Faculty Biography

Matthew Goetz, MD, is Professor of Oncology and Pharmacology at Mayo Clinic in Rochester, Minnesota.

Dr. Goetz received his medical degree from the University of North Dakota School of Medicine. He completed his post-graduate training with an internship and residency in internal medicine at the University of Michigan and a fellowship in hematology/oncology at the Mayo Clinic College of Medicine.

Dr. Goetz's clinical and research interests include pharmacogenomics of anticancer therapy and breast cancer drug development. Specifically, his research focuses on estrogen receptor-positive breast cancer and the development of new treatments for hormone receptor-positive breast cancers that resist hormonal therapies.

With funding from the National Institutes of Health, Dr. Goetz has served as principal investigator and co-principal investigator for a number of clinical trials, is co-PI for the Mayo Breast Cancer SPORE and co-leader of the Women's Cancer Program at the Mayo Clinic. He has devoted research to identifying specific genetic differences that may impact the effectiveness of breast cancer treatments. His other research has sought to identify genetic mutations and changes to cancer pathways before and after neoadjuvant chemotherapy.

Dr. Goetz is a member of the NCCN Breast Cancer Panel.

Faculty Biography

Sarika Jain, MD, MSCI, is Assistant Professor in the Division of Hematology/Oncology at Northwestern University Feinberg School of Medicine and the Northwestern Medicine Developmental Therapeutics Institute at Robert H. Lurie Comprehensive Cancer Center.

Dr. Jain received her medical degree from the Southern Illinois University School of Medicine. She completed an internship and residency in internal medicine at the University of Michigan and a hematology/oncology fellowship at Weill Cornell Medical College - New York Presbyterian Hospital. She is board-certified in internal medicine with subspecialties in hematology and medical oncology.

Dr. Jain's current clinical research focuses on investigating novel targeted agents in the treatment of breast cancer. She has received numerous awards for her research, including the Scott Wadler Memorial Fellow Clinical Research Award and the Lynn Sage Foundation Scholar Award.

Dr. Jain has served as an ad-hoc reviewer for the *Annals of Oncology* and *Breast Cancer Research and Treatment.* She also is a member of a number of professional societies, including the American Society of Clinical Oncology, the American Association for Cancer Research, Women in Cancer Research, and the ECOG-ACRIN Cancer Research Group.

Faculty Biography

Cesar A. Santa-Maria, MD, is Assistant Professor of Medicine in the Division of Hematology/Oncology at Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital.

Dr. Santa-Maria received his medical degree from the University of Texas at Houston Medical School. He completed his residency in internal medicine at the University of Texas Southwestern Medical School and a fellowship in medical oncology at the Sidney Kimmel Cancer Center at Johns Hopkins. He is board-certified in internal medicine with a subspecialty in medical oncology.

Dr. Santa-Maria's goal as a clinical translational investigator is to bring new therapeutic agents and strategies from the laboratory into clinical practice. In particular, his research examines ways of stimulating the immune system to fight breast cancer.

Dr. Santa-Maria has received numerous awards and grants for his research from several organizations, including the American Society of Clinical Oncology (ASCO), the San Antonio Breast Cancer Symposium (SABCS), and other research foundations. Additionally, Dr. Santa-Maria has served as an editorial reviewer for a number of scientific publications, including *Breast Cancer Research and Treatment*, *Cancer*, and the *Journal of Clinical Oncology*. He also is an active member of ASCO and the American Association for Cancer Research.

2016

NCCN CONGRESS SERIES™

National Comprehensive Cancer Network

Role of Multigene Assays in the Management of Early Stage Breast Cancer

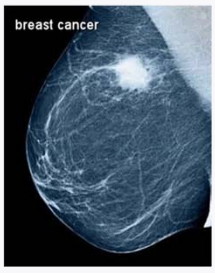
Matthew P. Goetz, MD

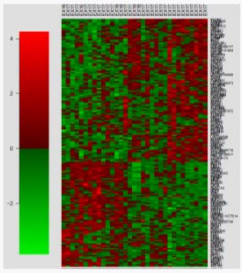
Mayo Clinic Cancer Center

Outline

- Precision Medicine
- The importance of the estrogen receptor
- Multi-gene assays in early stage cancer:
- Use of multi-gene assays for “prediction” of drug benefit
- Moving beyond multi-gene panels: what are the next steps?

Precision Medicine

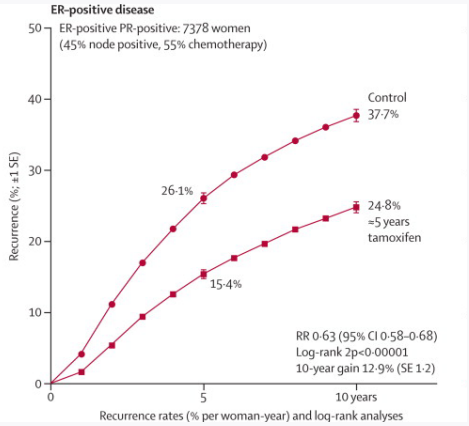




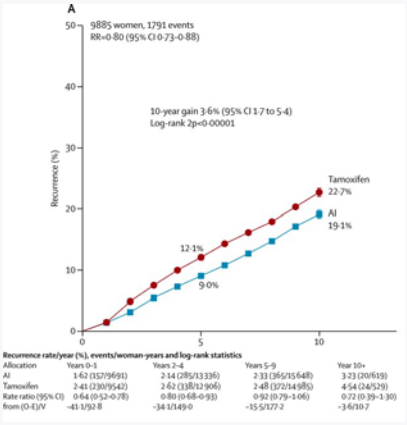
Application of “omic” analysis and systems biology to analyze the cause of the patient’s disease and to utilize targeted treatments to address the disease process.

Tamoxifen and Aromatase Inhibitors: Adjuvant Treatment of Postmenopausal ER+ Breast Cancer

Tamoxifen vs Control

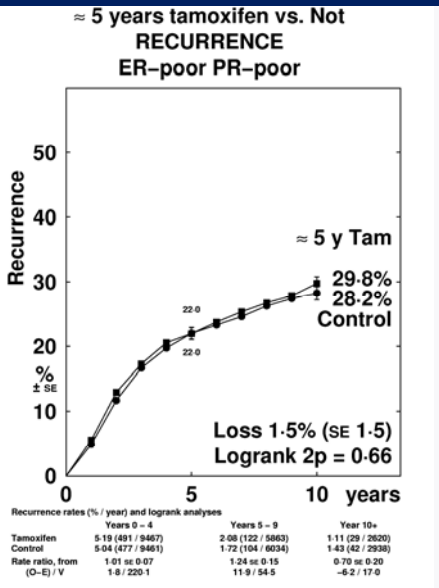


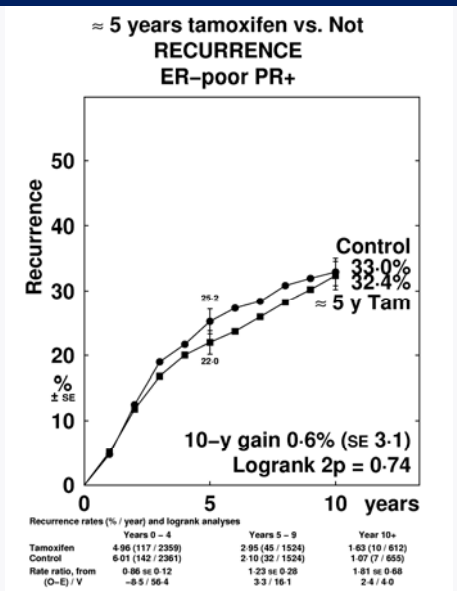
AI's vs Tamoxifen



Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2011 and 2015

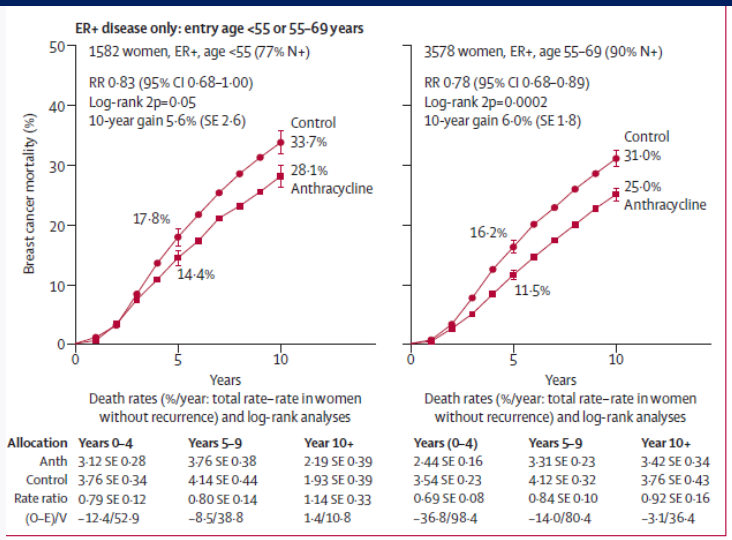
Tamoxifen for ER Negative Breast Cancer





Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2011

Modest benefit of Polychemotherapy (Oxford Overview)



Allocation	Years 0–4	Years 5–9	Year 10+	Years (0–4)	Years 5–9	Year 10+
Anth	3·12 SE 0·28	3·76 SE 0·38	2·19 SE 0·39	2·44 SE 0·16	3·31 SE 0·23	3·42 SE 0·34
Control	3·76 SE 0·34	4·14 SE 0·44	1·93 SE 0·39	3·54 SE 0·23	4·12 SE 0·32	3·76 SE 0·43
Rate ratio	0·79 SE 0·12	0·80 SE 0·14	1·14 SE 0·33	0·69 SE 0·08	0·84 SE 0·10	0·92 SE 0·16
(O–E)/V	−12·4/52·9	−8·5/38·8	1·4/10·8	−36·8/98·4	−14·0/80·4	−3·1/36·4

Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2012

Summary

- **Three decades of work focused on understanding the biology of ER breast cancer**
  - **Accurate identification of ER**
  - **Huge benefit of adjuvant hormonal therapy in ER+ but not ER- breast ca**
  - **Modest benefit of adjuvant chemotherapy**
- **Major goal: Identify molecular signatures to select patients that can avoid systemic chemotherapy**

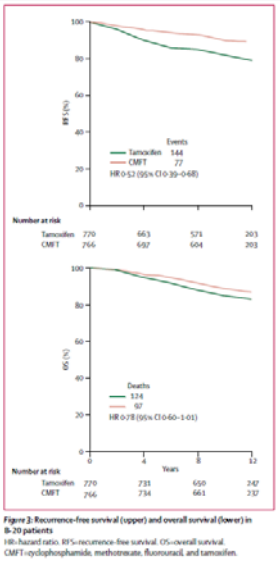
Common Clinical Scenario

- 58 y/o female with mammographically detected breast cancer
- Lumpectomy
  - Invasive Ductal, Grade 2
  - 3.5 cm
  - SLN: Negative
  - ER>75%+, PR > 75% +, HER2 1+ IHC
- Adjuvant! Online: 20-30% risk of recurrence

Chemotherapy and Tamoxifen Node Negative, ER+ Breast Cancer

Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials

Bernard Fisher, Jong-Hyeon Jeong, John Bryant, Stewart Anderson, James Dignam, Edwin R Fisher, Norman Wolmark

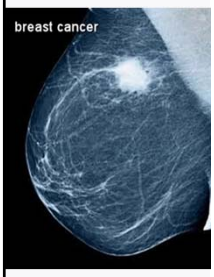


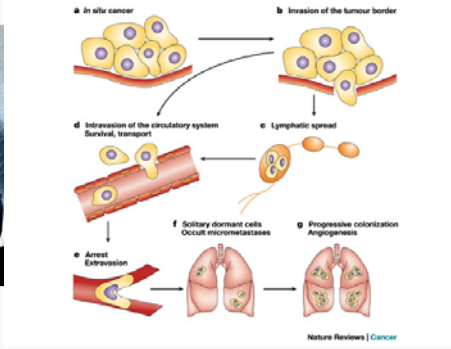
Benefit from CMF+ tamoxifen vs tamoxifen alone (HR for recurrence-free survival 0·52, 0·39–0·68, p<0·0001

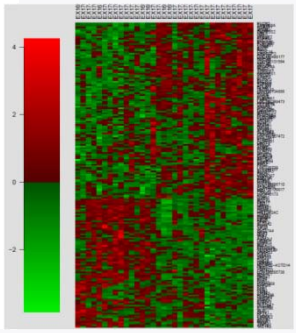
Question: Should all lymph node negative patients receive chemotherapy?

Fisher 2004 Lancet

Heterogeneity of Breast Cancer

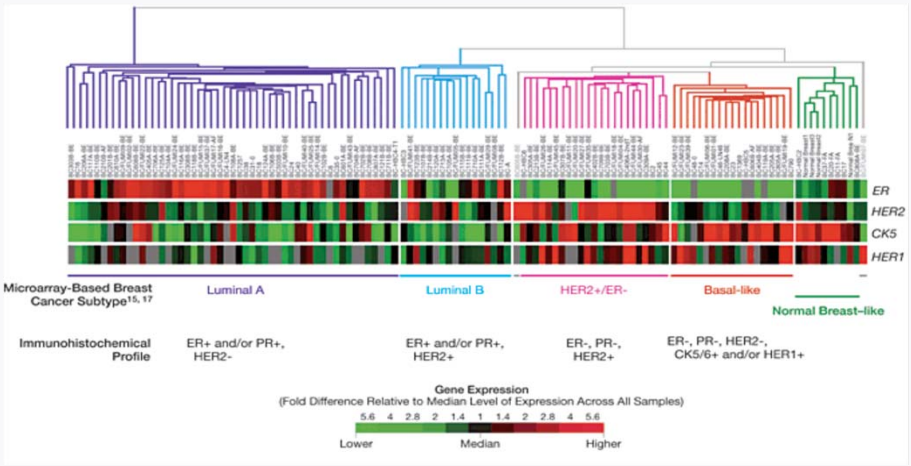






Sorlie et a al PNAS 2003

Breast Cancer Molecular Subtypes

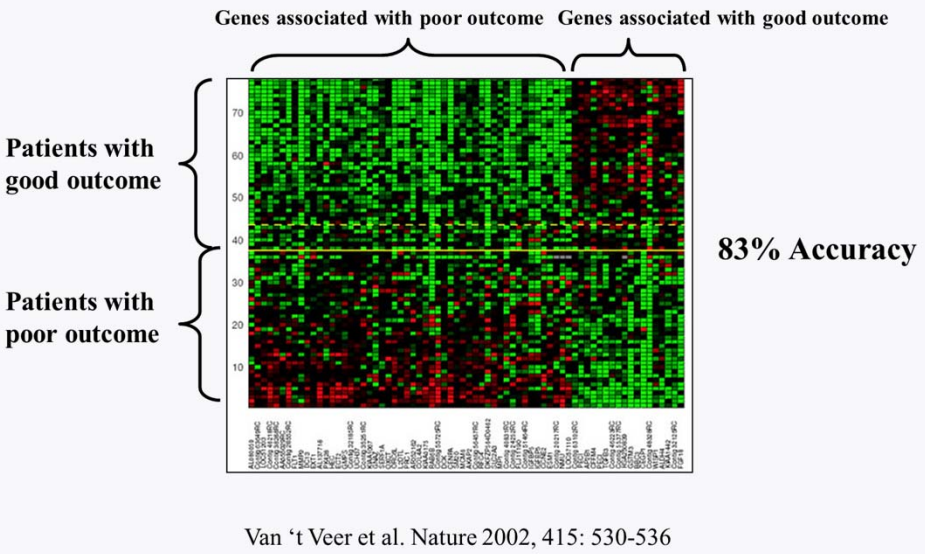


TCGA. Nature. 2012.

Gene Expression Profiling: Validated Breast Cancer Biomarkers

	Prognostic Overall recur(0-10 yrs)	Prognostic Late Recur (5-10 yrs)	Predicts Adjuvant Chemotherapy Benefit	Predicts Neo-Adjuvant Chemotherapy Benefit	Predicts Adjuvant Endocrine Benefit	Predicts Extend Adjuvant Endocrine Benefit
Mammaprint	Yes	No	Not assessed	Yes	Not Assessed	Not Assessed
OncotypeDx	Yes	No	Yes	Yes	Yes	Not Assessed
BCI	Yes	Yes	Not assessed	Yes	Yes	Yes
PAM50	Yes	Yes	Not assessed	Yes	Not assessed	Not assessed
GGI	Yes	No	Not assessed	Yes	Not assessed	Not assessed
Endopredict	Yes	Yes	Not assessed	Yes	Yes	Not assessed

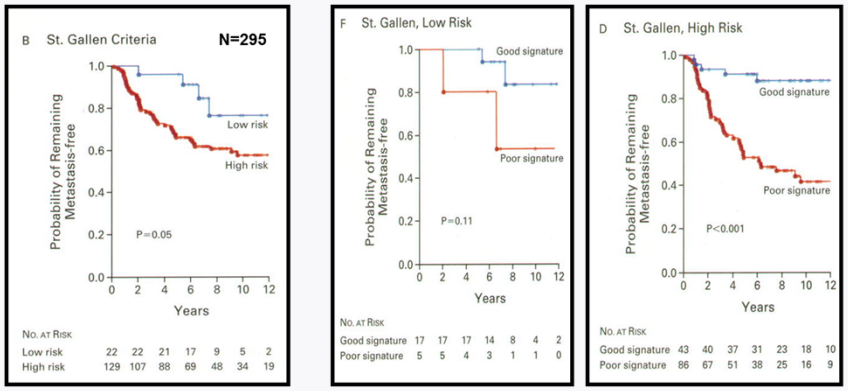
Mammaprint



Van 't Veer et al. Nature 2002, 415: 530-536

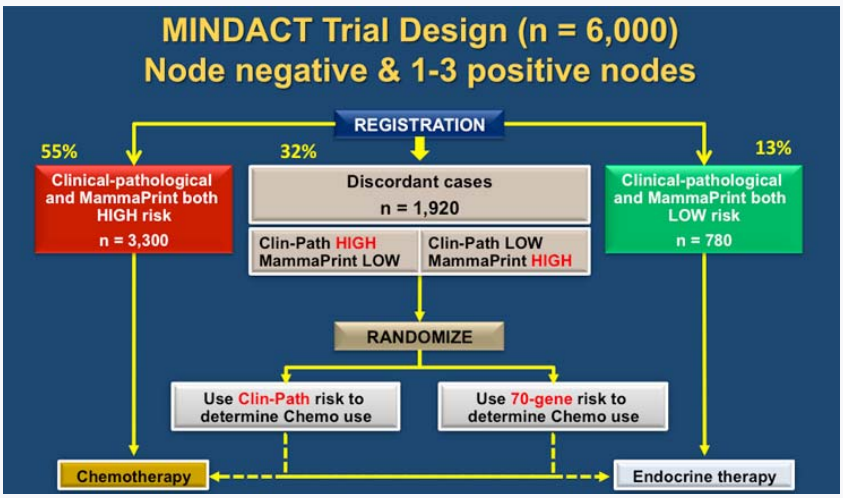
Mammaprint

Subgroup Analysis: St.Gallen High and Low Risk Patients Using 70-Gene Prognosis Signature

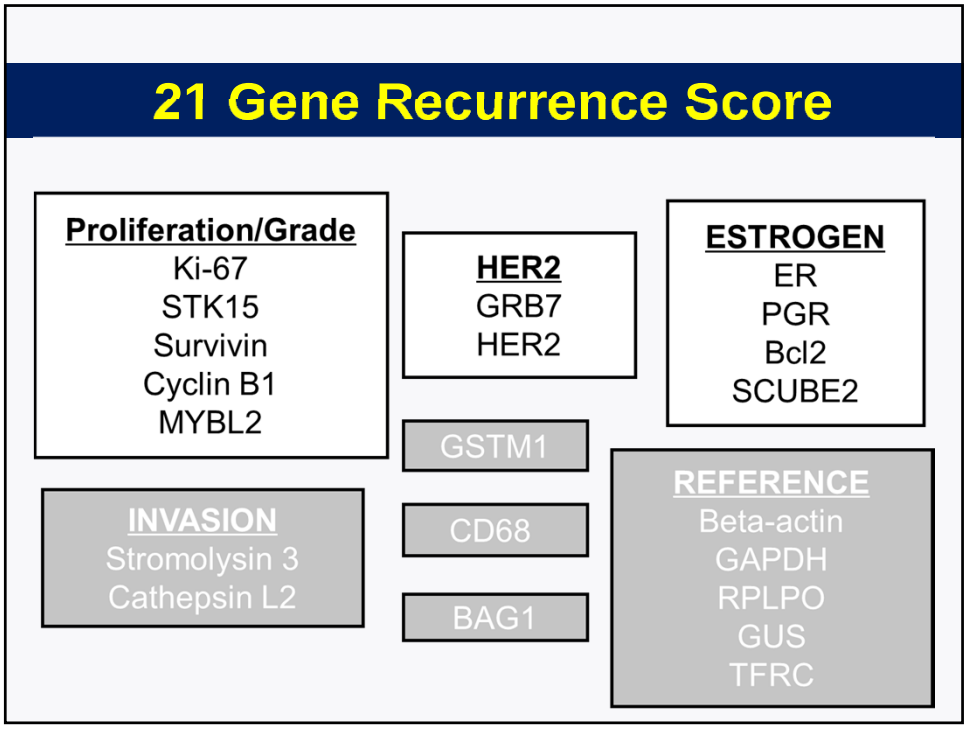


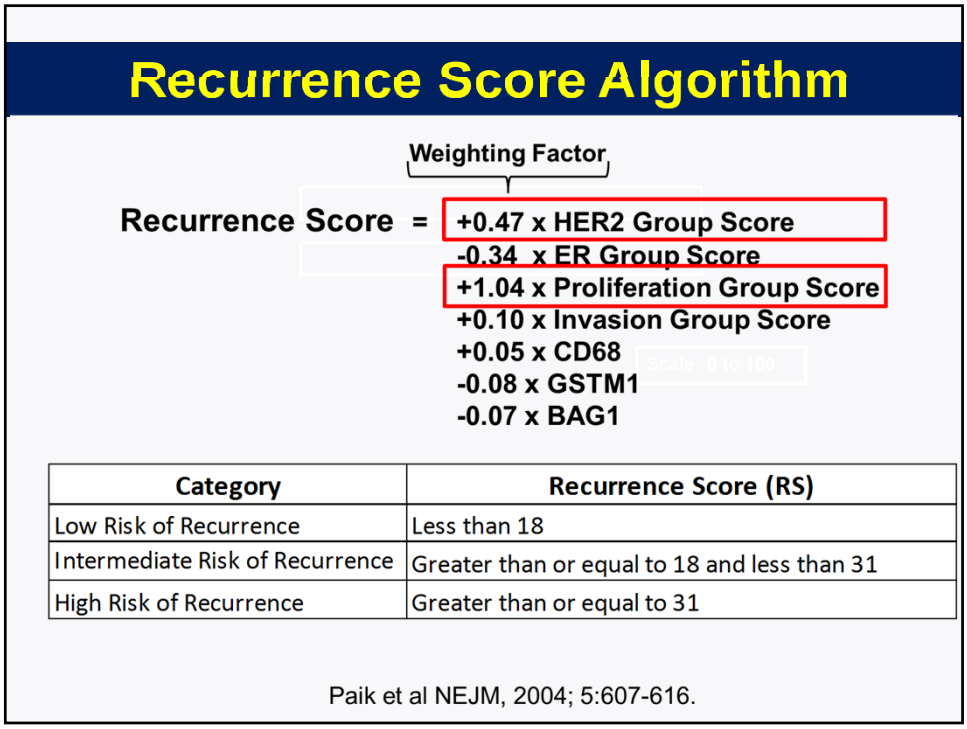
van de Vijver et al NEJM 2002, 347: 1999-2009

Prospective Validation of MammaPrint



Clinical Trial ID: NCT00433589

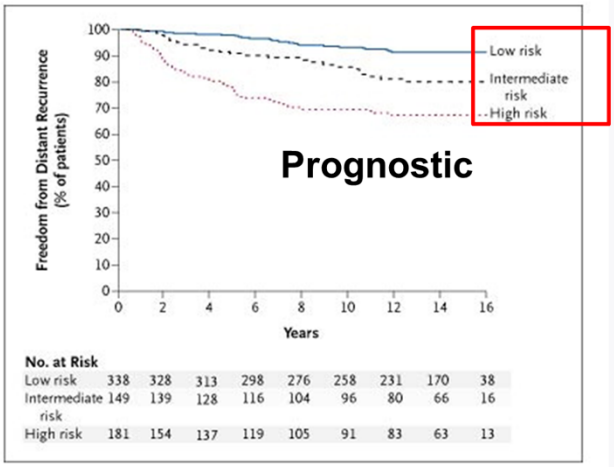




Category	Recurrence Score (RS)
Low Risk of Recurrence	Less than 18
Intermediate Risk of Recurrence	Greater than or equal to 18 and less than 31
High Risk of Recurrence	Greater than or equal to 31

Paik et al NEJM, 2004; 5:607-616.

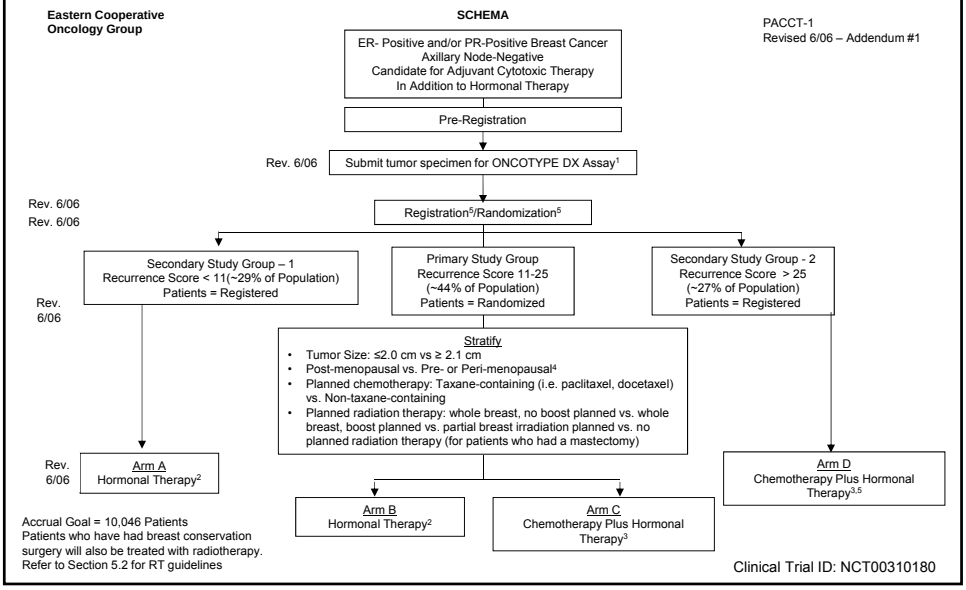
21 Gene Recurrence Score: Distant Recurrence in NSABP B14



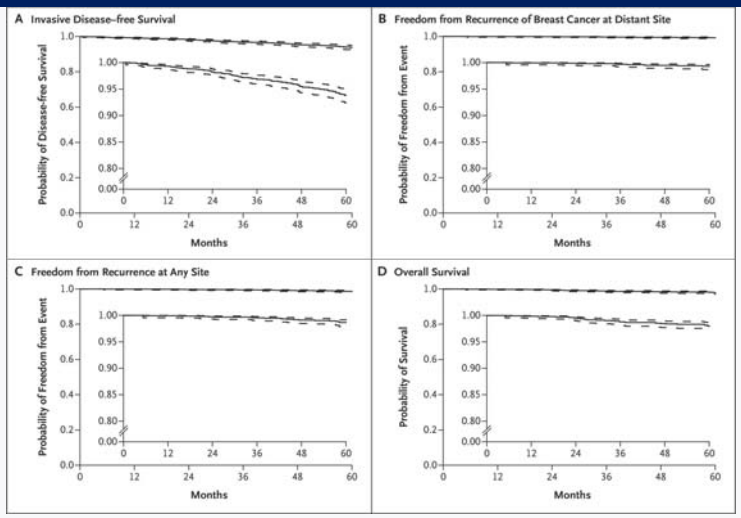
The difference among the three recurrence score (RS) groups is significant (P<0.001)

Paik et al. N Engl J Med 2004

Prospective Validation of 21 gene Recurrence Score (PACCT-1)

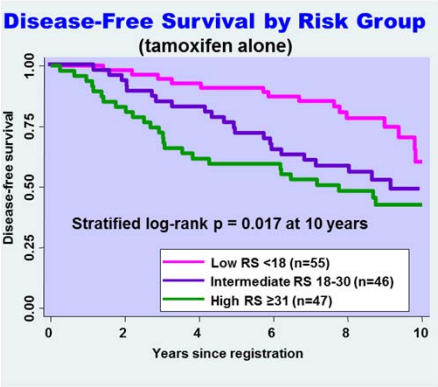


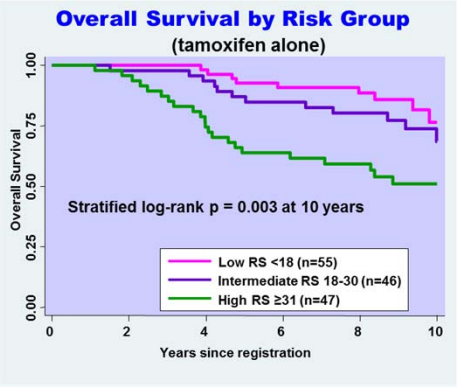
Kaplan–Meier Estimates of Key Endpoints
1626 patients with a recurrence score of 0 to 10.



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

OncotypeDx: SWOG 8814:





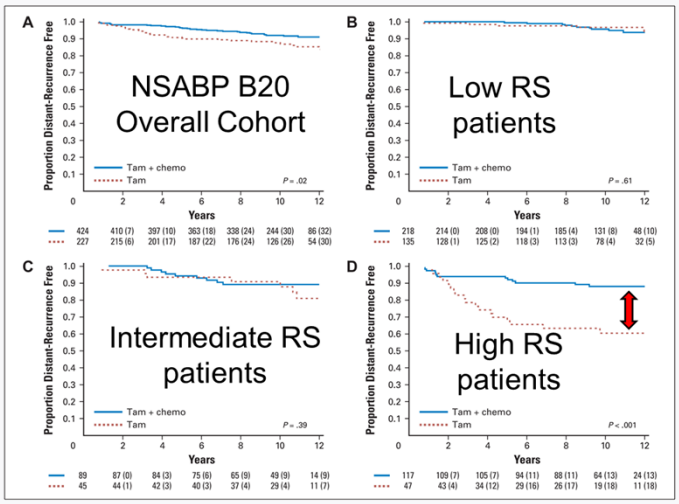
Albain KS et al. Lancet Oncol 2010, 11:55-65

Assessment of Chemotherapy Response

Can multi-gene panels predict drug response?

Most multi-gene panels are heavily weighted towards "proliferation" genes and thus "high risk" patients may gain the greatest benefit from systemic chemotherapy

Recurrence Score: Benefit of chemotherapy Restricted to High-Risk Group



Paik et al. JCO, 2006; 24: 3726

Recurrence Score Proliferation Gene Group Associated with Chemotherapy Benefit

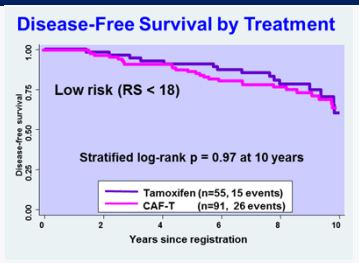
Table 2. Likelihood Ratio Tests of the Interaction of Chemotherapy Treatment With the Clinical Variables and the Gene Expression Variables

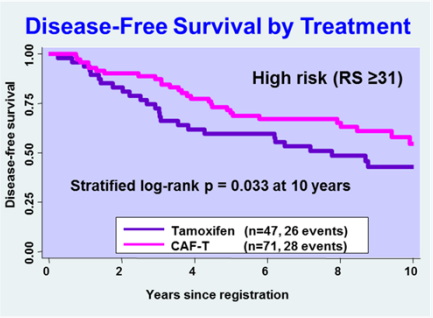
	Assessable B20 Patients (n = 651)				All B20 Patients (N = 2,299)			
Variable	HR	Lower 95%	Upper 95%	*P*	HR	Lower 95%	Upper 95%	*P*
Clinical variables								
Age ≥ 50 years*	2.02	0.75	5.47	.162	1.78	1.06	2.97	.029
Tumor size > 2 cm†	1.34	0.49	3.68	.569	0.76	0.45	1.27	.293
Quantitative ER ≥ 50‡	1.96	0.73	5.30	.183	1.54	0.92	2.57	.099
Quantitative PR ≥ 50‡	1.87	0.70	4.97	.214	0.76	0.45	1.27	.289
Grade site§								
Poor	0.27	0.02	3.01	.284	0.31	0.09	1.04	.057
Moderate	0.60	0.06	6.42	.672	0.51	0.15	1.70	.273
Grade, pathologist A								
Poor	0.73	0.19	2.89	.657	—	—	—	—
Moderate	1.04	0.23	4.58	.963	—	—	—	—
Grade, pathologist B					—	—	—	—
Poor	0.32	0.06	1.77	.192	—	—	—	—
Moderate	0.36	0.06	2.03	.244	—	—	—	—
Gene expression variables‖					—	—	—	—
Recurrence score¶	0.32	0.11	0.94	.038	—	—	—	—
Proliferation gene group-TH**	0.33	0.11	0.94	.039	—	—	—	—
MYBL2	0.67	0.45	1.00	.050	—	—	—	—

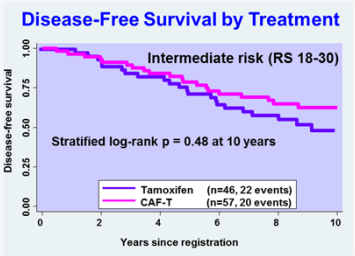
The 5 genes in the proliferation group display the same performance as the entire 16 genes in the OncotypeDx assay.

Paik et al. JCO, *2006;* 24: 3726

Recurrence Score and Chemotherapy Response in SWOG 8814

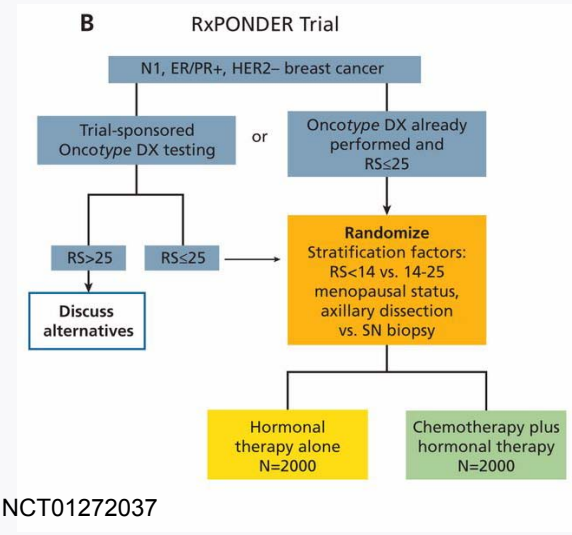




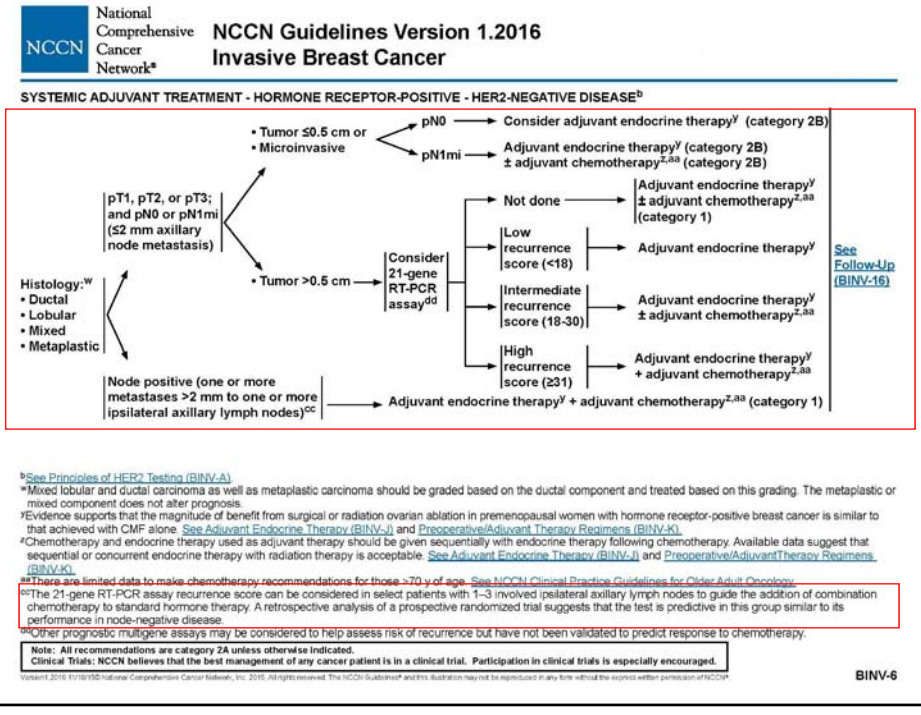


Albain KS et al. Lancet Oncol 2010, 11:55-65

Prospective Validation of Recurrence Score in Node Positive Breast Cancer



Clinical Trial ID: NCT01272037



ASCO Biomarker Guidelines:

Key Points and Recommendations

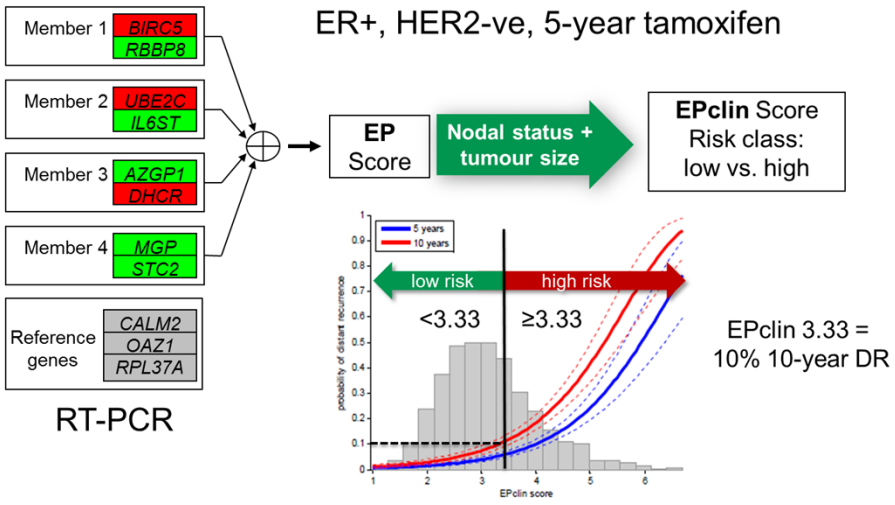
For women with early-stage invasive breast cancer and with known ER/PgR and HER2 status, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

Oncotype DX

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the 21-gene recurrence score (RS; Oncotype DX; Genomic Health, Redwood City, CA) to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 21-gene RS to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the 21-gene RS to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.

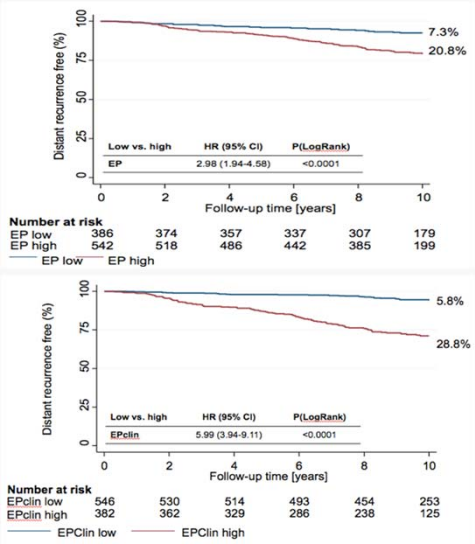
Harris LN et al. JCO published online on February 8, 2016; DOI:10.1200/JCO.2015.65.2289

EndoPredict



Filipits et al, Clin Cancer Res 2011, 17:6012

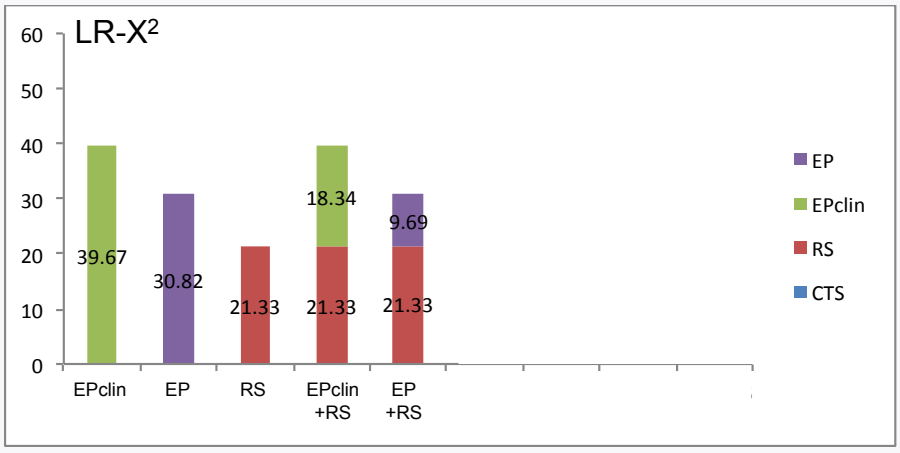
EP vs EPclin in ATAC



Distant recurrence rate according to pre-specified risk stratification in TransATAC: EP vs EPclin: all patients

Dowsett et al. SABC 2015

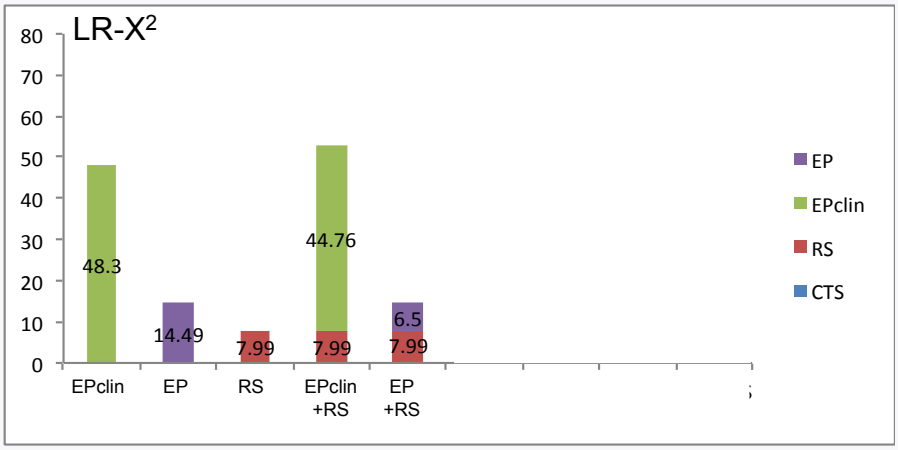
Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node negative



Based on 10-year risk of distant recurrence

Dowsett et al. SABC 2015

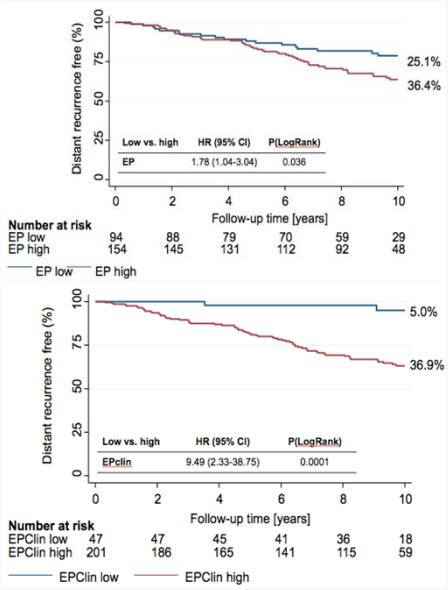
Comparison of prognostic information provided by EP, EPclin and RS in TransATAC: node positive



Based on 10-year risk of distant recurrence

Dowsett et al. SABC 2015

Epclin node positive in ATAC



Distant recurrence rate according to pre-specified risk stratification in TransATAC: EP vs EPclin: node positive

ASCO Biomarker Guidelines: Endopredict

EndoPredict

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Köln, Germany) to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: insufficient. Strength of recommendation: moderate.
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.

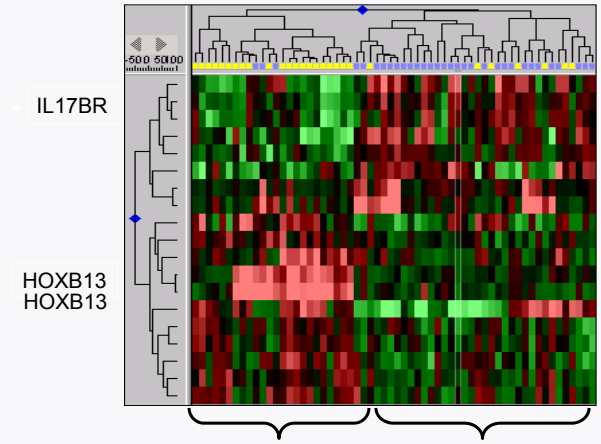
Harris LN et al. JCO published online on February 8, 2016; DOI:10.1200/JCO.2015.65.2289

Breast Cancer Index (BCI)

- The BCI biomarker consists of **two independently developed** biomarkers for ER+ LN- Breast Cancer:
  - *HOXB13:IL17BR (H/I) gene expression ratio*
    - Estrogen–signaling related genes that are both prognostic[1,2] and predictive for hormonal therapy benefit[3].
    - Developed independent of tumor grade/proliferation
  - *Molecular Grade Index (MGI)*
    - 5 cell cycle-related genes that predicts for distant recurrence (prognostic) beyond tumor grade[4]

[1] Goetz et al. CCR 2006,12: 2080-7. [2] Ma et al. JCO 2006, 24:4611-9.
[3]Sgroi et al. J Clin Oncol (2011) 29: (suppl 27; abstr 2). [4] Ma et al. CCR 2008,14: 2601-8.

HOXB13/IL17BR



High H/I

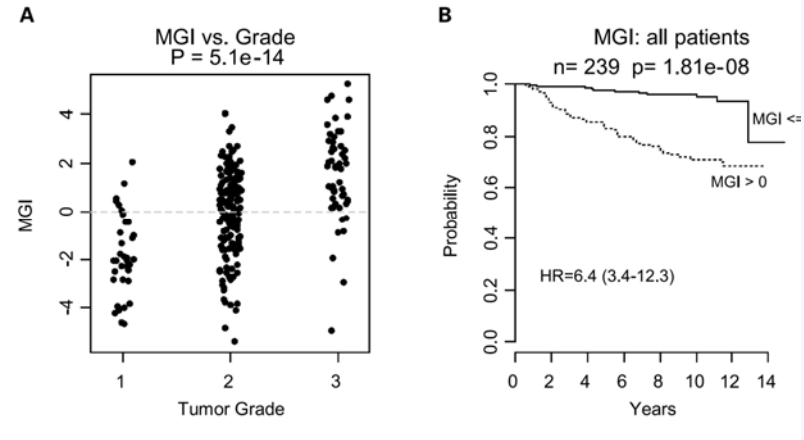
Poor Outcome: Relapse in setting of Adjuvant Tamoxifen

Good Outcome: Relapse-free in setting of Adjuvant Tamoxifen

Low H/I

Ma et al . Cancer Cell, 2004; 5: 607-616.

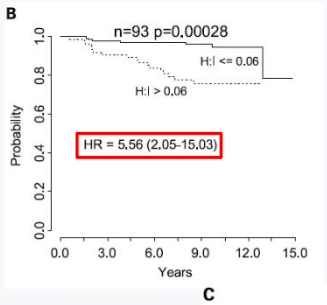
Molecular Grade Index (MGI)

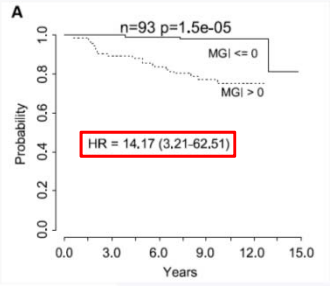


Ma et al. Clin Cancer Res., 2008; 14: 2601-2608.

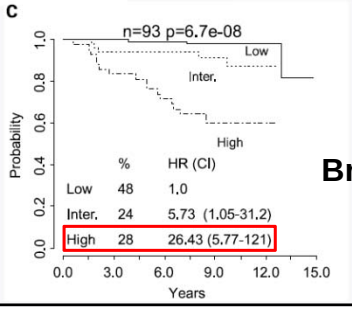
H/I and MGI are Additive in their Prognostic Value

H/I





MGI

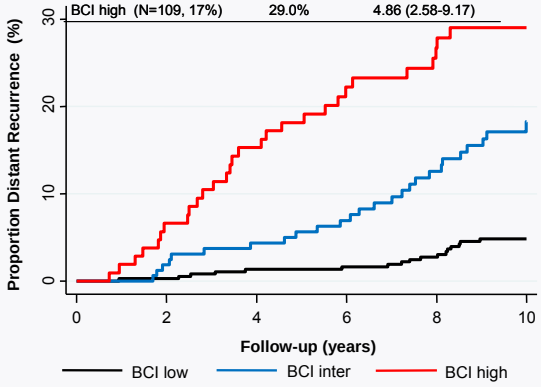


H/I + MGI = Breast Cancer Index (BCI)

Ma et al. Clin Cancer Res., 2008.

ATAC: BCI Distinguishes Three Risk Groups All Study Patients: (0-10 years)

	10-yr rate of distant recurrence	HR (95% CI) (adjusted for CTS)
BCI low (N=390, 58%)	4.8%	Reference
BCI inter (N=166,25%)	18.3%	2.89 (1.55-5.40)
BCI high (N=109, 17%)	29.0%	4.86 (2.58-9.17)

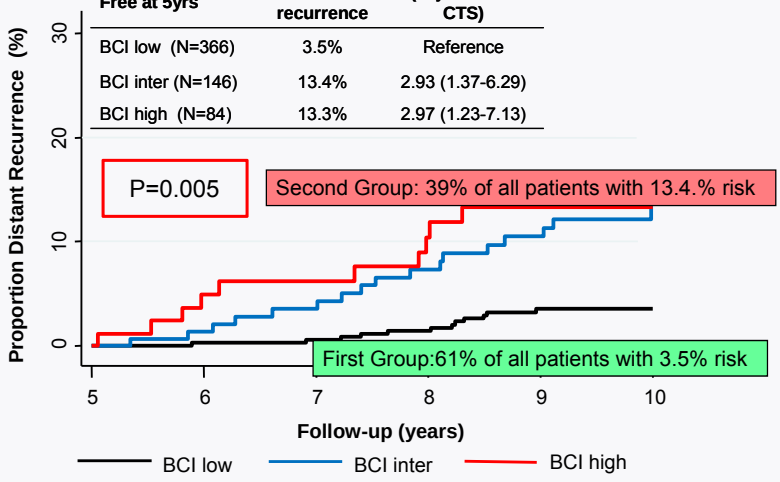


p<0.0001

Sgroi et al Lancet Oncology, 2013

ATAC: BCI Identifies Two Late (5-10 yr) Recurrence Risk Groups

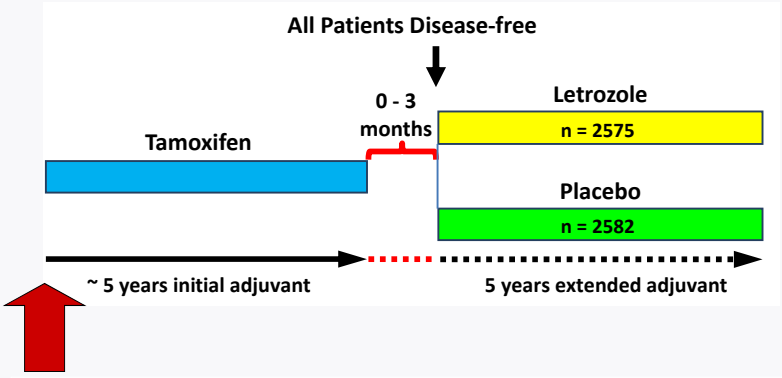
Patients disease-Free at 5yrs	10-yr rate of distant recurrence	HR (95% CI) (adjusted for CTS)
BCI low (N=366)	3.5%	Reference
BCI inter (N=146)	13.4%	2.93 (1.37-6.29)
BCI high (N=84)	13.3%	2.97 (1.23-7.13)



Sgroi et al Lancet Oncology, 2013

Prediction of Treatment Benefit: HOXB13/IL17BR (H/I)

MA.17 Trial Design: Benefit of Extended Hormonal Therapy



Tested tumor blocks at time of diagnosis to see if it would predict for benefit of extended letrozole therapy

MA.17: HOXB13/IL17BR Results

Variable	UnadjustedOR [95% CI]	*P* value	AdjustedOR [95% CI]	*P* value
Age (Post vs. Pre)	0.25 [0.02-2.76]	0.2583	0.13 [0.01-1.60]	0.1097
Tumor size (T2+T3 vs. T1)	1.00 [0.23-4.35]	1.0000	1.13 [0.21-6.00]	0.8832
Grade (3 vs. 1-2)	1.56 [0.82-2.98]	0.1753	1.23 [0.58-2.60]	0.5949
ER status (pos vs. neg)	0.67 [0.15-2.98]	0.5955	0.83 [0.15-4.72]	0.8349
PR status (pos vs. neg)	1.05 [0.53-2.09]	0.8802	1.33 [0.62-2.86]	0.4604
HER2 (pos vs. neg)	1.32 [0.55-3.18]	0.5382	0.99 [0.35-2.78]	0.9823
Node status (pos vs. neg)	1.00 [0.06-15.99]	1.0000	1.93 [0.11-33.77]	0.6519
Treatment effect (Letrozole vs. Placebo)				
H/I-low	0.68 [0.31-1.52]	0.3513	0.58 [0.25-1.36]	0.2100
H/I-high	0.35[0.16-0.75]	0.0070	0.33 [0.15-0.73]	0.0061

•High H/I is associated with a 67% reduction in the risk of recurrence with extended letrozole as compared with placebo (p=0.0061)

Sgroi et al JNCI 2013;105:1036-1042

ASCO Biomarker Guidelines: Breast Cancer Index

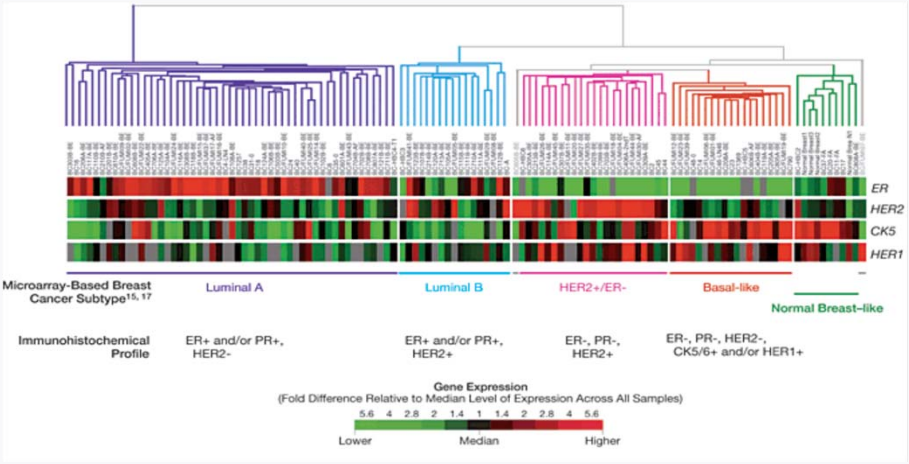
Breast Cancer Index

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.
- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.

US Medicare: Allows for the use of the test to predict the risk of breast cancer recurrence within 5 to 10 years in women with early-stage estrogen receptor-positive breast cancer

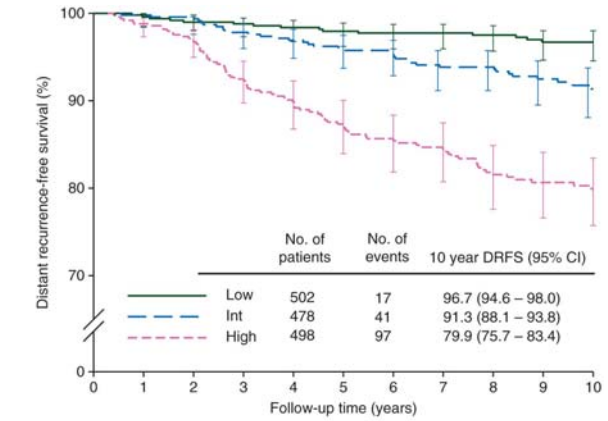
Harris LN et al. JCO published online on February 8, 2016; DOI:10.1200/JCO.2015.65.2289

Breast Cancer Molecular Subtypes



TCGA. Nature. 2012.

PAM50 ROR: DRFS according to 3 Risk Groups in ABCSG 8

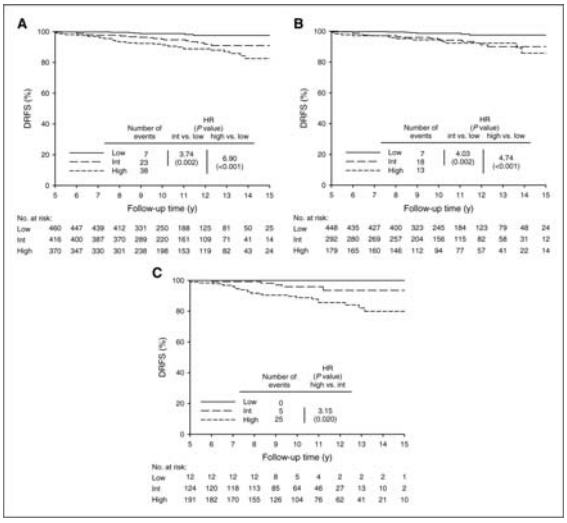


No. at risk:

Low	502	497	488	479	469	460	447	439	412	331	250
Int	478	466	454	437	423	416	400	387	370	289	220
High	498	484	465	428	399	370	347	330	301	238	198

M. Gnant et al. Ann Oncol 2014;25:339-345

PAM50 ROR: Late DRFS in ABCSG 8



Martin Filipits et al. Clin Cancer Res 2014;20:1298-1305

ASCO Biomarker Guidelines: PAM50 ROR

PAM50 risk of recurrence score

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 risk of recurrence (ROR) score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA), in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.
- If a patient has TN breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.

Harris LN et al. JCO published online on February 8, 2016; DOI:10.1200/JCO.2015.65.2289

Common Clinical Scenario

- 58 y/o female with mammographically detected breast cancer
- Lumpectomy
  - Invasive Ductal, Grade 2
  - 2.5 cm
  - SLN: Negative
  - ER>75%+, PR > 75% +, HER2 1+ IHC
- Recurrence Score: 18 (intermediate risk)

What are your recommendations?

1) Adjuvant radiation therapy, followed by endocrine therapy
2) Adjuvant chemotherapy followed by radiation and endocrine therapy
3) Adjuvant radiation therapy alone

Summary

- Multiple multi-gene panels validated in secondary analyses of prospective trials
- 21 gene recurrence score both prognostic and predictive of chemotherapy response
- BCI, Endopredict, and PAM50 prognostic for late relapse
- Data from MA17 suggests BCI (HOXB13/IL17BR) may identify patients responsive to letrozole

Future Directions

- Future studies will need to identify the best treatments for “higher risk” patients
  - Systemic Chemotherapy (TAILORx, MINDACT)
  - Other targeted therapies (e.g. CDK 4/6 inhibitors, PI3K inhibitors)
- Higher risk patients (e.g. luminal B) exhibit great heterogeneity and diversity of genomic variation
- “Window” studies may represent an opportunity to study new drugs in “high risk” ER+ patients

2016
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National Comprehensive Cancer Network

SABCS Updates: Adjuvant Therapy

Sarika Jain, MD, MSCI
Assistant Professor of Medicine
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Outline

- ER+ Her2- breast cancer
  - How much therapy is too much or not enough?
    - DBCG77B trial
    - ABCSG-18 trial
- HER2+ breast cancer
  - How much therapy is too much or not enough?
    - ExteNET trial
    - Netherlands study
    - BCIRG-006
- Residual disease after neoadjuvant chemotherapy in HER2- breast cancer
    - CREATE-X trial

Outline

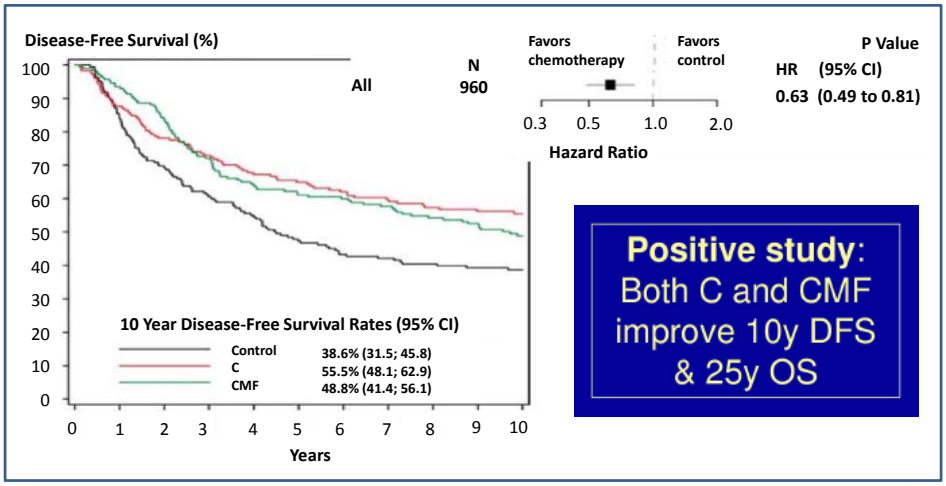
- **ER+ Her2- breast cancer**
  - **How much therapy is too much or not enough?**
    - **DBCG77B trial**
    - **ABCSG-18 trial**
- HER2+ breast cancer
  - How much therapy is too much or not enough?
    - ExteNET trial
    - Netherlands study
    - BCIRG-006
- Residual disease after neoadjuvant chemotherapy in HER2- breast cancer
    - CREATE-X trial

Chemotherapy is unnecessary in many ER+ BC

DBCG77B trial

- Background:
  - Intrinsic subtypes are proven prognostic in many settings and may predict benefit for chemotherapy.
  - Phase 3 trial in high-risk premenopausal breast cancer s/p mastectomy/ALND and RT, randomized to CMF, C, levamisole, or no adjuvant therapy
- Hypothesis:
  - Patients with IHC-defined luminal A tumors will derive no benefit from chemotherapy
    - C +CMF arms = chemotherapy
    - Levimasole + control arms = no chemotherapy

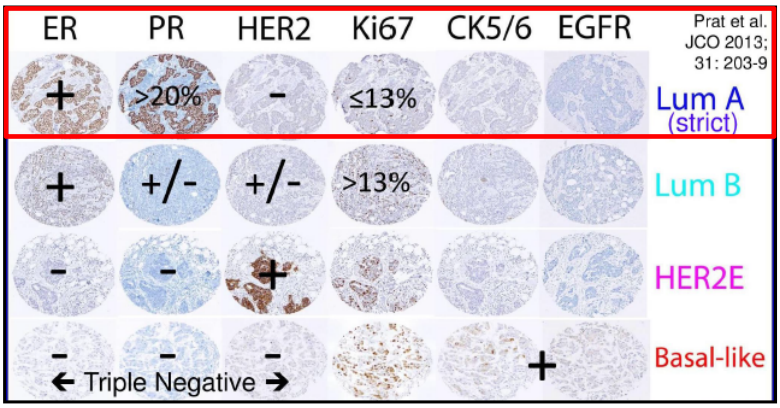
DBCG77B trial: DFS and OS improved with chemotherapy



Nielsen TO, et al. Oral presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S1-08.

DBCG77B trial

Intrinsic subtype determined by IHC



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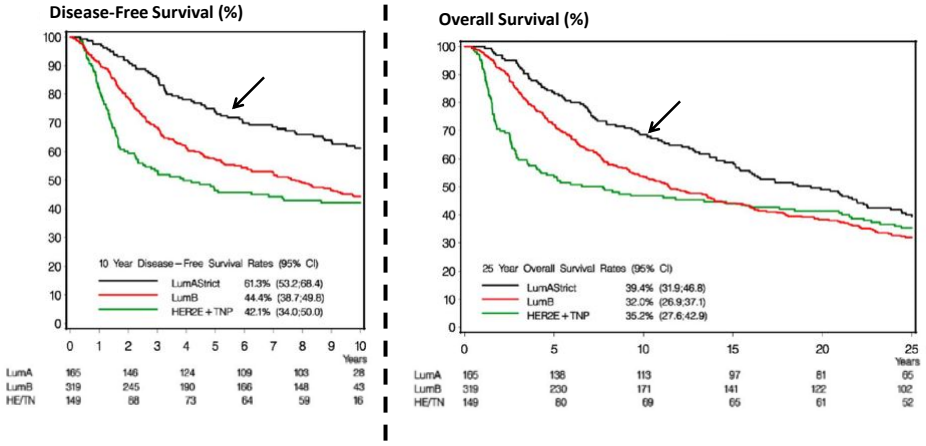
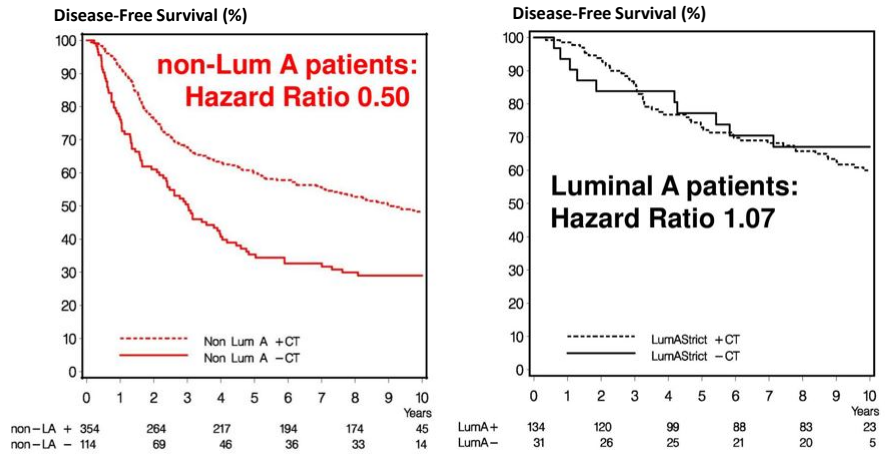
DBCG77B trial: Prognosis by Subtype



Increased 10-year DFS and 25-year OS in LumA

Nielsen TO, et al. Oral presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S1-08.

DBCG77B trial: Prediction of Chemotherapy Benefit by Subtype

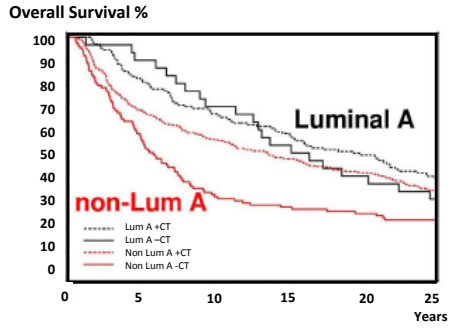


No improvement in DFS with chemotherapy in LumA

Interaction test: p<0.05

Nielsen TO, et al. Oral presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S1-08.

DBCG77B trial: Prediction by Subtype OS



LumA+ 134	110	91	80	68	55
LumA- 31	28	22	17	13	10
NonLA+ 354	245	202	173	153	127
NonLA- 114	65	38	33	30	27

No difference in OS with chemotherapy in LumA

Nielsen TO, et al. Oral presentation at: San Antonio Breast Cancer Symposium; December 9-12, 2015; San Antonio, TX. Abstract S1-08.

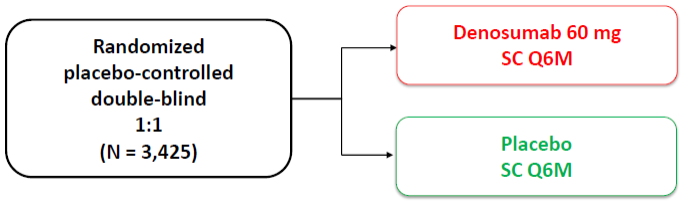
DBCG77B trial: Summary

- Conclusion:
  - Women with LumA breast cancers derive no benefit from chemotherapy
- Limitations:
  - Retrospective study
  - IHC has limited analytical validity
  - Small number of LumA patients (not powered)
  - Older trial: G1 chemo regimens, no endocrine tx, no HER2 tx
  - Materials difficult to find (blocks not saved or exhausted)
- However:
  - Phase 3 randomized trial to chemo vs not, very long follow-up

Who needs "more" therapy?

ABCSG-18

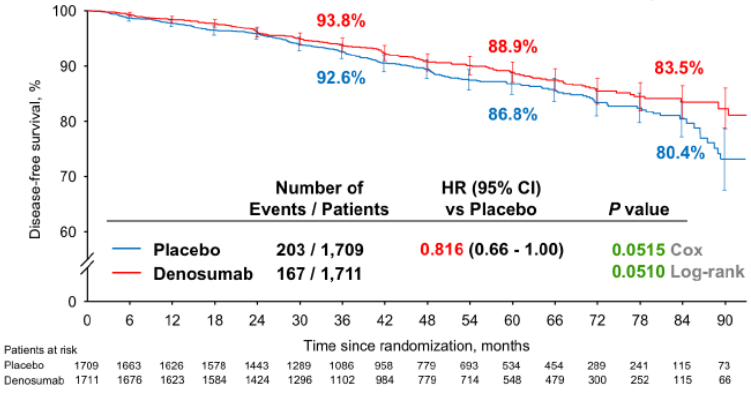
- Background:
  - Adjuvant bisphosphonates reduce recurrence and improve survival in postmenopausal breast cancer patients.
  - The primary analysis of ABSCG-18 (ASCO 2015) showed that adjuvant denosumab 60 mg twice yearly reduces clinical fractures (HR 0.5, *P*<.0001) and improves bone health, and can be administered without added toxicity.
  - Adjuvant denosumab might have a beneficial impact on survival outcomes
  - DFS reported at SABCS 2015



Gnant et al ASCO 2015

Gnant M, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S2-02.

ABCSG-18: DFS analysis

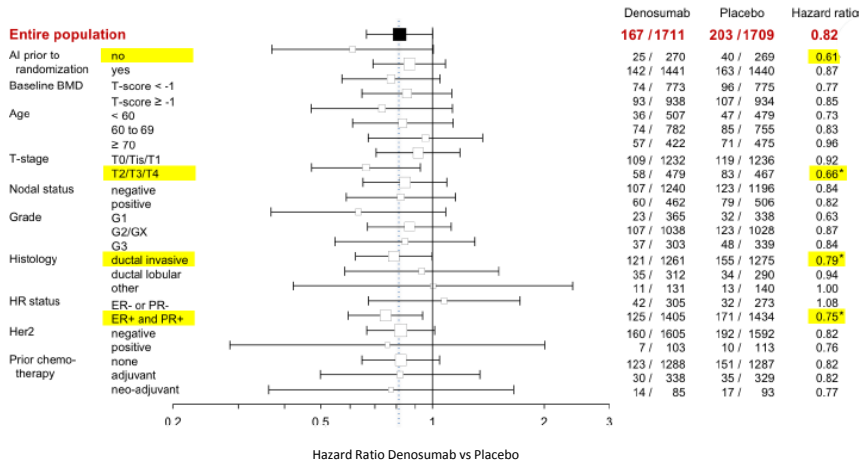


Stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density

In absolute numbers, the DFS benefit is about 1% after 3 years, 2% after 5 years, and 3% at 7 years of follow-up

Gnant M, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S2-02.

ABCSG-18: DFS analysis by subgroups



*Interactions were not statistically significant

Gnant M, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S2-02.

ABCSG-18: Summary

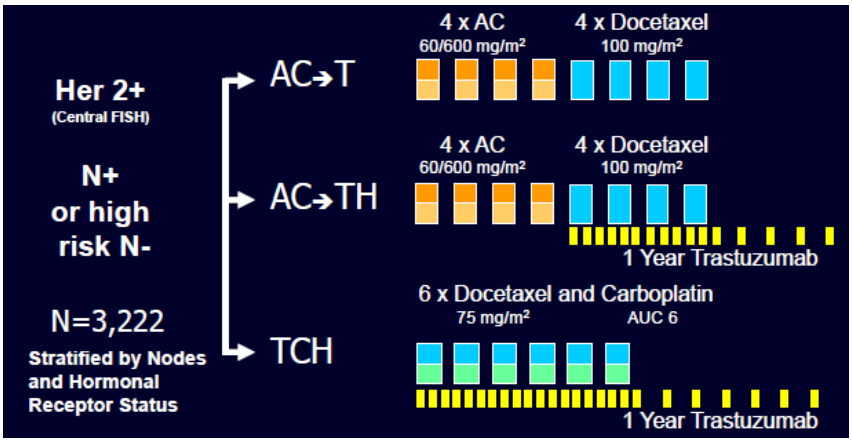
- Adjuvant denosumab improves DFS by 18%
  - HR 0.816, p=0.0510
- Safe treatment
  - No measurable differences in AEs
  - No confirmed ONJ or atypical fractures
- Similar DFS benefit seen in EBCTCG bisphosphonate meta-analysis
- "Should be offered to postmenopausal breast cancer patients on AI therapy irrespective of bone health status"
- Limitations: no OS data, cost

Outline

- ER+ Her2- breast cancer
  - How much therapy is too much or not enough?
    - DBCG77B trial
    - ABCSG-18 trial
- **HER2+ breast cancer**
  - **How much therapy is too much or not enough?**
    - **ExteNET trial**
    - **Netherlands study**
    - **BCIRG-006**
- Residual disease after neoadjuvant chemotherapy in HER2- breast cancer
    - CREATE-X trial

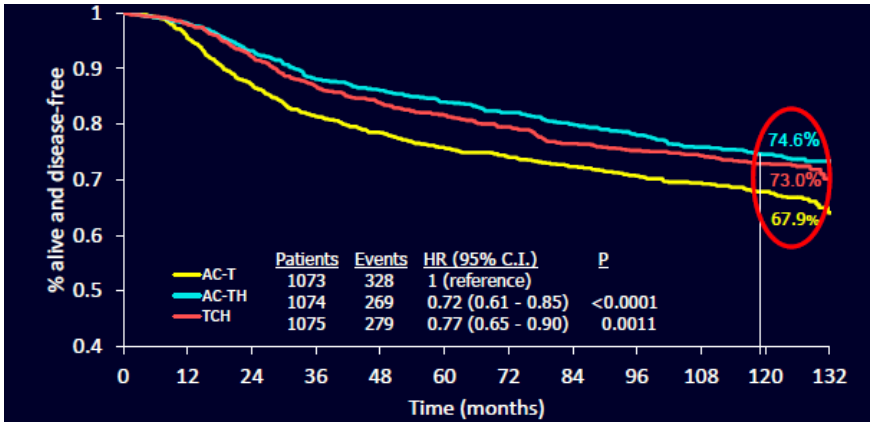
Can we avoid anthracyclines in early stage HER2+ BC patients?

BCIRG 006: 10 year follow-up analysis



Slamon D, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas.

BCIRG 006: 10 year DFS

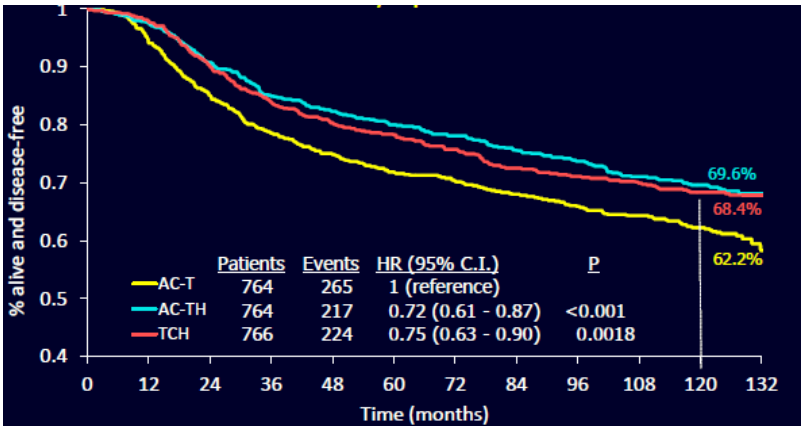


No significant difference between AC-TH and TCH (74.6 vs 73%)

Slamon D, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas.

BCIRG 006: DFS Lymph Node Positive

Do higher risk HER2+ tumors require anthracycline-based treatment? No



Slamon D, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas.

BCIRG 006: TCH appears to be safer and better tolerated

Grade 3/4 Non-Hematological Toxicity

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	%	%	%
Arthralgia	3.2	3.3	1.4*
Myalgia	5.2	5.1	1.8*
Fatigue	7.0	7.2	7.2
Hand-foot syndrome	1.9	1.4	0.0*
Stomatitis	3.5	2.9	1.4*
Diarrhea	3.0	5.6	5.4
Nausea	5.9	5.7	4.8
Vomiting	6.2	6.7	3.5*
Irregular menses	27.3	24.5	26.7

Yellow=*Statistically significant less events

Slamon D, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas.

BCIRG 006: TCH appears to be safer and better tolerated

Specific non-hematological toxicity (all grades)

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	%	%	%
Neuropathy-sensory	48.8	50.1	36.1*
Neuropathy-motor	5.2	6.4	4.3*
Nail changes	49.4	43.7	28.7*
Myalgia	53.0	55.4	38.9*
Renal failure	0.0	0.0	0.1
Creatinine Grade 3/4	0.6	0.3	0.1

Yellow=*Statistically significant less events

Slamon D, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas

BCIRG 006: TCH appears to be safer and better tolerated

Therapeutic Index – Most Recent 006 Data

	AC→TH	TCH
DFS Events	269	279
Grade 3 / 4 CHF	21	4
Totals	290	283
Rx-Related Leukemias	*6(8)** **Only in AC-Rx patients*	*0(1)*** ***Leukemia developed after CHOP Rx*
Sustained LVEF Loss >10%	200	97

Slamon D, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas.

BCIRG 006: Summary

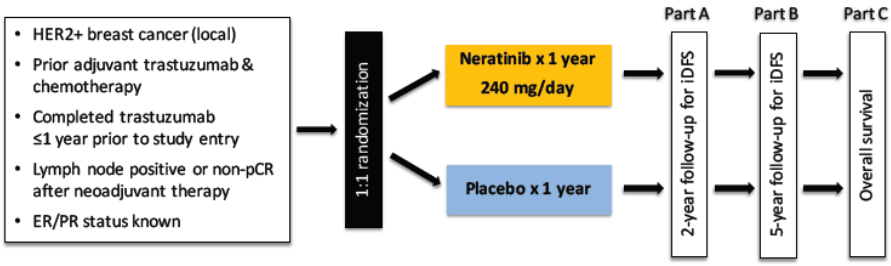
- At 10 year follow-up, DFS and OS data show sustained and significant efficacy advantage of AC-TH and TCH over AC-T
- No statistical advantage of AC-TH over TCH
- More CHFs, leukemias, and higher rate of sustained LVEF loss > 10% with ACTH compared to TCH.

Do HER2+ breast cancer patients need more treatment?

ExteNET study

- Background:
  - Following adjuvant trastuzumab, relapse occurs in up to 26% of patients at 8.4 years of follow-up.
  - Highest risk of relapse occurs in first 12 months following completion of trastuzumab.
  - Neratinib – oral TKI of HER 1, 2, 4
    - Effective in preclinical models, trastuzumab-treated MBC
    - Diarrhea most common adverse event

ExteNET: Final Study Design



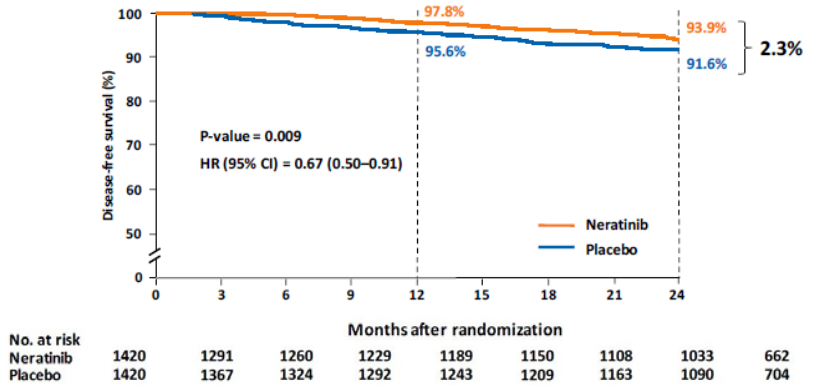
Primary analysis: invasive DFS (iDFS) in ITT population (n=2840)

- iDFS at 2 years: HR=0.67 (0.50–0.91); p=0.009
  - Hormone receptor-positive (n=1631; 57.4%); HR=0.51; p=0.001
  - Centrally-confirmed HER2-positive 60% (n=1463; 51%); HR=0.51; p=0.002

Chen A et al. Lancet Oncol 2015 in press

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

ExteNET: primary analysis at 2 years



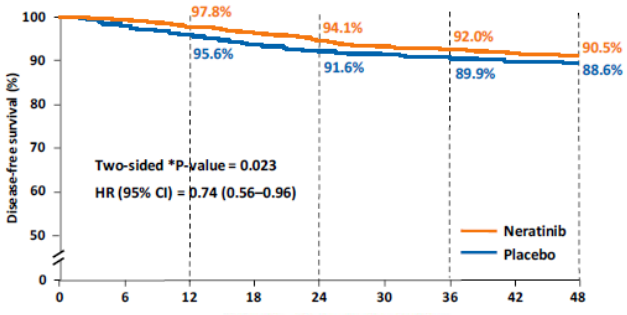
No. at risk									
Neratinib	1420	1291	1260	1229	1189	1150	1108	1033	662
Placebo	1420	1367	1324	1292	1243	1209	1163	1090	704

P-value and HR adjusted for hormone receptor status, prior trastuzumab (concurrent vs > sequential) and lymph node status

Chen A et al. Lancet Oncol 2015 in press

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

3-year iDFS analysis (ITT: n=2840)



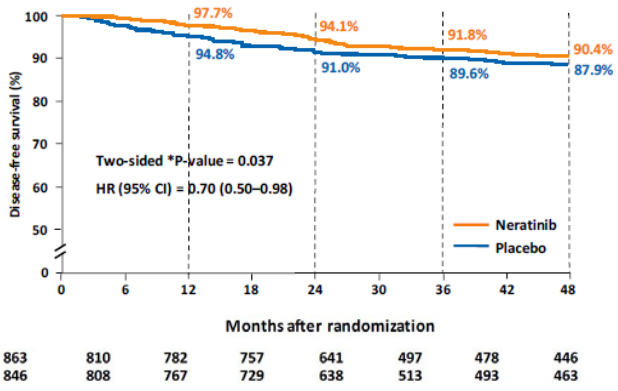
No. at risk									
Neratinib	1420	1302	1247	1196	1007	783	761	710	600
Placebo	1420	1350	1287	1223	1075	856	822	773	641

3 year iDFS – consistent benefit of pts receiving N with HR 0.74

* p value descriptive

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

3-year iDFS analysis:
Centrally confirmed HER2+



No. at risk									
Neratinib	863	810	782	757	641	497	478	446	376
Placebo	846	808	767	729	638	513	493	463	386

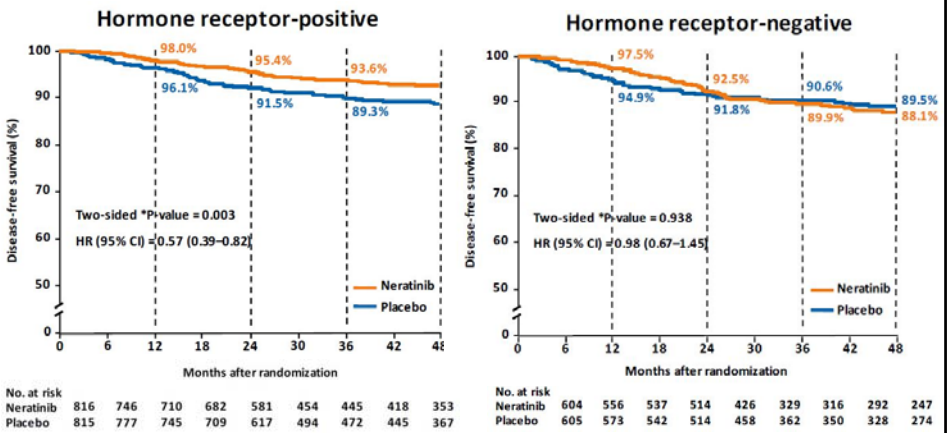
*HER2 DNA dual probe HER2 amplification defined as HER2:CEP17 ratio of >2.2

Wolff A et al. J Clin Oncol 2007

*p value descriptive

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

3-year iDFS analysis:
Hormone receptor status



No. at risk									
Neratinib	816	746	710	682	581	454	445	418	353
Placebo	815	777	745	709	617	494	472	445	367

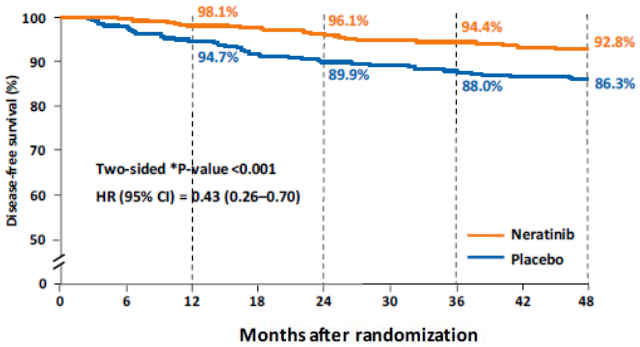
No. at risk									
Neratinib	604	556	537	514	426	329	316	292	247
Placebo	605	573	542	514	458	362	350	328	274

*p value descriptive

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

3-year iDFS analysis:

Hormone receptor-positive and centrally confirmed HER2+



No. at risk									
Neratinib	455	426	410	398	342	258	252	237	200
Placebo	448	426	406	385	336	275	262	245	205

*p value descriptive

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

Diarrhea prophylaxis

Loperamide pre-medication: (during 1st cycle of treatment only)
Day 1: 4 mg with neratinib, followed by
Day 1–3: 2 mg 4-hourly
Day 4–28: 2 mg 6–8-hourly

Target	HER2+ MBC[1]	HER2+ MBC[1]	HER2+ mutated NSCLC[1]	HER2+ mutated NSCLC[1]	HER2+ mutated solid tumors[1]
	Neratinib + Paclitaxel + Trastuzumab	Neratinib + Torisel	Neratinib + Torisel	Neratinib	Neratinib
Patients	6	41	14	13	81
Diarrhea grade 3	0	7 (17%)	2 (14%)	1 (8%)	10 (12%)
Non-compliance with loperamide	0	4 / 7 (57%)	1 / 2 (50%)	1 / 1 (100%)	–
Duration (days) grade 3		2	2	2	2

[1] Ustaris et al. Am J Hematol Oncol 2015

Chen A et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S5-02

ExteNET: Summary

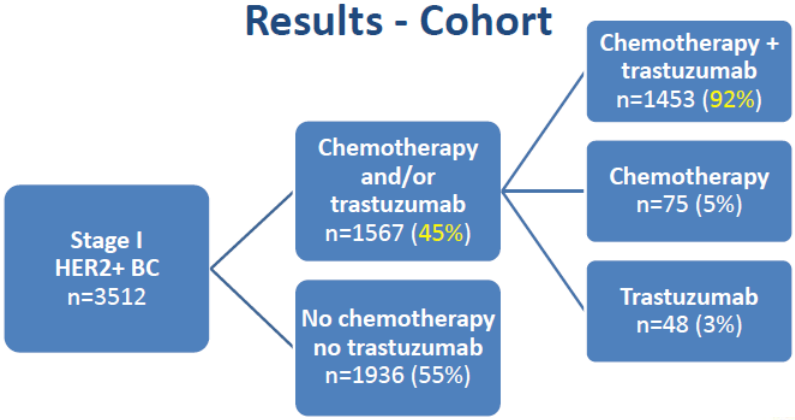
- 3-year exploratory analysis is consistent with the 2-year primary analysis that neratinib significantly improved DFS.
- Greater benefit seen in:
  - Centrally-confirmed HER2+
  - Patients who completed prior trastuzumab within 1 year
  - Hormone receptor-positive patients
- Ongoing data collection for 5-year DFS and OS
- Ongoing trial to confirm efficacy of loperamide prophylaxis

Small HER2 tumors:

To treat or not to treat?

- Background:
  - Trastuzumab-based therapy effective in stage 2-3 breast cancer.
  - Worse prognosis for small node-negative HER2 tumors (additional 15-30% risk of relapse in HER2+ T1a/T1b tumors per retrospective series)
  - Evidence to support systemic therapy in stage 1 is limited.

Results - Cohort



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Van Ramshorst MS, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-06.

Baseline characteristics not balanced

	No chemo no Tzt n=1936		Chemo and/or Tzt n=1576		
	n	(%)	n	(%)	*p-value*
Age (years)					*<0.001*
Median (range)	62	(26-90)	52	(19-75)	
Pathologic tumor stage					*<0.001*
T1a	357	(19%)	28	(1%)	
T1b	650	(34%)	150	(10%)	
T1c	929	(48%)	1398	(89%)	
Pathologic nodal stage					*0.003*
Negative	1833	(95%)	1453	(92%)	
Isolated tumor cells	103	(5%)	123	(8%)	
Grade					*<0.001*
I	267	(14%)	28	(2%)	
II	954	(49%)	472	(30%)	
III	599	(31%)	1033	(66%)	
Unknown	116	(6%)	43	(3%)	

NETHERLANDS CANCER INSTITUTE
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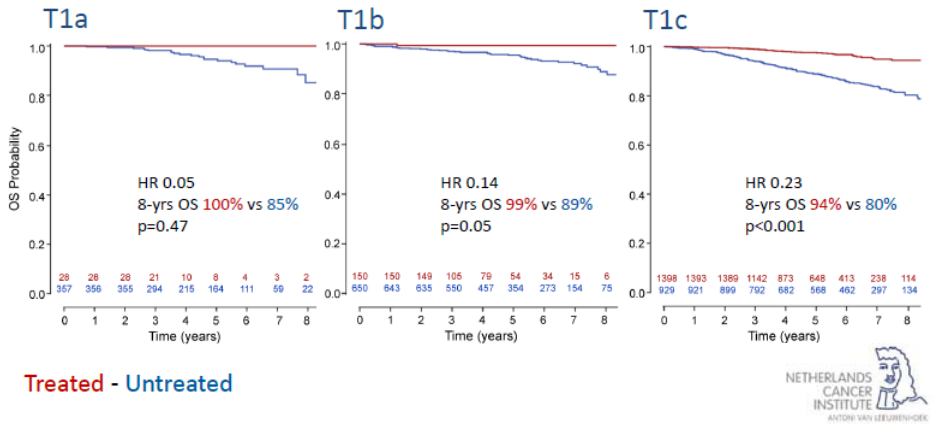
No tx: older, less hormone therapy
Tx: worse prognostic factors

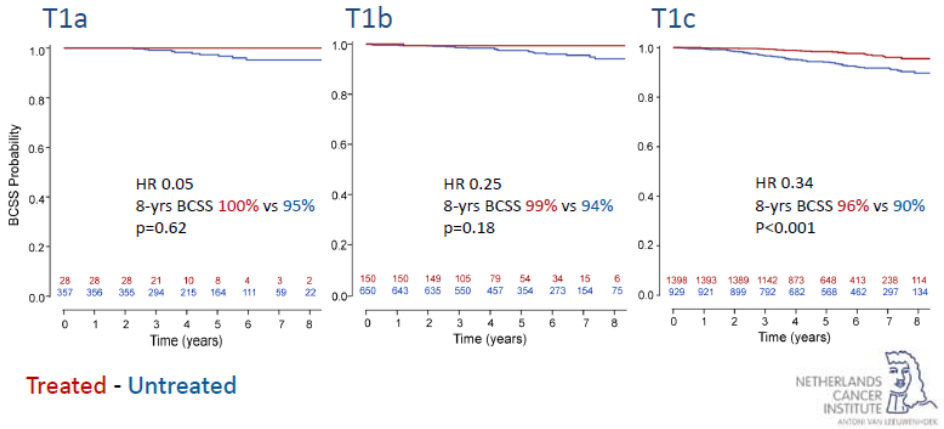
Van Ramshorst MS, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-06.

Results: Overall survival
Median follow-up of 61 months



Van Ramshorst MS, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-06.

Results: Breast cancer specific survival



Van Ramshorst MS, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-06.

Summary

- Systemic therapy improves OS and BCSS in stage 1 HER2+ breast cancer
- Limitations:
  - Observational study
  - No recurrence data was available
  - Low number of events in subgroups
- Absolute benefit must be discussed with the individual patient

Outline

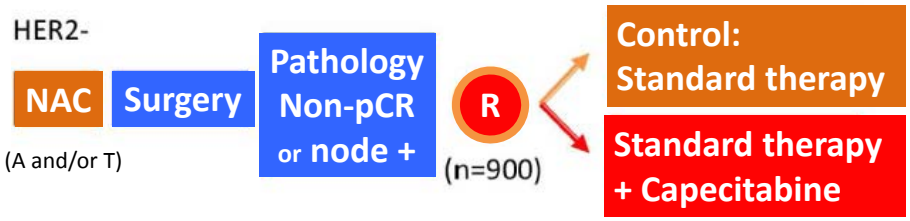
- ER+ Her2- breast cancer
  - How much therapy is too much or not enough?
    - DBCG77B trial
    - ABCSG-18 trial
- HER2+ breast cancer
  - How much therapy is too much or not enough?
    - ExteNET trial
    - Netherlands study
    - BCIRG-006
- **Residual disease after neoadjuvant chemotherapy in HER2- breast cancer**
    - **CREATE-X trial**

Should we give more chemotherapy for non-pCR after neoadjuvant chemotherapy?

CREATE-X trial

- Background
  - Patients with pathologic residual invasive disease after NAC have a higher risk for relapse.
  - Unclear if postoperative chemotherapy prolongs survival.

CREATE-X: Trial Design



Stratification factors:
ER, Age, NAC, ypN,
5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

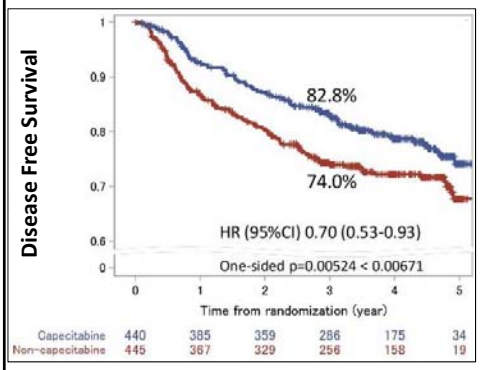
Capecitabine (X): 2,500 mg/m^2/day, po, day 1-14
Repeat every 3 weeks for 8 cycles

Primary endpoint:
DFS
Secondary endpoints:
OS, safety

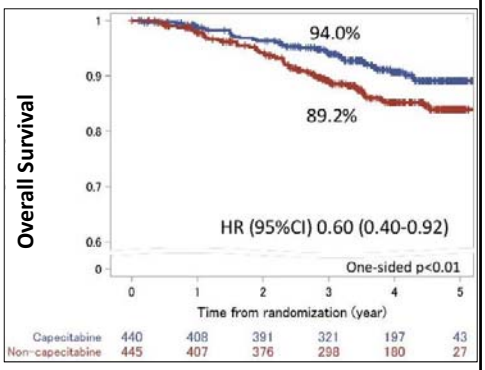
Lee S-J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S1-07.

CREATE-X: Results

Disease Free Survival

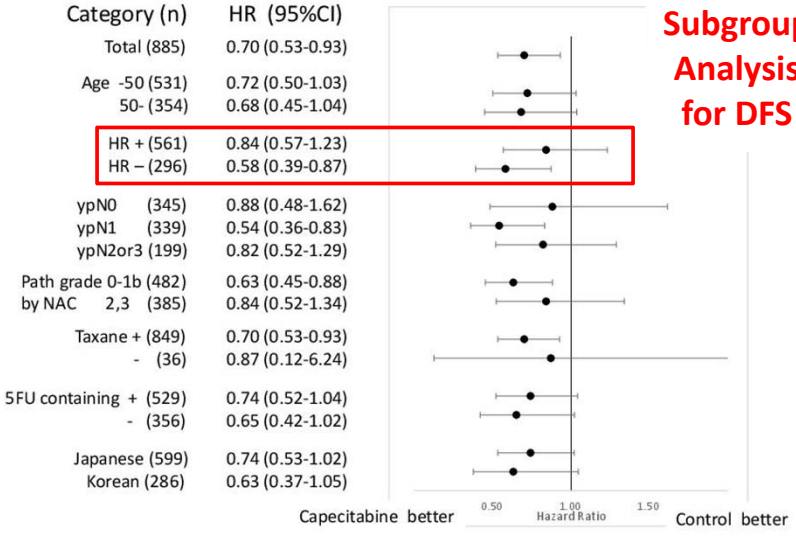


Overall Survival



Lee S-J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S1-07.

Subgroup Analysis for DFS



AEs: grade 3/4 neutropenia (7% vs. 2%) and diarrhea (3% vs. <1%), grade 3 HFS 11%

Lee S-J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S1-07.

CREATE-X: Summary

- Postoperative chemo after NAC containing A and/or T improved DFS and OS in HER2-negative breast cancer with residual invasive disease. Toxicities manageable.
- Limitations: unknown doses/duration of NAC, unclear benefit in HR+, higher doses of cape than typically used in US

2016 NCCN CONGRESS SERIES™ National Comprehensive Cancer Network

SABCS Updates: Neoadjuvant Therapy

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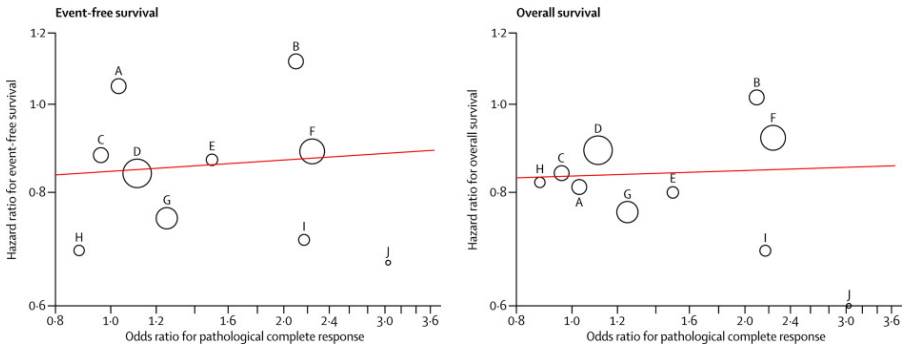
Northwestern University Feinberg School of Medicine
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University
Northwestern Medicine Developmental Therapeutics Institute

Overview

- pCR and Survival: Experience to Date
- Carboplatin in TNBC
  - Survival in GeparSixto and CALGB 40603
- BRCA Status and Response
  - Bevacizumab in GeparQuinto
  - Platinums in GeparSixto
- TKIs in HER2-positive
  - Neratinib in NSABP FB-7
  - NGS biomarkers in neoALTTO
- Novel Approaches
  - T-DM1 in WGS-ADAPT
  - Palbociclib

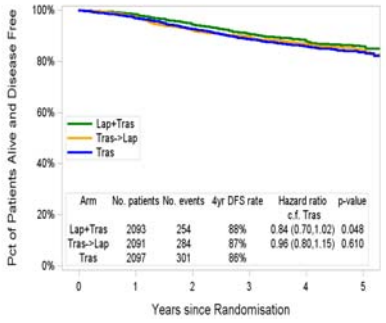
pCR is a Surrogate for Survival



Cortazar et al. Lancet 2014

Experience with Lapatinib

Study	Regimen	+ TRAS	+ LAP	+ TRAS/LAP
EORTC 10054	Doc → FEC	52%	36%	56%
NSABP B-41	AC → Pac	53%	53%	62%
CALGB 40601			%	52%
neoALTTO			%	51%



Burstein SABCS 2014
Piccart et al. ASCO 2014

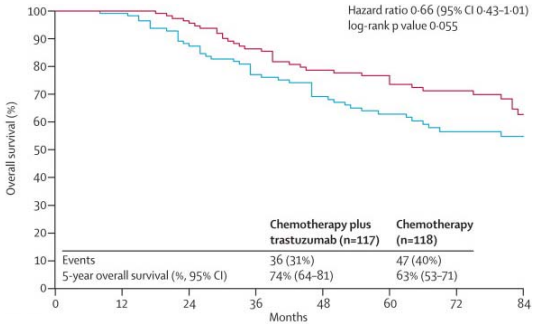
Bevacizumab in Early BC

	Trial	Subtype	pCR improved	DFS improved	OS improved
Neoadjuvant	GBG 44 24136883	HER2-	yes (ER-)	no	no
	NSABP B-40 22276821	HER2-	yes (ER+)	no	-
	ARTEMIS 25975632	HER2-	yes (ER-)	-	-
	CALGB 40603 25092775	TNBC	yes	-	-
	ABCSG-32	HER2-	yes (esp ER-)	-	-

Miller et al. ASCO 2014 Cameron et al. Lancet 2013, Steger et al. SABCS 2014
Bear et al. SABCS 2014 SABCS 2014 Nahleh et al. SABCS 2014
Sikov et al. SABCS 2014 Sikov et al. ASCO 2015 Ear. et al. SABCS 2014

NOAH: pCR Correlation with EFS/OS

	HER2-positive disease		p value*
	With trastuzumab (n=117)	Without trastuzumab (n=118)	
bpCR	50 (43%)	26 (22%)	0·0007
tpCR	45 (38%)	23 (19%)	0·001
OR‡	102 (87%)	87 (74%)	0·009



Gianni et al Lancet 2010
Gianni et al Lancet Oncology 2014

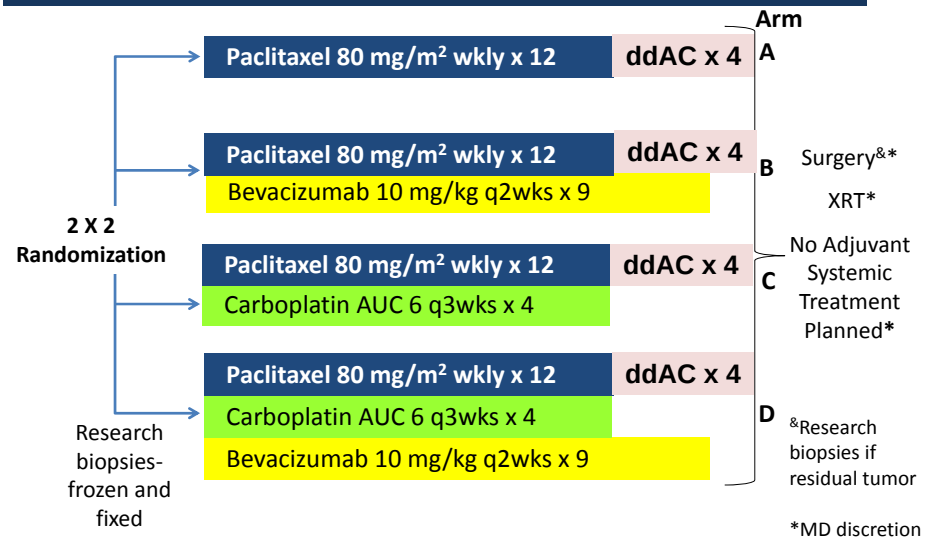
Carboplatin Improves pCR in TNBC

Study	N	Tumor Subtypes	Regimen (for TNBC)	Carboplatin dose/schedule	ypT0N0 rates TNBC
GeparSixto	588	1. *HER2+ 2. TNBC (315)	a) Paclitaxel/doxil/bev b) Paclitaxel/doxil/bev + Carbo	AUC 2→1.5, weekly	a) 36.9% **b) 53.2%**
CALGB 40603	443	1. TNBC	a) Paclitaxel → ddAC +/- bev b) Paclitaxel/Carbo → ddAC +/- bev	AUC6, q3wks during paclitaxel	a) 41% **b) 54%**
ISPY2	72	1. HR+/HER2- 2. HR-/HER2-	a) Paclitaxel → ddAC b) Paclitaxel → ddAC, Carbo/velaparib	AUC6, q3wks x4 cycles	a) 26% **b) 52%**

*Suggests benefit in HER2+

San Antonio Breast Cancer Symposium, December 8-12, 2015

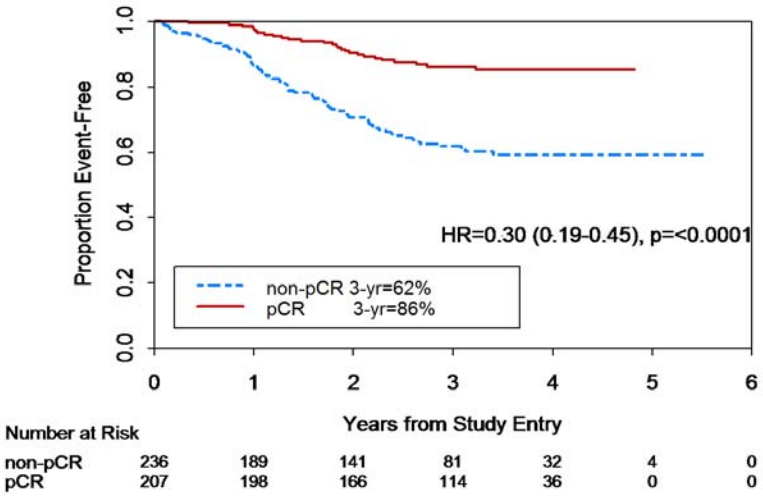
CALGB 40603: Schema – Randomized Phase II



Sikov SABCS 2015 (with permission)

San Antonio Breast Cancer Symposium, December 8-12, 2015

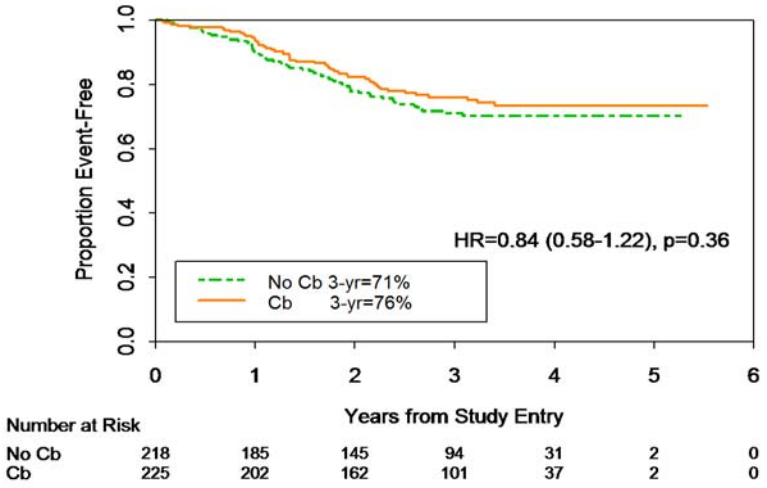
CALGB 40603 – EFS by pCR Breast/Axilla



Sikov SABCS 2015 (with permission)

San Antonio Breast Cancer Symposium, December 8-12, 2015

CALGB 40603 – EFS for carboplatin vs. not



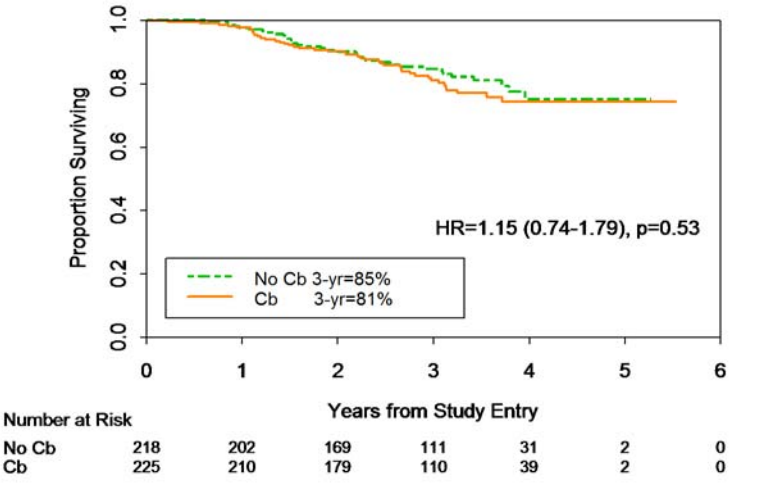
Number at Risk

No Cb	218	185	145	94	31	2	0
Cb	225	202	162	101	37	2	0

Sikov SABCS 2015 (with permission)

San Antonio Breast Cancer Symposium, December 8-12, 2015

CALGB 40603 – OS for carboplatin vs. not

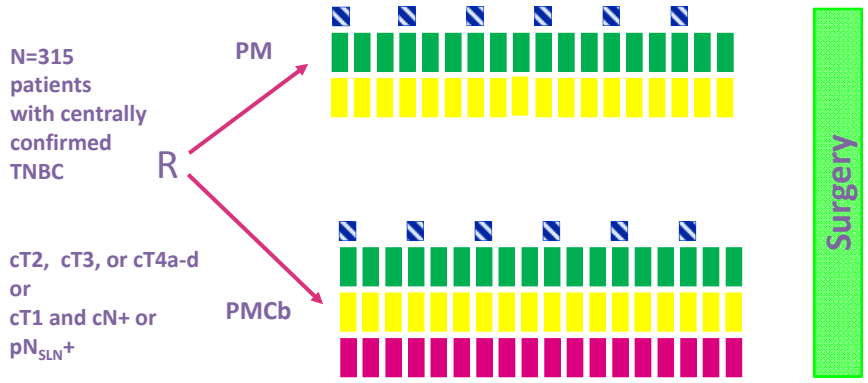


Number at Risk

No Cb	218	202	169	111	31	2	0
Cb	225	210	179	110	39	2	0

Sikov SABCS 2015 (with permission)

(GeparSixto) Design for Patients with TNBC



Paclitaxel (P) 80 mg/m² q1w

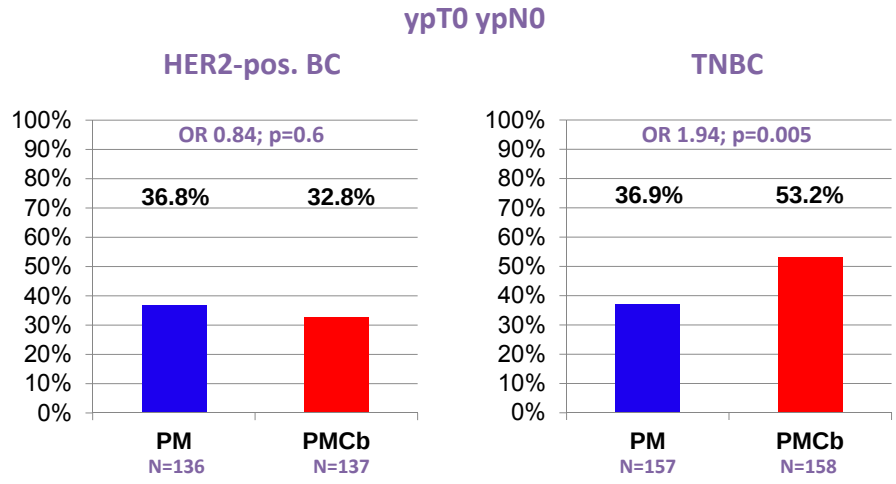
Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin (Cb) q1w
Dose of AUC 2 was reduced to AUC 1.5 after enrolment of 330 patients

Bevacizumab 15 mg/kg q3w

von Minckwitz SABCS 2015 (with permission)

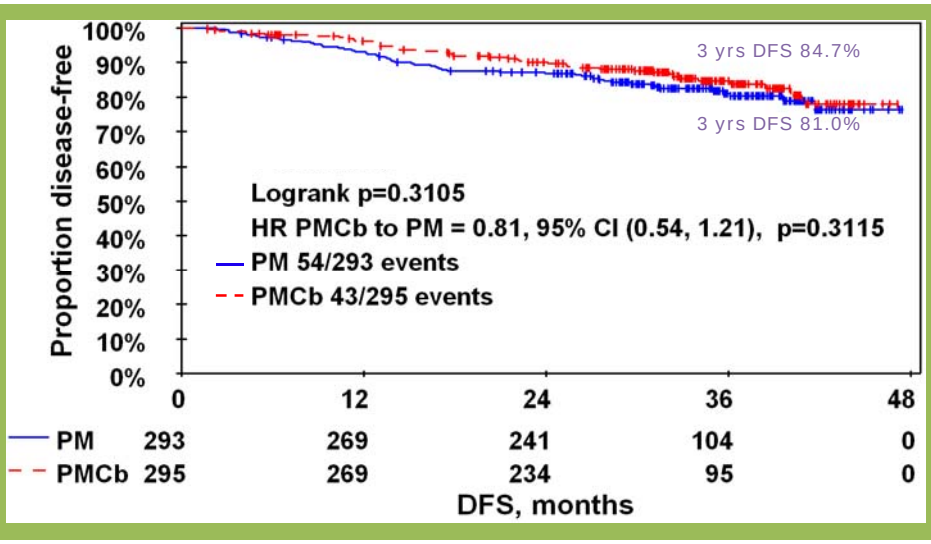
pCR Rates by Subtype



Test for interaction p=0.015

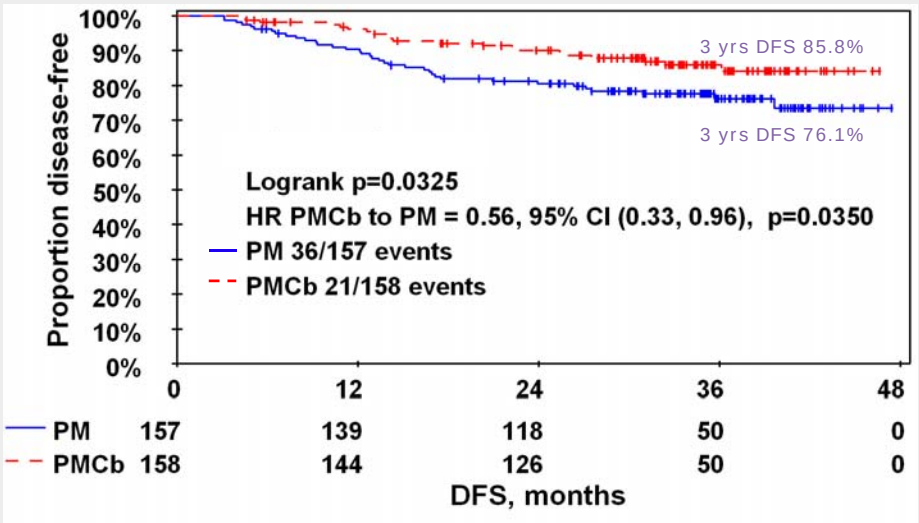
von Minckwitz SABCS 2015 (with permission)

DFS: Effect of Carboplatin in all Patients



von Minckwitz SABCS 2015 (with permission)

DFS: Effect of Carboplatin in TNBC



von Minckwitz SABCS 2015 (with permission)

Carboplatin in Neoadjuvant Setting

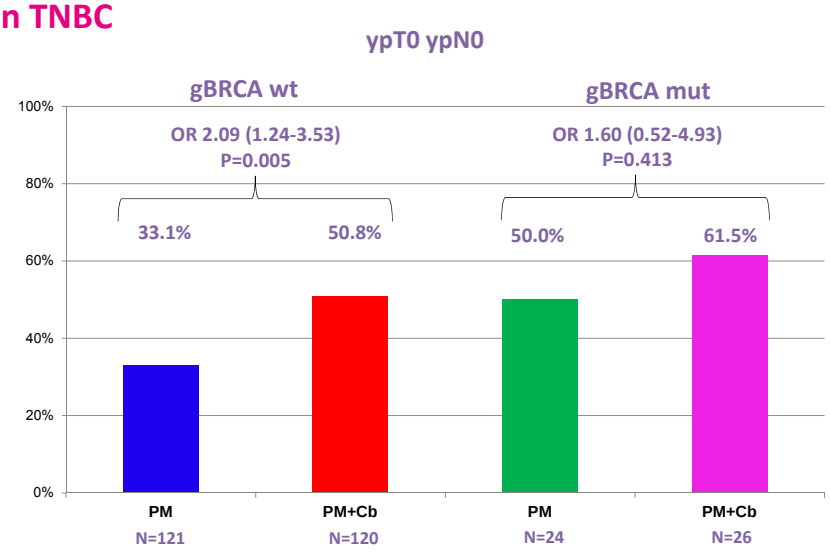
	CALGB 40603	GeparSixto
# with TNBC	443	315
Regimen	a)Paclitaxel → ddAC +/- bev b)Paclitaxel/Carbo → ddAC +/- bev	a)Paclitaxel/doxil /bev b)Paclitaxel/doxil /bev + Carbo
Carbo dosing	AUC6, q3wks during paclitaxel	AUC 2→1.5, weekly

- Nonstandard US regimens
- Carbo dose density?
- Increased toxicity
- May affect completion of standard therapy
- Not ready for routine use
- Encourage clinical trial participation

BRCA Status and Chemosensitivity

- Patients with BRCA mutations have defects in homologous recombination
- Platinum sensitivity in metastatic studies
  - TBCRC 009 (Isakoff JCO 2015) – improved ORR
  - TNT (Tutt SABCS 2014) – improved ORR
- Platinum sensitivity in neoadjuvant studies
  - PrECOG 0105 (Telli JCO 2015) – pCR 33→47% (wt vs mut)
  - PROGECT (Sharma ASC0 2014) – pCR 68→ 86%

(GeparSixto) pCR Rates by g*BRCA* Status and Carboplatin in TNBC



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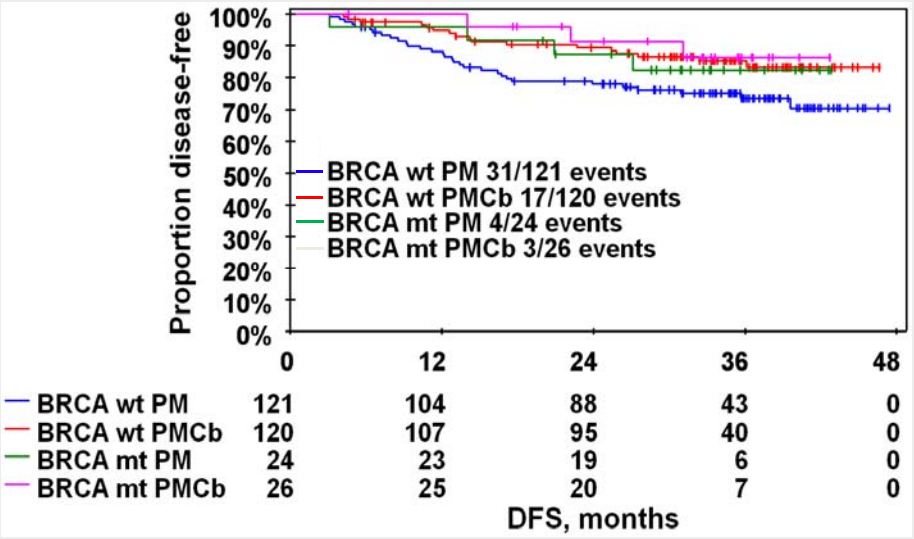
DFS by g*BRCA* Status and Carboplatin in TNBC



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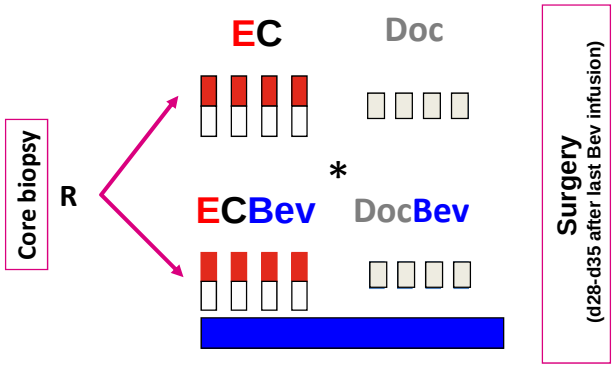
HER2-negative part of GeparQuinto



Recruitment of n=1948 HER2 negative patients,

N=678 having triple negative tumors.

E: Epirubicin 90 mg/m²
C: Cyclophosphamide 600 mg/m²
Doc:Docetaxel 100mg/m²
Bev: Bevacizumab 15 mg/kg
(all 3 week cycles)

* non responders continued with a prespecified non responder therapy

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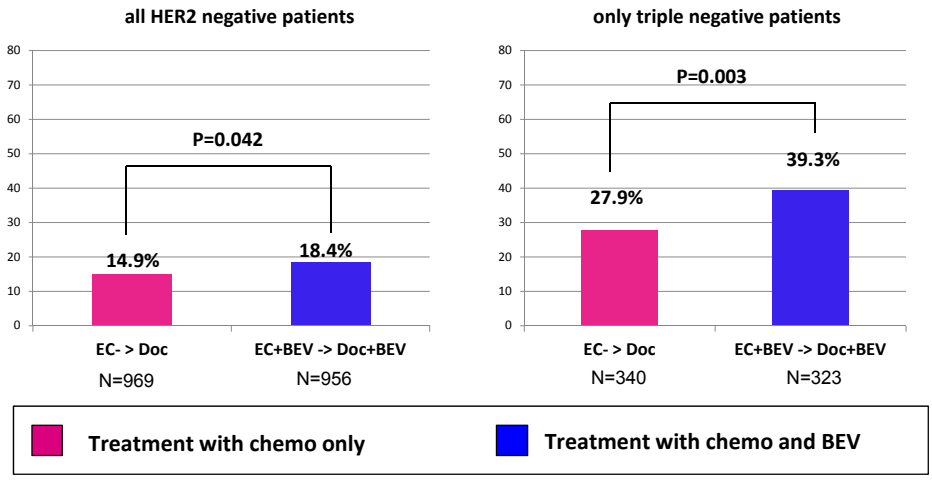
pCR (ypT0/ypN0) in all HER2 negative patients and in the triple negative subgroup



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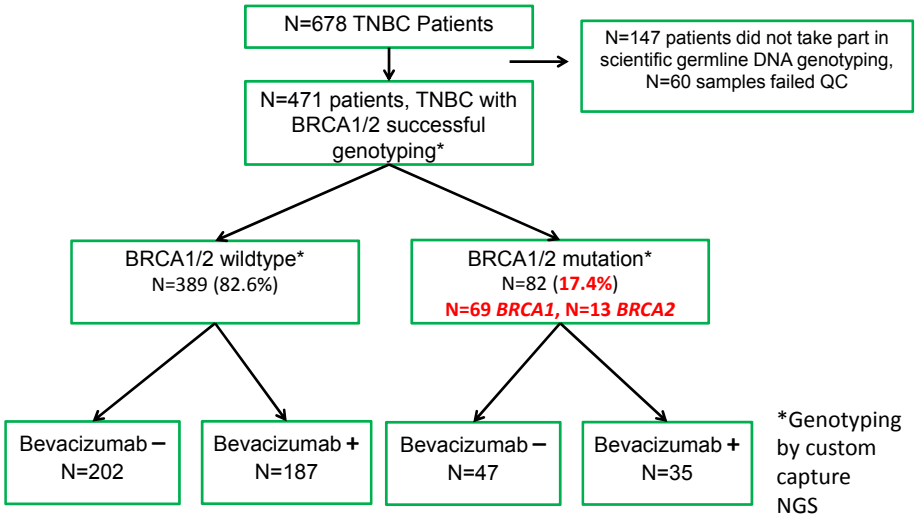
BRCA1/2 genotyping and treatment arms



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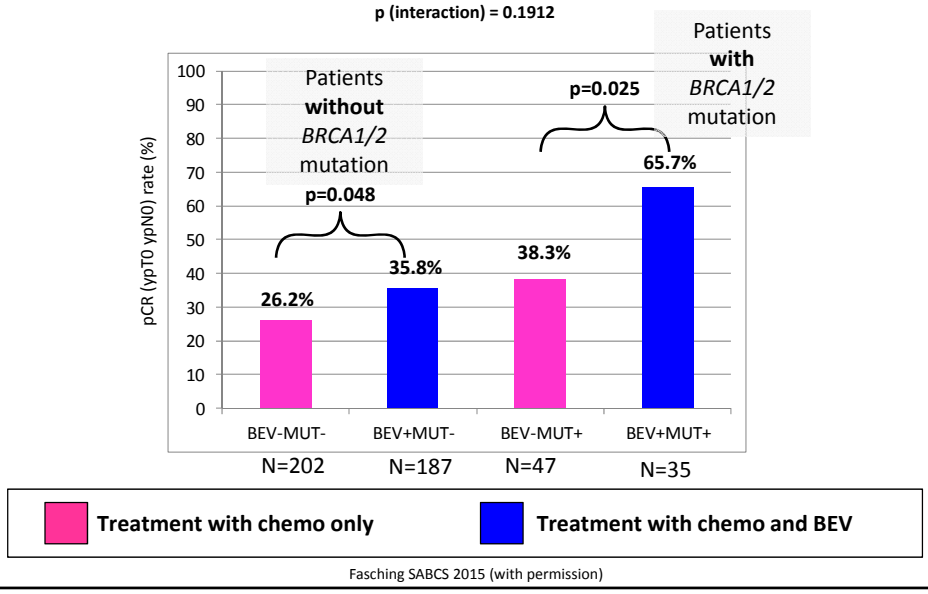
pCR according to treatment and *BRCA1/2 status*



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Exploratory subgroup analysis: pCR according to randomization arms

- Hypoxia has been described to cause DNA damage.
- Synthetic lethality is a described phenomenon in *BRCA1/2* mutation carriers.
- Angiogenic factors such as VEGF, Ang-1 and Ang-2 are overexpressed in *BRCA* mutated tumors.

[1]Bindra RS, et al. (2005) Cancer Res; [2]Bindra RS, et al. (2004) Mol Cell Biol, [3]Bristow et al (2008) Nat Rev Cancer
[4]de Bock et al. (2011) Nat Rev Clin Oncol [5]Danza et al. (2013) Eur J Hum Genet

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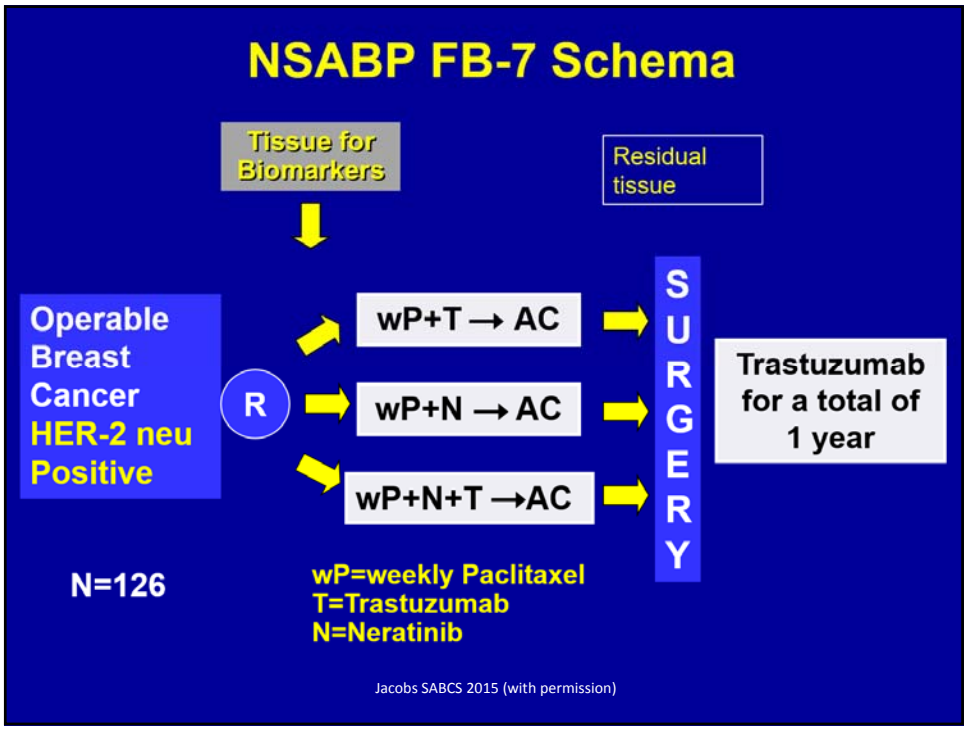
Neoadjuvant Therapy for Patients with BRCA 1/2 Mutations

- Respond well to chemotherapy
- Responsiveness to platinums not clear, future studies are required
- Other novel therapeutics require additional research (PARP inhibitors, anti-VGEF)
- Encourage clinical trial participation

TKIs in Neoadjuvant HER2-positive

- Lapatinib is a small molecule reversible inhibitor of HER2
  - consistently increases pCR rates, but no effect on survival
- Neratinib is a small molecule irreversible inhibitor of HER2
  - under investigation
- Biomarker predictive of response may help select appropriate patients



Treatment-Related Adverse Events During T+P, N+P, or T+N+P (All Cycles)

Event	Arm 1; N=42			Arm 2; N=42			Arm 3; N=42		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Nausea	12 (29%)	0	0	22 (42%)	0	0	16 (43%)	1 (2%)	0
Diarrhea	16 (38%)	0	0	29 (69%)	13 (31%)	0	28 (66%)	13 (31%)	0
Rash	7 (17%)	0	0	9 (22%)	0	0	6 (15%)	0	0
Trans-aminase elevation	14 (33%)	1 (2%)	0	28 (66%)	3 (7%)	0	29 (69%)	3 (7%)	0
Fatigue	18 (43%)	0	0	20 (48%)	1 (2%)	0	17 (40%)	1 (2%)	0
Neuropathy	17(40%)	0	0	17(40%)	0	0	11(26%)	1 (2%)	0

4 week prophylaxis (Europe)		
Diarrhea	Arm 2; N=12	Arm 3; N=21
Grade 3 Cycle 1	1 (8%)	4 (19%)
Grade 3 All cycles	2 (17%)	5 (24%)

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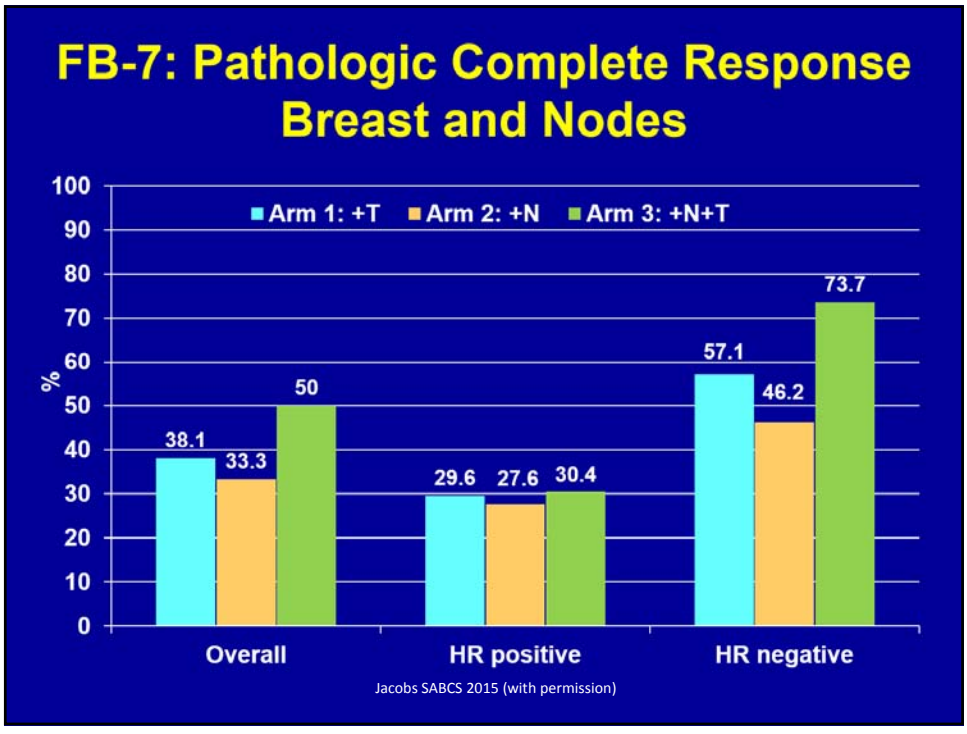

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Preliminary Analysis of Predictors of pCR (All Arms)

Preliminary Analysis of Predictors of pCR (All Arms)

	Total	No PCR	Yes PCR	P-value
FCGR3A				
F/F	27 (46.6%)	20 (74.1%)	7 (25.9%)	0.009
V/V or F/V	31 (53.4%)	12 (38.7%)	19 (61.3%)	
ER status				
ER negative	29 (44.6%)	10 (34.5%)	19 (65.5%)	0.003
ER positive	36 (55.4%)	26 (72.2%)	10 (27.8%)	

Biomarkers not Significant

PIK3CA
PTEN
FCGR2A
TILs

Analysis of Additional Biomarkers in Progress

4EBP	IGF1R
AKT	MEK
ALK	SHC
AR	mTOR
cMET	P70
EGFR	p70S6K
eIF4G	P95 HER2
ER alpha	PI3K
ERK	RAS40
ESR α	RET
HER2	RPS6
HER3	RSK
HER4	

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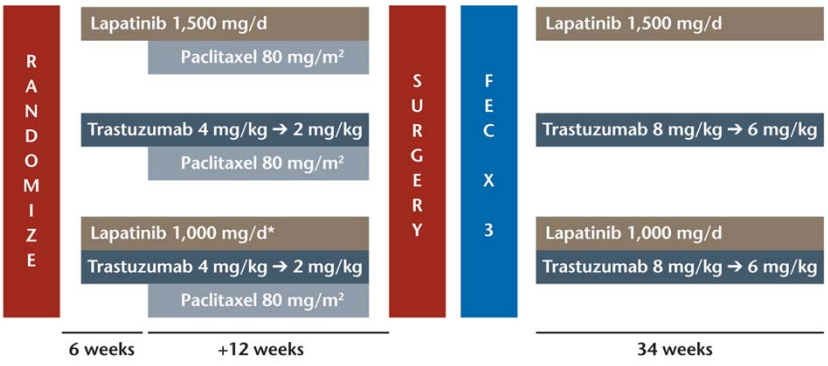
NeoALTTO Study

Trial Schema



d = day; FEC = fluorouracil, epirubicin, cyclophosphamide
**Amendment: October 2, 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel; 54/152 had protocol-driven reduction.*

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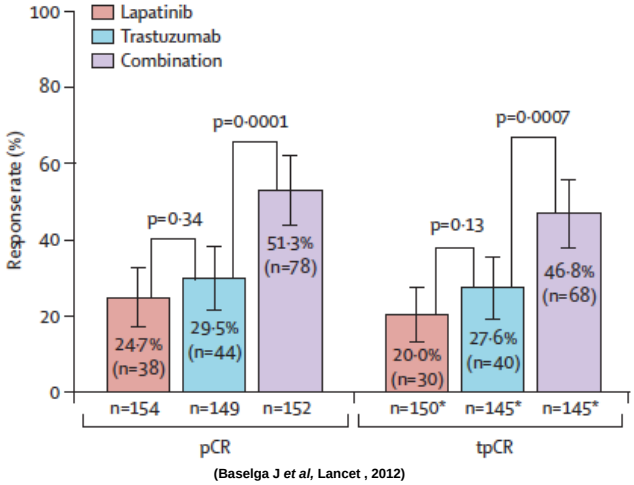
NeoALTTO Study

Pathologic Complete Response (pCR) rates by treatment arm



(Baselga J *et al*, Lancet , 2012)

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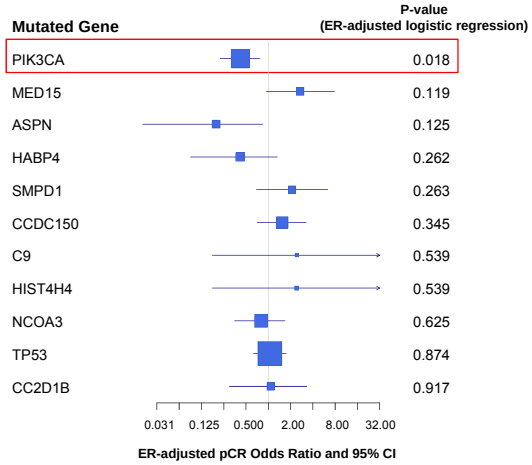
Results

Mean coverage = 150x
90% of target bases had >30x coverage in 99% of samples
Median number of somatic variants = 65 /sample
Median number of HFI variants = 34 / sample

At gene level, only PIK3CA mutations showed significant (negative) association with pCR



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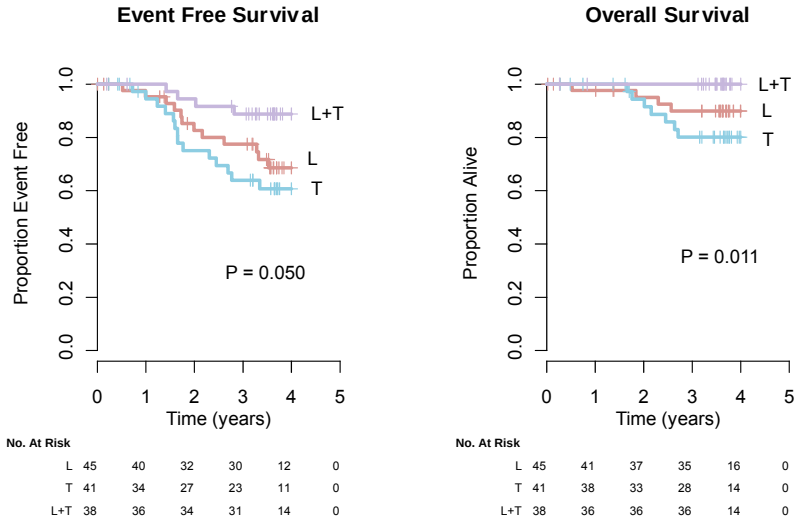
RhoA pathway wild-type and PIK3CA network mutant cancers (60%) have better outcome with L+T compared to T alone



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Novel Neoadjuvant Therapeutics

- Trastuzumab-emtansine (T-DM1) is a anti-body drug conjugate linking trastuzumab to the cytotoxic emtansine, it is approved for pts with HER2+ metastatic breast cancer
- Palbociclib is CDK 4/6 inhibitor approved with endocrine therapy for pts with ER+ metastatic breast cancer

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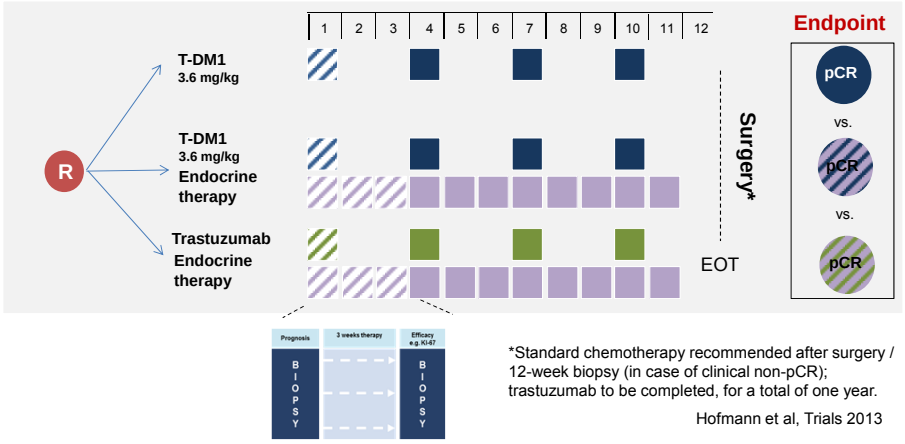
ADAPT HER2+/HR+: Trial design



*Standard chemotherapy recommended after surgery / 12-week biopsy (in case of clinical non-pCR); trastuzumab to be completed, for a total of one year.

Hofmann et al, Trials 2013

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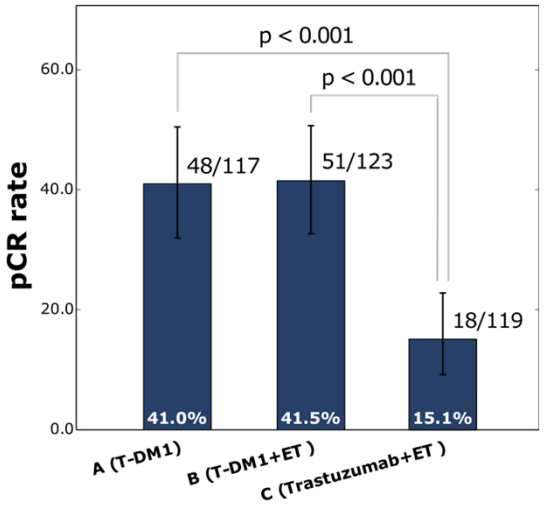
ADAPT HER2+/HR+: pCR (no invasive tumor in breast and nodes)



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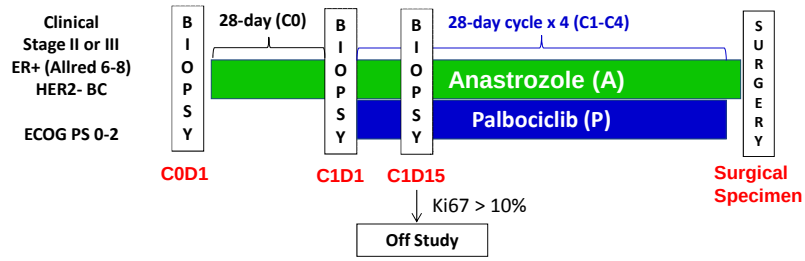
Neoadjuvant Palbociclib

Single Arm Phase II

Schema



Primary Endpoint: Complete cell cycle arrest (CCCA), defined as Ki67 ≤2.7% (LnKi67=1)#, on C1D15 biopsy post 2 weeks of both anastrozole (A) + palbociclib (P).

***# Ref:** Ellis et al JNCI 2008: 100, 1380-8*

Secondary Endpoints: Clinical, Radiographic and Pathologic Response, Safety profile; CCCA rate and changes in Ki67 by intrinsic subtype and *PIK3CA* mutation status; Molecular effect of palbociclib and NGS of an 83-gene panel to explore resistant mechanisms.

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Clinical Response

	Clinical Response	N	%
Completed study drug for at least 3 cycles (n=41)	Complete Response	11	24%
	Partial Response	20	43%
	Stable Disease	6	15%
	Unconfirmed progression*	2	2%
	Unknown	1	4%
Off study per protocol (n=5)	>10% Ki67 (n=4) Goserelin failure (n=1)	5	11%
Withdrew consent in C1 (n=3); Physician decision off in C1 (n=1)			

Clinical response was determined based on WHO criteria

*Ultrasound did not show progression

Total Evaluable: N=46; Overall response: N=31 (67%, 90% CI: 54-79%)

Surg Path

Path Stage	N
I	7
II	22
III	9
unknown	1
Total	39

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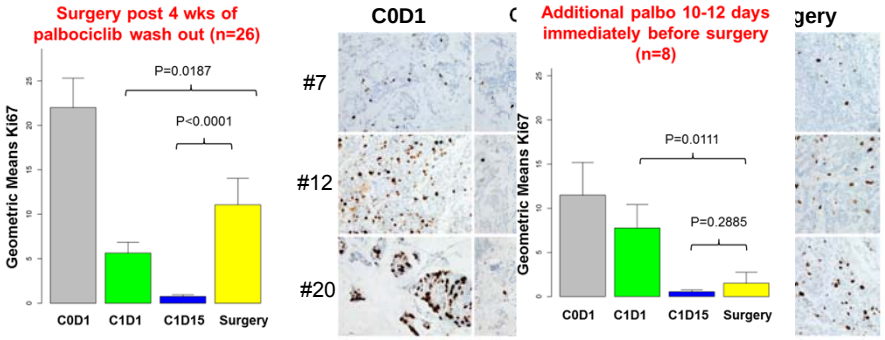
Ki67 Recovery at Surgery after 4 weeks of Palbociclib Wash out



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The Neoadjuvant Setting

- Indications: research, surgical, IBC
- A powerful research setting
  - Identifying biological and clinical activity
  - Tissue-based biomarkers
- pCR a surrogate for survival for individual patients BUT improvements to pCR rates due to a drug ≠ improvements in survival necessarily
  - Depth of pCR rate may matter
  - Drug definitely matters
- Caution when using neoadjuvant therapy with no survival validation
- Caution when extrapolating neoadjuvant data into adjuvant setting

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- Nadia Harbeck
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