Terapia sistemica adiuvante: quando e quale?

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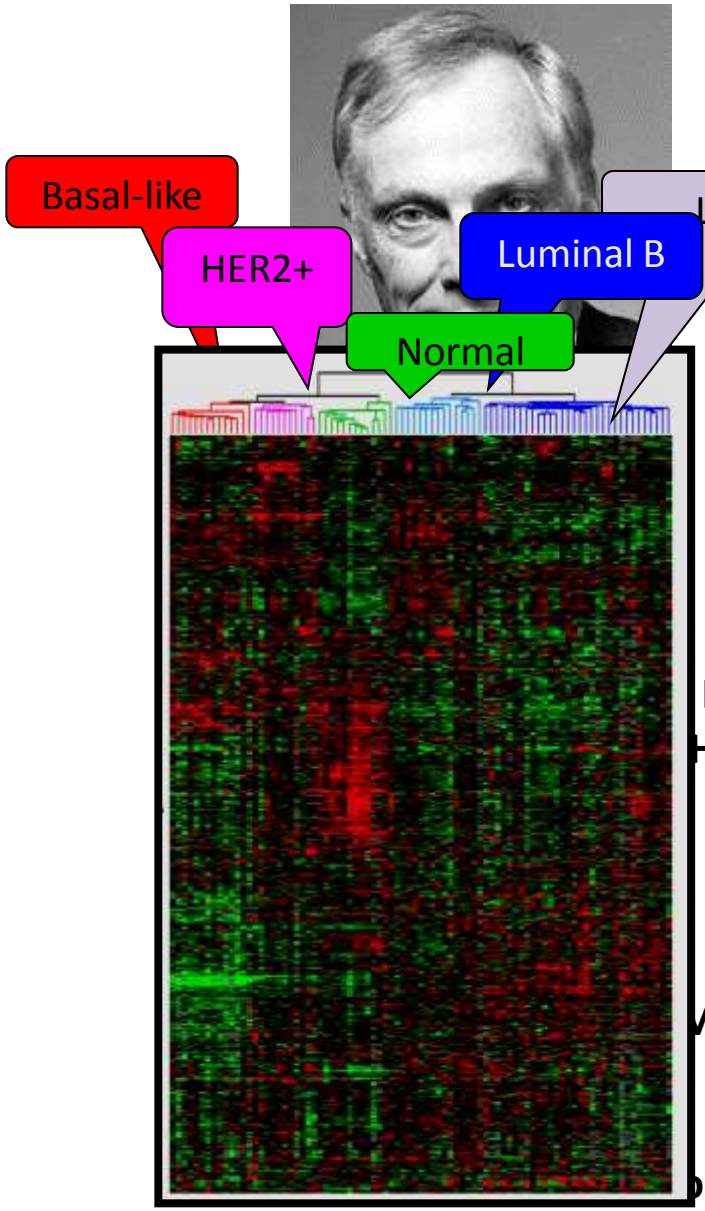
Milano

Breast Cancer – Was One Disease, Now Several



Simply "breast cancer"

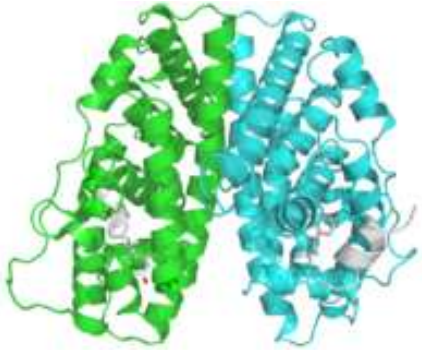
ER (-)

ER(+) HER2(-)
ER(-) HER2(+)
ER(+) HER2(+)
ER(-) HER2(-)

If ER(+) and HER2(-), either:
High grade, Low ER level – or
Low grade, High ER level

Multigene Assays
Molecular (intrinsic) Subtypes

ole genome/next gen sequencing



TAILORED / PERSONALIZED MEDICINE

"One size fits all"

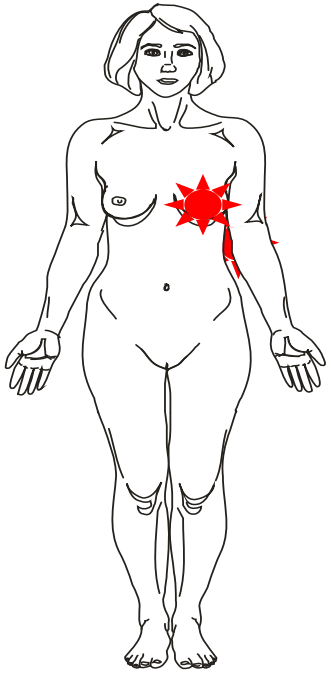
=

The right treatment

for the right patient

at the right time

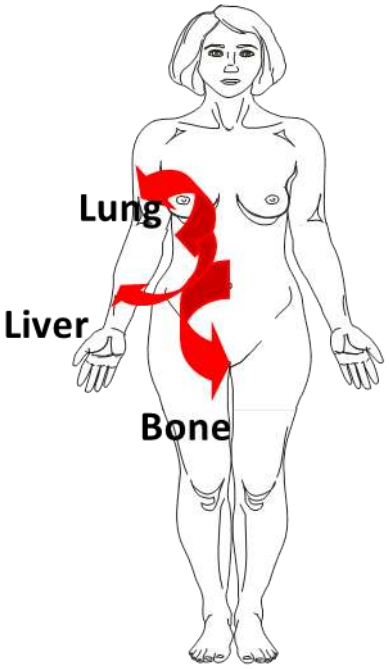
"The right size for the individual woman"



Early

Curable disease

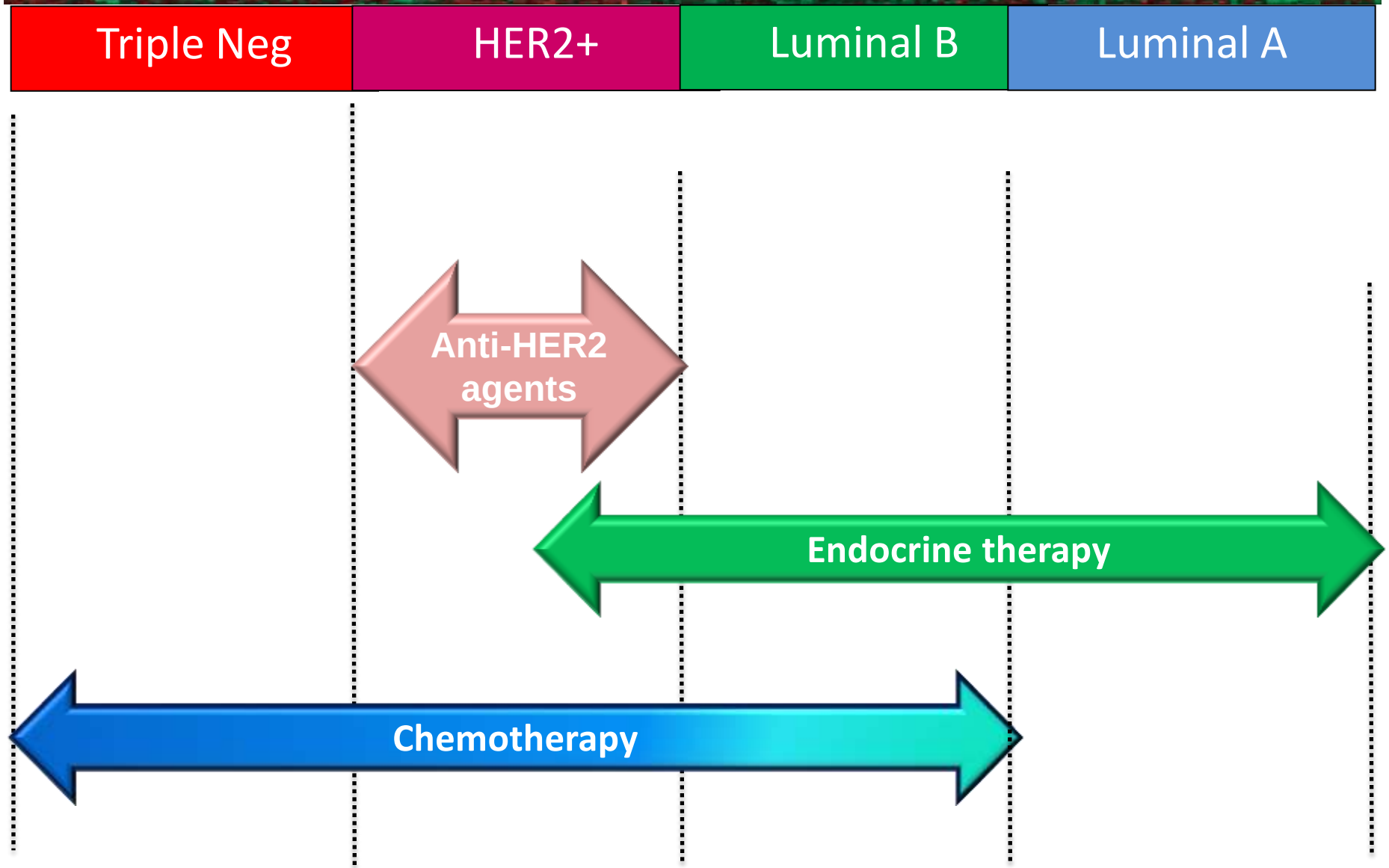
adjuvant therapy



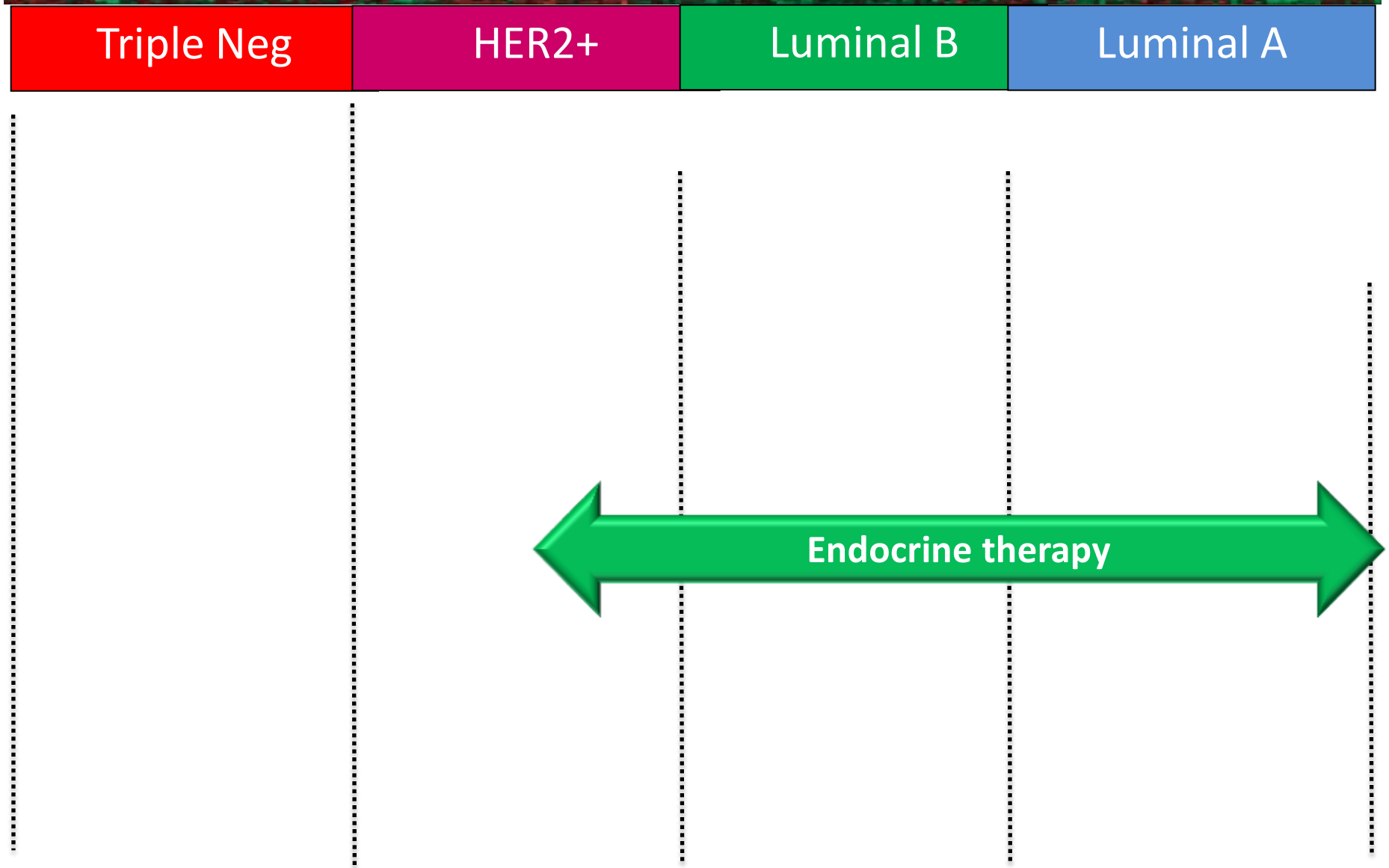
Metastatic

Non curable disease

Subtype driven approach



Subtype driven approach



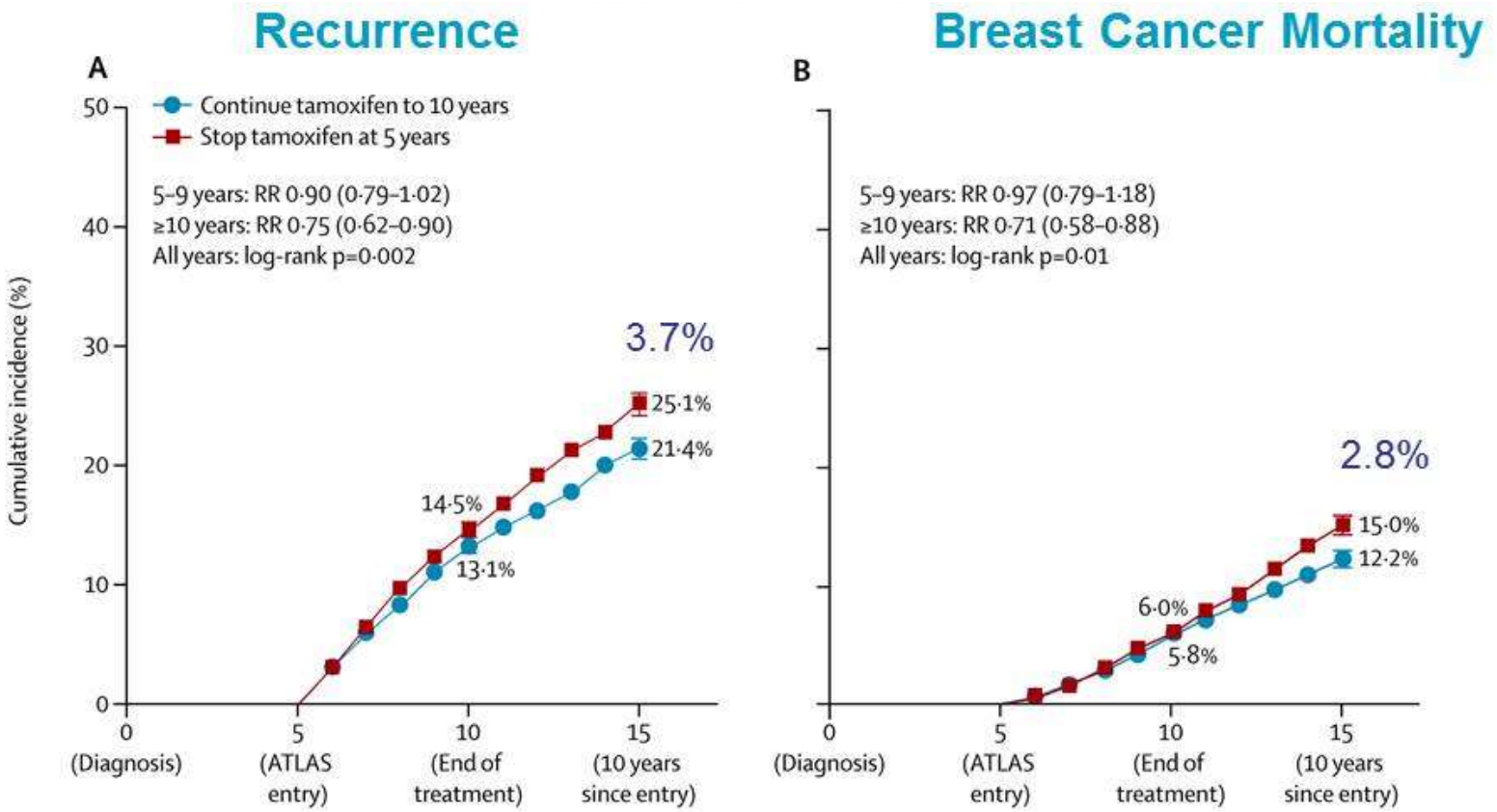
ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

Tamoxifen for premenopausal pts

- 1980 tamoxifen effective for premenopausal metastatic BC
- 1988 (1st) EBCTCG publication: adjuvant tamoxifen benefit in women ≥ 50 years
- 1998 EBCTCG publication: adjuvant tamoxifen effective in women < 50 yrs with ER+ BC; 5 years better than 2
- 2011 EBCTCG publication: tamoxifen 5 yrs reduced 15-year BC mortality by ~ 1/3 in women < 45 yrs

ATLAS: 10 vs 5 years of Tamoxifen

(6846 patients)



- Gain independent of age (<55 v ≥55) or nodes
- Reduced overall mortality (639 *vs* 722 deaths, p=0.01)
- Non-breast cancer deaths nsd (RR 0.99)

Davies et al. Lancet 2013

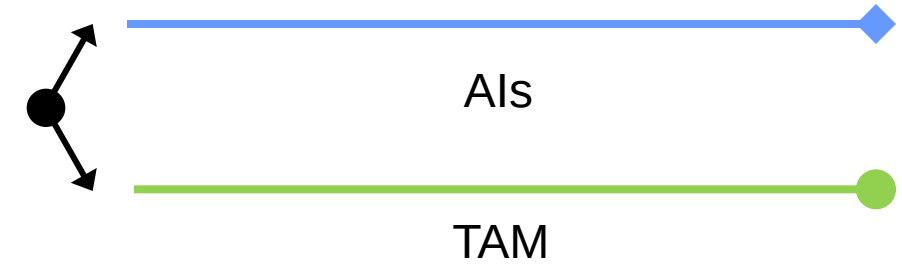
SOFT/TEXT

- SOFT showed:
  - DFS benefit with ovarian suppression only in higher risk patients receiving chemotherapy
  - Ovarian suppression + AI better, especially in pts under 35
- TEXT confirmed ovarian suppression + AI better DFS than ovarian suppression + Tamoxifen
- But no OS benefit so far
- Adverse QoL issues for many patients, and this requires discussion and choice

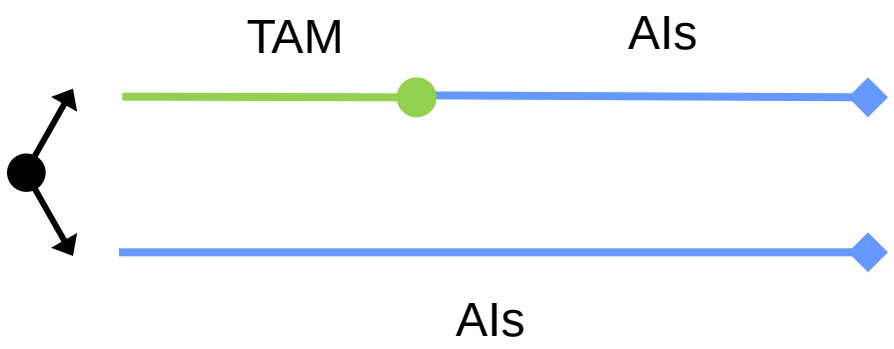
Francis et al. NEJM 2015

ADJUVANT ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN

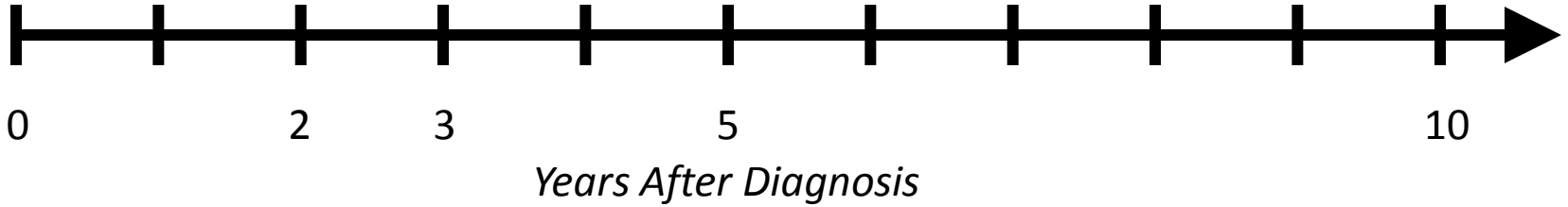
Upfront vs switch



Upfront
ATAC, BIG 1-98, ABCSG 12, TEAM

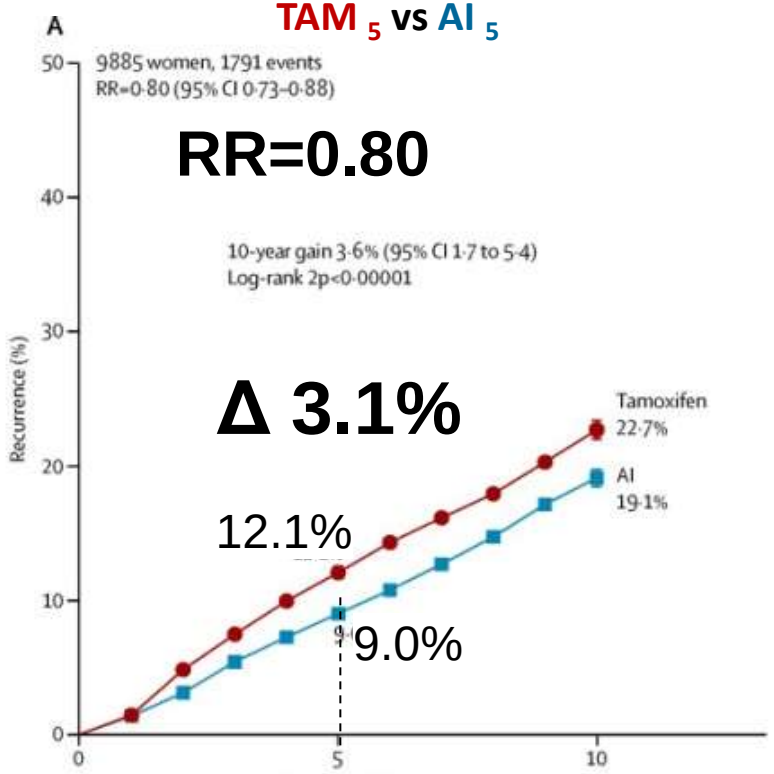


Switch
BIG 1-98, IES, ITA, NSAS BC-03, ARNO 95, ABCSG 8



Patient-level meta-analysis of RCTs with endocrine therapy

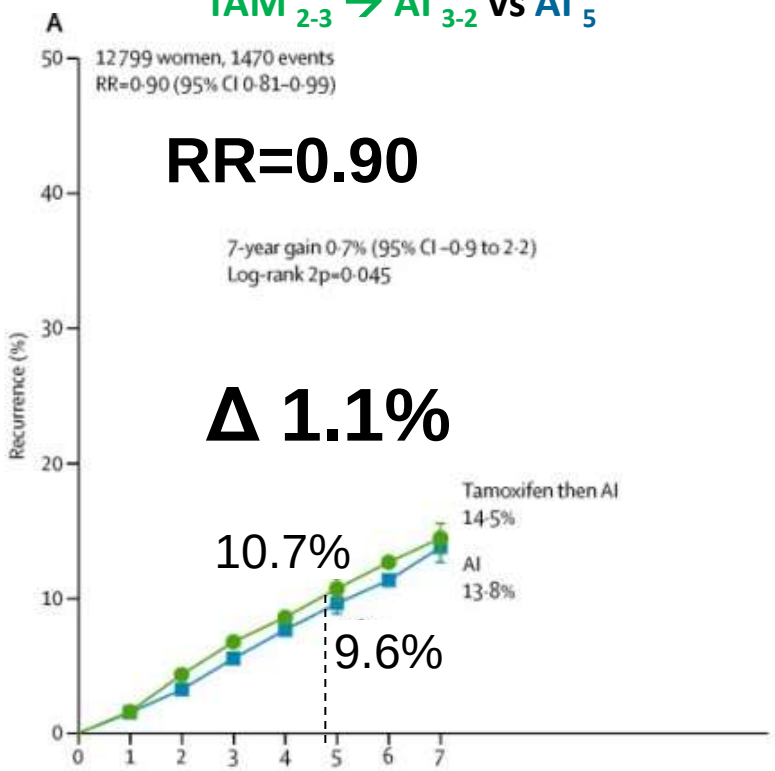
TAM $_5$ vs AI $_5$



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13336)	2·33 (365/15648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12906)	2·48 (372/14985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	-41·1/92·8	-34·1/149·0	-15·5/177·2	-3·6/10·7

TAM $_{2-3}$ → AI $_{3-2}$ vs AI $_5$

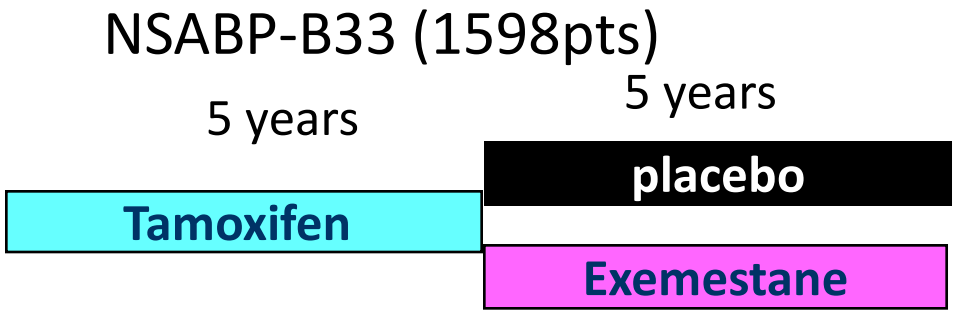


Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12435)	2·31 (360/15589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12290)	2·29 (348/15183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	-34·0/115·0	-1·2/170·6	-2·6/69·2

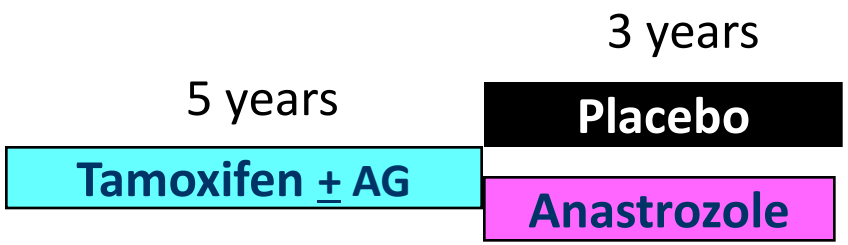
EBCTCG. Lancet 2015

Extended AIs after 5 yrs TAM significantly reduces recurrences, and likely improve OS



HR	p
0.44	0.004

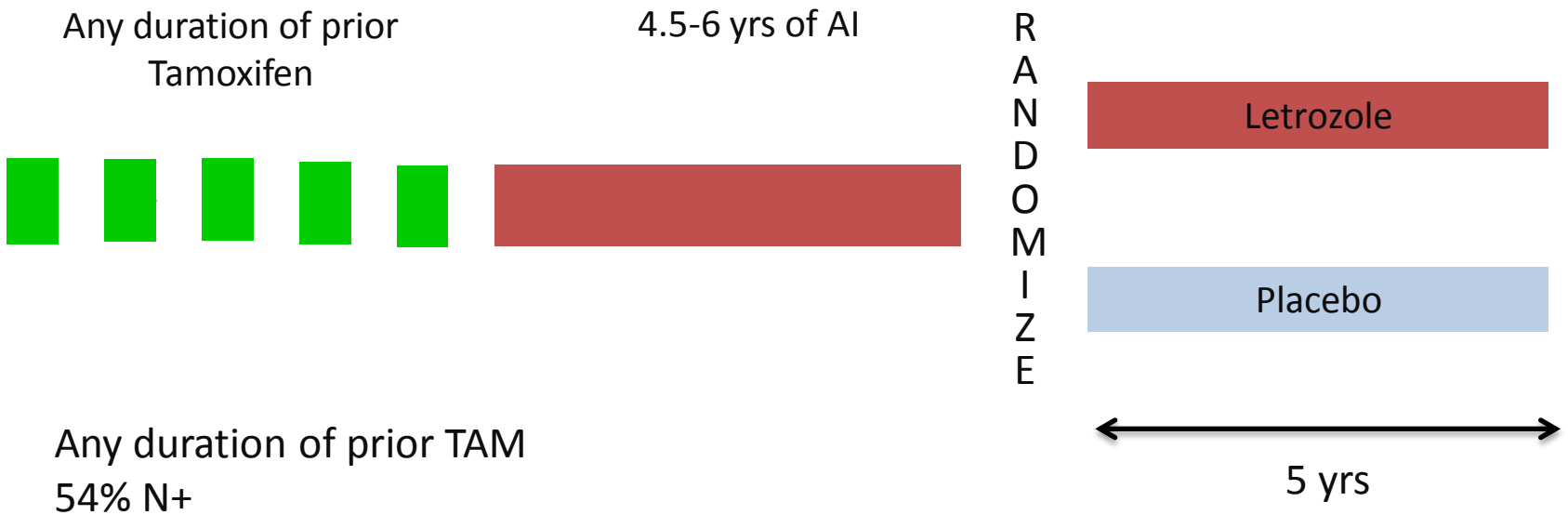
Mamounas et al. *JCO 2008 26*



0.64	0.05

Jakesz et al. J Clin Oncol. 2005

Extended AIs after AIs: MA.17R Trial

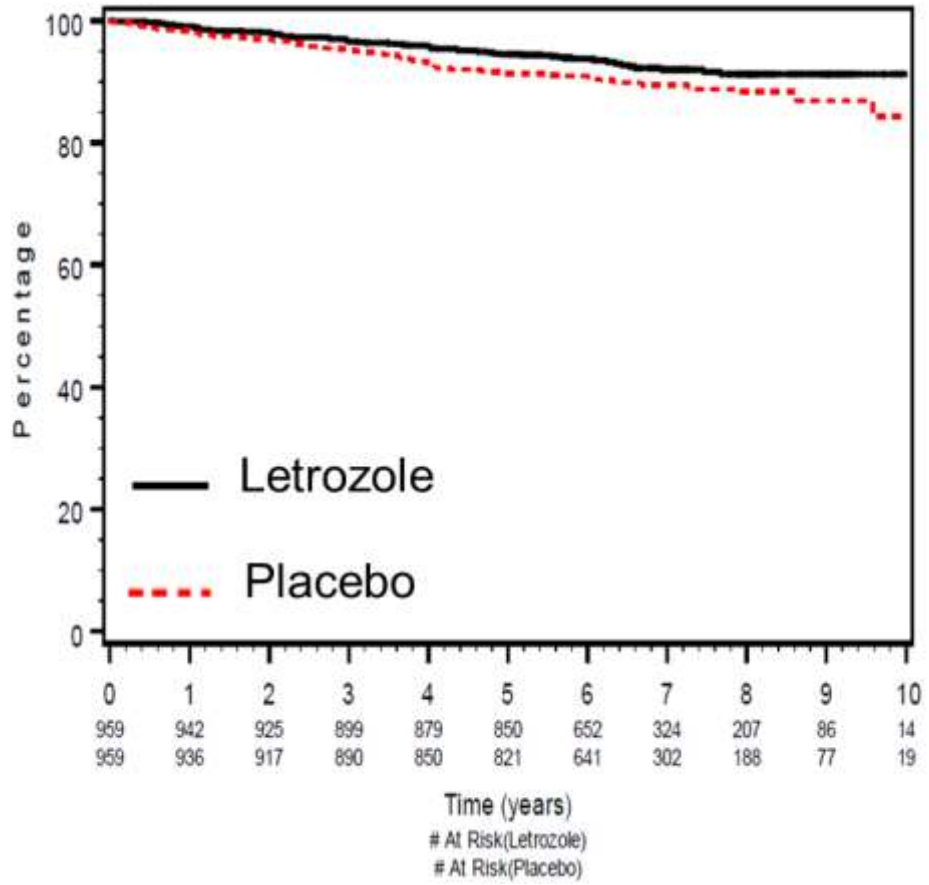


Any duration of prior TAM
54% N+
58% Adjuvant chemotherapy

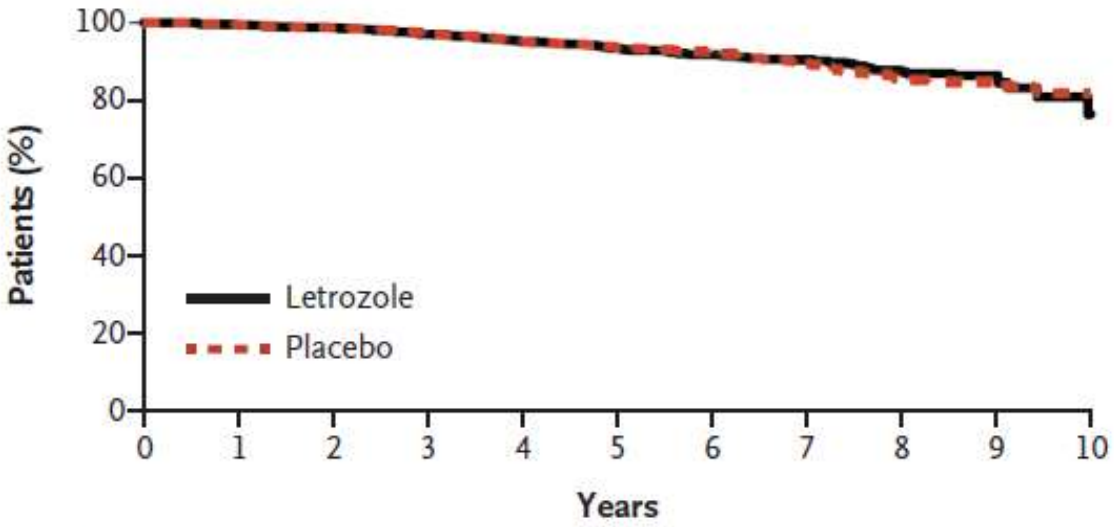
Goss et al, NEJM 2016

Extended AIs after AIs significantly reduces recurrences, but not OS benefit

DFS



OS



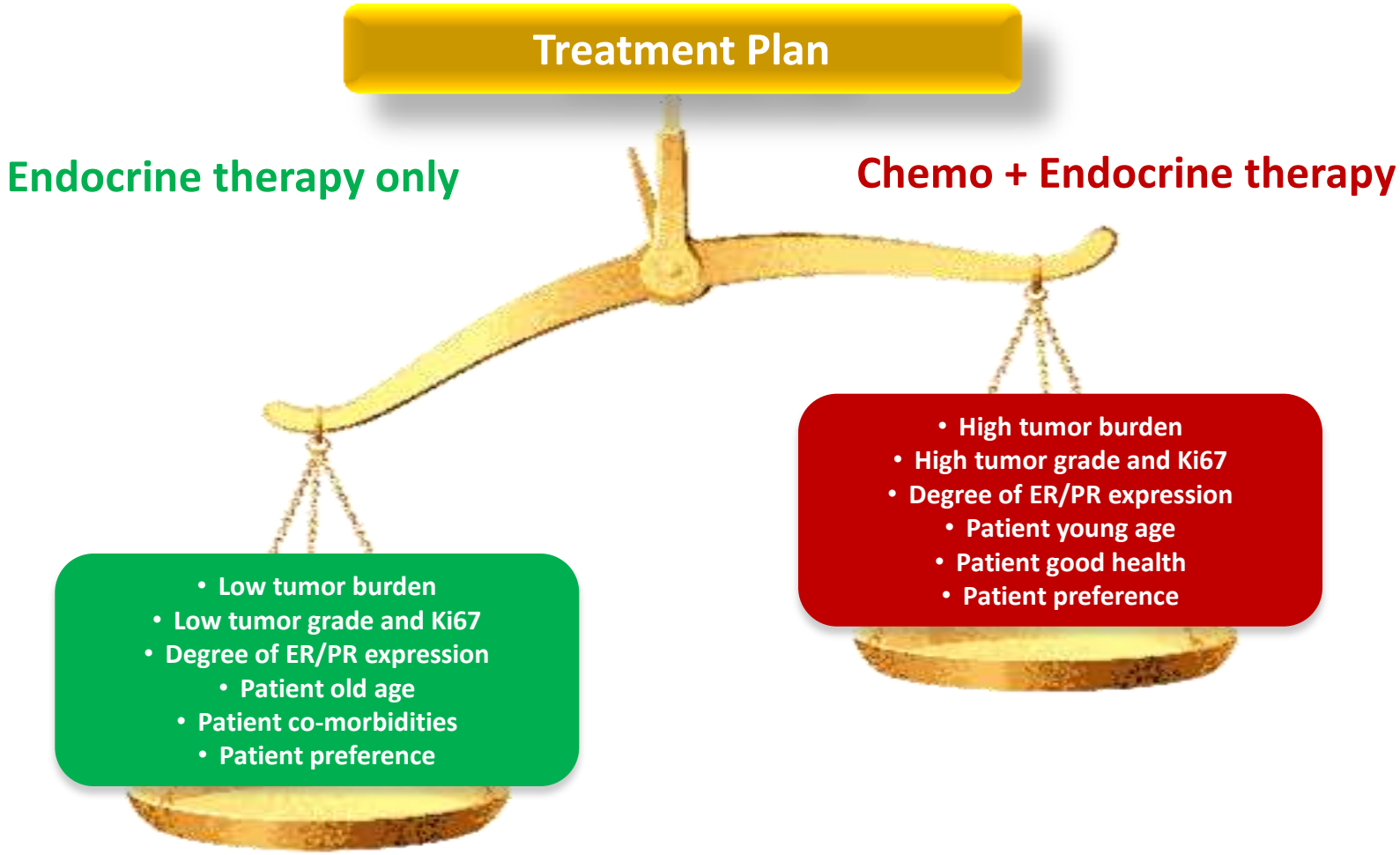
No. at Risk

Letrozole	959	952	941	921	903	880	680	343	221	93	14
Placebo	959	953	943	923	895	874	680	327	204	84	20

Median FU 6.3 yrs

Goss et al, NEJM 2016

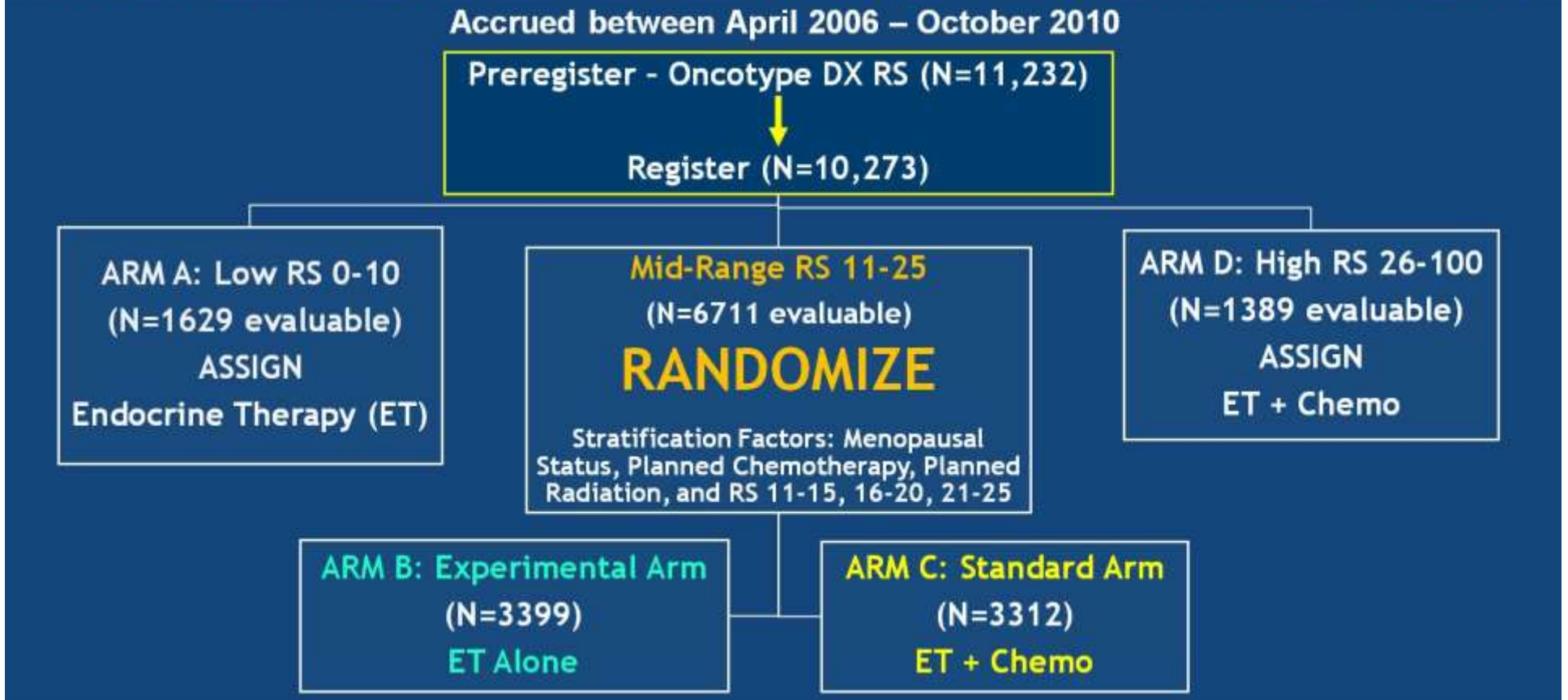
Adjuvant Treatment Decision in ER+/HER2- Breast Cancer



Multigene expression signatures to forego chemotherapy: 15 years of research efforts!

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

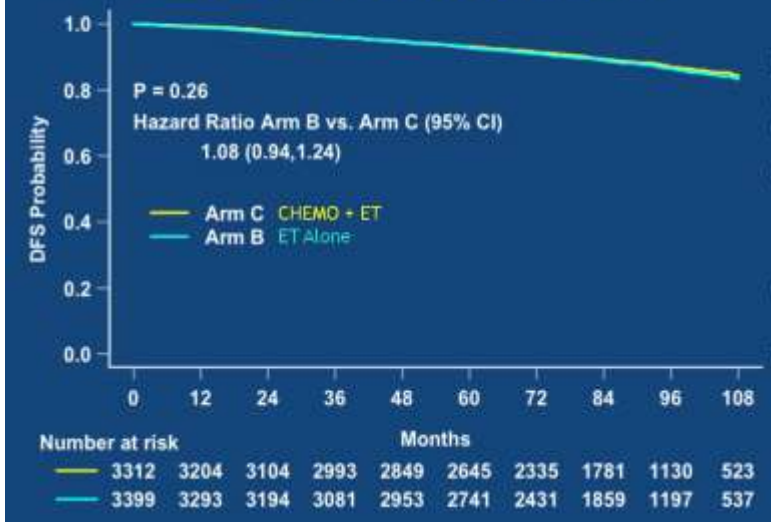


Sparano et al, NEJM 2018

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 fist event, of which 199 (23.8%) were distant

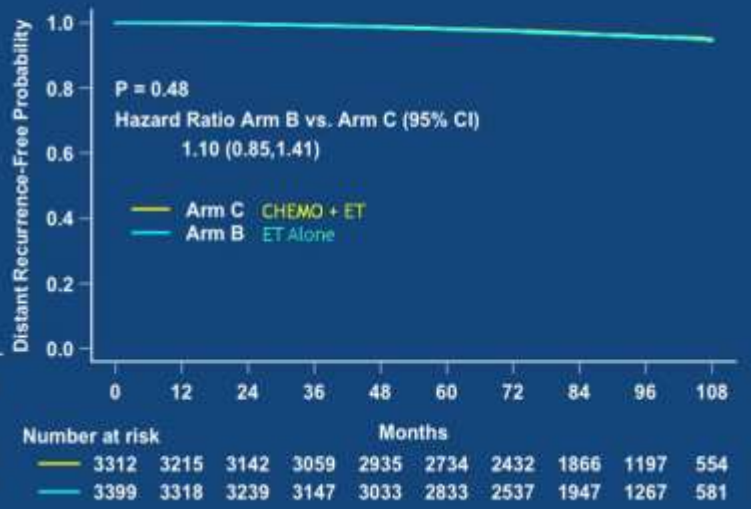
Primary Endpoint
Invasive Disease-Free Survival



Number at risk

Arm C	3312	3204	3104	2993	2849	2645	2335	1781	1130	523
Arm B	3399	3293	3194	3081	2953	2741	2431	1859	1197	537

Secondary Endpoint
Distant Relapse-Free Interval

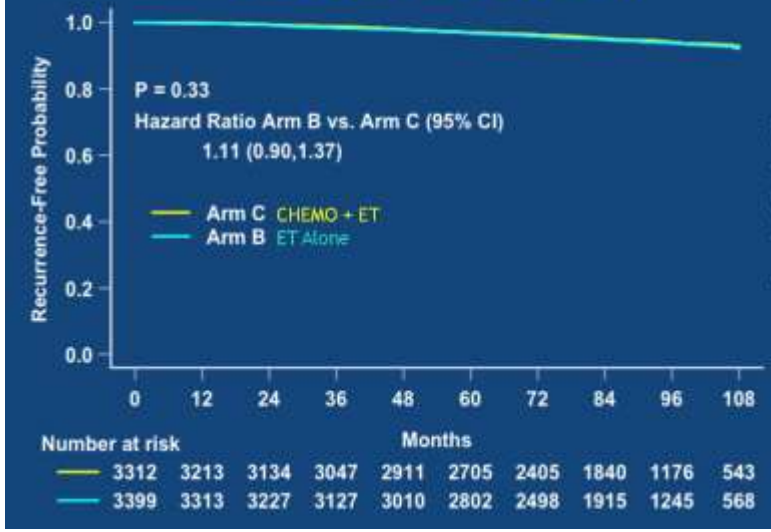


Number at risk

Arm C	3312	3215	3142	3059	2935	2734	2432	1866	1197	554
Arm B	3399	3318	3239	3147	3033	2833	2537	1947	1267	581

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

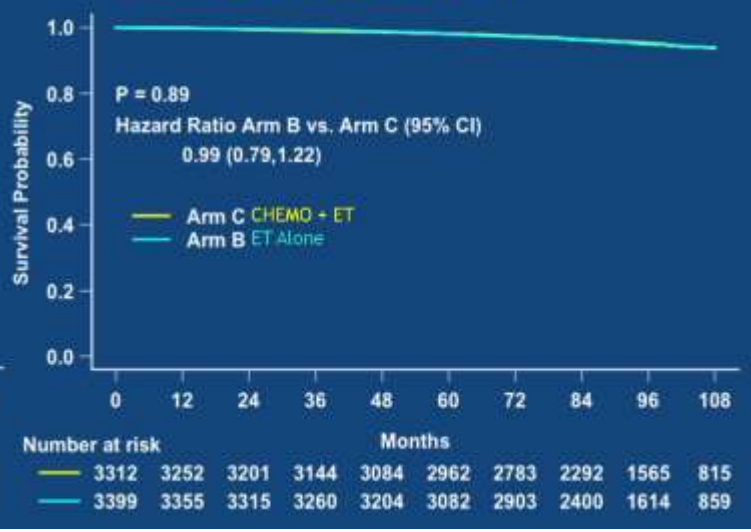
Other Secondary Endpoints
Relapse-Free Interval



Number at risk

Arm C	3312	3213	3134	3047	2911	2705	2405	1840	1176	543
Arm B	3399	3313	3227	3127	3010	2802	2498	1915	1245	568

Overall Survival

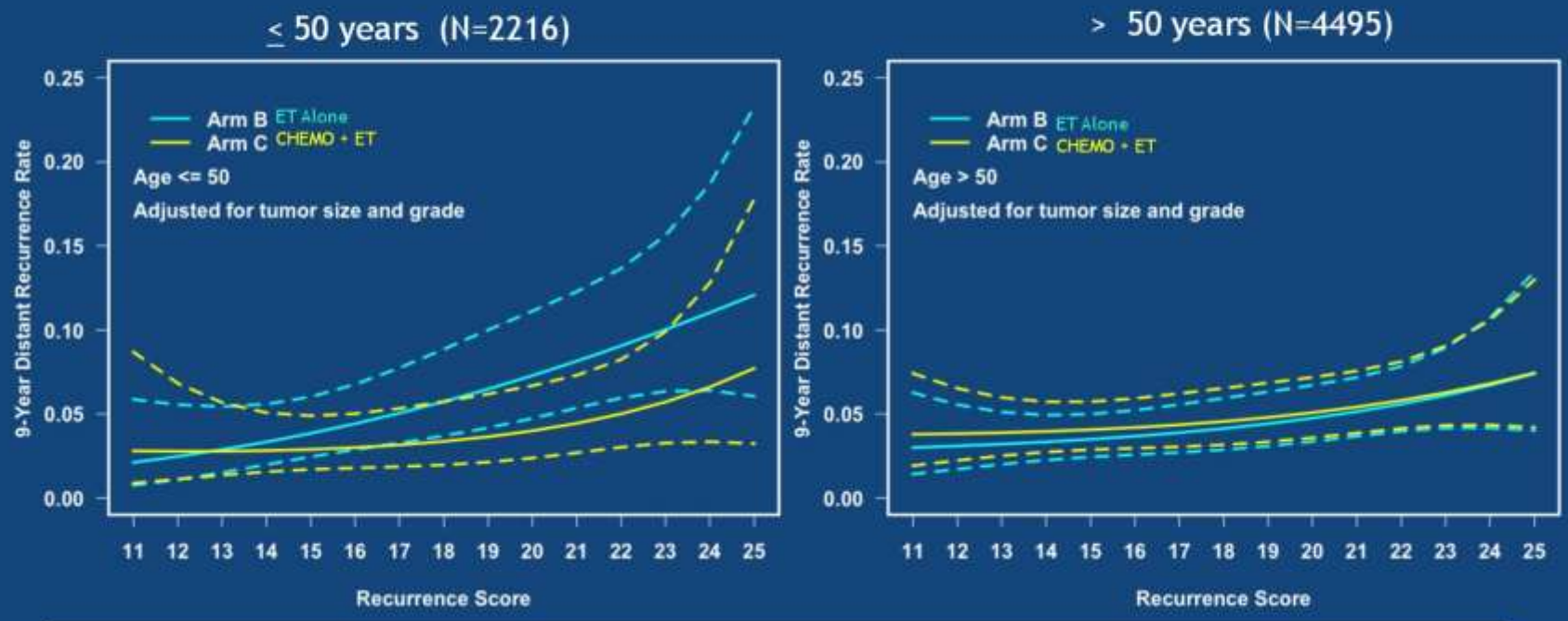


Number at risk

Arm C	3312	3252	3201	3144	3084	2962	2783	2292	1565	815
Arm B	3399	3355	3315	3260	3204	3082	2903	2400	1614	859

Sparano et al, NEJM 2018

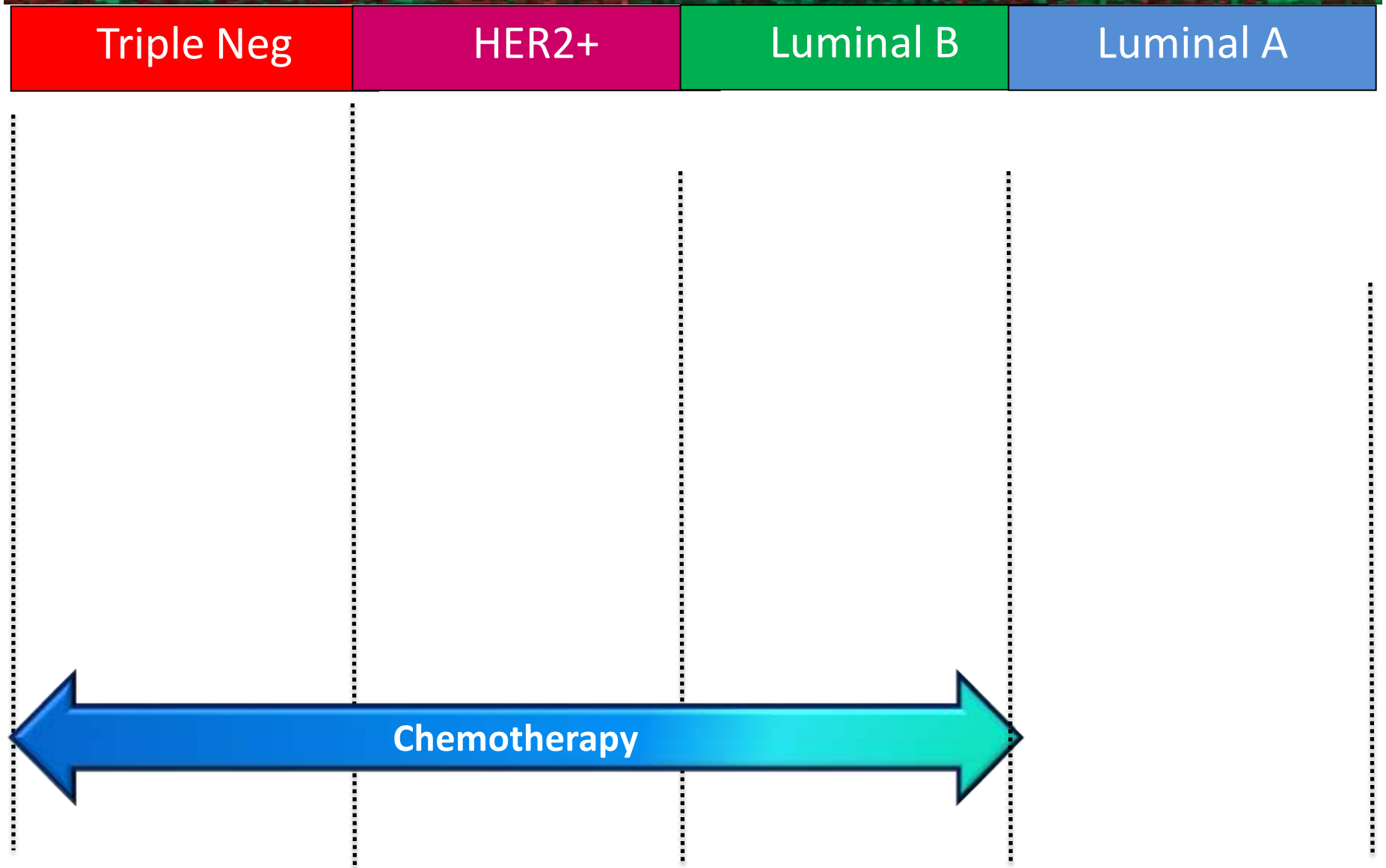
TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (</=50 vs. >50 Years)



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

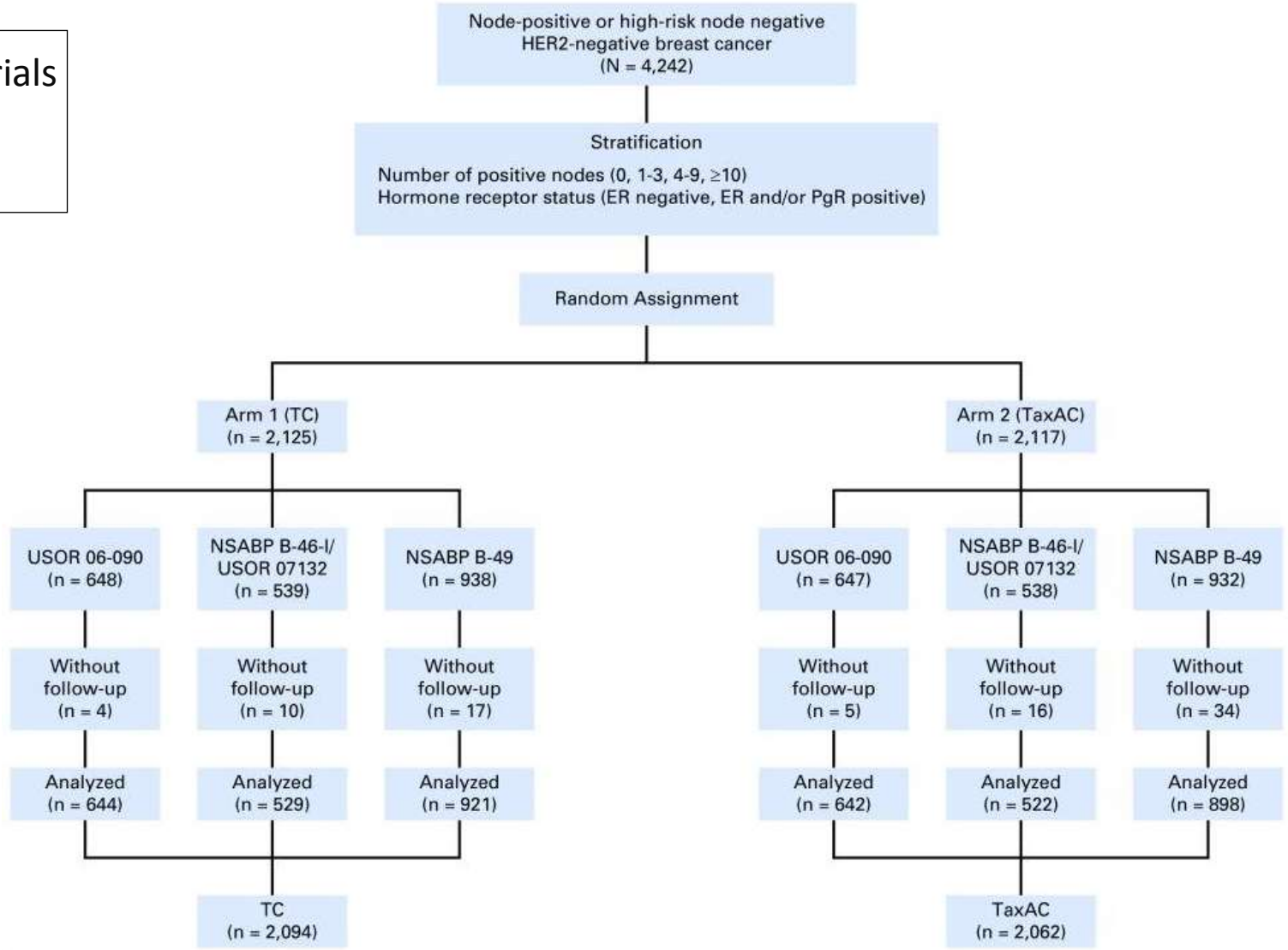
Sparano et al, NEJM 2018

Subtype driven approach



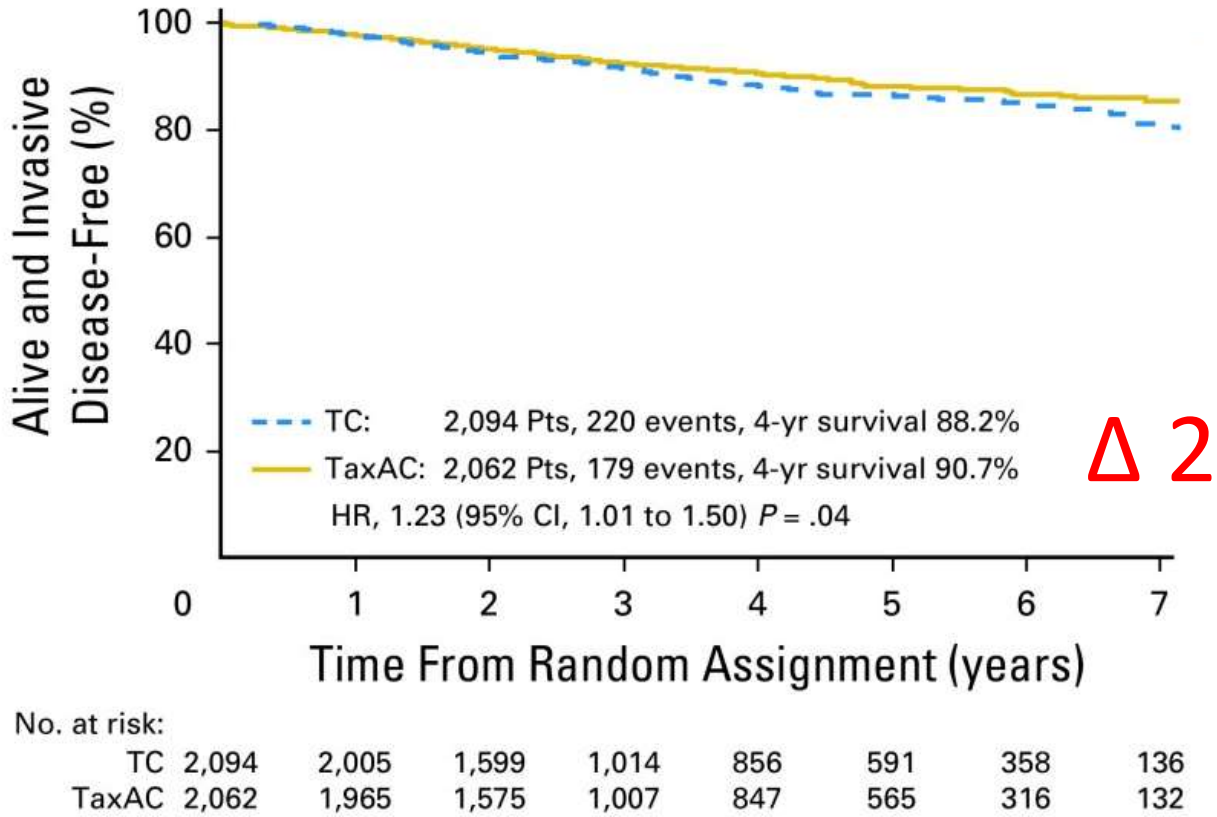
Looking for the optimal adjuvant chemotherapy

Joint Analysis of 3 ABC Trials
TC vs TaxAC
4242 high risk pts



Blum et al JCO 2017

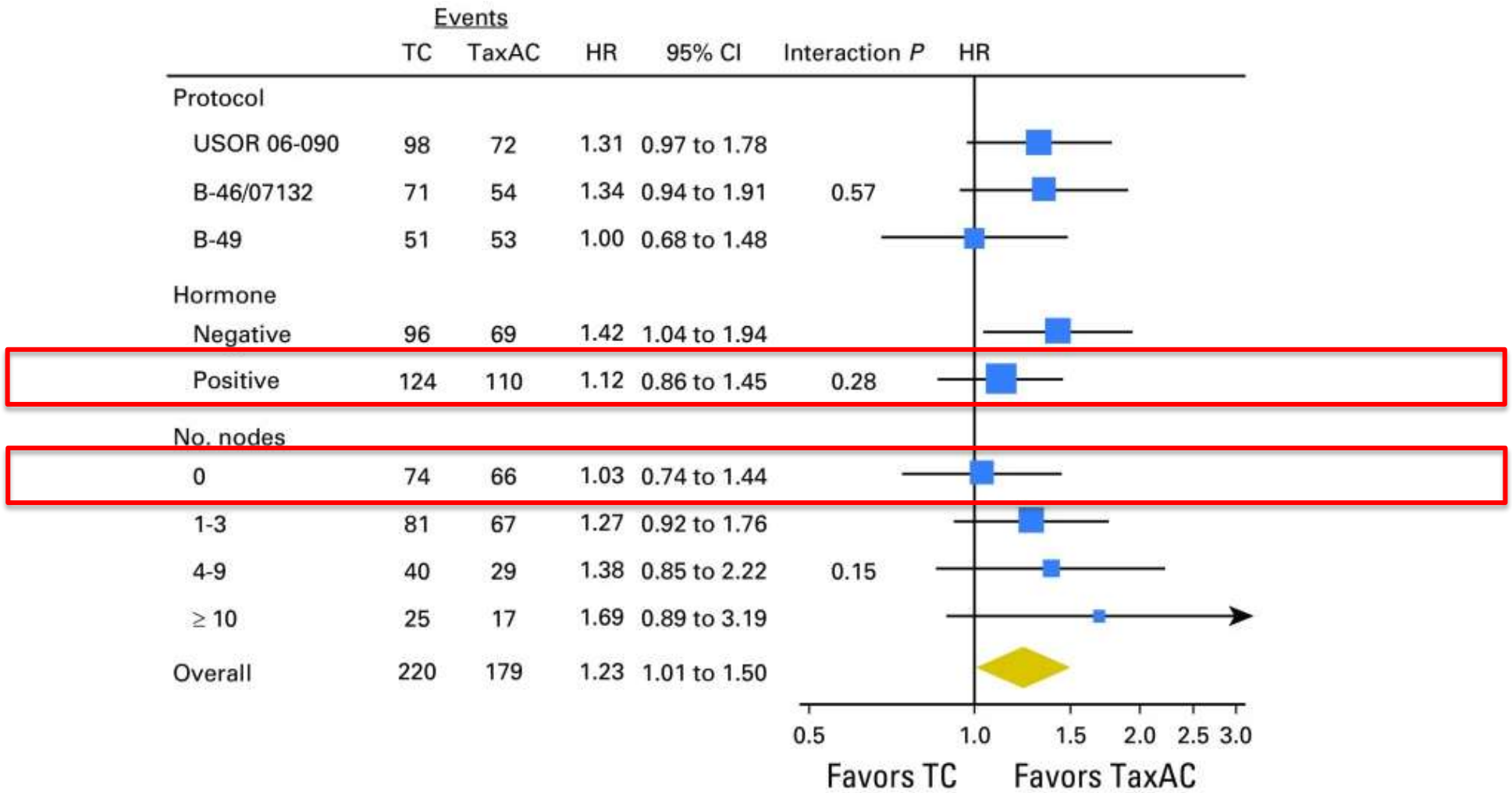
ABC trials: IDFS



Δ 2,5%

Blum et al JCO 2017

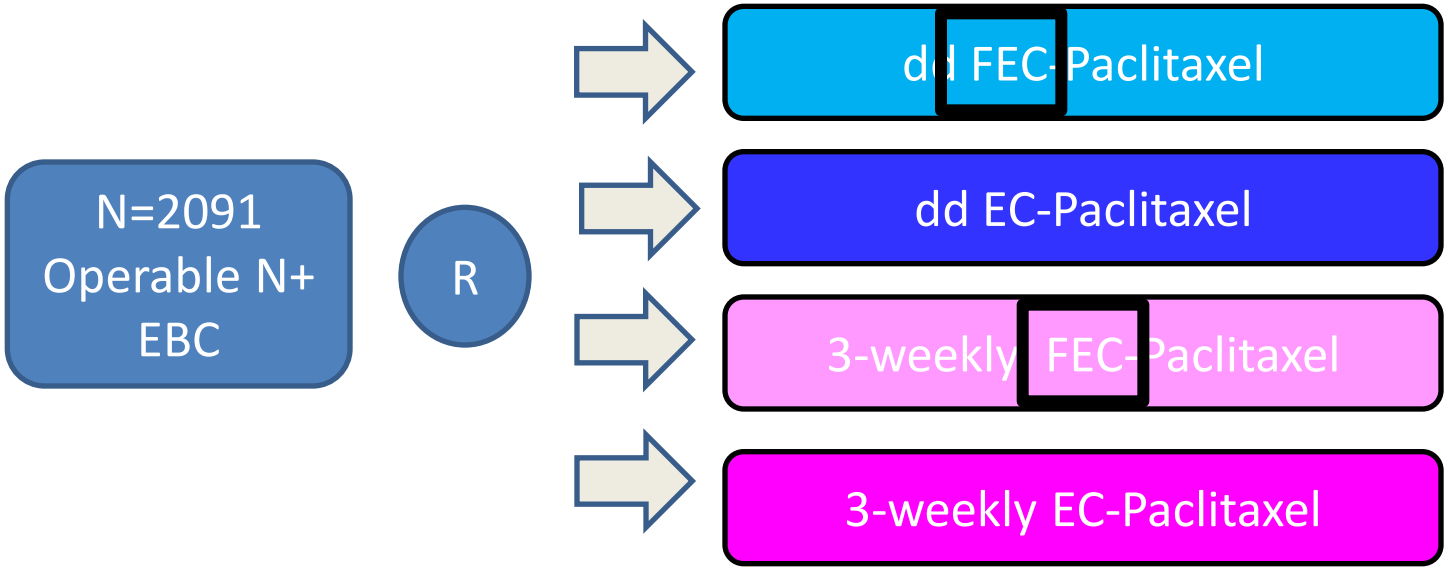
Forest plots of IDFS by stratification variables



Blum et al JCO 2017

The role of 5-FU in the adjuvant setting

- 5FU has been a component of adjuvant chemo since the development of CMF
- 2x2 design:



- Primary endpoint: DFS

Del Mastro et al, Lancet 2015

5-FU: NO improved outcome
Toxicity increased

	5-year DFS	5-year OS	Toxicity
5FU vs no 5FU (HR, 95% CI, p-value)	**78% vs 79%** (1.06, 0.89-1.25; p=0.561)	**91% vs 92%** (1.16, 0.91-1.46; p=0.234)	More G3-4 neutropenia, fever, nausea and vomiting with 5FU

So why are we still using it?

Del Mastro et al, Lancet 2015

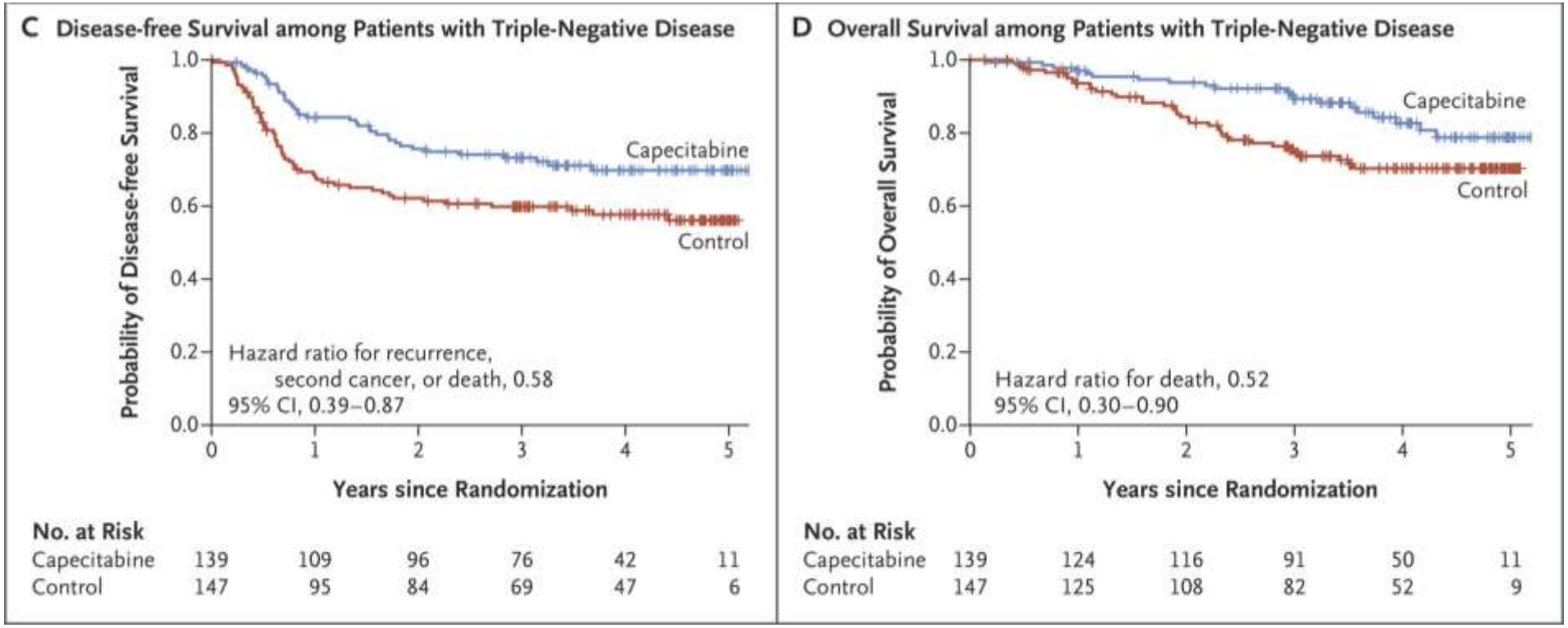
Selection of optimal adjuvant chemotherapy

- In patients who can tolerate it, use of **a regimen containing anthracycline-taxane is considered the optimal strategy for adjuvant chemotherapy**, particularly for patients deemed to be at high risk.

Denduluri N JCO 2016

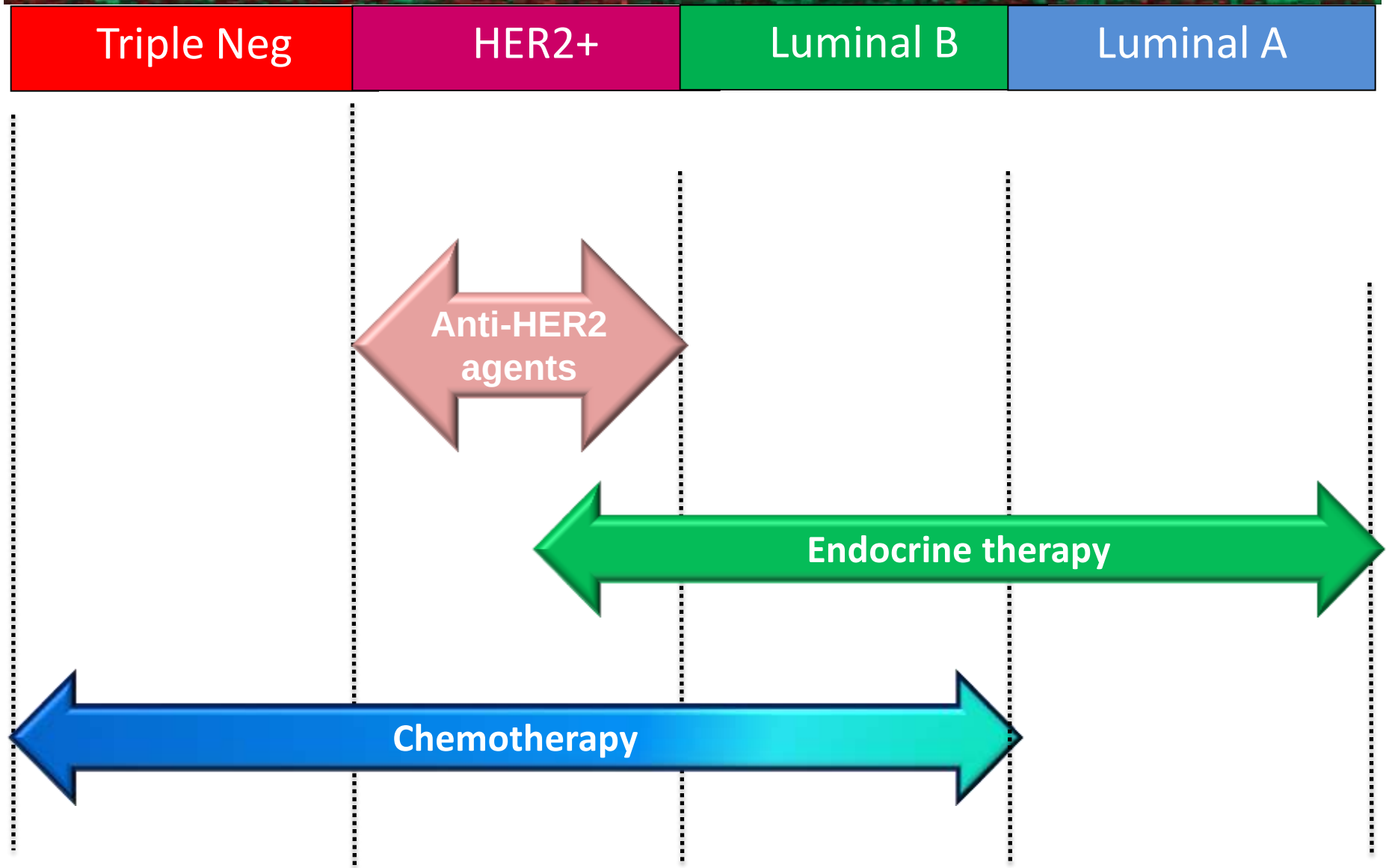
Adding capecitabine in TNBC?

910 HER2- pts with RD and N+ after neoadjuvant chemotherapy

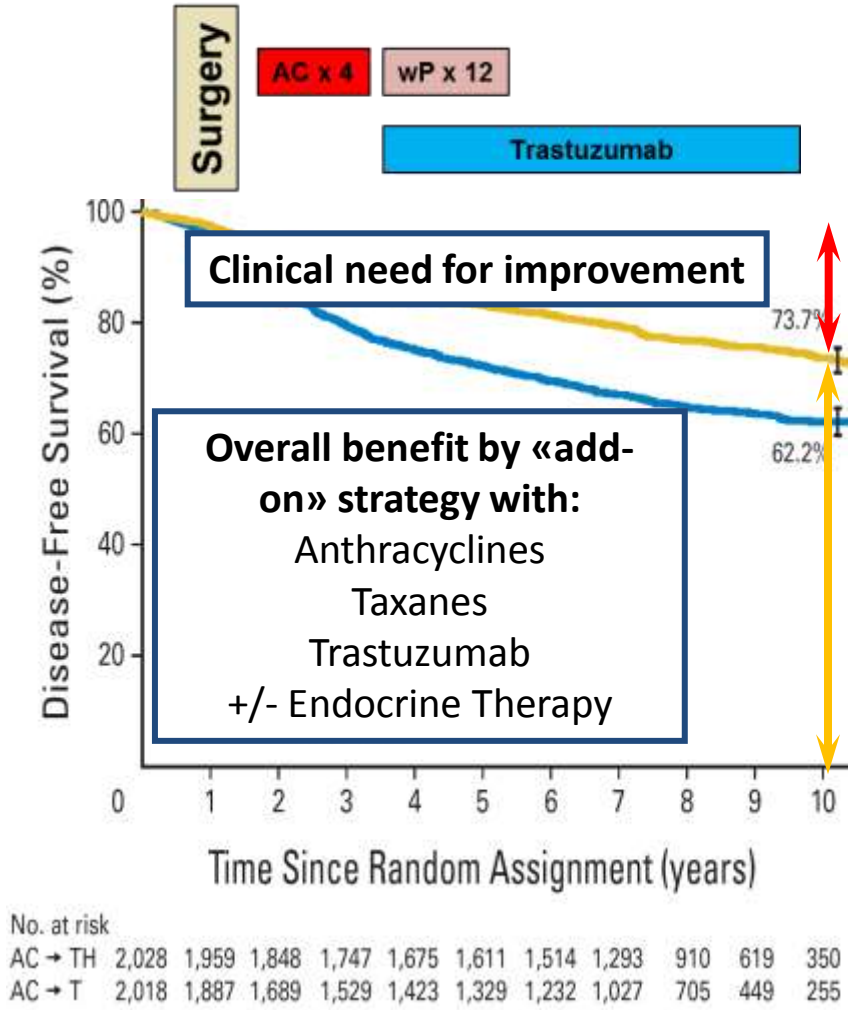


Masuda, et al. NEJM 2017

Subtype driven approach

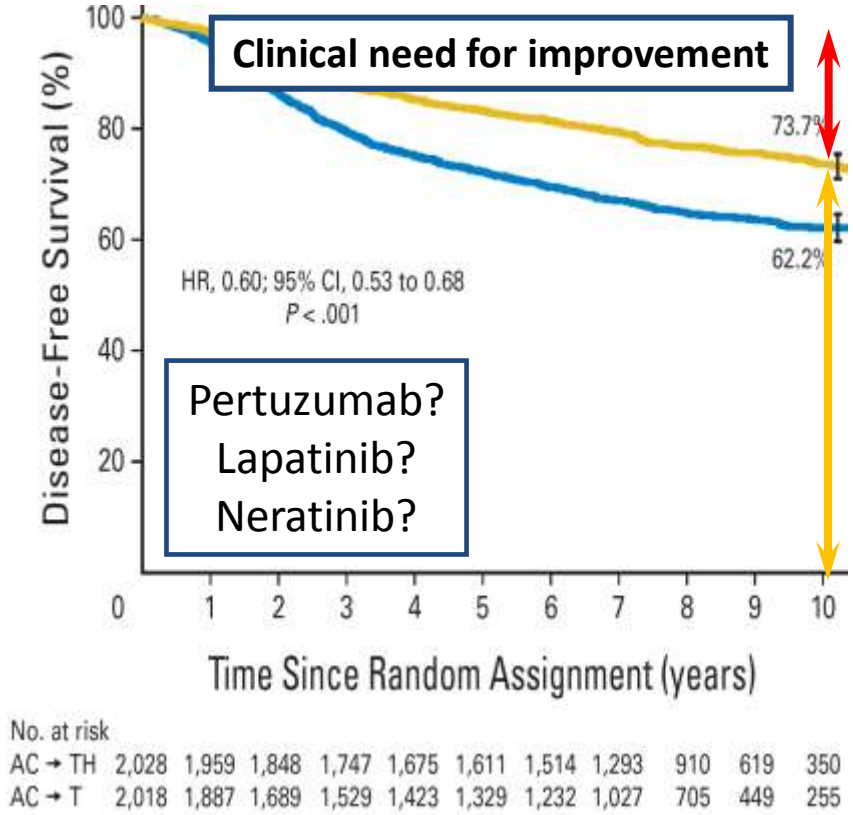


Trastuzumab + chemotherapy



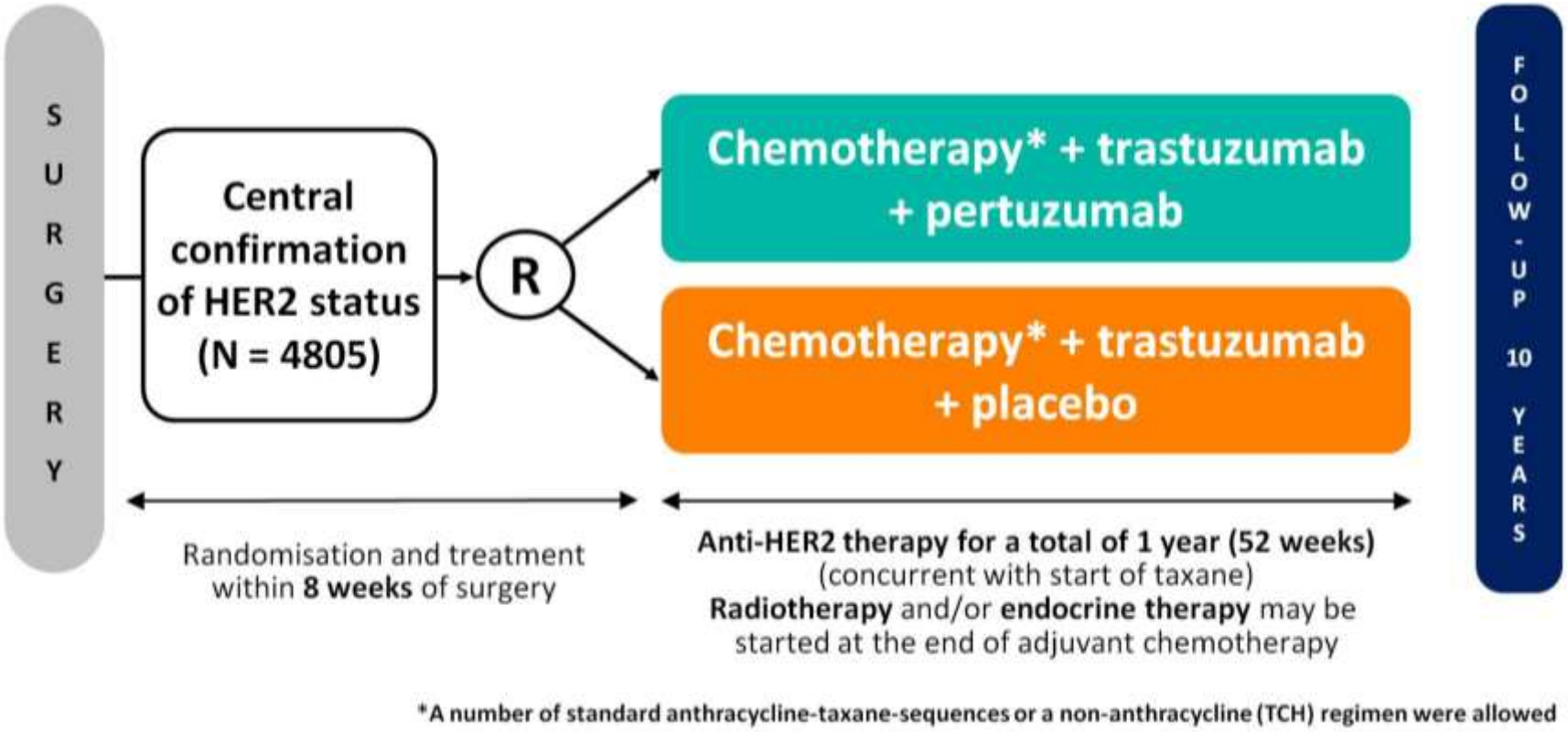
Perez EA JCO 2014

Esclation attempts



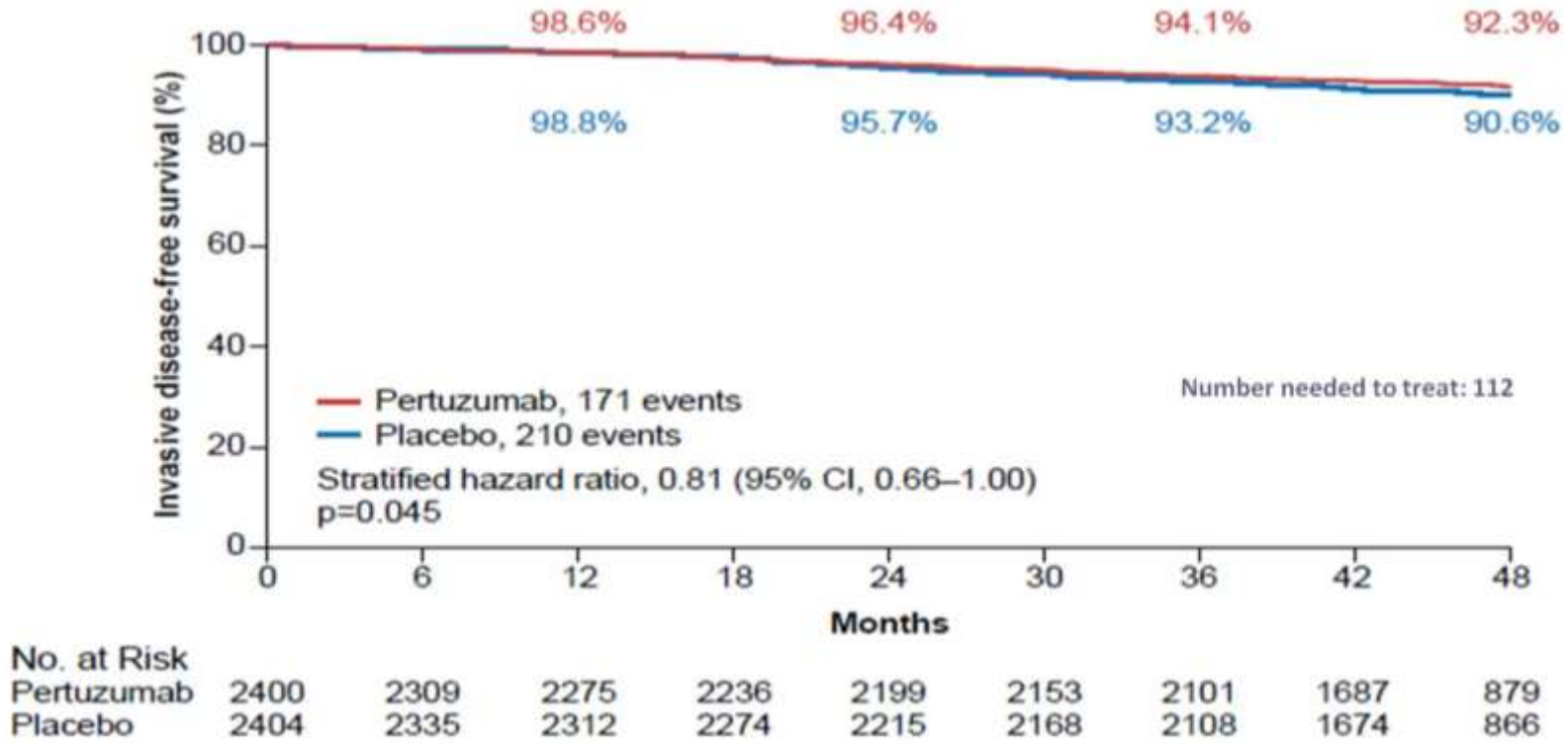
Perez EA JCO 2014

APHINITY trial



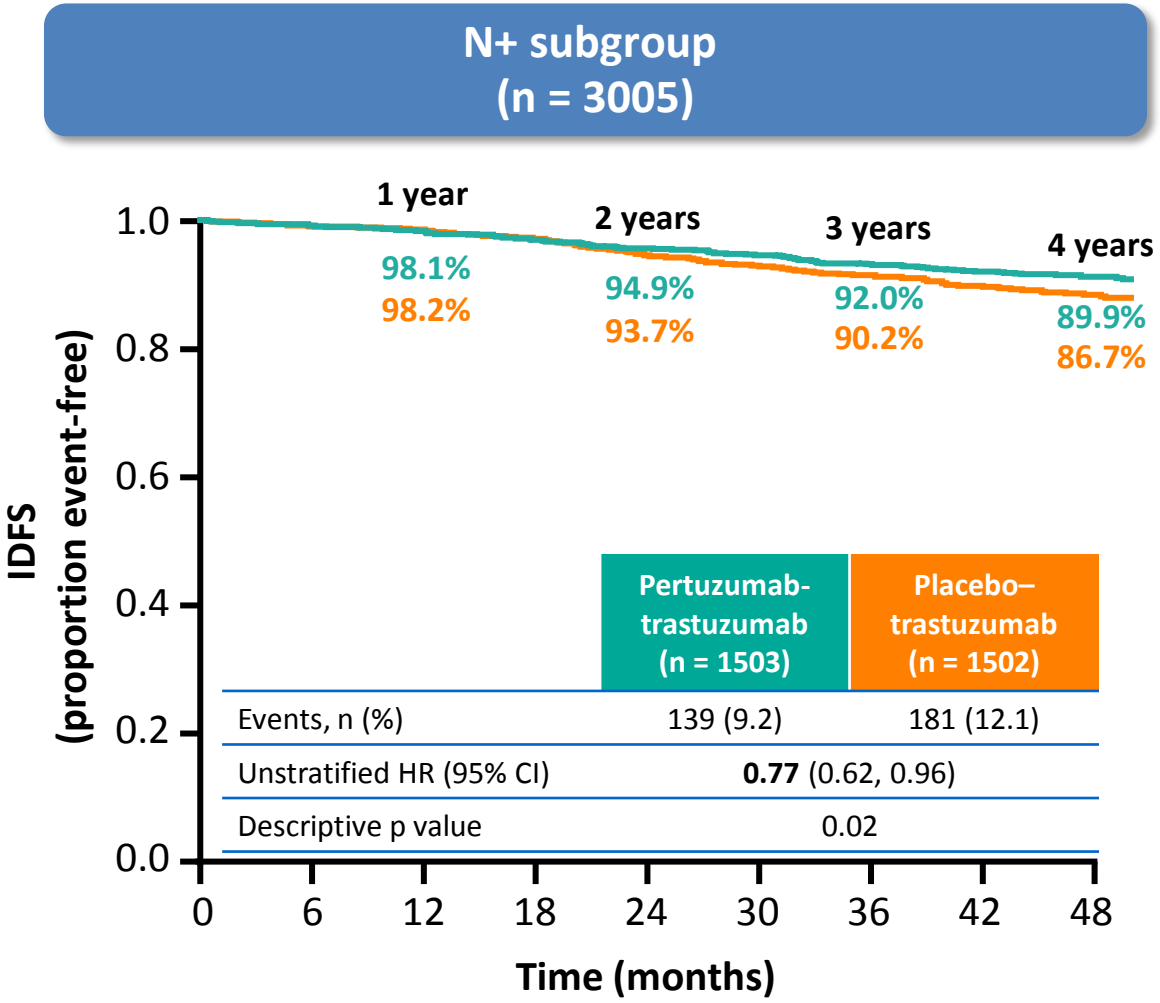
von Minckwitz G et al, NEJM 2017

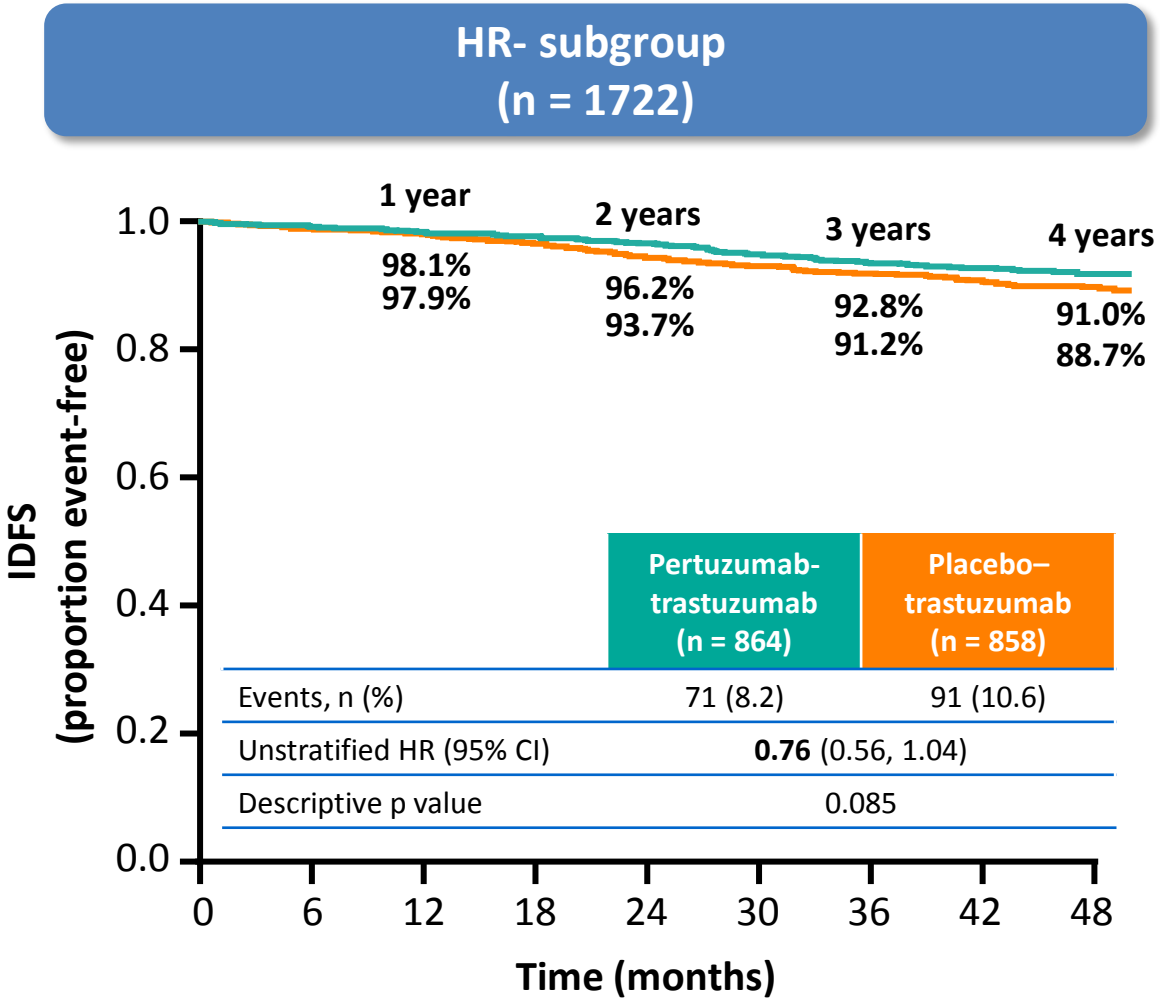
APHINITY trial: ITT IDFS



von Minckwitz G et al, NEJM 2017

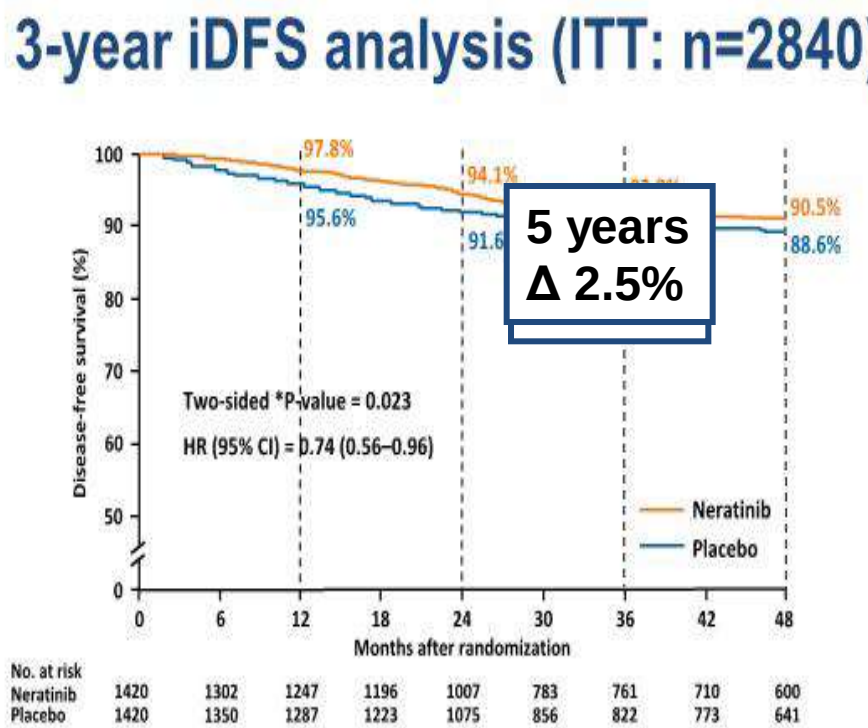
Who may derive more benefit from adjuvant pertuzumab?





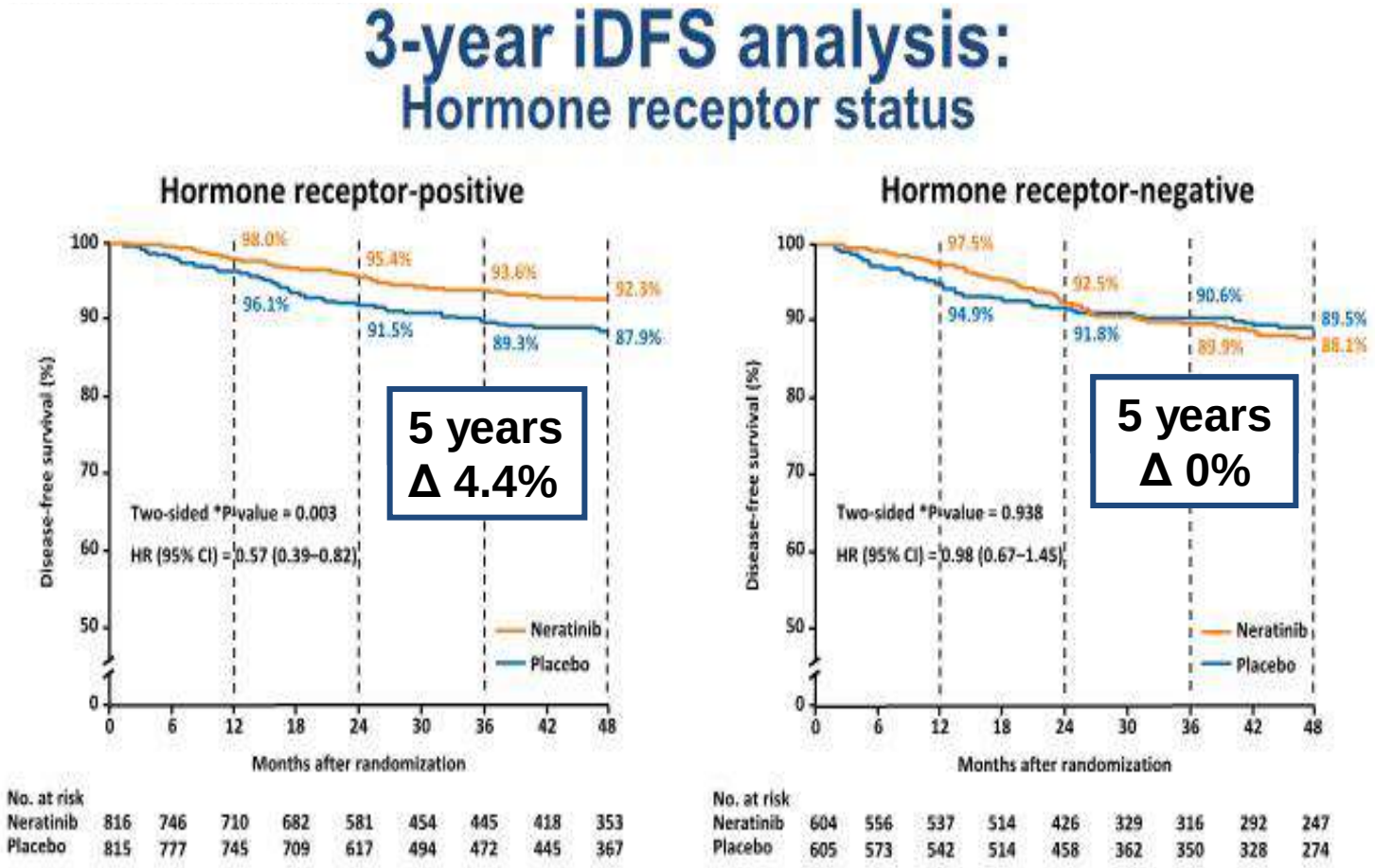
von Minckwitz G et al, NEJM 2017

Neratinib in high risk early BC?



Chan A SABCS 2015

Who may derive more benefit from neratinib?



Martin M ESMO 2017

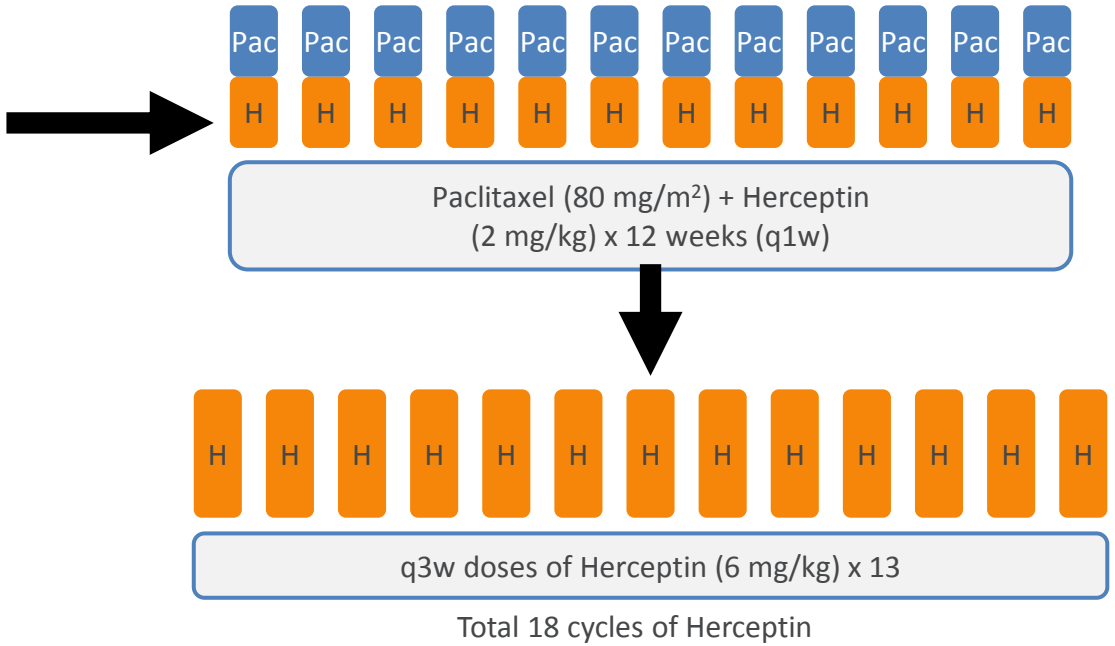
AVOID UNDUE OVERTREATMENT

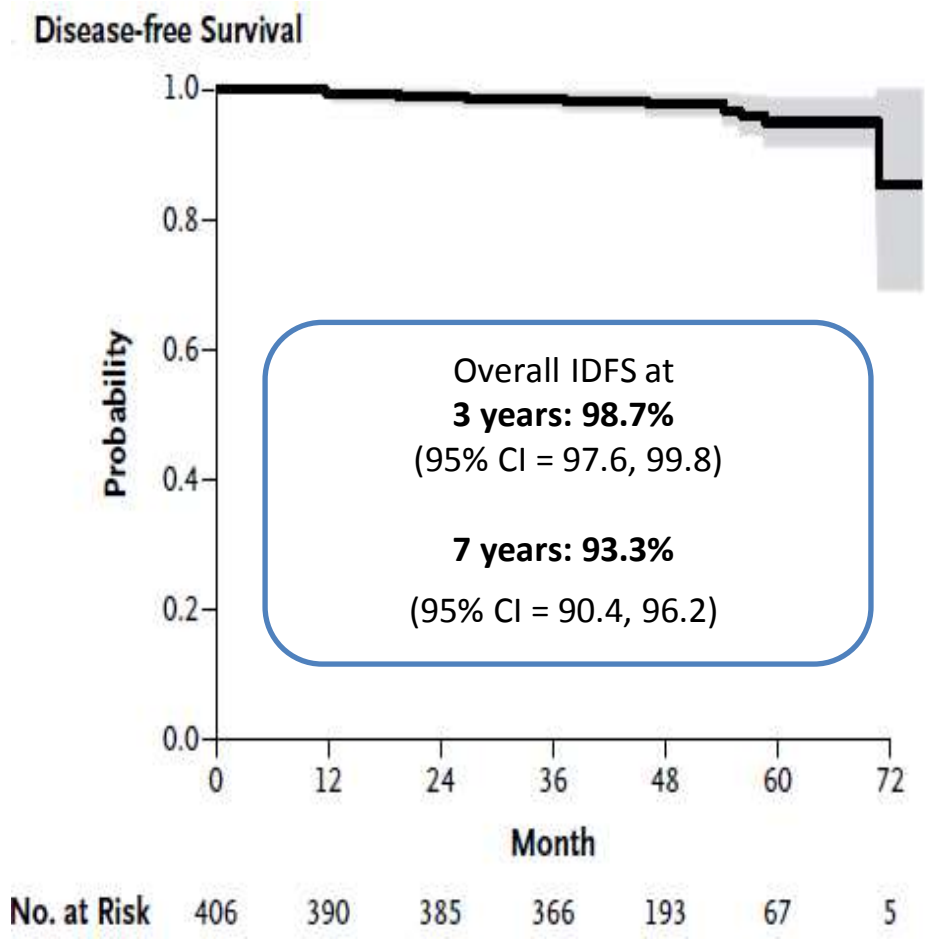
De-escalation attempts: APT trial

- HER2-positive
- ER+ or ER–
- Node-negative tumour ≤3 cm

N = 406

Primary endpoint: IDFS





Tolaney SM *et al. N Engl J Med* 2015

Is medicine art or science?

“If it were not for the great variability among individuals, medicine might have well been a science and not an art”

Sir William Osler (1849 –1919)


THE ONCOLOGIST WILL DISCUSS OPTIONS FOR ADJUVANT THERAPY AND HELP YOU DECIDE WHAT YOU WANT TO DO!
I WANT TO SURVIVE!
BATTUK
4-5

Thank you