Molecular Testing in Breast Cancer: An Oncologist's Perspective

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Disclosures

- I have no conflicts of interest to disclose.
- The views expressed here are mine alone and may not represent the views of the University of Utah, the State of Utah, or the Huntsman Cancer Institute

Objectives

- Understand how ER, PR, and HER2 testing are used in treatment decisions
- Recognize the options for genomic profiling of breast tumors
- Understand how genomic profiling is used in adjuvant treatment decisions
- Understand the potential roles for genomic profiling in metastatic treatment decisions


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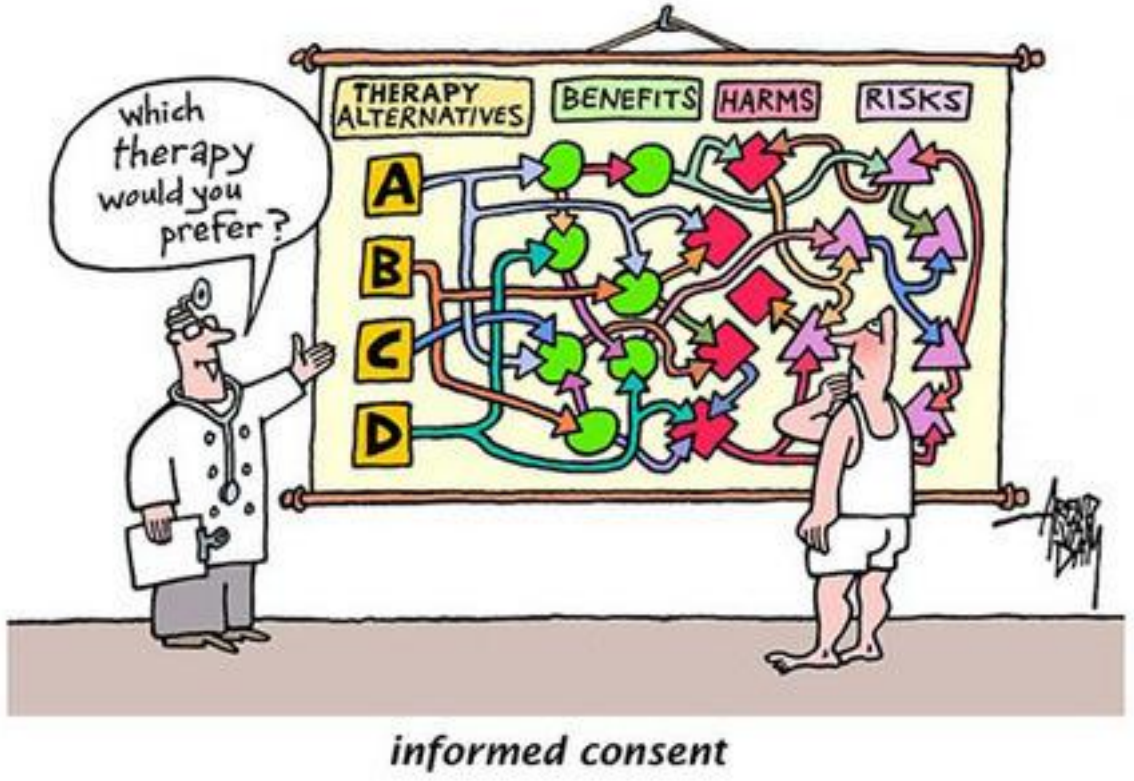
SURVIVOR

Decisions to be made

- Presentation
  - Surgery first or chemotherapy first?
  - Which neoadjuvant therapy to use?
- After surgery
  - What is the local recurrence risk?
  - What is the distant recurrence risk?
  - Is adjuvant chemotherapy needed, and if so which one?
  - Is adjuvant hormone therapy needed, and if so which one?
  - Is adjuvant biologic therapy needed?
- Metastatic disease
  - How long will she live?
  - What therapy to use when?

Options

- NCCN lists:
  - 21 adjuvant/neoadjuvant chemotherapies
  - 4 adjuvant endocrine therapies
  - 11 metastatic endocrine therapies
  - 34 metastatic chemotherapies
- How do we decide?

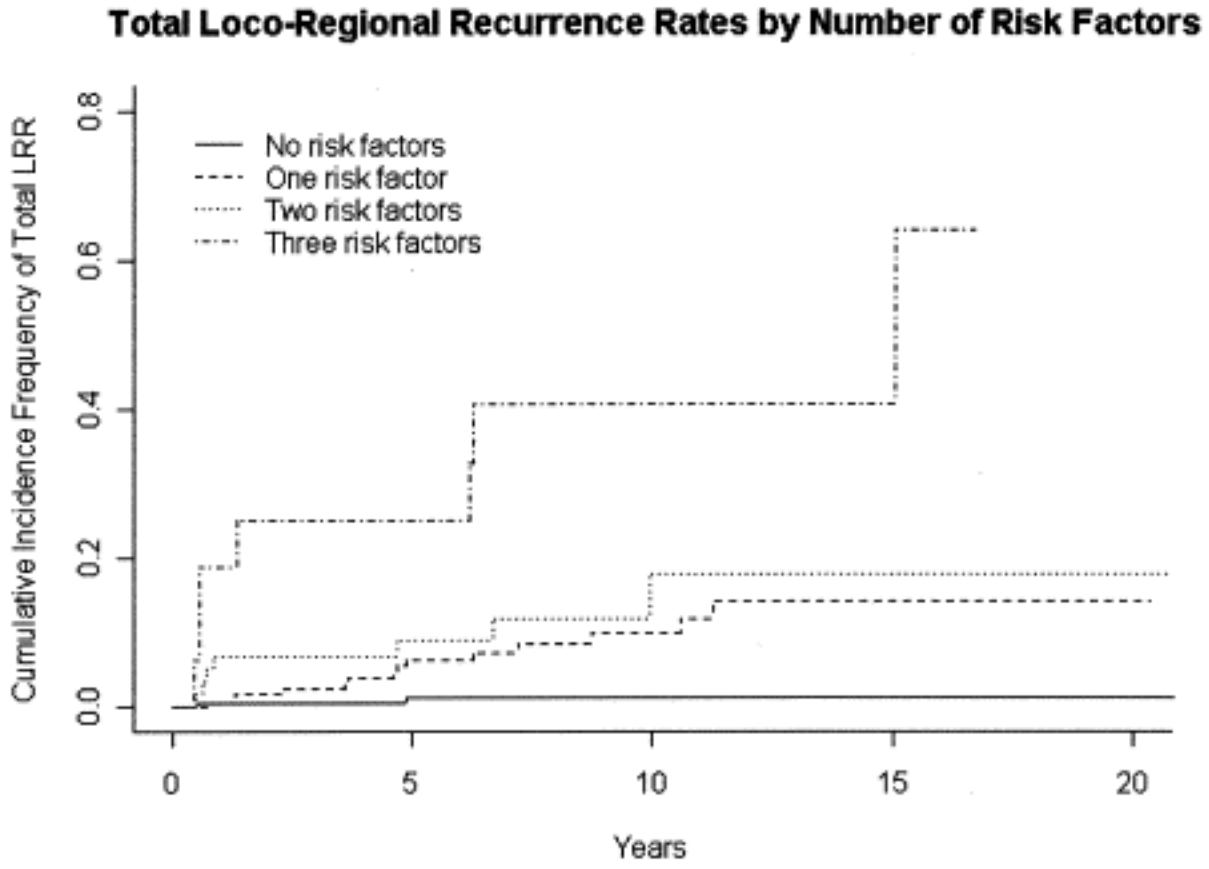


Decisions after surgery

- What is the local/distant recurrence risk?
  - Combination of biology and clinical factors
  - Clinical factors
    - Age
    - Size of primary tumor
    - Node positivity
    - Margins**
  - Biology
    - Estrogen receptor presence and activation
    - HER2 amplification
    - Proliferation
    - Grade
    - Lymphovascular invasion**

Local Recurrence after Mastectomy

- Margins ≥ 2mm
- Premenopausal
- Size > 2cm
- Lymphovascular invasion



International Journal of Radiation Oncology*Biology*Physics, Volume 62, Issue 4, 2005, 1035 - 1039

Decisions after surgery

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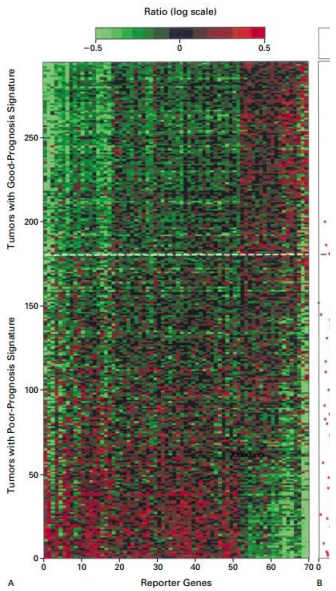
How do we measure estrogen receptor presence and activation?

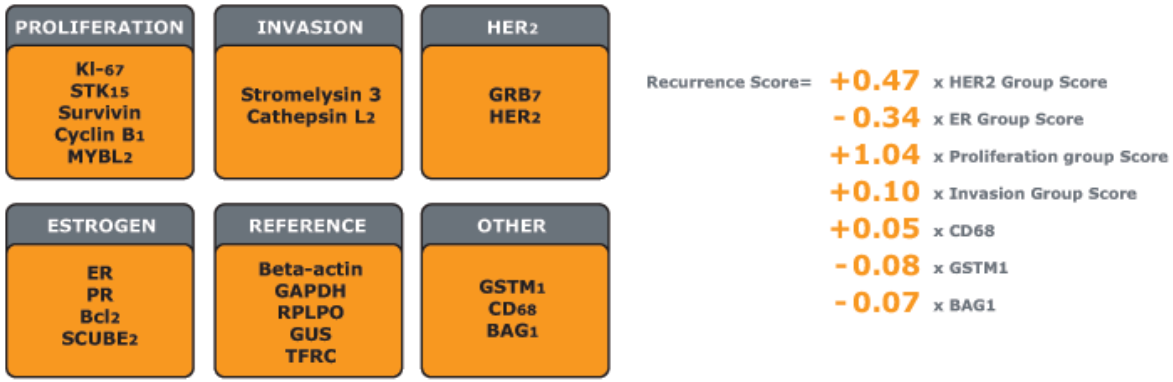
- Presence
  - Detected by immunohistochemistry
  - Number of positive cells and intensity are both important
  - Increasing ER by 1% decreases relapse by ~3%
- Activation
  - PR level
  - Gene expression analysis

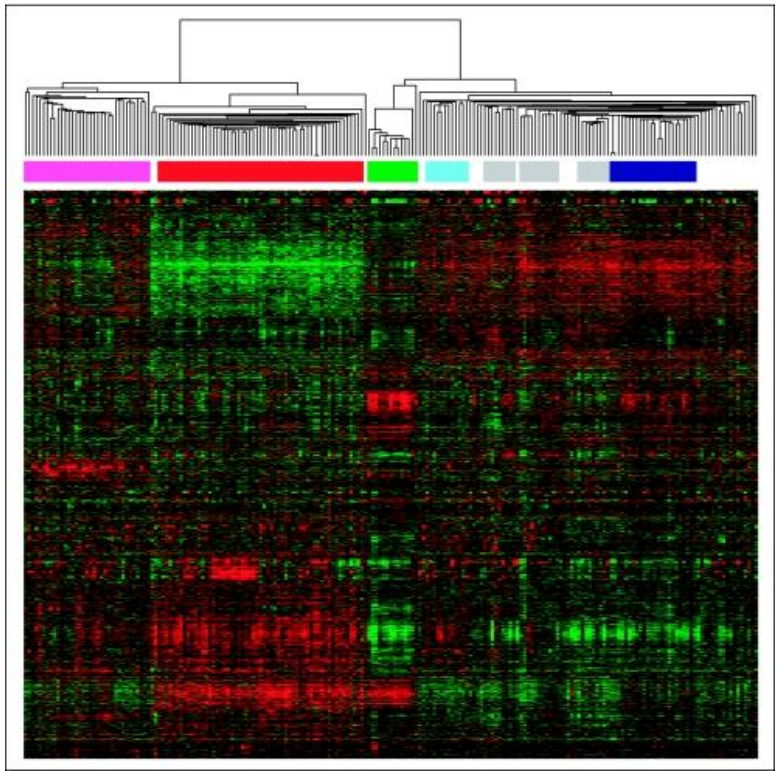
Modern Pathology (2013) **26,** 79–86;

Available gene expression tests

- Oncotype Dx recurrence score
- Mammaprint
- PAM50/Prosigna
- Breast Cancer Index



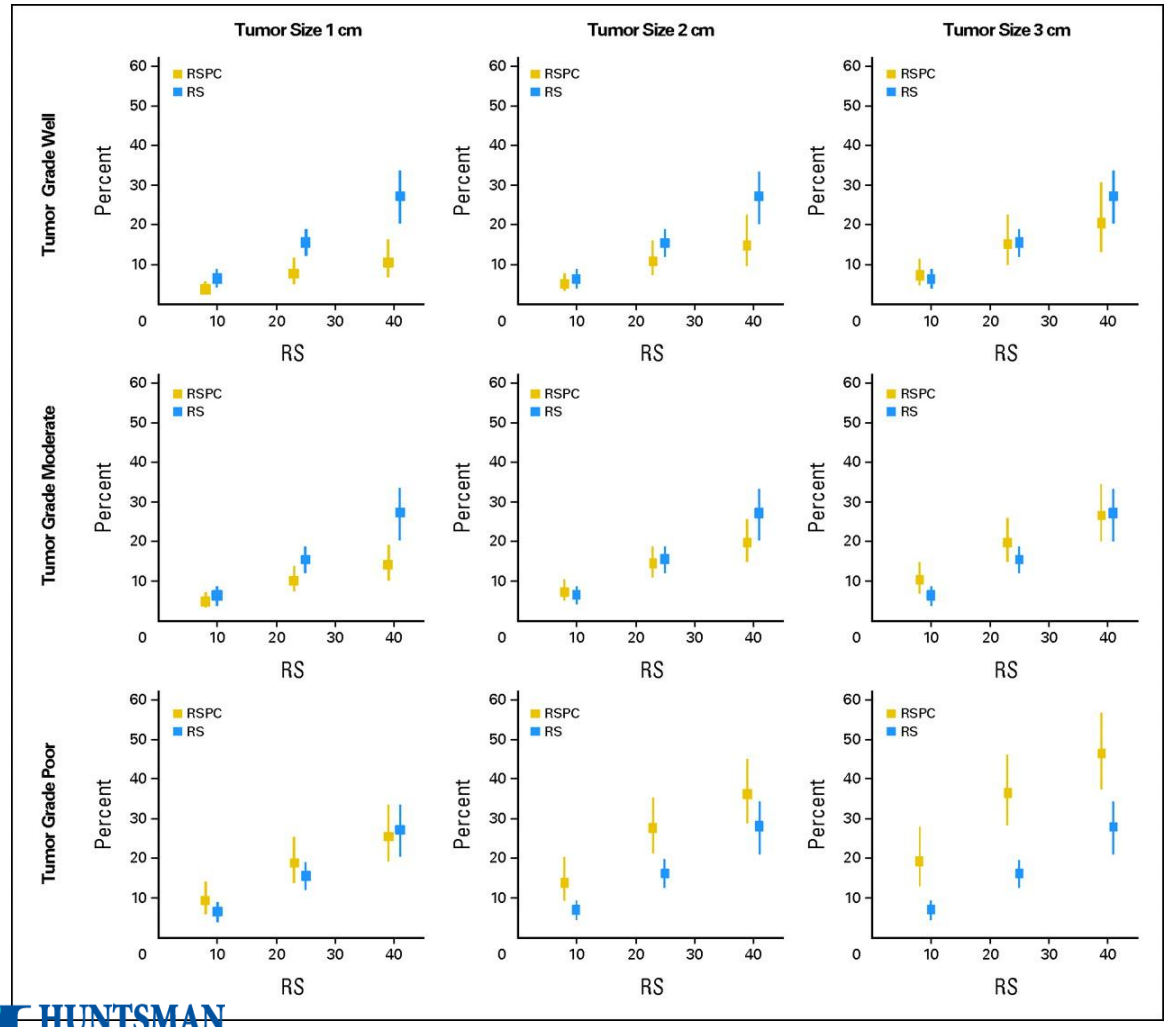




Features of gene expression tests

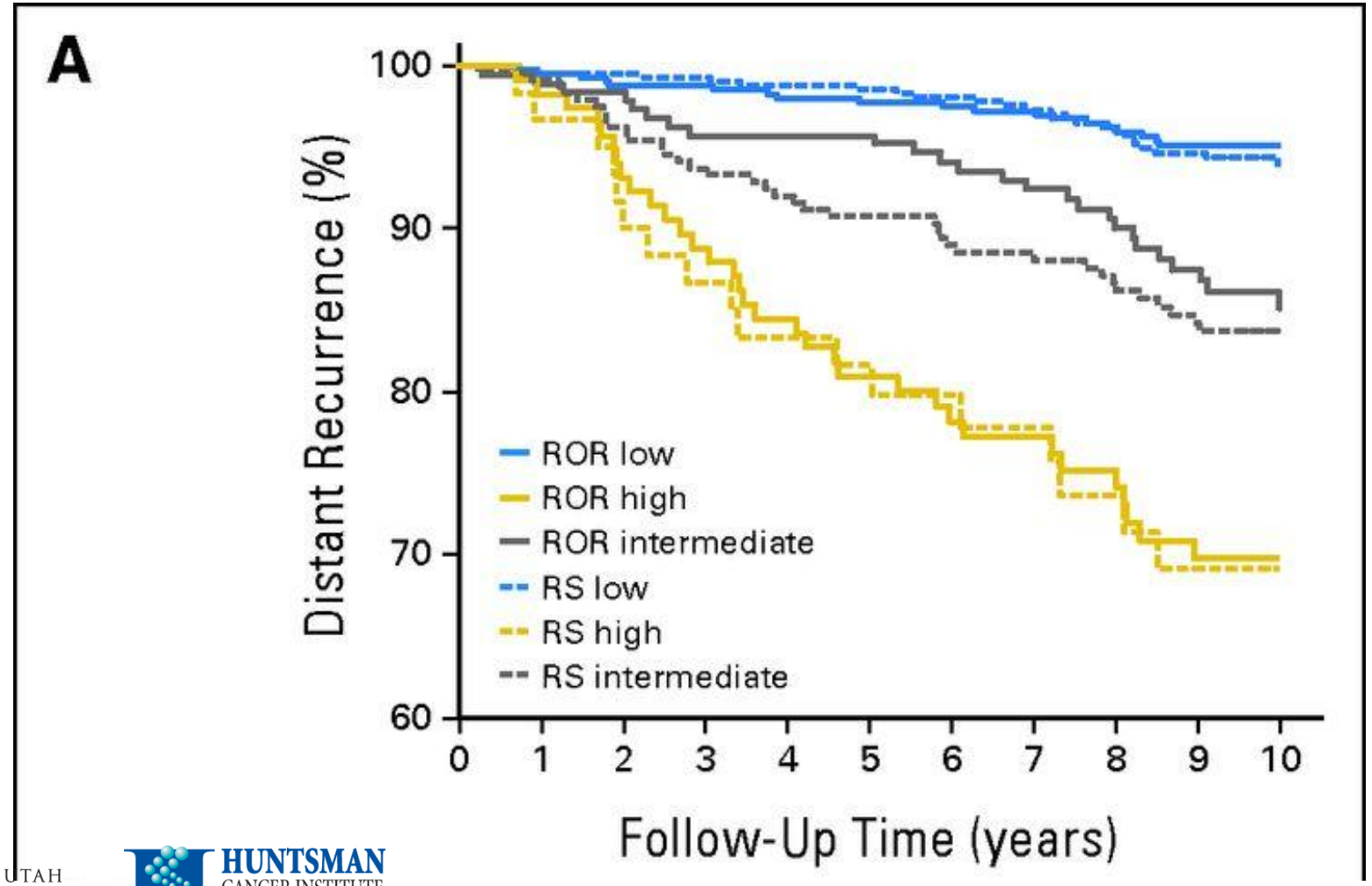
Feature	Oncotype	MammaPrint	Prosigna	Breast Cancer Index
Number of Genes	21	70	50	7
Able to be done on FFPE	Yes	Yes	Yes	Yes
Output	Score (0-100)	Binary (High/Low)	Score (0-100)	Score (0-10)
Population	ER-positive, HER2-negative Node negative (>1 validation) Node positive (1 validation)	<4 lymph nodes	ER-positive Node negative or node positive	ER-positive, node negative
Incorporates clinical variables	Calculator on website integrates age, size, and grade	No	Score incorporates tumor size	No
Predictive of chemotherapy benefit	Yes	Yes	Unknown	Unknown

Age, Size, and grade still matter



JCO **November 20, 2011** vol. 29 no. 33 **4365-4372**

Gene expression tests give similar data



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JCO **August 1, 2013** vol. 31 no. 22 **2783-2790**

What about immunohistochemistry?

- IHC4
  - Combines quantitative assessments of ER, PR, Ki-67, and HER2
  - Compares favorably to gene expression tests
  - Not clear how to lab-to-lab variability affects score
- Mammastrat
  - Five gene score
  - Prognostic, but not clearly predictive
  - Has not been compared to gene expression based assays
  - Benefit in premenopausal women not established

Table 3. Examples of Predicted 9-Year Distant Recurrence Probabilities for 25th and 75th Percentiles of the IHC4 and GHI-RS Scores for Different Grades and Nodal Status for a Women Age ≥ 65 Years With a 1- to 2-cm Tumor Treated With Anastrozole

Grade		Poor or Undifferentiated		Moderate		Well Differentiated	
Nodal Status	Percentile Score	IHC4	GHI-RS	IHC4	GHI-RS	IHC4	GHI-RS
Node Negative	25	7.1	8.3	4.8	5.8	2.2	2.5
	75	13.1	12.1	8.9	8.4	4.2	3.6
Node Positive	25	10.4	12.1	7.1	8.4	3.3	3.6
	75	18.8	17.3	13.0	12.2	6.2	5.3

Abbreviations: GHI-RS, Genomic Health recurrence score; IHC4, four immunohistochemical markers (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and Ki-67).

JCO November 10, 2011 vol. 29 no. 32 4273-4278

Mammostrat Biomarkers

Protein Markers	Function
p53 HTF9C	Cell Cycle Regulation
CEACAM5	Differentiation
NDRG1	Hypoxia
SLC7A5	Nutrient Supply

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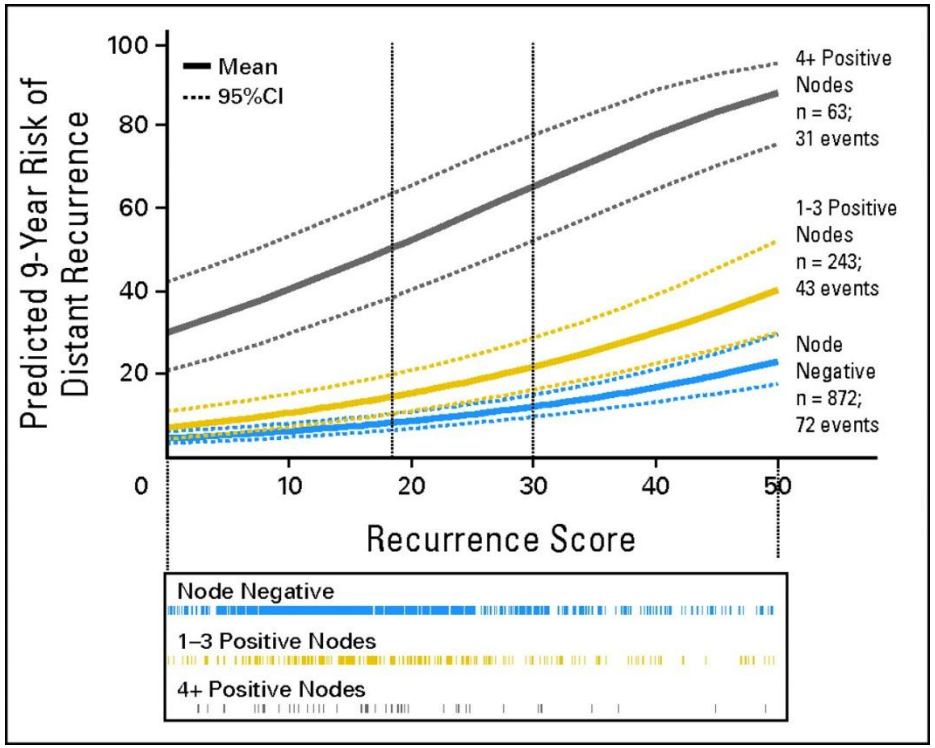
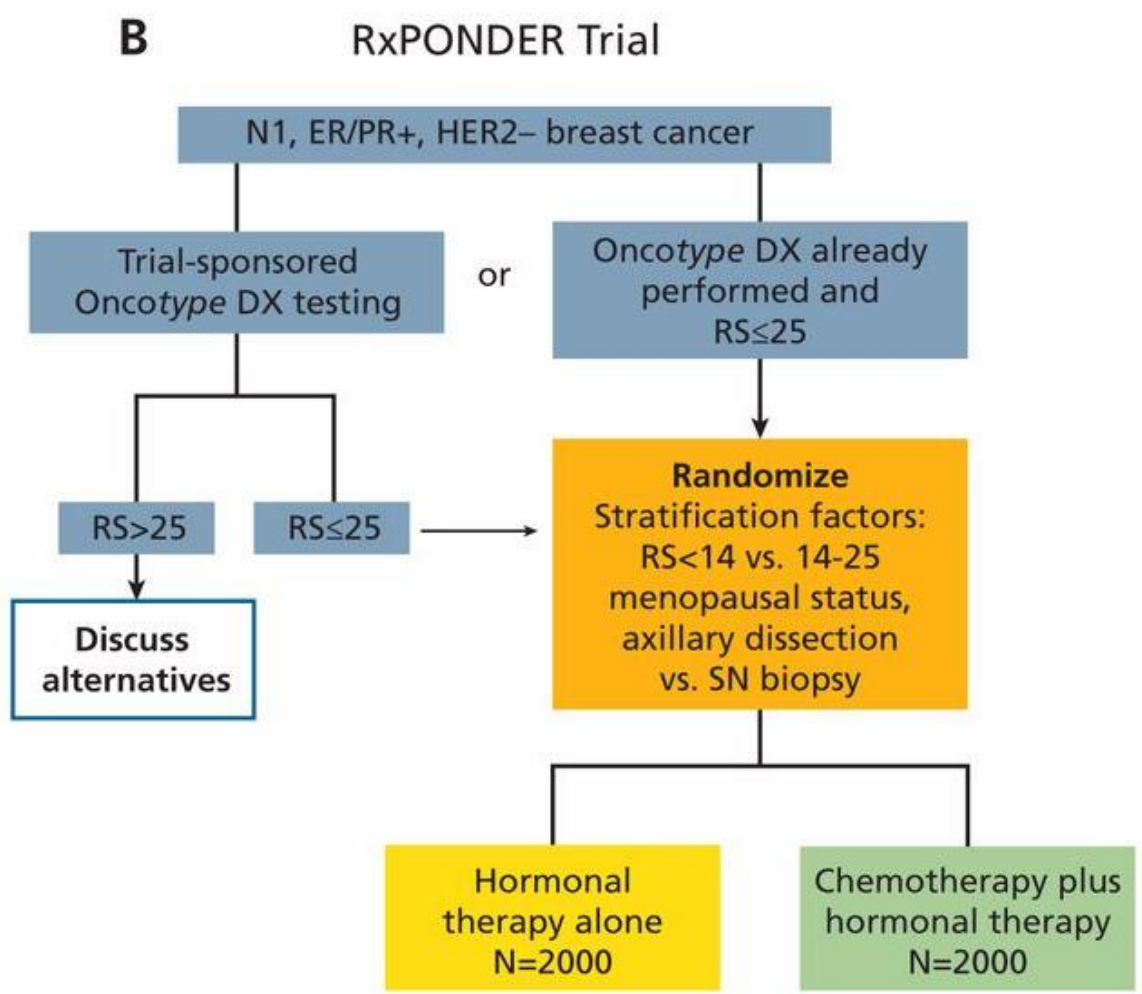
What about node-positive ER-positive disease

- Historically and per NCCN, chemotherapy is indicated.



Dowsett M et al. JCO 2010;28:1829-1834



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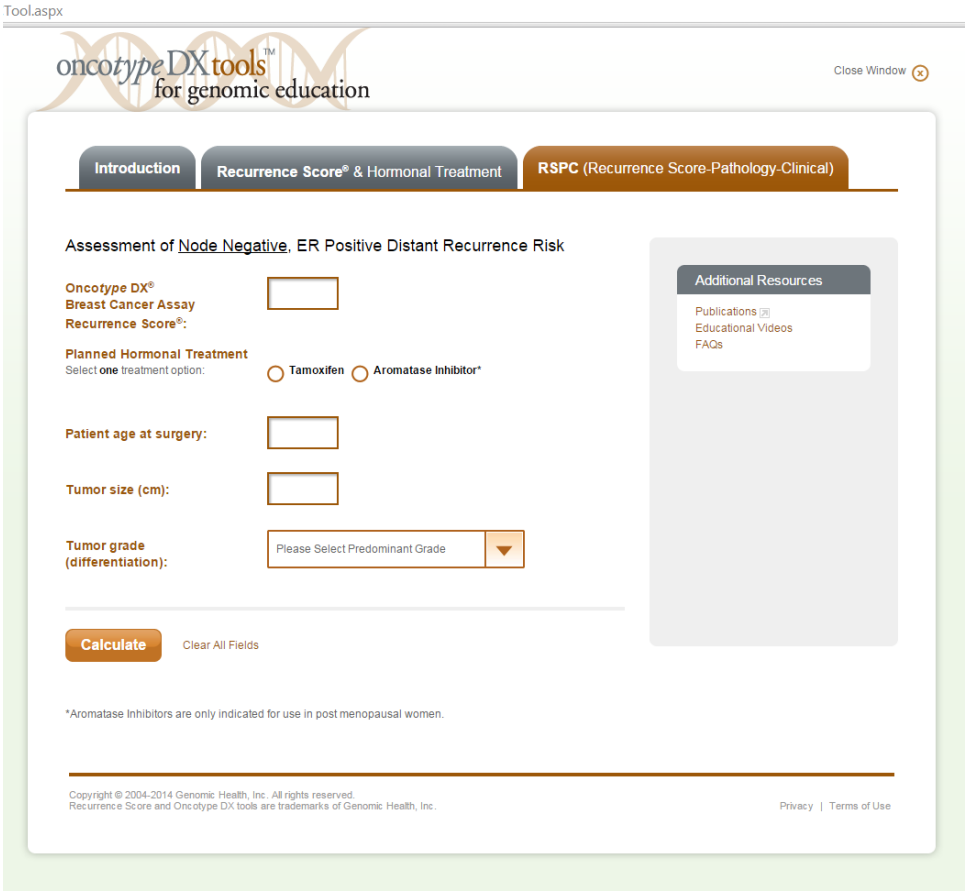
My approach in ER-positive, HER2-negative breast cancer

- > 4 nodes -> Chemotherapy followed by endocrine therapy
- Node-negative
  - Estimate range of possible recurrence risks based on clinical factors and recurrence scores
  - Determine chemotherapy based on recurrence risk and potential benefit from chemotherapy
- 1-3 nodes
  - Agonize
  - Consider enrolling on RxPonder
  - Recommend chemotherapy pending RxPonder results, but if gene expression test is low risk, strength of recommendation depends on clinical factors



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Gene expression does not replace traditional HER2 testing

		RT-PCR in OncotypeDx			
		Equivocal	Negative	Positive	Total
IHC/FISH	Equivocal	0	23	0	23
	Negative	5	779	0	784
	Positive	12	14	10	36
	Total	17	816	10	843

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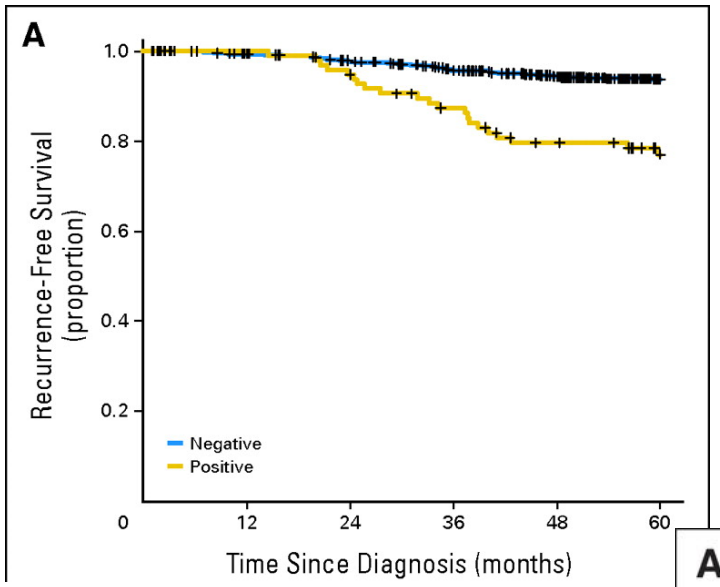
JCO **November 10, 2011** vol. 29 no. 32 **4279-4285**

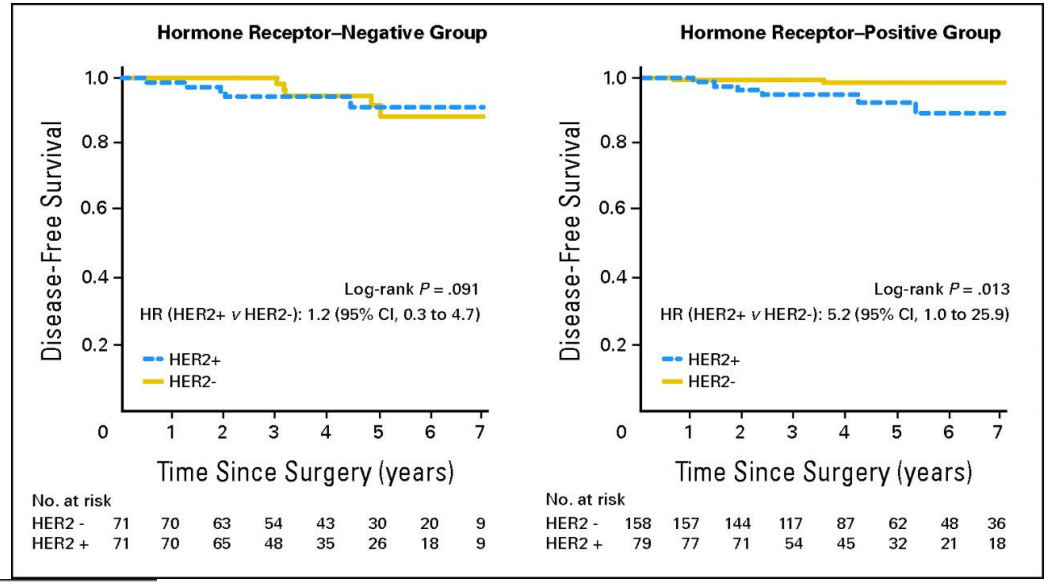
Choice of regimen for HER2-positive cancers is based on clinical factors

- No test for withholding trastuzumab based on biologic factors
- Since trastuzumab must be given with chemotherapy, want to limit chemotherapy exposure in low risk women
- Node-positive -> chemotherapy plus trastuzumab plus pertuzumab
- > 3 cm, node negative -> chemotherapy plus trastuzumab plus pertuzumab
- 1-3 cm -> taxol and trastuzumab
- < 1cm -> controversial

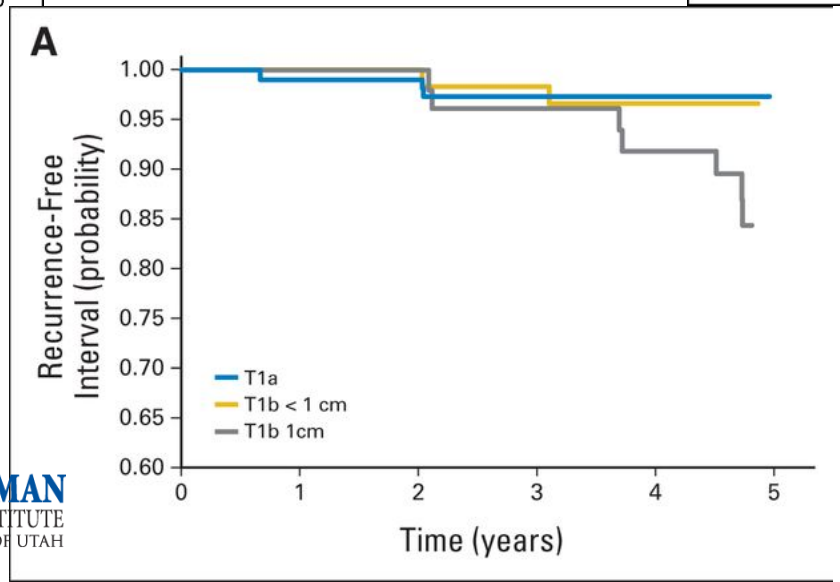
Small HER2-positive cancers



JCO December 1, 2009 vol. 27 no. 34 5700-5706



JCO December 1, 2009 vol. 27 no. 34 5693-5699



JCO July 10, 2014 vol. 32 no. 20 2151-2158

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Current Clinical Dilemmas

- Adjuvant chemotherapy for clinically high risk but biologically chemotherapy-resistant tumors?
- Neoadjuvant endocrine therapy for very estrogen-sensitive tumors?
- Can we predict which endocrine therapy to use in the adjuvant setting?
- What size cutoff should be used for anti-HER2 therapy?
- Utility of adjuvant endocrine therapy in tumors with low ER-positivity?

Decisions at presentation

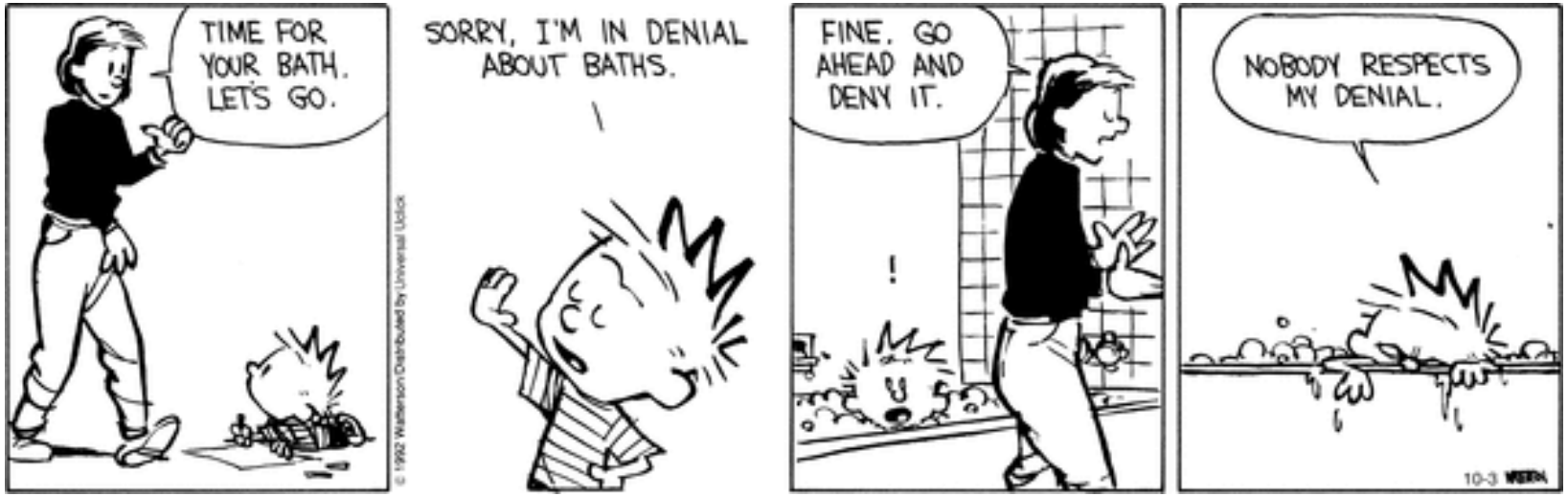
- Is therapy needed prior to surgery for localized disease?
  - Easy yes
    - Clinical T4 or Clinical N2
    - Why?
      - Surgeon needs easier surgery
      - Maximal therapy is needed
        - Anthracycline, taxane, trastuzumab, pertuzumab
  - Easy no
    - Anyone who may not need adjuvant therapy
    - Tumor < 1cm
    - Clinically node negative ER-positive
    - ER, PR, HER2 can’t be done on biopsy

Decisions at presentation

- Is therapy needed prior to surgery for localized disease?
  - Harder decisions
    - Adjuvant therapy will definitely be needed but no clear advantage to preoperative therapy
      - Triple-negative >1 cm
      - HER2-positive > 1 cm
      - Node-positive Triple-negative or HER2-positive
    - If I know what regimen is needed, based on clinical factors, comorbidities, or schedule, then may do preoperative therapy.

Metastatic breast cancer

- How long will she live?
- What therapy to use when?

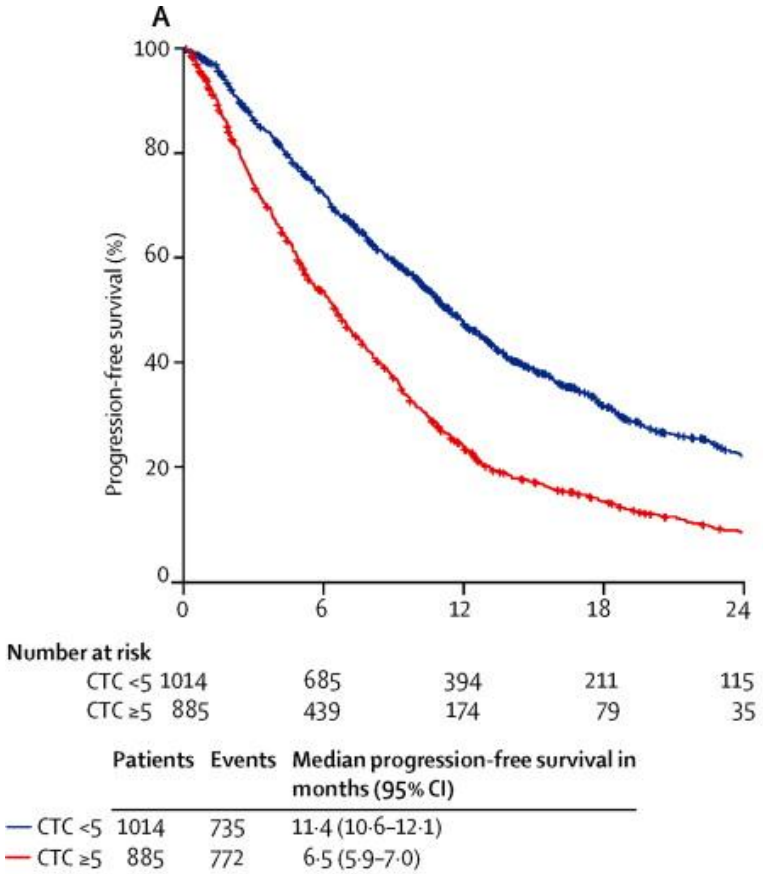


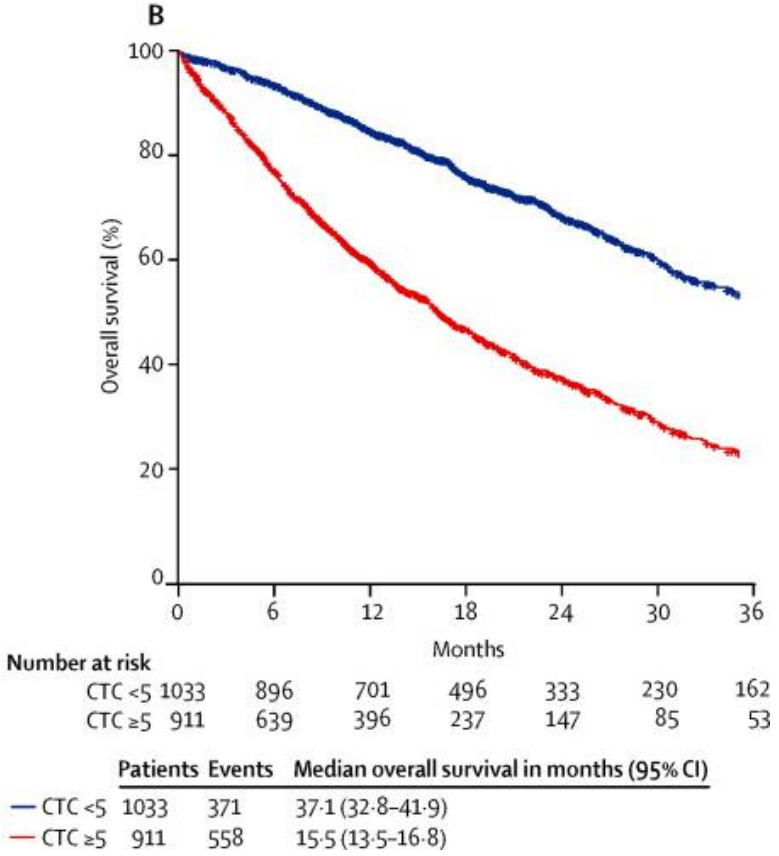
Metastatic breast cancer

- Prognosis is affected by:
  - Clinical factors
    - Location of metastases
    - Performance status
    - Prior therapies
  - Biologic factors
    - Histology
    - Molecular subtype
    - Location of metastases

Circulating Tumor Cells (CTCs)

- Add prognostic information to clinical variables
- Change in AUC is ~0.02





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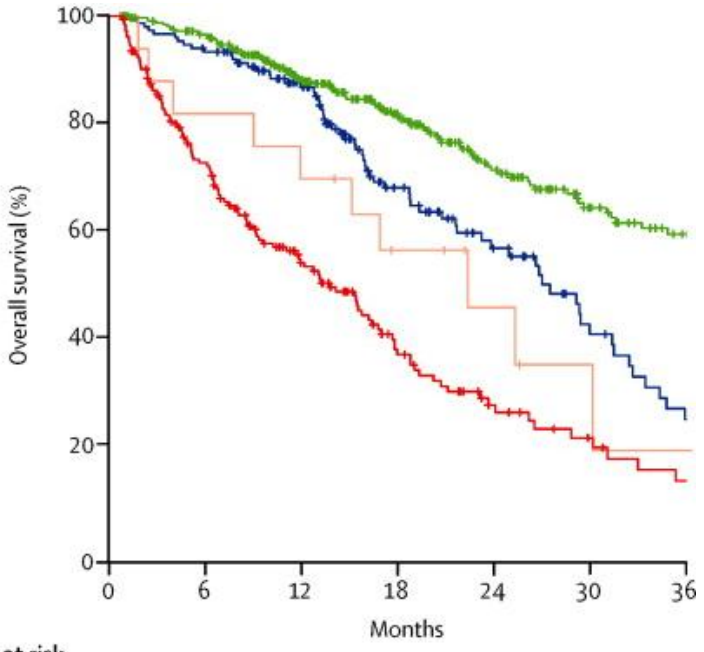
Lancet Oncol. 2014 Apr;15(4):406-14

Change in CTC count is prognostic



Number at risk							
Decrease	149	135	104	59	36	20	11
Increase	17	13	11	7	4	2	1
Stable negative	327	296	231	160	102	68	50
Stable positive	179	116	68	36	18	10	5

	Patients	Events	Median overall survival in months (95% CI)
Decrease ≥5–<5	149	70	27·0 (21·7–31·5)
Increase <5–≥5	17	10	22·4 (11·9–NA)
Stable negative <5–<5	327	104	41·5 (36·8–52·7)
Stable positive ≥5–≥5	179	116	13·1 (9·4–16·4)

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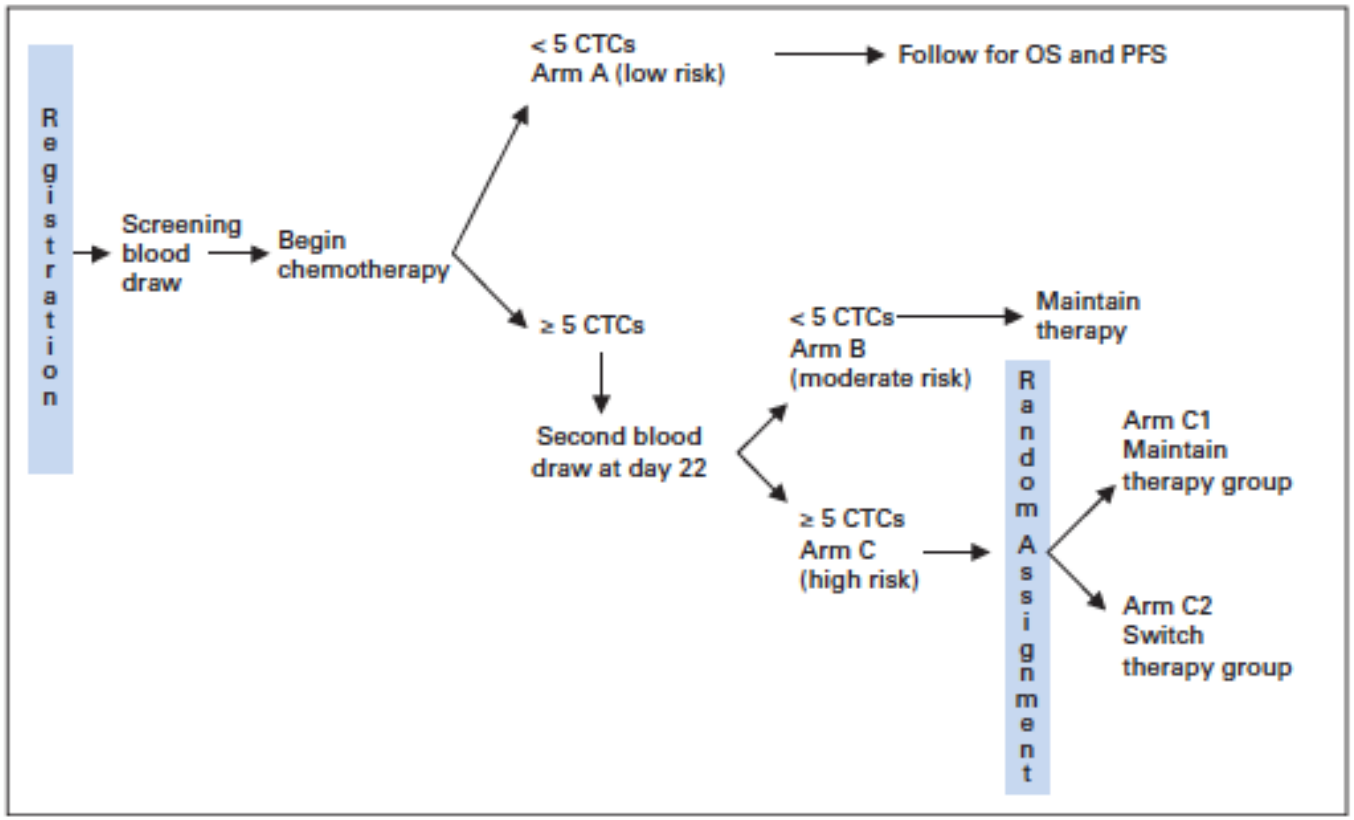
Lancet Oncol. 2014 Apr;15(4):406-14

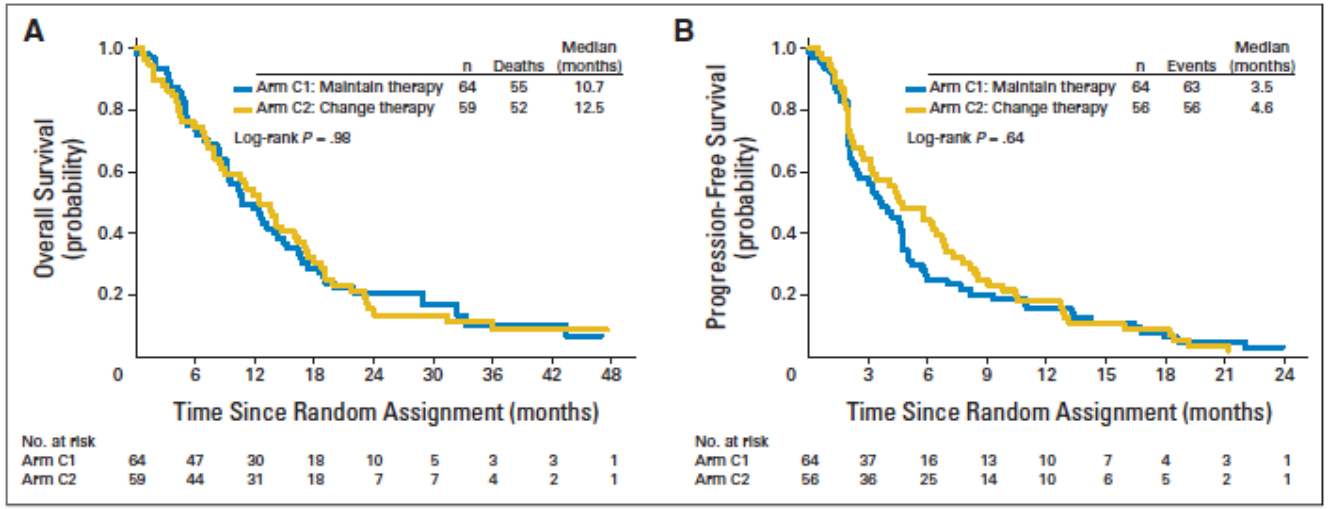
S0500: Does changing therapy base on CTC affect survival



Lancet Oncol. 2014 Apr;15(4):406-14

S0500 results

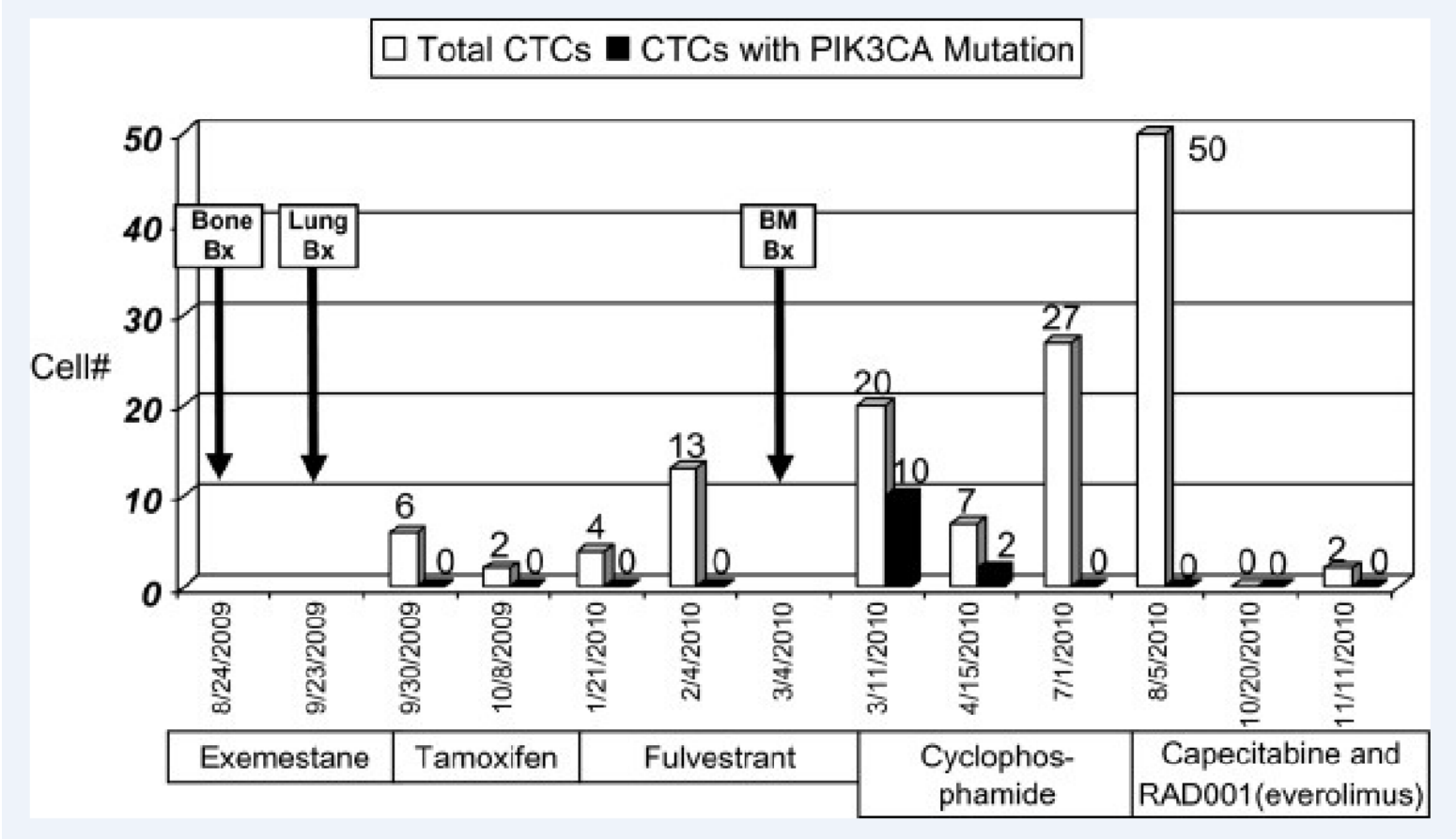
- Changing therapy for women with unchanged CTCs did not improve PFS or OS
- Why?
  - Underpowered study
  - Therapy options are similar in mechanism
  - Women tend to see sequentially all classes of drugs



J Clin Oncol. 2014 Nov 1;32(31):3483-9.

Can blood tests be used to identify targets for therapy?

- Mutations can be found in both CTCs and ctDNA
- Is knowledge of these mutations useful?



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Mol Oncol. 2013 Oct;7(5):976-86
Clin Cancer Res. 2012 Jun 15; 18(12): 3462–3469.

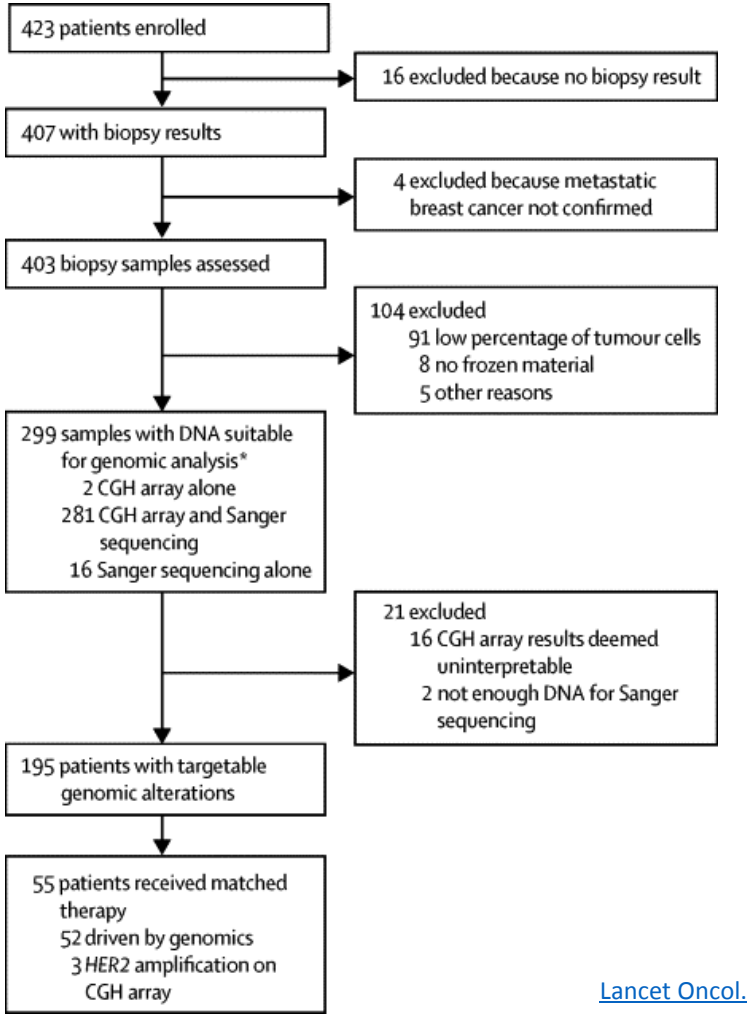
Can CTCs be used to identify targets for therapy?

- Targets in CTCs may not reflect the full biology
  - Phase 2 trial of lapatinib in women with HER2-positive CTCs but HER2-negative tumors
  - 7 of 96 women screened
  - No responses, 1 stable disease

Breast Cancer Res Treat. 2012 Jul;134(1):283-9

Molecular Profiling to Determine Treatment

- SAFIR01/UNICANCER trial
- Feasibility study to see how often targeted treatments could be identified for women with metastatic breast cancer



Lancet Oncol. 2014 Mar;15(3):267-74.

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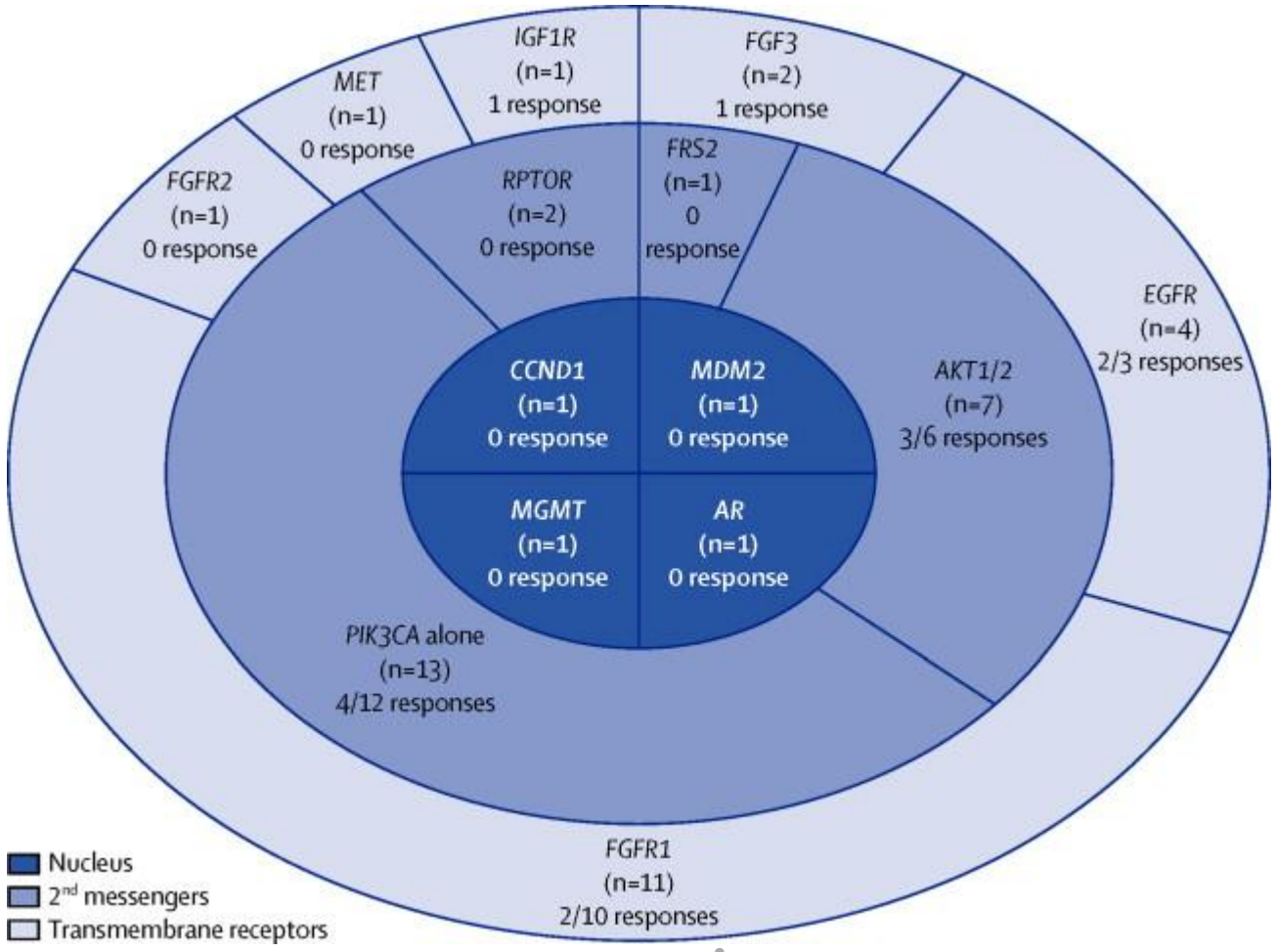
SAFIR01: A mixed success

- Issues with targeting somatic genetic alterations
  - Context matters
  - Current drugs are suboptimal
  - 50% of women don't have targetable alterations



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Question 1

- Which of the following is a predictor for distant relapse of early ER-positive breast cancer independent of molecular features?

A. Grade

B. Margin size

C. Ki-67

D. Germline BRCA status

Question 2

- RT-PCR testing for HER2 status in early breast cancer:

A. Has equivalent accuracy to FISH or immunohistochemistry
B. Is more likely to be called positive than FISH
C. Should not be used to withhold anti-HER2 therapy
D. Can be used when FISH is equivocal to decide whether to give anti-HER2 therapy

Question 3

- The presence of >5 circulating tumor cells/ml of blood in a woman with metastatic breast cancer:

A. Predicts increased sensitivity to chemotherapy

B. Decreases median overall survival by about 50%

C. Can be used to determine HER2 status

D. Determines the need for combination chemotherapy

Question 4

- Multigene mutation profiling of metastatic breast cancer:

A. Can detect actionable mutations in the vast majority of women
B. Can be performed on FFPE from most tumors
C. Leads to a greater than 50% response rate from targeted therapies
D. Works because targeted drugs will have the same effect regardless of histology

Question 5

- Multigene gene expression tests are most helpful for:

A. A 50 year-old woman with a 3cm, ER-positive, PR-positive, HER2-negative invasive ductal cancer and negative nodes

B. An 85 year-old wheelchair bound woman with a 3cm, ER-positive invasive ductal cancer and negative nodes

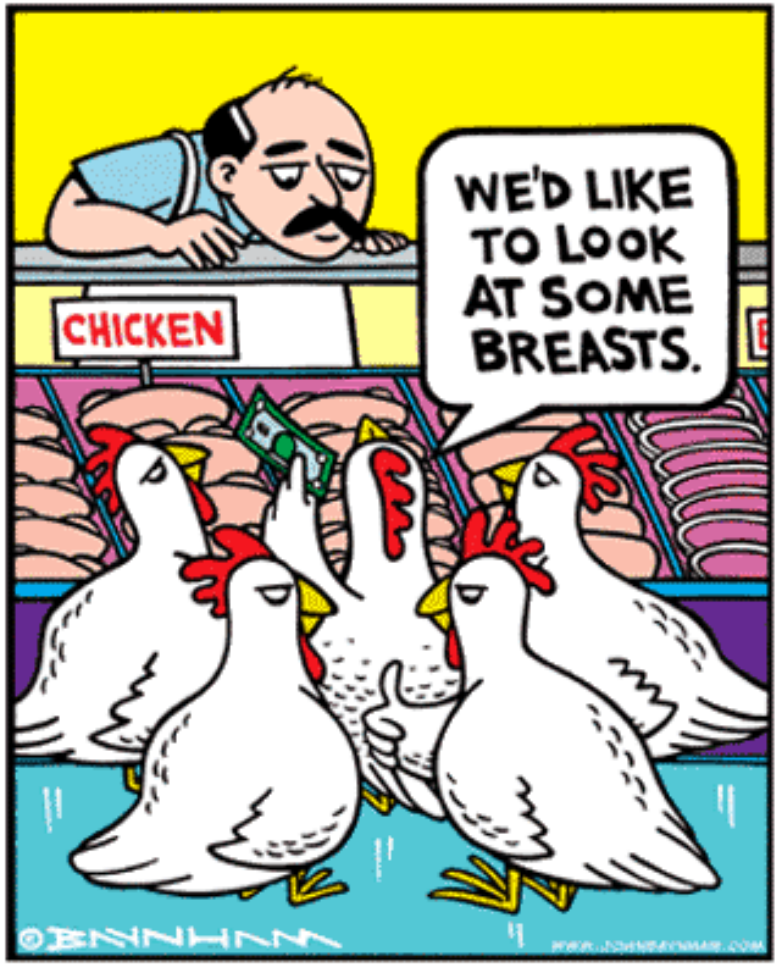
C. A 40 year-old woman with a 3 cm, ER-negative, PR-negative, HER2-negative invasive ductal cancer and negative nodes

D. A 60 year-old woman with a 3 cm, ER-positive invasive ductal cancer and 5 positive lymph nodes

E. A 55 year-old woman with a 3 cm, ER-positive, PR-positive, HER2-positive invasive ductal cancer with negative lymph nodes

Thank you

- Questions?



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