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Rational use of Genomic Tests in Early-Stage Breast Cancer

Rupert Bartsch

Department of Medicine 1, Clinical Division of Oncology
Comprehensive Cancer Center Vienna
Medical University of Vienna

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Disclosures

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- Research Support: Novartis, Roche

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Breast Cancer

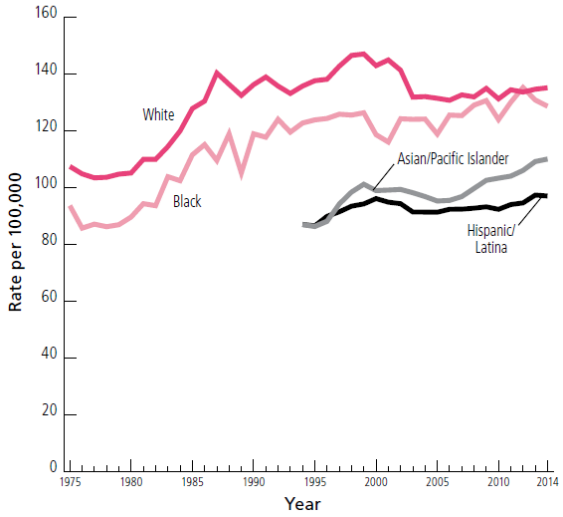
- Most common cancer in women worldwide [1]
- Age-dependent risk [2,3]
- Up until the early 2000s increasing breast cancer incidence [3]
- Reduced mortality due to screening and improved adjuvant treatment [3]

, Age-specific Probability of Developing Invasive Breast Cancer for US Women

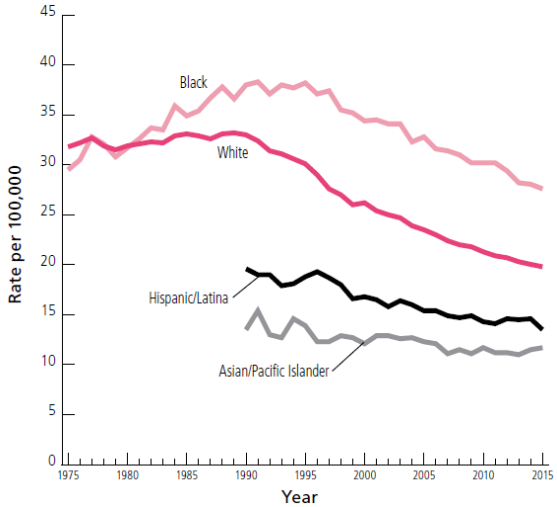
Current age	10-year probability:	or 1 in:
20	0.1%	1,567
30	0.5%	220
40	1.5%	68
50	2.3%	43
60	3.4%	29
70	3.9%	25
Lifetime risk	**12.4%**	**8**

Note: Probability is among those free of cancer at beginning of age interval. Based on cases diagnosed 2012-2014. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.

Trends in Female Breast Cancer Incidence Rates by Race/Ethnicity, 1975-2014, US



Trends in Female Breast Cancer Death Rates by Race/Ethnicity, 1975-2015, US



1 Available at http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics; last accessed January 23rd 2020.
2 Available at https://www.breastcancer.org/symptoms/understand_bc/risk/understanding; last accessed January 23rd 2020.
3 Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf; last accessed January 23rd 2020

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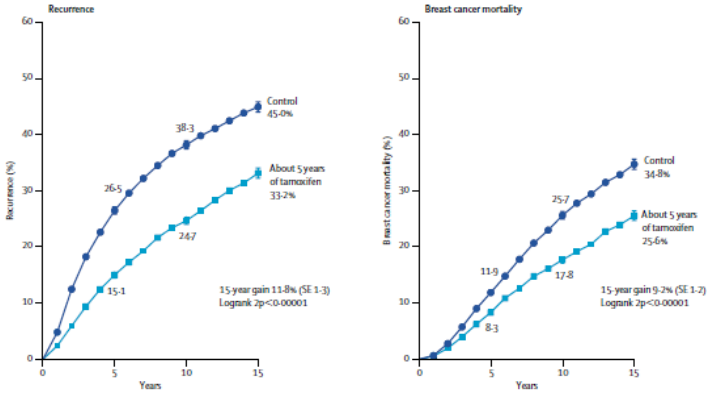
Endocrine Therapy in Breast Cancer

- ~60% of breast cancer cases are HR-positive
- Endocrine therapy accepted as backbone of systemic treatment in luminal breast cancer
- Five years of adjuvant tamoxifen reduces recurrence risk by 50% and breast cancer mortality by 30% [1,2]
- Aromatase-inhibitors superior to tamoxifen in postmenopausal and high-risk premenopausal patients (in combination with OFS) [3,4]
- Extension of adjuvant ET >5 a may reduce late recurrence risk [5,6]



1 EBCTCG. Lancet 2005;365:1687-1717.
2 EBCTCG. Lancet 2015;386:1341-1352.
3 BIG 1-98 Collaborative Group. N Engl J Med 2005;353:2747-2757.
4 Pagani O et al. N Engl J Med 2014; 371:107-118.
5 Davies C et al. Lancet 2013;381:805–816.
6 Goss PE et al. J Natl Cancer Inst 2005;97:1262-1271.

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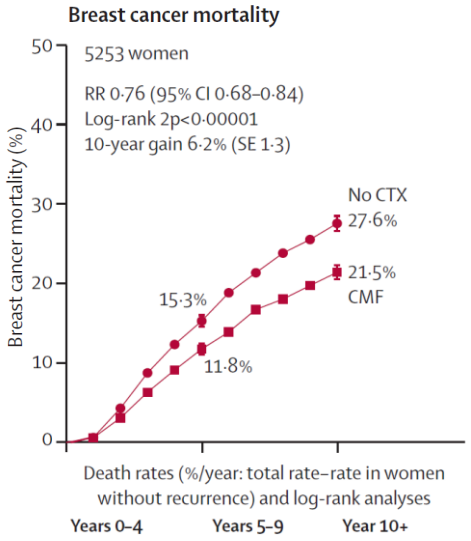
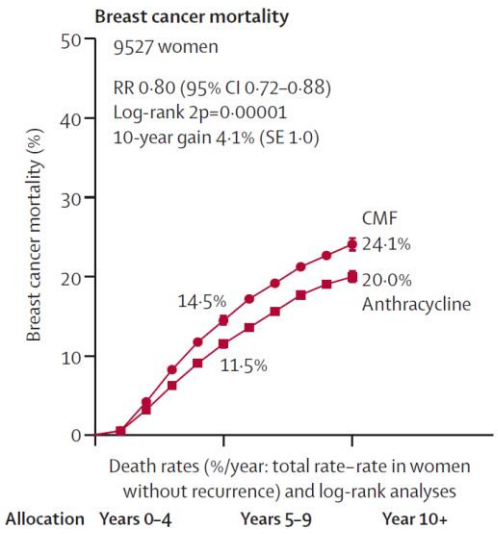
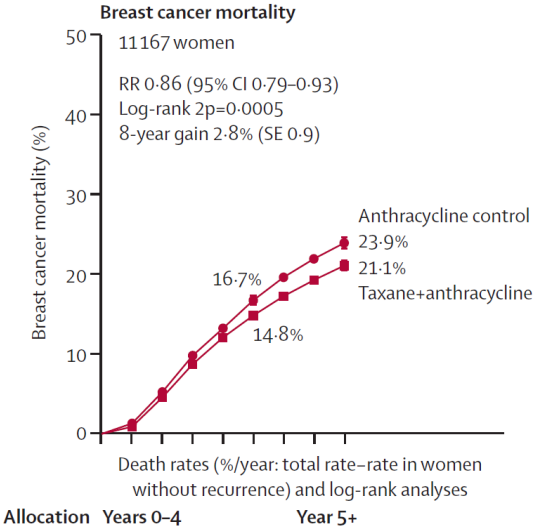
Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

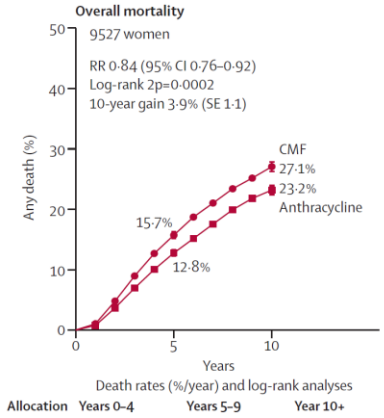
Gradual Improvement of Chemotherapy Acitivity

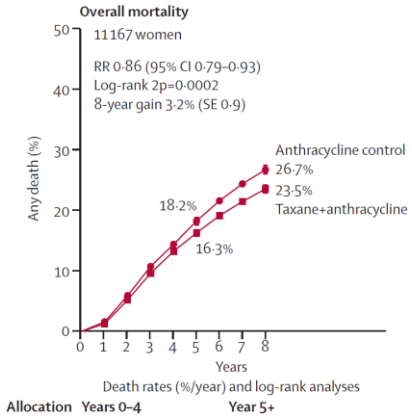






- No increase of alternative mortality



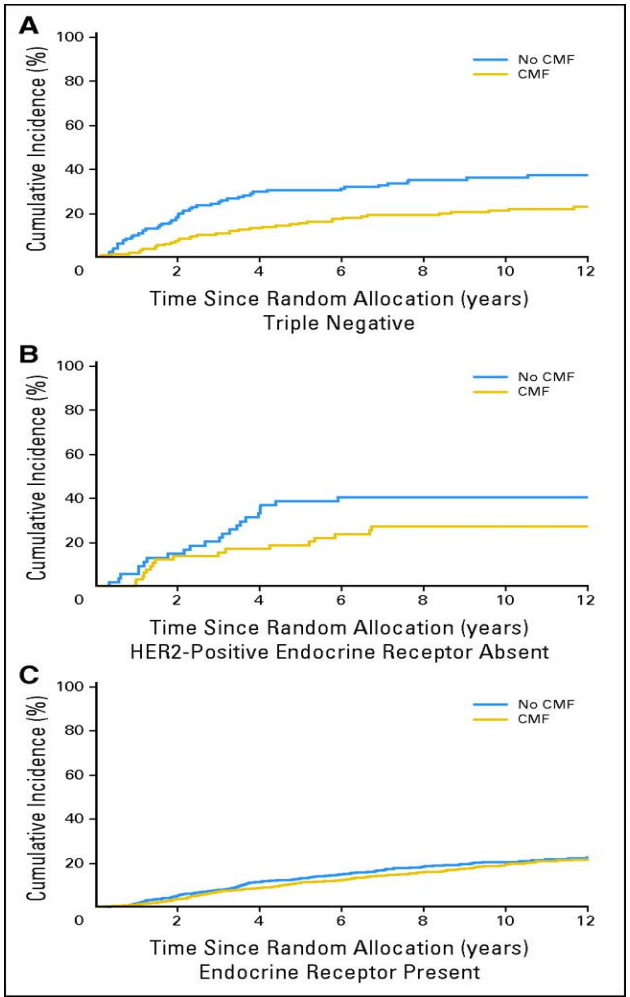


1 EBCTCG. Lancet 2012;379:432-444.

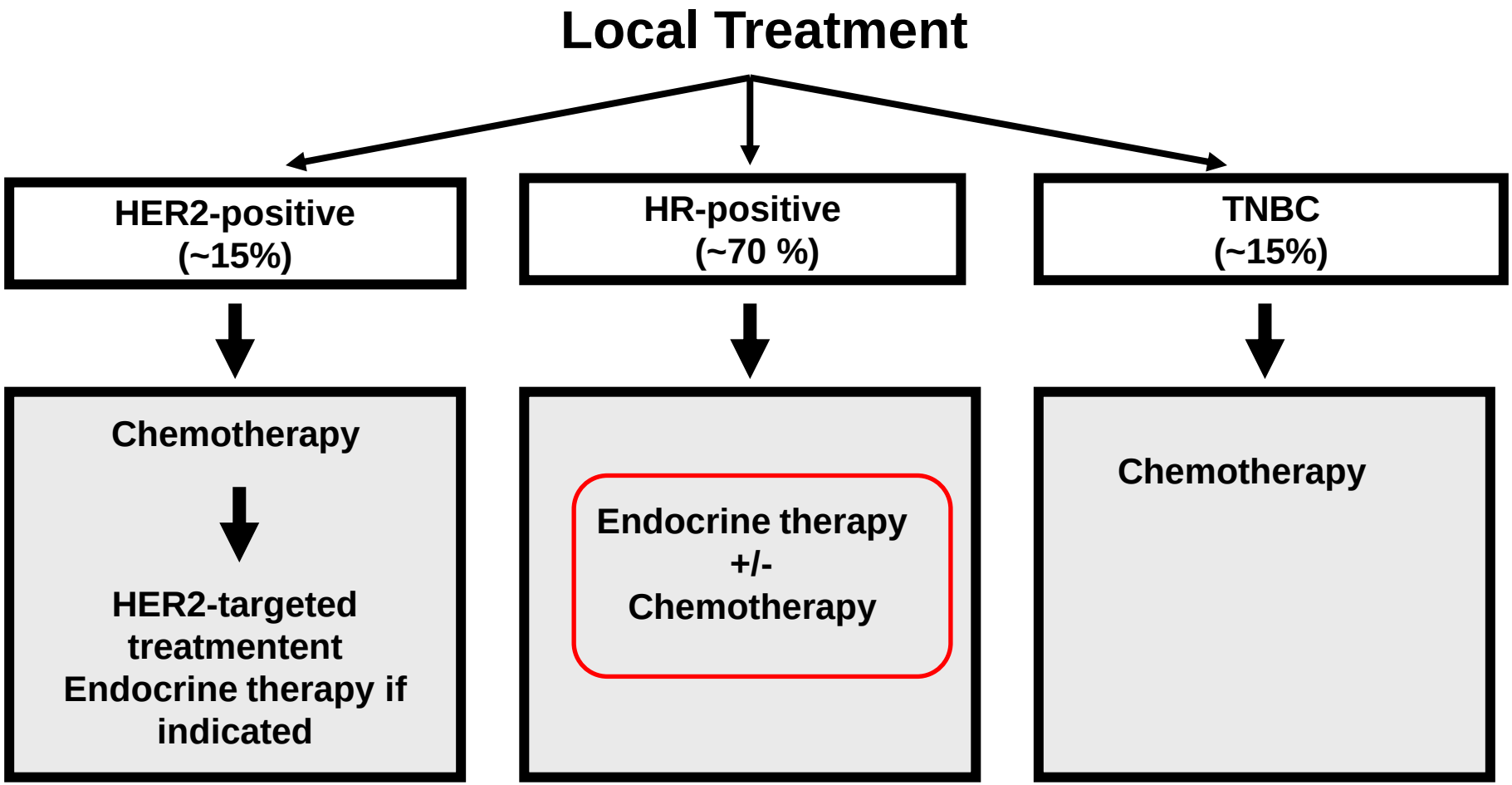
Chemotherapy Activity in Breast Cancer Subtypes[1]

- Activity of chemotherapy differs by breast cancer subtype

- A-C: Subtype-specific cumulative incidence of breast cancer recurrences over time in patients receiving CMF or no adjuvant chemotherapy in
  (A) TNBC
  (B) HER2-positive, HR-negative
  (C) HR-positive



1 Colleoni M. et al. J Clin Oncol 2010;28:2966-2973.


Local Treatment
HER2-positive (~15%)
HR-positive (~70 %)
TNBC (~15%)
Chemotherapy
HER2-targeted treatmentent
Endocrine therapy if indicated
Endocrine therapy +/- Chemotherapy
Chemotherapy

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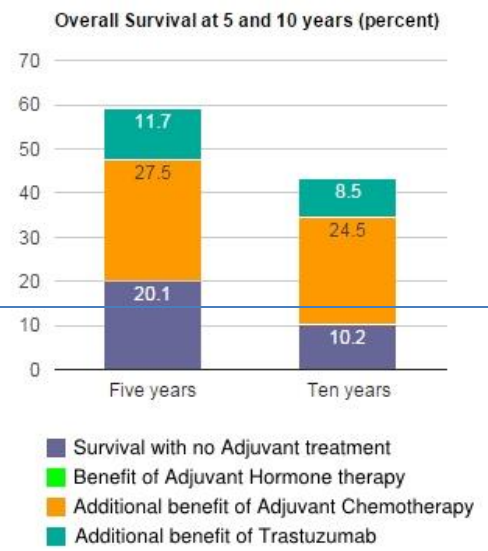

Decicison Making Tools[1]

- Disease Stage (prognostic)
  - Tumor size — Local therapy
  - Nodal status — Prognosis, type of systemic therapy (e.g. chemotherapy despite luminal A biology in case of extensive nodal involvement)
- Biomarker (prognostic, predictive)
  - Grading — Prognosis, prediction (chemotherapy)
  - Hormone-receptor — Prognosis, prediction (endocrine therapy)
  - HER2-stutus — Prognosis, prediction (HER2-targeted treatment)
  - Proliferation rate — Prognisi, prediction (chemoherapy)
- Risk scores — Web-based anaylsis of risk factors and graphic interpretation (e.g. Adjuvant Online!)

1 Curigliano G et al. Ann Oncol 2017;28:1700-1712..
2 Ravdin PM et al. J Clin Oncol 2001;19:980–991.

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Ki67

- Analysis of the prognostic and predictive role of Ki67 in GeparTrio [1,2]
- Ki67 was a significant predictive and prognostic marker over a wide range of cut-points
  - Significant Ki67 cut-points in GeparTrio:: 3%-94% (for pCR), 6%-46% (for DFS). 4%-58% (for OS)
  - Ki67 and pCR: Ki67 ≤15% pCR 4.2%; Ki67 15.1-35% pCR 12.8%; Ki67 >35% pCR 29.0% (p<0.0005)
  - Ki67 was a significant predictor of DFS and OS in HR-positive tumours
- No cut-point optimization may be possible – Ki67 is a continuous marker

- *Caveat:* Significant inter- and intraobserver variability in the analysis of Ki67 levels
- Poor reproducibility of test results
- More accurate and reproducibale capture of tumour biology by quantitative analysis of mRNA expression?

1 von Minckwitz G et al. J Natl Cancer Inst 2008;100,552-562..
2 Denkert C et al. Ann Oncol 2013;24:2786-2793.
3 Varga Z et al. PLoS One 2012;7(5):e37379.

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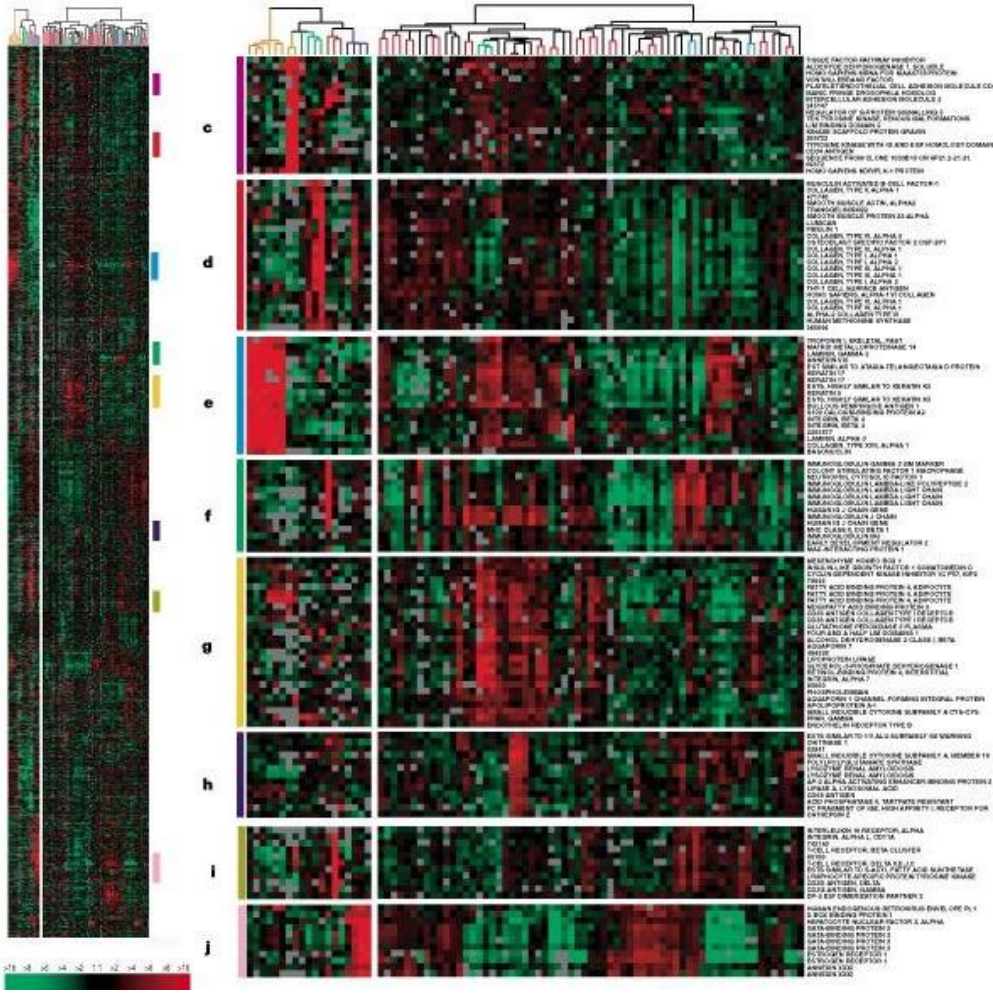
Intrinsic Classification[1]

- Analysis of differences in gene-expression patterns in 65 surgical specimens from 42 patients
- Gene expression patterns in two samples from the same individual were more similar to each other than to samples from other patients
- Variation in messenger RNA levels of genes were related to specific physiological variation – classification into subtypes



1 Perou CM et al. Nature 2000;406:747-752.

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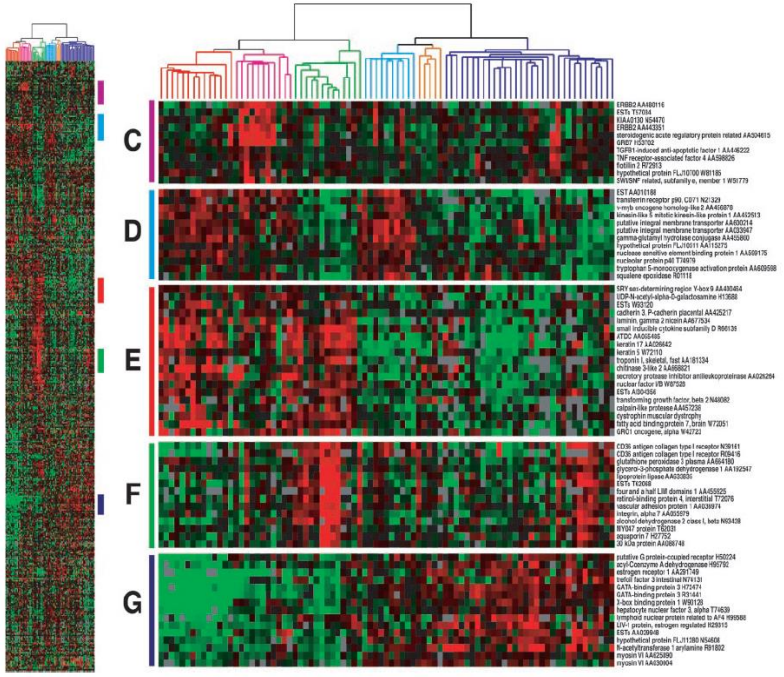
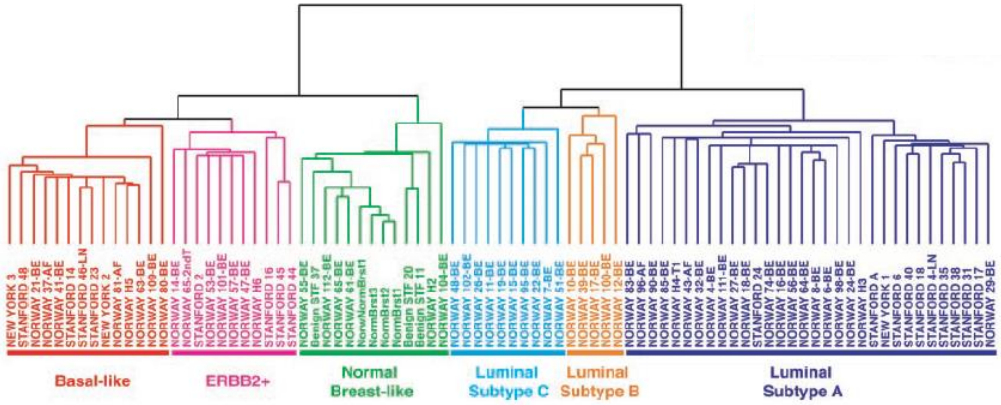
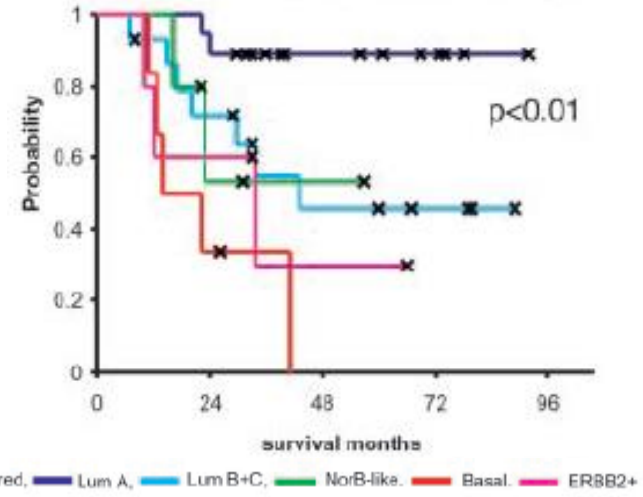
Intrinsic Classification[1]



- Aim: Classification of breast tumours based upon variations in gene-expression patterns and to correlate subytpes with clinical outcome
  - 85 cDNA samples (78 breast cancers; 71 ductal carcinoma, five lobular carcinoma, and two DCIS), three fibroadenoma, four normal breast tissues
  - Analysis by hierarchical clustering (full cluster diagram right)

OS (below)





1 Sørlie T et al. Proc Natl Acad Sci USA 2001;98:10869-10874.

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Development of Multigenomic Assays

- Data from the intrinsic classification lead to the development of several genomic tests to characterize breast cancer prognosis [1]
- Use of genomic tests may change treatment decision in 25-30% of cases [2-3]
- Several multigenomic assays commercially available
- In Europe commonly applied platforms include: 21-gene OncotypeDx risk of recurrence score, the 70-gene MammaPrint assay, the 12-gene Endopredict assay and the PAM50 risk of recurrence score [4-7]
- Multigenomic assays of the first generation, namely OncotypeDx and MammaPrint assess mostly tumor proliferation, while tests of the second generation, Endopredict and PAM50 also measure genes of ER signaling [8]

1 Azim Jr HA et al. Ann Oncol 2013;24:647–654.
2 Henry LR et al. J Surg Oncol 2009; 99: 319–323.
3 Lo SS et al. J Clin Oncol 2010; 28:1671–1676.
4 Paik S et al. N Engl J Med 2004;351:2817-2826.
5 van de Vijver MJ et al. N Engl J Med 2002;347:1999-2009.
6 Filipits M et al. Clin Cancer Res 2011;17:6012-6020.
7 Wallden B et al. BMC Med Genomics 2015;8:54.
8 Tendl K and Bargo-Hoyath Z. MEMO 2020:in press.

Multigenomic Assays

- Comercially available (validated) platforms [1]

Name	Tissue	Comment	Validation
OncotypeDX	FFPE	ROR; three groups	prospective
MammaPrint	FF, FFPE	Low/high risk	Prospective
Prosigna (PAM50)	FFPE	ROR, three groups	retrospective
Breast Cancaer Index	FFPE	Likelehood of late recurrence and benefit of extended adjuvant therapy	retrospective
Endopredict	FFPE	Low/high risk; Epclin incorporates clinical stage	retrospective
GenomicGrade	FFPE	Seperation of G2 tumours into low and high risk	retrospective
MammaTyper	FFPE	Descrimination of luminal A and B	retrospective

1 Adapted from:Fayanju OM et al. Ann Surg Oncol 2018;25:512-519.

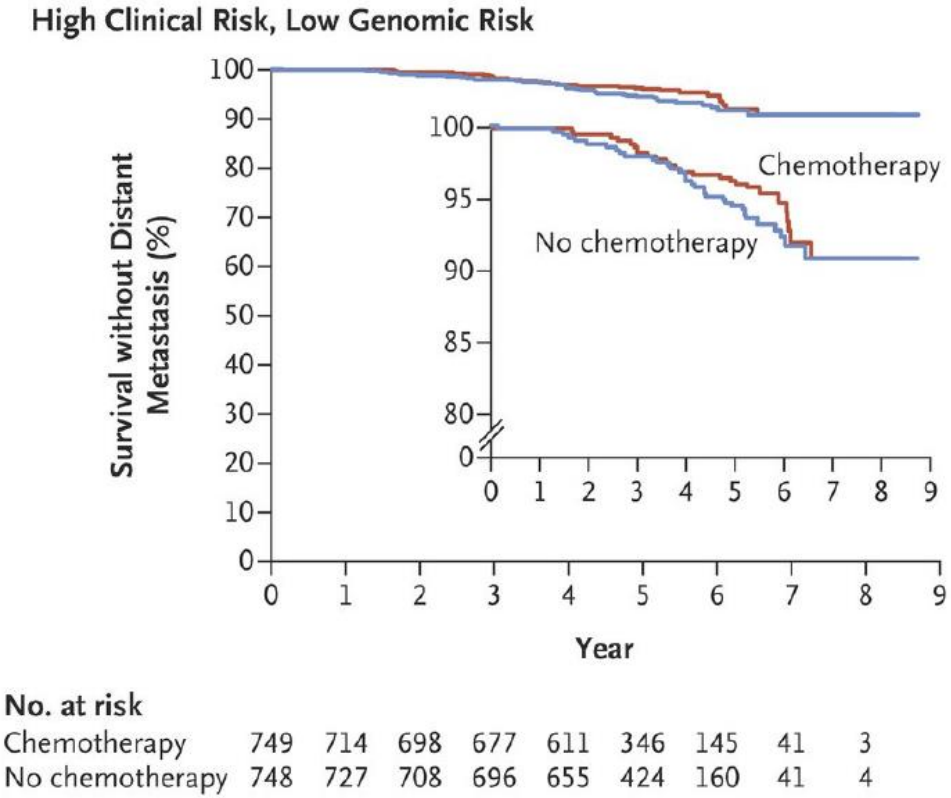
Multigenomic Assays

- MINDACT: MammaPrint [1,2]
  - Can multigenomic asssays reduce the rate of EBC patients receiving adjuvant chemotherapy?
  - Genomic *vs*. clinical risk assessment
  - MammaPrint *vs*. Adjuvant Online!
  - Prospective randomized phase III trial
  - 6.693 pts., EBC, 1-3 pos. axillary nodes allowed
  - 80% node-negative; 88% HR-pos., 10% HER2-pos.
  - Pts. with concordent clinical and genomic risk (i.e. MammaPrint high-risk/Adjuvant Online! High-risk and MammaPrint low-risk/Adjuvant Online! Low risk) received chemotherapy or no chemotherapy
  - Pts. with discordant results were rnadomized to adjuvant chemotherapy or no adjuvant chemotherapy

1 Cardoso F et al. Molecular Oncology. 2007;1:246-251.
2 Cardoso F et al. N Engl J Med. 2016;375:717-729.

Multigenomic Assays

- MINDACT [1]
  - 1,550 pts. with high clinical and low genomic risk
  - Rate of patients without distant metastases at five years
  - Chemotherapy 95.9% (95% CI 94.0-97.2) *vs*. no chemotherapy 94.4% (95% CI 92.3-95.9)
  - Absolute difference 1,5%;
    HR 0.78; 95% CI 0.50-1.21; *p*=0.27

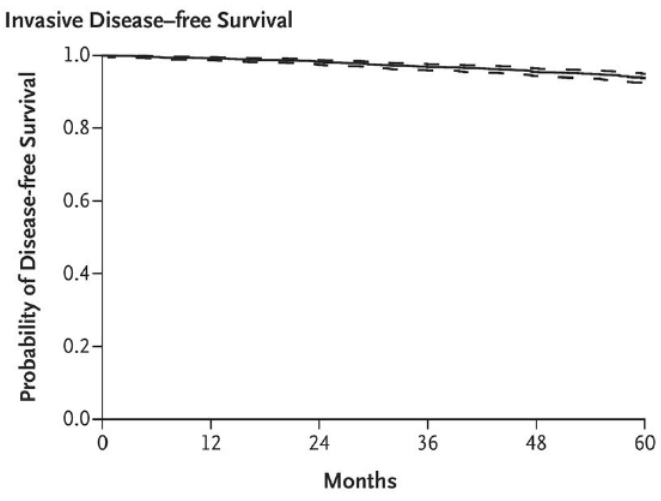


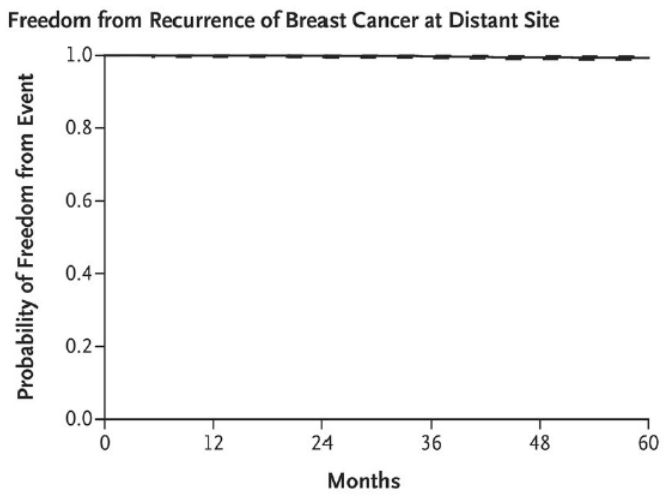
- N+ chemotherapy 96.3% (95% CI 93.1-98.1) vs. no chemotherapy 95.6 (95% CI 92.7-97.4)
- 592 pts. With low clinical and high genomic risk HR 1.17; 95% CI 0.59-2.28; *p*=0.66

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

Multigenomic Assays

- TaylorX: OncotypeDX [1,2]
  - Outcome of pts. with low RS without chemotherapy
  - Can chemotherapy be safely witheld in pts. with intermediate RS (11-25)
  - Prospective randomized phase III trial; n=10.273 pts., EBC, HR-positive, HER2-negative, node-negative EBC
  - RS 0-10: 5-years rate of invasive disease-free survival with endocrine therapy (ET) 93.8% (95% CI 92.4-94.9)

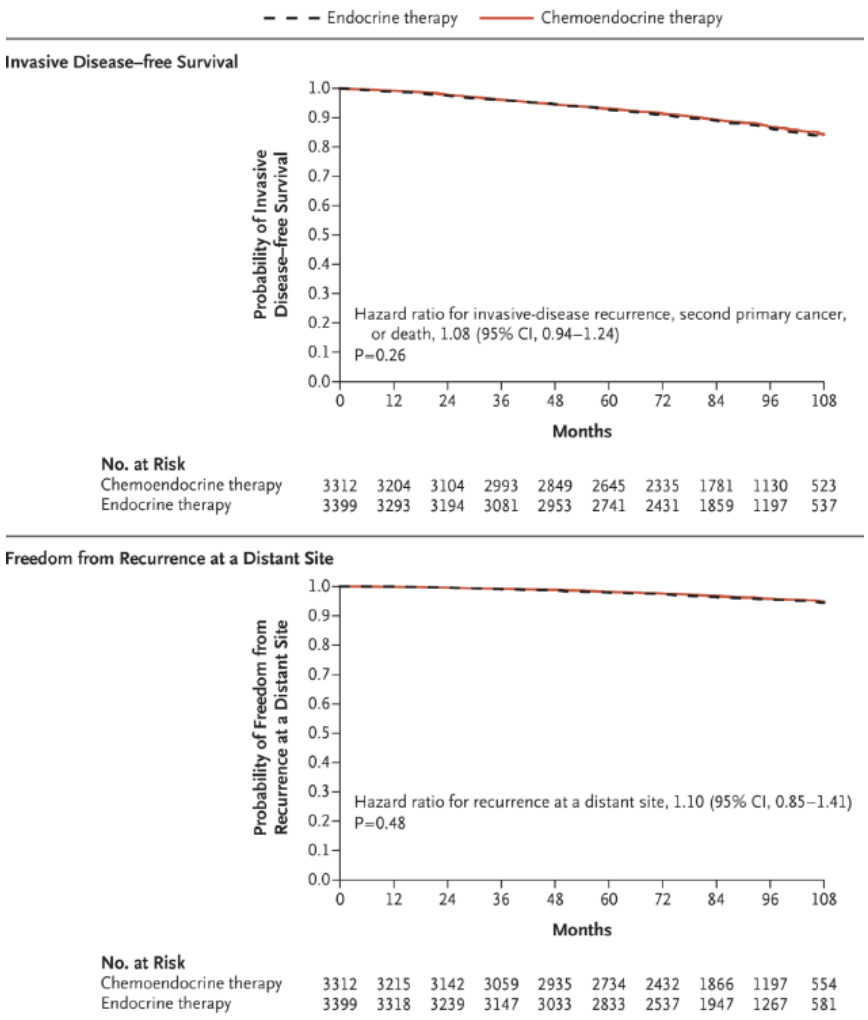




1 Sparano JA et al. N Engl Med 2015;373:2005-2014.
2 Sparano JA et al. N Engl J Med 2018:379:111-121.

Multigenomic Assays

- TaylorX
  - Intermediate RS 69%
  - Randomization ET +/- chemotherapy
  - Primary endpoint invasive disease-free survial
  - 9-years iDFS ET alone 83.3% *vs*. chemotherapy plus ET 84.3%
  - HR 1.08; 95% CI 0.94-1.24; *p*=0.26)
  - Subgroups:
  - ≤50 years: chemotherapy benefit in RS groups 21-25 (Δ6.5%) and 16-20 (Δ1.6%)
  - No difference in women with RS 0-15



1 Sparano JA et al. N Engl J Med 2018:379:111-121.

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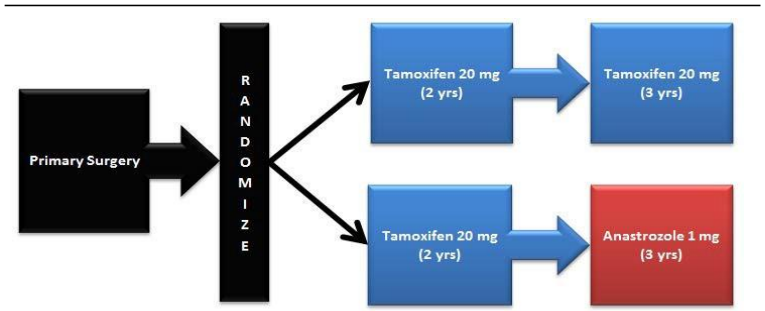
WSG Plan B[1]

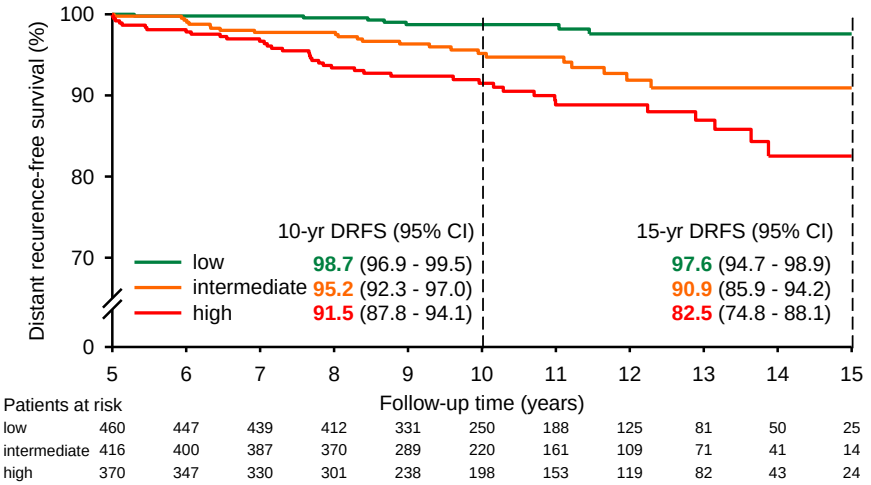
- Prospective randomized phase III trial, EBC, HER2-negative
- 6x docetaxel/cyclosphamide *vs.* EC-D
- 08/2009 amendment: endocrine therapy alone for pts. with RS ≤11
  - N+ (≤3 involved lymph nodes) or N0 with further risk-factors (≥pT2, grade 2/3, high uPA/PAI-1, <35 years)
  - 348 pts.; 238 pN0, 110 pN1
- Five-year DFS in pts. treated with ET alone:
  - pN0 94.2% (91.2-97.3%)
  - pN1 94.4% (89.5-99.3%)

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

Late Recurrence Risk in luminal BC

- Annual recurrence rate of 1-2% persists after five years in luminal BC [1]
- Extended adjuvant therapy may reduce the risk for late recurrences [2]
- Can multigenomic assays predict late recurrences?
- Late recurrence risk in ABCSG-8 [2]
  - Samples of 1.478 / 3.714 pts., PAM50



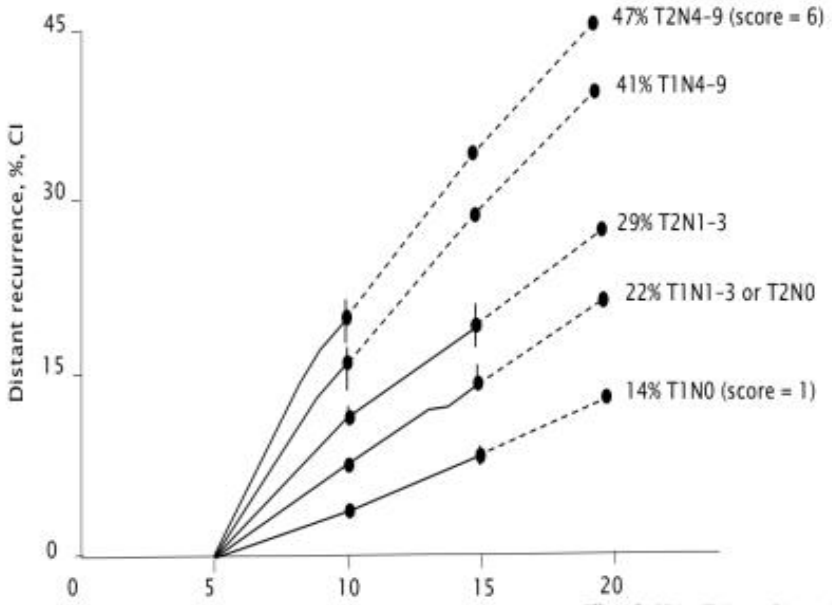


1 Pan H et al. N Engl J Med 2017;377:1836-1846.
2 Goss PE et al. N Engl J Med 2003;349:1793-1802.
2 Dubsky P et al. J Clin Oncol 2012;30:722-728.

Late Recurrence Risk in luminal BC

- EBCTCG metanalysis, 46,000 pts., EBC
- Recurrence risk after 5 years of adjuvant ET persists for 5-14 years
- Conventional clinical risk factors as predictors of late recurrenxe (tumour size, nodal status, grading)

- After 5 years' endocrine therapy, recurrences continue steadily to at least year 20
- Absolute recurrence risk in years 5–20 is appreciable even for T1N0 disease



1 Pan H et al. N Engl J Med 2017;377:1836-1846.

Discussion

- Several mRNA expression-based prognostic assays currently commercialy available
- Multigenomic platforms may optimze risk assessment in early-stage luminal/HER2.negative breast cancer
- OncotypeDX and MammaPrint validated in prospective randomized trials
- Patients with low genomic risk derive no benefit from chemotherapy
- Limited benefit of chemotherapy in patients with intermediate RS (TaylorX) or clinically high-risk/genomically low-risk (MINDACT)
- Multigenomic assays may reduce the use of adjuvant chemotherapy in selected breast cancer subgroups

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Backup

WSG Plan B[1]

- Correlation of RS and Ki67

	(semi-quantitative) Ki-67 group								
	0–10%	15%	20%	25%	30%	35%	40%	>40%	Total
RS ≤ 11									
N	223	87	68	23	1	1	2	0	405
% of Ki-67 group	22.7%	20.1%	19.1%	10.6%	1.0%	2.5%	4.7%	0.0%	0.0%
RS12-25									
N	680	283	219	108	42	16	5	2	1355
% of Ki-67 group	69.3%	65.5%	61.5%	50.0%	40.8%	40.0%	11.6%	6.3%	0.0%
RS > 25									
N	78	62	69	85	60	23	36	30	443
% of Ki-67 group	8.0%	14.4%	19.4%	39.4%	58.3%	57.5%	83.7%	93.8%	0.0%
Total									
N	981	432	356	216	103	40	43	32	2203
% of RS group	44.5%	19.6%	16.2%	9.8%	4.7%	1.8%	2.0%	1.5%	100.0%

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

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Late Recurrence Risk in luminal BC[1]

- 20-years recurrence-risk depending upon nodal-status 13%-34% in pts. treated between 1976 and 2011[2]
- Update SABCS 2019:
  - Changes in long-term risk in a more recently treated population?
  - Data from 82,598 pts. without recurrence event after five years of endocrine therapy
- Compared to pts. treated before 1995, the risk for developing distant metastases in years 5 to 9 was
  - 1995-1999 HR 0.82 (95% CI 0.77-0.90)
  - 2000-2004 HR 0.64 (95% CI 0.59-0.70)
  - 2005-2012 HR 0.58 (95% CI 0.52-0.65)

1 Pan H et al. GS2-04; SABCS 2019.
2 Pan H et al. N Engl J Med 2017;377:1836-1846.