# Neoadjuvant chemotherapy (NACT) in young women with breast cancer

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# ”Young women” according to EUSOMA guidelines


- Is under the age of 40
- Special issues related to:
  - Fertility preservation
  - Pregnancy and lactation
  - Contraception
  - Body image and sexuality
  - BRCA 1 and BRCA 2

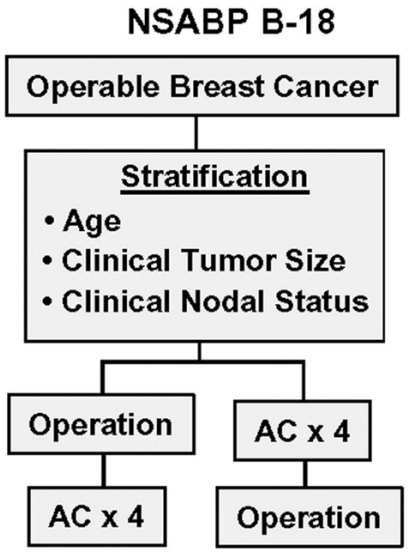
# Epidemiology

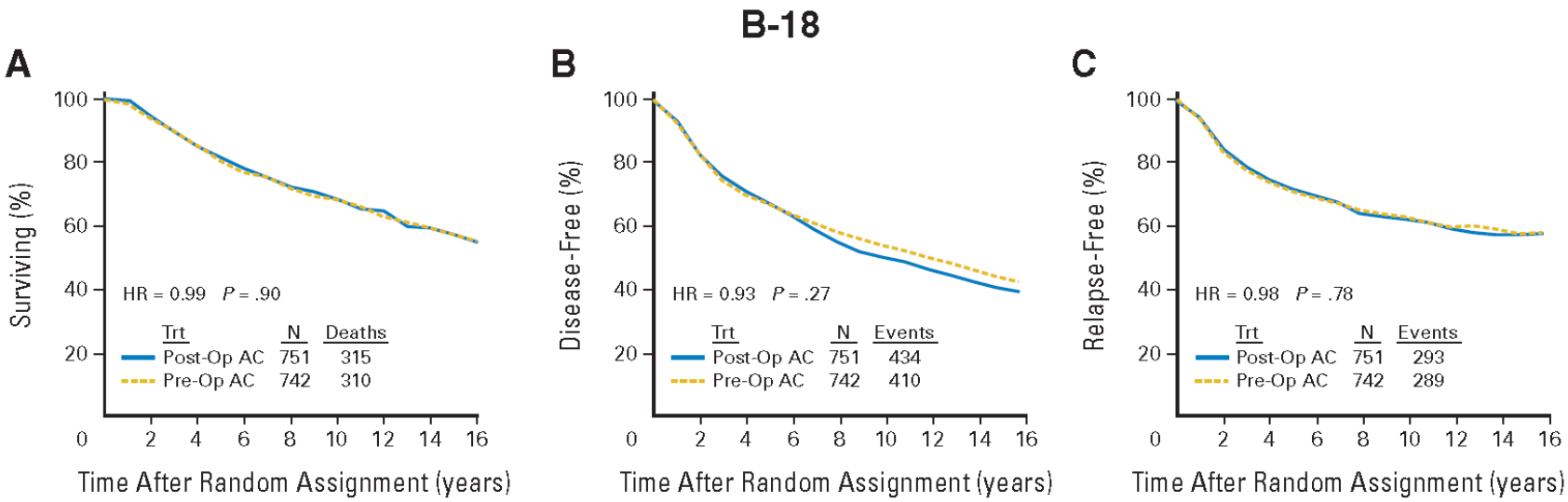
- Breast cancer accounts for 30-40% of all cancers in women below 40
- About 7% of all new breast cancers are in women below 40
- Only slightly increasing incidence over time
- More frequently associated with a family history

# Why consider neoadjuvant chemotherapy in young women with early breast cancer?

- According to DBCG guidelines women < 40 are recommended chemotherapy despite histopathology, so NACT because:
  - A need to preserve the breast
  - more often triple neg breast cancer
  - no co-morbidity
  - BRCA status not ready

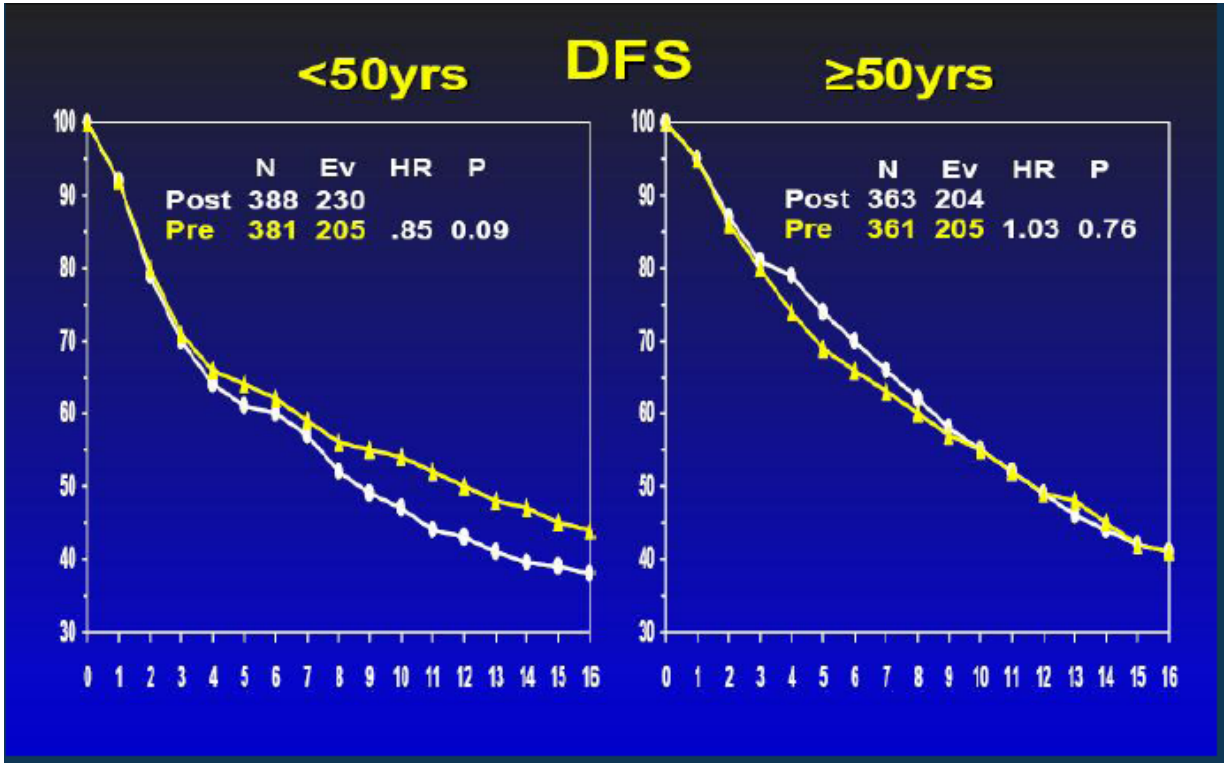
# Neoadjuvant vs. adjuvant chemotherapy: OS, DFS and RFS




***Rastogi and Wolmark 2008 JCO***

# Neoadjuvant vs. adjuvant chemotherapy: DFS and age < 50 years

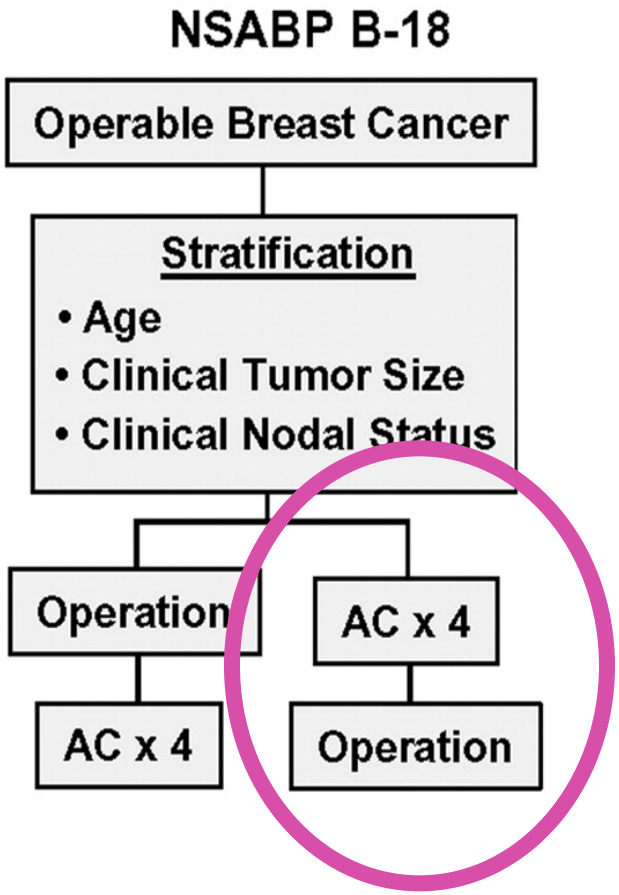



OS: HR=0.81, P=0.06

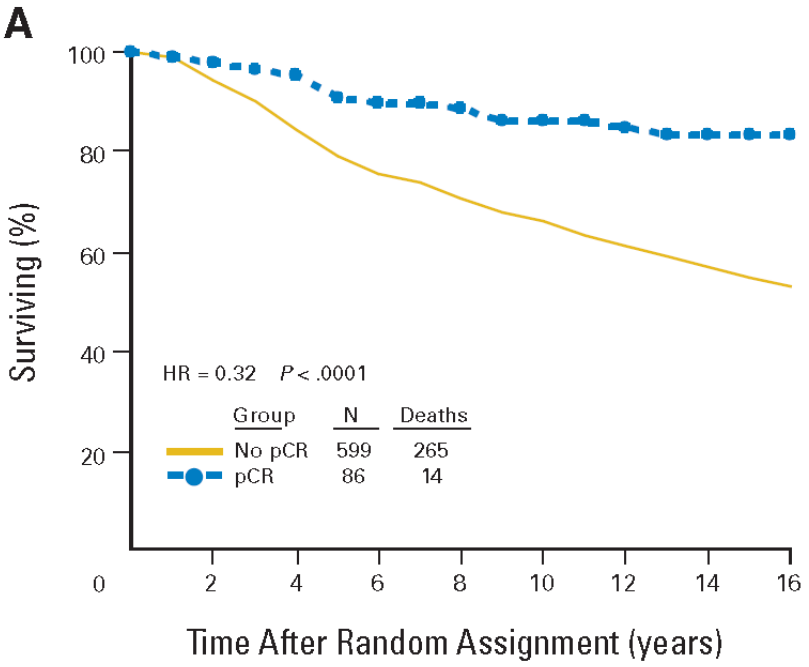
Trend in favor of preoperative chemotherapy in DFS and OS for women less than 50y

***Rastogi and Wolmark 2008 JCO***

# pCR and disease-free/overall survival

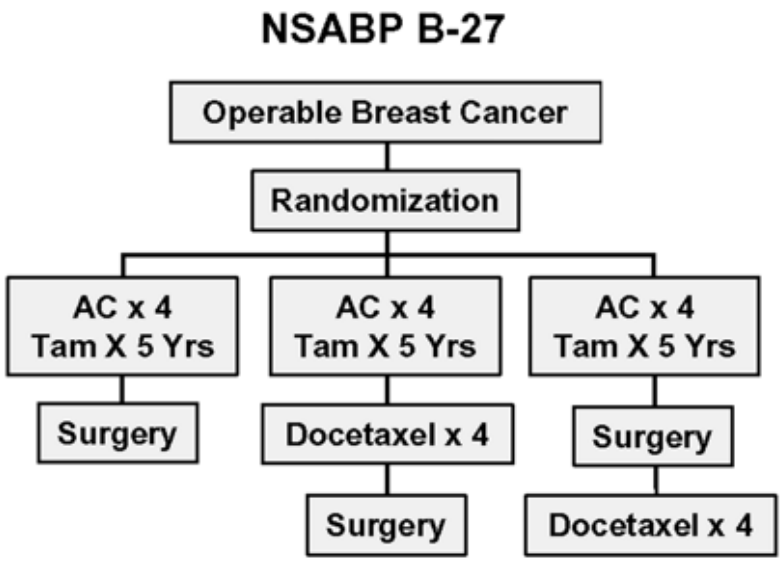



DFS HR = 0.47, P < 0.0001



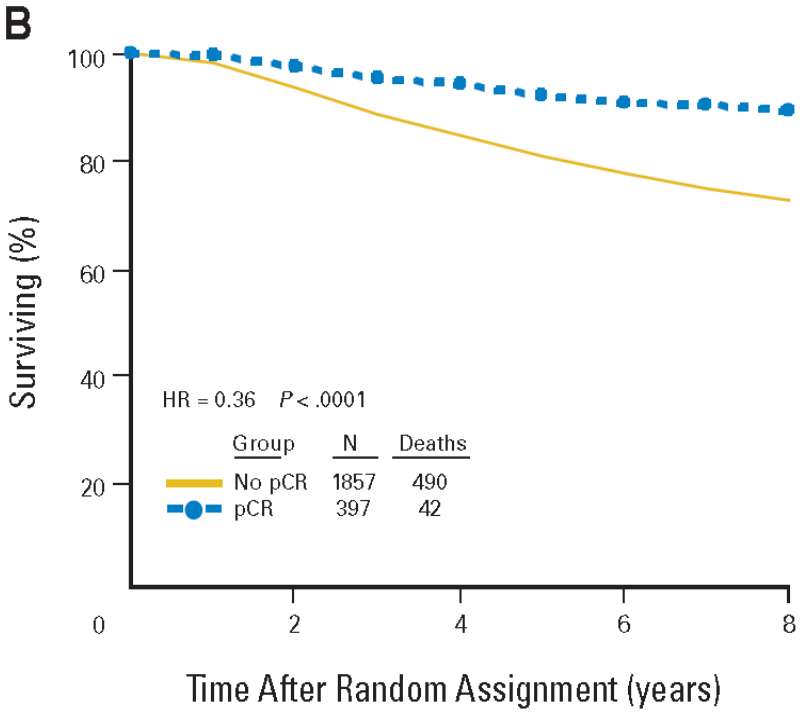

*Rastogi and Wolmark 2008 JCO*

# pCR and disease-free/overall survival



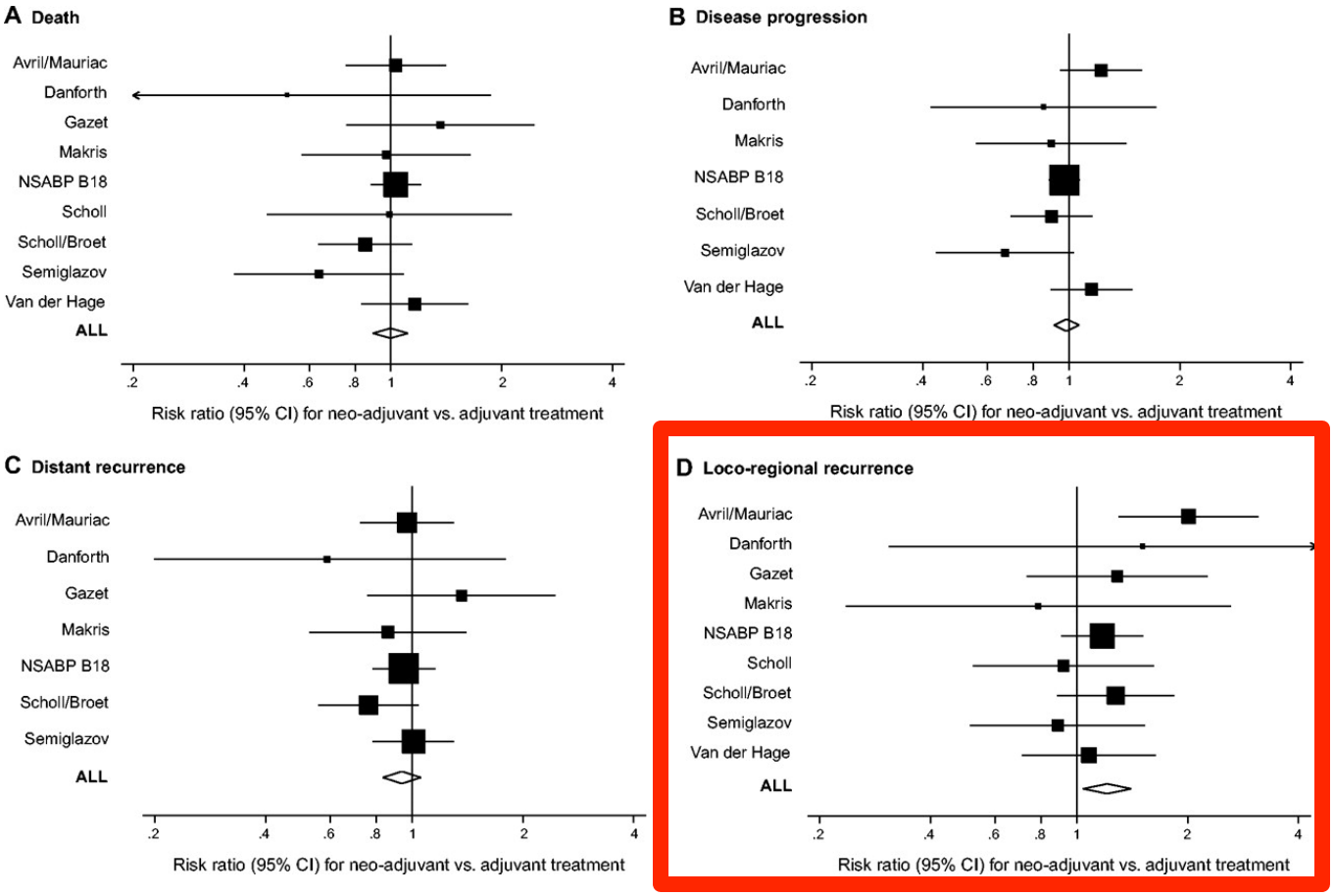

B-27: Effect of adding T to pre-operative AC

DFS HR = 0.49, P < 0.0001




*Rastogi and Wolmark 2008 JCO*

# Neoadjuvant vs. adjuvant chemotherapy: a meta-analysis

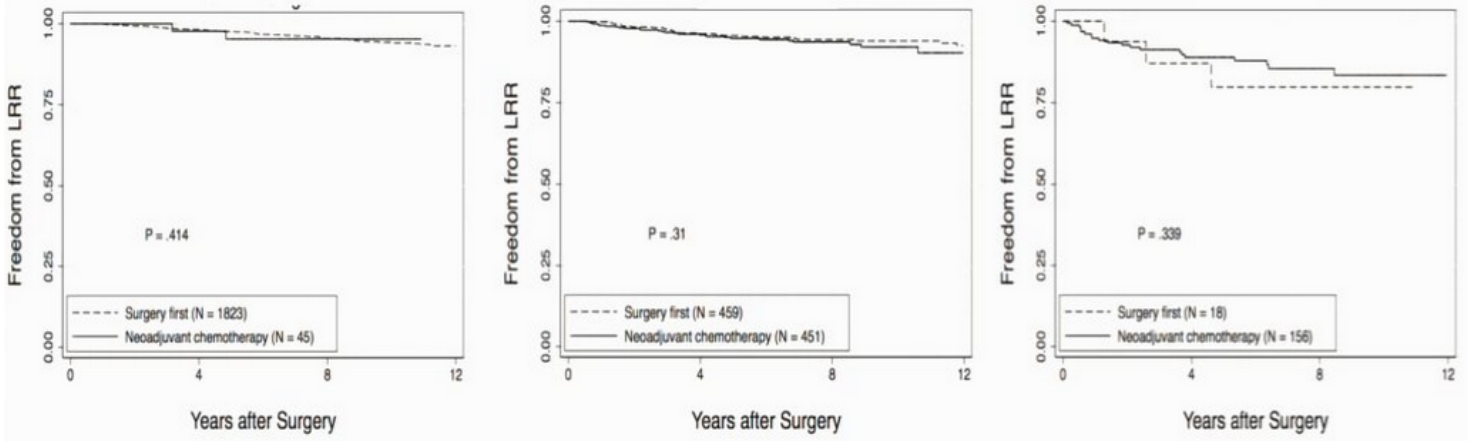



*Mauri, D. et al. J Natl Cancer Inst 2005;97:188-194*

# LRR-Free Survival Rates

- 1589 patients who underwent conservative surgery at MDACC
- 72% had initial surgery and 28% received neoadjuvant chemotherapy

| Clinical Stage I | Clinical Stage II | Clinical Stage III |
|---|---|---|

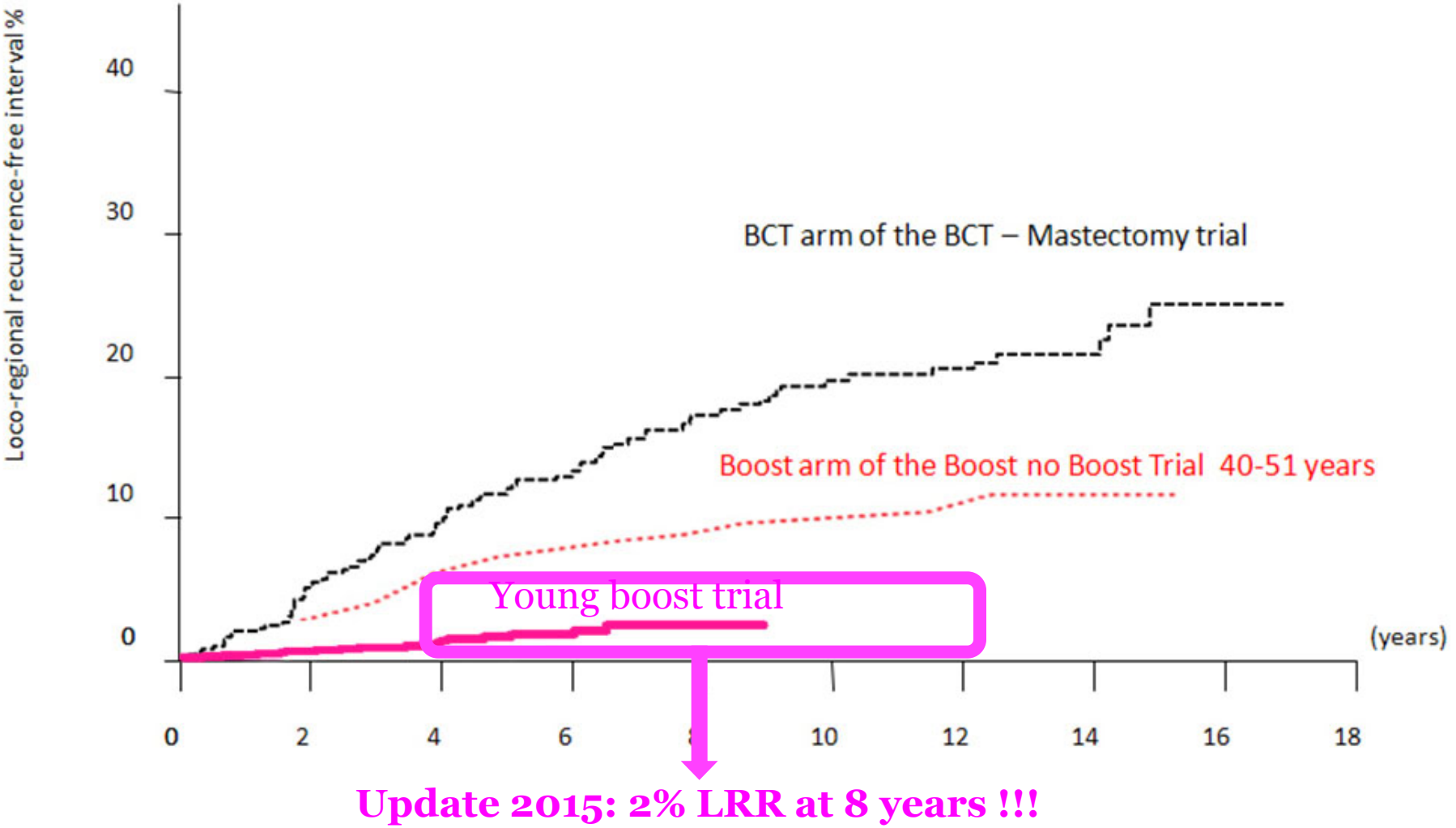



**Conservative Surgery Achieved Without Higher Local Recurrence Rate**
**In Multivariate Model, Neoadjuvant Chemotherapy Was Not Associated With High Local Recurrence**

The ability to do less surgery after NAC does not seem to be associated with any risk for the patient

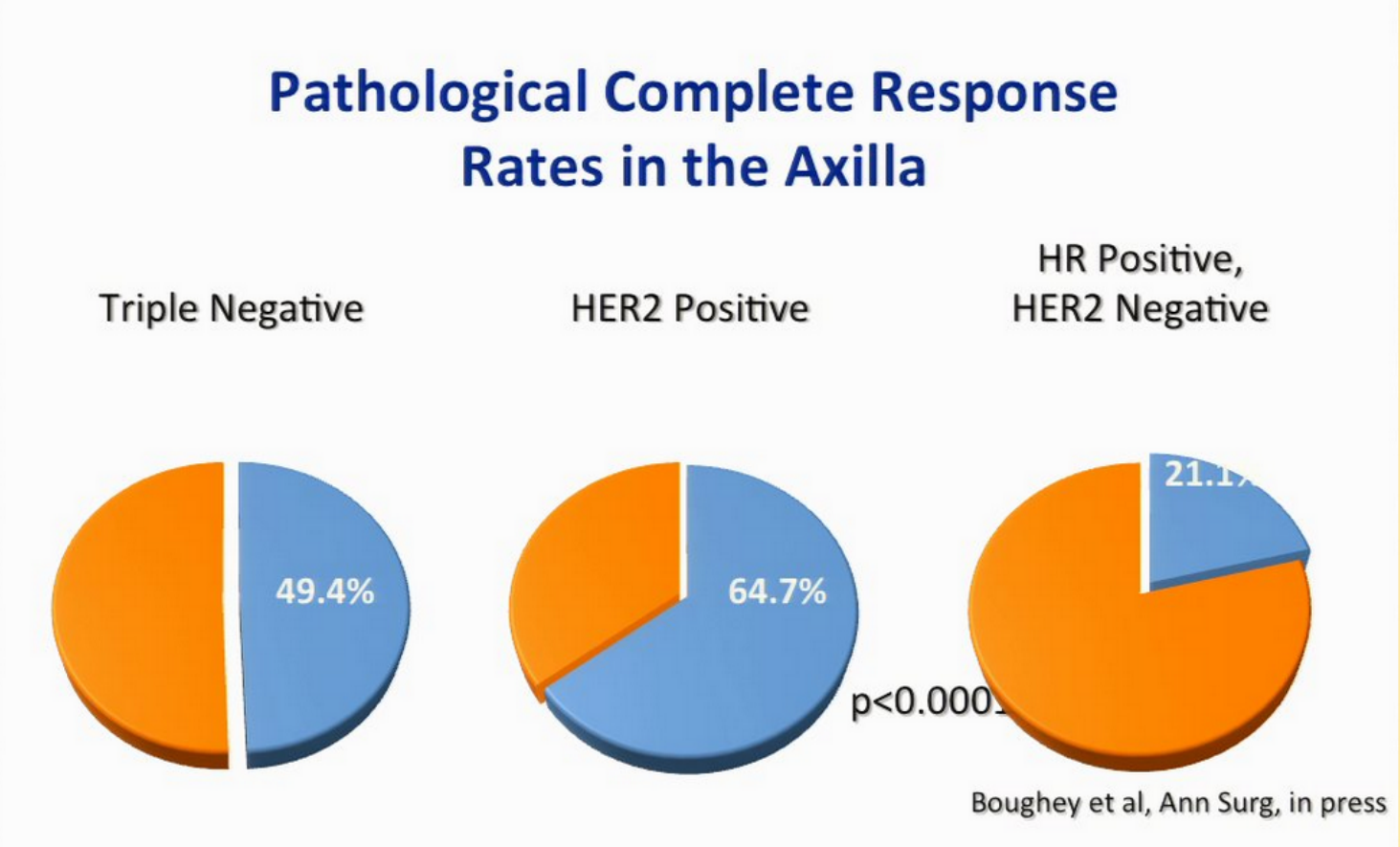
***Mittendorf E et al, Ann Surg 2013***

# RT & surgery




*Modified from Poortmans et al. Sem Rad Oncol 2012; Bartelink et al R&O 2012*

# Management of the axilla in case of NACT



# Timing of sentinel node procedure

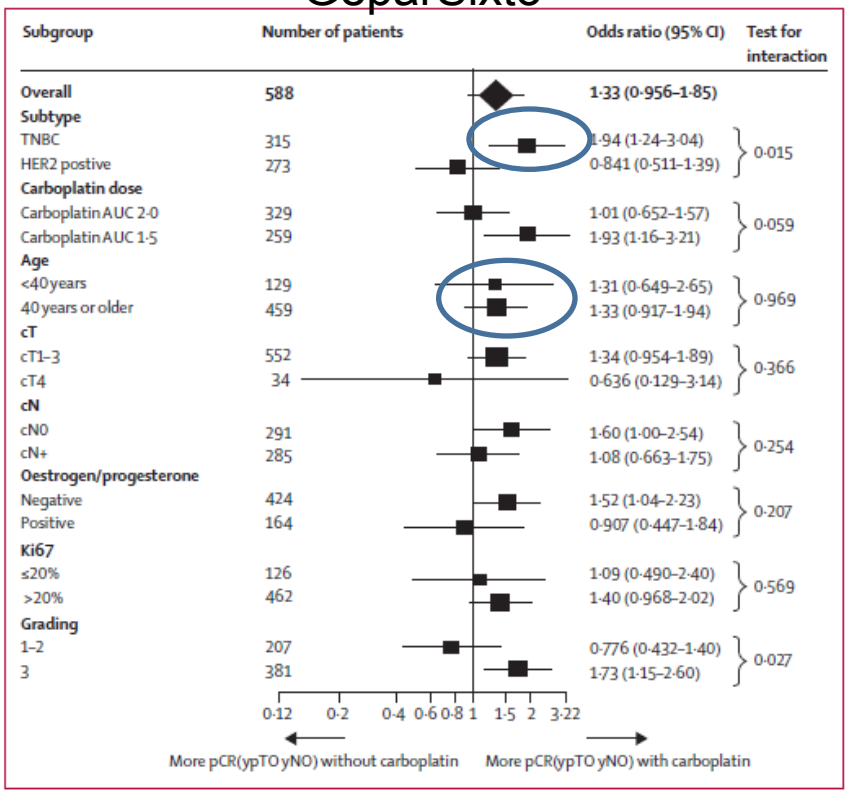
| Pre NACT | Post NACT |
|---|---|
| Optimal staging before start treatmtent | |
| Detection rate (99%) | Detection rate (80 - 90%) |
| FNR (8%) | FNR (10-15%) |
| | FNR < 7% if combined with removal of clipped node (TAD) |

*C. van Deurzen, EJC 2009*
*J. Boughey, JAMA 2013*
*T. Kuehn, Lancet Oncology 2013*
*J Boughey, Annals Surg 2016*
*S. Abigail, JCO 2016*

# Which neoadjuvant chemotherapy regimen to chose for young women?

- Consensus that the regimen should include anthracyclines and taxanes
- TNBC should not impact on choise of therapy
- Subsets of patients with BRCA mutations might need different treatment approach

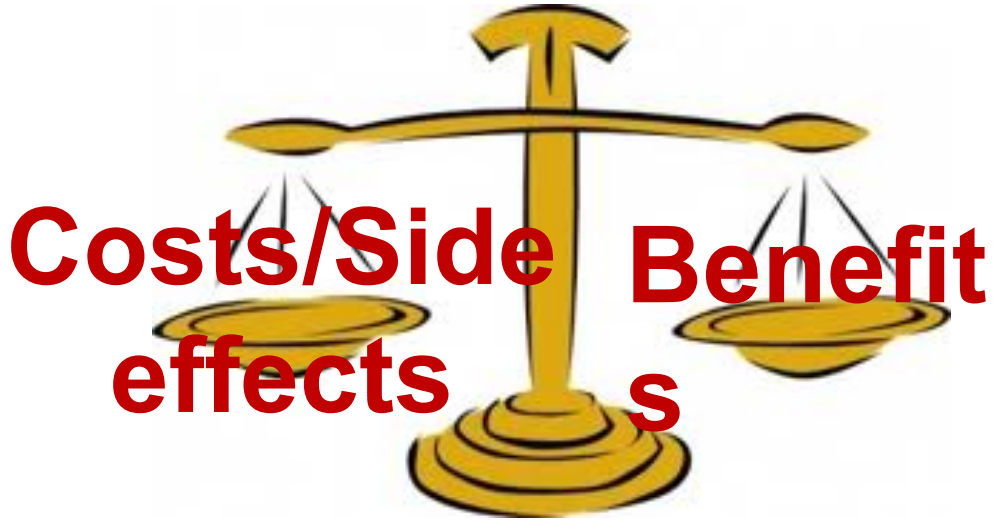
GeparSixto




*Von Minckwitz G, Lancet Oncol (2014)*

# Long term side effects of (neo) adjuvant chemotherapy – knowledge is important for the young women

- Chronic fatigue
- Ovarian failure
  - Infertility
    - Hot flushes
    - Bone loss
    - Sexual problems
- Cardiovascular disease
- Cognitive function
- Secondary malignancies



# ”Young women” according to EUSOMA guidelines


Table 3. Pregnancy Outcomes.

| Outcome | Chemotherapy Alone (N=113) | Chemotherapy plus Goserelin (N=105) | Odds Ratio with Goserelin | P Value* |
|---|---|---|---|---|
| Attempted pregnancy — no. of patients (%) | 18 (16) | 25 (24) | 1.78 | 0.12 |
| Achieved pregnancy — no. of patients (%) | 12 (11) | 22 (21) | 2.45 | 0.03 |
| ≥1 delivery — no. of patients (%) | 8 (7) | 16 (15) | 2.51 | 0.05 |
| Delivery or ongoing pregnancy — no. of patients (%) | 10 (9) | 19 (18) | 2.45 | 0.04 |
| Babies born — no.† | 12 | 18 | | |
| Ongoing pregnancies at last report — no. | 3 | 5 | | |
| Adverse pregnancy event — no. of events | | | | |
| Miscarriage | 5 | 4 | | |
| Elective termination | 3 | 2 | | |
| Delivery complication | 2 | 2 | | |

* P values were adjusted for the stratification factors of age and type of planned chemotherapy. The cutoff date for data analysis was January 22, 2014; data up to that date are included.
† This category may include more than one baby born to a woman.

***Moore H, NEJM 2015***

- Is under the age of 40
- Special issues related to:
  - Fertility preservation → Cryopreservation, Zoladex
  - Pregnancy and lactation → Centralized treatment
  - Contraception → Barriere, IUD, no hormones
  - Body image and sexuality → Mastectomy versus BCS
  - BRCA 1 and BRCA 2 → Accelerated genetic testing

# ”The German experience”

Breast Cancer Res Treat (2015) 152:377–387
DOI 10.1007/s10549-015-3479-z

CrossMark

CLINICAL TRIAL

## Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials

Sibylle Loibl[1,2] · Christian Jackisch[2] · Bianca Lederer[1] · Michael Untch[3] · Stefan Paepke[4] · Sherko Kümmel[5] · Andreas Schneeweiss[6] · Jens Huober[7] · Jörn Hilfrich[8] · Claus Hanusch[9] · Bernd Gerber[10] · Holger Eidtmann[11] · Carsten Denkert[12] · Serban Dan Costa[13] · Jens-Uwe Blohmer[14] · Valentina Nekljudova[1] · Keyur Mehta[1] · Gunter von Minckwitz[1]

# Pooled analysis of individual patient data from eight prospective randomized trials from 1998 to 2010

- Gepar Duo
- Gepar Trio
- Gepar Quattro
- AGO 1
- Prepare
- Techno
- Gepar Quinto
- The Gapardo trial

All trials used and anthracycline and taxane based chemotherapy backbone

*Loibl S, Breast Cancer Res Treat (2015)*

# Objectives and endpoints

- To evaluate the pCR rate in women < 40 years compared to age groups 40-49 years and >= 50 years
- To access the effect of age on disease free survival (DFS), local recurrence free survival (LRFS), distant free survival (DFS) and overall survial (OS) according to pCR status in different subgroups

*Loibl S, Breast Cancer Res Treat (2015)*

# Baseline characteristics of women undergoing treatment in 8 prospective trials of NACT

| Baseline characteristics | < 40 years N=1453 | | >= 40-49 years N=3073 | | > 50 years N=4423 | | All patients N=8949 | | P value |
|---|---|---|---|---|---|---|---|---|---|
| Tumor stage | | | | | | | | | < 0.001 |
| cT1 | 135 | 9.4 % | 251 | 8.2 % | 248 | 5.7 % | 634 | 7.1 % | |
| cT2 | 984 | 68.3 % | 1978 | 64.9 % | 2704 | 61.7 % | 5666 | 63.( % | |
| cT3 | 215 | 14.9 % | 537 | 17.6 % | 713 | 16.3 % | 1465 | 16.5 % | |
| cT4a-c | 56 | 3.9 % | 162 | 5.3 % | 388 | 8.8 % | 606 | 8.8 % | |
| cT4d | 50 | 3.5% | 120 | 3.9 % | 333 | 7.6 % | 503 | 7.6 % | |
| Nodal status | | | | | | | | | < 0.001 |
| cN0 | 731 | 51.6 % | 1499 | 49.7 % | 2069 | 47.6 % | 4299 | 49.0 % | |
| cN1 | 619 | 43.7 % | 1372 | 45.5 % | 1996 | 45.9 % | 3987 | 45.4 % | |
| cN2 | 50 | 3.5 % | 110 | 3.6 % | 216 | 5.0 % | 376 | 4.3 % | |
| cN3 | 18 | 1.3 % | 33 | 1.1 % | 68 | 1.6 % | 119 | 1.4 % | |

*Loibl S, Breast Cancer Res Treat (2015)*

# Baseline characteristics of women undergoing treatment in 8 prospective trials of NACT

| Baseline characteristics | < 40 years N=1453 | >= 40-49 years N=3073 | > 50 years N=4423 | All patients N=8949 | P value |
|---|---|---|---|---|---|
| Histological type | | | | | 0.001 |
| Ductale invasive | 1221 (85.7 %) | 2448 (81.6 %) | 3432 (78.9 %) | 7101 (81.0 %) | |
| Lobular invasive | 86 (6.0 %) | 354 (11.8 %) | 626 (14.4%) | 1066 (12.2%) | |
| Others | 117 (8.2 %) | 197 (6.6 %) | 290 (6.7%) | 604 (6.9%) | |
| Tumor grade | | | | | 0.002 |
| 1 | 42 (3.1%) | 124 (4.2%) | 149 (3.6%) | 315 (3.7 %) | |
| 2 | 684 (49.8%) | 1639 (55.9%) | 2334 (55.8%) | 4657 (54.9%) | |
| 3 | 647 (47.1%) | 1170 (39.9%) | 1698 (40.6%) | 3515 (41.4) | |

*Loibl S, Breast Cancer Res Treat (2015)*

# Baseline characteristics of women undergoing treatment in 8 prospective trials of NACT

| Baseline characteristics | < 40 years N=1453 | | >= 40-49 years N=3073 | | > 50 years N=4423 | | All patients N=8949 | | P value |
|---|---|---|---|---|---|---|---|---|---|
| Subtype | | | | | | | | | < 0.001 |
| ER pos/HER-2 neg (G1-2) | 330 | 31.2 % | 877 | 38.2 % | 1271 | 40.2 % | 2478 | 38.0 % | |
| ER pos/HER-2 neg (G3) | 133 | 12.6 % | 293 | 12.8 % | 440 | 13.9 % | 866 | 13.3 % | |
| ER pos/HER2 pos | 174 | 15.9 % | 379 | 15.9 % | 455 | 13.8 % | 1008 | 13.8 % | |
| ER neg/HER2 pos | 137 | 12.5 % | 243 | 10.2 % | 393 | 11.9 % | 773 | 11.9 % | |
| Triple neg | 323 | 29.4 % | 589 | 24.7 % | 733 | 22.3 % | 1645 | 22.3 % | |

*Loibl S, Breast Cancer Res Treat (2015)*

# Correlation between age and pCR

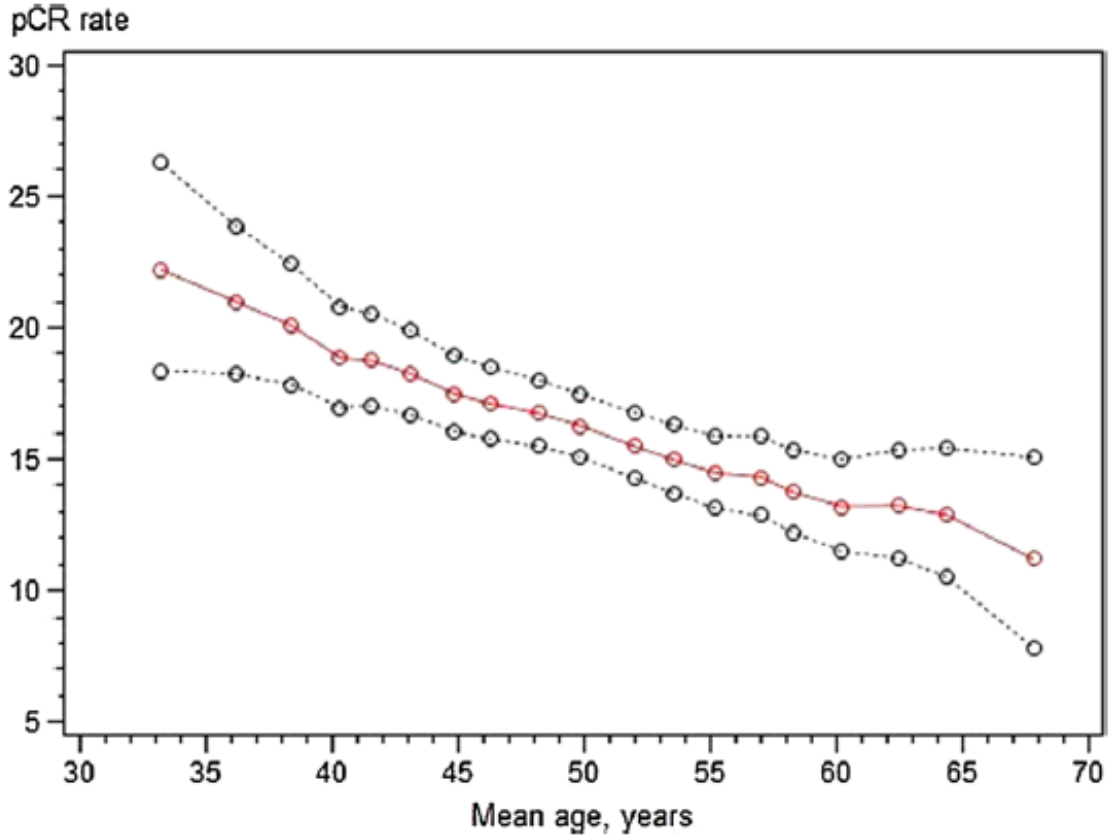
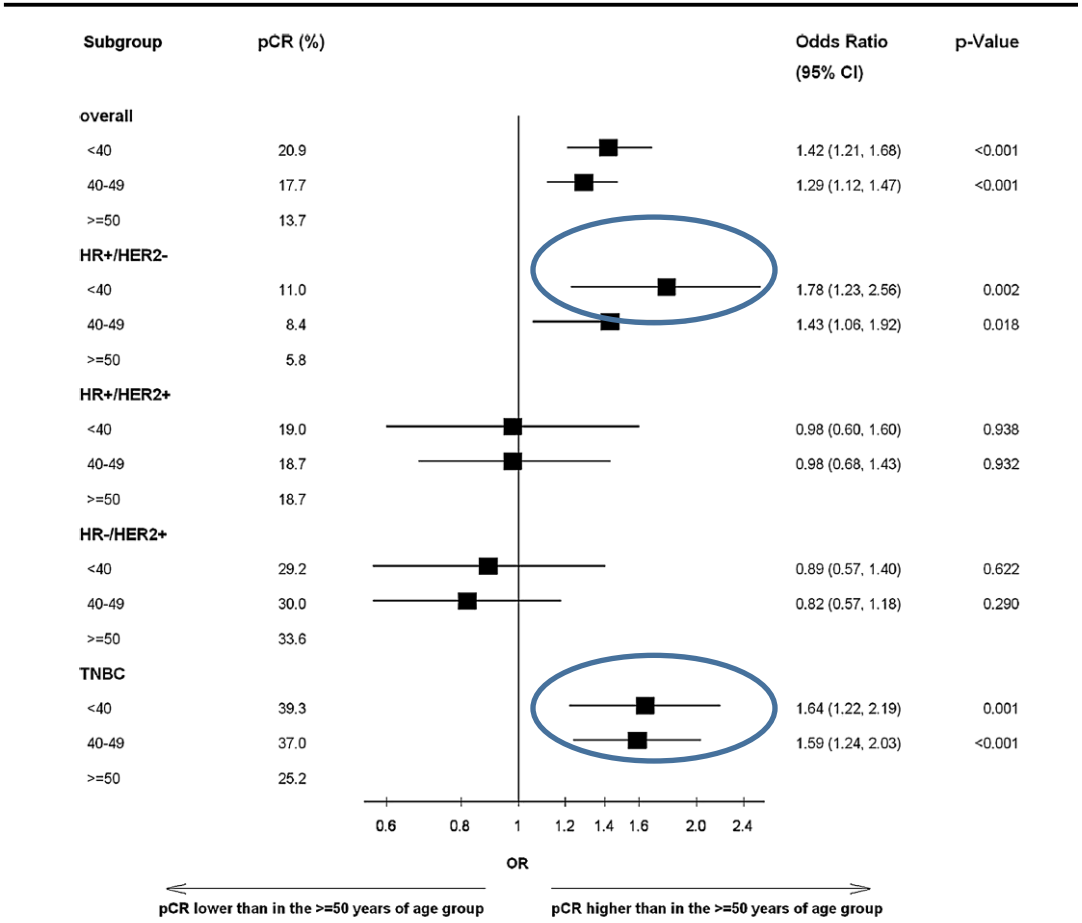



**Fig. 1** Correlation between age and pCR. STEPP-like analysis of age and pathological complete response (pCR, ypT0 ypN0)

*Loibl S, Breast Cancer Res Treat (2015)*

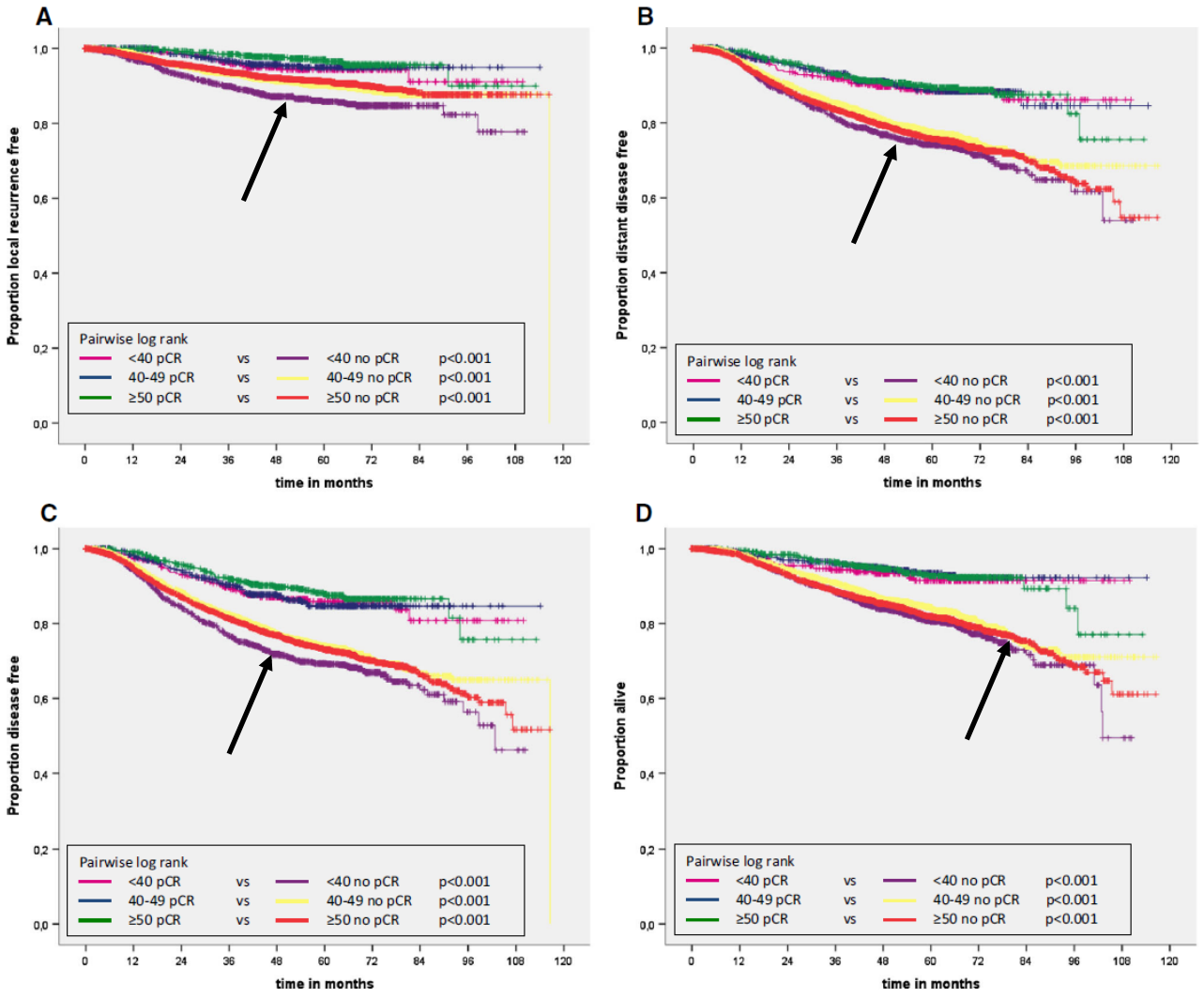
# The odds of achieving a pCR by subtype and age




CI, confidence interval; HR, hormone receptor; pCR, pathological complete response; TNBC, triple negative breast cancer

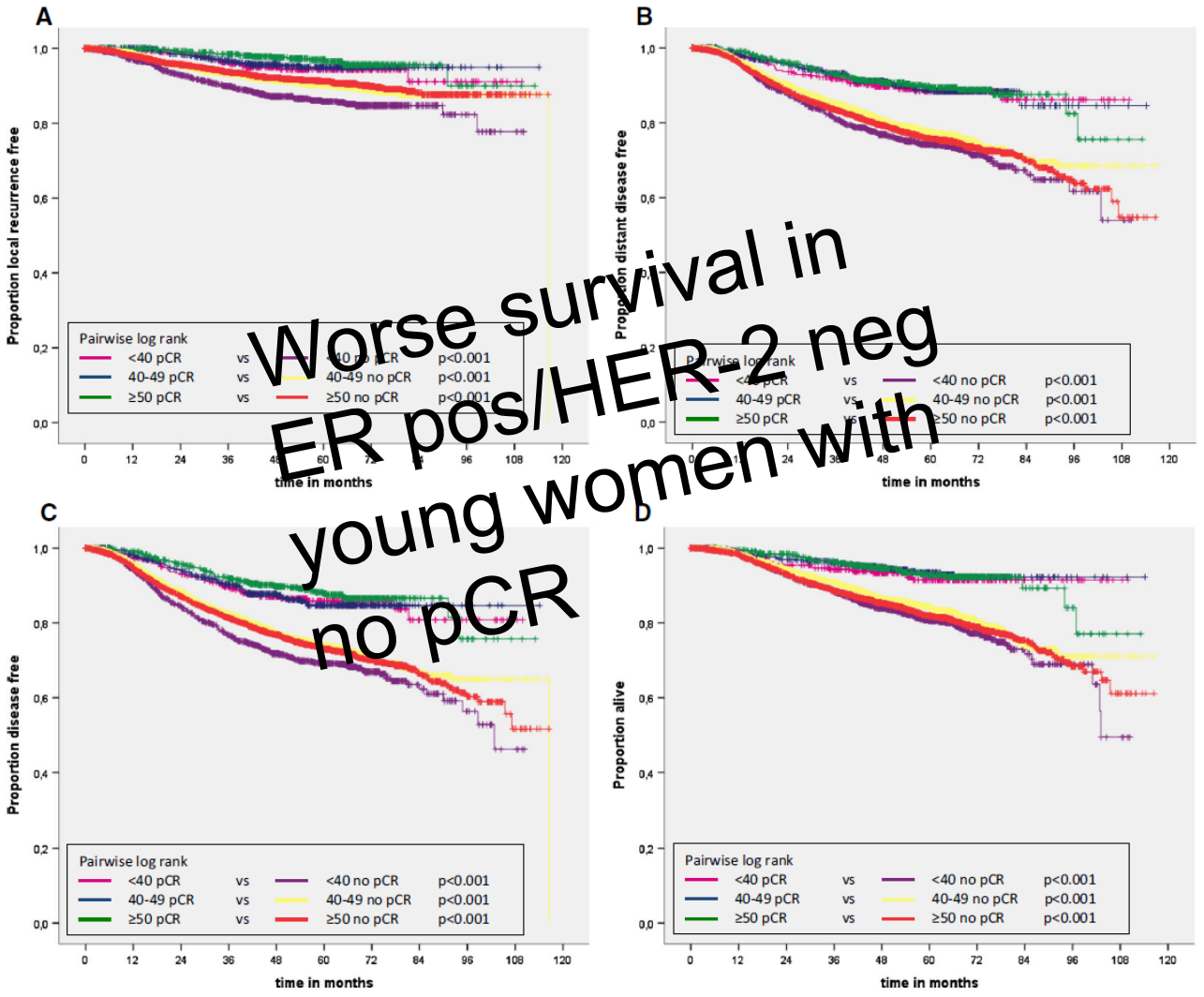
*Loibl S, Breast Cancer Res Treat (2015)*

# Survival in age groups with or without pCR




*Loibl S, Breast Cancer Res Treat (2015)*

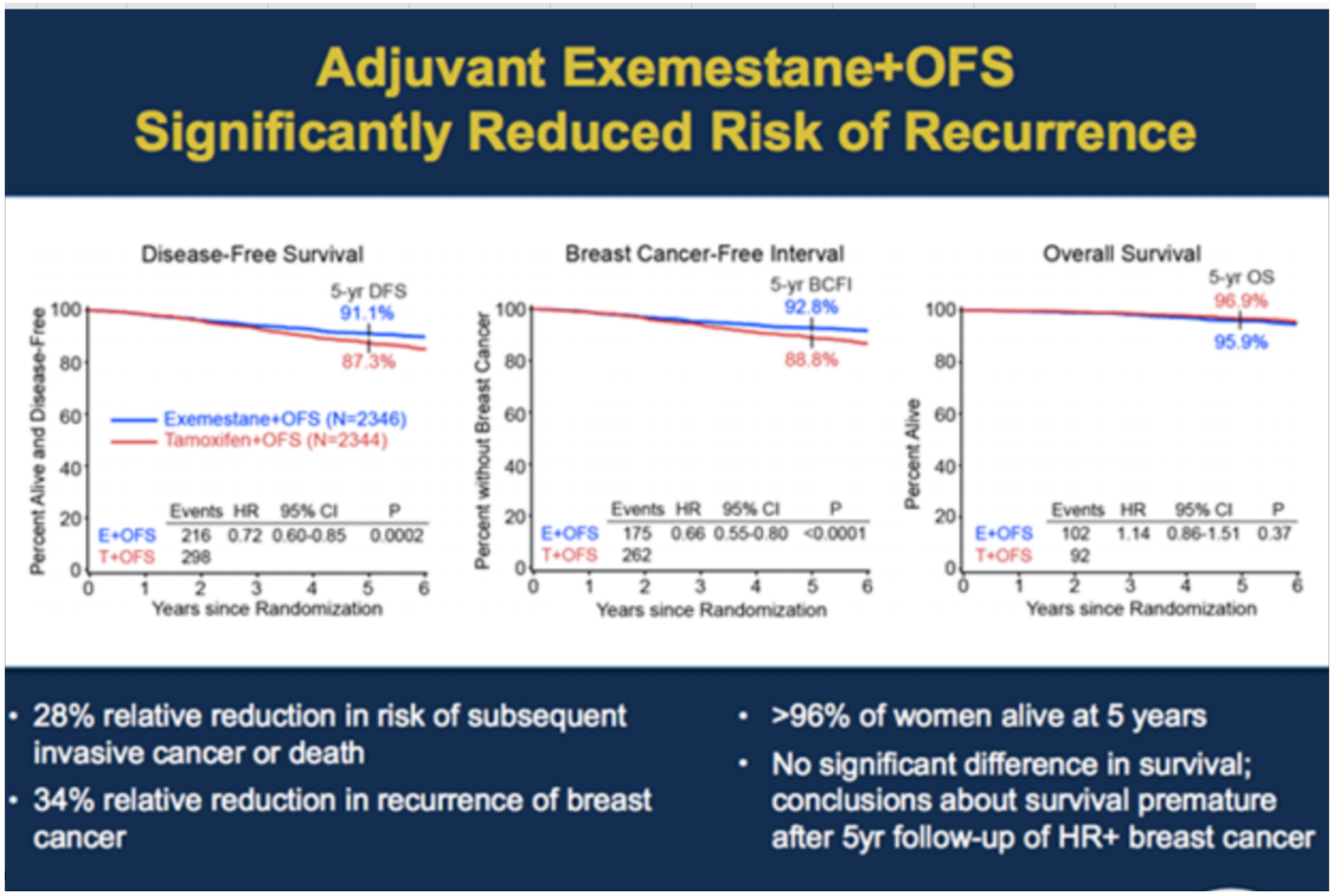
# Survival in age groups with or without pCR




Worse survival in ER pos/HER-2 neg young women with no pCR

*Loibl S, Breast Cancer Res Treat (2015)*

# Soft trial
# Exemestane + OFS beneficial among young women < 35 years with high risk disease




*Francis, PA NEJM (2015)*

# Future strategies will reduce chemotherapy prescription

"In the entire MINDACT population, the trial confirmed the hypothesis that the «genomic» strategy leads to a 14% reduction in CT prescription versus the «clinical» strategy"

"Among the High risk patients, the clinical use of MammaPrint® is associated with a 46% reduction in chemotherapy prescription"

# Future perspectives in young women

- To optimize adjuvant endocrine therapy in young women with ER pos/HER-2 neg BC having no pCR after NACT
- To do SN (sentinel node biopsi) after NACT in a safe manner and spare patients from ALND if downstaged from a positive to a negative LN status
- New prognostic tools in order not to overtreat young women!
- The optimal chemotherapy regimen regarding efficacy and long-term tolerance

Thank you