Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial

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Background

The neoadjuvant phase III GeparSepto study[1] showed that substituting nab-paclitaxel (nab-Pac) for standard solvent-based paclitaxel (Pac) significantly improved the pathological complete response (pCR) rate in patients receiving a sequential regimen of taxane, epirubicin and cyclophosphamide as neoadjuvant treatment for high-risk primary breast cancer. A dual HER2 targeted regimen of pertuzumab and trastuzumab achieved impressive rates of pCR in two phase II neoadjuvant studies, NeoSphere[2] and TRYPHAENA[3].

The present analysis focuses on efficacy and safety data of the HER2-positive patients from GeparSepto study treated with a dual HER2-blockade in comparison to the HER2-negative cohort.

Patients and Methods

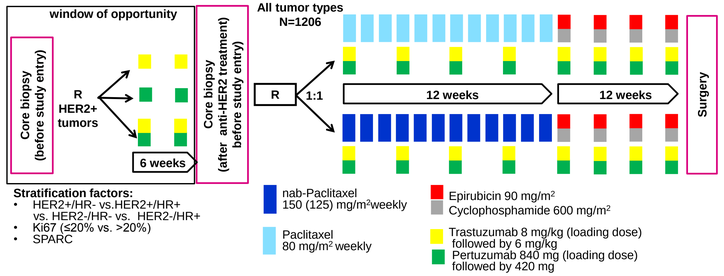
Trial design

GeparSepto (NCT01583426) was a multicentre, prospective, randomised, open-label, phase III trial comparing nab-paclitaxel and standard paclitaxel as part of a neoadjuvant regimen. The study design is shown in Figure 1.

Statistical consideration

Efficacy parameters were reported in subgroups with two-sided 95% confidence intervals (CI) and compared between treatment arms using continuity-corrected χ^2 test. Multivariable analysis was performed to identify predictive factors for pCR in trastuzumab-pertuzumab-treated HER2-positive breast cancer. Safety analysis of HER2+ vs. HER2-negative group was performed using the two-sided Fisher's test. Patients with missing response data were considered as having no response.

Figure 1: GeparSepto study design



Stratification factors:
- HER2+/HR- vs.HER2+/HR+ vs. HER2-/HR- vs. HER2-/HR+
- Ki67 (≤20% vs. >20%)
- SPARC

Primary objectives of the HER2+ subanalysis
- To assess the pCR defined as ypT0 ypN0

Secondary objectives of the HER2+ subanalysis:
- To assess the pCR rates by other definitions ;
- Safety in the HER2+ vs. HER2-negative cohort

Results

Table 1. Baseline characteristics of HER2+ & HER2- patients

Parameter	Category	HER2-positive N=396/1206 (32.8%) Overall N=396	HER2-negative N=810/1206 (67.2%) Overall N=810
Age, years	<30	12 (3.0)	25 (3.1)
	30-<40	61 (15.4)	112 (13.8)
	40-<50	133 (33.6)	298 (36.8)
	50-<60	102 (25.8)	219 (27.0)
	60-<70	74 (18.7)	119 (14.7)
	70+	14 (3.5)	37 (4.6)
cT	cT1-3	368 (92.9)	760 (94.1)
	cT4a-c	13 (3.3)	21 (2.6)
	cT4d	15 (3.8)	27 (3.3)
	Missing		2
Sentinel node biopsy	None	172 (43.4)	363 (44.8)
	Negative	132 (33.3)	291 (35.9)
	Positive	90 (22.7)	156 (19.3)
	Not detected	2 (0.5)	0 (0.0)
ER/PgR (central pathology)	both ER, PgR negative	107 (27.0)	276 (34.1)
	ER and/or PgR positive	289 (73.0)	534 (65.9)
Tumor grading	G1	5 (1.3)	20 (2.5)
	G2	192 (48.5)	332 (41.0)
	G3	199 (50.3)	458 (56.5)
Ki67 (central pathology)	≤20%	130 (32.8)	243 (30.0)
	>20%	266 (67.2)	567 (70.0)
SPARC	negative (IRS 0-5)	362 (91.4)	653 (80.6)
	positive (IRS 6-12)	34 (8.6)	157 (19.4)

Figure 2. pCR (ypT0 ypN0 or ypT0/is ypN0) by molecular subtypes

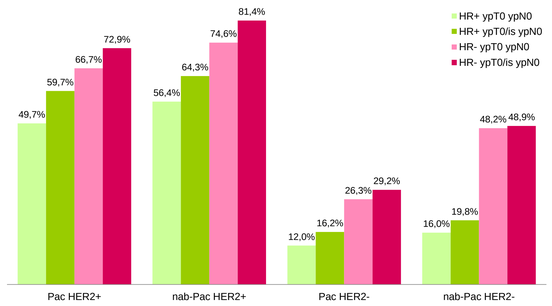


Table 2. Adverse events (AE) in HER2+ & HER2- patients

AE	Grade	HER2+ safety set Overall N (%)	HER2- safety set Overall N (%)	p-value (HER2+ vs. HER2-)
Any AEs	Any	396 (100)	809 (99.9)	1.00
	3-4	338 (85.4)	632 (78.0)	**0.003**
Hematological AEs	Any	390 (98.5)	792 (97.8)	0.513
	3-4	293 (74.0)	563 (69.5)	0.120
Anemia	Any	373 (94.2)	715 (88.5)	0.001
	3-4	10 (2.5)	7 (0.9)	**0.034**
	Missing	0	2	
Febrile neutropenia	Any	25 (6.3)	27 (3.3)	0.023
Thrombopenia	Any	113 (28.5)	176 (21.8)	0.012
	3-4	4 (1.0)	4 (0.5)	0.451
	Missing	0	2	
Non-hematological AE	Any	396 (100)	809 (99.9)	1.00
	3-4	152 (38.4)	244 (30.1)	**0.005**
Increased AP	Any	102 (25.8)	164 (20.3)	0.038
	3-4	1 (0.3)	1 (0.1)	0.550
	Missing	0	2	
Increased ALAT	Any	246 (62.1)	431 (53.3)	0.004
	3-4	11 (2.8)	16 (2.0)	0.410
	Missing	0	2	
Mucositis/stomatitis/esophagitis	Any	246 (62.1)	349 (43.1)	<0.001
	3-4	8 (2.0)	4 (0.5)	**0.025**
Diarrhea	Any	319 (80.6)	255 (31.5)	<0.001
	3-4	30 (7.6)	7 (0.9)	**<0.001**
Anorexia	Any	92 (23.2)	123 (15.2)	<0.001
	3-4	4 (1.0)	1 (0.1)	**0.043**
Maculo-papular rash	Any	165 (41.7)	180 (22.2)	<0.001
	3-4	7 (1.8)	4 (0.5)	**0.047**
Dyspnea	Any	71 (17.9)	137 (16.9)	0.685
	3-4	10 (2.5)	4 (0.5)	**0.003**
LVEF≥10% decrease from baseline and to <50%*		8 (2.0)	3 (0.4)	**0.008**
Serious AE	Any	104 (26.3)	179 (22.1)	0.112

*AE of special interest

- Overall, higher rates of pCR (ypT0 ypN0) were achieved in HER2+ than in HER2- tumors, with the highest rate in the HER2+/ hormone receptor negative (HER2+/HR-) cohort (Figure 2). A similar pattern of responses was seen using the ypT0/is ypN0 definition for pCR (Figure 2)
- A sensitivity analysis in the HER2+ cohort excluding the window-of-opportunity patients showed a pCR rate of 60.1% (52.5%, 67.8%) with nab-Pac and 52.7% (45.1%, 60.2%) with Pac (p=0.212).

- Multivariate regression analysis showed that the only significant predictor of pCR in HER2+ patients was the HR-negative status (OR 2.05 [95% CI 1.23-3.41; p=0.006).
- High-grade toxicities that were significantly more common in HER2+ than in HER2- group (85.4% vs. 78.0%; p=0.003) included anaemia (p=0.034), mucositis/stomatitis/esophagitis (p=0.025), diarrhea (p<0.001), anorexia (p=0.043), maculo-papular rash (p=0.047) and dyspnea (p=0.003).
- As reported previously[1], toxicities and treatment discontinuations were more frequent with nab-Pac than with Pac.
- LVEF decreases from baseline were uncommon, with 2.0% of the HER2+ vs. 0.4% of the HER2- patients showing decreases to <50% along with a ≥10% decrease from baseline.

Conclusions

This is the largest cohort of patients with HER2-positive early breast cancer receiving a dual HER2-targeted neoadjuvant therapy of pertuzumab and trastuzumab, together with nab-Pac or Pac followed by epirubicin and cyclophosphamide[3].

Although the HER2+ patients experienced more noteworthy toxicity, this treatment regime has acceptable toxicity and achieved higher rates of pCR in the HER2+ cohort, particularly in the HER+/HR- negative subgroup, supporting its use as part of the neoadjuvant treatment.

References

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