Neoadjuvant Chemotherapy in Breast Cancer: Patient Selection and Predictors of pCR

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Neoadjuvant Chemotherapy

- Indications:
- Management of locally advanced invasive breast cancers including inflammatory breast cancer
- **'Down-staging' of large inoperable cancers to permit surgical resection**

- Routine management of women with high risk disease who would require adjuvant chemotherapy based on biological tumour characteristics and clinical-radiological findings

Neoadjuvant Therapy

- Ability to monitor treatment response and tailor subsequent locoregional and systemic therapy -> more individualised patient care
  - Patients with pCR may not benefit from further regional therapy such as adjuvant radiotherapy
  - Patients with poor response can be identified and entered into trials of novel targeted agents
- Evaluation of treatment response to new agents using pathological complete response (pCR) as a surrogate marker of outcome
  - Neoadjuvant studies smaller, cheaper, faster results
  - Patient selection critical – well-characterised high risk pop'n

Pre Treatment Evaluation - Breast

- Pre treatment breast core biopsy must be adequate for unequivocal diagnosis of invasive carcinoma and assessment of key prognostic/ predictive factors
  - Histological type and grade
  - ER/ (PR) status
  - HER2 status
  - Other biomarkers
    - Ki67, multigene assays
    - additional markers needed for trial e.g. AR, TILs

- If multiple lesions biopsy of at least 2 foci is advised to confirm multifocality and look for heterogeneity

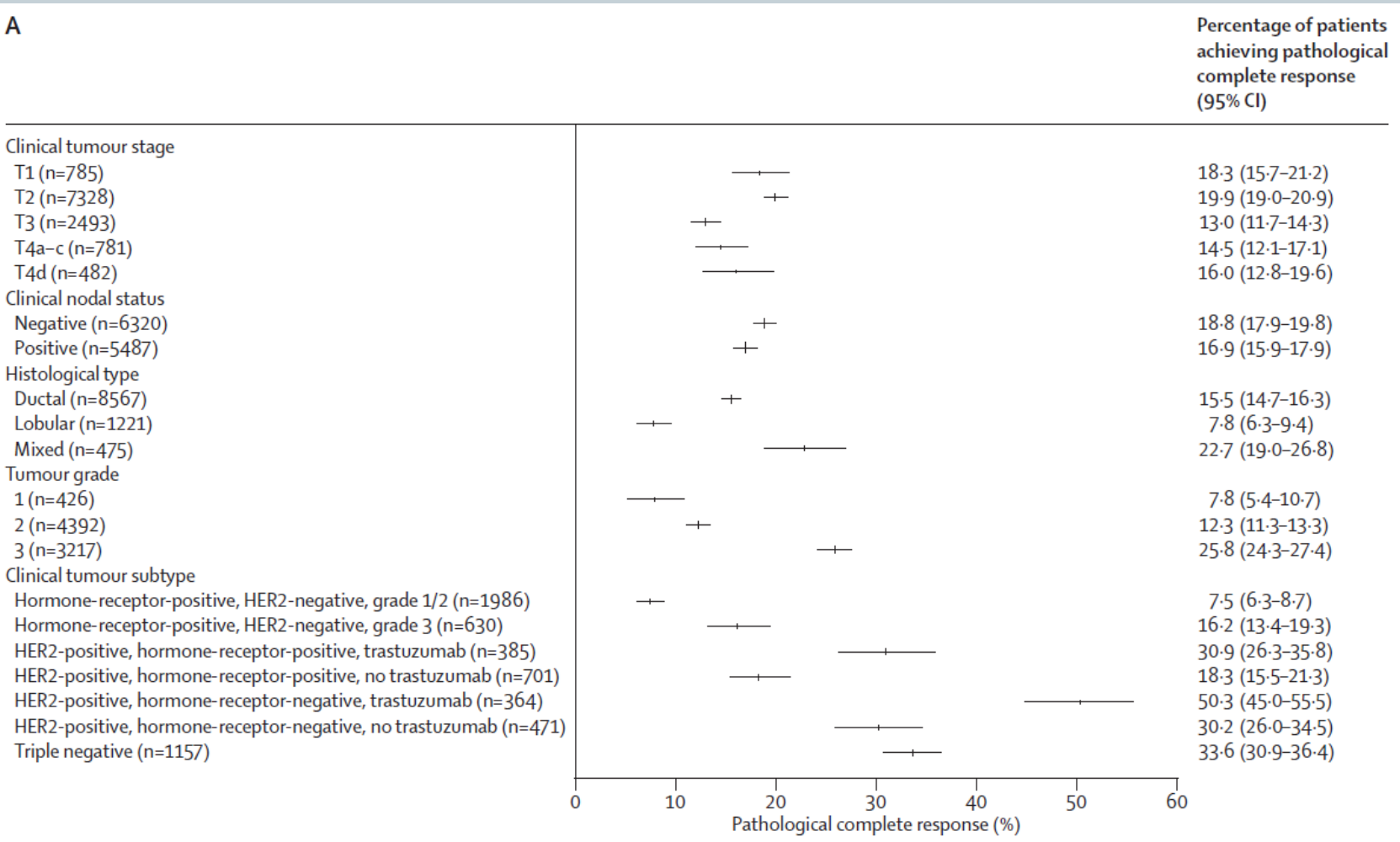
Pre Treatment Evaluation - Breast

- If there is an inadequate amount of invasive carcinoma in the core repeat biopsy should be considered
- Particular care should be taken if:

  Biopsy predominantly DCIS, especially in context of Ca++ with no mass

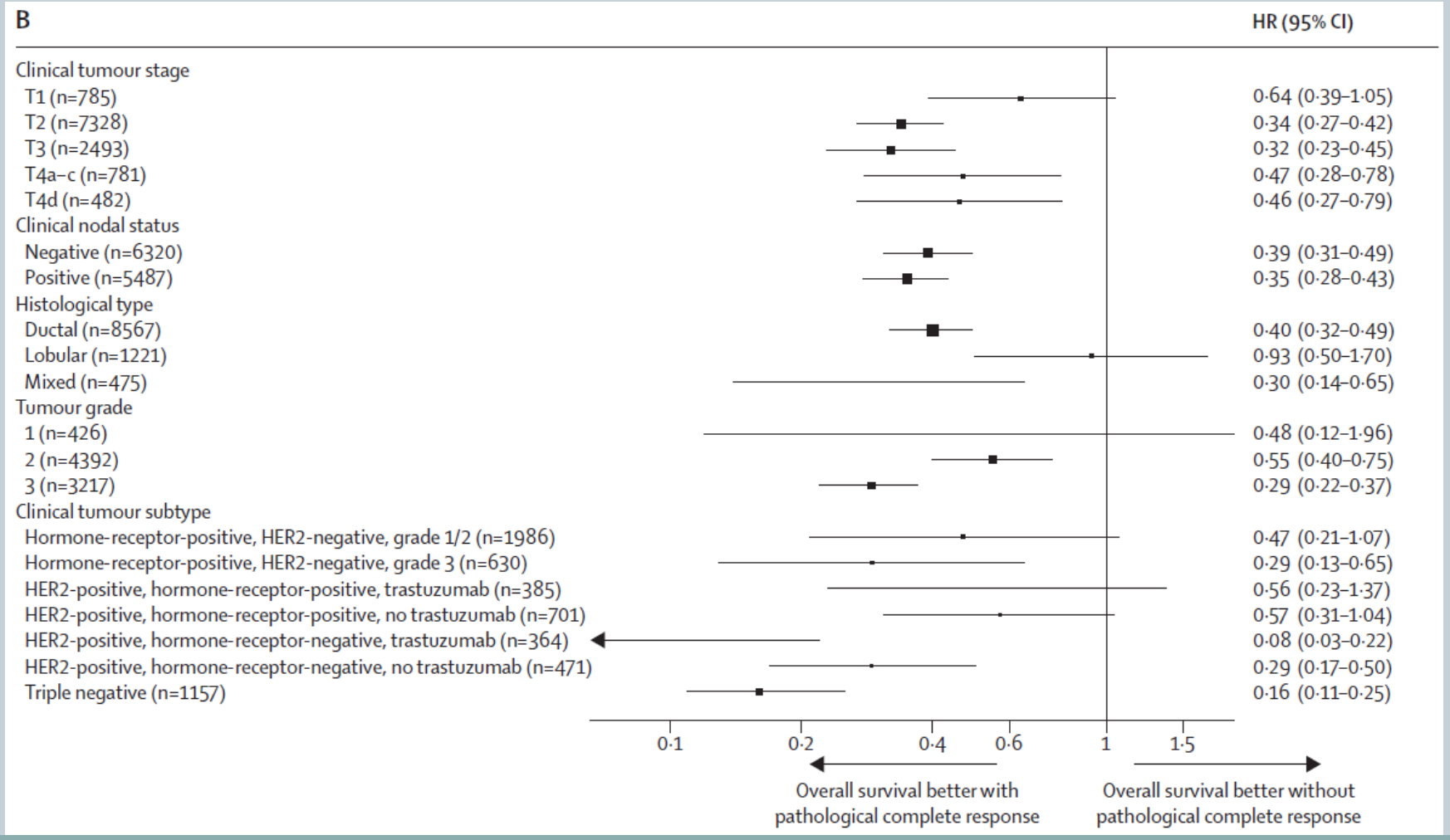
  Papillary carcinoma with focal invasion – radiological size may overestimate invasive component

Predictors of pCR



Cortazar et al., Lancet 2014;384(9938):164-72

Predictors of pCR



Cortazar et al., Lancet 2014;384(9938):164-72

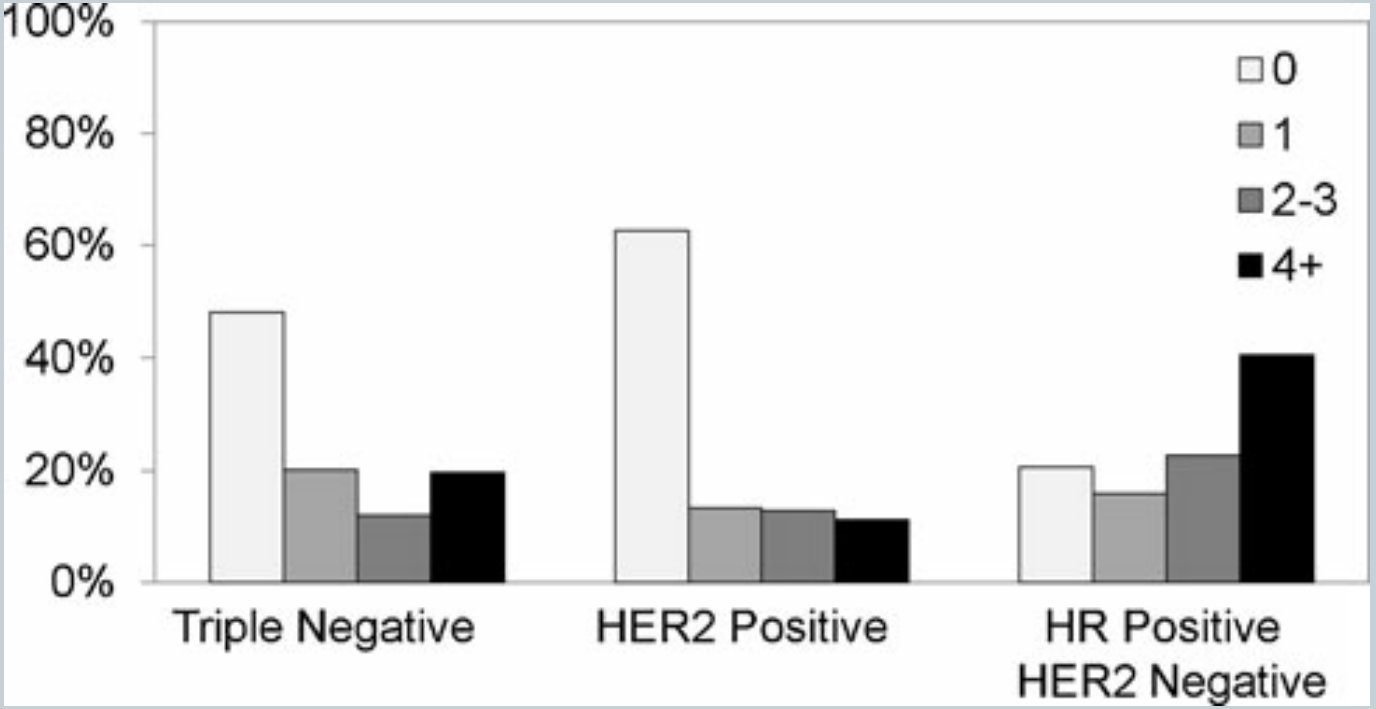
pCR by tumour subtype

- HR +ve tumours have low pCR rates BUT better survival
- HER2+ and triple negative cancers more likely to achieve pCR, but overall prognosis is worse with poor DFS and OS if no pCR

	pCR	3y DFS
HR+/HER2-	2-8%	91-96%
HR+/HER2+	8-33%	82-90%
HR-/HER2+	33-52%	33-68%
HR-/HER2-	24-38%	65-67%

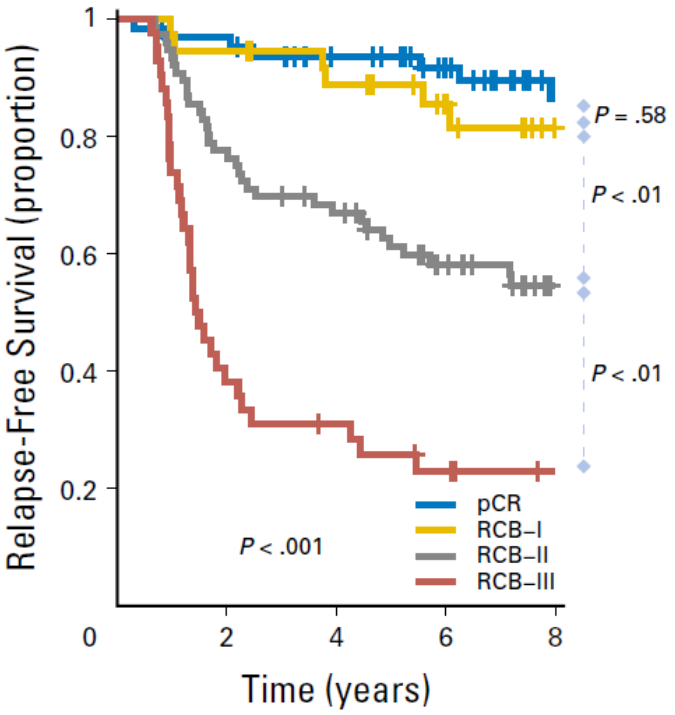
pCR by tumour subtype - axilla

- ACOSOG Z1071
- Nodal pCR rate 41%
- ER+/ HER2- = 21%, TN = 49%, HER2+ = 65%

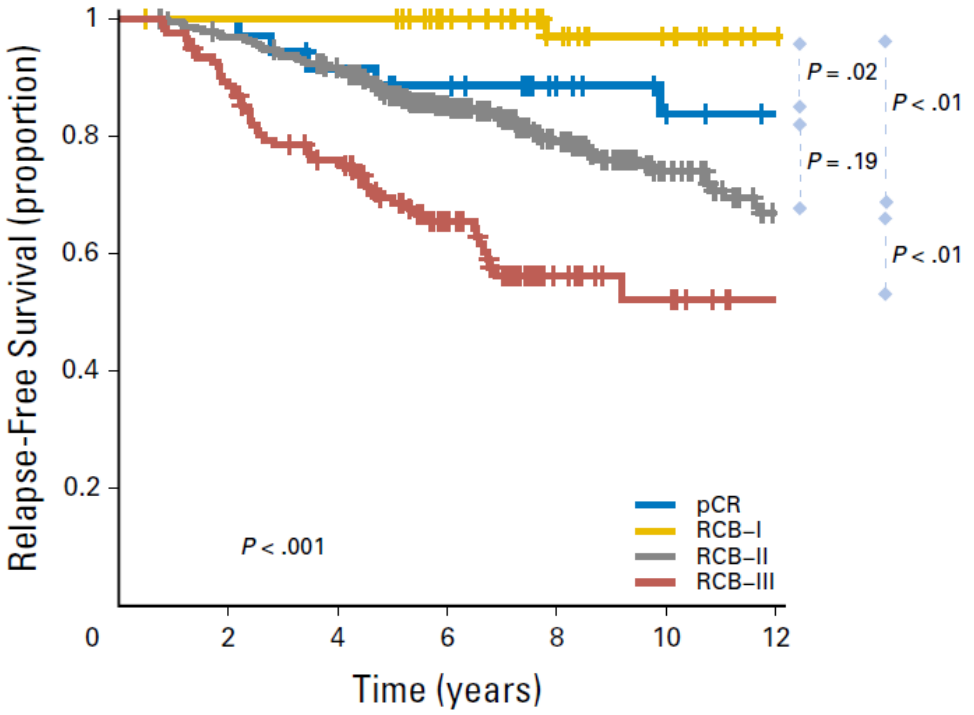


Boughey et al., Ann Surg Onc 2014;260:608-16.

Residual Cancer Burden



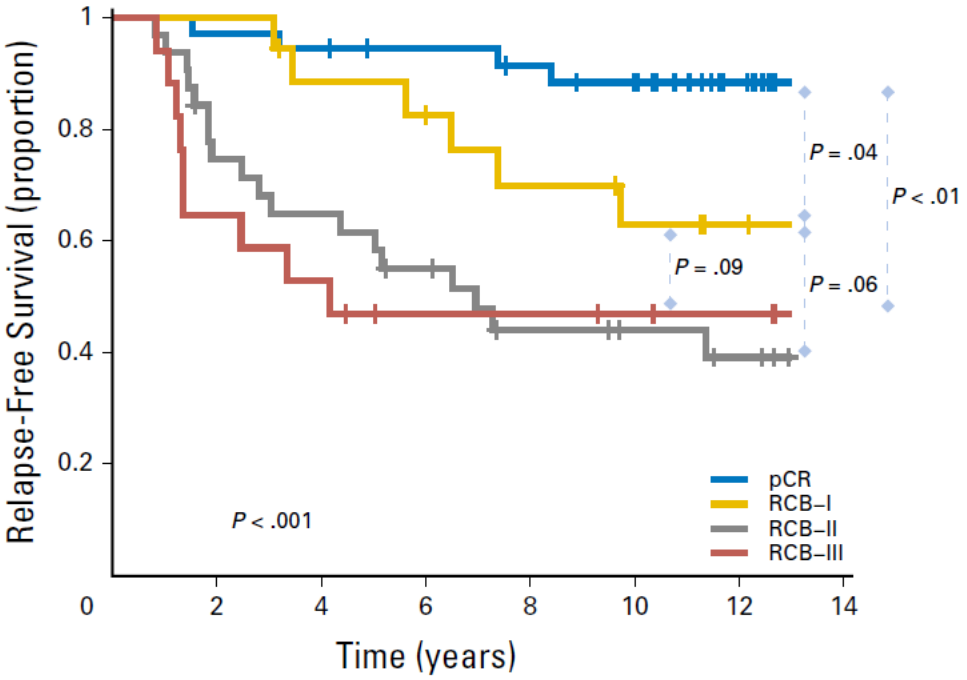
TNBC



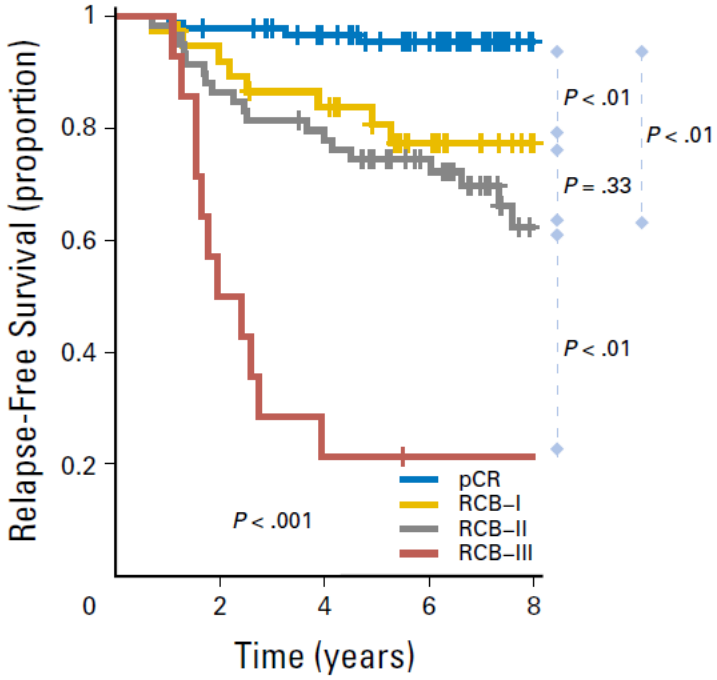
Luminal HER2-ve

Symmans W F et al. JCO 2017;35:1049-60.

Residual Cancer Burden



HER2+ Chemo only



HER2+ chemo plus anti-HER2 Rx

Symmans W F et al. JCO 2017;35:1049-60.

pCR by tumour subtype - Luminal

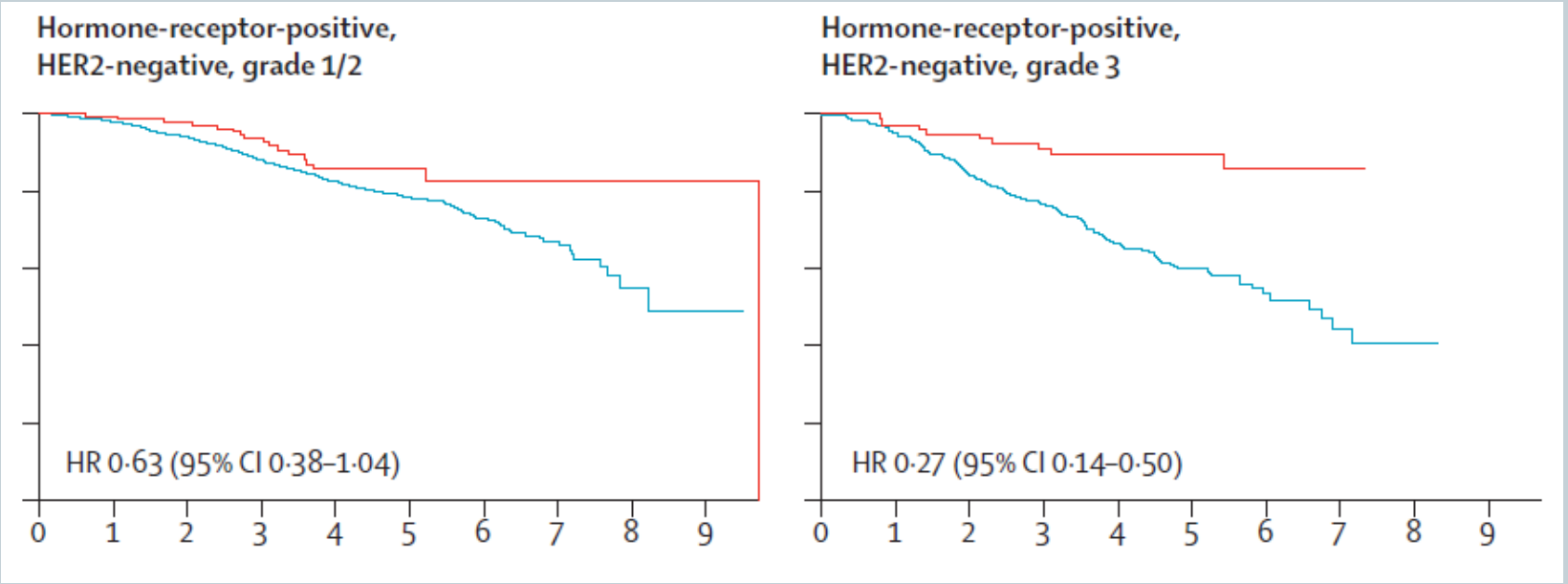
Predictors of response in ER+/HER2 negative cancers

- Grade
- PR status
- High Ki67
- Ductal NST tumours respond better than special types – lobular, tubular, mucinous

pCR by tumour subtype - Luminal

Predictors of response in ER+/HER2 negative cancers

- **Grade**
- Grade 1-2: pCR rate 7.5% (6-9%)
- Grade 3: pCR rate 16% (13-19%)



Cortazar et al., Lancet 2014;384(9938):164-72

pCR by tumour subtype - Luminal

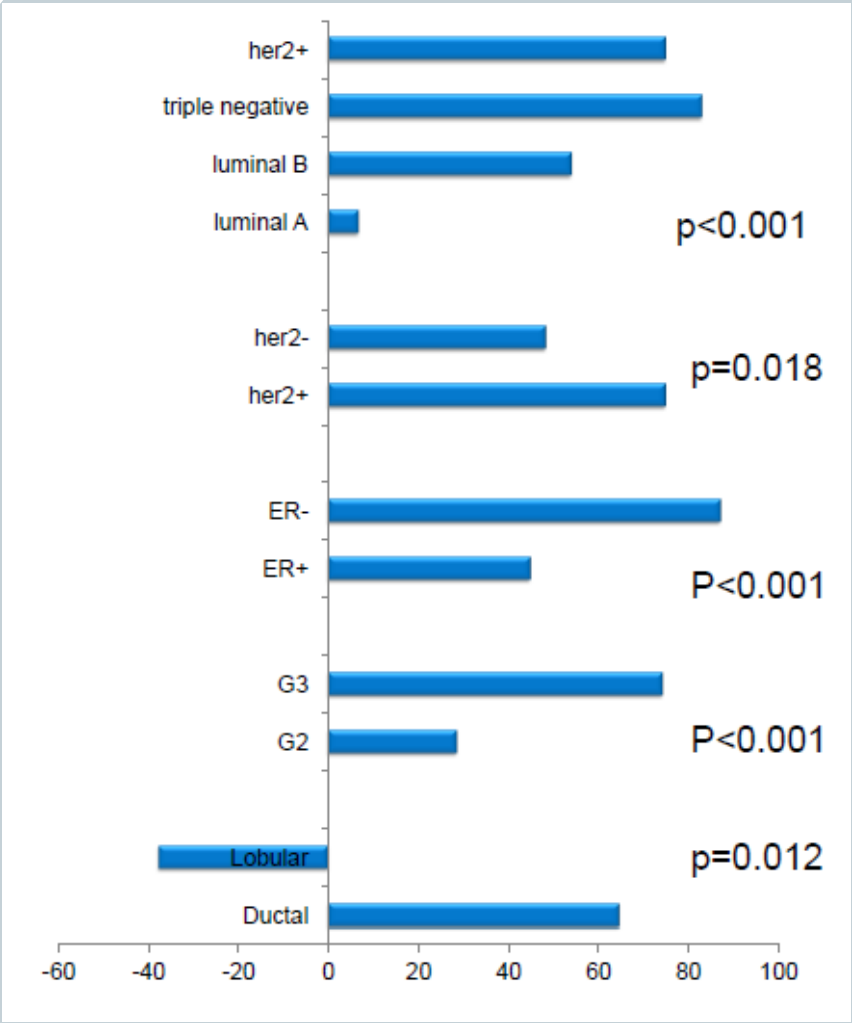
Predictors of response in ER+/HER2 negative cancers

- Invasive lobular carcinoma
- Lower rate of pCR compared with matched ER+ NST
  ILC = 3-6% v NST 14-17%
- Cortazar analysis:
  ILC = 7.8% (6.3-9.4%) v NST 15.5% (14.7-16.3%)
- BUT also lower rate of downstaging and BCS
  ILC = 35.4% v NST 54.8%
- Mastectomy rate remained higher in ILC on multivariate analysis
- Lobular phenotype a significant predictor of no response within luminal B cancers in one series

Petrelli et al., BCRT 2013:142;227-35. Balmoltivola et al., Breast Ca Res Tr 2014;148:511-23

Response by tumour subtype - Luminal

- Cambridge data
- Audit of tumour downstaging and response post NACT
- 6 lobular cancers – none showed a reduction in size post NACT
- 2 cases size underestimated by MRI



Courtesy of A. Agrawal.

Response by tumour subtype - Luminal

- MSKCC – review of ER+ /HER2- cancers who received NACT looking for predictors of downstaging
- Overall pCR rate 5% - breast 7%, cN+ - axilla 15%
- Downstaging to BCS - ILC 16% versus ductal NST 48%
- Axillary downstaging – ILC 7% versus NST 16% (N/S)
- Grade 3 – BCS 51% (v 33%) and axillary pCR 26% (v 5%)
- PR neg – BCS 52% (v 36%) and axillary pCR 22% (v 11%)
- Multivariate model – greatest benefit in PR-/G3 -> BCS 62% and axillary pCR 35%

Petruolo et al., Ann Surg Onc 2017;24:2556-62.

Biomarkers – ki67

- Neoadjuvant studies; high Ki67 associated with increase in pCR rate in several series but no data on benefit of specific Rx arms
- Difficult to interpret as often include all molecular subtypes
- Persisting questions regarding methodology and optimum cut offs
- One study suggests a cut off of >40% but includes HER2+ and TNBC. Luminal B higher rate than luminal A defined by cut off > 14% (pCR 3% vs 13%) Wang et al., Medicine 2016;95(18).

- Another proposed cut off of >50% but there were too few pCR in the ER+/HER2- group for meaningful analysis

Alba et al., The Oncologist 2016;21:150-55.

Biomarkers – ki67

- Denkert et al., Ann Onc 2013
- Pre treatment Ki67 levels in GeparTrio trial

- Low Ki67 (<15%) – pCR =4%
- Intermediate Ki67 (15-35%) – pCR = 13%
- High Ki67 (>35%) – pCR = 29%

- Ki67 predictive of pCR for luminal HER2- and TN but not HER2+ subtypes
- Ki67 only associated with survival in luminal HER2- group

Biomarkers – ki67

- Fasching et al., BMC Cancer 2011;11:486.
- Series looking specifically at ER+/HER2- tumours suggest cut off of 13-20%

- Chen et al., BCRT 2018 Epub
- Cut off of 25.5% to distinguish responders from non-responders amongst ER+ tumours

- Jones et al., BCRT 2009
- Pre treatment – High Ki67 predictive of pCR
- Post treatment – High Ki67 associated with worse RFS and OS

- Sheri et al., BCRT 2017;164:395-400
- Both pre treatment Ki67 and IHC4 score associated with pCR

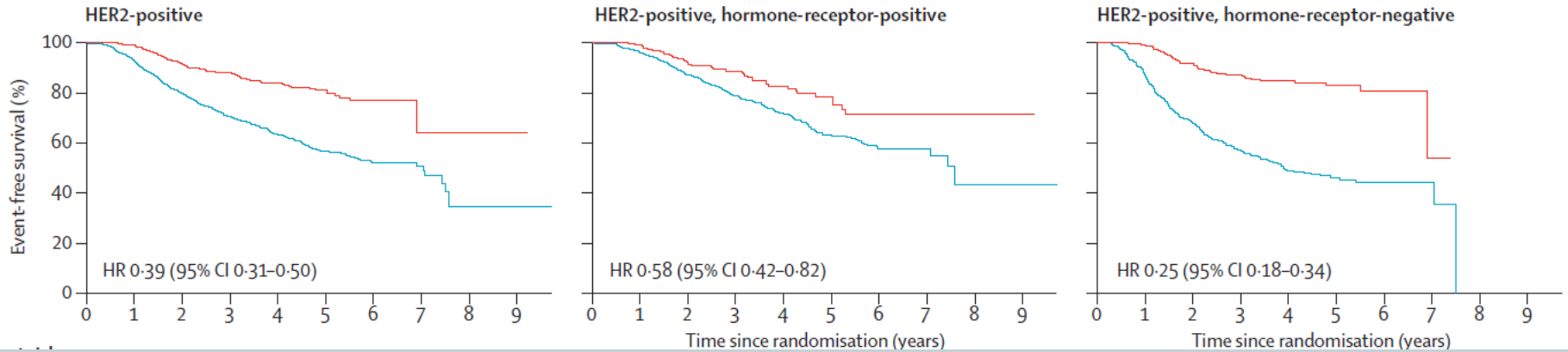
Genomic tests

- PAM50 has also been shown to predict survival outcomes in chemotherapy treated populations and pCR rates post neoadjuvant chemotherapy
- ISPY-1 and NOAH neoadjuvant trials both PAM50 subtype and high ROR score were associated with increased rates of pCR Esserman et al., Br Ca Res Tr 2012;132:1049-62. Prat et al., Clin Ca Res 2014;20:511-21.
- Oncotype Dx - an analysis of the chemotherapy arm of the NSABP B-20 trial showed chemotherapy benefit for patients with a high RS but minimal or no benefit with a low RS; no specific data in neoadjuvant chemotherapy setting Paik et al., J Clin Onc 2006;24:3726-34.
- EndoPredict - associated with pCR following neoadjuvant chemotherapy in a single study (EP low 7% pCR; EP high 17% pCR) Bertucci et al., Cancer Letts 2014;355:70-5.

pCR by tumour subtype – HER2+

Predictors of response in HER2 positive cancers

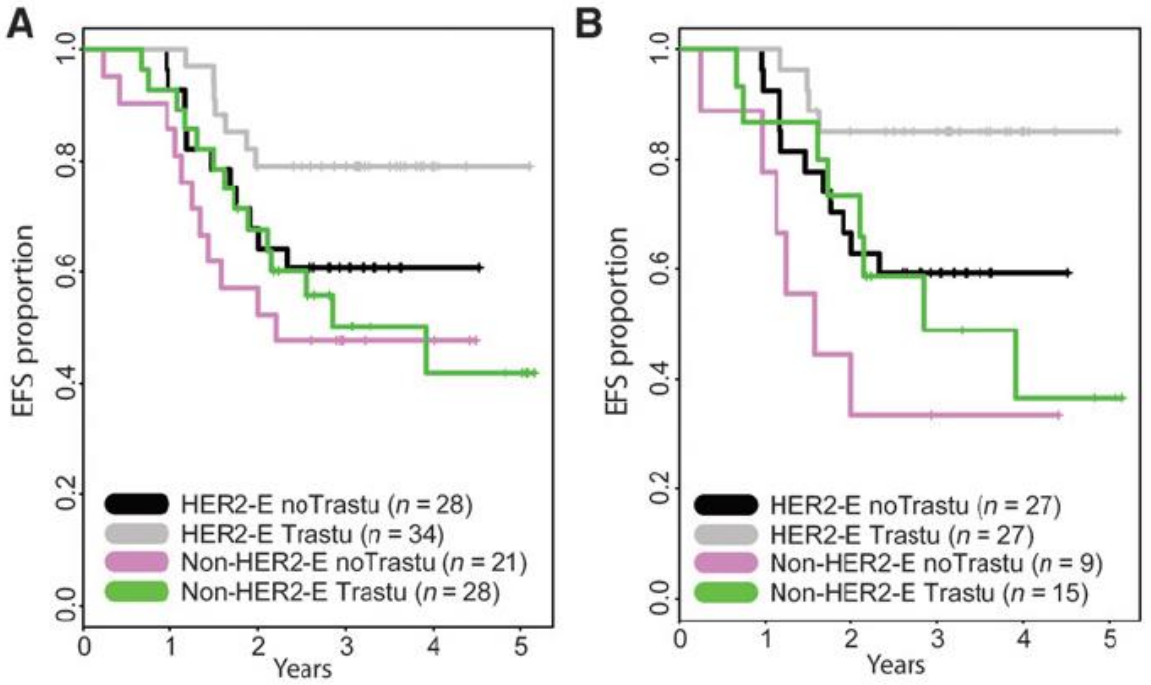
- **ER status**
- ER+: pCR rate with trastuzumab 31% (26-36%)
- ER-: pCR rate with trastuzumab 50% (45-56%)



Cortazar et al., Lancet 2014;384(9938):164-72

pCR by tumour subtype – HER2

- Retrospective analysis of NOAH study looking at PAM50 subtypes
- Only 55% of HER2+ tumours HER2-E subtype; 21% luminal, 7% basal-like, 18% normal-like
- Better pCR rates in HER2-E vs luminal HER2+ tumours (53% v 29%) with larger improvement in EFS with addition of Trastuzumab



Prat et al., Clin Cancer Res 2014;20(2):511-21.

pCR by tumour subtype – HER2+

Predictors of response in HER2 positive cancers

- In the NEOSPHERE trial, higher levels of HER2 protein expression associated with pCR after dual targeted Rx

Bianchini et al., Breast Ca Res 2017;19:16.

FISH:

- higher HER2:CEP17 ratio – OR = 2.11, optimum cut off 4.5
- higher HER2 copy number – OR = 1.15, optimum cut off 14

Wu et al., Oncotargets and Therapy 2018;11:801-8

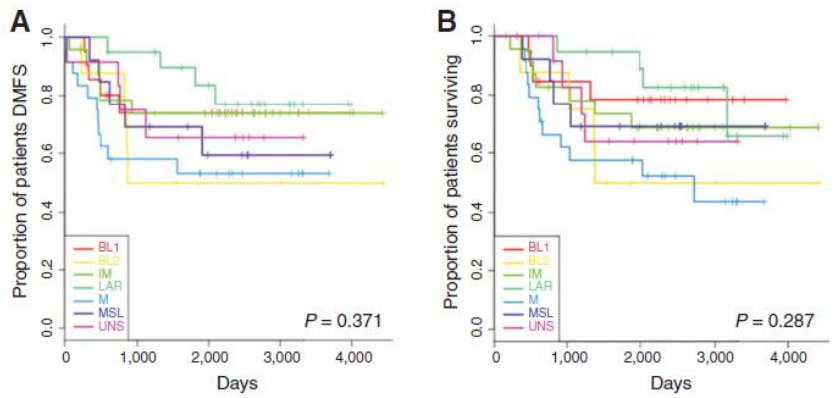
- Higher pCR rate with high level amplification (copy number >10) than low level amplification (6-10) – 55% v 24%
- No difference in RFS or OS

Guiu et al., BrJC 2010;103:1335-42.

pCR by tumour subtype - TNBC

- 7 subtypes of triple negative breast cancer
- Different rates of pCR between subtypes
- No difference in OS – LAR group had low pCR rate but best survival at 3 years

	pCR	Non-pCR	pCR rate
BL1	11	10	0.52
BL2	0	8	0.00
M	8	18	0.31
IM	8	19	0.30
MSL	3	10	0.23
LAR	2	18	0.10
UNS	5	10	0.33



Masuda et al., Clin Ca Res 2013;19(19):5533-40

pCR by tumour subtype - TNBC

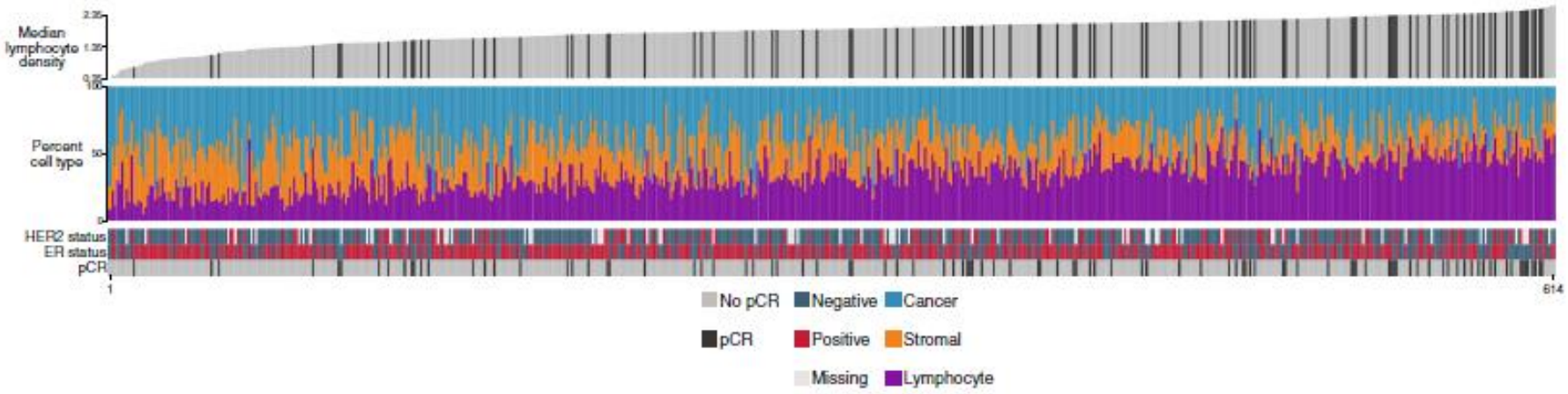
- Lower pCR rates amongst some special types of TNBC
- Metaplastic carcinoma – low rates of pCR in several series with higher rates of progressive disease
- Majority of studies not using current regimes with platinum based therapy

- Medullary-like carcinoma???
- High levels of TILS
- High proliferation
- BRCA1 dysfunction and impaired DNA repair

=> all associated with improved response to NACT

Immune response - TILS

- Increased levels of TILs pre Rx associated with pCR
- Highest lymphocyte density in HER2+ tumours



Ali et al., Breast Cancer Research 2016;18:21.

TILs

- High levels of TILs associated with pCR in a meta-analysis of 8 studies (OR 3.93)
- Subset analysis showed this was true for ER- (OR 3.30), HER2+ (OR 5.05) and TNBC (OR 2.49) but not ER+ disease
- Retained significance in multivariate analysis

  Mao et al. PlosOne, Dec 12, 2014.
- High pre treatment TILs associated with improved survival outcomes in HER2+ patients in neo-ALLTO trial

  Salgado et al., JAMA Oncol 2015; 1:448-54.
- Immune related gene expression signatures also associated with pCR
- Absence of inflammation a predictor of no response

  Balmoltivola et al., Breast Ca Res Tr 2014;148:511-23.