Aiom
Associazione Italiana di Oncologia Medica
SEZIONE REGIONE LAZIO

POST SAN ANTONIO
BREAST CANCER
SYMPOSIUM 2018

28 Gennaio 2019
POLICLINICO UMBERTO I - ROMA
Aula Bignami (Patologia Generale)
Viale Regina Elena 324

Early disease
Node positive:
chemotherapy to all women?

GIULIANA D'AURIA
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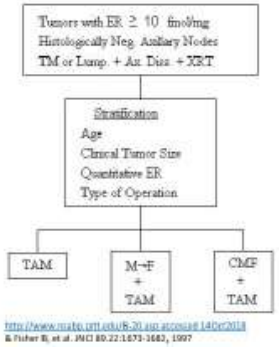
SABCS 2018 Session

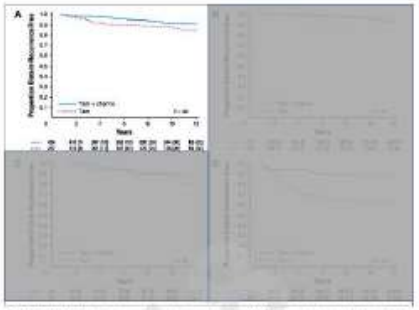
Should all women with breast cancer and positive lymph nodes receive chemotherapy?

SABCS 2018
9-9:45am Friday 7 December 2018
Moderator: Clifford Hudis, MD
Pro: Daniel F. Hayes, MD
Con: Harold J. Burstein, MD, PhD

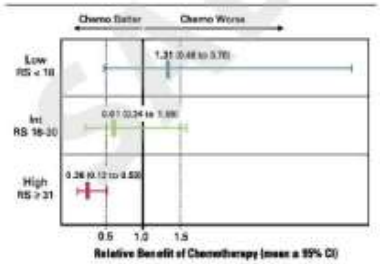
SABCS 2018 Session

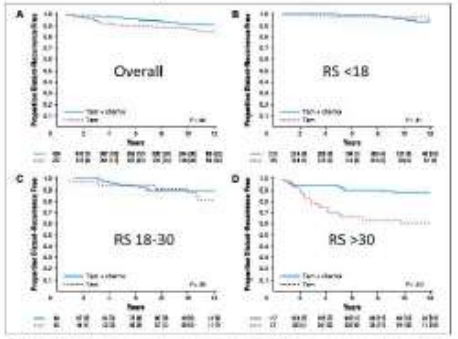
~1991 – Node Negative Disease: NSABP B-20 Suggested Chemotherapy For (Almost) All





2006 – Node Negative Disease: Genomic Assay-Stratified Outcomes And Said "Maybe Not All".





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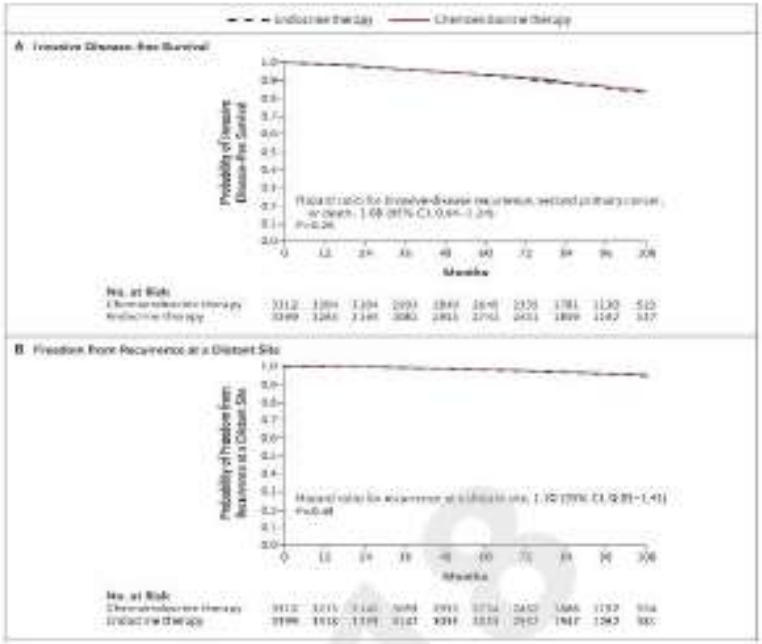
2018: TAILORx – RS 11-25: Limited Chemotherapy Impact (Node Neg)



JA Sparano et al. N Engl J Med 2018; DOI: 10.1056/NEJMoa1804710

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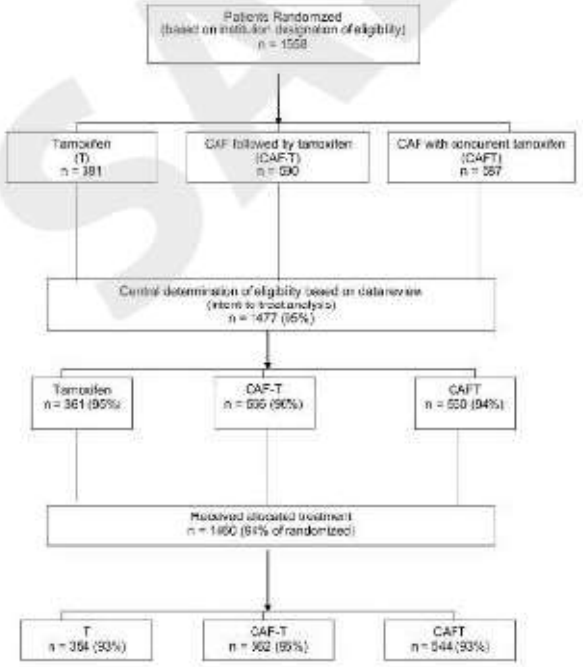
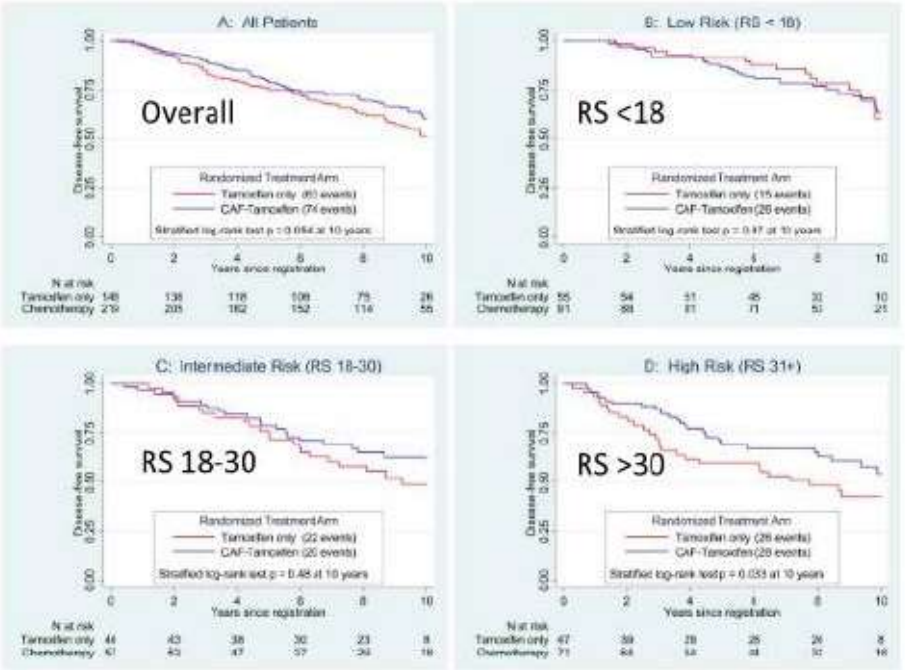
2010 – What do we do about node positives?



Lancet. 2005 Dec 10; 374(9707): 2055–2063.
Published online 2009 Dec 10. doi: 10.1016/S0140-6736(09)61523-3



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

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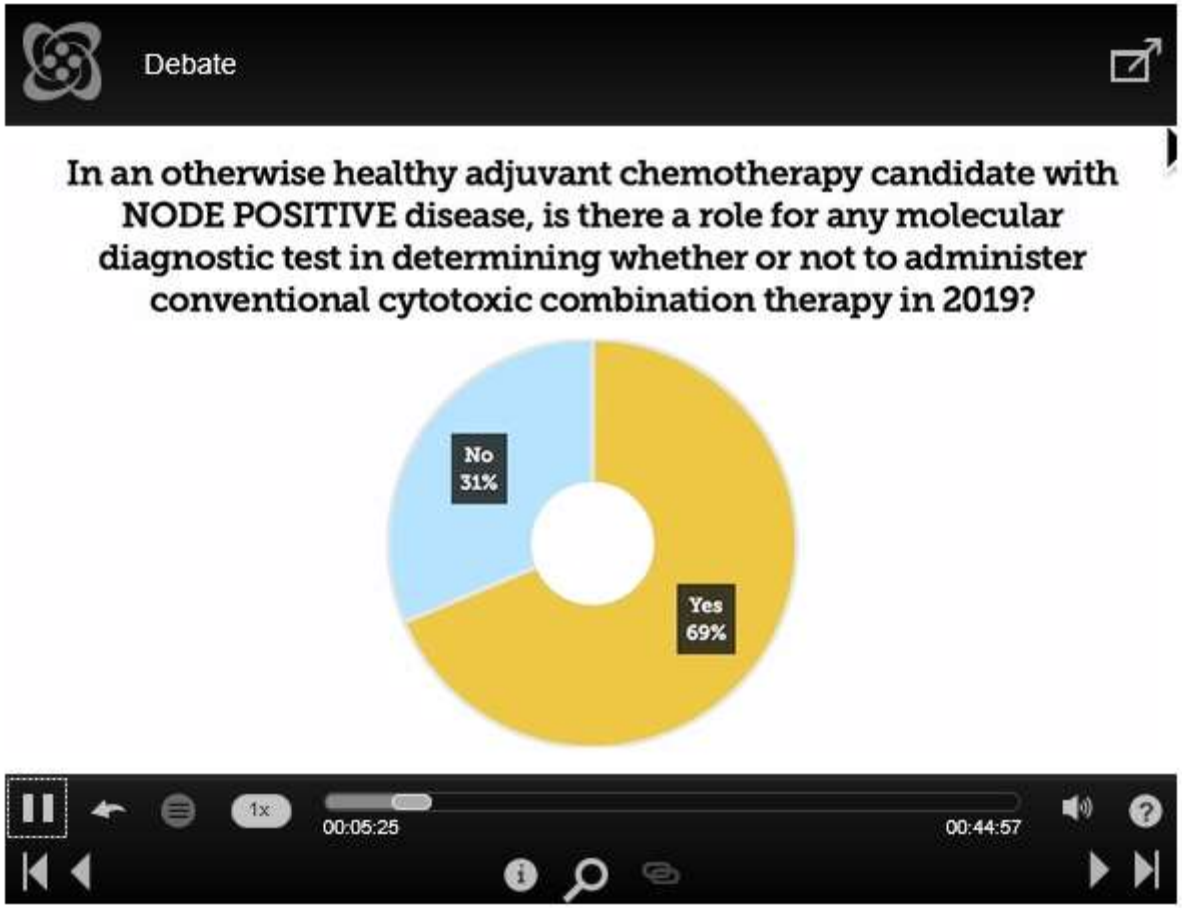
Harold Burstein, Daniel Hayes

UNLIKE



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Case 1.

- 43 y/o premenopausal woman has a right sided breast cancer found on screening mammography.
- Initial core biopsy confirms invasive ductal carcinoma
  - Grade 2-3 out of 3
  - ER positive 90%, PR positive 20% and HER2 1+ by IHC/negative by FISH
  - Ki67 is 14%.
- She undergoes lumpectomy and sentinel node mapping.
  - Tumor is 1.9 cm
  - Grade 3
  - 1 of 3 sentinel nodes positive for cancer: single focus measuring 4 mm in size.

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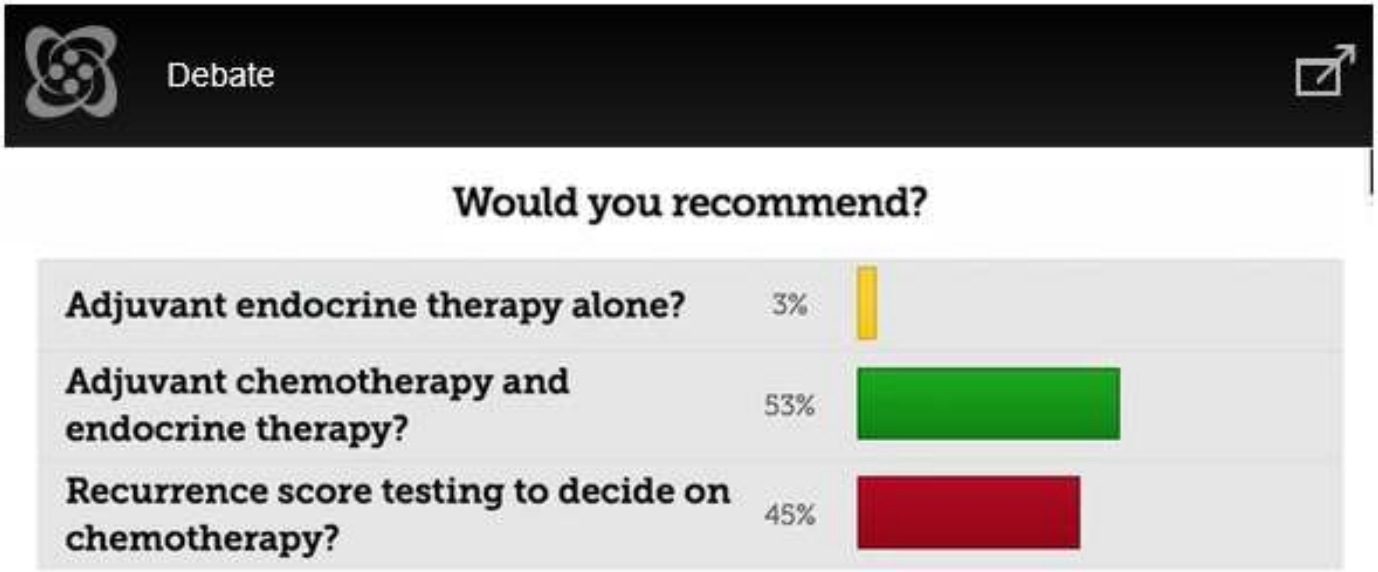
UNLIKE

Debate



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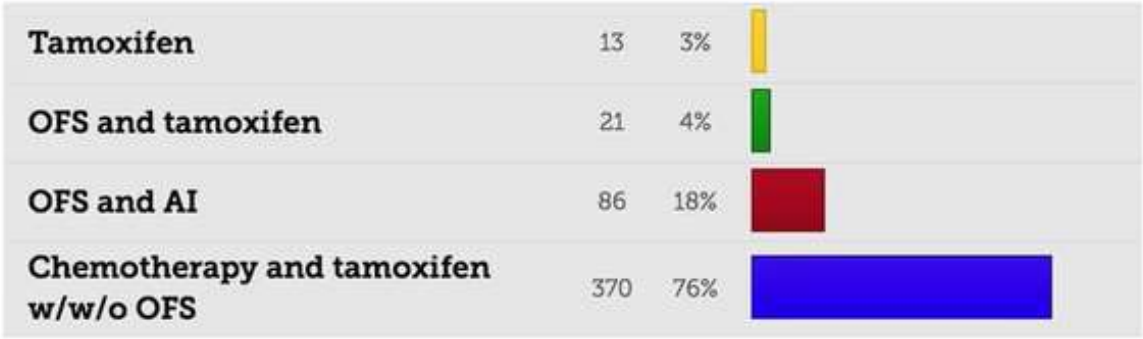
Harold Burstein, Daniel Hayes

UNLIKE

Debate

An OncotypeDX recurrence score is sent, and is "21". The patient is open to getting the "best" treatment. Now, would you recommend?



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Individualization of Adjuvant Chemotherapy

PROGNOSIS

ER Pos

"Few" (1-3) Node POSITIVE

Low Genomic Score (OncotypeDx)

Fundamental questions to consider:

Is nodal metastasis alone justification for recommending adjuvant chemotherapy?

Or, more precisely: Should we only use PROGNOSIS to make our decision?

1. PROGNOSIS:
- Are there node positive breast cancers with such a favorable prognosis that they do not NEED (cannot benefit from) chemo?

2. PREDICTION:
- Are there node positive breast cancers with a poor prognosis but for whom chemotherapy will not work?

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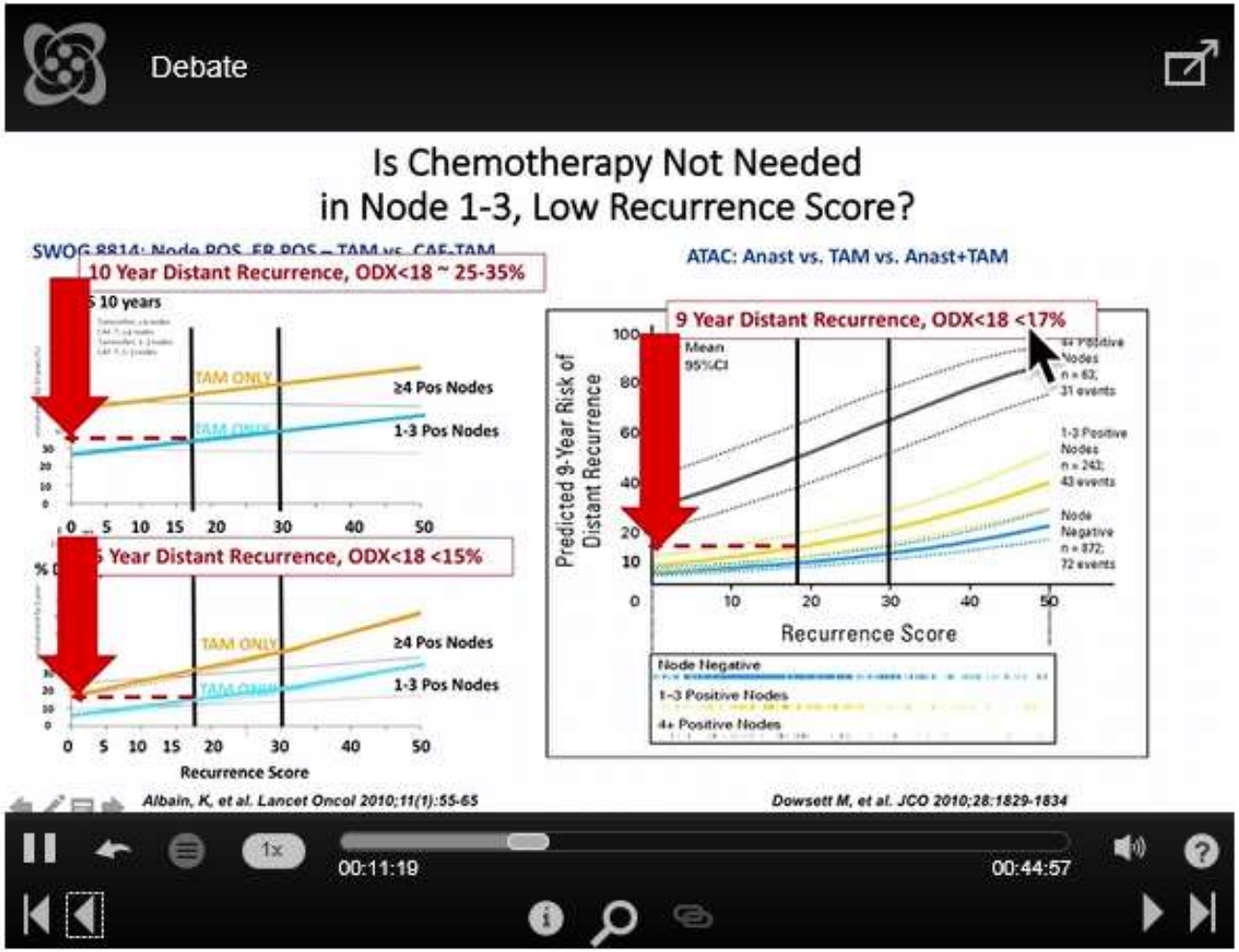

TransATAC
1231 tumor samples
306 N+
✓243 1-3 N+
✓63 ≥ 4 N+

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Is Chemotherapy Not Needed in Node 1-3, Low Recurrence Score?

- **Conclusions**
  - **Anatomic** Prognosis Still Important
    - Prognosis in Node positive patients worse than in node negative patients
  - **Genomic** Prognosis Does Pertain, But
    - Risk of Recurrence for patients with with POS Nodes and LOW RS still worse than NEG Node Low RS:

Node ≥4	(S8814)	*at 10 years*	*~50-60%!!*	*(High Early & LATE RECURRENCE).*
Node 1-3	(S8814)	*at 5 years*	*<15%*	*(But at 10 years ~ 30-35%).*
Node NEG	(B20,ATAC)	*at 10 years*	*<10%.*	

  - **MAYBE** avoid chemotherapy if Prognosis with
    - 1 pos node, especially if small (<2mm)

    BUT:
    - What about 2-5mm, ≥5mm, etc.?
    - What about 2 or 3 positive nodes?

Hayes' Conclusion

- For this patient based on **PROGNOSIS**
  - SINGLE <5 mm POS NODE, OncotypeDx Recurrence Score 21

It is probably reasonable to withhold adjuvant chemotherapy

Why?

BECAUSE:

- She would probably have have been called node negative 35 years ago
  - Many nodes resected instead of 2-3 sentinel nodes
  - Therefore, this patient is probably more like B20 and B14 than S8814
- Some evidence that patients are doing better today than in the past stage for stage
  - Screening
  - Better adjuvant ET
  - Other?

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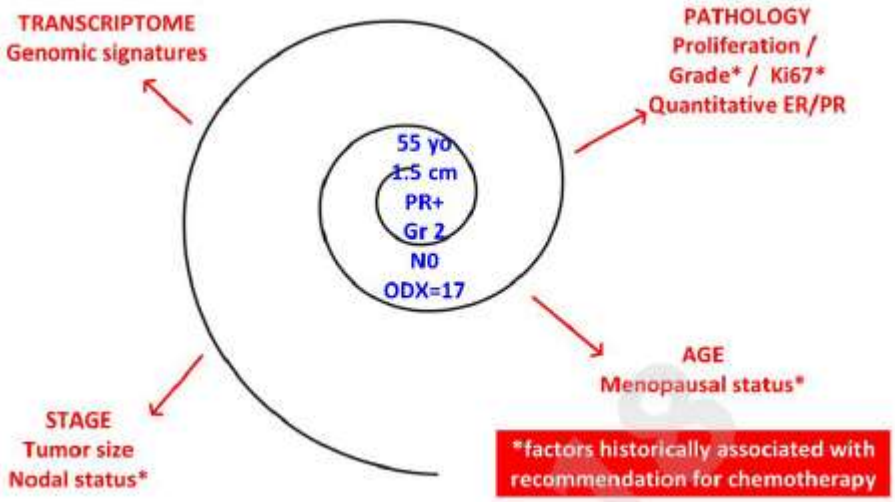
Should Chemotherapy Be Standard for All Node Positive Breast Cancer Patients?

Harold J. Burstein, MD, PHD

CASE #1

Of course not.

The challenge is to figure out who does or doesn't need it, and to discuss the reasons with patients in a shared decision making process.



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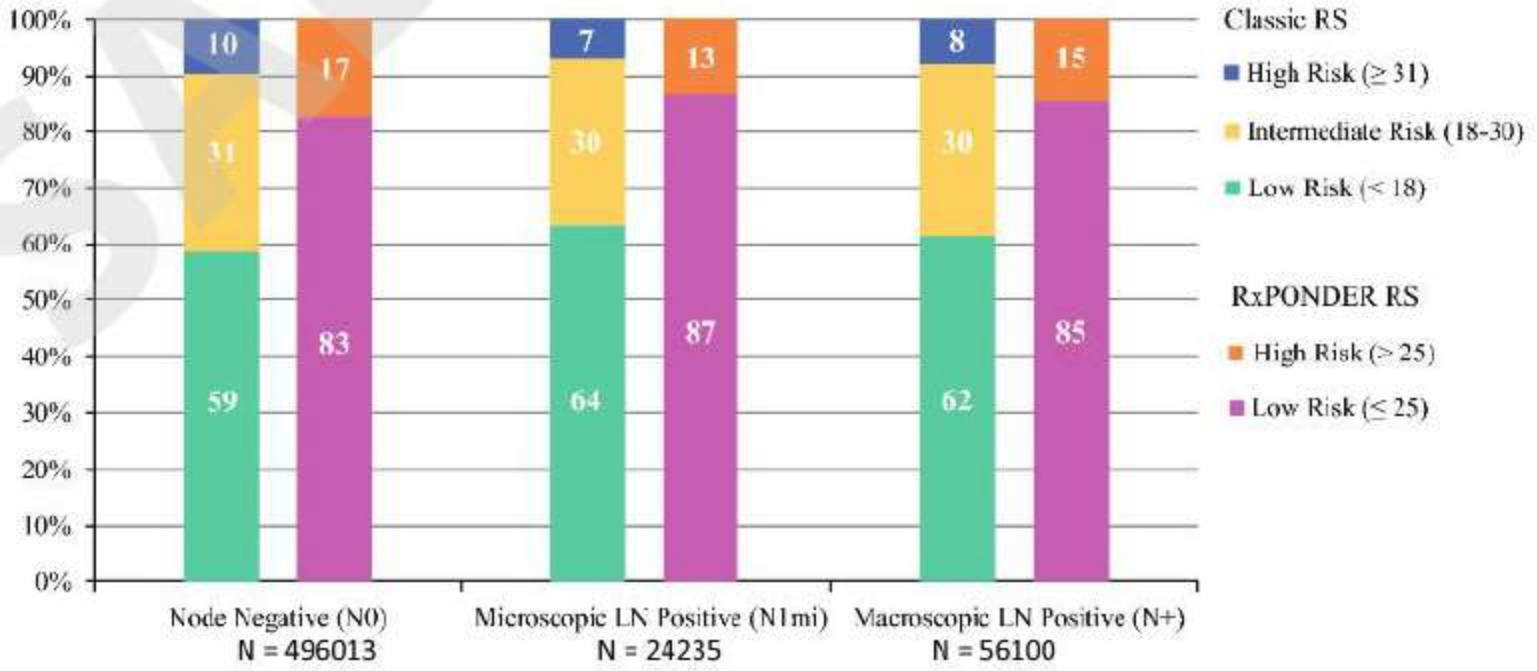
Recurrence score distribution does not differ between lymph node negative and positive tumors

*true for both ductal and lobular histologies



Bello DM, et al. Ann Surg Oncol 2018;25:2884-9

610 000 tumor specimens MSKCC

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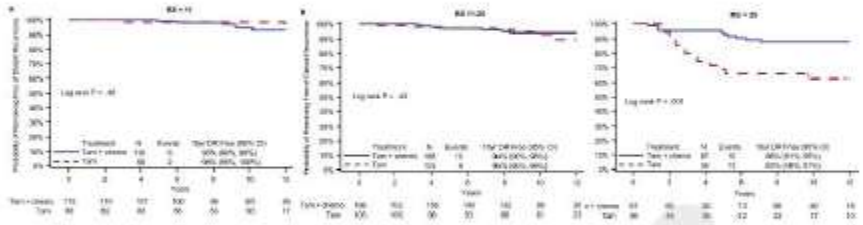
Is "25" the right number?
Re-analysis of NSABP B-20 outcomes after removal of HER2 positive cases and re-subsetting into TAILORx cohorts

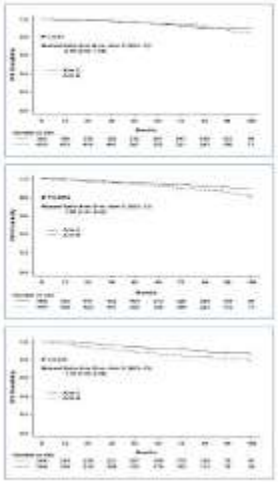


Geyer CE, et al. NPJ Breast Cancer. 2018 Nov 14;4:37. doi: 10.1038/s41523-018-0090-6. eCollection 2018.

HOW MUCH IS DUE TO
Ovarian suppression from chemo?

Is "25" the right number?
TAILORx Subset of Women < 50

Outcomes by recurrence score range in younger women with node-negative breast cancer.



11-15

16-20

21-25

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Clinical recommendation – Case 1.

- I think it is unlikely that chemotherapy adds significantly to her long-term clinical outcomes
  - Recurrence score suggests no/minimal benefit from chemo
  - "Limited" nodal involvement generally portends good prognosis
  - Not sure chemotherapy adds "nothing" but have ruled out >2% benefit
- I would carefully acknowledge that this is based in part on *extrapolation* and that the tumor grade and her younger age give me a bit less certainty
- I would recommend OFS and Tam/AI as the alternative to chemo/endocrine therapy

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Case 2

- Healthy 47 year old woman, no family hx, palpated a mass.
- Mastectomy reveals 3.8cm invasive lobular carcinoma, grade 1 of 3
- One of one sentinel node is positive.
- Axillary dissection: Two of 9 additional nodes for final of 3 of 10 LN+
- ER positive, PR positive, HER2 negative.
- 21 gene recurrence score: 10
- Plans on ovarian suppression & aromatase inhibitor for 5 years.

What chemotherapy regimen do you consider standard?

None?	48%	
Non-anthracycline-containing (TC)?	24%	
Anthracycline, taxane, and cyclophosphamide (such as AC-T)?	28%	

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Individualization of Adjuvant Chemotherapy

PREDICTION

ER Pos

≥3 Node POSITIVE

Low Genomic Score

(OncotypeDx)

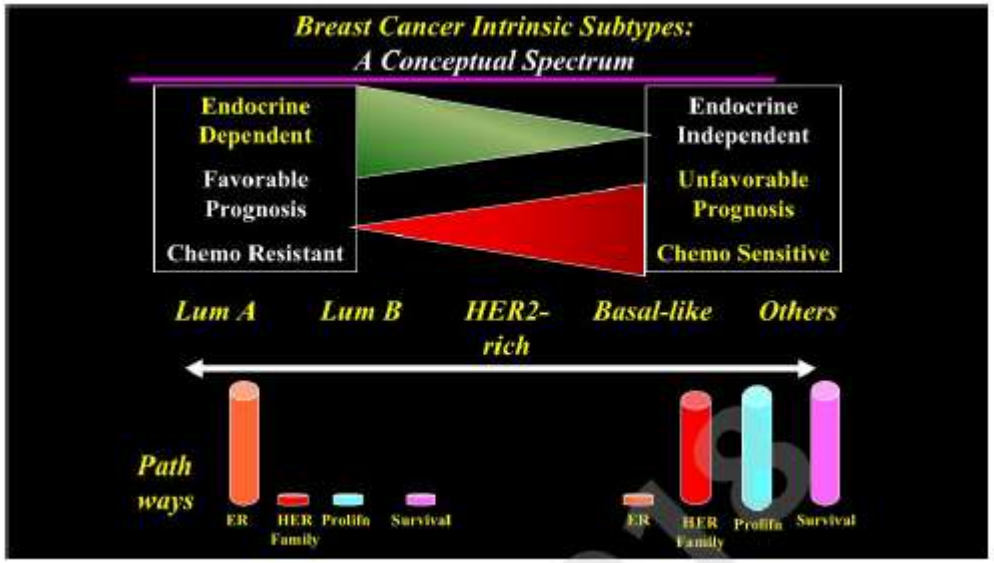
"Luminal A?"

The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer.

Lippman M.E., et al. N Engl J Med. 298:1223-1228, 1978

Conclusion:

ER NEG much more likely than ER POS patients to benefit from chemotherapy



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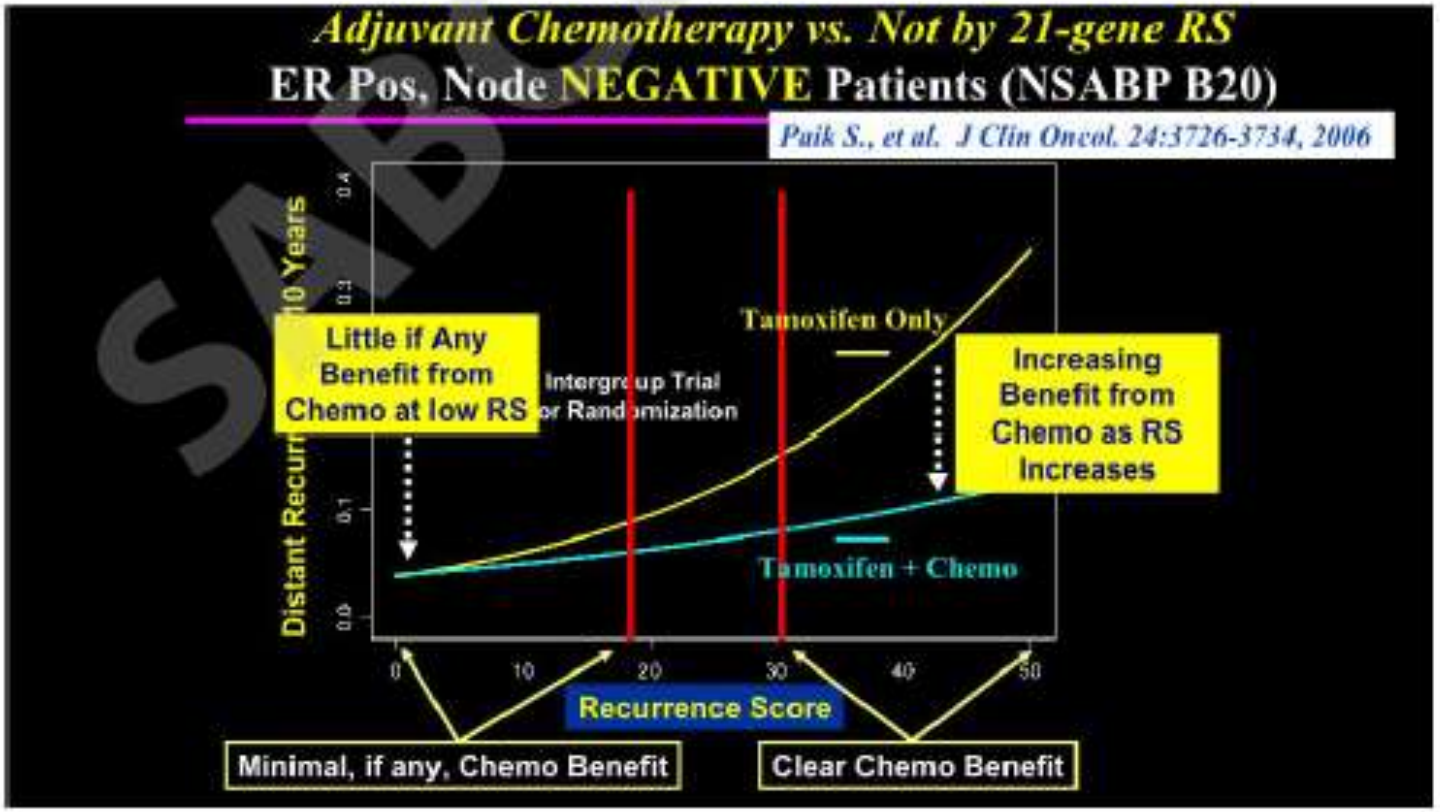

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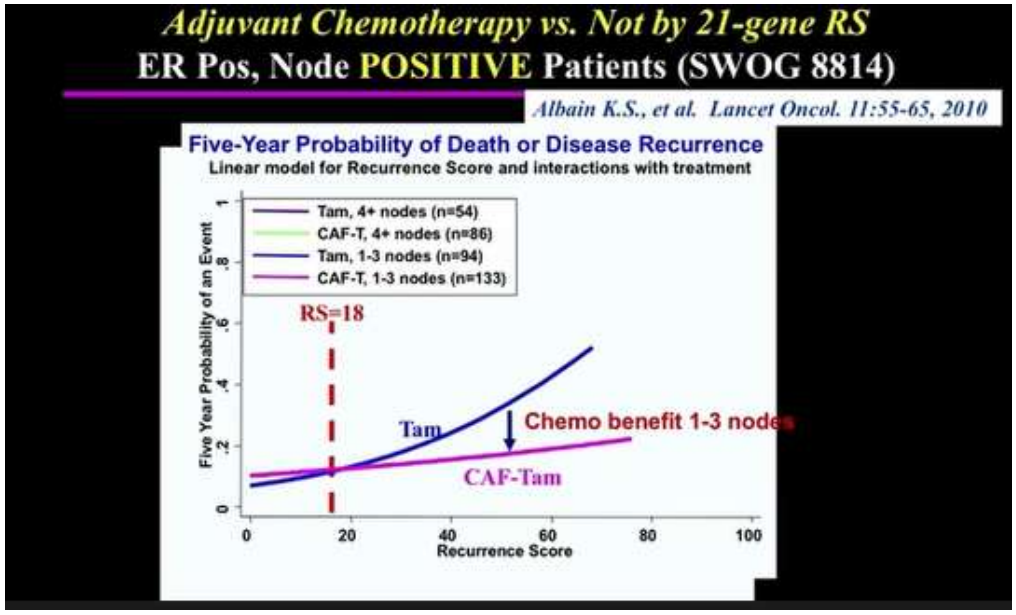

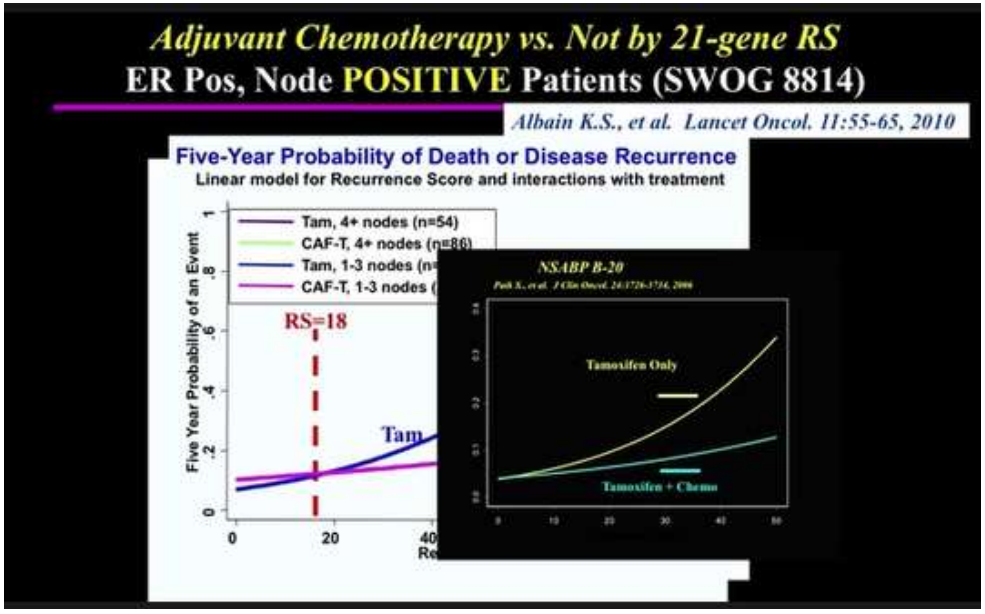

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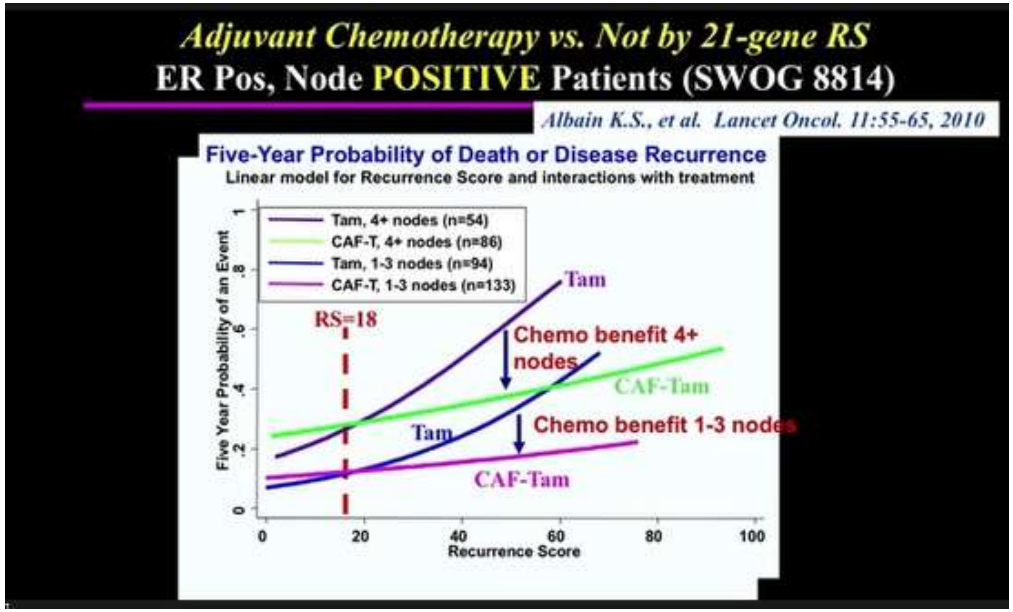

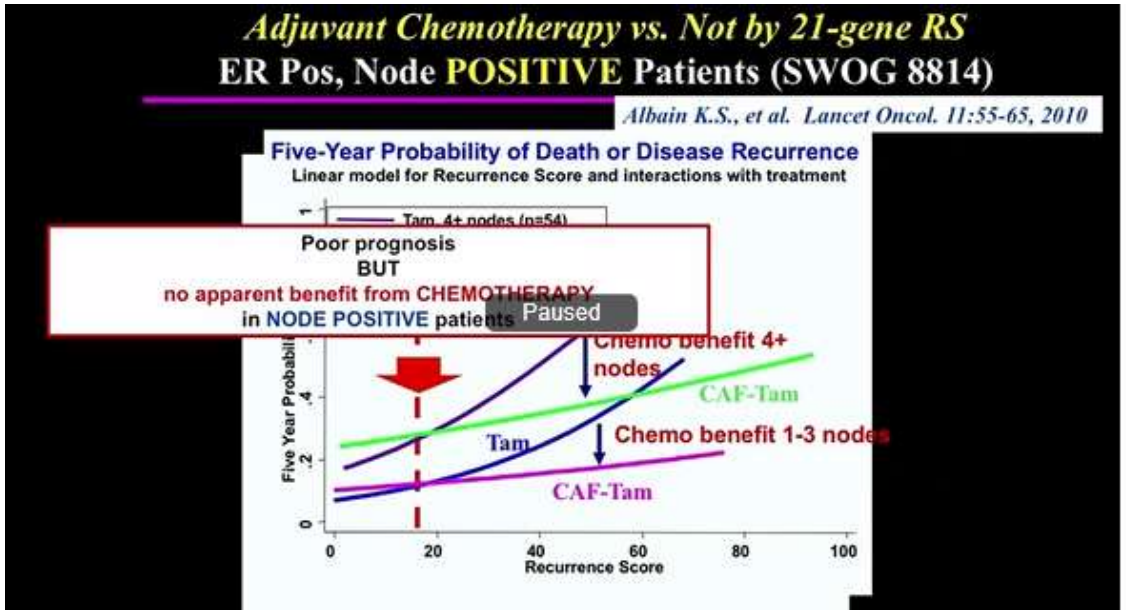

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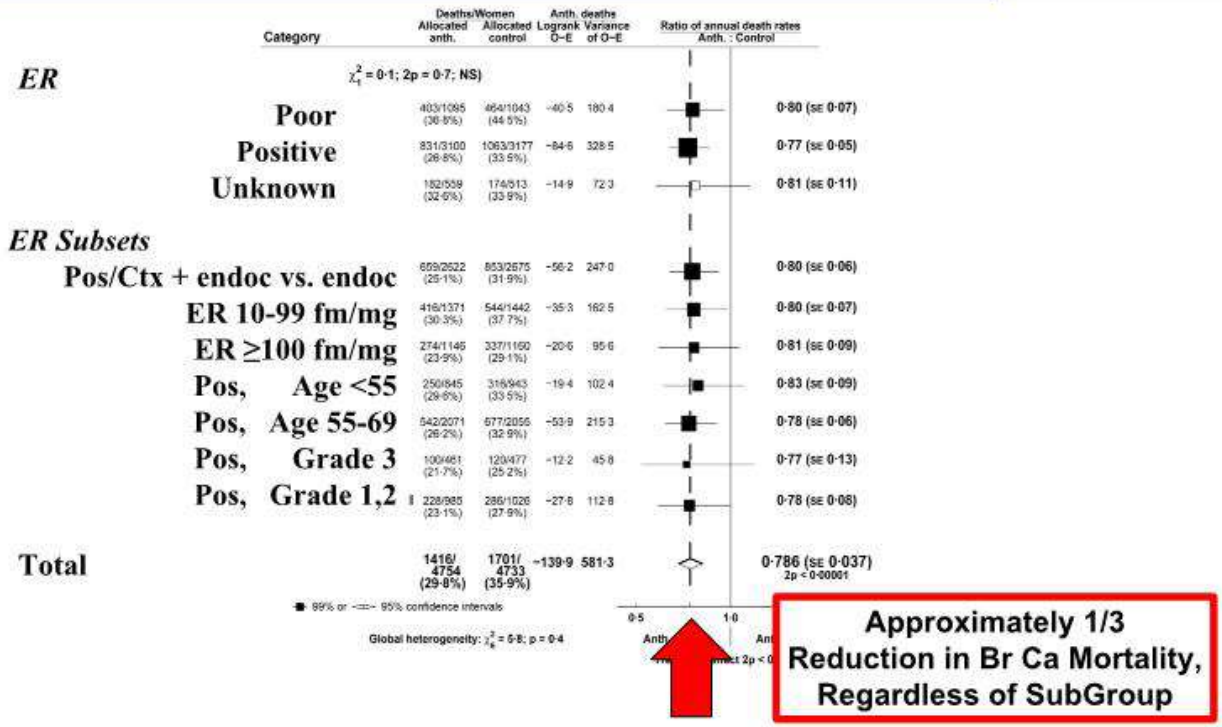
Breast cancer Mortality
Anthracycline-based regimen vs no adjuvant chemotherapy,
by ER STATUS and subsets of ER+

Oxford Overview
EBCTCG *Lancet* 2012,379,432-44



Approximately 1/3 Reduction in Br Ca Mortality, Regardless of SubGroup

After several analyses,
there is no apparent, significant interaction of ER,
PgR, or grade in any age group on the
proportional effect of chemotherapy
in the Oxford Overview Dataset

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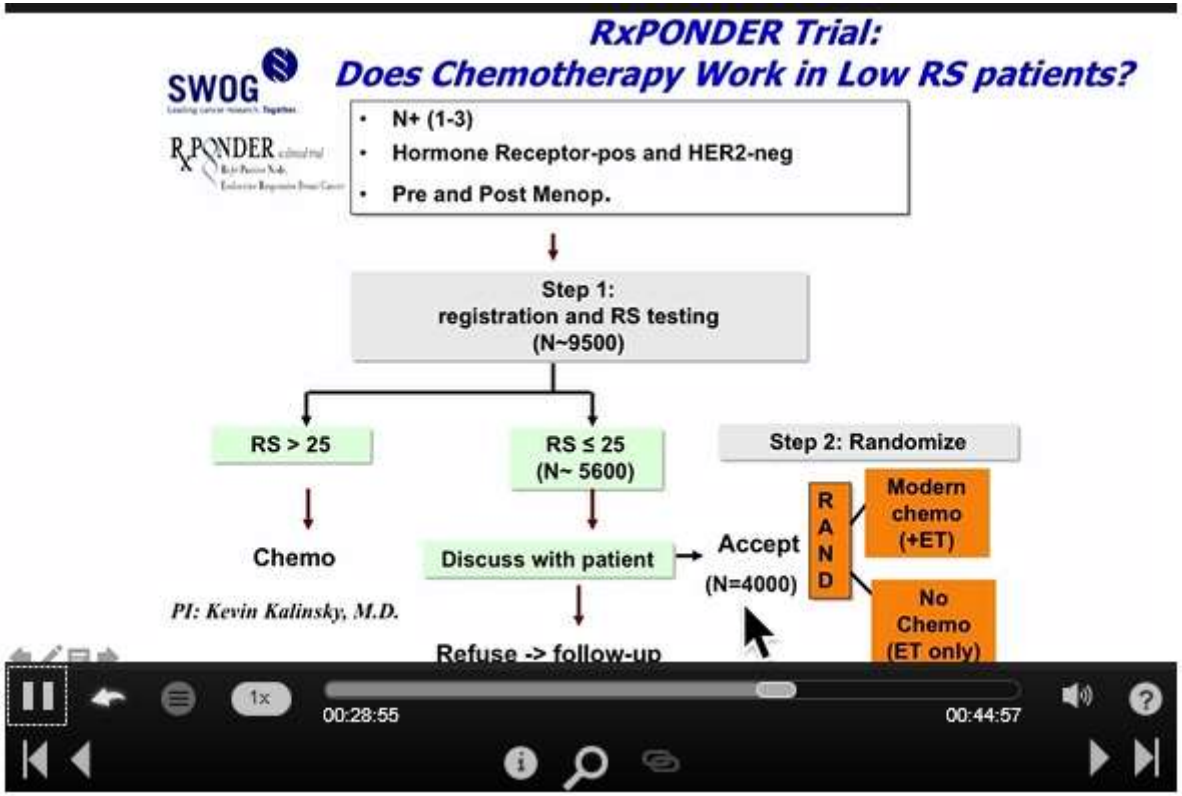

Closed to accrual in North America October 1, 2015!!

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Hayes' Conclusion

- For this patient, I would NOT have ordered a Genomic Test!

Why?

- *BECAUSE*
  - Her anatomic prognosis is poor no matter what the score (3/10 positive nodes)
  - Oxford Overview suggests NO Predictive Role of any biological subset for chemotherapy
  - S8814 provocative, but not validated
  - RxPonder Trial results pending

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Should Chemotherapy Be Standard for All Node Positive Breast Cancer Patients?

Harold Burstein, MD, PhD

CASE #2

No. This case even less than the first.

Outcome formula

Outcome = f (stage • biology • treatment)

Outcome formula

Outcome = f (stage • biology • treatment)

↑ Δ Chemo↓ Endo↑

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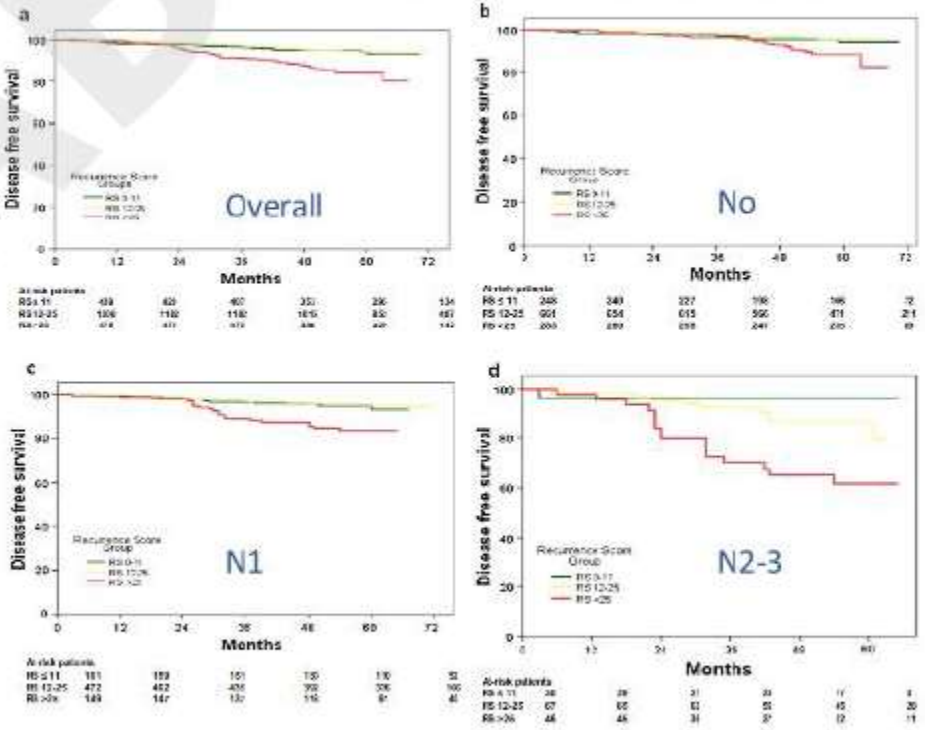
Prospective analysis of ER+ breast cancers by recurrence score: West German Plan B Study



RS ≤ 11, no chemo

5-year DFS

N0	94.2%
N1	94.4%

Nitz U, et al. Breast Cancer Res Treat 2017;165:573-583

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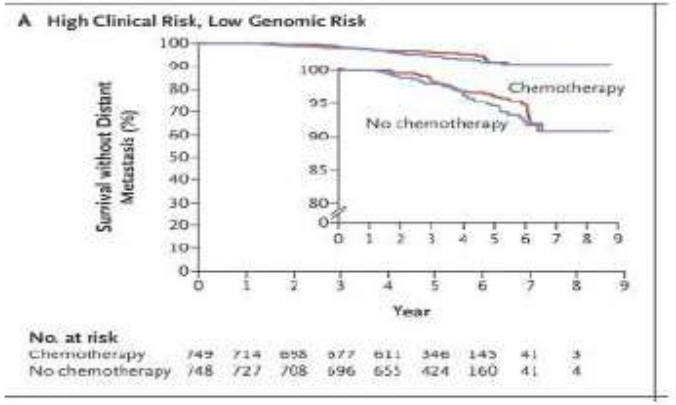
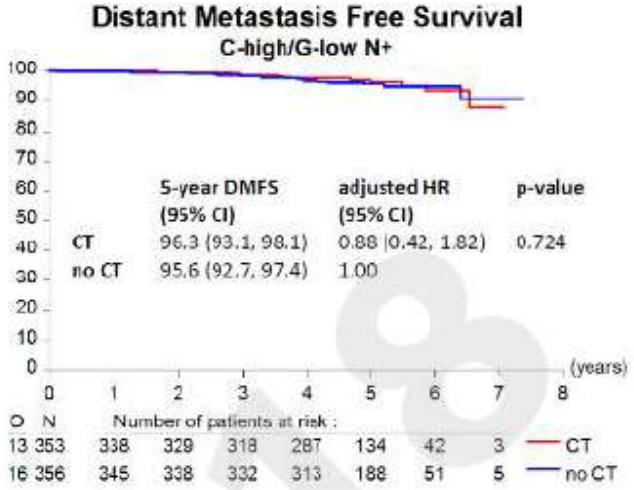
MINDACT:
Prospective evaluation of treatment w/w/o chemotherapy based on clinical and genomic risk stratification

Table S 13: Classification of patients according to clinical risk assessment by the modified version of Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high

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





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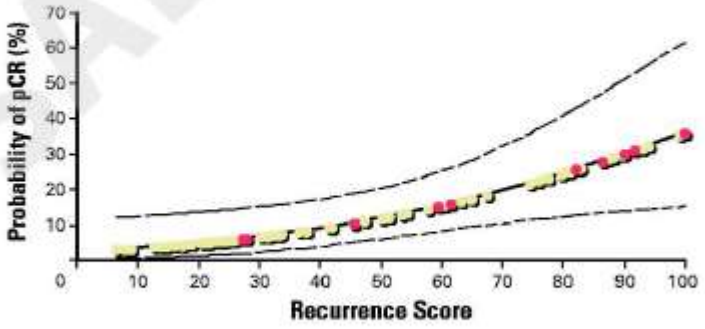
Relationship of recurrence score to pCR in locally advanced breast cancer treated with neoadjuvant chemotherapy



Gianni L, et al. J Clin Oncol 2005;23:7265-77

Neoadjuvant treatment in ER+ BC treated with ET or CT:
Impact of recurrence score on response

	RS < 11	RS 11 to 25		RS > 25
Treatment	ET	ET	CT	CT
N	12	18	11	14
Clinical Response Rate	83%	50%	72%	93%
pCR	0%	0%	0%	14%

Bear HD, et al. J Surg Oncol 2017;115:917-23

Neoadjuvant chemotherapy:
ER+ lobular vs ER+ ductal

Study	Endpoint	Invasive lobular	Invasive ductal	Reference
Loibl et al.	pCR	4.5%	9.6%	BRCT 2014;144:153
GBG				
Delpech, et al.	Breast pCR	3%	14%	Br J Cancer 2013;108:285
MDACC	Downstaging	41%	64%	
Petruolo, et al.	Axillary pCR	7%	16%	Ann Surg Onc 2017;24:2556
MSKCC	Downstaging	16%	48%	

Factors associated with low rates of pCR: lobular histology, low grade, strongly ER+, HER2 negative

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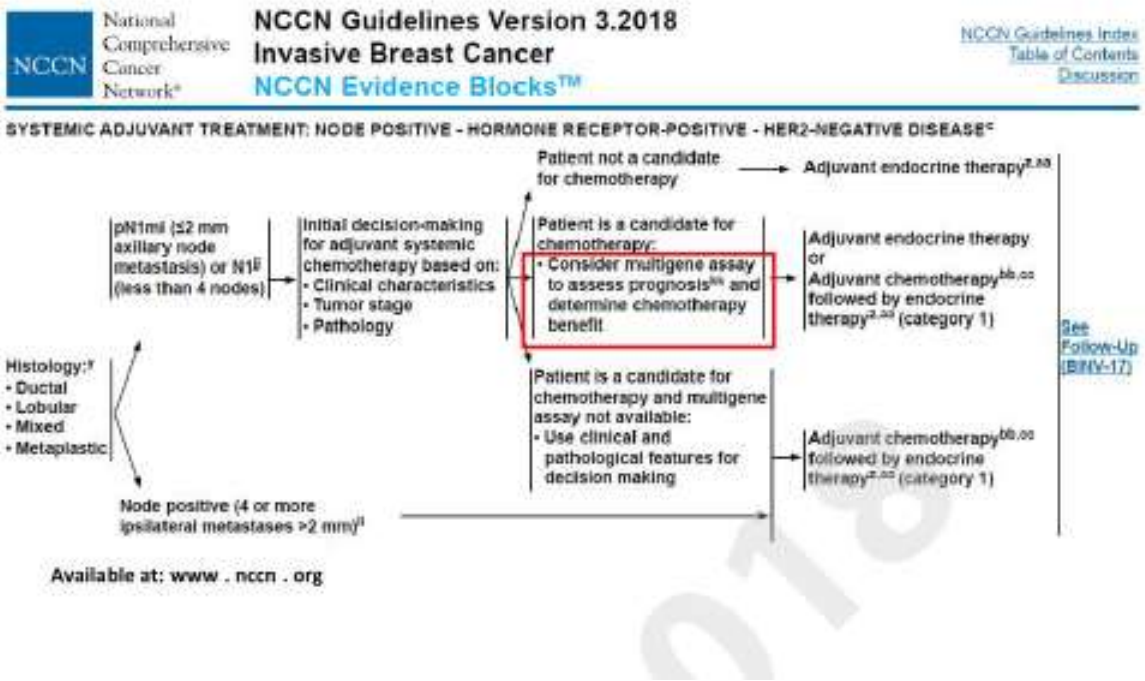

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Clinical recommendation – Case 2.

- I think it is unlikely that chemotherapy adds significantly to her long-term clinical outcomes – even more clear than in case 1
  - Recurrence score suggests no/minimal benefit from chemo
  - Multiple sources of data suggest little benefit to neo/adjuvant chemo in patients with tumors with these histological/genomic features
  - Oxford Overview may lack multivariate granularity to assess benefit of chemo
- I would carefully acknowledge that
  - We have limited prospective data
  - We cannot "rule out" a very small benefit
  - "Quantity has a quality all its own"
- Guidelines endorse genomic assays for guiding treatments in N1 cases
- I would recommend OFS and AI to this patient
- 10 years of endocrine therapy to address issues of residual risk

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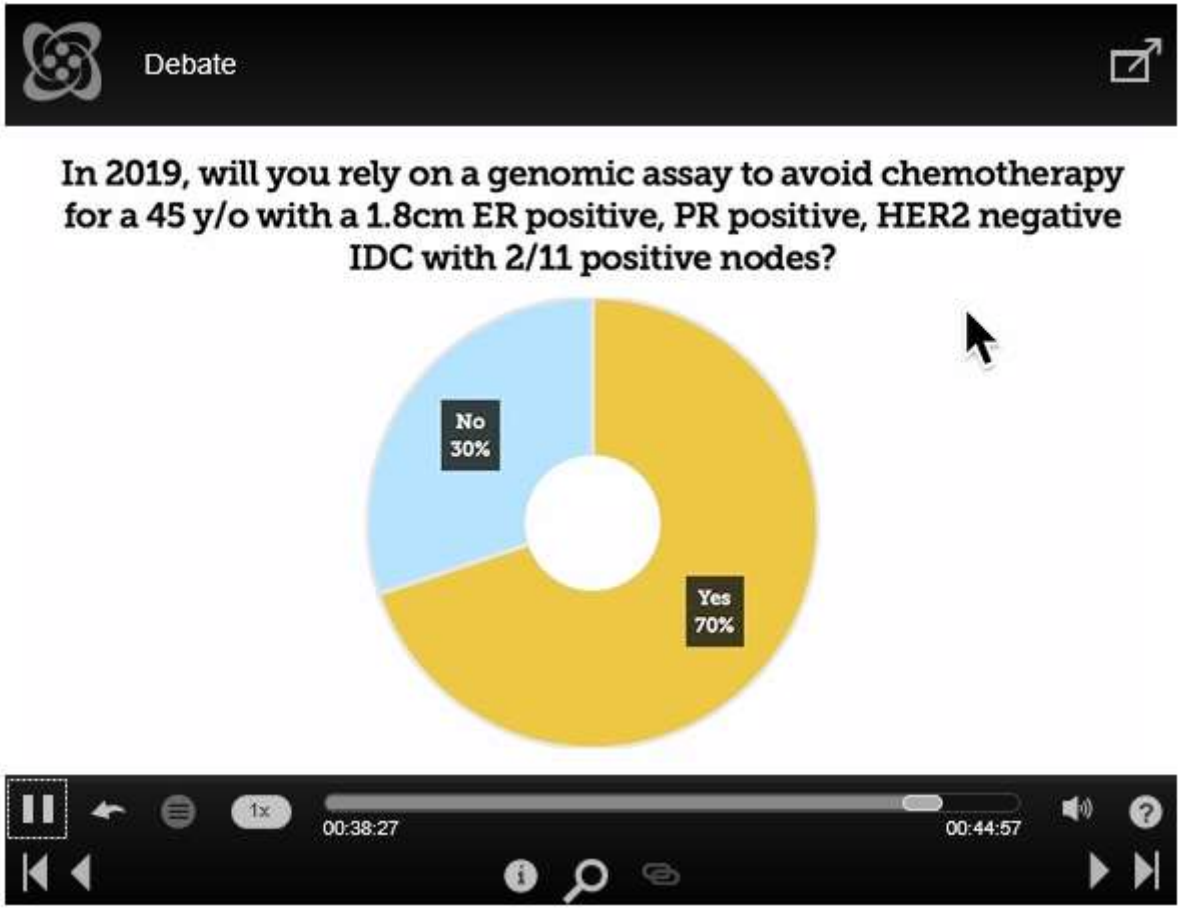

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POST SAN ANTONIO BREAST CANCER SYMPOSIUM 2018

28 Gennaio 2019

POLICLINICO UMBERTO I - ROMA

Aula Bignami (Patologia Generale)

Viale Regina Elena 324

Let's debate!