

Supplemental Online Content

Blohmer J-U, Link T, Reinisch M, et al; GBG and AGO-B. Effect of denosumab added to 2 different nab-paclitaxel regimens as neoadjuvant therapy in patients with primary breast cancer: the GeparX 2 × 2 randomized clinical trial. *JAMA Oncol*. Published online May 19, 2022. doi:10.1001/jamaoncol.2022.1059

eAppendix.

eTable 1. Patient and tumor baseline characteristics (ITT population)

eTable 2. Tumor baseline stratification parameters in 4 groups as randomized (ITT population)

eTable 3. Multivariable logistic regression analysis adjusted for primary endpoint pCR (ypT0 ypN0)

eTable 4. Comparison of short-term efficacy according to different pCR endpoints

eTable 5. Adherence to treatment

eTable 6. Hematological and non-hematological adverse events

eFigure 1. Patient-reported outcomes denosumab

eFigure 2. Patient-reported outcomes nab-paclitaxel

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix

Patient selection and study design

Further main eligibility criteria included normal cardiac function by ECG and cardiac ultrasound (left ventricular ejection fraction or shortening fraction) within 3 months prior to randomization, in case of HER2-positive disease with left ventricular ejection fraction >55%, no known or suspected cardiac disease, negative serum pregnancy test within 14 days prior to randomization for all women of childbearing potential with the result available before dosing, no history of significant neurological or psychiatric disorders, no pre-existing motor or sensory neuropathy of \geq grade 2 by National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0) criteria, no prior chemotherapy for any malignancy or radiation therapy for breast cancer, and no concurrent treatment with chronic corticosteroids, sex hormones or other experimental drugs or anticancer-therapy. Patients were excluded if they had inadequate general condition, previous malignant disease being disease-free for less than 5 years (except carcinoma in situ [CIS] of the cervix and non-melanomatous skin cancer), pure lobular carcinomas (lobular histology and G1/G2 and HR+/HER2-), stages cT1a, cT1b, or any M1, a history of disease with influence on bone metabolism (such as osteoporosis, Paget's disease of bone, primary hyperparathyroidism requiring treatment at the time of randomization or considered likely to become necessary within the subsequent six months), bisphosphonates or denosumab use within the past year, significant dental/oral disease, including prior history or current evidence of osteonecrosis/osteomyelitis of the jaw, active dental or jaw condition which requires oral surgery, non-healed dental/oral surgery, planned invasive dental procedure for the course of the study, last visit to a dentist > 1/2 year ago, currently active infection, incomplete wound healing, definite contraindications for the use of corticosteroids, known hypersensitivity reaction to one of the compounds or incorporated substances used in GeparX (inclusive calcium and vitamin D) or known hereditary fructose intolerance.

Laboratory requirements included absolute neutrophil count $\geq 2.0 \times 10^9/l$, platelets $\geq 100 \times 10^9/l$ and hemoglobin ≥ 10 g/dl (≥ 6.2 mmol/l); total bilirubin ≤ 1.5 x upper normal limit (UNL); ASAT (SGOT) and ALAT (SGPT) ≤ 1.5 x UNL; and alkaline phosphatase ≤ 2.5 x UNL.; serum calcium or albumin-adjusted serum calcium ≥ 2.0 mmol/L (8.0 mg/dL) and ≤ 2.9 mmol/L (11.5 mg/dL). Hypocalcaemia had to be corrected before study entry by supplementation of calcium and vitamin D.

Both randomizations were performed by dynamic allocation using the Pocock and Simon minimization method [1]. Complete baseline documentation was entered by study sites in the web-based electronic documentation system. After entering complete baseline data in the randomization database, patient number and treatment arm were assigned by the system and communicated to the participating site. Participants and investigators were not blinded. The stratification factors for randomization were defined as follows:

LPBC (negative defined as $\leq 50\%$ stromal tumor infiltrating lymphocytes vs present defined as $> 50\%$ stromal tumor infiltrating lymphocytes), breast cancer subtype (HER2-negative, hormone-receptor-positive vs triple-negative breast cancer vs HER2-positive), epirubicin/cyclophosphamide treatment (every two weeks vs every 3 weeks), and denosumab treatment (yes vs no) for the second randomization.

Study assessments

Pathological response was assessed considering all removed breast and lymphatic tissues from all surgeries. Patients with histologically positive nodes prior to treatment start and no axilla surgery after chemotherapy were counted as no pCR. Patients with negative sentinel node biopsy prior to treatment start and no axillary surgery after chemotherapy were counted as pCR, if they had no residual tumor detected in the removed breast tissue. Patients with positive sentinel node biopsy prior to treatment start and no residual tumor detected in the removed breast tissue and lymph nodes after chemotherapy were counted as pCR (preferably axillary dissection instead of sentinel node biopsy was strongly recommended in this situation). Patients with no axillary surgery at all were counted as no pCR. Patients who had not received breast surgery counted as no pCR. All local histopathological reports were centrally evaluated by an independent pathologist blinded to treatment and not otherwise involved in the trial.

Toxicity reported as adverse events (AE) was based on NCI-CTCAE v4.0. AEs of special interest (AESIs) included hypocalcemia grade ≥ 3 , osteonecrosis of the jaw, and atypical fractures of the femur for patients on denosumab, any adverse event affecting cranial nerves, anaphylaxis, and macular edema for patients on nab-paclitaxel, and cardiac failure, infusion reaction, pulmonary toxicity, hypersensitivity, and infections and infestations for patients treated with trastuzumab (ABP 980).

Patient-reported outcomes were assessed at baseline (BL), after nab-paclitaxel, at end of treatment and 90 days post-surgery using the Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) questionnaire, FACT-Taxane Trial Outcome Index (TOI), FACT-G total score, and FACT-Taxane total score scales. Higher mean scores indicate better functioning and quality of life (QoL).

Statistical analysis

Computation for sample size calculations was performed with nQuery Advisor 6.02. The sample size calculation was based on the following assumptions: An improvement of the pCR rate by denosumab in all patients was from 35% to 46% (OR=1.58) and an improvement of the pCR rate by different schedules of chemotherapy (nab-paclitaxel 125mg day 1,8 q22 (Cb) followed by EC arm to nab-paclitaxel 125mg weekly (Cb) followed by EC) from 36% to 45% (OR=1.45). With 778 recruited patients, the primary χ^2 -test of pCR rates between denosumab and no denosumab arms had 92% power to the 2-sided significance level $\alpha=0.10$. The χ^2 -test of pCR rates between nab-paclitaxel 125mg weekly (Cb) followed by EC to nab-paclitaxel 125mg day 1,8 q22 (Cb) followed by EC arms had 80% power to the 2-sided significance level $\alpha=0.10$. Co-primary objectives were tested according to the improved Bonferroni procedure: the smaller of the two p-values was compared with $\alpha = 0.1$ and the larger p-value was compared with $\alpha = 0.2$ to keep the overall significance level of the study of $\alpha = 0.2$.

The primary endpoint was also analyzed in subgroups defined by the stratification factors LPBC (no vs yes), breast cancer subtype (HER2-/HR+ vs TNBC vs HER2+), EC (every 2 vs every 3 weeks), and denosumab arm (for nab-paclitaxel comparison). The Breslow-Day test was used to test for interaction between treatment arm and binary subgroup variables, and the Wald p-value from the logistic regression including treatment arm, subtype and their interaction was used for interaction with the breast cancer subtype. There was no adjustment for the multiple comparisons in the analyses for the stratified subgroups.

Multivariable logistic regression analysis including both randomizations adjusting for stratification factors and the predefined covariates age (<40 vs \geq 40 years), tumor size (\leq 25 vs >25 mm), tumor stage (cT1-3 vs cT4), nodal status (cN0 vs cN+), and grade (1-2 vs 3); additionally, a multivariable logistic regression including interaction between denosumab and chemotherapy arms was performed.

For quality of life analyses, mixed models including BL value as a random effect and treatment, time, and treatment by time interaction as fixed effects were used to compare the quality of life scores.

All statistical analyses were performed using SAS® Version 9.4 with SAS Enterprise Guide Version 7.1 on Microsoft Windows 7 Enterprise.

Supplementary References

¹ Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; 31: 103-115.

eTable 1: Patient and tumor baseline characteristics (ITT population)

Parameter	1 st randomization		2 nd randomization	
	Dmab N=390 N (valid %)	no Dmab N=390 N (valid %)	nP wk N=390 N (valid %)	nP d1,8 q3 wk N=390 N (valid %)
Gender				
female	389 (99.7)	390 (100)	389 (99.7)	390 (100)
male	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Age (years)				
Median	49.0	48.5	49.0	49.0
Range	23.0, 78.0	22.0, 80.0	23.0, 78.0	22.0, 80.0
BMI (kg/m ²)				
Median	24.6	24.9	24.5	25.1
Range	17.6, 53.4	18.1, 54.4	17.6, 54.4	17.8, 53.4
Menopausal status				
pre- and perimenopausal	218 (55.9)	235 (60.3)	229 (58.7)	224 (57.4)
postmenopausal	171 (43.8)	155 (39.7)	160 (41.0)	166 (42.6)
n.a. (male patient)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Tumor focality, sonography				
Unifocal	323 (82.8)	324 (83.1)	323 (82.8)	324 (83.1)
Multifocal	47 (12.1)	46 (11.8)	50 (12.8)	43 (11.0)
Multicentric	20 (5.1)	20 (5.1)	17 (4.4)	23 (5.9)
Tumor stage, sonography				
cT1	135 (35.0)	156 (40.4)	132 (34.4)	159 (41.0)
cT2	222 (57.5)	213 (55.2)	230 (59.9)	205 (52.8)
cT3	18 (4.7)	11 (2.8)	13 (3.4)	16 (4.1)
cT4	11 (2.8)	6 (1.6)	9 (2.3)	8 (2.1)

missing	4	4	6	2
Nodal stage, sonography				
cN0	232 (59.9)	233 (60.2)	238 (61.0)	227 (59.1)
cN1	134 (34.6)	136 (35.1)	131 (33.6)	139 (36.2)
cN2	18 (4.7)	12 (3.1)	16 (4.1)	14 (3.6)
cN3	3 (0.8)	6 (1.6)	5 (1.3)	4 (1.0)
missing	3	3	0	6
Core- or fine needle biopsy of lymph node				
none	272 (69.7)	299 (76.7)	284 (72.8)	287 (73.6)
negative	27 (6.9)	18 (4.6)	23 (5.9)	22 (5.6)
positive	91 (23.3)	73 (18.7)	83 (21.3)	81 (20.8)
cN combined*				
cN0	242 (62.2)	239 (61.3)	246 (63.1)	235 (60.4)
cN+	147 (37.8)	151 (38.7)	144 (36.9)	154 (39.6)
missing	1	0	0	1
Sentinel node biopsy (not recommended)				
none	326 (83.6)	323 (82.8)	329 (84.4)	320 (82.1)
negative	45 (11.5)	46 (11.8)	45 (11.5)	46 (11.8)
positive	19 (4.9)	21 (5.4)	16 (4.1)	24 (6.2)
no sentinel detected	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor grading				
G1	7 (1.8)	7 (1.8)	7 (1.8)	7 (1.8)
G2	128 (32.8)	119 (30.5)	126 (32.3)	121 (31.0)
G3	255 (65.4)	264 (67.7)	257 (65.9)	262 (67.2)
Histological tumor type				
Invasive carcinoma NST	374 (95.9)	375 (96.2)	380 (97.4)	369 (94.6)
Invasive lobular carcinoma or mixed lobular carcinoma	6 (1.5)	9 (2.3)	5 (1.3)	10 (2.6)
other	10 (2.6)	6 (1.5)	5 (1.3)	11 (2.8)
ER/PgR, central				
both ER and PgR negative	185 (47.4)	180 (46.2)	177 (45.4)	188 (48.2)

ER and/or PgR positive	205 (52.6)	210 (53.8)	213 (54.6)	202 (51.8)
HER2, central				
negative	313 (80.3)	314 (80.5)	314 (80.5)	313 (80.3)
positive	77 (19.7)	76 (19.5)	76 (19.5)	77 (19.7)
Subtype (stratification)				
HER2-/HR+	153 (39.2)	157 (40.3)	155 (39.7)	155 (39.7)
TNBC	160 (41.0)	157 (40.3)	159 (40.8)	158 (40.5)
HER2+	77 (19.7)	76 (19.5)	76 (19.5)	77 (19.7)
Ki-67, central (stratification)				
≤20%	73 (18.7)	59 (15.1)	63 (16.2)	69 (17.7)
>20%	317 (81.3)	331 (84.9)	327 (83.8)	321 (82.3)
LPBC, central (stratification)				
no LPBC (≤50% sTILs)	359 (92.1)	359 (92.1)	359 (92.1)	359 (92.1)
LPBC (>50% sTILs)	31 (7.9)	31 (7.9)	31 (7.9)	31 (7.9)
Planned EC schedule (stratification)				
2-weekly	206 (52.8)	208 (53.3)	207 (53.1)	207 (53.1)
3-weekly	184 (47.2)	182 (46.7)	183 (46.9)	183 (46.9)
Germline BRCA				
wildtype	94 (24.1)	87 (22.3)	92 (23.6)	89 (22.8)
mutant	28 (7.2)	32 (8.2)	30 (7.7)	30 (7.7)
unknown	268 (68.7)	271 (69.5)	268 (68.7)	271 (69.5)

*combination of palpation, sonography and core- or fine needle biopsy;

BMI = Body mass index; EC = epirubicin, cyclophosphamide; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ITT = intent-to-treat; LPBC = lymphocyte-predominant breast cancer; NST = no special type; PgR = progesterone receptor; sTILs = stromal tumor-infiltrating lymphocytes; TNBC = triple-negative breast cancer; wk = weekly; d1,8 q3 wk = days 1 and 8 every-3-weeks

eTable 2: Tumor baseline stratification parameters in 4 groups as randomized (ITT population)

Parameter	Parameter value	nP wk with Dmab	nP wk without Dmab	nP d1,8 q3 wk with Dmab	nP d1,8 q3 wk without Dmab
Breast cancer subtype	HER2-/HR+	63 (32.3)	92 (47.2)	90 (46.2)	65 (33.3)
	TNBC	89 (45.6)	70 (35.9)	71 (36.4)	87 (44.6)
	HER2+	43 (22.1)	33 (16.9)	34 (17.4)	43 (22.1)
	missing	0	0	0	0
Ki-67, central pathology	<=20%	36 (18.5)	27 (13.8)	37 (19.0)	32 (16.4)
	>20%	159 (81.5)	168 (86.2)	158 (81.0)	163 (83.6)
	missing	0	0	0	0
LPBC, central pathology	no LPBC	179 (91.8)	180 (92.3)	180 (92.3)	179 (91.8)
	LPBC	16 (8.2)	15 (7.7)	15 (7.7)	16 (8.2)
	missing	0	0	0	0
Planned EC schedule	2-weekly	102 (52.3)	105 (53.8)	104 (53.3)	103 (52.8)
	3-weekly	93 (47.7)	90 (46.2)	91 (46.7)	92 (47.2)
	missing	0	0	0	0

Dmab = denosumab; EC = epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ITT = intent-to-treat; LPBC = lymphocyte-predominant breast cancer; nP = nab-Paclitaxel; TNBC = triple-negative breast cancer; wk = weekly; d1,8 q3 wk = days 1 and 8 every-3-weeks

eTable 3: Multivariable logistic regression analysis adjusted for primary endpoint pCR (ypT0 ypN0)

Parameter	Category	OR	90% CI	95% CI	p-value
Arm denosumab	no Dmab				
	Dmab	0.922	(0.707, 1.202)	(0.672, 1.265)	0.61
Arm nab-paclitaxel	nP d1,8 q3 wk				
	nP wk	1.361	(1.043, 1.776)	(0.992, 1.869)	0.06
Breast cancer subtype	HER2-/HR+				<0.001
	TNBC	3.526	(2.586, 4.808)	(2.437, 5.102)	<0.001
	HER2+	4.692	(3.227, 6.821)	(3.004, 7.327)	<0.001
LPBC	no				
	yes	2.477	(1.489, 4.123)	(1.350, 4.545)	0.003
EC schedule	2-wk				
	3-wk	1.004	(0.767, 1.314)	(0.728, 1.383)	0.98
Age, years	<40				
	>=40	0.855	(0.611, 1.198)	(0.572, 1.277)	0.44
Tumor size, mm	≤25				
	>25	0.571	(0.433, 0.753)	(0.410, 0.794)	0.001
cT	cT1-3				
	cT4	0.586	(0.205, 1.674)	(0.168, 2.046)	0.40
cN	cN0				
	cN+	0.892	(0.669, 1.189)	(0.633, 1.256)	0.51
Grading	G1-2				
	G3	2.531	(1.863, 3.441)	(1.756, 3.649)	<0.001

770 of 780 patients had no missing values and were included in the multivariable analysis.

CI = confidence interval; Dmab = denosumab; EC = epirubicin, cyclophosphamide; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; LPBC = lymphocyte predominant breast cancer; nP = nab-paclitaxel; OR = odds ratio; pCR = pathological complete response; TNBC = triple-negative breast cancer; wk = weekly; d1,8 q3 wk = days 1 and 8 every-3-weeks; q2 wk = every-2-weeks

eTable 4: Comparison of short-term efficacy according to different pCR endpoints

pCR#	Dmab N(%)	no Dmab N(%)	p-value Dmab stratified*	nP wk N(%)	nP d1,8 q3 wk N(%)	p-value nP stratified**	Overall N(%)
ypT0/is, ypN0							
yes	179 (45.9)	189 (48.5)	0.44	197 (50.5)	171 (43.8)	0.04	368 (47.2)
90% CI	(41.7%, 50.0%)	(44.3%, 52.6%)		(46.3%, 54.7%)	(39.7%, 48.0%)		
ypT0, ypN0/+							
yes	166 (42.6)	181 (46.4)	0.22	185 (47.4)	162 (41.5)	0.06	347 (44.5)
90% CI	(38.4%, 46.7%)	(42.3%, 50.6%)		(43.3%, 51.6%)	(37.4%, 45.6%)		
ypT0/is, ypN0/+							
yes	190 (48.7)	208 (53.3)	0.15	214 (54.9)	184 (47.2)	0.02	398 (51.0)
90% CI	(44.6%, 52.9%)	(49.2%, 57.5%)		(50.7%, 59.0%)	(43.0%, 51.3%)		
ypT(any), ypN0							
yes	291 (74.6)	297 (76.2)	0.59	302 (77.4)	286 (73.3)	0.26	588 (75.4)
90% CI	(71.0%, 78.2%)	(72.6%, 79.7%)		(74.0%, 80.9%)	(69.7%, 77.0%)		

CI = confidence interval; Dmab = denosumab; EC = epirubicin, cyclophosphamide; HR = hormone receptor; LPBC = lymphocyte-predominant breast cancer; nP = nab-paclitaxel; pCR = pathological complete response; TNBC = triple-negative breast cancer; wk = weekly; d1,8 q3 wk = days 1 and 8 every-3-weeks

* stratified test, primary analysis (stratified by 3 factors); **stratified test, primary analysis (stratified by 4 factors including denosumab arm)

primary endpoint significant to the 0.1 level; significance level for all further analyses is set to a two-sided $\alpha = 0.05$

eTable 5: Adherence to treatment

	Dmab N=377 N(%)	no Dmab N=391 N(%)	p-value Dmab	nP wk N=395 N(%)	nP d1,8 q3 wk N=373 N(%)	p-value nP	Overall N=768 N(%)
Discontinued nP treatment	56 (14.9)	48 (12.3)	0.34	81 (20.5)	23 (6.2)	<0.001	104 (13.5)
local progress	5 (1.3)	4 (1.0)		1 (0.3)	8 (2.1)		9 (1.2)
distant metastases/secondary malignancy	1 (0.3)	1 (0.3)		1 (0.3)	1 (0.3)		2 (0.3)
patient's death	1 (0.3)	0 (0.0)		0 (0.0)	1 (0.3)		1 (0.1)
AE	42 (11.1)	40 (10.2)		69 (17.5)	13 (3.5)		82 (10.7)
hematological toxicity	8 (2.1)	8 (2.0)		10 (2.5)	6 (1.6)		16 (2.1)
cardiac toxicity	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)
other non-hematological toxicity	32 (8.5)	28 (7.2)		55 (13.9)	5 (1.3)		60 (7.8)
AE not related to study medication	2 (0.5)	4 (1.0)		4 (1.0)	2 (0.5)		6 (0.8)
patient's decision	2 (0.5)	1 (0.3)		3 (0.8)	0 (0.0)		3 (0.4)
investigator's decision	5 (1.3)	2 (0.5)		7 (1.8)	0 (0.0)		7 (0.9)
Started EC	348	373		365	376		721
Discontinued EC	24 (6.9)	25 (6.7)	1.00	28 (7.7)	21 (5.9)	0.38	49 (6.8)
local progress	2 (0.6)	1 (0.3)		0 (0.0)	3 (0.8)		3 (0.4)
distant metastases/secondary malignancy	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)
patient's death	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)
AE	14 (4.0)	13 (3.5)		22 (6.0)	5 (1.4)		27 (3.7)
hematological toxicity	5 (1.4)	5 (1.3)		10 (2.7)	0 (0.0)		10 (1.4)
cardiac toxicity	1 (0.3)	1 (0.3)		1 (0.3)	1 (0.3)		2 (0.3)
other non-hematological toxicity	7 (2.0)	7 (1.9)		11 (3.0)	3 (0.8)		14 (1.9)
AE not related to study medication	1 (0.3)	0 (0.0)		0 (0.0)	1 (0.3)		1 (0.1)
patient's decision	5 (1.4)	8 (2.1)		3 (0.8)	10 (2.8)		13 (1.8)
investigator's decision	3 (0.9)	3 (0.8)		3 (0.8)	3 (0.8)		6 (0.8)

nP dose delay, any reason		253 (67.1)	257 (65.7)	0.70	301 (76.2)	209 (56.0)	<0.001	510 (66.4)
	due to organizational reason*	169 (44.8)	172 (44.0)	0.83	207 (52.4)	134 (35.9)	<0.001	341 (44.4)
	due to hematological toxicity	87 (23.1)	85 (21.7)	0.67	104 (26.3)	68 (18.2)	0.007	172 (22.4)
	due to cardiac toxicity	1 (0.3)	3 (0.8)	0.62	3 (0.8)	1 (0.3)	0.63	4 (0.5)
	due to other non-hematological toxicity	51 (13.5)	43 (11.0)	0.32	70 (17.7)	24 (6.4)	<0.001	94 (12.2)
	due to AE not related to study medication	40 (10.6)	23 (5.9)	0.02	45 (11.4)	18 (4.8)	<0.001	63 (8.2)
	due to other reason	27 (7.2)	28 (7.2)	1.00	31 (7.8)	24 (6.4)	0.49	55 (7.2)
	due to unknown reason	2 (0.5)	0 (0.0)	0.24	0 (0.0)	2 (0.5)	0.24	2 (0.3)
EC dose delay, any reason		192 (55.2)	222 (59.5)	0.26	213 (58.4)	201 (56.5)	0.65	414 (57.4)
	due to organizational reason*	74 (21.3)	97 (26.0)	0.14	77 (21.1)	94 (26.4)	0.10	171 (23.7)
	due to hematological toxicity	66 (19.0)	63 (16.9)	0.50	69 (18.9)	60 (16.9)	0.50	129 (17.9)
	due to cardiac toxicity	2 (0.6)	1 (0.3)	0.61	2 (0.5)	1 (0.3)	1.00	3 (0.4)
	due to other non-hematological toxicity	38 (10.9)	43 (11.5)	0.81	46 (12.6)	35 (9.8)	0.29	81 (11.2)
	due to AE not related to study medication	24 (6.9)	32 (8.6)	0.41	35 (9.6)	21 (5.9)	0.07	56 (7.8)
	due to other reason	52 (14.9)	37 (9.9)	0.04	40 (11.0)	49 (13.8)	0.26	89 (12.3)
	due to unknown reason	1 (0.3)	0 (0.0)	0.48	1 (0.3)	0 (0.0)	1.00	1 (0.1)
nP dose reduction, any reason		71 (18.8)	75 (19.2)	0.93	103 (26.1)	43 (11.5)	<0.001	146 (19.0)
	due to hematological toxicity	21 (5.6)	19 (4.9)	0.75	23 (5.8)	17 (4.6)	0.52	40 (5.2)
	due to cardiac toxicity	1 (0.3)	0 (0.0)	0.49	1 (0.3)	0 (0.0)	1.00	1 (0.1)
	due to other non-hematological toxicity	48 (12.7)	57 (14.6)	0.46	79 (20.0)	26 (7.0)	<0.001	105 (13.7)
	due to AE not related to study medication	1 (0.3)	1 (0.3)	1.00	2 (0.5)	0 (0.0)	0.50	2 (0.3)
	due to other reason	2 (0.5)	2 (0.5)	1.00	4 (1.0)	0 (0.0)	0.13	4 (0.5)
	due to unknown reason	1 (0.3)	1 (0.3)	1.00	2 (0.5)	0 (0.0)	0.50	2 (0.3)
EC dose reduction, any reason		69 (19.8)	73 (19.6)	1.00	86 (23.6)	56 (15.7)	0.009	142 (19.7)
	due to hematological toxicity	28 (40.6)	44 (60.3)	0.03	42 (48.8)	30 (53.6)	0.61	72 (50.7)
	due to cardiac toxicity	0 (0.0)	0 (0.0)	n.a.	0 (0.0)	0 (0.0)	n.a.	0 (0.0)

	due to other non-hematological toxicity	39 (56.5)	30 (41.1)	0.09	45 (52.3)	24 (42.9)	0.31	69 (48.6)
	due to AE not related to study medication	4 (5.8)	2 (2.7)	0.43	4 (4.7)	2 (3.6)	1.00	6 (4.2)
	due to other reason	3 (4.3)	2 (2.7)	0.67	2 (2.3)	3 (5.4)	0.38	5 (3.5)
	due to unknown reason	1 (1.4)	1 (1.4)	1.00	1 (1.2)	1 (1.8)	1.00	2 (1.4)

*up to 3 days

AE = adverse event; Dmab = denosumab; nP = nab-paclitaxel; EC = epirubicin, cyclophosphamide; wk = weekly; d1,8 q3 wk = days 1 and 8 every-3-weeks

eTable 6: Hematological and non-hematological adverse events

Predefined AEs	Grade	with Dmab nP wk N=195 N(%)	with Dmab nP d1,8 q3 wk with Dmab N=182 N(%)	without Dmab nP wk N=200 N(%)	without Dmab nP d1,8 q3 wk N=191 N(%)	p-value ⁺	p-value ⁺⁺
Anemia	any	185 (94.9)	172 (94.5)	197 (98.5)	182 (95.3)	0.15	0.28
	3-4	18 (9.2)	5 (2.7)	16 (8.0)	20 (10.5)	0.14	0.35
Leukopenia	any	185 (94.9)	170 (93.4)	195 (97.5)	181 (94.8)	0.24	0.18
	3-4	98 (50.3)	83 (45.6)	110 (55.0)	96 (50.3)	0.22	0.22
Neutropenia	any	178 (91.3)	161 (88.5)	183 (91.5)	171 (89.5)	0.81	0.28
	3-4	122 (62.6)	107 (58.8)	130 (65.0)	123 (64.4)	0.26	0.55
Febrile neutropenia	any	9 (4.6)	8 (4.4)	17 (8.5)	15 (7.9)	0.04	0.88
Thrombocytopenia	any	99 (50.8)	98 (53.8)	101 (50.5)	109 (57.1)	0.72	0.19
	3-4	15 (7.7)	8 (4.4)	19 (9.5)	20 (10.5)	0.06	0.60
Blood bilirubin increased	any	6 (3.1)	6 (3.3)	16 (8.0)	3 (1.6)	0.27	0.03
	3-4	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.49	1.00
Blood AP increased	any	65 (33.3)	59 (32.4)	76 (38.0)	68 (35.6)	0.26	0.65
	3-4	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.49	1.00
ASAT increased	any	86 (44.1)	72 (39.6)	83 (41.5)	68 (35.6)	0.38	0.14
	3-4	3 (1.5)	0 (0.0)	6 (3.0)	3 (1.6)	0.14	0.15
ALAT increased	any	133 (68.2)	101 (55.5)	123 (61.5)	110 (57.6)	0.51	0.02
	3-4	10 (5.1)	4 (2.2)	9 (4.5)	7 (3.7)	0.85	0.20
Blood creatinine increased	any	23 (11.8)	17 (9.3)	22 (11.0)	32 (16.8)	0.19	0.51
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.	n.a.
Fatigue	any	146 (74.9)	124 (68.1)	146 (73.0)	127 (66.5)	0.63	0.05
	3-4	11 (5.6)	9 (4.9)	9 (4.5)	7 (3.7)	0.50	0.73
Headache	any	40 (20.5)	36 (19.8)	45 (22.5)	35 (18.3)	0.93	0.42
	3-4	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1.00	1.00
Nausea	any	109 (55.9)	116 (63.7)	113 (56.5)	125 (65.4)	0.77	0.02

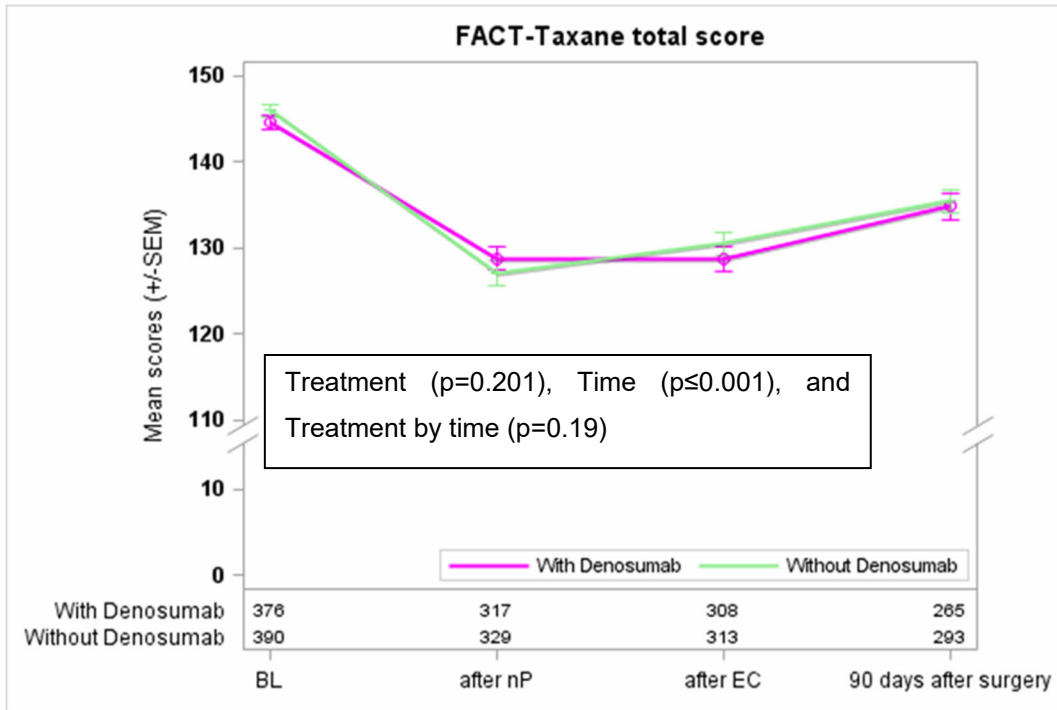
	3-4	2 (1.0)	3 (1.6)	6 (3.0)	4 (2.1)	0.30	1.00
Decreased appetite	any	26 (13.3)	22 (12.1)	35 (17.5)	16 (8.4)	0.92	0.03
	3-4	0 (0.0)	2 (1.1)	2 (1.0)	1 (0.5)	1.00	0.68
Vomiting	any	27 (13.8)	31 (17.0)	30 (15.0)	21 (11.0)	0.41	0.92
	3-4	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.5)	1.00	1.00
Diarrhea	any	83 (42.6)	57 (31.3)	81 (40.5)	67 (35.1)	0.88	0.02
	3-4	5 (2.6)	0 (0.0)	5 (2.5)	5 (2.6)	0.30	0.30
Hypertension	any	14 (7.2)	12 (6.6)	12 (6.0)	18 (9.4)	0.78	0.49
	3-4	2 (1.0)	2 (1.1)	1 (0.5)	0 (0.0)	0.21	1.00
Peripheral sensory neuropathy	any	142 (72.8)	84 (46.2)	154 (77.0)	91 (47.6)	0.46	<.001
	3-4	12 (6.2)	2 (1.1)	9 (4.5)	2 (1.0)	0.55	<.001
Arthralgia	any	53 (27.2)	41 (22.5)	47 (23.5)	30 (15.7)	0.08	0.04
	3-4	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0.50	0.50
Myalgia	any	34 (17.4)	29 (15.9)	22 (11.0)	21 (11.0)	0.03	0.83
	3-4	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)	1.00	0.25
Epistaxis	any	53 (27.2)	27 (14.8)	53 (26.5)	25 (13.1)	0.72	<.001
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.	n.a.
Dyspnea	any	29 (14.9)	21 (11.5)	25 (12.5)	21 (11.0)	0.59	0.33
	3-4	3 (1.5)	1 (0.5)	1 (0.5)	0 (0.0)	0.21	0.37
Alopecia	any	169 (86.7)	158 (86.8)	176 (88.0)	161 (84.3)	0.83	0.53
Palmar-plantar erythrodysesthesia syndrome	any	16 (8.2)	8 (4.4)	18 (9.0)	5 (2.6)	0.88	0.004
	3-4	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1.00	0.50
Embolicism	any	7 (3.6)	7 (3.8)	7 (3.5)	8 (4.2)	1.00	0.85
	3-4	0 (0.0)	3 (1.6)	3 (1.5)	1 (0.5)	1.00	0.72
Pyrexia	any	47 (24.1)	19 (10.4)	29 (14.5)	25 (13.1)	0.17	0.005
	3-4	6 (3.1)	1 (0.5)	2 (1.0)	3 (1.6)	0.57	0.39
≥10% decrease in LVEF from baseline and < 50%	any	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)	0.62	0.61
Osteonecrosis of jaw*	any	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0.49	0.49
	3-4	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0.49	0.49

Hypocalcaemia*§	any	98 (50.3)	95 (52.2)	62 (31.0)	50 (26.2)	<0.001	0.66
	3-4	1 (0.5)	3 (1.6)	1 (0.5)	3 (1.6)	1.00	0.17
Anaphylactic reaction****	any	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0.12	1.00
Cranial nerve disorder****	any	1 (0.5)	0 (0.0)	4 (2.0)	0 (0.0)	0.37	0.06
	3-4	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0.50	0.50
Infusion related reaction**	any	6 (3.1)	4 (2.2)	4 (2.0)	3 (1.6)	0.47	0.63
	3-4	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)	0.62	0.61
Hypersensitivity**	any	5 (2.6)	5 (2.7)	8 (4.0)	7 (3.7)	0.42	1.00
	3-4	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	1.00	0.61
Cardiac failure, NYHA**	any	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1.00	1.00
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.	n.a.
Pneumonitis**	any	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.12	0.25
	3-4	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.49	1.00
Cough	any	25 (12.8)	14 (7.7)	25 (12.5)	21 (11.0)	0.57	0.17
	3-4	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1.00	0.50
Other pulmonary toxicity**	any	2 (1.0)	0 (0.0)	3 (1.5)	5 (2.6)	0.11	1.00
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.	n.a.
Pneumonia**	any	8 (4.1)	2 (1.1)	4 (2.0)	0 (0.0)	0.11	0.01
	3-4	4 (2.1)	1 (0.5)	3 (1.5)	0 (0.0)	0.50	0.07
Infection other than pneumonia**	any	89 (45.6)	70 (38.5)	78 (39.0)	79 (41.4)	0.61	0.56
	3-4	9 (4.6)	5 (2.7)	15 (7.5)	9 (4.7)	0.14	0.18
Other AE***	any	183 (93.8)	163 (89.6)	190 (95.0)	172 (90.1)	0.69	0.02
	3-4	35 (17.9)	37 (20.3)	30 (15.0)	23 (12.0)	0.04	0.92

AE = Adverse event; AESI = Adverse event of special interest; ALAT = Alanine aminotransferase; AP = Alkaline phosphatase; ASAT = Aspartate aminotransferase; Dmab = denosumab; LVEF = Left ventricular ejection fraction; nP = nab-paclitaxel; NYHA = New York Heart Association; wk = weekly; d1,8 q3 wk = days 1 and 8 every-3-weeks

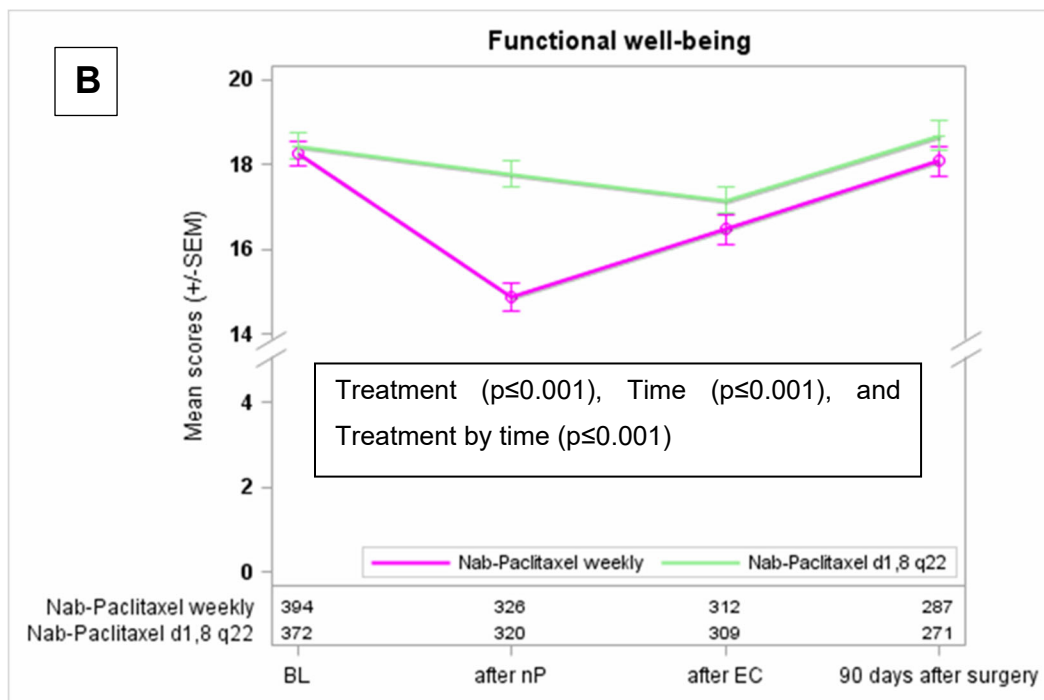
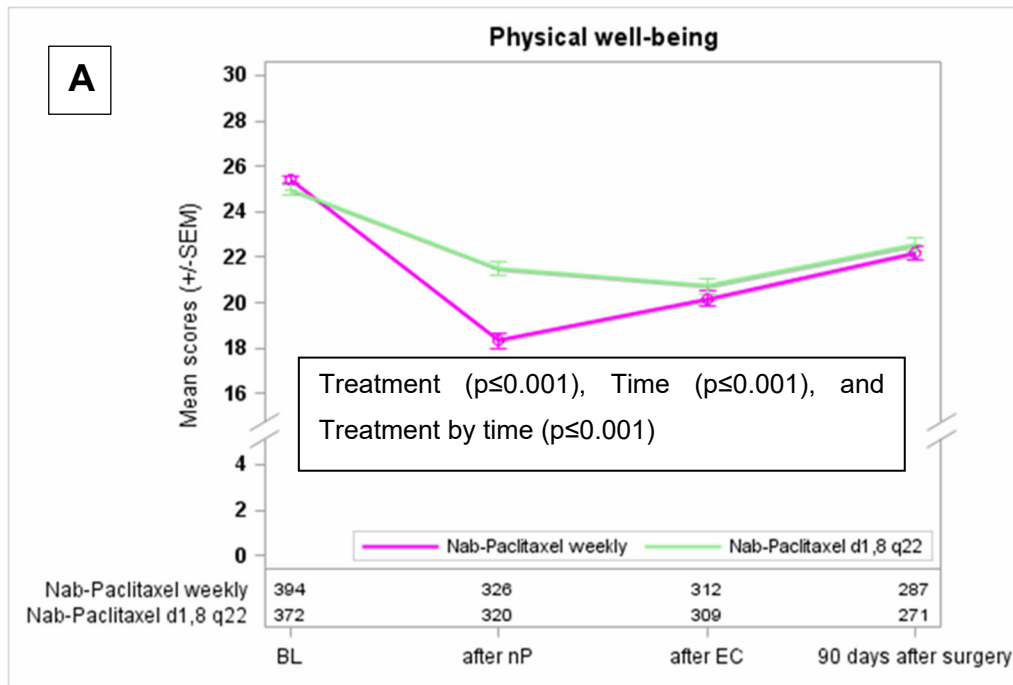
*AE of special interest for denosumab; **AE of special interest for HER2-positive patients treated with ABP 980; ***Reported as free-text; ****AE of special interest for nab-paclitaxel; § NOTE: One high grade hypocalcemia occurred before amendment 1 and was therefore not reported as AESI; + comparing with vs without Denosumab; ++ comparing nab-paclitaxel weekly vs nab-paclitaxel d1,8 q3w

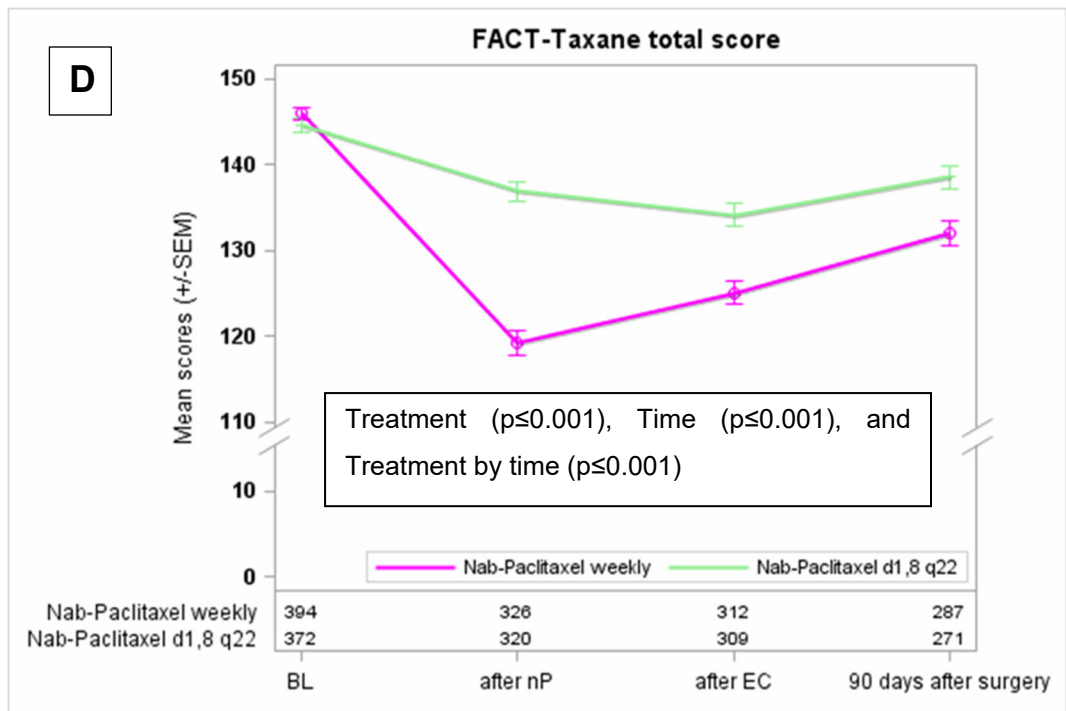
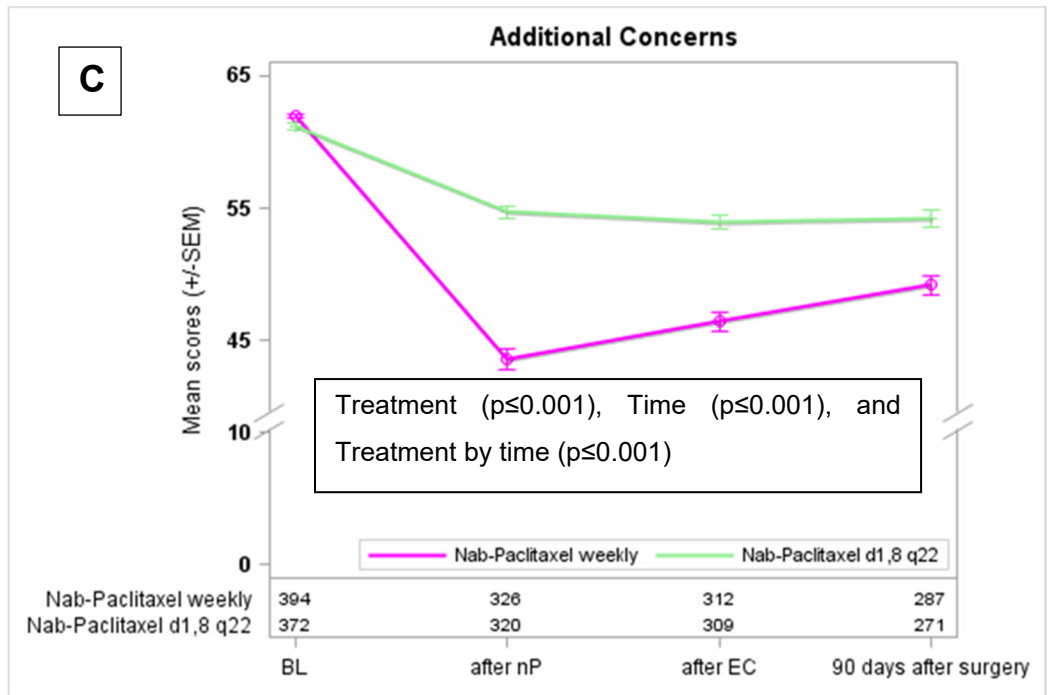
eFigure 1: Patient-reported outcomes Denosumab: FACT-Taxane total score

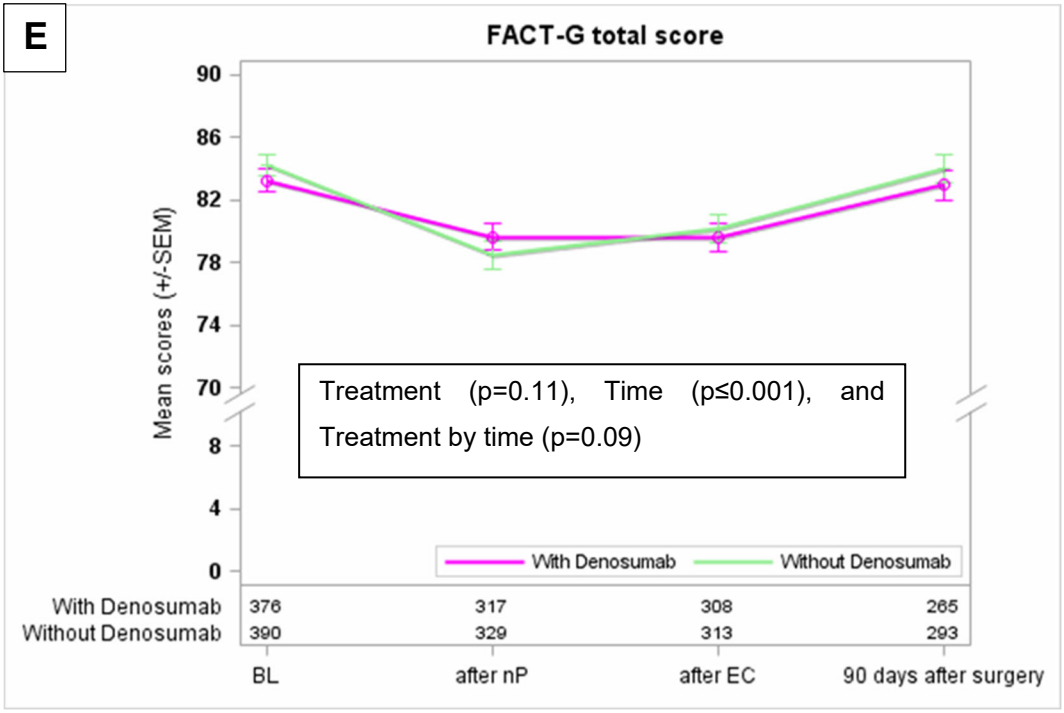


BL = baseline; EC = epirubicin, cyclophosphamide; FACT = Functional Assessment of Cancer Therapy; nP = nab-Paclitaxel; SEM = standard error of the mean

eFigure 2: Patient-reported outcomes nab-Paclitaxel: Physical well-being (A), Functional well-being (B), Additional concerns (C), FACT-Taxane total score (D), FACT-G total score (E)







BL = baseline; EC = epirubicin, cyclophosphamide; FACT = Functional Assessment of Cancer Therapy; nP = nab-Paclitaxel; SEM = standard error of the mean