ADJUVANT THERAPY IN BREAST CANCER

Quo vadis?

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Université Libre de Bruxelles
Breast International Group (BIG asbl), Chair

DISCLOSURES

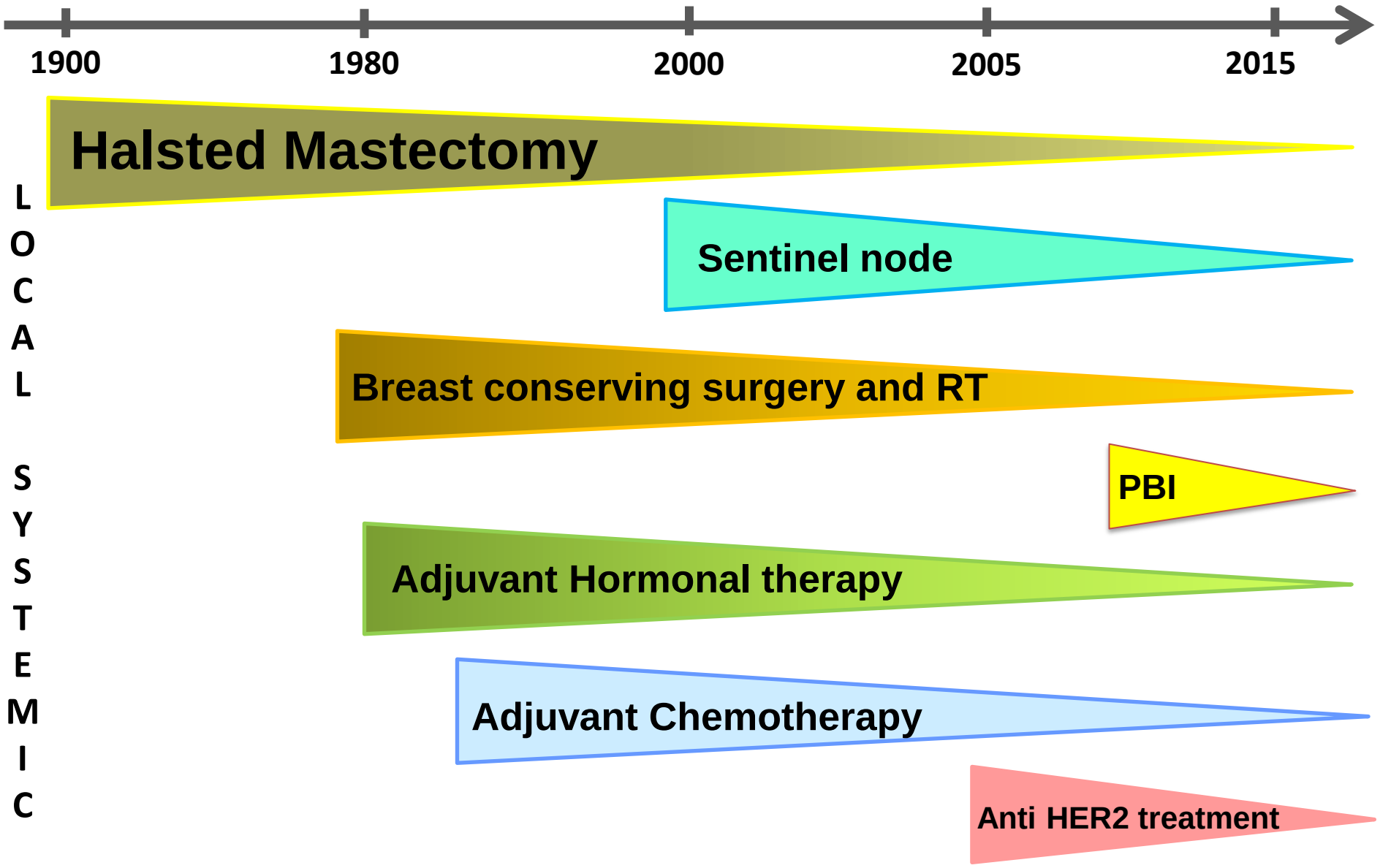
- **Board member**: PharmaMar
- **Consultant (honoraria)**: Amgen, Astellas, AstraZeneca, Bayer, Invivis, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Sanofi-Aventis, Symphogen, Synthon, Verastem
- **Research grants to Jules Bordet Institute**: most companies
- **Speakers bureau/stock ownership:** none

Plan of the talk

- **Rapid overview of current adjuvant treatment practice**

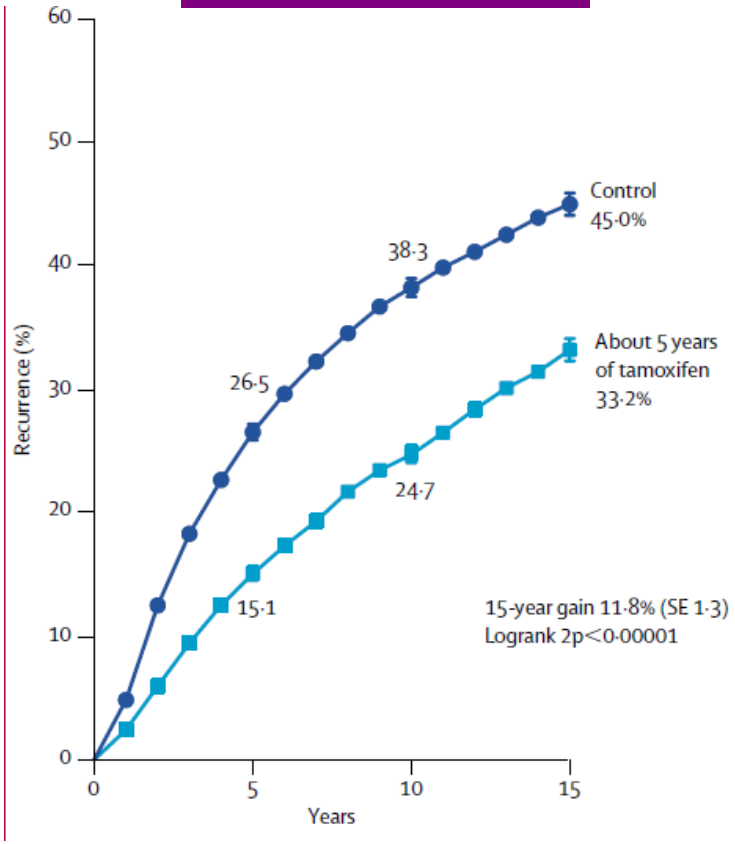
- **Lessons and questions in :**
  1. **Luminal BC**
  2. **Triple Negative BC**
  3. **HER2 positive BC**

Changes in clinical practice for early Breast Cancer

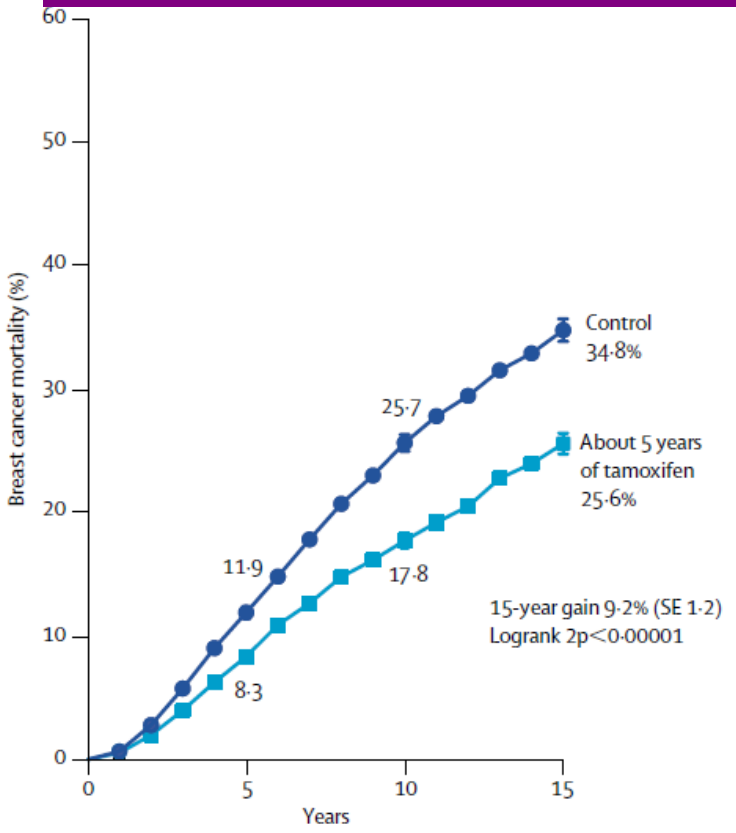


ADJUVANT HORMONAL THERAPY (Tamoxifen) IMPROVES SURVIVAL

Recurrence

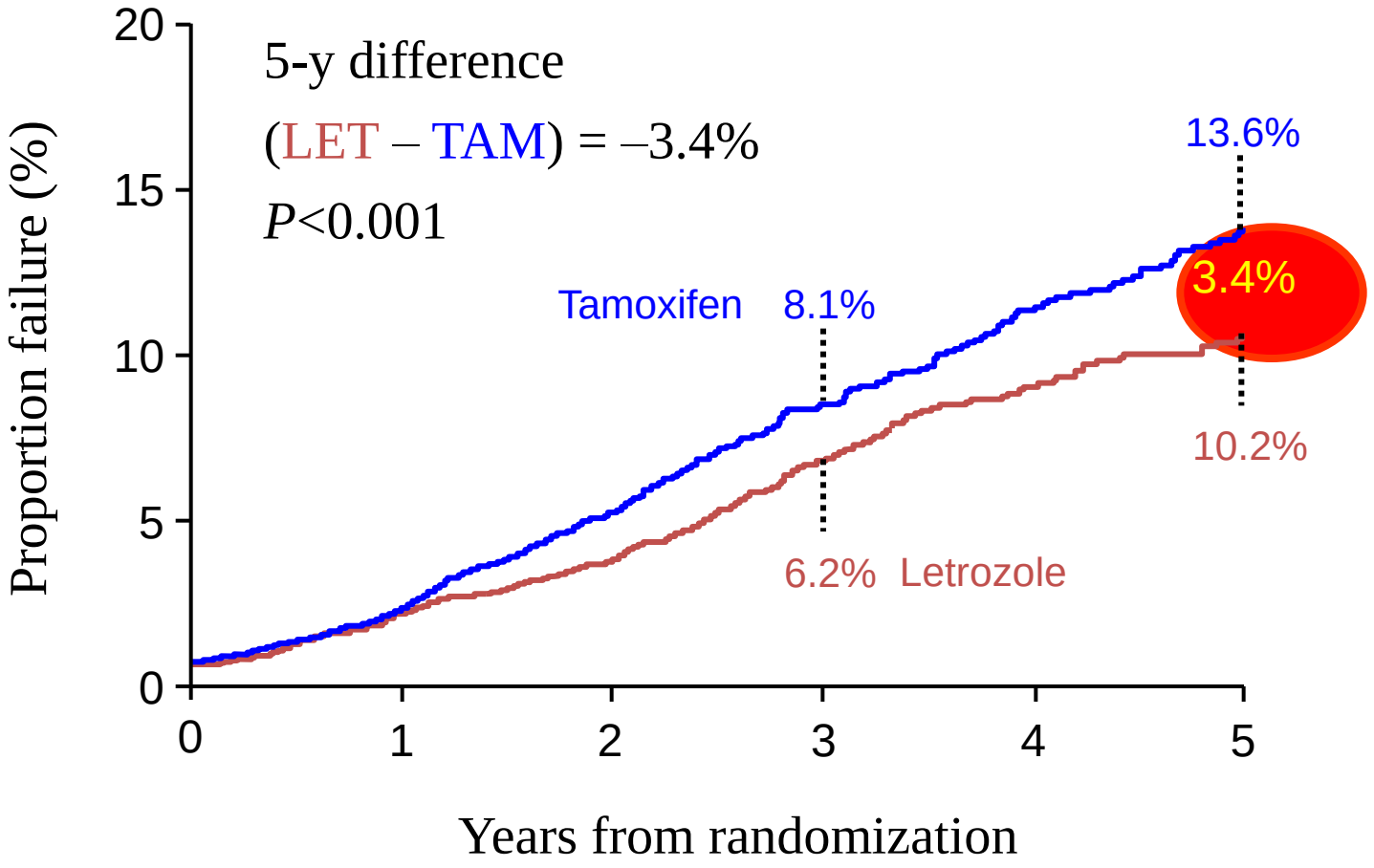


Breast cancer mortality



EBCTCG, Lancet 2005

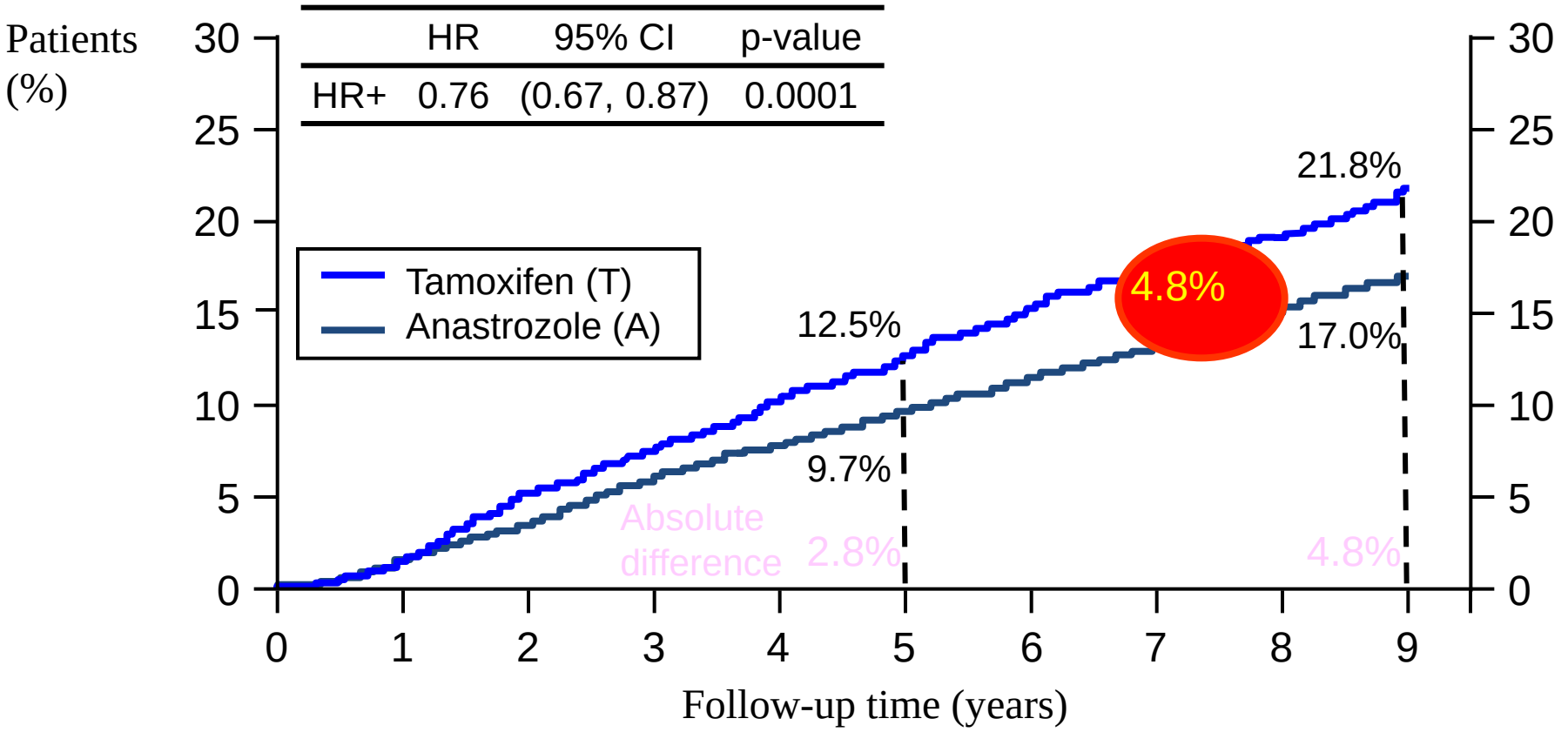
BIG 1-98: CUMULATIVE INCIDENCE OF BREAST CANCER EVENTS - ABSOLUTE BENEFIT



Thürlimann et al. N Engl J Med. 2005;353:2747.

Courtesy of R. Gelber

ATAC: TIME TO RECURRENCE HR+ PATIENTS CARRY OVER EFFECT



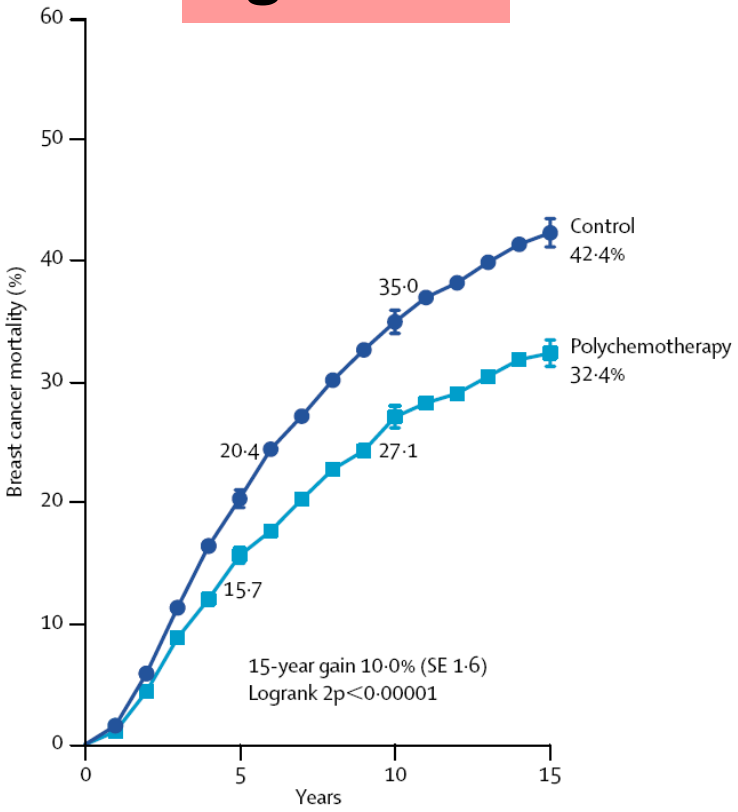
At risk:

A	2618	2541	2453	2361	2278	2159	1995	1801	1492	608
T	2598	2516	2400	2306	2196	2075	1896	1711	1396	547

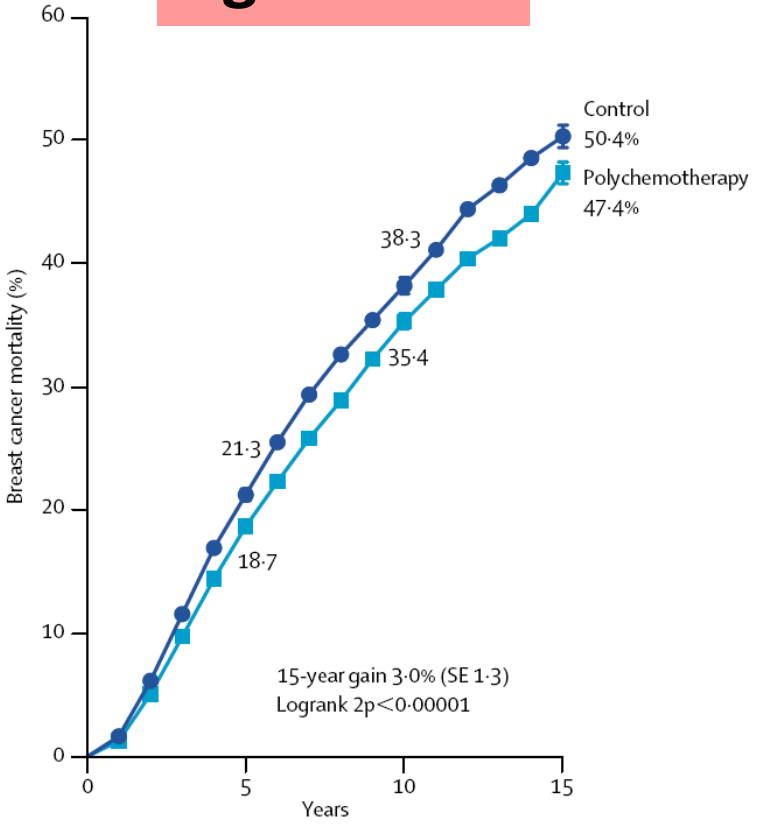
ADJUVANT CHEMOTHERAPY IMPROVES SURVIVAL

Breast cancer mortality

Age: < 50

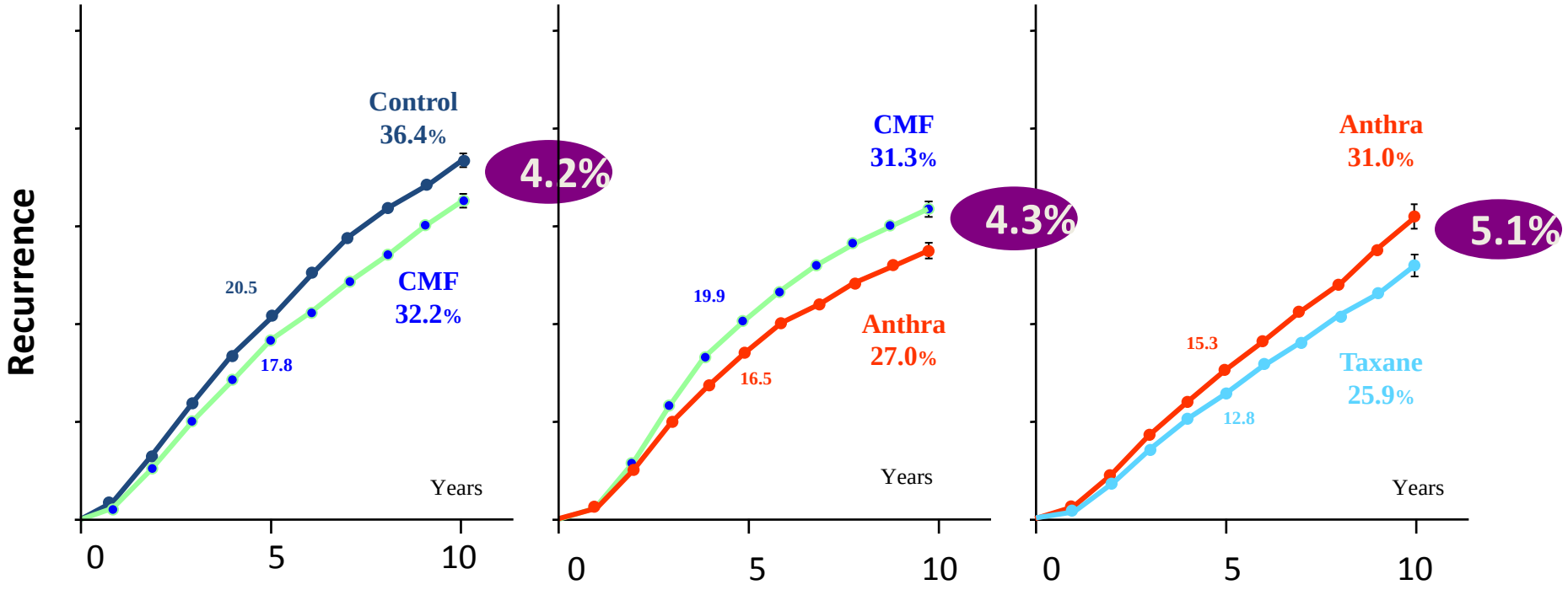


Age: 50-69



EBCTCG, Lancet 2005

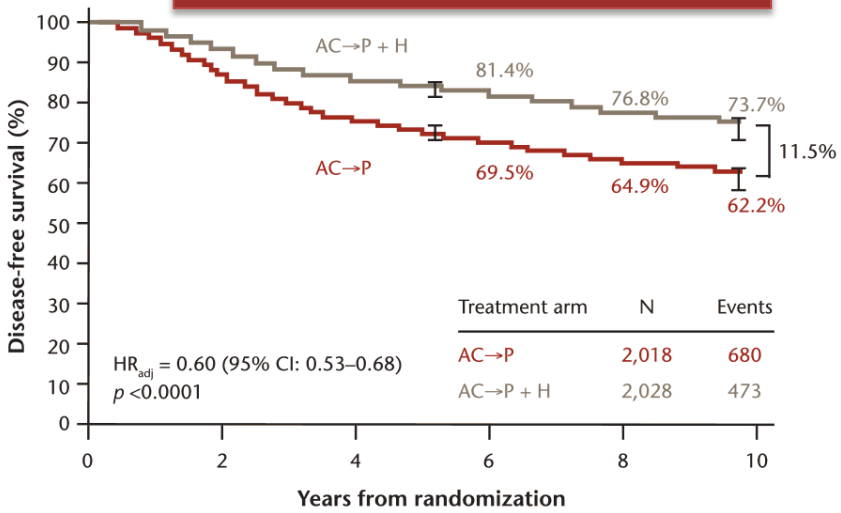
Taxanes + Anthracyclines > CMF > none



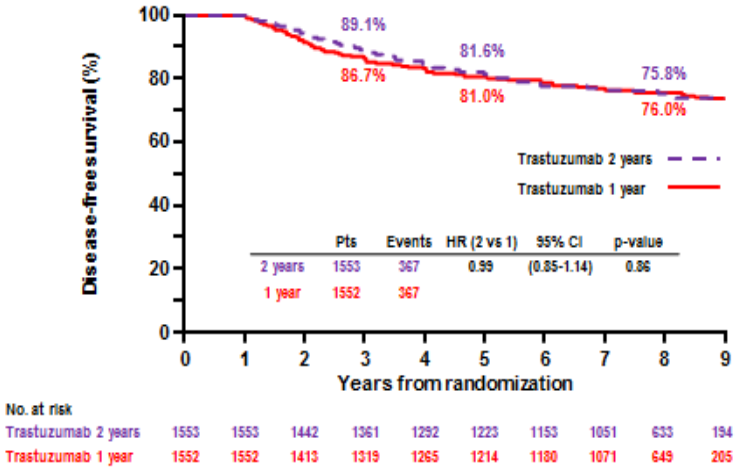
EBCTCG

ADJUVANT TRASTUZUMAB IMPROVES SURVIVAL

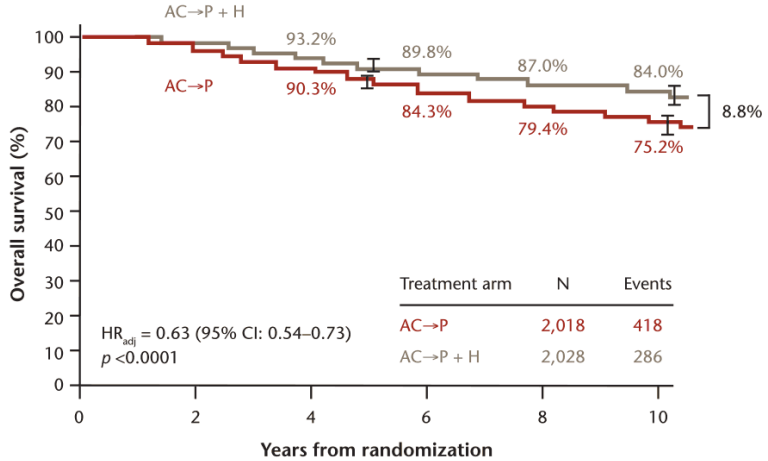
B-31 and NCCTG N9831 10-year disease free survival



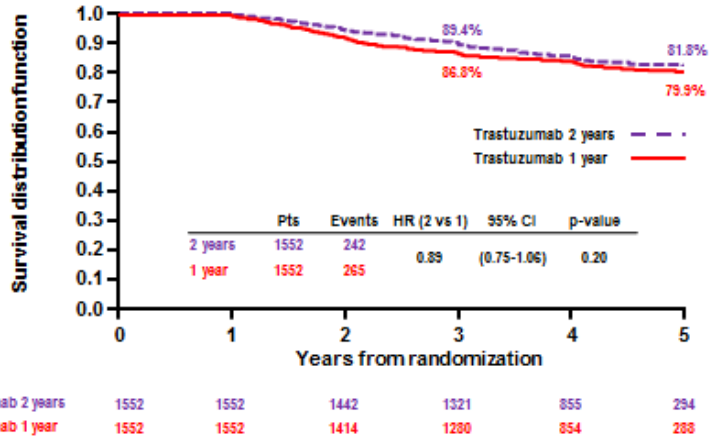
HERA 8-year disease free survival



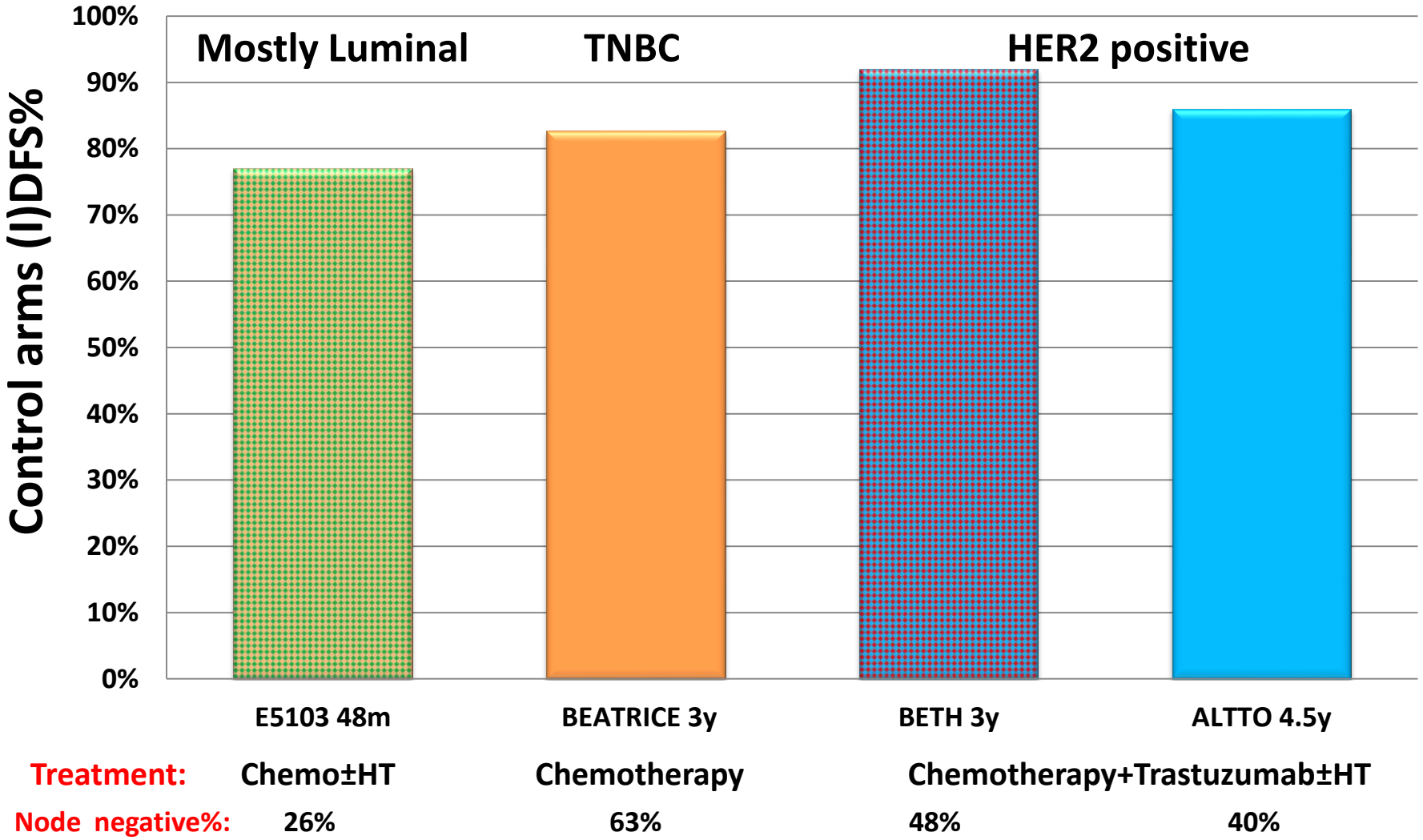
10-year overall survival



HERA 8-year over all survival



Patients in control arms of recent adjuvant BC trials do very well !

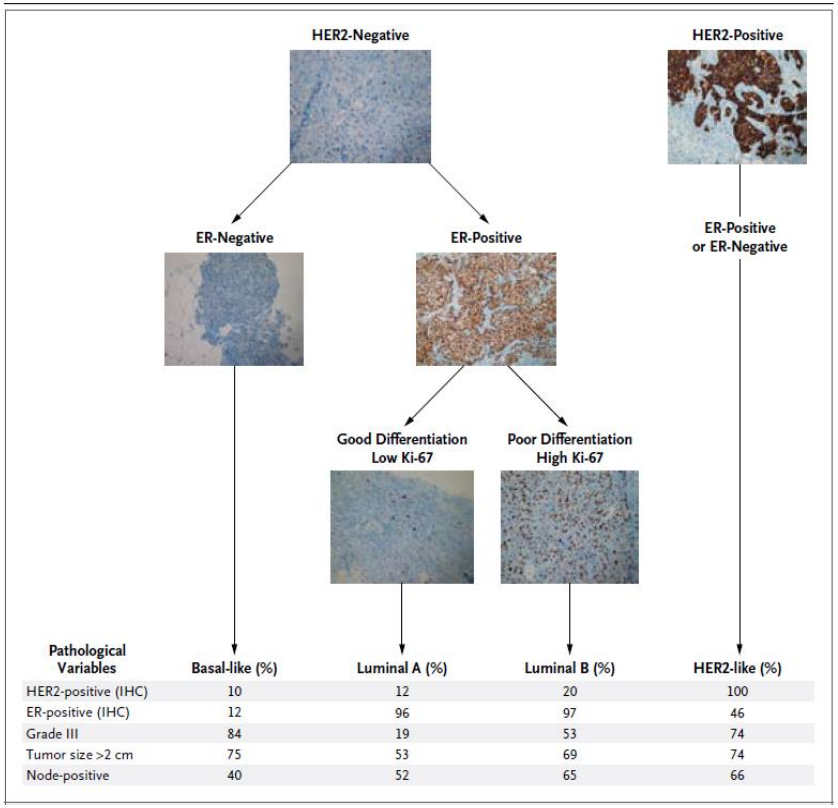


PROGRESS IN BREAST CANCER TREATMENT

- Breast cancer = 2 diseases (HR+ or -)
- Rough estimation of relapse risk
- « One size fits all » treatment strategy

- Breast cancer = 4 diseases (luminal A/B, HER2+, triple negative)
- Improved estimation of relapse risk
- Improved tailoring of adjuvant treatment

CLASSIFICATION Surrogates



Pathological Variables	Basal-like (%)	Luminal A (%)	Luminal B (%)	HER2-like (%)
HER2-positive (IHC)	10	12	20	100
ER-positive (IHC)	12	96	97	46
Grade III	84	19	53	74
Tumor size >2 cm	75	53	69	74
Node-positive	40	52	65	66

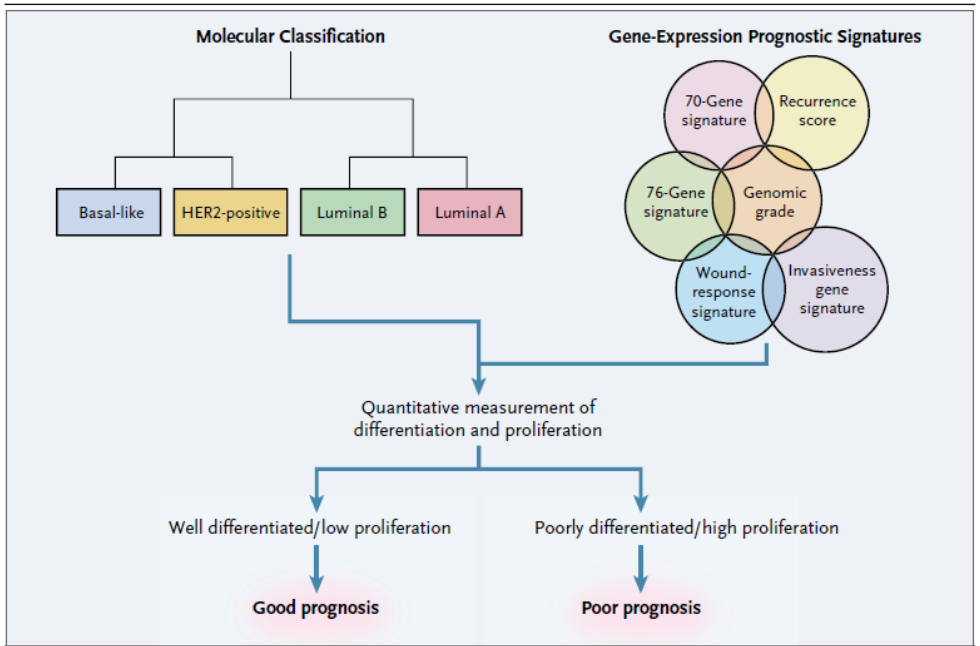


Figure 3. Molecular Classification, Gene-Expression Signatures, and Clinical Outcome.
Genes that are associated with tumor differentiation and cell cycle drive the prognostic power of the intrinsic molecular classification and several gene-expression signatures.

Simple tools

Complex tools

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Gene-Expression Signatures in Breast Cancer

Christos Sotiriou, M.D., D.Phil., and Lajos Pusztai, M.D., D.Phil.

Systemic treatment recommendations for early breast cancer subtypes

ESMO Guidelines 2013

Subtype	Recommended therapy	Comments
Luminal A-like	ET alone in the majority of cases.	Consider CT if (i) high tumour burden (four or more positive LN, T3 or higher) (ii) grade 3
Luminal B-like (HER2-negative)	ET + CT for the majority of cases	
Luminal B-like (HER2-positive)	CT + anti-HER2 + ET for all patients	If contraindications for the use of CT, one may consider ET + anti-HER2 therapy,although no randomised data exist.
HER2-positive (non-luminal)	CT + anti-HER2	
Triple-negative (ductal)	CT	

Focus on Luminal B.C.

- **What did we learn ?**
- **Which questions do we still have to answer ?**

Adjuvant therapy for Luminal Breast Cancers

What did we learn?

- ✓ **Some patients do not need chemotherapy**
- ✓ **Consideration for the incorporation of an "AI" in the treatment scheme should be given (in post menopausal women)**
- ✓ **Some patients benefit from extended (10y) hormonal treatment**
- ✓ **Exemestane+OFS is an emerging option for premenopausal women**
- ✓ **Bisphosphonates (mostly zoledronic acid) are to be considered for some women**
- ✓ **There is no role for adjuvant Bevacizumab**
- ✓ **BC mortality is increased in high BMI premenopausal women**

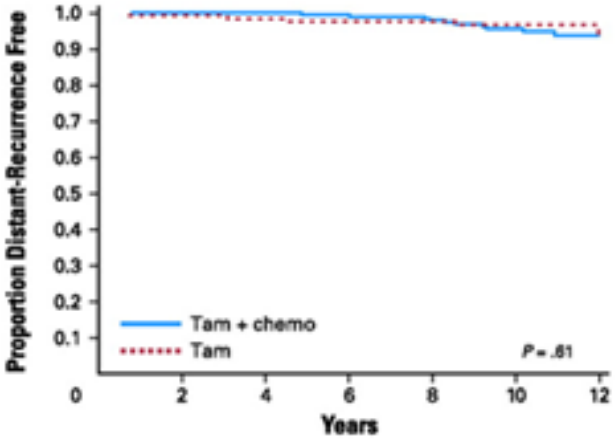
MULTIGENE "PROGNOSTIC" SIGNATURES

Name	Oncotype DX™	MammaPrint™	GGI	PAM50	Breast Cancer Index	EndoPredict
Provider	Genomic health	Agendia	Ipsogen	nanoString	Biotheranostics	Sividon Diagnostics
Type of Assay	21 gene recurrence score	70 Gene Assay	97 Gene Assay	50 Gene Assay	2 gene ratio HOXB13 to IL17R and molecular grade index	combines RNA score with nodal status and tumor size
Tissue samples	FFPE	From fresh moving to FFPE	From fresh moving to FFPE	FFPE	FFPE	FFPE
Technique	qRT-PCR	Microarray	From Microarray moving to qRT-PCR	qRT-PCR	qRT-PCR	qRT-PCR

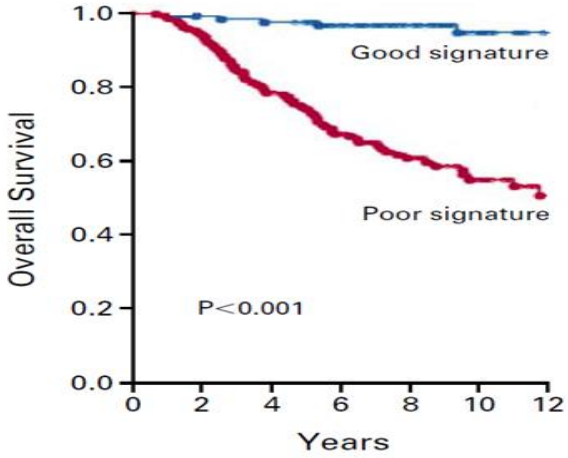
- **More than a decade of translational research…**
- **Rapid uptake of ONCOTYPE DX in the USA (<18 = no chemotherapy)**
- **Slower uptake of any of the signatures by European oncologists**

Very good RFS in patients with "low-risk" genomic signatures

OncotypeDx (JCO 2006)

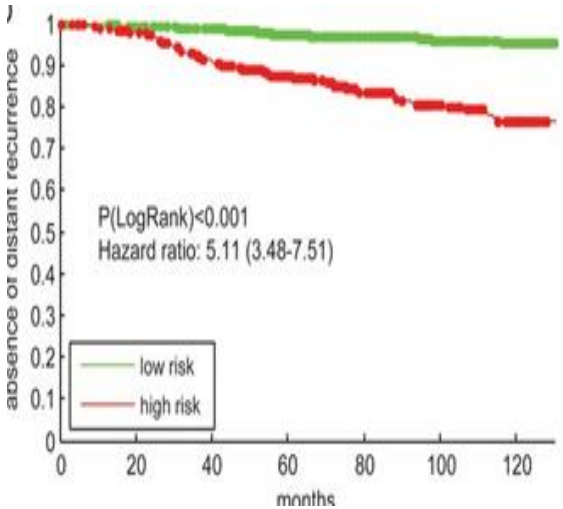


mammaprint (NEJM 2002)

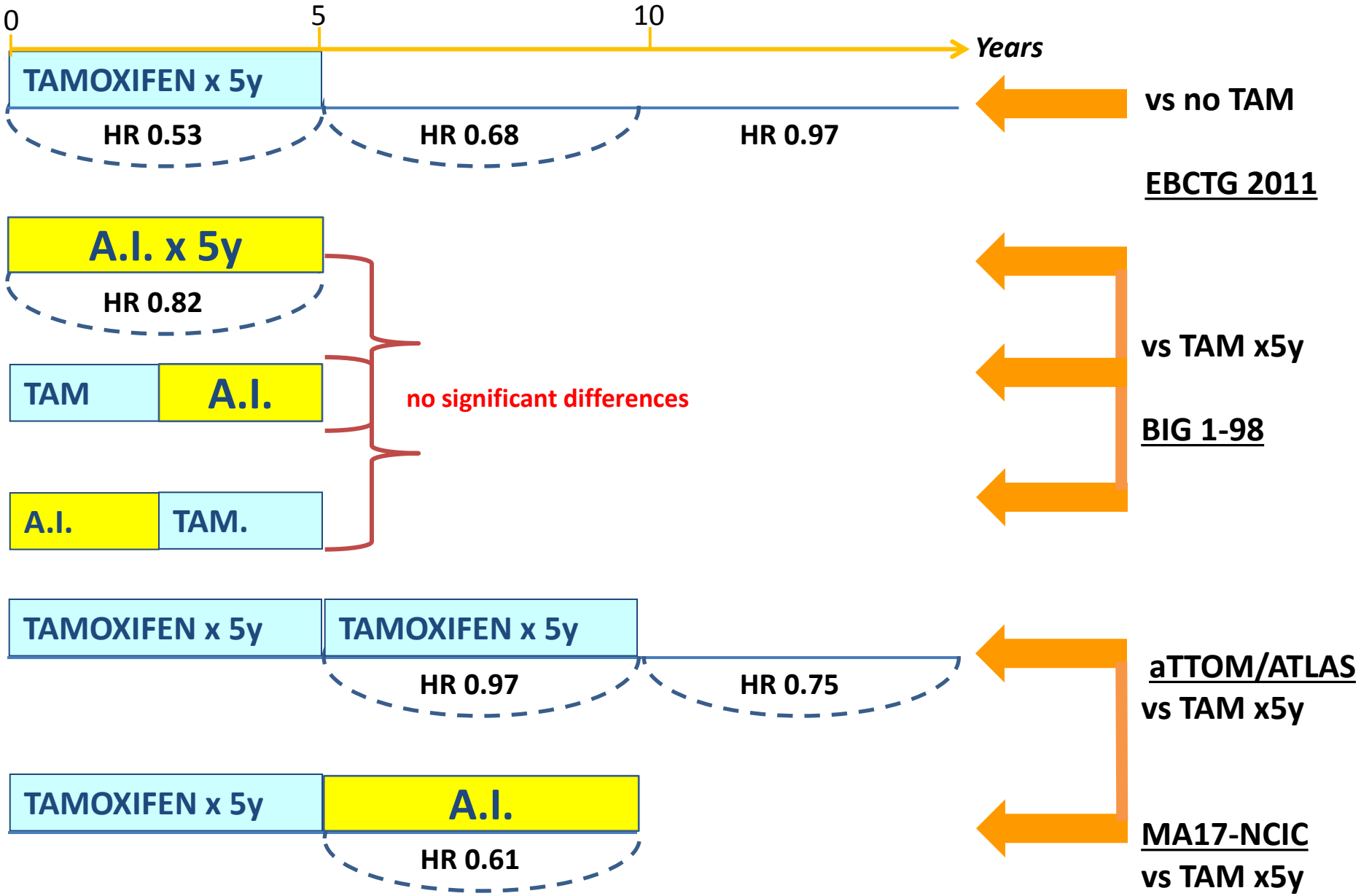


ENDOPREDICT

(Annals of Oncology 2013)



Impact of adjuvant endocrine treatment strategies on breast cancer mortality



10 vs 5-yr BREAST CANCER MORTALITY IN ER+

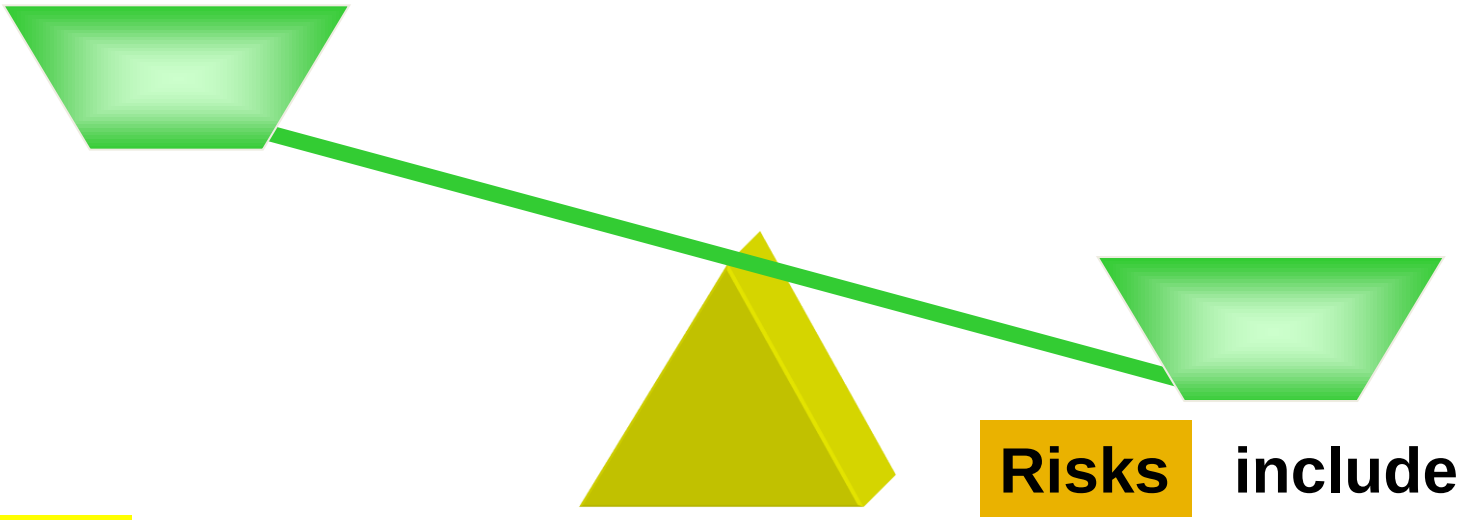
rate ratio* by period in aTTom and ATLAS

	10 yrs tam. vs 5: aTTom trial (n=6934 ER+/UK)	10 yrs tam. vs 5: ATLAS trial* (n=10,543 ER+/UK)	10 yrs tam. vs 5: aTTom & ATLAS combined (n=17,477 ER+/UK)
years 5-9	**1.08** (0.85-1.38)	**0.92** (0.77-1.09)	**0.97** (0.84-1.15)
years 10+	**0.75**† (0.63-0.90)	**0.75**§ (0.63-0.90)	**0.75**† (0.65-0.86)
All years	**0.88**‡ (0.74-1.03)	**0.83**‡ (0.73-0.94)	**0.85**‡ (0.77-0.94)
	†p=0.007 ‡p=0.1	§p=0.002 ‡p=0.004	†p=0.00004 ‡p=0.001

***Inverse−variance−weighted estimate of the effect in ER+.(ATLAS, *Lancet* 2013)

Courtesy of R. Gray

Assessing benefits and risks of prolonged tamoxifen



Benefits will depend on

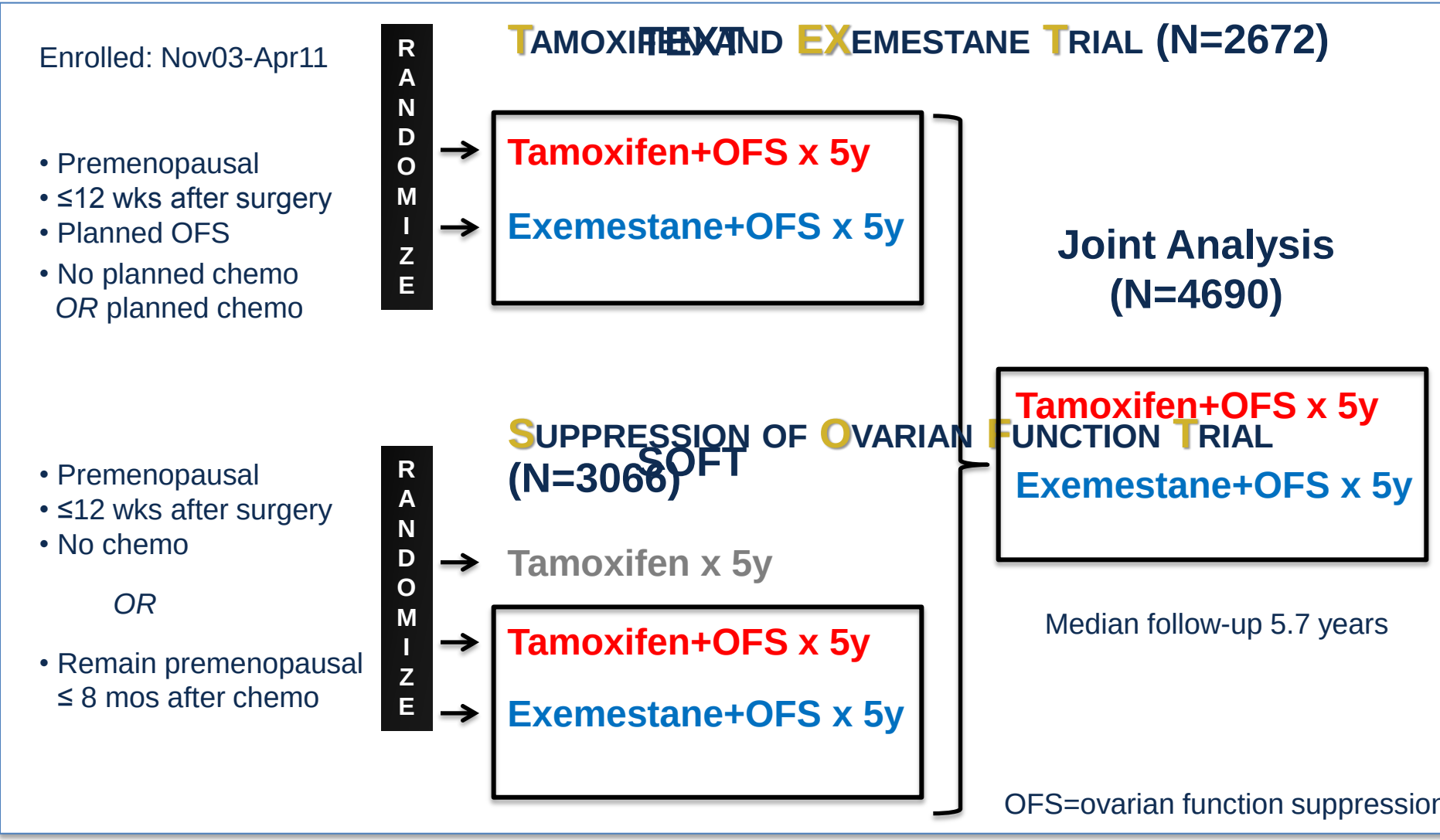
- Tumor burden
- Tumor biology
- Comorbidity & age

Risks include

- « SAE 's »
  - ↑ end.cancer from 1.6% to 3.1%
  - ↑ pulm embolism
    (but ↓ ischemic heart disease)
- Quality of life alteration
  - Vasomotor symptoms
  - Mood alterations
  - Sexual dysfunctions

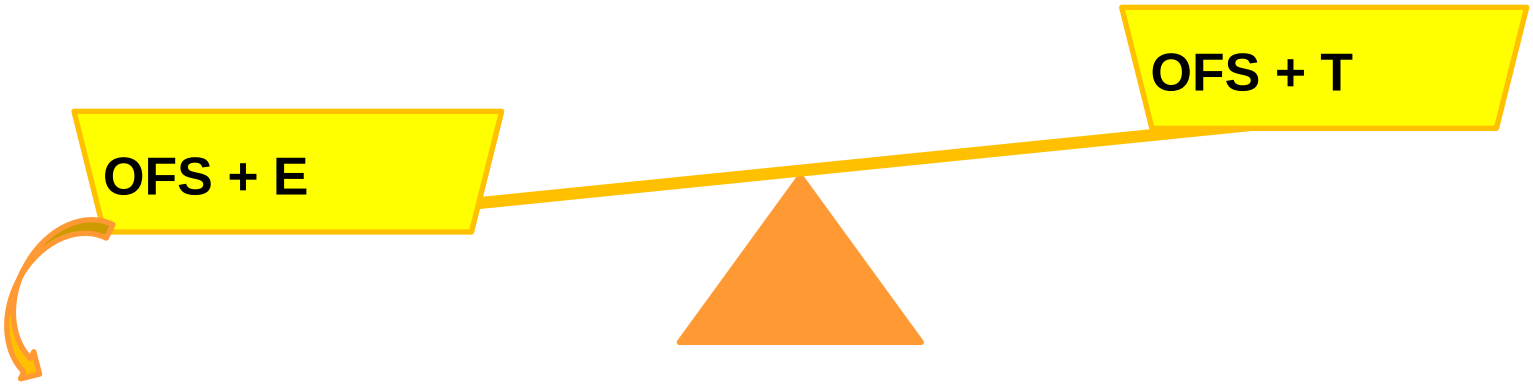
Exemestane+OFS is an emerging option for premenopausal women

TEXT and SOFT trials



Olivia Pagani, NEJM 6/2014

TEXT/SOFT



	H.R.	
DFS	0.72	All significant
BCFI	0.66	
DDFI	0.78	
OS	1.14	Not yet significant

… but

Long accrual : 2003-2011
Heterogenous populations
Revised analysis plan needed
Results different from ABCSG12

Goserelin + A vs Goserelin + T (3y)
(± zoledronic acid)
DFS H.R. 1.08 (0.81- 1.44)
OS H.R. 1.75 (1.08 - 2.83)

First results of TEXT/SOFT combined

Absolute gain in 5y DFS of 3.8% to be balanced against grade 3 or 4 side effects

	E > T
Musculo-skeletal	11% > 5%
Fractures	1.3% > 0.8%
Cardiac ischemia	0.3% > 0.1%
Dyspareunia	2.3% > 1.4%
Discontinuation of therapy	16% > 11%

	T > E
Thromboembolic events	1.9% > 0.8%

Effects of bisphosphonate treatment on recurrence in women with early breast cancer: a meta-analysis

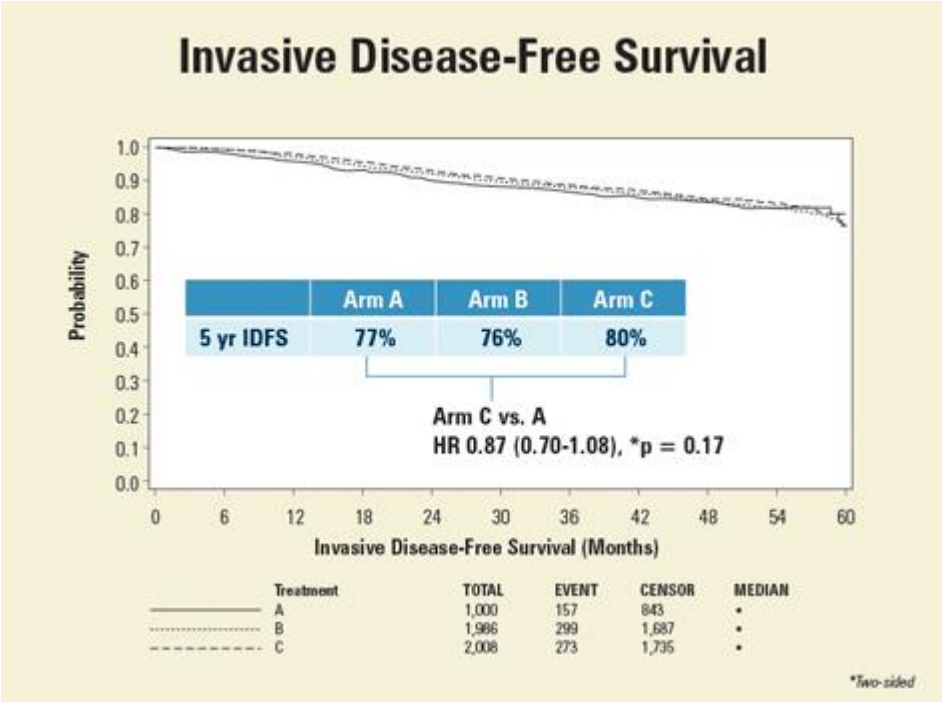
- 41 randomised trials, 17,751 women
- There were no improvements in recurrence for premenopausal women
- **In Post menopausal: 3.1% decrease in breast cancer mortality**

	No. events	HR	10 year gain	p value
Postmenopausal women (n = 10,540)				
Breast cancer mortality	1,107	0.83 (0.06)	3.1%	0.004
Breast cancer recurrence	1,809	0.86 (0.05)	3.0%	0.002
Distant recurrence	1,503	0.83 (0.05)	3.3%	0.0007
Bone recurrence	445	0.65 (0.08)	2.9%	0.00001
Other distant recurrence	1,058	0.93 (0.06)	0.7%	0.26

R Coleman, SABCS 2014, abstract S4-07

E5103 Adjuvant Bevacizumab (64% ER+)

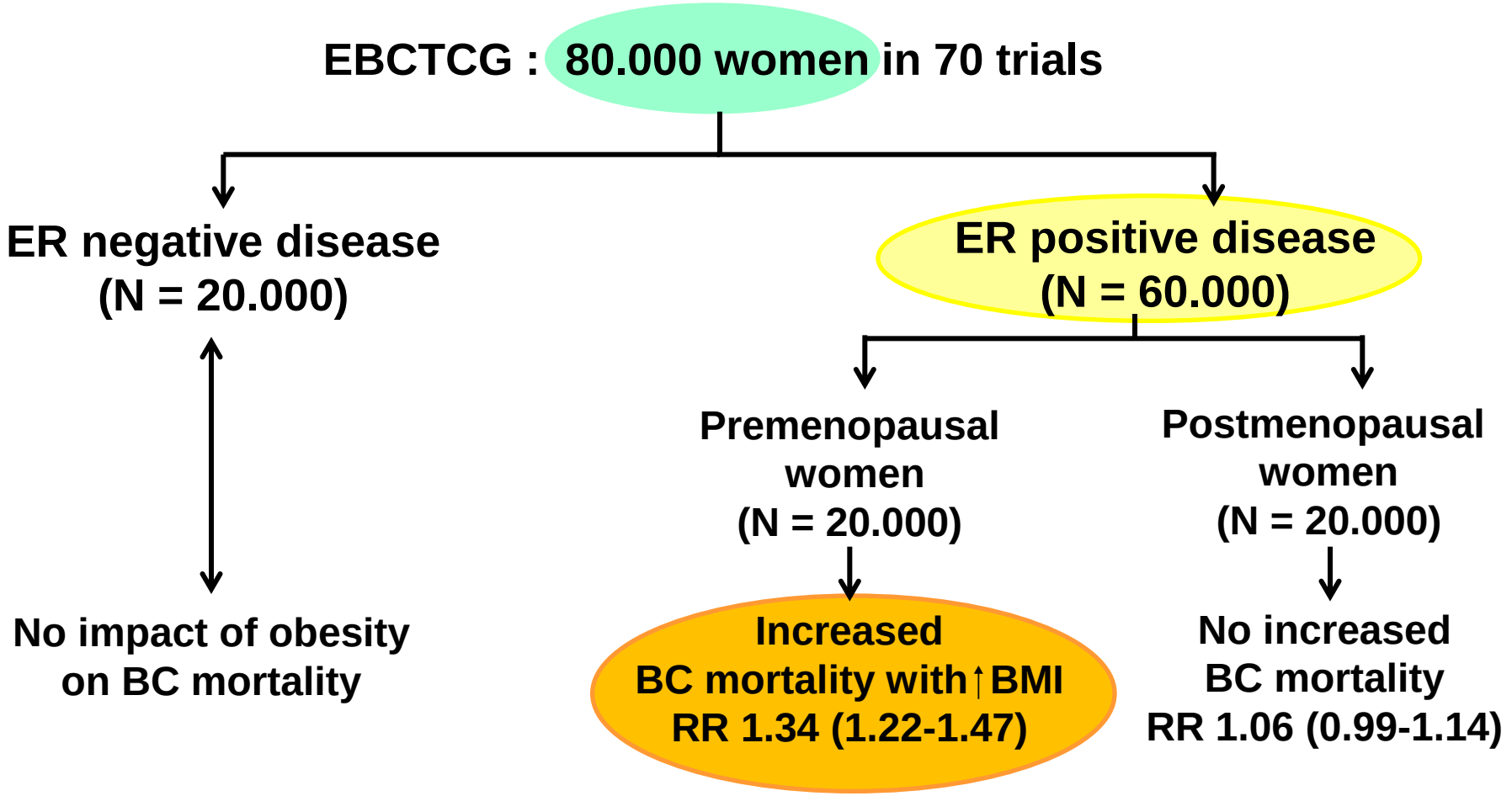
A large, well powered adjuvant trial – E5103 – fails to show any benefit from the incorporation of bevacizumab into adjuvant chemotherapy regimens !



K. Miller, SABCS 2013

ASCO 2014

The negative impact of obesity in early BC



- CTX dose reductions or biology ?
- No information on subsequent weight gain

H. Pau, abst 503

Adjuvant therapy for Luminal Breast Cancers

Interesting questions for the future

- ✓ **Can patients with intermediate genomic risk or discordant risk (low genomic risk/high clinical risk) be treated safely with endocrine therapy only ?**

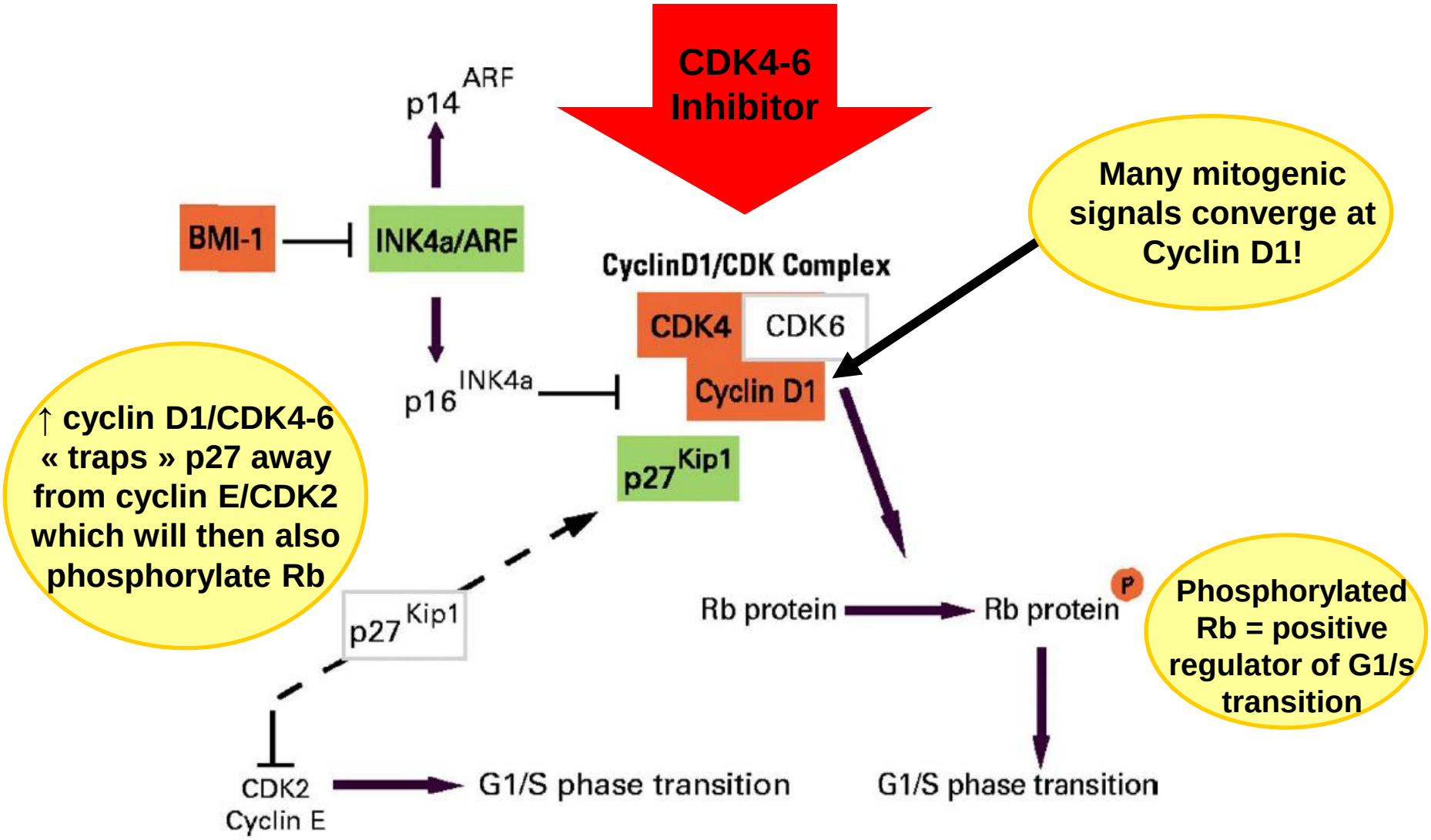
- ✓ **Will manipulation of endocrine resistance further improve outcome ? (CDK4-6 inhibitors/Everolimus)**

Should patients with intermediate risk or Discordant risk be treated with chemotherapy
Ongoing trials TAILORX AND MINDACT

	TAILORx	MINDACT
Groups	TBCI	BIG/EORTC
Population	Node-neg, ER+	N0-N1 ER+/-
Assay	21 gene ODX™	Mammaprint®
Utility Scale & Level of Evidence	+ or ++ II	
Tissue	FPFT	Fresh Frozen
No.		6,700
No. randomized		2,142
Randomized group	RS 11-25 (40%)	Discordant risk (32%)
Randomization	*Treat with hormones +/- chemotherapy*	*Treat by clinical vs genomic risk*
Non-randomized groups	RS<11: Hormones RS> 25: Chemo+ hormones	Both low risk (41%): Hormones Both high risk (27%): Chemo +/- hormones

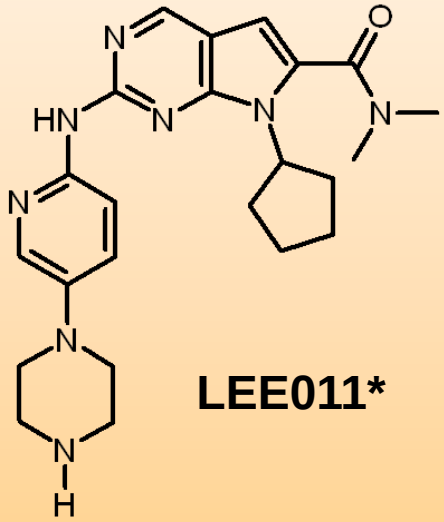
Results in 2015-2016

Circumventing endocrine resistance
Blocking CDK's



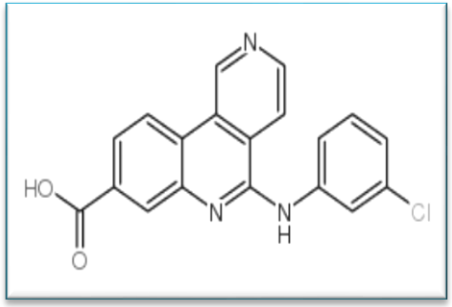
Fernàndez V et al. JCO 2005; 23:6364-6369

CDK4-6 inhibitors in clinical trials for advanced BC

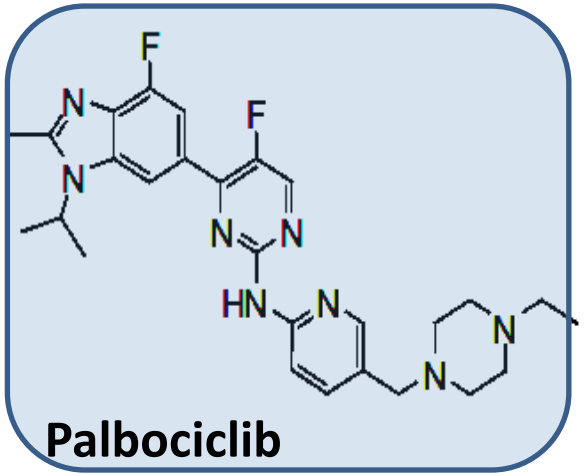


LEE011*

7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide



Abemaciclib



Palbociclib

Started Phase 3

- **Mild GI toxicity**
- **Reversible Neutropenia ± thrombocytopenia**

Ongoing Phase 3 Studies assessing CDK4/6 inhibition

PALOMA-2	Palbociclib + Letrozole vs. Letrozole For 1st Line Treatment Of Postmenopausal Women (NCT01740427)
PALOMA-3	Palbociclib + Fulvestrant vs. Fulvestrant + Placebo After Endocrine Failure (NCT01942135)
PEARL	Palbociclib + Exemestane vs. Capecitabine in Resistance to NSAI (NCT02028507)
MONARCH2	Fulvestrant With or Without Abemaciclib (LY2835219) (NCT02107703)
MONALEESA2	LEE011 in Combination With Letrozole (NCT01958021)

The Alliance – ABCSG – BIG

"Pallas" adjuvant trial

« High risk »
luminal BC

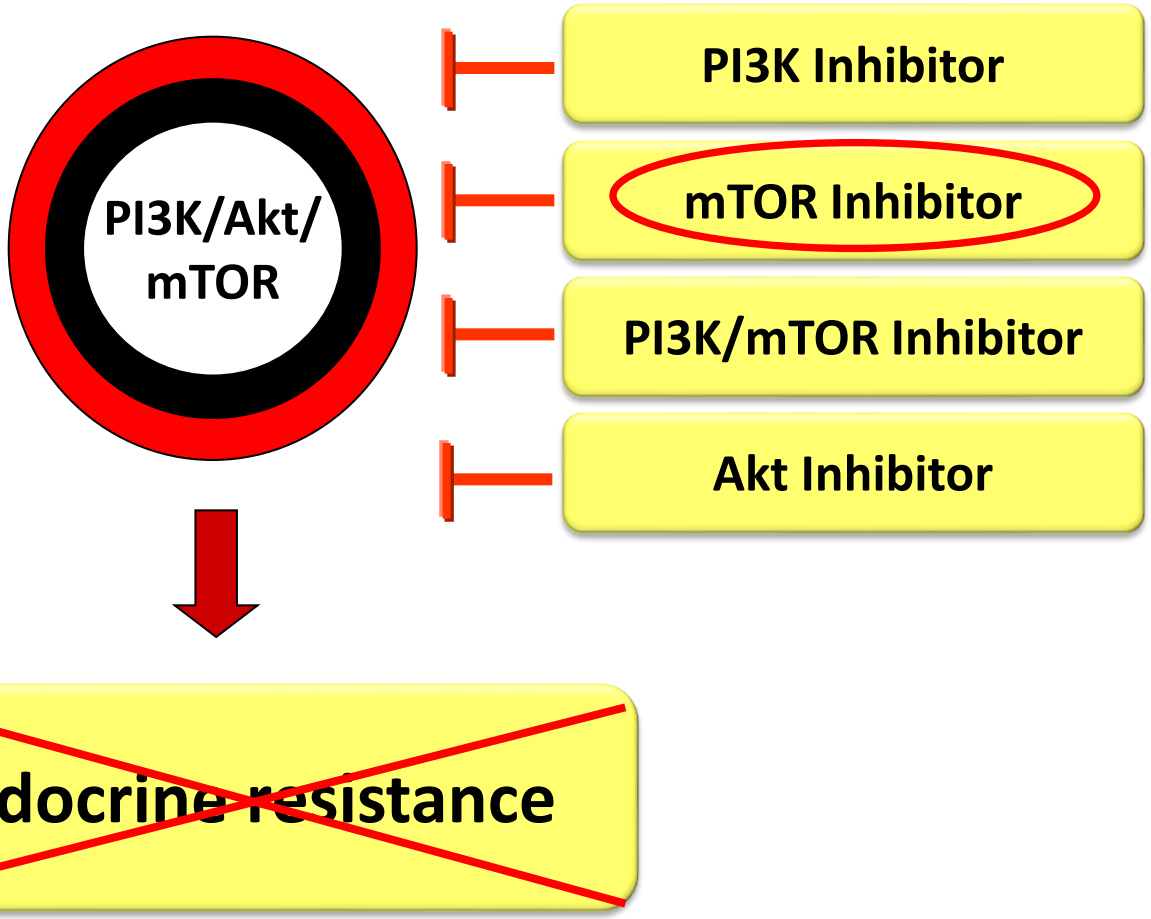
→ **Standard adjuvant therapy**

→ + palbociclib

→ or placebo

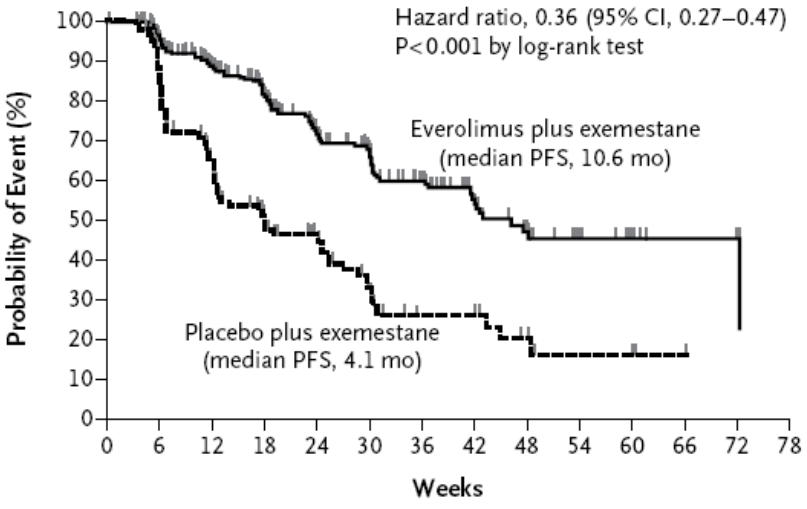
... under construction!

Fueling endocrine resistance
Circumventing endocrine resistance

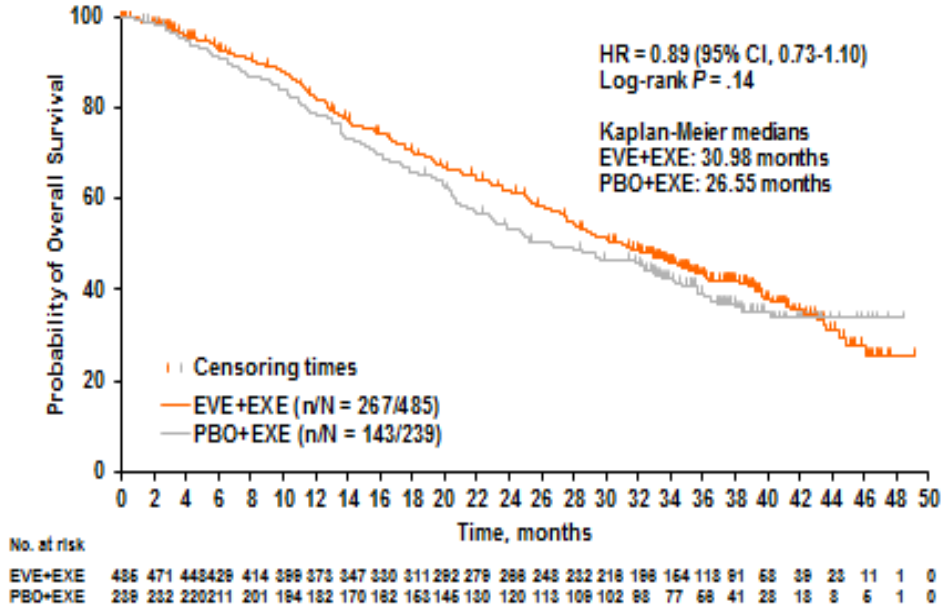


BOLERO-2 Study in advanced luminal BC with secondary resistance to non-steroidal AI

PFS Central Assessment



OS



PFS benefit but no OS benefit

Baselga, J. et al. N. Engl. J. Med. 366, 520–529 (2012)

Piccart M.J. et al., Annals of Oncology, in press.

S1207/SWOG and UNIRAD studies : Adjuvant endocrine therapy +/- Everolimus

Phase III randomized double-blind trial adding everolimus to adjuvant endocrine therapy who are disease-free following 3y of adjuvant ET for a total adjuvant therapy duration of 5y

UNIRAD

Planned Number = 1984

Population:
>18y
Non metastatic
ER+/Her2-
PN+
Disease free 3y HT

RANDOMIZE

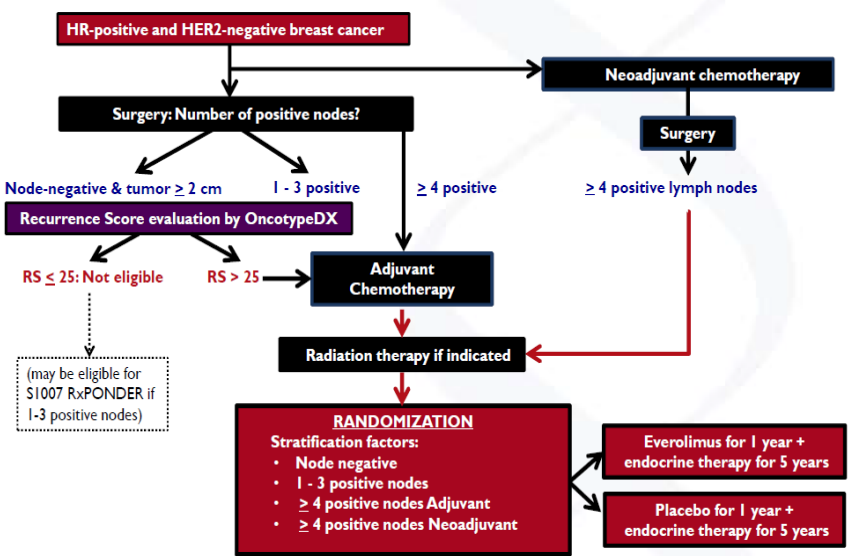
- **Eeverolimus** + **ongoing ET to 5y**
- **Placebo**

End points:
Primary:
DFS
Secondary:
OS, DMFS
Saftey

Phase III randomized, placebo-controlled trial adding 1 year of everolimus to adjuvant endocrine therapy for patients with high-risk, HR+, HER2- breast cancer.

SWOG-S1207

Planned Number = 3,500 an effective hazard ratio of 0.75 for everolimus versus placebo corresponding to a gain in DFS of approximately 4.3% at 5 years



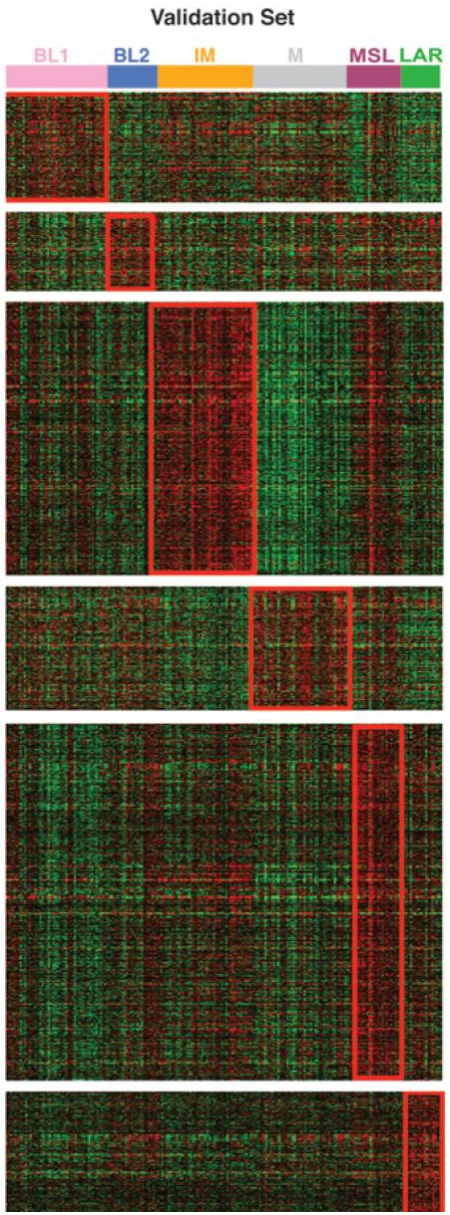
Focus on Triple negative B.C.

- **What did we learn ?**
- **Which questions do we still have to answer ?**

Adjuvant Therapy for triple negative BC

What did we learn?

- ✓ **TNBC is a heterogeneous disease**
- ✓ **There is a potential role for chemotherapy dose intensity**
- ✓ **There is no role for adjuvant bevacizumab**
- ✓ **There is a potential role for Platinum based therapy (confined to BRCA mutations carriers ?)**



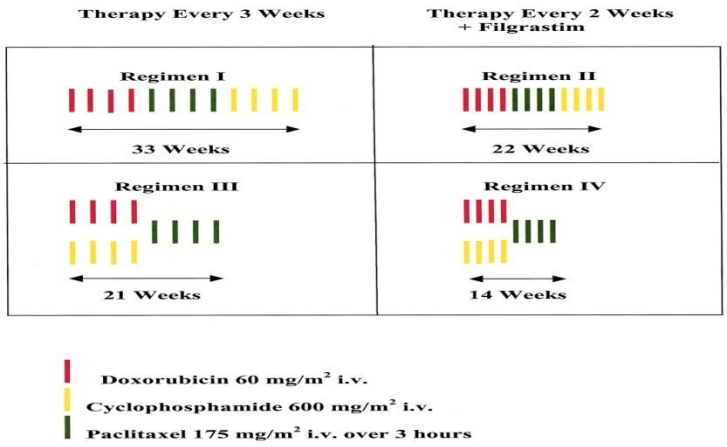
Subtyping of TNBC reveals marked heterogeneity in probabilities of pCR to neoadjuvant CT (anthracycline + docetaxel)

	pCR
Basal-like 1	++
Basal-like 2	-
Immunomodulatory	+(+)
Mesenchymal-like	+(+)
Mesenchymal stem-like	±
Luminal androgen-receptor	±
Unclassified	+(+)

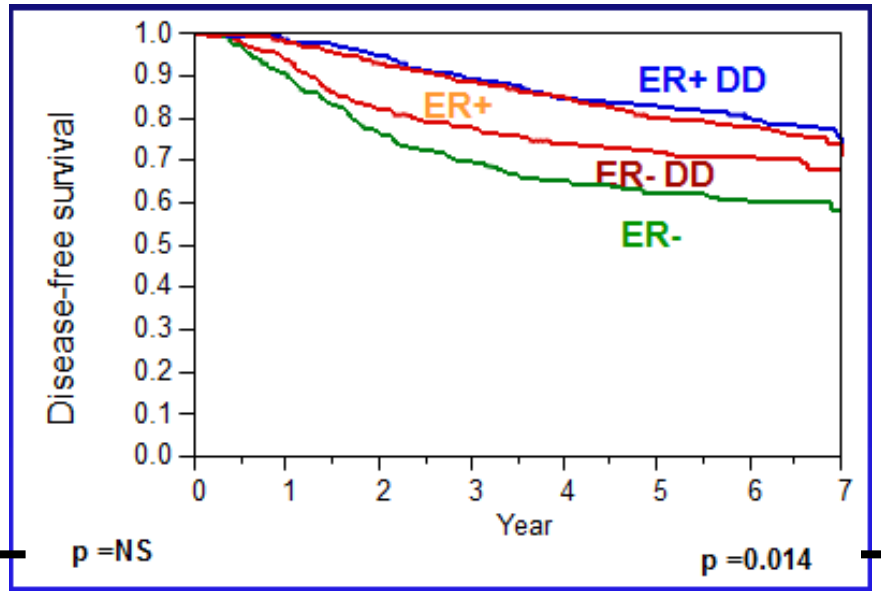
B. D. Lehmann, J Clin Invest 2011

H. Masuda ASCO 2013

DOSE-DENSE (DD) CHEMOTHERAPY IS AN OPTION FOR TNBC –CALGB 6y update



- Number: 2,005
- Population: LN +
- Dose dense > conventional
  - DFS [RR: 0.80; p=0.018]
  - OS [RR: 0.85; p=0.07]
- ER- DFS [RR: 0.75; p=0.03]



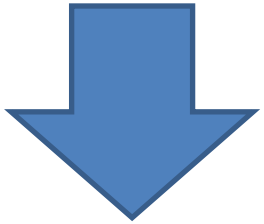
ER+ ← → ER-

UPDATE

Citron M et al; JCO 2003, Hudis SABCC 2005

Adjuvant CTX for TNBC

2009 - 2014



Renewed interest in Platinum compounds

PLATINUM SALTS & TNBC

Data from neo-adjuvant studies

Study	Year	N	Regimen	Efficacy
Gronwald et al	2009	25	Cisplatin x 4 (Q3w)	pCR: 72%
Garber et al	2006	28	Cisplatin x 4 (Q3w)	pCR: 22%
Torrisi et al	2008	30	Cisplatin + Epi +5Fu – Pac x 3	ORR: 86% pCR: 40%
Frasci et al	2009	74	Cisplatin + Epi + Pac x 8 (Q1w) + GCSF	pCR: 62% 5y DFS •90% (pCR) •56% (no pCR)

Randomized neoadjuvant trials in TNBC suggest a benefit from the addition of carboplatin to chemotherapy

	Sikov et al.	Von Minckwitz et al.
Pt population	N = 443 ♀ with TNBC	N = 595 ♀ with HER2+ and TNBC
Chemo backbone	Weekly paclitaxel (80mg/sqm)	Weekly paclitaxel (80mg/sqm) + Weekly pegylated doxo (20mg/sqm)
Carboplatin	AUC 6 q3wks	AUC 1.5 weekly
Bevacizumab	By randomization (2x2)	Added automatically for TNBC (15mg/kg q3wks)
Incremental pCR gain	41% → 54% (13%)	38% → 58% (20%)
Who benefits?	Ongoing analyses may lead to the identification of clinically relevant subsets	BRCA+ or strong familial Hx or TILs +++

Optimal adjuvant chemotherapy for TNBC

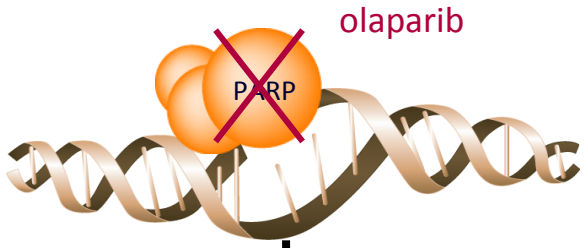
No consensus – as of today – on the role of Platinum compounds !
(will the incremental 20% gain in pCR translate into improved DFS, OS ?)

Adjuvant Therapy for triple negative BC

Interesting questions for the future

- ✓ **The role of PARP inhibitors in BRCA mutation carriers**
- ✓ **The role of metronomic chemotherapy**

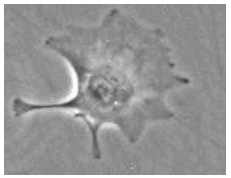
Exploiting DNA Damage Repair Deficits to Kill Cancer Cells



PARP plays a pivotal role in repairing single strand DNA breaks (SSBs). PARPi traps PARP on SSBs

Normal cell

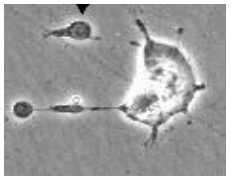
Repair by Homologous Recombination



Survival

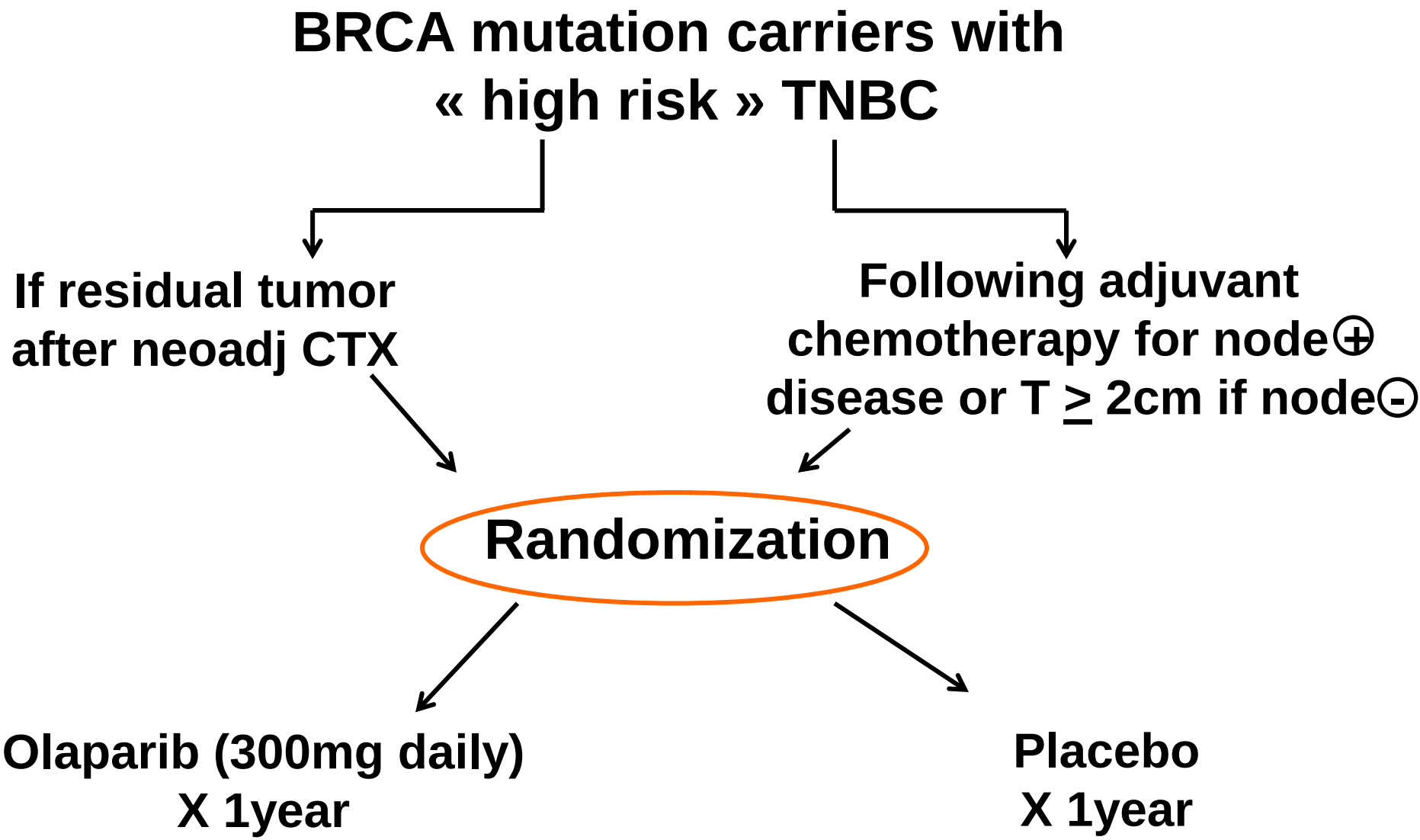
Cancer cell with BRCA mutation

continuous PARP inhibition leads to CUMULATIVE DNA DAMAGE GENOMIC INSTABILITY AND CELL DEATH



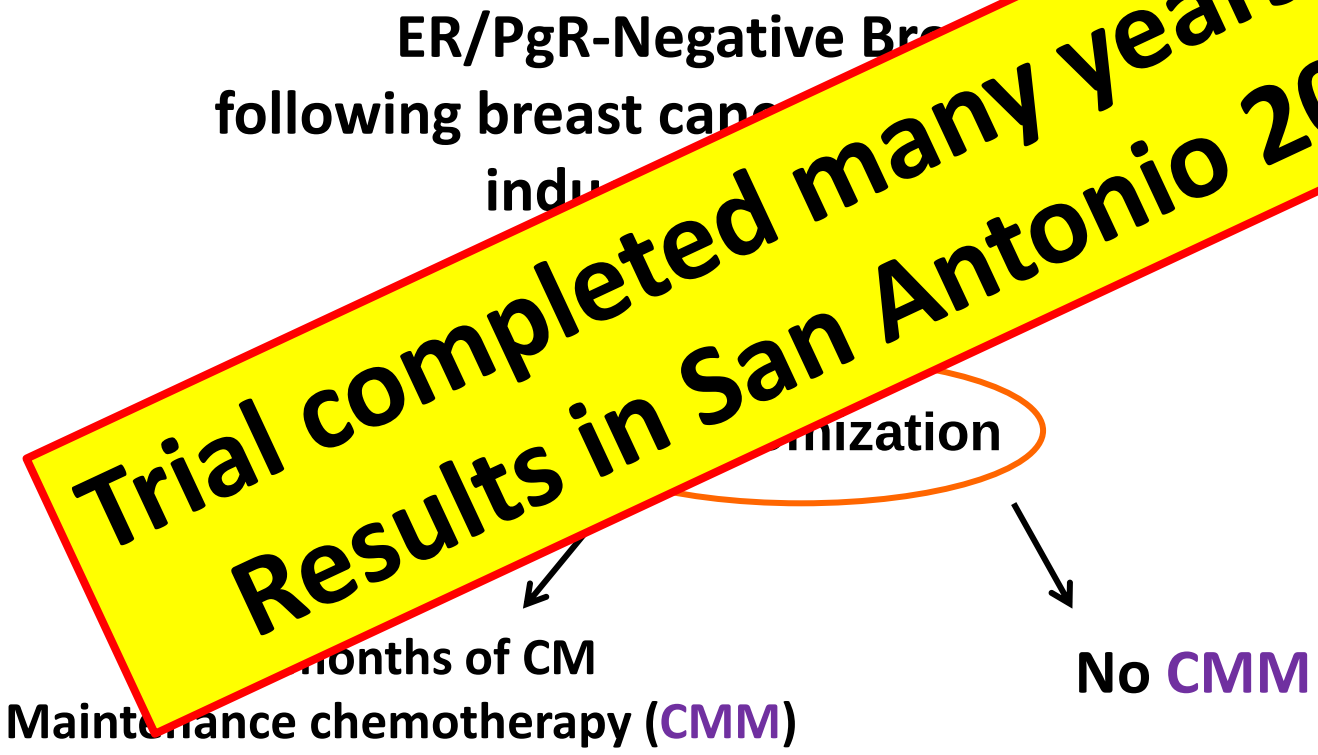
Death

Flow Chart- Olympia study design
(a collaboration between BIG and NSABP)



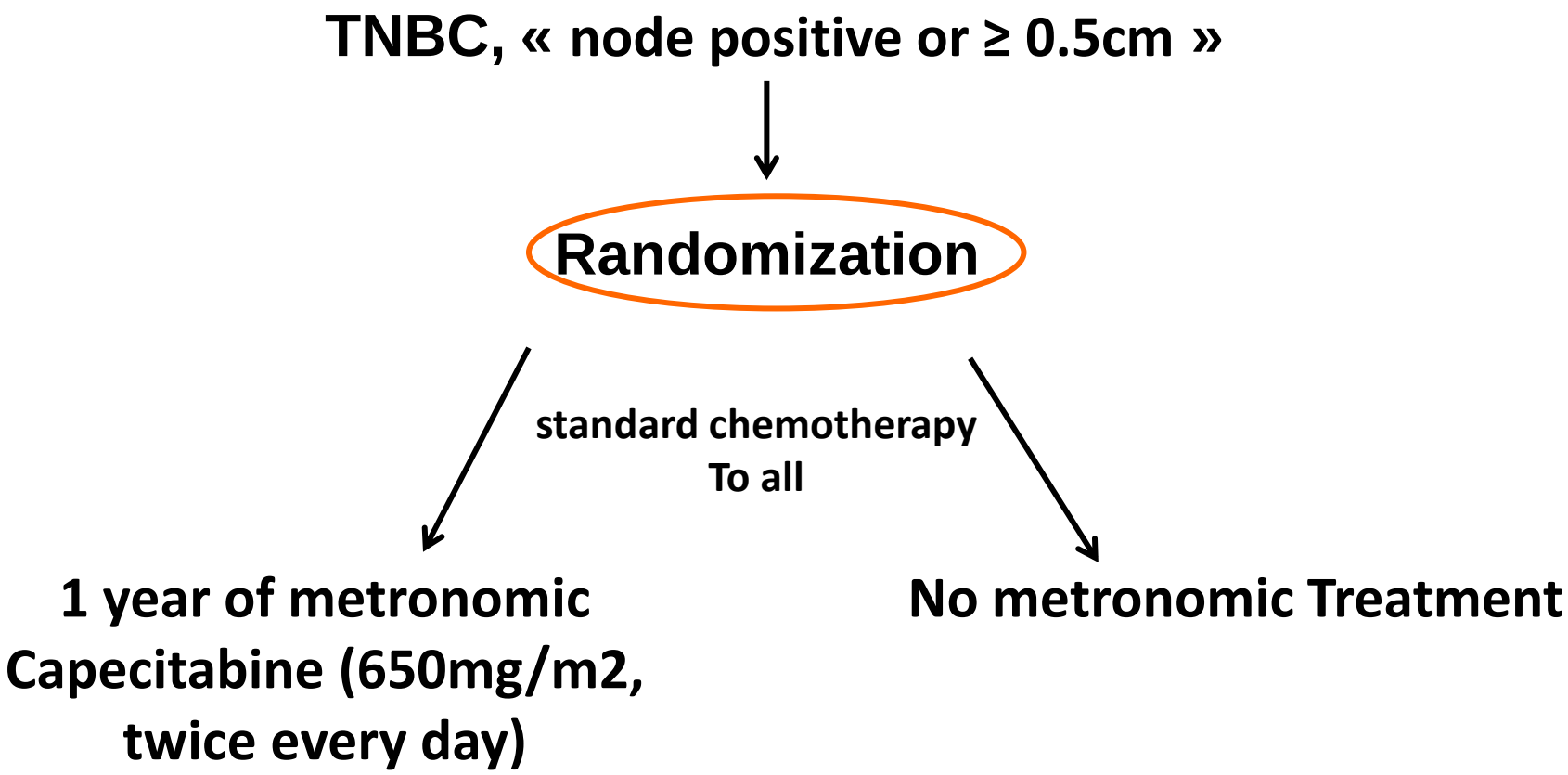
Metronomic Chemotherapy
International Breast Cancer Study Group
(IBCSG Trial 22–00)

Trial completed many years ago.
Results in San Antonio 2014!



CMM- Cyclophosphamide 50/mg/day orally continuously;
Methotrexate 2.5 mg/twice a day orally days 1 and 2 of every week for 1 year

Efficacy of Capecitabine Metronomic Chemotherapy in Triple-negative Breast Cancer (SYSUCC-001)



This study is currently recruiting participants

Focus on HER2+ B.C.

- **What did we learn ?**
- **Which questions do we still have to answer ?**

Adjuvant Therapy for HER2+ BC

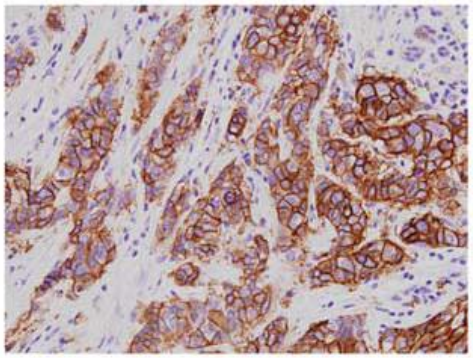
What did we learn?

- ✓ HER2+ BC is an heterogeneous disease
- ✓ There is no role for dual adjuvant blockade using T+L in the presence of aggressive chemotherapy
- ✓ There is still benefit from delayed adjuvant antiHER2 therapy
- ✓ For T_1N_0 tumors, the Dana Farber regimen offers a very favourable Benefit/Harm ratio
- ✓ TILs are now accepted as important stratification and prognostic factor in clinical trials for HER2+ BC
- ✓ There is no role for adjuvant bevacizumab

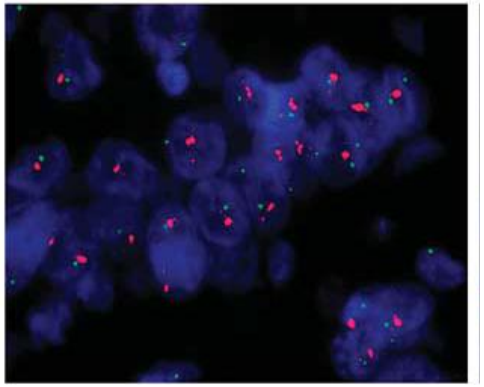
HER2 positive breast cancer

HER2+ BC
by IHC /FISH

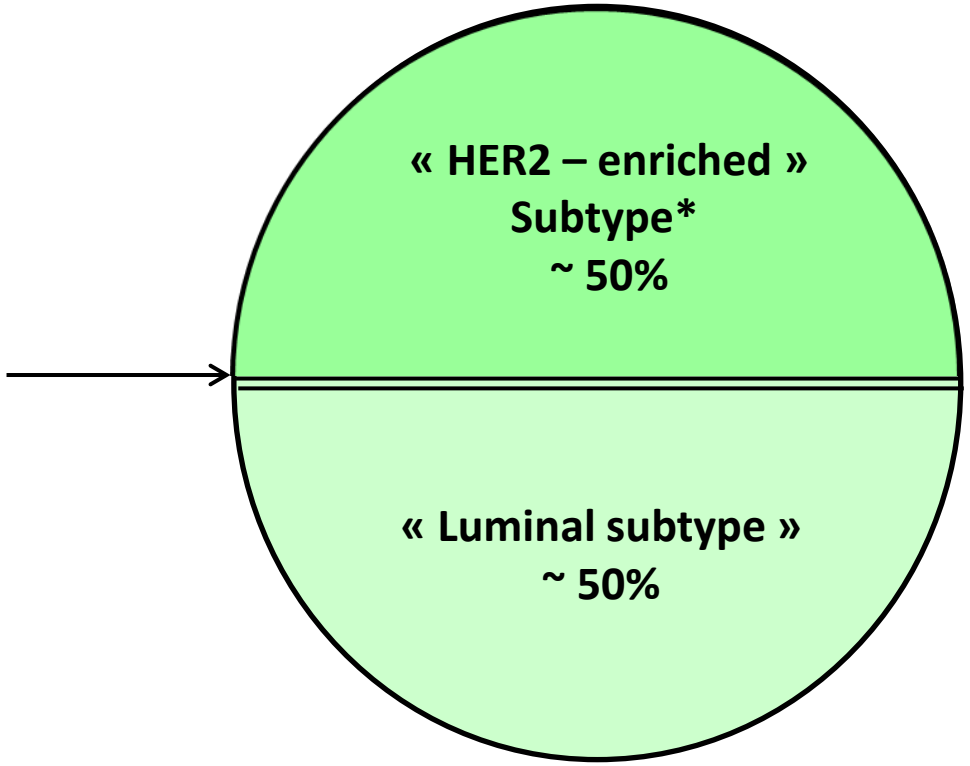
HER2 IHC



HER2 FISH



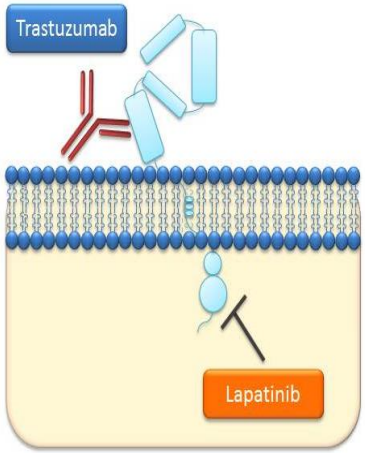
Gene-expression (PAM_{50}) analysis



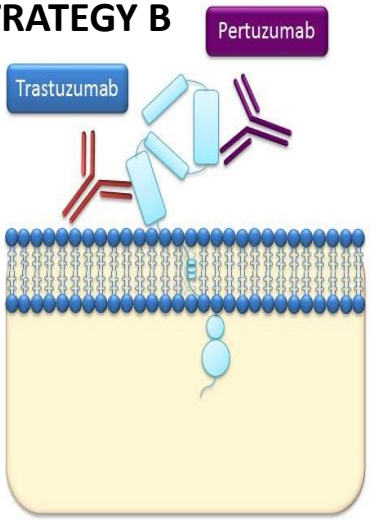
*** Enrichment for proteins encoded by genes in the HER2 amplicon (EGFR, FGFR, CDK4, Cyclin D1…)**

AVAILABLE RESULTS OF DUAL HER2 BLOCKADE PRIOR TO ASCO 2014

STRATEGY A



STRATEGY B



Advanced Disease
↑ PFS and OS
(2 trials)

EGF104900 (N= 296)

Cleopatra (N= 808)

Neoadjuvant setting
Significant ↑ ↑ pCR
(4 trials)

NeoALTTO (N= 455)

Cherlob (N= 121)

LPT 109096 (N= 78)

NeoSPHERE (N= 417)

Non significant ↑ pCR
(2 trials)

NSABP B-41 (N= 529)

CALGB 40601 (N= 305)

Adjuvant setting

ALTTO (N= 8,381)

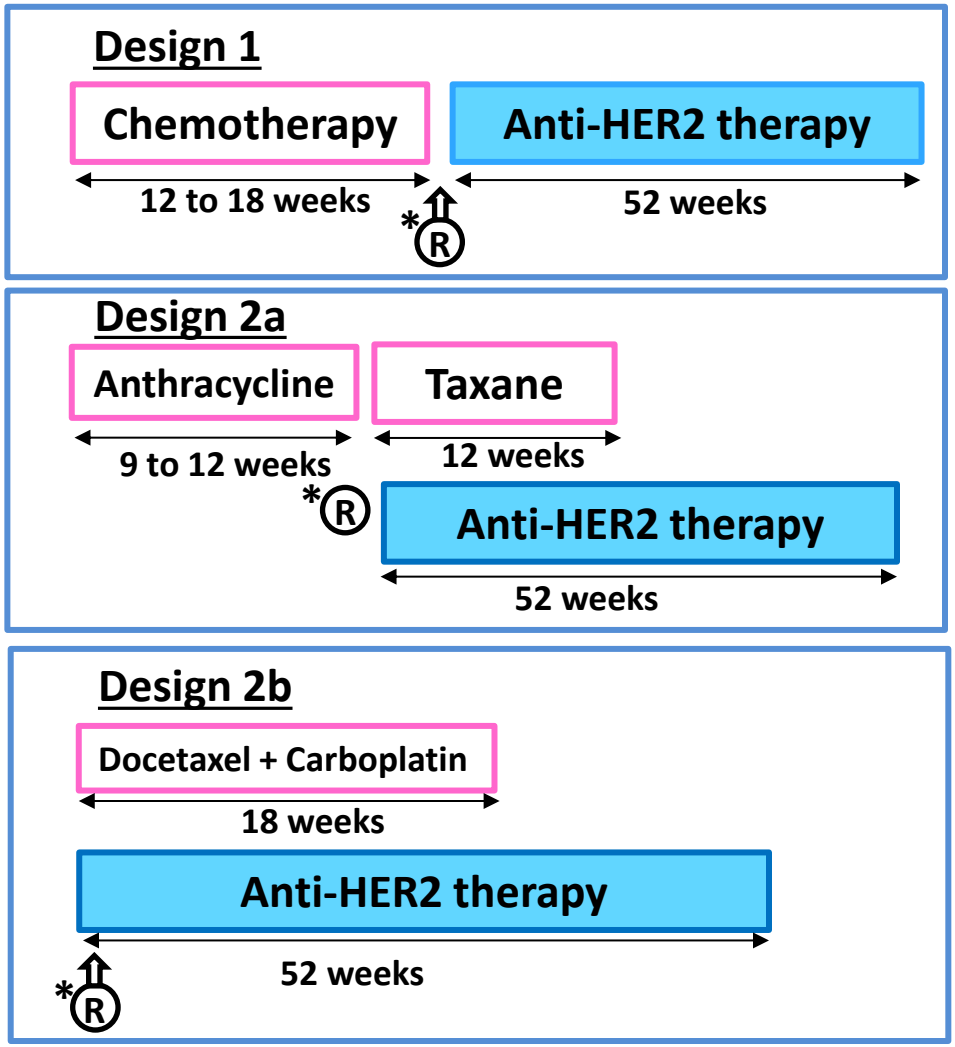
APHINITY (N= 4,805)

ALTTO STUDY DESIGN

Anti-HER2 therapy: 4 groups assigned by randomization

- Trastuzumab (T) x 52 weeks
- Lapatinib (L) x 52 weeks
- T x 12 wks ⟷ L x 34 weeks (6 weeks)
- Trastuzumab x 52 weeks and Lapatinib x 52 weeks

3 modalities of adjuvant CT administration per physician's choice



* R: refers to the timing of randomization

ASCO 2014

Comparison	Assumptions	Result (HR, 97.5% CI, P-value)
L + T vs. T	Test superiority in intention-to-treat (ITT) population at alpha = **0.025**	0.84 (0.70, 1.02), p = **0.048**
T→ L vs. T	Test non-inferiority in per protocol population (PPP) at alpha = **0.025**	0.93 (0.76, 1.13), p = **0.044**

CONCLUSIONS

- **The ALTTO trial did not meet its endpoints (DFS): Neither the L + T vs. T comparison nor the T → L vs. T comparison.**

- **The doubling in pCR observed with L + T in NeoALTTO did not translate into improved survival outcomes in ALTTO**

LESSONS LEARNED from the ALTTO TRIAL RESULTS

- ✓ **A substantial proportion of women with HER2+ BC are cured by today's adjuvant chemotherapy and trastuzumab**
- ✓ **Moving a new drug (eg: lapatinib) too quickly to the adjuvant setting carries significant risks**
- ✓ **For the neoadjuvant model to have a chance to predict outcome in the adjuvant setting, most « key players » must be given prior to surgery (in NeoALTTO, anthracyclines were given postoperatively)**
- ✓ **The best use of dual HER2 blockade might be in the context of adjuvant chemotherapy de-escalation**

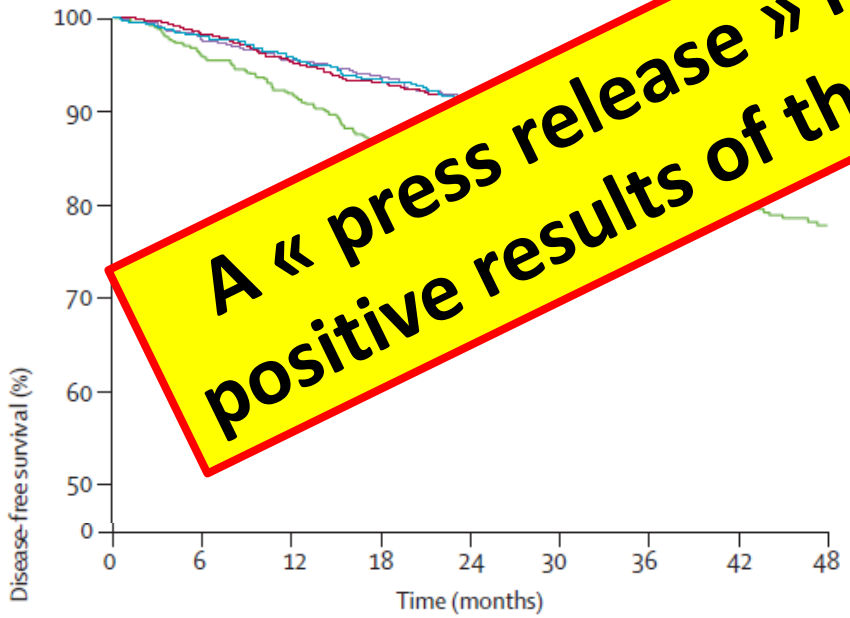
Does Lapatinib have some activity in the adjuvant setting?

	ITT population				FISH+ group		
	Lapatinib group (n=1571)	Placebo group (n=1576)	HR (95% CI)	p value	Lapatinib group (n=1230)	Placebo group (n=1260)	p value
Disease-free survival	210 (13%)	264 (17%)	0·83 (0·70–1·00)	0·053	157 (13%)		
Overall survival	92 (6%)	97 (6%)	0·99 (0·74–1·31)	0·96	79 (6%)		
Time to first recurrence	172 (11%)	220 (14%)	0·82 (0·67–1·00)	0·051			0·033
Time to distant recurrence	125 (8%)	156 (10%)	0·84 (0·67–1·06)	0·16			0·11
CNS recurrence as first recurrence	13 (<1%)	21 (1%)	0·65 (0·33–1·28)			0·66 (0·33–1·34)	0·28

Data are n (%) unless otherwise stated. HRs are unadjusted. ITT=intention-to-treat. FISH+=*HER2*-positi… …ation.

Table 2: Primary and secondary outcomes for the intention-to-treat populatio… …rmed centrally by fluorescence in-situ hybridisation

A « press release » in the US has announced positive results of the Neratinib adjuvant trial !



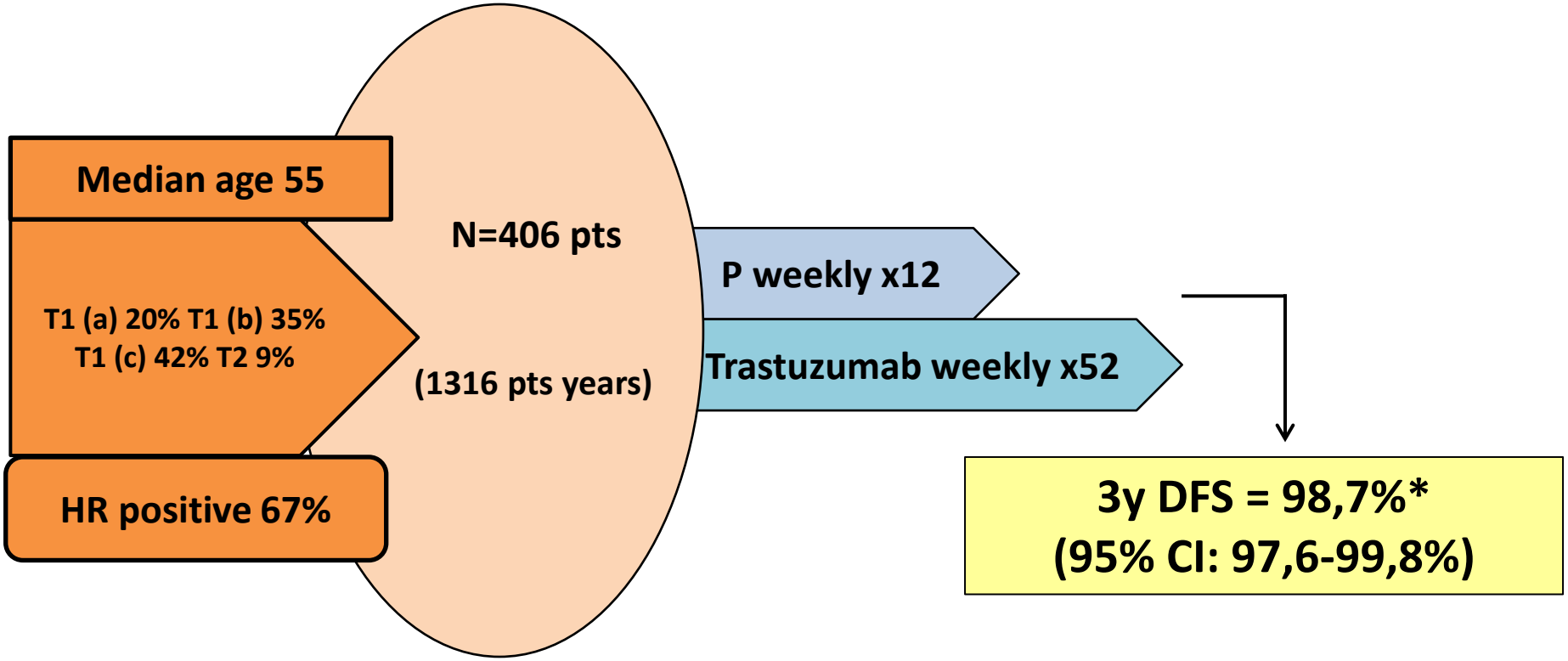
…ithout Trastuzumab

Lapatinib shows efficacy especially in ER-

Paul E Goss Lancet Oncology 2013

Small HER2+ BC: the Dana Farber prospective phase II study

Can aggressive chemotherapy be avoided?

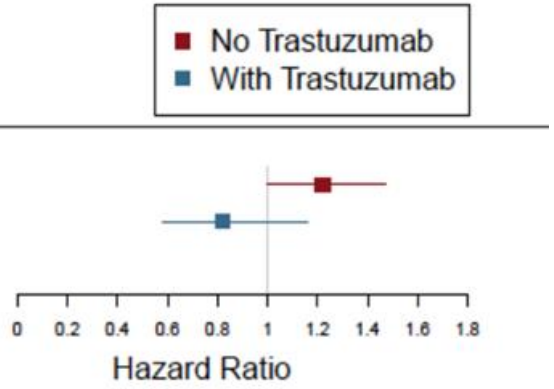


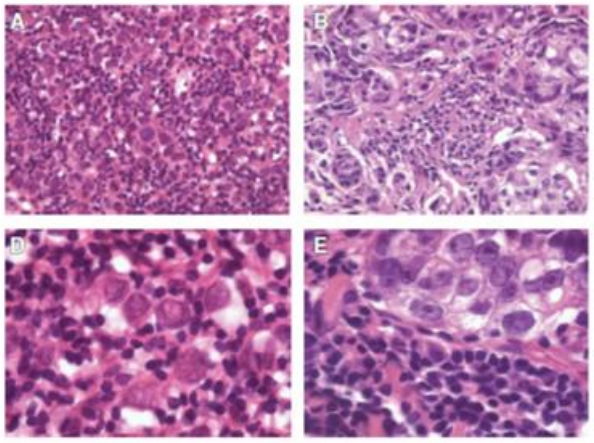
*10 « events », only 2 distant metastases

Tolaney SM et al., abst S1-04, SABCS 2013

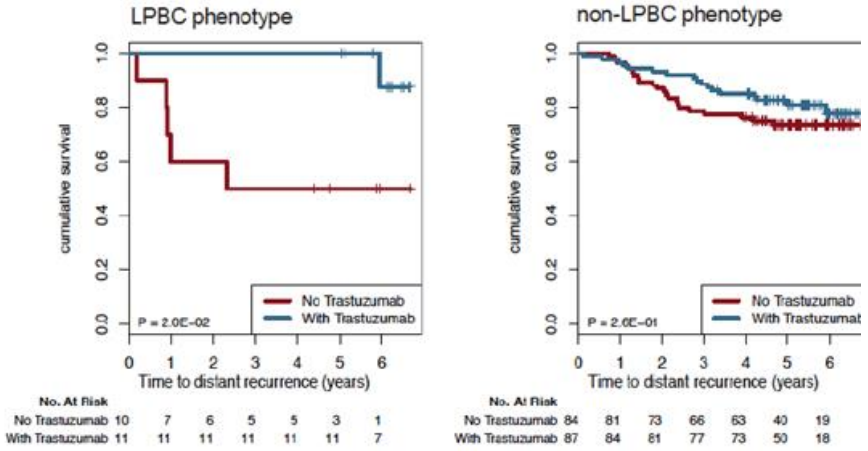
LYMPHOCYTIC INFILTRATION PREDICTS FOR TRASTUZUMAB RESPONSE IN THE FINHER TRIAL

TILs (10% increments)	HR	95% CI	DDFS interaction P Value
No Tras	1.22	1.0 to 1.47	2.5e−02
WithTras	0.82	0.58 to 1.16	





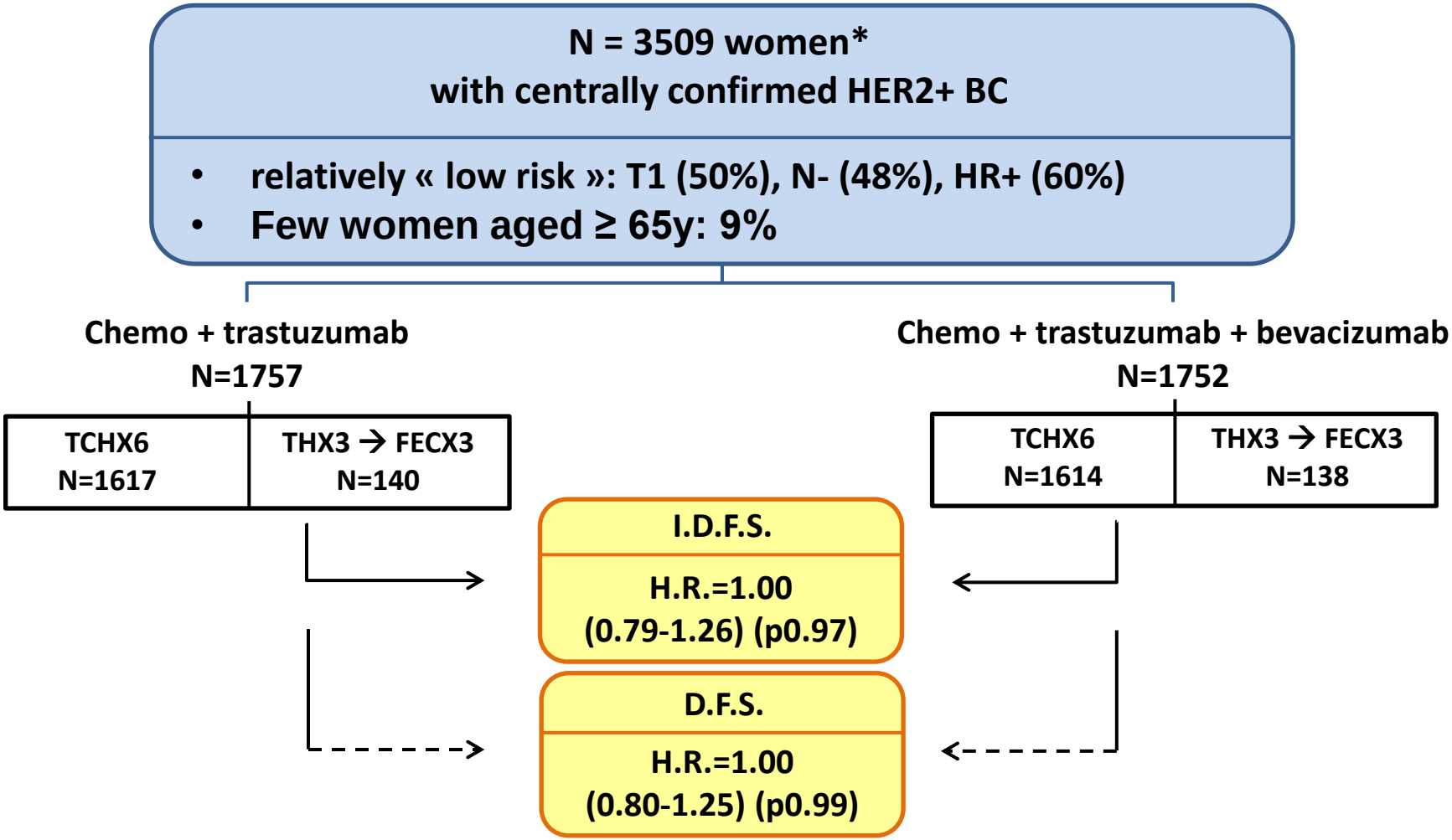
Denkert et al, JCO 2010; Loi et al, JCO 2013
Loi et al, ASCO 2012



Lymphocyte Predominant Phenotype LPBC >50% infiltration

Sherene LOI Annals of Oncology 2014

The negative results of the BETH trial (BCRIG + NSABP + independent centers) at a median followup of 38 months



* Study with 86% power to detect HR0,70 in IDFS

D. Slamon, abst 51-03, SABCS 2013

Adjuvant Therapy for HER2+ BC
Interesting questions for the future

- ✓ **Who is cured by current practice?**
- ✓ **Who can be cured with less aggressive chemotherapy ?**
  TDM1 neoadjuvant trial in preparation!
- ✓ **Will there be a role for Pik3 CA inhibitors?**
  Or for anti PD1 / PDL1 drugs?

Possible reasons for failure in incorporating new drugs in the adjuvant treatment scheme

- **Stage shifting- Improved radiological examination (PET-CT)**
- **Improved local treatments.**
- **Benefit in the metastatic or neoadjuvant settings not large enough (bevacizumab) or not optimally demonstrated (lapatinib)**
- **Lack of imagination or "courage" to move to innovative clinical trial designs**

ADJUVANT THERAPY IN BREAST CANCER

Quo vadis?

General conclusions

« Tailored » adjuvant systemic treatment = ??

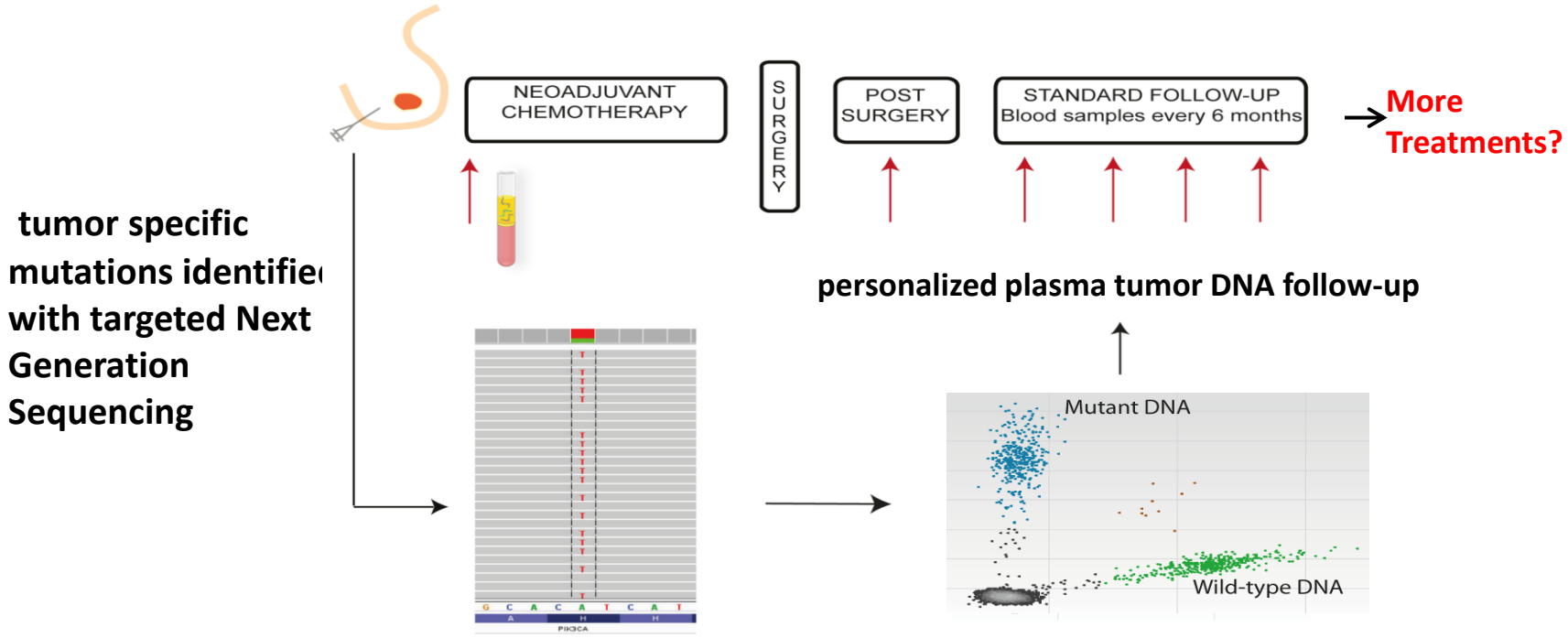
The present...

- **Avoiding chemotherapy in case of a genomically-defined low risk luminal cancer**

The future?

- **Improving the selection of cytotoxic drugs (± PARP inh) in the case of TNBC**
- **De-escalating chemotherapy in case of exquisit sensitivity to targeted drugs (in the case of HER2+ BC)**

The future of management of early BC could change dramatically !

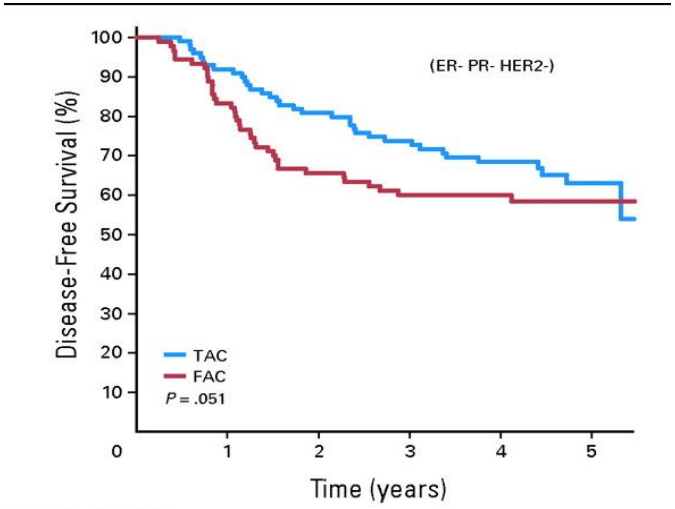


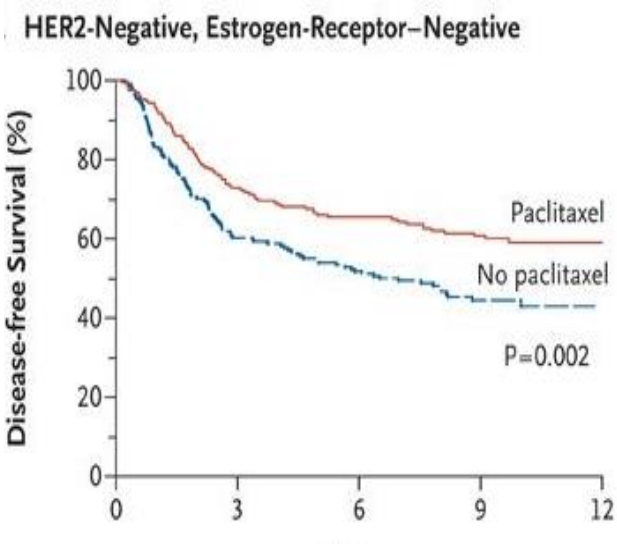
N. Turner, ASCO 2014

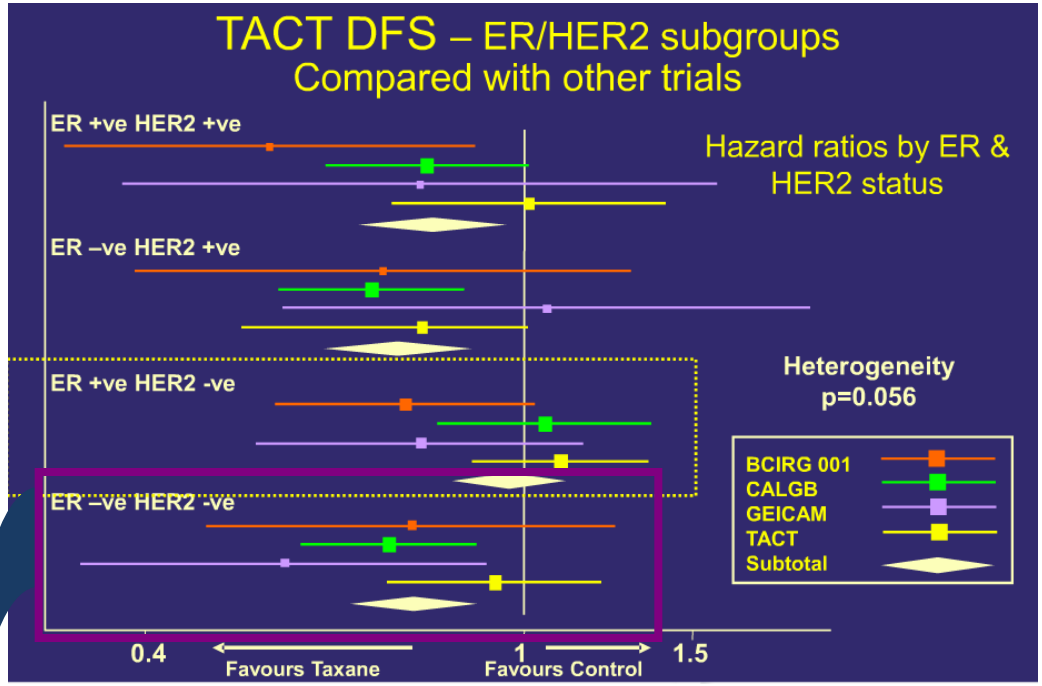
THANK YOU !

Back-up

TAXANES IN TNBC

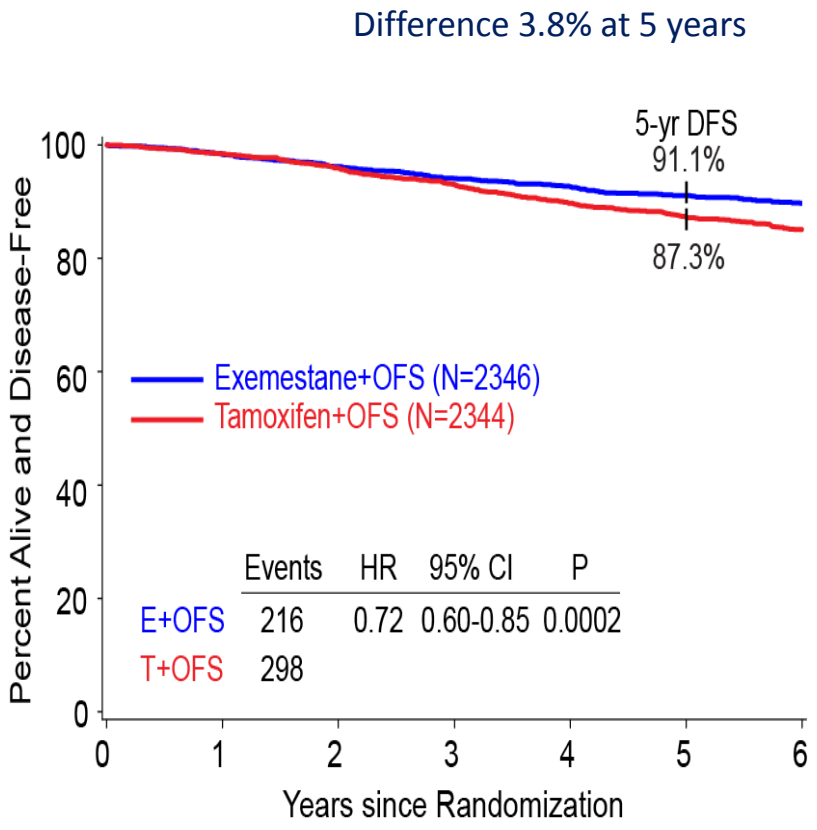


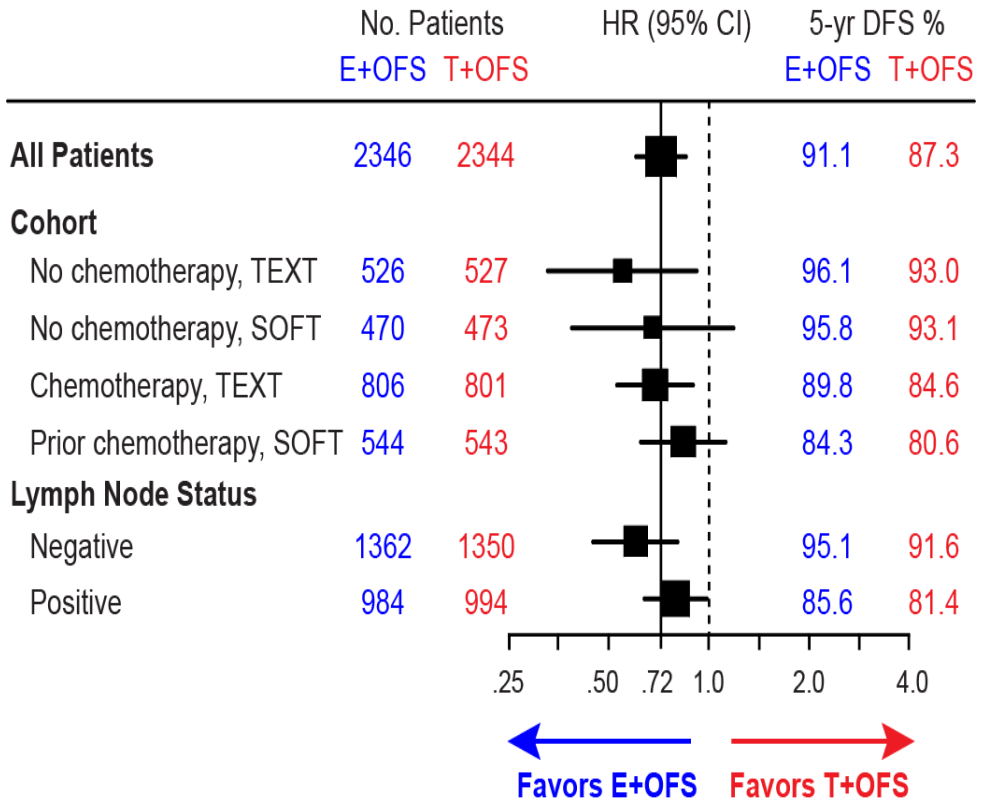




Triple –ve tumors seem to derive higher benefit when taxanes are added to anthracyclines

Exemestane+OFS Improved DFS

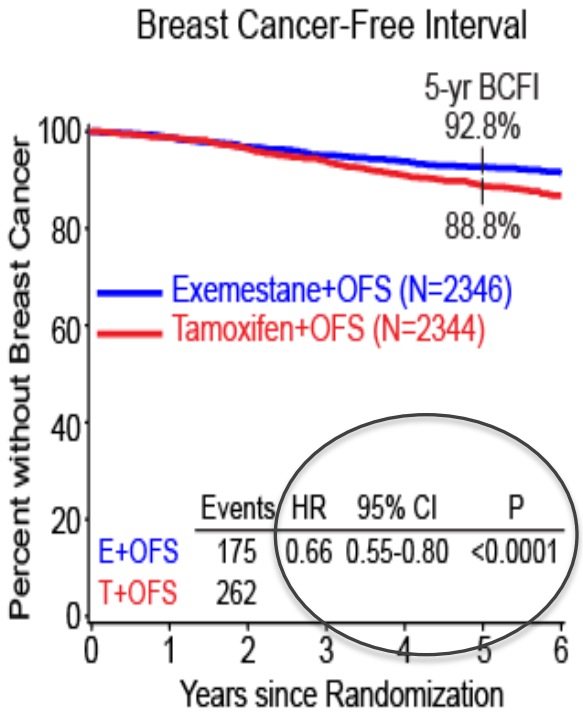


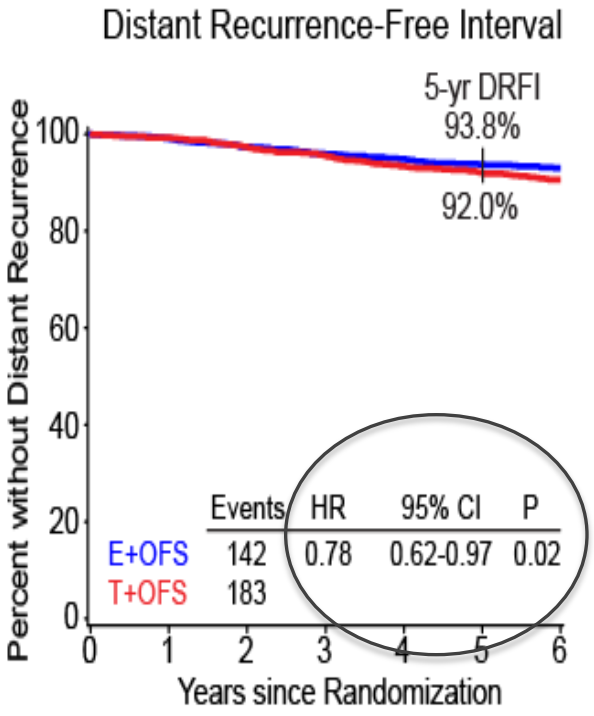


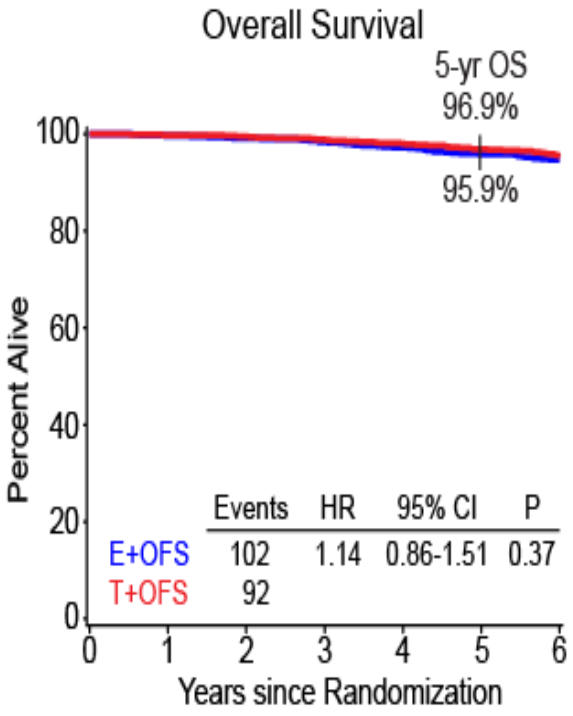
5.7 years median follow-up

Olivia Pagani, NEJM 6/2014

Exemestane+OFS Reduced Recurrence



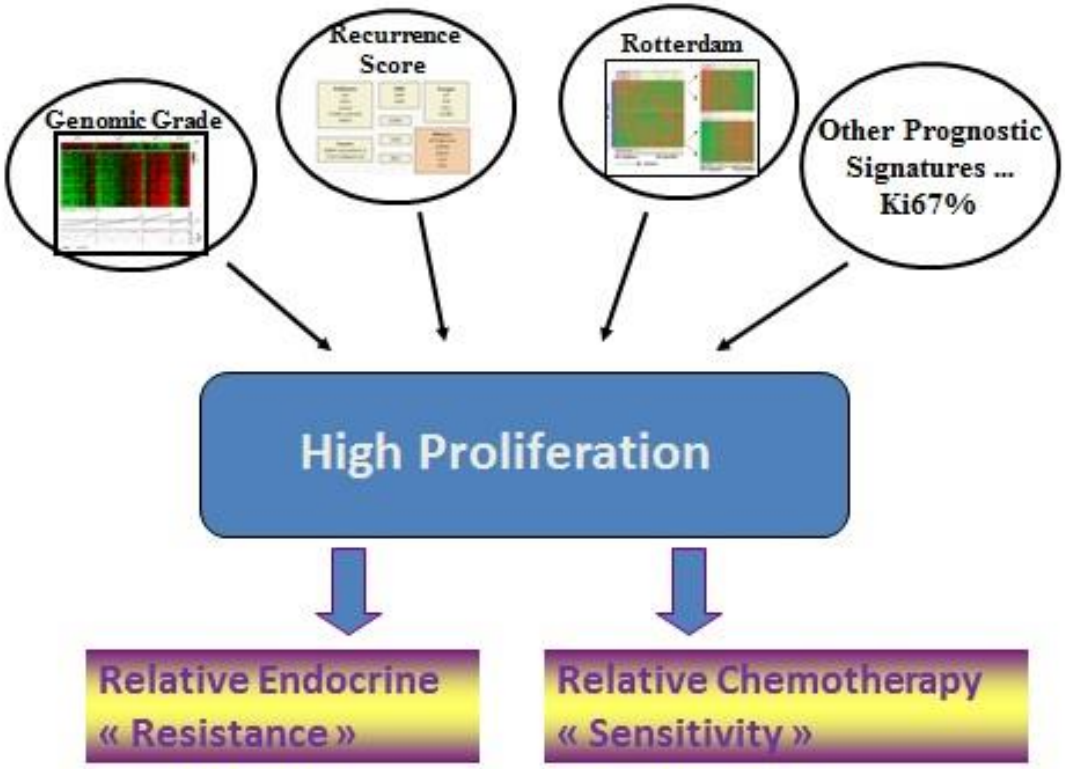




No Survival effect

Olivia Pagani, NEJM 6/2014

Luminal ER+ Cancers

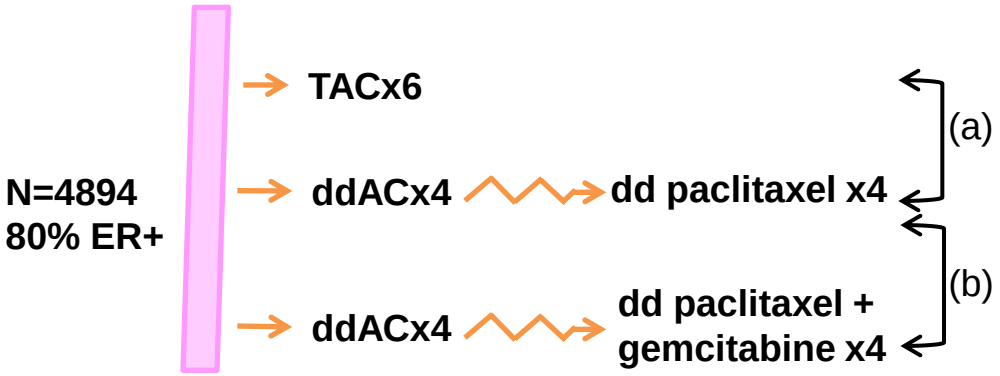


Luminal ER+ Cancers
What did we learned

- ✓ Increased BC mortality in high BMI premenopausal woman
- ✓ Extending tamoxifen to 10y is preferred over 5y – after risk assessment
- ✓ **Exemestane+OFS** is an emerging option for premenopausal woman
- ✓ Paclitaxel alone not proven equivalent to AC
- ✓ Low proliferating tumours probably can be spared from taxanes
- ✓ No role for adjuvant Bevacizumab

Adjuvant Chemotherapy trials
5 year follow-up

NSABP-B38 (N+)

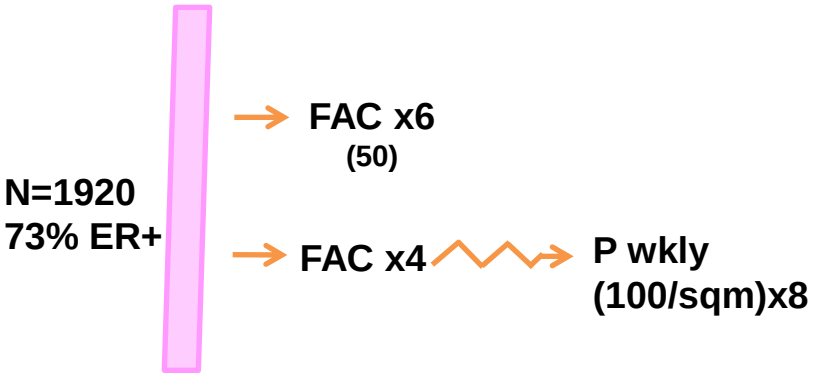


All arms equal as far as DFS/OS
(a): no difference
(b): no difference

Sequential arms : more neuropathy and anemia

Combination arm : more neutropenia, diarrhea

Geicam 2003-02 (N- high risk)



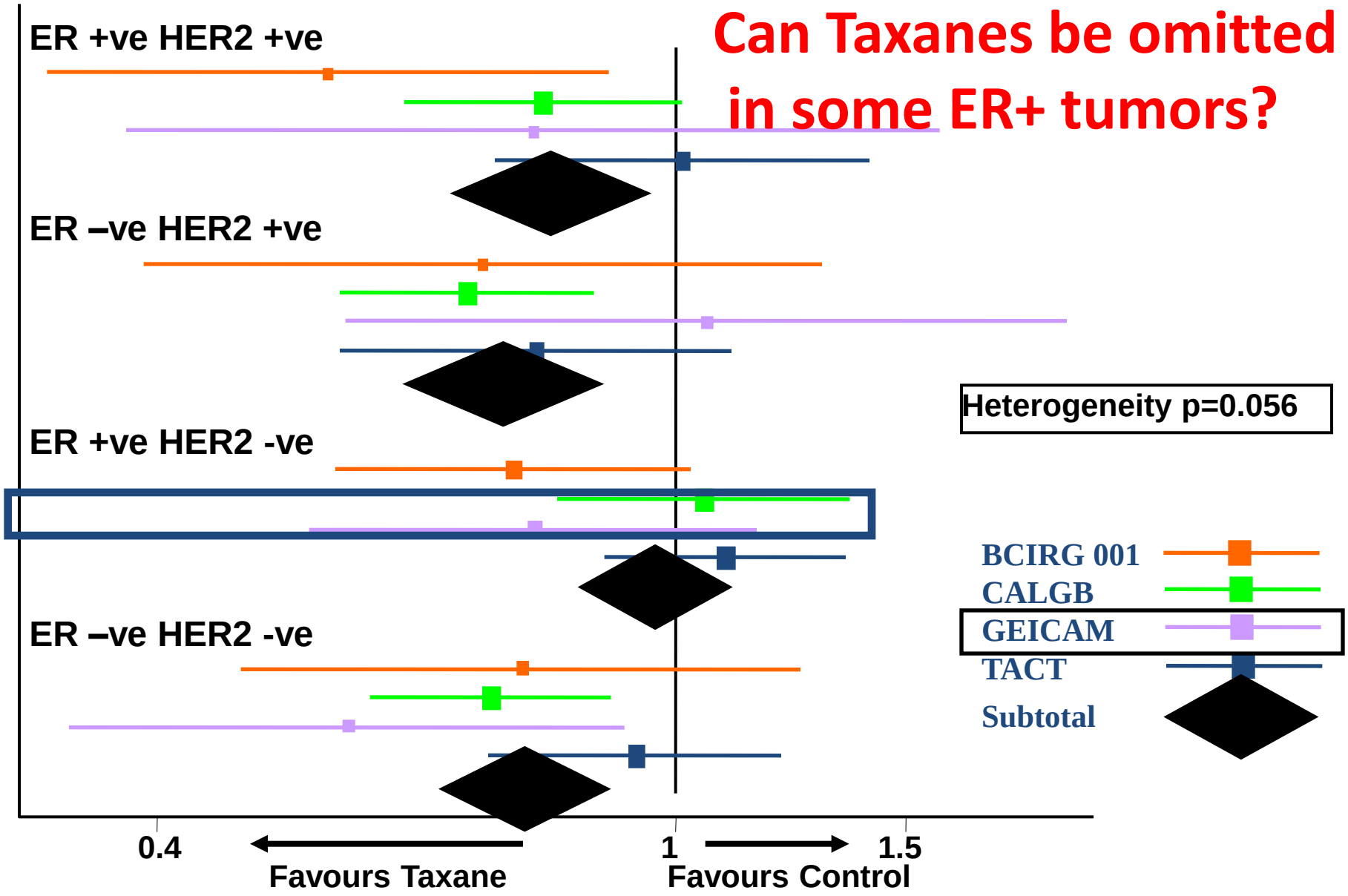
Sequential arm better
H.R. DFS = 0.73 (p0.04) (90%→93%)
H.R. OS = 0.76 (p0.26)

Sequential arm : more short term toxicity
(fatigue + neurotoxicity)

Combination arm : 5 late cardiac deaths!

META-ANALYSIS OF 4 TRIALS

BCIRG 001, CALGB 9344, GEICAM & TACT



TAXANES IN ADDITION TO ANTHRACYCLINES ARE NOT OF UNIVERSAL BENEFIT

EVIDENCE SUGGESTS LITTLE BENEFIT IN ER+ HER-ve TUMOURS WHICH ALSO HAVE KI67 OR ARE LUMINAL A

Smith I; SABCS 2009

Clinical Advances in Adjuvant Triple negative BC
Take home messages

- ✓ TNBC is a heterogeneic group
- ✓ There is potential role for dose intensity.
- ✓ There is no role for adjuvant bevacizumab
- ✓ Potential fertility preservation using LHRH agonist Goserelin during adjuvant treatment
- ✓ BRCA germline testing should be encouraged in TNBC especially in Pt<60.
- ✓ Potential role for Platinume

  -Potential enrolment to the Olympia trial(PARP inhibitor)

Predictive tools in TNBC

Neoadjuvant setting

Anthracycline benefit

Multidimensional gene signature incorporating topo2/apoptosis and immune genes : AUC = 0.71

(N = 147 TNBC receiving A but no T; 28 with pCR)

Neoadjuvant setting

Platinum benefit in GeparSixto

TILLs, better than immune mRNAS predict for ↑ pCR and carboplatin benefit

(N = 481/595 pts
pCR overall 53% vs 37
pCR if TILLs 74% vs 43

BRCA status and family Hx predict carbo effect with 25% absolute ↑ pCR

(N = 315/41 BRCA)

Metastatic setting

Platinum benefit (single agent)

Only Homologous Recombination Deficiency assays predictive !

(N = 86 pts incl. BRCA mut carriers)

abst 1025 (Di Leo), 510 (Denkert), 1005 (Von Minckwitz) and 1020 (Boston)

Early disease : fertility preservation

The « POEM » trial for < 50y women with ER-/PgR- tumors*

Standard adjuvant CTX (with cyclophosphamide)

Goserelin started ≥ 1wk prior to CTX (q4wk administration) Standard adjuvant CTX (with cyclophosphamide)

Primary goal : detect an absolute ↓ by 15% in « ov failure » at 2y (80% power)
Secondary : pregnancy outcomes
Exploratory : EFS, OS

N = 416 women needed

** Cutoff : <10% ⊕ cells*

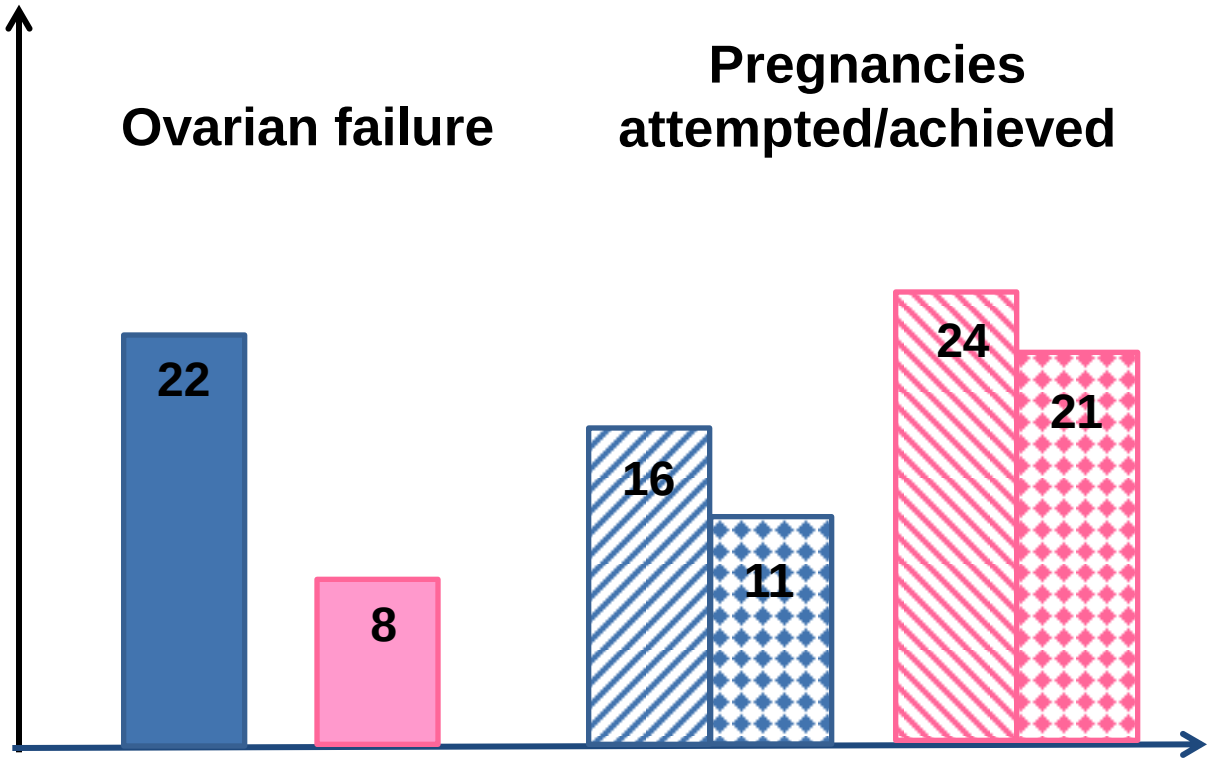
LBA 505 ASCO 2014

ASCO 2014 Breast Cancer Highlights

Early disease : fertility preservation

The « POEM » trial

N = 218 analyzable women among 257 randomized



DFS HR : 0.47 (0.24 – 0.95)

OS HR : 0.45 (0.19 – 1.04)

CTX

CTX + Goserelin

Clinical Advances in Adjuvant HER2+ BC
Take home messages

- ✓ S.C. trastuzumab is likely to « take over » the role of I.V. trastuzumab
- ✓ For T_1N_0 tumors, the Dana Farber regimen offers a very favourable Benefit/Harm ratio but the f-up is only 3 years
- ✓ Older women (≥ 65y) should not be denied adjuvant CT + trastuzumab in view of a favorable benefit/harm ratio
- ✓ There is no role for adjuvant bevacizumab
- ✓ There is no role for dual adjuvant blockade using T+L
- ✓ TILs are accepted as important stratification and prognostic factor in clinical trials for HER2+ BC and standardization efforts among pathologists are ongoing

TARGETING HER2 IN BREAST CANCER: EVOLVING CONCEPTS

Single HER2 blockade with trastuzumab ↑↑ DFS (B-31, N9831, HERA)

ALTTO Recruitment

Will dual HER2 blockade further ↑ DFS? (ALTTO)

ASCO 2005 — 2006 — 2007 — 2011 — 2012 — 2013 — ASCO 2014

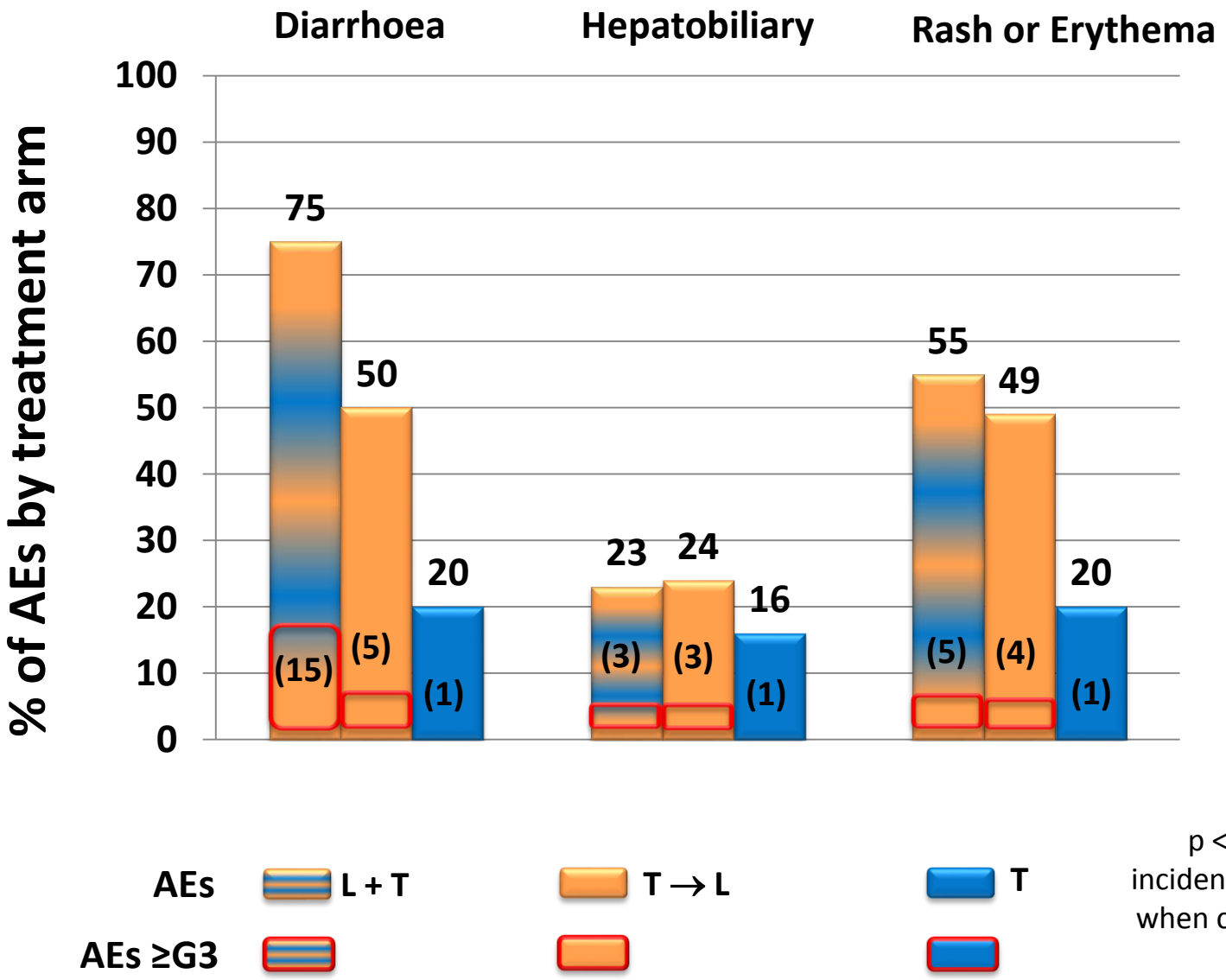
Trastuzumab (T): immune mechanism of action poorly appreciated

Lapatinib: more potent signalling network inhibitor with additional attractive features (oral drug, low cardiotoxicity, some activity against brain mets, encouraging single agent activity in pts, no cross resistance with T)

Trastuzumab + Lapatinib: synergistic in the lab and, potentially, in the clinic

Further clinical evidence supporting dual HER2 blockade in the clinic

MAIN DIFFERENCES IN AEs BY TREATMENT ARM



$p < 0.001$ for incidence for all arms when compared to T

Adjuvant trastuzumab (T) benefits/risks in Older women

- The prevalence of abnormal baseline LVEF (<50%) in 702 women considered for anthracycline or trastuzumab is low: 2% and unrelated to age, BMI, preexisting cardiac risk factors [1]

- A large observational study of adjuvant T use in Germany shows similar 5y recurrence free survival in 2927 women aged < 65y and 1013 women aged ≥ 65y, with only a slight increase in grade 3-4 cardiac function toxicity in the latter (1.6% vs 0.9 %) [2]

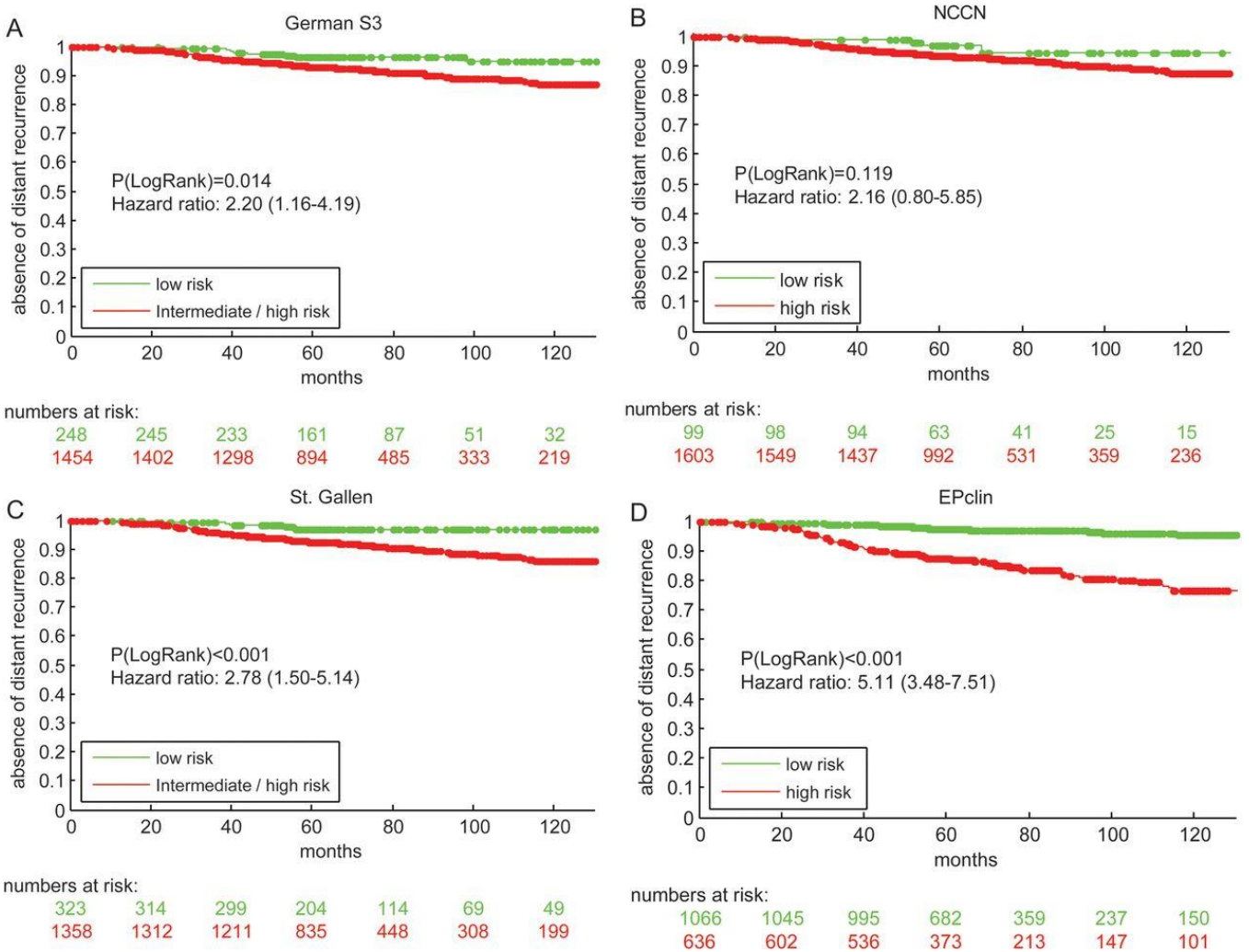
SABCC 2013

(1) Abst P6-06-09
(2) Abst P2-15-02

Subcutaneous trastuzumab preferred to i.v. trastuzumab

Results from Cohort 2 of the PrefHER trial (handheld syringe) are consistent with those of cohort 1 (single use injection device) and indicate a clear preference of patients (and health care professionals) for the sc delivery method!

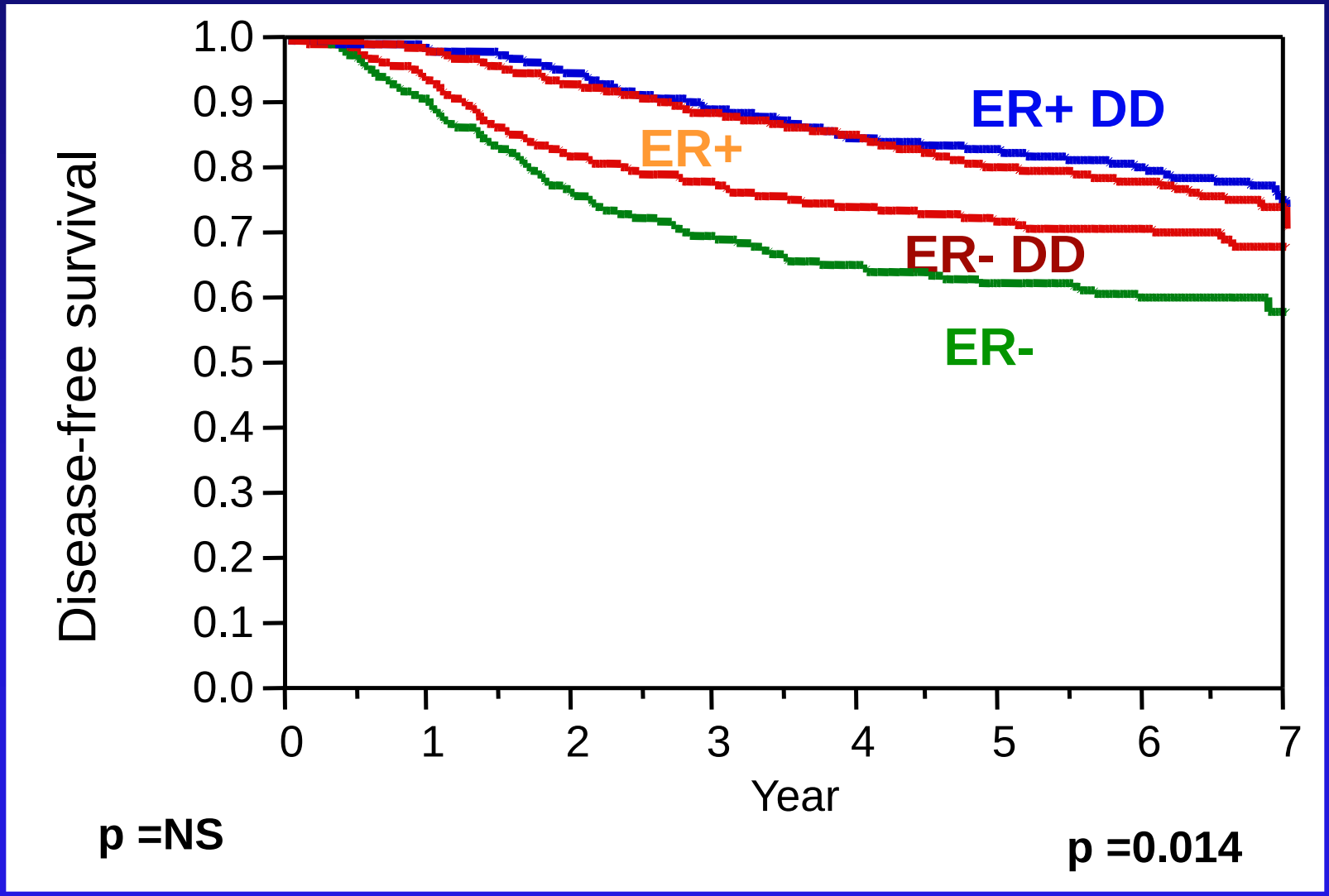
Kaplan–Meier plot of distant metastasis-free survival (MFS) by (A) German S3, (B) National Comprehensive Cancer Center Network (NCCN), (C) St Gallen guidelines and (D) EPclin risk groups. 95% confidence intervals (CI) of hazard ratios (HR) are indicated.



Dubsky P et al. Ann Oncol 2013;24:640-647

Annals of Oncology

C9741: DFS by ER Status & Dose Density



Hudis C, et al: San Antonio, 2005

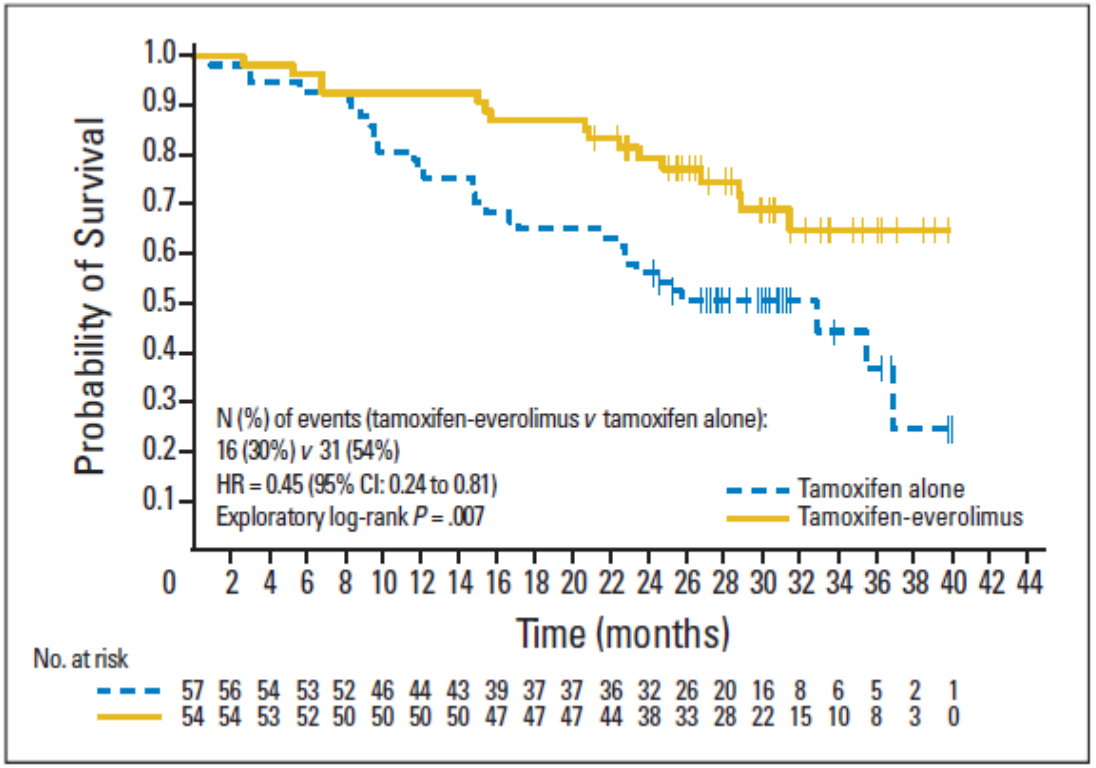
MAY BE AN OPTION FOR TNBC

	Q 2 wk		Q 3 Wk		HR	P value
	Pts (n)	Failures	Pts (n)	Failures		
Disease Free Survival						
ER-	335	98	327	122	0.75 (0.57 - 0.97)	0.031
ER+	636	113	639	130	0.86 (0.67 - 1.11)	0.26
Total	988	215	984	260	0.80 (0.67 - 0.96)	0.018
Overall Survival						
ER-	335	81	327	100	0.77 (0.57 - 1.03)	0.073
ER+	636	74	639	80	0.92 (0.67 - 1.26)	0.61
Total	988	159	984	185	0.85 (0.68 - 1.05)	0.12

Huuis C et al. SABC 2005. Abstract 41.

Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With ER=/HER2-, Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors

Overall survival benefit in the intention-to-treat population



Thomas Bachelot JCO 2012

Phase 3 Trials in breast cancer inhibiting CKDs

PALOMA1-3

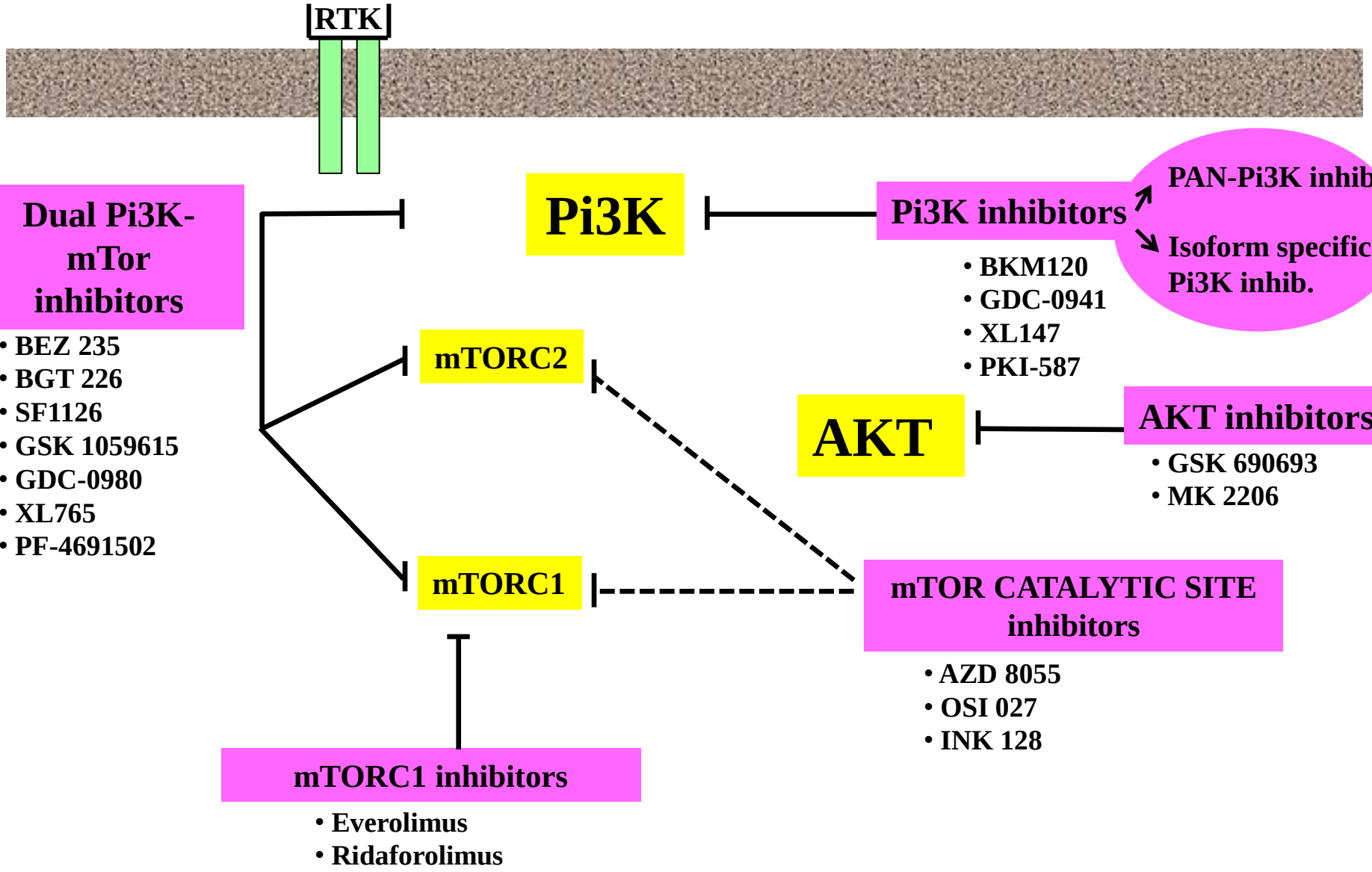
palbociclib (PD-0332991)	CDK 4,6 Kinase Inhibitor	1st Line Advanced Breast Cancer, *Cancer	Phase 3
▶palbociclib (PD-0332991)	CDK 4,6 Kinase Inhibitor	High Risk Early Breast Cancer	Phase 3
palbociclib (PD-0332991)	CDK 4,6 Kinase Inhibitor	Recurrent Advanced Breast Cancer	Phase 3

MONARCH 2 :
A Study of Abemaciclib (CDK 4/6 Dual Inhibitor) Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer

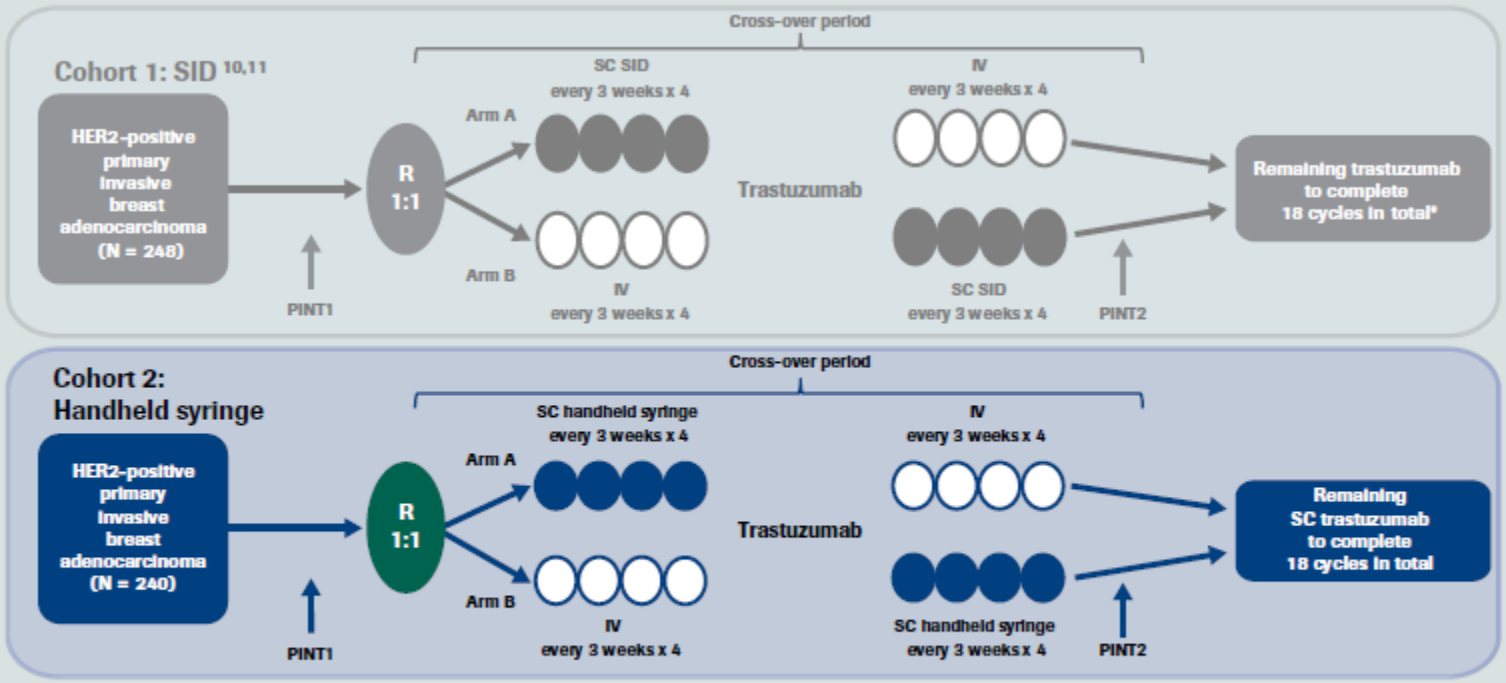
Phase 3 Trials in breast cancer inhibiting CKDs

Compund	Trial name	Company	design	NCT
LEE011	MONALEESA-2	Novartis	A Randomized Double-blind, Placebo-controlled Study of LEE011 in Combination With Letrozole for the Treatment of Postmenopausal Women With Hormone Receptor Positive, HER2 Negative, Advanced Breast Cancer Who Received no Prior Therapy for Advanced Disease	NCT01958021
Abemaciclib	MONARCH 2	Lilly	Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer	NCT02107703
Palbociclib	PENELOPE-B	Pfizer	A Study of Palbociclib in Addition to Standard Endocrine Treatment in Hormone Receptor Positive Her2 Normal Patients With Residual Disease After Neoadjuvant Chemotherapy and Surgery	NCT01864746
Palbociclib	PEARL	Pfizer	Phase III Study of Palbociclib in Combination With Exemestane Versus Chemotherapy (Capecitabine) in Hormonal Receptor (HR) Positive/HER2 Negative Metastatic Breast Cancer (MBC) Patients With Resistance to Non-steroidal Aromatase Inhibitors	NCT02028507
Palbociclib	PALOMA-2	Pfizer	A Study of Palbociclib (PD-0332991) + Letrozole vs. Letrozole For 1st Line Treatment Of Postmenopausal Women With ER+/HER2- Advanced Breast Cancer	NCT01740427

PiK3CA pathway inhibitors



Subcutaneous trastuzumab preferred to i.v. trastuzumab



Includes optional time-and-motion sub-study in both cohorts.[7-9]

Patients completed surgery and (neo)adjuvant chemotherapy (concurrent or sequential with IV trastuzumab) and had at least 8 out of the total of 18 planned trastuzumab cycles remaining in their adjuvant trastuzumab therapy. Stratification factor: *de novo* vs non-*de novo* trastuzumab (to balance the sequence groups for the proportion of patients with prior IV trastuzumab treatment).

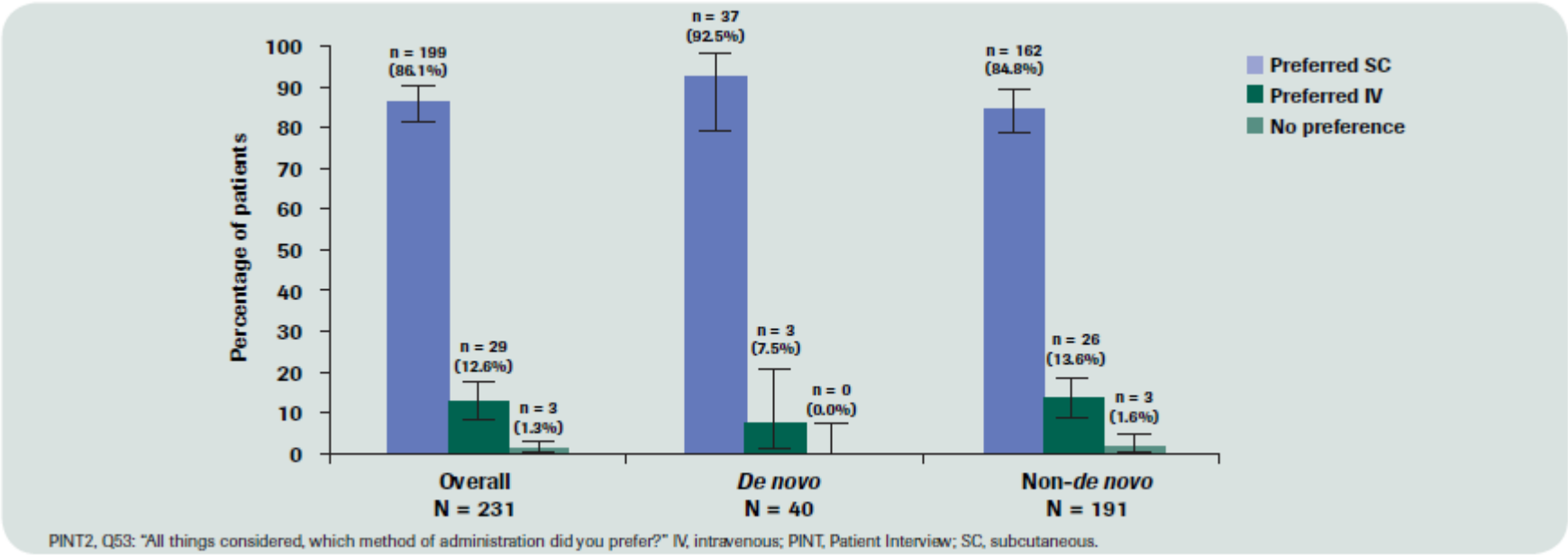
* Initially, 22 cycles were planned; however, the protocol was amended to 18 once non-inferiority of SC trastuzumab was demonstrated.[4] Remaining trastuzumab was administered by IV infusion unless patients participated in SID self-administration.

HER2, human epidermal growth factor receptor 2; IV, intravenous; PINT, patient interview; R, randomized; SC, subcutaneous; SID, single-use injection device.

Pivot et al. *Lancet Oncol* 2013; 14: 962-70

Pivot et al. Poster SABCS 2013

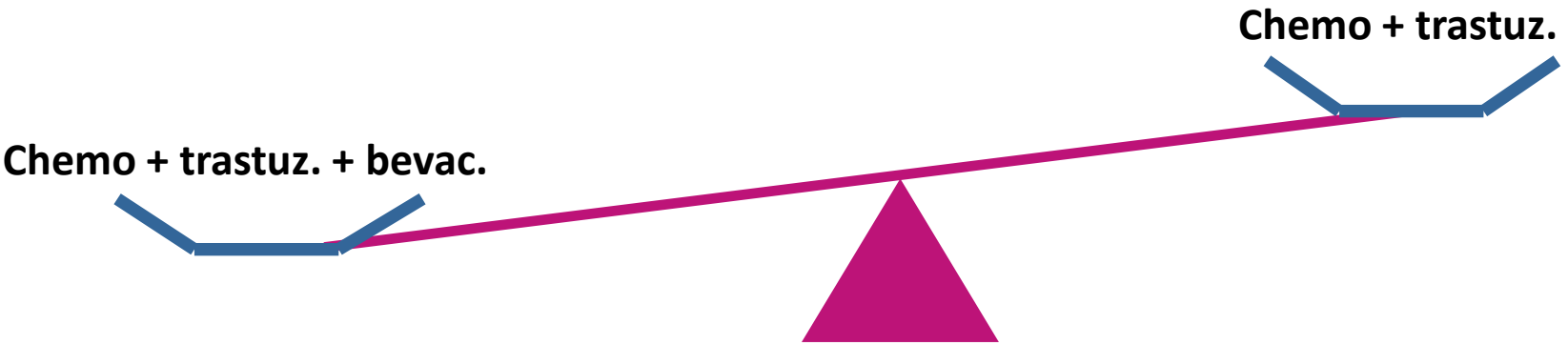
Results Cohort 2 – Handheld syringe



- In total, 199 **(86,1%) of** 231 **patients preferred SC trastuzumab**
- **Overall preference for subcutaneous trastuzumab was "very strong" in 62,3% of patents**, "fairly strong" in 15,6%, and "not very strong" in 8,2%.

Pivot et al. *SABCS 2013.*

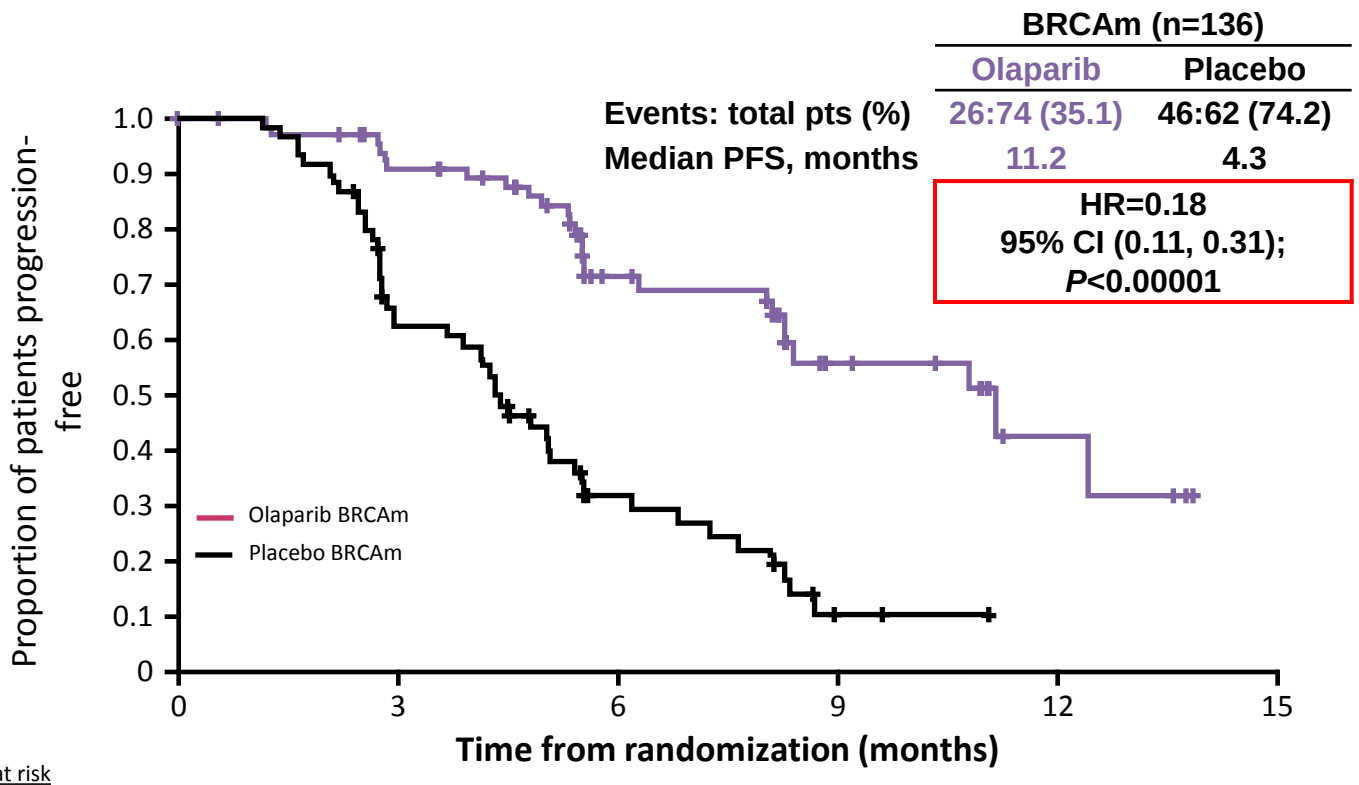
Beth trial: more toxicity in bev. arm



88%	←	Trastuzumab completion	→	92%
70%	←	Bevacizumab completion	→	NA
21%	←	Grade 3-4 A.E.	→	5%
n=3 (2 cardiac)	←	Grade 5 A.E.	→	n=0
9%	←	L.V. systolic dysfunction	→	7%
2,1%	←	CHF	→	< 1%
n=19	←	Cardiac Ischemia	→	n=3

D. Slamon, abst S1-03, SABCS 2013

PFS by BRCAm status



Number at risk

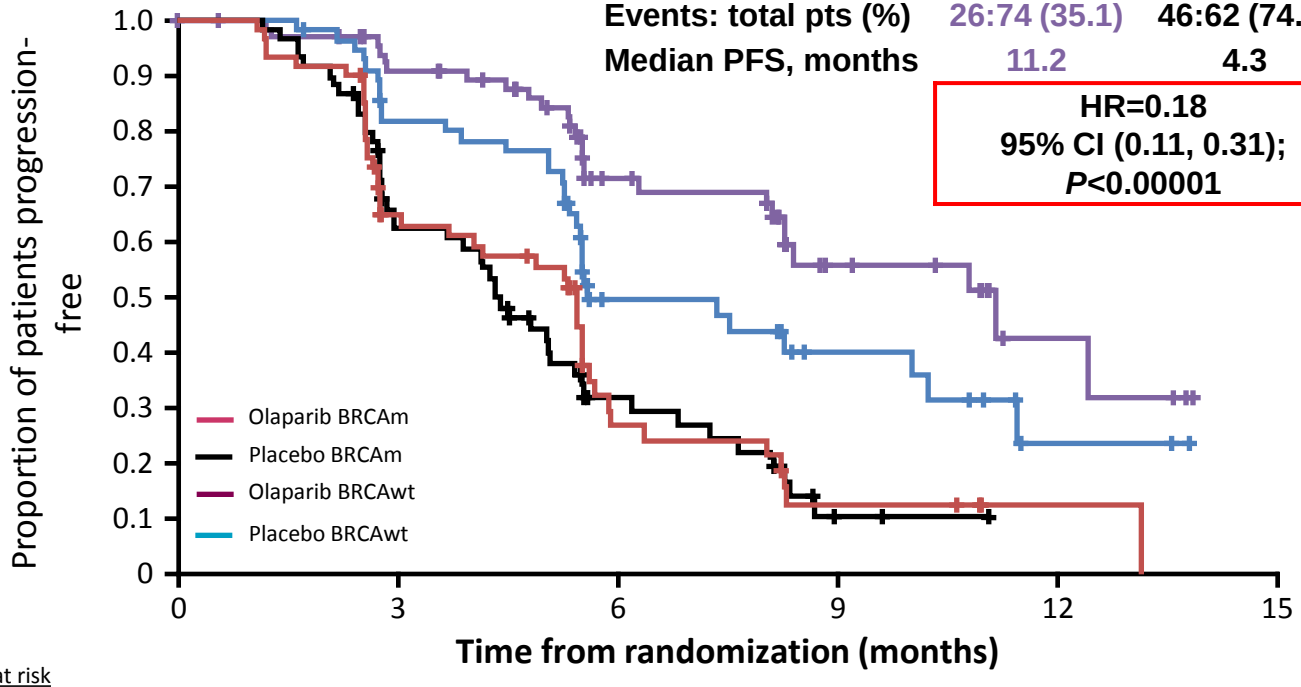
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

- **82% reduction in risk of disease progression or death with olaparib**

Ledermann JA et al. *J Clin Oncol* 2013;31(15 suppl):abst 5505

Most compelling evidence in BRCAg

	BRCAm (n=136)		BRCAwt (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Events: total pts (%)	26:74 (35.1)	46:62 (74.2)	32:57 (56.1)	44:61 (72.1)
Median PFS, months	11.2	4.3	5.6	5.5
	HR=0.18 95% CI (0.11, 0.31); *P*<0.00001		HR=0.53 95% CI (0.33, 0.84); *P*=0.007	



Number at risk						
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0
Olaparib BRCAwt	57	44	17	9	2	0
Placebo BRCAwt	61	35	10	4	1	0

BRCAwt, wild type (includes patients with no known BRCAm or a mutation of unknown significance)

Ledermann JA et al. J Clin Oncol 2013;31(15 suppl):abst 5505

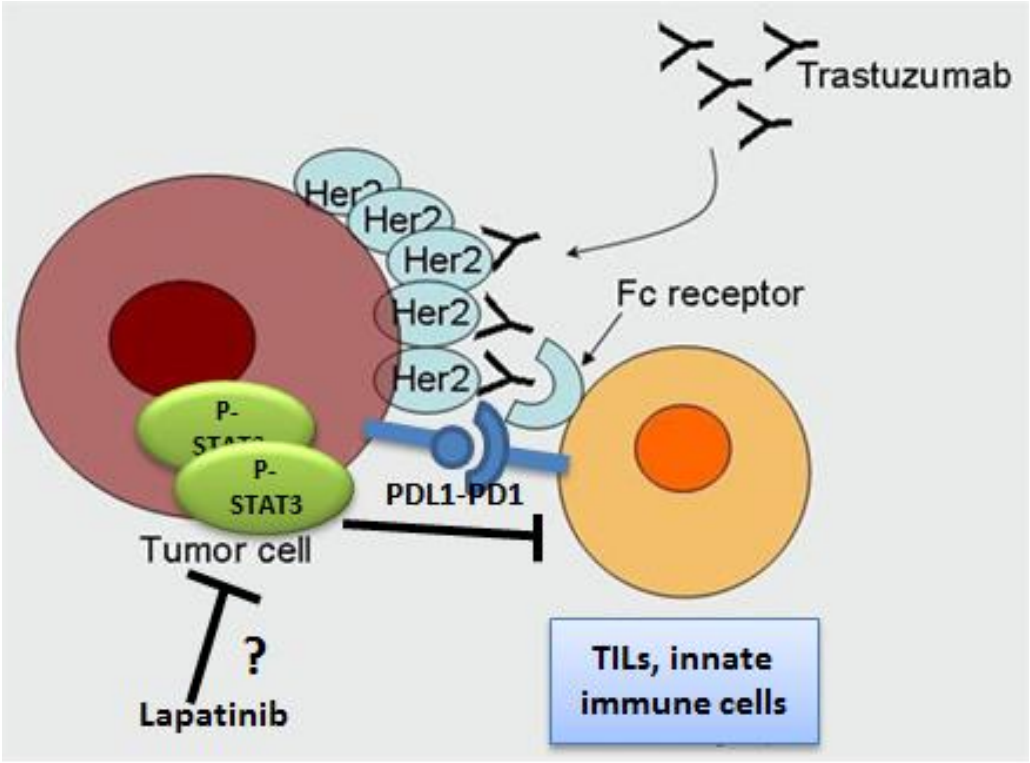
Can we identify sub-groups that will benefit from dual blockade?

Immune signatures ?

TILs?

P-STAT3 ?

Immune tolerance:
less benefit from Trastuzumab and maybe more benefit from Lapatinib ?



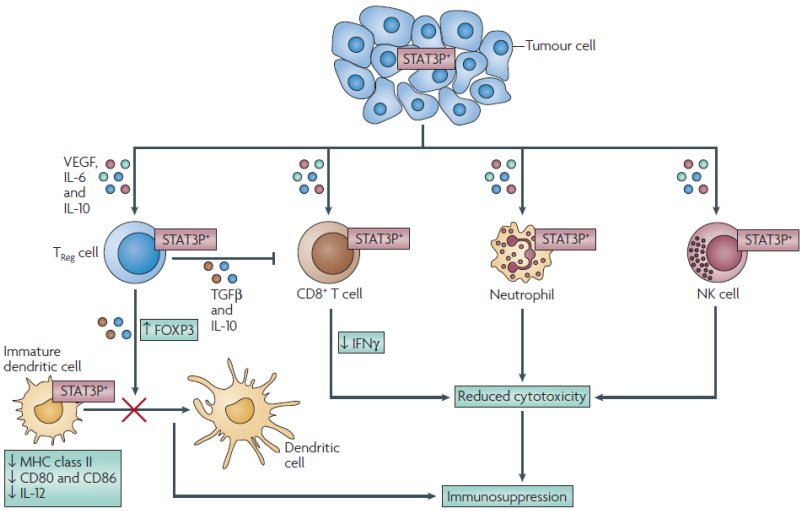
TIL- Tumor infiltrating lymphocytes

Rational P-STAT3 :
Potential role in Anti-Immunity

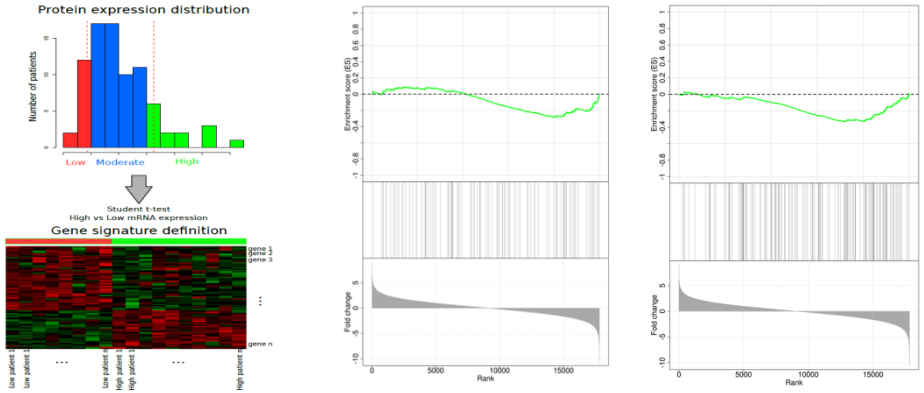
TUMOUR IMMUNOLOGY

Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment

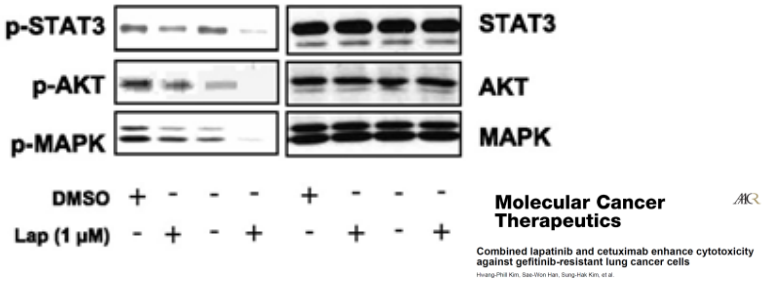
Hua Yu, Marcin Kortylewski* and Drew Pardoll‡*



Preliminary data evidence for immune inhibition in p-STAT3+ tumors



Can P-STAT3 be inhibited by Lapatinib?

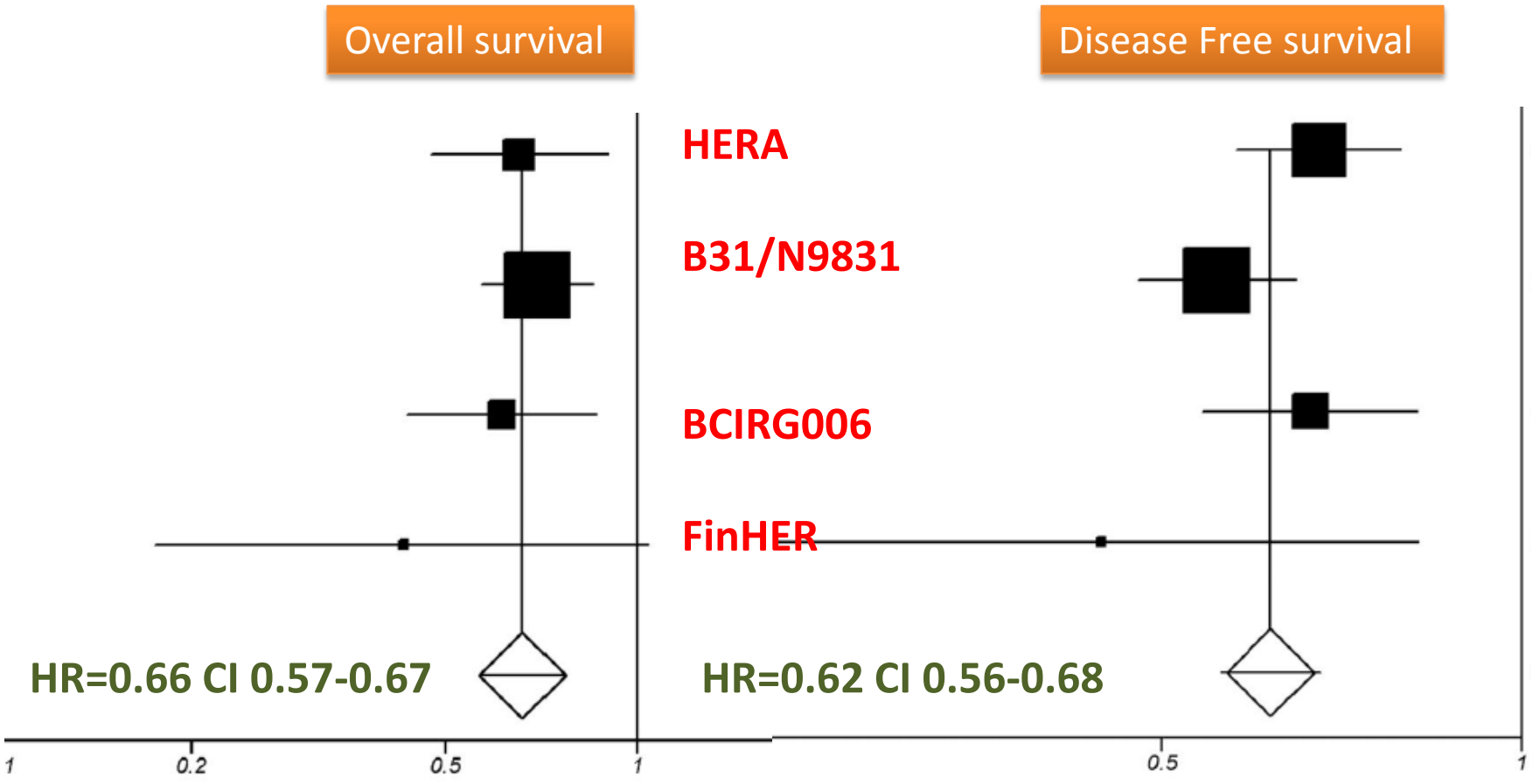


Examples and suggestions

Problems	Suggestion	Good examples	Wrong example
Heterogeneity	Predefine the sub-set of population most likely to benefit from the drug	HER2 -trastuzumab BRCA carriers- PARP inhibitors?	ER and TNBC in the same trial HER2/ER+ and HER2/ER- in the same trial ?
Stage shifting (PET-CT) Improved local and systemic management.	Take action in advance to overcome stage shifting and improved local and systemic treatments	Statistical power considerations based on present practice	Statistical power considerations based on previous studies
Launching adjuvant trials without clear evidence of benefit in the metastatic or neoadjuvant setting	Have clear evidence of benefit in the metastatic a/o neoadjuvant setting	Tamoxifen, Aromatase inhibitors, taxanes, trastuzumab	Controversies about the efficacy of the drug in the metastatic or neoadjuvant setting

ADJUVANT TRASTUZUMAB IMPROVES SURVIVAL

Relative Risk Meta-analysis plot



Issa J. Dahabreh, The Oncologist

ST. GALLEN 2005

INTRODUCED A FUNDAMENTAL CHANGE IN THE TREATMENT ALLOCATION PARADIGM

"First select the target in the tumor based on the biology of the tumor… then think about risk to « fine-tune » adjuvant therapy

Adjuvant therapy for Luminal Breast Cancers

What did we learn?

- ✓ Some patients do not need chemotherapy
- ✓ Consideration for the incorporation of an “AI” in the treatment scheme should be given (in post menopausal women)
- ✓ Some patients benefit from extended (10y) hormonal treatment
- ✓ Exemestane+OFS is an emerging option for premenopausal women
- ✓ Bisphosphonates (mostly zoledronic acid) are to be considered for some women
- ✓ When chemotherapy is indicated, shorter regimens can be considered in certain circumstances
- ✓ There is no role for adjuvant Bevacizumab
- ✓ BC mortality is increased in high BMI premenopausal women

Adjuvant Therapy for HER2+ BC

What did we learn?

- ✓ HER2+ BC is an heterogeneous disease
- ✓ There is no role for dual adjuvant blockade using T+L in the presence of aggressive chemotherapy
- ✓ There is still benefit for delayed adjuvant antiHER2 therapy
- ✓ For T_1N_0 tumors, the Dana Farber regimen offers a very favourable Benefit/Harm ratio
- ✓ TILs are now accepted as important stratification and prognostic factor in clinical trials for HER2+ BC
- ✓ There is no role for adjuvant bevacizumab

What chemotherapy should we give (ER+)?

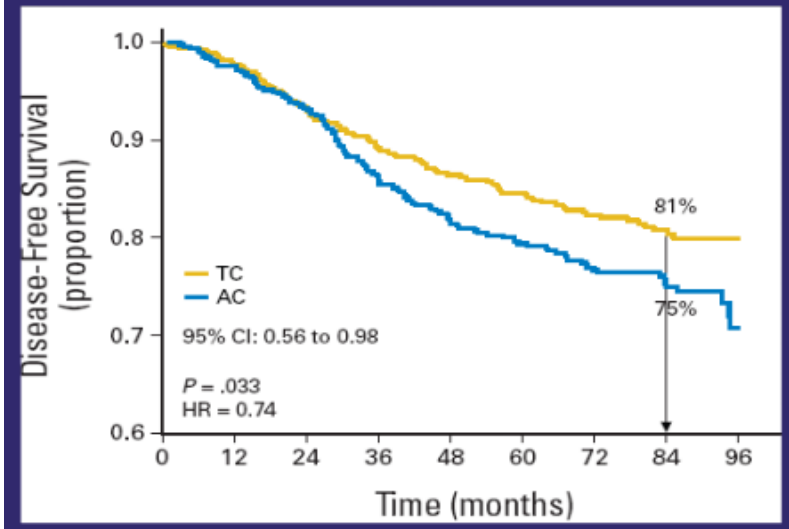
CAN WE OMIT ANTHRACYCLINES ?

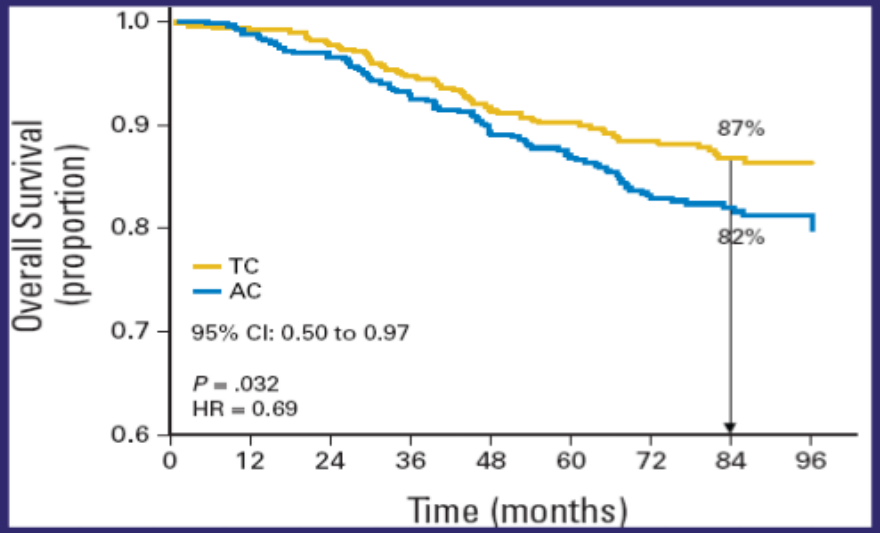
US Oncology Trial 9735

Docetaxel + Cyclo x4 v Doxorubicin + Cyclo x4:

Overall Survival Benefit with 7-Year Follow-Up

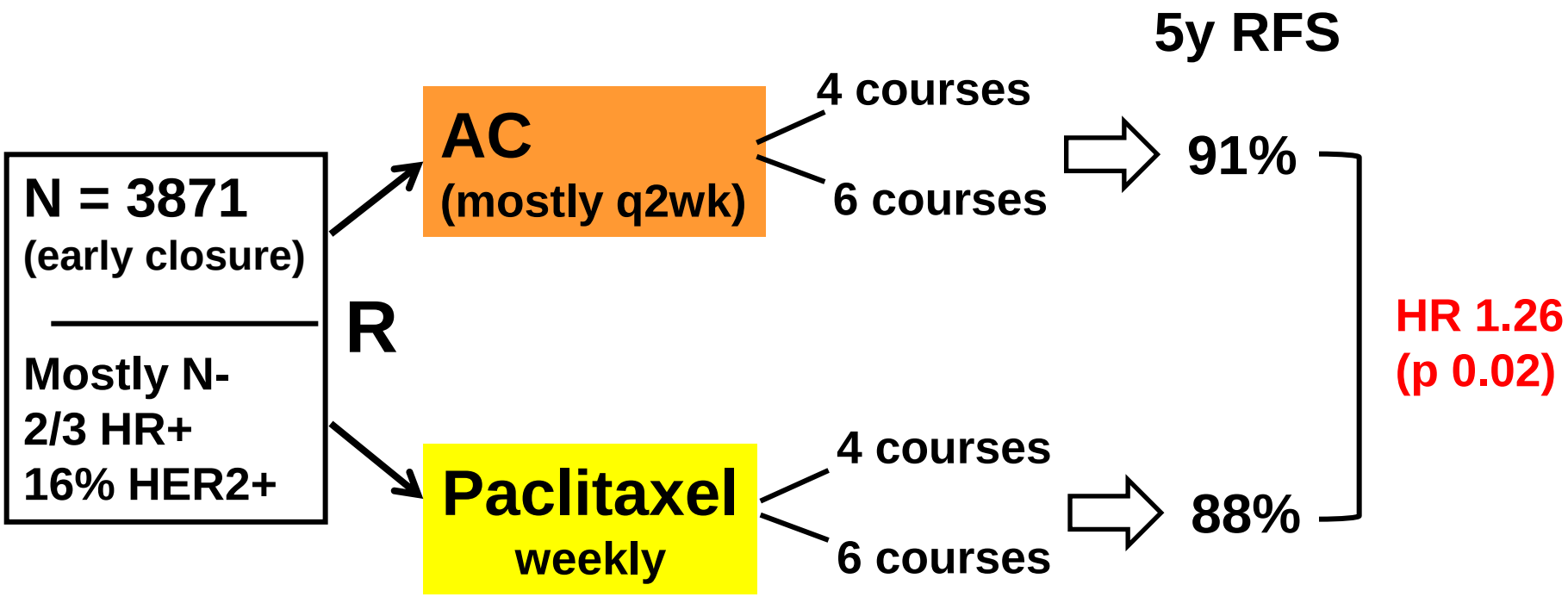
- 1016 women
- 48% N-ve
- Around 70% ER+ve





Jones S et al; JCO 2009

Paclitaxel alone not proven equivalent to AC

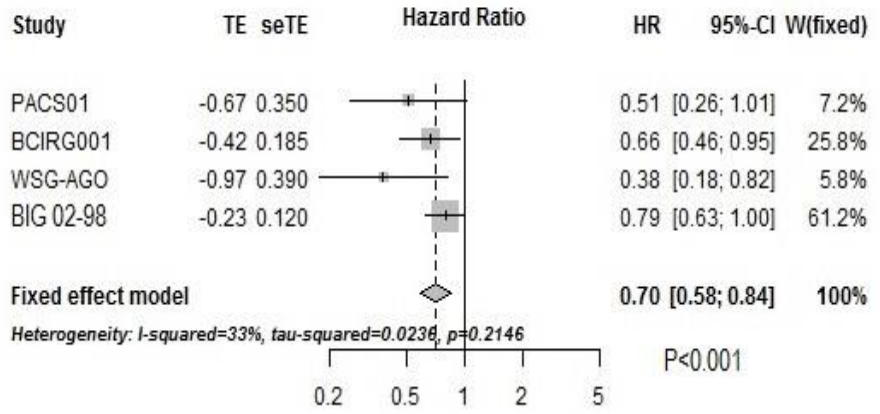


… but more « toxic » deaths on AC (7 AML/MDS, 2 cardiac)

L.Shulman, CALGB 40101,JCO 2014

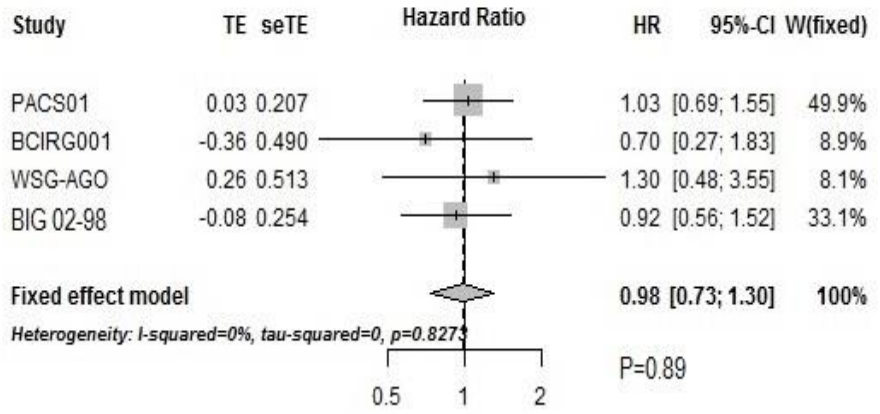
CAN WE OMIT Taxanes?
Exploratory pooled analysis (4 trials) on the role of Ki67% in predicting benefit of adjuvant taxanes in ER+ patients

High Ki67



DFS

Low Ki67



DFS

Benefit of taxanes appears to be restricted to highly proliferative tumors

But…

Heterogeneity in the design of these trials and different Ki67% cut-offs

Sonnenblick A, ESMO 2014

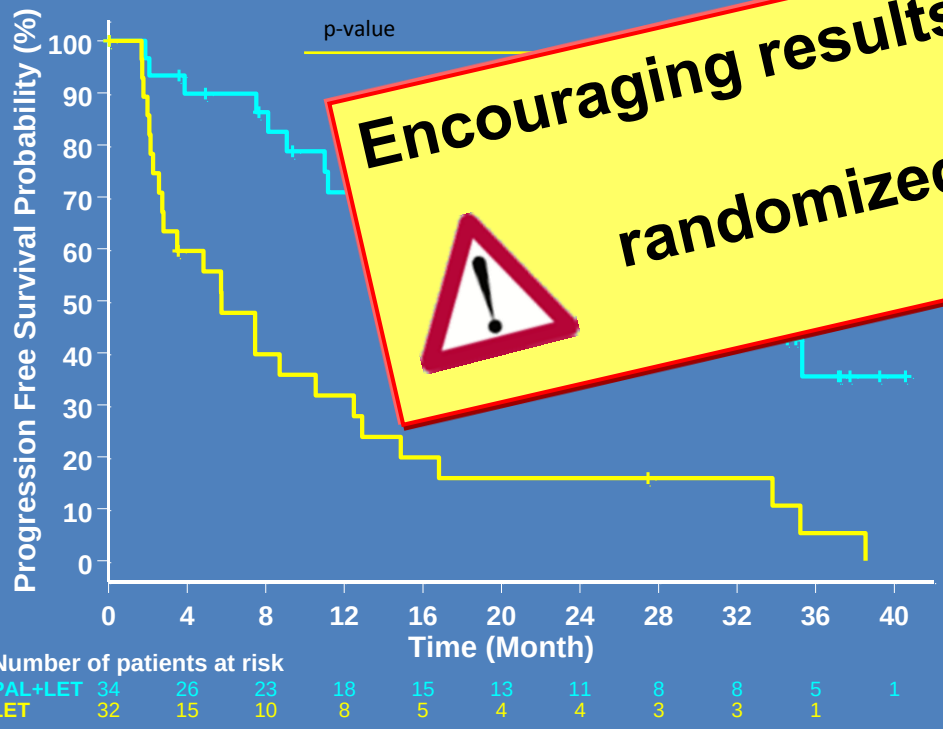
PALOMA-1 : Progression-Free Survival (ITT) Part 1 and Part 2

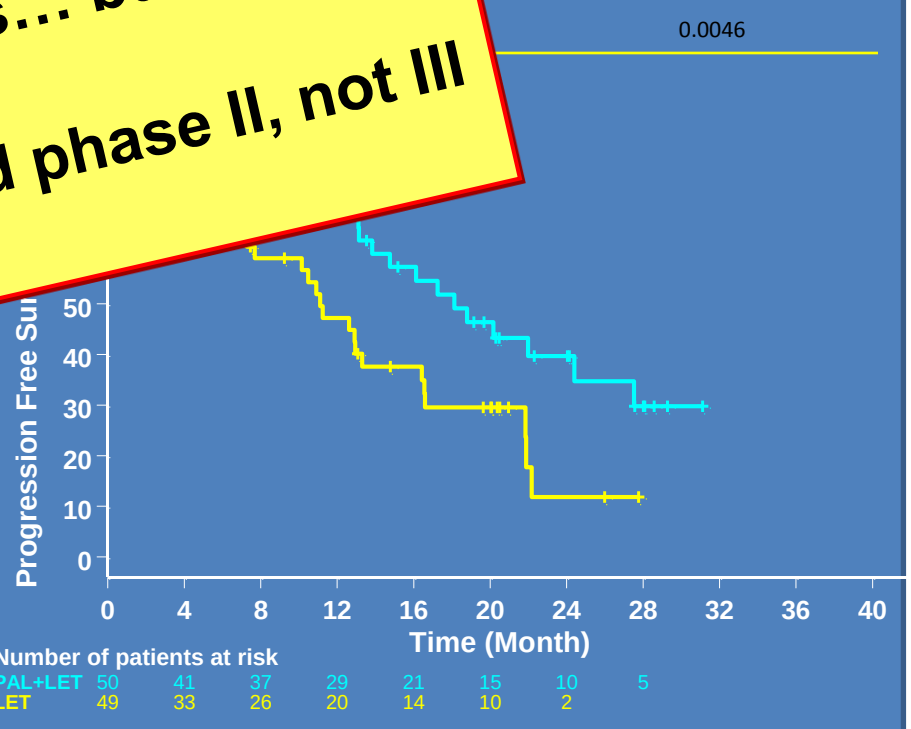
Part 1	PAL + LET (N=34)	LET (N=32)
Number of Events (%)	15 (44)	25 (78)
Median PFS, months (95% CI)	26.1 (11.2, NR)	5.7 (2.6, 10.5)
Hazard Ratio (95% CI)	0.299 (0.156, 0.572)	
p-value		

Part 2	PAL + LET (N=50)	LET (N=49)
Number of Events (%)	26 (52)	34 (69)
Median PFS, months	18.1 (13.1, 27.5)	11.1 (7.1, 16.4)
Hazard Ratio (95% CI)	0.508 (0.303, 0.853)	
p-value	0.0046	

Encouraging results… but

randomized phase II, not III





RS Finn et al, AACR 2014

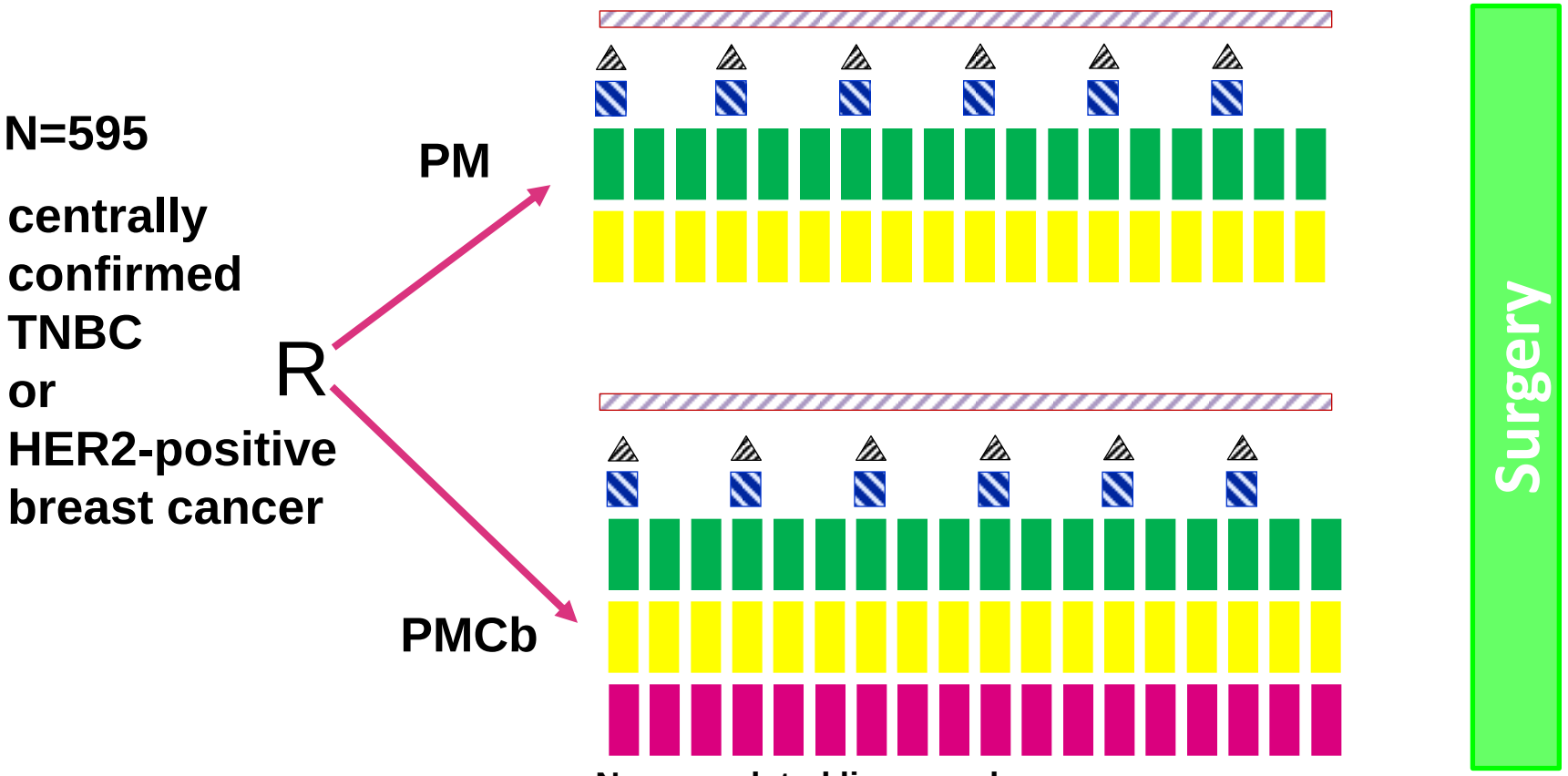
Phase 3 trials in breast cancer inhibiting PI3K-Akt

Belle-2 — buparlisib plus fulvestrant in HR+/HER2– advanced breast cancer (NCT01610284)

Belle-3 — buparlisib plus fulvestrant in HR+/HER2– advanced breast cancer previously treated with AI and mTOR inhibitor (NCT01633060)

Many other drugs are in earlier phases
GDC-0032 , GSK2636771 , GDC-0941

Platinum benefit- in GeparSixto

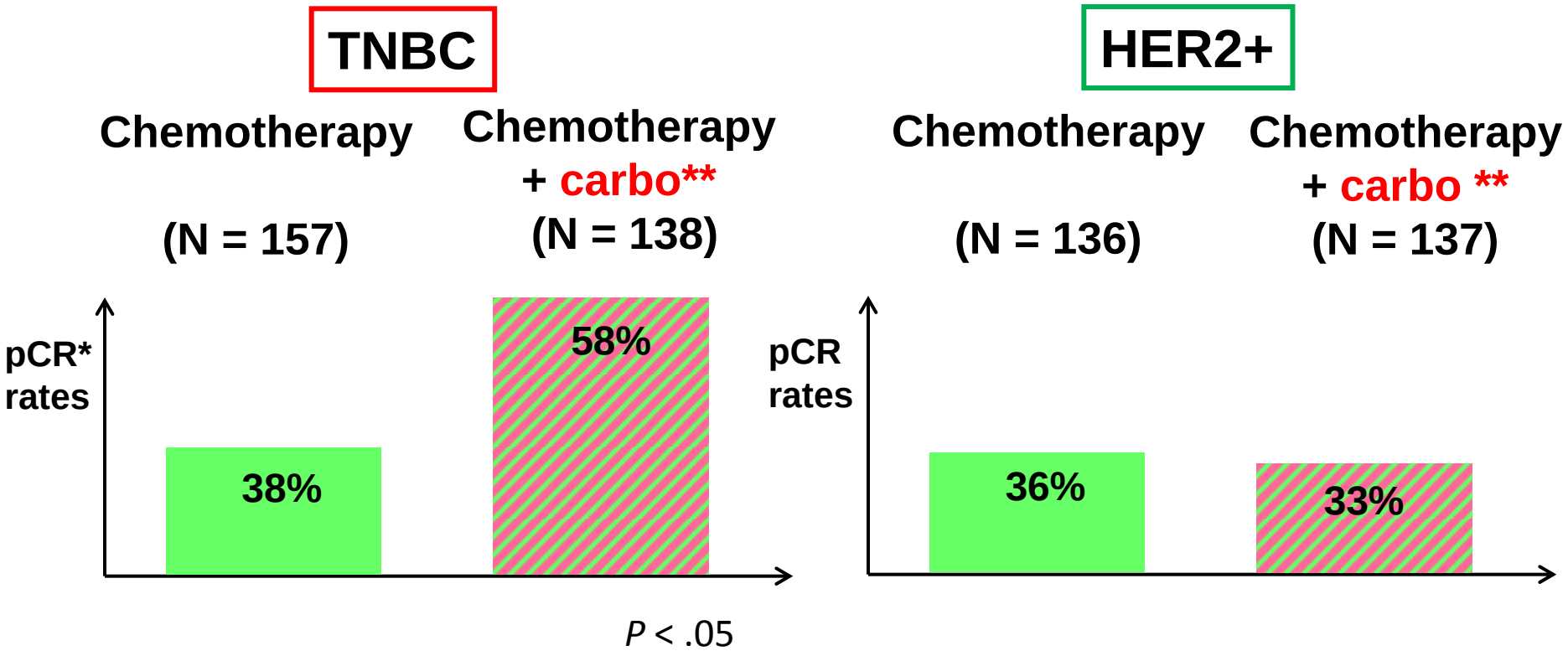


*reduced from AUC 2 at amendment 1 after enrolment of 330 patients

G. Von Minckwitz, Lancet Oncology 2014

Does carboplatin add benefit to neoadjuvant CT with paclitaxel and non-pegylated doxorubin given weekly ?

(+ bevacizumab in TNBC; + trastuzumab and lapatinib in HER2+ BC)



* *Strict definition : in situ not allowed*

** *Carboplatin weekly x 18 at AUC 1.5*

G. Von Minckwitz, Lancet Oncology 2014

Predictive tools in TNBC

Neoadjuvant setting

↓

Platinum benefit in GeparSixto

↓

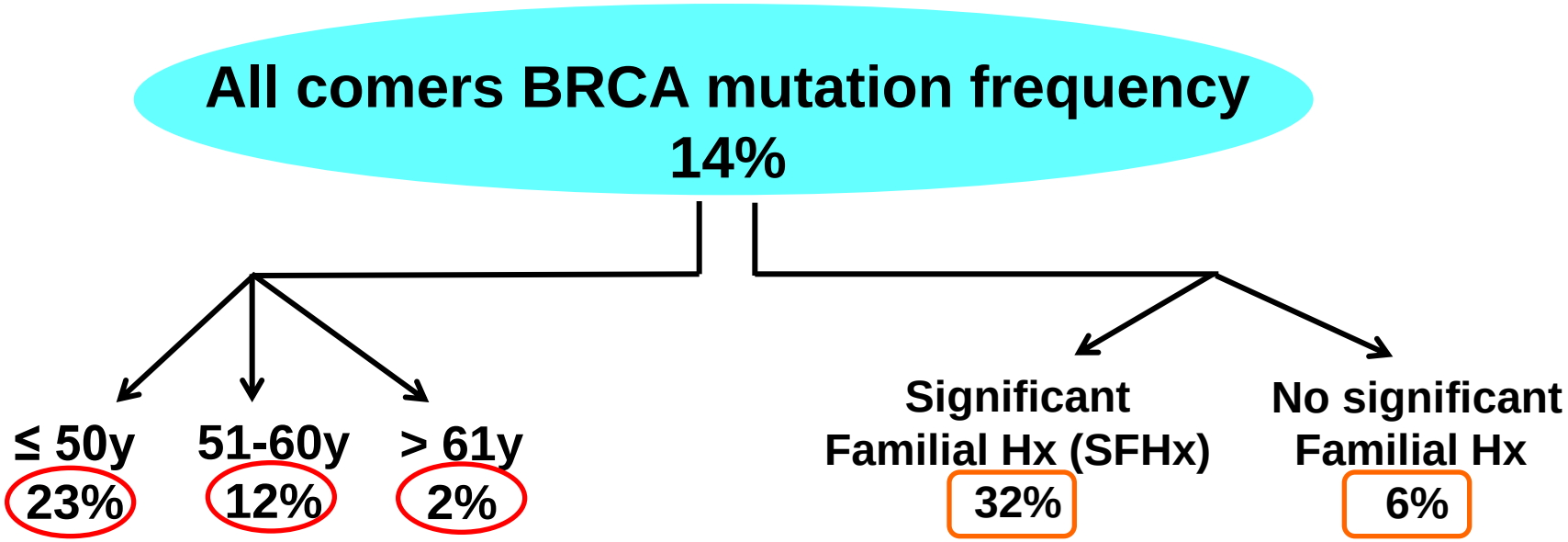
TILs, better than immune mRNAS, predict for ↑ pCR and carboplatin benefit

BRCA status and family history predict carbo effect with 25% absolute ↑ pCR

Denkert S1-06 SABCC 2013 , Von Minckwitz 1005 ASCO 2014

BRCA germline testing : in all TNBC below 60y !

N = 186 unselected women with TNBC in the Kansas City area are submitted to BRCA (Myriad) testing



If SFHx or age < 50y were the only criteria used
≈ one third of mutation carriers would have been missed !

P. Sharma, abst 1026, ASCO 2013

Olaparib data in breast cancer:

- **Tutt et al 2010; Ph II monotherapy olaparib in patients with *BRCA1 or BRCA2* mutations and with advanced breast cancer (doses; 100mg BD or 400mg BD); Median 3 prior lines of chemotherapy. ORR for 400mg BD 41% (11/27)**

- **Gelmon et al 2011; Ph II monotherapy Olaparib in patients with *BRCA1 or BRCA2* mutations and with advanced breast cancer or ovarian cancer (dose 400mg BD) Median 3 prior lines of chemotherapy overall – breast cancer patient more heavily pretreated. No RECIST responses for breast cancer patients – 38.5% had SD**

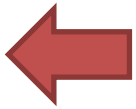
- **Kauffman et al 2013; Ph II monotherapy olaparib in patients (multiple tumours) with *BRCA1 or BRCA2* mutations (dose 400mg BD). 62 breast cancer patients with median number of 6 prior lines of chemo. ORR for breast cancer patients = 12.9% (8/62), At 4 mo, disease control in 37% (23/62)**

"Olympia" is currently open in the adjuvant setting: Olaparib for BRCAg TNBC

Why do we fail to incorporate new targeted drugs in the adjuvant setting ??

Recent Negative trials with new targeted drugs in the adjuvant setting

Trial	Drug	BC subtype	N status	End point	Needed Events	Actual Events
BEATRICE	Bevacizumab	TNBC	63% N-	3y IDFS: 82.7 VS 83.7 HR:0.87 p=0.18	388	393/2591
BETH	Bevacizumab	HER2+	48% N-	38m IDFS: **92% Vs 92%** HR: 1 p=0.9	**296**	**116/3509**
E5103	Bevacizumab	ER+ 64%	26% N-	47.5m IDFS 77% Vs 80% HR: 0.87 p=0.17	426	430/3008 (arm A vs C)
ALTTO	Lapatinib	HER2+	40% N-	4.5y IDFS **88% Vs 86%** HR: 0.84 p=0.048	850	555/6281



HER2 control arms did extremely well!