Selection criteria for post neoadjuvant therapy concepts

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DISCLOSURE SLIDE

My institution receives research grants and honoraria from AstraZeneca, Novartis, Pfizer, and Roche.

The model of neoadjuvant cytotoxic therapy (NACT)

Prognostic factors

e.g. stage
and many others

e.g. clinical response

e.g. pCR, ypTN, RCB

Predictors of chemotherapy response:

baseline

e.g.
- ***Grade***
- ***Ki-67***
- ***TILs***
- ***Pi3KCa***

functional

Ultrasound
- **e.g. GeparTrio**

Ki-67
- **e.g. Poetic, Adapt**

PET-CT
- **e.g. GeparPET**

surrogate endpoint

pCR based on
- **GBG-meta-analysis**
- **CtNeoBC**
- **literature-based meta-analysis**

Rationale of post-neoadjuvant treatment

Use neoadjuvant therapy to individualize subsequent treatment:

Those with pCR:

- **To reduce extend of subsequent treatment**

Those without pCR:

- **To overcome treatment resistance**

NEO-ADJUVANT TRIAL ADD-ON

NATAN

Study design

Stratification factors

- **Center**
- **Hormone receptor status (<10 or ≥ 10 % ER or PgR)**
- **Age (<50 / ≥50 years)**
- **Time since surgery (within 3 months, 1 year, 2 years, or 3 years)**

RANDOMIZATION

Observation

Zoledronate 4 mg iv.

- Every 4 weeks for the first 6 doses (year 0- 0.5)
- Every 3 months for 8 doses (year 0.5-2.5)
- Every 6 months for 5 doses (year 2.5- 5.0)

Prior and/or simultaneous endocrine/trastuzumab treatment or radiotherapy

AGO-B BREAST STUDY GROUP

von Minckwitz et al, SABCS 2013

GBG GERMAN BREAST GROUP

NEO-ADJUVANT TRIAL ADD-ON

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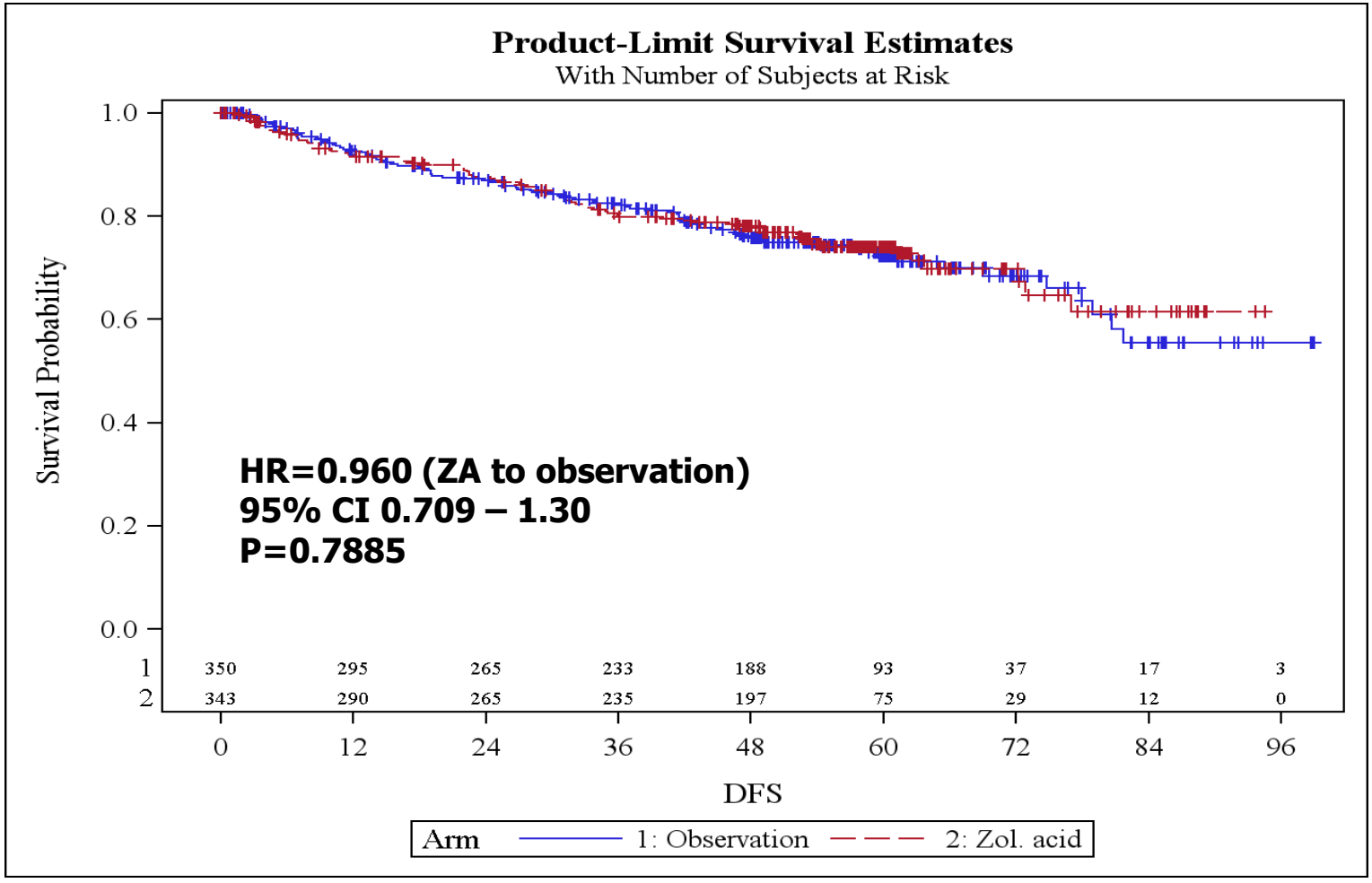
Disease-free survival



NEO-ADJUVANT TRIAL ADD-ON

NATAN

Patients & Tumor Characteristics

Total n=693	Observation n=350	Zoledronate n=343
Age (median yrs)	50	49
>55 years	34.0%	33.3%
Ductal invasive	70.4%	72.4%
Grade 3	31.7%	31.3%
Hormone receptor positive	79.9%	78.7%
HER2 positive	17.3%	17.5%
ypT 3 or 4	16.2%	14.7%
ypN0	26.5%	29.8%
ypN1	48.0%	41.2%
ypN2 or 3	25.6%	28.9%
SD or PD after neoadjuvant chemotherapy	15.0%	15.1%
>1 year after axillary surgery	17.4%	16.1%

AGO-B BREAST STUDY GROUP

von Minckwitz et al, SABCS 2013

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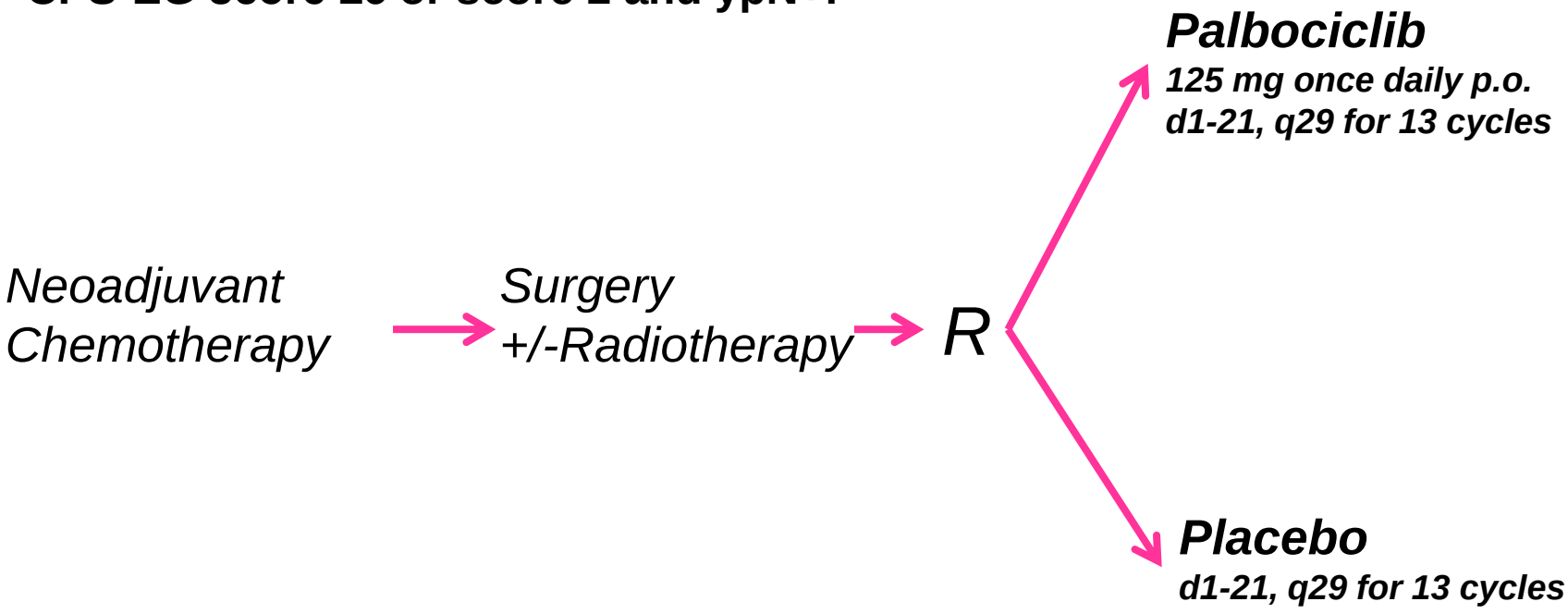
PENELOPE^{B} Study Design

N=1100 pts. with
HR+/HER2- breast cancer
no pCR and
CPS-EG score ≥3 or score 2 and ypN+:



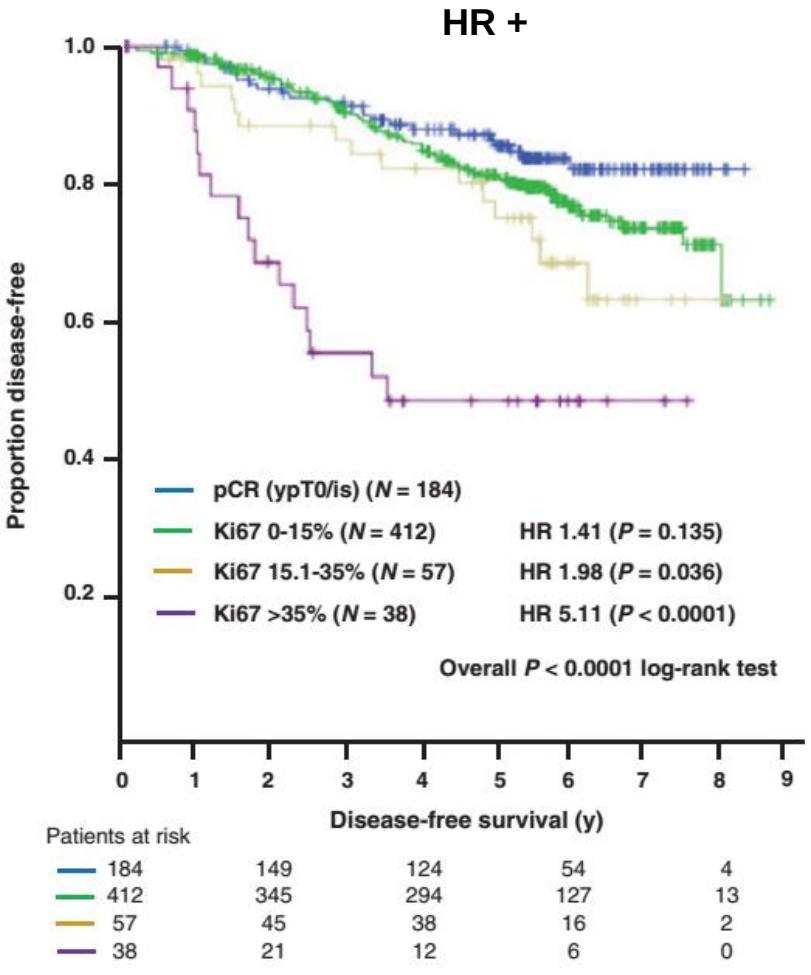
All patients will receive concomitantly endocrine therapy according to local standards

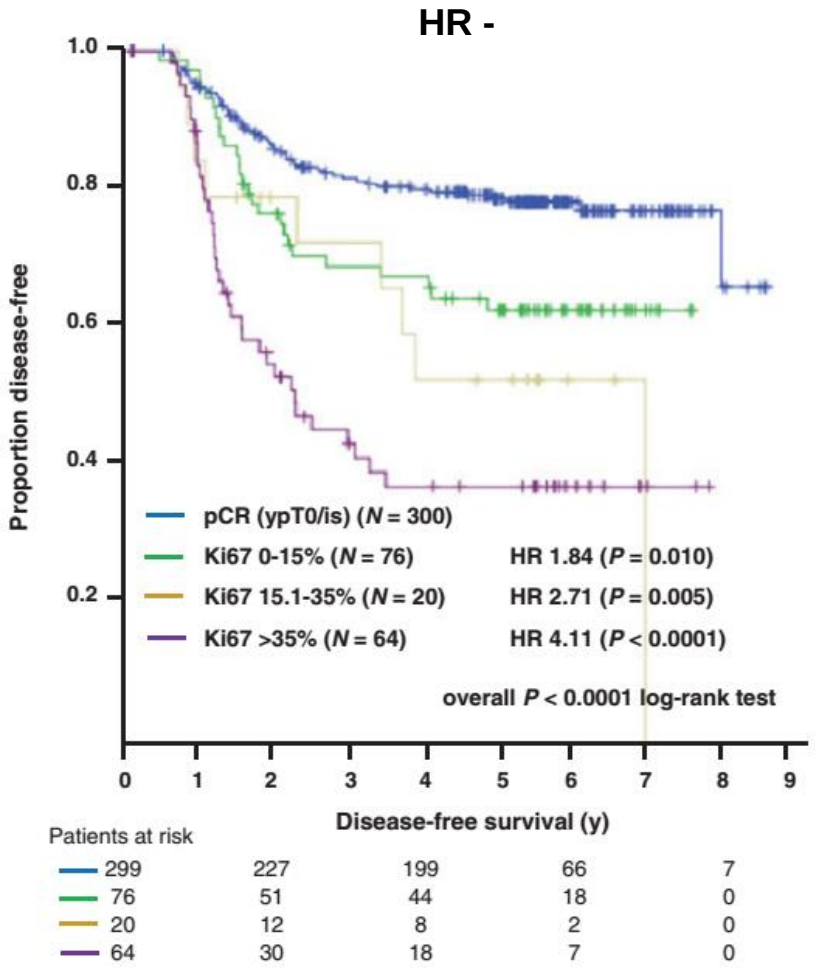
Trio-18 (Paloma 1) study
Prediction of PFS by
CCND1 amplification and/or loss of p16

Population	Comparison	Number of Patients	HR (95% CI) / P value
Biomarker Positive	PD 0332991 + Letrozole vs. Letrozole	12 9	0.37 (0.10, 1.40) / 0.13
Biomarker Negative	PD 0332991 + Letrozole vs. Letrozole	10 15	0.19 (0.05, 0.67) / <0.01
Biomarker Status Unknown	PD 0332991 + Letrozole vs. Letrozole	12 8	0.59 (0.11, 3.08) / 0.53
PD 0332991 + Letrozole	Biomarker Positive vs. Biomarker Negative	12 10	1.42 (0.31, 6.43) / 0.65
Letrozole	Biomarker Positive vs. Biomarker Negative	9 15	0.68 (0.24, 1.94) / 0.47

Finn RS et al, IMPACT 2012

Prognostic impact of Ki-67 measured in postneoadjuvant surgical tissue





PENELOPE-B

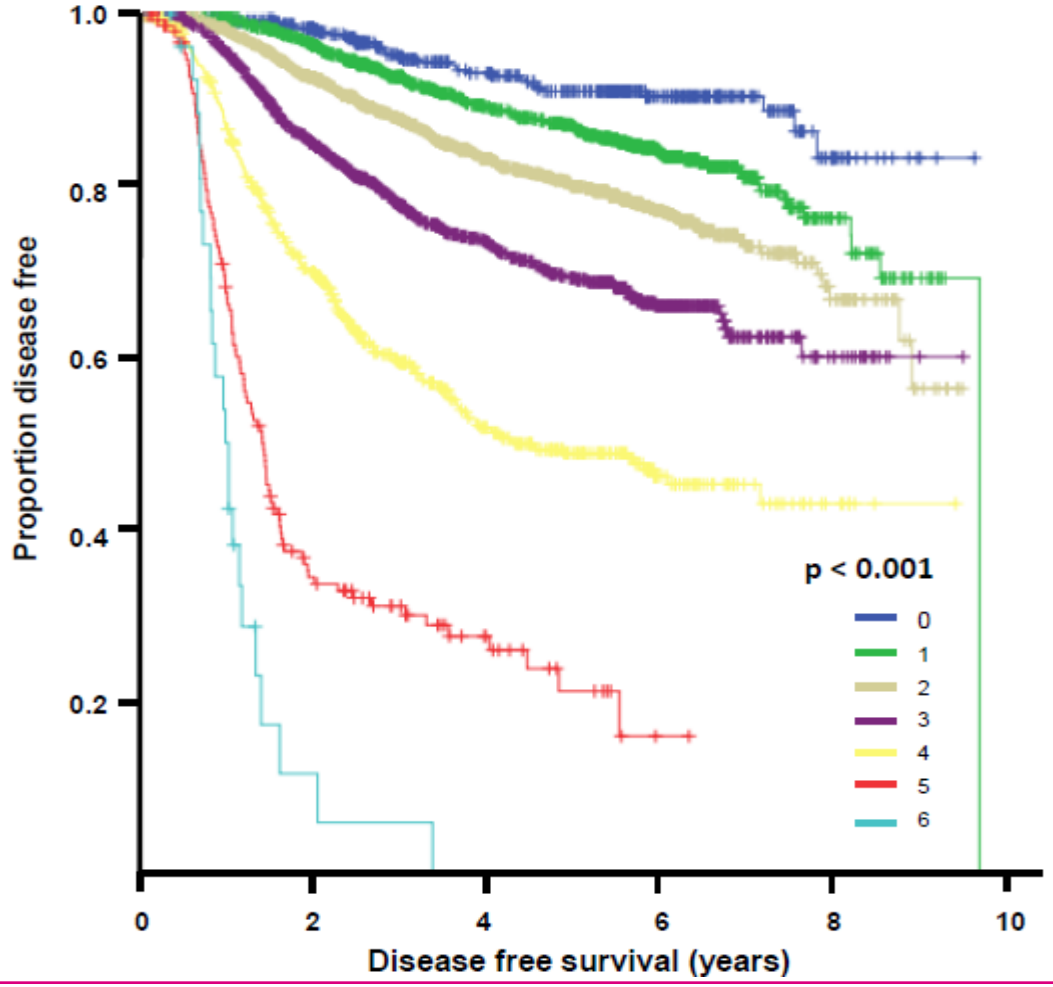
CPS + EG Staging System

Table 1. Point Assignments for the CPS + EG Staging System

Stage	Points
Clinical stage	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic stage	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER negative	1
Nuclear grade 3	1

Abbreviations: CPS + EG, clinical-pathologic staging system incorporating ER-negative disease and nuclear grade 3 tumor pathology; ER, estrogen receptor.

German meta-database
(N=2454 HR+/HER2- tumors)



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Mittendorf EA, J Clin Oncol 2011
Marmé F, manuscript in prep

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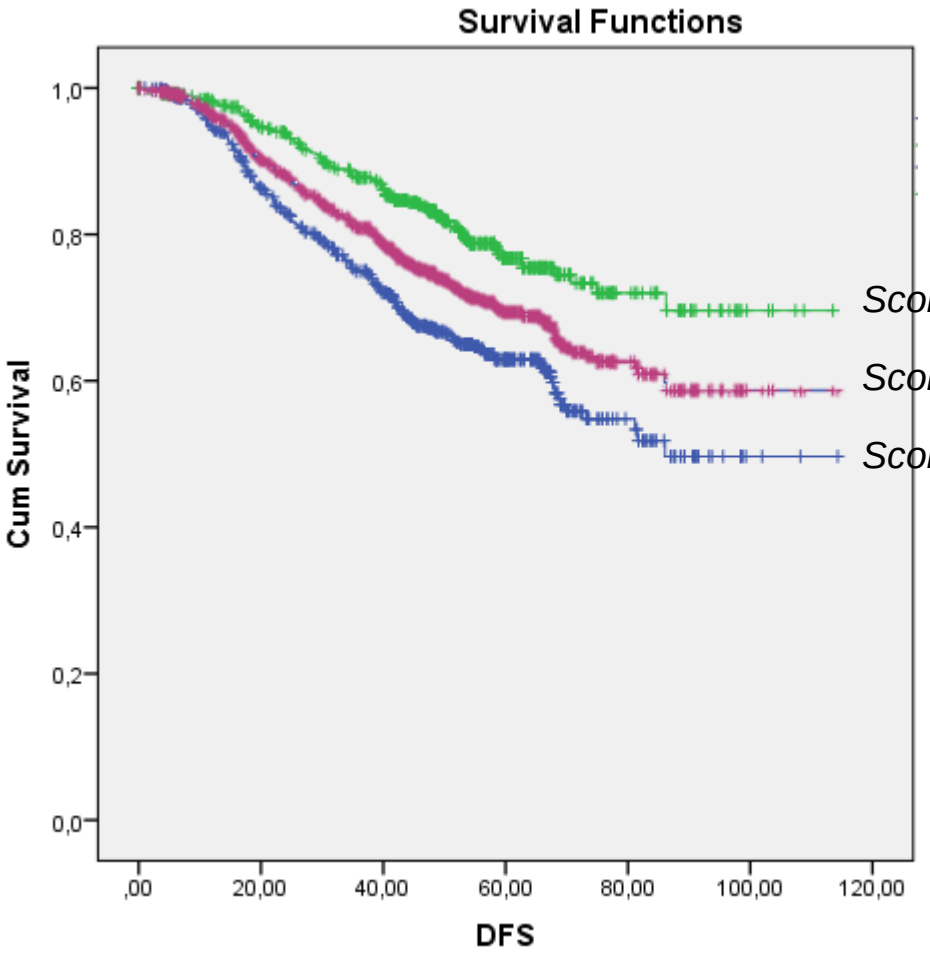
iDFS by CEP- EG Score



Score 2 ypN+ (N=488)

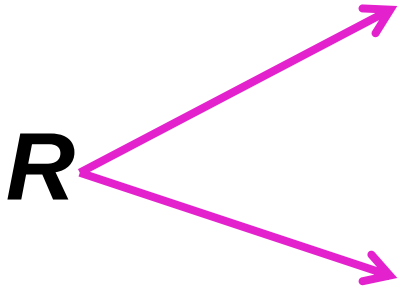
*Score 3+ & Score 2 ypN+ (N=1076)**

Score 3+ (N=588)

** Includes all patients of the curves above and below*

Katherine
BO27938 / NSABP B-50-I / GBG-77

N=1484 pts.
with HER2+ EBC
and no pCR
after NACT



T-DM1 3.6 mg/kg q3w

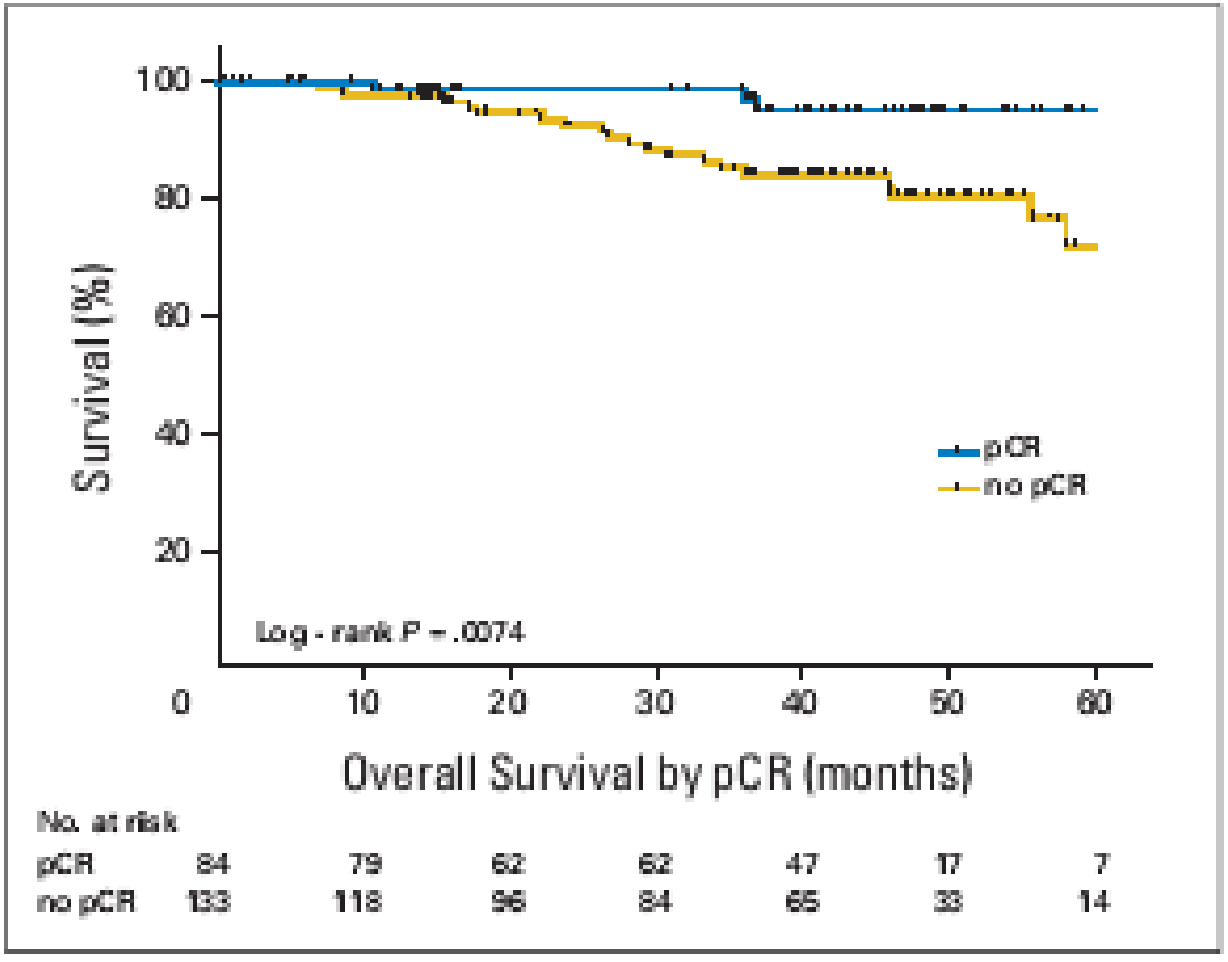
F-up 10 yrs

Trastuzumab 6 (8) mg/kg q3w

Duration: 14 cycles (42 weeks)
+ endocrine tx (if HR+)
+ RTX (if indicated)

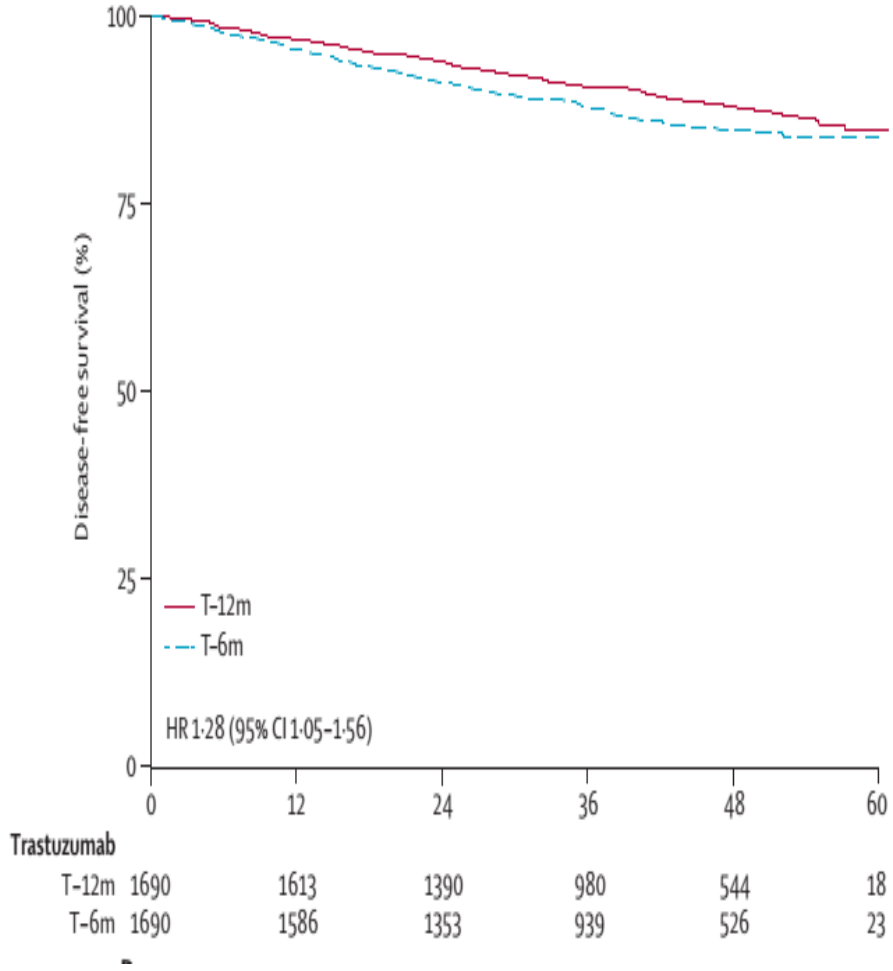
Sponsor: Roche

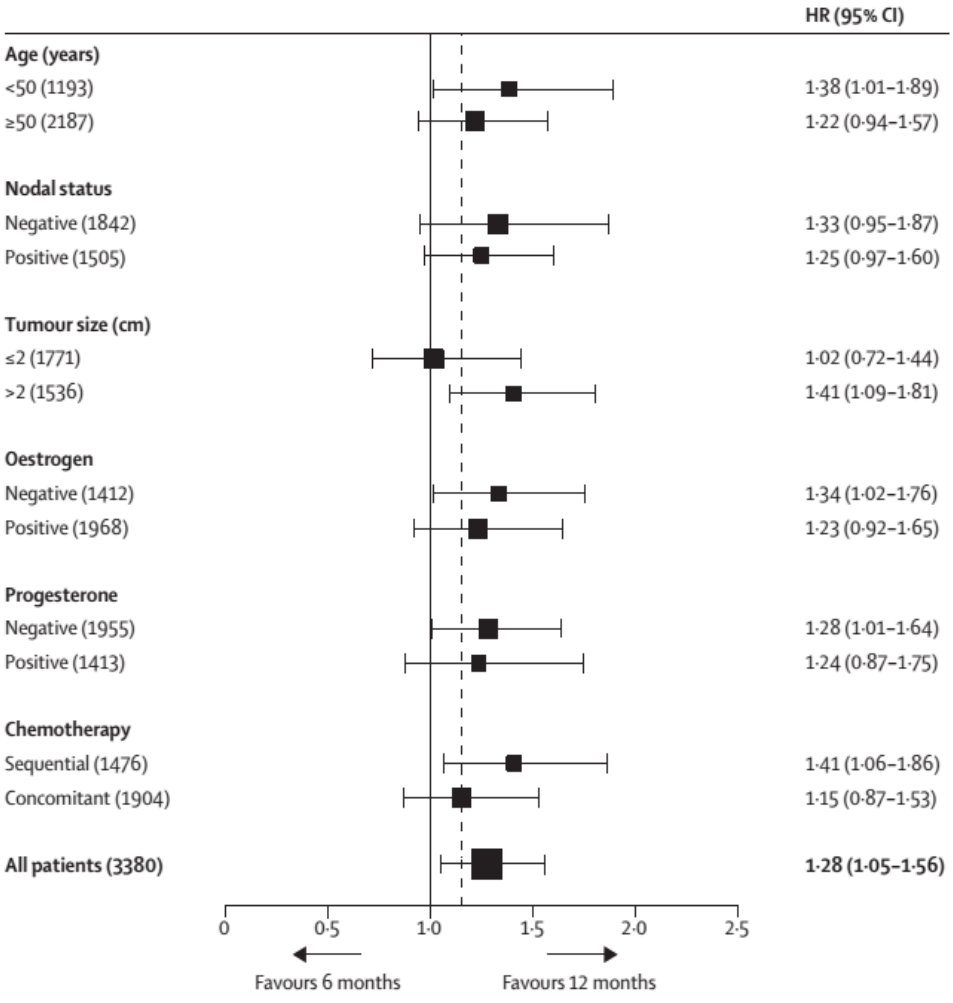
TECHNO Study
Overall survival after neoadjuvant EC-TH



Untch M, et al. J Clin Oncol 2011

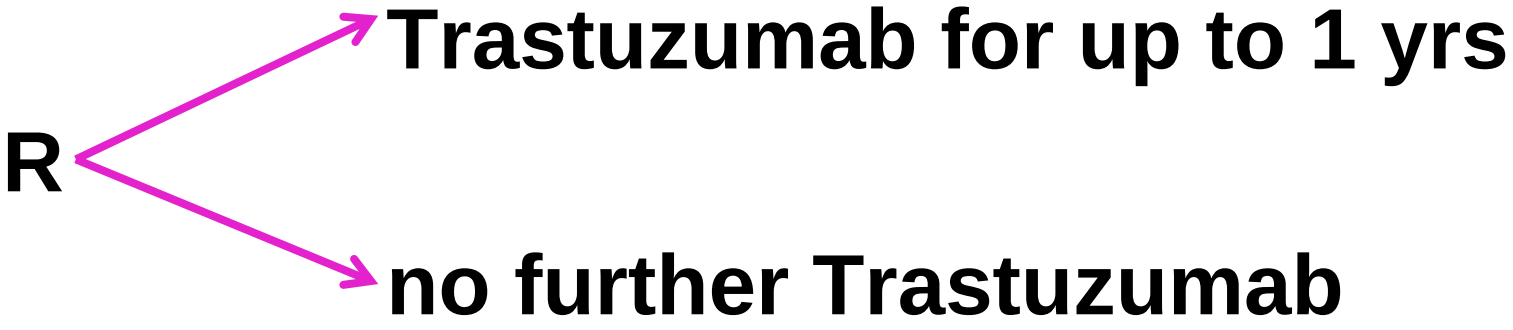
Phare – Study
6 vs 12 m adjuvant trastuzumab





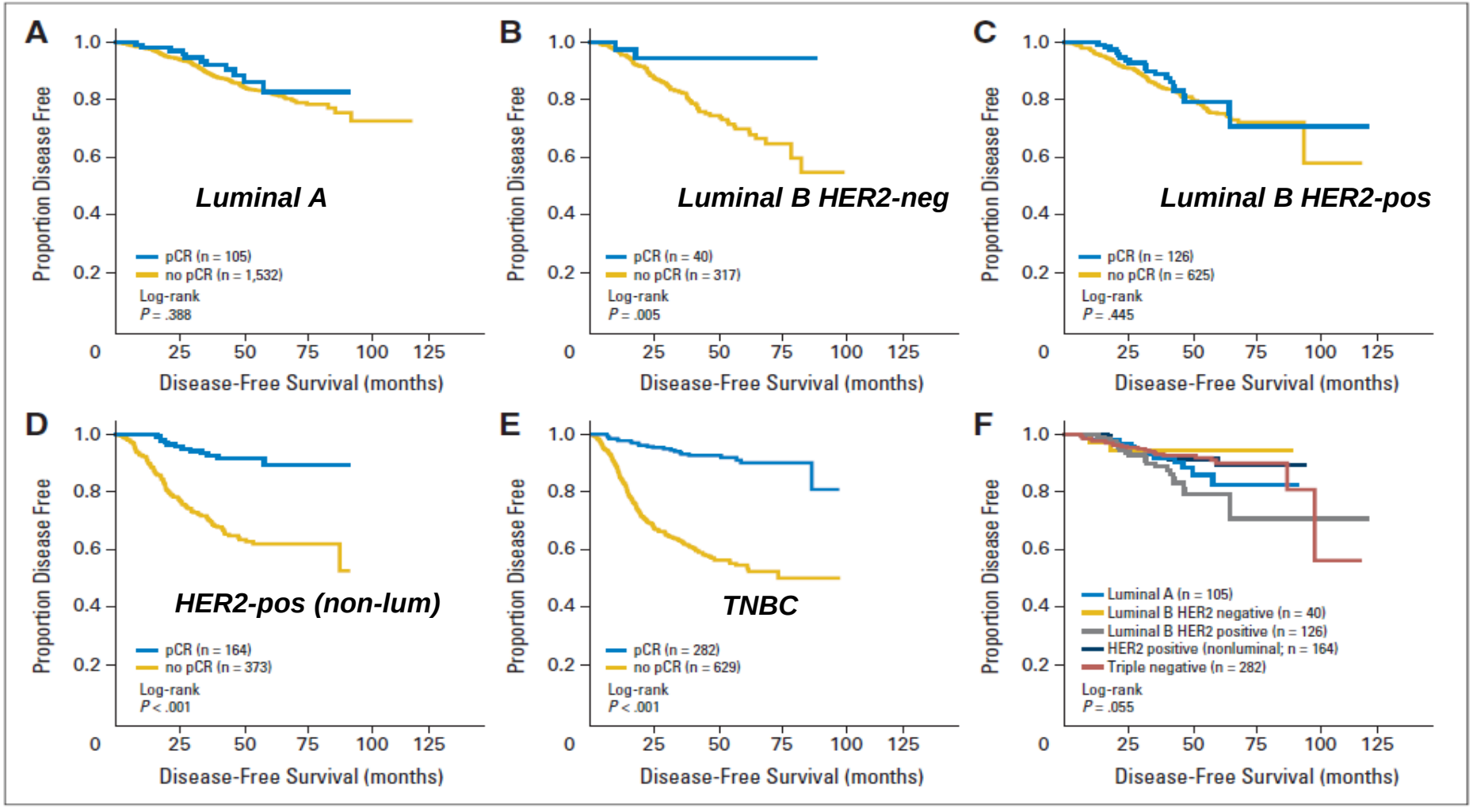
Pivot X, Lancet Oncology 2013

Proposed post-neoadjuvant GBG study for patients with HER2-pos tumors and pCR



Funding possibilities?

Prognosis information of pCR by Subtype (N=4193)



von Minckwitz G et al, J Clin Oncol 2012

Post-neoadjuvant treatment with Rucaparib BREA 09-146

N=128 pts. with

TNBC or gBRCA-Muation

ypN+ or ypT≥2

1 yr DFS

Neoadjuvant Chemotherapy → *Surgery +/- Radiotherapy* → ***R***

Cisplatin *82.7%*

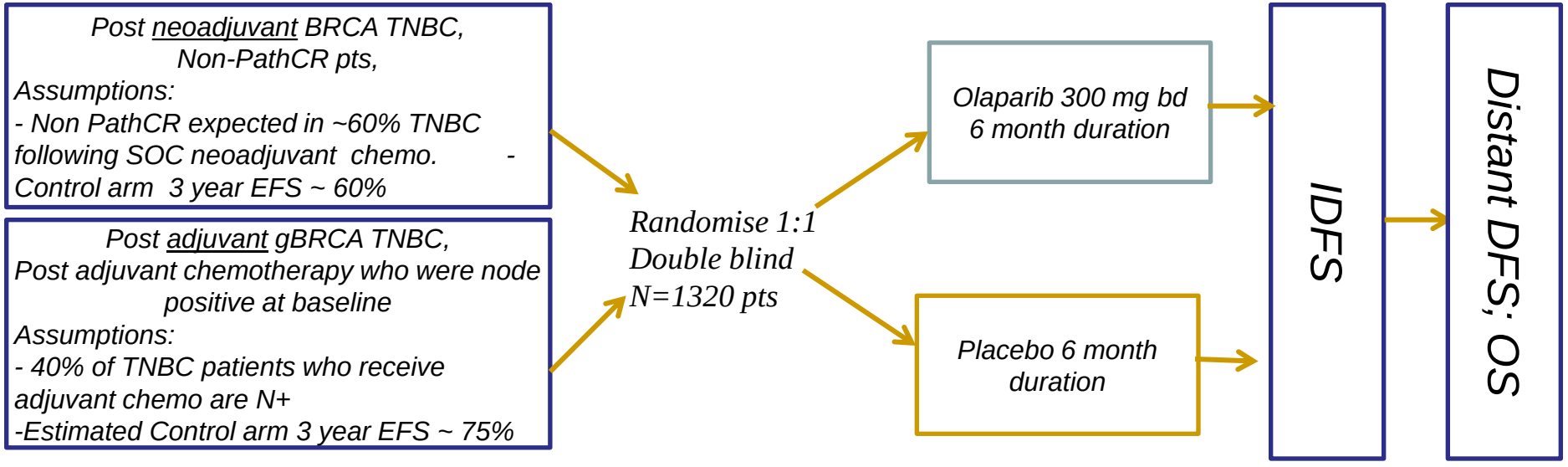
75 mg 4 cycles

Cisplatin + Rucaparib *82.5%*

30 mg IV or 100 mg orally wkly for 24 wks

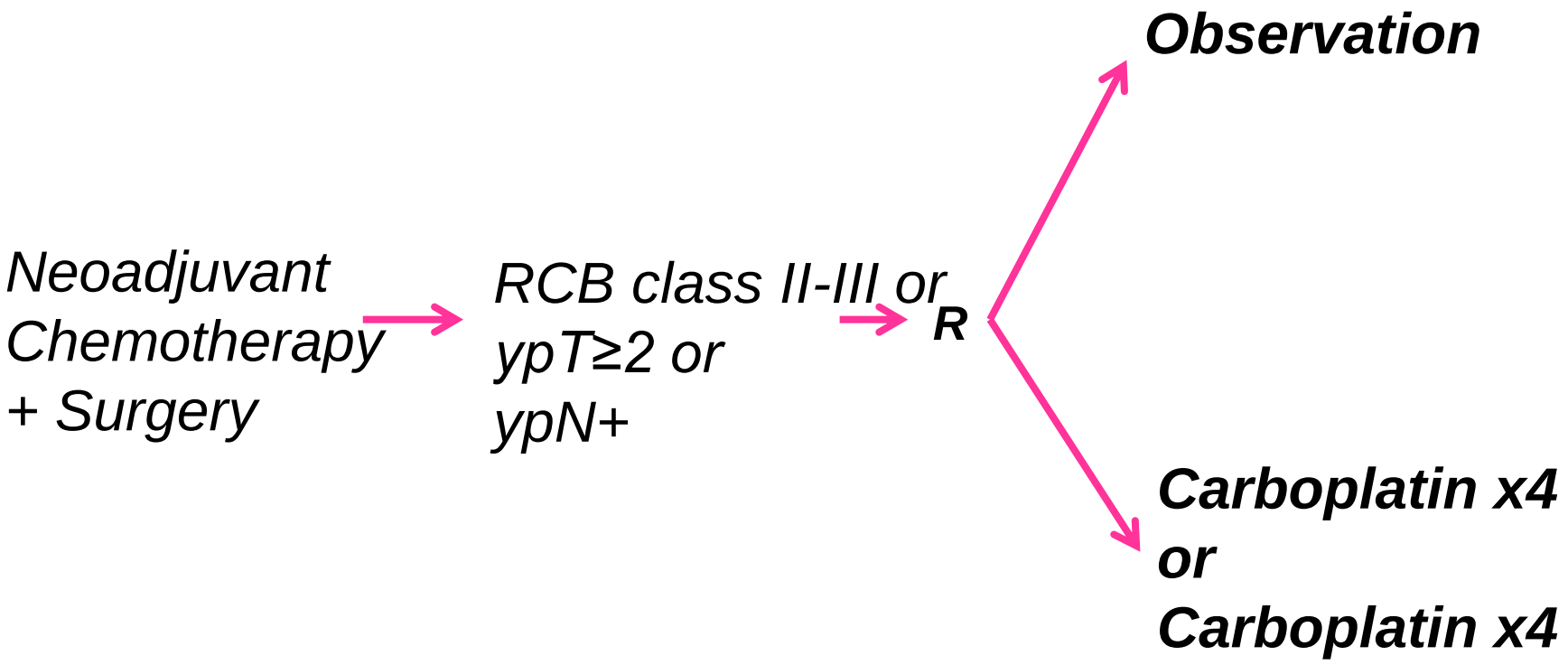
Dwadasi S, …. Miller K. ASCO 2014 abst 1019

Olympia

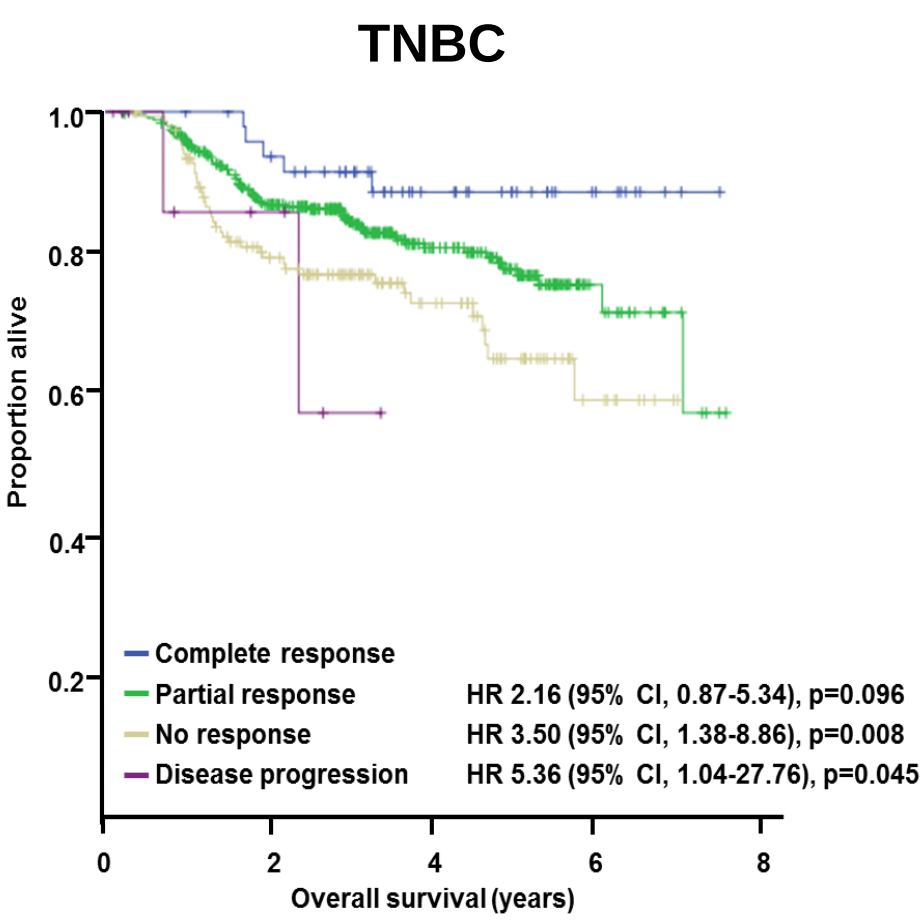


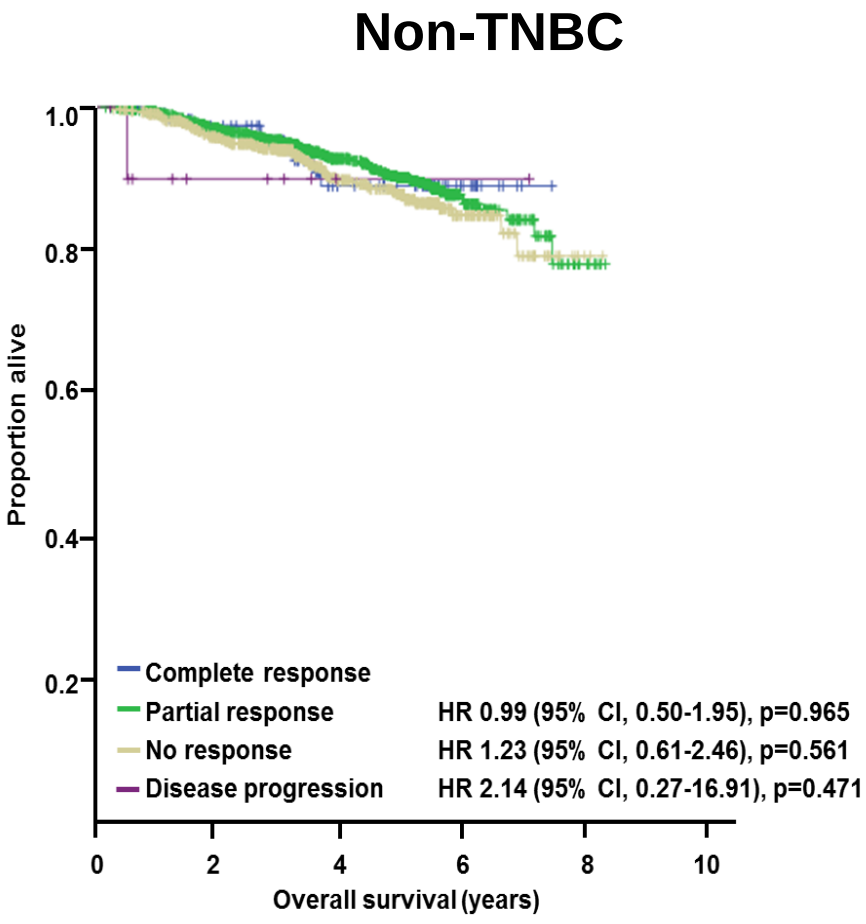
Sponsor: AstraZeneca; in cooperation with BIG and NSABP

New ECOG 1113 design

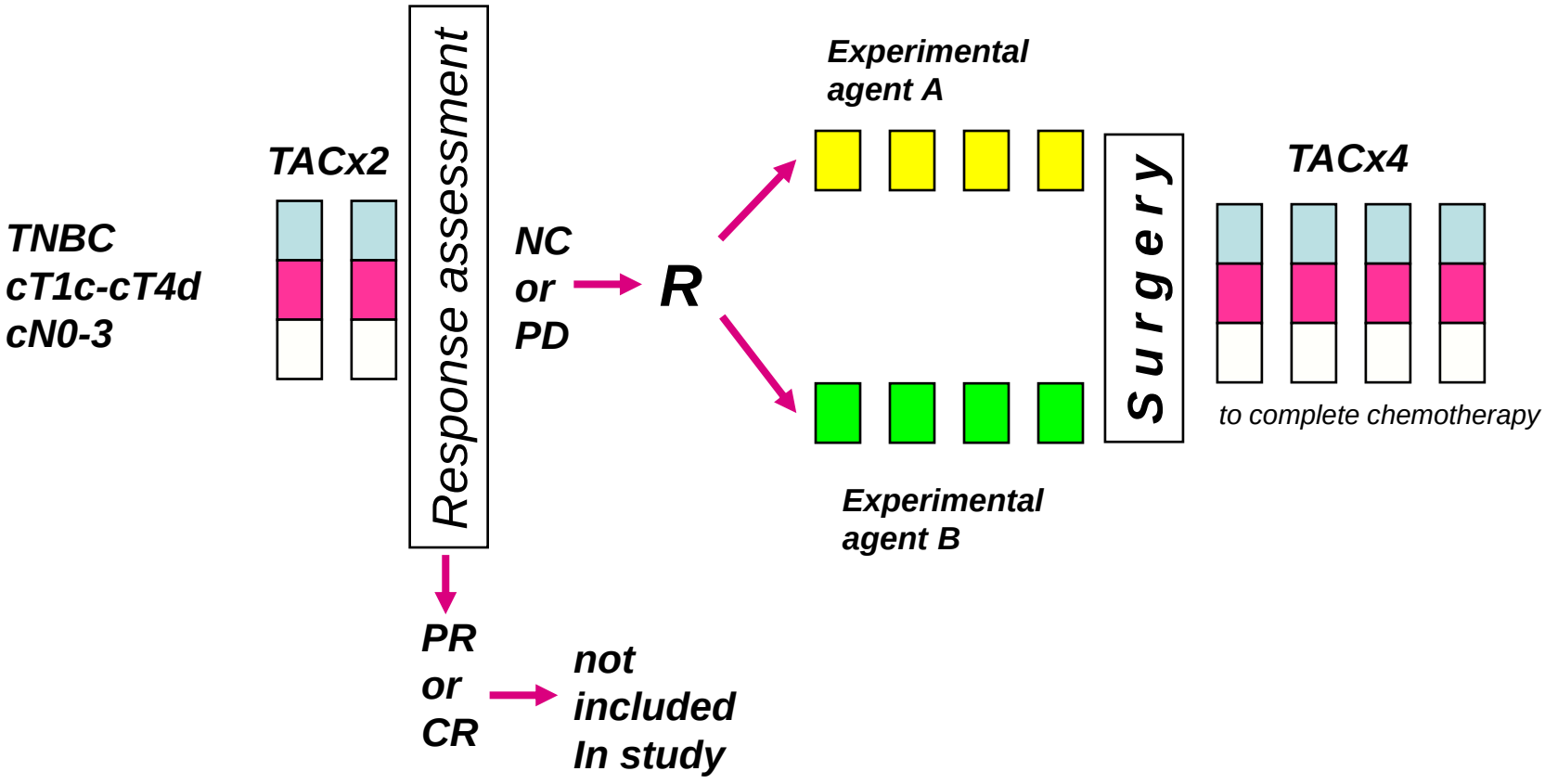


Interim clinical response as a prognostic factor for overall survival





Trial Design for chemo-insensitive TNBC



Conclusion

- **Selection criteria for postneoadjuvant studies are a prerequisite!**
- **Beyond HR and HER2, only classical prognostic markers have so far been implemented in trials**
  - **CPS-EG score**
  - **ypN status**
- **Better and more b.c. subtype-specific criteria are required**
- **Intermediate prognostic markers might help to design small investigational trials after early failure of neoadjuvant treatment**