NEOADJUVANT CHEMOTHERAPY FOR BREAST CANCER

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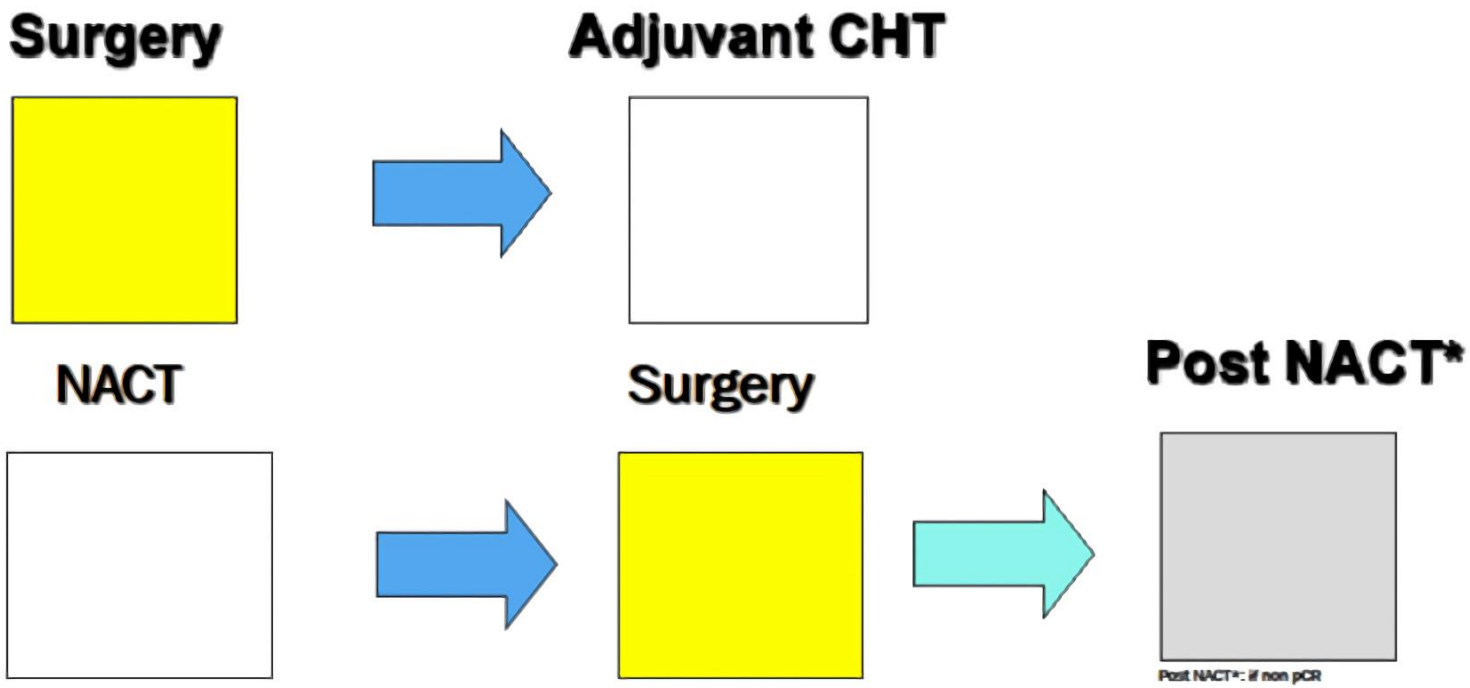
NZAGS

New Plymouth 2021

Neoadjuvant Therapy – Changing the Sequence



NEOADJUVANT CHEMOTHERAPY - RATIONALE

NACT is a safe procedure with improved survival and less recurrence

High pathological complete response rate (pCR) in HER2+ and TNBC

Fast track procedure to evaluate new therapies

Increase the rate of breast conservation

Avoids delay due to surgical complications

Reduce the impact of surgery to the axilla

NACT is at tool of “in-vivo chemo-sensitivity testing”

Option of post neoadjuvant therapy in non pCR

NEOADJUVANT CHEMOTHERAPY – WHICH PATIENTS?

Large locally advanced/inoperable tumours

Inflammatory breast cancer

Down stage tumours so BC possible

Smaller ca with aggressive features

Allows time for BRCA testing if required

Allows ability to assess response

St Gallen and European Soc. of Med Oncol (ESMO) recommend NACT for stage 2-3 Ca, HER2+ BC regardless of size

NEOADJUVANT CHEMOTHERAPY - LIMITATIONS

Not indicated if no role for adjuvant chemotherapy – low risk Ca

Risk of delaying surgery

- Rare to get progression on NACT (3% vs >90% response)

Lack pathological data for prognosis

- Have to rely on clinical and radiological staging

Lesser role in certain sub-types

- Low grade ER+ (?Eliminate trial)
- Lobular ca
- Multicentric (>1 quadrant)

NEOADJUVANT CHEMOTHERAPY: RATE

- Australia
  3.08% 2011
- 6.65 % 2016
- 10.35% HER2+, 9.71% triple negative (2011-2016)

- US National Cancer Database 24% 2011
- Canada 8.53% 2012-14
- Dutch National Audit 14% 2015

- What should the figure be? 20%??
-

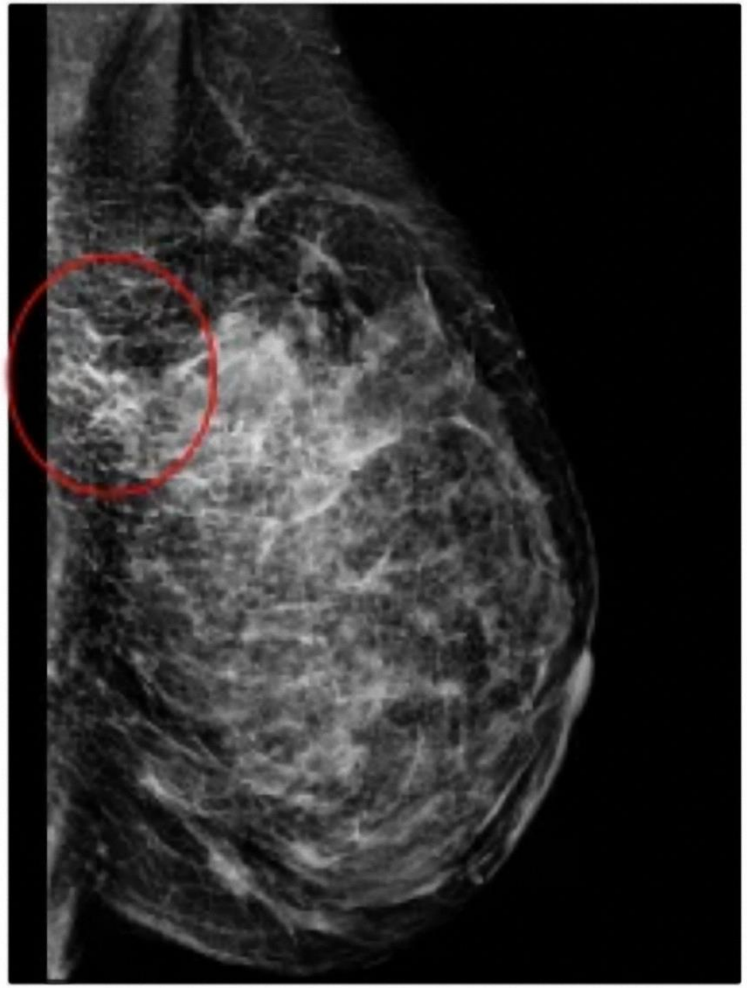
  (Pattiniott et al, *Ann Breast Surg* 2019)

- CHCH Breast Cancer Registry 14% 2013-18

NACT: THE WORK UP

1. Mammogram
2. Ultrasound - Core Bx mass + receptors + Her 2
3. Core distant disease (US or stereo), often after MRI
4. US axilla – FNA/core abnormal nodes
5. Clip - breast Ca and increasing clip abnormal node(s)
6. MRI breast – younger, higher density, extent of Ca/ DCIS?, extent of lymphadenopathy?, check contralateral breast
7. +/- Staging – FDG PET, or CT/bone scan, routine bloods
8. MDM

PRE NACT



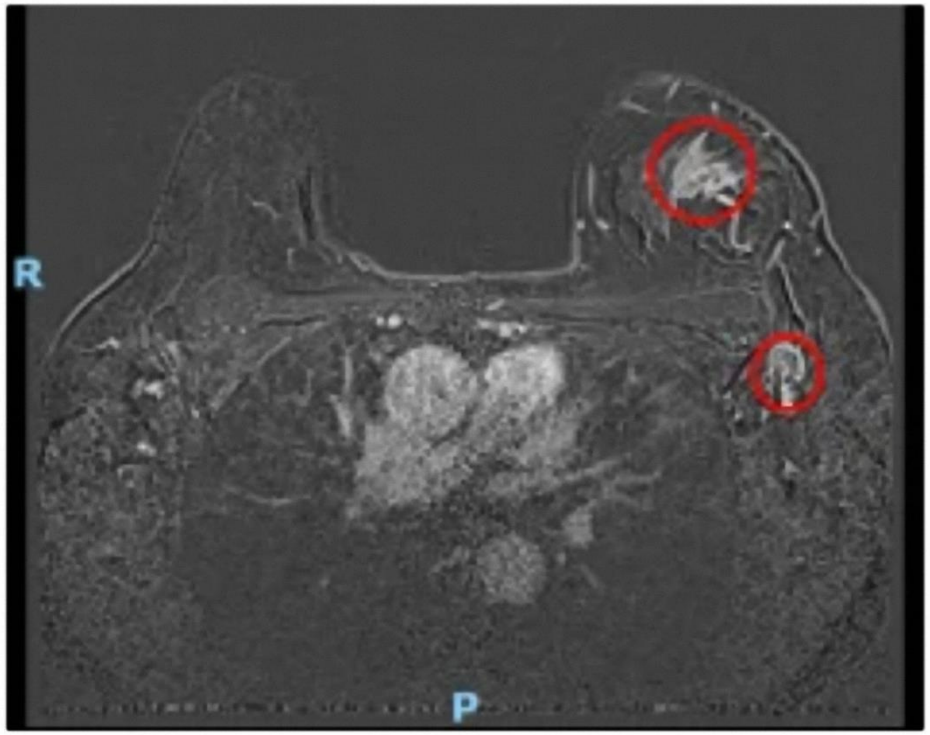
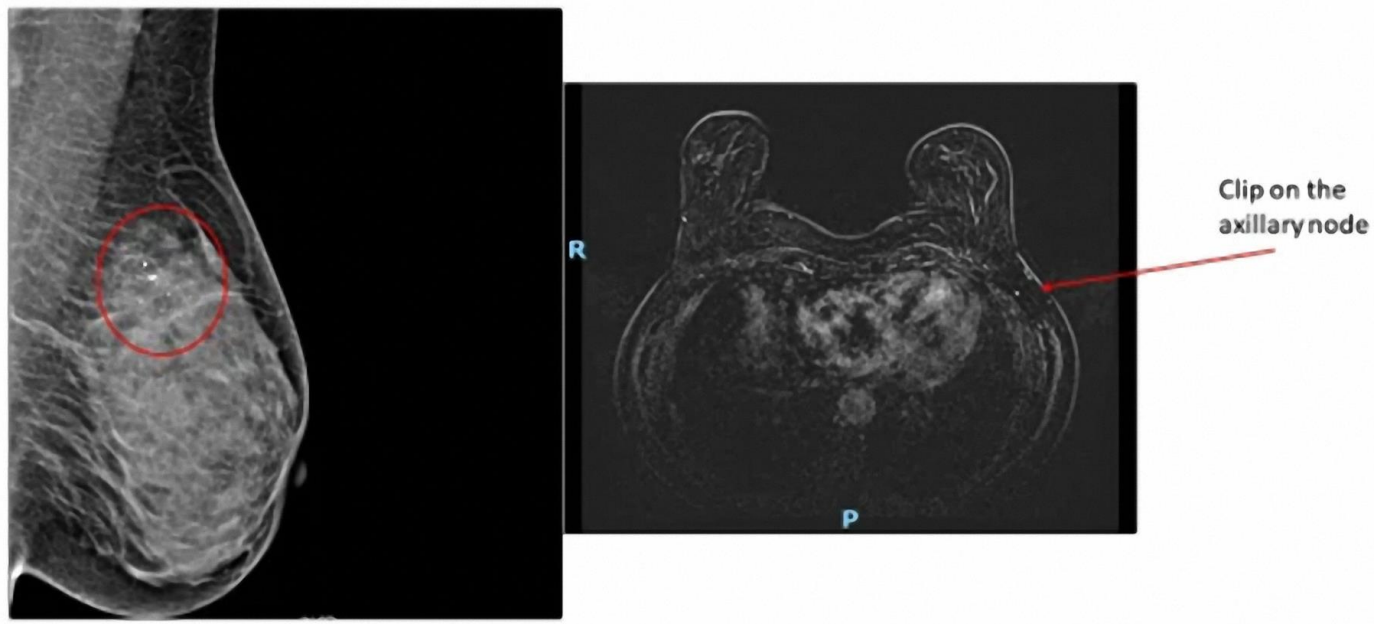


Figure 2. Mammogram and MRI Following Neoadjuvant Therapy Showing Complete Radiologic Response in the Breast and Axilla



IMAGING AND SURGICAL DECISIONS: NACT

-Mammography and US – may give all the necessary information initially and to assess response

-MRI – useful especially if dense breast or complex on mammography. Help assess extent

-Repeat imaging at end of NACT looking for evidence of response in the breast and axilla

-Some centres image during NACT to assess response

-MRI - complete response for HER2+ BC – high correlation with pCR

-Final surgical decision based on initial extent and clinical/radiology response – BC v Mastectomy, SNB/AND

-Excise clip/residual disease and residual calcification

Based on the European Medicines Agency (EMA) definition, does Ruby have a pCR?

- ◯ No, pCR is defined as no invasive disease or in situ disease in breast and lymph nodes (ypT0 ypN0)
- ◯ Yes, pCR is defined as no invasive disease in breast and lymph nodes (ypT0/is ypN0)
- ◯ Yes, pCR is defined as no invasive or in situ disease in breast (ypT0)
- ◯ Yes, pCR is defined as no invasive disease in breast (ypT0/is)

Definition of pCR

Vary between studies

EMA definition

- no invasive disease in the breast or nodes (ypT0/isypN0)
- appropriate end point of clinical trials of NACT

ADRIAMYCIN (ANTHRACYCLINE), CYCLOPHOSPHAMIDE --- (AC)
+ PACLITAXEL (TAXANE)

5-FLUOROURACIL, EPIRUBICIN (ANTHRACYCLINE),CYCLOPHOSPHAMIDE --
(FEC)
+ DOCETAXEL (TAXANE)

+ TRASTUZAMAB +/- (PERTUZUMAB – NOT FUNDED IN NZ) - 1 YEAR

ST GALLEN AND ESMO RECOMMEND DUAL TRASTUZUMAB +
PERTUZUMAB IF HIGHER RISK DISEASE, NODE +VE, HORMONE RECEPTOR
NEGATIVE. PHASE 2 CLINICAL TRIALS SHOW SUPERIOR EFFICACY

Examples of Neoadjuvant Regimes:
Stage 2 or 3 or HER2+ Breast Cancer

RESPONSE RATE
COMPLETE, PARTIAL, STABLE, PROGRESSION

Path pCR rates in the breast and axilla varies by phenotype

	Triple Negative	HER2+	HE+HER2-	
Breast pCR	47.9%	50.2%	15.5%	p<0.0001
Axilla pCR	49.4%	64.7%	21.1%	p<0.0001

Boughey J et al, *Ann Surg* 2014

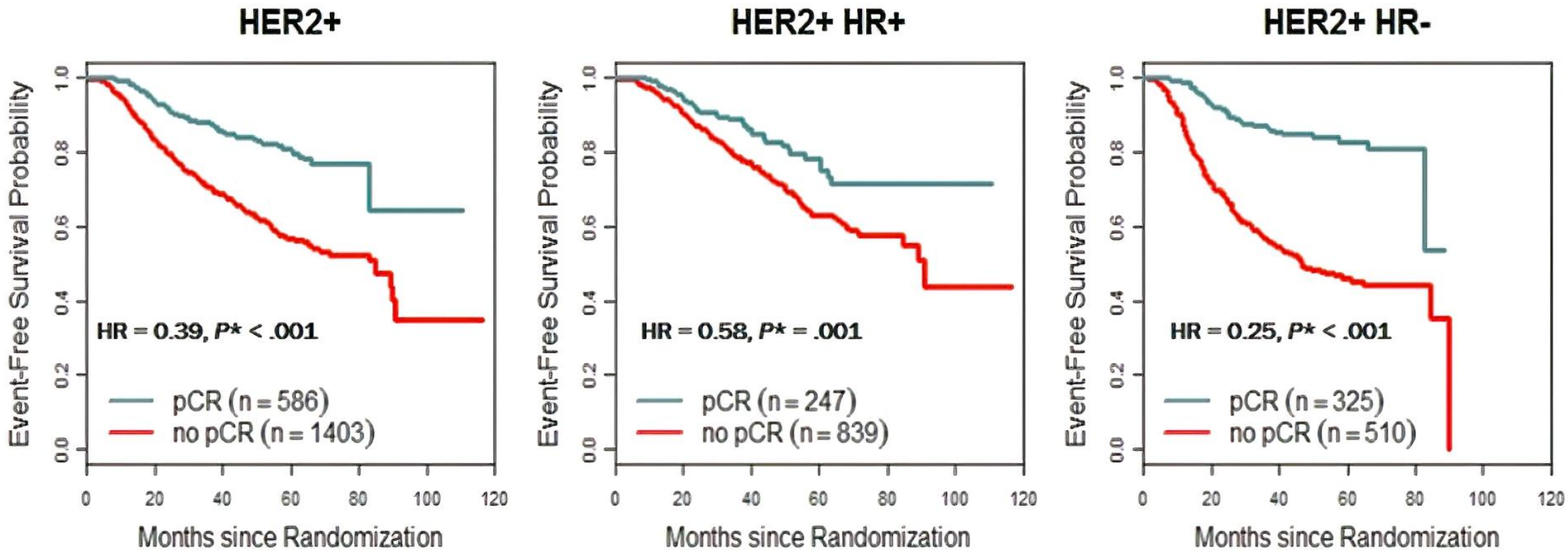
HER2+

Approx 10-15% of early BC

Adjuvant - anthracycline/taxane based chemotherapy or taxane/platinum with HER2-directed antibody transtuzumab

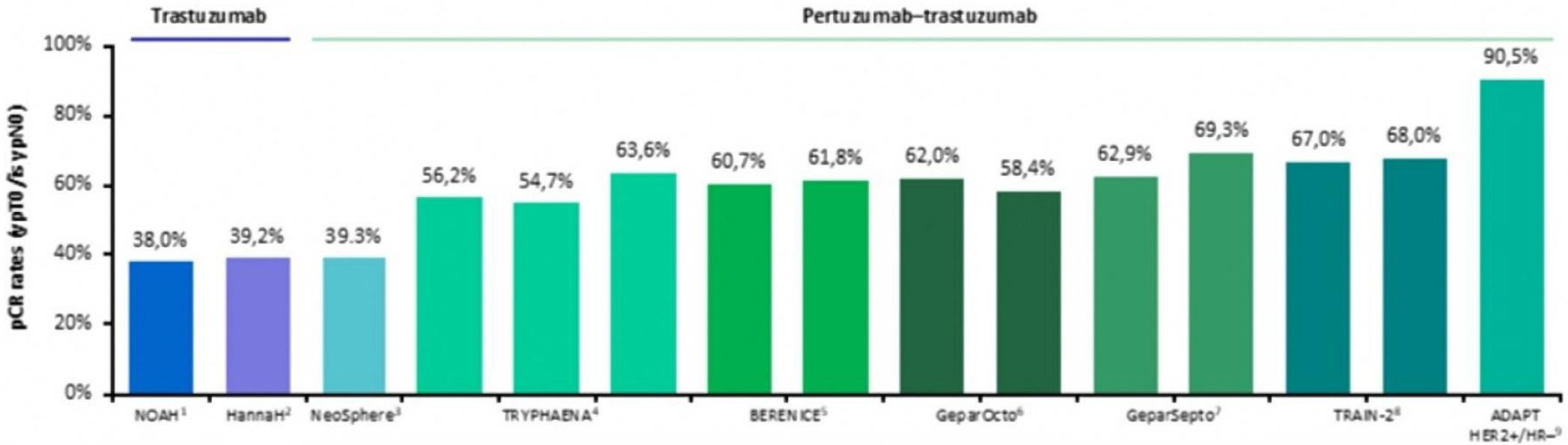
10yr DFS 73.7% and 37% reduction in death

Neoadjuvant Therapy – What Is the Evidence? (cont)



*Nominal *P* value.
pCR = ypT0/is ypN0.
Cortazar P, et al. *Lancet*. 2014;384:164-172.

Neoadjuvant Therapy – Improvement of pCR



Phase	II[1]	III[2]	II[3]	II[4]			II[5]		III[6]		III[7]		III[8]		II[9]
n*	117	260	107	73	75	77	201	199	192	190	197	199	212	206	42
Regimen	AT+H – T+H – CMF+H	Doc+H – FEC+H	Doc/PH	FEC-Doc/PH	FEC-Doc/PH	Cb/Doc/PH	FEC-Doc/PH	ddAC-Pac/PH	E-TC/PH	Pac/NPLD/Cb/PH	Pac-EC/PH	nabPac-EC/PH	FEC-Pac/Cb/PH	Pac/Cb/PH	Pac weekly/PH
Duration of anti-HER2 therapy	33 weeks	24 weeks	12 weeks	18 weeks	9 weeks	18 weeks	18 weeks	20 weeks	12 weeks	18 weeks	24 weeks		27 weeks		12 weeks

* n-values represent number of patients in particular treatment arm.

1. Gianni L, *et al. Lancet* 2010; 2. Ismael G, *et al. Lancet Oncol* 2012; 3. Gianni L, *et al. Lancet Oncol* 2012; 4. Schneeweiss A, *et al. Ann Oncol* 2013; 5. Swain SM, *et al. Ann Oncol* 2018; 6. Schneeweiss A, *et al. Eur J Cancer* 2018 (incl. suppl. info.); 7. Loibl S, *et al. Ann Oncol* 2017; 8. van Ramshorst MS, *et al. Lancet Oncol* 2018; 9. Nitz UA, *et al. Ann Oncol* 2017.

EBC HER2-Positive: Treatment Options 2020 (cont)

Adjuvant "low risk"

$Paclitaxel_{weekly\ x\ 12}$ + Trastuzumab 1 yr

- Low risk of recurrence
- Elderly or frail patients
- T < 2 cm, cN0 (Tolaney)

Adjuvant "at risk"

CHT + Trastuzumab + Pertuzumab

- High risk of recurrence
- Node positive
- ER negative

NACT

Trastuzumab & Pertuzumab

- High risk of recurrence
- Not feasible for "Tolaney regimen"
- Node positive
- T > 2 cm
- Additional risk factor

- pCR: Total duration up to 12 months

Post NACT

T-DM1

- pCR:
- Trastuzumab
- Trastuzumab & pertuzumab

- npCR:
- T-DM1

- Total duration up to 12 months

Courtesy of Christian Jackisch, MD, PhD.

Clin Cancer Res. 2020 June 15; 26(12): 2838–2848. doi:10.1158/1078-0432.CCR-19-3492.

Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis

Laura M. Spring[*,1,3], Geoffrey Fell[*,2], Andrea Arfe[5,*], Chandni Sharma[1], Rachel Greenup[6], Kerry L. Reynolds[1,3], Barbara L. Smith[1,3], Brian Alexander[2,3], Beverly Moy[1,3], Steven J. Isakoff[1,3], Giovanni Parmigiani[2,4], Lorenzo Trippa[#,2,4], Aditya Bardia[#,1,3]

A NEW META-ANALYSIS ADDRESSING MANY OF THE CONCERNS OF SCEPTICS TO NEOADJUVANT CHEMOTHERAPY

PATH CR VS EVENT FREE AND OVERALL SURVIVAL AFTER NACT: SPRING L ET AL

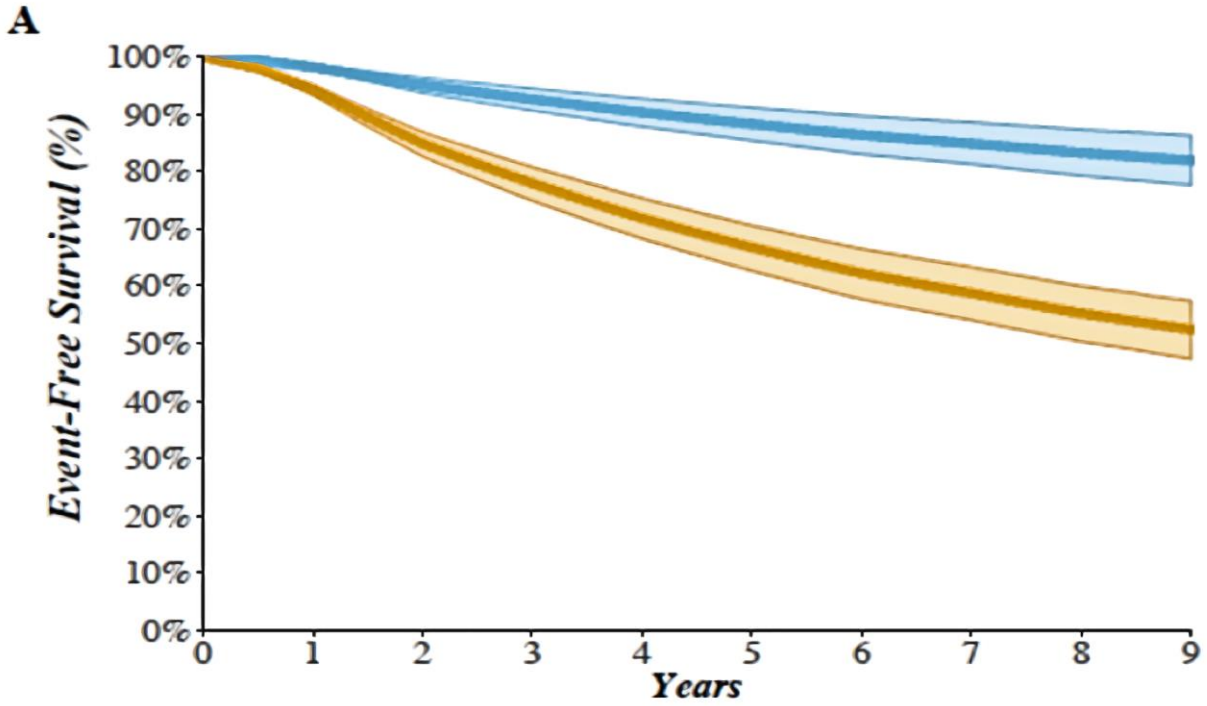
Patients with pCR vs patients with residual disease had significantly better EFS

HR 0.31 (95% CI 0.24 – 0.39)

N=26738

Clin Cancer Res. 2020 June 15; 26(12): 2838–2848. doi:10.1158/1078-0432.CCR-19-3492.

RELATIONSHIP BETWEEN PCR AND EVENT FREE SURVIVAL: SPRING L ET AL



5yr EFS pCR vs RD:
88% vs 67%

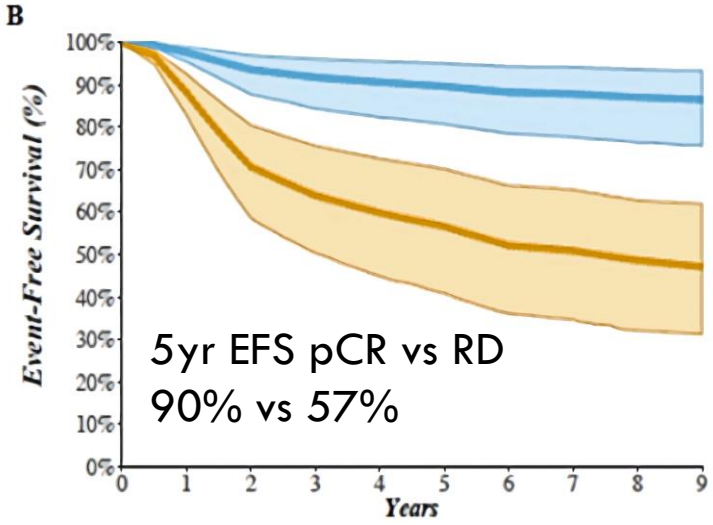
OS:
94% vs 75%

Blue line: pCR group. Orange line: RD group

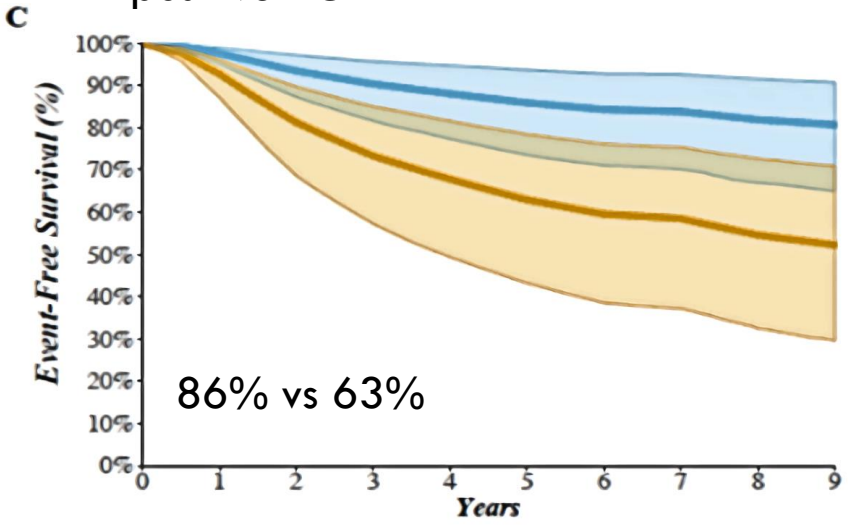
Clin Cancer Res. 2020 June 15; 26(12): 2838–2848. doi:10.1158/1078-0432.CCR-19-3492.

EVENT FREE SURVIVAL PATH CR VS RESIDUAL DISEASE: SUBTYPES

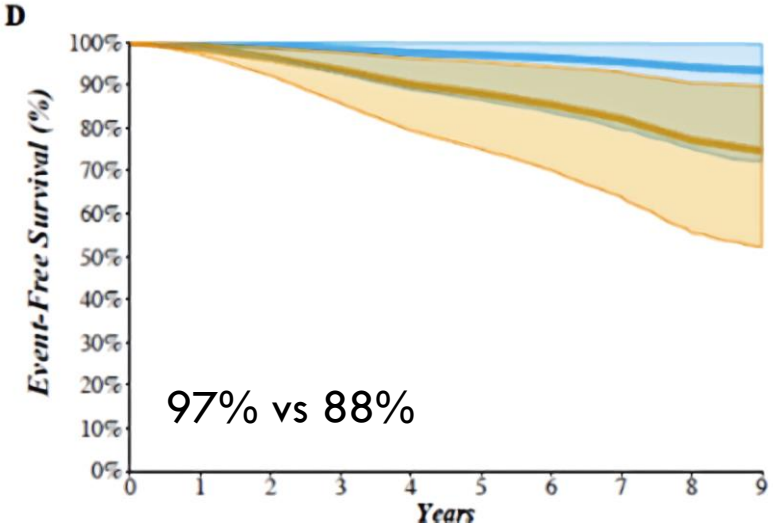
Triple negative BC



HER2 positive BC



Hormone Receptor positive BC



Similar results seen with OS

Blue line: pCR group. **Orange line: RD** group

Clin Cancer Res. 2020 June 15; 26(12): 2838–2848. doi:10.1158/1078-0432.CCR-19-3492.

Tumour size

Breast Size

Patient preference

Response/lack of response

Radiotherapy acceptance for BC

BREAST SURGERY AND NACT
MASTECTOMY VS BREAST CONSERVATION

Preoperative and Intraoperative Localization

Several localization techniques – develop your in-house standard

- Wire-guided techniques (intra- or preoperative)[a]
- Radio-guided occult lesion localization[a]
- Carbon marking[b]
- Clips with bio-resorbable material[c]
- Iodine-125 seeds[d]
- Magnetic seeds
- Intraoperative ultrasound[e]

a. Sajid MS, et al. *J Surg Oncol*. 2012;105:852-858; b. Canavese G, et al. *Eur J Surg Oncol*. 1995;21:47-49; c. Eby PR, et al. *Acad Radiol*. 2010;17:340-347; d. van der Noordaa ME, et al. *Eur J Surg Oncol*. 2015;41:553-558; e. Krekel NM, et al. *Lancet Oncol*. 2013;14:48-54.

THE AXILLA AND NACT: TIMING OF AXILLARY SURGERY

SNB Pre NACT – not recommended, Sentina Trial FNR 52%

Axilla after NACT

- originally negative axilla =>SNB +/- AND
- originally nodes ++ and even with good MRI /clinical resolution =>AND
- originally only few positive nodes (N1) and resolution on MRI – targeted axillary dissection (TAD) + SNB +/- AND. Or go directly to AND

NOTE

1. If micro or macro metastases in SN =>AND
2. Removal of the clipped node during SLN biopsy reduces the false negative rate (FNR) after neoadjuvant therapy from 13.4% to 6.8%
3. Dual localization and 3-4 nodes to reduce FNR

WHEN TO GIVE ADDITIONAL CHEMOTHERAPY?

NACT – only way to identify patients who need additional chemotherapy

pCR – nil further chemotherapy except complete Herceptin

Residual disease (HER2 positive or negative) - 20-30% chance of relapse

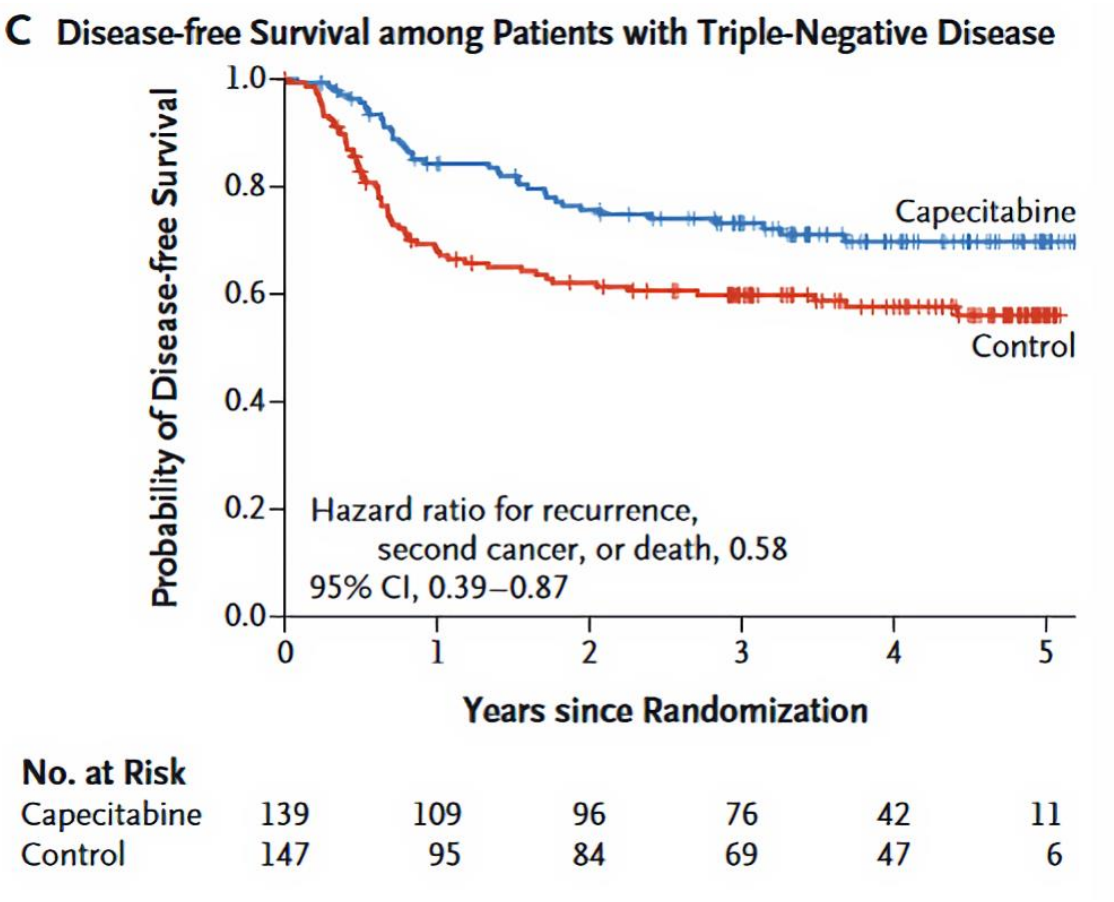
HER2 negative – Capecitabine – oral prodrug of fluorouracil

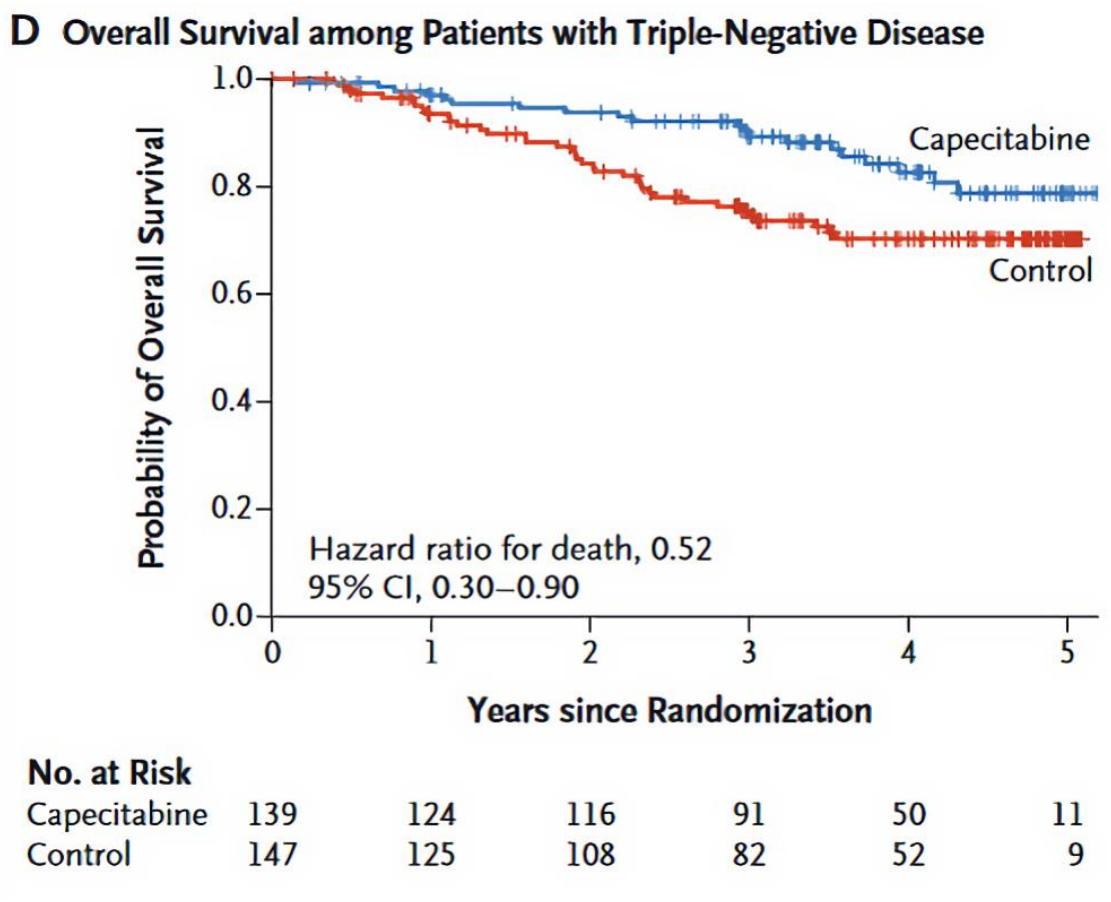
HER2 positive – T-DM1 (in NZ funded for advanced BC and not as adjuvant Rx)

Study of Post NACT in Her2 Negative (Triple Negative) Patients without pCR

Capecitabine vs Control (CREATE-X trial):455 patients in each arm of study at initial randomization.

Masuda N Engl J Med 2017; 376: 2147-59





The NEW ENGLAND JOURNAL of MEDICINE

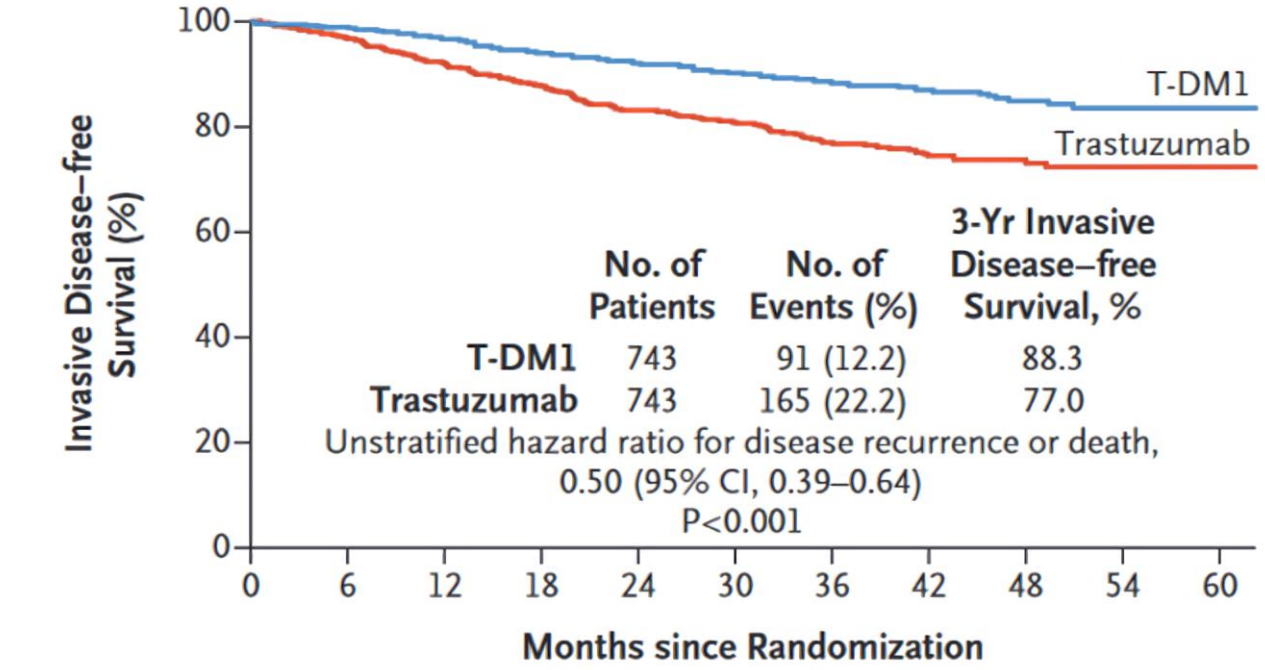
ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

Katherine study: Trastuzumab Emtansine for Residual Invasive HER-2 Positive Breast Cancer

A subgroup with residual disease can benefit from TDM1



KATHERINE STUDY DESIGN AND CONCLUSIONS

Initial Her2+ BC Rx Chemo, Trastuzumab +/- Pertuzumab

Subgroup with residual disease in breast or axilla

Randomized to T-DM1 (Trastuzumab emtansine = Kadcyla) v Trastuzumab after surgery

50% reduction of breast cancer recurrence at 3 years

Increase of DFS 77.0% to 88.3%

Reduced distant recurrence 15.9% to 10.5%

Without NACT this group would not have been identified

Conclusions

- Neoadjuvent therapy is not a risk factor for local failure
- Resection within the new margins after NACT seems to be safe and is a major goal in multidisciplinary treatment
- No patient should be excluded from BCT, as long as negative margins can be obtained
- Surgeons have to learn to trust in the capabilities of neoadjuvant therapy to reduce the extent of surgery for better cosmetic outcomes without oncologic compromise

GENE EXPRESSION ASSAYS ASSESSMENT OF RISK

Early-Stage ER+/PR+/HER2- Breast Cancer
Introduction

- Treatment consists primarily of endocrine therapy
- In recent years, the role of chemotherapy has changed to be used mainly in patients at high risk or possibly intermediate risk for recurrence
- Assessing risk levels poses some challenges
- Several factors are involved in determining risk level

Assessing Risk for Recurrence

Determining Risk

NCCN includes[a]:

- Clinical characteristics
- Axillary status
- Pathology

ESMO includes[b]:

- Tumor burden (≥ 4 LNs, T3 or higher)
- Luminal A-like vs luminal B-like subtype
  - Luminal A: good prognostic factor
  - Luminal B: bad prognostic factor

a. NCCN Guidelines®. Breast cancer. V5.2020; b. Cardoso F, et al. *Ann Oncol*. 2019;30:1194-1220.

Other Approaches to Assessing Risk

- Ki67 cell proliferation marker
  - Difficult to reproduce results between institutions
  - Use is controversial
  - Very low or very high expression is precise in predicting risk
    - Low-risk tumor vs high-risk tumor
  - However, most luminal tumors express Ki67 within a small range, so distinguishing luminal A vs luminal B tumors is difficult
- Tumor grading
  - Analysis is subjective
  - Pathologists don't have equal expertise
  - Reproducing results is not consistent

Dowsett M, et al. *J Natl Cancer Inst*. 2011;103:1656-1664.

Gene Expression Assays in ER-Positive, HER2-Negative Breast Cancer: The Latest Evidence, Guidelines, and Implications

Commonly used gene expression assays for early stage breast cancer include:

- Oncotype DX® (21-gene panel).
- MammaPrint® (70-gene panel; "Amsterdam signature").
- EndoPredict® (EP and EPclin scores).
- Prosigna® PAM50-ROR® (Breast Cancer Intrinsic Classifier)

Luminal Early Breast Cancer Pn0-1: Chemotherapy Indications

- Need to be well substantiated clinical by tumour burden and tumour biology (ER, PR, HER2, Ki67, grade)
- Gene expression assays may help in decision-making.
  - Several assays are evidence-based, but not all are well validated for all patient groups
  - Utilization and reimbursement differ in different countries.
  - Prospective data for chemotherapy decision-making are available for Oncotype DX®,(21-gene panel) and MammaPrint® (70-gene panel; "Amsterdam signature").

Gene Expression Assay Options

NCCN Guidelines

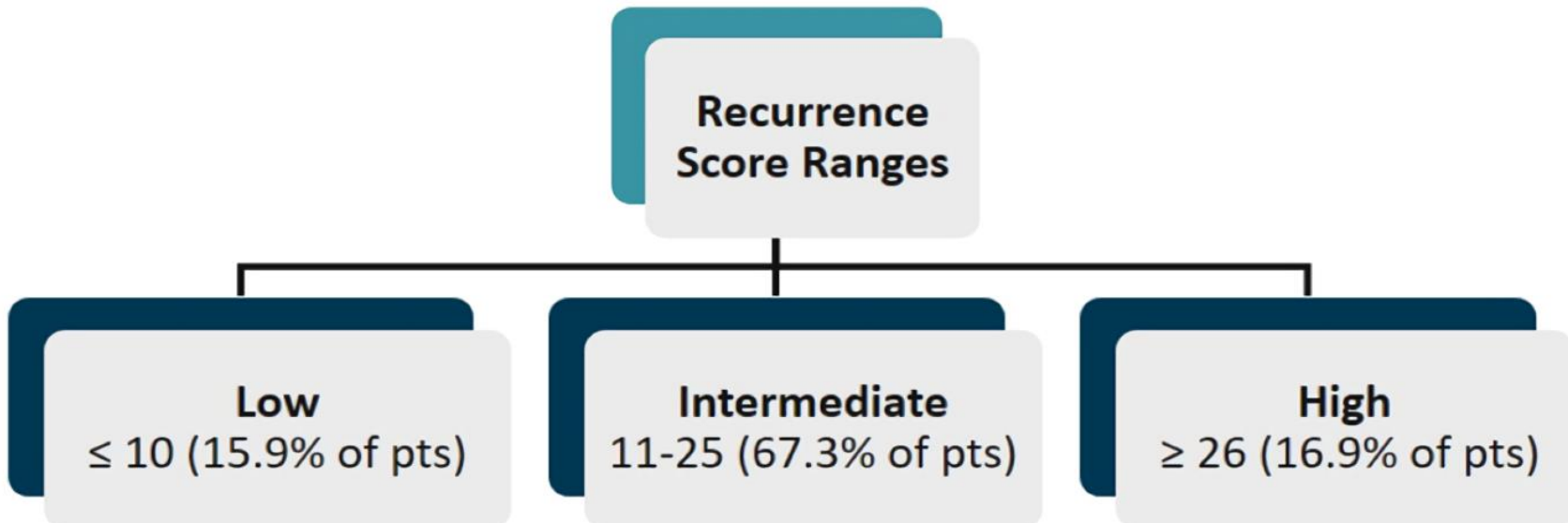
Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus
21-gene (Oncotype Dx) (for pN0 or node negative)	Yes	Yes	Preferred	1
21-gene (Oncotype Dx) (for pN+ or node positive)	N/A*	Yes	Other	2A
70-gene (MammaPrint) (for node negative and 1-3 positive nodes)	Not determined	Yes	Other	1
50-gene (PAM50) (for node negative and 1-3 positive nodes)	Not determined	Yes	Other	2A
12-gene (EndoPredict) (node negative and 1-3 nodes)	Not determined	Yes	Other	2A
Breast Cancer Index (BCI)	Not determined	Yes	Other	2A

*Awaiting results of RxPONDER study.
NCCN Guidelines®. Breast cancer. V5.2020.

TAILORx: 21-Gene (Oncotype Dx)

Study Design

- Conducted in North America by ECOG
- 10,253 patients with ER+/PR+/HER2-, node-negative, invasive BC



- Low- and high-recurrence score groups were registry studies, whereas intermediate-recurrence score group was randomized to either ET or CET

Sparano JA, et al. *N Engl J Med*. 2015;373:2005-2014.

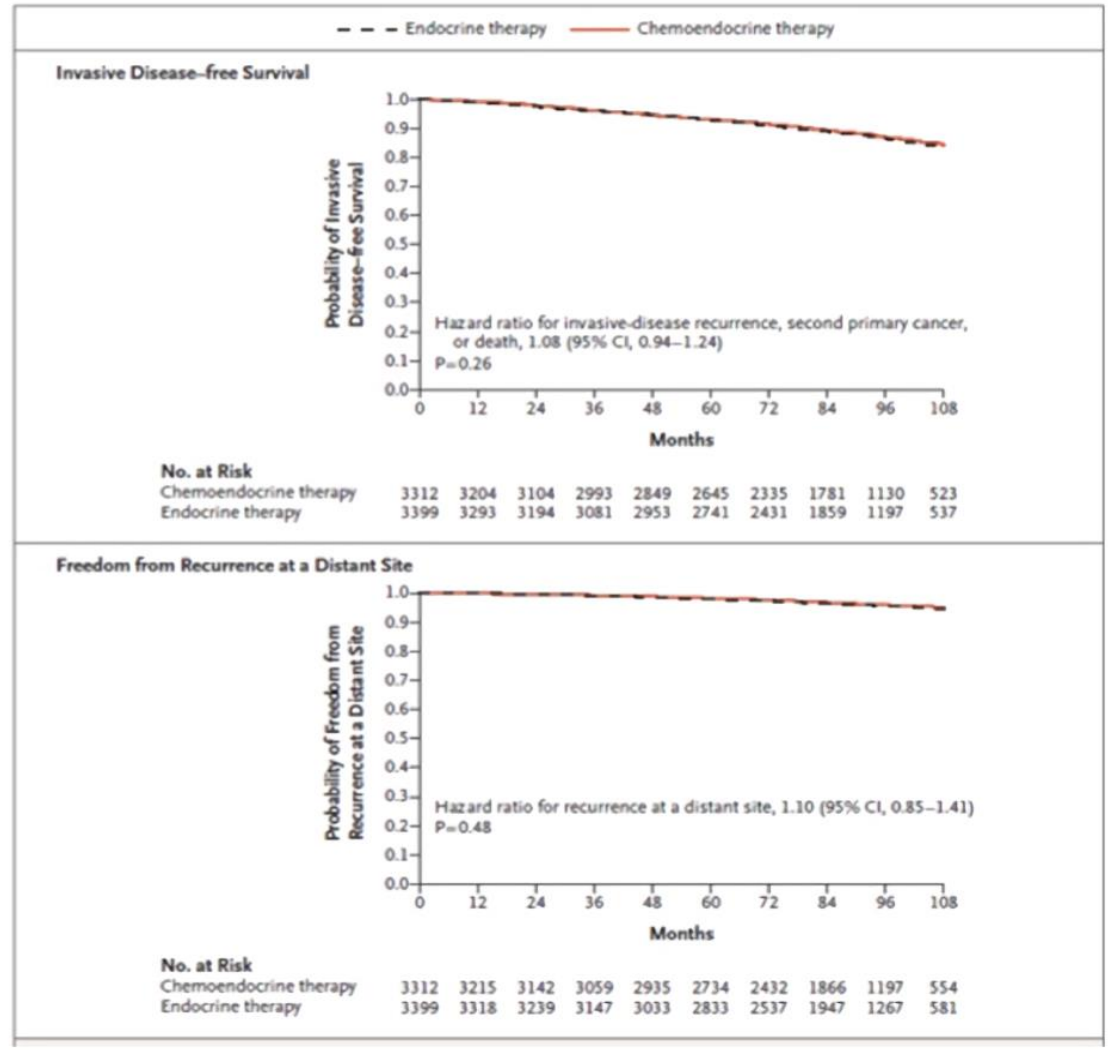
TAILORx: 21-Gene (Oncotype Dx)

Intermediate Score Group

- Patients randomized to either ET or CET
- Results at 9 years
- No benefit from chemotherapy for overall group
- Benefits from chemotherapy in women aged < 50 years
  - May be due to CT-induced ovarian suppression

Endpoint	ET	CET
Freedom from disease recurrence at distant or local-regional site, %	92.2	92.9
OS, %	93.9	93.8

Sparano JA, et al. *N Engl J Med.* 2018;379:111-121.



Integrating Clinical Factors With Genomic Scores
TAILORx Analysis

- Clinical-risk stratification (based on tumor size and histologic grade) added to the 21-gene recurrence score provided prognostic information about recurrence

Women aged < 50 years had estimated chemotherapy benefit in reducing distant recurrence at 9 years if they had either:

- Recurrence score of 16-20 with high clinical risk, OR
- Recurrence score of 21-25 regardless of clinical risk

Sparano JA, et al. *N Engl J Med*. 2019;380:2395-2405.

Oncotype DX test costs about $4,000.00

Public Summary Document

Application No. 1342.5 Gene expression profiling of 21 genes in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit

Applicant: Specialised Therapeutics Australia Pty Ltd

Date of MSAC consideration: MSAC 76th Meeting, 1-2 August 2019

Australian Government

Medical Services Advisory Committee

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for this gene expression profiling test for patients with breast cancer primarily because its ability to identify those who could safely be spared the addition of chemotherapy to endocrine therapy was not demonstrated by the new trial. The re-analysis of previously provided evidence was also insufficient to change the previous conclusion that the test could not satisfactorily identify those intermediate-risk patients who would benefit from the addition of chemotherapy to endocrine therapy.

70-Gene Signature Test (MammaPrint)
Overview

Comparison With 21-Gene Oncotype Dx[a]

- Developed around the same time
- Developed for a different population of patients
- Signature derived from a study with a distinct population of patients
  - Younger and all-comers population vs ER+ population (Oncotype Dx)
- Exceptionally well-validated assay
  - **NCCN Guidelines[b]**
    - Category 1 recommendation
    - Level 1 evidence

a. Cardoso F, et al. *N Engl J Med*. 2016;375:717-729; b. NCCN Guidelines®. Breast cancer. V5.2020.

MINDACT Trial

Study Design

- Phase 3 trial; N = 6693 women
- Early-stage breast cancer
- Looked for genomic risk using MammaPrint and clinical risk
- Low clinical risk
  - Low-grade tumor, < 3 cm
  - Intermediate-grade tumor, < 2 cm
  - High-grade tumor, < 1 cm

Goal of Study

Assess whether chemotherapy is necessary in patients with high-risk clinical features and low-risk gene expression profile (n = 1550)

Cardoso F, et al. *N Engl J Med*. 2016;375:717-729.

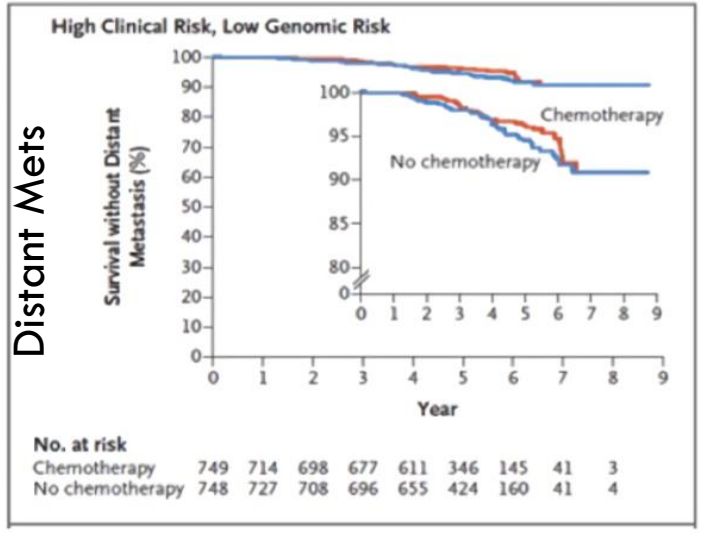
MINDACT Trial

Results

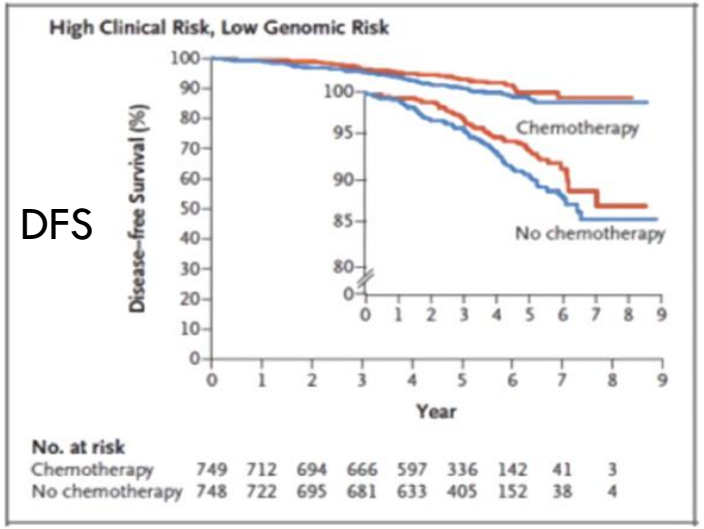
High Clinical Risk + Low Genomic Risk

- Rate of survival at 5 years without distant metastasis: 94.7%
  - Absolute difference in survival rate between those who received and did not receive chemotherapy was 1.5%

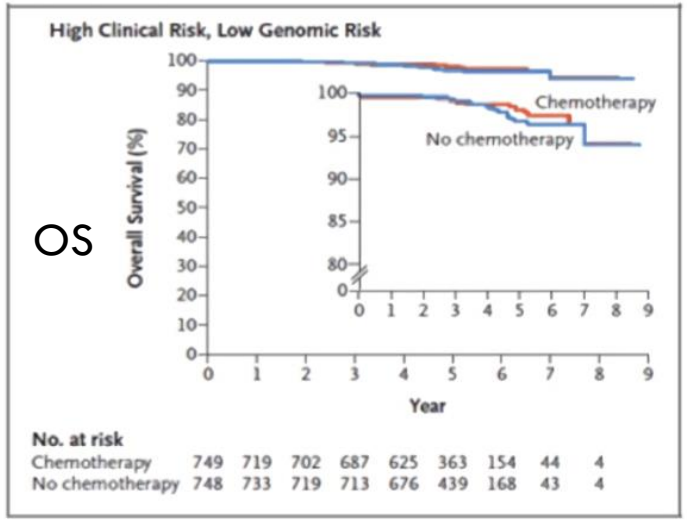
Survival & No Distant Mets



DFS



OS



Determining genomic risk in patients with high clinical risk for BC recurrence is important in deciding who might benefit from adjuvant chemotherapy

Cardoso F, et al. *N Engl J Med*. 2016;375:717-729.

Integrating Clinical Factors With Genomic Scores
MINDACT Analysis

Unplanned Analysis: 5-year DMFS

Patients aged > 50 years	• Similar among those who received and did not receive chemotherapy (95.2% vs 95.4%)
Patients aged 40-50 years	• 96.2% for patients who received chemotherapy vs 92.6% for those who did not

- One possible reason for this age-based benefit from chemotherapy may be that women who are near menopause but whose ovaries are still producing estrogen are rendered postmenopausal by the chemotherapy
- Findings require confirmation due to small subsets of these populations

Piccart MJ, et al. SABCS 2019. Abstract GS4-05.

Faculty Discussion on Management of Breast Cancer Based on Oncotype Dx and MammaPrint

- Used to overtreat patients with chemotherapy
  - Guideline recommendations: treat all tumors ≥ 1 cm with chemotherapy
- ER+/HER2- patients and all-comers were treated to get 5% absolute benefit in DFS but caused a lot of AEs
  - Chronic irreversible toxicity (eg, cardiotoxicity, leukemias, etc) and acute adverse effects (eg, alopecia)
- Genomic platforms have changed management of early-stage breast cancer
  - Help determine appropriate therapy and minimize risk by avoiding use of chemotherapy in majority of patients
  - Should be integrated into decision-making process in all countries

Late Relapse in Breast Cancer

Faculty Discussion

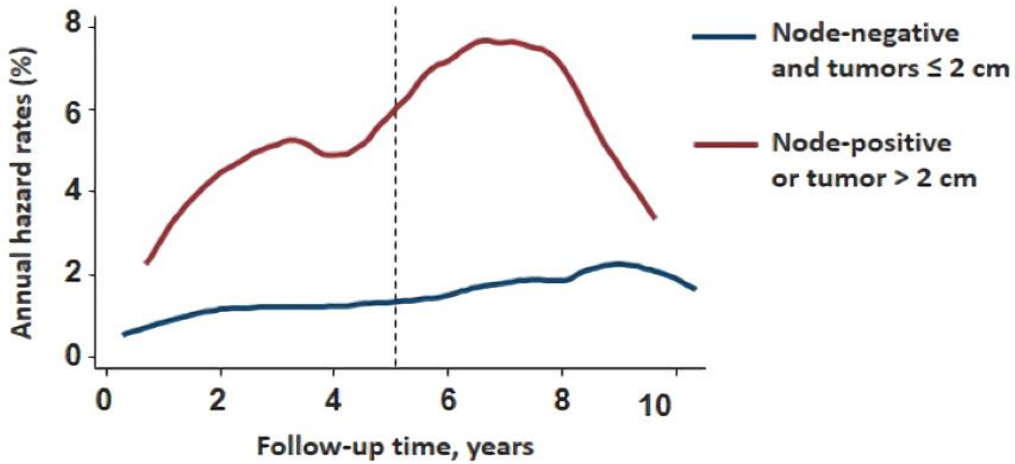
~50% of ER+ patients will have a recurrence ≥ 5 years from diagnosis

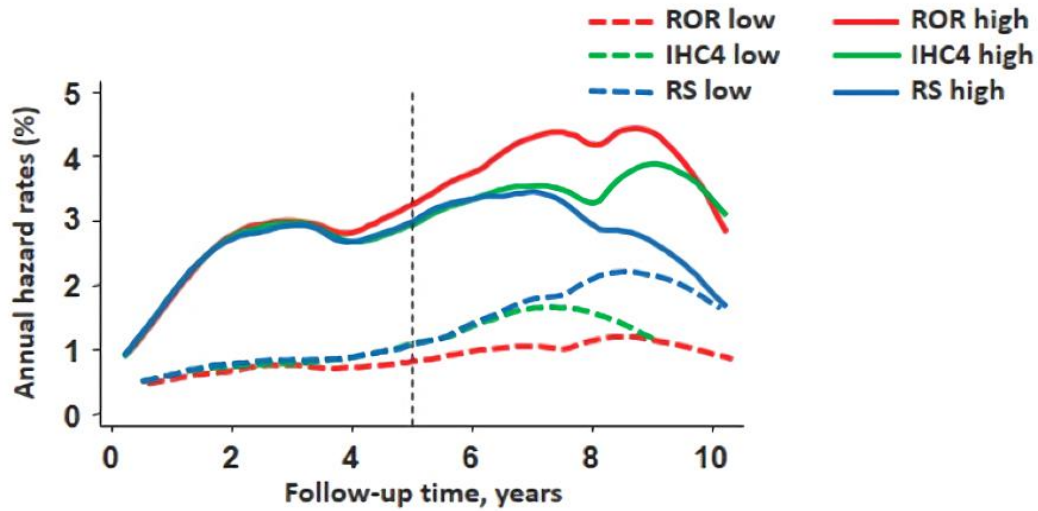
Assays (eg, 21-gene Oncotype Dx) are good at identifying which patients will benefit, in terms of early recurrence, with a reduction in chemotherapy

Late recurrence, as far out as 20 years, continues to be an issue

Even when assays predict who might have a recurrence, they don't indicate what treatment to offer patients who are fated to have a late recurrence

Late Recurrence: PAM50 ROR Score vs Oncotype Dx and IHC4 for Predicting Risk of Distant Recurrence After ET





- Nodal status and tumor size are key prognostic indicators of both early and late recurrence
- PAM50 ROR risk groups provide wider separation of hazards for death beyond 5 years compared with IHC4 and Oncotype DX

Hope for novel, biologic assays (eg, circulating tumor DNA, cell-free DNA) to provide a better handle on late recurring cancers

Sestak I, et al. *J Natl Cancer Inst.* 2013;105:1504-1511.

Concluding Remarks

- Toxicity associated with chemotherapy should be avoided if possible
- Genomic assays -- such as the 21-gene Oncotype Dx, the 70-gene MammaPrint, EndoPredict, and Prosigna -- allow us to predict patient populations that do not benefit from chemotherapy
- Data up until now has focused on patients with HR+/HER2- BC who are at high risk for early recurrence
- Work still needs to be done to identify patients who are at risk for late recurrence and to define therapies for that population