Should We Consider Neoadjuvant Therapy in Operable Breast Cancer?

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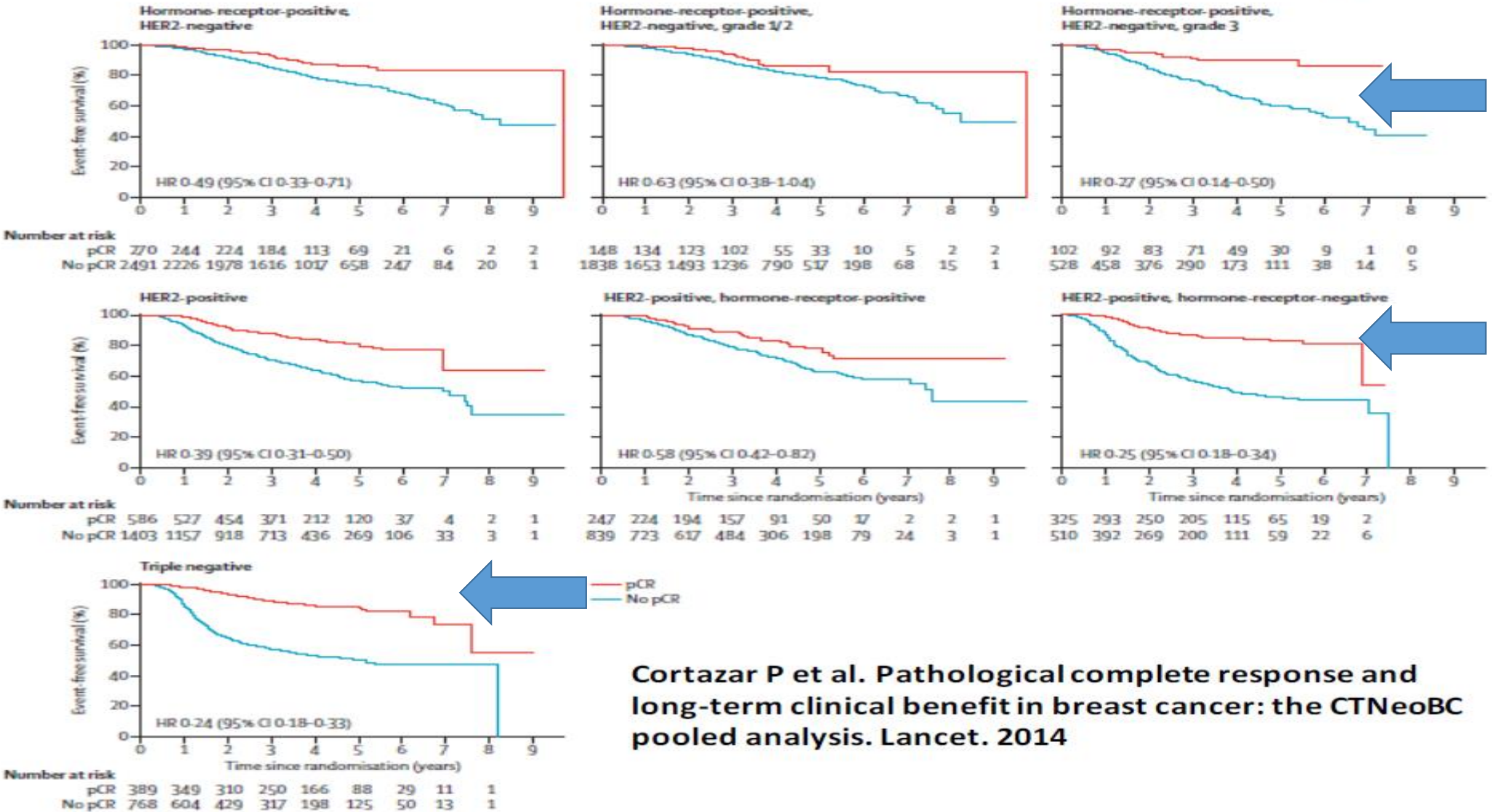
Inoperable	• **Conversion to operable**
Operable **BCS desired**	• **Downsizing for BCS**
Operable **No downsizing is needed**	• **Upfront surgery** • **?? Neoadjuvant therapy**

Operable BC- No downsizing is needed

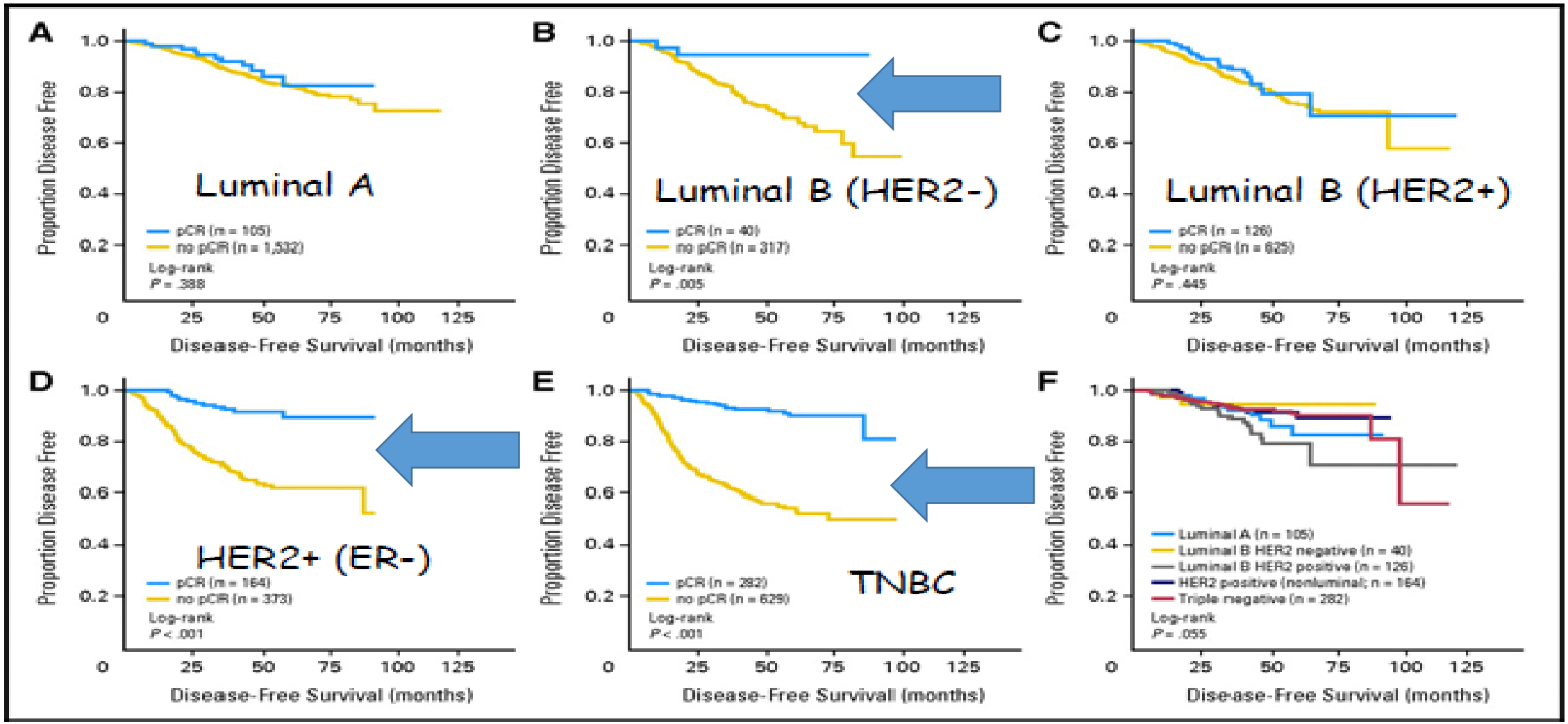
- **Achieving pCR**
- **Converting Node+ to Node-negative (Avoiding ALND)**
- **Buy the time for genetic testing**

Association between pCR and EFS by BC subtype



Cortazar P et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014

Prognostic impact of pathologic complete response (pCR) on disease-free survival according to breast cancer intrinsic subtype.



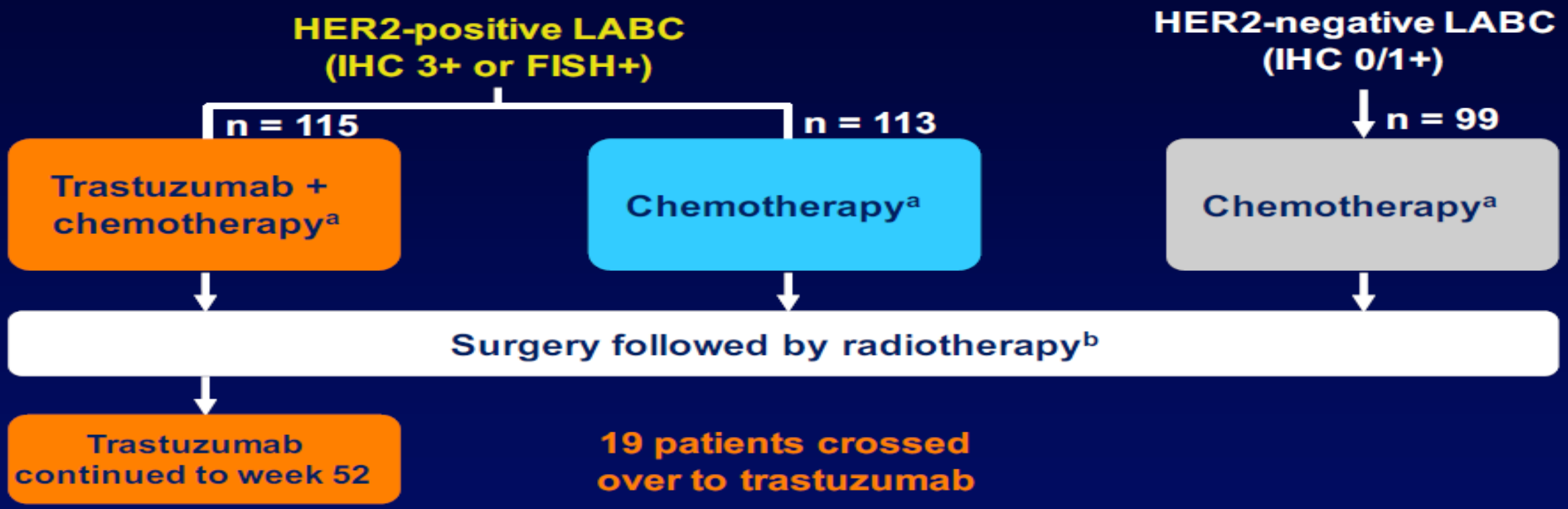
von Minckwitz G et al. JCO 2012;30:1796-1804

JOURNAL of CLINICAL ONCOLOGY ASCO

pCR after NAC: Open questions

- **Do we make the prognosis?**
- **Do we pick tumours with good prognosis?**
- **Specific considerations in TNBC**
- **How pCR is achieved? Does it matter?**
- **Operable ER+ breast cancer; do we need neoadjuvant therapy?**

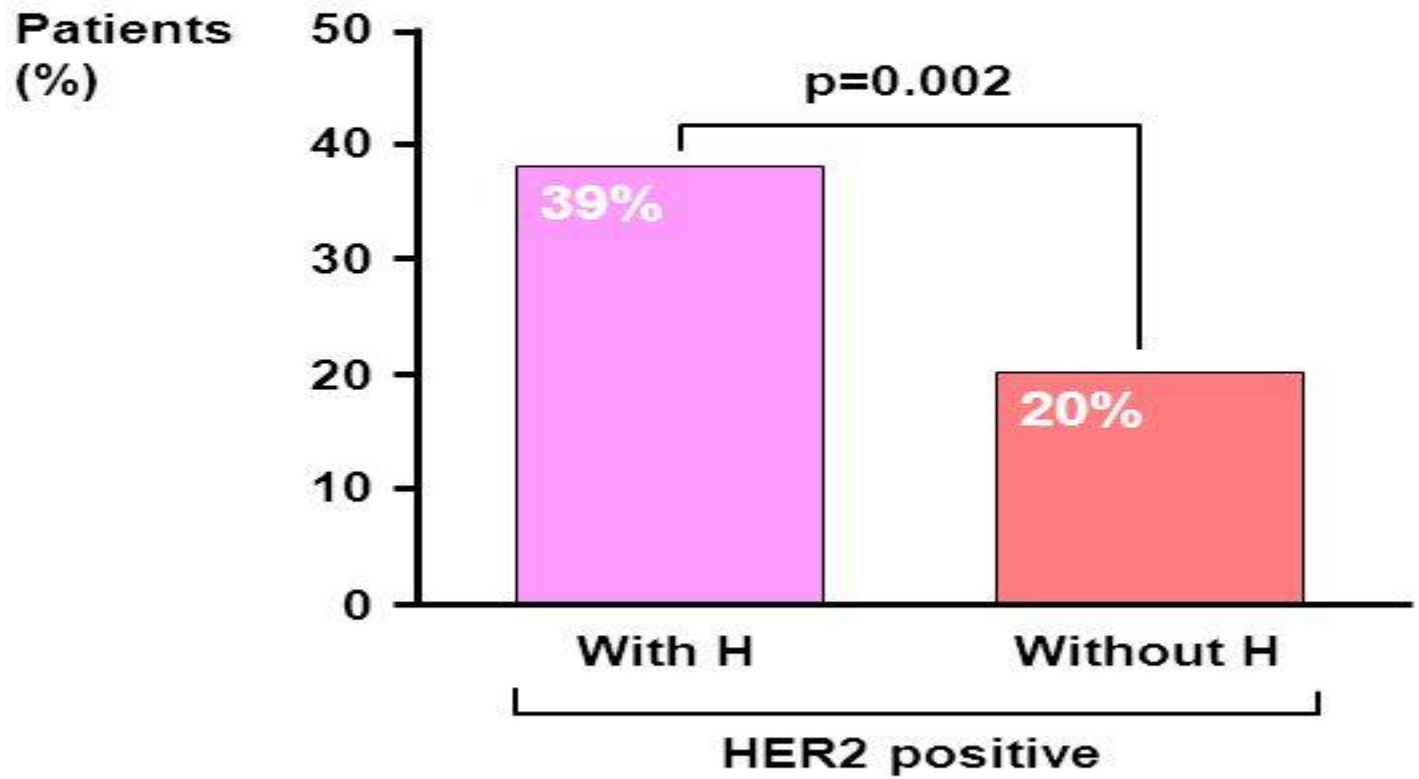
NOAH: Phase III, Open-Label Trial of Neoadjuvant Trastuzumab



[a] CT: AP x 3 followed by P x 4, followed by CMF x 3
[b] HR+ pts received adjuvant tamoxifen

Gianni L, et al. *Lancet.* 2010;375(9712):377-384.

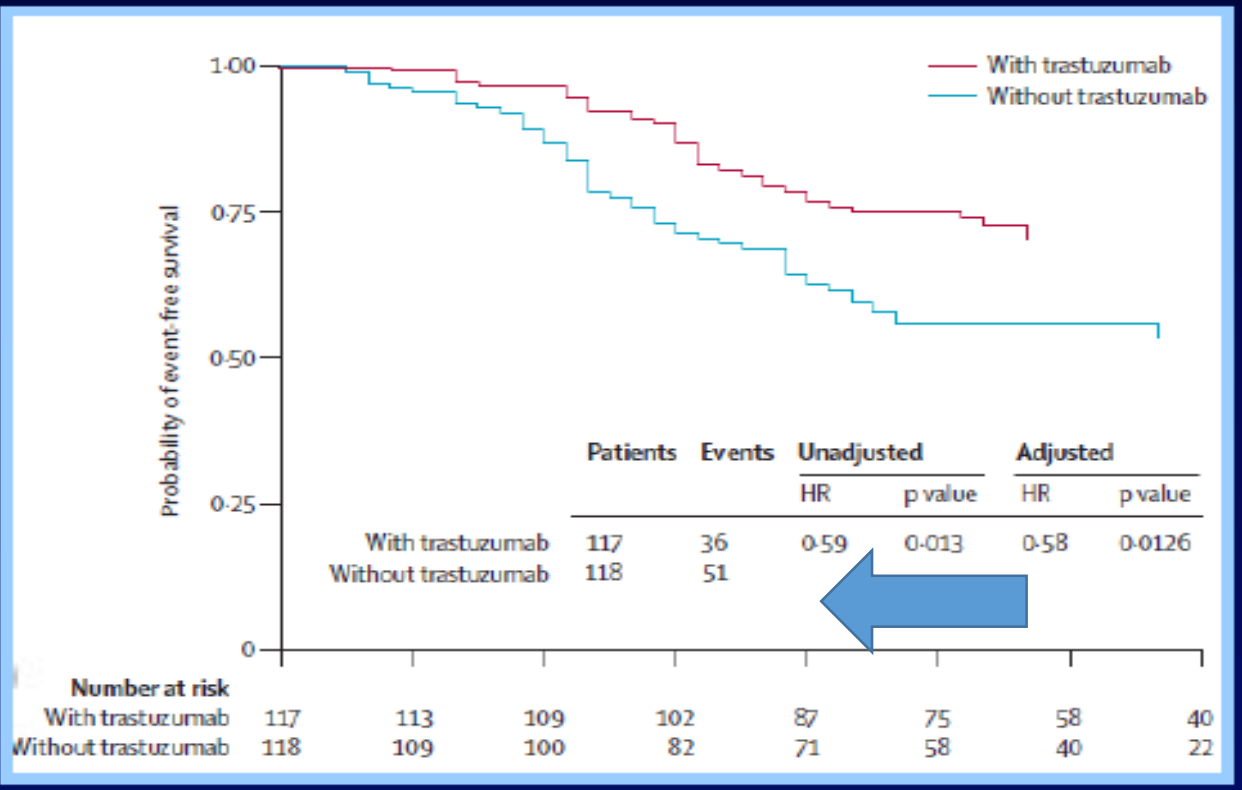
pCR rates in the NOAH trial: intent-to-treat population



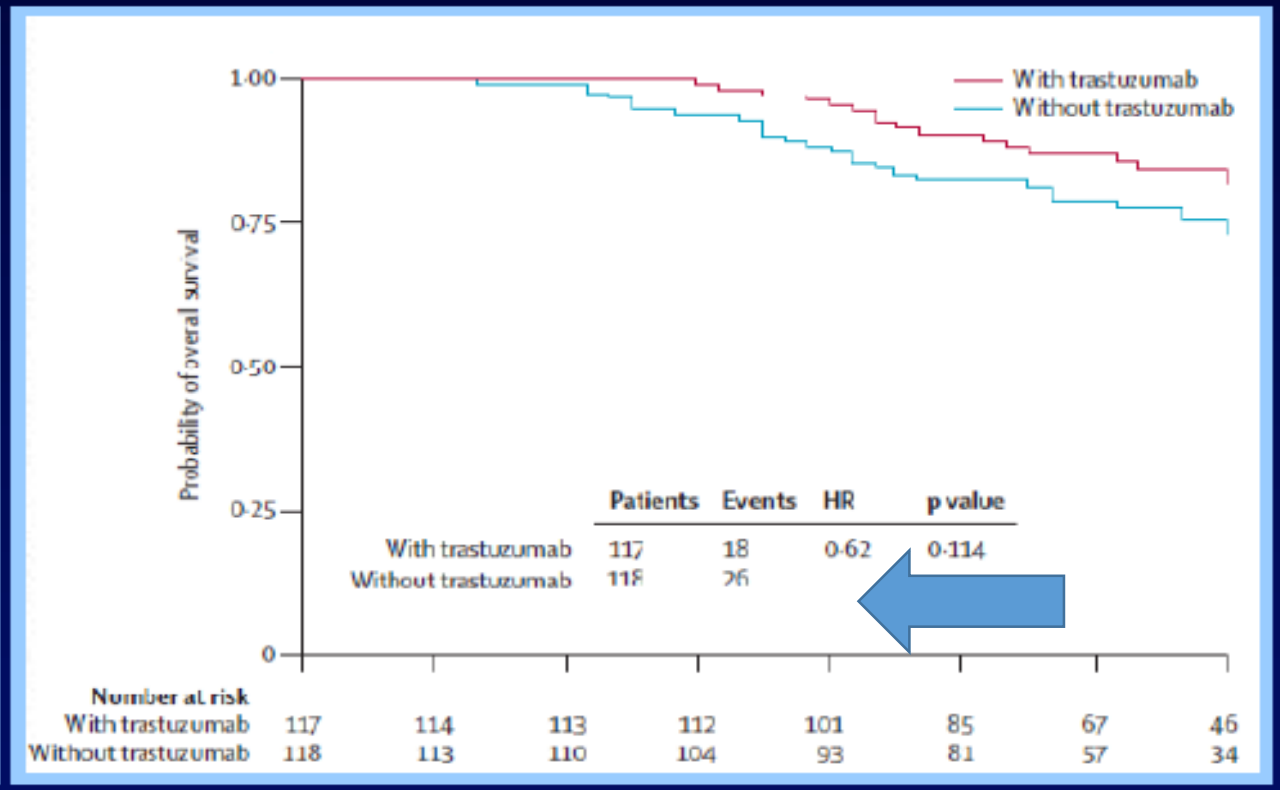
Gianni L et al. Lancet 2010; 375: 377–84

NOAH: Event-Free Survival (EFS) and OS in HER2-Positive Population (ITT)

EFS

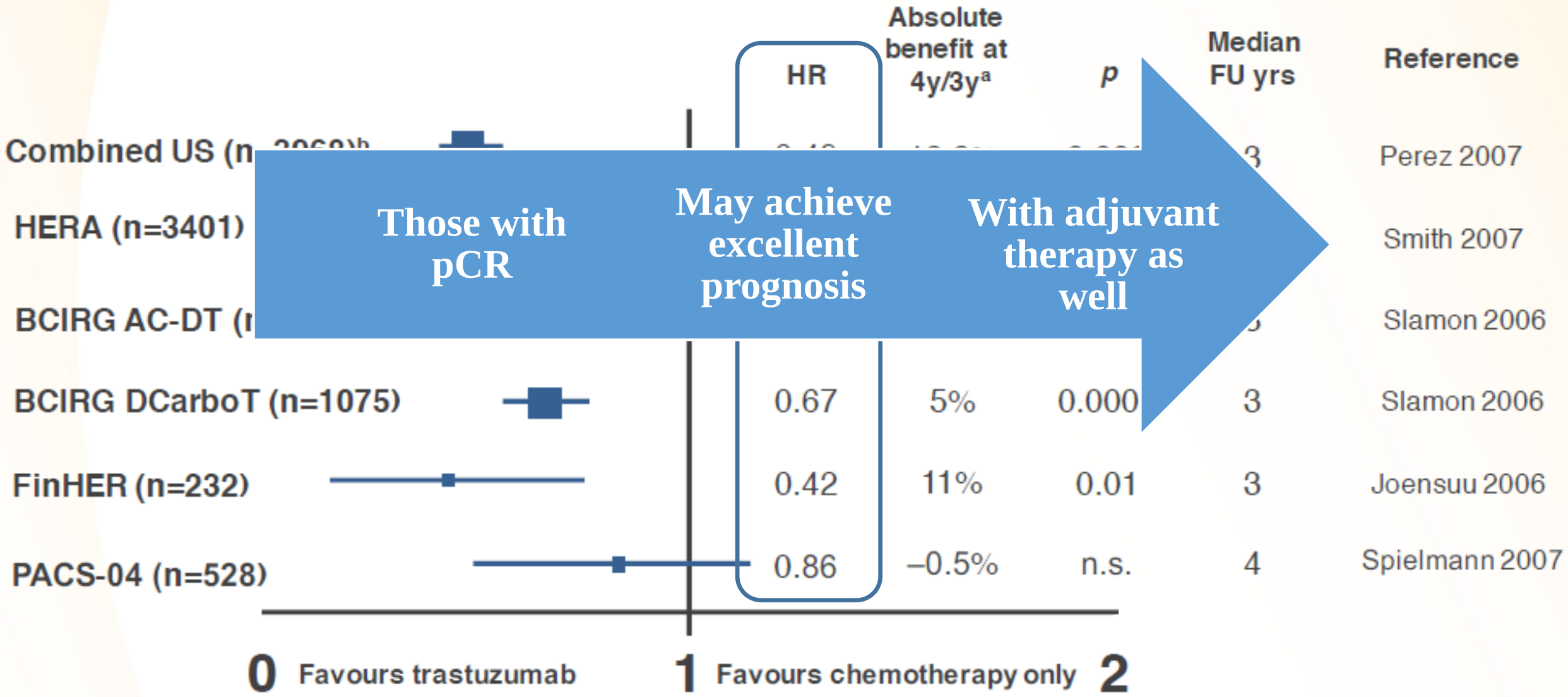


OS



Gianni L, et al. *Lancet.* 2010;375(9712):377-384.

Adjuvant chemotherapy ± trastuzumab trials: disease-free survival

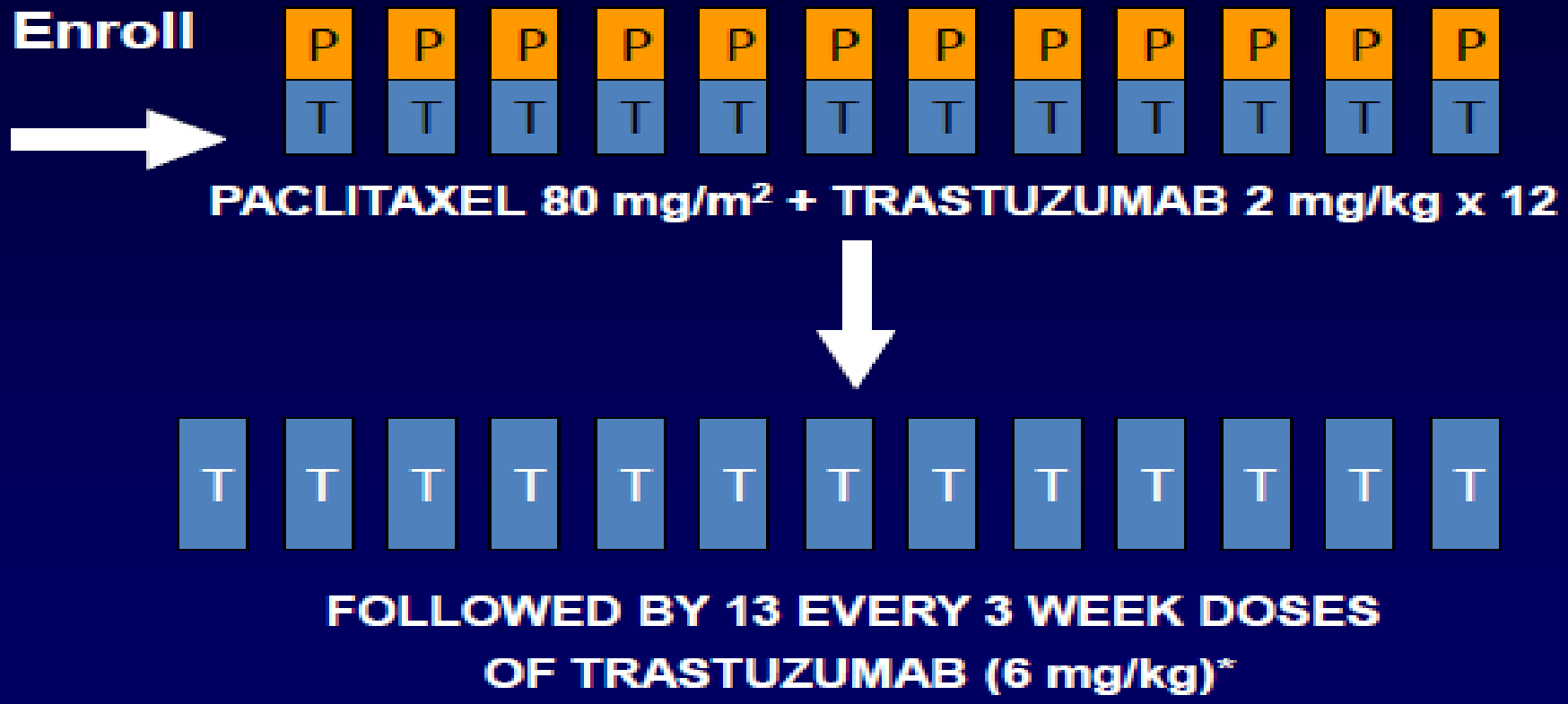


Risk of overtreatment

Study Design (APT Trial)

HER2+
ER+ or ER-
node negative
≤3 cm

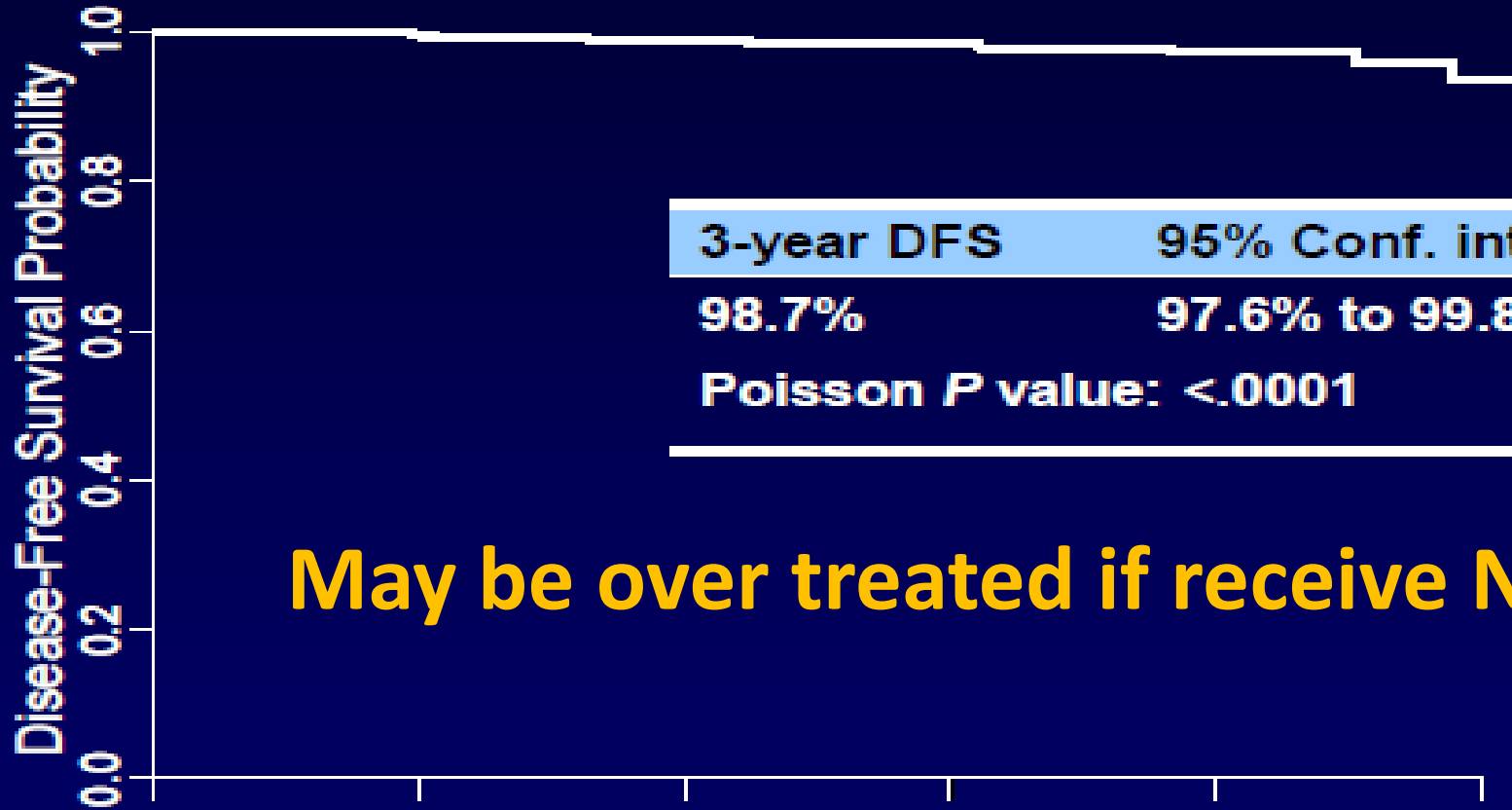
Planned N = 400



*Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks
**Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

Disease-Free Survival



3-year DFS	95% Conf. interval
98.7%	97.6% to 99.8%
Poisson *P* value: <.0001	

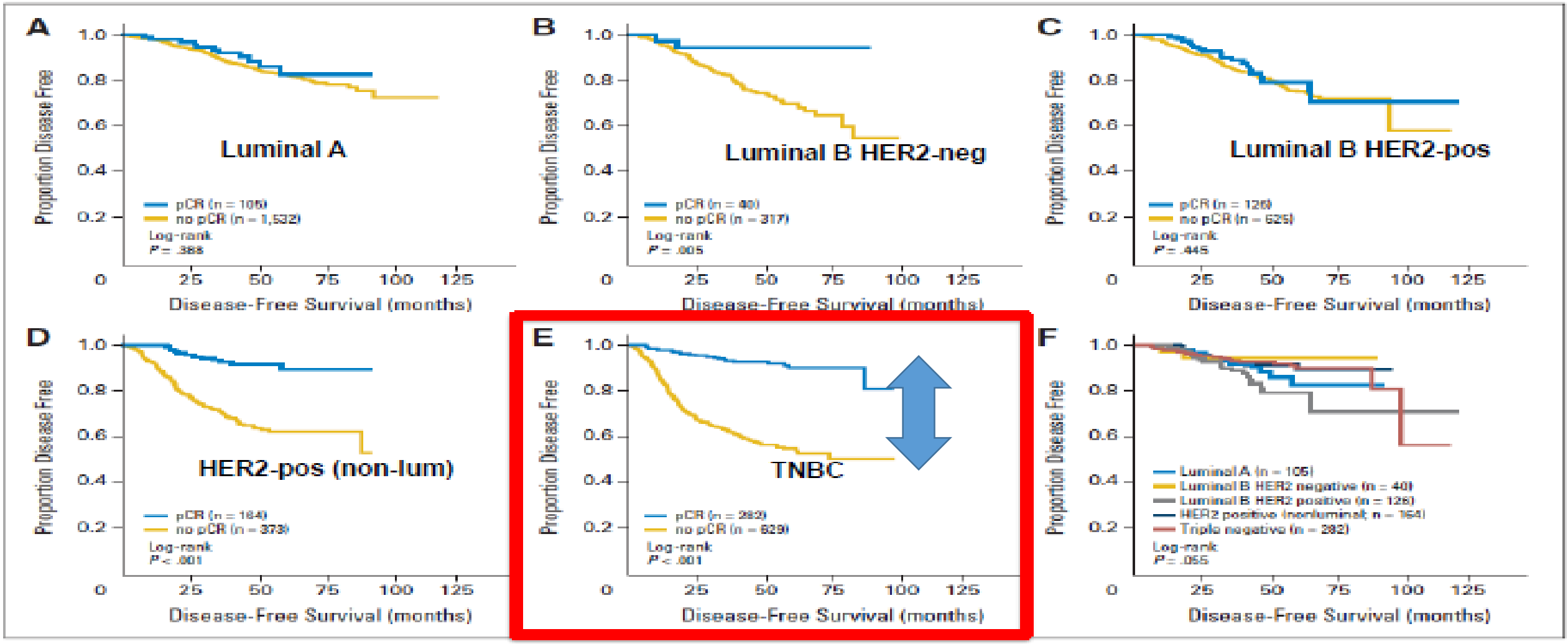
May be over treated if receive NAC A-T

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

pCR after NAC: Open questions

- **Do we make the prognosis??????????**
- **Do we pick tumours with good prognosis?**
  ???yes/risk of overtreatment
- **Specific considerations in TNBC**
- **How pCR is achieved? Does it matter?**
- **Operable ER+ breast cancer; do we need neoadjuvant therapy?**

pCR vs. PFS by Subtype
(N=4193)



von Minckwitz G et al, J Clin Oncol 2012

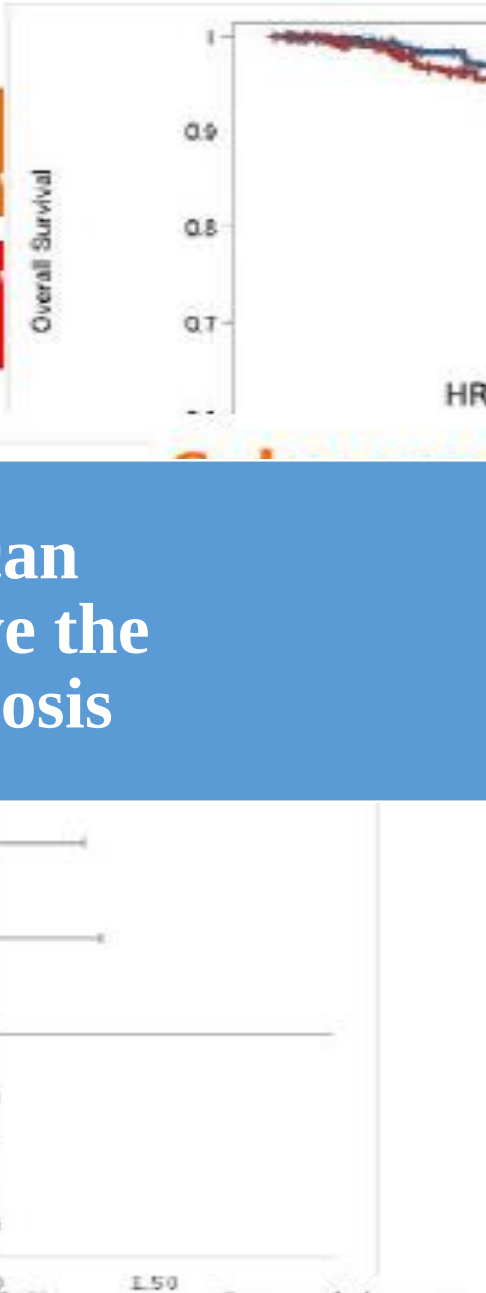
CREATE-X: Trial Design

HER2-

NAC → Surgery → Pathology Non-pCR or node + → R (n=900)

- Control: Standard therap
- Standard therap + Capecitabine

Category (n)	HR (95%CI)
Total (885)	
Age -50 (531)	
50- (354)	
HR + (561)	
HR – (296)	
ypN0 (345)	
ypN1 (339)	0.54 (0.36-0.83)
ypN2or3 (199)	0.82 (0.52-1.29)
Path grade 0-1b (482)	0.63 (0.45-0.88)
by NAC 2,3 (385)	0.84 (0.52-1.34)
Taxane + (849)	0.70 (0.53-0.93)
- (36)	0.87 (0.12-6.24)
5FU containing + (529)	0.74 (0.52-1.04)
- (356)	0.65 (0.42-1.02)
Japanese (599)	0.74 (0.53-1.02)
Korean (286)	0.63 (0.37-1.05)

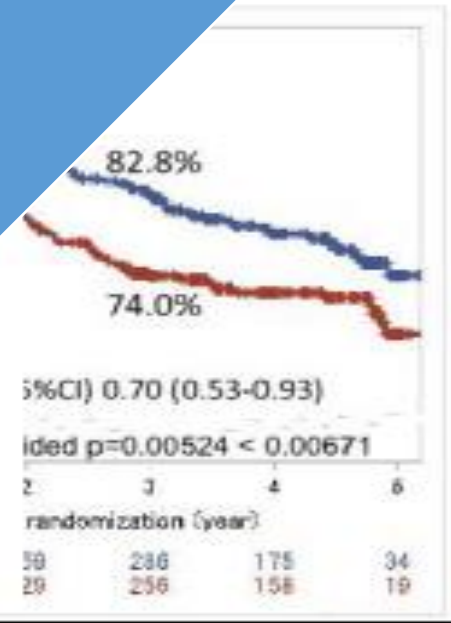


Overall Survival

If no pCR

We can improve the prognosis

vival



Gene Expressions in TNBC

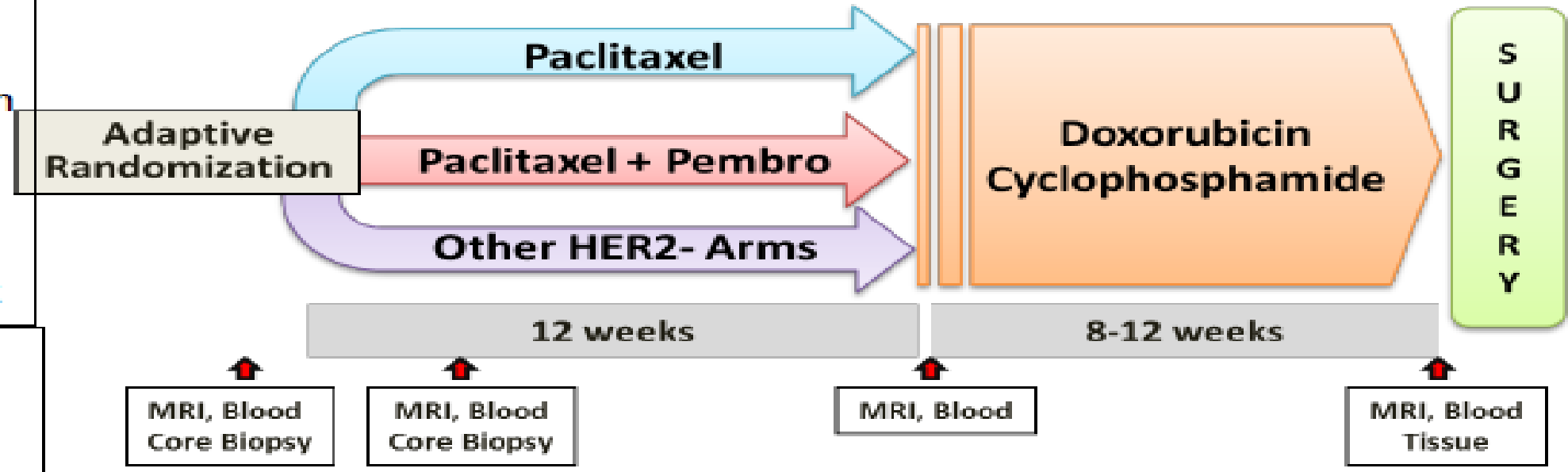
Subtype	Gene Expression Profile / High Expression of Genes
Basal-like 1 (BL-1)	cell cycle progression, cell division, and DNA damage response pathways
Basal-like 2 (BL.2)	cell cycle progression, cell division and growth factor signalling
Immunomodulatory	immune processes and cell signaling
Mesenchymal	motility and extracellular matrix
Mesenchymal stem-like	motility, extracellular matrix, growth factor signalling (consistent with claudin-low)
Luminal androgen receptor	hormonally regulated pathways

I-SPY 2 TRIAL Schema: HER2- Signatures

Screening

- Tumor size ≥ 2.5 cm
- MRI and biopsy
- **HER2-**
- **Triple negative**
- **HR+, MP High Risk**

NOT ELIGIBLE
Her2+ or
HR Positive *and*
MammaPrint Low Risk



Control
Paclitaxel 80 mg/m2 every wk x 12

Experimental
Paclitaxel 80 mg/m2 every wk x 12
Pembro 200 mg every 3 wks x 4

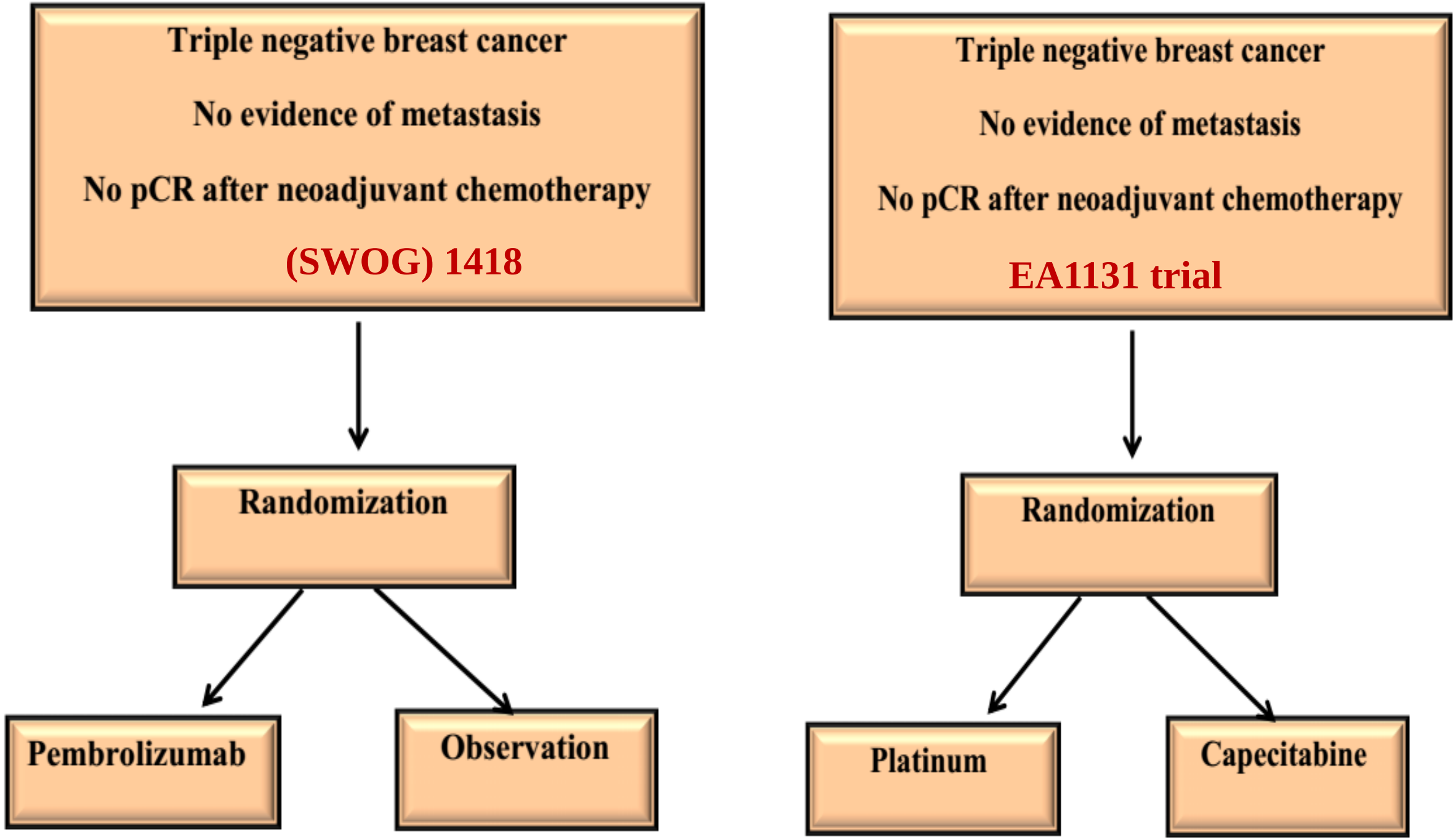
Nanda R et al, J Clin Oncol 35, 2017 (suppl; abstr 506)

Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

The Bayesian model estimated pCR rates appropriately adj… …acteristics of the I-SPY 2 population.
The raw pCR rates (not shown) are higher than the model es… …e of 0.604 in TNBC.

Nanda R et al, J Clin Oncol 35, 2017 (suppl; abstr 506)


Triple negative breast cancer
No evidence of metastasis
No pCR after neoadjuvant chemotherapy
(SWOG) 1418
Randomization
Pembrolizumab
Observation
Triple negative breast cancer
No evidence of metastasis
No pCR after neoadjuvant chemotherapy
EA1131 trial
Randomization
Platinum
Capecitabine

NAC in operable TNBC

pCR

- Excellent prognosis

No pCR

- Alternative therapy

Katherine (POST-NEOAJUVANT)

Primary endpoint : IDFS

1400 patients; recruitment ongoing

pCR after NAC: Open questions

- Do we make the prognosis?
- Do we pick tumours with good prognosis?
- Specific considerations in TNBC: alternative therapy in non-pCR
- How pCR is achieved? Does treatment intensity matter?
- Operable ER+ breast cancer; do we need neoadjuvant therapy?

NeoALTTO Study Design

- Invasive operable HER2+ BC
- T >2 cm (inflammatory BC excluded)
- LVEF ≥50%

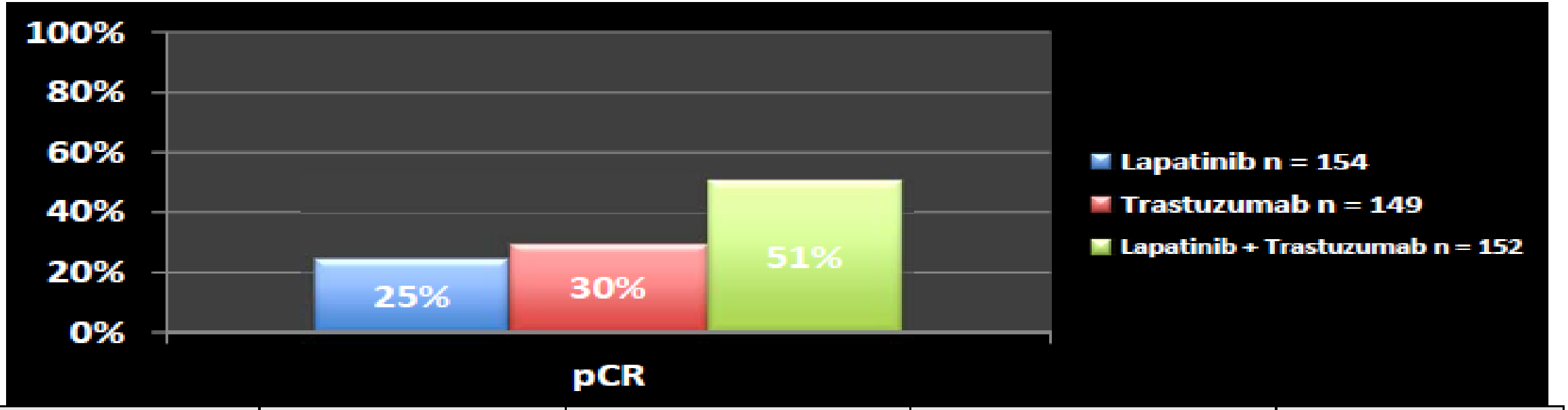
N = 450

Stratification
- T≤5 cm vs T>5 cm
- ER or PgR+ vs ER & PgR-
- N0-1 vs N≥2
- Conservative surgery or not

IBC exclusion criteria

Baselga J, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-3.

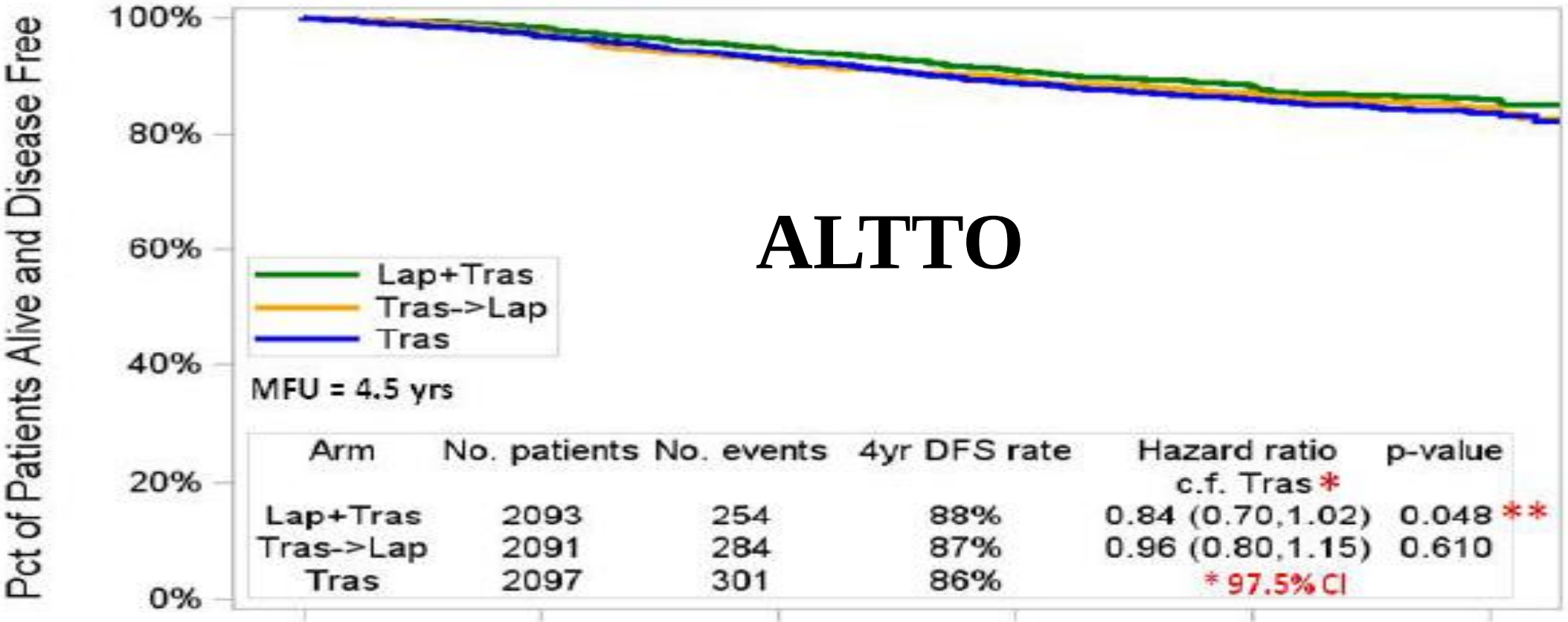
NeoALTTO Primary Outcome Measure: pCR*



	Lapatinib n = 154	Trastuzumab n = 149	Lapatinib + Trastuzumab n = 152	P Value
pCR HR+ Subset	16%	23%	42%	0.03
pCR HR- Subset	34%	37%	61%	0.005

*Pathologic complete response (pCR) rate defined as the absence of invasive cancer in the breast at the time of surgery.

DISEASE-FREE SURVIVAL (DFS) ANALYSIS



ALTTO

Arm	No. patients	No. events	4yr DFS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	254	88%	0.84 (0.70,1.02)	0.048 **
Tras->Lap	2091	284	87%	0.96 (0.80,1.15)	0.610
Tras	2097	301	86%		

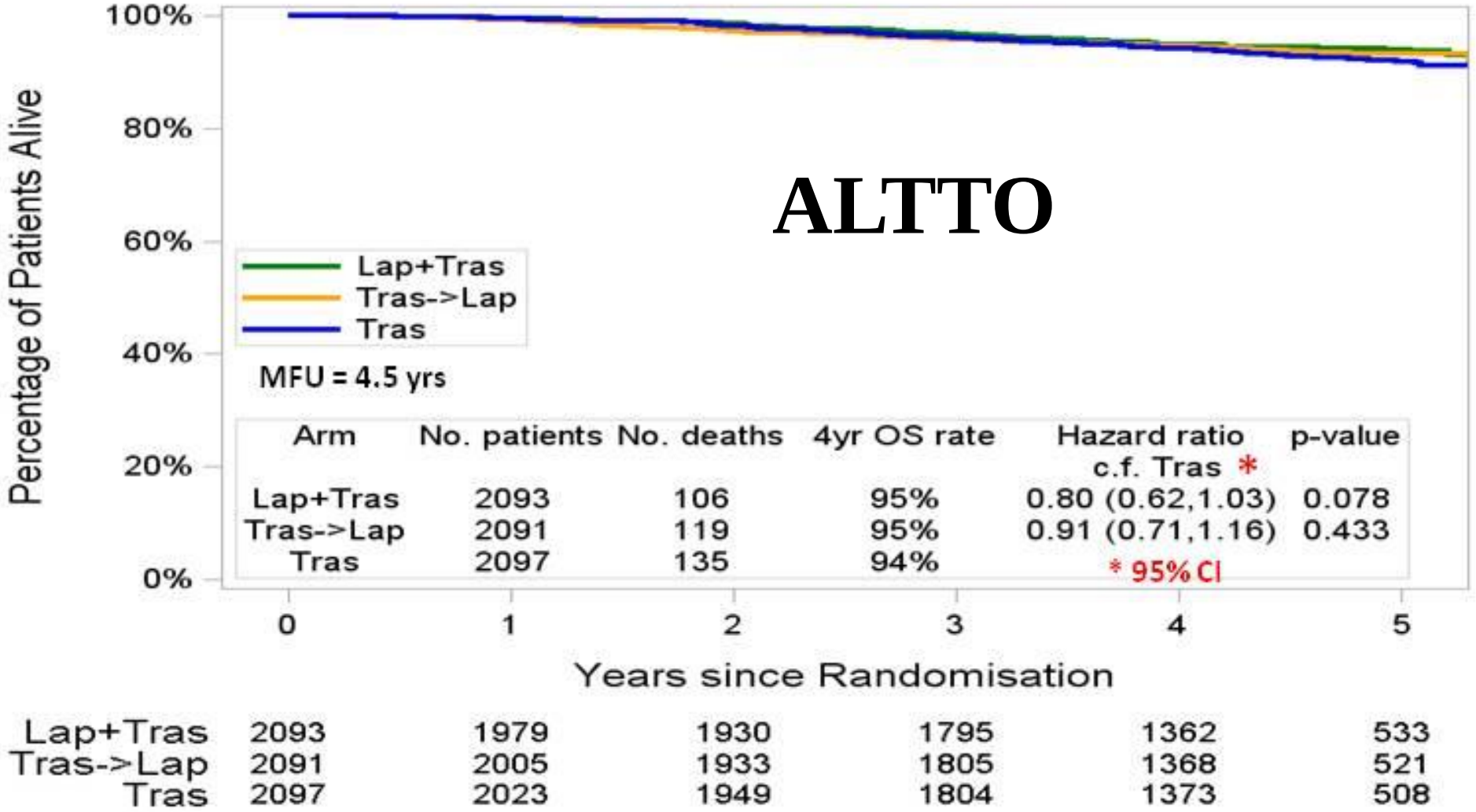
* 97.5% CI

Lap+Tras	2093	1938	1832	1672	1256	474
Tras->Lap	2091	1957	1822	1684	1261	476
Tras	2097	1959	1838	1658	1246	448

**p-value ≤ 0.025 required for statistical significance

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

OVERALL SURVIVAL (OS) ANALYSIS



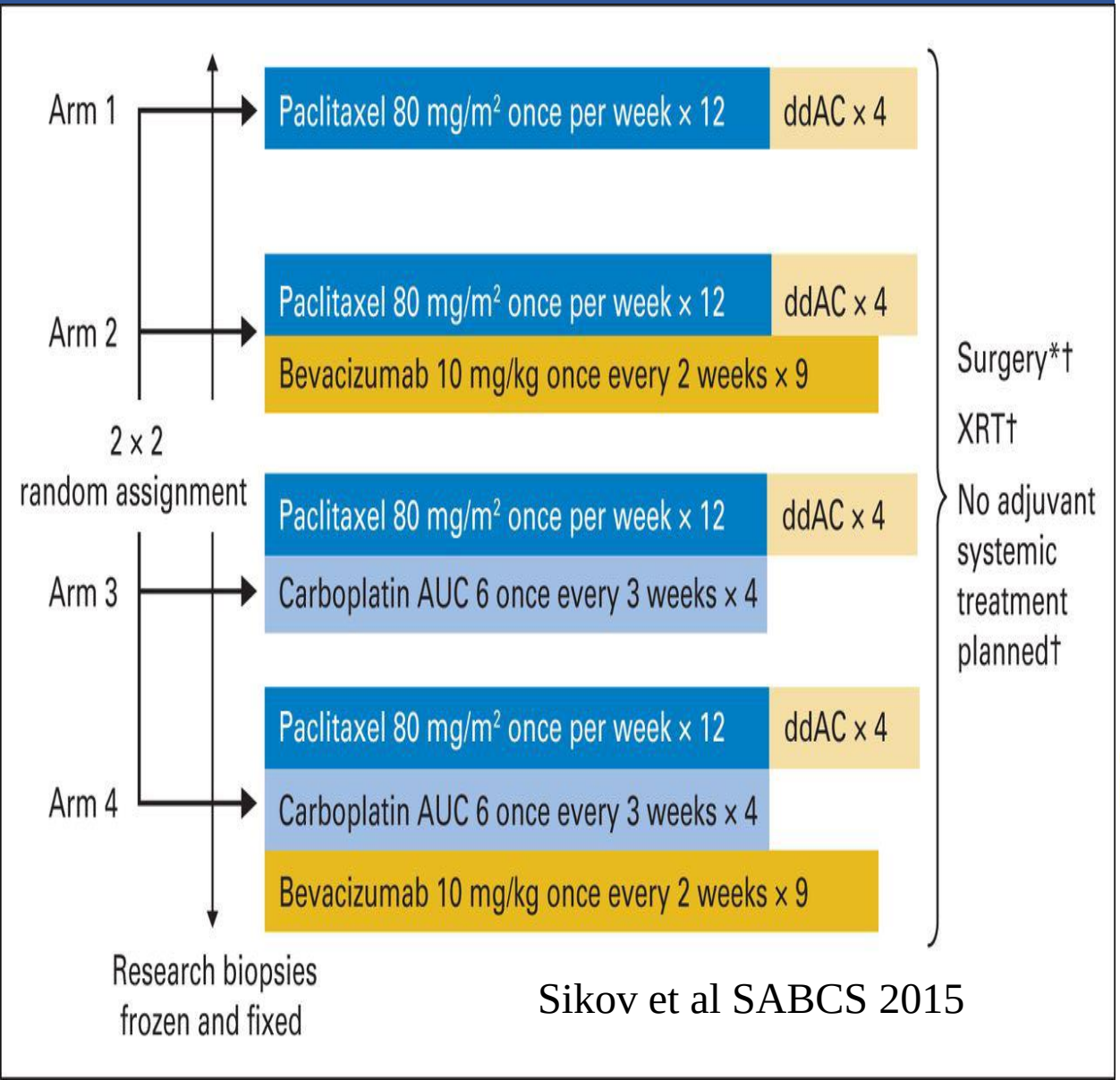
ALTTO

Arm	No. patients	No. deaths	4yr OS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	106	95%	0.80 (0.62,1.03)	0.078
Tras->Lap	2091	119	95%	0.91 (0.71,1.16)	0.433
Tras	2097	135	94%		

* 95% CI

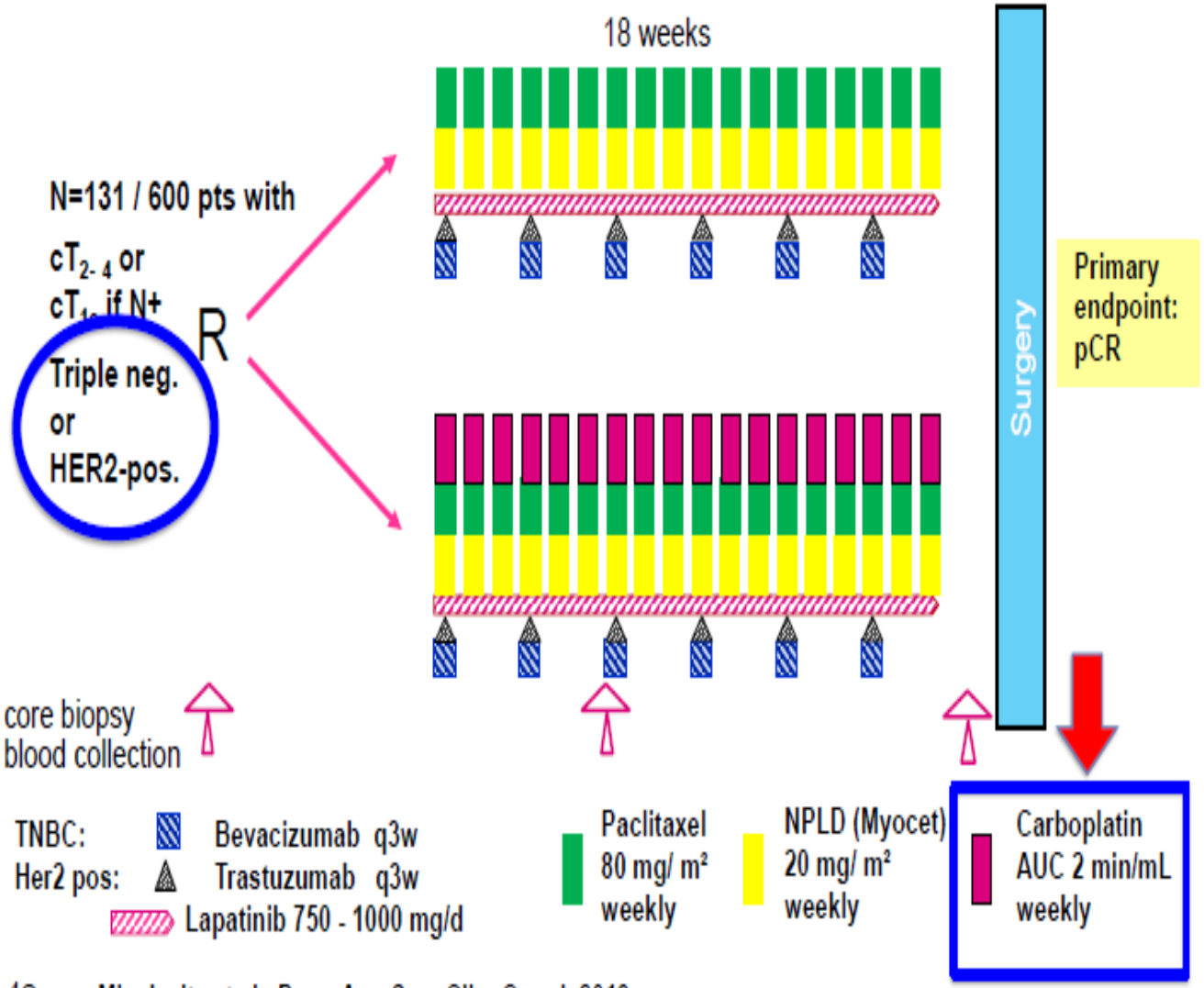
Lap+Tras	2093	1979	1930	1795	1362	533
Tras->Lap	2091	2005	1933	1805	1368	521
Tras	2097	2023	1949	1804	1373	508

CALGB 40603



Sikov et al SABCS 2015

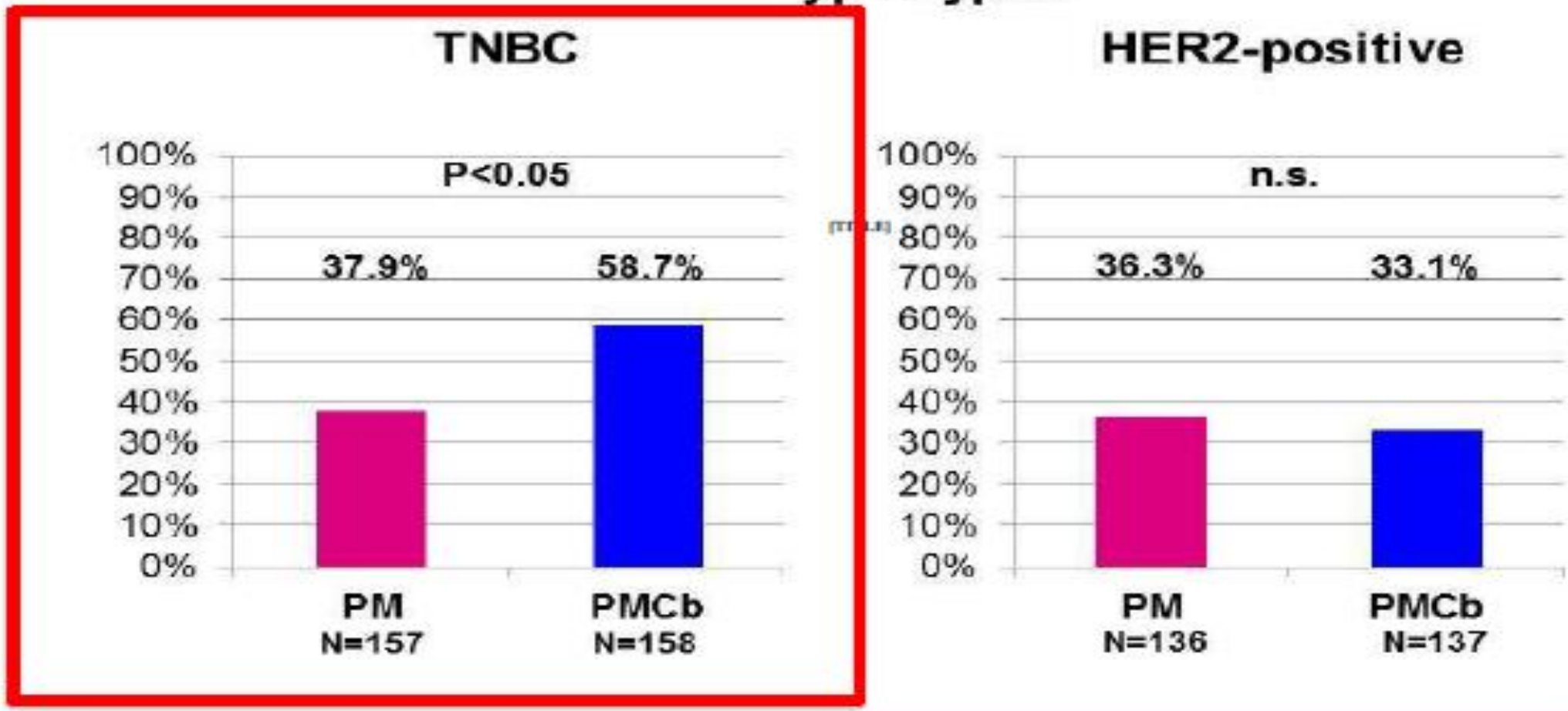
GeparSixto[1]



[1]G. von Minckwitz et al., Proc. Am. Soc. Clin. Oncol. 2013

GeparSixto: pCR by Subtypes[1]

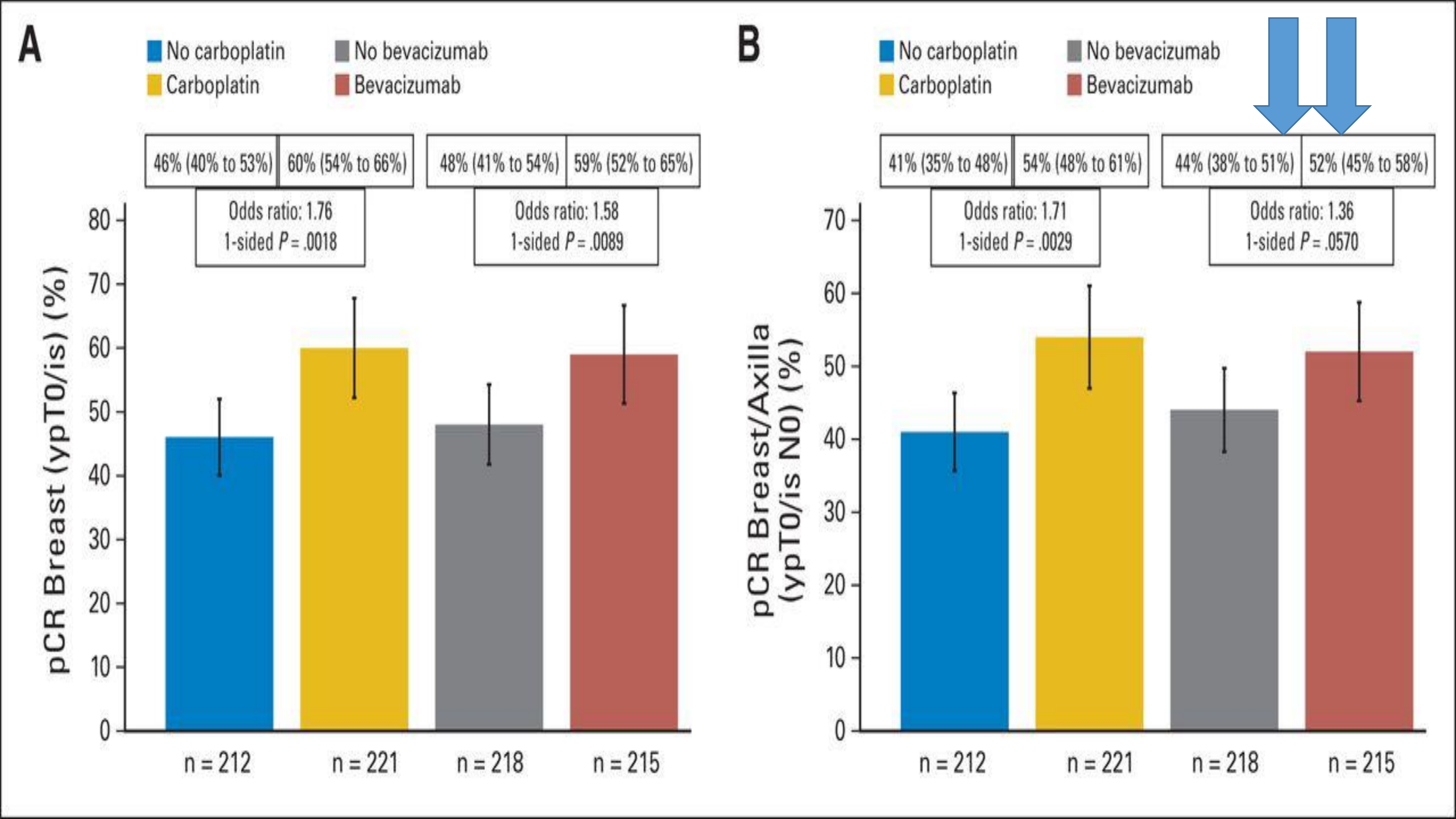
ypT0 ypN0



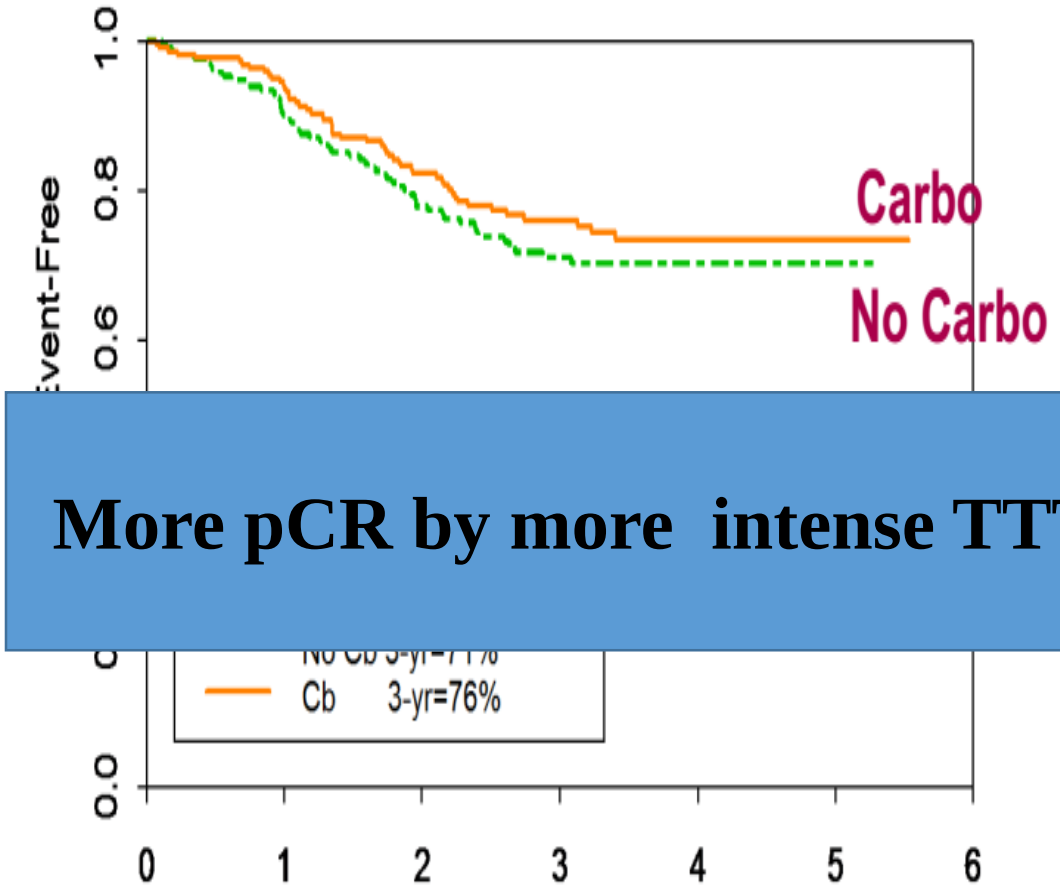
AGO-B BREAST STUDY GROUP

GBG GERMAN BREAST GROUP

[1]G. von Minckwitz et al., Proc. Am. Soc. Clin. Oncol. 2013


A
No carboplatin
Carboplatin
No bevacizumab
Bevacizumab
46% (40% to 53%)
60% (54% to 66%)
48% (41% to 54%)
59% (52% to 65%)
Odds ratio: 1.76
1-sided P = .0018
Odds ratio: 1.58
1-sided P = .0089
pCR Breast (ypT0/is) (%)
80
70
60
50
40
30
20
10
0
n = 212
n = 221
n = 218
n = 215
B
No carboplatin
Carboplatin
No bevacizumab
Bevacizumab
41% (35% to 48%)
54% (48% to 61%)
44% (38% to 51%)
52% (45% to 58%)
Odds ratio: 1.71
1-sided P = .0029
Odds ratio: 1.36
1-sided P = .0570
pCR Breast/Axilla (ypT0/is N0) (%)
70
60
50
40
30
20
10
0
n = 212
n = 221
n = 218
n = 215

CALGB 40603 – Event –free survival for carboplatin vs. not

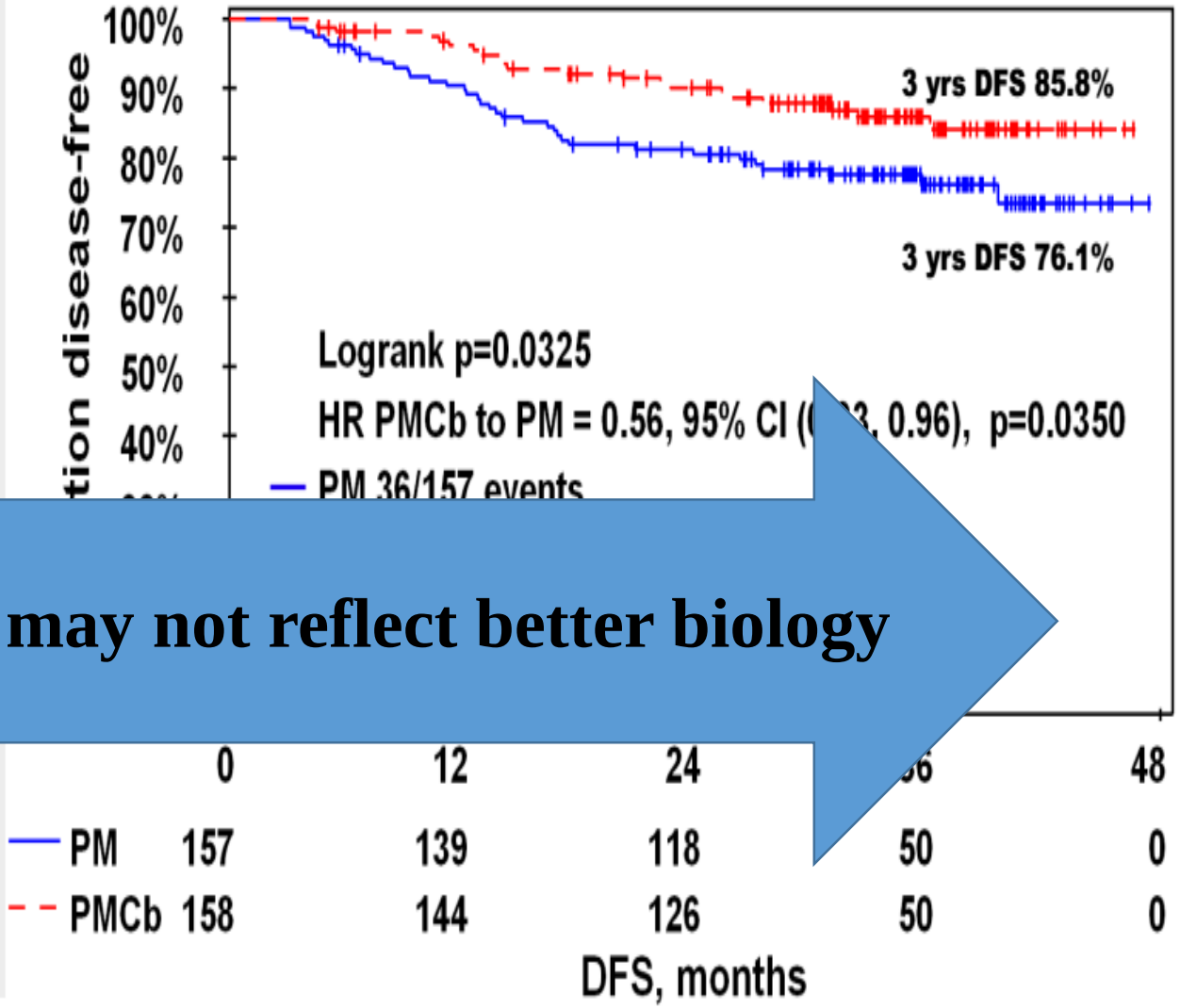


Number at Risk

No Cb	218	185	145	94	31	2	0
Cb	225	202	162	101	37	2	0

Sikov et al 2015

Disease-free Survival: Effect of Carboplatin in TNBC



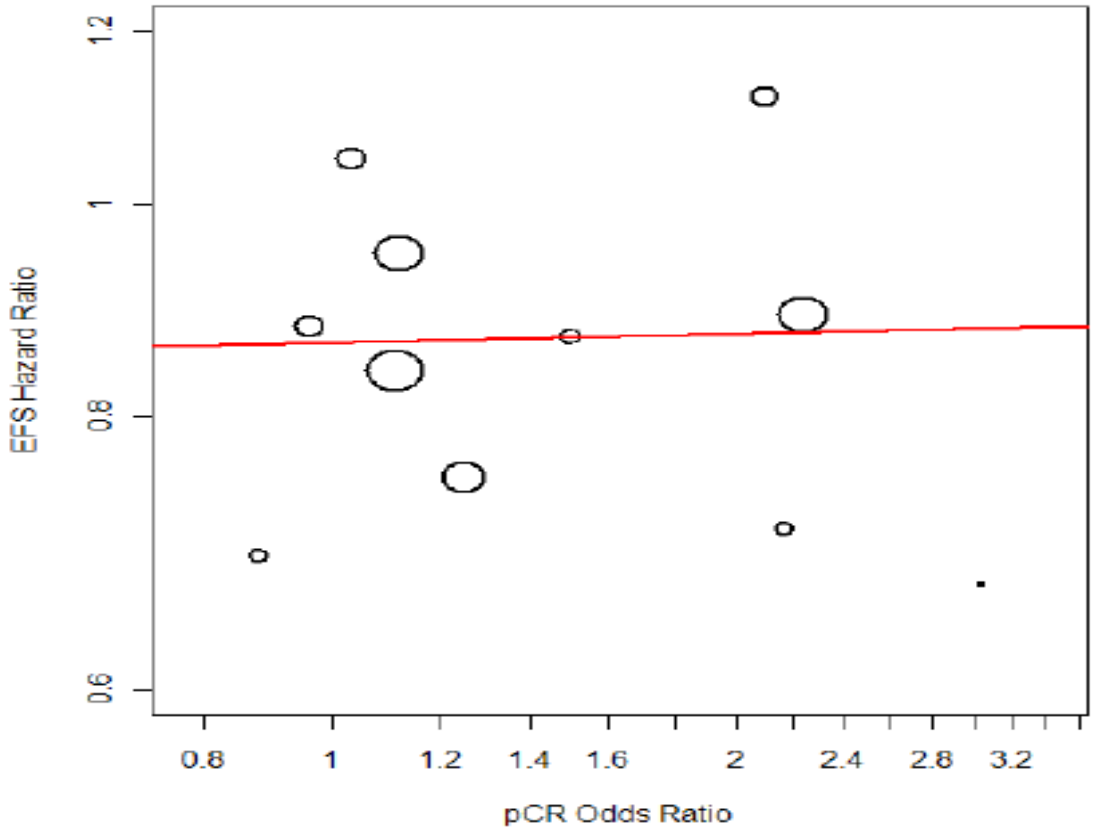
More pCR by more intense TTT may not reflect better biology

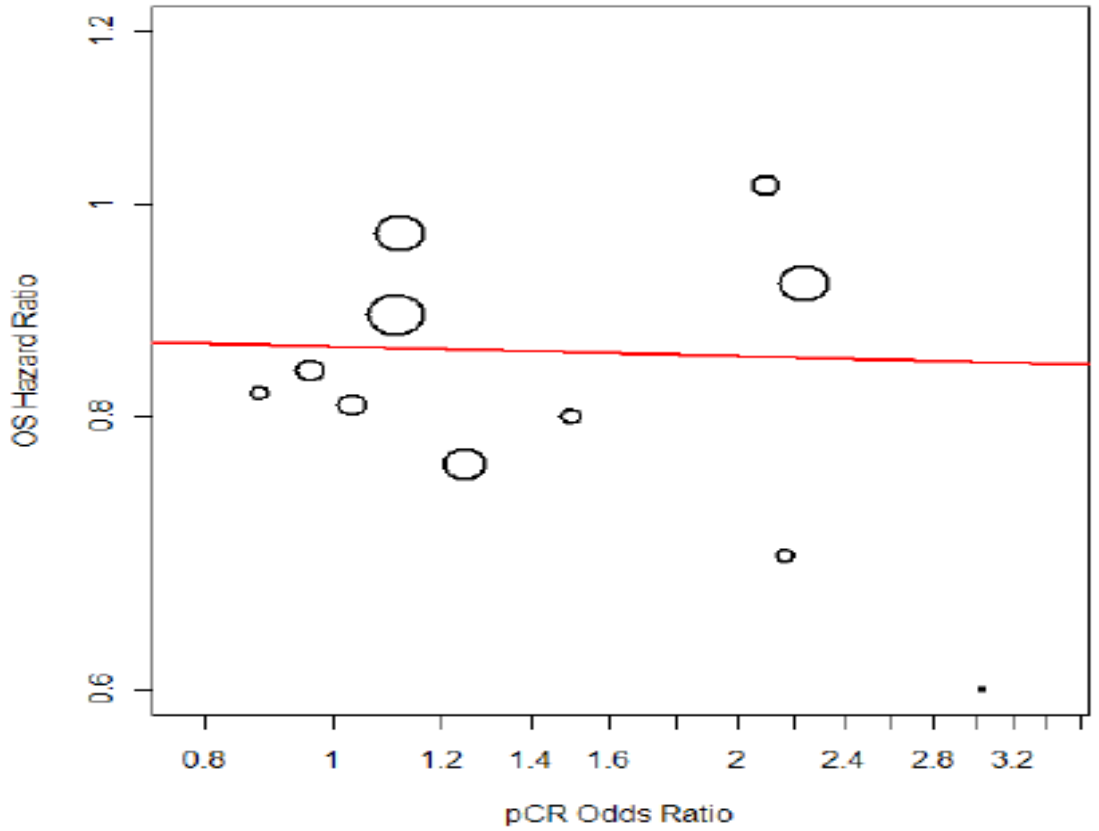
Geparsixto

von Minckwitz et al. SABCS 2015

Median DFS Follow-up = 35 months

The magnitude of improvement in pCR rate **did not** predict EFS and OS effect





Cortazar P et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014

pCR as a surrogate to survival ???

- **Effect on micrometastases should be the same as in 1ry tumour**
- **More pCR (gross tumour) by more intense therapy may not be translated to more effect elsewhere (microscopic disease)**
- **Non-pCR with more intense therapy may do very poorly**

pCR after NAC: Open questions

- Do we make the prognosis?
- Do we pick tumours with good prognosis?
- Specific considerations in TNBC
- How pCR is achieved? Does it matter? May be
- Operable ER+ breast cancer; do we need neoadjuvant therapy?

P024

4 months

ER+
Stage 2/3

Letrozole

Tamoxifen

SURGERY

Ellis et al 2008

PEPI Score

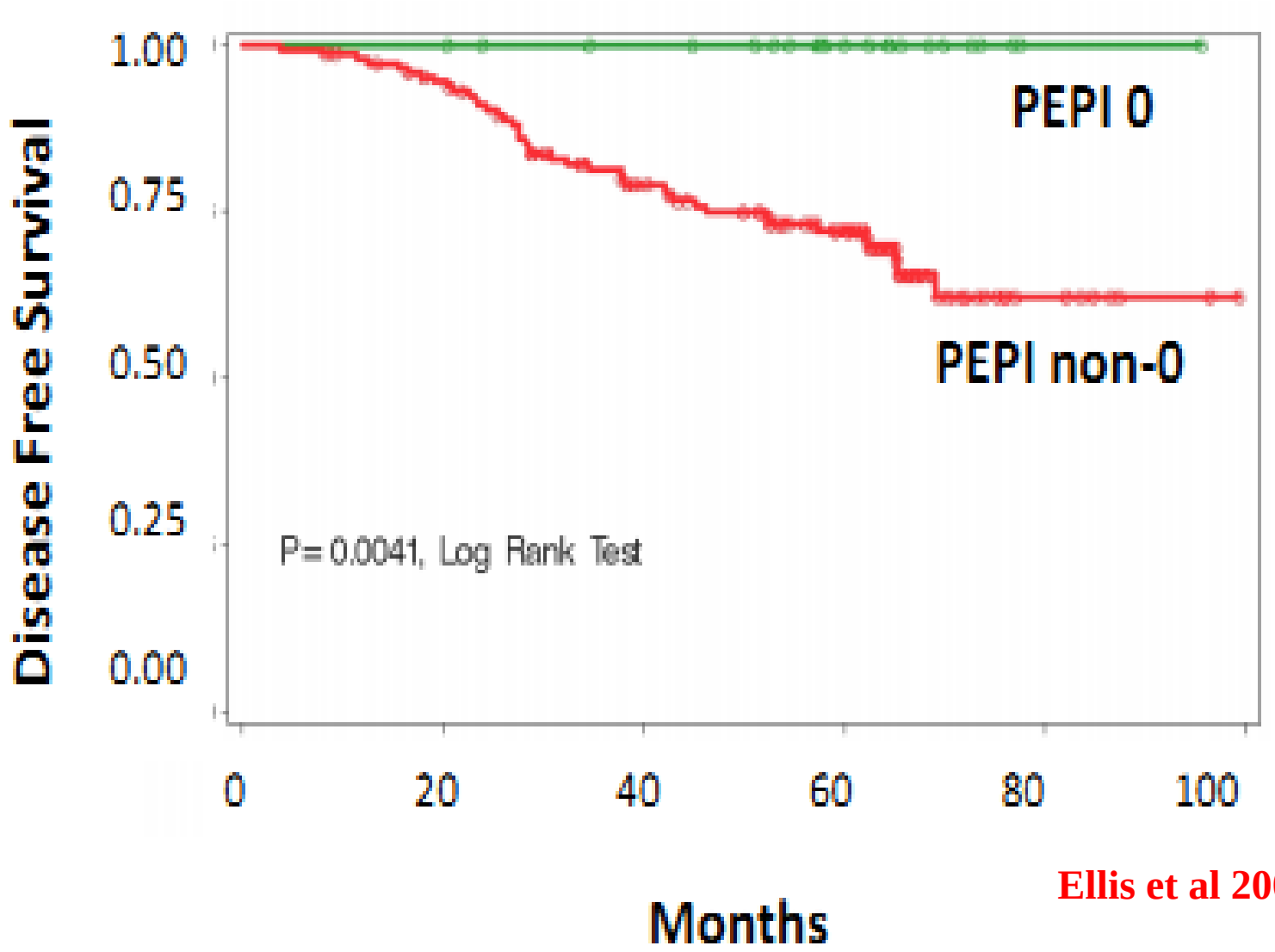
Preoperative Prognostic Index (PEPI)				
Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Tumor Size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0–2.7%	—	0	—	0
>2.7–7.3%	1.3	1	1.4	1
>7.3–19.7%	1.7	1	2.0	2
>19.7–53.1%	2.2	2	2.7	3
>53.1%	2.9	3	3.8	3
ER, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0

Modified PEPI excludes ER

PEPI score was developed using results of PO24 trial to assess the risk of relapse based on pathologic tumor size, lymph node status, Ki67 level, and ER status of surgery specimen post neoadjuvant endocrine therapy.

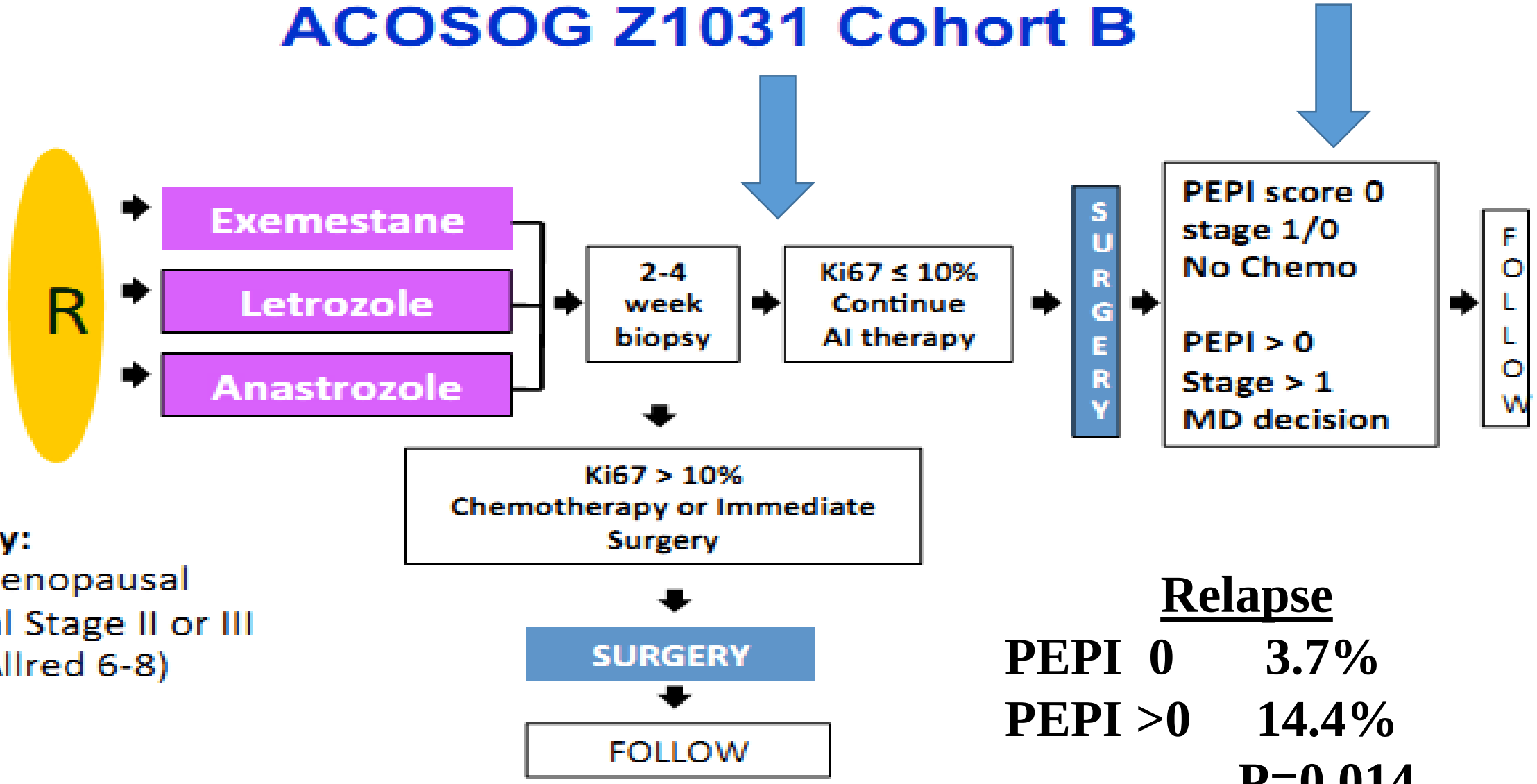
Ellis MJ, et al, J Natl Cancer Inst 100:1380-8, 2008

PEPI 0 Predicts Disease Free Survival



Ellis et al 2008

ACOSOG Z1031 Cohort B



Eligibility:

- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2-

Relapse

PEPI 0 3.7%

PEPI >0 14.4%

P=0.014

This trial demonstrated the feasibility of using 2-4 week Ki67 and PEPI sore at surgery to tailor subsequent treatment.

Ellis et al J Clin Oncol 2017

ALTERNATE Schema

Eligibility

Post-menopausal
Clinical Stage II or III
ER+ (Allred 6-8) HER2-

REGISTRATION → BIOPSY → RANDOMIZE

BEFORE SURGERY

6 cycles (each cycle is 4 weeks)

- Arm I
- Arm II
- Arm III

4w
12 w
BIOPSY

Ki67 ≤10%
- Arm I
- Arm II
- Arm III

Ki67>10%

Neoadjuvant Chemotherapy Group
Chemotherapy (4-6 cycles)

Cycle 1 day 2 optional biopsy
(if receiving paclitaxel)

SURGERY

AFTER SURGERY
Therapy of Physician Choice

FOLLOW

SURGERY

AFTER SURGERY

Modified PEPI 0
Chemo NOT recommended
- Arm I
  A x 4.5 yrs
- Arm II
  F x 1.5 yrs then A x 3 yrs
- Arm III
  (A+F) x 1.5 yrs then Ax3 yrs

FOLLOW

Modified PEPI > 0
Chemo recommended
- Endocrine therapy of Physician's Choice

FOLLOW

Arm I: Anastrozole (A)
Arm II: Fulvestrant (F)
Arm III: Anastrozole + Fulvestrant

Red: required tissue collection
Blue: optional tissue collection

Primary Endpoints:
1st Phase: Modified PEPI 0 rate
2nd Phase: RFS in Modified PEPI 0

Sample size: n=2820
1st phase: n=400 each arm
2nd phase: n=540 each arm

Suman et el 2015

pCR after NAC: Open questions

- **Do we make the prognosis?**
- **Do we pick tumours with good prognosis?**
- **How pCR is achieved? Does it matter?**
- **Do we need adjuvant chemotherapy after 4 cycles of NAC?**
- **Specific considerations in TNBC: alternative therapy in non-pCR**
- **Operable ER+ breast cancer; do we need neoadjuvant therapy?**

  May be used in selected patients (strong ER+/low Ki67/ poor chemo candidate)

Operable BC- No downsizing is needed

- **Achieving pCR**
- **Converting Node+ to Node-negative (Avoiding ALND)**
- **Buy the time for genetic testing**

Feasibility and Accuracy of Sentinel Lymph Node Biopsy in Clinically Node-Positive Breast Cancer after Neoadjuvant Chemotherapy: A Meta-Analysis (15 studies)

Jian-Fei Fu, Hai-Long Chen, Jiao Yang, Cheng-Hao Yi, Shu Zheng

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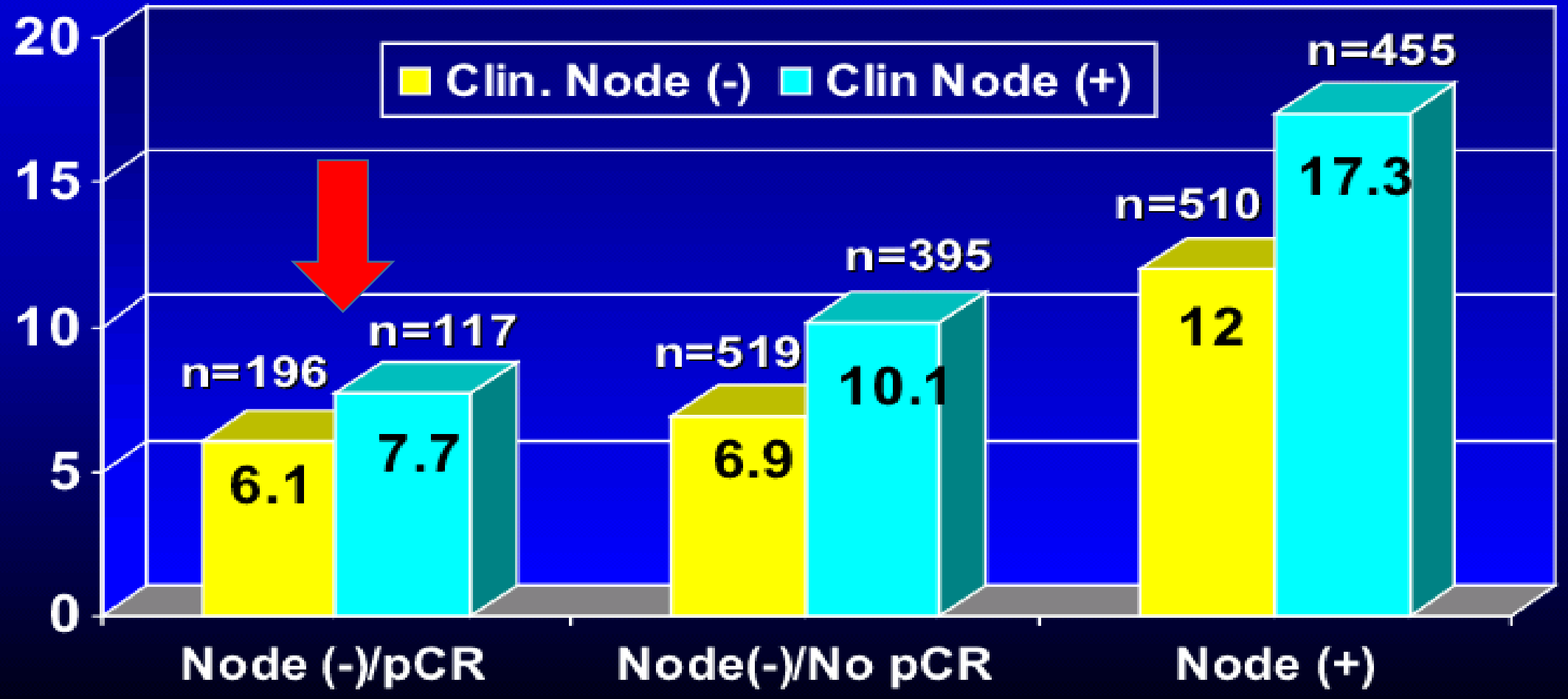
8-Year Cum. Incidence of LRF by According to Path Nodal Status/pCR and Clinical Nodal Status



SLNB after NAC in cN-positive

- **Nodal Response**
- **Response in the breast**
- **Number of retrieved LNS ≥3.**
- **Dual mapping agents**
- **Clipping of LNs**

Conclusion

Conclusion

- Achieving pCR may pick those with good biology/prognosis
- Those patient may do well with adjuvant therapy as well
- More pCR with more intense therapy is not essentially translated into better survival outcome
- Risk of overtreatment (NAC) in small tumours

Conclusion

- Operable HER2+: NAC is a valid option but still no alternative adjuvant therapy in non-pCR
- Operable TNBC: NAC should be considered to guide treatment strategy after surgery
- Operable ER+/HER2-: selected cases to pick those with PEPI score 0
- Avoiding ALND in clinically node-positive

Conclusion

- **We have new data, new treatment strategies**

but

- **Always we have open questions, new challenges**


Thank you
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