Lo Studio Geparsepto

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Oncologia Medica 1

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ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

nab-Paclitaxel Versus Solvent-Based Paclitaxel in Neoadjuvant Chemotherapy for Early Breast Cancer (GeparSepto—GBG 69): A Randomised, Phase III Trial

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FIRST UP DATE SABCS 2014

FINAL ANALYSIS SABCS 2015

PUBLICATION 8 FEBRUARY 2016

Lancet Oncol 2016; 17: 345–56

I Giudici

“Testimone”

“Persona informata sui fatti”

“Il PM”

Rationale

To determine if neoadjuvant treatment with weekly *nab*-P improves pCR rate compared with weekly Pac, both followed by EC

1. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Breast Cancer v1. 2016. 2. Earl M, et al. *Lancet Oncol*. 2014;15:212. 3. Gianni L, et al. *Lancet Oncol*. 2012;13:32. 4. Gradishar W, et al. *J Clin Oncol*. 2009;27:3619.

Untch M, et al. *Lancet Oncol*. 2016

From 30 July 2012 to 23 December 2013

16 Months duration of study

Principal Inclusion Criteria

T >2 cm (cT2 to cT4a–d) without additional risk factors,
or
T 1 cm and 2 cm (cT1c) with one of the following additional criteria:

- either clinical or pathological nodal involvement
- or HR -,
- or HER2+,
- or Ki67 > 20%

Tumors of 1 cm or smaller were not accepted

FFPE tissue centrally available for HER2, HR, KI67, SPARC testing

Gepar septo

Sample size Calculation

Assumptions

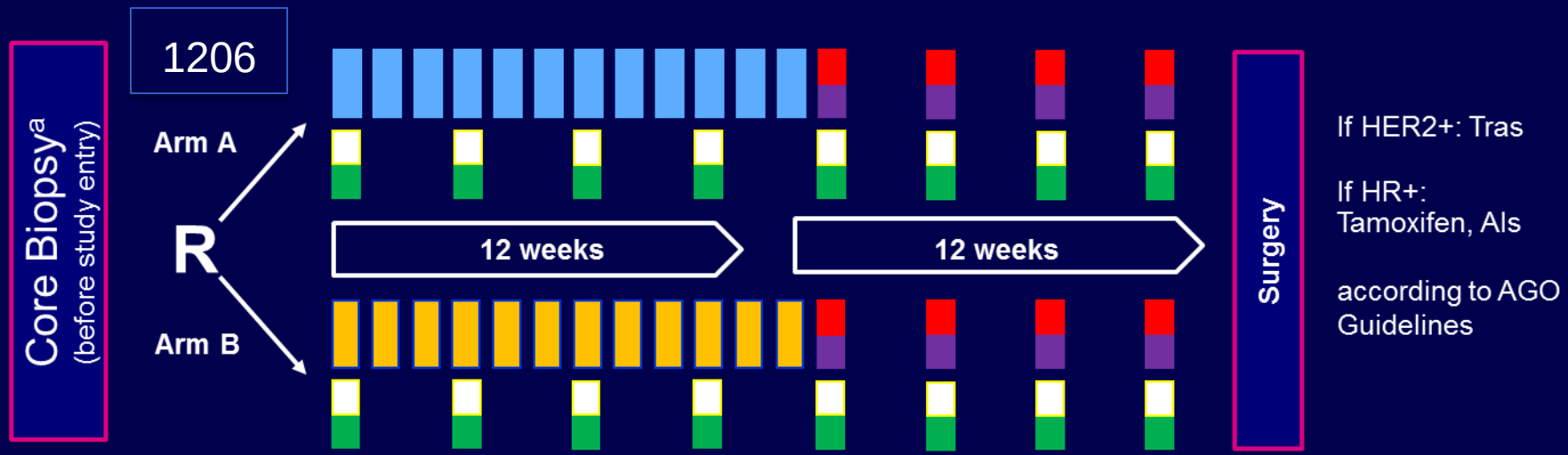
- **pCR with P-EC will be 33%**
- **pCR with nabP-EC will be 41%**
- **Odds ratio 1.41**
- **Two stage sequential testing**
  - **First exclude 10% non-inferiority margin**
  - **Second, if positive, superiority test with 2-sided α=0.05, ß=0.8**
- **1200 patients (400 with HER 2+ tumors)**

Endpoints

- Primary
  - pCR (ypT0 ypN0)
- Secondary
  - Other pCR definitions: ypT0/is ypN0; ypT0/is ypN0/+; ypN0
  - Response by clinical and imaging assessments
  - Proportion of patients with breast conserving surgery and axillary surgery
  - Efficacy by HR, HER2, SPARC, and Ki-67 status
  - Tolerability
  - Treatment adherence
  - Time of resolution of grade 3/4 neuropathy to grade ≤ 1

Untch M, et al. *Lancet Oncol*. 2016

Initial Study Design (Before March 2012)



Core biopsy

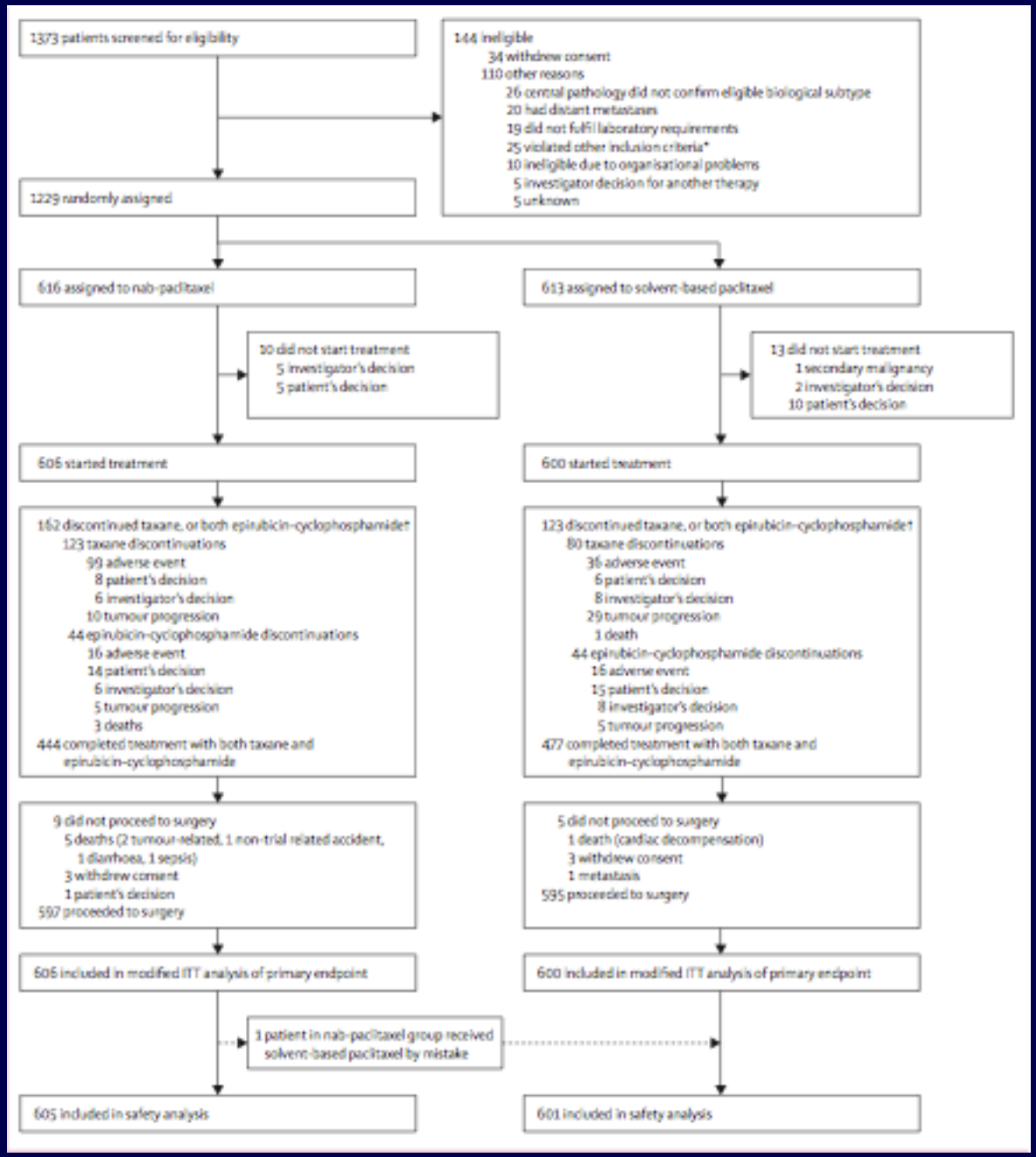
Pac 80 mg/m² weekly

nab-P 150 mg/m² weekly

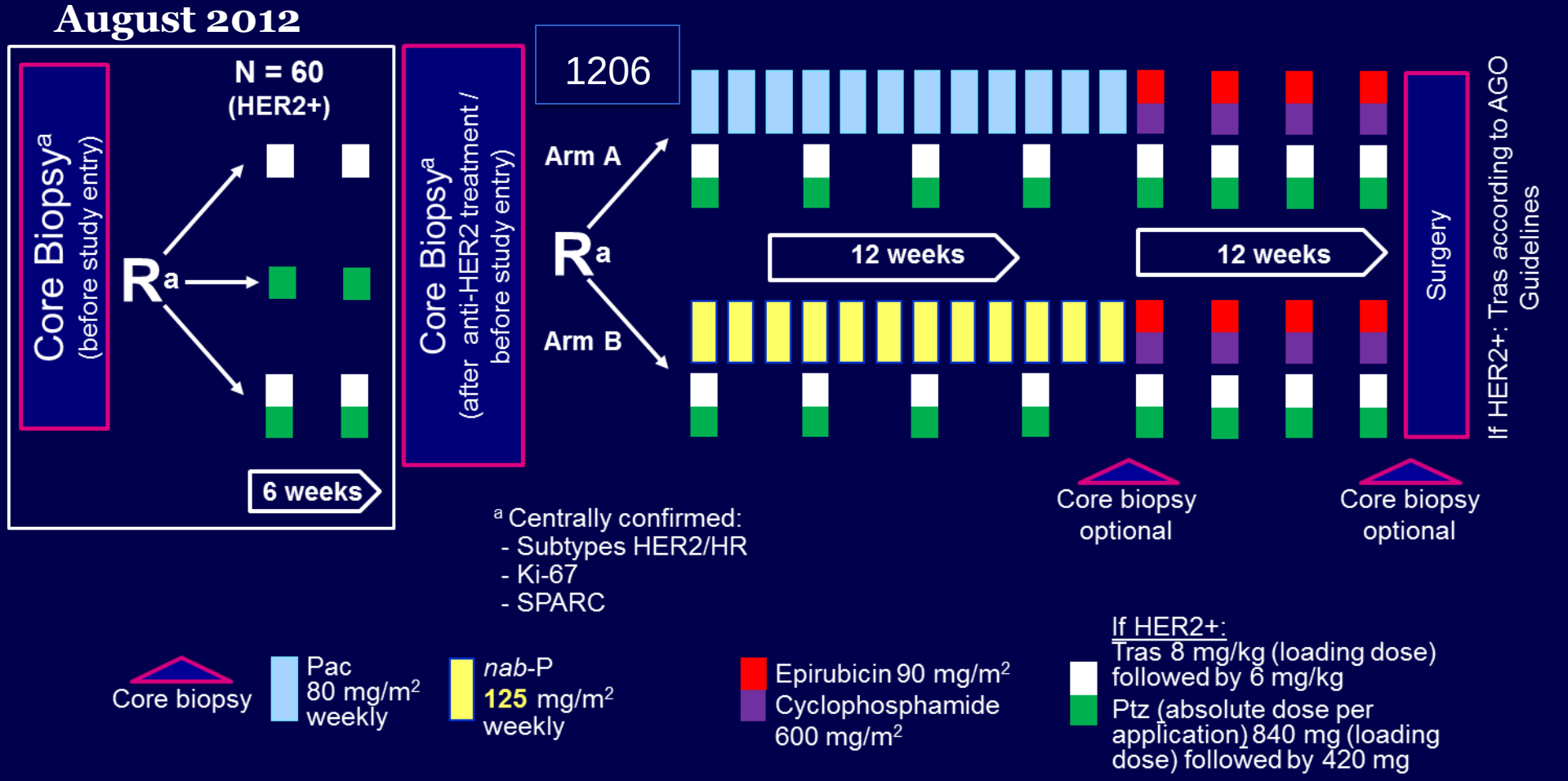
Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²

If HER2+:
Tras 8 mg/kg (loading dose) followed by 6 mg/kg
Ptz (absolute dose per application) 840 mg (loading dose) followed by 420 mg

Untch M, et al. *Lancet Oncol*. 2016.


1373 patients screened for eligibility
144 ineligible
34 withdrew consent
110 other reasons
26 central pathology did not confirm eligible biological subtype
20 had distant metastases
19 did not fulfil laboratory requirements
25 violated other inclusion criteria*
10 ineligible due to organisational problems
5 investigator decision for another therapy
5 unknown
1229 randomly assigned
616 assigned to nab-paclitaxel
613 assigned to solvent-based paclitaxel
10 did not start treatment
5 investigator's decision
5 patient's decision
13 did not start treatment
1 secondary malignancy
2 investigator's decision
10 patient's decision
606 started treatment
600 started treatment
162 discontinued taxane, or both epirubicin-cyclophosphamide†
123 taxane discontinuations
99 adverse event
8 patient's decision
6 investigator's decision
10 tumour progression
44 epirubicin-cyclophosphamide discontinuations
16 adverse event
14 patient's decision
6 investigator's decision
5 tumour progression
3 deaths
444 completed treatment with both taxane and epirubicin-cyclophosphamide
123 discontinued taxane, or both epirubicin-cyclophosphamide†
80 taxane discontinuations
36 adverse event
6 patient's decision
8 investigator's decision
29 tumour progression
1 death
44 epirubicin-cyclophosphamide discontinuations
16 adverse event
15 patient's decision
8 investigator's decision
5 tumour progression
477 completed treatment with both taxane and epirubicin-cyclophosphamide
9 did not proceed to surgery
5 deaths (2 tumour-related, 1 non-trial related accident, 1 diarrhoea, 1 sepsis)
3 withdrew consent
1 patient's decision
597 proceeded to surgery
5 did not proceed to surgery
1 death (cardiac decompensation)
3 withdrew consent
1 metastasis
595 proceeded to surgery
606 included in modified ITT analysis of primary endpoint
600 included in modified ITT analysis of primary endpoint
1 patient in nab-paclitaxel group received solvent-based paclitaxel by mistake
605 included in safety analysis
601 included in safety analysis

Final Study Design (After 464 Patients), Preplanner safety analysis



[a] Randomizations carried out simultaneously.

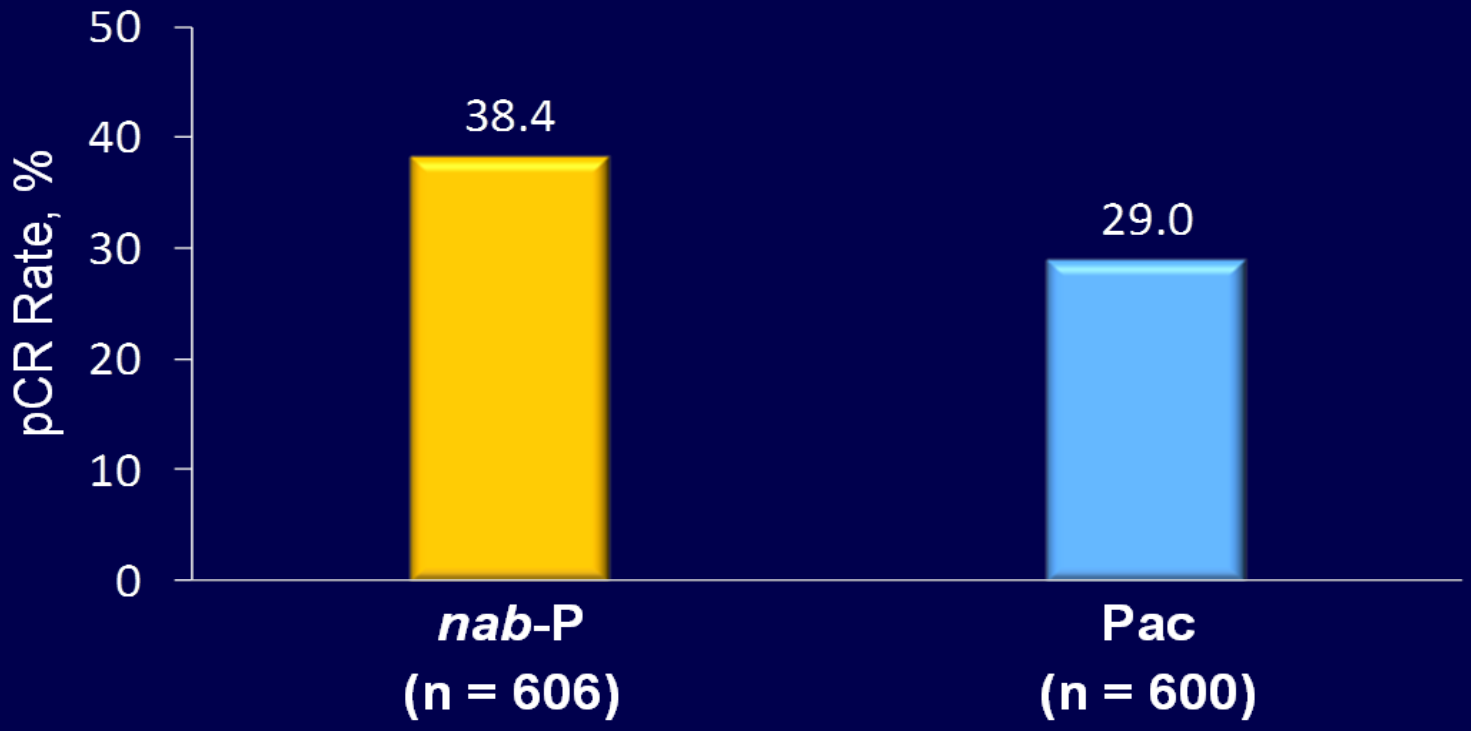
Key Baseline Characteristics (ITT)

	***nab*-P n = 606**	**Pac n = 600**
Age, median (IQR), years	49 (43 - 57)	48 (41 - 56)
Premenopausal, n (%)	336 (55)	368 (61)
Tumor stage by palpation Size, median (IQR), mm cT3, n (%) cT4a-c, n (%) cT4d, n (%)	 30 (20 - 40) 41 (8) 20 (4) 20 (4)	 30 (20 - 40) 50 (10) 14 (3) 22 (4)
Nodal stage by palpation, n (%) cN1 cN2 cN3	 190 (33) 9 (2) 2 (< 1)	 176 (31) 12 (2) 6 (1)
HER2 central pathology Positive Negative	 199 (33) 407 (67)	 197 (33) 403 (67)
Tumor subtype, n (%) HER2−, HR+ HER2−, HR− HER2+, HR+ HER2+, HR−	 268 (44) 139 (23) 140 (23) 59 (10)	 266 (44) 137 (23) 149 (25) 48 (8)
Ki-67 (central) > 20%, n (%)	418 (69)	415 (69)
SPARC+ (IRS 6 - 12), n (%)	97 (16)	94 (16)

Untch M, et al. *Lancet Oncol*. 2016. Epub ahead of print.

RESULTS

Primary End Point
pCR (ypT0 ypN0)

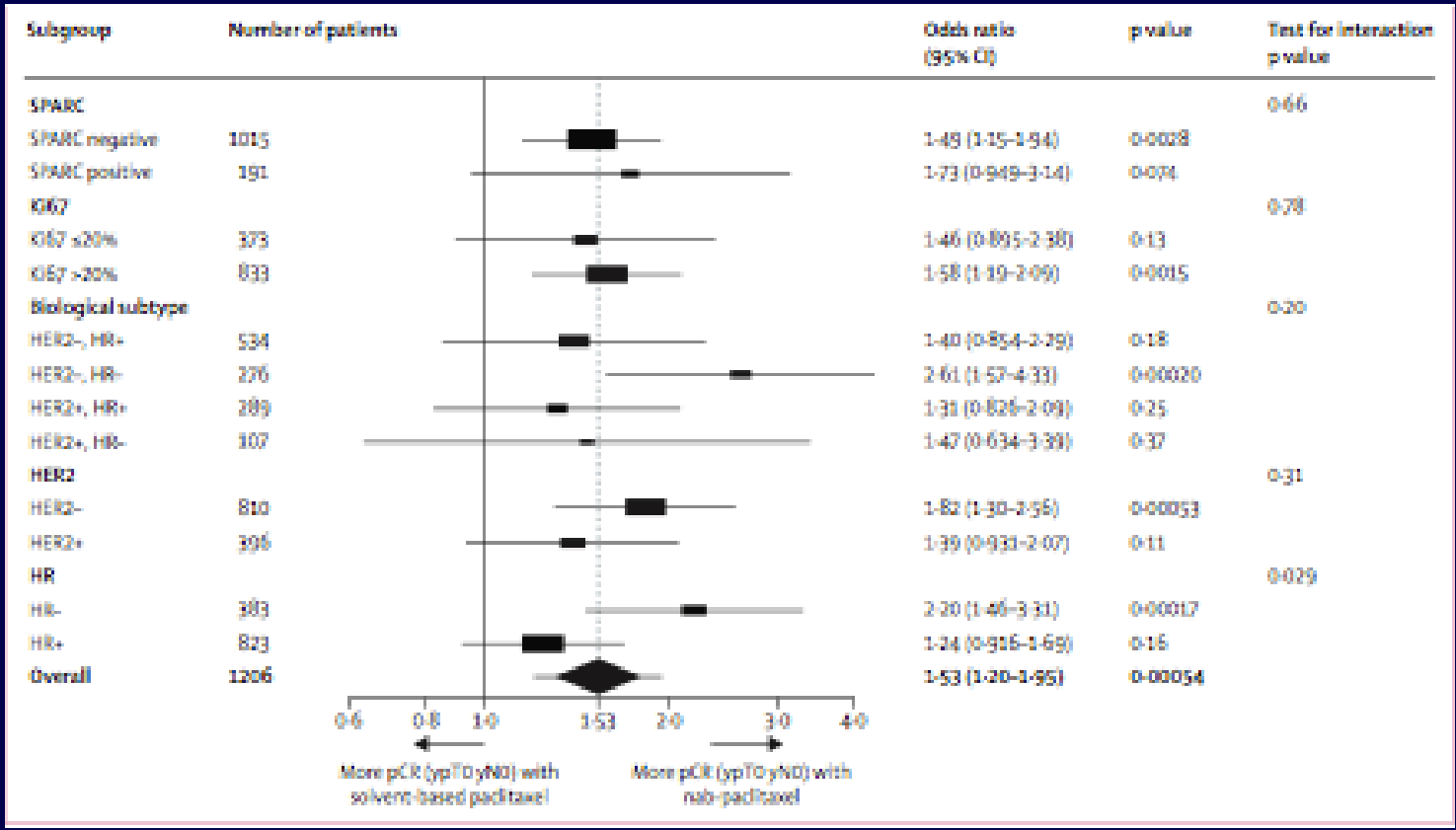


- *nab*-P remained an independent predictor for pCR after adjustment for baseline and minimization factors (OR 1.66; 95% CI, 1.25 - 2.19; *P* = 0.00043)

[a] Unadjusted.

Untch M, et al. *Lancet Oncol*. 2016.

pCR in the Subgroups

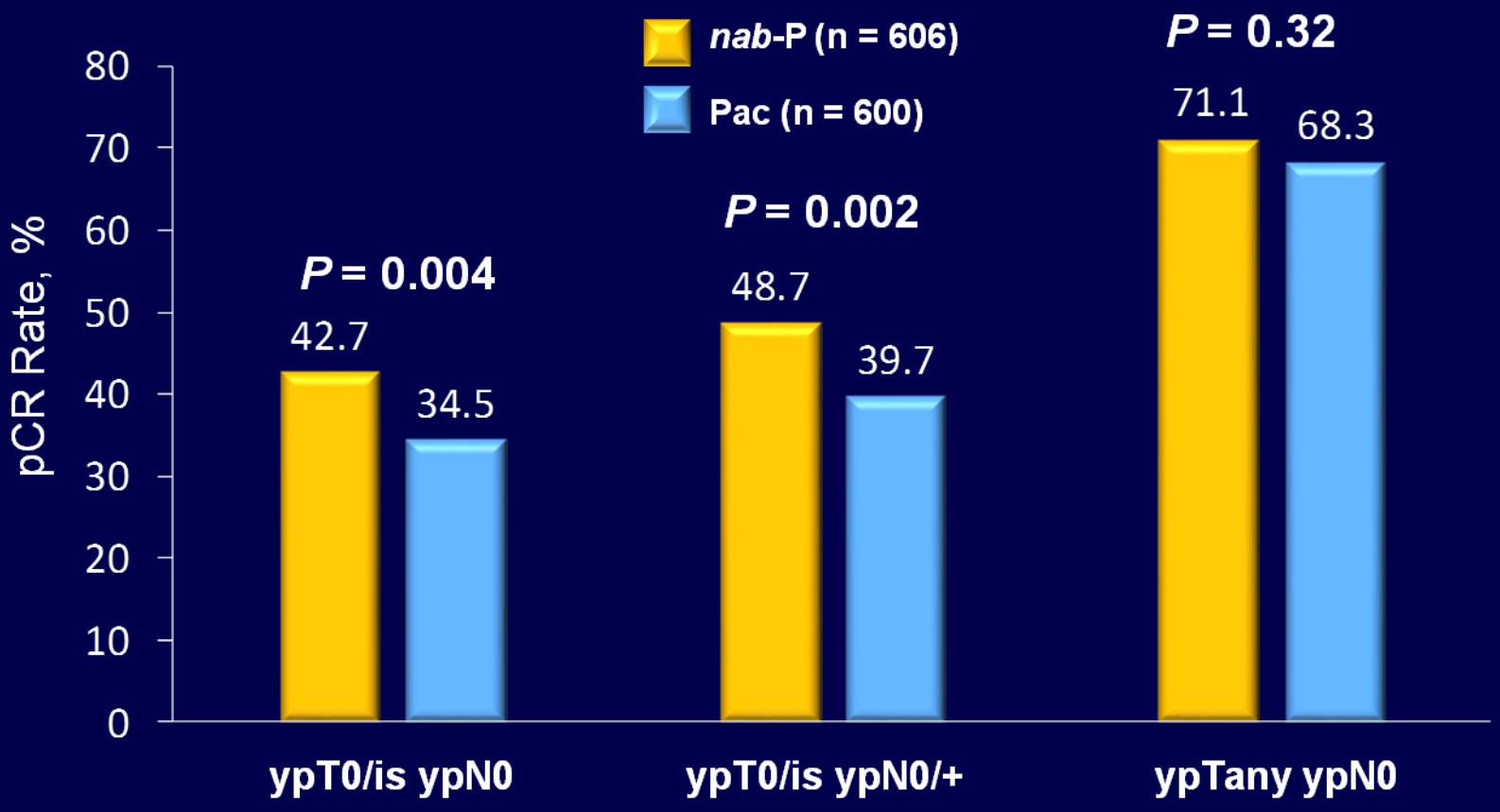


Untch M, et al. *Lancet Oncol*. 2016

pCR in the Subgroups

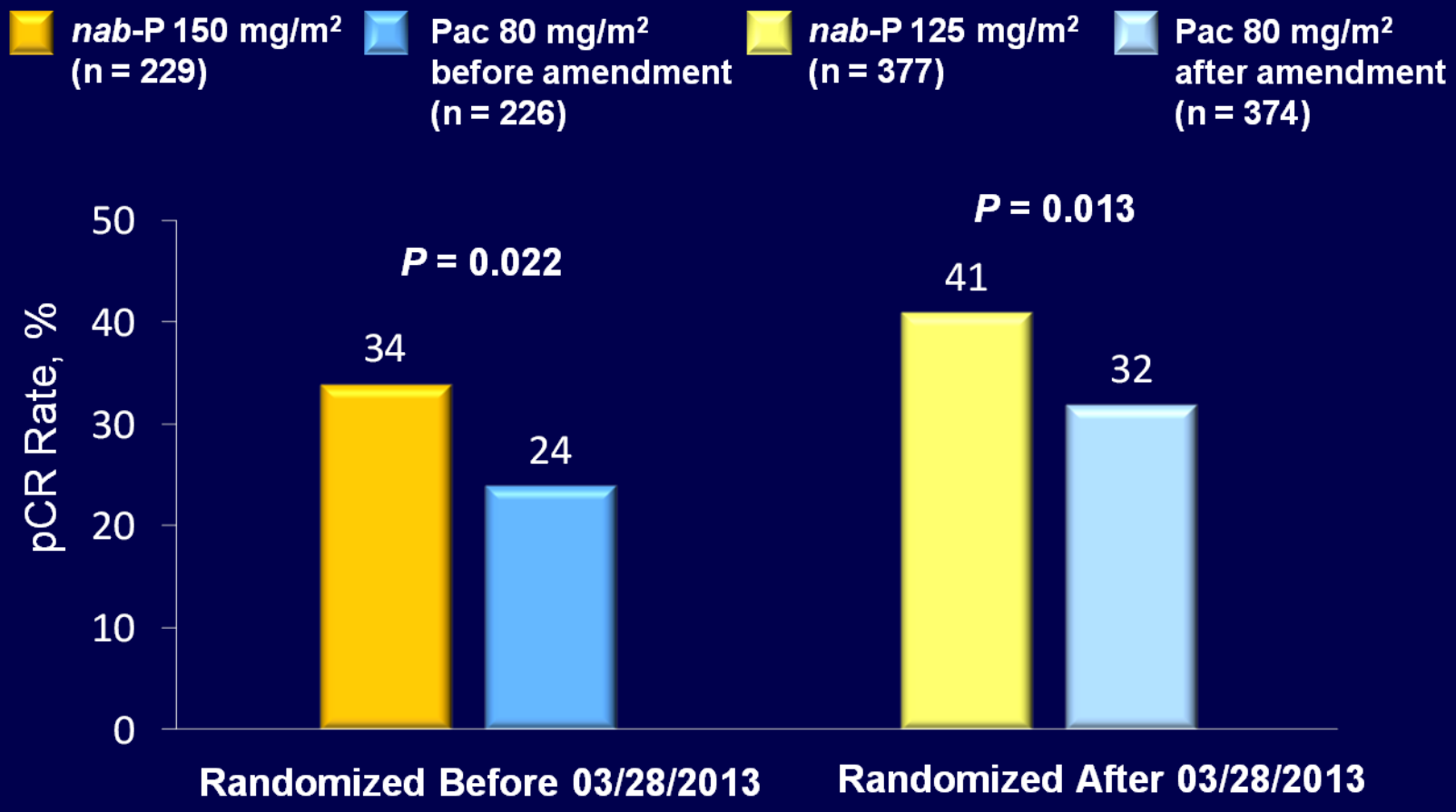
	pCR	Nab-paclitaxel (N=606)	Sb-Paclitaxel (N=600)	Overall (N=1206)	p-value
SPARC negative	no	317 (62·3)	360 (71·1)	677 (66·7)	0·0034
	yes	192 (37·7, 33·5 - 41·9)	146 (28·9, 24·9 - 32·8)	338 (33·3, 30·4 - 36·2)	
SPARC positive	no	56 (57·7)	66 (70·2)	122 (63·9)	0·10
	yes	41 (42·3, 32·4 - 52·1)	28 (29·8, 20·5 - 39·0)	69 (36·1, 29·3 - 42·9)	
Ki67≤20%	no	139 (73·9)	149 (80·5)	288 (77·2)	0·16
	yes	49 (26·1, 19·8 - 32·3)	36 (19·5, 13·8 - 25·2)	85 (22·8, 18·5 - 27·0)	
Ki67>20%	no	234 (56·0)	277 (66·7)	511 (61·3)	0·0018
	yes	184 (44·0, 39·3 - 48·8)	138 (33·3, 28·7 - 37·8)	322 (38·7, 35·3 - 42·0)	
HER2-, HR+	no	225 (84·0)	234 (88·0)	459 (86·0)	0·23
	yes	43 (16·0, 11·7 - 20·4)	32 (12·0, 8·1 - 15·9)	75 (14·0, 11·1 - 17·0)	
HER2-, HR-	no	72 (51·8)	101 (73·7)	173 (62·7)	0·00027
	yes	67 (48·2, 39·9 - 56·5)	36 (26·3, 18·9 - 33·6)	103 (37·3, 31·6 - 43·0)	
HER2+, HR+	no	61 (43·6)	75 (50·3)	136 (47·1)	0·30
	yes	79 (56·4, 48·2 - 64·6)	74 (49·7, 41·6 - 57·7)	153 (52·9, 47·2 - 58·7)	
HER2+, HR-	no	15 (25·4)	16 (33·3)	31 (29·0)	0·49
	yes	44 (74·6, 63·5 - 85·7)	32 (66·7, 53·3 - 80·0)	76 (71·0, 62·4 - 79·6)	
HER2-	no	297 (73·0)	335 (83·1)	632 (78·0)	0·00066
	yes	110 (27·0, 22·7 - 31·3)	68 (16·9, 13·2 - 20·5)	178 (22·0, 19·1 - 24·8)	
HER2+	no	76 (38·2)	91 (46·2)	167 (42·2)	0·13
	yes	123 (61·8, 55·1 - 68·6)	106 (53·8, 46·8 - 60·8)	229 (57·8, 53·0 - 62·7)	
HR-	no	87 (43·9)	117 (63·2)	204 (53·3)	0·00023
	yes	111 (56·1, 49·1 - 63·0)	68 (36·8, 29·8 - 43·7)	179 (46·7, 41·7 - 51·7)	
HR+	no	286 (70·1)	309 (74·5)	595 (72·3)	0·19
	yes	122 (29·9, 25·5 - 34·3)	106 (25·5, 21·3 - 29·7)	228 (27·7, 24·6 - 30·8)	

pCR by Other Definitions



Untch M, et al. *Lancet Oncol*. 2016.

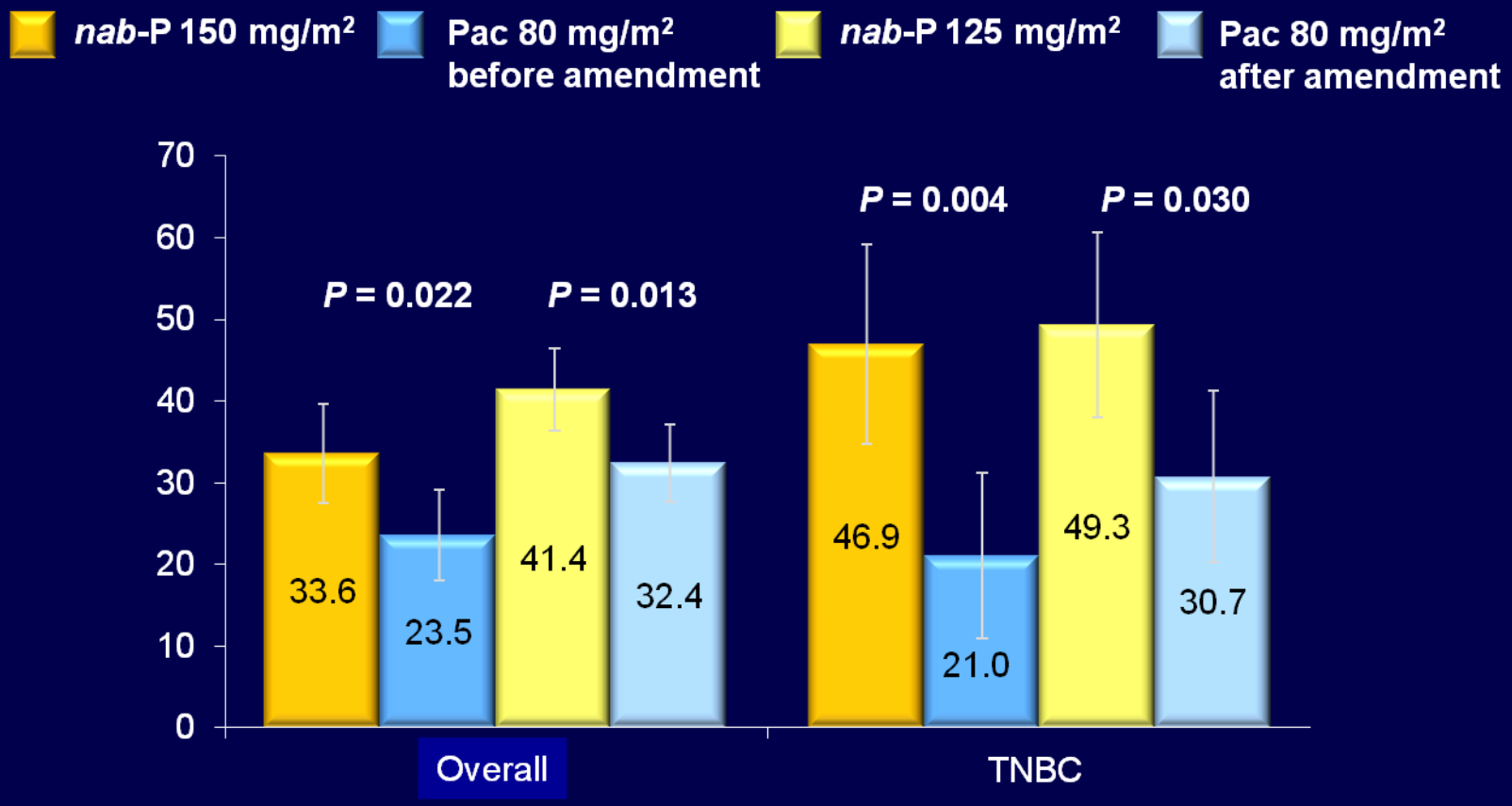
pCR (ypT0 ypN0) by nab-*P Dosing*



Untch M, et al. *Lancet Oncol*. 2016.

Comparison to Nab-Pac 150 vs 125

Difference in terms of pCR Rates



- Differences in pCR rates between *nab*-P 125 mg/m² and Pac 80 mg/m² were greatest in the overall cohort and the TNBC subgroup

Other Secondary Endpoints

Endpoints	*nab*-P	Pac	*P* Value
Breast conserving surgery, %	69.5	69.6	1.0
Axillary conserving surgery, %	43.8	44.7	0.80
Clinical response before surgery, % ORR CR PR PD	 81.7 20.6 61.1 4.1	 79.2 18.2 61.0 5.3	0.3[a]

[a] *P* value for response (CR or PR) vs no response.

Untch M, et al. *Lancet Oncol*. 2016.

Select Grade ≥ 3 AEs

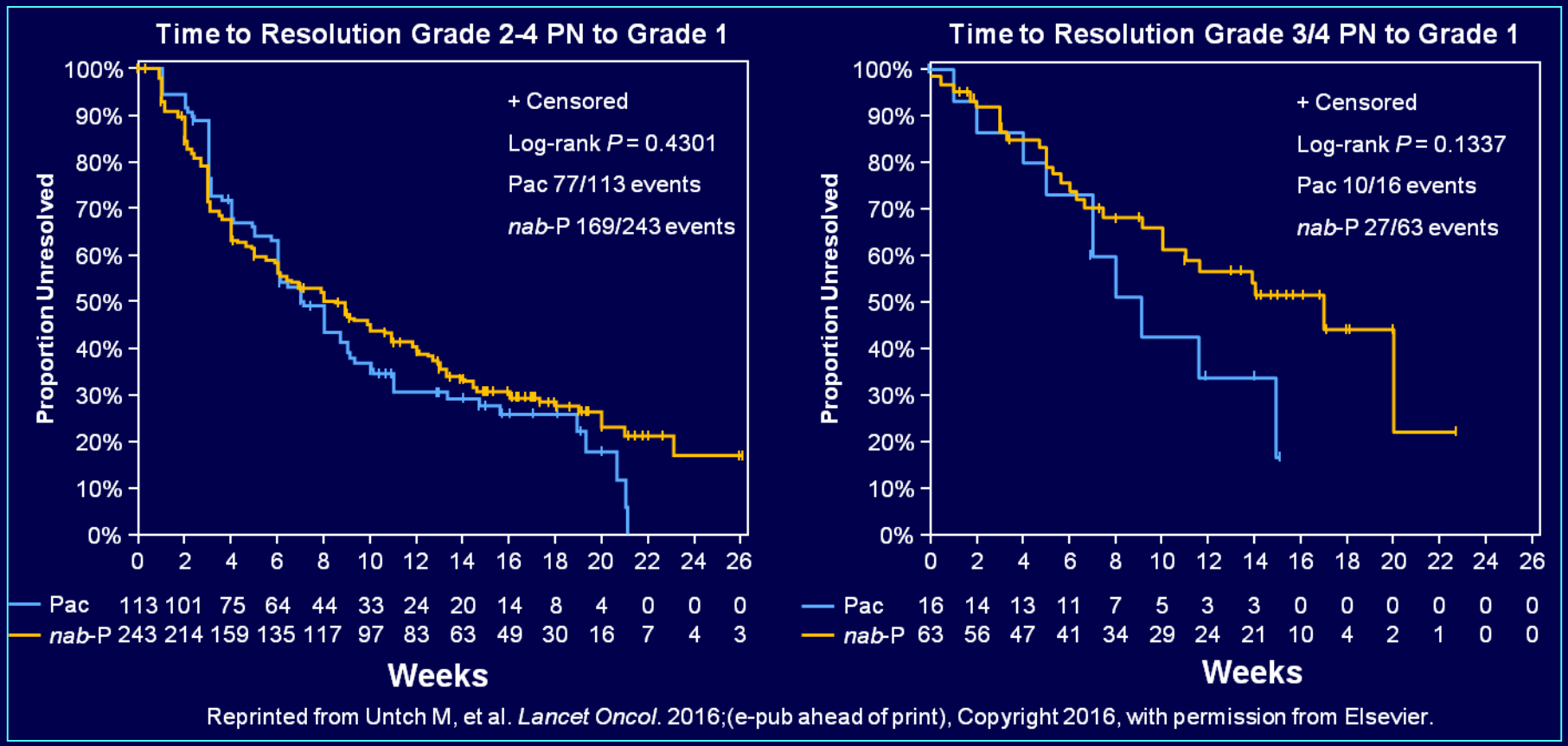
AE, n (%)[a]	*nab*-P n = 605		Pac n = 601		*P* Value[b]
	Grade 3	Grade 4	Grade 3	Grade 4	
Neutropenia	139 (23)	229 (38)	153 (26)	218 (36)	0.72
Leukopenia	224 (37)	56 (9)	219 (37)	52 (9)	0.73
Lymphopenia	46 (12)	20 (5)	41 (11)	14 (4)	0.23
Peripheral neuropathy	59 (10)[c]	4 (1)[c]	16 (3)	0	< 0.0001
Infection	32 (5)	4 (1)	34 (6)	2 (< 1)	1.0
Fatigue	30 (5)	–	25 (4)	–	0.58
Febrile neutropenia	20 (3)	8 (1)	19 (3)	5 (<1)	0.67

Grade 5 AEs occurred in 3 patients in the *nab*-P group (1 diarrhea,1 infection, and 1 with other nonhematologic AE) and 1 patient in the Pac group (congestive heart failure)

[b] *P* value reported for grade 3-5.
[c] Grade 3/4 PN was 8% in patients treated with 125 mg/m^2 *nab*-P vs 15% with 150 mg/m^2

Untch M, et al. *Lancet Oncol*. 2016.

Time to Neuropaty Resolution



- Median time to resolution of PN
  - Grade 2-4 to grade 1, 8.4 vs 7.1 weeks for *nab*-P vs Pac (*P* = 0.43)
  - Grade 3/4 to grade 1, 17.0 vs 9.1 weeks for *nab*-P vs Pac (*P* = 0.13)

Untch M, et al. *Lancet Oncol*. 2016

Taxane Dose Modifications

Parameter, n (%)	*nab*-P n = 605	Pac n = 601	*P* Value
Completed taxane and EC treatment	444 (73)	477 (79)	0.012
Reason for taxane discontinuation			
AEs	99 (16)	36 (6)	NR
Local progression	10 (2)	29 (5)	NR
Patient's or investigator's decision	14 (2)	14 (2)	NR
Death	0	1 (< 1)	
Dose reduction	182 (30)	75 (12)	< 0.0001
Reason for taxane dose reduction			
Hematologic AEs	34 (6)	15 (2)	0.008
Nonhematologic AEs	131 (22)	53 (9)	< 0.001

Untch M, et al. *Lancet Oncol*. 2016

Comparison to Nab-Pac 150 vs 125

Nonhematologic Toxicities

AE, n (valid %)	Grade	*nab*-P 150 mg/m^2 n = 220	*nab*-P 125 mg/m^2 n = 385	Pac 80 mg/m^2 n = 601[a]
Any nonhematologic AE	Any 3/4	220 (100.0) 188 (85.5)	385 (100.0) 306 (79.5)	600 (99.8) 458 (76.2)
Peripheral sensory neuropathy	Any 3/4	194 (88.2) 32 (14.5)	320 (83.1) 32 (8.1)	392 (65.2) 16 (2.7)
Hand-foot syndrome	Any 3/4	54 (24.5) 3 (1.4)	117 (30.4) 10 (2.6)	107 (17.8) 6 (1.0)

[a]For safety analysis, patients were grouped according to their dose on day 1.

von Minckwitz G, et al. Poster at SABCS 2015 [Abstract P1-14-11].

Author Conclusions (and our Conclusions)

- GeparSepto is the first trial in primary breast cancer directly comparing the 2 taxanes weekly and one of the largest studies replacing an established agent
- Demonstrated a significantly higher pCR rate using weekly *nab*-P vs Pac for patients with primary breast cancer
- *nab*-P 125 mg/m^2 should therefore be considered instead of *nab*-P 150 mg/m^2
- Patients with TNBC had particular benefit from *nab*-P, resulting in pCR rates 20% higher than with Pac
- Results also in HER2 +

Untch M, et al. *Lancet Oncol*. 2016.

Considerations

All patients were randomly assigned according to central pathology assessment and were considered high risk.

About half of the patients underwent sentinel node biopsy before start of chemotherapy and 37% of patients who underwent sentinel node biopsy had involved lymph nodes.

After about a third of the population was enrolled, the dose of nab-paclitaxel was reduced to 125 mg/mq, resulting in less peripheral sensory neuropathy but without affecting the frequency of pathological complete response. The overall results for pathological complete response in this trial can te be considered to be reflective of the pathological response with the lower nab-paclitaxel dose.

70 patients with HER2-positive BC were enrolled into the window of opportunity part of the study. Exclusion of these patients did not affect the results.

Patient-reported outcomes were not collected in this study so far, but will be collected after a recent protocol amendment for patient-reported outcomes.

..... it remains to be shown if this increase in pathological complete response can be translated into improved disease-free survival

“IL PM”