Who Needs Systemic Chemotherapy?
Tailoring Adjuvant Systemic Therapy

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DISCLOSURE SLIDE

Personal COI:

Consultancy/Honoraria/Travel/Research Support

- Astra Zeneca, Eisai, Lilly, Novartis, Pfizer, Roche

Outline

- Introduction
  - Key Milestones in Adjuvant Chemotherapy

- Who needs chemotherapy?
  - Guidelines
  - Standard Clinicopathological Factors
  - Molecular Assays

- Limitations and Future Directions

- Conclusions

Chemotherapy Evolution Timeline

| 1600 BC	17th–19th century	Early-mid 20th century	Late 20th century		
Reports of breast cancer appear in early medical texts	Radical surgery used to 'treat' breast cancer	First effective chemotherapy regimen developed – CMF	Surgery becomes less radical as merits of radiotherapy recognised	First anthracycline-containing regimen introduced – AC	Taxanes added to chemotherapy armamentarium

Verrill, BJC 2009

Stepwise Improvements with Adjuvant Chemotherapy in Breast Cancer

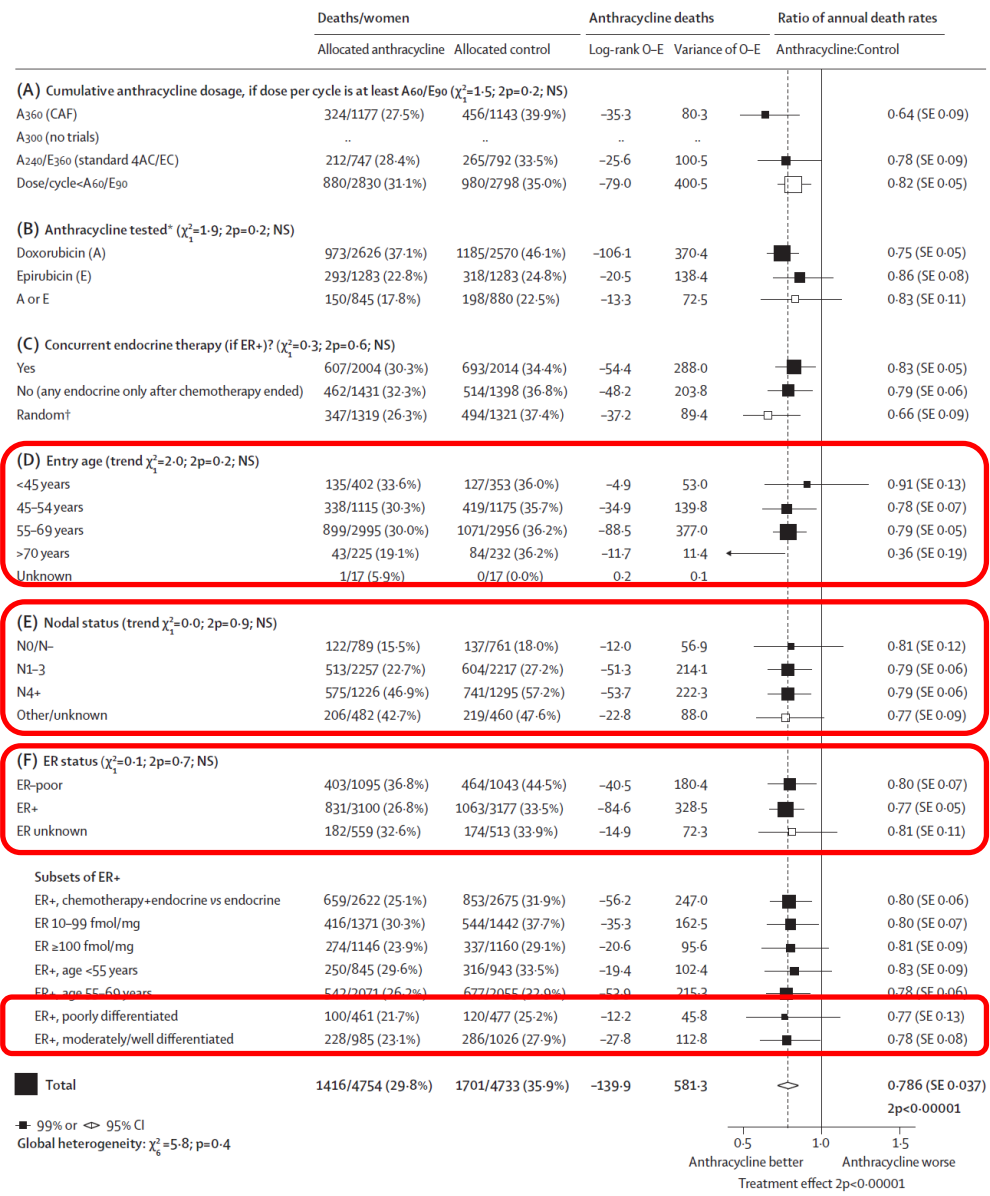No chemotherapy < CMF < Anthracyclines < Taxanes
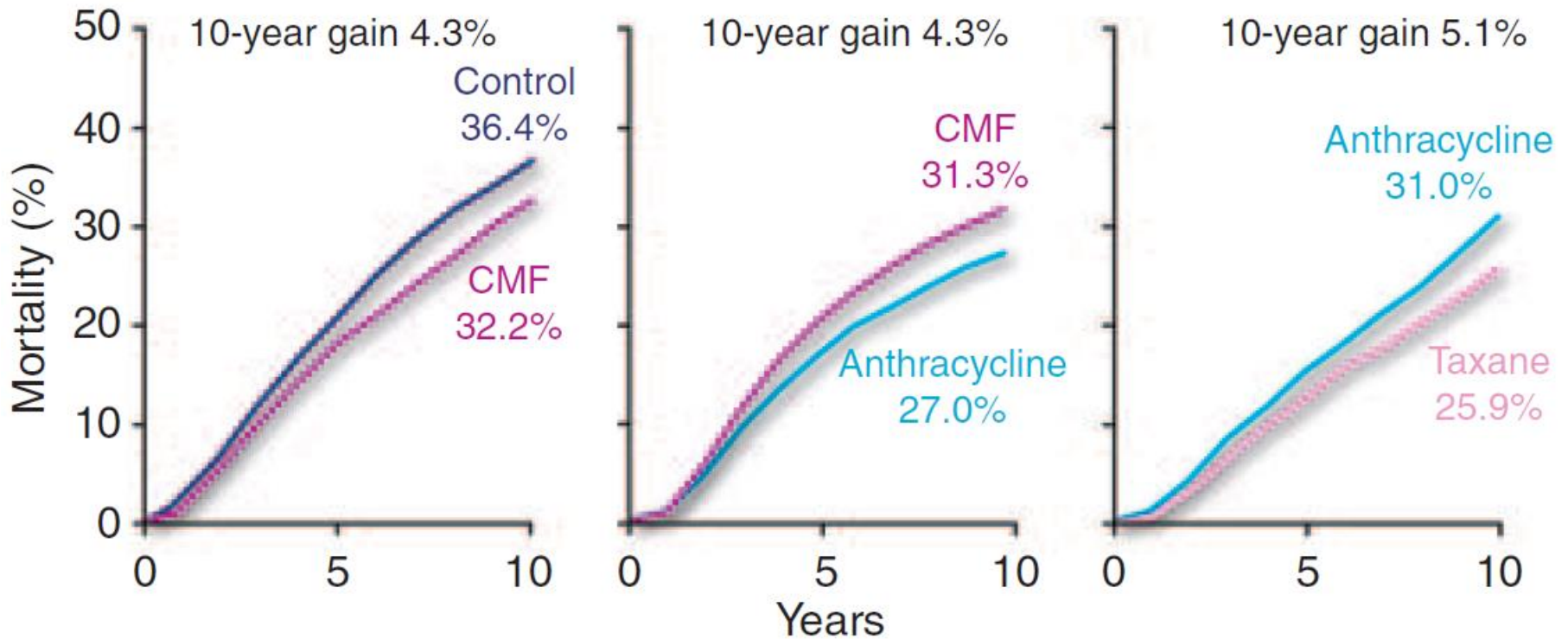
Verrill, BJC 2009   Peto, SABCS 2007;

Who Needs Adjuvant Chemotherapy for Breast Cancer?

- Who has occult micrometastases?
  - Residual disease after local therapy
  - Tumor burden
  - Tumor biology

- What do the guidelines say?
  - ASCO, St Gallen/ESMO, NCCN etc

- What is the evidence behind the recommendations?
  - Clinicopathological Factors
  - Molecular Assays

Who Needs Adjuvant Chemotherapy?

	Deaths/women		Anthracycline deaths		Ratio of annual death rates		
	Allocated anthracycline	Allocated control	Log-rank O–E	Variance of O–E	Anthracycline:Control		
(A) Cumulative anthracycline dosage, if dose per cycle is at least A60/E90 (χ^2_1=1·5; 2p=0·2; NS)							
A360 (CAF)	324/1177 (27·5%)	456/1143 (39·9%)	−35·3	80·3			0·64 (SE 0·09)
A300 (no trials)	..	..	..	..			
A240/E360 (standard 4AC/EC)	212/747 (28·4%)	265/792 (33·5%)	−25·6	100·5			0·78 (SE 0·09)
Dose/cycle<A60/E90	880/2830 (31·1%)	980/2798 (35·0%)	−79·0	400·5			0·82 (SE 0·05)
(B) Anthracycline tested* (χ^2_1=1·9; 2p=0·2; NS)							
Doxorubicin (A)	973/2626 (37·1%)	1185/2570 (46·1%)	−106·1	370·4			0·75 (SE 0·05)
Epirubicin (E)	293/1283 (22·8%)	318/1283 (24·8%)	−20·5	138·4			0·86 (SE 0·08)
A or E	150/845 (17·8%)	198/880 (22·5%)	−13·3	72·5			0·83 (SE 0·11)
(C) Concurrent endocrine therapy (if ER+)? (χ^2_1=0·3; 2p=0·6; NS)							
Yes	607/2004 (30·3%)	693/2014 (34·4%)	−54·4	288·0			0·83 (SE 0·05)
No (any endocrine only after chemotherapy ended)	462/1431 (32·3%)	514/1398 (36·8%)	−48·2	203·8			0·79 (SE 0·06)
Random†	347/1319 (26·3%)	494/1321 (37·4%)	−37·2	89·4			0·66 (SE 0·09)
(D) Entry age (trend χ^2_1=2·0; 2p=0·2; NS)							
<45 years	135/402 (33·6%)	127/353 (36·0%)	−4·9	53·0			0·91 (SE 0·13)
45–54 years	338/1115 (30·3%)	419/1175 (35·7%)	−34·9	139·8			0·78 (SE 0·07)
55–69 years	899/2995 (30·0%)	1071/2956 (36·2%)	−88·5	377·0			0·79 (SE 0·05)
>70 years	43/225 (19·1%)	84/232 (36·2%)	−11·7	11·4			0·36 (SE 0·19)
Unknown	1/17 (5·9%)	0/17 (0·0%)	0·2	0·1			
(E) Nodal status (trend χ^2_1=0·0; 2p=0·9; NS)							
N0/N−	122/789 (15·5%)	137/761 (18·0%)	−12·0	56·9			0·81 (SE 0·12)
N1–3	513/2257 (22·7%)	604/2217 (27·2%)	−51·3	214·1			0·79 (SE 0·06)
N4+	575/1226 (46·9%)	741/1295 (57·2%)	−53·7	222·3			0·79 (SE 0·06)
Other/unknown	206/482 (42·7%)	219/460 (47·6%)	−22·8	88·0			0·77 (SE 0·09)
(F) ER status (χ^2_1=0·1; 2p=0·7; NS)							
ER-poor	403/1095 (36·8%)	464/1043 (44·5%)	−40·5	180·4			0·80 (SE 0·07)
ER+	831/3100 (26·8%)	1063/3177 (33·5%)	−84·6	328·5			0·77 (SE 0·05)
ER unknown	182/559 (32·6%)	174/513 (33·9%)	−14·9	72·3			0·81 (SE 0·11)
Subsets of ER+							
ER+, chemotherapy+endocrine vs endocrine	659/2622 (25·1%)	853/2675 (31·9%)	−56·2	247·0			0·80 (SE 0·06)
ER 10–99 fmol/mg	416/1371 (30·3%)	544/1442 (37·7%)	−35·3	162·5			0·80 (SE 0·07)
ER ≥100 fmol/mg	274/1146 (23·9%)	337/1160 (29·1%)	−20·6	95·6			0·81 (SE 0·09)
ER+, age <55 years	250/845 (29·6%)	316/943 (33·5%)	−19·4	102·4			0·83 (SE 0·09)
ER+, age 55–69 years	542/2071 (26·2%)	677/2055 (32·9%)	−52·9	215·2			0·78 (SE 0·06)
ER+, poorly differentiated	100/461 (21·7%)	120/477 (25·2%)	−12·2	45·8			0·77 (SE 0·13)
ER+, moderately/well differentiated	228/985 (23·1%)	286/1026 (27·9%)	−27·8	112·8			0·78 (SE 0·08)
Total	1416/4754 (29·8%)	1701/4733 (35·9%)	−139·9	581·3			0·786 (SE 0·037) 2p<0·00001

■– 99% or ◇ 95% CI
Global heterogeneity: χ^2_6=5·8; p=0·4

0·5   1·0   1·5
Anthracycline better   Anthracycline worse
Treatment effect 2p<0·00001

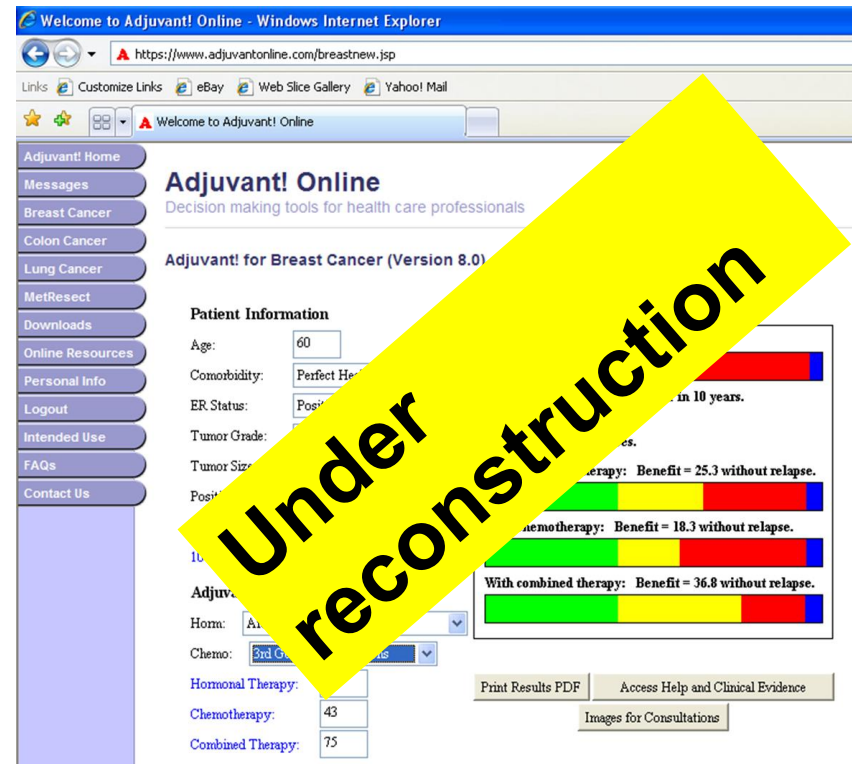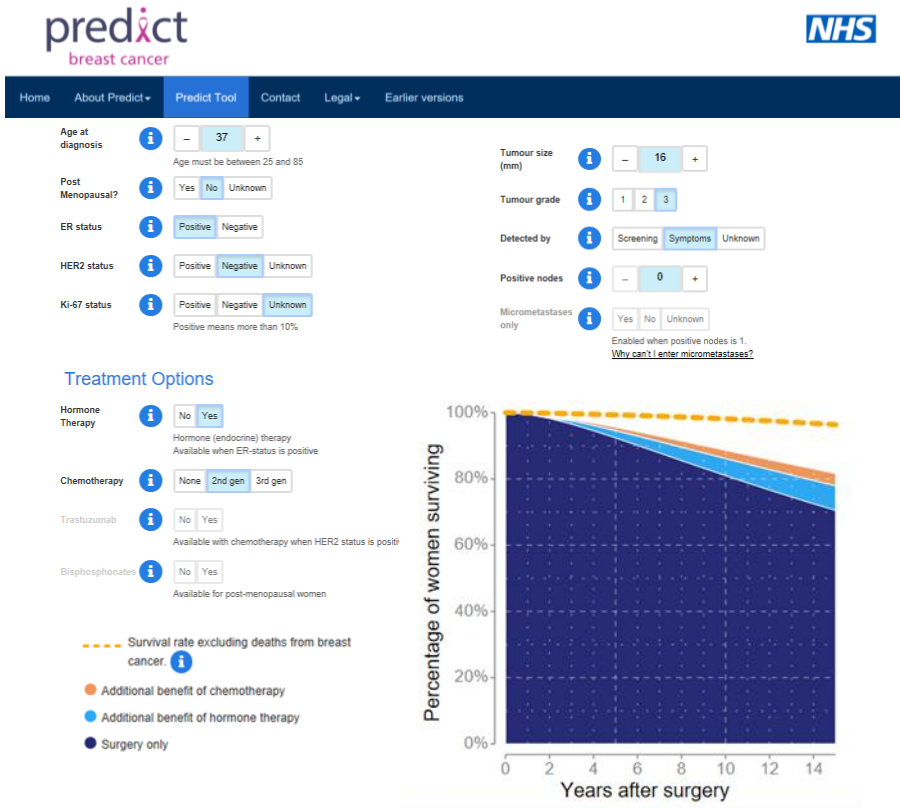Reduction in BC mortality by >20-30% (relative).
Appears largely independent of
- age,
- nodal status,
- tumor size,
- grade or
- ER status

But absolute risk reduction depends on risk of relapse.

EBCTCG Lancet 2012

Benefit-Risk Calculators

- These calculators should not, however, be considered a substitute for multigene assays.

ASCO Guidelines (Adaptation of the Cancer Care Ontario Clinical Practice Guideline)

- Decisions regarding adjuvant chemotherapy regimens should take into account baseline recurrence risk, toxicities, likelihood of benefit, and host factors such as comorbidities.
    - In high-risk HER2-negative populations with excellent performance status, anthracycline- and taxane-containing regimens are the standard of care.
    - Docetaxel and cyclophosphamide for four cycles is an acceptable non-anthracycline regimen.

  Denduluri et al, JCO 2016

- Patients with early-stage HER2-negative breast cancer with pathologic, invasive residual disease at surgery following standard anthracycline- and taxane-based preoperative therapy may be offered up to 6 to 8 cycles of adjuvant capecitabine.

  Denduluri et al, JCO 2017

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De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

Table 5. Adjuvant systemic treatment recommendations for triple negative and *HER2* positive early breast cancer

| Subtypes according to clinical-pathologic and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
Ductal triple negative pT1a node negative		No routine adjuvant chemo-therapy for stage pT1a pN0.	
Higher T and N stage	Neoadjuvant therapy for stage II or III is suggested as initial treatment approach. Chemotherapy should include anthracycline and taxanes	Dose-dense adjuvant chemo-therapy preferred by only a minority of the consensus panel	No consensus on post-neoadjuvant treatment in case of residual disease. In *BRCA1/2* associated cancers, the Panel was evenly split on whether to recommend (neo)ad-juvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.

Curigliano et al, Ann Onc 2017

St Gallen Expert Consensus

Table 4. (Neo)-Adjuvant systemic treatment recommendations for ER positive/*HER2* negative early breast cancer			
Subtypes according to clinical-pathological and genomic risk assessment	**Treatment recommendation**	**De-escalation**	**Escalation**
High/Intermediate degree of ER and PgR expression, intermediate tumour burden pT1c, pT2, pN0 or pN1 (1-3), intermediate or high proliferation or grade, and/or intermediate "genomic risk"	Endocrine therapy according to menopausal status plus adjuvant chemotherapy		
Premenopausal Uncertain "clinical risk" (node negative) "intermediate genomic risk"	OFS plus tamoxifen or OFS plus exemestane		Consider addition of chemotherapy in selected cases Extended adjuvant endocrine therapy with tamoxifen in some cases
Premenopausal intermediate/high "clinical risk" (node positive) "intermediate/high genomic risk"	OFS plus exemestane plus adjuvant chemotherapy in many cases		Chemotherapy Extended adjuvant endocrine therapy with tamoxifen
Post-menopausal Uncertain "clinical risk" (node negative) "intermediate genomic risk"	AI up front Chemotherapy in many cases		Bisphosphonates
Postmenopausal "intermediate/high genomic risk" and intermediate/high "clinical risk" (node positive)	Chemotherapy AI as first endocrine therapy for at least 3-5 years		Extended adjuvant AI according to risk and tolerability Bisphosphonates
			Denosumab has been shown to reduce bone-health related events in breast cancer patients

St Gallen Expert Consensus

Table 4. (Neo)-Adjuvant systemic treatment recommendations for ER positive/*HER2* negative early breast cancer

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
Intermediate to low ER and PR expression Higher tumor burden (typically T3 and/or N2-3) More proliferative / higher Ki67 "Intermediate to high genomic risk markers"	Adjuvant chemotherapy plus endocrine therapy according to menopausal status		
Premenopausal high risk	Adjuvant chemotherapy and OFS + AI (if premenopausal after chemo)		Extended adjuvant AI according to risk and tolerability
Postmenopausal high risk	Adjuvant chemotherapy and AI		Extended adjuvant AI according to risk and tolerability Bisphosphonates Denosumab has been shown to reduce bone-health related events in breast cancer patients

Curigliano et al, Ann Onc 2017

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SYSTEMIC ADJUVANT TREATMENT: HORMONE RECEPTOR-NEGATIVE - HER2-NEGATIVE DISEASE[d,v]
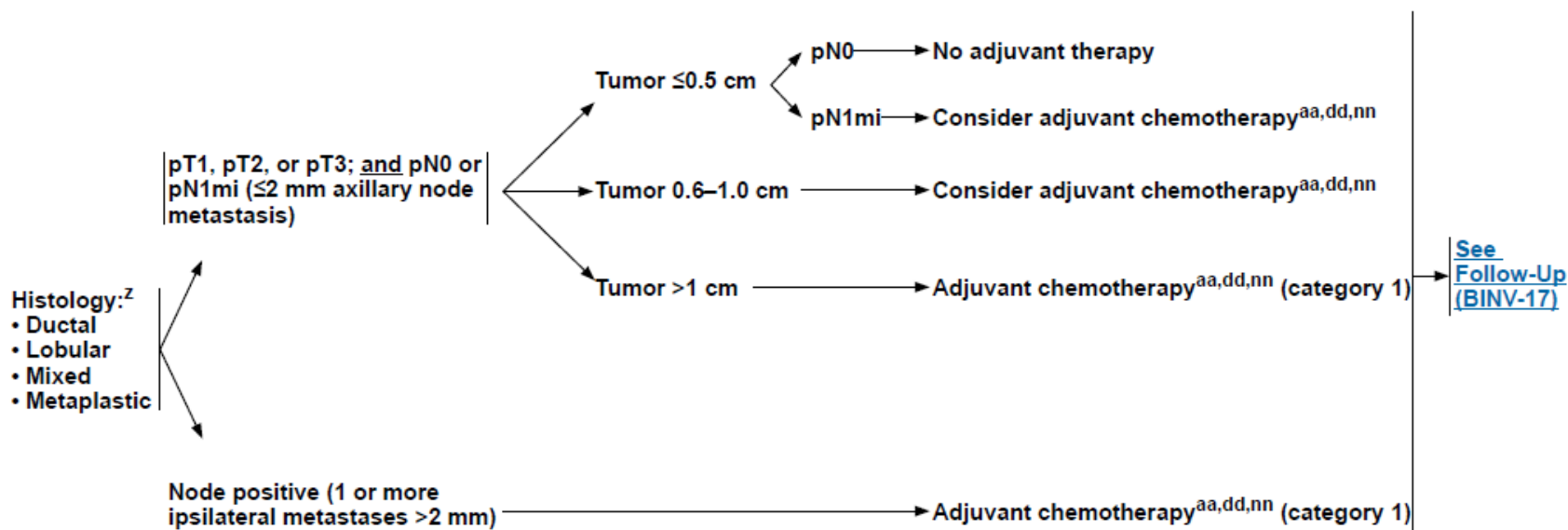
z Mixed lobular and ductal carcinoma, should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

aa Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.
dd There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.
nn See Preoperative/Adjuvant Therapy Regimens (BINV-L).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-9

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SYSTEMIC ADJUVANT TREATMENT: NODE-NEGATIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[d,v]

Histology:[z]
- Ductal
- Lobular
- Mixed
- Metaplastic

→ pT1, pT2, or pT3; and pN0

Tumor ≤0.5 cm → pN0 → Consider adjuvant endocrine therapy[aa,bb] (category 2B)

Tumor >0.5 cm → Strongly consider 21-gene RT-PCR assay (category 1)[hh,ii]

- **Not done** → Adjuvant endocrine therapy[aa,bb] or Adjuvant chemotherapy[cc,dd] followed by endocrine therapy[aa,bb] (category 1)

- **Recurrence score <26[jj]** → Adjuvant endocrine therapy[aa,bb,jj]

- **Recurrence score 26–30** → Adjuvant endocrine therapy[aa,bb] or Adjuvant chemotherapy[cc,dd] followed by endocrine therapy[aa,bb]

- **Recurrence score ≥31** → Adjuvant endocrine therapy[aa,bb] + adjuvant chemotherapy[cc,dd]

See Follow-Up (BINV-17)

[d] See Principles of HER2 Testing (BINV-A).
[v] See Special Considerations for Breast Cancer in Men (BINV-J).
[z] Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.
[aa] Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.
[bb] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

[cc] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).
[dd] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.
[hh] Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).
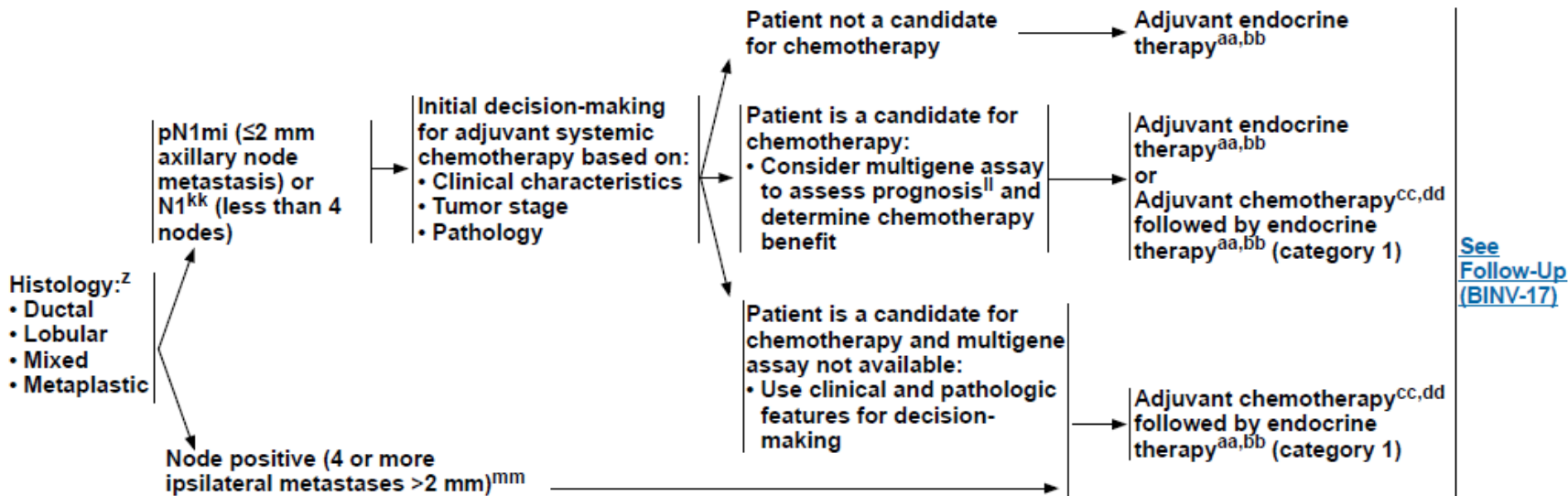[ii] Patients with T1b tumors with low-grade histology should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[jj] Consider the use of adjuvant chemotherapy in women 50 years of age or younger with a recurrence score of 16–25 based on an exploratory analysis from the TAILORx study demonstrating lower distant recurrences in women 50 years of age or younger randomized to chemotherapy.

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BINV-6

PATIENTS. AT THE HE♥RT OF ALL WE DO.

SYSTEMIC ADJUVANT TREATMENT: NODE-POSITIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[d,v]

Histology:[z]
• Ductal
• Lobular
• Mixed
• Metaplastic

→ pN1mi (≤2 mm axillary node metastasis) or N1[kk] (less than 4 nodes)

→ Initial decision-making for adjuvant systemic chemotherapy based on:
• Clinical characteristics
• Tumor stage
• Pathology

→ Patient not a candidate for chemotherapy → Adjuvant endocrine therapy[aa,bb]

→ Patient is a candidate for chemotherapy:
• Consider multigene assay to assess prognosis[ll] and determine chemotherapy benefit
→ Adjuvant endocrine therapy[aa,bb] or Adjuvant chemotherapy[cc,dd] followed by endocrine therapy[aa,bb] (category 1)

→ Patient is a candidate for chemotherapy and multigene assay not available:
• Use clinical and pathologic features for decision-making
→ Adjuvant chemotherapy[cc,dd] followed by endocrine therapy[aa,bb] (category 1)

→ Node positive (4 or more ipsilateral metastases >2 mm)[mm]

See Follow-Up (BINV-17)

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[d] See Principles of HER2 Testing (BINV-A).

[v] See Special Considerations for Breast Cancer in Men (BINV-J).

[z] Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

[aa] Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.

[bb] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

[cc] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy Regimens (BINV-L).

[dd] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

[kk] In N1mi and N1, multigene assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low-risk population that when treated with proper endocrine therapy may derive little absolute benefit from chemotherapy. Regarding the 21-gene RT-PCR assay, a secondary analysis of a prospective trial suggests that the test is predictive for women with 1–3 involved ipsilateral axillary lymph nodes. Other multigene assays have not proven to be predictive of chemotherapy benefit.
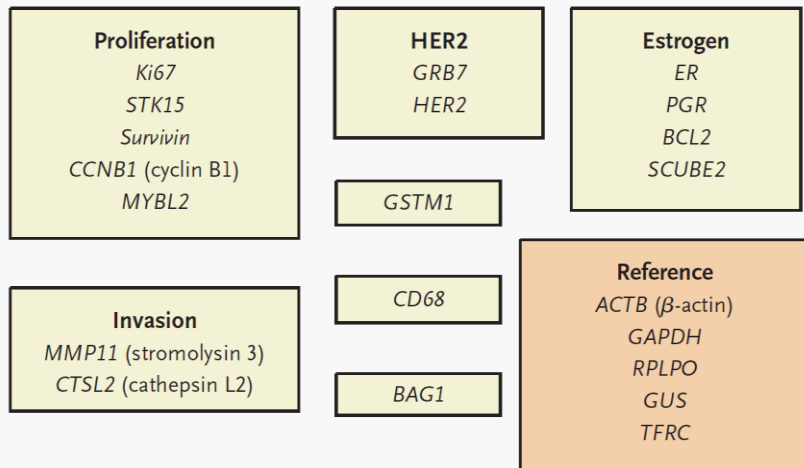
[ll] See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).

[mm] There are few data regarding the role of multigene assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.

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BINV-7

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Need for Genomic Assays?

Proliferation
Ki67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

HER2
GRB7
HER2

GSTM1

Estrogen
ER
PGR
BCL2
SCUBE2

Invasion
MMP11 (stromolysin 3)
CTSL2 (cathepsin L2)

CD68

BAG1

Reference
ACTB (β-actin)
GAPDH
RPLPO
GUS
TFRC

Panel of 21 genes in Oncotype

Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.*

Risk Category	Percentage of Patients	Rate of Distant Recurrence at 10 Yr (95% CI)†
		percent
Low	51	6.8 (4.0–9.6)
Intermediate	22	14.3 (8.3–20.3)
High	27	30.5 (23.6–37.4)‡

* A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher.
† CI denotes confidence interval.
‡ $P<0.001$ for the comparison with the low-risk category.

The overall agreement in tumor grade among the 3 pathologists in the study was 43%.

Paik et al, NEJM 2004

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Benefit of Adjuvant Chemotherapy is mainly in High risk subgroups (recurrence score ≥31)

Node Negative (NSABP-B20)
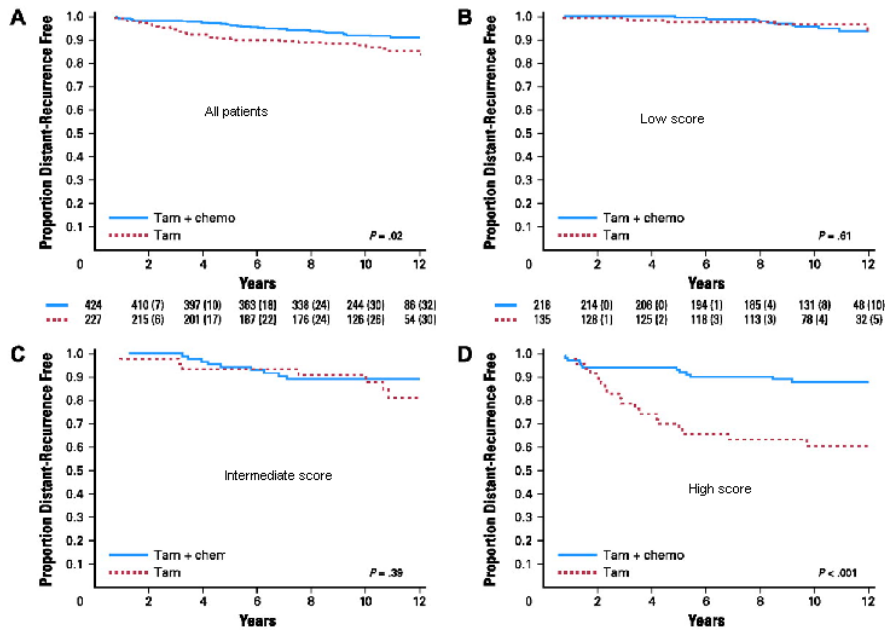
Node Positive (SWOG 8814)

Paik et al, JCO 2006
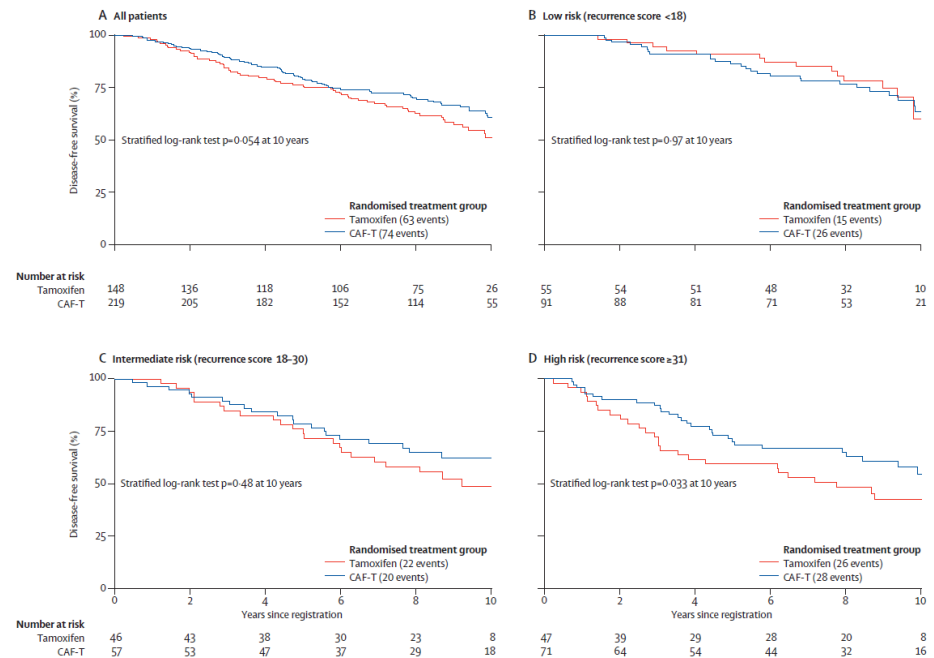
Albain et al, Lancet Onc 2010

TAILORx
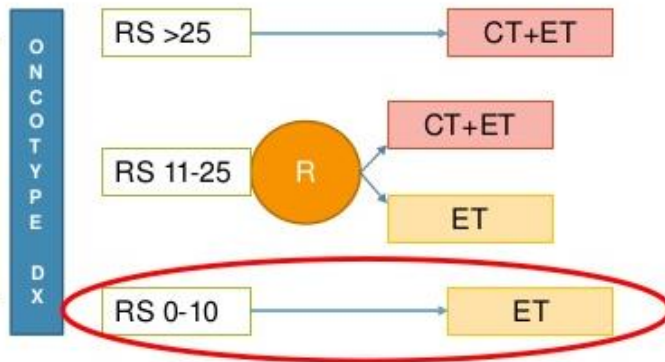
For RS ≤10 (n =1,626 (15.9%))
Rate of invasive disease–
free survival at 5 years was 93.8%;
5-yr rate of freedom from recurrence of
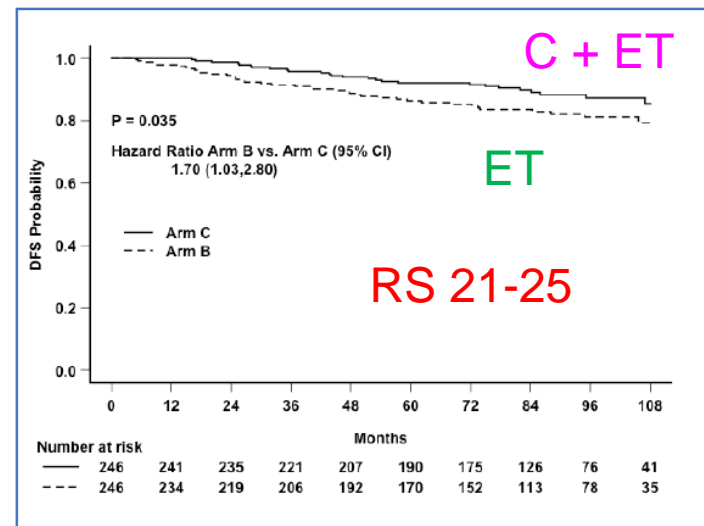breast cancer at a distant site was 99.3%.

TAILORx: Design   n = 10,253
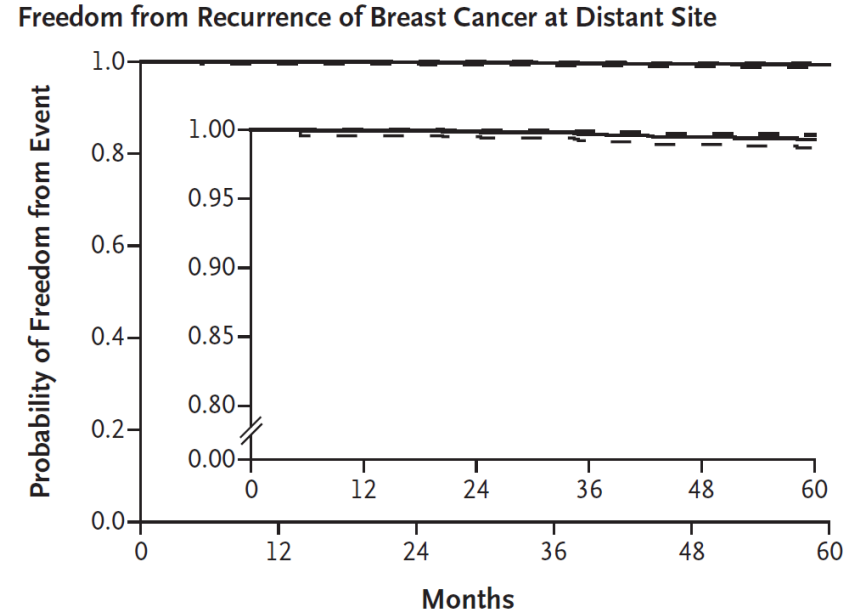
Sparano et al, NEJM 2015

Other prospective studies in node positive patients are ongoing.

TAILORx

RS 11-25

A Invasive Disease–free Survival

B Freedom from Recurrence at a Distant Site

C + ET

ET

RS 16-20

C + ET

ET

RS 21-25

Sparano et al, NEJM 2018
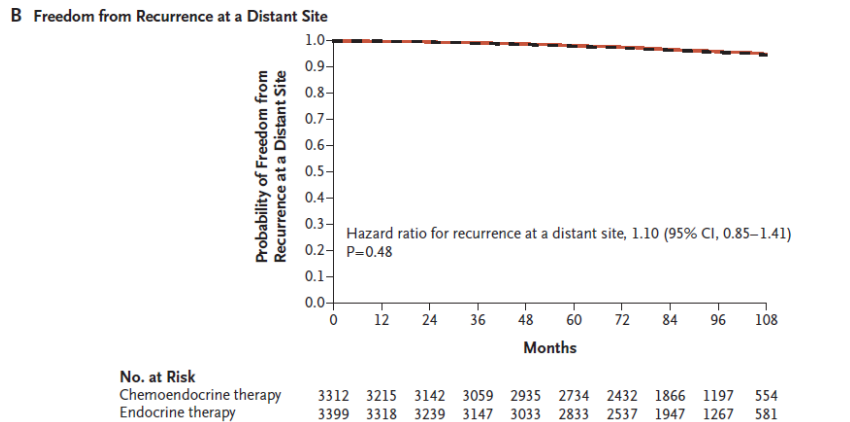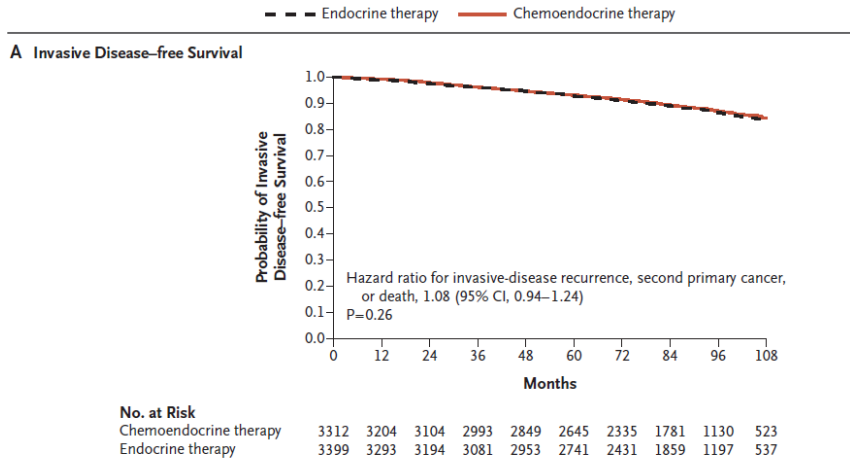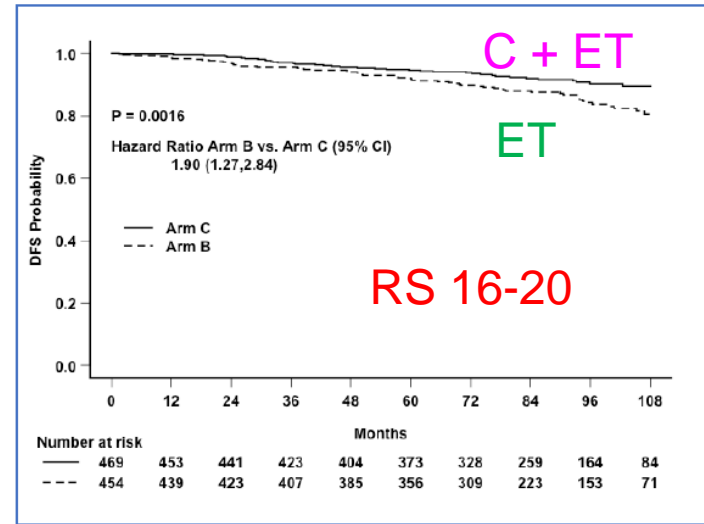
Effect of chemotherapy induced amenorrhoea?

Who Needs Adjuvant Chemotherapy for Breast Cancer?

Cardoso et al, NEJM 2016

MINDACT
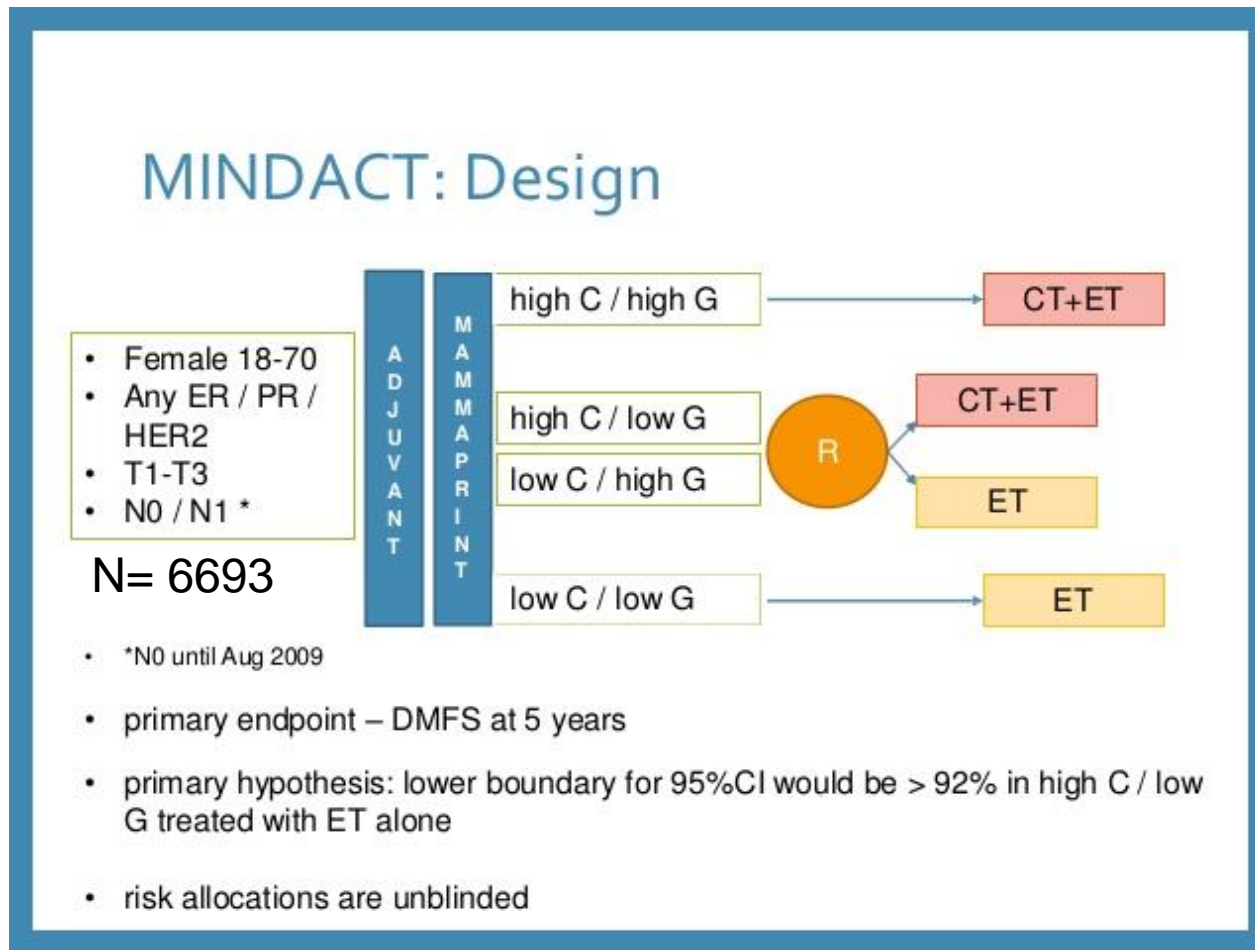
Survival without Distant Metastasis in the Four Risk Groups.

Cardoso et al, NEJM 2016

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MINDACT

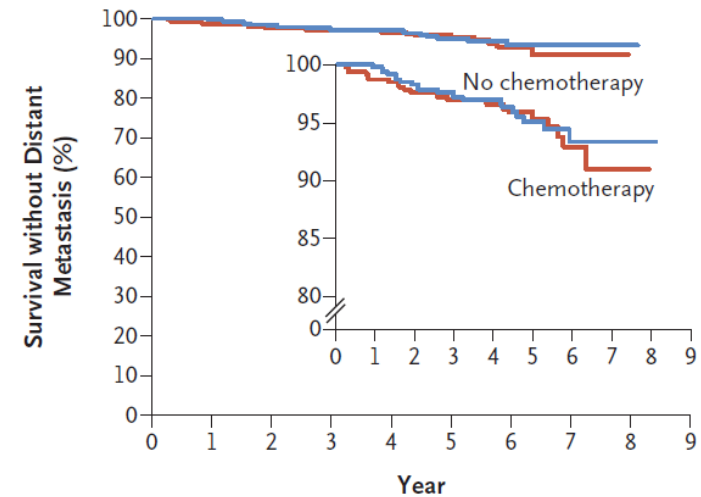**A** High Clinical Risk, Low Genomic Risk

B Low Clinical Risk, High Genomic Risk
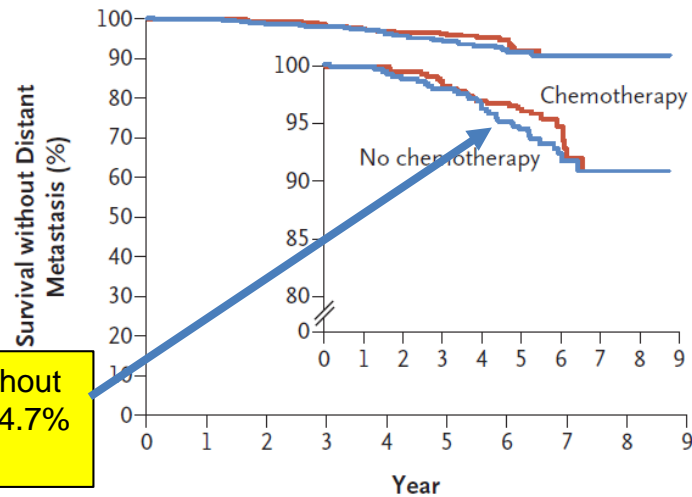
5-yr rate of survival without distant metastasis of 94.7% (95% CI, 92.5 to 96.2)

No. at risk (Panel A)

Chemotherapy	749	714	698	677	611	346	145	41	3
No chemotherapy	748	727	708	696	655	424	160	41	4

No. at risk (Panel B)

|									
Chemotherapy	344	321	316	306	281	179	81	22	0
No chemotherapy	346	336	327	319	291	178	82	24	3

Cardoso et al, NEJM 2016

ASCO Recommendations re Mammaprint

May be used in those with high clinical risk to identify a good-prognosis population with potentially limited chemotherapy benefit. However, a benefit from chemotherapy cannot be excluded, particularly in patients with >1 node involved. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group. Therefore, it does not have clinical utility in such patients. Krop et al, JCO 2017

Comparison of 6 Prognostic Signatures for ER+ BC - Secondary Analysis of ATAC Trial
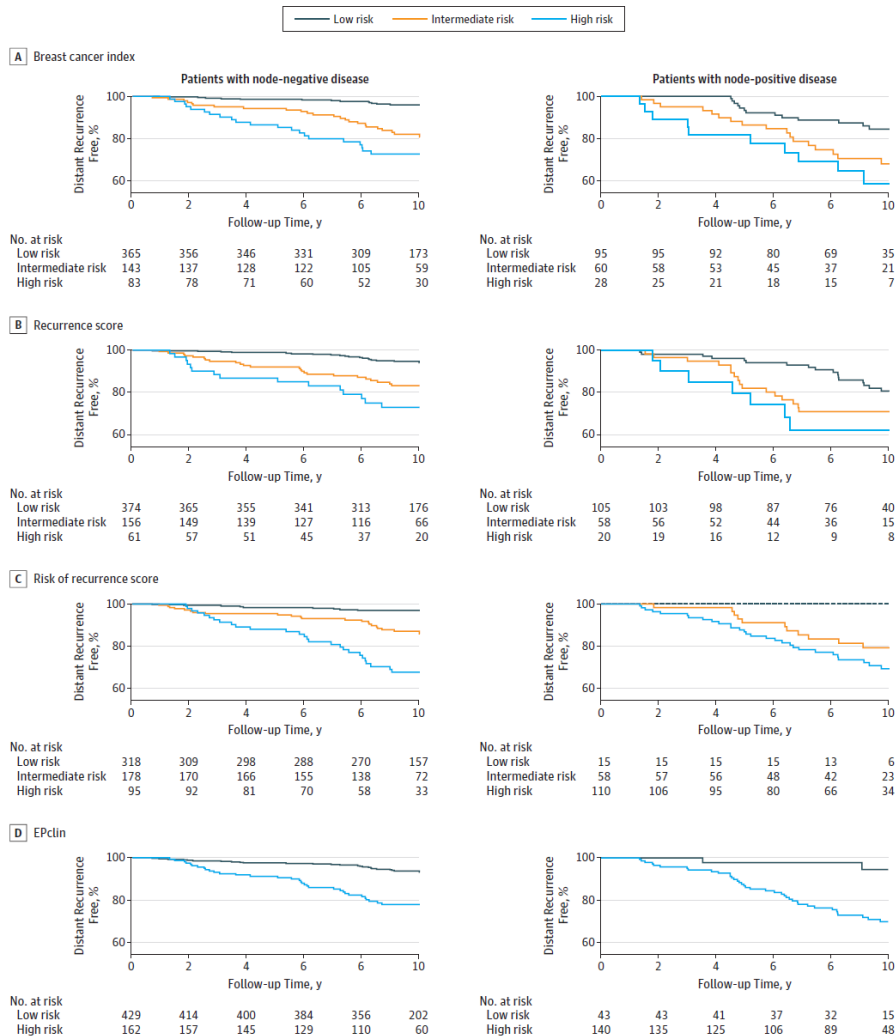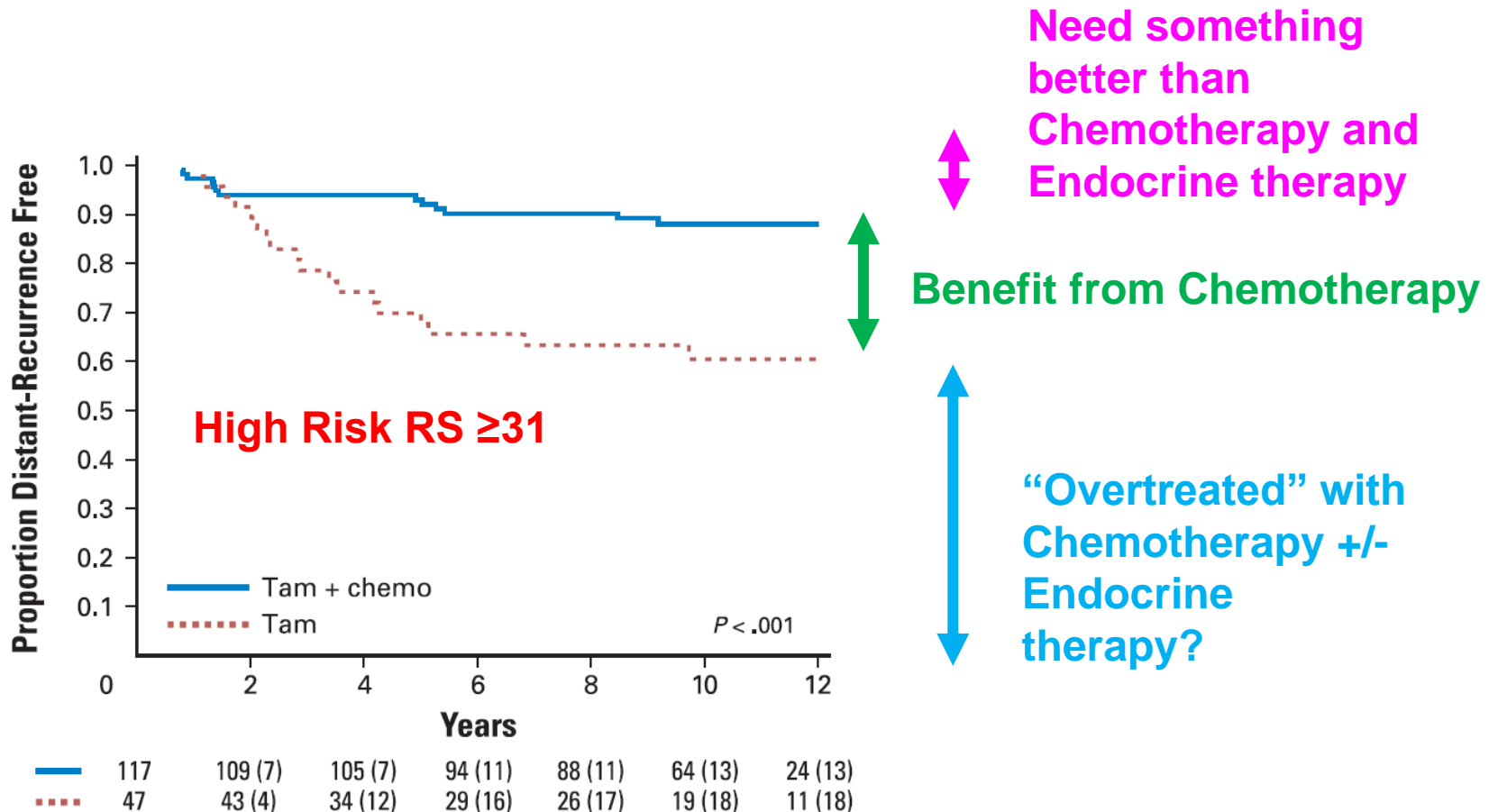

Each signature provided significantly more information than the Clinical Treatment Score.

For women with node-negative disease, the ROR (PAM50-based Prosigna risk of recurrence), BCI (Breast Cancer Index), and Epclin (EndoPredict) were significantly more prognostic for overall and late distant recurrence.

For women with 1-3+ nodes, limited independent information was available from any test.

Sestak et al, JAMA Oncology 2018

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Genomic Assays for Early BC

- Who needs it?
  - HR+HER2-
  - Mainly node negative
  - If it changes the clinical decision

- Which one is the best?
  - All are prognostic, though ROR, BCI, and EPclin were significantly more prognostic for overall and late distant recurrence.

- Which has the highest level of evidence to support its use?
  - Oncotype currently

Limitations of Current Practice

Need something better than Chemotherapy and Endocrine therapy

Benefit from Chemotherapy

High Risk RS ≥31

"Overtreated" with Chemotherapy +/- Endocrine therapy?

Tam + chemo
Tam
$P < .001$

| 117 | 109 (7) | 105 (7) | 94 (11) | 88 (11) | 64 (13) | 24 (13) |
| 47 | 43 (4) | 34 (12) | 29 (16) | 26 (17) | 19 (18) | 11 (18) |

KM Curve from Paik et al, JCO 2006 (subset of NSABP-B20)

Conclusions and Future Directions

- Improvements continue to be made to refine selection of who needs adjuvant chemotherapy.
  - Prediction Tools using Clinicopathological factors
  - Guidelines
  - Molecular Assays

- However, there are still limitations with truly personalising treatment.
  - Still overtreating substantial proportion of patients
    - Better detection of residual microscopic disease?
  - Need to develop better treatments to reduce risk of relapse further.

Thank you for your attention!
감사합니다