Neoadjuvant therapy When and How

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Neoadjuvant chemotherapy

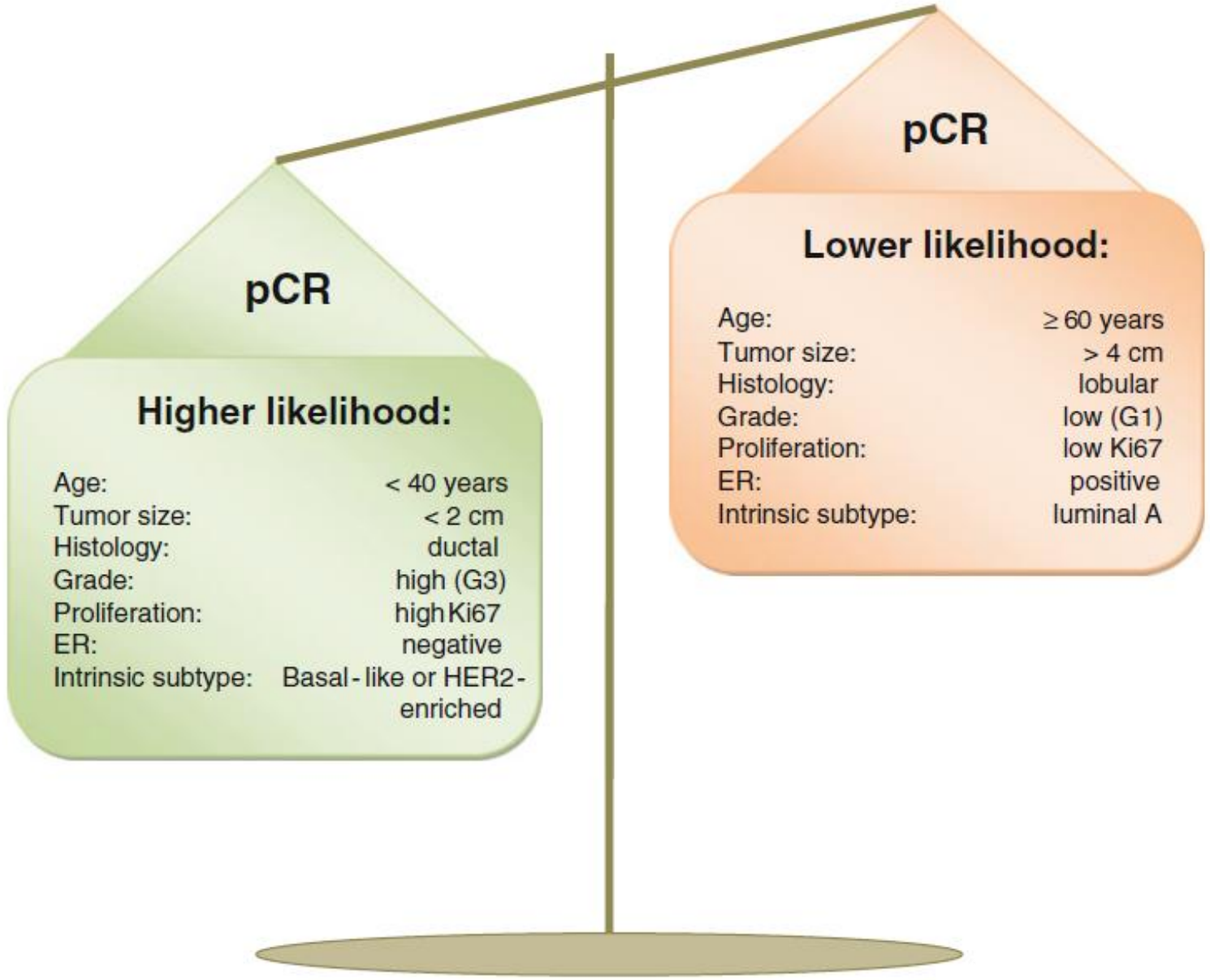
- Women with large tumours or inflammatory disease
- Neoadjuvant chemotherapy is commonly used for the treatment of patients with high-risk operable primary breast cancer
- Guidelines for the use of neoadjuvant chemotherapy in operable breast cancer, with recommendations for patient selection and treatment regimens

Recommendations from an International Consensus Conference on the Current Status and Future of Neoadjuvant Systemic Therapy in Primary Breast Cancer

- The largest benefit by NST is realized in those patients who have a high likelihood for a pathologic complete response (triple-negative or high-grade estrogen receptor [ER]- positive, and HER2-positive breast cancer)
- Patients with small (<2 cm) tumors and those with ER positive low-grade cancers or pure (classic) invasive lobular cancers have the smallest expected benefit from NST
- NST should not be recommended routinely when there is uncertainty regarding the appropriateness of chemotherapy (i.e., small [<2 cm], ER-positive/HER-2neu negative, or low or intermediate grade with clinically negative nodes). Such a patient may be treated with adjuvant hormone therapy only

Ann Surg Oncol (2012) 19:1508–1516

http://www.mdanderson.org/pcr/



Likelihood of pCR in NST of breast cancer

Neoadjuvant chemotherapy

- Pooled analysis of 12 international trials. 11 955 patients included
- Four objectives:
  - Establish the association between pCR and EFS and OS
  - Establish the definition of pCR that correlate best with long term outcome
  - Identify the breast cancer sub-types in which pCR is best correlated with long term outcome
  - Assess whether an increase in frequency of pCR between different treatments predicts an improved EFS and OS

Cortazar P, Lancet 2014

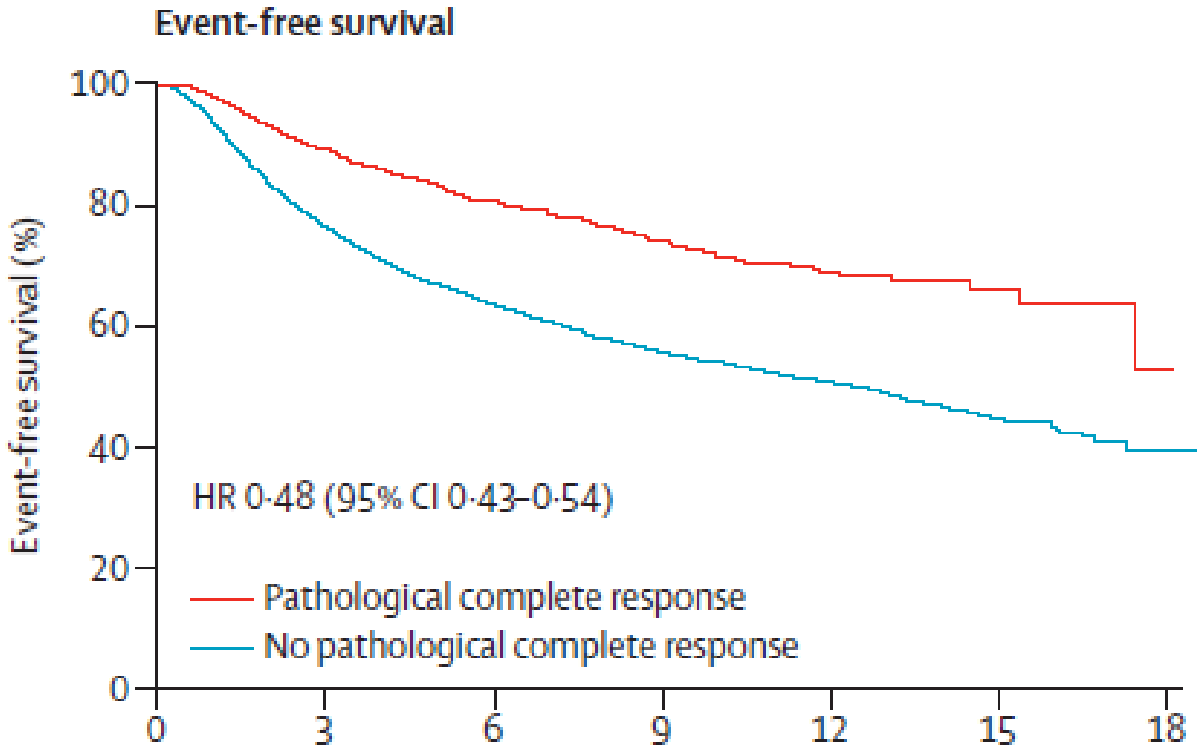
Pathological response

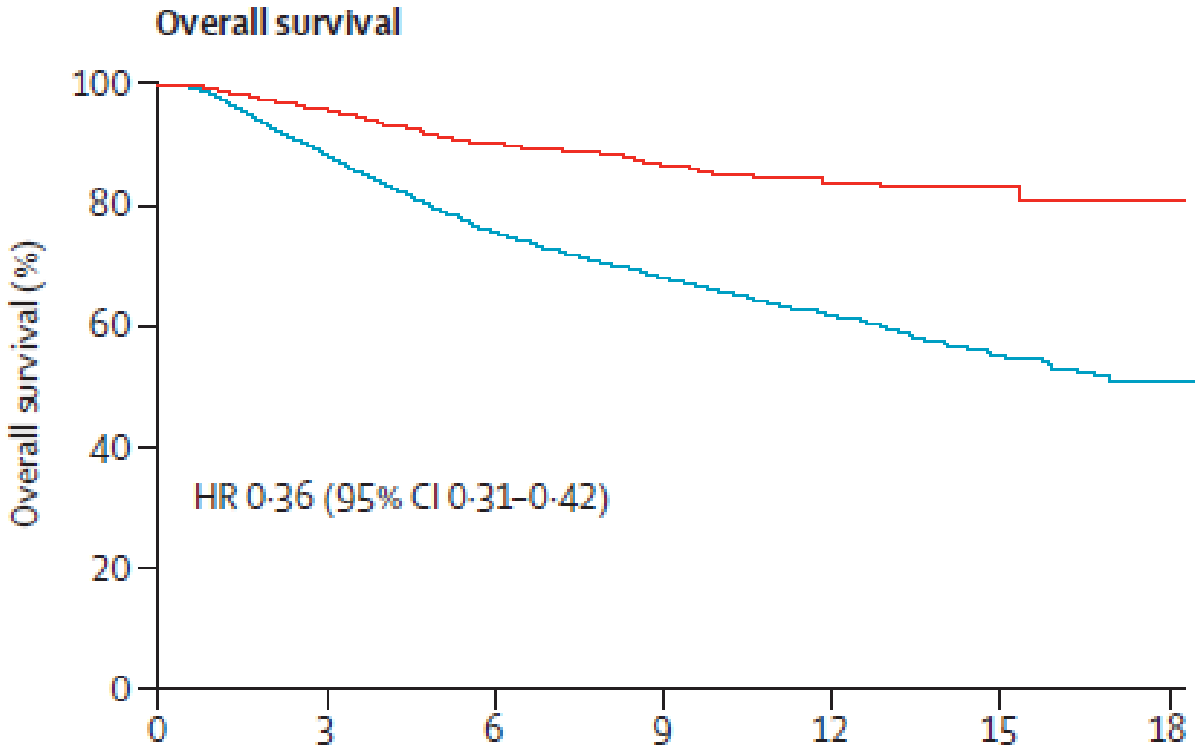
- Overall the frequency of pathological complete response was low
- The frequency decreased with stringent definitions:
    - 22 % (21-22) of patients achieved ypT0/is
    - 18% (17-19) achieved ypT0/is ypN0
    - 13% (12-14) achieved ypT0 ypN0

Clinical tumor subtype and complete pathological response

Clinical tumor subtype	N	pCR	CI
HR positive, HER2 negative, grade 1/2	1986	7,5%	6,3-8,7
HR positive, HER2 negative grade 3	630	16,2%	13,4-19,3
HER2 positive, HR positive, trastuzumab	385	30,9%	26,3-35,8
HER2 positive, HR positive no trastuzumab	701	18,3%	15,5-21,3
HER2 positive, HR negative, trastuzumab	364	50,3%	45,0-55,5
HER2 positive, HR negative, no trastuzumab	471	30,2%	26,0-34,5
Triple negative n = 1157	1157	33,6%	30,9-36,4

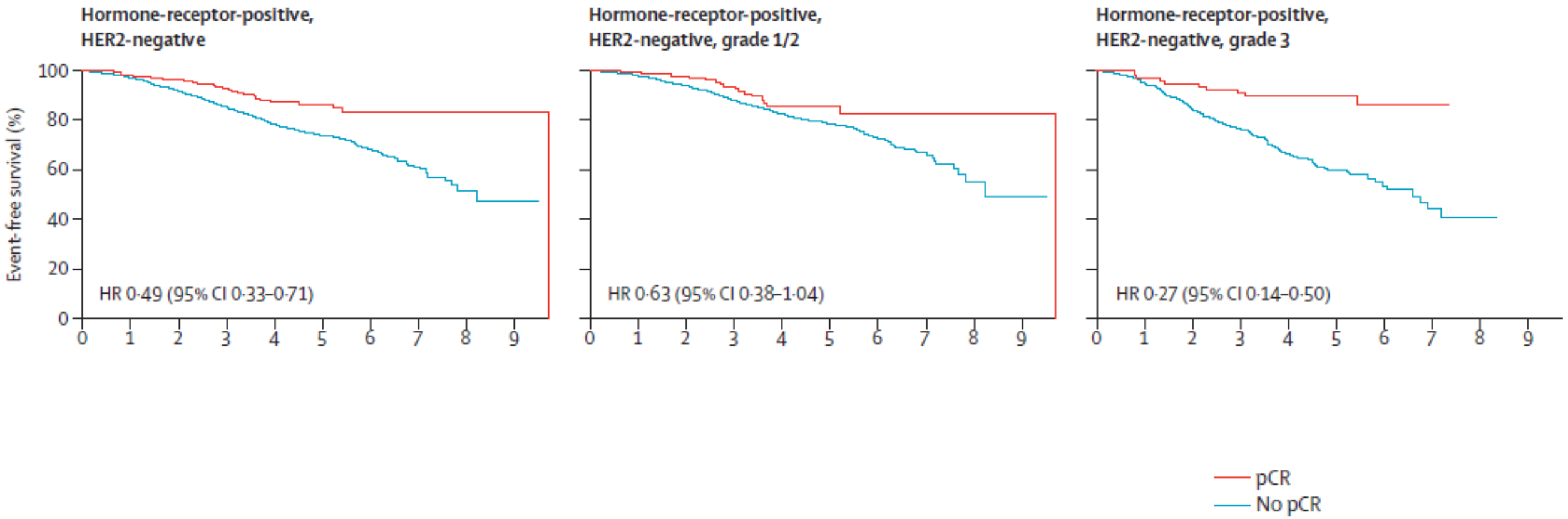
Associations between pathological complete response and event-free survival and overall survival



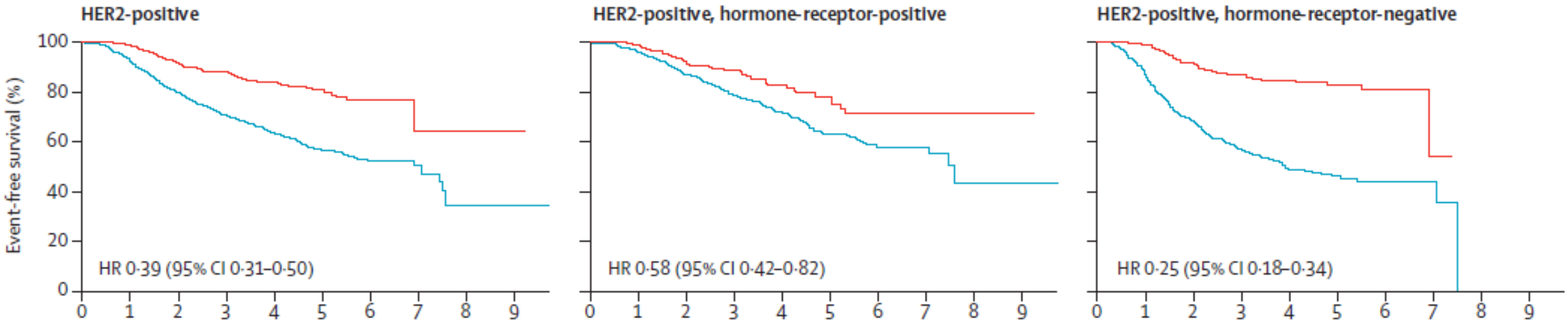


pCR: absence of invasive cancer in the breast and axillary nodes irrespective of DCIS

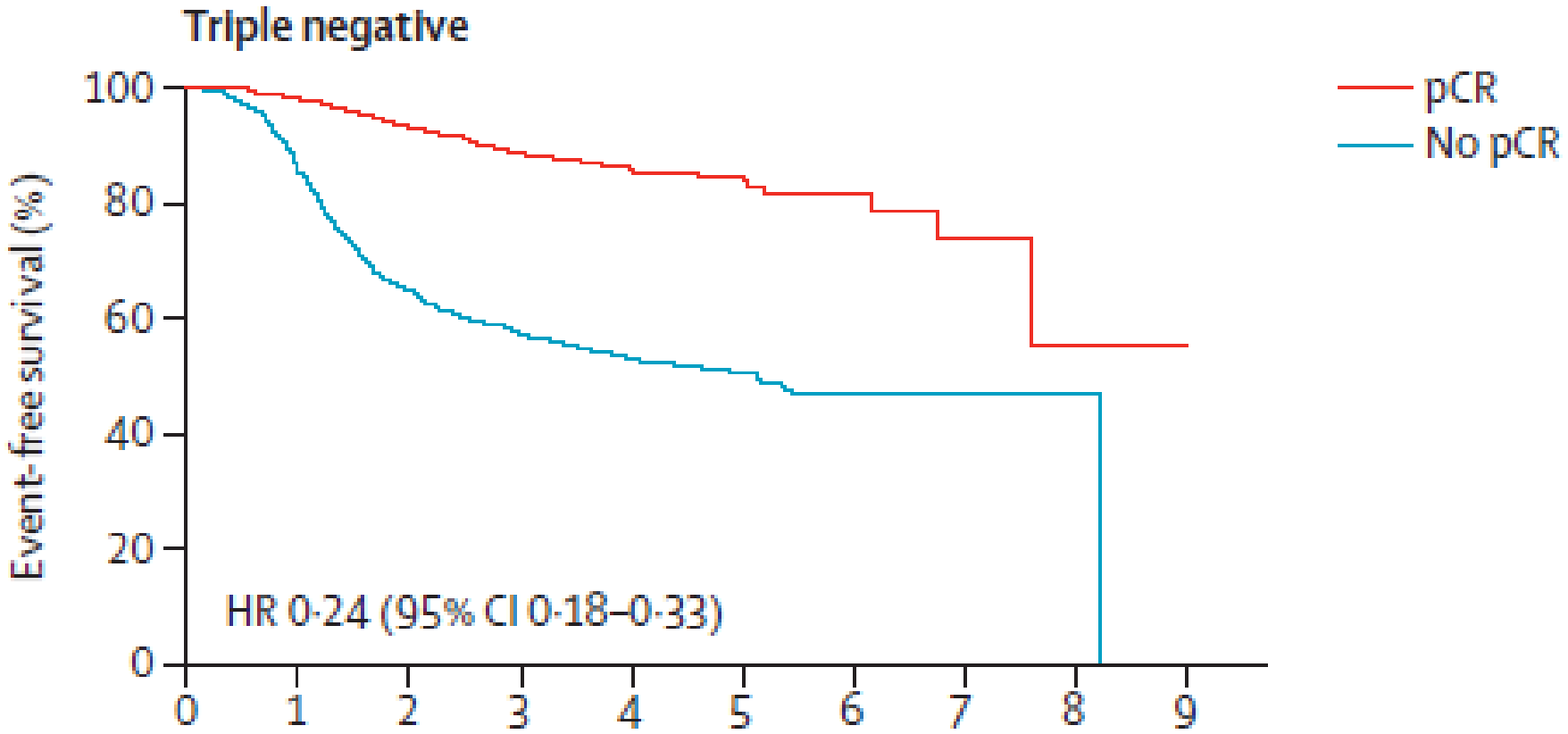
Association between pCR and breast cancer subtype: 1) HR+ HER2 negative



Association between pCR and breast cancer subtype: 2) HER2 positive



Association between pCR and breast cancer subtype: triple negative



Pathological complete response

- Standardization of the definition of pathological complete response is very important
- The authors propose that pathological complete response is defined as either
  - ypT0/is ypN0 or
  - ypT0 ypN0
- Presence or absence of ductal carcinoma in situ did not affect long term outcome in their analysis. A retrospective analysis of a database find the same results (Mazouni 2007) but a German pooled analysis of seven neoadjuvant trials showed that patients without DCIS had longer survival than did patients with residual DCIS (von Minckwitz 2012)
- Residual cancer burden

Triple negative breast tumors

- In TNBC the survival difference between pCR and non pCR patients is the largest. The primary aim is therefore to increase pCR in order to improve survival
- Anthracycline and taxane containing therapies are the standard regimen used today
- But TNBC is a very heterogeneous group
- The basal group seems to be the most chemosensitive one, reaching the highest pCR rates, whereas the luminal androgen receptor positive group achieves a pCR rate of around 10%

pCR and TNBC patients

- Von Minckwitz et al. published a meta-analysis confirming the impact of pCR in DFS and OS in TNBC patients
- Patients who did not achieve a pCR had a 6-fold higher risk of relapse (HR = 6.02, 95% CI,3.92–9.25), and a 12-fold higher risk of death (HR = 12.41,95% CI, 5.82–26.49) compared to patients with pCR
- Cortazar et al. confirmed that in TNBC patients who achieved a pCR, the risk of recurrence and mortality decreased significantly (DFS: HR 0.24, 95% CI [0.18–0.33];OS: 0.16, 95% CI [0.11–0.25]).

Von Minckwitz G, BCRT 2011
Cortazar P Lancet 2014

Chemotherapy and triple negative tumor

- Carboplatin?
  - Geparsixto study : Of the patients with triple-negative breast cancer, 84 of 158 patients achieved a pathological complete response with carboplatin, compared with 58 of 157 without (p=0·005)
  - CALGB 40603 (Alliance) carboplatin significantly increased pCR breast/axilla (ypT0/is, ypN0): (54% v 41%; P = 0.0029)
- Preliminary data from the Geparsixto study support the hypothesis that mainly BRCA 1/2 mutation carriers derive a benefit from the use of carboplatin

Triple negative tumours and tumour infiltrating lymphocytes (TIL)

- The amount of TILs predicts, independently of the breast cancer subtype, a significantly higher pathological response and seems to be prognostic in some (Denckert 2010, Issa Nummer 2013, Loi 2014)
- In TNBC, TIL measured on postsurgical tissue or in primary tumour tissues shows the more stromal TILs are present the better is the DFS and OS (Dieci 2014)
- In the GeparSixto trial increased levels of stromal TILs predicted pCR in univariable ($P < .001$) and multivariable analyses ($P < .001$) particularly in patients treated with Cb (Denkert 2015)

Chemotherapy and triple negative tumor

- St Louis experience: dose dense chemotherapy
- We reported the survival of two consecutive series of 267 locally advanced breast cancers (LABC) treated with two different neoadjuvant regimens, either a dose-dense and dose-intense cyclophosphamide–anthracycline (AC) association (historically called SIM) or a conventional sequential association of cyclophosphamide and anthracycline, followed by taxanes (EC-T)
- We compared pathological responses and survival rates of these two groups and studied their association with tumour features

Giacchetti S; BJC 2014; 110: 1413-1419

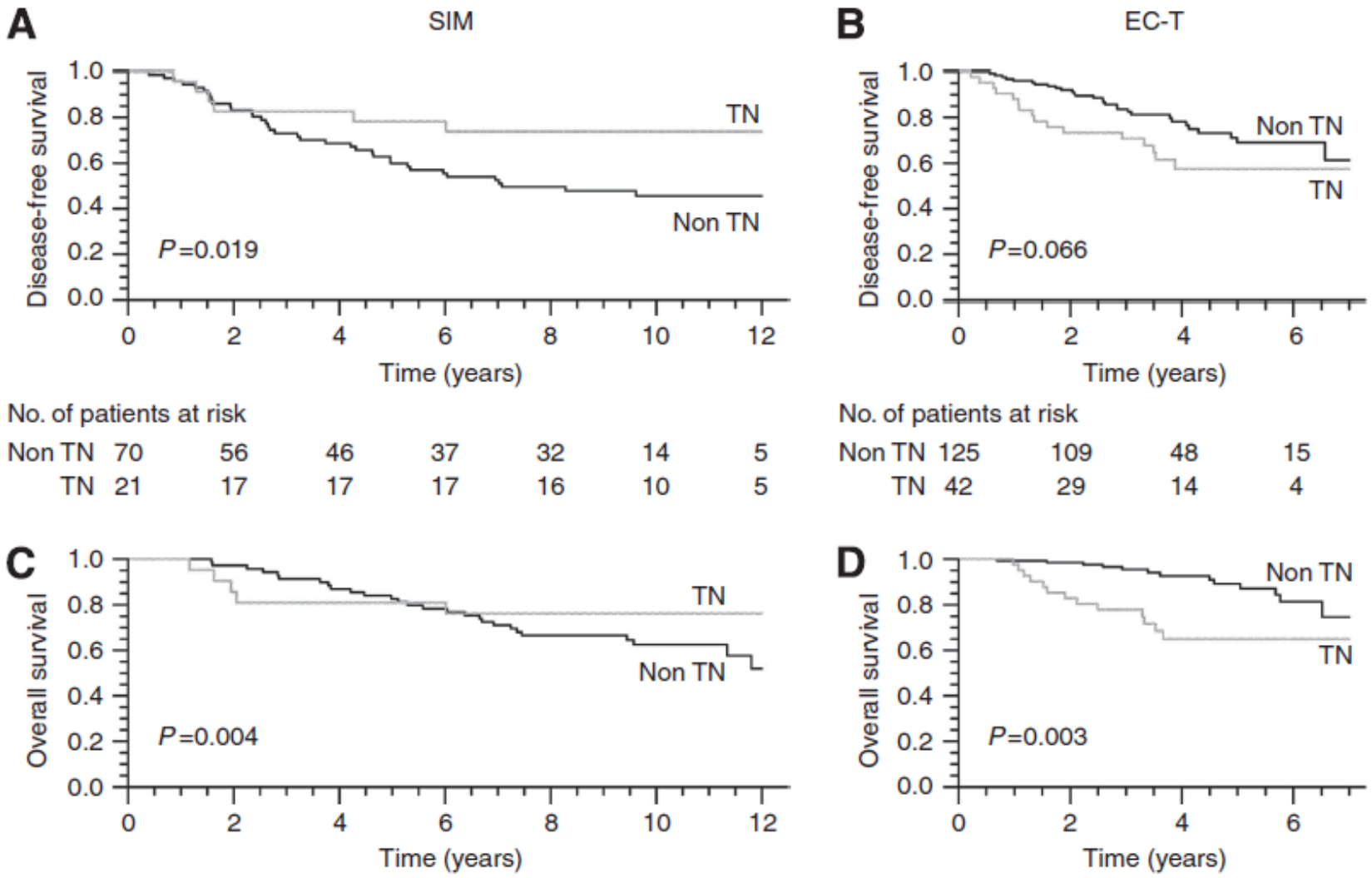
Neoadjuvant treatment: dose dense chemotherapy

- The two regimens showed equivalent pathological complete response (pCR) in the whole population (16 and 12%)
- The SIM regimen yielded a higher pCR rate than EC-T (48% vs 24%, P=0.087) in TN tumours
- In the SIM protocol, DFS was statistically higher for TN than for non-TN patients (P = 0.019)
- After 2 years, TN was associated with a significantly decreased likelihood of relapse in SIM-treated LABC :HR = 0.25 (95% CI: 0.07–0.86), P = 0.028

Giacchetti S; BJC 2014; 110: 1413-1419

Dose dense chemotherapy

DFS at 7 years:
SIM:76%
EC-T: 57%

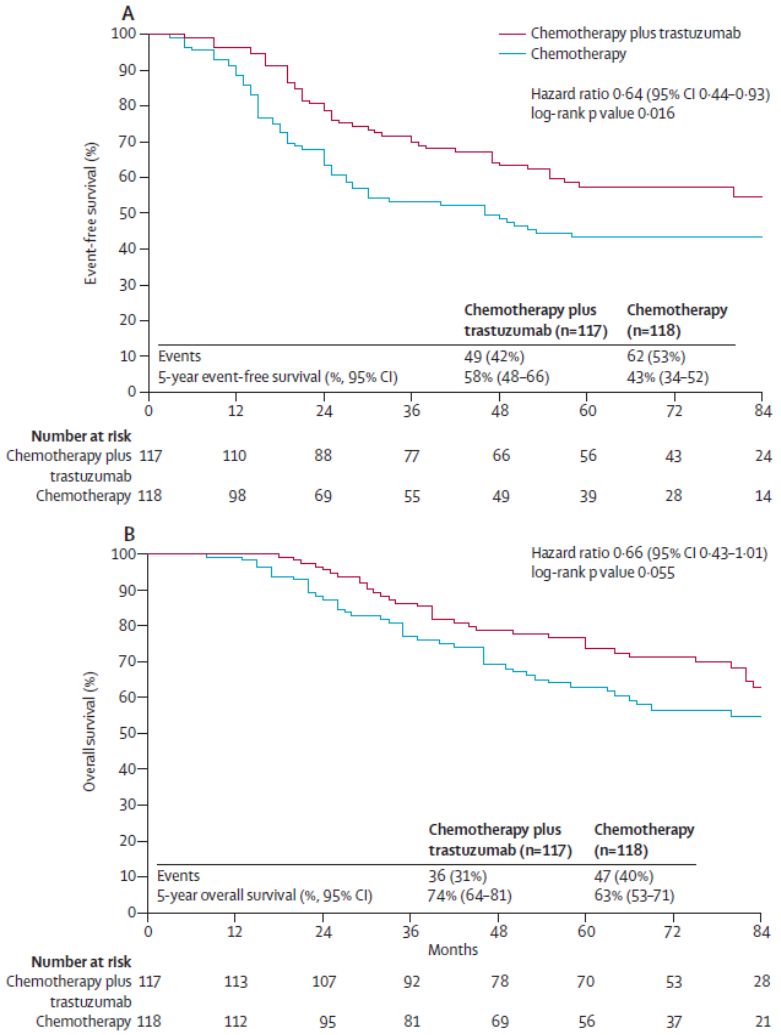


Neoadjuvant chemotherapy and HER2

- The prognosis of patients with HER2 breast cancer has made a quantum leap forward since the introduction of trastuzumab as part of the primary treatment
- The previously unfavourable prognosis of HER2 breast cancer changed to a favourable one, especially if patients experienced a pCR after neoadjuvant therapy

Neoadjuvant chemotherapy and HER2

- NOAH trial:
  - Median follow-up: 5.4 years
  - 5 years EFS: 58% (48-66) in the trastuzumab group and 43% in the chemotherapy group
  - EFS strongly associated with pathological complete response HR = 0,29 (0,11-0,78)



NeoALTTO

- 455 patients randomized between:
  - Trastuzumab (152)
  - Lapatinib(154)
  - Trastuzumab + lapatinib (149)

Paclitaxel
hebdo x 12

- Trastuzumab+ lapatinib : CR = 51.3% (43.1-59.5)
- Trastuzumab: CR = 29.5%; (22.4-37.5); difference: 21.1%, p=0.0001
- Lapatinib: CR = 24.7%, (18.1-32.3)

Baselga J; Lancet 2012; 379: 633-640

NeoALTTO

- 3 year Disease Free survival:
  - Trastuzumab: 76% (62-82)
  - Lapatinib: 78% (68-82)
  - Trastuzumab + Laptinib: 84% (77-89)
- HR = 1.06 (0.66-1.69) Lapatinib / trastuzumab and HR = 0.78 (0.47-1.28) in the combination
- 3 year overall survival : lapatinib 93%, trastuzumab 90% and combination 95% (NS)

E de Azambuja, Lancet Oncol 2014

NeoALTTO

- Three year event free survival was significantly improved for women who achieved pathological complete response compared with those who did not as was three year overall survival
- EFS: HR = 0.38 (0.22-0.63) p = 0.0003
- OS: HR = 0.35 (0.15-0.70) p = 0.005

E de Azambuja, Lancet Oncol 2014

Trastuzumab Pertuzumab (neosphere)

- Phase II randomized study: 417 patients
  - Trastuzumab + Docetaxel (A)
  - Trastuzumab + Pertuzumab + Docetaxel (B)
  - Pertuzumab + trastuzumab (C)
  - Pertuzumab + docetaxel (D)
- The primary endpoint, examined in the intention-to-treat population, was pathological complete response in the breast

Gianni L, Lancet Oncol 2012; 13:25-32

Neosphere

- Pertuzumab + trastuzumab + docetaxel (groupe B): RC = 45.8% (36.1-55.7)
- Trastuzumab + docetaxel (groupe A): RC = 29.0% (20.6–38.5); p=0.0141
- Pertuzumab + docetaxel (groupe D): RC = 24.0% (15.8–33.7)
- Pertuzumab + Trastuzumab (groupe C): RC = 16.8% (10.3–25.3)

Gianni L, Lancet Oncol 2012; 13:25-32

Neosphere ASCO 2015

- 3 year DFS:
  - trastuzumab plus pertuzumab plus docetaxel: 90%,
  - Trastuzumab- docetaxel: 86%
  - HR = 0,69 (0,34–1,40) NS
- In case of pCR versus absence of pCR:
  - DFS: HR = 0,68 (0,36-1,26)
  - PFS: HR = 0,54 (0,29–1,00)
- The benefit may be less than expected?

Impact of neoadjuvant single or dual HER2 inhibition and chemotherapy upon pathological complete response: a metaanalysis

- The dual HER2 inhibition significantly improves pCR rate (breast + Nodes)

➢RR = 1.37 (1.23-1.53) p< 0.0001

- pCR and the rate of breast conserving surgery was higher when anthracyclines were added to taxanes: RR = 1.74 (1.37-2.16)
- pCR was significantly higher in the hormonal receptor negative population

Bria R, CTR 2014; 40: 847-856

HER2 positive, HR positive

- Much lower pCR rate for the hormone-receptor positive tumours
- The TBRC006 study investigated a chemofree neoadjuvant therapy consisting of trastuzumab plus lapatinib ± letrozole for 12 weeks
- pCR rate (ypT0/is, ypN0) : 22% (ER- : 28%; ER+: 18%)
- Adding an endocrine therapy to anti-HER2 treatment could increase the pCR rate in HER2+, HR+ patients
- the patients with a hormone-receptor positive disease probably benefit from a longer treatment duration

Rimawi MF, J Clin Oncol 2013; 31:1726-1731

HER2 and neoadjuvant chemotherapy conclusion

- Using anti-HER2 therapy combined with chemotherapy has significantly increased the pCR rates
- All large series, without stratification according to HER2 status (luminal or pure HER2), confirmed the predictive value of pCR on DFS/OS
- When separating HER2+ tumors to luminal (HR+) and pure (HR−) pCR (ypT0 ypN0) is a surrogate marker for DFS ($p < 0.001$) and OS ($p = 0.01$) for pure HER+ tumors, but not for luminal HER+ tumors
- The CTNeoBC meta-analysis emphasized that pCR significantly predicted DFS and OS in pure or enriched HER2-positive but not in luminal/HER2+ subgroup

New anti HER2 agents

- New and potentially more potent anti-HER2 agents irreversibly blocking the HER2 pathway have been tested in neoadjuvant studies
- The DAFNE study investigated the addition of afatinib, a panHER2 family blocker which is orally bioavailable, in addition to trastuzumab and paclitaxel
- Neratinib another irreversible HER2 inhibitor is being tested in a similar study by the ISYP-2 programme

Conclusion

- pCR rate varies significantly among different breast cancer molecular sub-groups and depends on pre-treatment tumor biological profile
- Reaching a pCR strongly predicted improved survival in TNBC and HER2-enriched BC subgroup, while data remain controversial for the luminal subtypes
- It is still not clear whether pCR could be used as a “surrogate marker” of treatment benefit
- pCR can be considered as a “surrogate marker” for accelerated drug registration only in aggressive BC subtypes such as TN and HER2+ and exclusively in the neoadjuvant setting

Conclusion

- We have to explore response guided neoadjuvant chemotherapy
- The neoadjuvant platform offers unique research opportunities to delineate the biologic action of targeted compounds in vivo, identify predictive biomarkers of sensitivity and/or resistance, and finally identify patients at high risk of relapse, where investigational agents should be assessed.
- Taken together, these data indicate how the neoadjuvant setting changes BC management, offering a valuable platform to advance personalized cancer medicine

What can we suggest?

- T≤ 2 cm < N2, M0: No neoadjuvant therapy
- Inflammatory cancer, LABC: neoadjuvant chemotherapy
- T> 2 cm ∀ N:
  - HER2 +++, TNBC: neoadjuvant chemotherapy +/- anti HER2 agents
  - RH+ HER2-
    - Luminal B: neoadjuvant chemotherapy or surgery?
    - Luminal A: surgery or hormonal neoadjuvant treatment?
    - But in some cases chemotherapy can shrink the tumor allowing conserving treatment
  - Classical lobular carcinoma : surgery or hormonal neoadjuvant treatment

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Thank you for your attention