Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline/cyclophosphamide for patients with early breast cancer – GBG69

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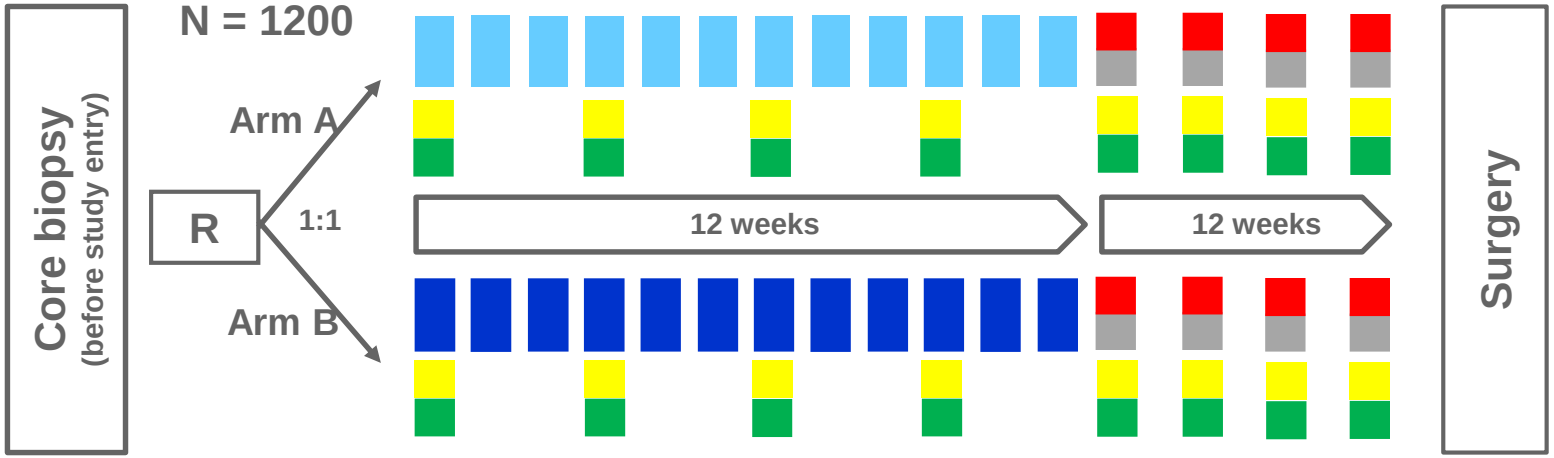
- A joint study of the AGO Breast and the German Breast Group -

Study Design



STRATIFICATION FACTORS:

- HER2+/HR- vs. HER2+/HR+ vs. HER2-/HR- vs. HER2-/HR+
- Ki67 (≤20% vs. >20%)
- SPARC (positive vs. negative)

Paclitaxel
80 mg/m² weekly

Nab-paclitaxel 150 mg/m² weekly
The dose was reduced to 125 mg/m² after recruitment of 464 patients

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²

HER2 positive patients:
Trastuzumab 8 mg/kg (loading dose) → 6 mg/kg
Pertuzumab 840 mg (loading dose) → 420 mg

Untch et al. Lancet Oncol 2016

Main Eligibility Criteria

- **Unilateral or bilateral primary breast cancer**
- **Stages**
  - cT2 - cT4a-d
  - cT1c and additional high risk
    - cN+ *or*
    - pN_{SLN+} *or*
    - ER-neg and PR-neg *or*
    - Ki67 > 20% *or*
    - HER2-positive
- **Central testing for HER2, HR, Ki67, and SPARC[1]**

[1]Lindner J et al. Ann Oncol 2015

Study Endpoints

Primary endpoint:

- pCR rate (ypT0 ypN0)

Secondary efficacy endpoints (overall and according to stratified subpopulations):

- disease-free survival (DFS)
- distant disease-free survival (DDFS)
- overall survival (OS)

Patient and tumor characteristics (baseline)

	Paclitaxel N=600 (%)	Nab-paclitaxel N=606 (%)	Overall N=1204 (%)
Age (median, yrs)	48 (22 - 76)	49 (21 - 75)	49 (21 - 76)
Palpable tumor size (median, mm)	30 (5 - 150)	30 (4 -150)	30 (4 - 150)
cT3 / 4 (palpation)	86 (16.5)	81 (15.8)	167 (16.2)
cN+	265 (45.1)	275 (46.3)	540 (45.7)
Ki67 >20%	415 (69.2)	418 (69.0)	833 (69.1)
SPARC positive (IRS 6-12)	94 (15.7)	97 (16.0)	191 (15.9)
Grade 3	338 (56.3)	319 (52.6)	657 (54.5)
Breast cancer subtype			
TNBC	137 (22.8)	139 (22.9)	276 (22.9)
HER2-negative / HR-positive	266 (44.3)	268 (44.2)	534 (44.3)
HER2-positive / HR-positive	149 (24.8)	140 (23.1)	289 (24.0)
HER2-positive / HR-negative	48 (8.0)	59 (9.7)	107 (8.9)

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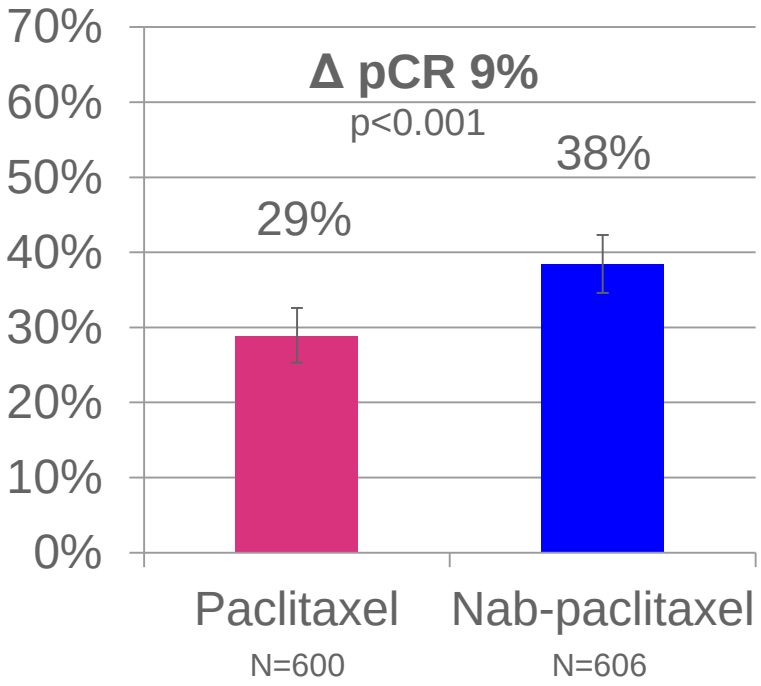
Primary Endpoint: pCR (ypT0 ypN0)



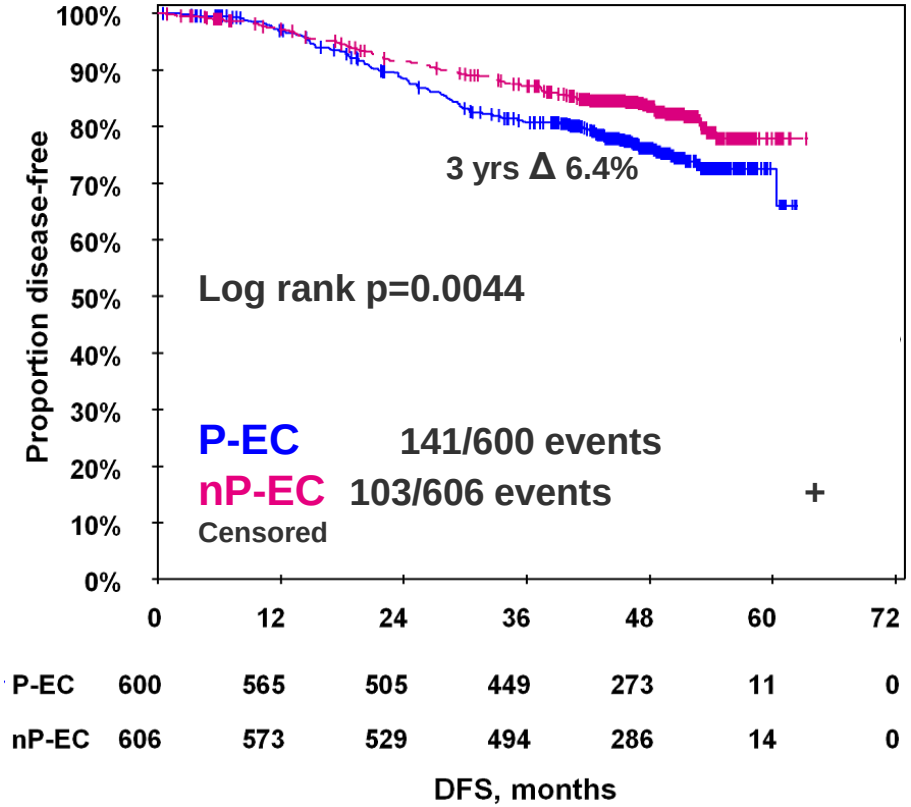
- The substitution of solvent-based paclitaxel (P) with nab-paclitaxel (nP) as neoadjuvant chemotherapy significantly increased the pathological complete response rate (pCR; ypT0 ypN0) overall from 29% to 38% (p<0.001).
- The largest pCR improvement of absolute 22% (from 26% to 48%; p<0.001) was achieved in patients with TNBC.
- It has not yet been shown whether this will translate into an improved survival.

Untch et al. Lancet Oncol 2016

Power Calculation

- The analysis of DFS (and other time-to-event endpoints) was planned to be performed after 248 events had occurred.
- In this case the log-rank test would have 80% power to detect an improvement of the 5 year DFS from 75% to 81.8% (HR=0.70) with a 2-sided significance level of α=0.05.
- The cut-off date of this analysis was November 16th 2017.
- At that time, 244 confirmed events were in the database with a median follow-up of 49 months (IQR 44.6 - 52.9).

Disease-Free Survival



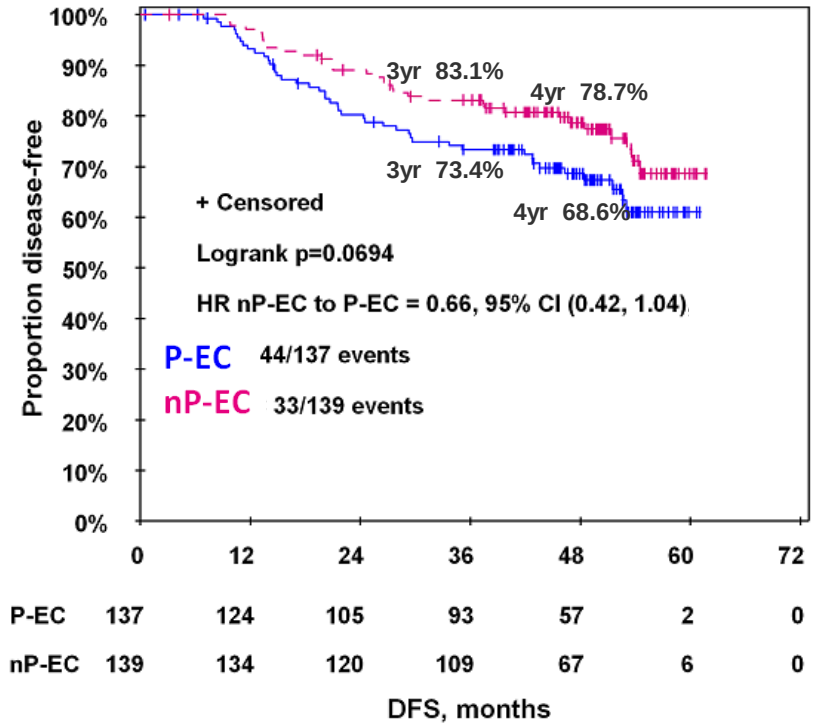
- Median follow-up of 49 months (IQR 44.6 - 52.9)
- HR (nP-EC vs. P-EC) = 0.69 (95% CI 0.54-0.89)
- Number needed to treat (NNT; 3yrs) = 16 pts

DFS rates (estimated):

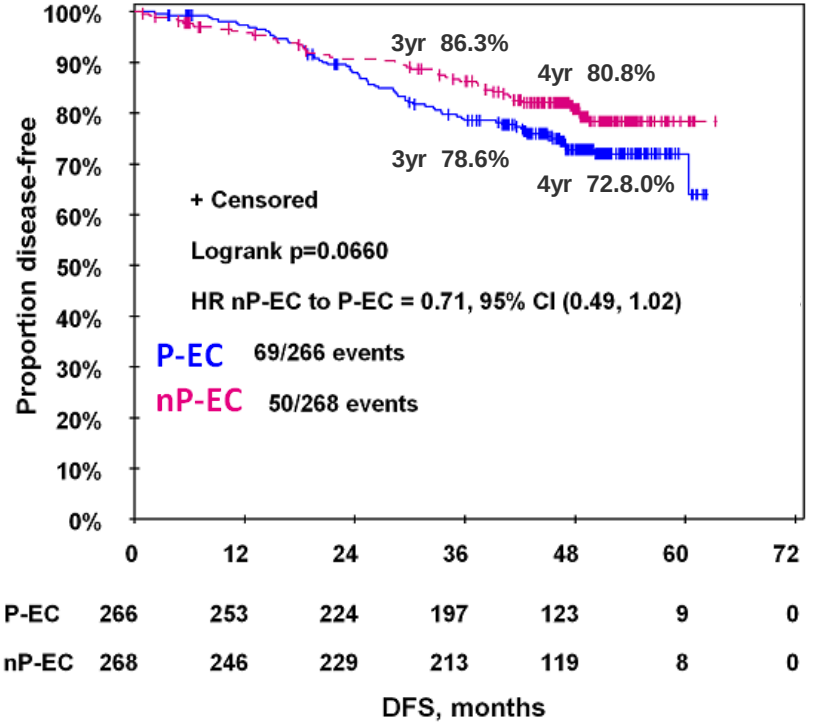
Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	80.7%	(77.2-83.7)	87.1%	(84.1-89.6)
4 yrs	76.2%	(72.3-79.5)	83.5%	(80.2-86.4)

Disease-Free Survival per Subtype

TNBC

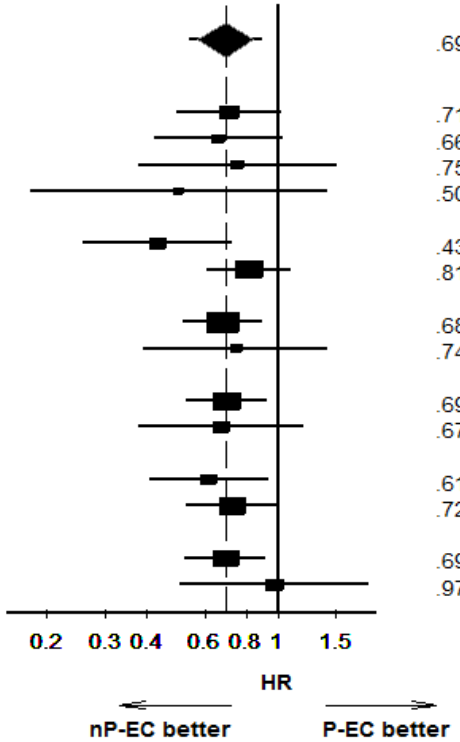


HR+HER2-

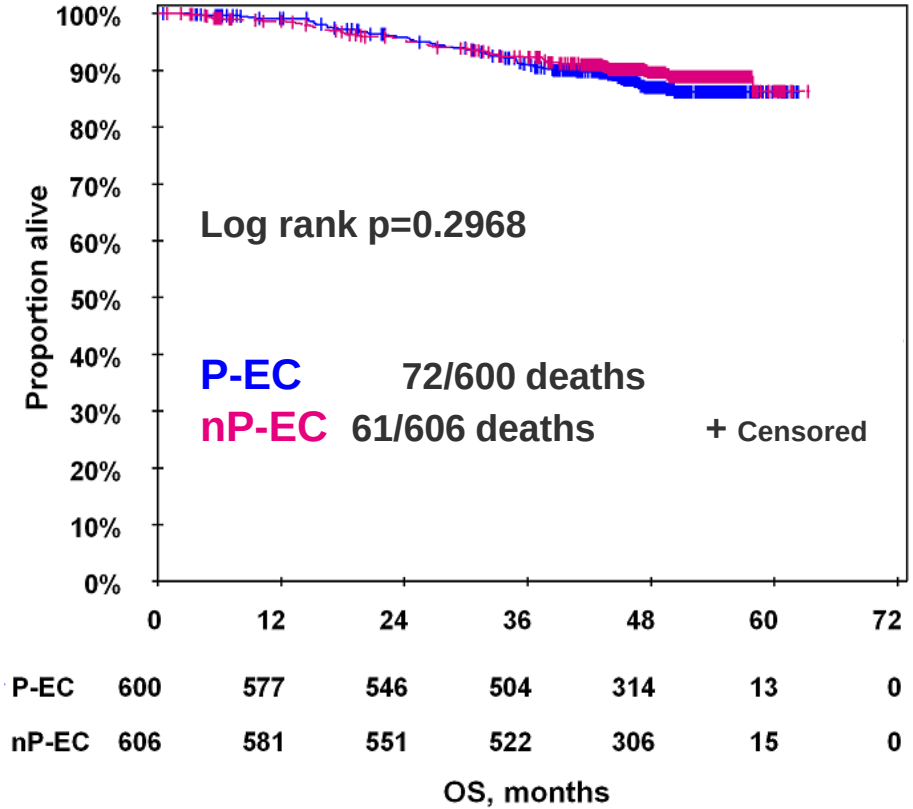


Forest Plot: Disease-Free Survival

Subgroup	N patients	Hazard Ratio (95% CI)	p-Value	Test for Interaction
Overall	1206	.693 (.537, .893)	.005	
Biological subtype				.913
HER2-/HR+	534	.712 (.495, 1.02)	.067	
HER2-/HR-	276	.660 (.420, 1.04)	.072	
HER2+/HR+	289	.753 (.377, 1.50)	.420	
HER2+/HR-	107	.500 (.178, 1.41)	.189	
Ki67				.046
<=20%	373	.431 (.256, .724)	.001	
>20%	833	.813 (.606, 1.09)	.168	
SPARC				.795
negative (IRS 0-5)	1015	.681 (.516, .898)	.007	
positive (IRS 6-12)	191	.744 (.392, 1.41)	.365	
HER2				.927
negative	810	.698 (.526, .927)	.013	
positive	396	.675 (.380, 1.20)	.180	
ER/PgR				.530
negative	383	.618 (.409, .935)	.023	
positive	823	.727 (.527, 1.00)	.052	
pCR ypT0 ypN0				.350
no pCR	772	.693 (.520, .922)	.012	
pCR	404	.975 (.502, 1.89)	.941	



Overall Survival: Overall



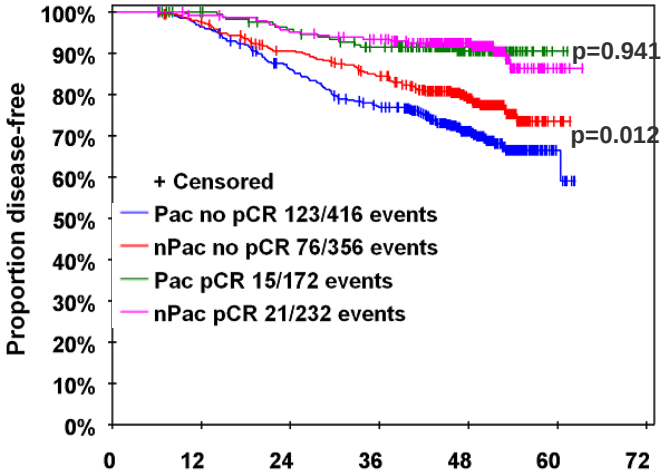
- **HR (nP-EC vs. P-EC) = 0.83 (95% CI 0.59-1.17)**

OS rates (estimated):

Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	**91.1%**	(88.4-93.1)	**92.3%**	(89.8-94.2)
4 yrs	**87.0%**	(83.8-89.6)	**89.6%**	(86.8-91.9)

Surrogate Value of pCR (exploratory analysis)

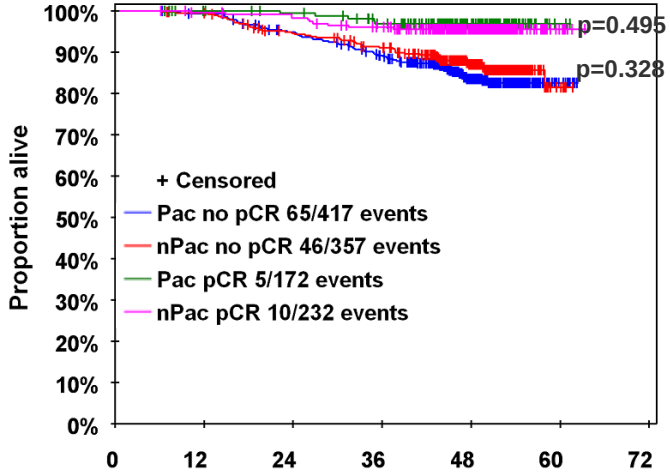
Disease-Free Survival



Pac no pCR	416	398	348	305	194	9	0
nPac no pCR	356	346	312	286	163	7	0
Pac pCR	172	167	157	144	79	2	0
nPac pCR	232	227	217	208	123	7	0

DFS, months

Overall Survival



Pac no pCR	417	410	383	352	229	11	0
nPac no pCR	357	353	327	308	180	8	0
Pac pCR	172	167	163	152	85	2	0
nPac pCR	232	228	224	214	126	7	0

OS, months

Summary

- GeparSepto demonstrates a significantly improved DFS when patients received
  nab-paclitaxel instead of paclitaxel (HR=0.69, 95% CI [0.54-0.89; log rank p=0.0044).
- A similar treatment effect was observed for patients with TNBC and HR+/HER2- tumors.
- The interaction with Ki67 suggests that nab-paclitaxel generates a long term benefit in particular in tumors with lower proliferation.
- Irrespective of the treatment group, patients achieving a pCR had a significantly better DFS.
- Patients without pCR have a significantly better DFS with nab-paclitaxel than paclitaxel.