Azienda Ospedaliera Nazionale
SS. Antonio e Biagio e Cesare Arrigo
Alessandria

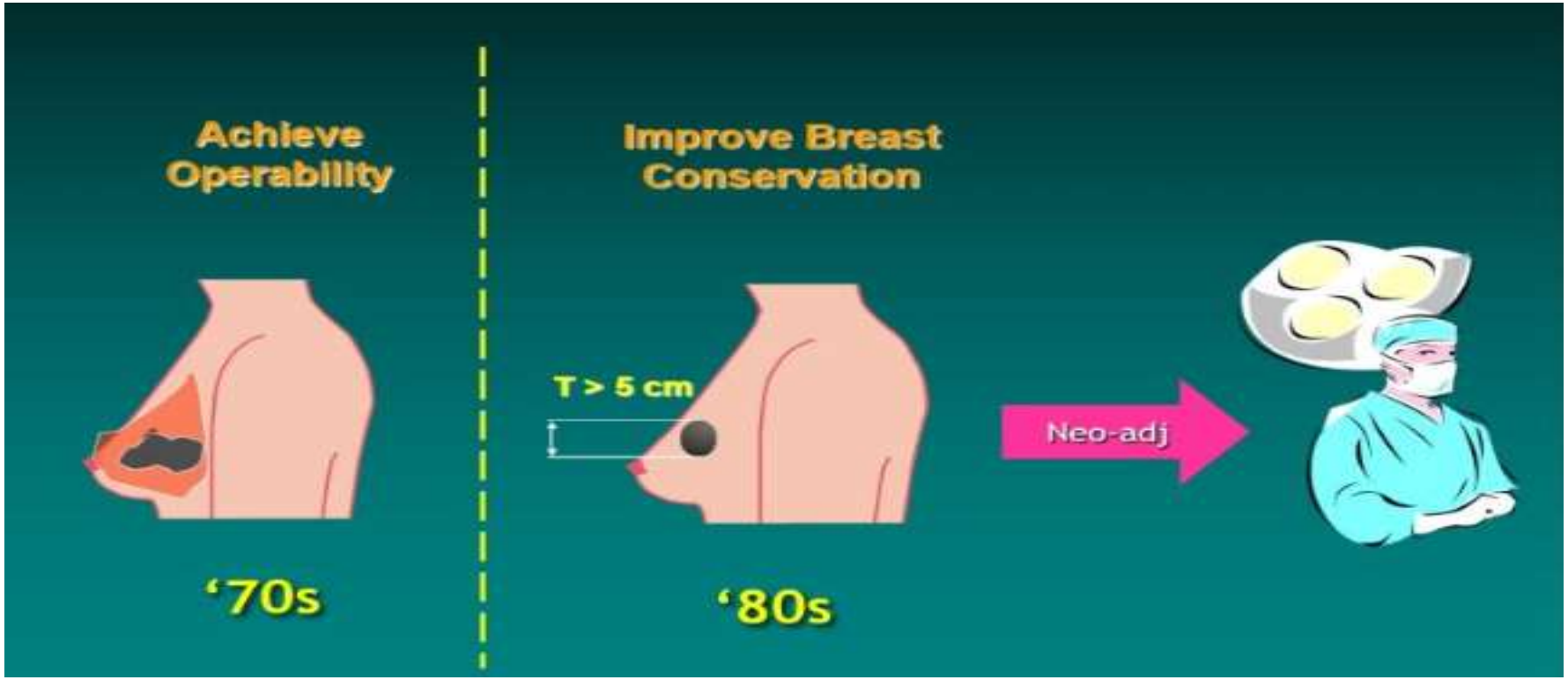
REGIONE PIEMONTE

Valutazione del rischio. Terapia neoadiuvante e adiuvante

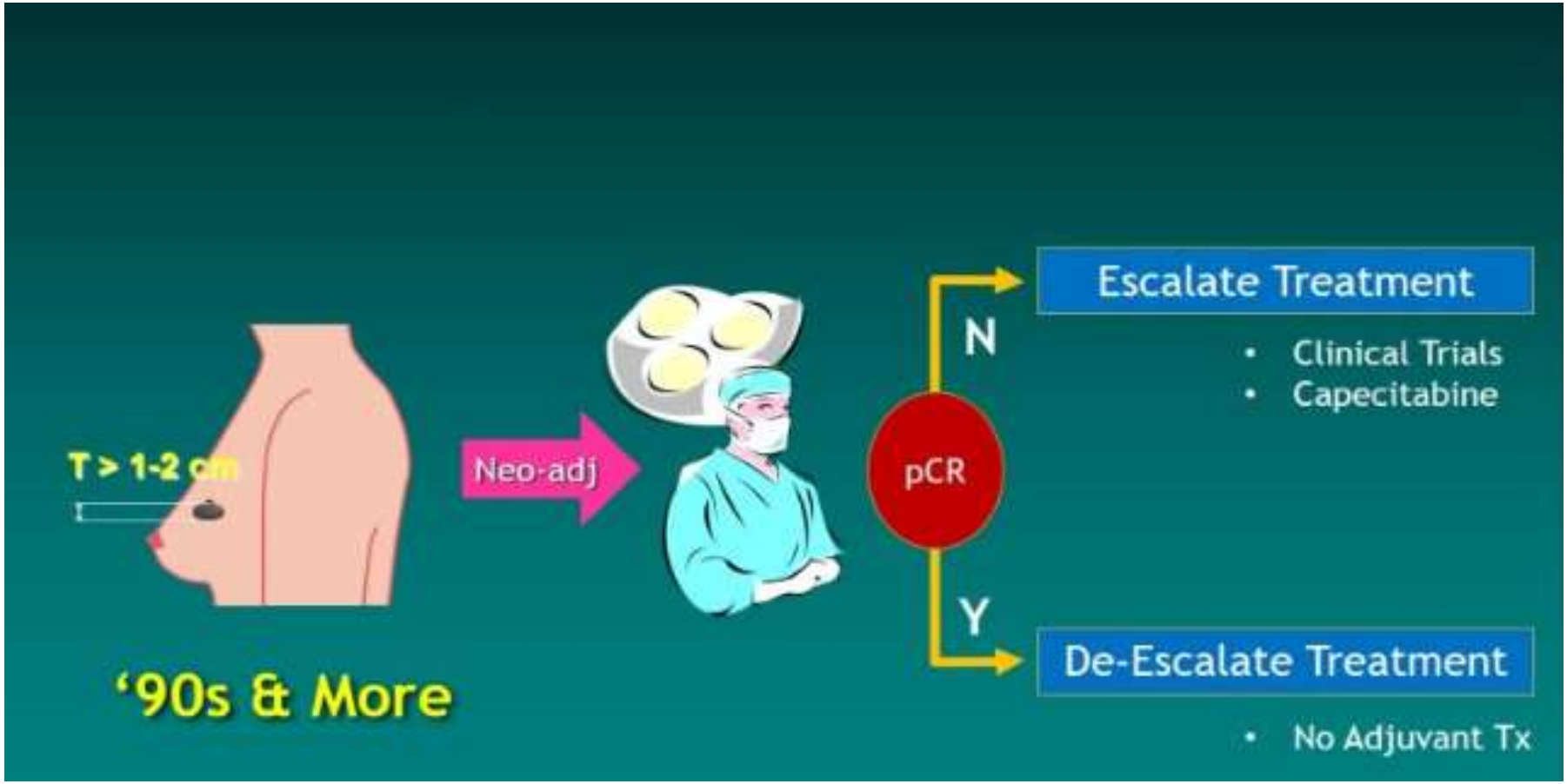
Dott. ssa Pamela Guglielmini

SC Oncologia Medica
Azienda Ospedaliera Nazionale "SS. Antonio e Biagio e C. Arrigo" Alessandria

NEOADIUVANTE:
Aiming at surgical outcome

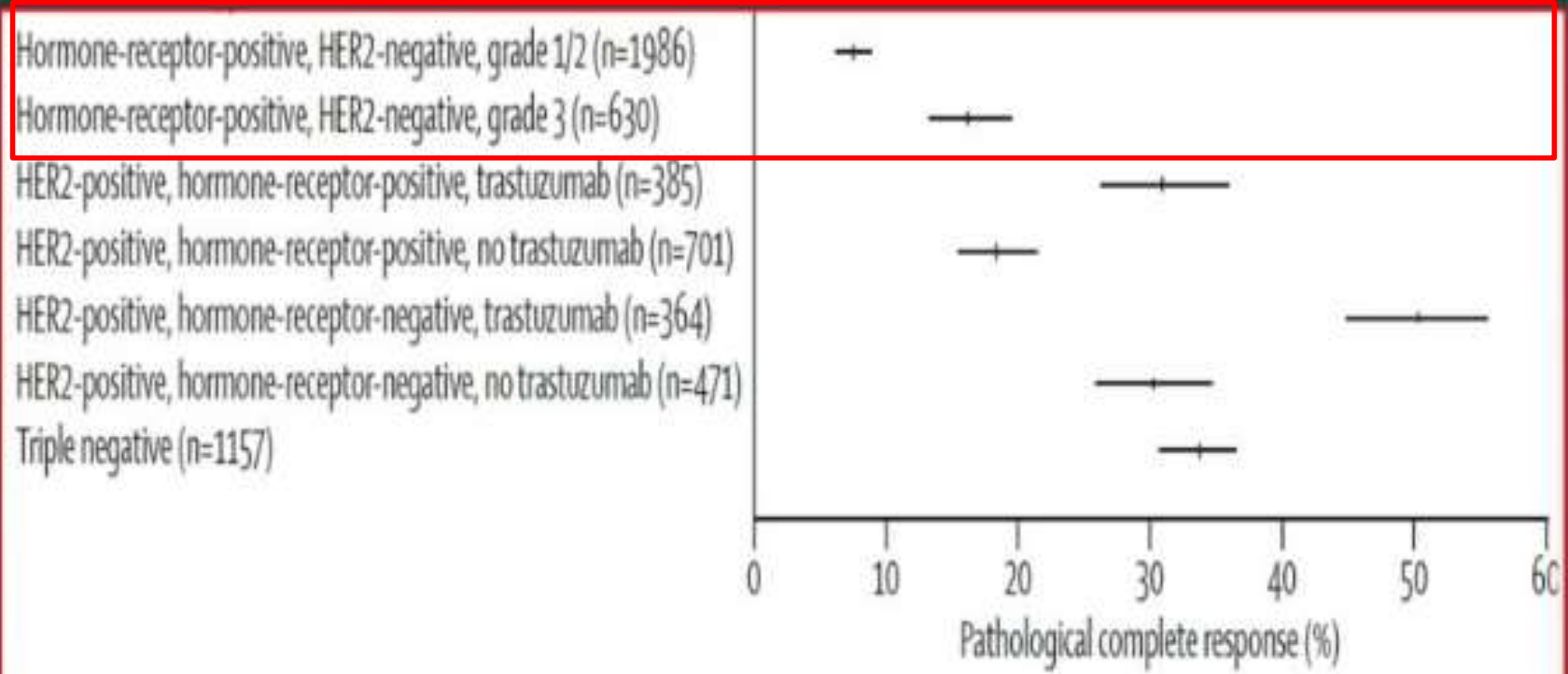


Aiming at prognostic prediction



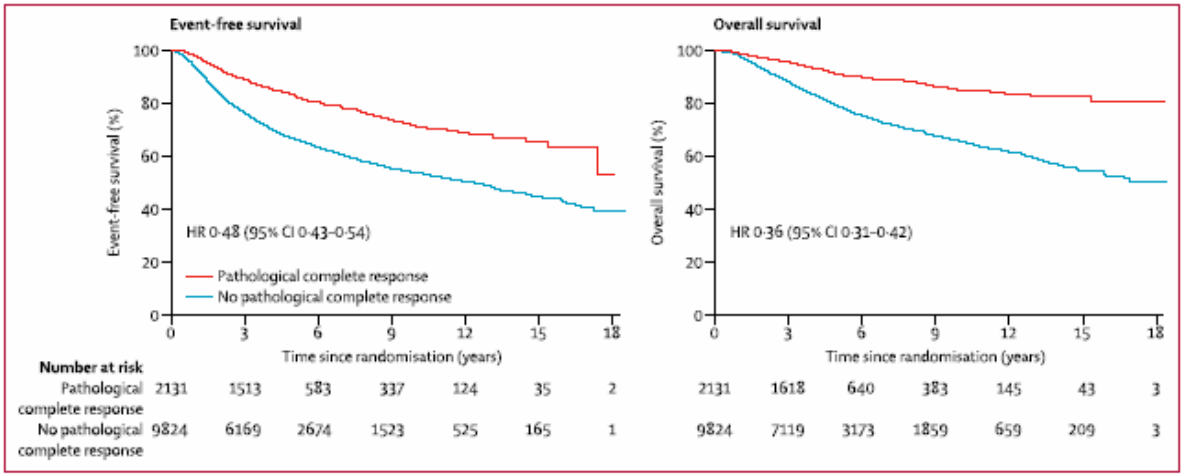
Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

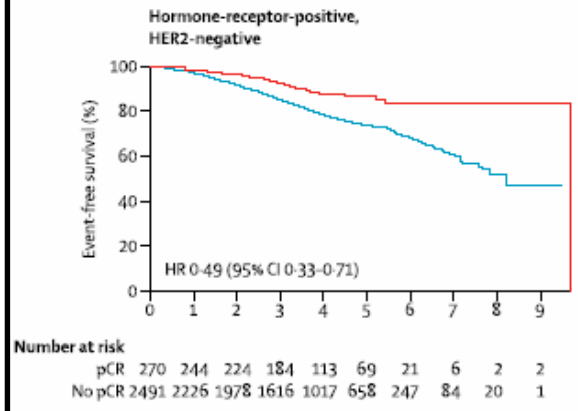
Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

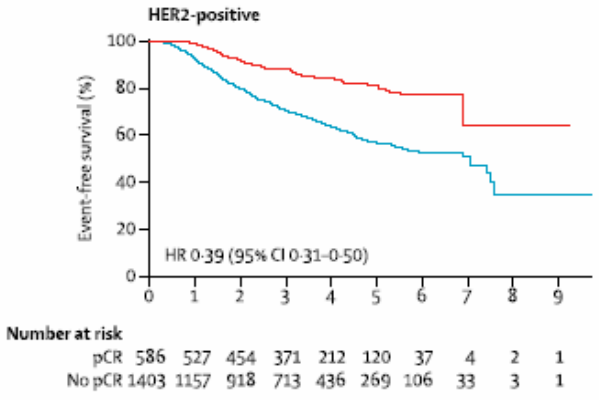


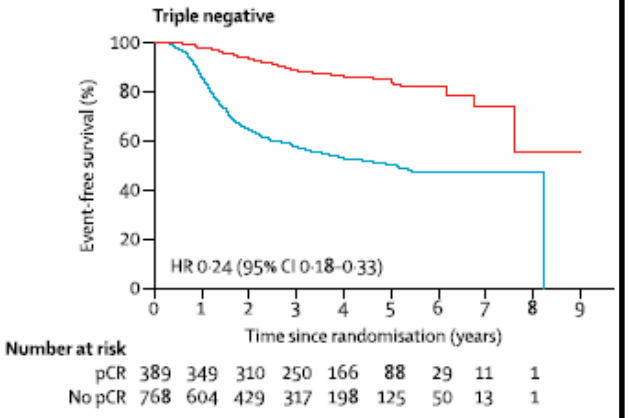
Lancet 2014

The role of pCR according to BC subtypes







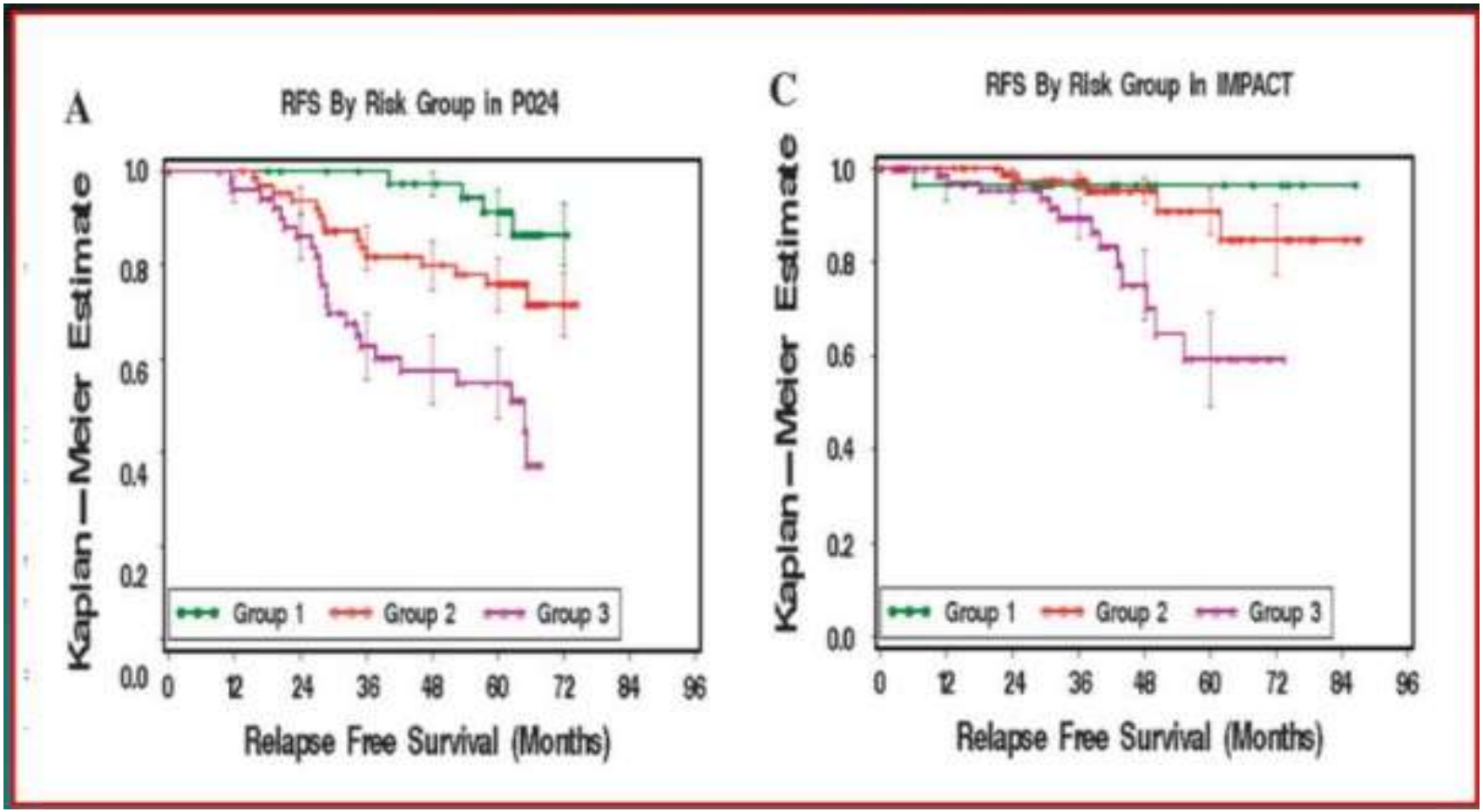


PEPI score

Pathology, biomarker status	RFS	
	HR	Points
Pathological tumor size		
T1/2	—	0
T3/4	2.8	3
Node status		
Negative	—	0
Positive	3.2	3
Ki67 level		
0%–2.7% (0–1†)	—	0
>2.7%–7.3% (1–2†)	1.3	1
>7.3%–19.7% (2–3†)	1.7	1
>19.7%–53.1% (3–4†)	2.2	2
>53.1% (>4†)	2.9	3
ER status, Allred score		
0–2	2.8	3
3–8	—	0

Ellis et al. J Natl Cancer Inst 2008

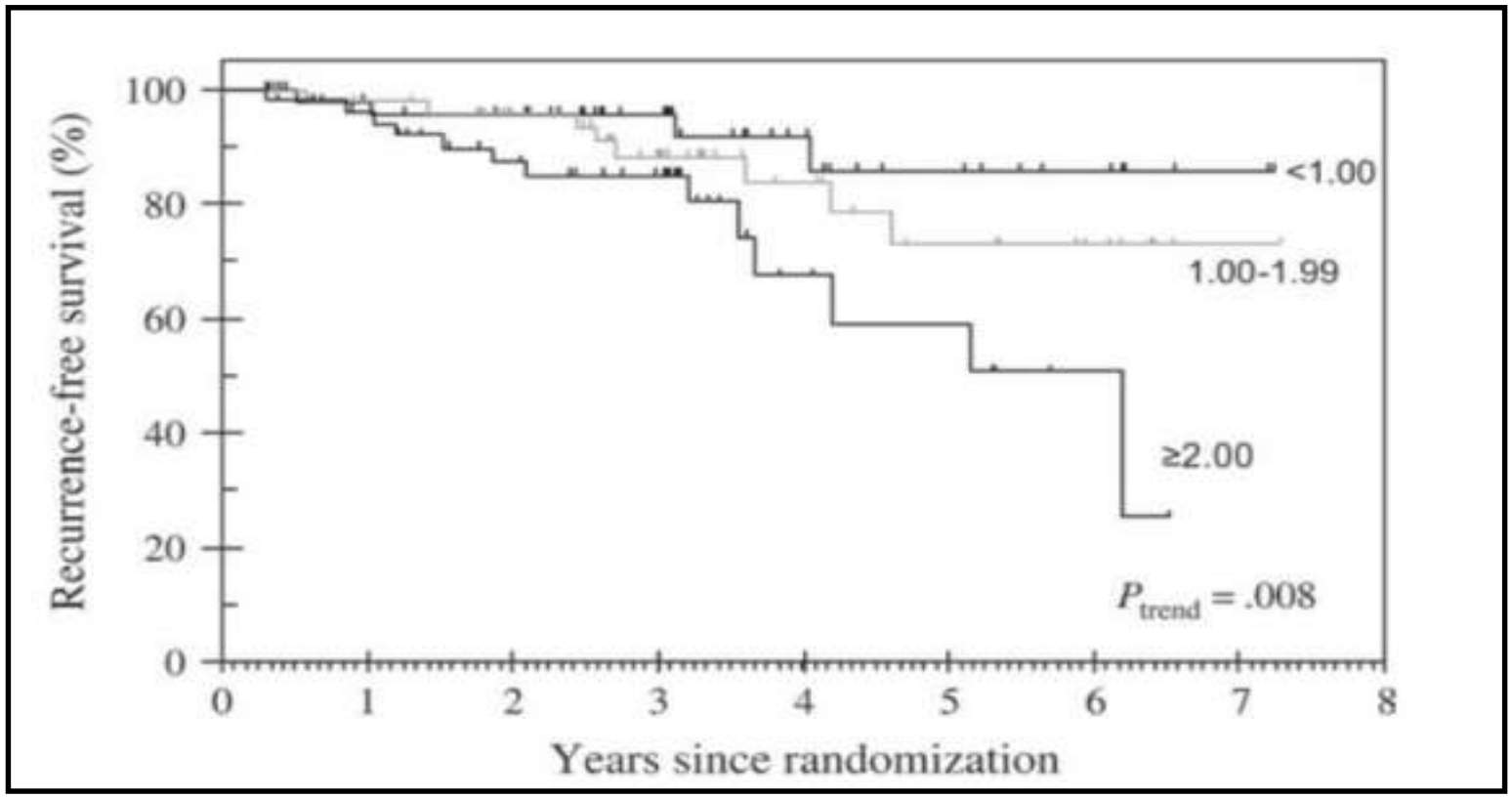
PEPI score



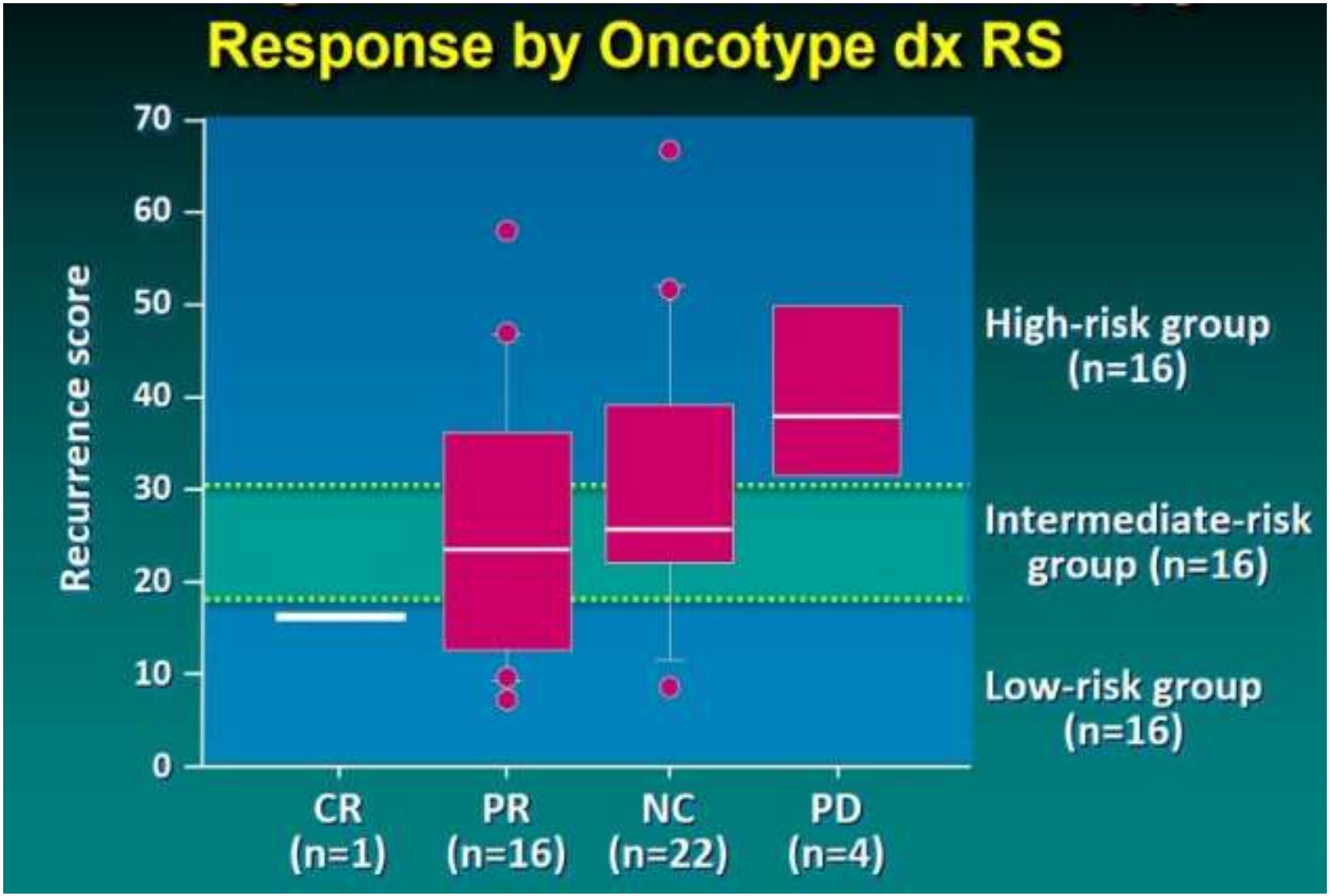
Ellis et al. J Natl Cancer Inst 2008

Identification of early markers of response

Ki67 at 2 weeks

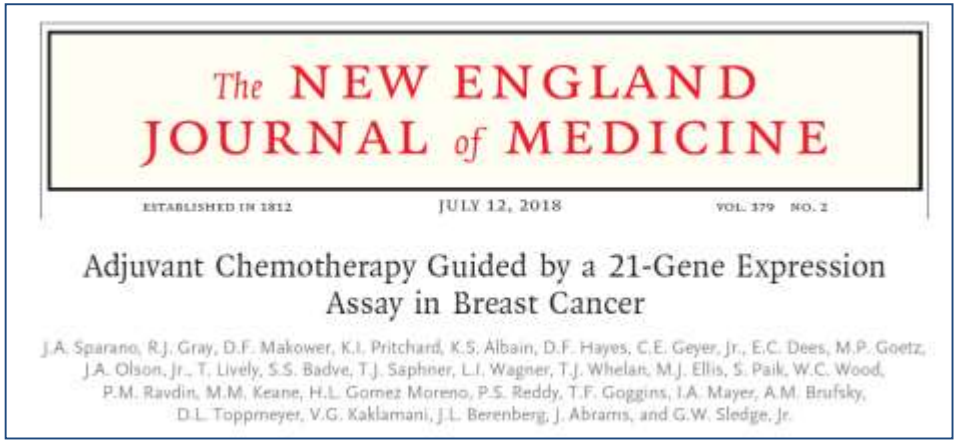


Dowsett et al. J Natl Cancer Inst 2007



Akashi-Tanakaetal et al. The Breast 2009

ADIUVANTE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

Trial Assigning IndividuaLized Options for TReatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score

Joseph A. Sparano, Robert J. Gray, William C. Wood, Della F. Makower, Tracy G. Lively, Thomas J. Saphner, Maccon M. Keane, Henry L. Gomez, Pavan Reddy, Timothy F. Goggins, Ingrid A. Mayer, Deborah Toppmeyer, Adam Brufsky, Matthew P. Goetz, Daniel F. Hayes, Elizabeth Claire Dees, Kathleen I. Pritchard, Charles E. Geyer, John A. Olson, & George W. Sledge

on behalf of the TAILORx investigators

Canadian Cancer Trials Group

Alliance for Clinical Trials in Oncology

ECOG-ACRIN cancer research group

Reshaping the future of patient care

NATIONAL CANCER INSTITUTE

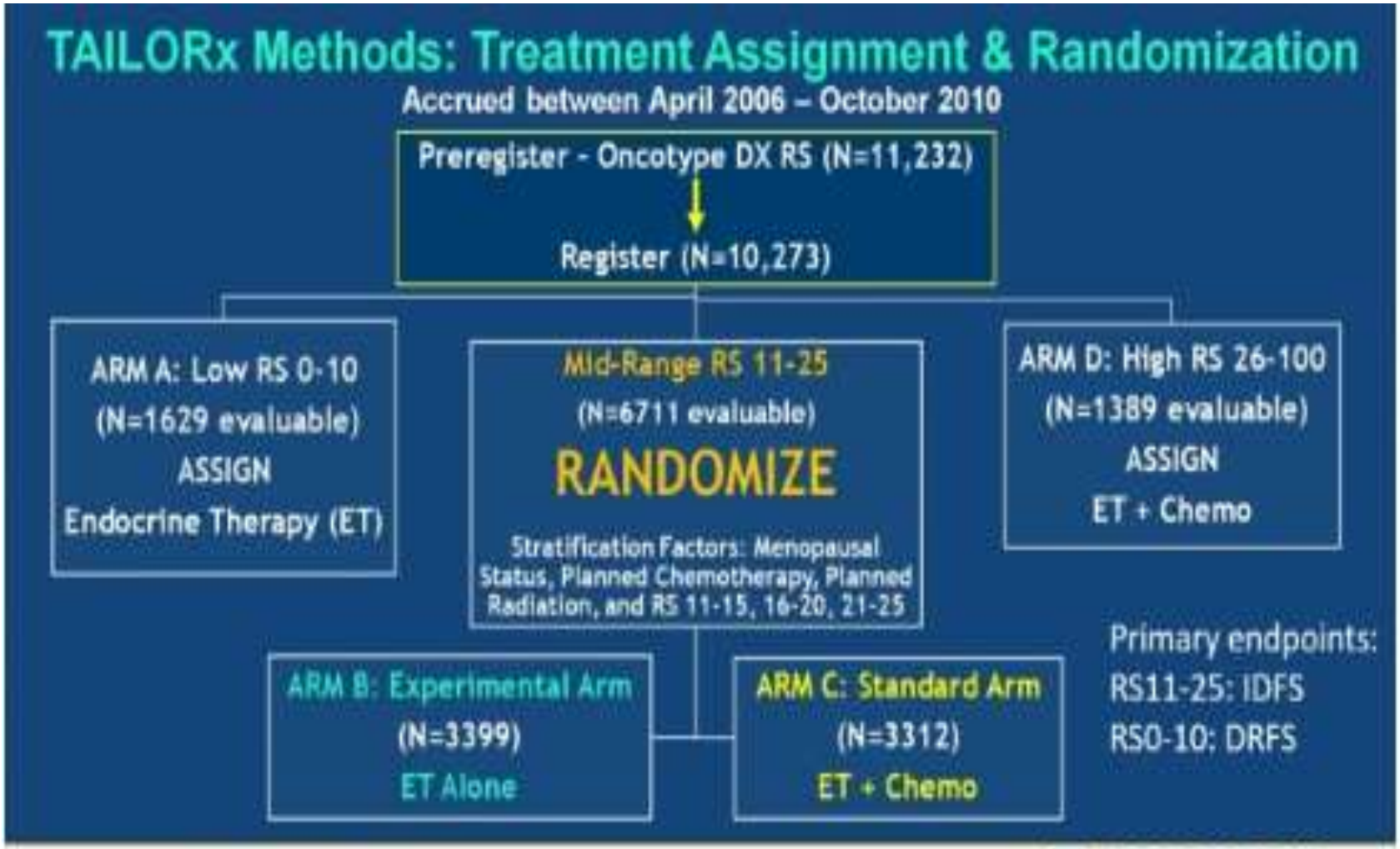
SWOG

NRG

Sparano J et al.
NEJM 2018

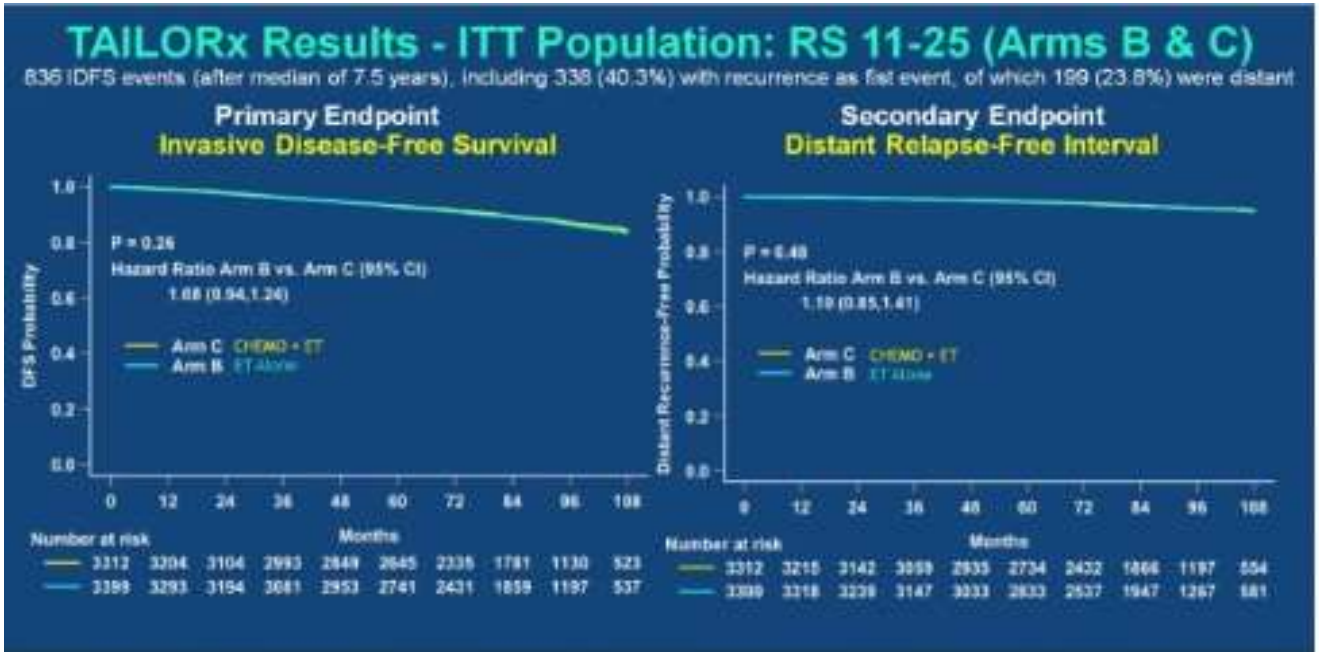
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010



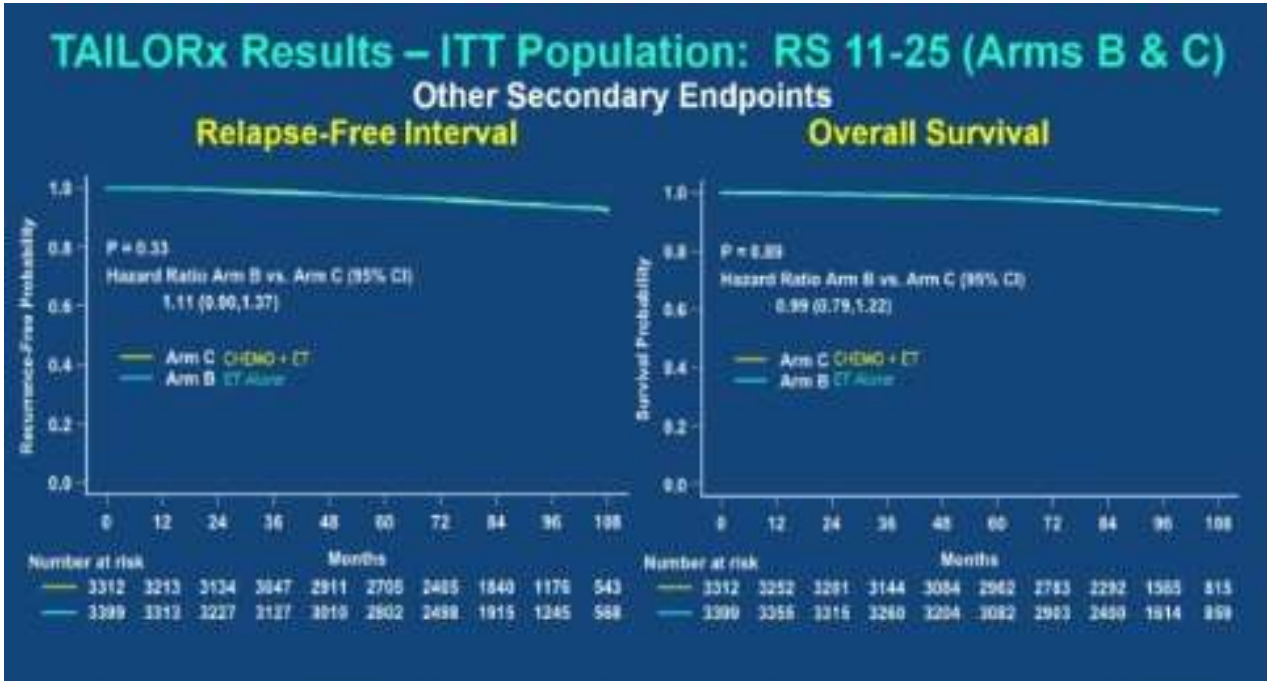
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as 1st event, of which 199 (23.8%) were distant

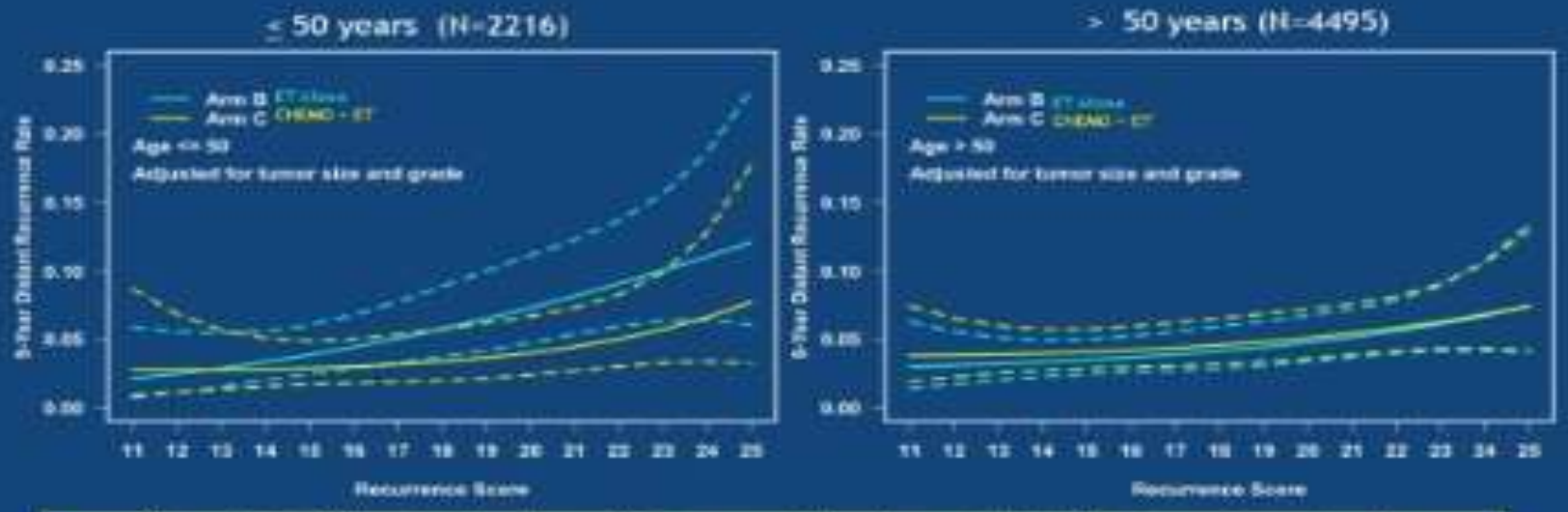


TAILORx Results – ITT Population: RS 11-25 (Arms B & C)

Other Secondary Endpoints



TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (</=50 vs. >50 Years)



RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade

- **Age – RS – Chemo treatment interaction:**
  - Some chemo benefit in women 50 or younger with a RS 15-25 — Δ 2% DRFI events
  - Greatest impact on distant recurrence with RS 21-25 — Δ 6% IDFS events, mainly distant

DUBBI….

- **73%** delle pazienti ad alto rischio (G1 > 3 cm, G2 > 2 cm, G3 > 1 cm) possono essere sovratrattate (?)

- **43%** delle pazienti con RS 26-100 ha basso rischio sulla base dei soli parametri clinico-patologici (sottotrattate?)

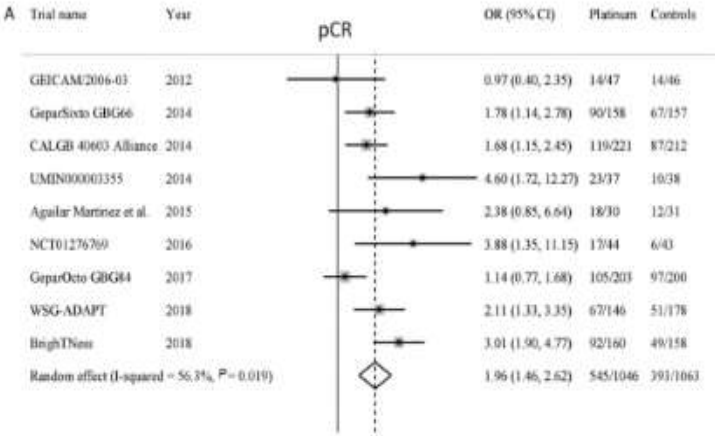
QUALE TERAPIA NEOADIUVANTE?

- Chemioterapia: antra-taxani
- TNBC: antra-taxani-sali di platino
- Pazienti anziane a basso rischio: AI
- HER2+: antra→ taxani (+ Sali di platino) + trastuzumab…Domani doppio blocco anti HER2?

Platinum-based Neoadjuvant Chemotherapy in TNBC: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Nine RCTs, 2109 pts included

Study	Treatment arms	TNBC patients, n
GEICAM/2006-03 *Breast Cancer Res Treat 2012*	EC→DCb	47
	EC→D	46
GeparSixto GBG66 *Lancet Oncol 2014*	P+Dox+Bev+Cb	158
	P+Dox+Bev	157
CALGB 40603 Alliance *J Clin Oncol 2015*	P+Cb+Bev→ddAc	221
	P/Bev→ddAc	212
UMIN000003355 *Breast Cancer Res Treat 2014*	PCb→FEC	37
	P→FEC	38
Aguilar Martinez et al *J Clin Oncol 2015 (abstract)*	Cb+P → Cb+Dox	30
	P→FAC	31
NCT01276769 *Oncotarget 2016*	PCb	44
	EP	43
Gepar Octo GBG84 *J Clin Oncol 2017 (abstract)*	PDexCb	203
	DdEPC	200
WSG-ADAPT *J Natl Cancer Inst 2017*	Nab-P+Cb	146
	Nab-P+Gem	178
BrighTNess *Lancet Oncol 2018*	P+Cb→AC	180
	P→AC	158



pCR rate 37.0% (ctrl) vs 52.1% (exp)
(OR 1.96, 95% CI 1.46–2.62, P<0.001)

Poggio F, et al. Annals of Onc 2018

QUALE TERAPIA ADIUVANTE?

SE CT: DOSE-DENSE

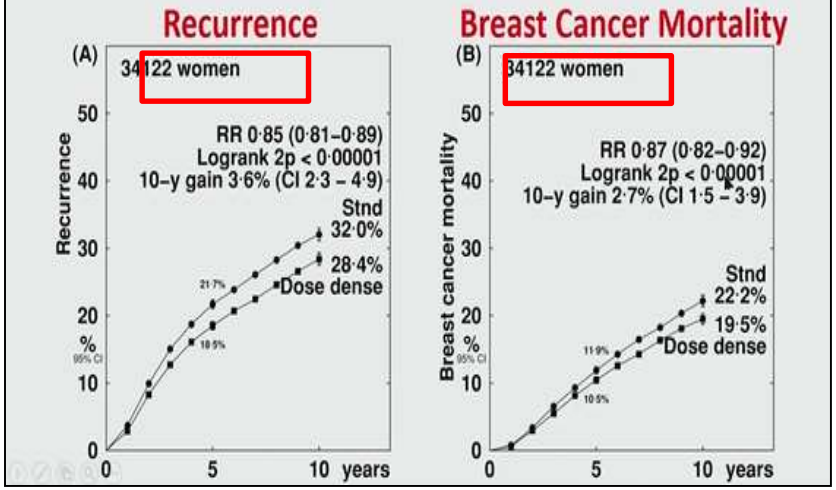
SAN ANTONIO BREAST CANCER SYMPOSIUM

SABCS, December 5 -9, 2017

Increasing the dose intensity of adjuvant chemotherapy : an EBCTCG meta-analysis

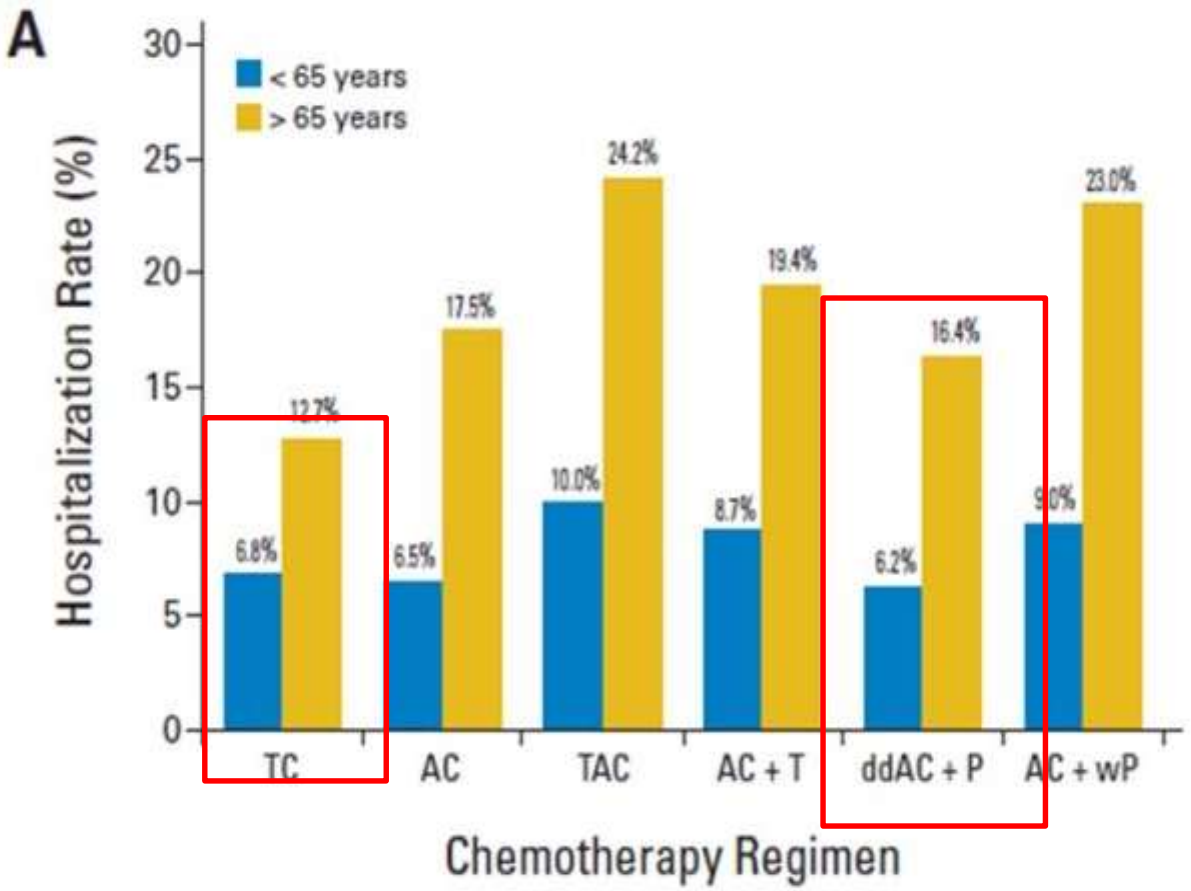
Richard Gray, Rosie Bradley, Jeremy Braybrooke, Christina Davies, Hongchao Pan, Richard Peto, Judith Bliss, David Cameron, John Mackey, Lucia Del Mastro, Sandra Swain, Michael Untch, Jonas Bergh, Kathleen Pritchard, Larry Norton, for the

Pooled analysis of all 25 dose-dense and sequential trials



- Shortening the interval between cycles and sequential administration of anthracycline and taxane chemotherapy reduces recurrence and death from breast cancer
- Reductions in recurrence of about 15% were similar in ER positive and ER-negative disease and did not differ significantly by any other tumour or patient characteristic
- No increase seen in death without recurrence (overall or during chemotherapy)

Newer Regimens and Hospitalization

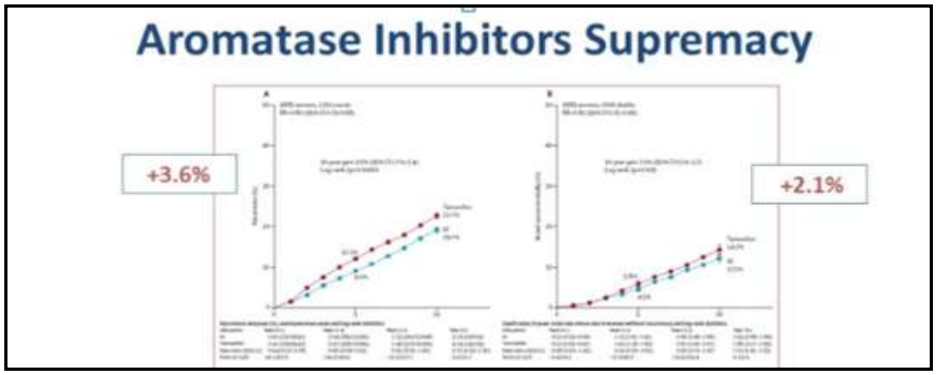


CH Barcenas, JCO 2014

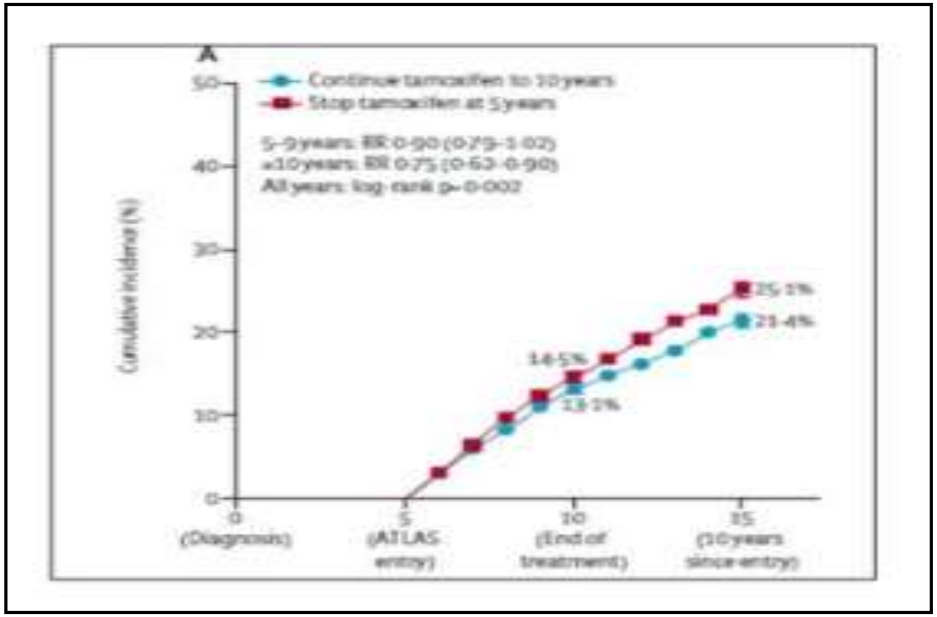
QUALE TERAPIA?
ORMONOTERAPIA

POST-MENOPAUSA

- AI up-front 5 yrs

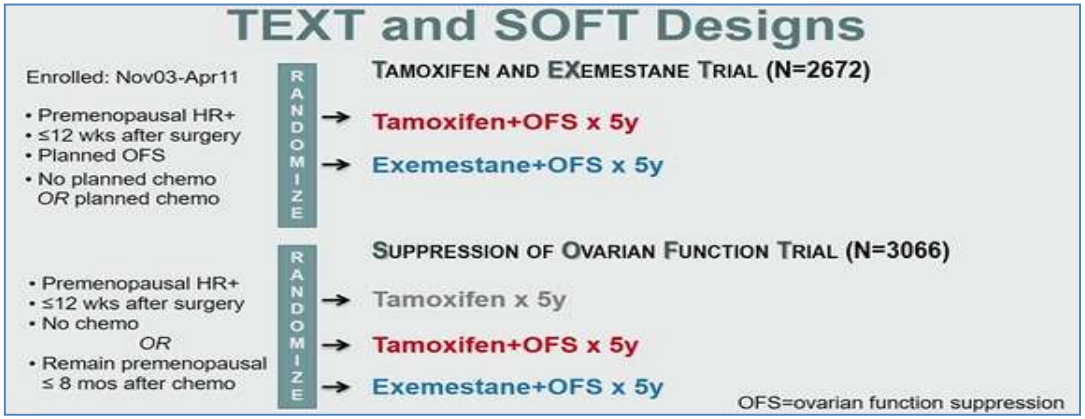


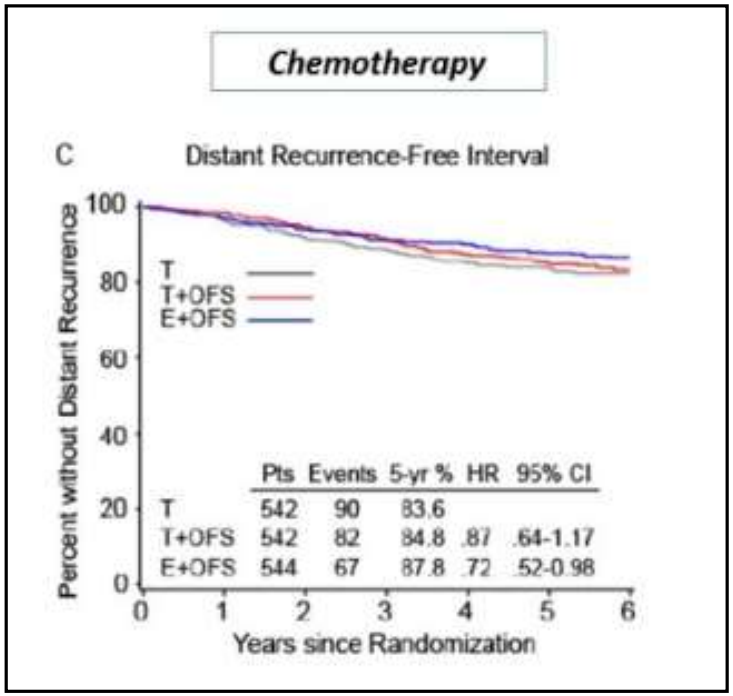
- 10-yr TAM vs 5-yr AI



QUALE TERAPIA?

ORMONOTERAPIA





PRE-MENOPAUSA:

- **Pazienti a rischio intermedio – alto: OFS + EXE**
- **Pazienti a basso rischio: OFS+TAM**

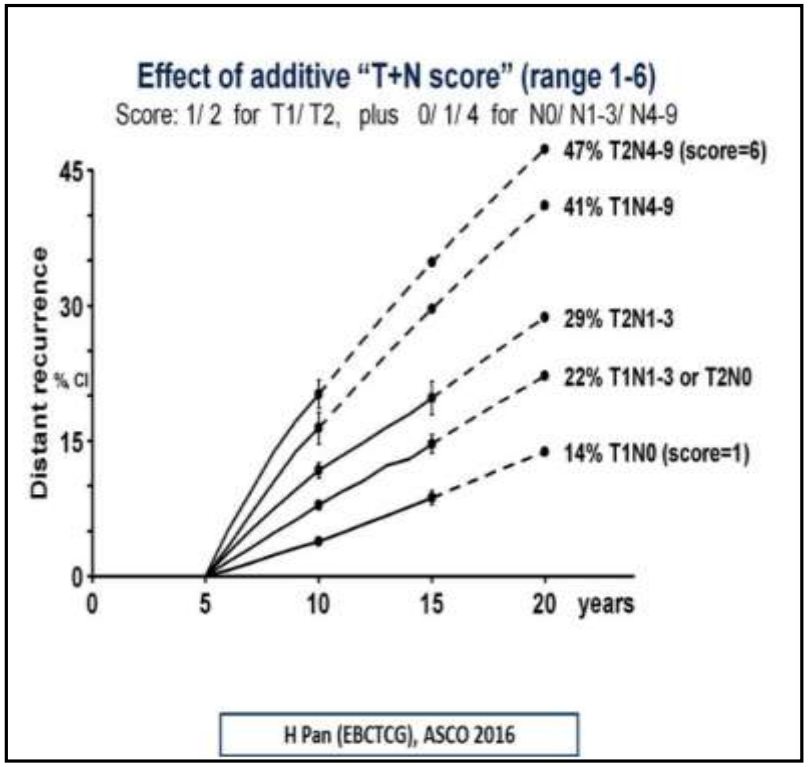
QUANTO A LUNGO?

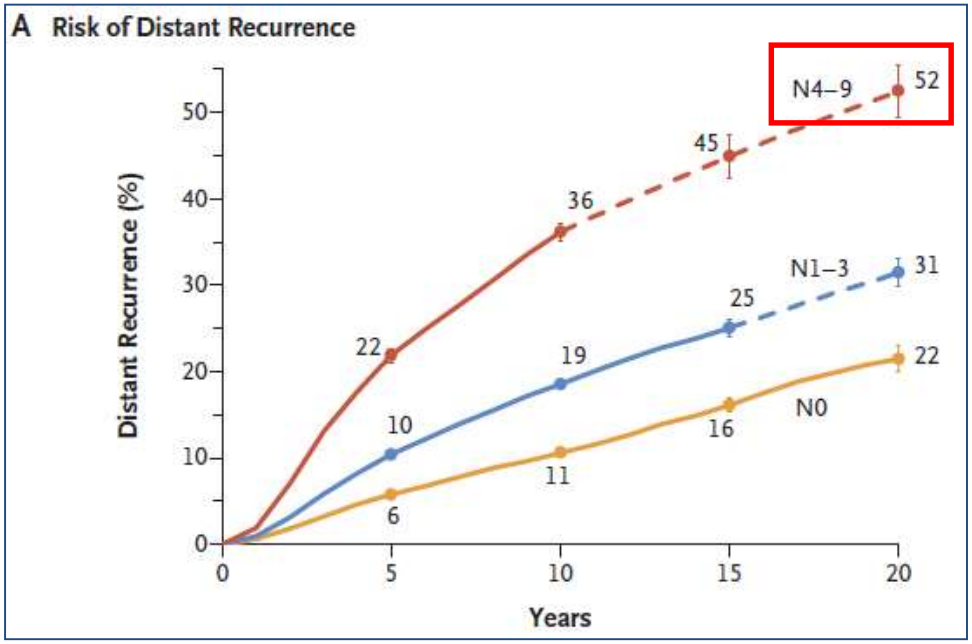
The NEW ENGLAND JOURNAL of MEDICINE

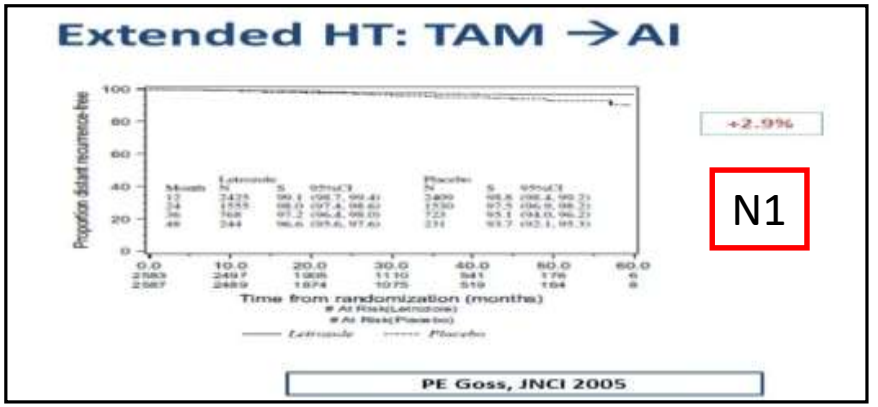
ORIGINAL ARTICLE

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years

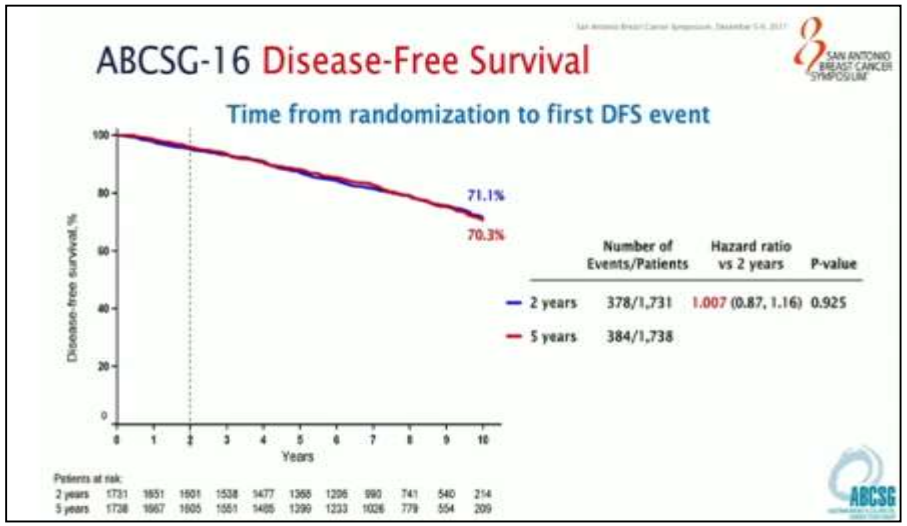
Hongchao Pan, Ph.D., Richard Gray, M.Sc., Jeremy Braybrooke, B.M., Ph.D., Christina Davies, B.M., B.Ch., Carolyn Taylor, B.M., B.Ch., Ph.D., Paul McGale, Ph.D., Richard Peto, F.R.S., Kathleen I. Pritchard, M.D., Jonas Bergh, M.D., Ph.D., Mitch Dowsett, Ph.D., and Daniel F. Hayes, M.D., for the EBCTCG*

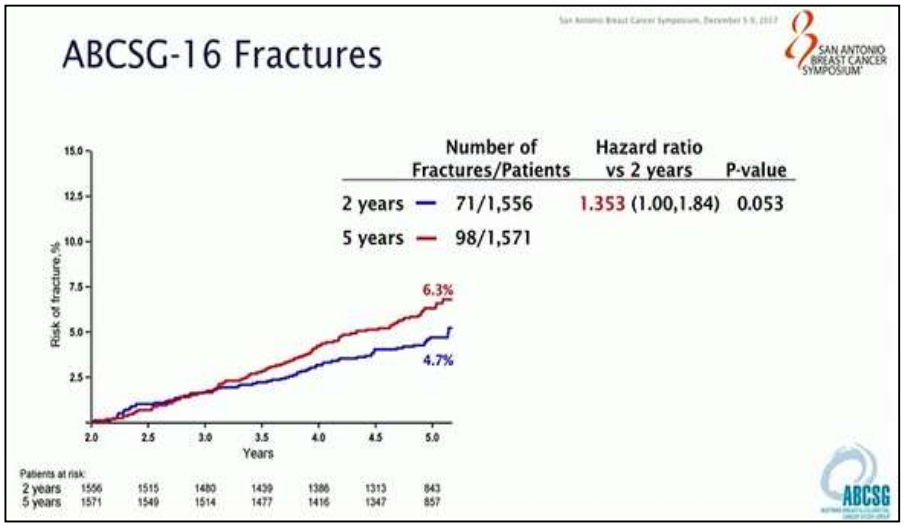






A prospective randomized multi-center phase-III trial of additional 2 versus additional 5 years of Anastrozole after initial 5 years of adjuvant endocrine therapy – results from 3,484 postmenopausal women in the ABCSG-16 trial





Conclusion and Perspectives

- After 5 years of standard endocrine therapy, 2 additional years of Anastrozole are sufficient – there is no benefit of continuing/escalating

- In the future, translational research may identify molecular characteristics that indicate benefit of prolonged extended therapy.

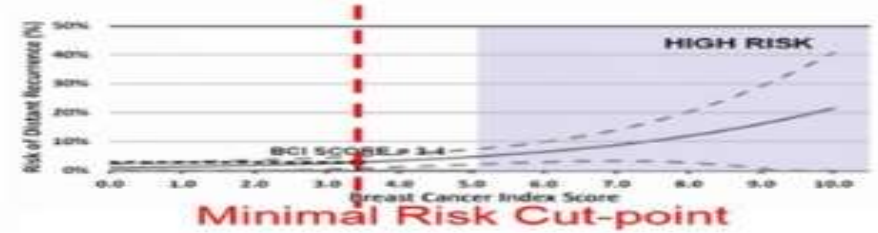
Some Potential Factors to Support Use of Extended Adjuvant Endocrine Therapy

- Higher stage at diagnosis
- Limited or absent toxicity
- Absence of life-threatening comorbidities
- Younger age
- Patient preference
- **Biomarkers for late recurrence?**

Genomic stratification with BC Index (BCI) of ER+ EBC pts with limited long-term risk of BC death

- To use the BCI genomic tool to identify a minimal risk cohort of ER+ EBC pts who might not need extended adjuvant ET

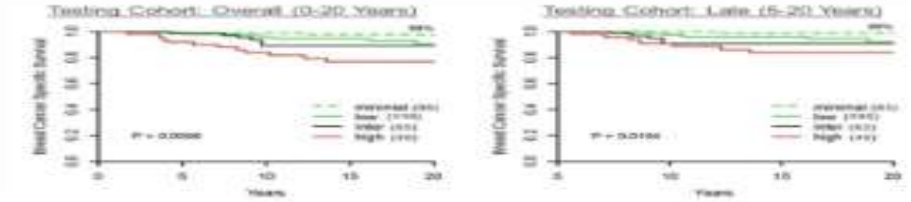
- Studied population: n=600, postmenopausal, ER+/HER2-, stage I-II, no chemo. Randomized to 2-5 years of tamoxifen vs not. Followed for 17 years.



Kaklamani, et al. Abstract 516

Trial results

- ~~Four risk groups identified~~
- Minimal risk group (28% of cohort) had 99% BCSS years 5-20



- Only BCI score and tumor size were independent predictors of 20-year BCSS in a multivariate model

	HR (95% CI)	p-value
Age at surgery (per 10 years)	0.65 (0.33-1.24)	0.25
Tumor size (T2 vs T1)	3.19 (1.41-7.21)	0.005
Tumor grade (G2 & G3 vs G1)	1.41 (0.31-6.43)	0.66
PR status (pos vs neg)	0.84 (0.36-1.99)	0.70
HER2 status (pos vs neg)	0.38 (0.08-1.73)	0.21
BCI (per 5 unit)	3.92 (1.27-12.11)	0.02

Kaklamani, et al. Abstract 516

Her2 positivi

Chemioterapia più 1 anno di terapia anti-HER2 rimane lo standard

Domani…pazienti ad **alto rischio:** Trastuzumab + Pertuzumab (Aphinity)

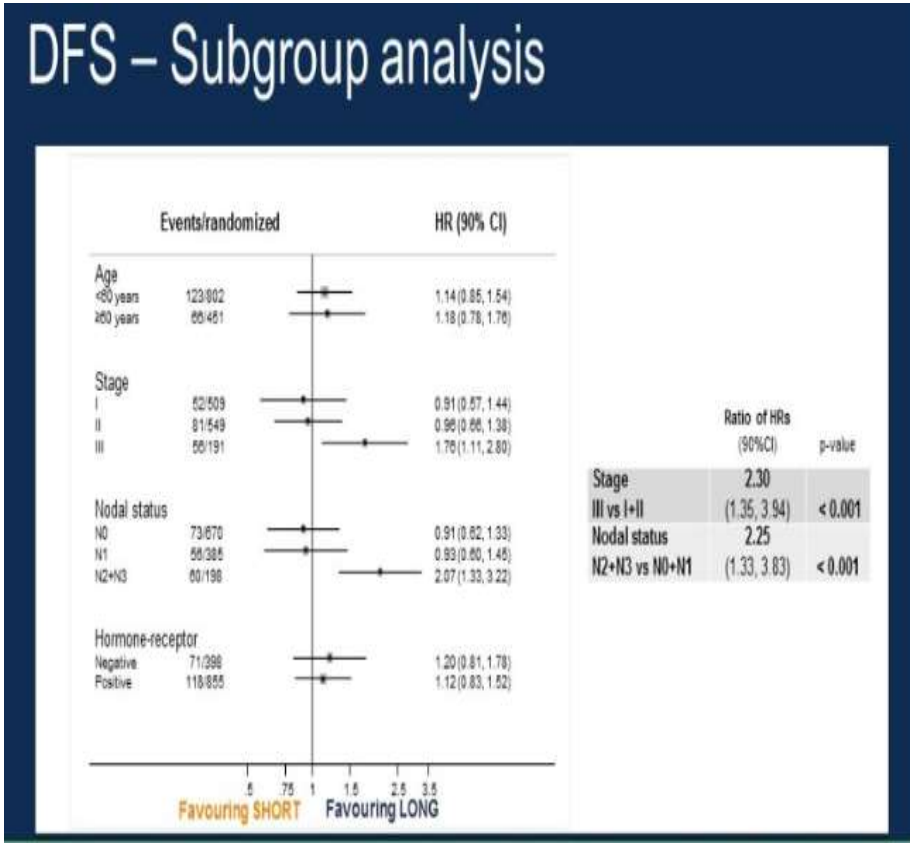
MA...pazienti a **basso rischio** (o alto rischio di tossicità cardiaca)

Persephone Study
Patient Characteristics

Accrual: 4088 from 2007 to 2015
152 sites in the UK

T1	48%
N –ve	59%
ER +ve	69%
Concurrent CHT/T	47%

Her2 positivi
SHORT-HER Study
DFS in long and short treatments arms stratified by risk groups



		Patients	DFS events
Low Risk **T≤ 2cm N0**	**Long** **Short**	**233** **234**	**26** **25**
Intermediate Risk **T≤ 2cm N1-3 or** **T≥ 2cm N0-3**	**Long** **Short**	**295** **291**	**45** **41**
High Risk **Any T N 4**	**Long** **Short**	**96** **95**	**23** **37**

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy

30 APRIL 2015 | VOL 520 | NATURE | 611

Illustration by Greg Clarke

Personalised Medicine

Precision biology does not grant personalised medicine

Overtreatment /undertreatment is a failure as a scientist, as a clinician, as a socially responsible person

Adattato da Conte PF, 2018

Grazie per l’attenzione…