Jonas Bergh M.D., Ph.D., FRCP (London, UK)
Professor of Oncology, Mimi Althainz' donation
DPA, Karolinska Institutet & University Hospital,
Director Breast Cancer Theme Network, Stockholm,
Sweden, Co-Chair EBCTCG, Vice- Chair SAG, EMA

Evidence- guideline based strategies for the early- and metastatic breast cancer setting

Fundamental breast cancer questions

Prevention
-Interplay life style factors & genes

Early diagnosis

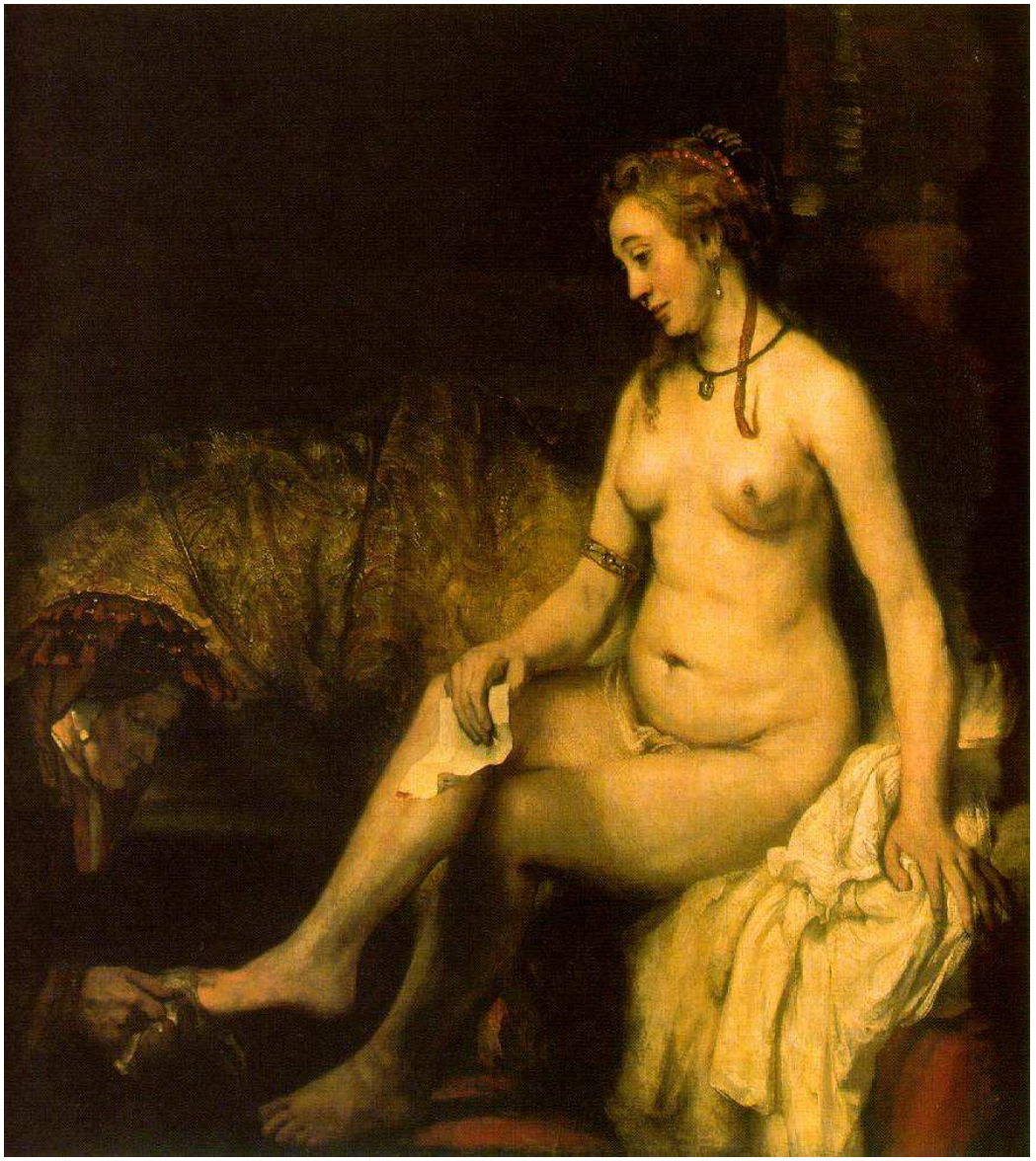
Which pts will only need loco-regional therapy?

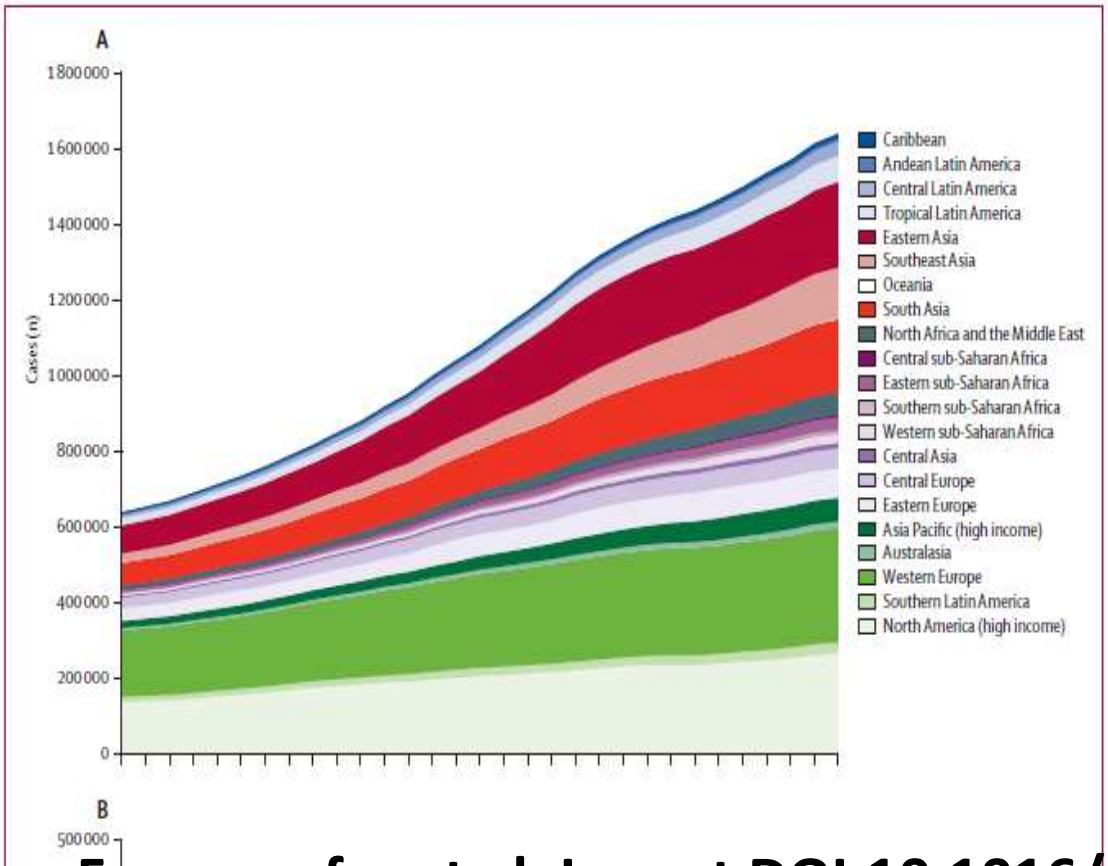
To whom addition of systemic therapies? Avoiding both over & under treatment

Therapy prediction-How to be more rational in drug selections?

Understand breast cancer biology – growth & met regulatory genes –proteins & stem cells

Macrometastatic disease

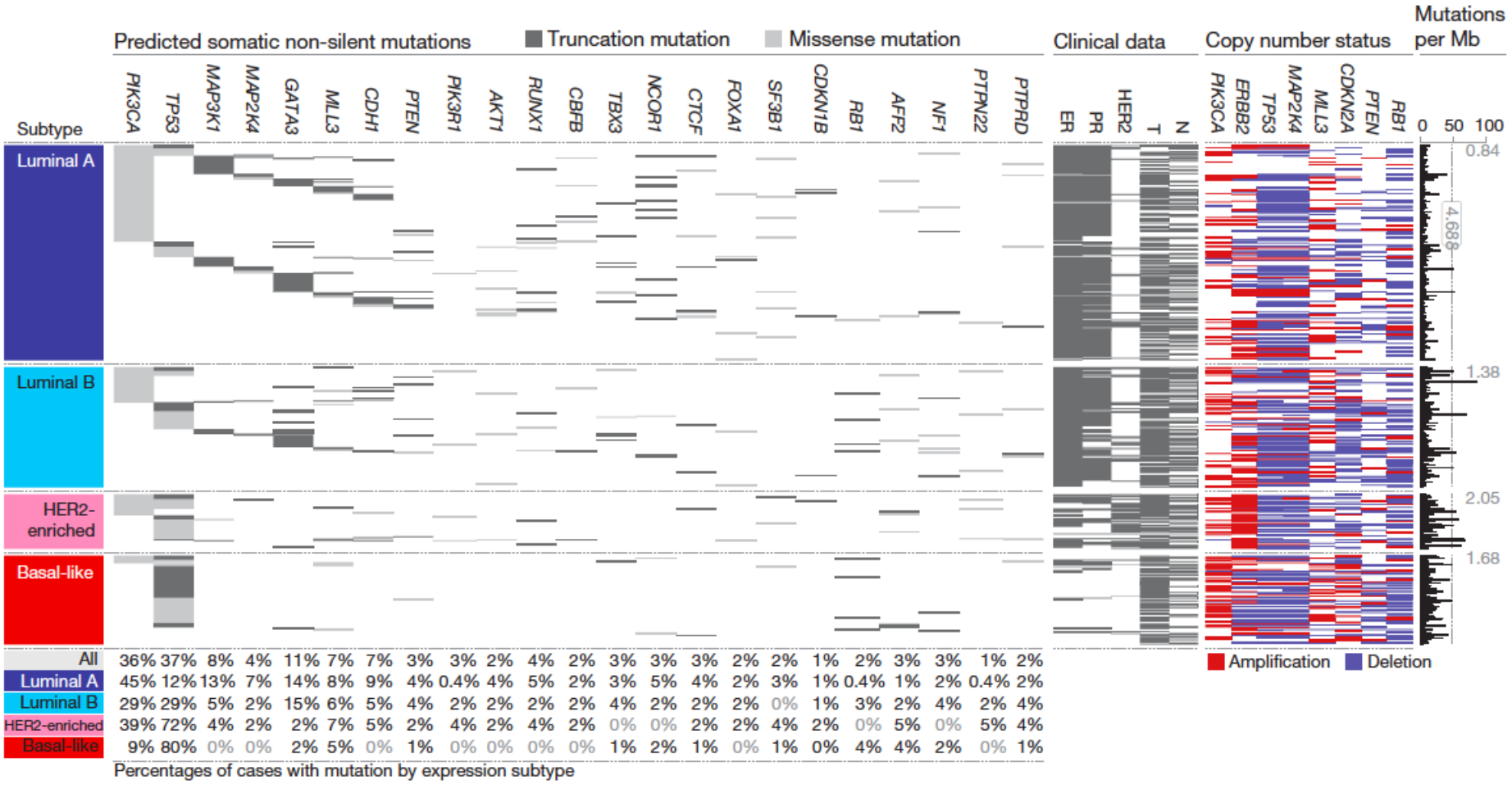




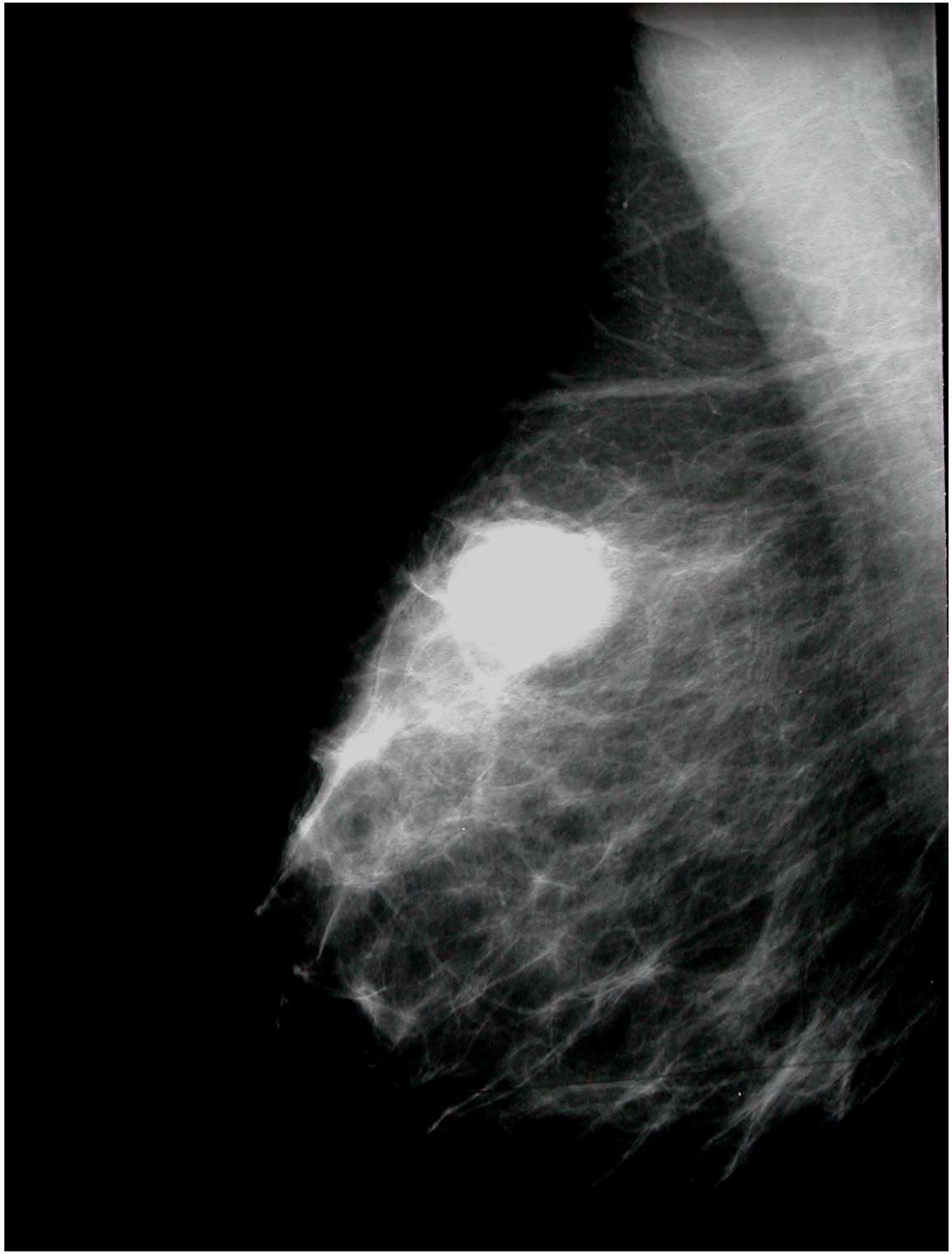
Breast cancer incidence 1980-2010 per region

Forouzanfar et al. Lancet DOI:10.1016/S0140-6736(11)61351-2, 2011

First- Breast cancer is to be split into several clinically relevant entities


Predicted somatic non-silent mutations
Truncation mutation
Missense mutation
Clinical data
Copy number status
Mutations per Mb
Subtype
PIK3CA TP53 MAP3K1 MAP2K4 GATA3 MLL3 CDH1 PTEN PIK3R1 AKT1 RUNX1 CBFB TBX3 NCOR1 CTCF FOXA1 SF3B1 CDKN1B RB1 AFF2 NF1 PTPN22 PTPRD
ER PR HER2 T N
PIK3CA ERBB2 TP53 MAP2K4 MLL3 CDKN2A PTEN RB1
0 50 100
0.84
4.688
1.38
2.05
1.68
Luminal A
Luminal B
HER2-enriched
Basal-like
All 36% 37% 8% 4% 11% 7% 7% 3% 3% 2% 4% 2% 3% 3% 3% 2% 2% 1% 2% 3% 3% 1% 2%
Luminal A 45% 12% 13% 7% 14% 8% 9% 4% 0.4% 4% 5% 2% 3% 5% 4% 2% 3% 1% 0.4% 1% 2% 0.4% 2%
Luminal B 29% 29% 5% 2% 15% 6% 5% 4% 2% 2% 2% 2% 4% 2% 2% 2% 0% 1% 3% 2% 4% 2% 4%
HER2-enriched 39% 72% 4% 2% 2% 7% 5% 2% 4% 2% 4% 2% 0% 0% 2% 2% 4% 2% 0% 5% 0% 5% 4%
Basal-like 9% 80% 0% 0% 2% 5% 0% 1% 0% 0% 0% 0% 1% 2% 1% 0% 1% 0% 4% 4% 2% 0% 1%
Amplification
Deletion
Percentages of cases with mutation by expression subtype

NEOADJUVANT THERAPY

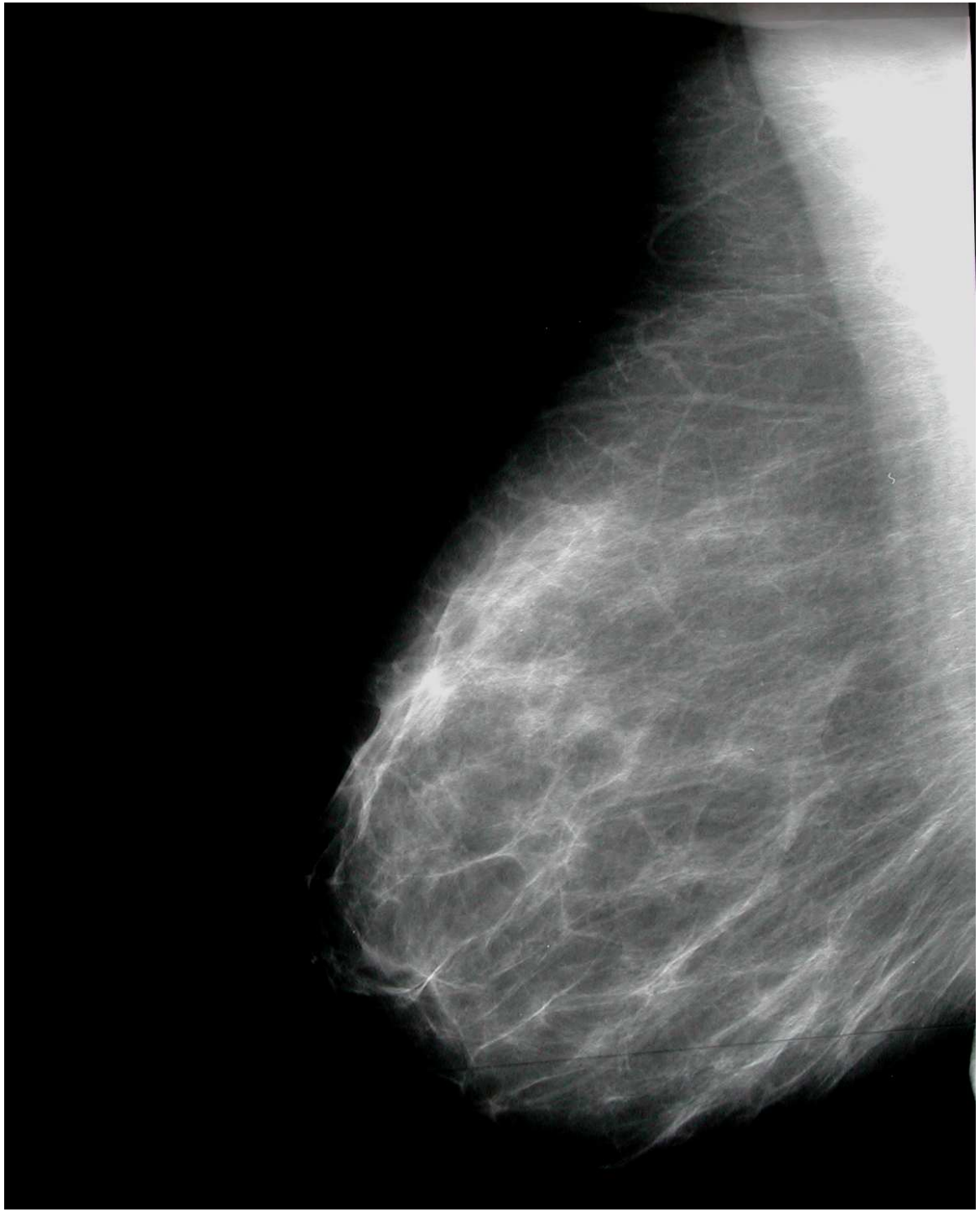


B. 45 year old female

Slides from assoc. Prof Edward Azavedo

Neoadjuvant therapy results in similar survival expectations as adjuvant therapy, 5500 pts-14 studies (Cochrane Review, 2007) Mieog JSD, van der Hage JA, van de Velde CJH)

Gepartrio-Swicth strategy – DFS improvements Von Minckwiz et al, JCO on line 2013



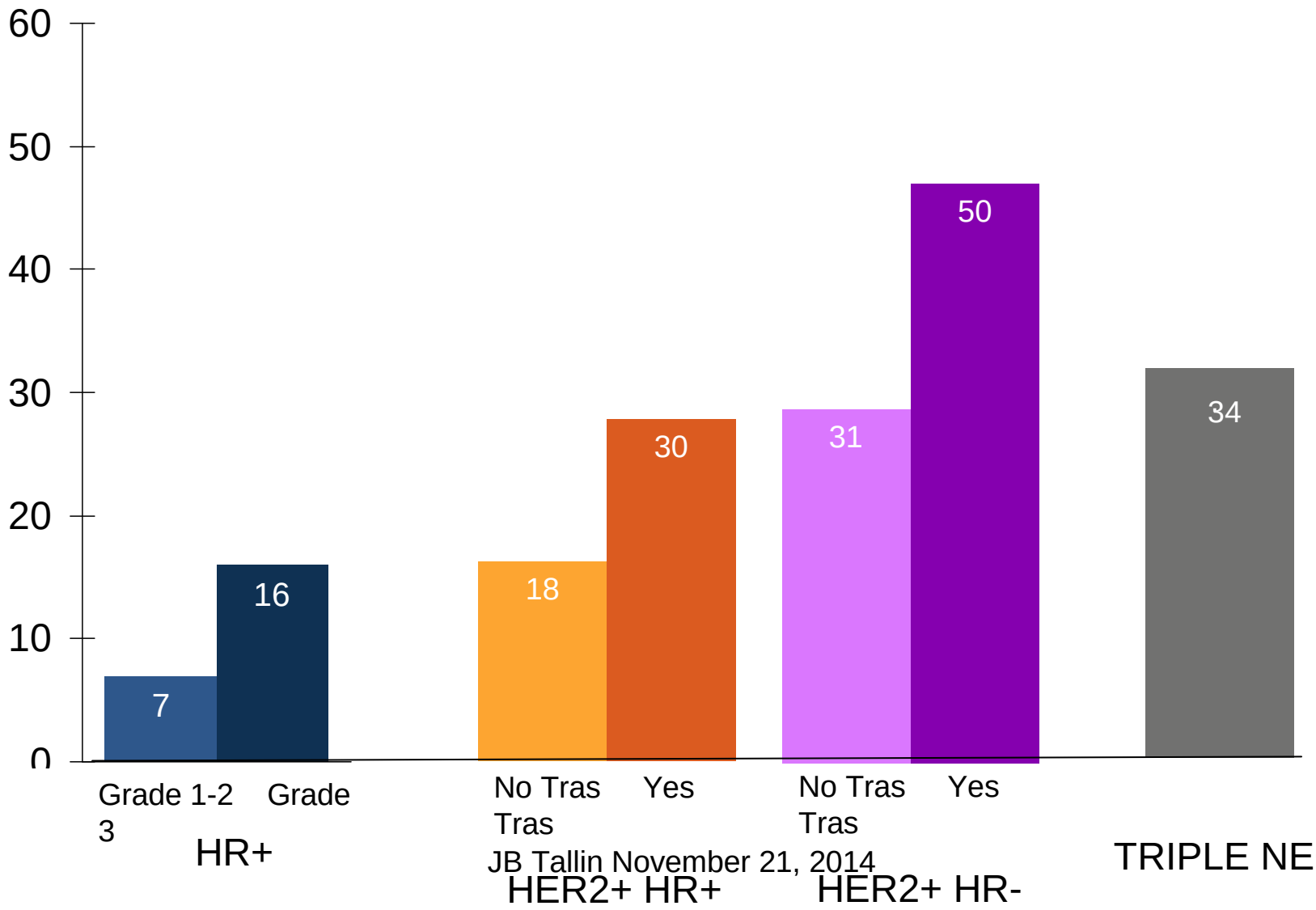
After 4 courses of tFEC, sector resection Histological CR, both in breast & axillary nodes (29/1-02-conf. Rah)

CTNeoBC Selected Trials

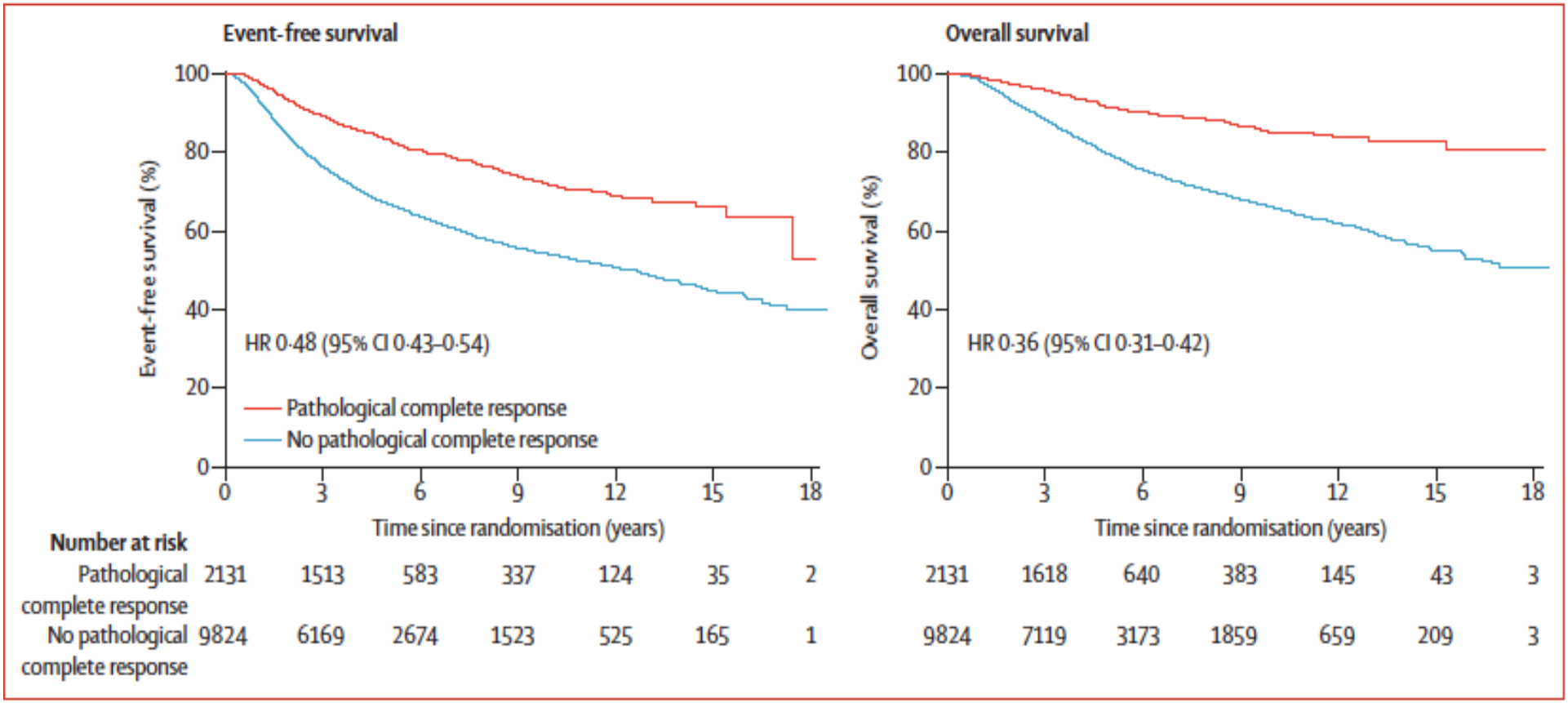
- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected

TRIALS	Patients (n)
GBG/AGO: 7	6377
NSABP: 2	3171
EORTC/BIG: 1	1856
ITA: 2	1589
Total # patients	12993

pCR Rates by Tumor Subtypes



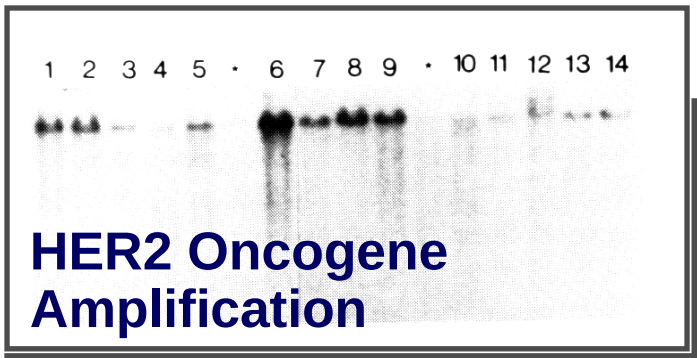
Importance of pCR for prognostication

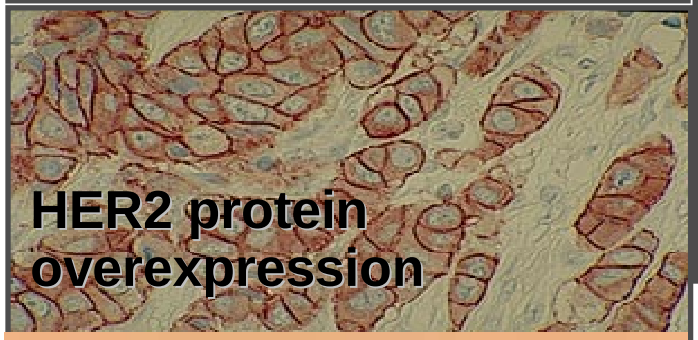


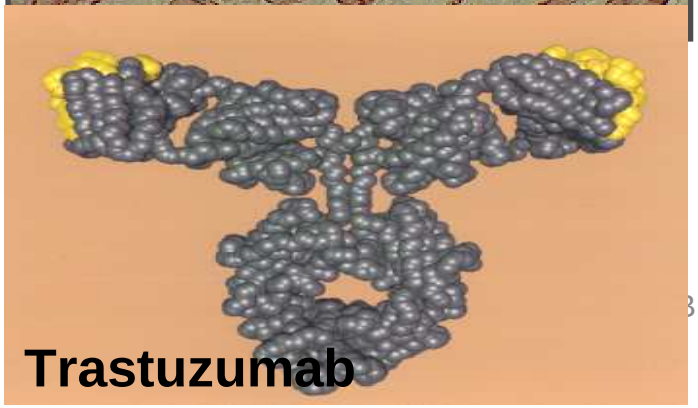
Cortozar et al, Lancet 2014

HER-2/neu positive breast cancers

Breast Cancer **From Slamon et al, Science 1987**

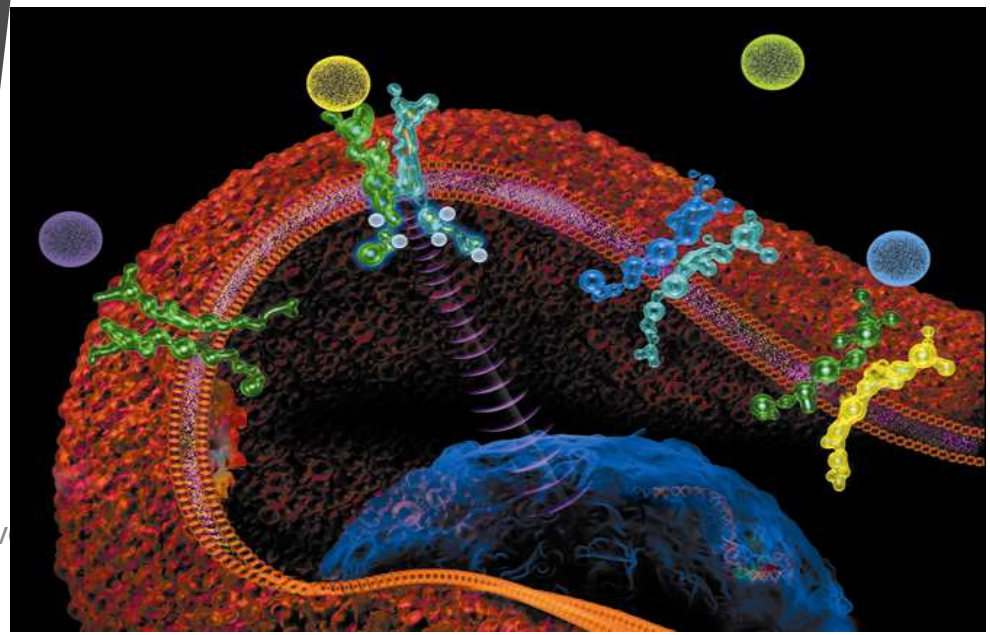






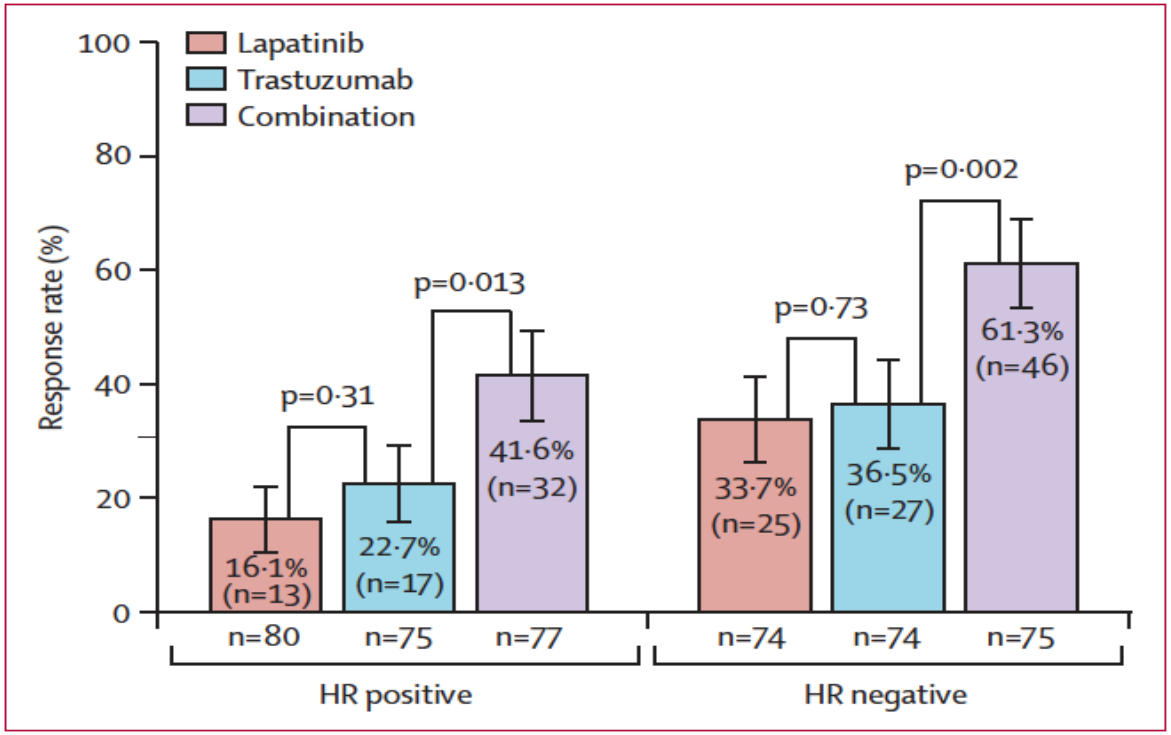
Shortened Median Survival

HER2 overexpressing	3 yrs
HER2 normal	6 - 7 yrs



Neoadjuvant – pre operative therapy
Single vs. double blockade – backbone of CT

Six weeks of lapatinib +-trastuzumab – Twelve weeks of of paclitaxel Neoallto



Basegla et al., Lancet 379;633-640, 2012

Trastuzumab +- pertuzumab +- docetaxel
NEOSPHERE

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Pathological complete response in ITT population	31 (29·0%, 20·6–38·5)	49 (45·8%, 36·1–55·[illegible])*	18 (16·8%, 10·3–25·3)†	23 (24·0%, 15·8–33·7)‡
Pathological complete response and N– at surgery	23 (21·5%, 14·1–30·5)	42 (39·3%, 30·0–49·2)	12 (11·2%, 5·9–18·8)	17 (17·7%, 10·7–26·8)
Pathological complete response and N+ at surgery	8 (7·5%, 3·3–14·2)	7 (6·5%, 2·7–13·0)	6 (5·6%, 2·1–11·8)	6 (6·3%, 2·3–13·1)
Pathological complete response in ER positive or PR positive, or both, women	10/50 (20·0%, 10·0–33·7)	13/50 (26·0%, 14·6–40·3)	3/51 (5·9%, 1·2–16·2)	8/46 (17·4%, 7·8–31·4)
Pathological complete response in ER negative and PR negative women	21/57 (36·8%, 24·4–50·7)	36/57 (63·2%, 49·3–75·6)	15/55 (27·3%, 16·1–41·0)	15/50 (30·0%, 17·9–44·6)

Data are n (%, 95% CI) or n/N (%, 95% CI). ITT=intention-to-treat. N–=lymph-node negative. N+=lymph-node positive. ER=oestrogen receptor. PR=progesterone receptor. *p=0·0141 vs group A. †p=0·0198 vs group A. ‡p=0·003 vs group B.

Table 2: **Pathological complete responses in the ITT population, by hormone-receptor status, and by axillary lymph node status at surgery**

Gianni et al, Lancet Oncol 2012

Adjuvant endocrine therapy, five years of tamoxifen is still a good standad

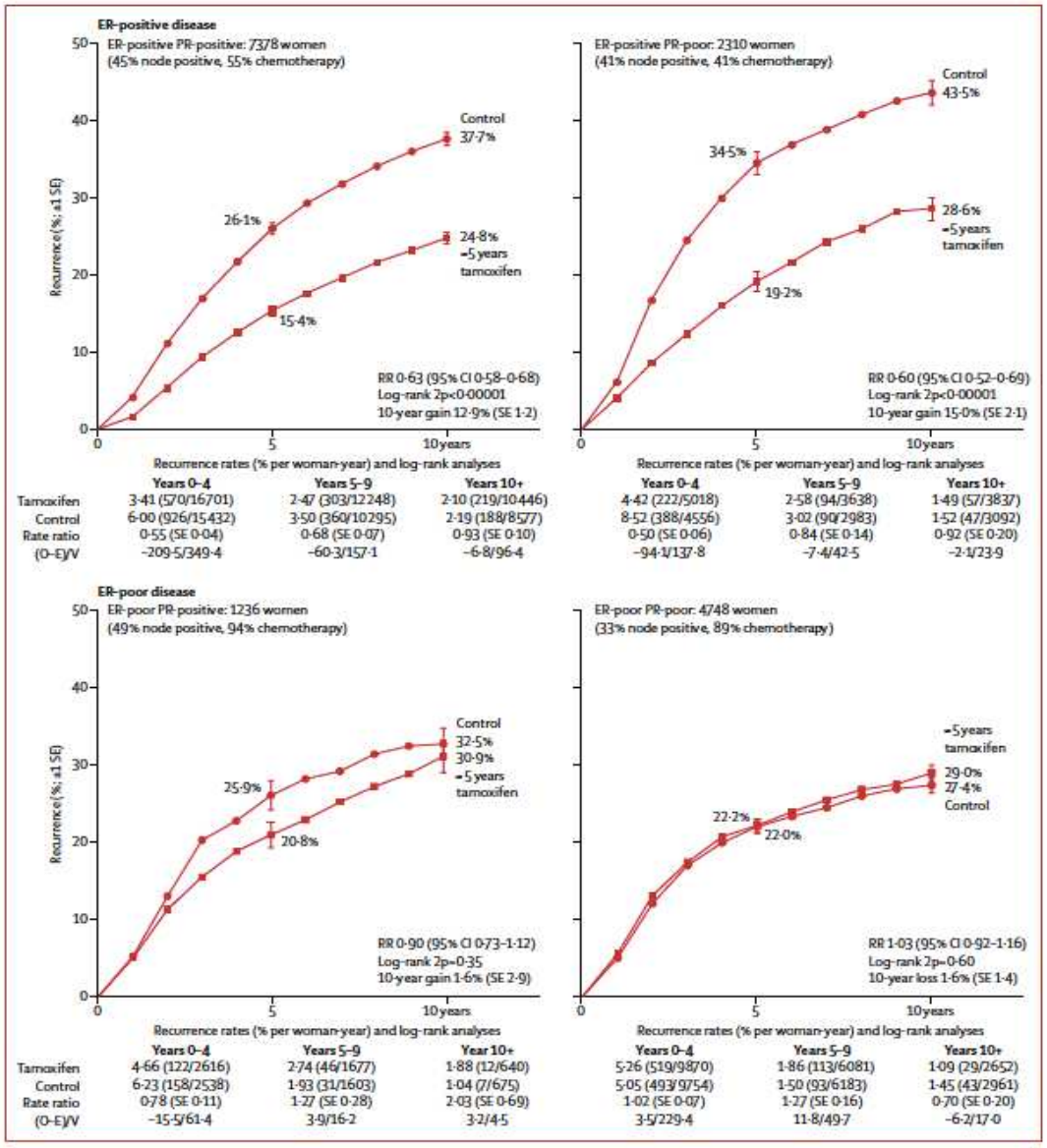


Figure 1: **Relevance of measured ER and PR status to the effects of about 5 years of tamoxifen on the 10-year probability of recurrence**
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain

EBCTCG, Lancet Published Online July 29, 2011

20,187 women with ER-positive or ER-unknown disease randomised in 5 trials of 10 vs 5 years of tamoxifen:

ECOG, Scottish & NSABP B-14	**1,588**
ATLAS*	**11,646**
aTTom	**6,953**
ALL TRIALS	**20,187**

***ATLAS, *Lancet* 2013; 381: 805–16**

Slide from Richard Gray, EBCTCG, CTSU

Adjuvant AI vs Tam
Five years of an AI – improves RFS by 4%

A new update with > 30.000 pts is presently analysed

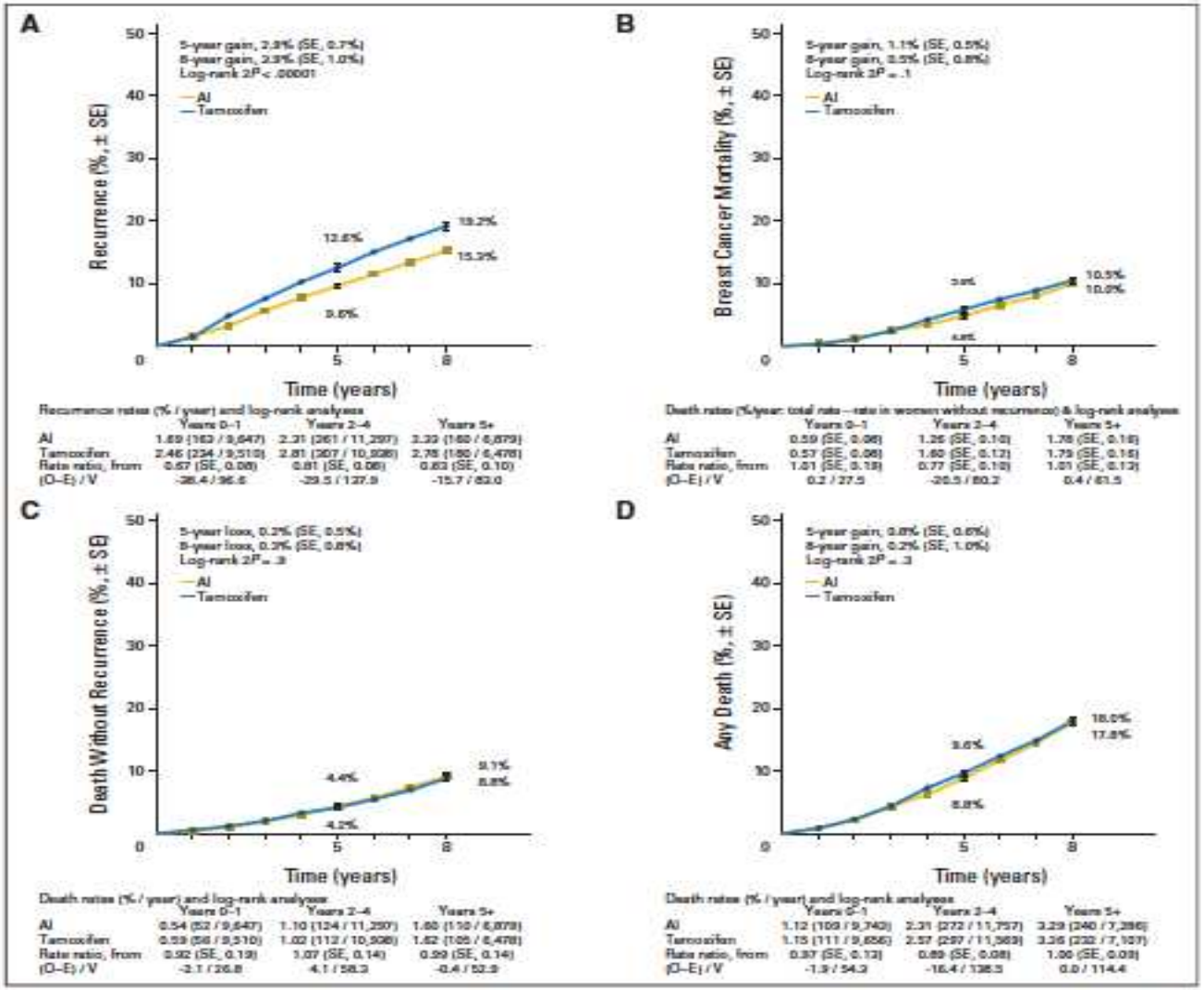


Fig 1. Life-table curves of (A) recurrence; (B) breast cancer mortality; (C) death without recurrence; and (D) any death, for estrogen receptor–positive patients in trials of approximately 5 years of aromatase inhibitor (AI) versus tamoxifen. O, observed; E, expected; V, variance.

Dowsett et al,
J Clin Oncol
28:509-518.

Adjuvant Chemotherapy

Group statistical based therapy of micrometastatic disease

St Gallen guidelines 2013

'Subtype'	Type of therapy	Notes on therapy
'Luminal A-like'	Endocrine therapy is the most critical intervention and is often used alone.	Cytotoxics may be added in selected patients. Relative indications for the addition of cytotoxics accepted by a majority of the Panel included: (i) high 21-gene RS (i.e. >25), if available; (ii) 70-gene high risk status, if available; (iii) grade 3 disease; (iv) involvement of four or more lymph nodes (a minority required only one node). The Panel was almost equally divided as to whether young age (<35 years) *per se* was an indication to add cytotoxics. Studies suggest a wide geographical divergence in the threshold indications for the inclusion of cytotoxics for the treatment of patients with luminal disease [96].
'Luminal B-like (HER2 negative)'	Endocrine therapy for all patients, cytotoxic therapy for most.	
'Luminal B-like (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive (non-luminal)'	Cytotoxics + anti-HER2	Threshold for use of anti-HER2 therapy was defined as pT1b or larger tumour or node-positivity.
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'[a]		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine non-responsive	Cytotoxics	Adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

[a]Special histological types: endocrine responsive (cribriform, tubular and mucinous); endocrine non-responsive (apocrine, medullary, adenoid cystic and metaplastic).

Goldhirsch et al, Ann Onc 2013

Direct and indirect comparisons between different polychemotherapy regimens, based on ~100,000 randomised women

45,000 taxane vs no taxane*
(44,000 with anthracycline in both arms)

22,000 anthracycline vs CMF
(18,000 vs “standard” CMF)

5,000 more vs less anthracycline
(2000 comparing currently relevant doses)

31,000 polychemotherapy vs no adjuvant chemo
(13,000 CMF vs Nil; 10,000 anthr.-based regimen vs Nil)

* Excludes trials of one taxane regimen vs another

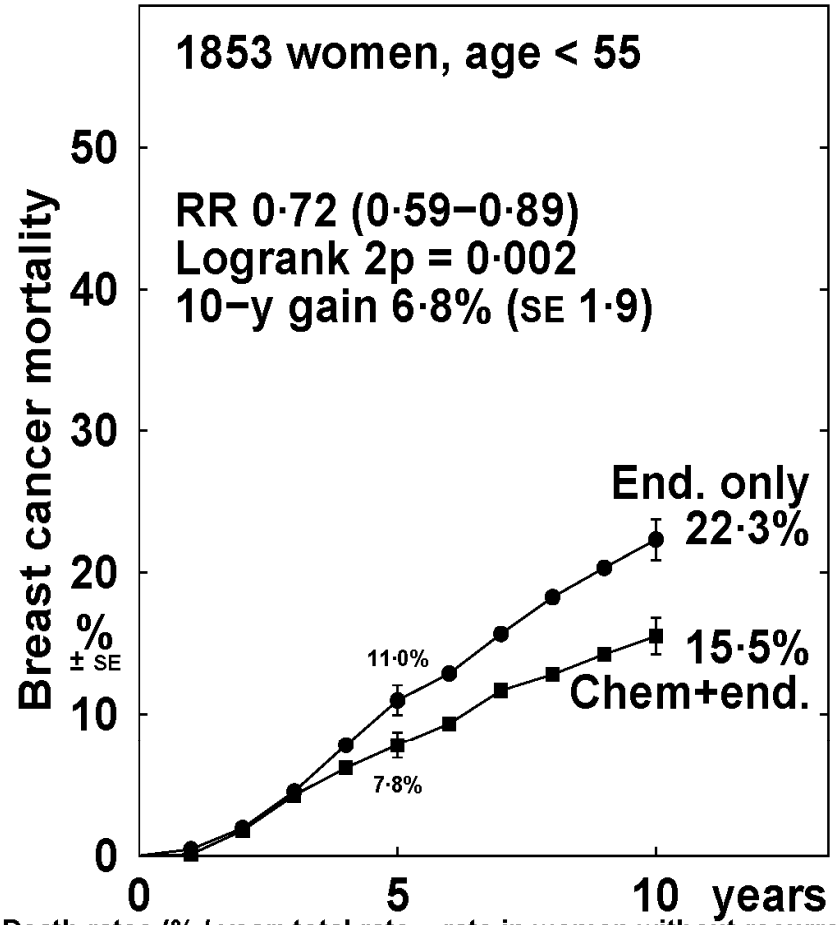
EBCTCG, Lancet 2012

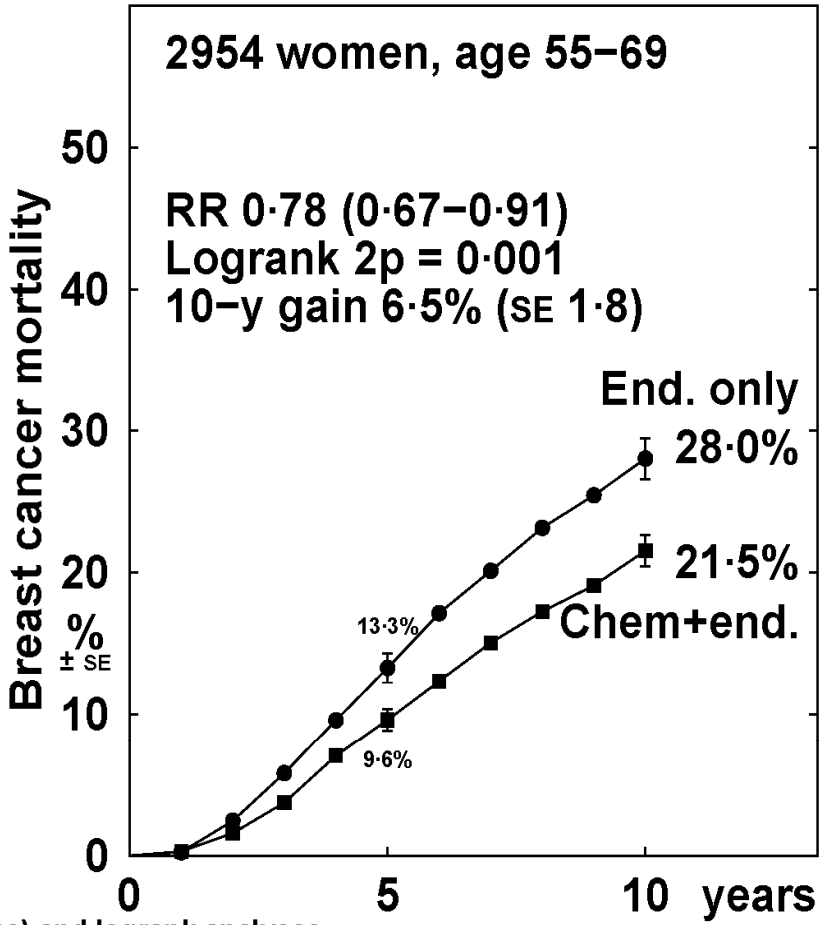
Halving big risks and halving small risks by chemotherapy

- **Proportional risk reduction does not depend much on age, ER status or nodal status (or on tumour grade or tumour diameter)**
- **Absolute risk reduction, however, depends on the prognosis – and, for ER+ disease, this is the prognosis with endocrine therapy**
- Information lacking on tumour gene expression and on quantitative immunohistochemistry

EBCTCG, Lancet 2012

Chemotherapy (anthracycline-based regimen or standard CMF) + 5 year endocrine therapy vs 5 year endocrine therapy only, ER+ disease only: by ENTRY AGE



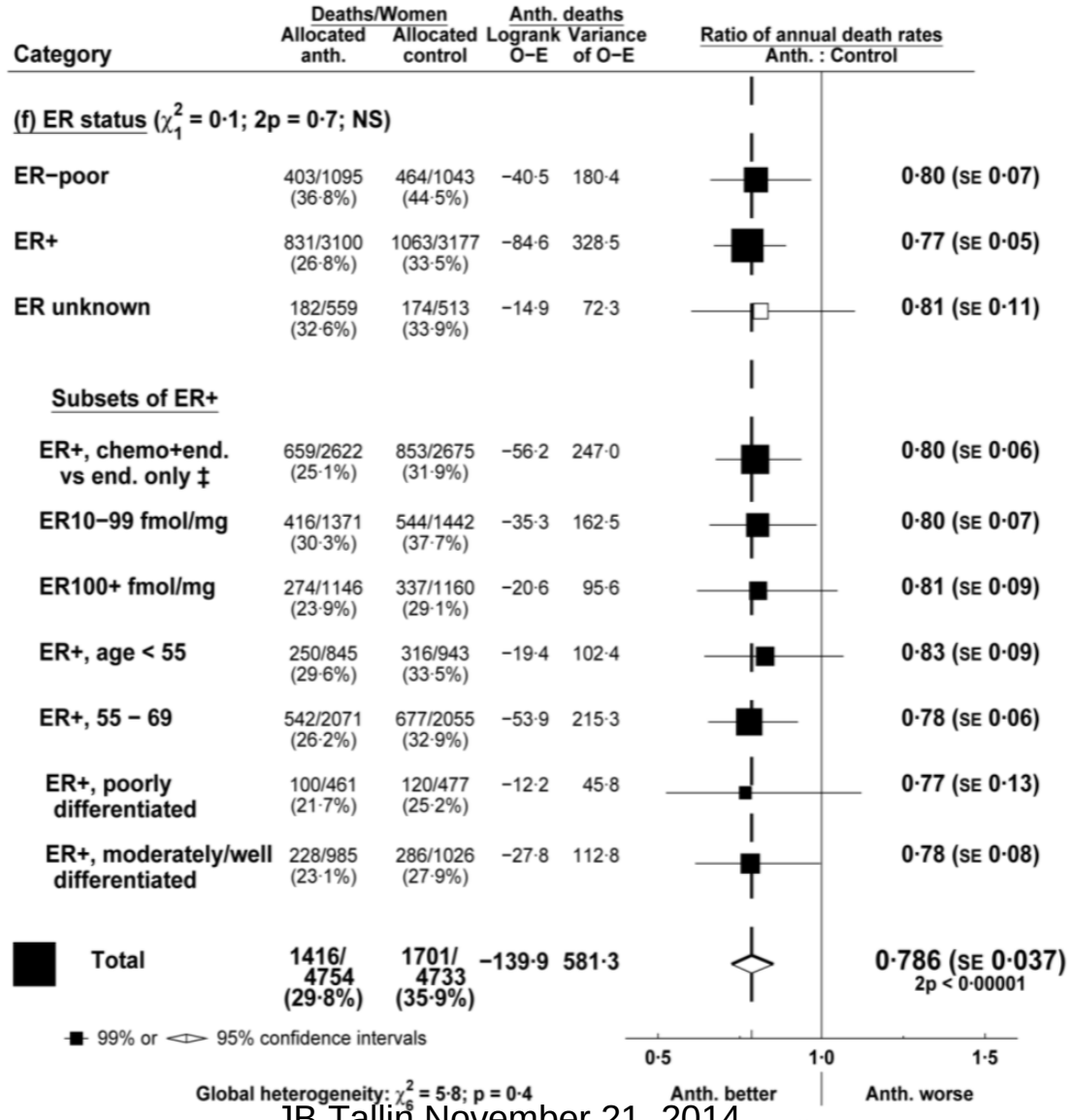


Death rates (% / year: total rate − rate in women without recurrence) and logrank analyses

Allocation	Years 0 − 4	Years 5 − 9	Year 10+	Years 0 − 4	Years 5 − 9	Year 10+
Chem+end.	1·72 SE 0·19	1·99 SE 0·23	1·77 SE 0·28	2·09 SE 0·16	2·88 SE 0·22	3·03 SE 0·31
End. only	2·20 SE 0·23	2·53 SE 0·28	1·69 SE 0·29	2·75 SE 0·23	3·96 SE 0·32	2·88 SE 0·35
Rate ratio	0·71 SE 0·14	0·65 SE 0·14	0·96 SE 0·24	0·70 SE 0·10	0·75 SE 0·10	1·03 SE 0·17
(O−E) / V	−13·0 / 37·8	−14·7 / 33·8	−0·6 / 16·2	−23·1 / 66·0	−19·7 / 69·4	1·0 / 34·5

EBCTCG, Lancet 2012

Breast cancer mortality ratio: any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ER STATUS and subsets of ER+



EBCTCG, Lancet 2011

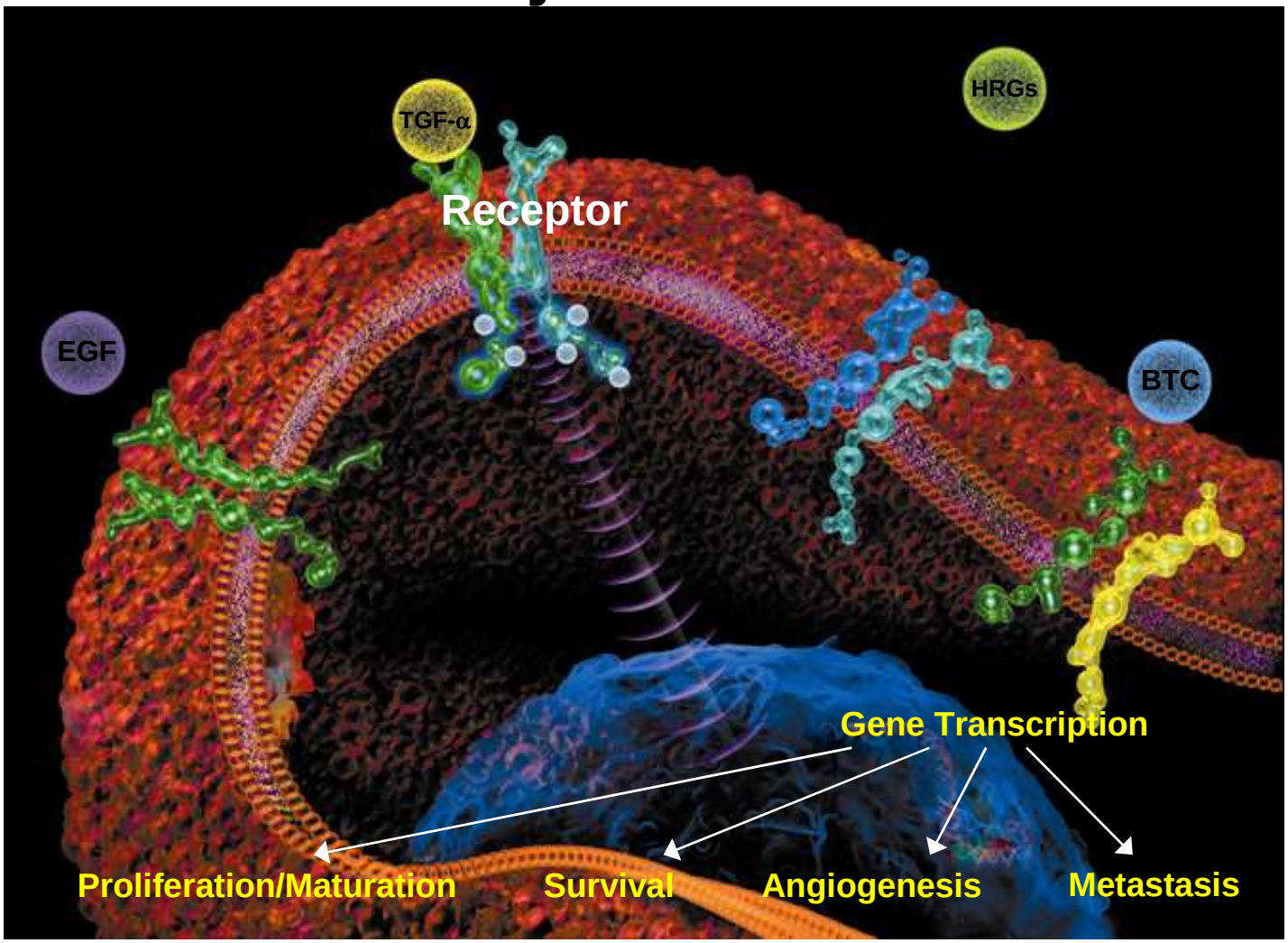
Dose dense therapies

A better way to deliver chemotherapy-same doses with G-CSF support but with a bi-weekly interval instead of the standard q three weeks?

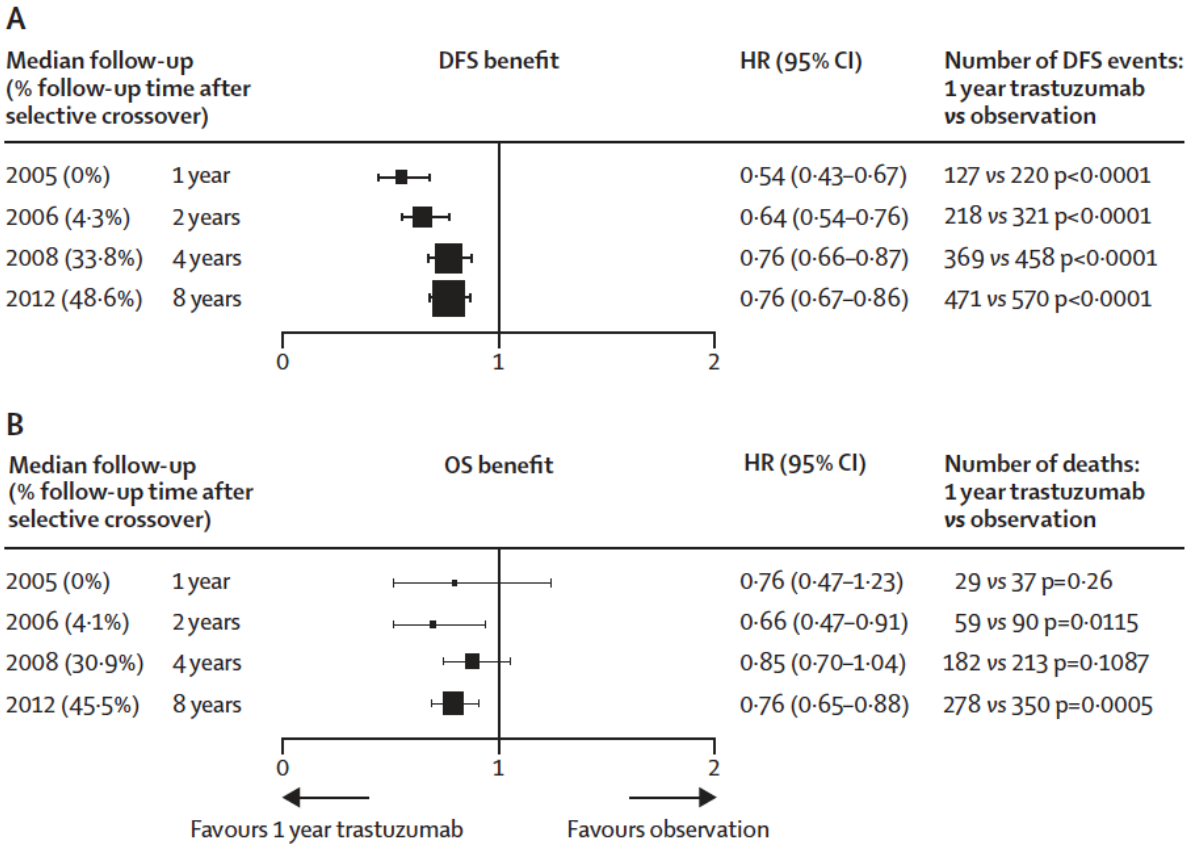
Bonilla et al, JNCI 2010

Survival gain

Her-2 (Her-2/neu, c-erbB2)
Her familjens funktioner



Huang et al, 1999. Woodburn, 1999. Slide from Pfizer

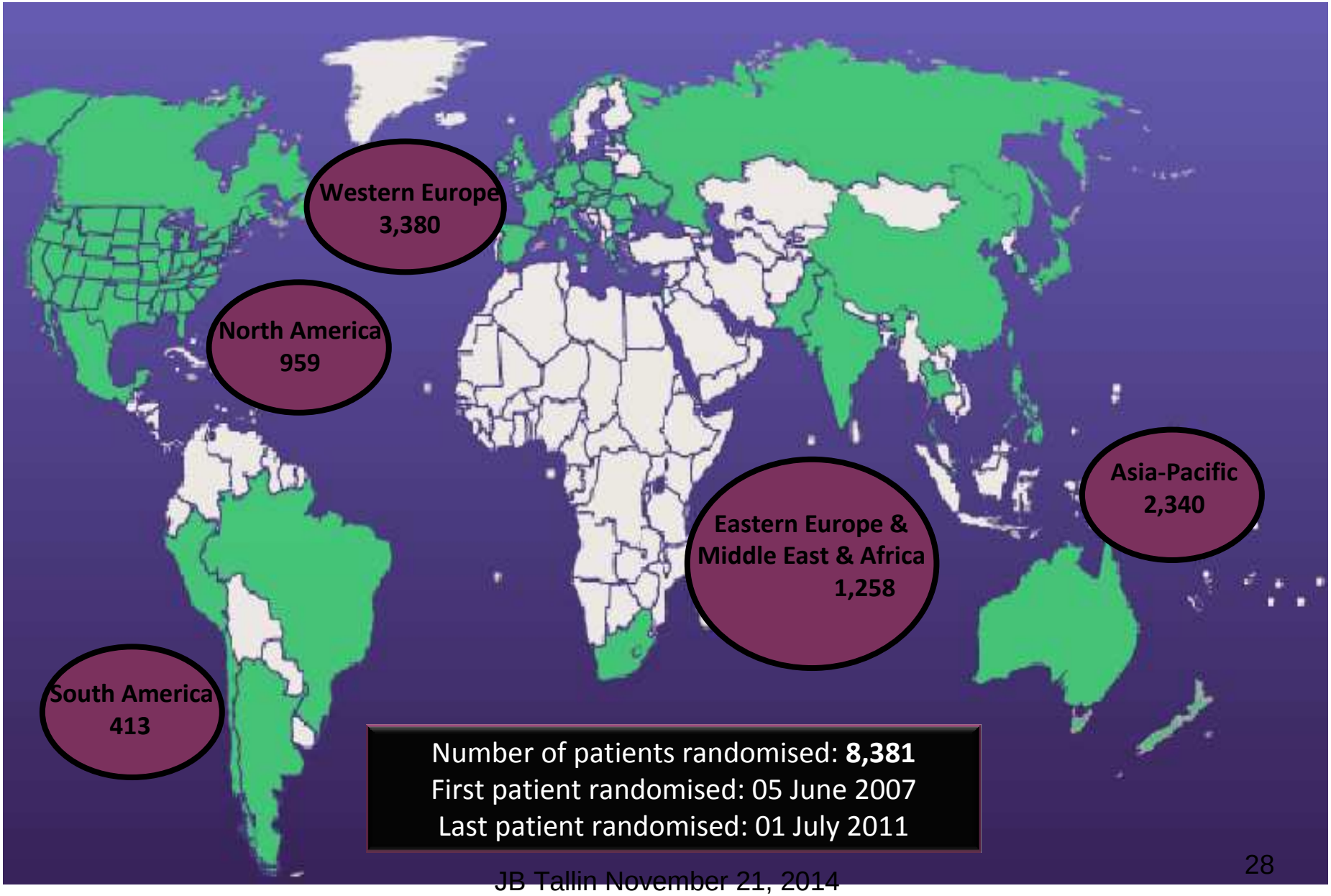


Hazard ratios and confidence intervals in a comparison of 1 year trastuzumab treatment versus observation (intention-to-treat analysis)

(A) Disease-free survival. (B) Overall survival. Results for 1, 2 and 4 years' median follow-up are found in references 1,3 and 4, respectively. These intention-to-treat analyses are affected by selected crossover of 884 (52%) of patients in the observation group who received trastuzumab after the first results were released in 2005. The number in parentheses show the percentage of follow-up time in the intention-to-treat analysis that was accrued after selective crossover for patients assigned to the observation group. DFS=disease-free survival HR=hazard ratio. OS=overall survival.

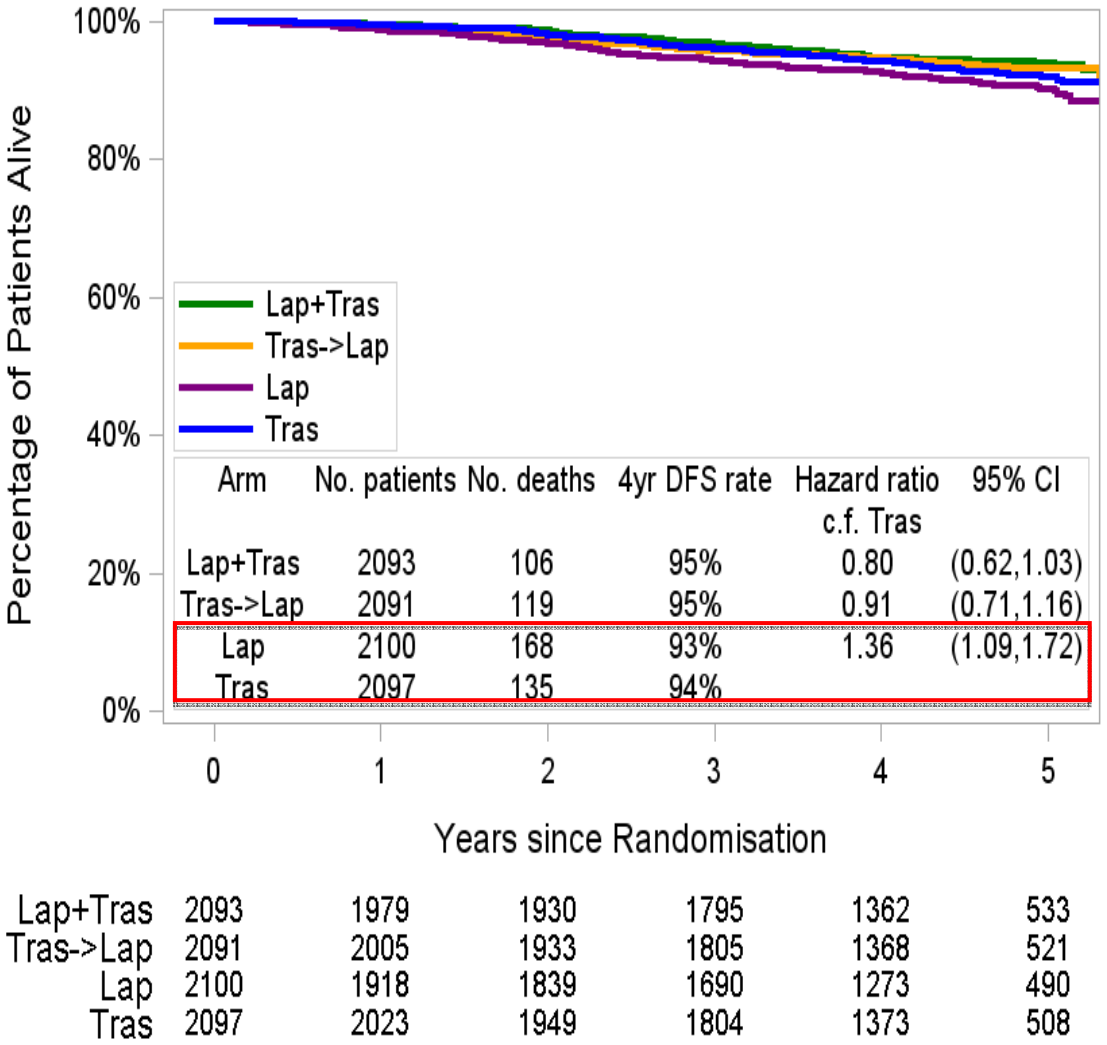
Goldhirsch et al., Lancet 382:1021-1028, 2013

ALTTO Recruitment



Slide from Prof Edith Perez 29-9-

Overall Survival (OS) Analysis

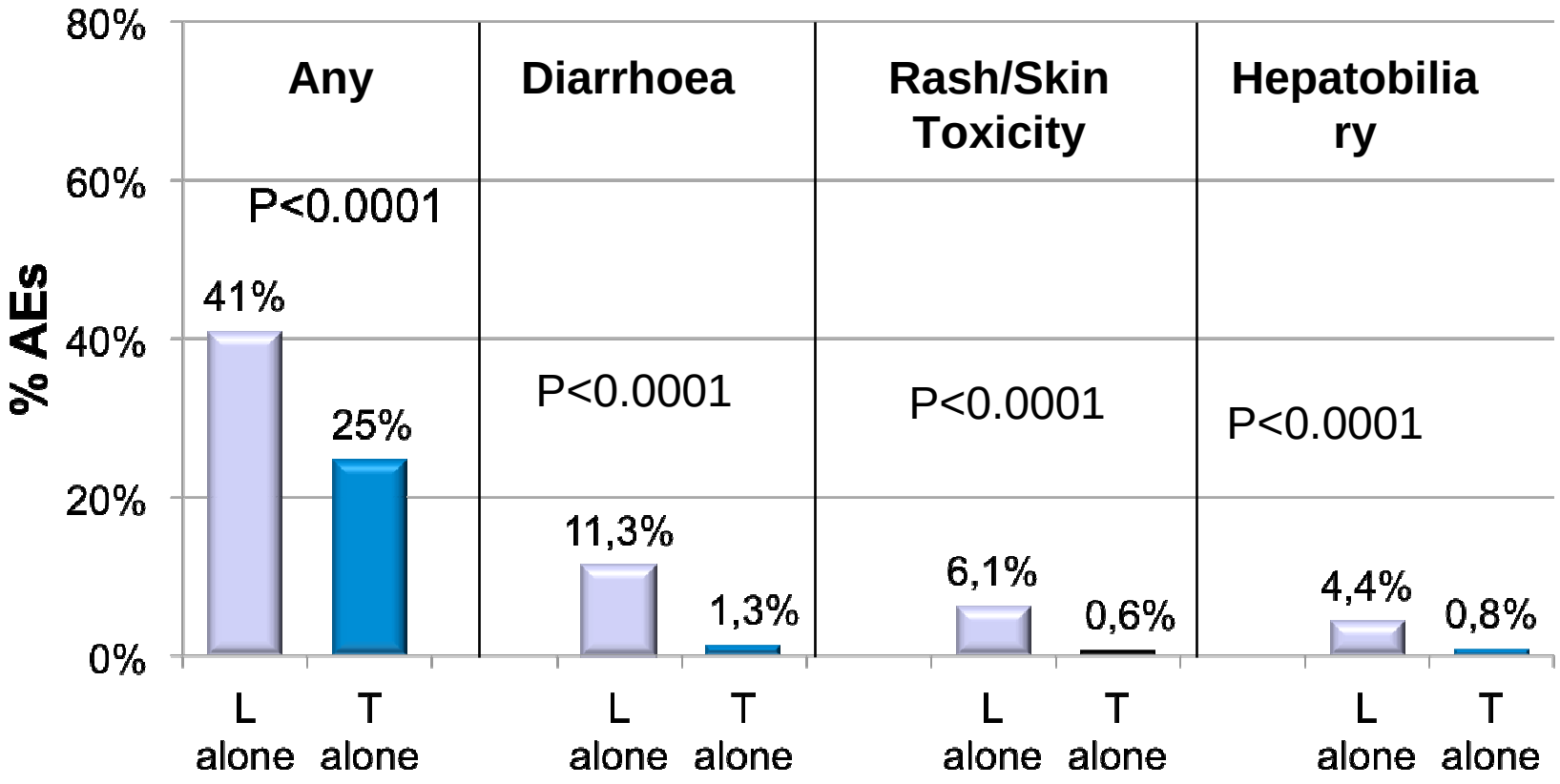


Arm	No. patients	No. deaths	4yr DFS rate	Hazard ratio c.f. Tras	95% CI
Lap+Tras	2093	106	95%	0.80	(0.62,1.03)
Tras->Lap	2091	119	95%	0.91	(0.71,1.16)
Lap	2100	168	93%	1.36	(1.09,1.72)
Tras	2097	135	94%		

Lap+Tras	2093	1979	1930	1795	1362	533
Tras->Lap	2091	2005	1933	1805	1368	521
Lap	2100	1918	1839	1690	1273	490
Tras	2097	2023	1949	1804	1373	508

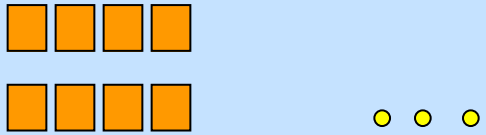
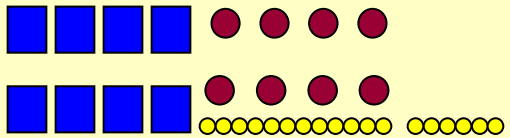
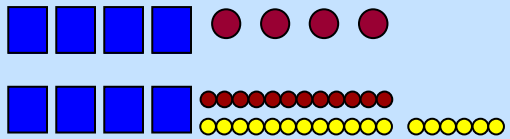
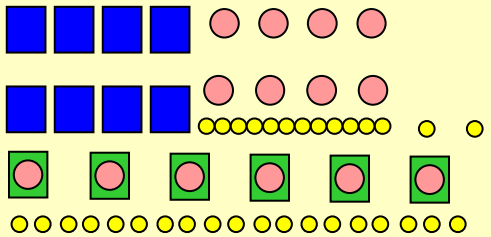
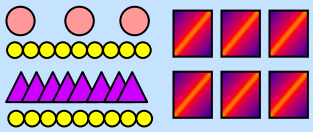
Slide from Prof Edith Perez 29-9-14

Main Differences in Grade 3-4 AEs by Treatment Arm



Slide from Prof Edith Perez 29-9-14

Adjuvant Trastuzumab BC Trials

		Severe CHF	Syst. Dysf.
HERA CT CT → Trast		0.6%	3.0%
NSABP B-31 AC → Ptx AC → Ptx+Trast		3.6%	15.9%
NCCTG N 9831 AC → Ptx AC → Ptx+Trast		2.5 / 3.3%	14 / 17 %
BCIRG 006 AC → Docet AC → Docet+Trast TC+Trast → Trast		1.9 % 0.4 %	18.1 % 8.6 %
FinHER Docet → +/- Trast Vinblast → +/- Trast		0 %	3.5 %

Generous gift from Assoc Prof. Suter

”For middle-aged women with ER-positive disease (the commonest type of breast cancer), the breast cancer mortality rate throughout the next 15 years would be approximately halved by 6 months of anthracycline-based chemotherapy (with a combination such as FAC or FEC) followed by 5 years of adjuvant tamoxifen.”

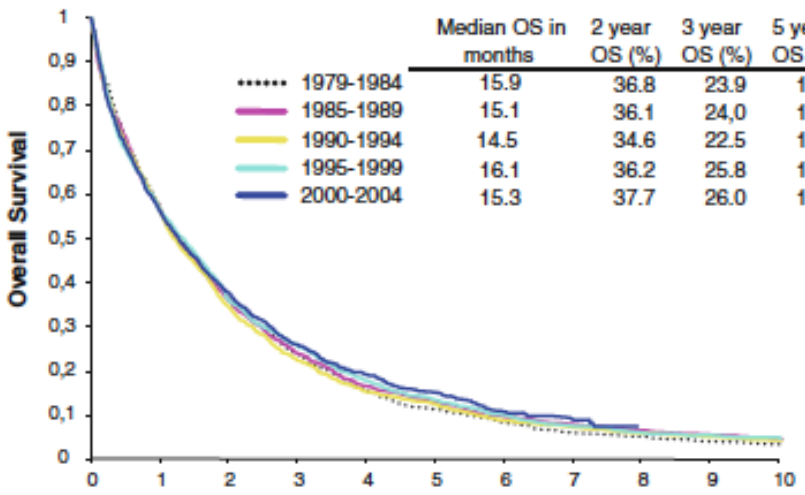
Lancet, EBCTCG 2005

BREAST CANCER METASTATIC DISEASE

ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)

Annals of Oncology and The Breast On line September 2014

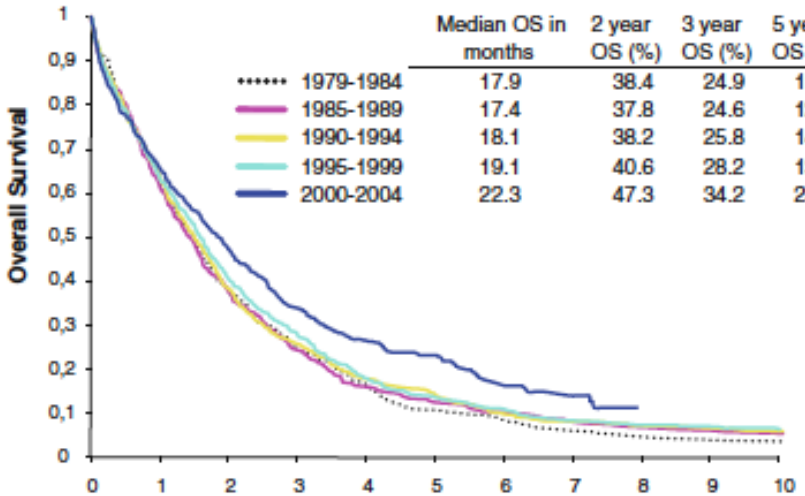
A



	Median OS in months	2 year OS (%)	3 year OS (%)	5 year OS (%)
1979-1984	15.9	36.8	23.9	11.4
1985-1989	15.1	36.1	24,0	12.9
1990-1994	14.5	34.6	22.5	12.5
1995-1999	16.1	36.2	25.8	13.6
2000-2004	15.3	37.7	26.0	15.2

No. at risk						
1979-84	899	332	143	75	48	32
1985-89	1078	390	180	105	72	51
1990-94	1158	402	179	103	70	51
1995-99	1196	435	216	122	74	47
2000-04	1132	429	174	52	11	0

B

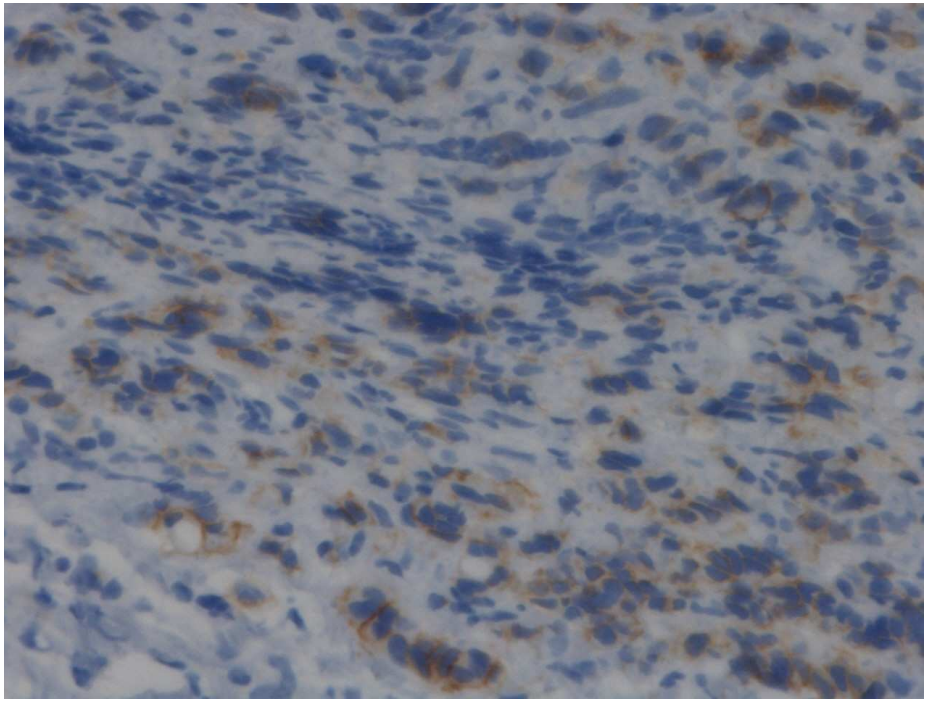


	Median OS in months	2 year OS (%)	3 year OS (%)	5 year OS (%)
1979-1984	17.9	38.4	24.9	11.1
1985-1989	17.4	37.8	24.6	12.8
1990-1994	18.1	38.2	25.8	14.4
1995-1999	19.1	40.6	28.2	13.8
2000-2004	22.3	47.3	34.2	23.3

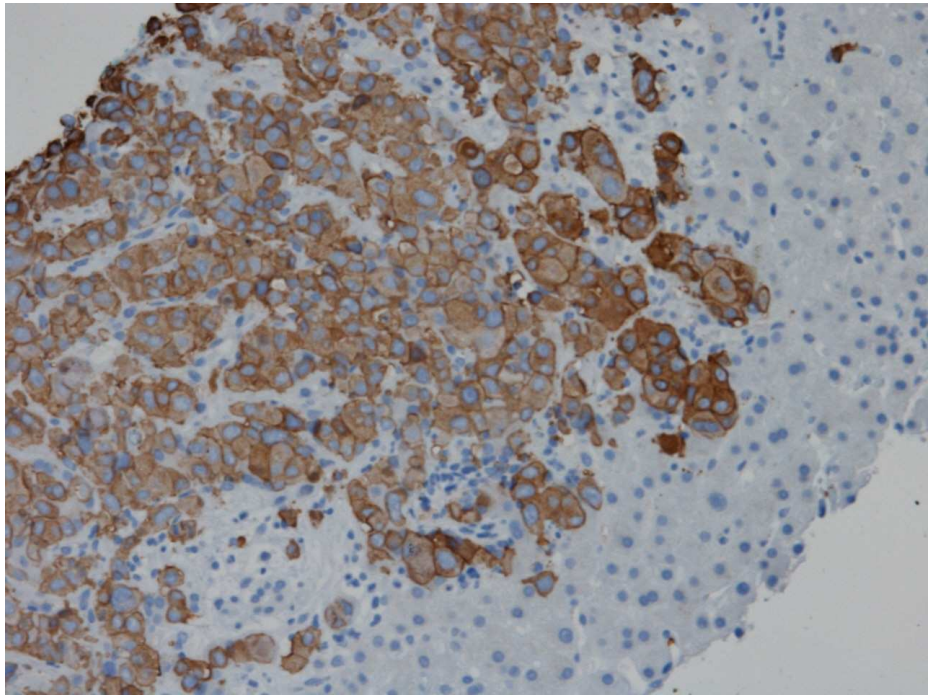
No. at risk						
1979-84	362	140	62	32	19	15
1985-89	439	167	72	46	32	26
1990-94	492	189	89	50	37	31
1995-99	515	211	94	58	39	28
2000-04	488	233	108	37	9	0

Foukakis et al, Breast Cancer Research and Treatment, 2011

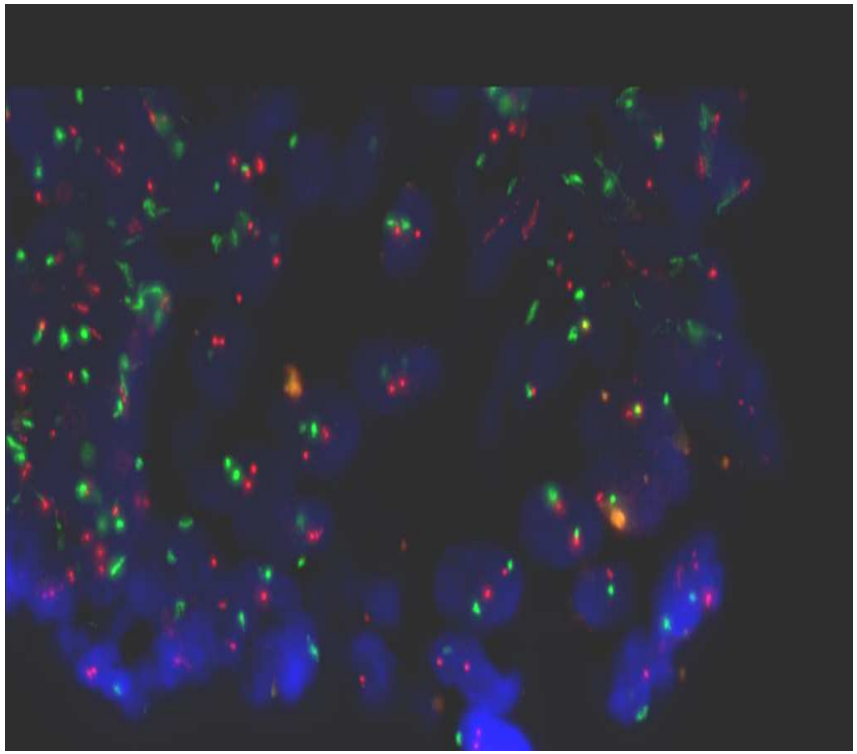
Ax LN core



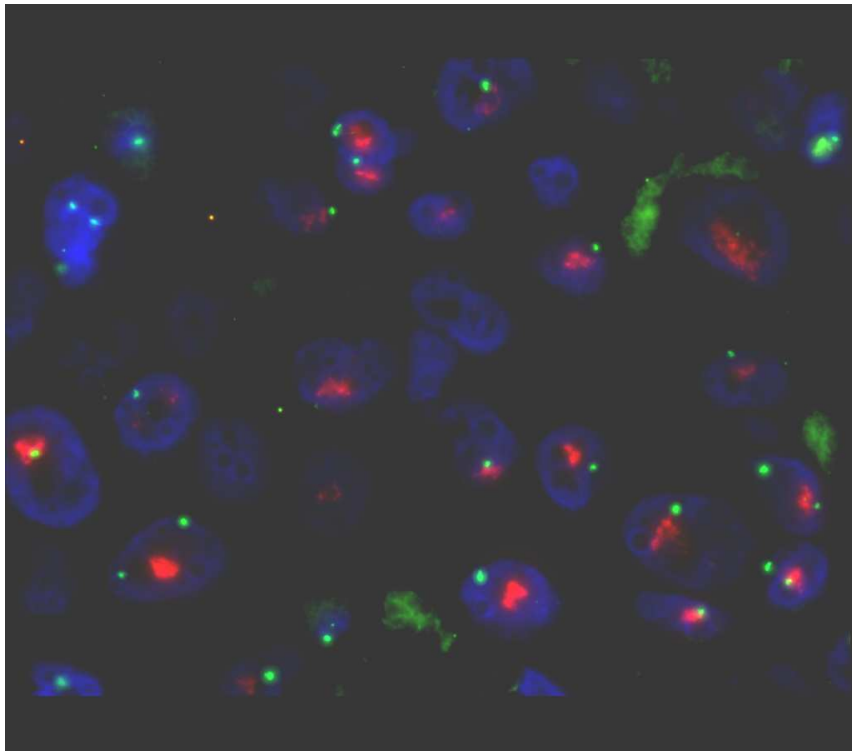
Liver core



Ax LN



Liver



Prospective studies comparing on ER & PR and HER-2 during metastatic development

By taken biopsies, when you have a “radiological relapse of breast cancer”, you change management in 1/6- 1/7 patient

(Thompson et al, 2010, Amir et al, 2011)

Retrospective studies

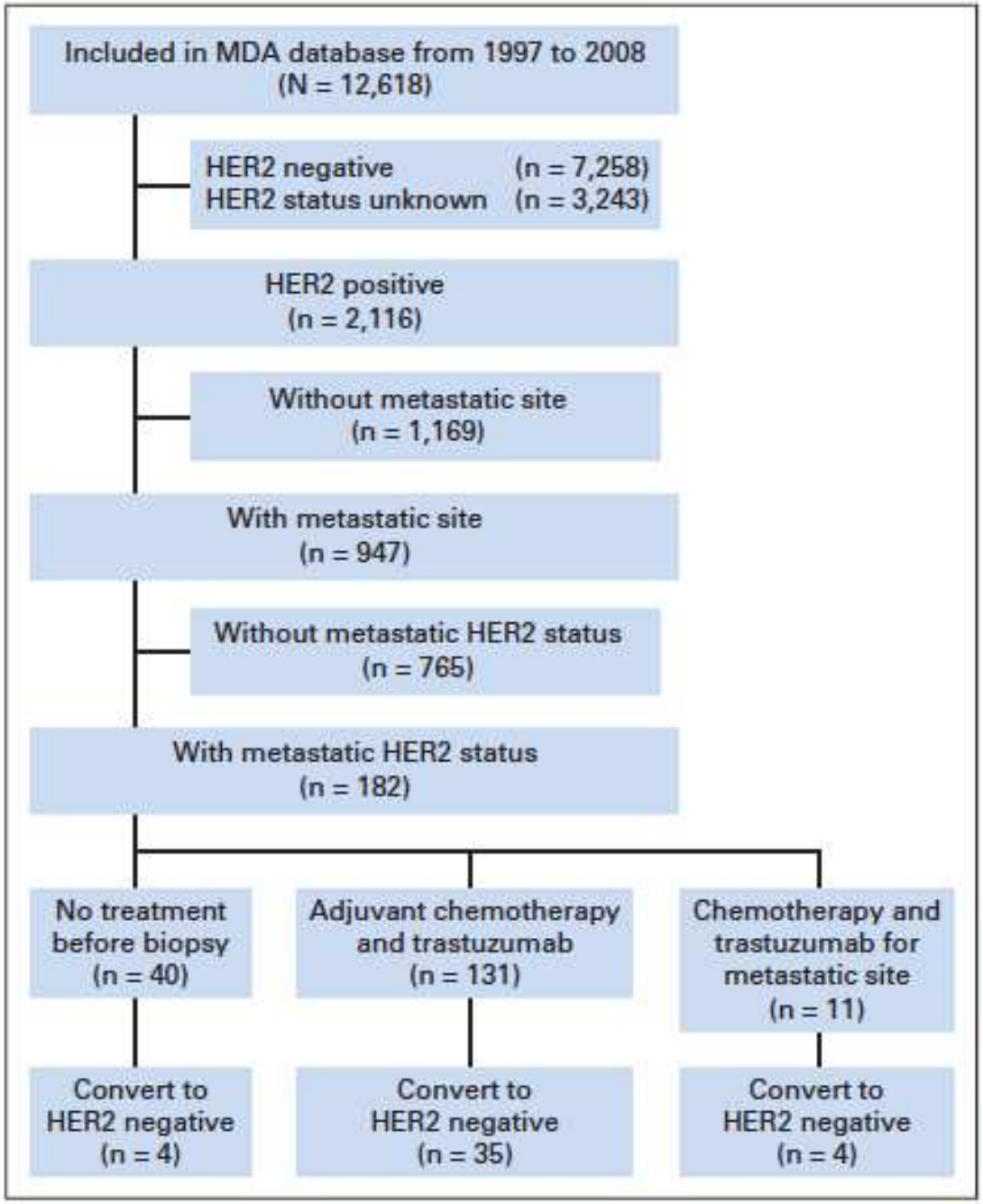


Fig 1. Study diagram. HER2, human epidermal growth factor receptor 2; MDA, MD Anderson Cancer Center.

Niikura et al, JCO on line 2011

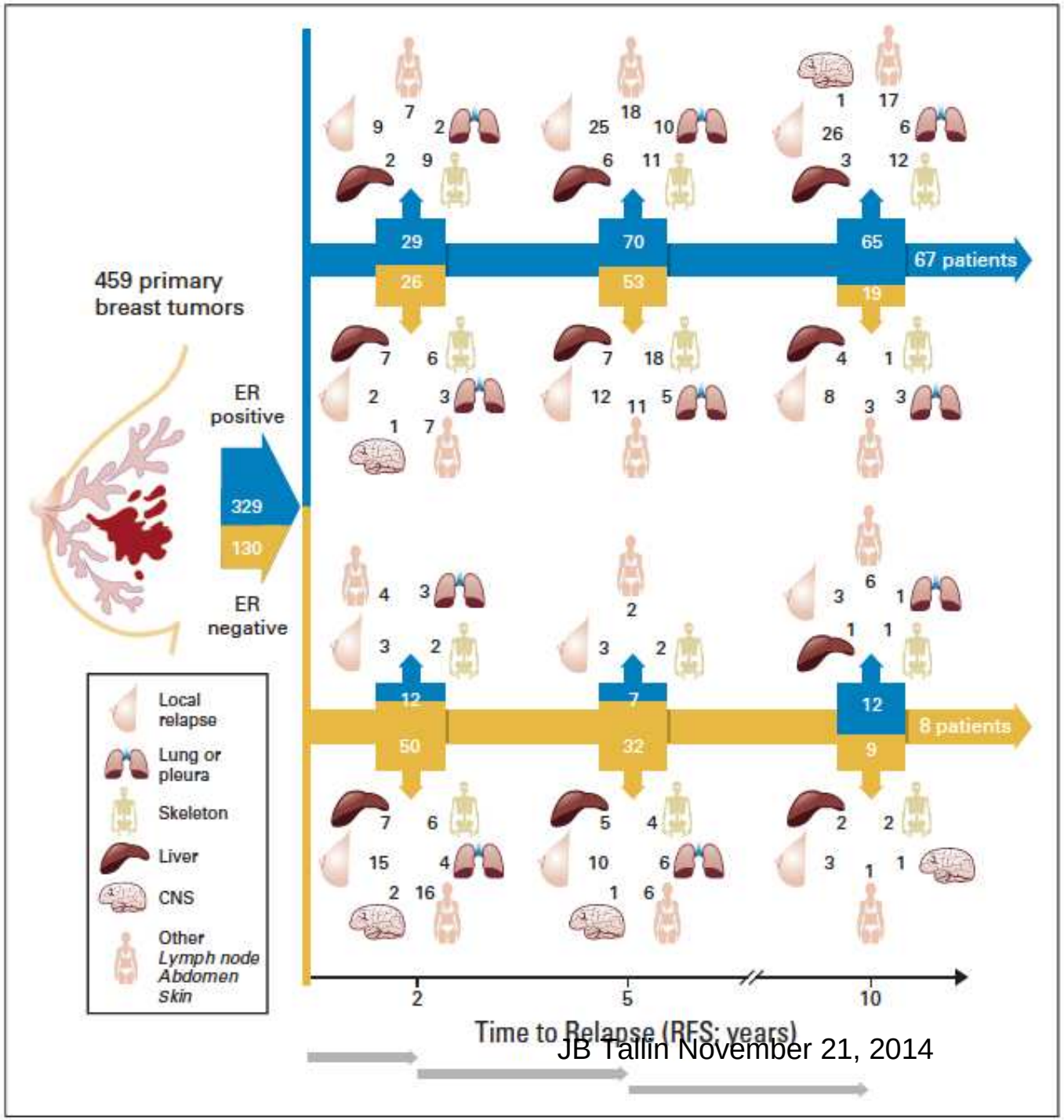
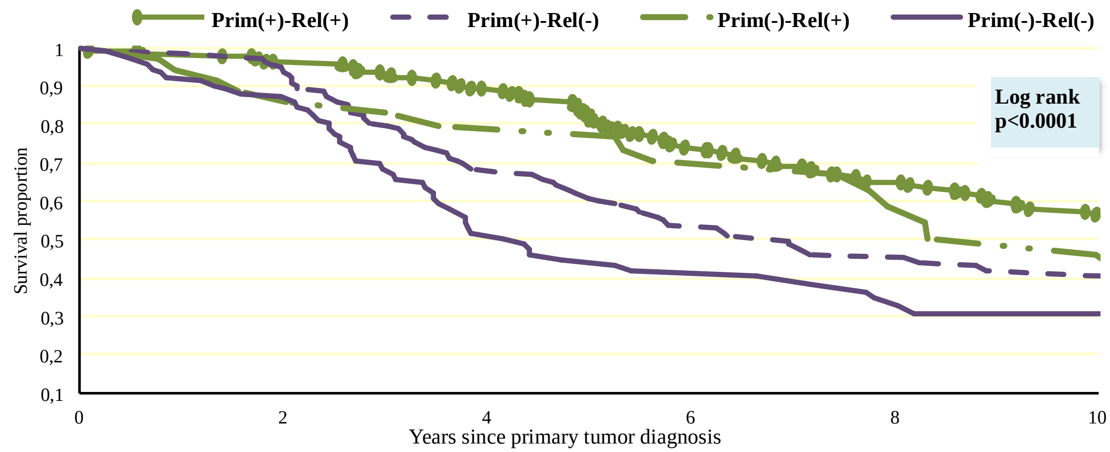


Fig 2. Patients by intraindividual estrogen receptor (ER) status (in primary tumor and first diagnosed site of relapse) were stratified according to relapse-free survival (RFS) at ≤ 2, 5, and 10 years. The sites of relapse were grouped into local relapse (ipsilateral breast), skeleton, lung and pleura combined, liver, CNS, or other (mainly defined as lymph node, abdomen, or skin).

Lindström/Karlsson et al, JCO 2012

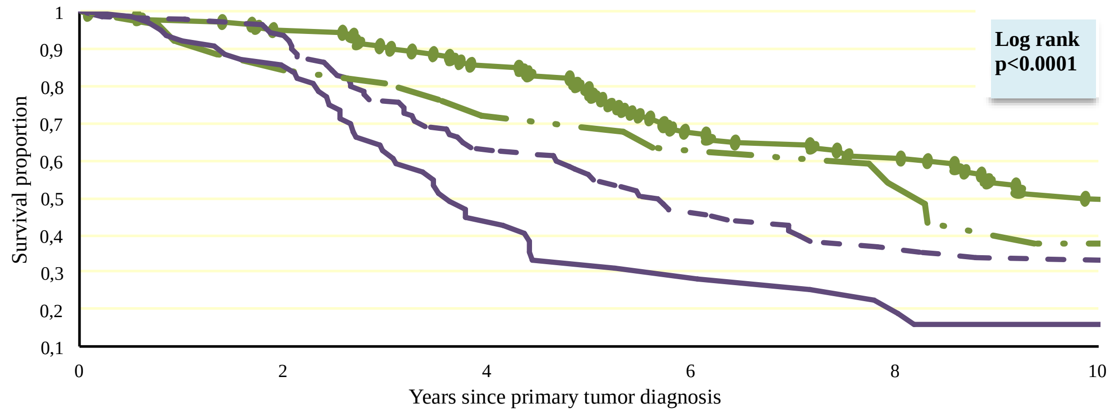
Overall survival
from the time of primary tumour diagnosis to death or censoring contrasting intra-patient ER status

Local and systemic relapses included



20 of 36 pts gaining Er+ received endocrine therapy

Only systemic relapses included



Lindström/Karlsson et al Journal of Clinical Oncology 2012

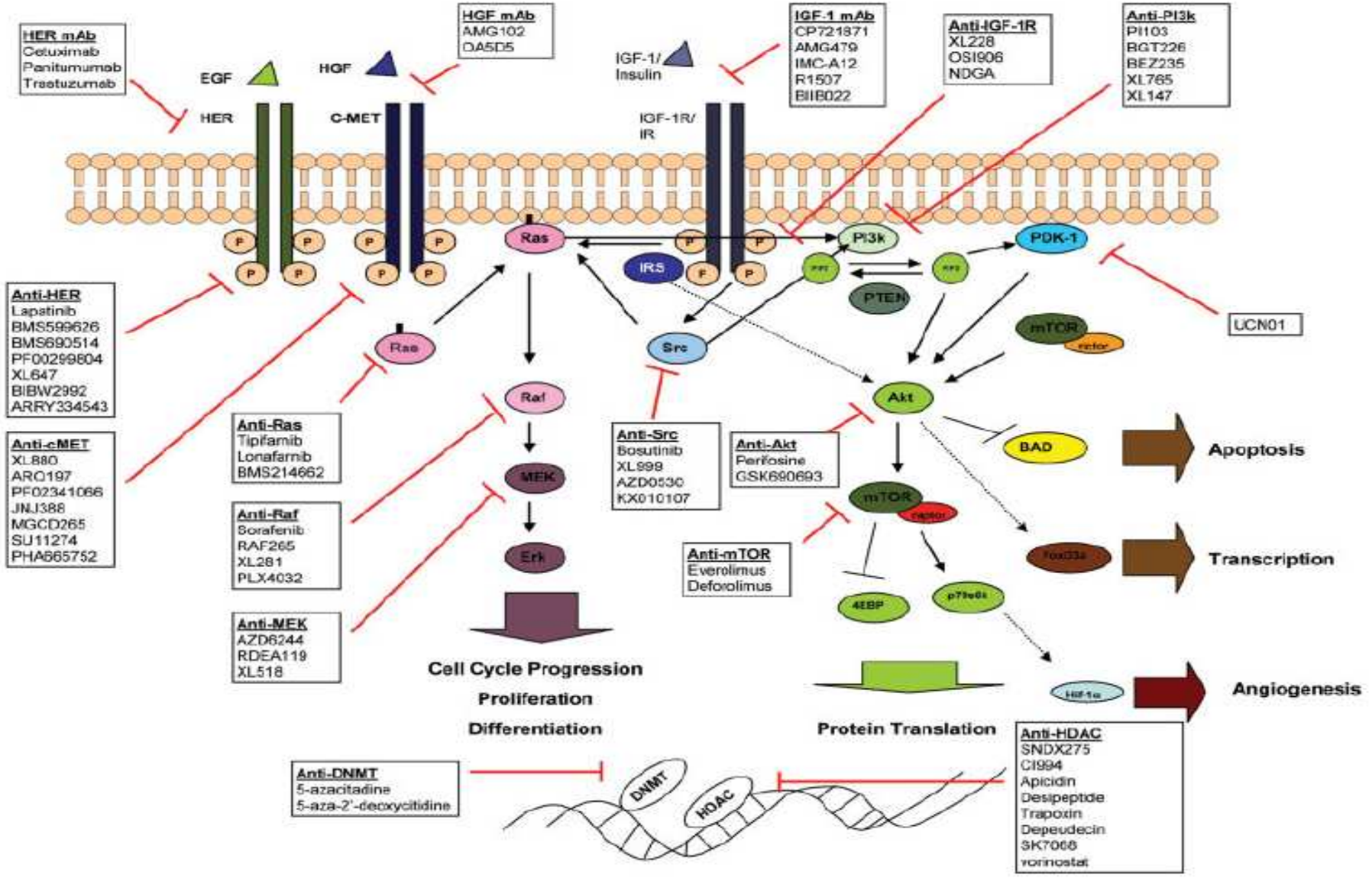


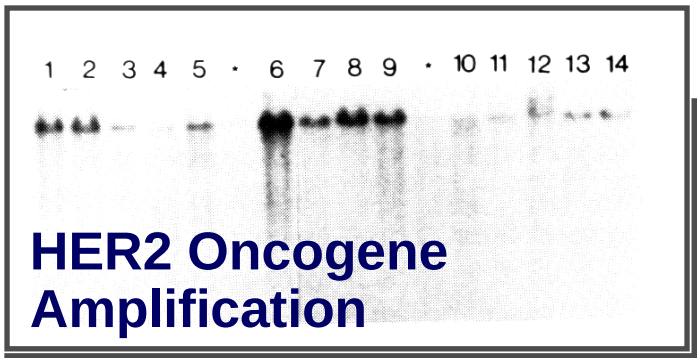
FIGURE 1. Depicted are the cellular signaling pathways involved in the proliferation, angiogenesis, and differentiation in neoplasms with the targets amenable to therapeutic interventions in cancer therapy. Membrane-bound human epidermal growth factor receptors (HER), c-MET, and insulin-like growth factor 1 receptor (IGF-1R) mediate mitogenic signals from extracellular ligands, such as epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin growth factors (IGF), respectively. The Ras/Raf/MEK/Erk (mitogen-activated protein kinase, MAPK) and PI3k/Akt/mTOR pathways are major intracellular axes that regulate intracellular signaling traffic. DNA methytransferases (DNMT) and histone deacetylases (HDAC) are "epigenetic switches" that modulate the expression of oncogenes and tumor suppressor genes. The agents targeting the signaling proteins are indicated in boxes.

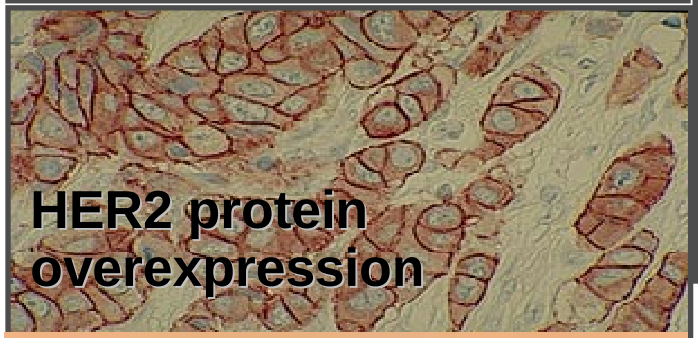
Ma & Adjei, CA Cancer J Clin 59:111-137, 2009

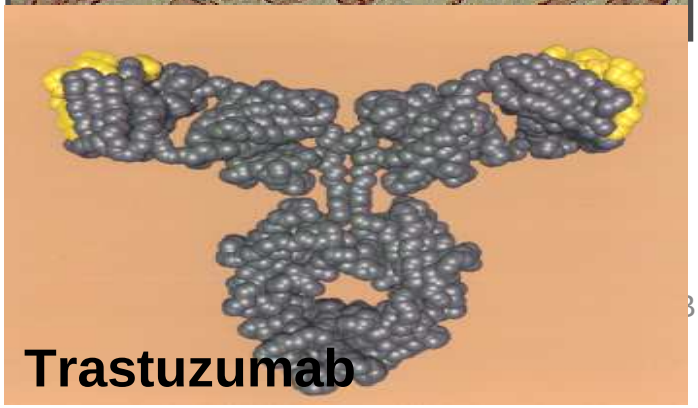
HER-2/neu positive metastatic breast cancer

Breast Cancer

From Slamon et al, Science1987

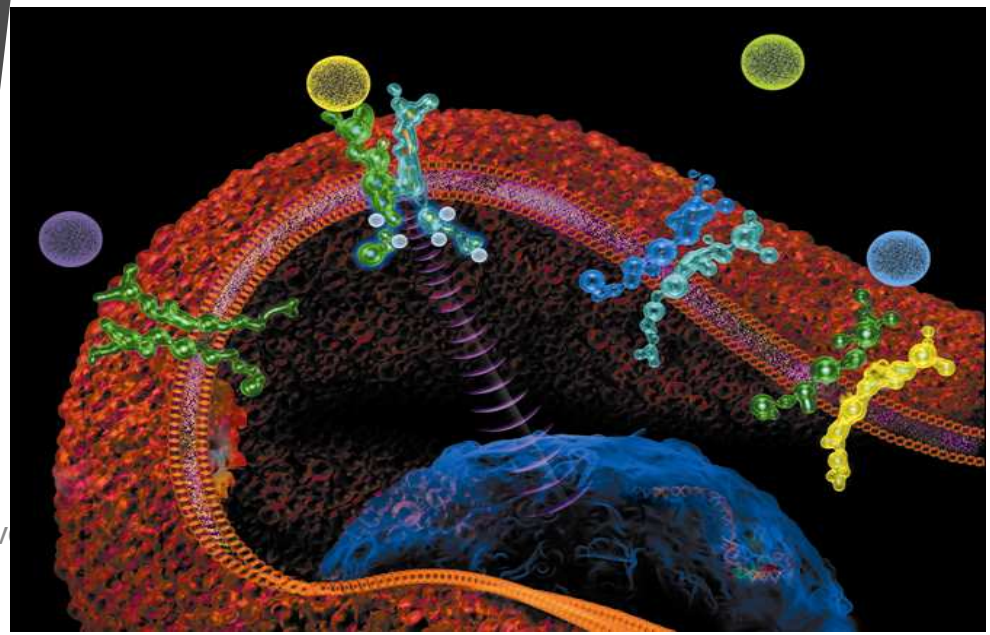






Shortened Median Survival

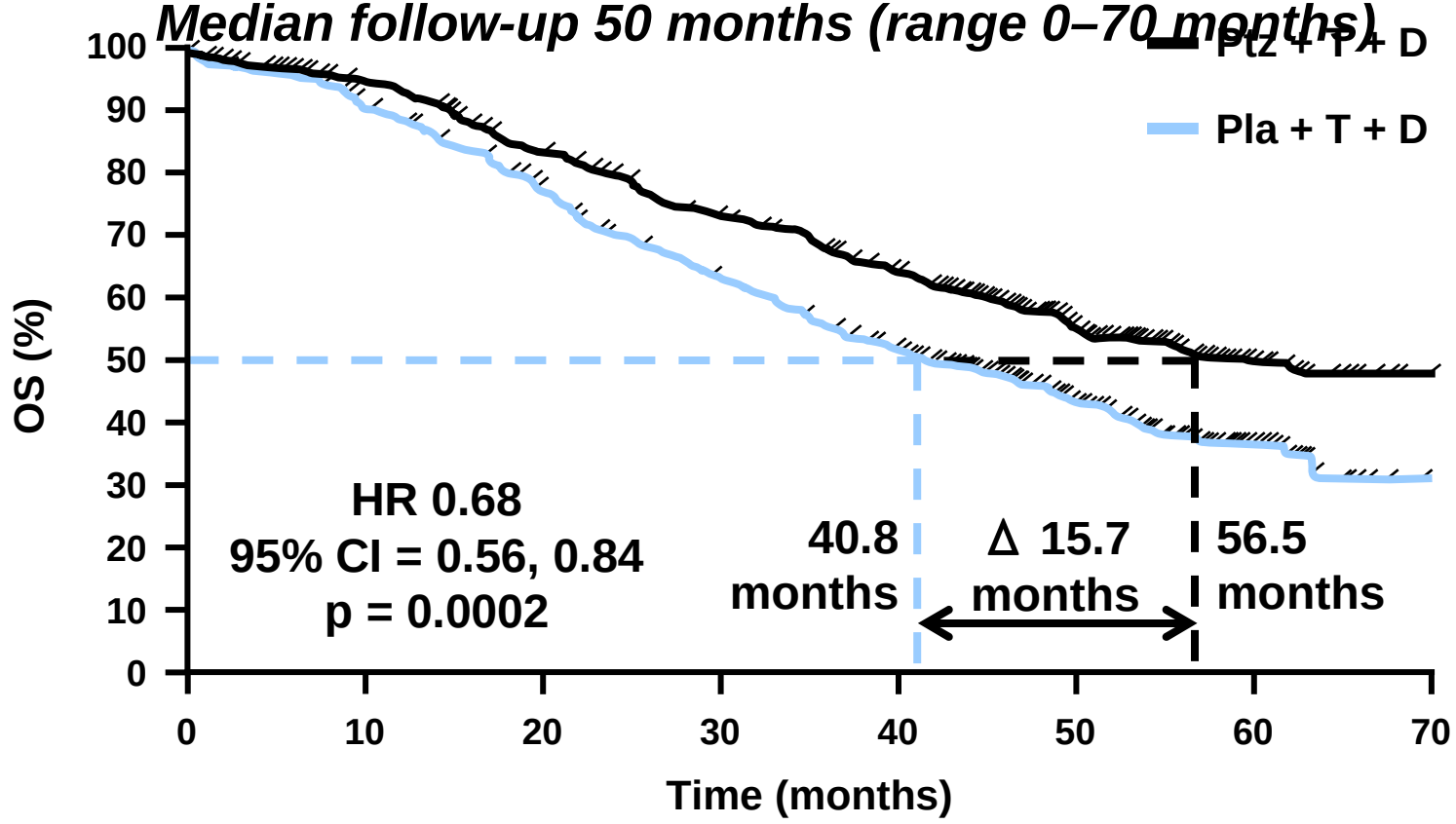
HER2 overexpressing	3 yrs
HER2 normal	6 - 7 yrs



Trastuzumab+ pertuzumab+ docetaxel – 15.7 månaders (vs trast + doc) medianöverlevnadsvinst

FINAL OS Analysis

Median follow-up 50 months (range 0–70 months)

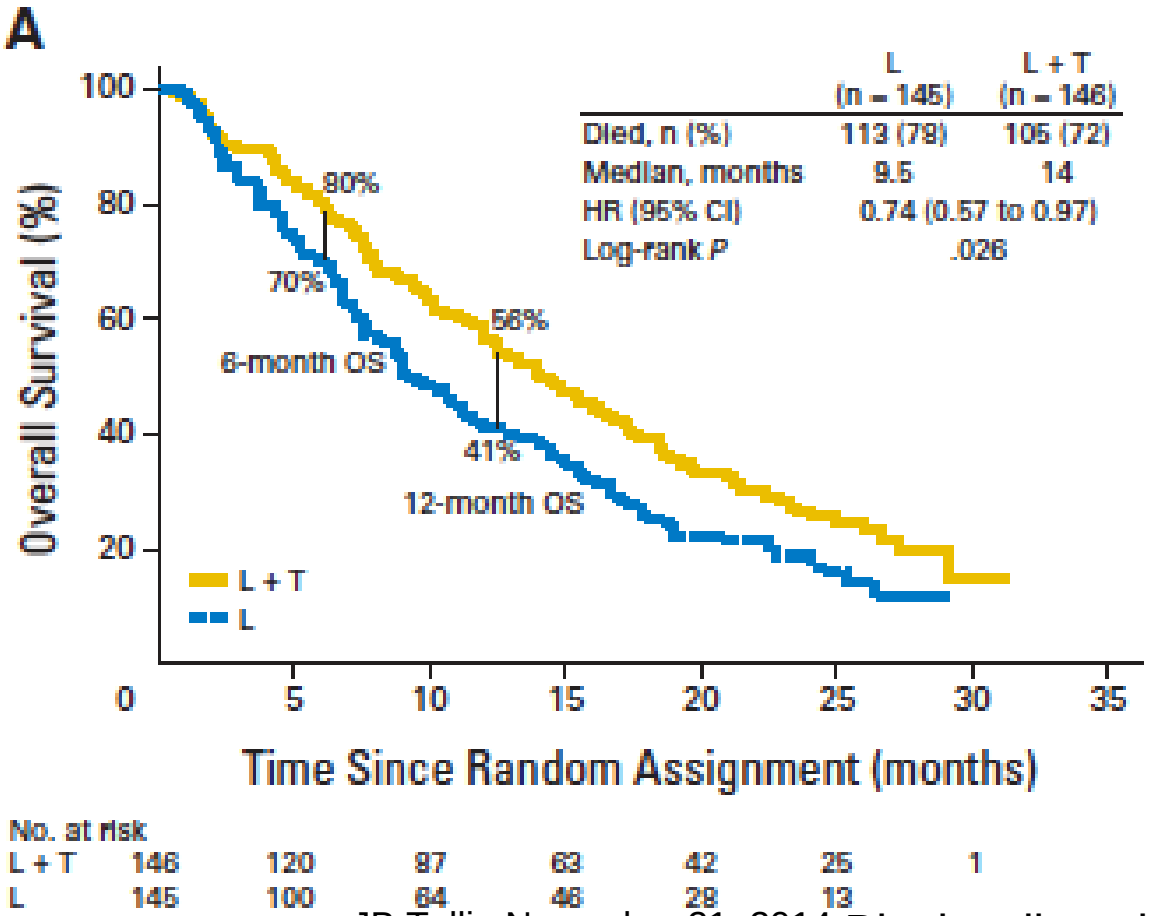


n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

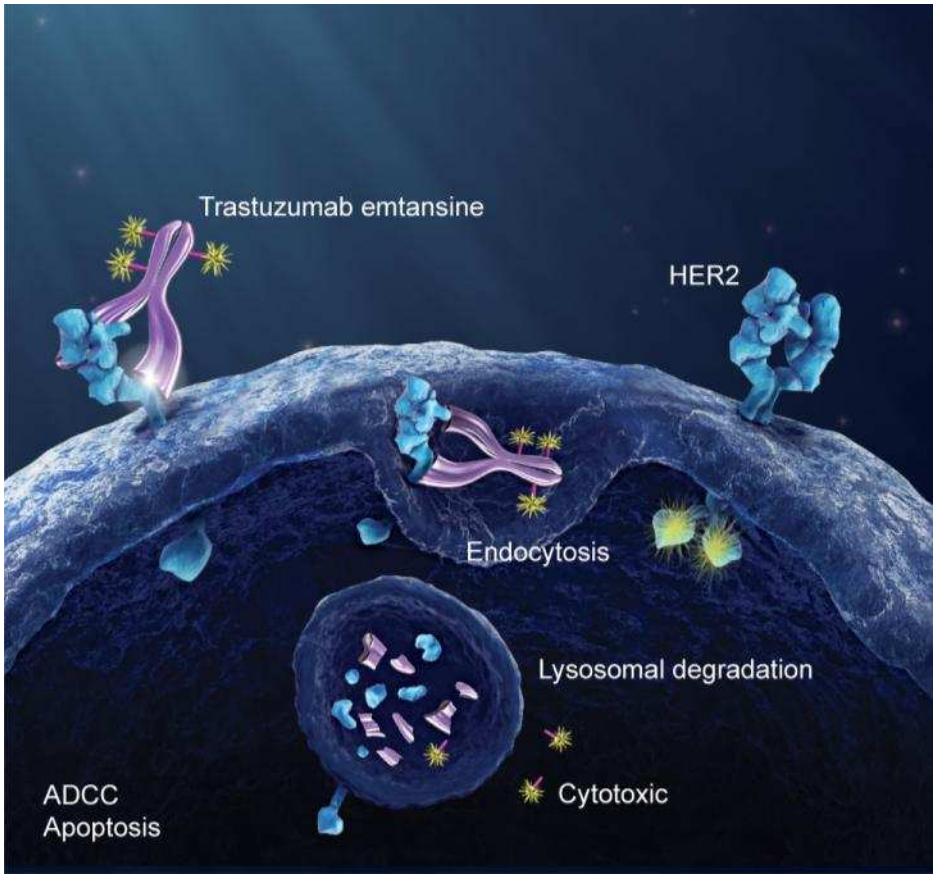
ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Slide from Prof Sandra Swain 45
28-9-14, ESMO 2014

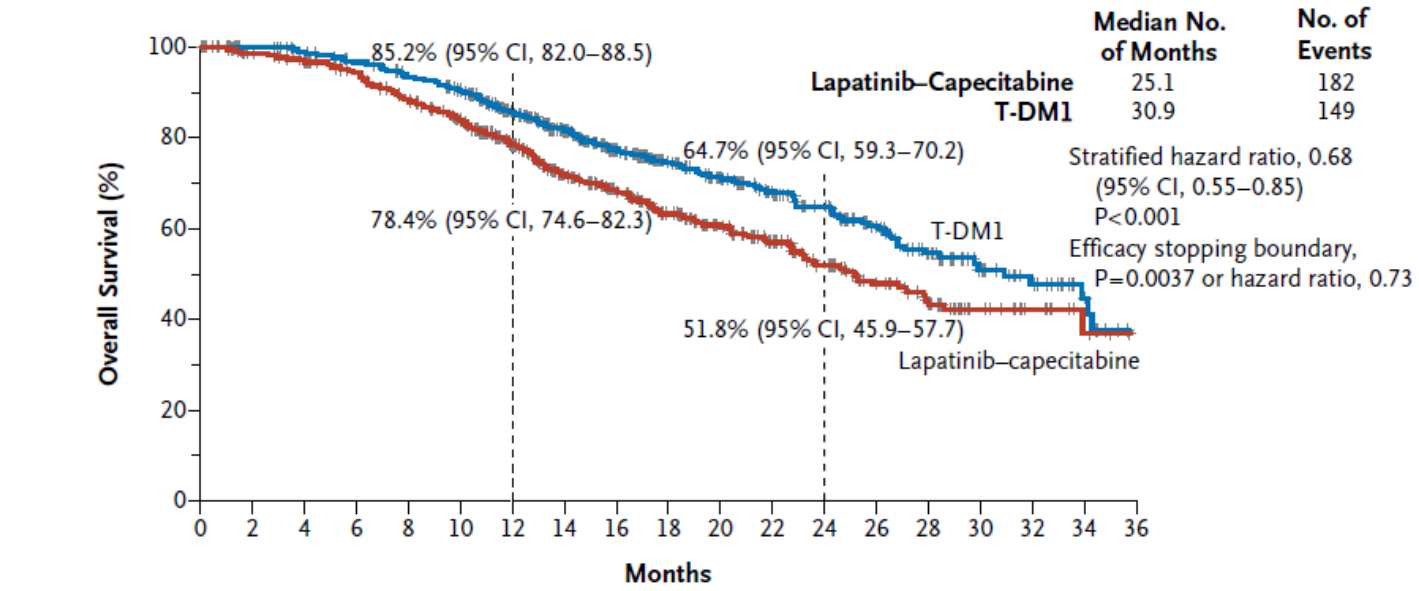
Double blockade, trastuzumab + lapatinib, after failure on previous anti-Her-2 therapy



Other HER-2 interacting drugs; lapatinib, neratinib pertuzumab, TDM-1

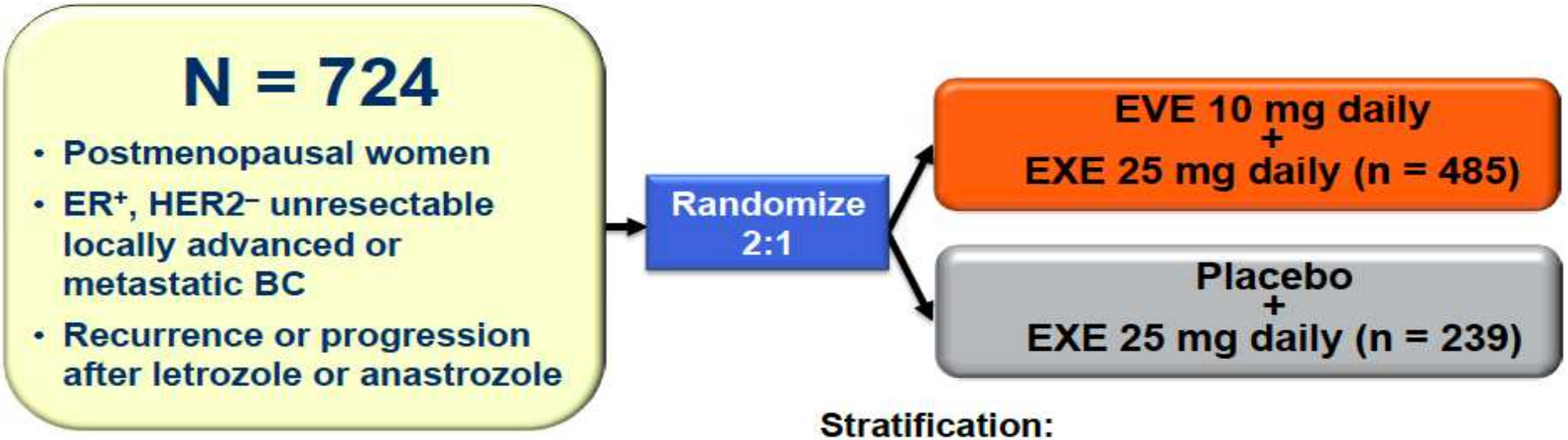


Efter progress, trastuzumab-emtansin, 5,8 månaders medianöverlevnadsvinst



Verma et al., NEJM online 2012

BOLERO-2: Study Design



Stratification:

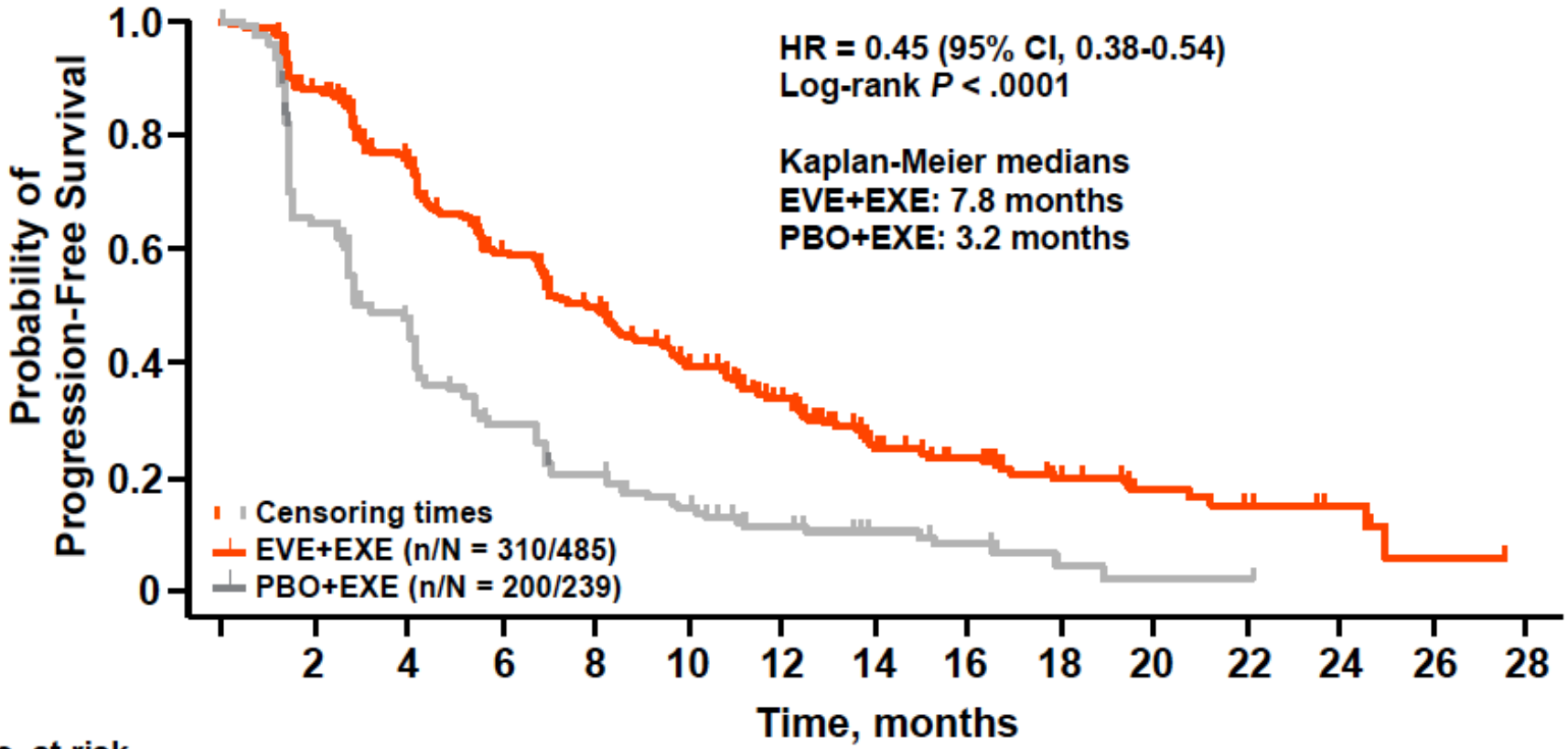
- **Sensitivity to prior hormone therapy**
- Presence of visceral metastases

Endpoints

- **Primary**: PFS (local assessment)
- **Secondary**: **OS**, ORR, CBR, QOL, safety, PK
- **Exploratory**: Biomarkers

Piccart et al, EBCC, Glasgow 2014

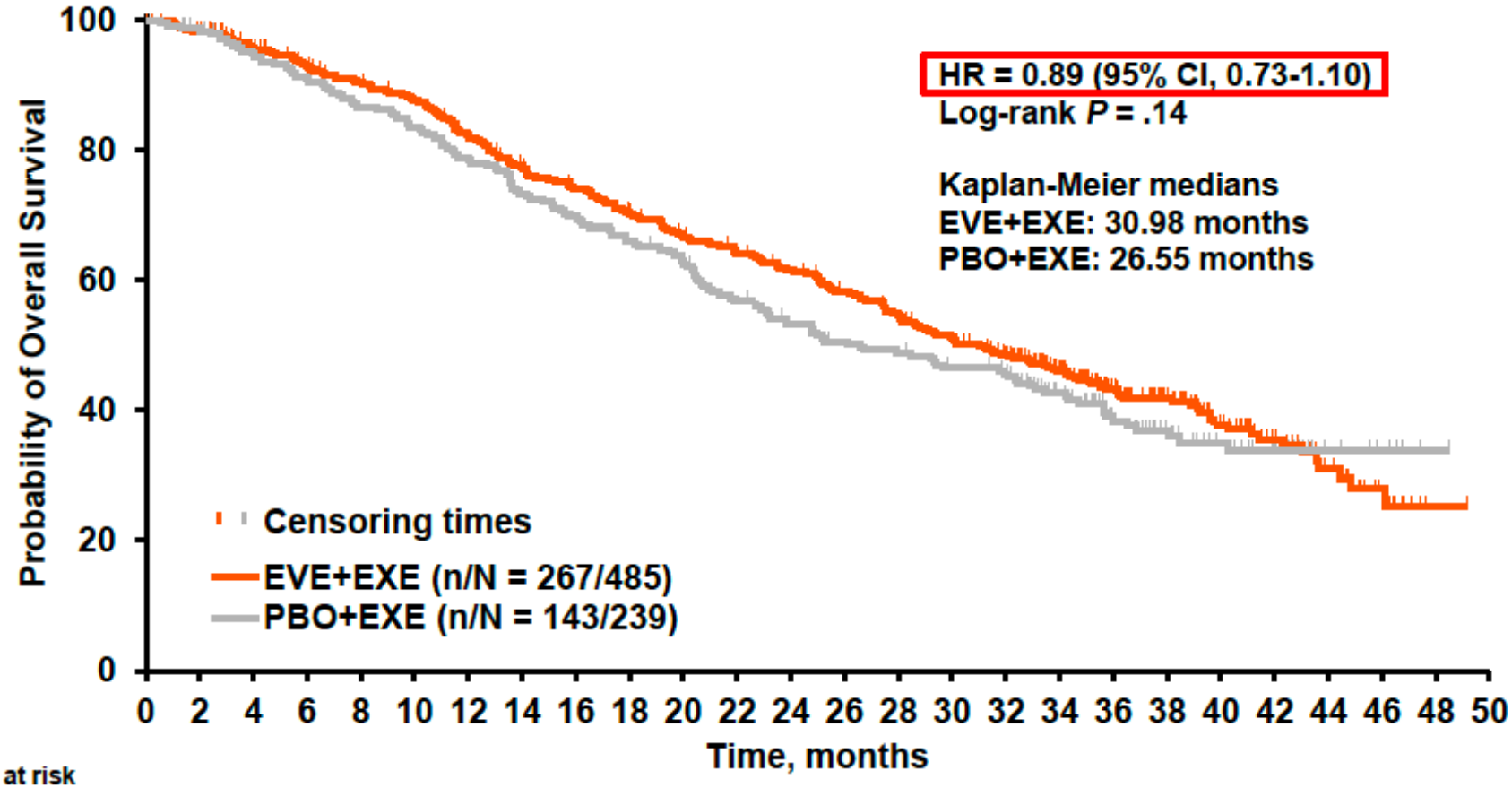
BOLERO-2 Met Primary Endpoint: Final PFS Analysis (18-mo) Based on Local Assessment Demonstrated a 4.6-mo Prolongation of PFS



No. at risk															
EVE+EXE	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
PBO+EXE	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

Piccart et al, EBCC, Glasgow 2014

BOLERO-2 (39-mo): Final OS Analysis



No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

One-sided *P* value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.

Piccart et al, EBCC, Glasgow

Abstract CT101

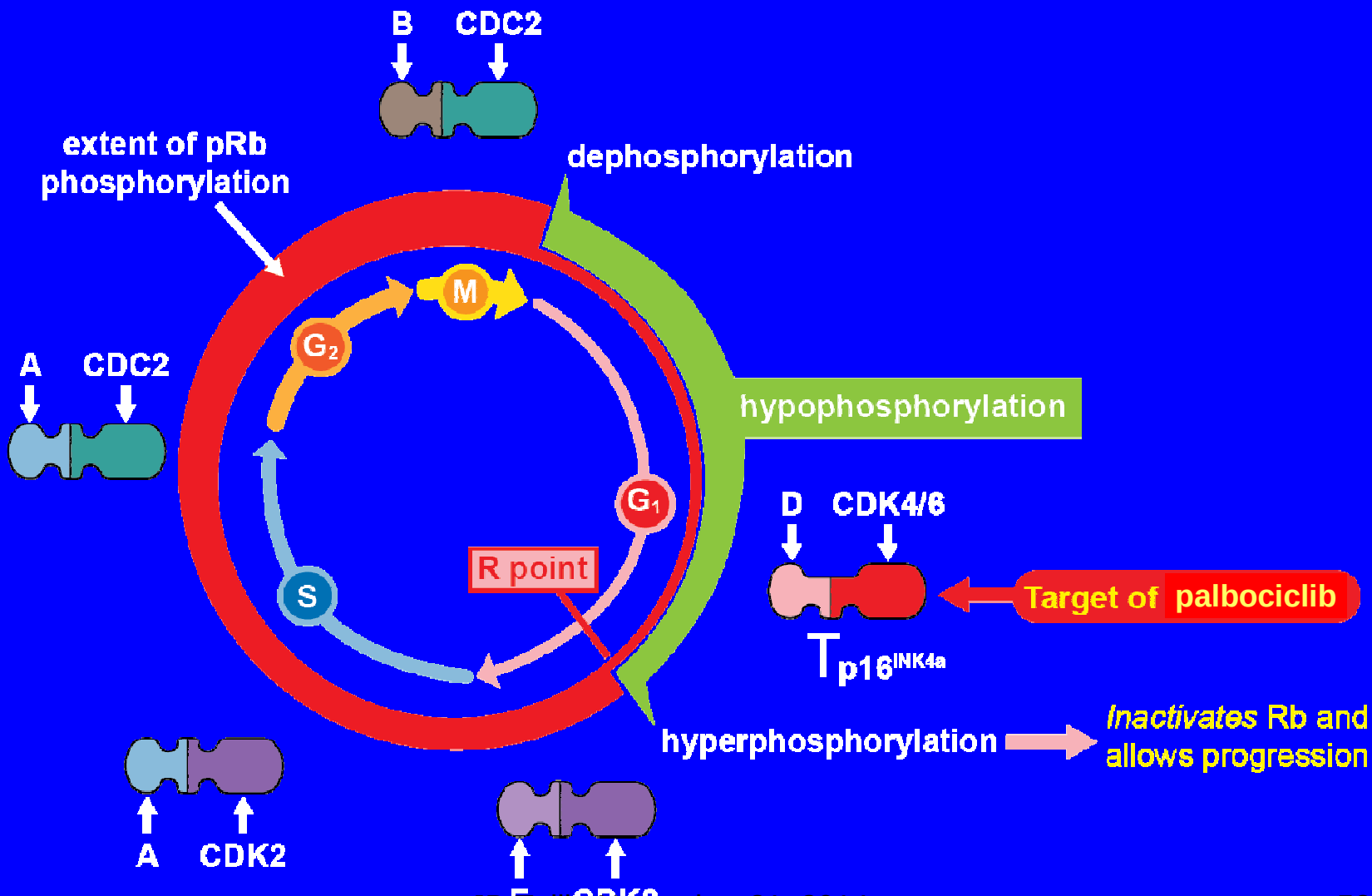
Final Results of a Randomized Phase 2 Study of Palbociclib (PD 0332991) a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer (PALOMA-1/TRIO-18)

RS Finn,[1] JP Crown,[2] I Lang,[3] K Boer,[4] IM Bondarenko,[5] SO Kulyk,[6] J Ettl,[7] R Patel,[8] T Pinter,[9] M Schmidt,[10] Y Shparyk,[11] AR Thummala,[12] NL Voytko,[13] X Huang,[14] ST Kim,[14] S Randolph,[14] DJ Slamon[1]

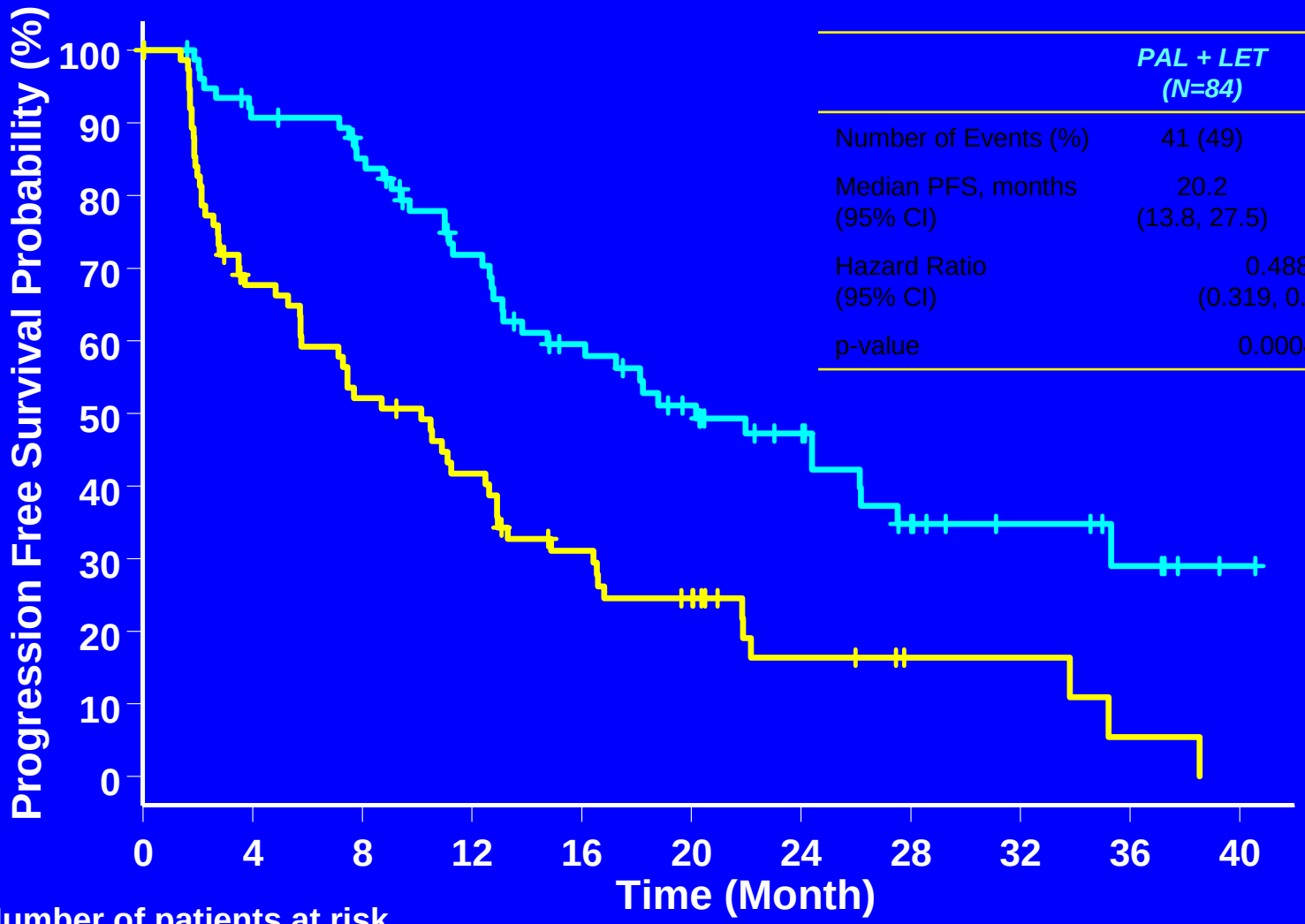
[1]University of California Los Angeles, Los Angeles, CA, USA; [2]Irish Cooperative Oncology Research Group, Dublin, Ireland; [3]Orszagos Onkologiai Intezet, Budapest, Hungary; [4]Szent Margit Korhaz, Onkologia, Budapest, Hungary; [5]Dnipropetrovsk City Multiple-Discipline Clinical Hospital, Dnipropetrovsk, Ukraine; [6]Municipal Treatment-and-Prophylactic Institution, Donetsk, Ukraine; [7]Technical University of Munich, Munich, Germany; [8]Comprehensive Blood and Cancer Center, Bakersfield, CA, USA; [9]Petz Aladar Megyei Oktato Korhaz, Gyor, Hungary; [10]University Hospital Mainz, Mainz, Germany; [11]Lviv State Oncologic Regional Treatment and Diagnostic Center, Ukraine; [12]Comprehensive Cancer Centers of Nevada, Henderson, NV, USA; [13]Kyiv City Clinical Oncology Center, Ukraine; [14]Pfizer Oncology, San Diego, CA, USA

Presented at AACR 2014; April 6, 2014; San Diego, CA USA

Rb as Master-Regulator of the R-point



Progression-Free Survival (ITT)

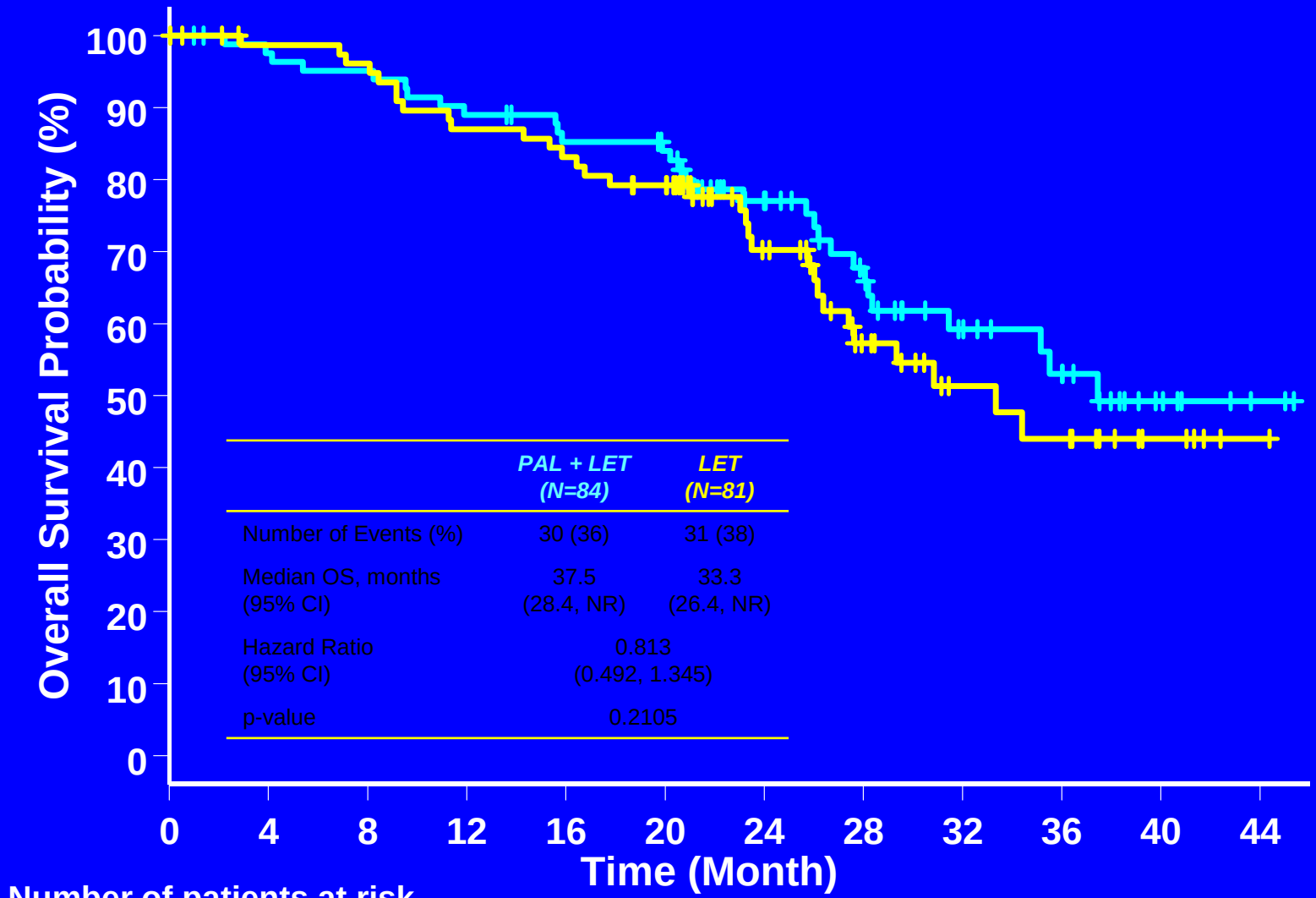


	PAL + LET (N=84)	*LET (N=81)*
Number of Events (%)	41 (49)	59 (73)
Median PFS, months (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)
Hazard Ratio (95% CI)	0.488 (0.319, 0.748)	
p-value	0.0004	

Number of patients at risk

PAL+LET	84	67	60	47	36	25	21	13	8	5	1
LET	81	48	36	28	19	14	6	3	3	1	

Overall Survival (ITT)
At Time of Final PFS Analysis



	PAL + LET (N=84)	LET (N=81)
Number of Events (%)	30 (36)	31 (38)
Median OS, months (95% CI)	37.5 (28.4, NR)	33.3 (26.4, NR)
Hazard Ratio (95% CI)	0.813 (0.492, 1.345)	
p-value	0.2105	

Number of patients at risk

PAL+LET	84	80	78	73	68	65	47	35	22	17	7	2
LET	81	76	74	67	64	59	37	23	14	12	5	1

Most Common All-Causality AEs ≥15% (AT)

	PAL + LET (N=83)			LET (N=77)		
	G1/2 (%)	G3 (%)	G4 (%)	G1/2 (%)	G3 (%)	G4 (%)
Neutropenia	20	48	6	4	1	0
Leukopenia	24	19	0	3	0	0
Fatigue	36	2	2	20	1	0
Anemia	29	5	1	5	1	0
Nausea	23	2	0	12	1	0
Arthralgia	22	1	0	13	3	0
Alopecia	22	0	0	3	0	0
Diarrhea	17	4	0	10	0	0
Hot flush	20	0	0	12	0	0
Thrombocytopenia	14	2	0	1	0	0
Decreased appetite	14	1	0	6	0	0
Dyspnea	13	2	0	6	1	0
Nasopharyngitis	16	0	0	10	0	0
Back pain	13	0	1	14	1	0

AT=As Treated Population

Conclusions neoadjuvant/adjuvant therapies

- Neoadjuvant CT is a safe option with a similar outcome as adjuvant therapy, 15% increased rate of BCS.
- Switch strategy in non-responding pts - improved DFS
- Adjuvant chemotherapy reduces the risk to die by the relative same magnitude (independent age, Er, stage, grade etc.)
- The risk to die in a middle age woman with an Er pos disease will be reduced by 50% by CT followed by five years of tamoxifen

Conclusions neoadjuvant/adjuvant therapies

- Anthracyclines should still be the cornerstone in the adjuvant/neoadjuvant CT regimens
- Taxanes add 1-3% absolute survival gain to anthracycline based regimens

Conclusions neoadjuvant/adjuvant therapies

- “All” patients with Er+ positive disease should be offered adjuvant endocrine therapy, for at least five years
- AIs are slight better than tamoxifen, 4% reduction in recurrence rate, so far no OAS advantage
- 10 years of adjuvant endocrine (tamoxifen) therapy provides an additional improvement in in breast cancer mortality ‘
- 5 years of tamoxifen plus some further years of an AI, statistically significantly survival improvement for pts with node positive disease

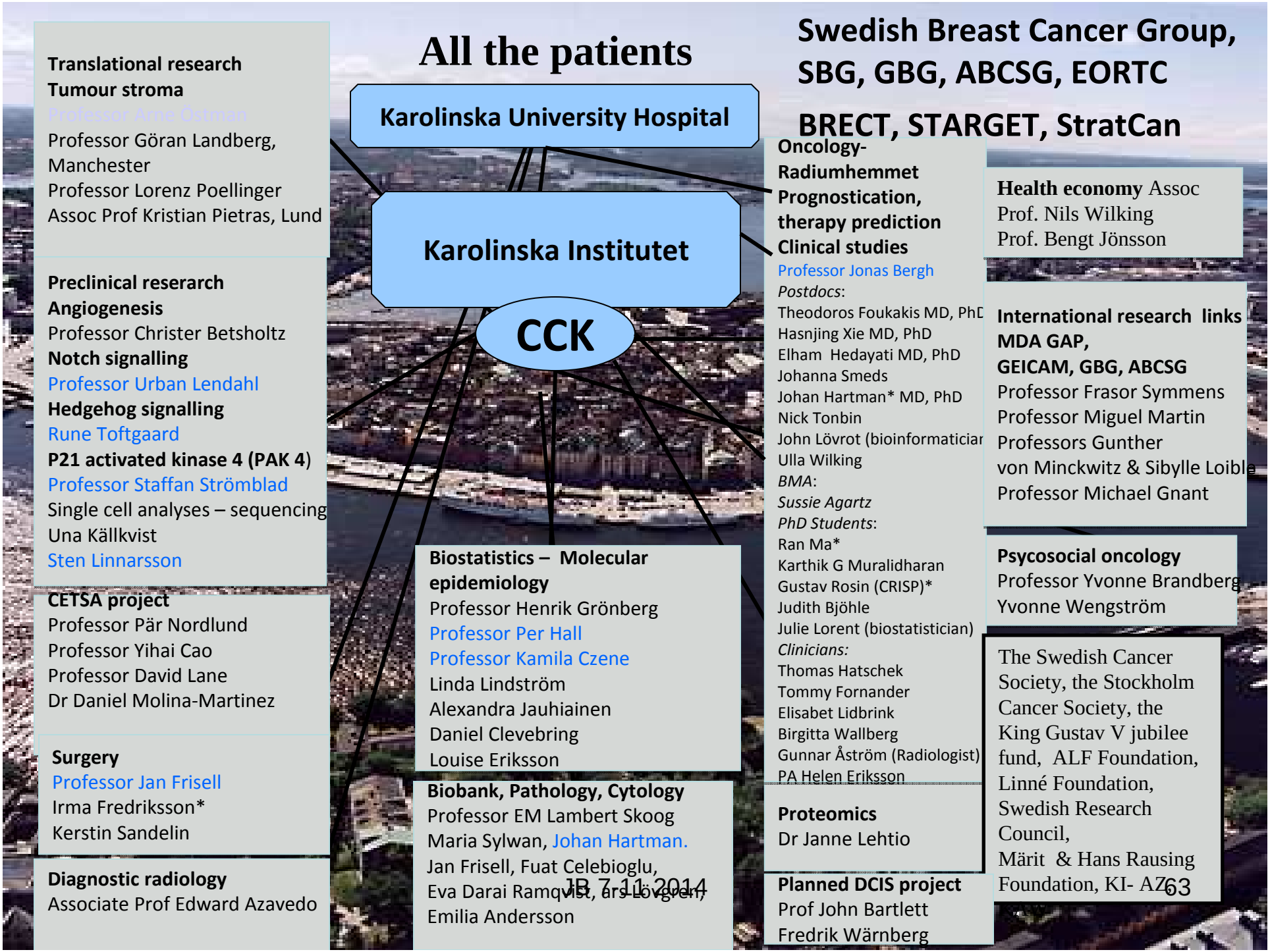
Conclusions neoadjuvant/adjuvant therapies

- Double HER-2 blockade results in a doubled chance for pCR, lapatinib has more side-effects
- One year of duration of trastuzumab is presently the best proven option, two years not better
- Single agent lapatinib results in an inferior outcome

Conclusions Metastatic disease-chemotherapy

- Effective therapies provide QOL improvement
- The tumour characteristics seem to change during progression
- Endocrine therapies cornerstone in the management, *patient selection*
- CT should be offered to pts with rec negative disease and those with biologically aggressive disease
- Chemotherapy prolongs survival and improve QoL
- How many lines? Evidence?
- Please use with sense- Responding on previous lines-offer the pts very many lines of therapy
- In pts with HER-2 pos disease: Maintain HER-2 blockade, change cytostatics, and use the different HER-2 agents
- mTOR and CDK 4/6 are promising drug targets

Thank you


All the patients
Swedish Breast Cancer Group, SBG, GBG, ABCSG, EORTC
BRECT, STARGET, StratCan
Karolinska University Hospital
Karolinska Institutet
CCK
Translational research
Tumour stroma
Professor Arne Östman
Professor Göran Landberg, Manchester
Professor Lorenz Poellinger
Assoc Prof Kristian Pietras, Lund
Preclinical reserarch
Angiogenesis
Professor Christer Betsholtz
Notch signalling
Professor Urban Lendahl
Hedgehog signalling
Rune Toftgaard
P21 activated kinase 4 (PAK 4)
Professor Staffan Strömblad
Single cell analyses – sequencing
Una Källkvist
Sten Linnarsson
CETSA project
Professor Pär Nordlund
Professor Yihai Cao
Professor David Lane
Dr Daniel Molina-Martinez
Surgery
Professor Jan Frisell
Irma Fredriksson*
Kerstin Sandelin
Diagnostic radiology
Associate Prof Edward Azavedo
Biostatistics – Molecular epidemiology
Professor Henrik Grönberg
Professor Per Hall
Professor Kamila Czene
Linda Lindström
Alexandra Jauhiainen
Daniel Clevebring
Louise Eriksson
Biobank, Pathology, Cytology
Professor EM Lambert Skoog
Maria Sylwan, Johan Hartman.
Jan Frisell, Fuat Celebioglu,
Eva Darai Ramqvist, Ars Lövgren,
Emilia Andersson
Oncology-Radiumhemmet
Prognostication, therapy prediction
Clinical studies
Professor Jonas Bergh
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Theodoros Foukakis MD, PhD
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Johan Hartman* MD, PhD
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Ulla Wilking
BMA:
Sussie Agartz
PhD Students:
Ran Ma*
Karthik G Muralidharan
Gustav Rosin (CRISP)*
Judith Björhle
Julie Lorent (biostatistician)
Clinicians:
Thomas Hatschek
Tommy Fornander
Elisabet Lidbrink
Birgitta Wallberg
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PA Helen Eriksson
Proteomics
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The Swedish Cancer Society, the Stockholm Cancer Society, the King Gustav V jubilee fund, ALF Foundation, Linné Foundation, Swedish Research Council,
Märit & Hans Rausing Foundation, KI- AZ