Lo studio GEPARsepto: Quali ricadute nella pratica clinica?

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Gepar7 potential clinical implications

- Sentinel node biopsy in the neoadjuvant setting: moving toward routine?
- Is it there an optimal anthracycline-taxane sequence?
- Neoadjuvant chemotherapy in luminal subtypes: needs for alternative options
- HER2 positive subtype: chemotherapy backbone still matters
- TN subtype: superior activity of nabP or suboptimal P performance?
- Gepar7 schedule and dose: transferability in the metastatic setting

Nodal staging and SNB

Nodal stage by palpation		
cN0	378 (65%)	377 (66%)
cN1	190 (33%)	176 (31%)
cN2	9 (2%)	12 (2%)
cN3	2 (<1%)	6 (1%)
Missing	27	29
Nodal stage by sonography		
cN0	324 (55%)	320 (55%)
cN1	252 (43%)	235 (41%)
cN2	10 (2%)	14 (2%)
cN3	4 (1%)	9 (2%)
Missing	16	22
Sentinel node biopsy		
None	267 (44%)	268 (45%)
Negative	219 (36%)	204 (34%)
Positive	118 (20%)	128 (21%)
Missing	2	0

Untch M, Lancet Oncol 2016

SLNB before or after NACT

	Before	after
Clinical Utility	+	+++
Feasibility	+++	++
Accuracy	+++	++
Oncologic Safety	+++	?

Courtesy C Khune

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First author	Design	*n*	Comparisons of interest	Main results
Alvarez [16]	Retrospective	1414	FAC/FEC followed by paclitaxel versus paclitaxel followed by FAC/FEC	Rates of pCR of 12.4% for anthracycline first and 20.9% for taxane first; higher risk of relapse for anthracycline first, but no difference in risk of death
Thiery-Vuillemin [22]	Retrospective	123	Anthracycline-based chemotherapy X 4, followed by docetaxel X 4 versus Docetaxel X 4, followed by anthracycline-based chemotherapy X 4	RDI of anthracycline similar in both groups, but RDI of docetaxel significantly higher in with the taxane first; no difference in pCR rates, but clinical complete responses more frequent with the taxane first
Stearns [23]	Randomized pilot	29	Doxorubicin followed by paclitaxel versus paclitaxel followed by doxorubicin	Rates of pCR of 10% for anthracycline first and 7% for taxane first, with similar clinical responses in both arms
Miller [24]	Randomized phase II	70	Doxorubicin X 3, followed by weekly docetaxel X 6 versus Weekly docetaxel X 6, followed by doxorubicin X 3	Rates of pCR of 8.6% for anthracycline first and 17.1% for taxane first (no statistical significance)
Taghian [25]	Randomized phase II	54	Doxorubicin X 4, followed by weekly paclitaxel X 9 versus Weekly paclitaxel X 9, followed by doxorubicin X 4	Mean decrease in ultrasound tumor volume of 79.5% with anthracycline first and 70.6% with taxane first (no statistical significance)
Earl [26]	Randomized phase III, 2 × 2 factorial	831	Epirubicin and cyclophosphamide X 4, followed by paclitaxel ± gemcitabine X 4 versus paclitaxel ± gemcitabine X 4, followed by epirubicin and cyclophosphamide X 4	Rates of pCR of 15% with anthracycline first and 20% with taxane first ($P = 0.03$), with no benefit from the addition of gemcitabine; similar RDIs across groups
Buzdar [27]	Randomized phase III	280	FEC X 4, followed by weekly paclitaxel plus trastuzumab X 12 versus Weekly paclitaxel plus trastuzumab X 12, followed by FEC X 4 plus trastuzumab X 12	No significant differences in pCR rates in both arms; slightly higher rates of grade 3/4 neutropenia, fatigue, and neurosensory problems with taxane first
INCA	Randomized phase II	112[a]	FAC X 3, followed by docetaxel X 3 versus docetaxel X 3, followed by FAC X 3	Ongoing study

Gepar7

- Almost 5% of the patients in the solvent-based paclitaxel group progressed during the first 12 weeks, whereas primary progressions with nab-paclitaxel occurred as expected in less than 2% of patients

- The proportion of patients who completed the taxane treatment was 483 (80%) patients treated with nab-paclitaxel compared with 520 (87%) patients treated with solvent-based paclitaxel.

- This did not affect the completion of the anthracycline treatment, which followed the taxane therapy.

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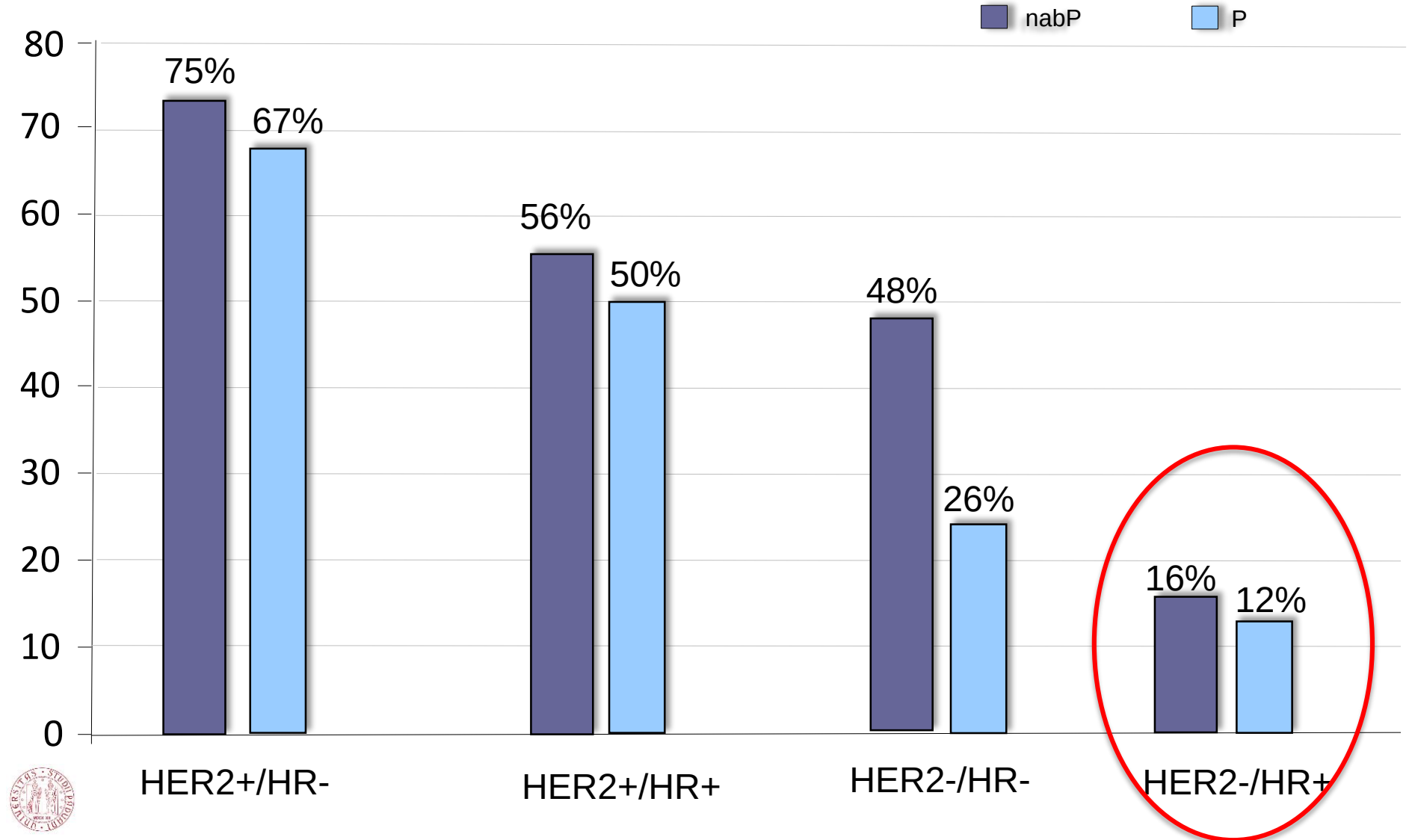
pCR rates (ypT0N0) according to BC subtype



Neoadjuvant endocrine therapy vs CT in postmenopausal women with HR+ BC

R → Doxo60+TXL200 q3w X 4 (118 pts) → **Surgery**

R → ET for 3 mos (121 pts) Exemestane or Anastrozole → **Surgery**

	ChemoRx	Endocrine Rx
Clinical OR %	63.6	64.5
USG response %	46	40
Mammography %	63	60
BCS %	24	33
pCR %	6	3
LRF at 3y %	2.3	3.3

Semiglazov VF, Cancer 2007

Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study

E. Alba[1*], L. Calvo[2], J. Albanell[3], J. R. De la Haba[4], A. Arcusa Lanza[5], J. I. Chacon[6], P. Sanchez-Rovira[7], A. Plazaola[8], J. A. Lopez Garcia-Asenjo[9], B. Bermejo[10], E. Carrasco[11], & A. Lluch[10]
on behalf of GEICAM

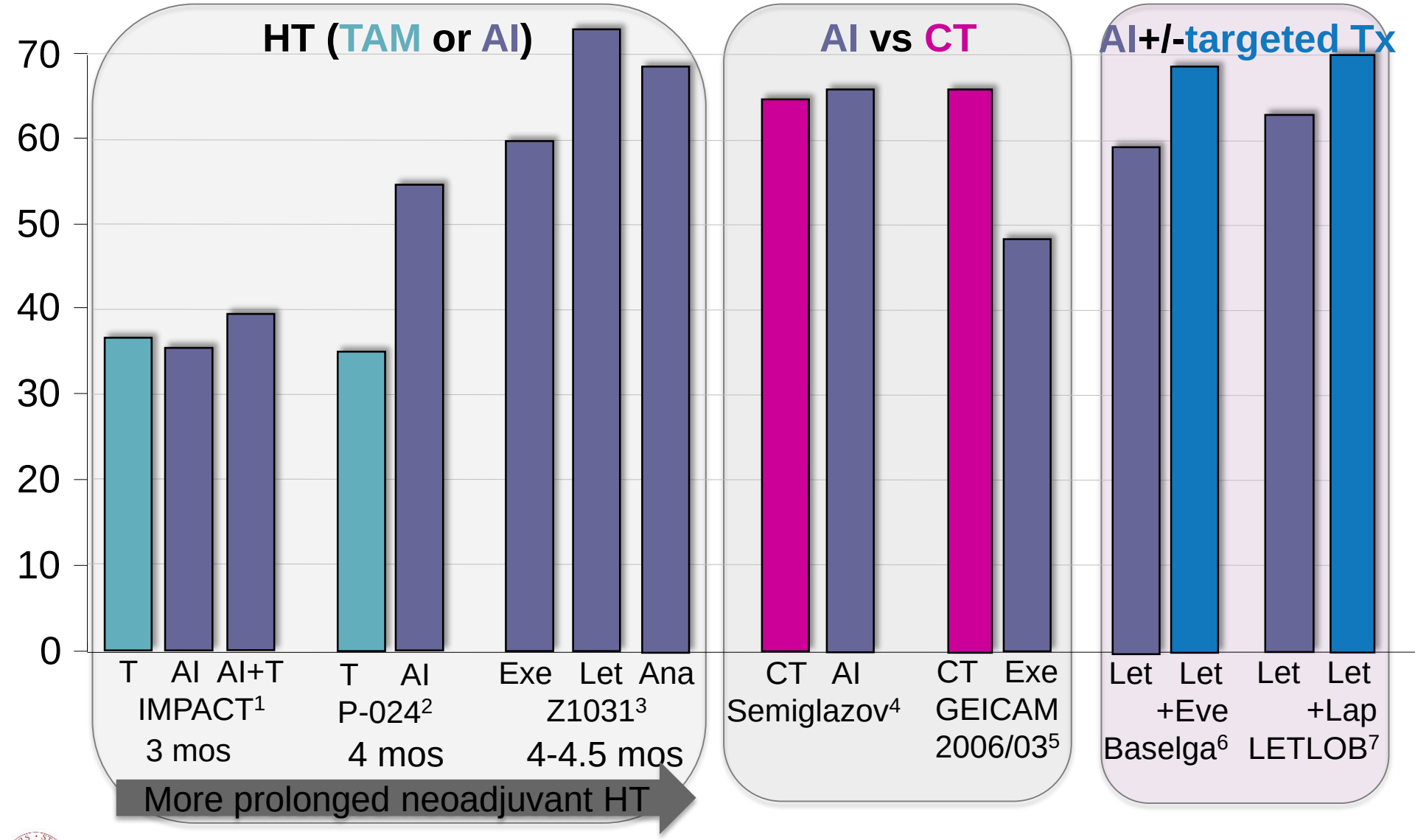
95 ER+/ PgR +/HER2- patients randomized to:

- EC x 4 → Docetaxel 100 x 4
- Exemestane x 24 weeks (+ goserelin if pre-menopausal)

	CT arm	HT arm	p-value
ORR	66%	48%	0.075
BCS	47%	56%	0.23
pCR	2%	-	0.6
pN0	36%	29%	0.47

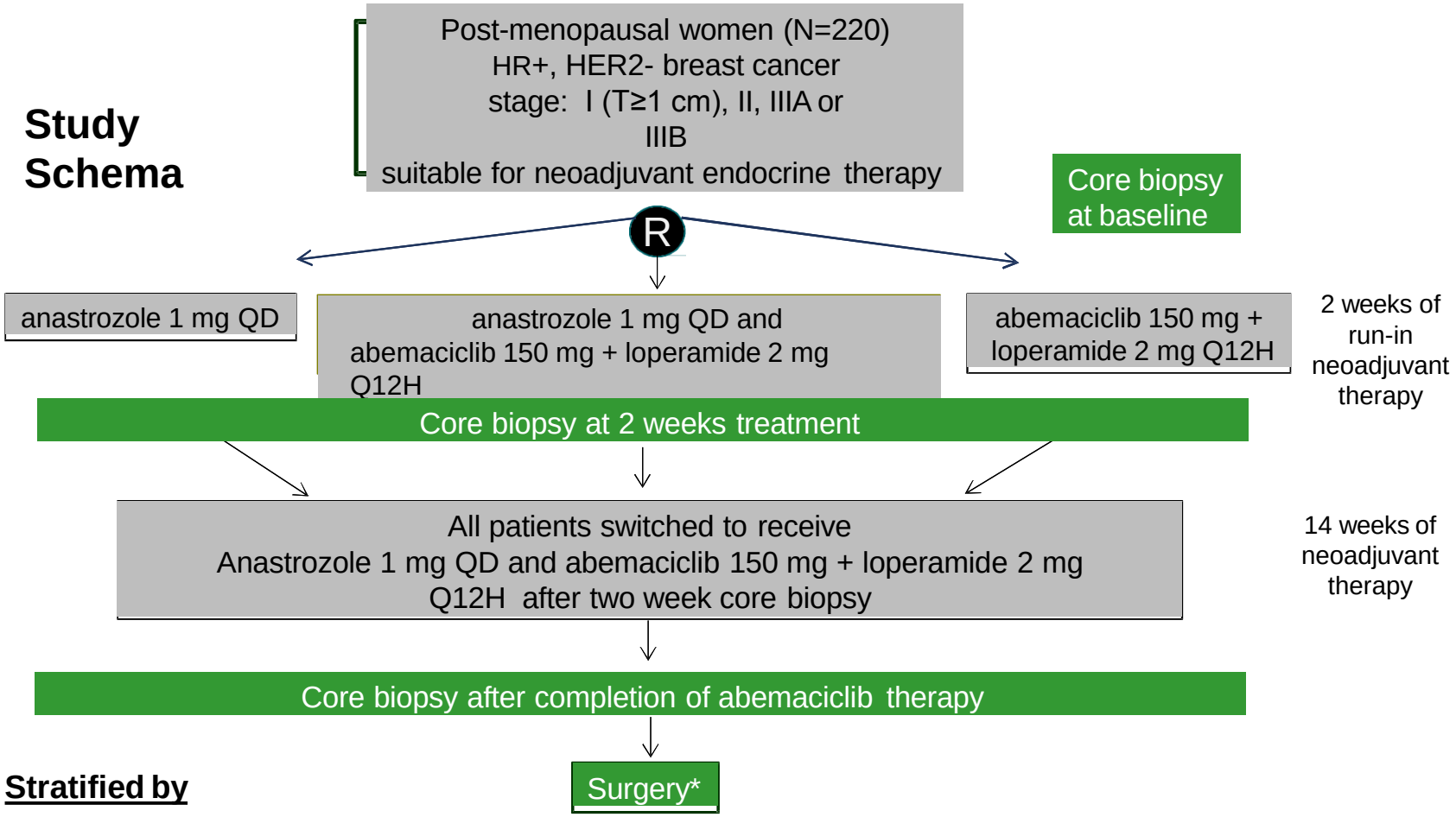
Alba et al, Ann Oncol 2012

ORR rates in HR+/HER2- BC



1. Smith I.E., J Clin Oncol 2005; 2. Eiermann W. Ann Oncol 2001; 3. Ellis M.J. J Clin Oncol 2011; 4. Semiglazov V.F., Cancer 2007;

Study Schema



Stratified by

PgR status: positive, vs.
negative/unknown

Tumor size: < 2 cm, vs.
≥ 2 cm & < 5 cm, vs.
≥ 5 cm

*Surgery is not required and not considered a study procedure.

neoMONARCH

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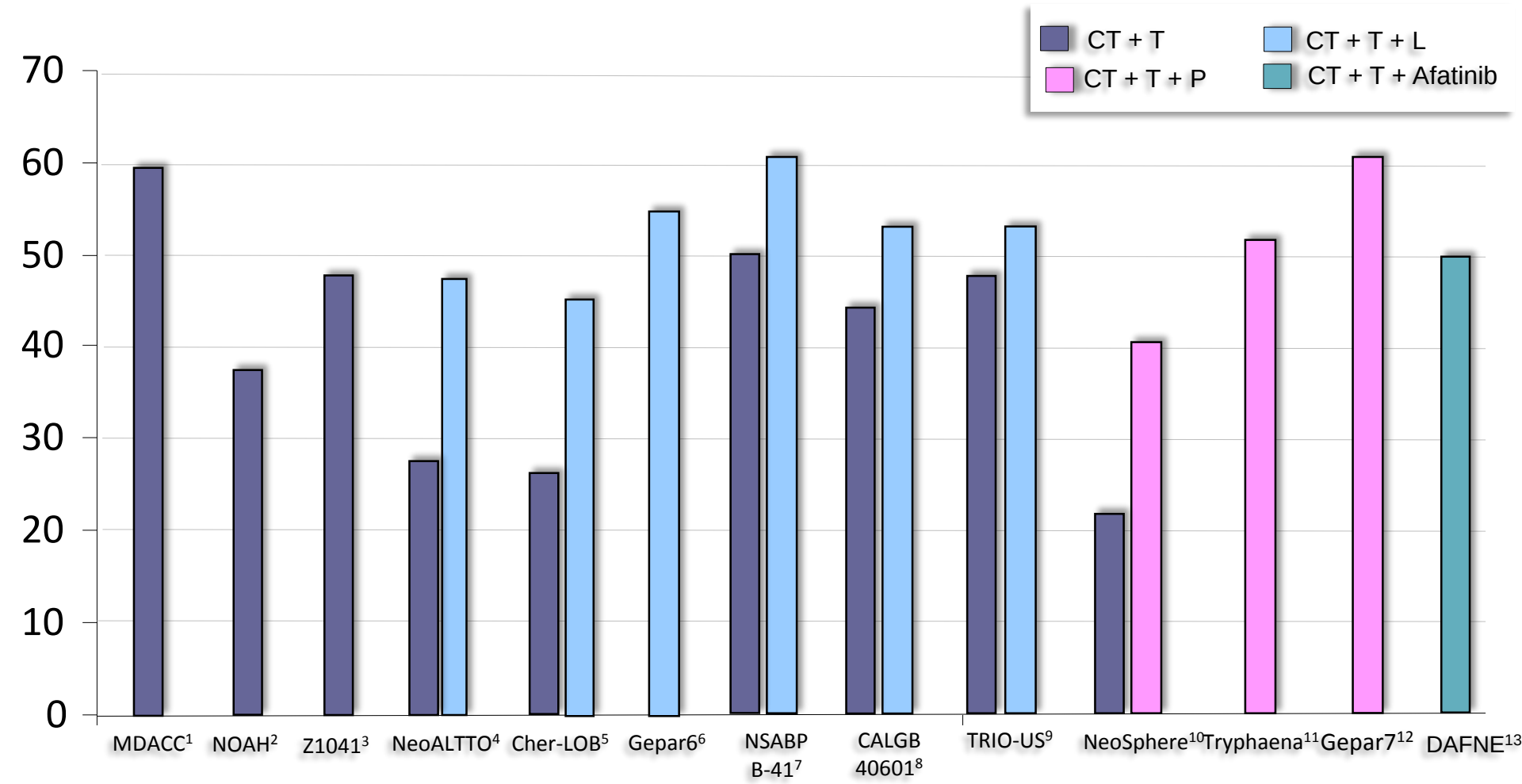
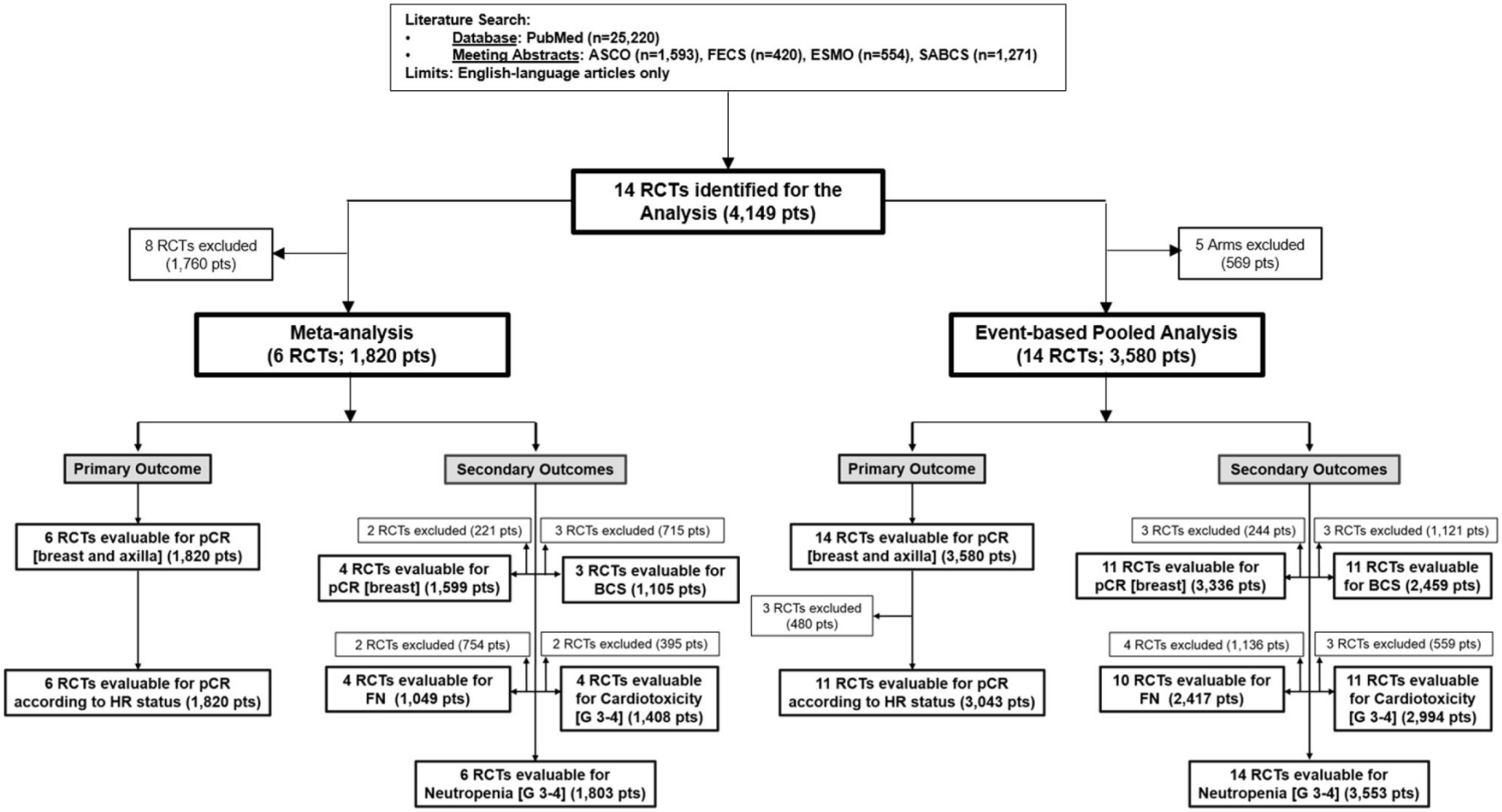
pCR rates (breast/axilla) in HER2+ BC



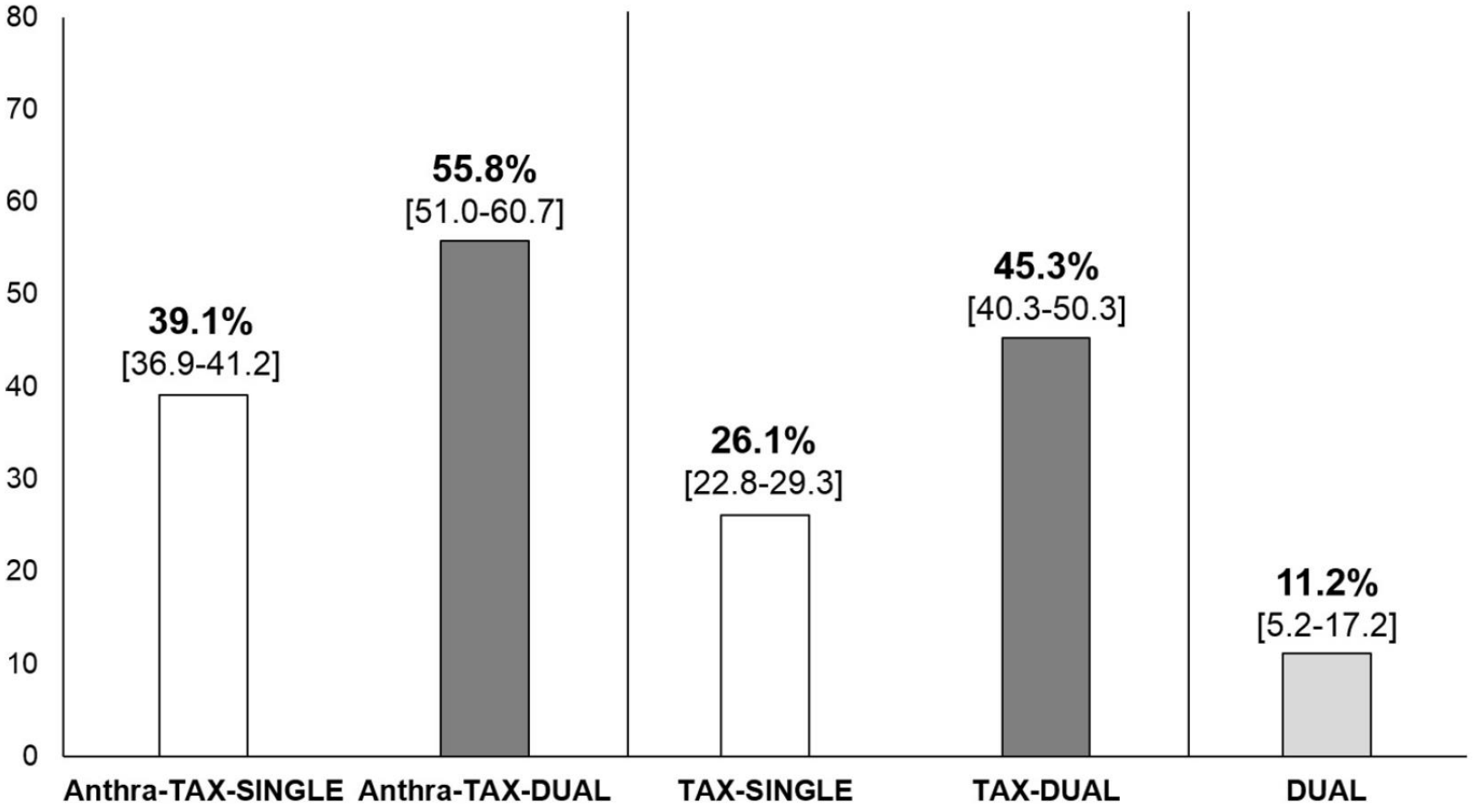
1. Buzdar AU, CCR 2007; 2. Gianni L, Lancet 2010. 3. Buzdar AU, Lancet Oncol 2013. 4. Baselga J. Lancet 2012; 5. Guarneri V. J Clin Oncol 2012; 6. von Minckwitz. Lancet Oncol 2014; 7. Robidoux A. Lancet Oncol 2013; 8. Carey L .ASCO 2013; 9. Hurvitz S SABCS 2013 10. Gianni L . Lancet Oncol 2012; 11. Schneeweiss A . Ann Oncol 2013 ; 12 Untch M. SABCS 2014; 13. Hanusch C. Clin Cancer Res 2015

Impact of neoadjuvant single or dual HER2 inhibition and chemotherapy backbone upon pathological complete response in operable and locally advanced breast cancer: Sensitivity analysis of randomized trials

Emilio Bria [a,*], Luisa Carbognin [a], Jenny Furlanetto [a], Sara Pilotto [a], Maria Bonomi [a], Valentina Guarneri [b], Cecilia Vicentini [a], Matteo Brunelli [c], Rolando Nortilli [a], Francesca Pellini [d], Isabella Sperduti [e], Diana Giannarelli [e], Giovanni Paolo Pollini [d], Pierfranco Conte [b], Giampaolo Tortora [a]

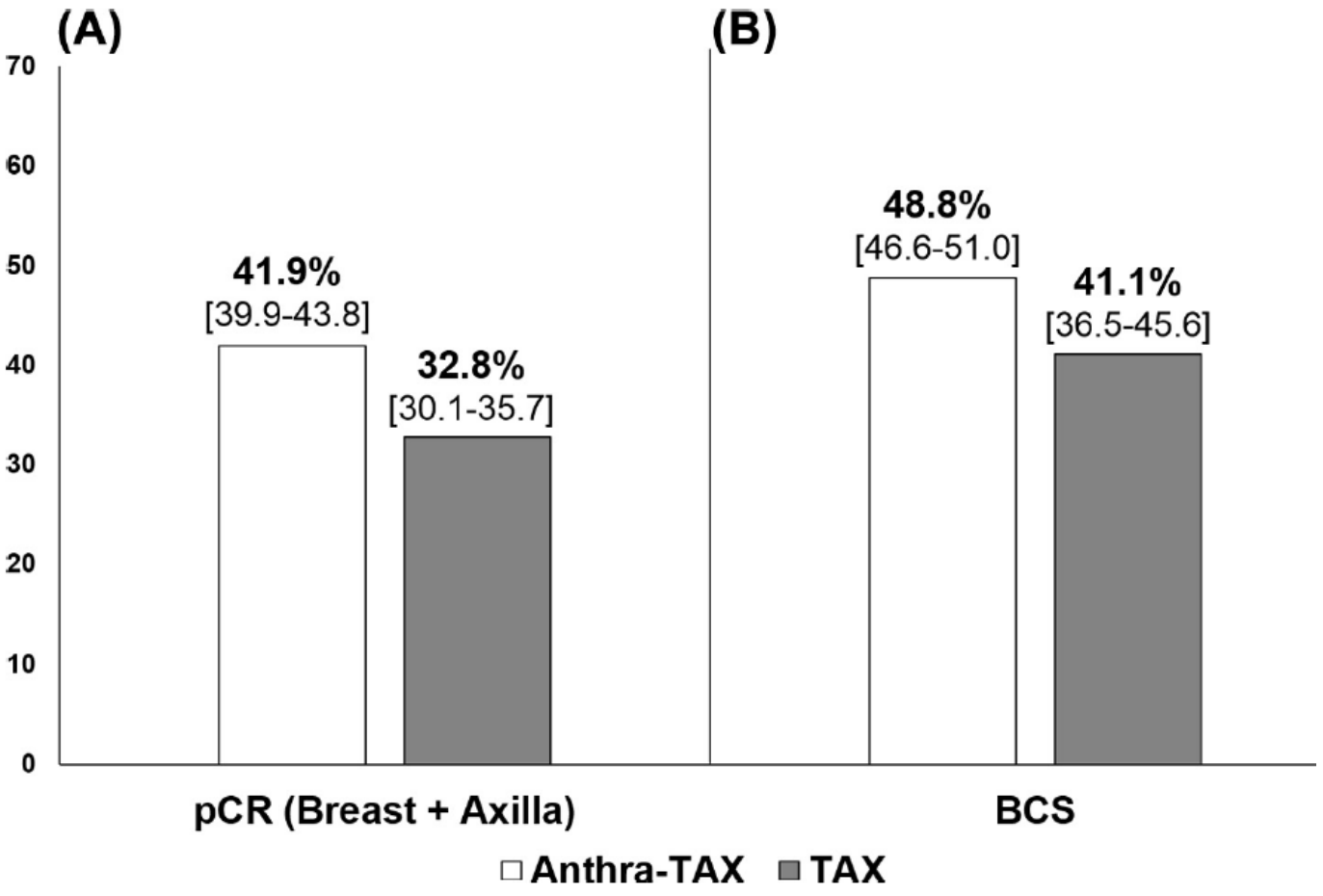


Breast & axillary pCR: single vs dual anti-HER2 blockade



Bria E. et al, Cancer Treatment Reviews 2014

Breast & axillary pCR and BCS: anthra-TAX vs TAX



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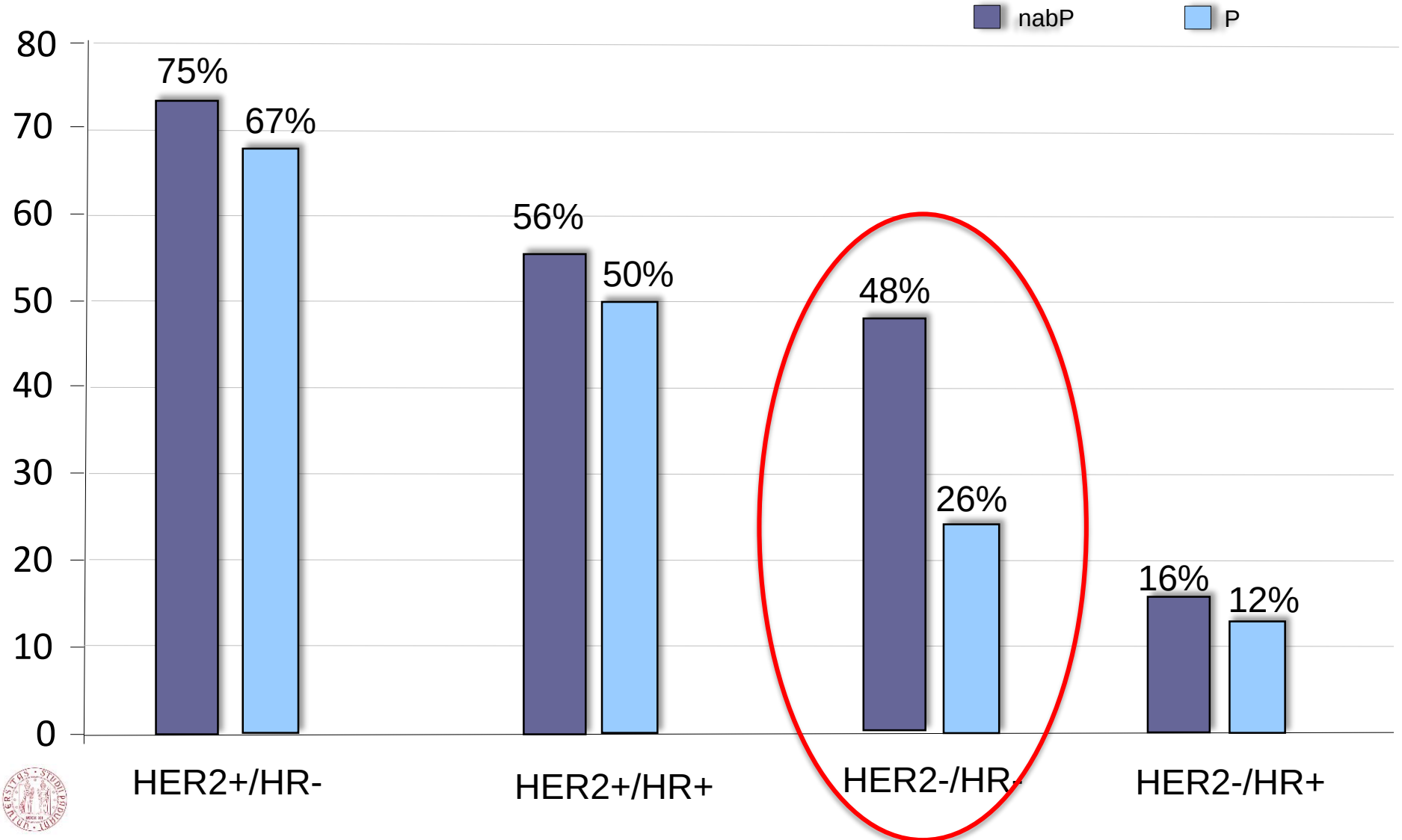
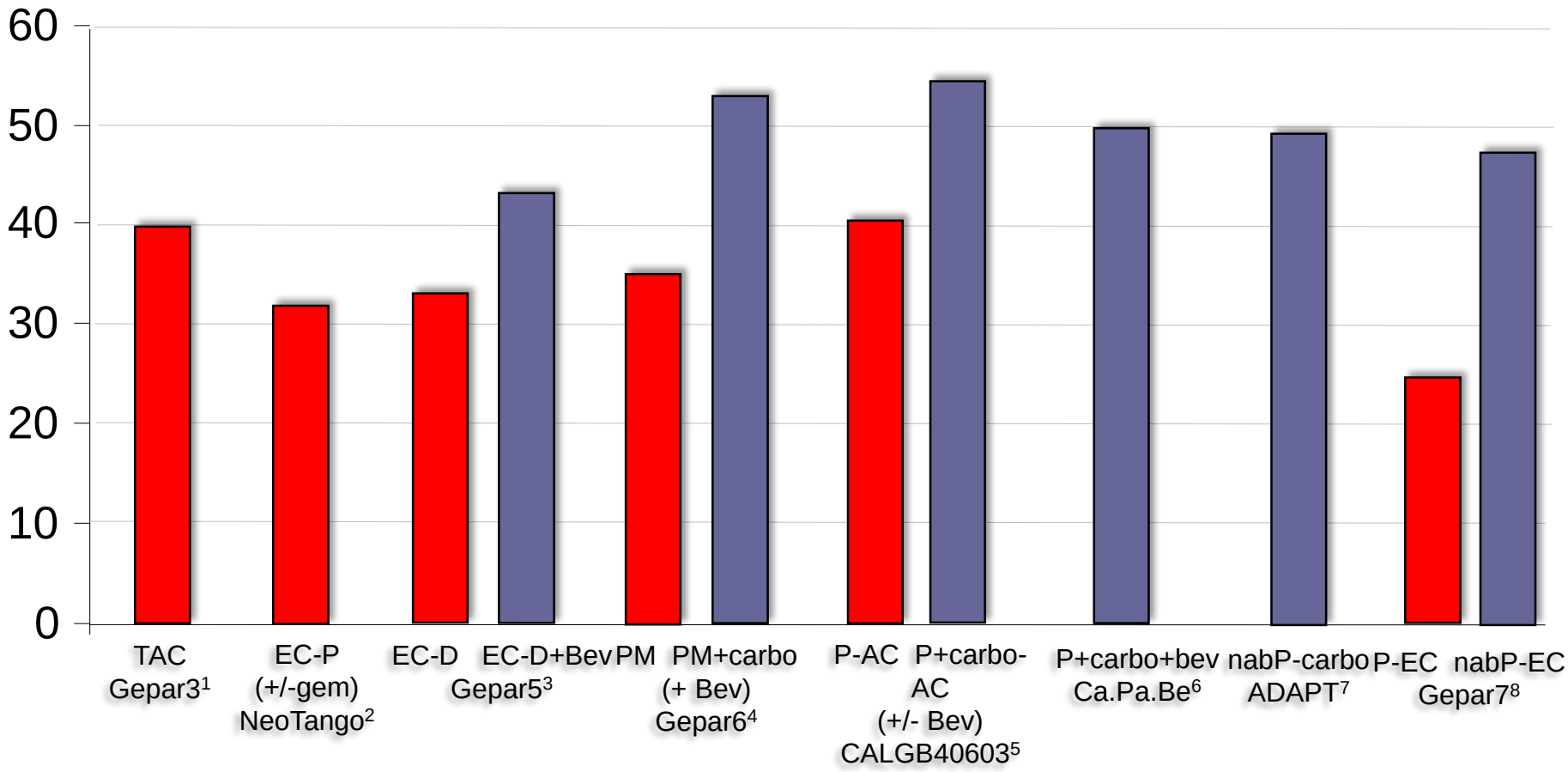


pCR rates (breast/axilla) in TNBC



1. Huober J, BCRT 2010; 2. Earl HM, Lancet Oncol 2014; 3. von Minckwitz, NEJM 2012; 4. von Minckwitz, Lancet Oncol 2014; 5. Sikov, J Clin Oncol 2015; 6. Guarneri V, Ann Surg Oncol 2015; 7. Gluz O, ASCO 2015; 8. Untch M, Lancet Oncology 2016

Gepar7 selected AEs

	Nab-Paclitaxel Grade				Paclitaxel Grade				p value G1-5	p value G3-5
	1-2	3	4	5	1-2	3	4	5		
Neutropenia	27	23	38	-	19	25	36	-	**0.0018**	**0.72**
Fatigue	76	5	-	-	72	4	-	-	**0.025**	**0.58**
Diarrhoea	48	3	-	<1	41	2	<1	-	**0.016**	**0.74**
Skin rash	32	1	-	-	23	1	-	-	**0.00028**	**0.55**
Hand-foot	26	2	-	-	17	1	-	-	**<0.0001**	**0.16**
Allergic reactions	16	<1	-	-	20	1	-	-	**0.076**	**0.51**
Anaphylaxis	-	<1	-	-	-	<1	<1	-	**-**	**0.62**
Peripheral neuropathy	75	10	1	-	63	3	-	-	**<0.0001**	**<0.0001**
Myalgia	31	<1	-	-	25	-	-	-	**0.025**	**0.50**

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Gepar7 schedule and dose

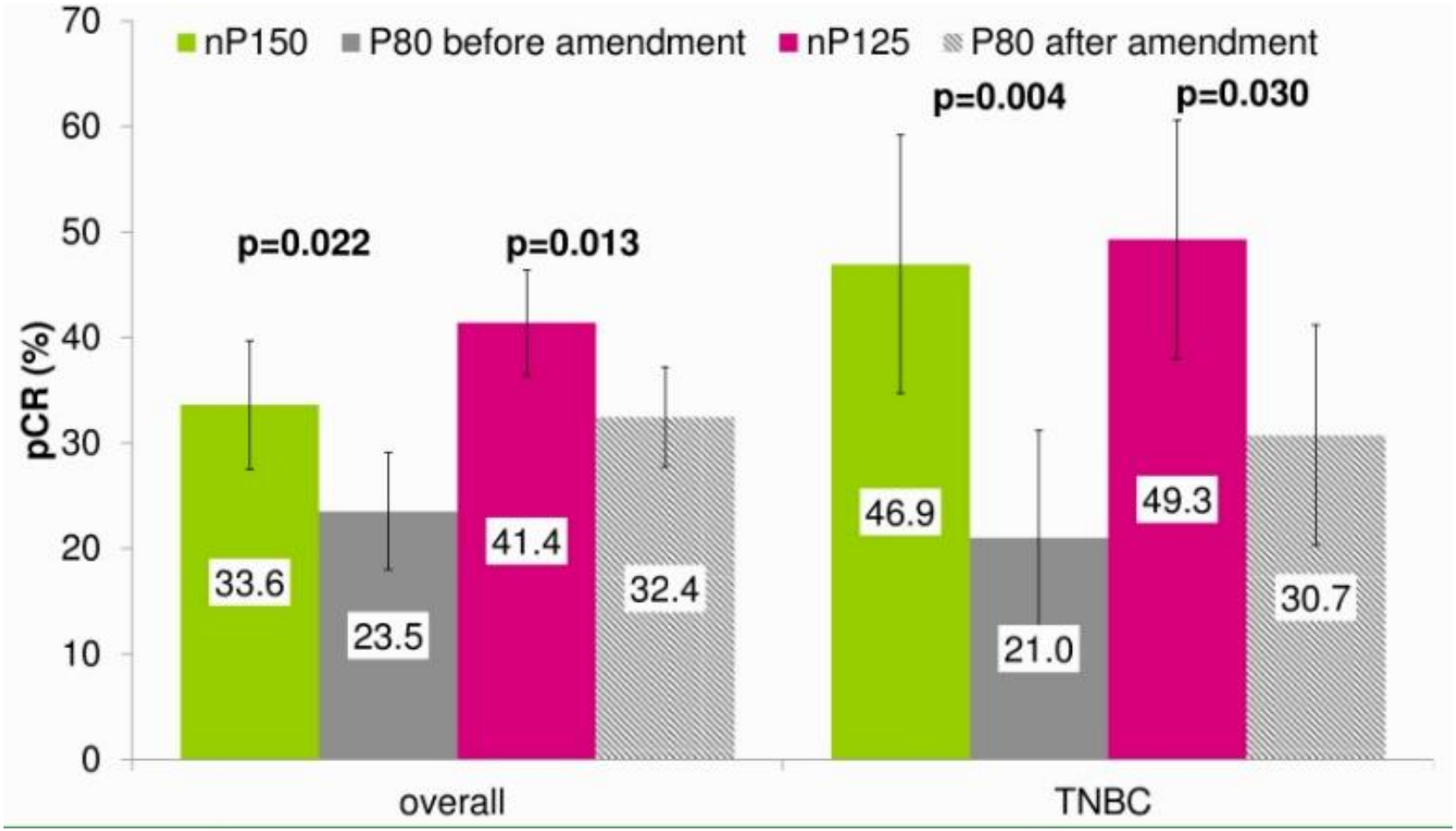
- NabP doses in studies in MBC:
  - 260 mg/sqm q 3 weeks (Gradishar J Clin Oncol 2005)
  - 260 mg/sqm q 3 wks, 150 mg/sqm wkly 3 out of 4, 100 mg/sqm wkly 3 out of 4 (Gradishar J Clin Oncol 2009, Rugo J Clin Oncol 2016)

- In the Gepar7, because of un unacceptable imbalance of discontinuations and sensory neuropathy for nab-paclitaxel, the IDMC recommended adjusting the nab-paclitaxel dose.

- The scientific committee decided to reduce the dose from 150 mg/sqm to 125 mg/sqm weekly.

- Etna Study is investigating nabP 125 mg/sqm wkly 3 out of 4

pCR rates according to nP dose overall and in TNBC



SABCS 2015

Hematologic and relevant non hematologic toxicities

Adverse Event (AE)	Grade	nP150 (N=220) N (valid %)	nP125 (N=385) N (valid %)	P80 (N=601) N (valid %)
Anemia	any	206 (93.6)	354 (91.9)	528 (88.1)
	3-4	5 (2.3)	8 (2.1)	4 (0.7)
Leukopenia	any	209 (95.0)	358 (93.0)	550 (91.8)
	3-4	110 (50.0)	170 (44.2)	271 (45.2)
Neutropenia	any	197 (90.0)	334 (86.8)	487 (81.3)
	3-4	140 (63.9)	228 (59.2)	371 (61.9)
Thrombocytopenia	any	51 (23.2)	93 (24.2)	145 (24.2)
	3-4	2 (0.9)	3 (0.8)	3 (0.5)
Febrile neutropenia	3-4	10 (4.5)	18 (4.7)	24 (4.0)
Any non-hematological AE	any	220 (100.0)	385(100.0)	600 (99.8)
	3-4	188 (85.5)	306 (79.5)	458 (76.2)
Peripheral sensory neuropathy	any	194 (88.2)	320 (83.1)	392 (65.2)
	3-4	32 (14.5)	31 (8.1)	16 (2.7)
Hand-foot-syndrome	any	54 (24.5)	117 (30.4)	107 (17.8)
	3-4	3 (1.4)	10 (2.6)	6 (1.0)

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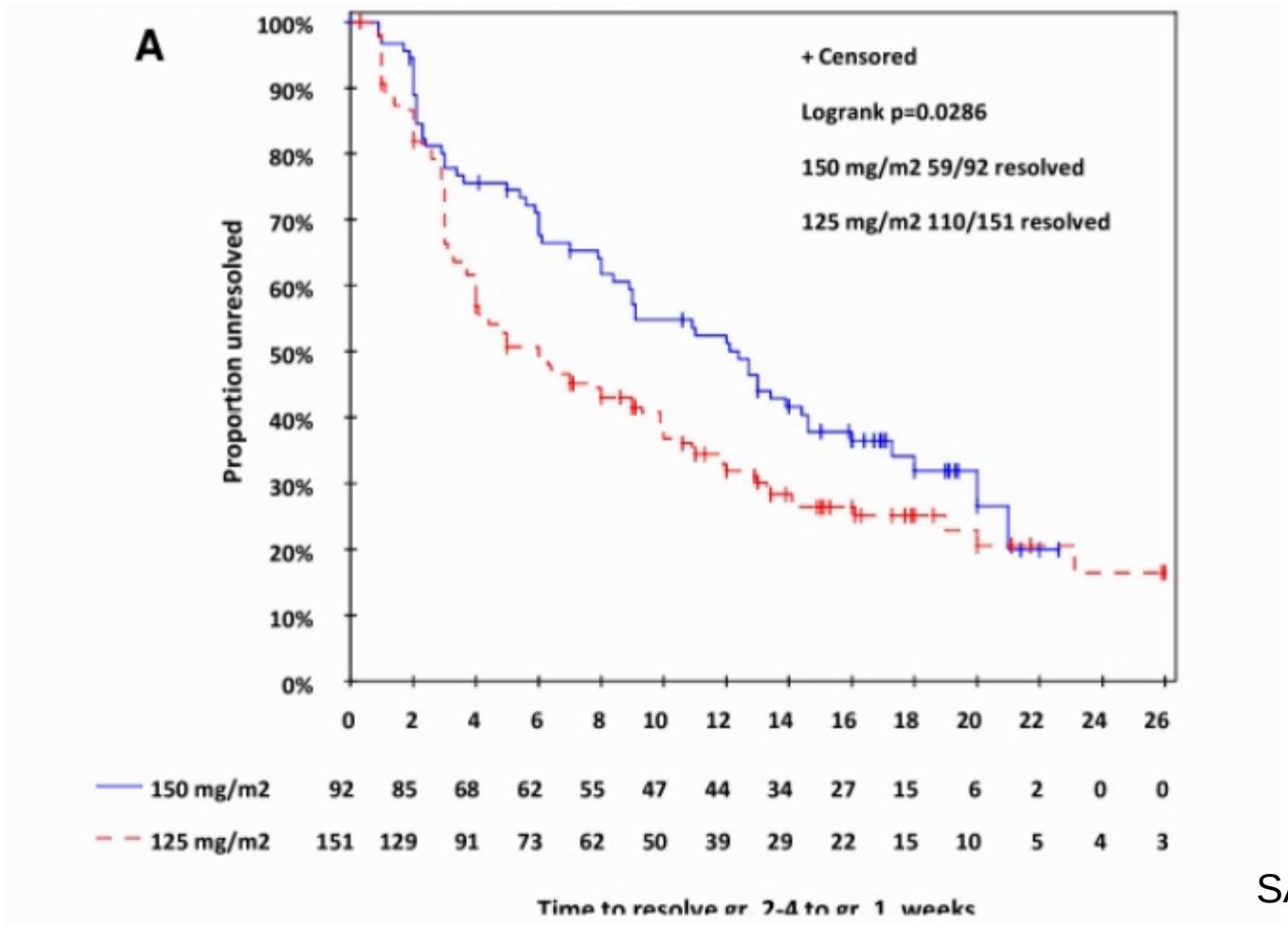
Time to resolve PSN of G2-4 to grade </=1



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