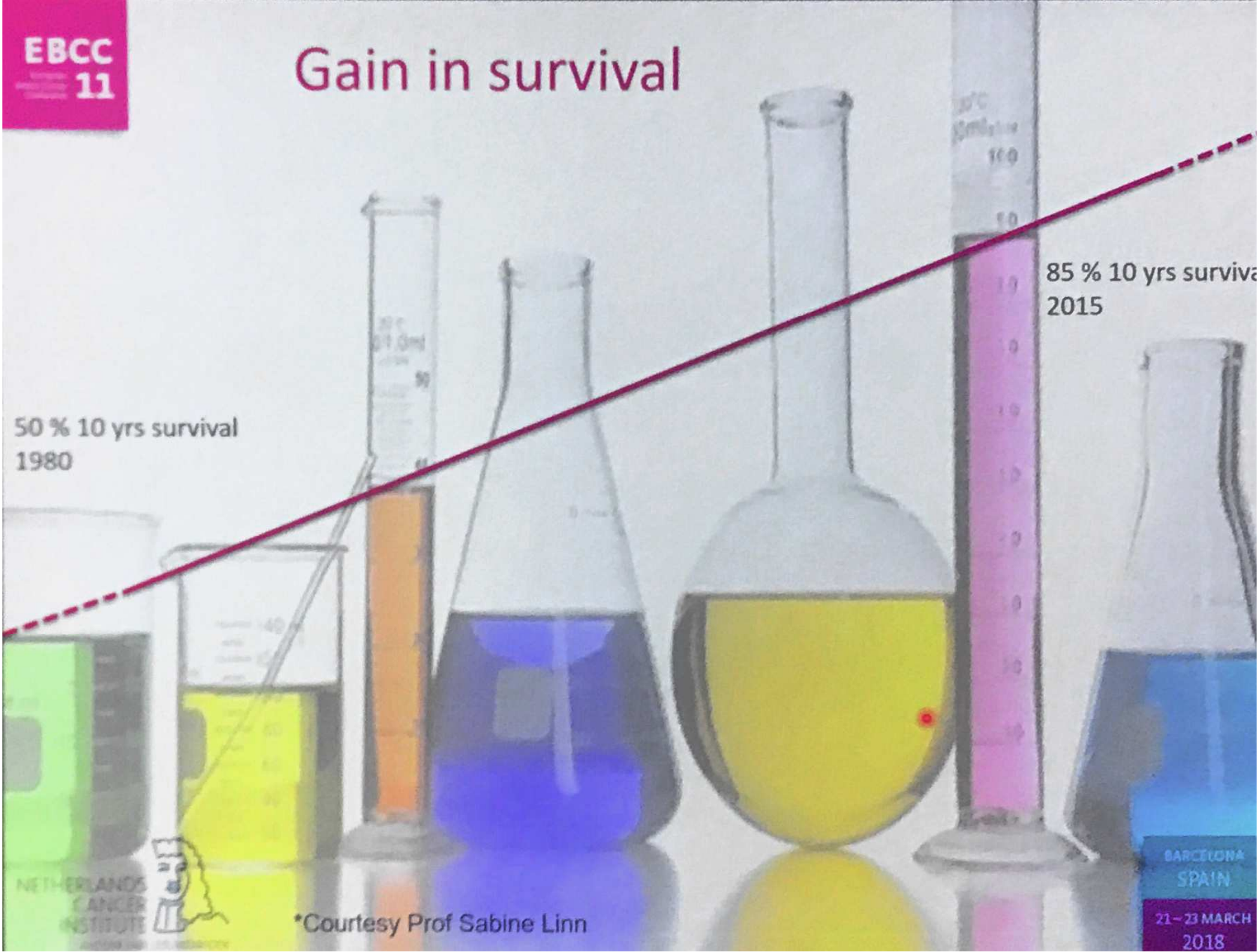
Novità in oncologia e radioterapia

Maria Grazia Baù

FIM 11aprile 2018


EBCC 11
Gain in survival
85 % 10 yrs survival
2015
50 % 10 yrs survival
1980
*Courtesy Prof Sabine Linn
NETHERLANDS CANCER INSTITUTE
BARCELONA
SPAIN
21 – 23 MARCH
2018

Gain in survival and higher pCR rates

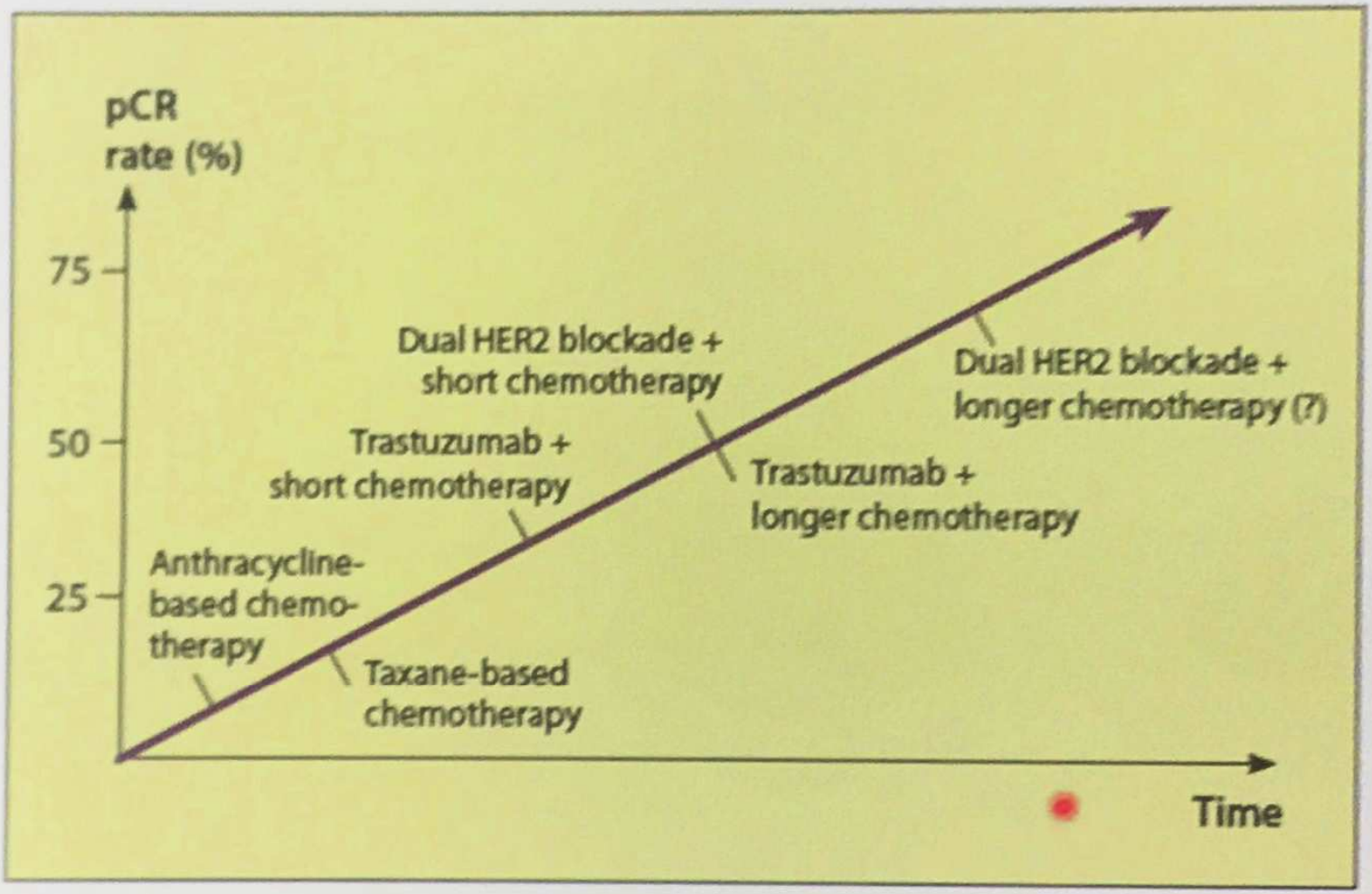
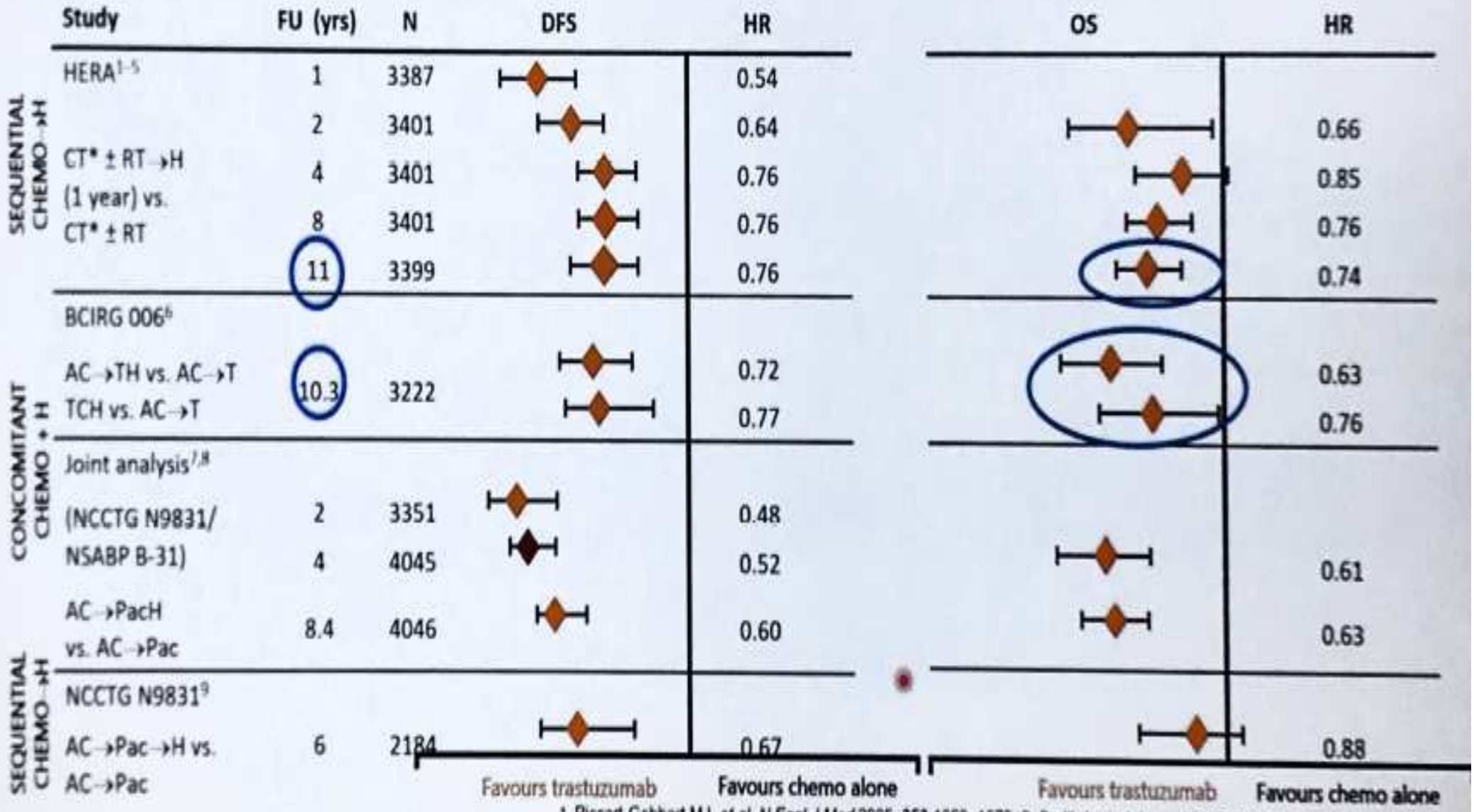


Figure 1: Incremental Improvement in Pathologic Complete Remission (pCR) Rates by Optimizing Systemic Neoadjuvant Treatment of HER2-Positive Breast Cancer.

These adjuvant trials demonstrated consistent DFS and OS benefit over time with 1 year trastuzumab treatment vs. observation

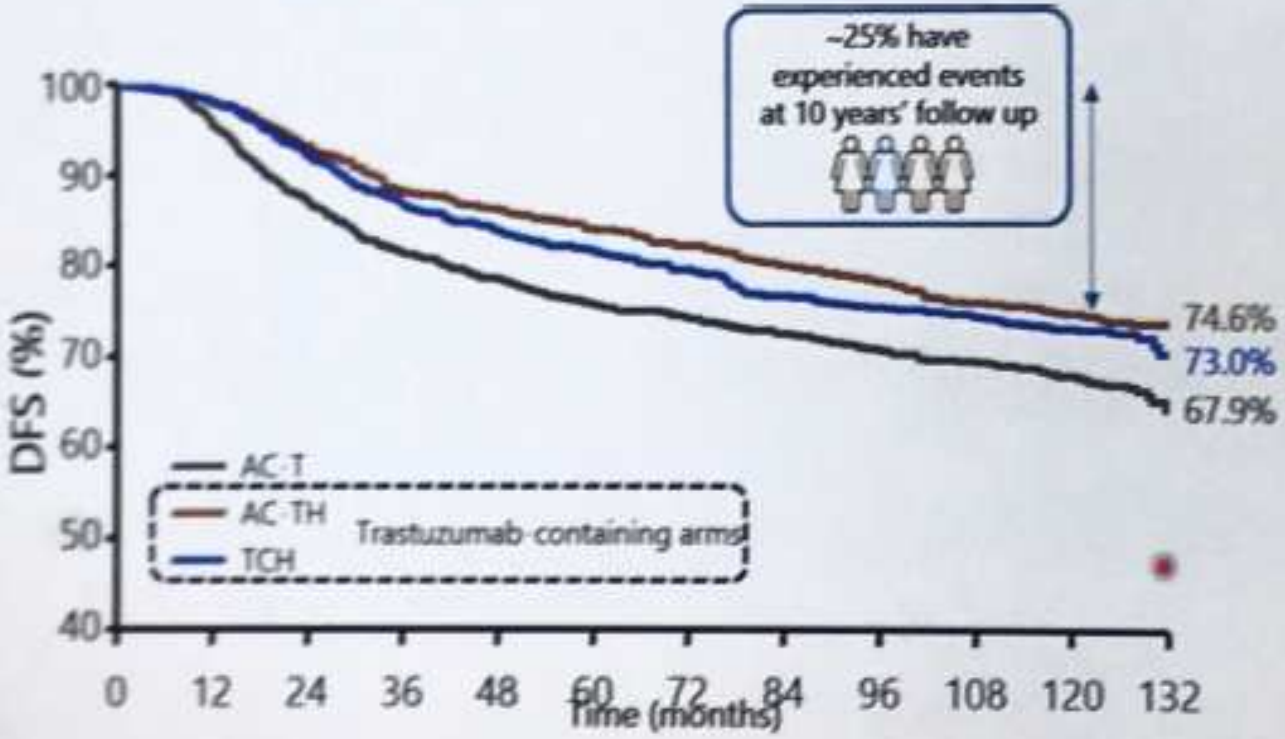


* Selected from a list of approved regimens consisting of ≥4 cycles.
AC, doxorubicin plus cyclophosphamide; CT, chemotherapy; DFS, disease free survival; FU, follow up; ; OS, overall survival; Pac, paclitaxel; RT, radiotherapy; T, docetaxel; TCH, docetaxel, carboplatin.

1. Piccart-Gebhart MJ, *et al. N Engl J Med* 2005; **353**:1659–1672; 2. Smith I, *et al. Lancet* 2007; **369**:29–36; 3. Gianni L, *et al. Lancet Oncol* 2011; **12**:236–244; 4. Goldhirsch A, *et al. Lancet* 2013; **382**:1021–1028; 5. Cameron D, *et al. Lancet* 2017; **389**:1195–1205; 6. Slamon D, *et al.* SABCS 2015 (Abstract S5-04); 7. Perez EA, *et al. J Clin Oncol* 2011; **29**:3366–3373; 8. Perez EA, *et al. J Clin Oncol* 2014; **32**:3744–3752; 9. Perez EA, *et al. J Clin Oncol* 2011; **29**:4491–4497.

BCIRG 006: Relapse rates in HER2-positive eBC remain high despite the significant impact of trastuzumab-based therapy

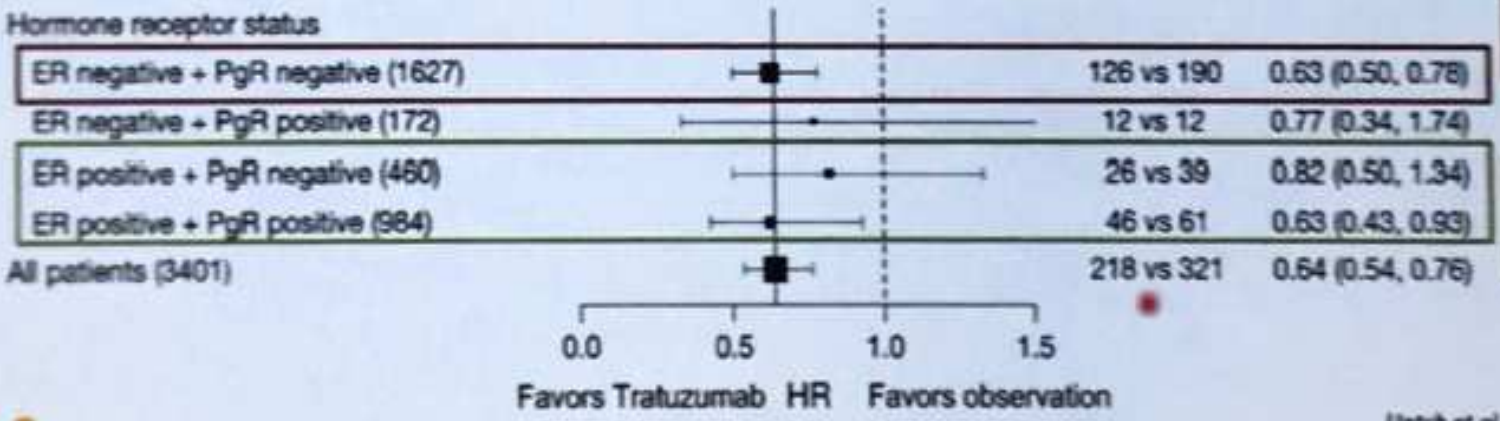
DFS final analysis (10.3 years' median follow-up)



1 in 4 patients will still experience recurrence and death despite 1 year of adjuvant trastuzumab-based therapy

HERA trial

- Arms: Observation vs. Trastuzumab 1 year vs. Trastuzumab 2 years after adjuvant chemotherapy (total: n=5099)
- Sub-analysis of **3-years DFS** (Trastuzumab 1 year vs. Observation arms) by HR status → n=3401, **48% HR+** (ER and/or PgR **≥10%** by **local testing)**
- **Similar benefit from Trastuzumab** in HR- and HR+ patients:



HR: 0.63 (0.50-0.78)

HR: 0.68 (0.51-0.89)

Untch et al., Ann Oncol 2008

INSTITUT JULES BORDET INSTITUUT

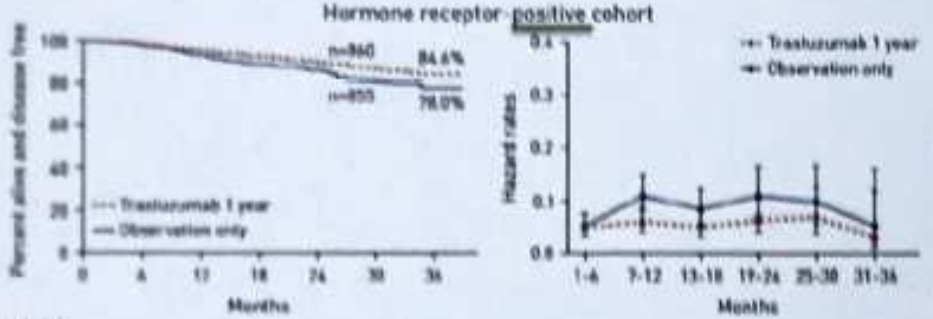
ULB

HERA trial

- Different **patterns of relapse** → different patterns of trastuzumab effect:

B

Hormone receptor-positive cohort



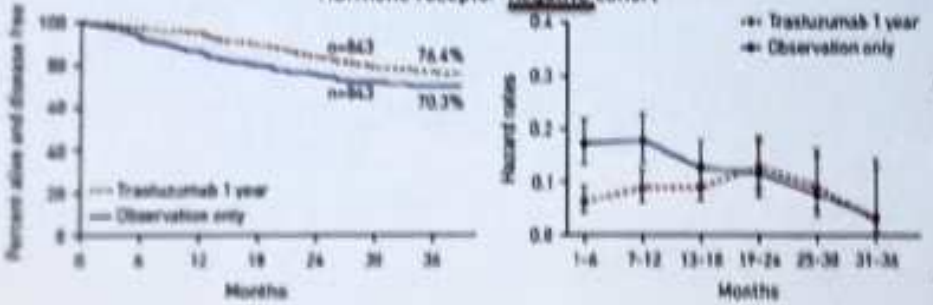
Number at risk

Trastuzumab 1 year (=E1)	736	397	73
Observation only (=E1)	697	337	48

Risk of relapse is **consistent over time**

C

Hormone receptor-negative cohort



Number at risk

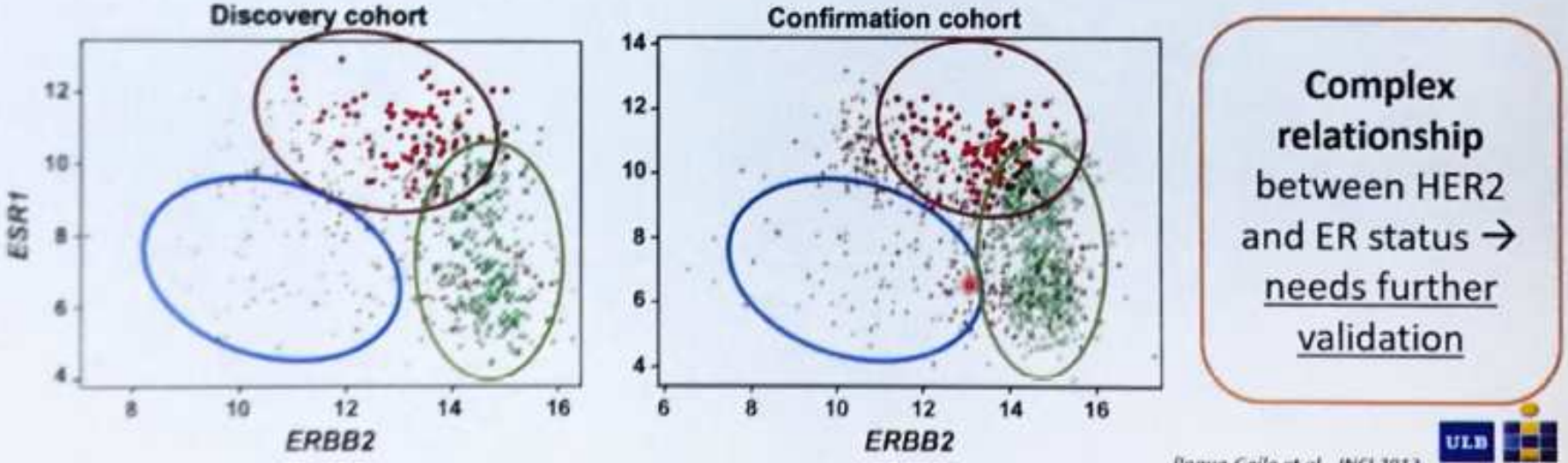
Trastuzumab 1 year	703	345	67
Observation only	633	302	59

Observation group:
- very high risk of **early relapse** → decreases over time

Untch et al., Ann Oncol 2008

NSABP B-31 – GEP model

- **8-gene prediction model**: no linear correlation between *ERBB2* and *ESR1* mRNA levels and each of the groups → Group with **no benefit**: **high levels of *ESR1*** mRNA, but **intermediate overexpressed levels of *ERBB2*** mRNA
- Group with **moderate benefit**: also included HER2-negative patients

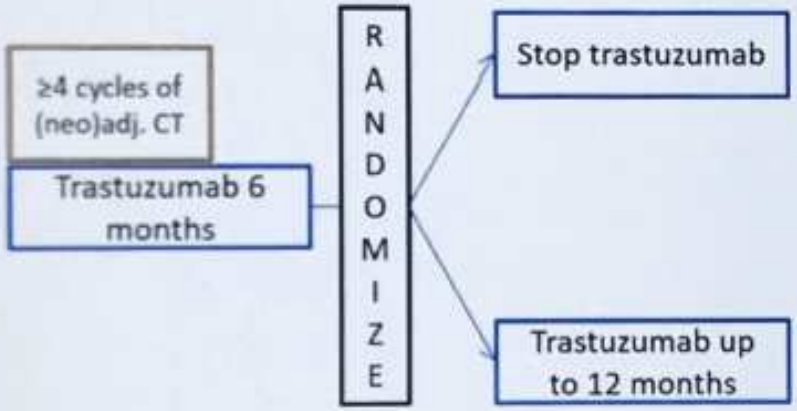


Complex relationship between HER2 and ER status → needs further validation

Pogue-Geile et al., JNCI 2013

PHARE design

Pivot et al., Lancet Oncol 2013

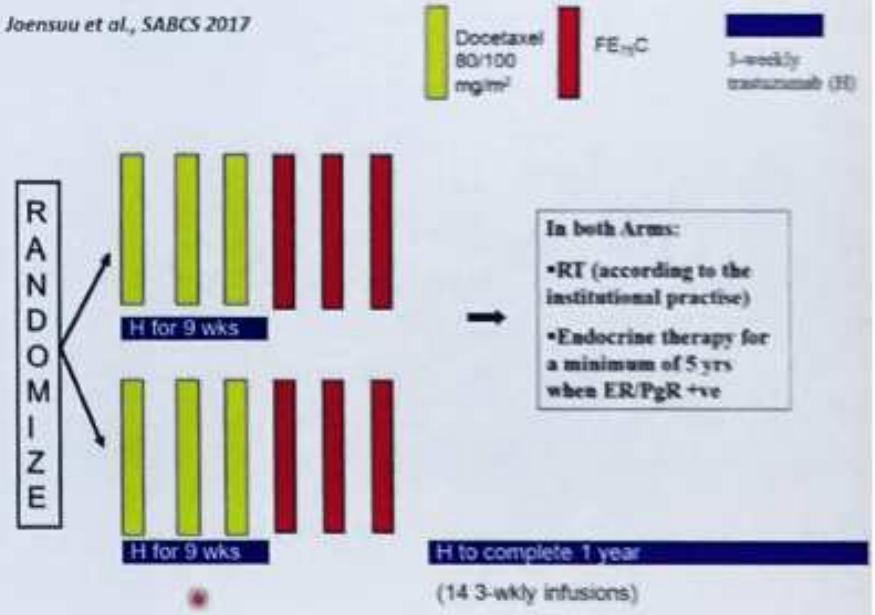


Primary endpoint: **DFS**

Non-inferiority design: 2% variation in absolute difference in recurrence; 95%CI HR margins should not cross the 1.15 boundary

SOLD design

Joensuu et al., SABCS 2017

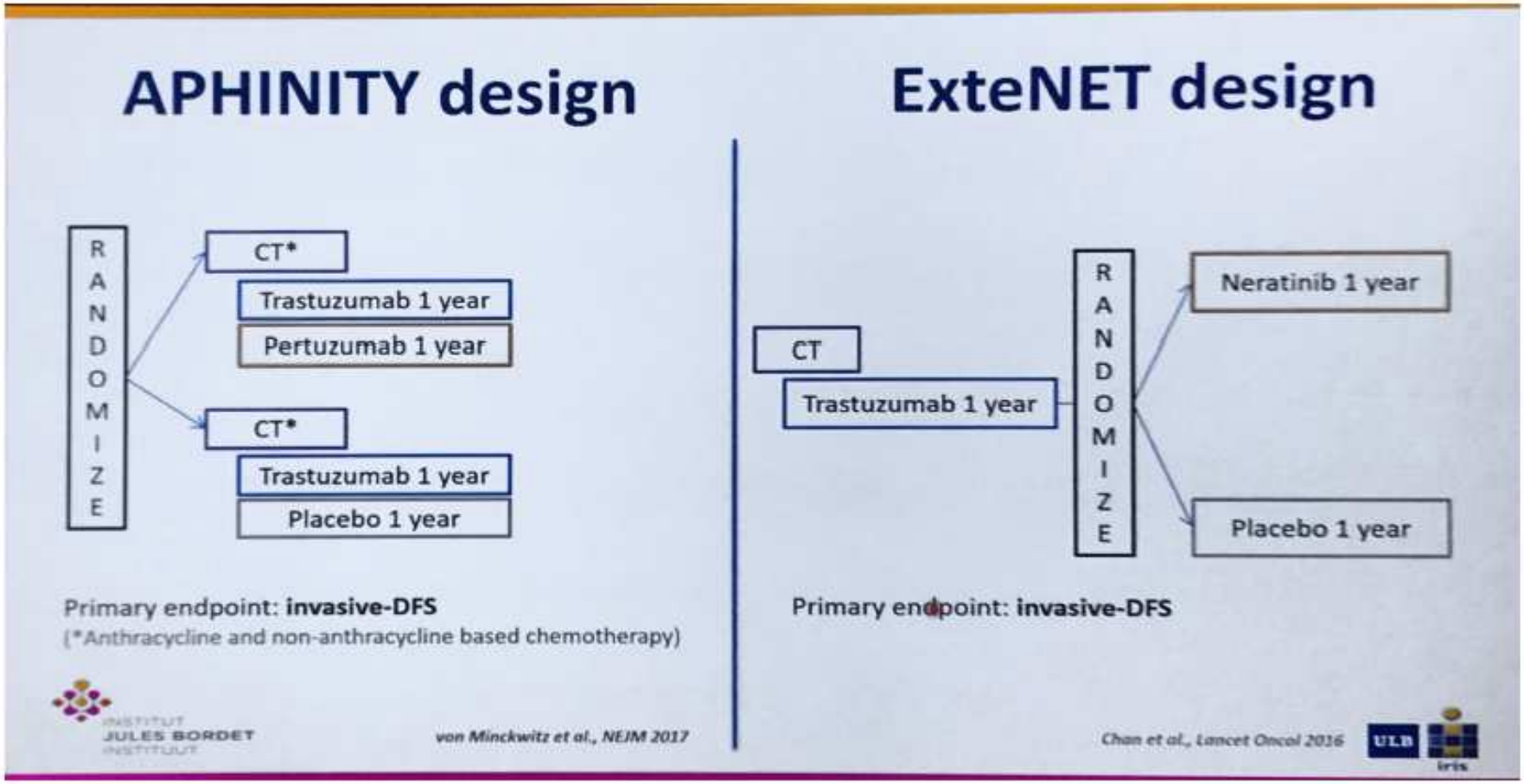


Primary endpoint: **DFS**

(After revision): Non-inferiority design: absolute 5-yr DFS differences ,4% were considered not clinically significant; non-inferiority margin of 1.3

First and second generation of adjuvant Trastuzumab trials : Lessons learned about subgroups by hormone receptor status

- HR+ and HR- subgroups show similar degrees of risk reduction with Trastuzumab ; the absolute benefit is slightly larger in HR-
- A subgroup of "high ESR1"/"low-intermediate HER2" tumors might derive no benefit from Trastuzumab !
- HR- have a some what worse prognosis and do relapse much earlier ; the relapse rate is more constant over time in HR+ disease
- Duration of Trastuzumab might matter more for HR- than HR+ tumors, particularly when Trastuzumab is given after chemotherapy rather than concomitantly

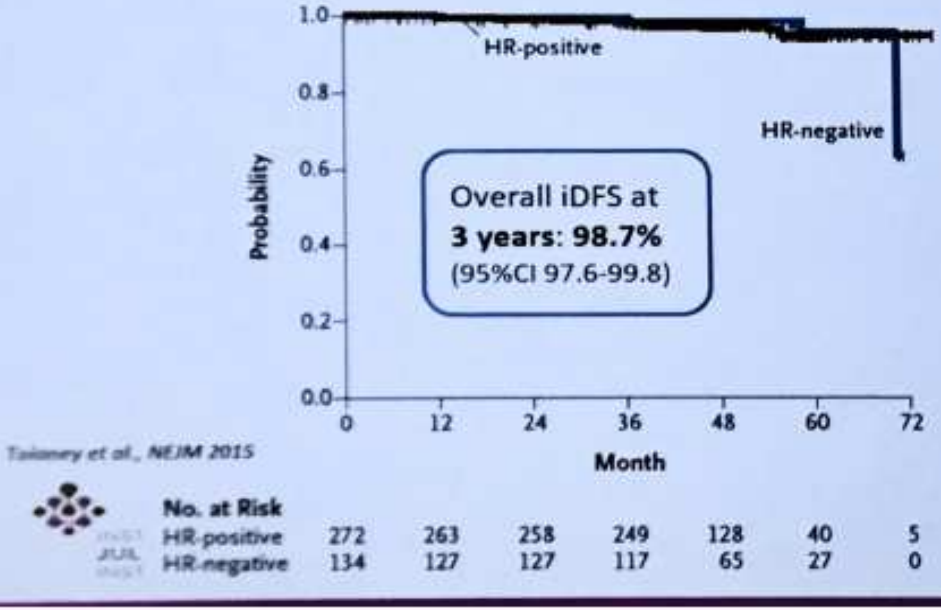


Third generation of adjuvant Trastuzumab trials : Lessons learned about subgroups by hormone receptor status

- Dual HER2 blockade administered early seems to have a more profound effect in HR- disease
- Dual HER2 blockade administered later (sequential Trastuzumab → Neratinib) is effective only in HR+ disease

Small tumors: APT trial

- Paclitaxel 12 weeks + Trastuzumab in **small tumors** (≤3 cm), **N0/N$_{mic}$ → 67%** HR+ (higher proportion than in the other trials); median FU: 4 years
- No significant differences in **3-years iDFS** according to HR status:



Overall iDFS at **3 years: 98.7%** (95%CI 97.6-99.8)

Tolaney et al., NEJM 2015

Updated results → iDFS at **7 years**:

- Overall: 93.3% (95%CI 90.4-96.2)
- **Very safe for HR+ disease : 94.6%** (95%CI 91.8-97.5)
- **HR-: 90.7%** (95%CI 84.6-97.2)

Tolaney et al., ASCO Congress 2017

General comments on the data presented

- Local **assessment** of HR status, only: **HERA, APT, PHARE, ExteNET**
  - **Different cut-points** to define positivity (1% vs. 10%)

vs.

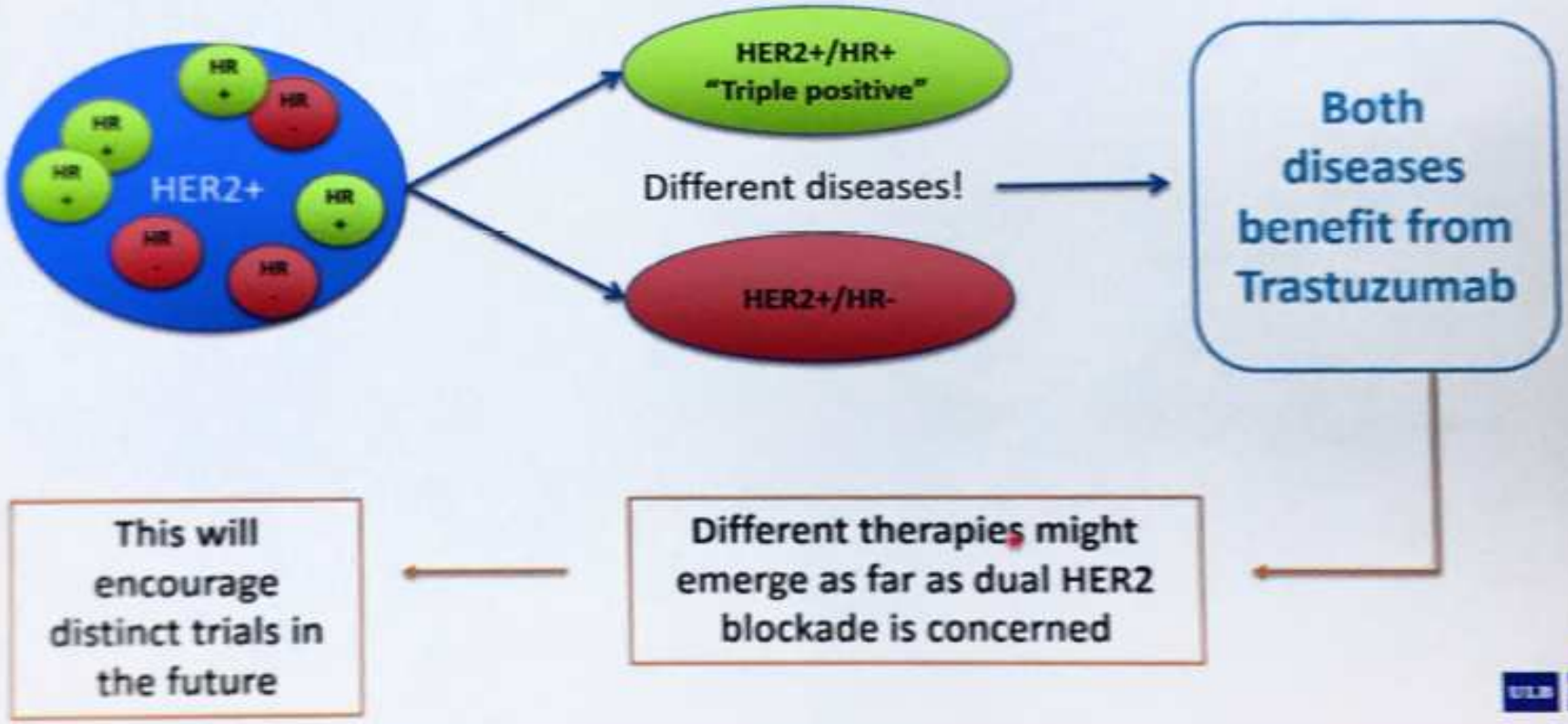
- **Central confirmation** of HR status: **BCIRG-006, ALTTO, APHINITY**

- Most trials: only HR Positive vs. Negative → **no quantification of HR expression !**

- **Gene expression levels measurements** (*ESR1* and *ERBB2*) – no cross-trial validation of the intriguing findings in HERA and NSABP B-31

- **Longer FU needed** for several trials

Conclusions



Gain in survival and higher pCR rates

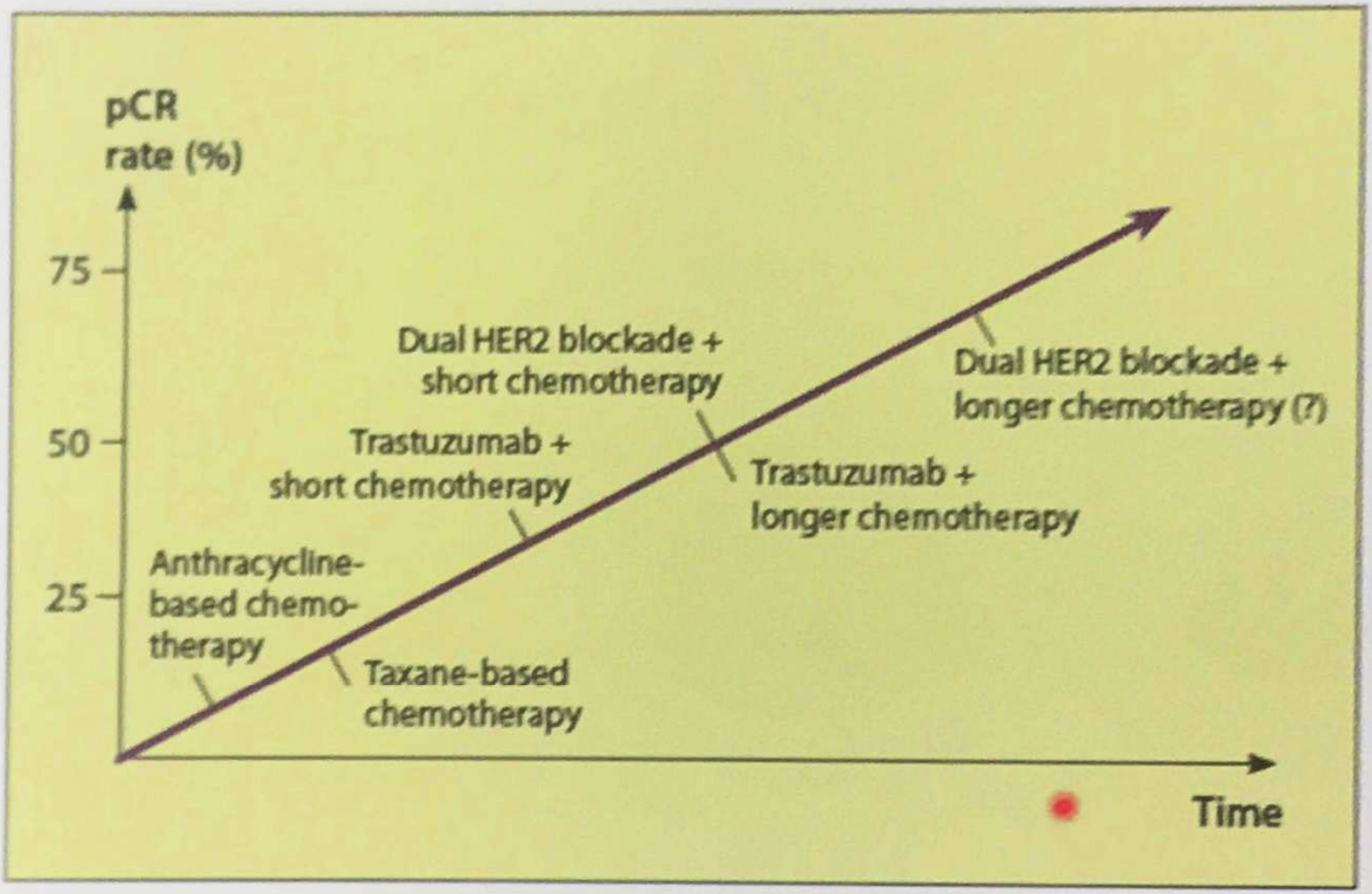


Figure 1: Incremental Improvement in Pathologic Complete Remission (pCR) Rates by Optimizing Systemic Neoadjuvant Treatment of HER2-Positive Breast Cancer.

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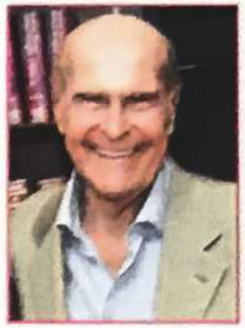
Gains in local regional treatment

- Radical mastectomy
- Modified radical mastectomy
- Breast conserving surgery



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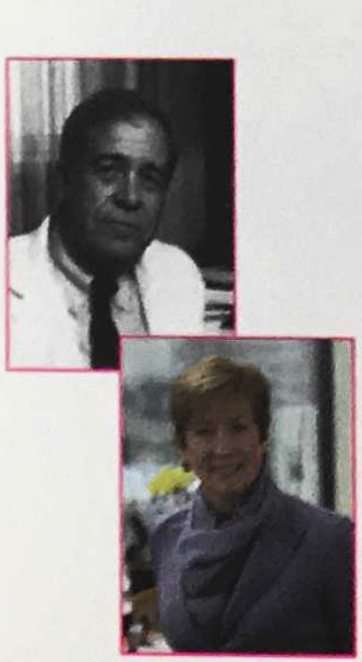
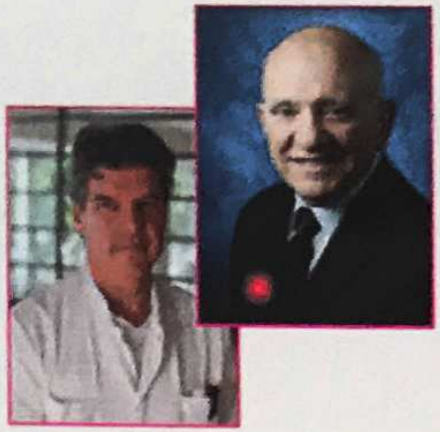
Gains in local regional treatment

- Axillary Lymph node dissection
- Sentinel node procedure in cN0
- Axillary radiation or observation in pt with positive SN





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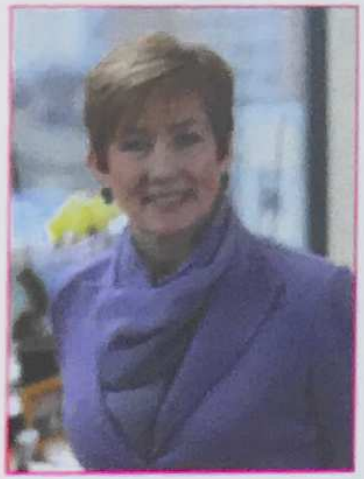
Principles of axillary surgery

- Quotes of Monica Morrow

1998

Breast surgery in general, and axillary dissection in particular, Have come to be regarded by many as staging procedures that are usefulfor maintaining local control but do not affect survival.



2017

The overarching goal when selecting an axillary management strategy is to reduce the use of ALND. The optimal approach to achieve this goal will depend on the type of breast surgery being performed, and the hormone receptor and *ERBB2/HER2* status of the tumor; however, ALND should no longer be considered routine management of the node-positive breast cancer patient.

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M Morrow, Ann Surg Oncol 1999 6 (1) 17-18, Morrow 2017

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Clinical Trials: c T1-2N0 with pos SLN

	Z011 n=856	AMAROS n=1425	OTOASOR n=474	IBCSG 23-01 n=933	AATRM n=233
Axillary recurrence : other Tx	1.1 %	1.2 %	1.7 %	1 %	1.7 %
Axillary recurrence: ALND	0.5 %	0.4 %	2 %	0.2 %	1.0 %
Additional positive nodes ALND	27.3 %	32.8 %	38.5 %	13 %	13 %
Median Follow Up	9.25 yrs	6.1 yrs	8 yrs	5 yrs	5.1 yrs

No difference in axillary recurrence rates between ALND and 'other' treatment (observation of axillary RT)

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Giuliano, Ann Surg 2016, Donker Lancet oncol 2014, Galimberti Lancet Oncol 2013, Sola Ann Surg Oncol 2013, Savolt EJSO 2017

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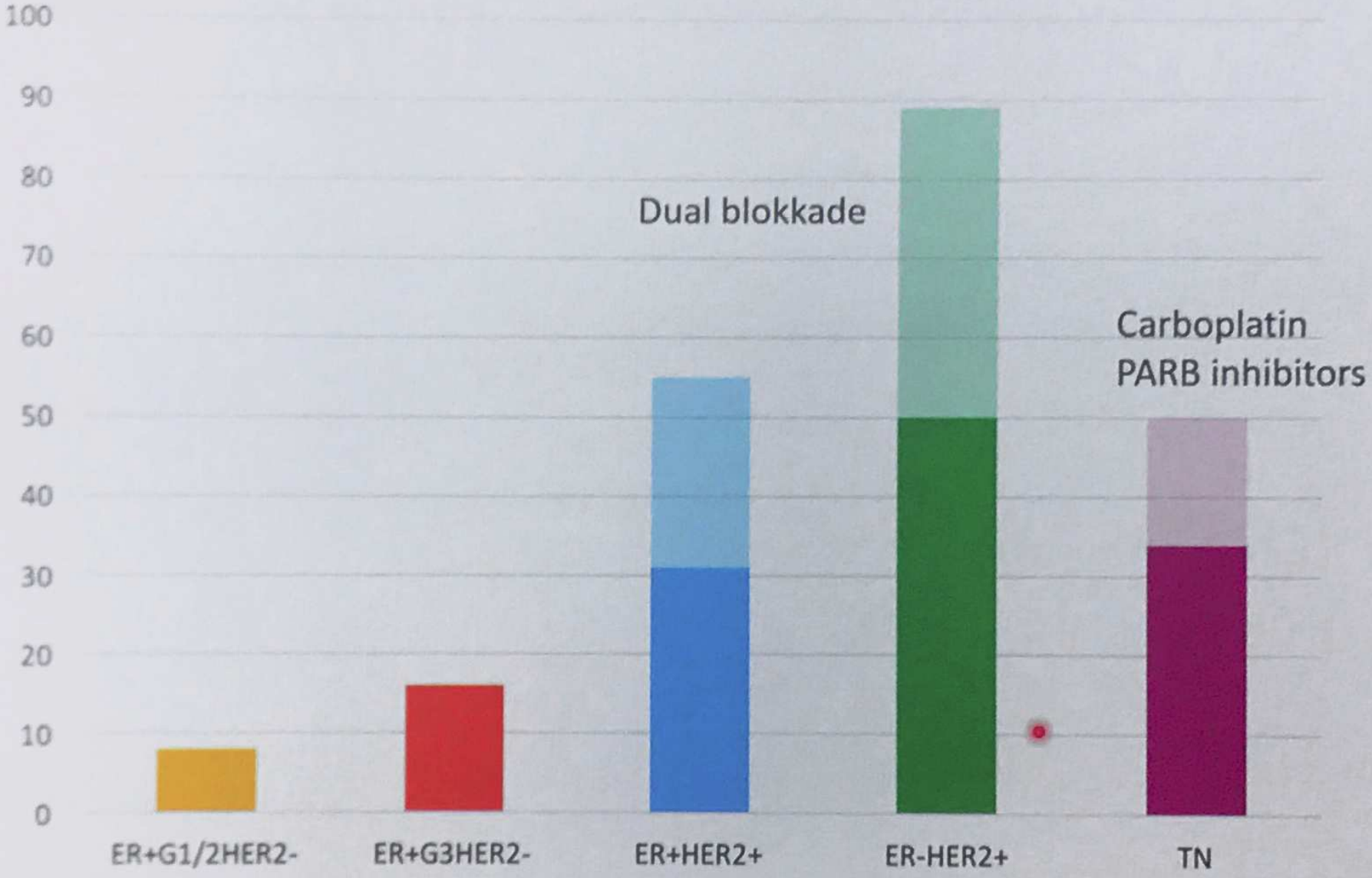
Current pCR rates after NST



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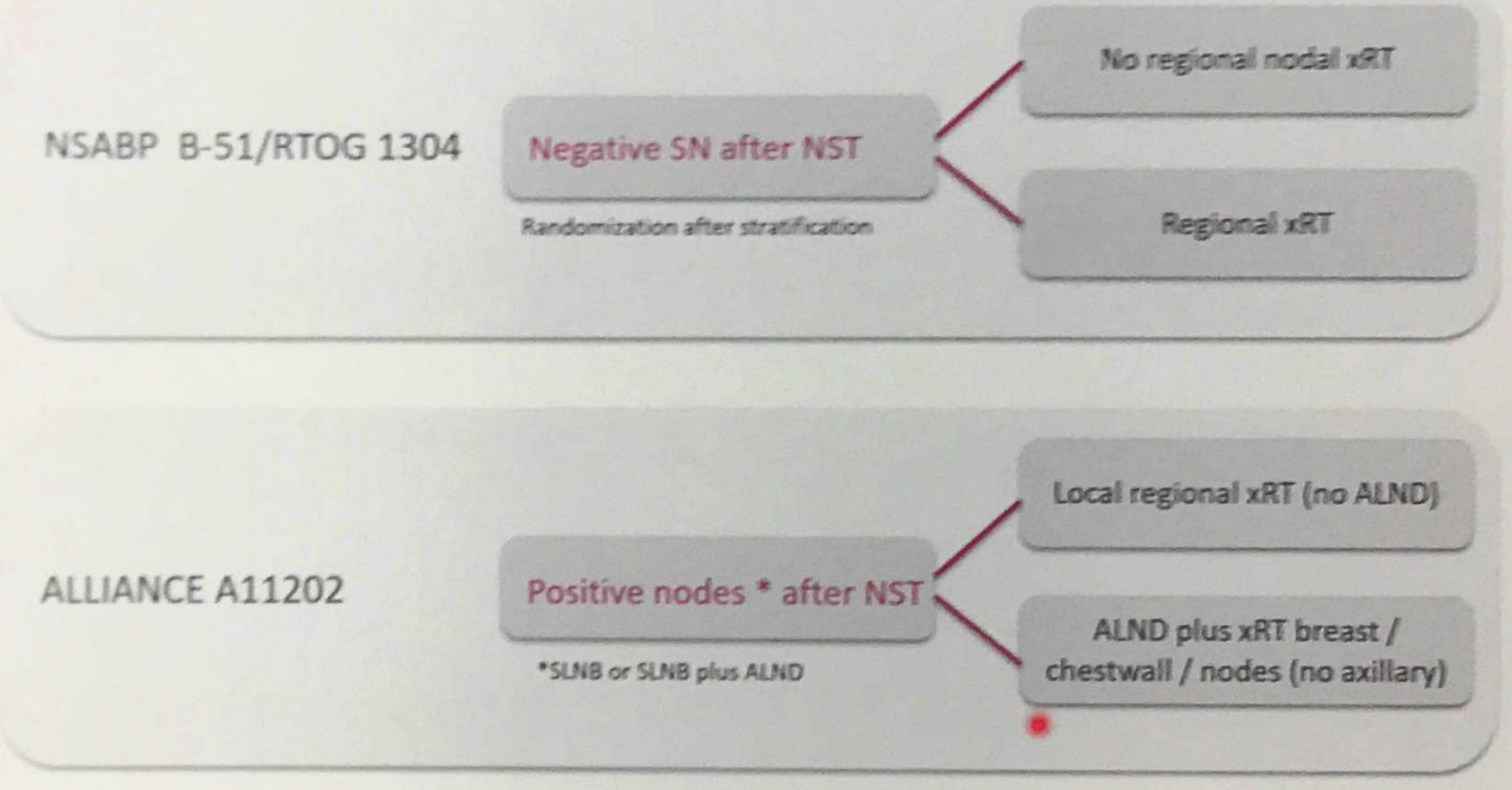
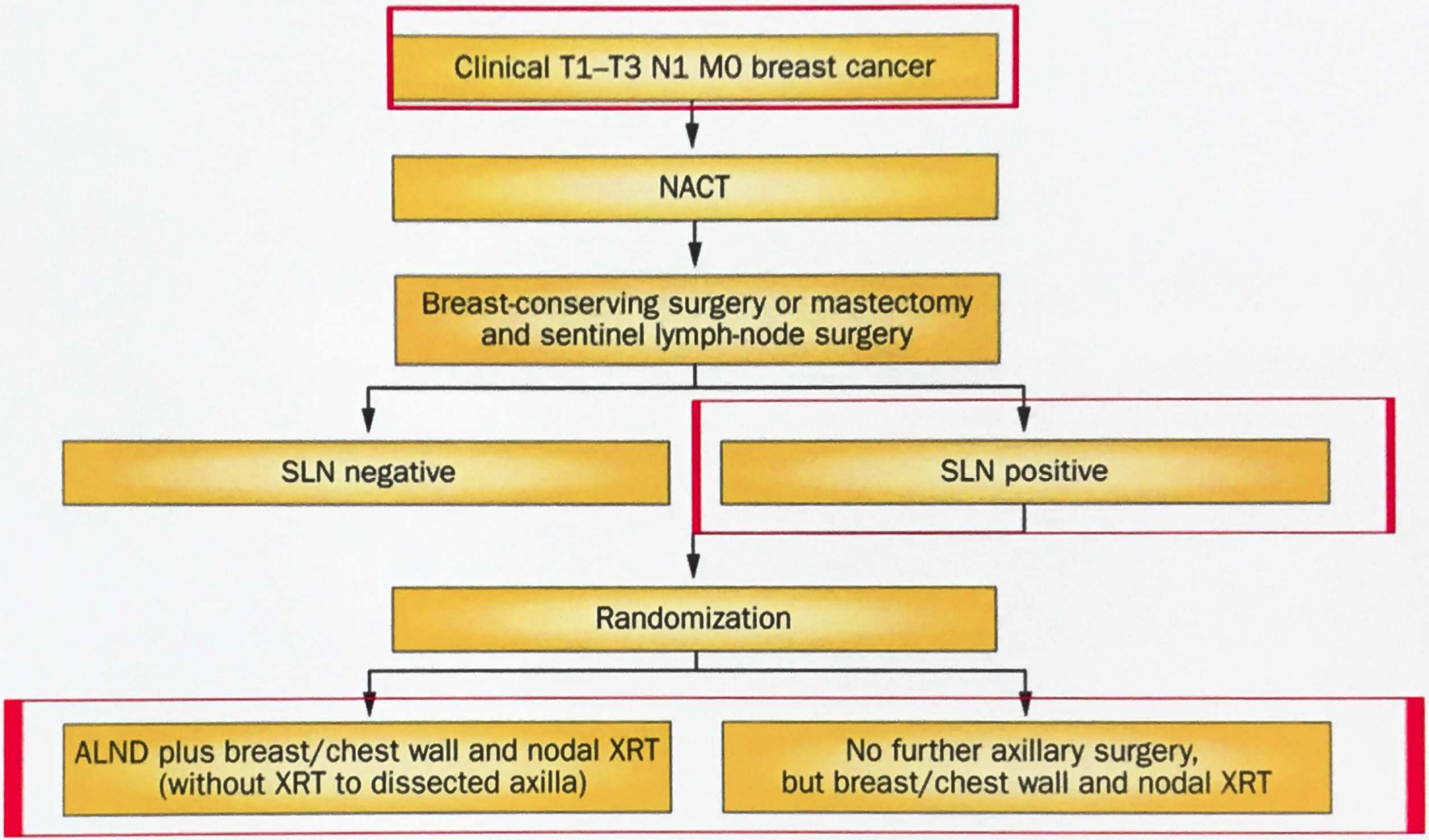
Cotazar Lancet Oncol 2014; Sikov SABCS 2015; van Ramshorst ASCO 2017

Current important trials **c N1** patients



ALLIANCE A11202



Nature Reviews | Clinical Oncology

NSABP B-51

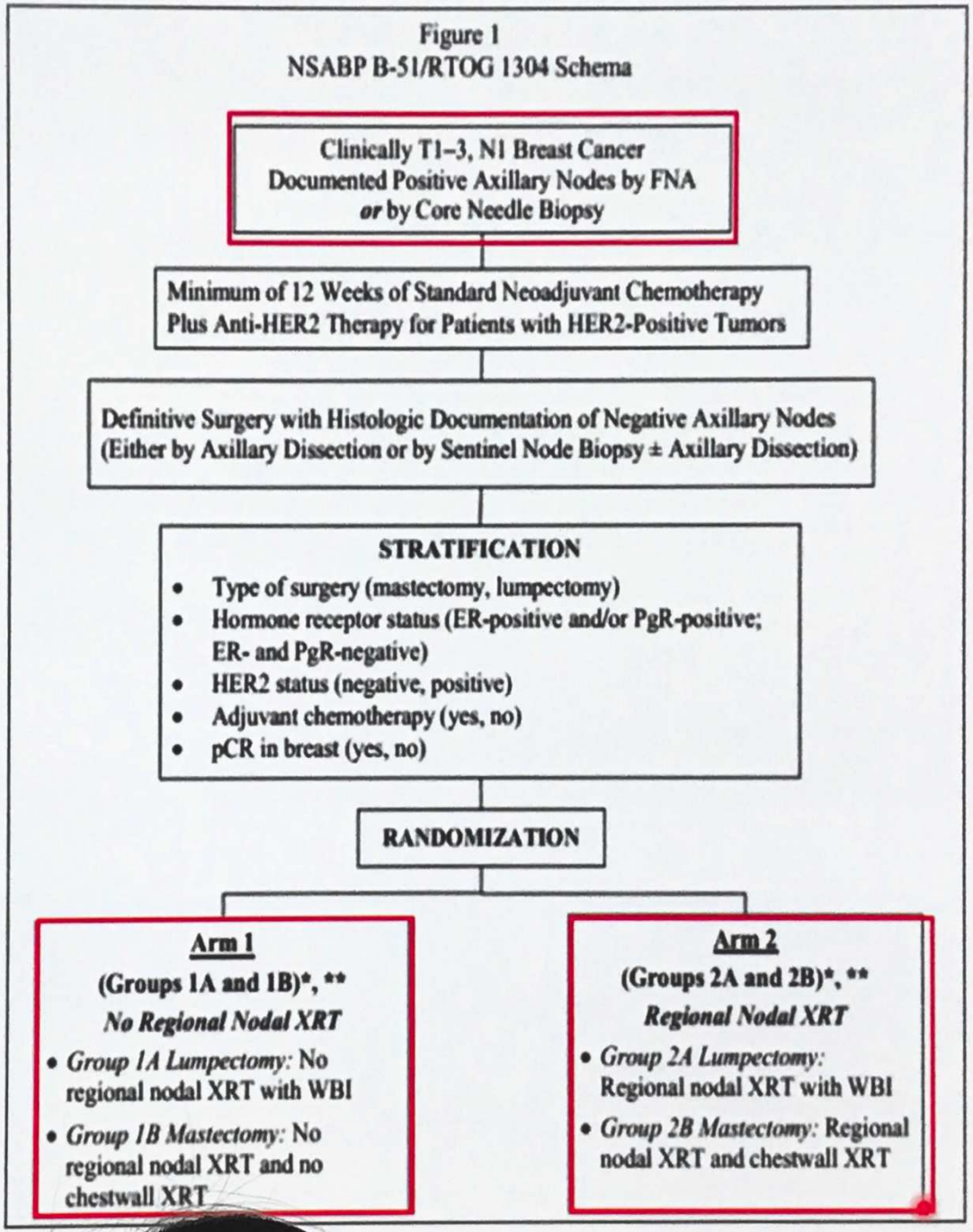


Figure 1
NSABP B-51/RTOG 1304 Schema
Clinically T1–3, N1 Breast Cancer
Documented Positive Axillary Nodes by FNA
or by Core Needle Biopsy
Minimum of 12 Weeks of Standard Neoadjuvant Chemotherapy
Plus Anti-HER2 Therapy for Patients with HER2-Positive Tumors
Definitive Surgery with Histologic Documentation of Negative Axillary Nodes
(Either by Axillary Dissection or by Sentinel Node Biopsy ± Axillary Dissection)
STRATIFICATION
Type of surgery (mastectomy, lumpectomy)
Hormone receptor status (ER-positive and/or PgR-positive; ER- and PgR-negative)
HER2 status (negative, positive)
Adjuvant chemotherapy (yes, no)
pCR in breast (yes, no)
RANDOMIZATION
Arm 1
(Groups 1A and 1B)*, **
No Regional Nodal XRT
Group 1A Lumpectomy: No regional nodal XRT with WBI
Group 1B Mastectomy: No regional nodal XRT and no chestwall XRT
Arm 2
(Groups 2A and 2B)*, **
Regional Nodal XRT
Group 2A Lumpectomy: Regional nodal XRT with WBI
Group 2B Mastectomy: Regional nodal XRT and chestwall XRT

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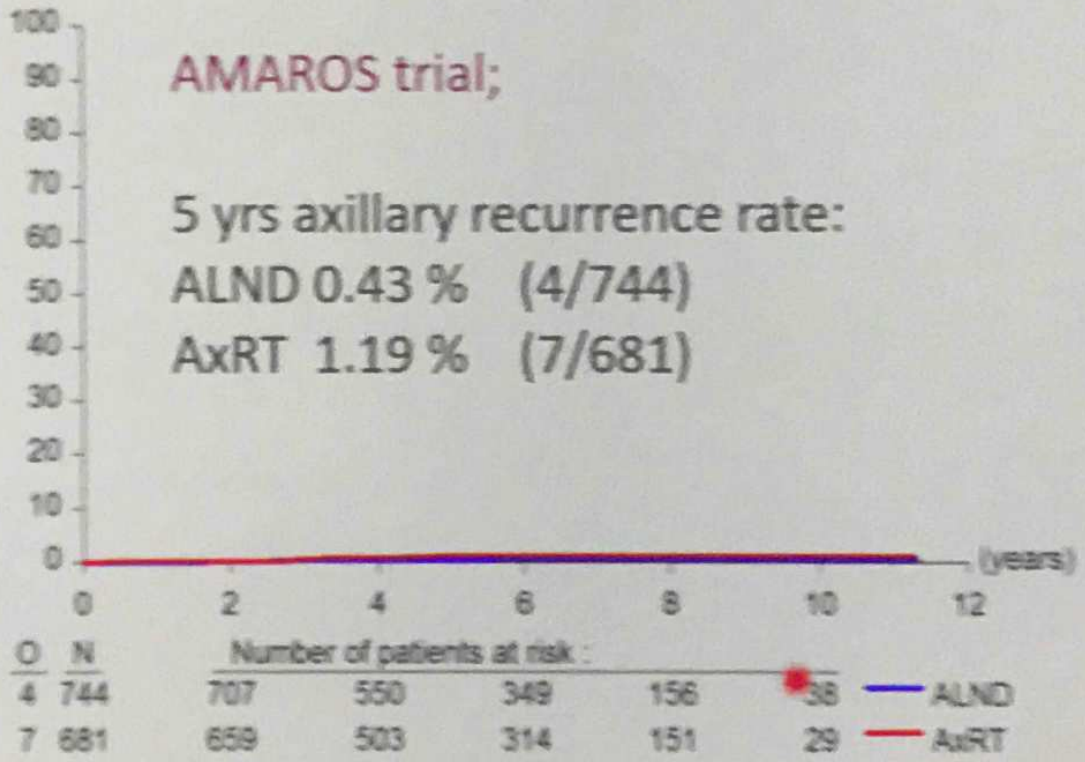
Current important trials **c N1** patients

- However, trials might be underpowered



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Current important trials **c N1** patients

- However, trials might be underpowered
- We will have to wait another ten years for results
- No N2-3 patients included in these trials

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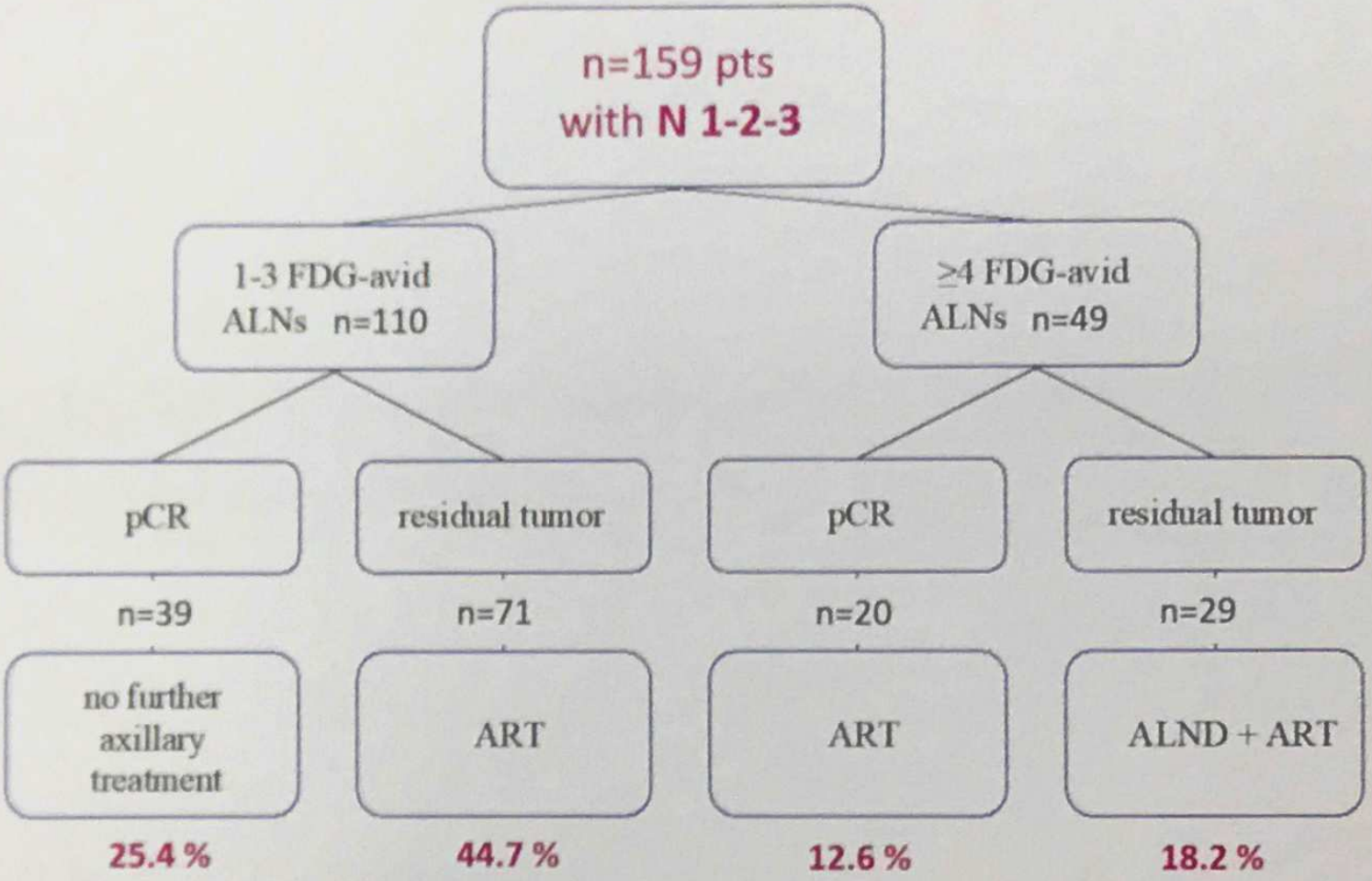
BARCELONA SPAIN 21–23 MARCH 2013

Current NCI strategy

PET-CT before NST

Response MARI

Axillary Treatment



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Tailored axillary treatment after NST

- Low FNR
- Minimal residual disease
- Axillary RT as a safe alternative for ALND

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Vd Noordaa et al, Ann Surg Oncol 2018

BARCELONA SPAIN
21 – 23 MARCH 2018

Are false-negative rates important?

Kantonsspital St.Gallen

- False-negative rates: 13-14% after „traditional SNB“
- „Random sampling“ not recommended

- Maybe not so much in primary surgery:
  - NSABP-B32: FNR 9.8% - only 0.7% recurrence rate
  - Z0011: 27% pos. nodes were left behind – 0.9% recurrence rate

- Systemic therapy and radiation are there to help us out!

Morrow M et al., JAMA 2013
Krag DN et al., Lancet Oncol 2010
Giuliano AE et al., JAMA 2011

Are false-negative rates important?

Kantonsspital St.Gallen

- Maybe very much after neoadjuvant surgery!

  - resistance of tumor cells against systemic therapy might warrant more aggressive local treatment

  - Information about residual tumor (in the lymph nodes) might be important for clinical trials in the „post-neoadjuvant“ setting

  - Capecitabine post-neoadjuvant: Create-X

Morrow M et al., JAMA 2013
Krag DN et al., Lancet Oncol 2010
Giuliano AE et al., JAMA 2011
Masuda N et al., NEJM 2017

Opposing trends in axillary treatment

Kantonsspital St.Gallen

MA20
EORTC22922

AMAROS

IBCSG 23-01
ACOSOG Z0011

Patients & Methods

JPRAS

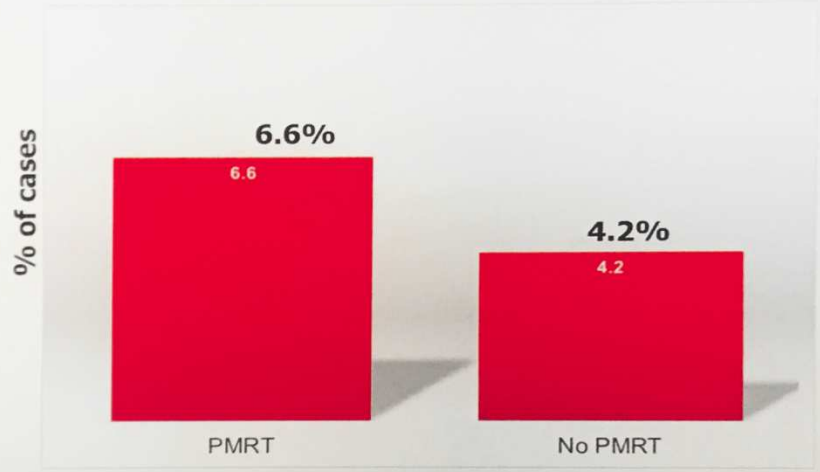
Does post-mastectomy radiotherapy affect the outcome and prevalence of complications in immediate DIEP breast reconstruction? A prospective cohort study☆

R. Taghizadeh, M. Moustaki, S. Harris, P. Roblin, J. Farhadi

Standardised radiotherapy protocol

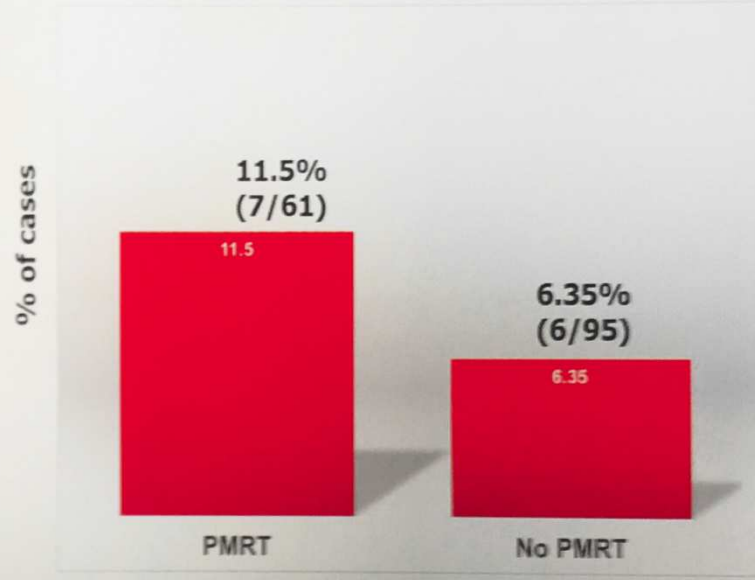
- 40 Gray in 15 fractions
- Start RT 4/52 Post operatively or 4/52 following adjuvant chemotherapy

Surgical excision of fat necrosis



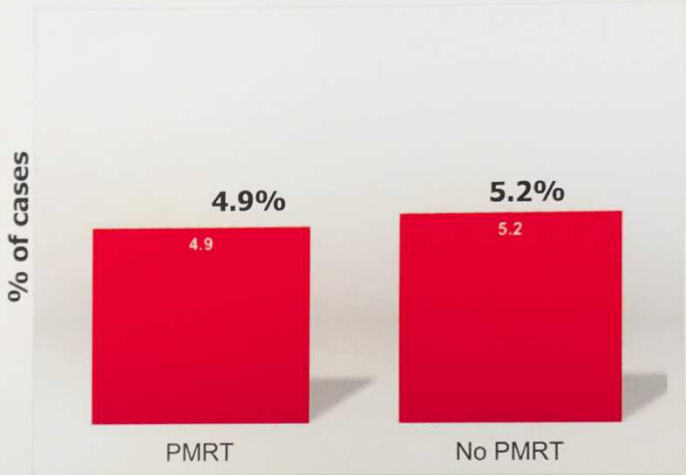
- Surgery for fat necrosis removal: PMRT 6.6%, NO PMRT 4.2%
- **p=0.383** Fisher' s exact Chi square test , p>0.05

Fat Necrosis



- Fat necrosis: PMRT 11.5%, NO PMRT 6.35%
- **p=0.199**, Fisher' s exact Chi Square test

Volume enhancement



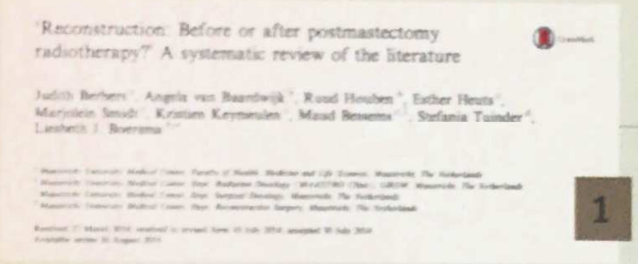
- Volume enhancement: PMRT 4.9%, NO PMRT 5.2%
- **p=0.617** Fisher's exact Chi square test , P>0.05

Maalouf C et al
Impact of autologous breast reconstruction using DIEP flap on the oncologicefficacy of radiation therapy.
Ann Chir Plast Esthet. 2017

Berbers J et al.
"Reconstruction: before or after postmastectomy radiotherapy?" A systematic review of the literature.
Eur J Cancer. 2014

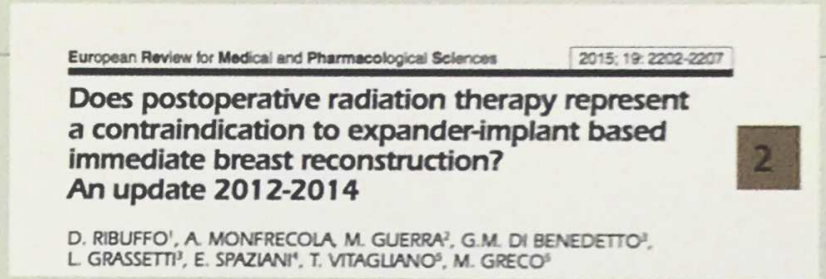
Schaverien MV etr al.
Is immediate autologous breast reconstruction with postoperative radiotherapy good practice?: a systematic review of the literature
JPRAS 2013

Implant BEFORE RT: high complications



"Reconstruction: Before or after postmastectomy radiotherapy?" A systematic review of the literature

1

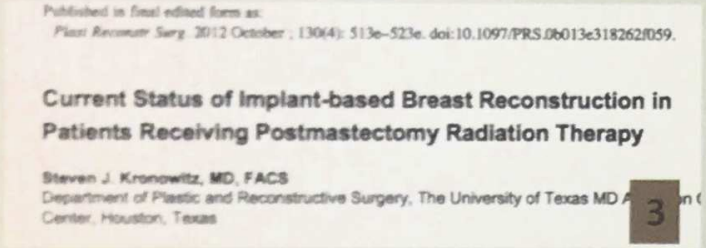


European Review for Medical and Pharmacological Sciences 2015; 19: 2202-2207

Does postoperative radiation therapy represent a contraindication to expander-implant based immediate breast reconstruction? An update 2012-2014

D. RIBUFFO[1], A. MONFRECOLA, M. GUERRA[2], G.M. DI BENEDETTO[3], L. GRASSETTI[3], E. SPAZIANI[4], T. VITAGLIANO[5], M. GRECO[5]

2

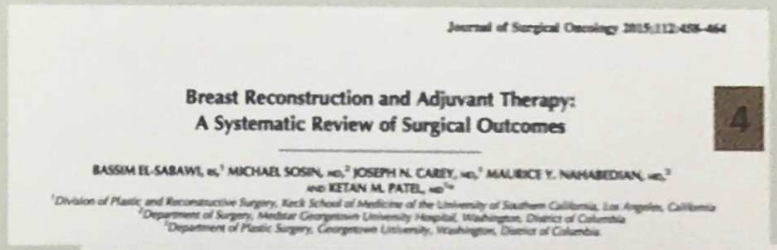


Published in final edited form as:
Plast Reconstr Surg. 2012 October ; 130(4): 513e–523e. doi:10.1097/PRS.0b013e318262f059.

Current Status of Implant-based Breast Reconstruction in Patients Receiving Postmastectomy Radiation Therapy

Steven J. Kronowitz, MD, FACS
Department of Plastic and Reconstructive Surgery, The University of Texas MD A[illegible]n C[illegible] Center, Houston, Texas

3



Journal of Surgical Oncology 2015;112:458–464

Breast Reconstruction and Adjuvant Therapy: A Systematic Review of Surgical Outcomes

BASSIM EL-SABAWI, BS,[1] MICHAEL SOSIN, MD,[2] JOSEPH N. CAREY, MD,[2] MAURICE Y. NAHABEDIAN, MD,[3] AND KETAN M. PATEL, MD[1]*

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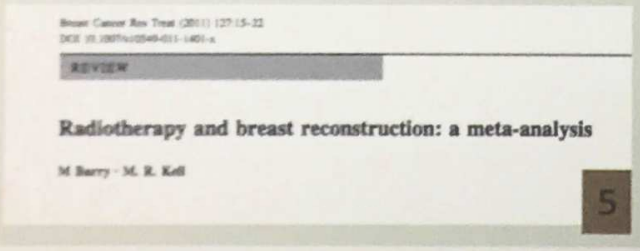

Breast Cancer Res Treat (2011) 127:15–22
DOI 10.1007/s10549-011-1401-x

REVIEW

Radiotherapy and breast reconstruction: a meta-analysis

M Barry · M. R. Kell

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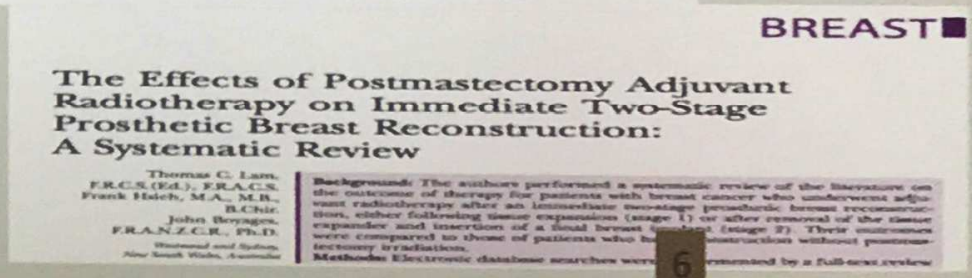

BREAST

The Effects of Postmastectomy Adjuvant Radiotherapy on Immediate Two-Stage Prosthetic Breast Reconstruction: A Systematic Review

Thomas G. Lam, F.R.C.S.(Ed.), F.R.A.C.S.
Frank Hoch, M.A., M.B., B.Chir.
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Westmead and Sydney, New South Wales, Australia

Background: The authors performed a systematic review of the literature on the outcome of therapy for patients with breast cancer who underwent adjuvant radiotherapy after an immediate two-stage prosthetic breast reconstruction, either following tissue expansion (stage 1) or after removal of the tissue expander and insertion of a final breast [illegible] (stage 2). Their outcomes were compared to those of patients who had [illegible] reconstruction without postmastectomy irradiation.
Methods: Electronic database searches were [illegible] determined by a full-text review

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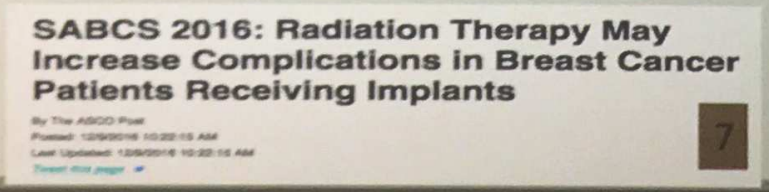

SABCS 2016: Radiation Therapy May Increase Complications in Breast Cancer Patients Receiving Implants

By The ASCO Post
Posted: 12/9/2016 10:22:15 AM
Last Updated: 12/9/2016 10:22:15 AM

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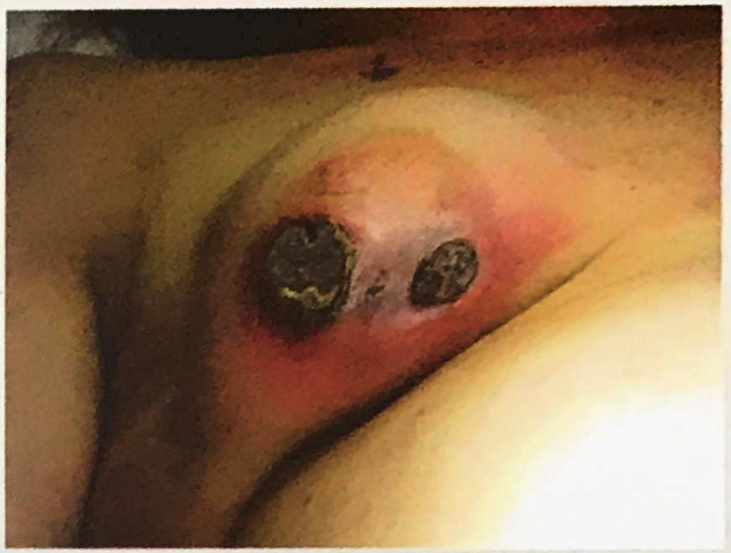
Multiple systematic reviews

Implants and RT
Adverse outcomes



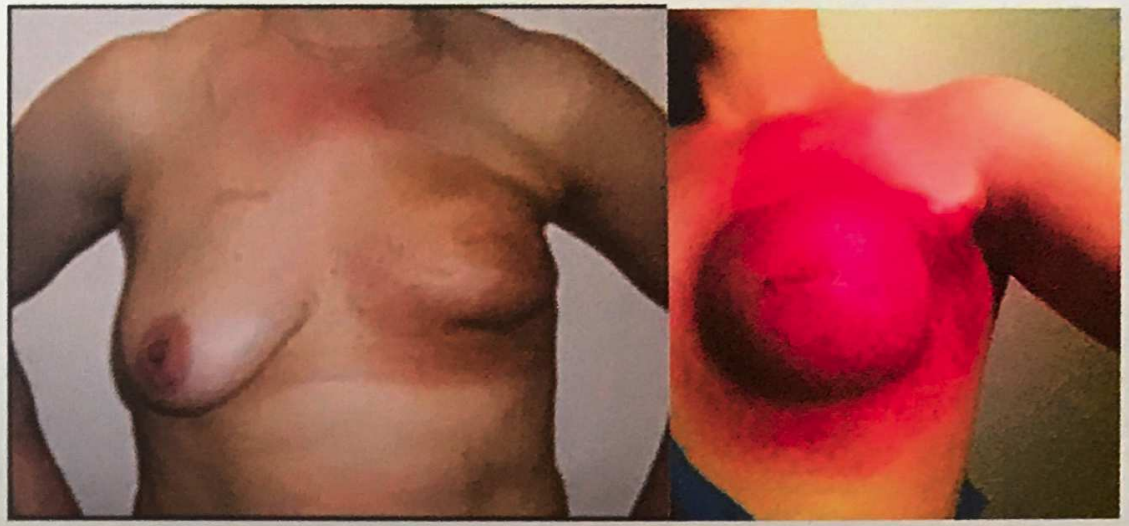
Immediate:

- wound breakdown
- implant extrusion

Delayed:

- Malposition, rippling
- capsule formation, pain
- poor cosmesis

Reconstruction ‘cripples’

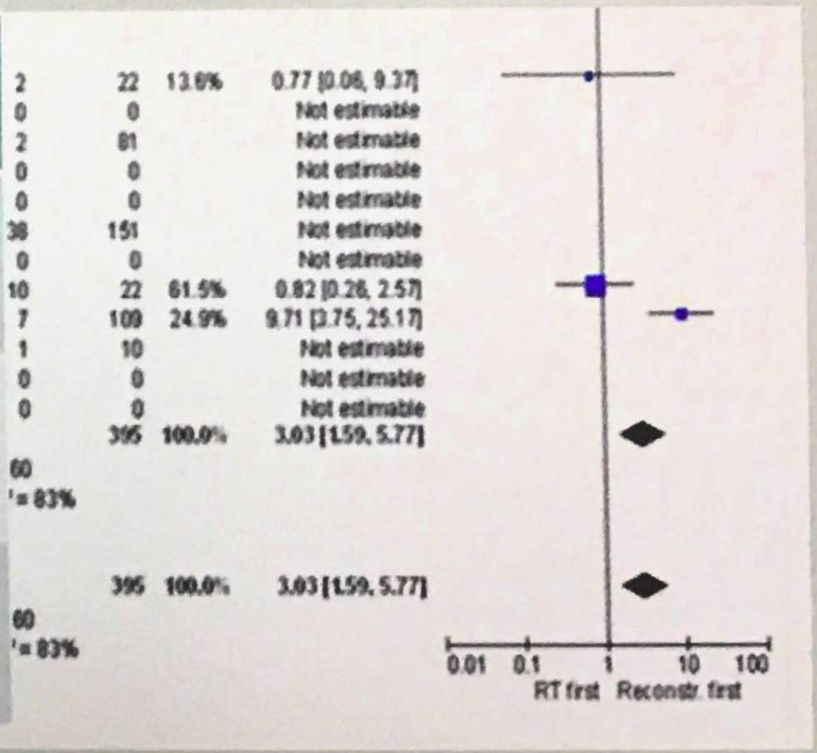


Implants BEFORE RT: high complications

- 16% implant extrusion[1]
- 20-30% implant loss at 5 years[1,2,4,6]
- 8-53% severe capsular contracture[4,6]
- 40-50% unplanned corrective surgery at 5 years [1,2,3]
- 8-10% autologous conversion[1]
- Decreased patient satisfaction (breast Q) : 40% at 2 years[4,5]

Implant AFTER RT even higher complications

Implant recon	After RT	Before RT
Total complications	49%	20%
Revision surgery	42%	9%
Implant failures	Odds ratio 3.03 (1.59-5.77)	



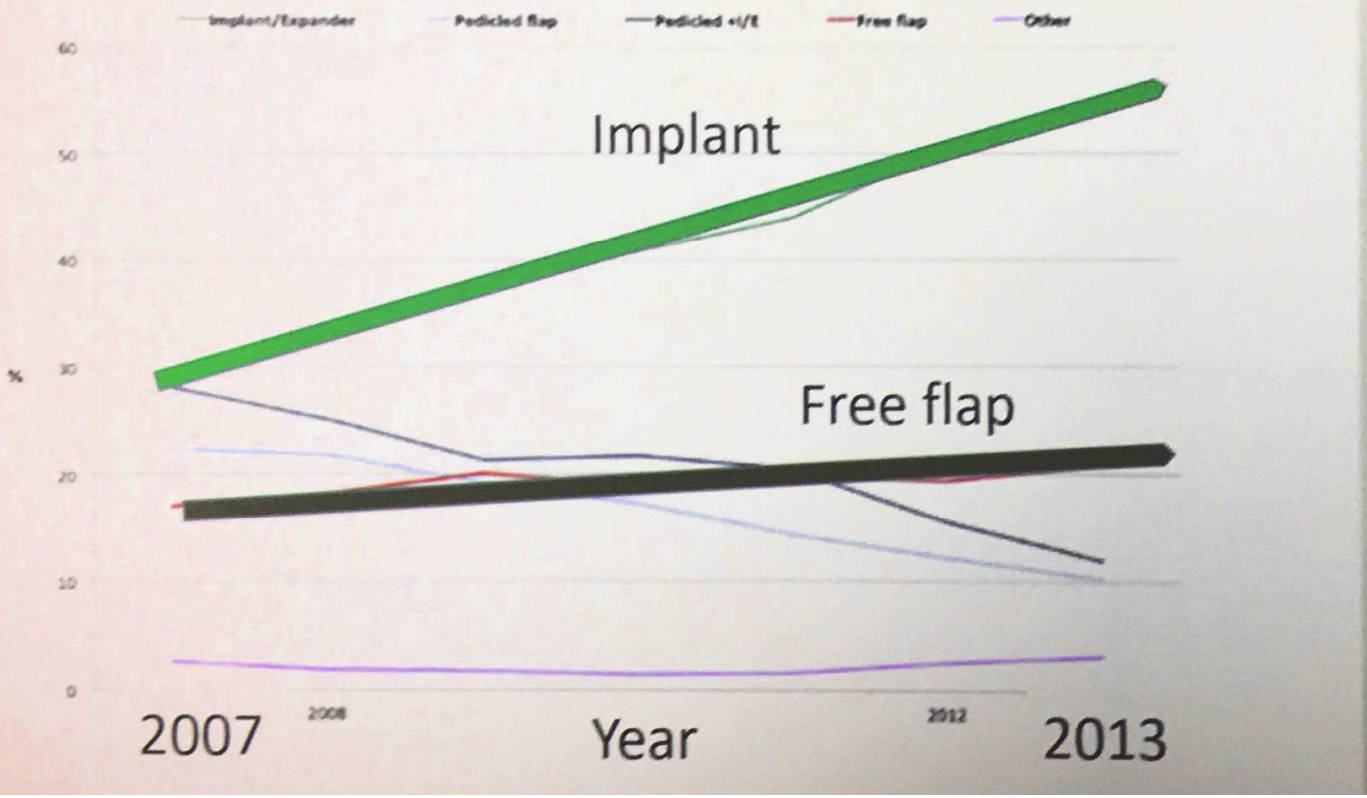
Berbers et al, EJC 2014; 50: 2752-2762

Regardless of reconstruction timing.....

Implant reconstruction has poorer outcomes when compared to autologous reconstruction. (immediate or delayed) *Jagsi et al JNCI 2018*

	PMRT N=622 IBR 83%		No RT N=1625 IBR 95%	
Type or recon	Complications 2yrs	PROM	Complications 2yrs	PROM
Autologous	26%	64%	22%	68%
Implant	**39%**	**48%**	28%	61%
	P = 0.007	P = 0.002	NS	NS

Implant Reconstruction is increasing – 30 to 54%



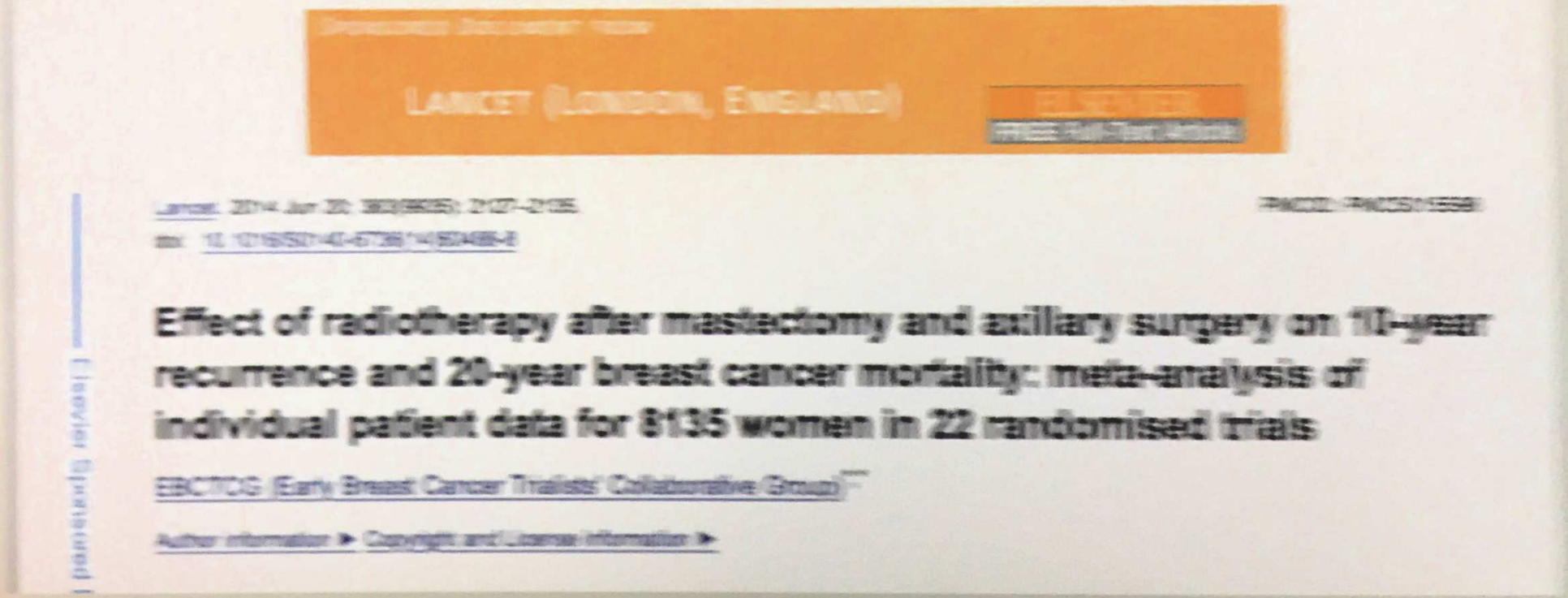
2007-2013:Enlgand

Immediate implant BR increased

from 30% to 54%

(Mennie et al EJSO 2017

We seem to be finding more reasons for recommending PMRT.....



LANCET (LONDON, ENGLAND)

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)

A personal agenda first....

- We do too many 'unnecessary' mastectomies
  - Mastectomy drives reconstruction
  - Need for reconstructive symmetry drives bilateral mastectomy and implant recon

- Avoid mastectomy where possible
  - Biology + multimodality therapies determine LRR, OS
  - Use primary systemic therapies to support risk adapted BCS
  - Use oncoplastic conservation to support more BCS

The Impact of Postmastectomy Radiotherapy on Two-Stage Implant Breast Reconstruction: An Analysis of Long-Term Surgical Outcomes, Aesthetic Results, and Satisfaction over 13 Years

Cordeiro, Peter G. M.D.; Albornoz, Claudia R. M.D., M.Sc.; McCormick, Beryl M.D.; Hu, Qunying M.D.; Van Zee, Kimberly M.D.

92% :good aesthetic result

94%: would choose implants again

Not so bad in the right hands.....

	RT N= 319 (15%)	No RT N=1789
EARLY Implant removal	9%	0.5%
Grade 4 capsule	7%	0.5%
Predicted implant replacement	13%	9%
Converted to autologous	2%	o%

PRS 2014; 134 (4) : 588–595

Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience

Salzberg, C. Andrew M.D.; Ashikari, Andrew Y. M.D.; Berry, Colleen A.R.N.P., F.N.P.-B.C.; Hunsicker, Lisa M. M.D.

- 1584 reconstructions; N=106 RT (7%)
- mean follow up 4.7 years
- Capsule contracture 4.7% vs 0.7%, (P= 0.003)
- capsular contracture stabilized at 2 years

EBCC 11

Can we decrease radiation treatment after excellent response to preoperative systemic therapy?

Meritxell Mollà, MD, PhD

Radiation Oncology Department. Hospital Clínic Barcelona

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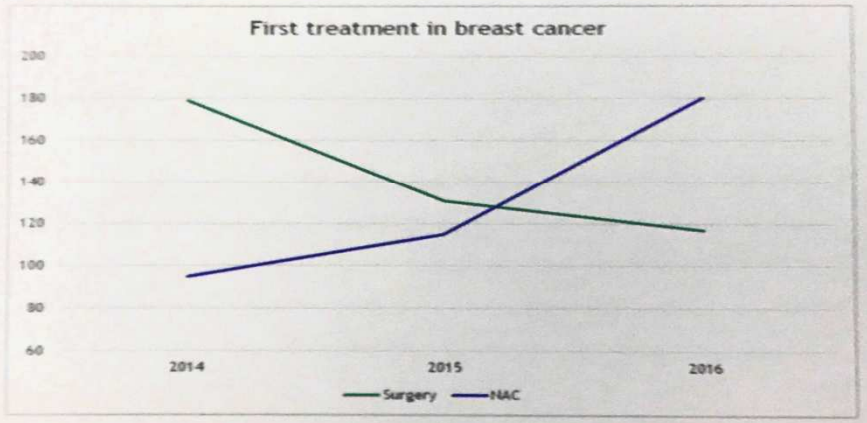
CLÍNIC BARCELONA Hospital Universitari

Background

- Neoadjuvant chemotherapy (NAC) is increasingly used in breast cancer, particulary those with more advanced node positive disease
- The use of radiation therapy following mastectomy and/ or regional nodal irradiation following breast conserving therapy after neoadjuvant chemotherapy is highly variable

Use of NAC in Hospital Clinic Barcelona 2014-2016



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Current controversies in local therapy following NAC

1. What is the adequate **management of the axilla** following NAC in node- positive breast cancer at initial diagnosis?

2. Do all patients with node-positive disease at presentation **need RT** after NAC?

3. Can **biological subtypes** help to decide local therapy options?

1- What is the adequate **management of the axilla** following NAC in node- positive breast cancer at initial diagnosis?

- False negative rate of sentinel node sampling following NAC in patients with initially node + disease

- Can axillary radiation replace ALND? Is **AMAROS** trial applicable?

pT1-T2N1(sn)

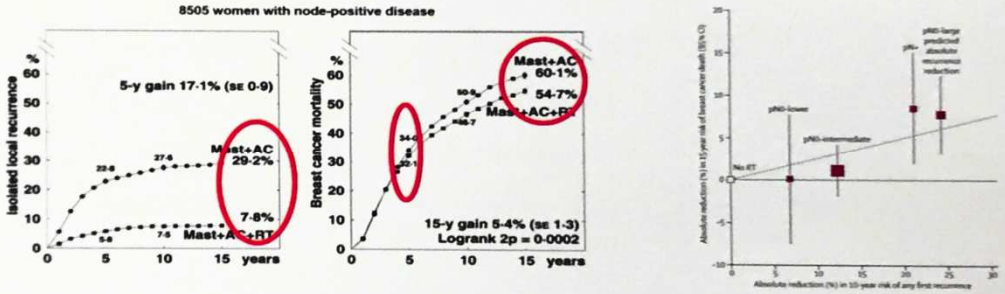
Median f/u: 6.1 y
Median age: 55 y/o
Median T size: 17 mm
ER +: 83% G3: 28%
Median SN removed: 2
Micrometastases: 40%
Systemic therapy: 91%

	cALND N=744	AxRT N=681
5-y Axillary recurrence	0.54% (n=4)	1.03% (n=7)
5 y DFS	87%	83%
5 y OS	94%	94%
5 y Clinical Lymphedema	23%	11% p<0.0001

Donker M et al. Lancet Oncol 2014

2- Do all patients with node-positive disease at presentation **need RT** after NAC?

- In adjuvant setting, EBCTCG trial showed that RT in high risk factors decreased LRR and improved OS



- In neoadjuvant setting, clinical decision making is unclear, because there are no data from randomized trials.

Lancet 2011; 378: 1707-16

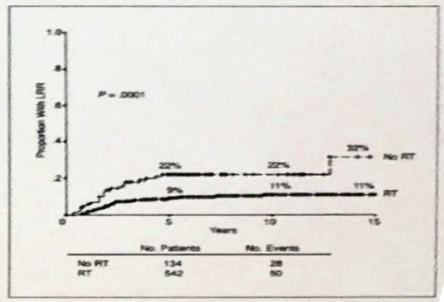
Lessons from retrospective series:

MDACC. Hung et al JCO 2004

- 6 prospective NAC. 100% doxorrubicine based. 15% taxans
- Mastectomy n=536 → RT 542 (EII: 30%. EIII: 70%)
  No RT 134

- RT significantly reduced the risk of LRR at 10 years in:

locally advanced disease at presentation and/ or
pathological T>2 cm (14% vs. 31%) and N≥4 (16% vs. 59%)



pCR retrospective series

	Le Scodan 2012	Shim 2014	Mc Gaire 2007
N	134	151	106
E I-II III	63% 37%	60% 40%	34% 66%
NAC	90% Antracycline 10% taxans	56% Antracycline 6% taxans	92% Antracycline 38% taxans
FU (m)	91	59	62
LRR (RT/ non RT)	3.8% / 13.2%	1.9% / 6.5%	5% / 10% EI-II: 0 EIII: 7% / 33%*
OS (RT/ non RT)	77.2% / 87.7%	93.3% / 89.9%	EIII: 77% / 33%*

* $p<0.05$

These data suggest:

- Patients with **Stage II** → No evidence that omission of radiation had a significant impact on LRR or OS
- Patients with **Stage III** → Higher LRR rates and decrease with RT

Lessons from NSABP B18 / B27

B18: 1523 patients. T1-3 N0-1M0

ACx4 NAC vs. Adj (1:1 RND) >50y/o→TAM

No PMRT or regional nodal RT

pCR:13%

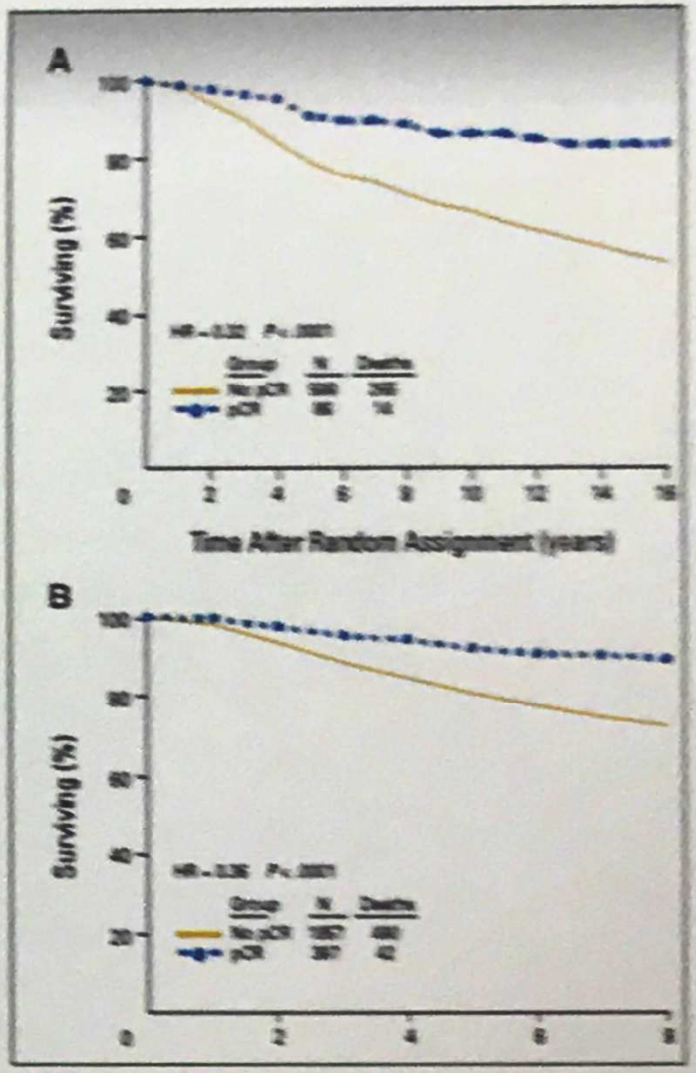
B27: 2x2 design with Taxotere added

All women received TAM (75% ER+)

No PMRT or regional nodal RT

pCR: 26% adding Taxol

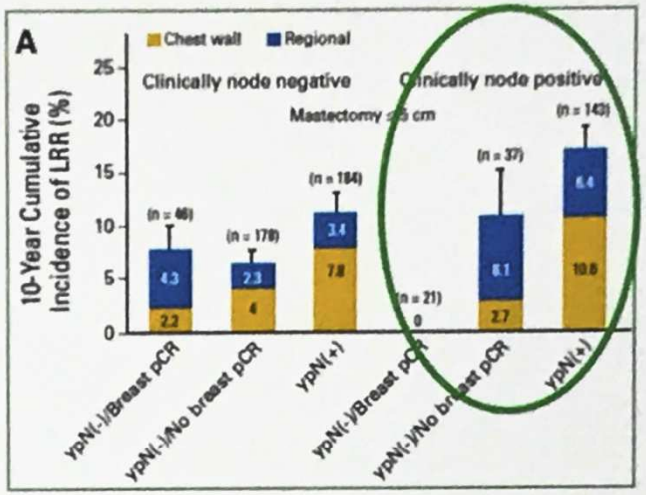
- Predominant EII population
- pCR impact in OS

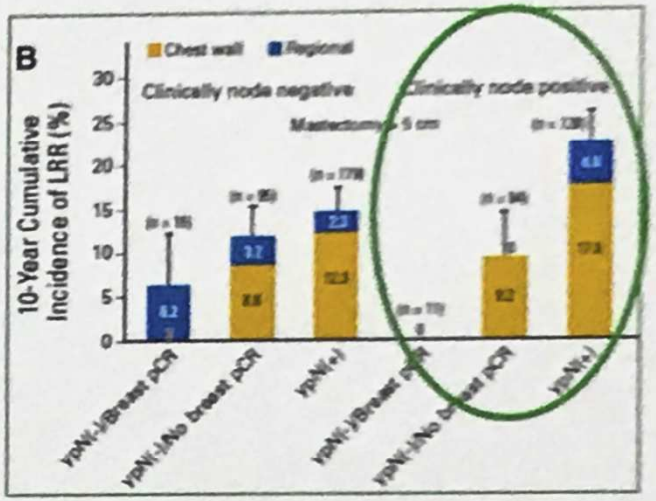


Mamounas et al, JCO 2012. Rastogi et al, J Clin Oncol 2008

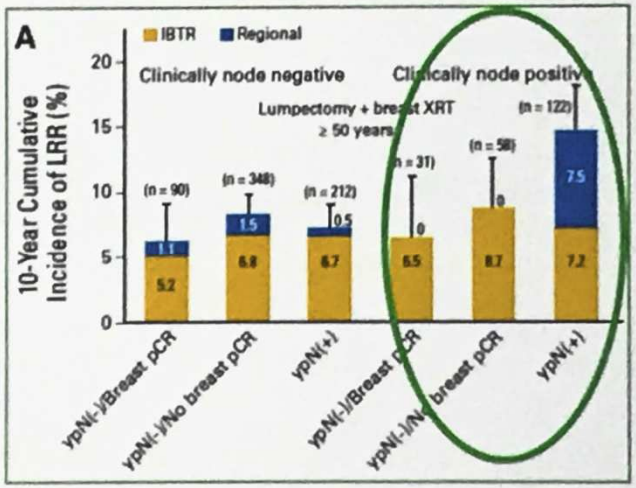
NSABP B18 / B27:

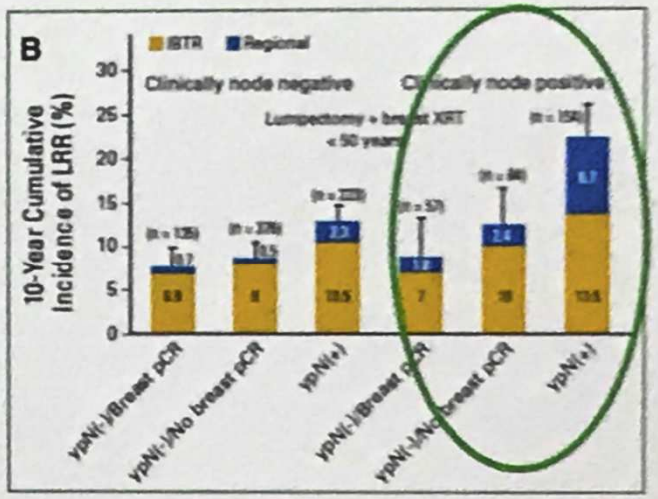
Mastectomy
LRR: 12.3%





Lumpectomy +
Breast RT
LRR: 10.3%



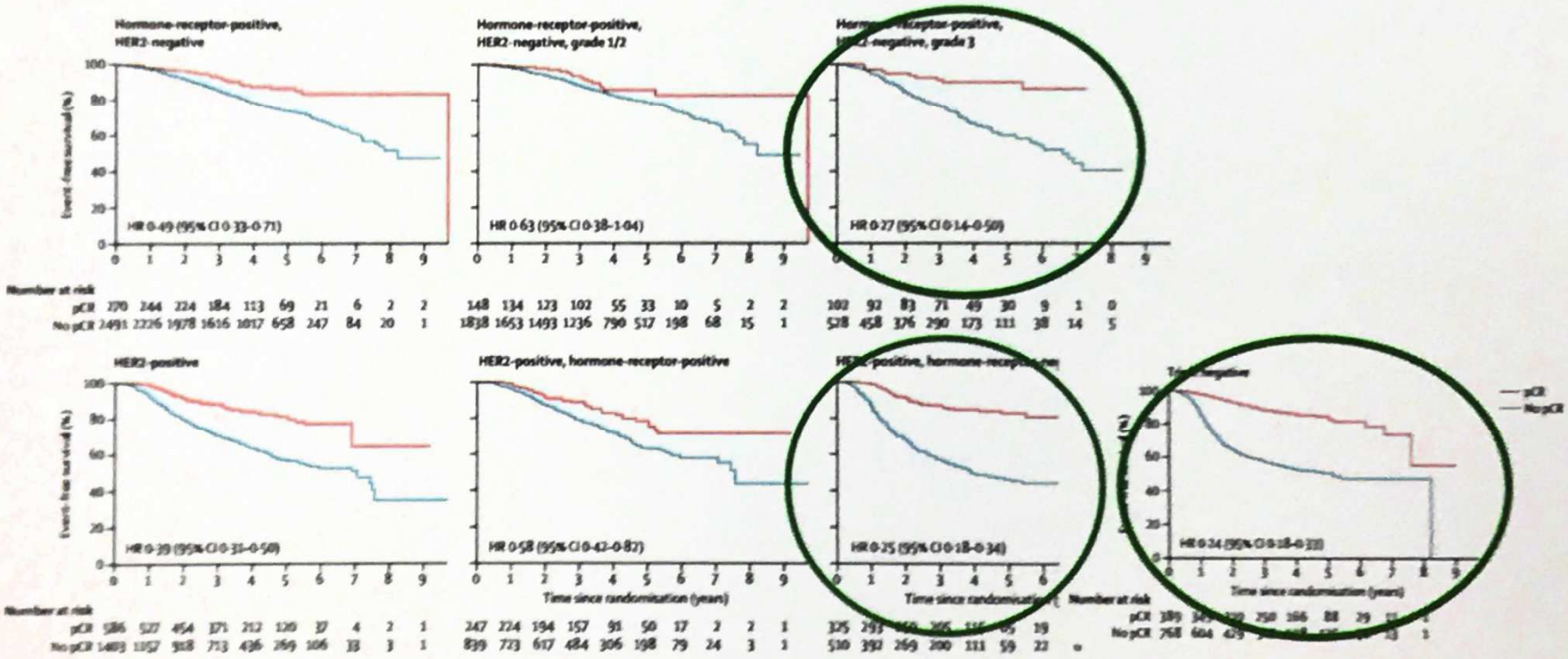


- Higher rates of LRR with tumor >5cm or ypN+
- Low LRR in pCR with negative nodes irrespective of tumor size or clinical nodal status

Mamoumas et al. J Clin Oncol 2012

3- Can **biological subtypes** help to decided local therapy options?

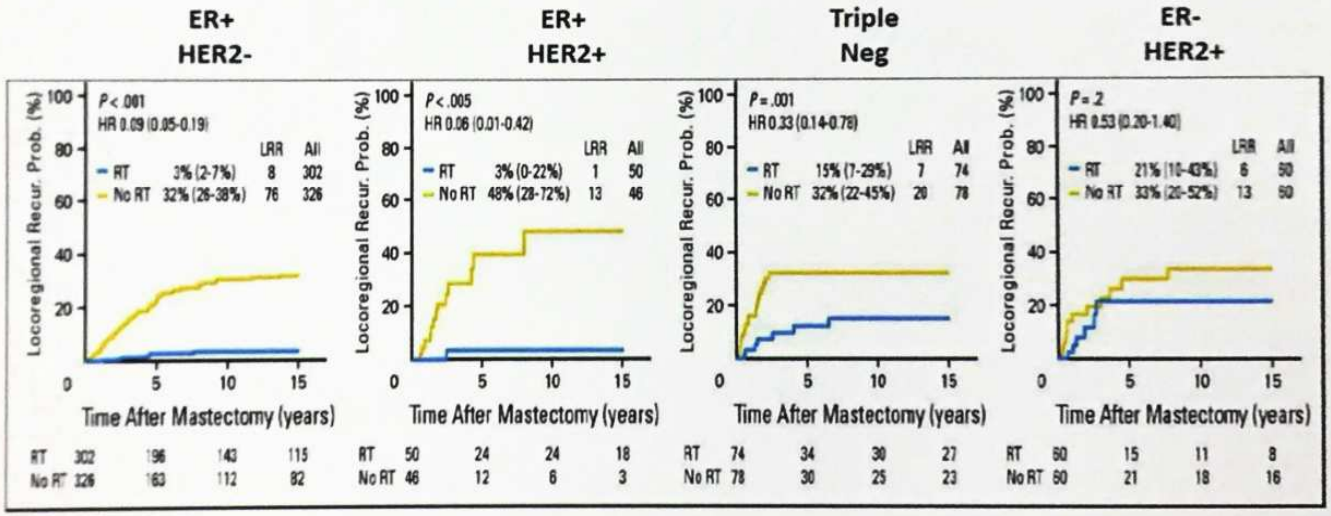
- Intrinsec subtyping at diagnosis was independently associated with **pCR**
- Patients who obtain **pCR** have **improved survival with** the prognostic value greatest <u>in aggressive breast cancer subtypes</u>: TN, HER2+/RH-, HER2-/RH+/G3



Prat et al. BMC Med 2015

Intrinsic subtypes and benefit from PMRT- Results from Danish 82b and 82c

- LRR +/- RT by Subtype approximation. Pre-Trastuzumab



Kyndi et al. JCO 2008

- Association between pCR and Survival by tumor subtype:

Long-term Follow-up From ACOSOG Z1071 (Alliance) Impact of pCR on BCSS and OS by tumor subtype in node-positive breast cancer patients treated with NAC

	11.5%	45%	42%			
	pCR			Residual Disease		
	HR (hormone receptor) Pos/ HER2 Neg	HER2 Positive	Triple Negative	HR (hormone receptor) Pos/ HER2 Neg	HER2 Positive	Triple Negative
BCSS						
HR (hazard ratio)	1.00	—	—	1.00	0.11	2.35
95% CI	Ref	—	—	Ref	0.03–0.44	1.50–3.68
5 yrs	100%	96.0%	89.8%	78.3%	95.8%	65.8%
P value		0.018			<0.0001	
OS						
HR (hazard ratio)	1.00	1.14	4.02	1.00	0.32	2.18
95% CI	Ref	0.12–10.96	0.50–32.71	Ref	0.15–0.71	1.42–3.34
5 yrs	97.1%	94.6%	87.8%	74.4%	92.8%	64.4%
P value		0.086			<0.0001	

Boughey J et al. Annals of Surgery 2017

Suggested approaches cN+/NAC: Radiotherapy management

Clinical Stage at presentation	Pathological stage after NAC	Treatment recommendations
Stage III	Any	PMRT/ nodal RT BCT
Stage II	-Residual disease in lymph nodes	PMRT/nodal RT BCT (Alliance11202 is testing whether axillary RT is not inferior to ALND)
	-Non residual disease in lymph nodes:	(RTOG1304 is testing de-escalation of RT as prognostic is much improved)
	- Low risk LRR(<10%): >40 y/o, ER+, Non LVI, pCR in breast and nodes	No PMRT/non nodal RT BCT
	- Risk of LRR >10%	PMRT/nodal RT BCT

Adapted from: Recht et al. JCO 2016, Fowble et al. Int J Radiat Oncol Biol and Phys

The future: Less aggressive **breast** therapy in pCR

- **pCR** rates are greatly improving, especially in **HER2-positive** subgroup. Are breast surgery and radiotherapy now redundant procedures?

  - Safe omission of surgery and radiotherapy are dependent on the ability to accurately **estimate pCR** imaging sensitivity and specificity and successful evaluation of percutaneous biopsy
  - Currently studies are focused on evaluating the **omission of breast surgery** in patients with excellent response to NAC

  ➢ As non- surgery strategies become more common, there will be **radiotherapy** questions to resolve:

  Optimal fractionation? Boost? Is radiotherapy needed?

Conclusions

- Modification of locoregional therapy has emerged as a clear benefit of preoperative systemic therapy
- Preoperative systemic therapy can potentially select a low risk group of patients who may do well with less agressive locoregional therapy
- Tumor biology had a significant impact on LRR, also in NAC
- Additional prospective data are needed to guide adjuvant radiotherapy decisions

Gain in survival and higher pCR rates

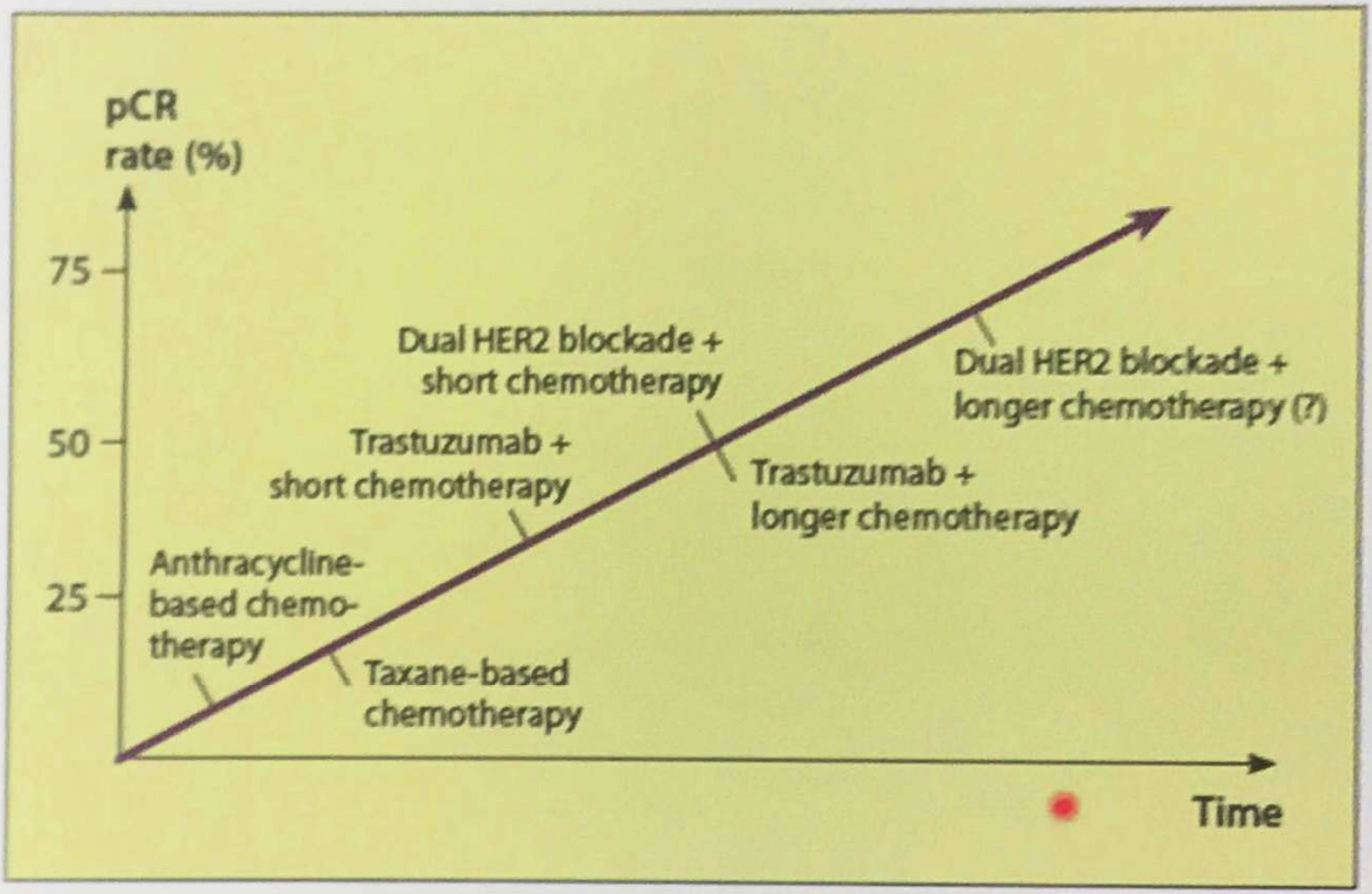
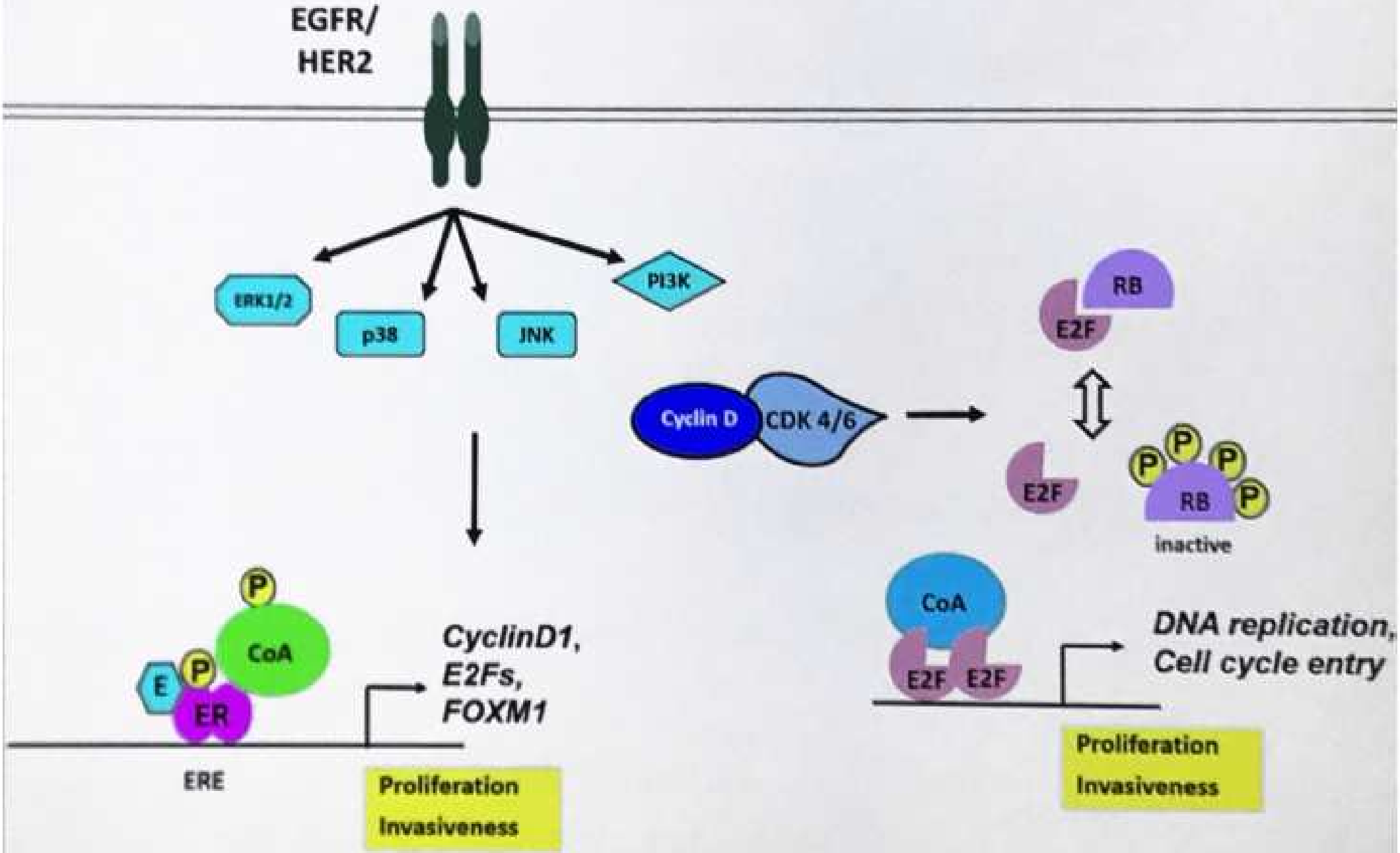
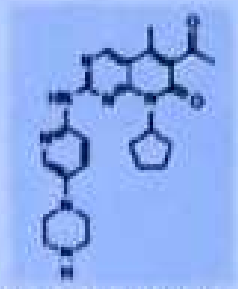


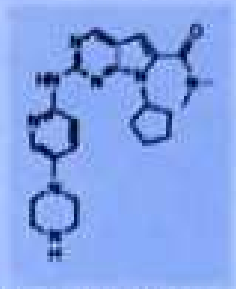
Figure 1: Incremental Improvement in Pathologic Complete Remission (pCR) Rates by Optimizing Systemic Neoadjuvant Treatment of HER2-Positive Breast Cancer.

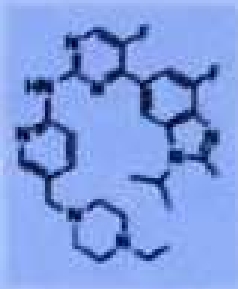
Biology of HER2+ and ER+ BC



Modern CDK 4/6 inhibitors





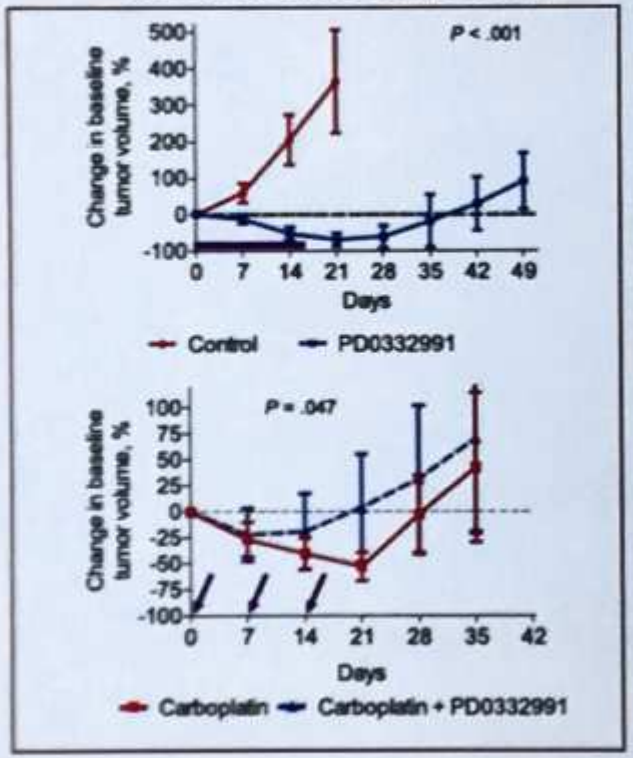


Drug	Palbociclib (Pfizer) (PD0332991, Ibrance)	Ribociclib (Novartis) (LEE011)	Abemaciclib (Eli Lilly) (LY2835219)
IC_{50} (*in vitro* kinase assay, recombinant proteins)	CDK4 (D1): 11 nmol/L CDK4 (D3): 9 nmol/L CDK6 (D2): 15 nmol/L CDK1: >10 μmol/L CDK2: >10 μmol/L (66, 67)	CDK4: 10 nmol/L CDK6: 39 nmol/L CDK1: >100 μmol/L CDK2: >50 μmol/L (1, 89)	CDK4 (D1): 0.6–2 nmol/L CDK6 (D1): 2.4–5 nmol/L CDK 9: 57 nmol/L CDK1: >1 μmol/L CDK2: >500 nmol/L (1, 88)
PK	T_{max} 4.2–5.5 hr $t_{1/2}$ 25.9–26.7 hr (69, 70)	T_{max} 4 hr $t_{1/2}$ 24–36 hr (90, 91)	T_{max} 4–6 h $t_{1/2}$ 17–38 h (crosses blood:brain barrier; refs. 92, 93)
Dosing	125 mg daily (3 weeks, 1-week drug holiday) or 200 mg daily (2 weeks, 1-week drug holiday; refs. 69, 70)	600 mg daily (3 weeks, 1-week drug holiday; ref. 90)	200 mg twice daily (continuous dosing; ref. 92)
Major dose-limiting toxicities	Neutropenia, thrombocytopenia	Neutropenia, thrombocytopenia	Fatigue
Other reported adverse events	Anemia, nausea, anorexia, fatigue, diarrhea (69, 70)	Mucositis Prolonged EKG QTc interval Elevated creatinine Nausea (90)	Diarrhea Neutropenia (92)

Sherr CJ, Cancer Discovery 20

Interaction of CDK 4/6 inhibition with chemotherapy

MMTV-neu (Rb competent)



CDK4/6i is an effective treatment in a HER2+transgenic model of BC

but it REDUCES the efficacy of concomitant chemotherapy

Roberts P.J. et al. *JNCI* 2012

NAPHER2 neoadjuvant trial

Pts with early and locally advanced centrally confirmed HER2+ AND ER+ (>10%) BC

N=30

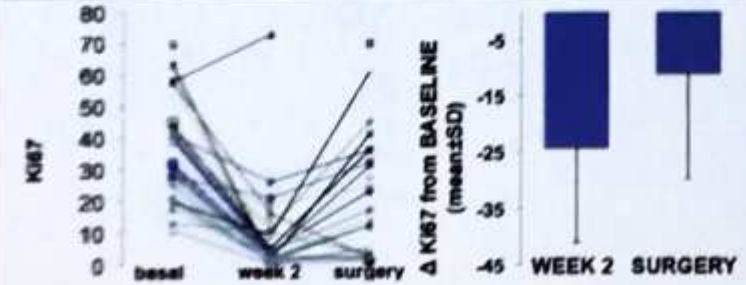
Trastuzumab, 8 mg/kg on first dose, 6 mg/kg thereafter q 3 weeks X 6
Pertuzumab, 840 mg on first dose, 420 mg thereafter q 3weeks X 6
Palbociclib 125 mg po q.d. x 21 q. 4 weeks X 5
Fulvestrant im at 500 mg q 4 weeks X 5 (+500 mg two weeks after 1st dose)

Primary endpoints:
- Ki67 changes from baseline, at 2 weeks and at surgery
- Changes in apoptosis from baseline and at surgery

Secondary endpoints:
- Rate of pCR (ypT0-ypTis ypN0) at surgery
- Clinical objective response rate
- Tolerability

Ki67 Changes

	Baseline (n=27)	Week 2 (n=25)	Surgery (n=22)
*Geometric mean (SD)	31.9 (15.7)	4.3 (15.0)	12.1 (20.0)
Mean change 95% CI		-24.0 (-31.0; - 17.1)	-10.9 (-19.3; -2.6)
Paired T-test P-value		-7.11 < 0.0001	-2.72 0.013



Pathological and Clinical Response - ITT population (30)

pCR (no invasive cells in breast and axilla)	8 (27%)
pCR in breast only	9 (30%)
Overall clinical response	**29 (97%)**
• complete clinical response	15 (50%)
• partial response	14 (47%)
• stable disease	3 (3%)

L. Gianni et al, Lancet Oncology 2018

- Palbociclib in combination with ET and anti-HER2 therapy shows signals of activity in ER+ and HER2+ BC warranting further studies
- The standard of care in this setting is mainly chemotherapy + anti-HER2 therapy

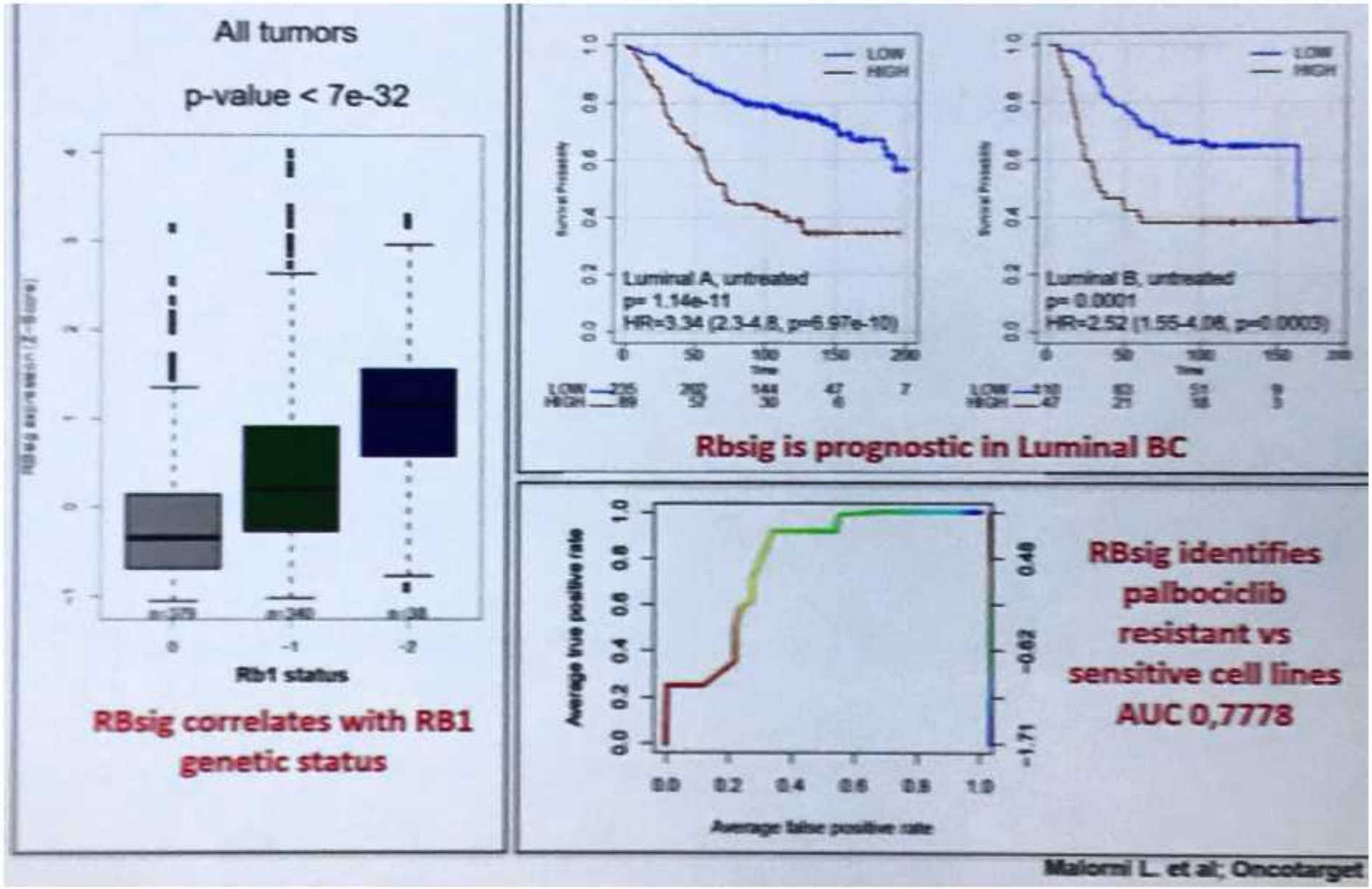
Questions:

Can CDK4/6 inhibitor substitute for chemotherapy in ER+ and HER2+ BC?

Will it be active in all patients?

We do not know!

Biomarkers would help building new trials in this setting



RBsig in ER+/HER2+ BC

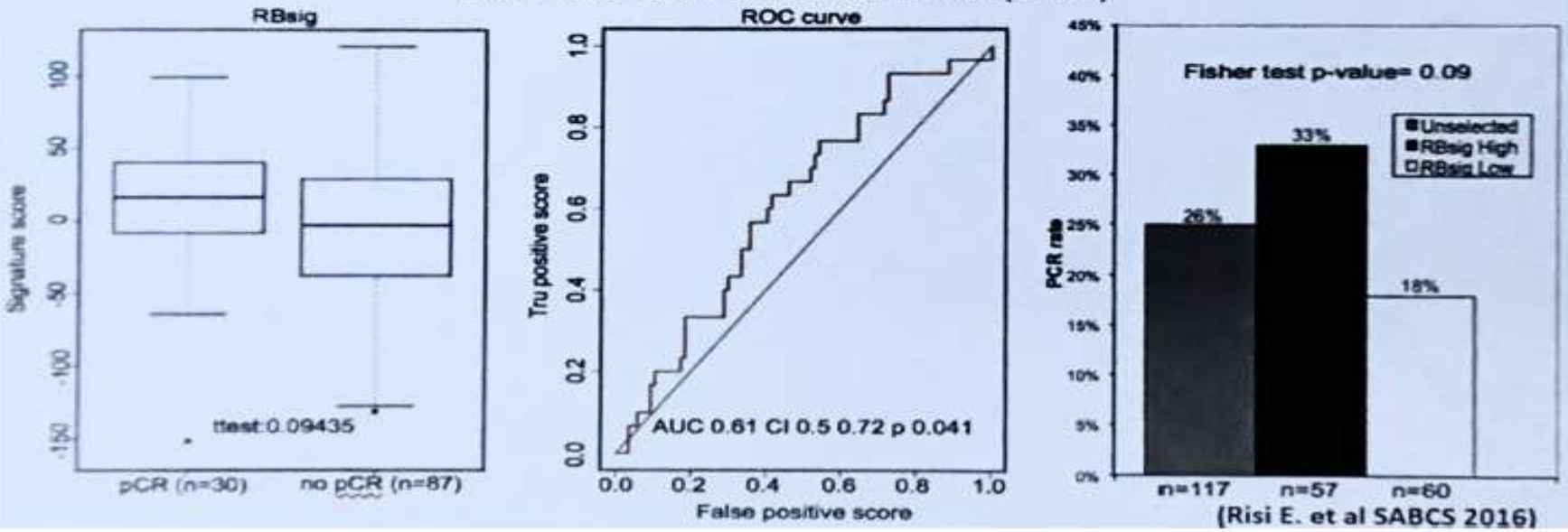
- **Meta-dataset of 10 neoadjuvant trials of CHT +/- anti-HER2 therapy with GEP data available on pre-treatment biopsies (ER+ /HER2+ pts N= 211)**
- **RBsig was computed and the correlation with pCR was explored**

In ER+/HER2+ pts treated with CHT+ anti-HER2:

- **Pre-treatment RBsig was lower in patients not achieving pCR**
- **RBsig LOW* tumors had lower pCR rates compared to RBsig HIGH***

* The RBsig was dichotomized as High/Low in correspondence to the 50th percentile

ER+/HER2+ dataset - CT+ anti-HER2 (n=117)



(Risi E. et al SABCS 2016)

Trial hypothesis

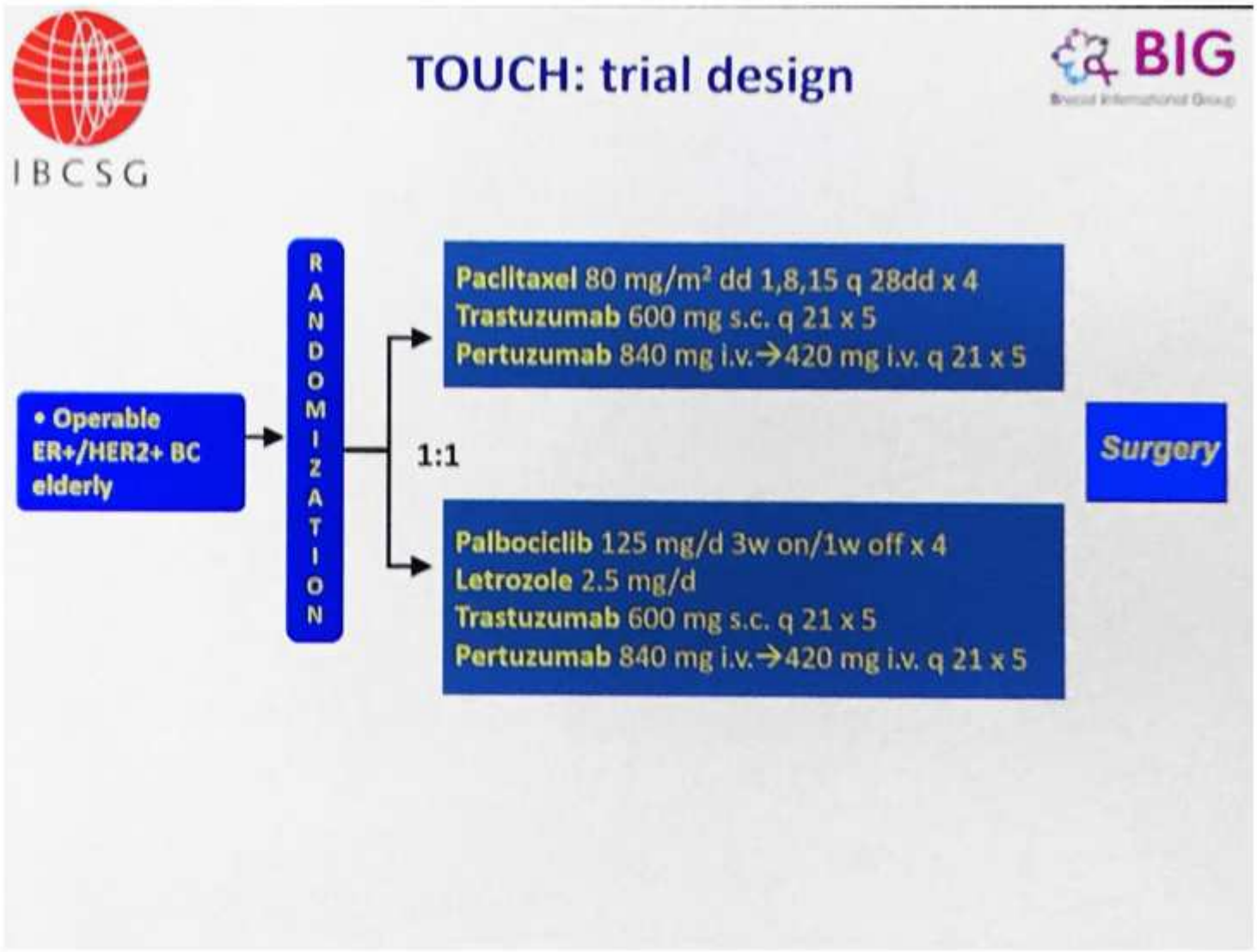
RBsig may help selecting pts with ER+/HER2+ BC who could be spared CHT and treated with ET+ anti-HER2 + palbociclib

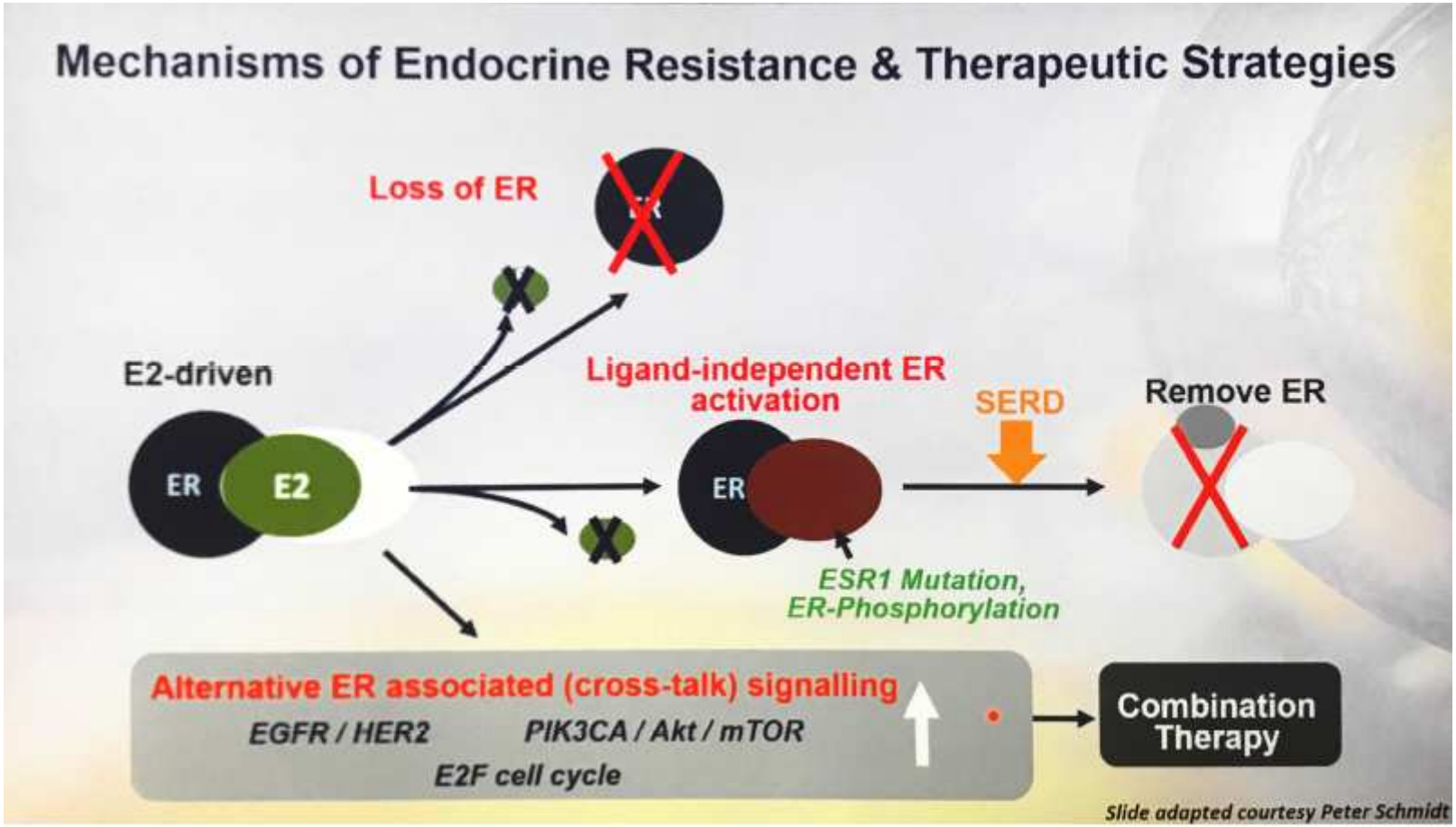
- Pts with **RBsig LOW**

  ET+ anti-HER2+ palbociclib will be **more active** than CHT+ anti-HER2

- Pts with **RBsig HIGH**

  CHT+ anti-HER2 will be **more active** than **ET+ anti-HER2+ palbociclib**




Mechanisms of Endocrine Resistance & Therapeutic Strategies
Loss of ER
E2-driven
ER
E2
Ligand-independent ER activation
ER
SERD
Remove ER
ESR1 Mutation, ER-Phosphorylation
Alternative ER associated (cross-talk) signalling
EGFR / HER2
PIK3CA / Akt / mTOR
E2F cell cycle
Combination Therapy
Slide adapted courtesy Peter Schmidt

Introduction

- AI resistance is very diverse
  - ESR1 mut ~ 50% of pts
  - KRAS mut ~ 15-20%
  - FGFR mut ~ 5-10%
  - NF1 mut ~ 5%
- Moreover mutations are often sub-clonal
- How to adress this double issue ?

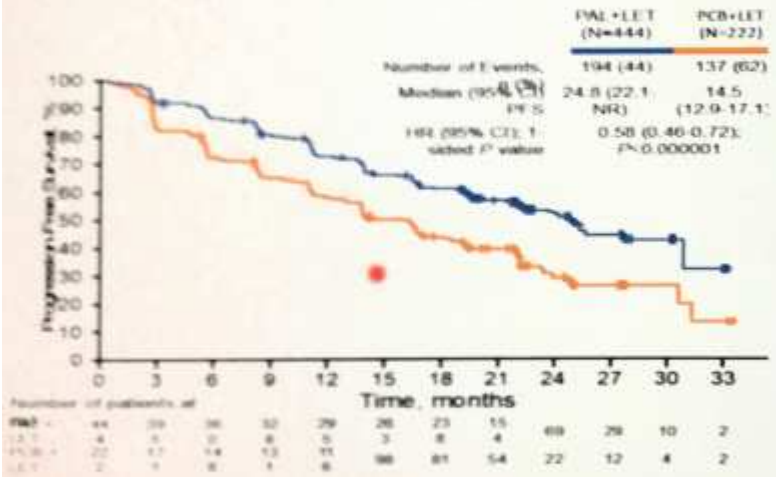
→ Target what these cells have in commun

Cyclin D1-CDK4/6

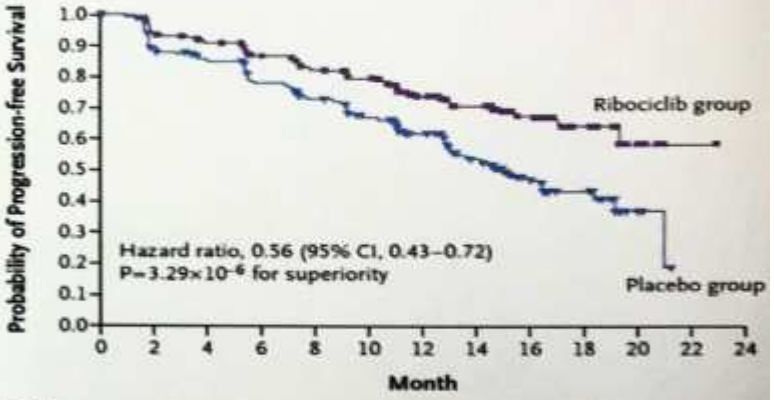
(the growth of ER+ breast cancer is dependent on Cyclin D1-CDK4/6)

First line AI sensitive trials with CDK4/6 inhibitors

PALOMA2



MONALEESA2



No. at Risk

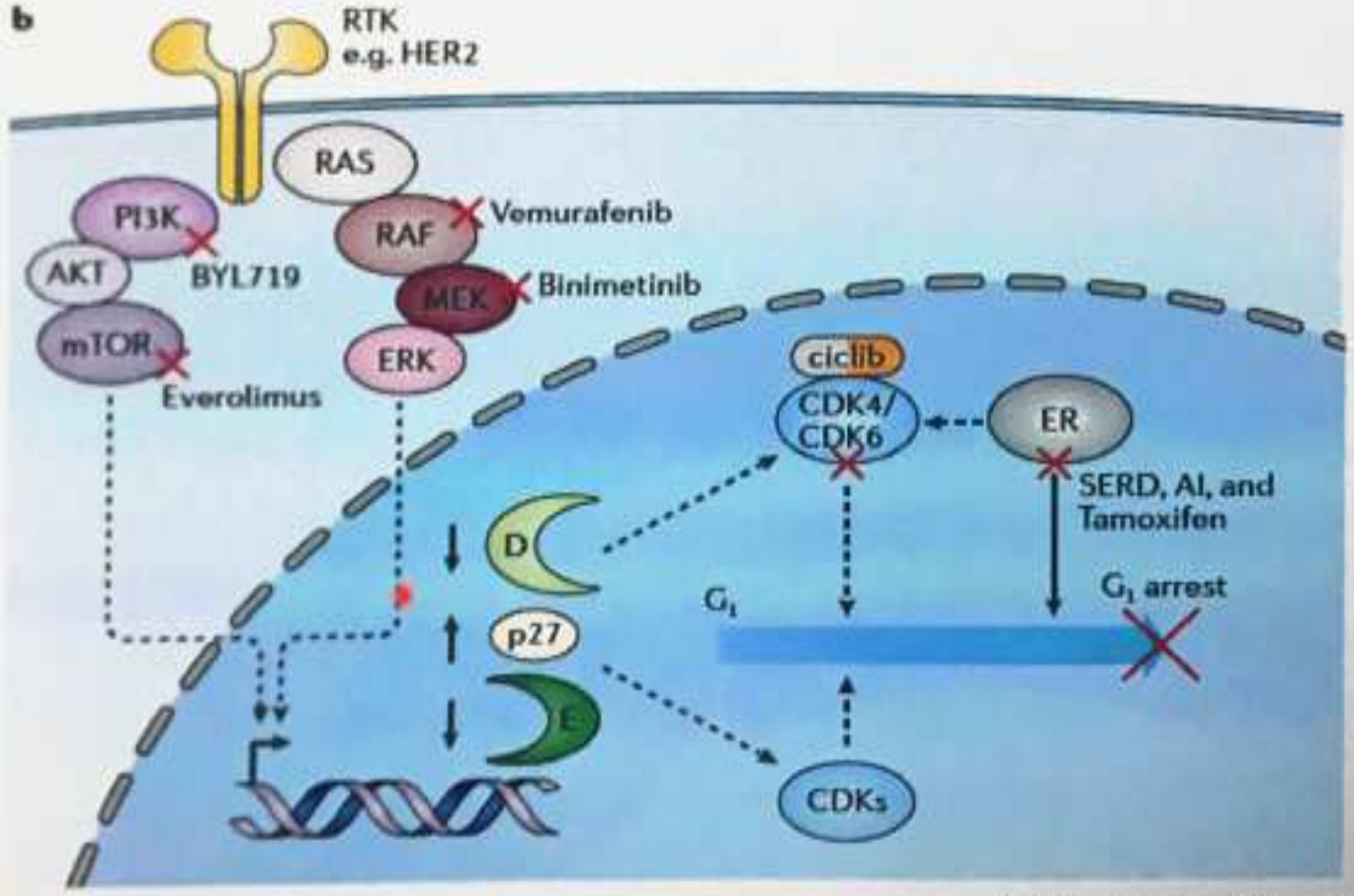
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

Finn *et al* NEJM 2016

Hortobagyi *et al* NEJM 2016

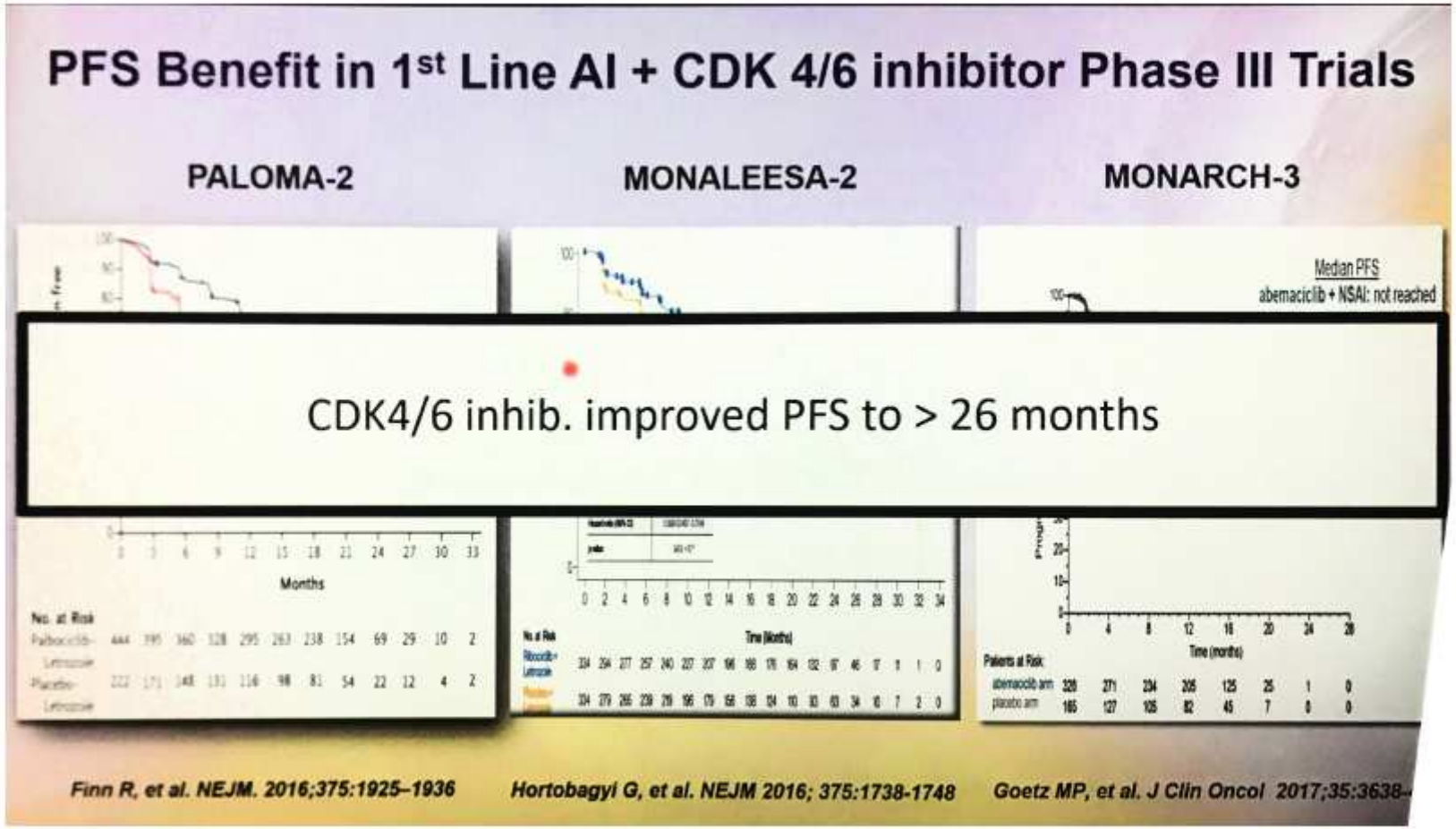
How to block resistance ?

Combination therapy augments CDK4/6 inhibition and prevents acquired resistance



O'Leary et al Nat Rev Clin Oncol 2016

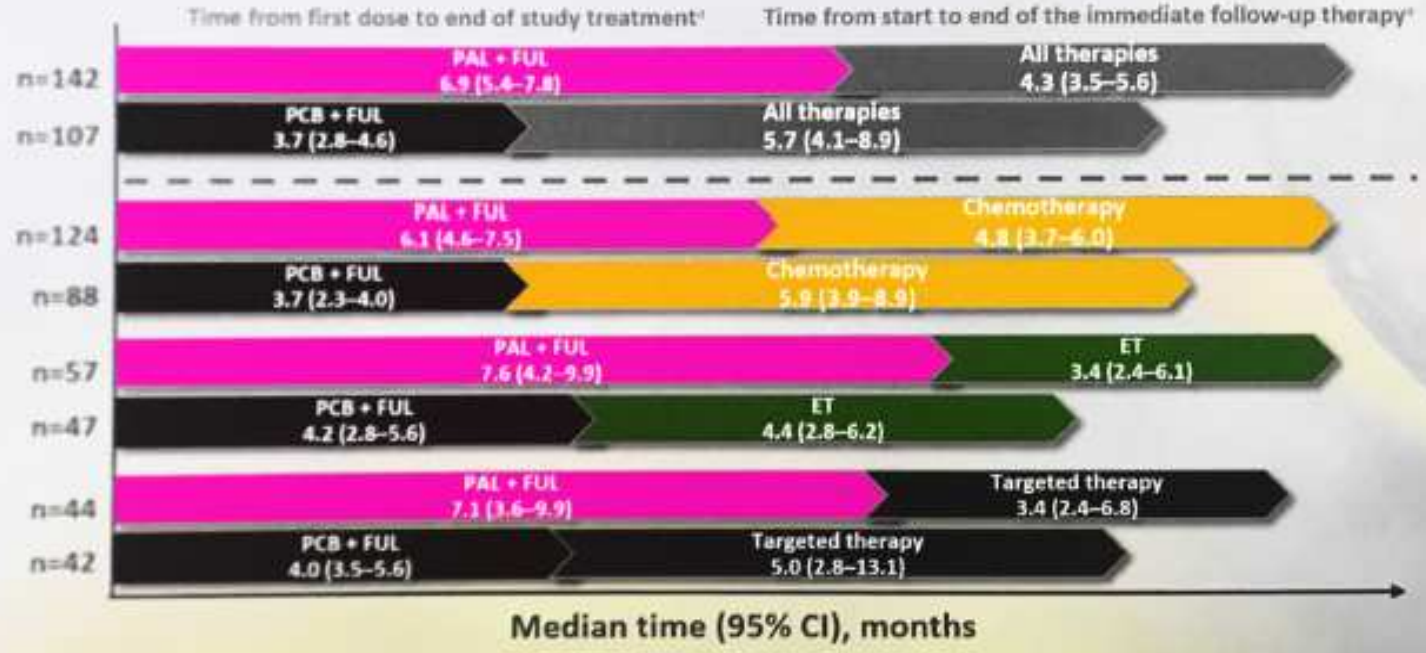
PFS Benefit in 1st Line AI + CDK 4/6 inhibitor Phase III Trials



How effective are subsequent therapies after CDK 4/6 inhibitors ?

PALOMA-3: Median duration on 1st treatment after progression

Most common treatments were everolimus, capecitabine, paclitaxel and exemestane (with or without everolimus)



Determined using the Kaplan-Meier method
CI, confidence interval; ET, endocrine therapy; FUL, fulvestrant; PAL, palbociclib; PCB, placebo

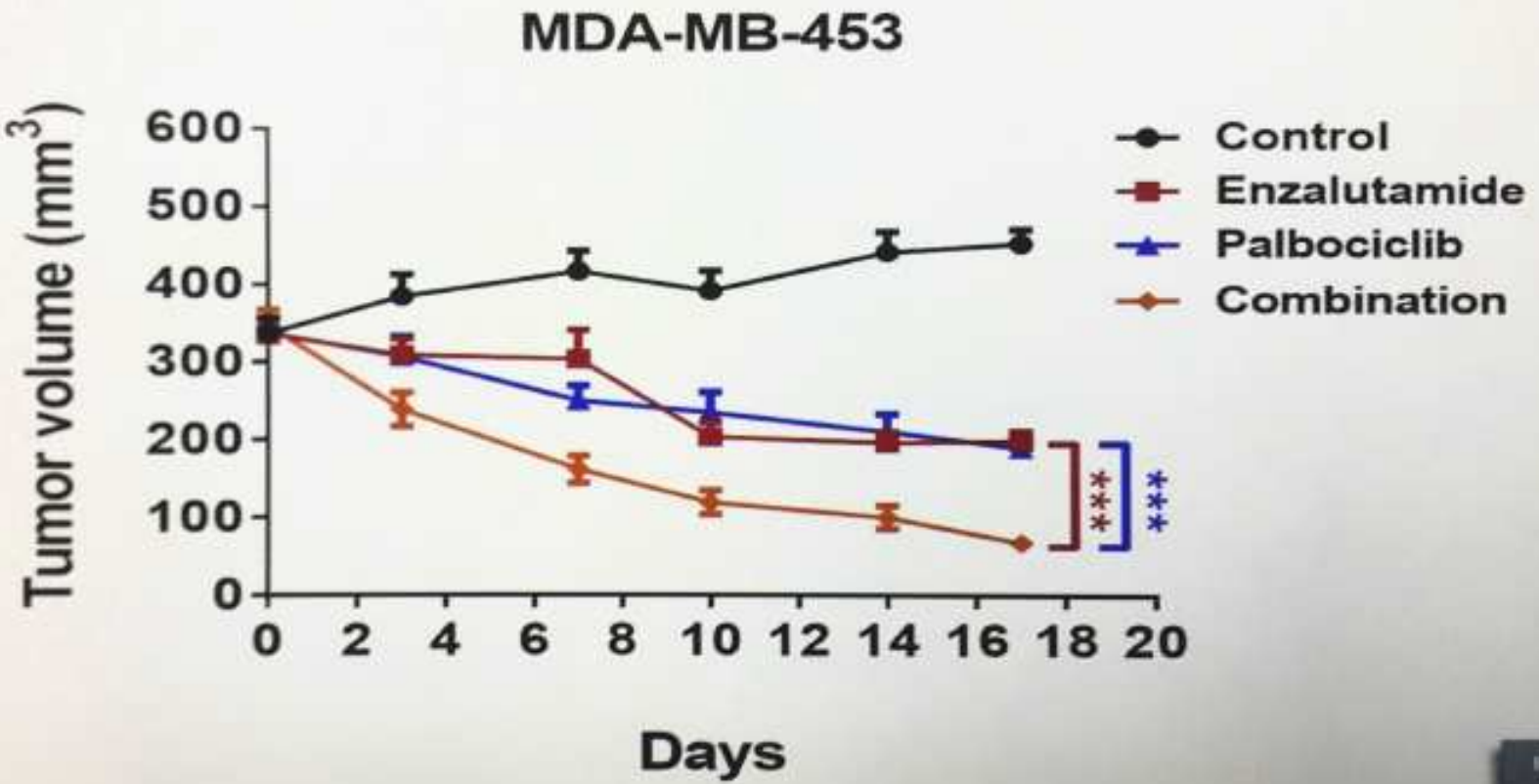
Turner NC, et al. SABCS 2016 (Abstract P4-22-06)

Novel combination of AR inhibitor and CDK4/6 inh. and MEK inh. In AR+ER and PR- BC preclinical models (Lim et al MDA Houston)

- 20-30% of TNBC are AR+ (molec apocrine, LAR)
- 3 clinical trials with a 20% CBR (bicalutamide, enza., abiraterone acetate)
- Cases with long responses to anti-androgen treatments

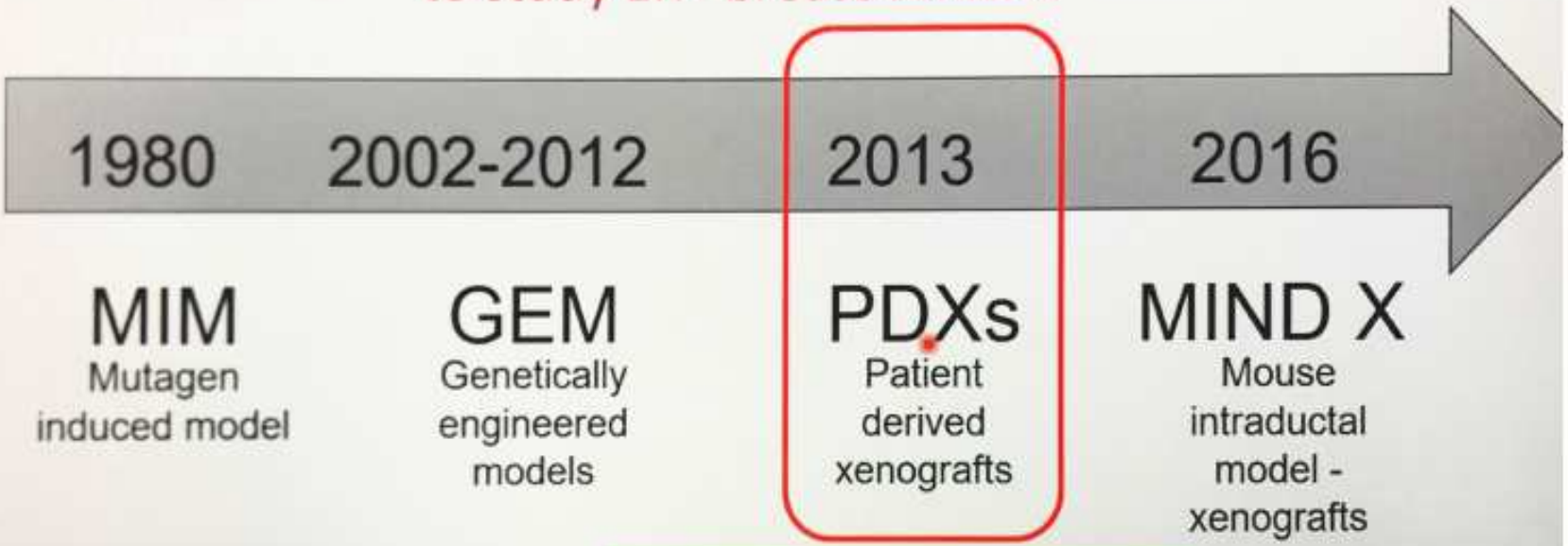
EBCC 11

In vivo tumor growth inhibition



Introduction

There is a lack of physiologicaly relevant animal models to study ER+ breast cancers

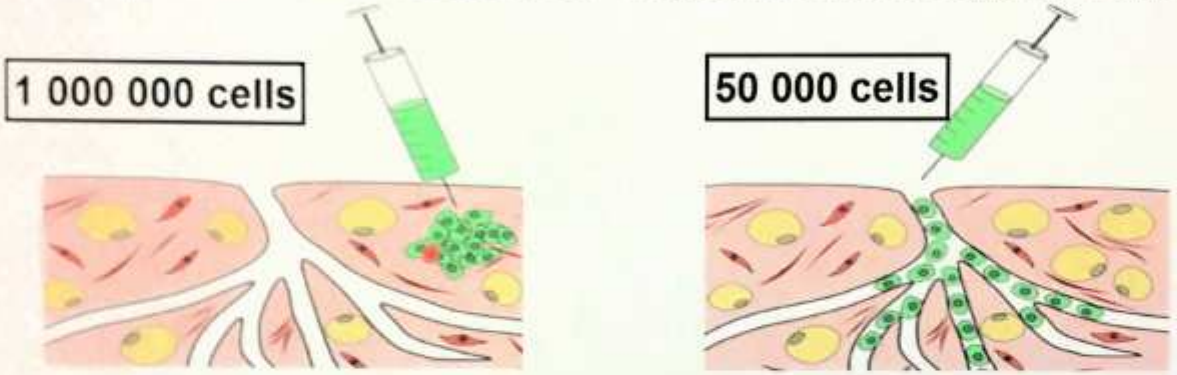


ER+ tumour do not growth unless
- high E2 sup +++ is used
- Or ER mut

Adapted from Haricharan, Lei, Ellis Cancer Cell 2016

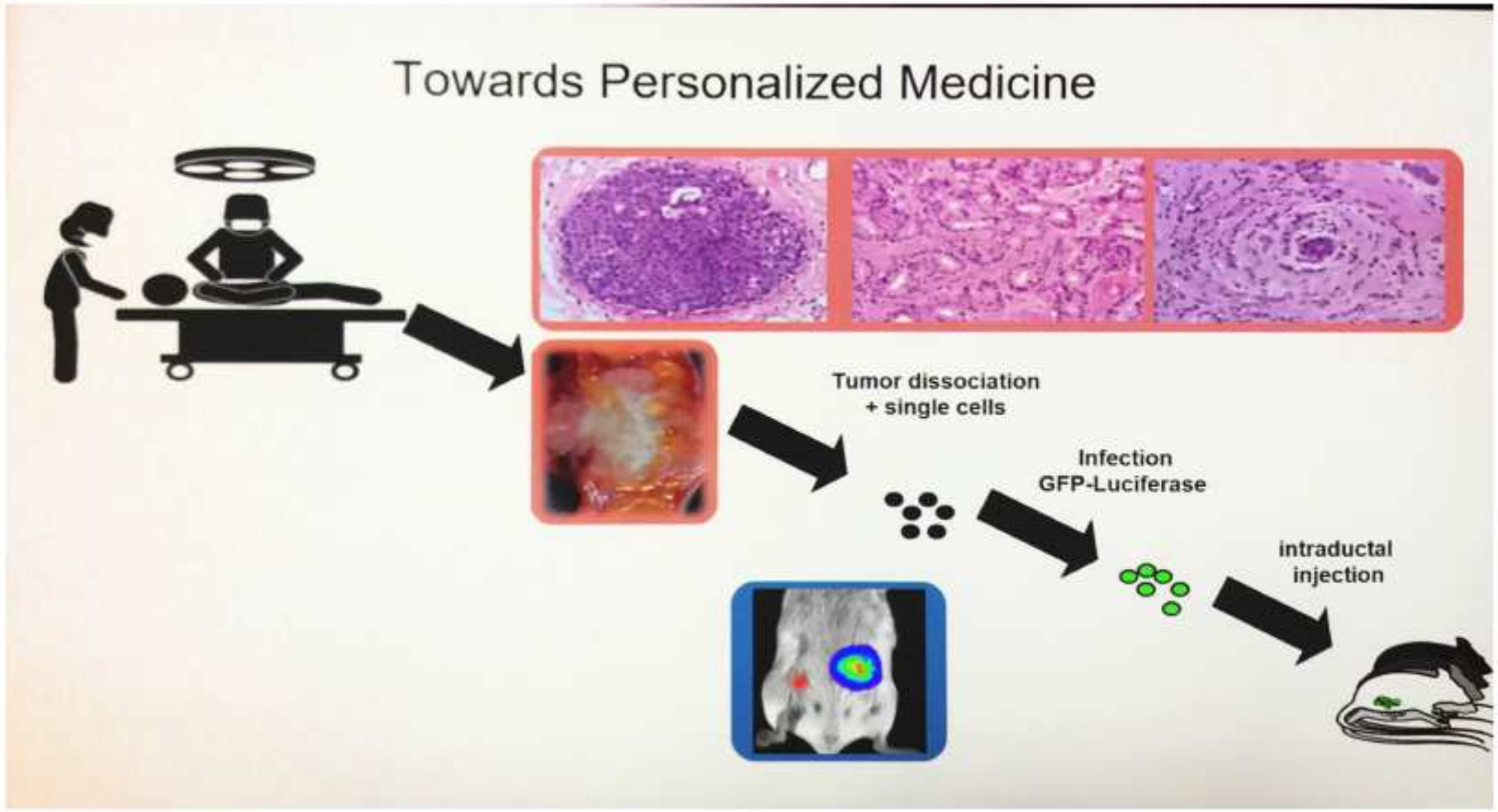
Sflomos G,… Brisken C Cancer Cell 2016

Fat pad versus Intraductal engraftment of tumor cells



1. Mind Xenografts become invasive
2. … Metastasise
3. Can be used to test treatments

Sflomos G,… Brisken C Cancer Cell 2016



Grazie

HTTPS://WWW.ECCO-ORG.EU/EVENTS/ebcc11/WEBCAST

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