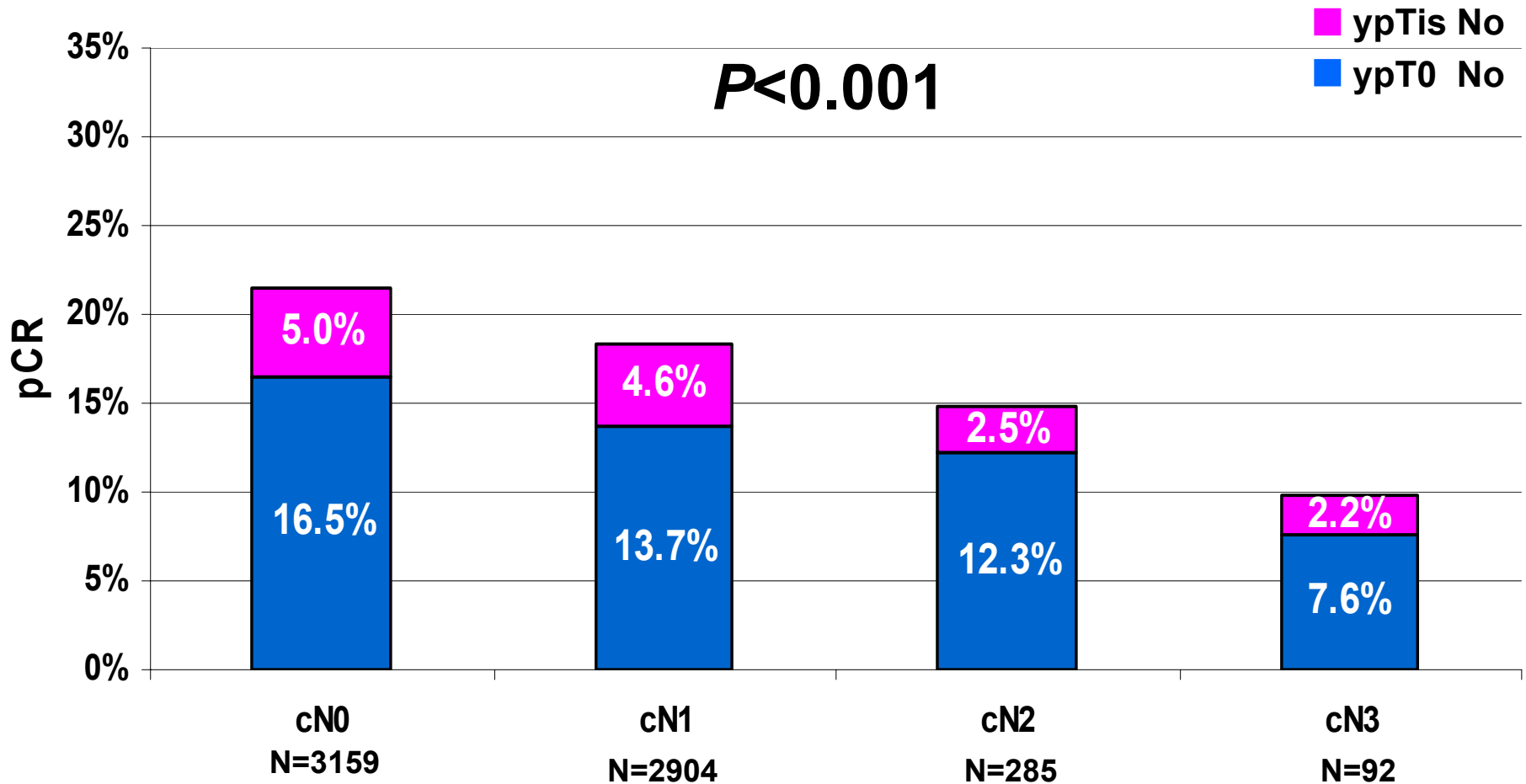
Gruppe	Neoadjuvant AC			Adjuvant AC		
	N	Event	Cum. Inc. (95% CI)	N	Event	Cum. Inc. (95% CI)
pCR	88	7	6.8 (3.1, 14.8)	--	--	--
pINV	159	22	12.9 (8.6, 19.5)	--	--	--
cPR	295	49	16.2 (12.4, 21.0)	--	--	--
cNR	140	25	17.3 (12.1, 25.0)	--	--	--
N-	434	48	10.3 (7.8, 13.6)	319	25	7.8 (5.3, 11.5)
N+ 1 – 3	180	32	18.1 (13.2, 24.8)	222	40	16.9 (12.6, 22.6)
N+ <u>≥</u> 4	121	29	22.5 (16.1, 31.4)	202	31	15.0 (10.7, 20.8)

CI: Konfidenzintervall

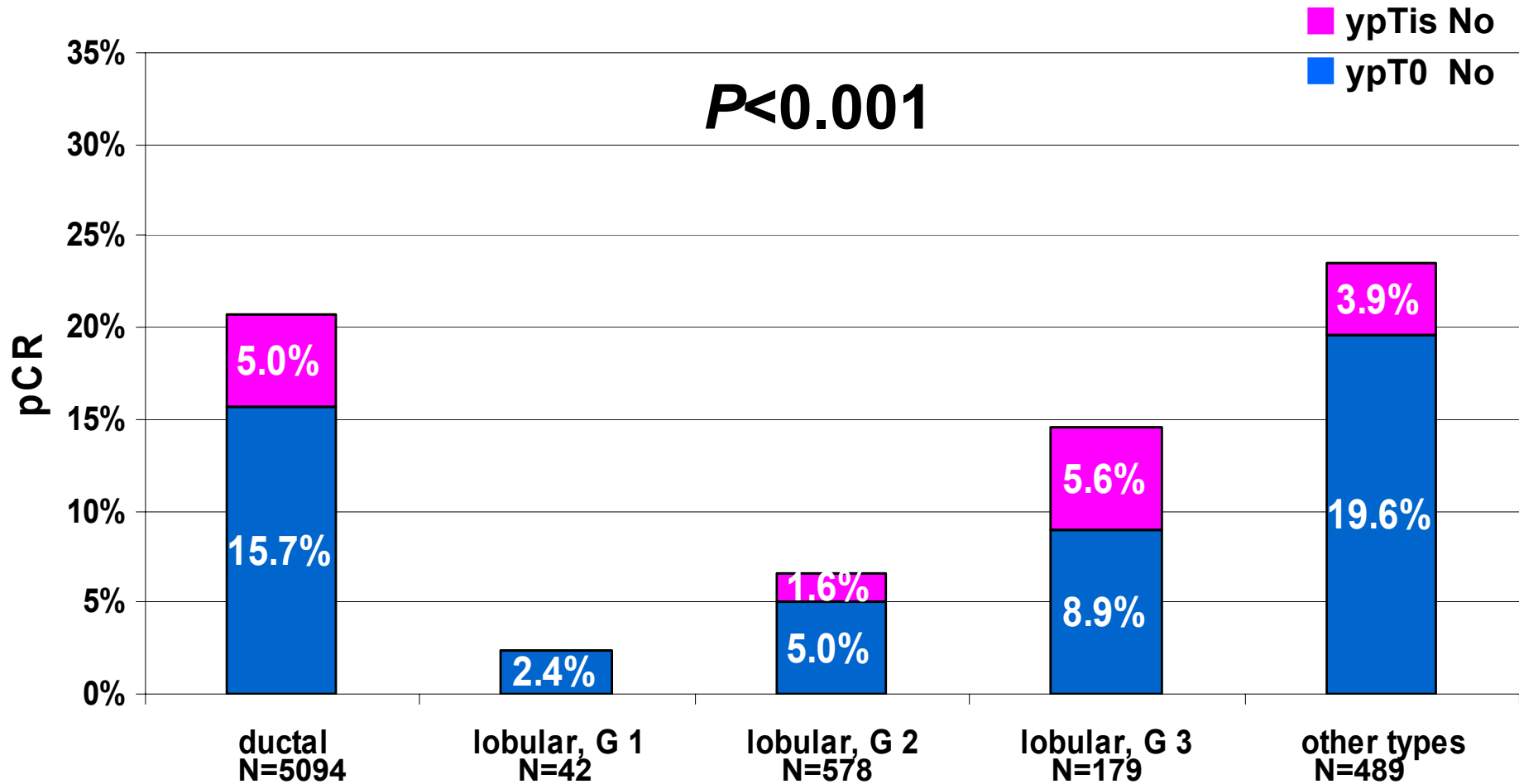
Predictive Factors Clinical Tumor Stage



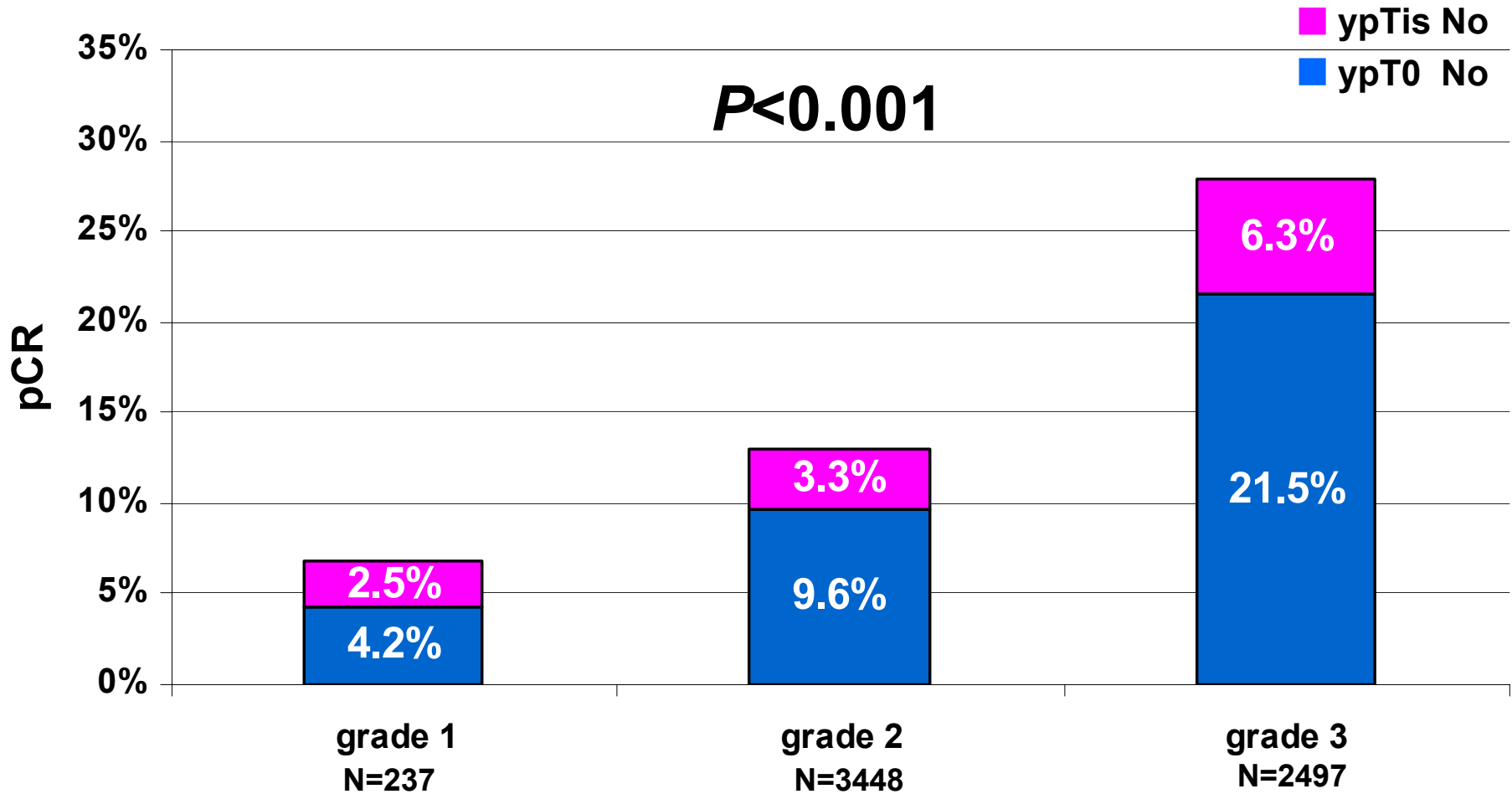
Predictive Factors Clinical Nodal Stage



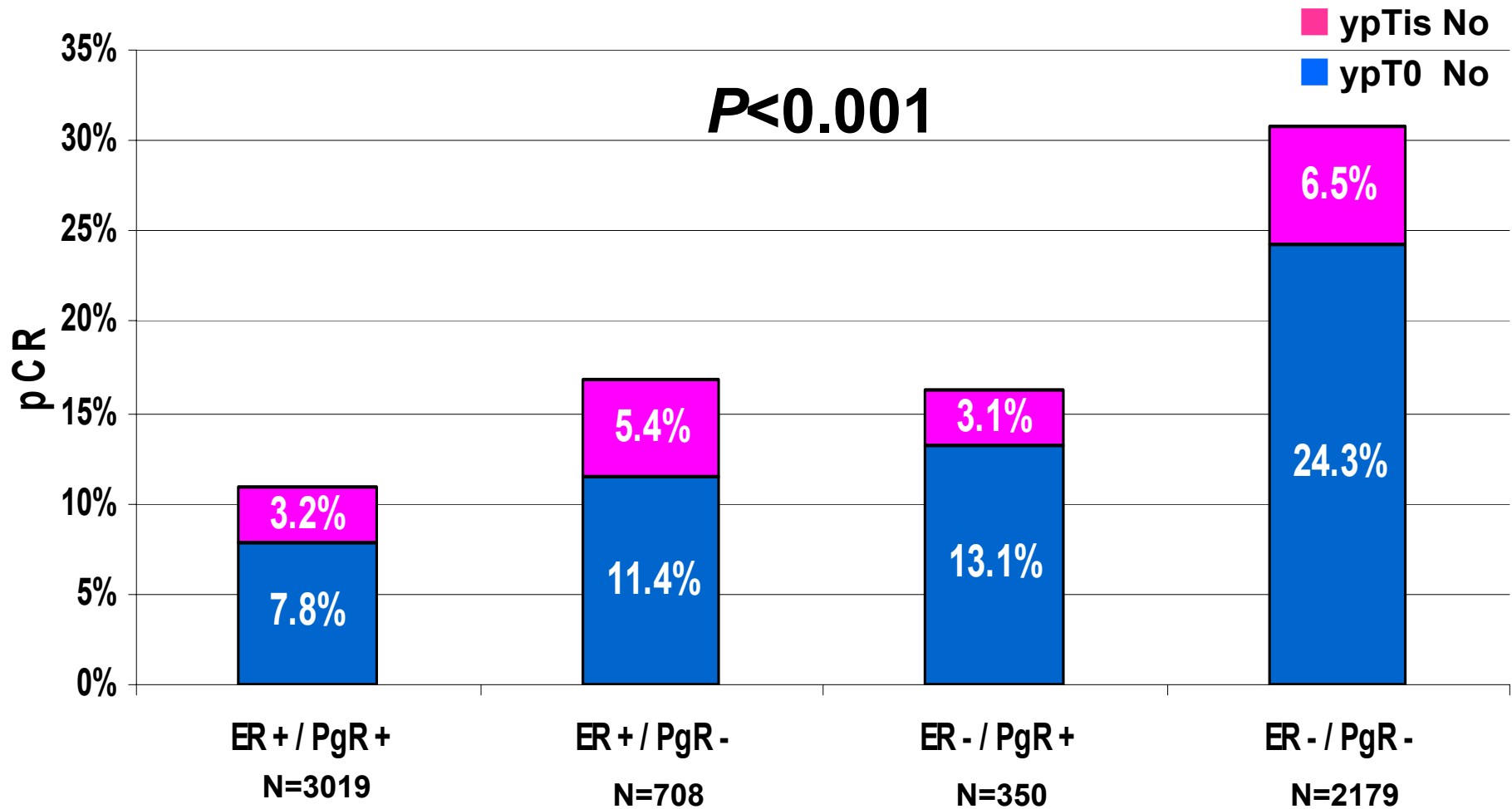
Predictive Factors Histological Type



Predictive Factors Histological Grade



Predictive Factors Hormone Receptor Status



Neoadjuvant Systemic Chemotherapy in HER-2 Positive Tumors

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LOE / GR

- **Chemotherapy concomitantly with trastuzumab** **1b A ++**
- **Chemotherapy concomitantly with lapatinib (+/- trastuzumab)** **2b^a C -***

Further
information

References

FORSCHEN
LEHREN
HEILEN

* Study participation recommended

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

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- | | | | | |
|--|----|---|----|--|
| ➤ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy | 1a | A | | |
| ➤ Pathological complete response (no invasive residuals in breast and axilla) is associated with high survival probability | 1b | A | | |
| ➤ May achieve operability in primary inoperable tumors | 1b | A | ++ | |
| ➤ Improved options for breast conserving surgery | 1b | A | ++ | |
| ➤ Allows individualization of therapy according to mid-course treatment effect | 1b | B | +* | |

* Study participation recommended

Further
information

References

FORSCHEN
LEHREN
HEILEN

Neoadjuvant Systemic Chemotherapy Response Prediction

Oxford / AGO
LOE / GR

Factors predicting a high chance for a pathological complete response:

➤ Age < 35 yrs	1a ^a	A	++
➤ cT1 / cT2 tumor	1a ^a	A	++
➤ Negative nodal status	1a ^a	A	++
➤ Grade 3 tumor	1a ^a	A	++
➤ Negative ER and PgR status	1a ^a	A	++
➤ Positive HER2 status	1a ^a	A	++
➤ Non-lobular tumor type	1a ^a	A	+/-
➤ Prediction algorithm/score	2b	B	+/-

Further
information

References

FORSCHEN
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Primary systemic therapy

Procedures in case of insufficient response

Oxford / AGO
LoE / GR

In case of stable disease:

- | | | | |
|--|----|---|-----|
| ➤ Completion of PST, followed by surgery | 5 | D | ++ |
| ➤ Continuation of PST with non cross-resistant regimen | 2b | B | + |
| ➤ AC X 4 → D X 4 | 2b | B | + |
| ➤ DAC X 2 → NX x 4 | 2b | B | +/- |

In case of progressive disease:

- | | | | |
|---|---|---|------|
| ➤ Stop of PST and immediate surgery or radiotherapy | 4 | D | +++* |
| ➤ Additional adjuvant chemotherapy with non cross resistant regimen | 4 | D | +/- |

* Study participation recommended