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## **STATISTICAL ANALYSIS PLAN**

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### **GeparX**

**Investigating Denosumab as an add-on to neoadjuvant chemotherapy in RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules in a 2x2 factorial design**

**GBG 88**

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

<b>Version:</b>	<b>1.0</b>
<b>Date:</b>	<b>20.03.2020</b>
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**Protocol number: GBG 88**

**Protocol title: GeparX**

**Author: Dr. Valentina Nekljudova**

**Version: 1.0**

**Version Date: 20.03.2020**

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## 1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the statistical methods used for planning, conducting and analyzing the GeparX study. The SAP is based on the protocol of the GeparX Study incl. Amendment 3, version 11.04.2019 [1] and includes the final analysis of safety, short-term and long-term efficacy. Analysis of HER2+ substudy, DTC substudy and RANK is included, all other biomarker analyses and analysis of other substudies will be performed according to separate SAPs.

The analysis will be performed in accordance with the principles stated in the Consensus Guidelines E9 (Statistical Principles for Clinical Trials) [2] and E3 (Structure and Content of Clinical Study Reports) [3] of the International Conference on Harmonization (ICH).

## 2. ABBREVIATIONS

ABP 980	Trastuzumab biosimilar APB 980
AC	Additional concerns
AD	Actual dose (in cycle or week)
AE	Adverse event
AESI	Adverse event of special interest
ALAT	Alanine aminotransferase
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
AP	Alkaline phosphatase
ASAT	Aspartate aminotransferase
ATD	Actual total dose
ATDI	Actual total dose intensity
AUC	Area under curve
BCS	Breast conserving surgery
BMI	Body mass index
<i>BRCA</i>	Breast cancer gene 1 or 2
C	Cyclophosphamide
Cb	Carboplatin
CI	Confidence interval
CIF	Cumulative incidence function
CR	Complete response
CRF	Case report form

(NCI-)CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
D	Denosumab
DDFS	Distant disease-free survival
DTC	Disseminated tumor cells
E	Epirubicin
EFS	Event-free survival
EOT	End of treatment
ER	Estrogen receptor status
EWB	Emotional well-being
FWB	Functional well-being
GBG	German Breast Group
gBRCA	Germline BRCA
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HR	Hormone receptor status
ICH	International Conference on Harmonization
IDFS	Invasive disease-free survival
ITT	Intent-to-treat
LN	Lymph node(s)
LPBC	Lymphocyte-predominant breast cancer
LRRFI	Loco-regional relapse-free interval
LVEF	Left ventricular ejection fraction
MD	Mammographic density
MedCODES	Medical CRF Online Documentation & Evaluation System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NACT	Neo-adjuvant chemotherapy
NC	No change (stable disease)
nPac	Nab-paclitaxel
NST	Invasive carcinoma of no special type
NYHA	New-York Heart Association
OR	Odds ratio
ORR	Overall response rate
ORes	Overall (clinical) response

OS	Overall survival
pCR	Pathological complete response
PD	Progressive disease
PgR	Progesteron receptor status
PnD	Planned dose (in cycle or week)
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response
PSN	Peripheral sensory neuropathy
PT	(MedDRA) preferred term
PTD	Planned total dose
PTDI	Planned total dose intensity
PhWB	Physical well-being
QoL	Quality of Life
RANK	Receptor activator of nuclear factor $\kappa$ B
RTD	Relative total dose
RTDI	Relative total dose intensity
SABCS	San-Antonio Breast Cancer Symposium
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis Software
SFWB	Social/Family well-being
SNB	Sentinel node biopsy
SOP	Standard operation procedure
SOC	(MedDRA) system organ class
StD	Standard deviation
STEPP	Subpopulation treatment effect pattern plot
TILs	Tumor-infiltrating lymphocytes
TNBC	Triple-negative breast cancer
TOI	FACT-Taxane Trial Outcome Index
ULN	Upper limit normal

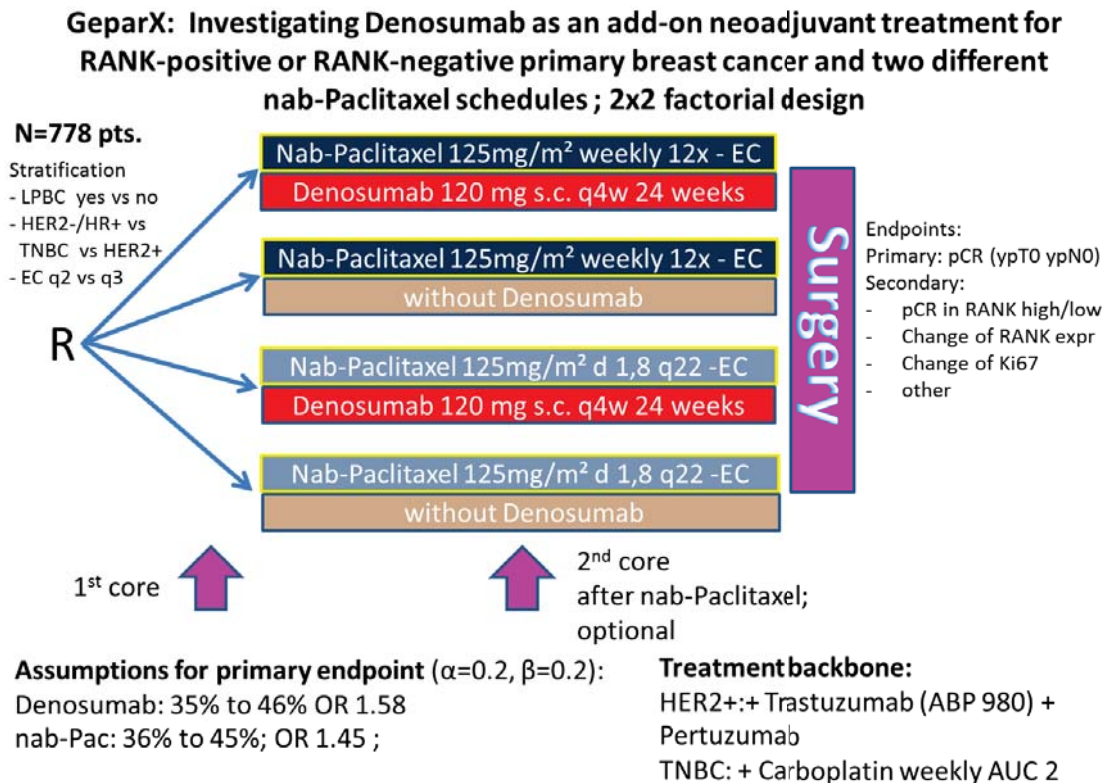


### 3. STUDY DESIGN

#### 3.1 Overall design and treatment

This is a multicenter, prospective, 2x2 randomized, open-label phase IIb study to compare neoadjuvant treatment with and without denosumab in patients with untreated early breast cancer and two different nab-paclitaxel schedules.

Figure 1 GeparX study design



Patients were first randomized to one of the following two treatments in addition to neoadjuvant therapy:

- Denosumab (120 mg s.c. q4w)
- No denosumab

Secondarily patients were randomized to:

- nPac 125mg/m<sup>2</sup> weekly (Cb)→EC
- nPac 125mg/m<sup>2</sup> day 1,8 q22 (Cb)→EC

Figure 2 GeparX treatment schedule, EC 2 weekly

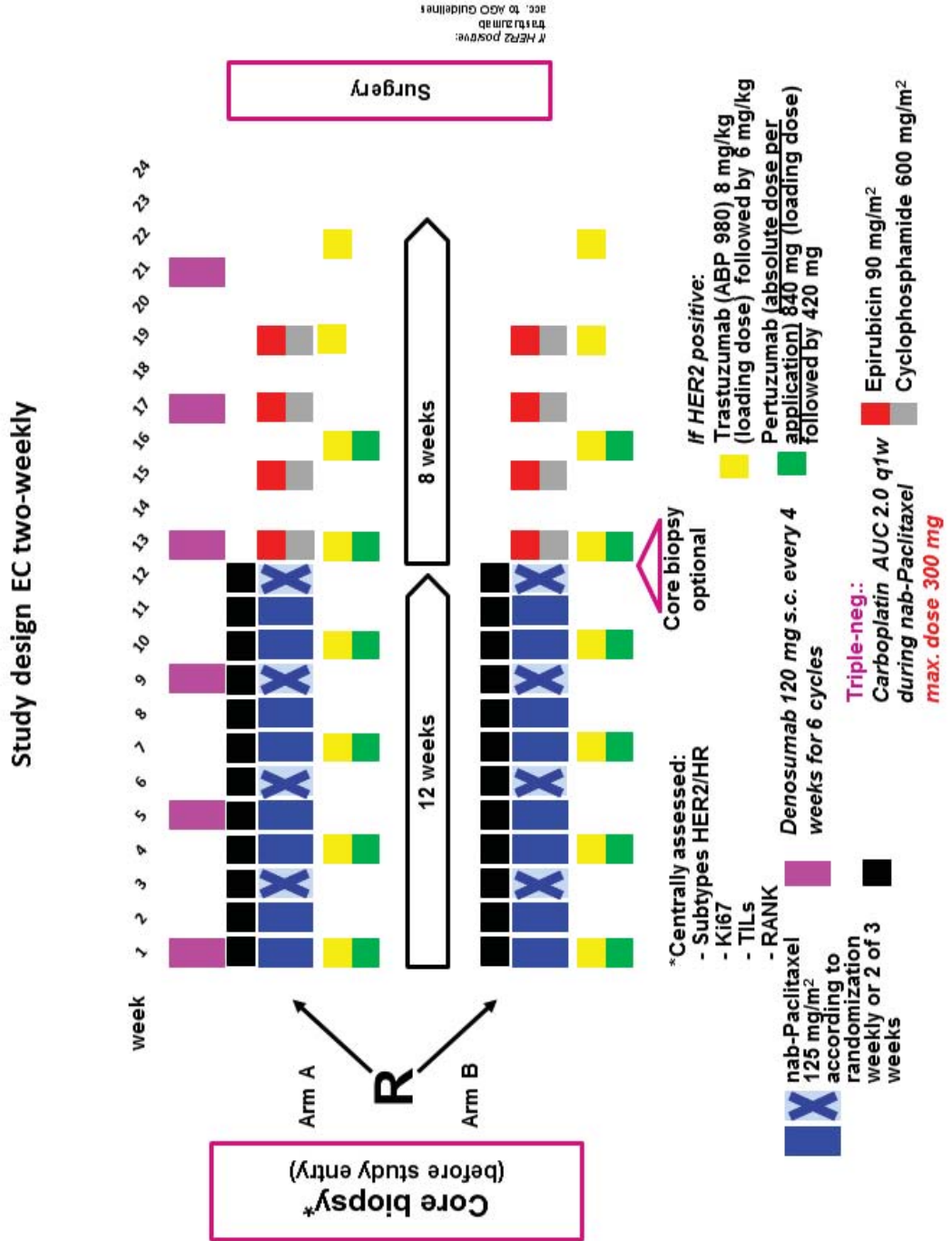
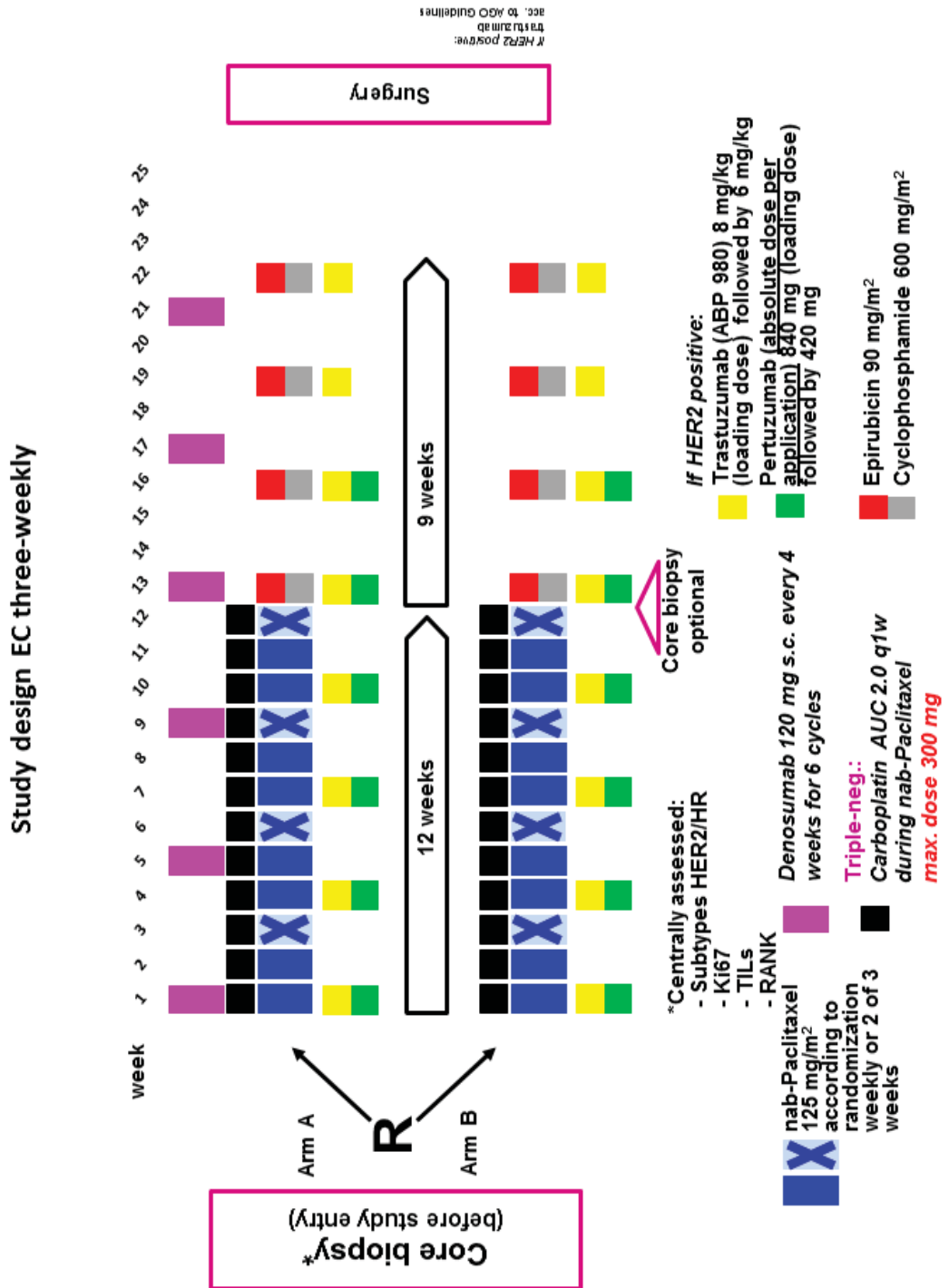


Figure 3 GeparX treatment schedule, EC 3 weekly



Carboplatin was given in TNBC in addition to nPac and the HER2+ substudy is a cohort study investigating open label non- randomized use of trastuzumab biosimilar ABP 980 in combination with pertuzumab in patients with HER+ breast cancer.

Patients with primary cT1c-cT4a-d BC and centrally assessed HR, HER2, Ki-67, and sTILs on core biopsy could be enrolled.

In all study arms, treatment was to be given until surgery, disease progression, unacceptable toxicity, withdrawal of consent of the patient, or termination by the Sponsor.

### **3.2 Randomization/stratification**

Patients were first randomized (using Pocock minimization [4]) to one of the following two treatments in addition to neoadjuvant therapy:

- Denosumab (120 mg s.c. q4w)
- No denosumab

Stratification (minimization) factors for the randomization are:

- LPBC (negative (defined as  $\leq 50\%$  stromal tumor infiltrating lymphocytes) / present (defined as  $> 50\%$  stromal tumor infiltrating lymphocytes))
- Subtype (HER2-/HR+ vs TNBC vs. HER2+)
- EC every 2 vs EC every 3 weeks

Secondarily patients were randomized (using Pocock minimization) to:

- nPac 125mg/m<sup>2</sup> weekly (Cb) → EC
- nPac 125mg/m<sup>2</sup> day 1,8 q22 (Cb) → EC

The first randomization (denosumab) was an additional minimization factor for the second randomization (chemotherapy regimen).

### **3.3 Sample size computation**

The sample size calculation was based on the following assumptions for the primary endpoint:

- Improvement of the pCR rate by denosumab in all patients from 35% to 46% (OR=1.58)
- Improvement of the pCR rate by different schedules of chemotherapy (nPac 125mg day 1,8 q22 (Cb) → EC arm to nPac 125mg w (Cb) → EC) will be 36% to 45% (OR=1.45)

With 778 recruited patients, the primary  $\chi^2$ -test of pCR rates between denosumab and no denosumab arms will have 92% power to the 2-sided significance level  $\alpha=0.10$ . The  $\chi^2$ -test of pCR rates between nPac 125mg w (Cb) → EC) to nPac 125mg day 1,8 q22 (Cb) → EC arms will have 80% power to the 2-sided significance level  $\alpha=0.10$ .

Sample size for the  $\chi^2$ -test was computed using nQuery Advisor 6.02.

It was planned to recruit 778 subjects into this study.

The sample size calculation for the HER2+ substudy was based on the primary endpoint of the main study:

All patients with HER2+ disease enrolled into the study will receive ABP 980 in addition to pertuzumab and backbone chemotherapy.

It was planned to recruit approximately 150 subjects into this substudy.

#### 4. STUDY OBJECTIVES, ENDPOINTS AND COVARIATES

##### 4.1 Objectives and endpoints

###### 4.1.1 Primary efficacy

There are two co-primary objectives:

- A: To compare the pathological complete response (pCR= ypT0 ypN0) rates of neoadjuvant treatment with or without denosumab in addition to backbone treatment consisting of nPac 125mg/m<sup>2</sup> weekly (Cb)→EC or nPac 125mg/m<sup>2</sup> day 1,8 q22 (Cb)→EC plus anti-HER2 treatment (i. e. ABP 980/pertuzumab in case of positive HER2-status) in patients with early breast cancer.
- B: To compare the pathological complete response (pCR= ypT0 ypN0) rates of nPac 125mg/m<sup>2</sup> weekly(Cb)→EC or nPac 125mg/m<sup>2</sup> day 1,8 q22 (Cb)→EC plus anti-HER2 treatment (i. e. ABP 980/pertuzumab in case of positive HER2-status) in patients with early breast cancer.

The primary efficacy endpoint is **pathological complete response (pCR=ypT0 ypN0)** defined as no microscopic evidence of residual viable invasive or non-invasive tumor cells in any resected specimens of the breast and axillary nodes (ypT0, ypN0). Pathological response will be 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 will be counted as no pCR. Patients with negative sentinel node biopsy prior to treatment start and no axillary surgery after chemotherapy will be counted as pCR, if they have 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 will be counted as pCR (preferably axillary dissection instead of

sentinel node biopsy was strongly recommended in this situation). Patients with no axillary surgery at all will be counted as no pCR.

Patients who have not received breast surgery count as no pCR.

#### 4.1.2 Secondary efficacy, short-term

- To assess the pCR rates per arm for patients with RANK high and RANK low prospectively and centrally by IHC; to test for interaction of denosumab treatment with RANK expression.
- To assess the pCR rates per arm in subgroups according to stratification (minimization) factors.
- To determine the rates of ypT0/Tis ypN0; ypT0 ypN0/+; ypT0/Tis ypN0/+; ypT(any) ypN0 for both randomizations.
- To determine the response rates of the breast tumor and axillary nodes based on physical examination and imaging tests (sonography, mammography, or MRI) after treatment in both arms for each randomization.
- To determine the breast conservation rate after each treatment.
- To correlate response (complete vs. partial vs. no change) measured by best appropriate imaging method after the first two cycles of treatment with pCR.
- To assess mammographic density—changes induced by denosumab.

The corresponding endpoints definitions are:

- **ypT0/Tis ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0** are defined according to the TNM classification [5], the same algorithm as for the primary pCR definition will be used to assess ypN0 for ypT0/is ypN0, ypT(any) ypN0 in case of no axilla surgery after chemotherapy
- **Clinical (c) and imaging (i) response** was assessed every 6 weeks and before surgery by physical examination and imaging tests. Sonography is the preferred examination, however, if sonography appears not to provide valid results or is not performed, MRI or mammography will be considered with decreasing priority for all categories except complete response which must be confirmed in all available imaging tests. The same imaging method should be considered for the measurement before and after treatment. If no imaging is available, palpation will be considered. Clinical (imaging) response of the breast is defined as:

- **Complete response (CR)**

Complete disappearance of all tumor signs in the breast as assessed by all imaging tests. The response of the axillary nodes is not to be considered.

- **Partial response (PR)**

Reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more assessed by imaging test or palpation. In patients with multifocal or multicentric disease, the lesion with the largest diameters should be chosen for follow-up. The response of the axillary nodes is not to be considered.

- **Stable disease (NC)**

No significant change in tumor size during treatment. This category includes no change, an estimated reduction of the tumor area by less than 50%, or an estimated increase in the size of the tumor area lesions of less than 25% measured by imaging test or palpation.

- **Progressive disease (PD)**

Development of new, previously undetected lesions, or an estimated increase in the size of pre-existing lesions by 25% or more after at least 6 weeks of therapy.

To derive the overall clinical/imaging response, response for each reported method will be taken as reported by the investigator. Clinical/imaging response will be reported before surgery (end of treatment) and early response after 2 cycles of treatment. If a patient discontinued treatment, the last available assessment will be used for the clinical response before surgery.

- **Response of the axillary nodes** is defined (only in cN+ patients without SNB at baseline) as a) conversion from cN+ at baseline to cN0 before surgery and b) conversion from cN+ at baseline to ypN0 at surgery; both definitions will be presented separately.

cN+ vs cN0 at baseline is defined as follows (SNB is not taken into account):

- cN+, if
  - LN biopsy (core or fine needle) positive, irrespective of sonography or palpation
  - cN+ by sonography, no biopsy

- cN+ by palpation, no sonography, no biopsy
- cN0, if
  - LN biopsy (core or fine needle) negative, irrespective of sonography or palpation
  - cN0 by sonography and no biopsy, irrespective of palpation
  - cN0 by palpation, no sonography, no biopsy

cN before surgery is defined as

- cN0, if
  - cN0 by sonography, irrespectively of palpation
  - cN0 by palpation, if no sonography performed
- cN+, if
  - cN+ by sonography, irrespectively of palpation
  - cN+ by palpation, if no sonography performed
- **Breast conservation (BCS)** is defined as tumor resection, segmental resection, or quadrant resection as last surgical procedure.
- Additionally (not specified in the protocol), the **axilla conservation** defined as SNB only (before or after chemotherapy).
- **Mammographic density** score is defined as follows:
  1. The breast is almost entirely fatty.
  2. There are scattered areas of fibroglandular density
  3. The breast is heterogenously dense, which may obscure small masses.
  4. The breast is extremely dense, which lowers the sensitivity of mammography

The difference in the mammographic density score between pre-surgery and baseline mammography will be computed.

#### 4.1.3 Secondary efficacy, long-term

- To determine invasive disease-free survival (iDFS), EFS (event free survival), loco-regional invasive recurrence free interval (LRRFI), distant-disease-free survival (DDFS), and overall survival (OS) for all treatment arms and according to stratified subpopulations.

The corresponding endpoints are:

- **Invasive disease-free survival (iDFS)** is defined according to [6] as time in months from randomization until any invasive loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant



recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Progression under therapy is not considered as an event for iDFS. Patients without event will be censored at the date of the last contact.

- **Event-free survival (EFS)** is defined according to [6, 7] as time in months from randomization until any progression of disease rendering the tumor inoperable, any invasive loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Patients without event will be censored at the date of the last contact.
- **Loco-regional invasive recurrence free interval (LRRFI)** is defined according to [6] as time in months from randomization until any loco-regional (ipsilateral breast (invasive), chest wall, local/regional lymph nodes) recurrence of disease or any invasive contralateral breast cancer whichever occurs first. Progression under therapy is not considered as an event for LRRFI. Distant recurrence, secondary malignancy, and death are considered competing risks. Patients without event or competing event will be censored at the date of the last contact.
- **Distant disease free survival (DDFS)** is defined according to [6] as time in months from randomization until any distant recurrence of disease, any secondary malignancy or death due to any cause whichever occurs first. Patients without event will be censored at the date of the last contact.
- **Overall survival (OS)** is defined as time in months from randomization until death due to any cause. Patients alive will be censored at the date of the last contact.

As no study specific treatment or investigation is planned after end of systemic treatment, follow up is not part of this study. However, information on the health status of the patients is collected either based on yearly chart reviews at the sites or based on information deriving from the GBG registry of previous study participants. All time-to-event endpoints will be derived based on the actual report time.

#### 4.1.4 Safety

- To assess the toxicity, including time to onset of peripheral sensory neuropathy grade 2-4 and resolution of peripheral sensory neuropathy grade 2-4 to grade

The corresponding endpoints are:

- **Toxicity (adverse events)** will be assessed according to the NCI-CTCAE version 4.0 [8] and will be reported for the whole treatment duration and for the nab-paclitaxel and EC portion of the treatment separately. Congestive heart failure will be assessed by NYHA class. LVEF assessment had to be performed according to guidelines for anti-HER2 treatment and anthracycline therapy (e.g. after taxane and prior to surgery); LVEF decreased by  $\geq 10\%$  and to  $< 50\%$  will be reported.
- **Time of onset** of grade 2-4 PSN is defined as the first cycle in which the peripheral sensory neuropathy of grade  $\geq 2$  occurred; additionally, time to onset of grade 3-4 PSN will be considered.
- **Time of resolution of grade 2-4 PSN to at least grade 1** is defined as time in weeks between first occurrence of grade 2-4 peripheral sensory neuropathy and its resolution to grade  $\leq 1$ . Patients in which peripheral sensory neuropathy persists grade  $\geq 2$  will be censored at the date of the last assessment of peripheral sensory neuropathy grade. Additionally, time to resolution of grade 3-4 PSN will be analyzed.

#### 4.1.5 Compliance

- To assess compliance

The corresponding endpoints are:

- **premature treatment discontinuations** (with reasons)
- **dose reductions** (with reasons)
- **treatment delays** (with reasons)
- **treatment interruptions** (skipped infusions, with reasons)
- additionally, for nab-paclitaxel d1, 8 q22 arm **not respecting the pause in week 3** will be reported, as well as any case of overdose
- **Relative total dose** and **relative total dose intensity**.

##### 4.1.5.1 *Relative total dose (RTD) and Relative total dose intensity (RTDI) of chemotherapy*

RTDI is the dose intensity achieved by a patient relative to intended dose intensity based on the planned schedule.

RTDI will be calculated according to the following step-by-step algorithm.

**Planned dose (PnD)** is the amount of a drug planned to be given in a cycle/week. PnD is calculated separately for each component of a therapy.

**Planned total dose (PTD)** is the planned cumulative dose over the entire treatment duration; i.e. if a patient was planned to receive  $n$  cycles/weeks of drug, then sum the total amount of drug planned during those  $n$  cycles/weeks.

$$\text{i.e. } PTD(\text{mg}) = \sum_{i=1}^n PnD_i$$

**Planned total dose intensity (PTDI)** is the planned average dose intensity over the entire treatment duration.

$$\text{i.e. } PTDI(\text{mg/week}) = \frac{PTD}{\text{planned duration of therapy (weeks)}}$$

**Actual dose (AD)** is the total amount of drug that the patient has received over one cycle/week.

**Actual total dose (ATD)** is the cumulative doses of the drug that have been given over the treatment duration of  $n$  cycles/weeks.

$$\text{i.e. } ATD(\text{mg}) = \sum_{i=1}^n AD_i$$

**Actual total dose intensity (ATDI)** is defined as the dose intensity of what has actually been administered over the  $n$  cycles/weeks, calculated as actual total dose divided by the treatment duration in weeks.

$$\text{i.e. } ATDI(\text{mg/week}) = \frac{ATD}{\text{duration of therapy (weeks)}}$$

For those patients who die on study, or those who withdraw from chemotherapy due to disease progression, the planned total dose intensity as well as planned total dose will be calculated based on the actual duration of treatment in weeks: [(treatment end date) - (treatment start dated)]/7.

For all other patients who discontinued chemotherapy prematurely, including those due to toxicity, the remaining cycles/weeks will be considered to be a zero dose without delay, and the PTD will be as initially planned.

The last cycle/week (the regular one or the last one before the withdrawal) is always assumed to have the planned length, the treatment end date is the last day of the last cycle/week.

If a patient has not received some drug at all, ATD and ATDI for this drug are considered to be 0.

**Relative Total Dose (RTD)** is the ratio of ATD and PTD, expressed as a percentage.

$$\text{i.e. } RTD(\%) = \frac{ATD}{PTD} \times 100$$

**Relative Total Dose Intensity (RTDI)** is the ratio of ATDI and PTDI, expressed as a percentage.

$$\text{i.e. } RTDI(\%) = \frac{ATDI}{PTDI} \times 100$$

Note that RTDI expresses the effect of reductions, interruptions and delays as well as premature discontinuation in a treatment.

The RTD (RTDI) of EC will be computed as an average from RTD (RTDI) of E and C; for the triple-negative patients the RTD (RTDI) of the taxane portion of the treatment will be computed as an average from RTD (RTDI) of nab-paclitaxel and carboplatin. The overall RTD (RTDI) of chemotherapy will be computed as an average from RTD (RTDI) of EC and nab-paclitaxel ± carboplatin. It will be reported as a continuous endpoint and in groups  $RTDI < 85\%$  vs  $RTDI \geq 85\%$ .

Additionally, RTDI and RTD of nab-paclitaxel based on the weekly schedule will be computed for both arms.

#### 4.1.6 Quality of life (QoL)

- To assess quality of life with a focus on persisting peripheral sensory neuropathy using the FACT-Taxane (Version 4) questionnaire.

The corresponding endpoints are:

- FACT Taxane scores at baseline, after nab-paclitaxel treatment, prior to surgery and 90 days after surgery.

#### 4.1.7 Objectives of the HER2+ substudy

Primary:

- To assess the pathological complete response (pCR= ypT0 ypN0) rate of neoadjuvant treatment with ABP 980 and pertuzumab in the overall HER2+ cohort and compare them with the results obtained in the GeparSepto study (the results will be presented separately for nab-paclitaxel 150 mg/m<sup>2</sup> GeparSepto, nab-paclitaxel 125mg/m<sup>2</sup> GeparSepto and for each chemotherapy arm of GeparX study, all in ITT sets).

- To compare the pathological complete response (pCR= ypT0 ypN0) rate of nPac 125mg/m<sup>2</sup> weekly followed by EC or nPac 125mg/m<sup>2</sup> day 1,8 q22 followed by EC plus anti-HER2 treatment (i. e. ABP 980 / pertuzumab in case of positive HER2-status) in patients with early breast cancer.

The endpoint pCR is the same as for the main study.

Secondary:

- To assess the pCR rate in subgroups by denosumab.
- To assess the pCR rates in HER2+ patients treated with ABP 980 in subgroups according to HR status.
- To determine the pCR rates in the overall HER2+ cohort of ypT0/Tis ypN0; ypT0 ypN0/+; ypT0/Tis ypN0/+; ypT(any) ypN0 for both randomizations.
- To determine the response rates on the HER2+ cohort of the breast tumor and axillary nodes based on physical examination and imaging tests (sonography, mammography, or MRI) after treatment in both arms for each randomization.
- To determine the breast conservation rate in the HER2+ cohort.
- To assess the toxicity and compliance for the HER2+ cohort treated with ABP 980 and by systemic therapy (nabPaclitaxel 125mg/m<sup>2</sup> continuously vs. 2/3; EC, Denosumab yes vs. no).
- To specifically address the incidence of diarrhea and cardiovascular events overall and by subgroup
- To assess the toxicity with EC and ABP 980/pertuzumab.
- To determine loco-regional invasive recurrence free interval (LRRFI), distant-disease-free survival (DDFS), invasive disease-free survival (IDFS), EFS (event free survival) and overall survival (OS) for all HER2+ patient treated with ABP 980/pertuzumab.

The corresponding endpoints are the same as for the main study.

#### **4.1.8 Objectives of the DTC substudy**

Primary:

- Does the application of denosumab in terms of an add-on neoadjuvant treatment eradicate DTCs in the bone marrow (BM) of breast cancer patients?

Corresponding endpoint is the absence of DTCs after NACT in patients with DTCs detected at baseline.

Secondary:

- Does a potential eradication of DTCs by add-on neoadjuvant denosumab treatment correlate with the pCR rate?

Corresponding endpoint is pCR (primary definition).

#### **4.1.9 Other substudies and correlative science objectives**

All other substudies (urinary miRNA sampling, pharmacogenetic substudy) and correlative science objectives defined in the study protocol will be analyzed according to the separate SAPs.

## **4.2 Subgroups or covariates of interest**

### **4.2.1 Subgroups**

#### **4.2.1.1 Subgroups for efficacy analysis**

The primary endpoint pCR (ypT0 ypN0) as well as secondary endpoints pCR (ypT0/is ypN0), IDFS, DDFS and OS will be analyzed in the subgroups defined by the stratification factors:

- LPBC (negative (defined as  $\leq 50\%$  stromal tumor infiltrating lymphocytes) / present (defined as  $> 50\%$  stromal tumor infiltrating lymphocytes))
- Subtype (HER2-/HR+ vs TNBC vs. HER2+)
- EC every 2 vs EC every 3 weeks
- Denosumab arm (for nab-paclitaxel comparison)
- Nab-paclitaxel arm (for denosumab comparison, not a stratification but will be included for the sake of symmetry)

Additionally, a subgroup analysis of pCR (ypT0 ypN0) according to the *gBRCA* mutation- status will be performed:

- No mutation/unknown vs *gBRCA 1* or 2 mutation

Additionally, the primary endpoint pCR (ypT0 ypN0) will be analyzed in the subgroups according to RANK high vs low for both randomizations. Since there is no well-established cutoff for the RANK expression high vs low, the cutoff will be defined based on the distribution of RANK expression (e.g. 75% percentile).

Additionally, the endpoints pCR (ypT0 ypN0), pCR (ypT0/Tis ypN0), ypT0 ypN0/+, ypT0/Tis ypN0/+, ypT(any) ypN0, breast conservation, response of breast and LN, LRRFI, iDFS, DDFS, EFS and OS will be analyzed for the HER2+ subgroup (trastuzumab biosimilar substudy) by both randomizations.

#### **4.2.1.2 Subgroups for safety and compliance analysis**

Key safety (brief summary of AEs, AEs any grade and high grade for the whole treatment duration and reported under nab-paclitaxel for nab-paclitaxel randomization, SAEs) and key compliance (treatment discontinuations, dose reductions, dose delays and interruptions, RTD and RTDI) will be analyzed in the subgroups according to the additional treatment according to the biological subtype (since HER2-positive patients receive additionally trastuzumab biosimilar (ABP 980) and pertuzumab and TNBC patients receive carboplatin).

For the subgroup of the HER2-positive patients treated with trastuzumab biosimilar ABP 980 AEs any grade and high grade reported under EC will be additionally analyzed.

#### **4.2.2 Covariates**

For the primary endpoint pCR (ypT0 ypN0) a multivariate analysis including both randomizations and adjusting for the stratification parameters

- LPBC (negative (defined as  $\leq 50\%$  stromal tumor infiltrating lymphocytes) / present (defined as  $> 50\%$  stromal tumor infiltrating lymphocytes))
- Subtype (HER2-/HR+ vs TNBC vs. HER2+)
- EC every 2 vs EC every 3 weeks

will be performed.

For the primary endpoint pCR (ypT0 ypN0) as well as secondary endpoints pCR (ypNT0/is ypN0), IDFS, DDFS and OS a multivariate analysis including both randomizations will be performed adjusting for stratification factors and additionally for

- Age (<40 years vs.  $\geq 40$  years)
- Tumor size by sonography ( $\leq 25$ mm vs  $> 25$  mm, as in GeparSepto)
- cT1-3 vs. cT4
- Nodal status (cN0 vs. cN+ combined, (by sonography, palpation and core- or fine needle biopsy, as described in 4.1.2))
- Grade (1-2 vs. 3)
- pCR (ypT0 ypN0 definition, for time-to-event endpoints)

In the study protocol also histological tumor type was listed as a potential covariate for the multivariate analysis but will be omitted (the vast majority of the patients is expected to be NST).

#### **4.2.3 STEPP analysis**

A STEPP analysis [9] will be performed in each arm to explore influence of the nab-paclitaxel RTDI and RTD (both based on the weekly schedule) on the pCR rate.

### **5. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL**

In Amendment 1 the HER2+ substudy was added to the protocol; no other changes in any amendment (Amendments 1 to 3) were relevant for the statistical analysis.

### **6. ANALYSIS SUBSETS**

The primary analysis set is the ITT set.

#### **6.1 Data subsets**

##### **6.1.1 Intent-to-treat set/full analysis set**

A 'intent-to-treat' (ITT) analysis set includes all patients who were randomized.

##### **6.1.2 Per protocol (PP) set**

Patients who fulfilled all relevant study criteria at the time of randomization, started treatment and in whom no major protocol violation occurred in the course of the study will be included into the per-protocol analysis. Major protocol violations according to protocol are:

- Prior chemotherapy treatment for any malignancy or endocrine treatment for breast cancer
- Absence of documentation of protocol specified tumor
- Axilla dissection at baseline
- No surgery unless due to progression/death
- No LN surgery at all or no LN surgery after chemotherapy in case of positive SNB at baseline
- Additional off-study chemotherapy or radiotherapy before surgery, except patients with disease progression, those are included and are counted as no pCR
- Patients who did not started treatment



- Patients, who did not receive at least 2 cycles of the treatment, except those who progressed earlier on.

Premature termination of the treatment after second cycle is not per se a major protocol deviation, i.e. patients in whom the study was prematurely terminated for reasons which might be related to the study medication (e.g. adverse events) are included in the per protocol analysis.

Patients who were treated not according to the randomized arm (for details s. 6.1.4.1) will be included in the per protocol analysis as treated, as for safety.

### **6.1.3 Evaluable subsets for efficacy**

For the analysis of breast conservation rate only patients who received breast surgery will be included. For the analysis of axilla conservation rate only patients who received axilla surgery (SNB or axilla dissection) before or after neo-adjuvant treatment will be included.

For the time-to-event analysis according to pCR or adjusted by pCR a landmark analysis set will be used, with the 28 weeks landmark (24 weeks treatment as per 3-weekly EC-schedule) plus 4 weeks for surgery).

### **6.1.4 Evaluable subsets for safety**

#### **6.1.4.1 Safety set**

Patients from the ITT population will be included into the safety analysis, if they received at least one dose of study drug.

If a patient randomized to no denosumab has accidentally received denosumab, this patient is analyzed for safety, compliance and QoL in the denosumab arm. Patients randomized to denosumab who did not receive at least one dose of denosumab will be analyzed in the no denosumab arm.

Patients randomized in the nab-paclitaxel day 1,8 q22 arm in whom there was no pause at day 15 in at least 2 cycles will be analyzed for safety, compliance and QoL in the nab-paclitaxel weekly arm; 1 cycle with no pause will be tolerated.

#### **6.1.4.2 Safety subset according to the treatment by biological subtype**

As described in section 4.2.1.2, key safety and compliance endpoints will be analyzed in the subsets defined by the treatment added to the backbone according to the biological subtype:

- HER2-/HR+ (no additional treatment)
- TNBC (Carboplatin)
- HER2+ (trastuzumab biosimilar (ABP 980)+ pertuzumab)

Patients who are not TNBC but received carboplatin by mistake will be included in the carboplatin group.

#### **6.1.5 Evaluable subsets for QoL**

The safety set is the basis subset for QoL analysis. For each time point only patients providing QoL questionnaire at this time point will be included in the analysis of QoL; the number of patients included for each time point will be reported.

### **6.2 Interim analyses**

First 202 randomized patients were included in the interim analysis for safety (200 planned in the protocol, but all patients randomized on the day when 200th patient was randomized were included).

### **6.3 Subgroup analyses**

For each subgroup analysis all patients belonging to the corresponding subgroup will be included; since the subgroup variables except *gBRCA* and RANK are the minimization factors, it is expected that there will be no missings and it will be possible to include each patient in one of the categories for each subgroup variable. For the analysis according to RANK only patients with known RANK result will be included. For the analysis according to *gBRCA* all patients will be included, patients with missing *gBRCA* assessment will be included in the subgroup together with the *gBRCA* negative in the “*gBRCA* negative/unknown” group.

## **7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES**

One interim analysis for safety defined in the protocol was performed in the first 202 patients randomized according to the separate SAP.

## **8. DATA SCREENING AND ACCEPTANCE**

### **8.1 General principles**

The documentation and verification procedure is described in the study protocol and the Data Management Plan [10].

## **8.2 Database lock**

A database snapshot to analyze top line results for the SABCS 2019 was done prior to database lock of the complete trial.

Final Database lock is planned for Q3/2020.

## **8.3 Data handling and electronic transfer of data**

The data will be exported from the clinical database of the MedCODES system running on MySQL 5.0 into MS ACCESS 2010 database. Histology data reviewed by an independent pathologist are entered by the independent pathologist into MedCODES histology database and will be handled in the same way.

RANK data will be transferred from the central pathology to GBG as an Excel table. DTC data will be transferred from the laboratory as an Excel table.

All data will be converted to the SAS format. The data will be analyzed using SAS® (Statistical Analysis Software) Version 9.4 with SAS Enterprise Guide Version 7.1 on Microsoft Windows 7 Enterprise.

## **8.4 Handling of missing and incomplete data, drop-outs**

Patients from the ITT set in whom success cannot be determined (e.g. patients in whom histology is not evaluable) will be included in the denominator, i.e. these patients will be evaluated as treatment failures.

For all time-to-event endpoints, missing or incomplete dates of events will be imputed as follows: when day is missing, the first day of the month will be assigned. However, if it is in the month and year of first study drug dose, then the date of first dose of study drug will be assigned. If month is missing, January will be assigned. However, if it is in the year where there was a follow-up report for the patient, then the date of the last event-free contact to the patient in this year plus one day will be taken.

All other missing values will be reported explicitly. All percent values will be valid percent.

## **8.5 Outliers**

Most variables in the analysis are categorical so the outlier problems are not applicable to them.

Before converting hematology values in CTC-grades by Data Management, outliers will be examined and queries will be sent out by the Data Management.

Outliers in RTD and RTDI (overdose) will be carefully checked, queries will be sent out by the Data Management. Cases of confirmed overdose will be listed.

#### **8.6            Distributional characteristics**

No tests for distribution will be performed. Non-parametrical tests will be used for all continuous baseline variables.

#### **8.7            Testing/validation plan**

The data will be analyzed using SAS<sup>®</sup> (Statistical Analysis Software) Version 9.4 with SAS Enterprise Guide Version 7.1 on Microsoft Windows 7 Enterprise.

Analysis programs will be validated according to the GBG SOPs.

All computer programs will be clearly documented (using commenting facilities within programs) and stored. All SAS-logs will be stored.

### **9.            STATISTICAL METHODS OF ANALYSIS**

#### **9.1            General principles**

All categorical variables will be summarized as number and percent of patients in each category. Continuous parameters will be summarized as mean, standard deviation, median, minimum and maximum. Time-to-event variables will be presented using Kaplan-Meier product-limit estimator.

Primary objectives A and B will be tested according to the improved Bonferroni procedure: the smaller of the two p-values will be compared with  $\alpha = 0.1$  and the larger p-value will be compared with  $\alpha = 0.2$  to keep the overall significance level of the study of  $\alpha = 0.2$  [11]. All confidence intervals for the primary endpoint will be 90% CI (for the second comparison additionally 80%); additionally, 95% CIs will be reported.

The significance level for all further analyses is set to a two-sided  $\alpha = 0.05$ ; 95% CIs will be reported as appropriate (90% CIs additionally only for the secondary pCR definitions and time-to-event endpoints).

All multivariate models will be fit as full models without variable selection. Multivariate analyses will be presented in tables and as forest plots.

Subgroup analyses will be presented in tables and as forest plots. No adjustment of  $\alpha$  is planned for the subgroup analysis which should be considered as explorative.

## 9.2 Subject accountability

The number of patients in each of the following categories will be reported:

- Screened patients
- Screen failure patients and reasons for screen failure, if available
- Randomized patients (ITT set)
  - Of them HER2-/HR+
  - Of them TNBC
  - Of them HER2+
- Randomized but not treated patients with reason for not starting treatment
- Randomized and treated patients
  - Of them HER2-/HR+
  - Of them TNBC
  - Of them HER2+
- Patients who received treatment not according to the randomized arm
- Patients who completed both nab-paclitaxel and EC treatment
- Patients who completed nab-paclitaxel treatment
- Patients who discontinued nab-paclitaxel treatment by main reason for permanent treatment discontinuation
- Patients who started EC treatment (after completion or discontinuation of nab-paclitaxel)

- Patients who completed EC treatment
- Patients who discontinued EC treatment by main reason for permanent treatment discontinuation
- Patients who did not have surgery (with reasons)
- Patients who received surgery
- Status at the last study contact – will be reported with the time-to-event outcome analysis
- Included in different additional analysis sets, as appropriate – will be presented together with the corresponding analyses.

It will be checked for each patient enrolled whether she violates any of the inclusion or exclusion criteria.

Median follow-up time will be estimated with the inverse Kaplan-Meier method and the completeness of the follow-up will be assessed according to [12].

For the composite time-to-event endpoints the frequency table for different types of events (and competing events, if applicable) will be included.

### **9.3 Randomization irregularities**

Following randomization irregularities will be reported if occurred:

- an ineligible patient is randomized
- a patient is randomized based on an incorrect stratum
- a patient is randomized twice
- a computer program error in a dynamic randomization scheme.

### **9.4 Demographic and baseline characteristics**

The demographic and baseline characteristics will be reported descriptively per treatment arm and overall. The Pearson  $\chi^2$ -test (for categorical parameters with more than 2 categories), Fisher exact test (for binary parameters), Wilcoxon-Mann-Whitney test (for continuous parameters) will be used to assess the comparability of two randomized treatment arms.

These statistical tests are to be considered descriptive, no adjustment for minimization is planned.

Following demographic and baseline characteristics will be included:

- Age at randomization
- Gender
- Height, weight, BMI
- Karnofsky index
- Menopausal status
- Unilateral vs bilateral tumor, unifocal vs multifocal vs multicentric by palpation/sonography
- Tumor size by palpation/sonography, cT, cN – by palpation, by sonography
- Core- or fine needle biopsy of lymph node none/negative/positive
- Combined cN0 vs cN+ (by sonography, palpation and core- or fine needle biopsy, as described in 4.1.2)
- SNB yes/no, positive/negative/not detected, if yes
- ER/PgR, HER2, breast cancer subtype (stratification)
- Grading, histological tumor type
- Ki67, continuous and  $\leq 20\%$  vs  $> 20\%$  (stratification)
- LPBC yes vs no (stratification,  $\geq 50\%$  vs  $< 50\%$ )
- Family risk yes vs no
- gBRCA (local test) mt vs wt vs unknown
- LVEF and other cardiac medical history at baseline
- General medical history
- Concomitant medication

Continuous data will be summarized using the number of available data, mean, standard deviation, median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

## **9.5 Primary efficacy analyses**

Primary objectives A and B will be tested according to the improved Bonferroni procedure: the smaller of the two p-values will be compared with  $\alpha = 0.1$  and the larger p-value will be compared with  $\alpha = 0.2$  to keep the overall significance level of the study of  $\alpha = 0.2$  [11].

### **9.5.1 Estimation of outcomes**

The primary endpoint will be summarized as pathological complete response rate for each treatment group for both randomizations. Two-sided 80%, 90% and 95% confidence intervals will be calculated according to Pearson and Clopper. [13]

The difference in the rates of pathological complete response will be evaluated as rate difference (for primary objective A denosumab arm minus no-denosumab arm; for primary objective B nPac 125w (Cb) →EC minus nPac day 1,8 q22 (Cb) →EC arm) with 90% and 95% confidence interval. Additionally, an odds ratio with the 90% and 95% confidence intervals will be reported.

### **9.5.2 Hypotheses to be tested**

The null hypothesis is that there is no difference in pCR rates between treatment arms; the alternative hypothesis is that there is a difference for both randomizations. The significance will be tested with the two-sided Cochran-Mantel-Haenszel  $\chi^2$ -test stratified by the minimization factors as well as the other randomization; according to the improved Bonferroni procedure.

The minimization factors for the stratified analysis will be taken according to the value reported in the clinical database, irrespectively of misclassifications at the time of randomization.

Secondarily, the unstratified continuity-corrected  $\chi^2$ -test will be reported.

### **9.5.3 Regression analysis**

Uni- and multivariate logistic regressions will be performed for pCR to adjust for the minimization factors as well as for the other factors listed in 4.2.2, based on the ITT population. The odds ratios will be reported with the 90% and 95% confidence interval

Additionally, a multivariate logistic regression including all factors listed in 4.2.2 and interaction between denosumab and chemotherapy arms will be performed.

### **9.5.4 Subgroup analysis**

The primary endpoint will be analyzed in the subgroups listed in 4.2.1.1.



For both randomizations, pathological complete response rates for each treatment group will be reported with two-sided 90% and 95% confidence intervals.

The difference in the rates of pathological complete response will be evaluated as rate difference (for primary objective A denosumab arm minus no-denosumab arm; for primary objective B nPac 125w (Cb) →EC minus nPac day 1,8 q22 (Cb) →EC arm) with 90% and 95% confidence interval. Additionally, an odds ratio with the 90% and 95% confidence interval will be reported. The significance will be tested with the two-sided Cochran-Mantel-Haenszel  $\chi^2$ -test stratified by the minimization factors (except the one defining the subgroup) as well as the other randomization. Additionally, the unstratified continuity-corrected  $\chi^2$ -test will be reported.

Additionally, odds ratios between arms (for each randomization) with 90% and 95% CI will be calculated in subgroup using the logistic regression; Breslow-Day test will be used to test for interaction between treatment arm and binary subgroup variable, for the biological subtype the interaction p-value will be the Wald p-value from the logistic regression including treatment arm, subtype and their interaction.

There will be no adjustment for the multiple comparisons in the analyses for the stratified subgroups.

Analysis of the primary endpoint in the subgroups RANK high vs RANK low is exploratory; further exploratory analysis according to RANK may be performed.

#### **9.5.5 STEPP analysis**

A tail-oriented STEPP analysis [9] will be performed in each arm to explore influence of the nab-paclitaxel RTD and RTDI (based on the weekly schedule) on the pCR rate. It is to be considered explorative and will be presented graphically.

### **9.6 Secondary efficacy analyses**

Secondary efficacy endpoints will be analyzed in ITT set.

Short-term secondary efficacy endpoints (clinical and imaging response rates, ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT<sub>(any)</sub> ypN0, breast and axilla conservation), mammographic density changes will be analyzed together with the primary efficacy.

The time-to-event efficacy endpoints (IDFS, DDFS, LRRFI, EFS and OS) will be analyzed at a later time point: the analysis of the time-to-event endpoints will be event-driven and will occur after 248 iDFS events occurred (which will give 80% power to the stratified log-rank test with  $\alpha=0.05$

to detect the HR of 0.7 between the nab-paclitaxel treatment arms (similar to the GeparSepto iDFS analysis plan).

### 9.6.1 Estimation of outcomes

The following secondary endpoints

- Clinical and imaging response rates after 6 weeks of treatment and before surgery
- ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT<sub>(any)</sub> ypN0
- breast conservation
- axilla conservation

will be summarized as number and percent of patients for each treatment group. Two-sided 90% (only for secondary pCR definitions) and 95% confidence intervals will be calculated according to Pearson and Clopper and odds ratios between treatment groups from univariate logistic regression will be reported for all of them, as well as the difference in the rates and its 90% (only for secondary pCR definitions) and 95% CI correspondingly.

Cross-table of pCR (primary definition) vs early (after 2 cycles) clinical response will be reported, overall and per arm for each randomization.

Mammographic density at baseline and pre-surgery as well as its change will be presented in the frequency tables as well as mean, median, StD, minimum and maximum for denosumab vs no denosumab arms.

The time-to-event efficacy outcomes will be analyzed after the end of the study by referring to data from GBG patient's registry. Curves will be estimated using the Kaplan-Meier method, based on the ITT population (patients who did not start treatment will be censored at day 1). Kaplan-Meier estimates of 3-, 4- and 5-year (if median follow-up is sufficient) probability of survival will be provided together with the 95% and 90% CI.

### 9.6.2 Hypotheses to be tested

2-sided Cochran-Mantel-Haenszel  $\chi^2$ -test to the significance level of  $\alpha = 0.05$  stratified by the minimization factors as well as the other randomization will be used to compare clinical and imaging response rates of breast and lymph nodes, ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT<sub>(any)</sub>, ypN0, breast conservation, axillary conservation between arms.

2-sided log-rank test stratified by the same factors to the significance level of  $\alpha = 0.05$  will be used to compare time-to-event efficacy outcomes between treatment arms, except LRRFI where stratified Gray test will be used.

2-sided Wilcoxon-Mann-Whitney rank-sum test will be used to compare mammographic density changes with vs without denosumab.

### **9.6.3 Regression analysis**

Univariate and multivariate logistic regression will be performed for ypT0/is ypN0 to report odds ratios with 90% and 95% CI and to adjust for the factors listed in 4.2.2.

Univariate and multivariate Cox proportional hazards model will be used for IDFS, EFS, DDFS, OS, to report hazard ratios with 90% and 95% CI and (for IDFS, DDFS and OS) to adjust for the factors listed in 4.2.2.

The results will be presented in tables and graphically as forest-plots.

Fine-Gray model will be used for LRRFI to report hazard ratio with 90% and 95% CI.

### **9.6.4 Subgroup analysis**

The key secondary endpoints (ypT0/is ypN0, IDFS, DDFS, OS) will be analyzed in the subgroups listed in 4.2.1.1. There will be no adjustment for multiple comparisons in the analyses in subgroups which are to be considered explorative.

In the subgroup analysis of ypT0/is ypN0, a Breslow-Day interaction test will be performed to assess interaction between treatment arm and binary subgroup; for the breast cancer subtype a logistic regression with an interaction term will be performed to assess interaction.

The interaction with treatment arm for IDFS, DDFS, and OS will be assessed by including and interaction term into Cox proportional model.

## **9.7 Safety analyses**

All safety analyses will be performed using the evaluable subset for safety.

AE data will be aggregated based on the maximal grade that the patient experienced within each PT during the reporting period. If a patient experiences more than one AE within a PT for the same summary period, only the AE with the worst NCI CTCAE v. 4.0 severity grade will be included in the summaries of severity ('patients-based'). For summaries of relationship the AEs

classified as related with the worst NCI CTCAE v.4.0 severity grade and will be included. No imputation of missing grades will be performed.

Predefined, free-text AEs, and Adverse Events of Special Interest (AESIs) are documented with CTC grades (NCI-CTCAE version 4.0, NYHA for cardiac events) on the CRFs. The hematological parameters will be converted into CTC grades according to the GBG Laboratory Value Guideline 8 [14] and all AEs will be classified using MedDRA classification system version 19.1 by Data Management.

Unless otherwise specified, AEs will be summarized by frequency and percentage of patients with the AE in the category of interest, by treatment arm (for both randomizations) and overall.

Anemia, leucopenia, neutropenia, febrile neutropenia and thrombocytopenia will be merged into 'Any hematological toxicity'. All other AEs will be merged into 'Any non-hematological toxicity'. All AEs will be aggregated into 'Any AE'.

Hematological and non-hematological SAEs will be included into analysis of AEs and will be additionally reported per patient in the same categories and aggregated as 'any SAE' per patient.

Free text AEs occurred in at least 5% of patients will be reported according to MedDRA preferred terms, less frequent AEs will be included into "other AE SOC XX".

Grades for the AESIs assessed only as "yes/no" on the AESI page will be taken from the AESI reported on the SAE form; AESI page will be reconciled by Data Management with the reports on SAE form.

### **9.7.1 Estimation of outcomes**

A "Brief summary of AEs" table will be included summarizing the above mentioned categories, both for the whole treatment duration and separately for nab-paclitaxel and EC part of treatment, for all AEs and for treatment-related AEs:

- Any hematological AE any grade (with 95% CI)
- Any hematological AE grade 3-4 (with 95% CI)
- Any non-hematological AE any grade (with 95% CI)

- Any non-hematological AE grade 3-4 (with 95% CI)
- Any hematological SAE
- Any non-hematological SAE
- Any AESI

The occurrence of each AE category will be displayed for the whole treatment duration and separately for nab-paclitaxel and EC part of treatment, for all AEs and for treatment-related AEs, as

- a. number and percentage of grades 1-4 (any grade) vs no AE per treatment group and overall,
- b. number and percentage of grades 3-4 (high grade) vs no AE or grade 1-2 per treatment group and overall,
- c. number and percentage of patients per grade (none, grade 1, grade 2, grade 3, grade 4) per treatment group and overall.

No grade 5 will be used in the AE tables. Any death of patients under therapy (during the chemotherapy and within 30 days following the last treatment) will be listed together with the treatment arms, cycle number, and primary death cause.

AEs leading to treatment discontinuation will be reported in following categories per each treatment arm and overall:

- Hematological toxicity
- Cardiac toxicity
- Dental event (for denosumab only)
- Other non-hematological toxicity
- AE not related to study medication

They will also be listed with the AE term and the cycle/week after which treatment was discontinued.

Decreased LVEF in any assessment (by  $\geq 10\%$  and to  $< 50\%$ ) during therapy will be reported per patient, per treatment arm and overall.

### **9.7.2 Hypotheses to be tested**

Occurrence rates of each AEs (any grade and high grade) and decreased LVEF will be compared between treatment arms for both randomizations using the exact test of Fisher. These p-values are descriptive in nature and no adjustment for alpha inflation will be performed.

### **9.7.3 Subgroup analysis for safety**

Key safety analyses (brief summary of AEs, AEs any grade and high grade for the whole treatment duration and reported under nab-paclitaxel for nab-paclitaxel randomization, SAEs), will be also performed according to the biological subtype (s. 4.2.1.2).

## **9.8 Compliance analyses**

Compliance will be analyzed using the evaluable subset for safety.

### **9.8.1 Estimation of outcomes**

The incidence and reasons of permanent chemotherapy discontinuation will be reported per patient, for each treatment arm and overall.

The incidence and reasons of permanent denosumab discontinuation will be reported per patient, per chemotherapy arm and overall for patients who received denosumab.

The incidence and reasons of permanent targeted treatment discontinuation before chemotherapy will be reported per HER2-positive patient for each treatment arm and overall.

Reasons for treatment discontinuation will be grouped as (single choice)

- Local progression
- Distant relapse/secondary malignancy
- Death
- Adverse event:
  - Hematological toxicity
  - Cardiac toxicity
  - Dental event (only for denosumab)
  - (Other) non-hematological toxicity
  - AE not related to study medication

- Patient's decision
- Investigator decision

Following measures of treatment completeness will be reported (for each treatment arm and overall):

- Number of chemotherapy weeks (infusions) for nab-paclitaxel
- number of cycles (infusions) for EC and anti-HER2 treatment
- number of injections for denosumab.

The incidence and reasons of nab-paclitaxel, EC delays will be reported per patient for each treatment arm and overall.

The incidence and reasons of denosumab delays will be reported per patient for each chemotherapy treatment arm and overall for patients who received denosumab.

The incidence and reasons of chemotherapy dose reductions and interruptions (omitted infusions) will be reported per patient, for each treatment arm and overall; the premature discontinuation of a single chemotherapy drug will be counted as an interruption.

The incidence and reasons of targeted treatment (trastuzumab biosimilar ABP 980, pertuzumab) delays and interruptions will be reported per HER2-positive patient, for each treatment arm and overall.

Reasons for dose delays, dose reductions and interruptions will be grouped according to CRF as (multiple choice):

- Organizational (for delays, up to 3 days)
- AE:
  - Cardiac toxicity
  - Hematological toxicity
  - (Other) non-hematological toxicity
  - AE not related to study medication
- Other

Completeness of treatment for each drug will be presented graphically as a bar chart, per week for nab-paclitaxel and carboplatin and per cycle for EC arm.

Relative total dose and relative total dose intensity of chemotherapy (each drug and overall) and of denosumab will be reported descriptively per treatment arm and overall, as continuous variables and in cross-tables  $\geq 85\%$  vs  $< 85\%$ . Additionally, RTD and RTDI of nab-paclitaxel based on the weekly schedule will be reported as continuous variables per chemotherapy arm and overall.

### **9.8.2 Hypotheses to be tested**

Fisher exact test will be used to compare the incidence of treatment discontinuations and modifications. Wilcoxon-Mann-Whitney test will be used to compare the chemotherapy duration, RTD and RTDI. The p-values will be reported as is without adjusting for multiple comparisons and are to be considered descriptive.

### **9.8.3 Subgroup analysis for compliance**

Key compliance analyses (discontinuations, dose reductions, delays and interruptions, RTD and RTDI) will be performed in the subgroups according to the biological subtype in the similar way.

## **9.9 Quality-of-life analyses**

FACT-Taxane Questionnaire is available together with the scoring guideline under <http://www.facit.org/FACITOrg/Questionnaires>.

5 scales (Physical well-being, Social/Family well-being, Emotional well-being, Functional well-being and Additional Concerns) as well as the FACT-Taxane Trial Outcome Index (FACT-Taxane TOI), the FACT-G total score and the FACT-Taxane total score will be computed per completed questionnaire according to the scoring guideline [15] and will be presented per treatment arm for both randomizations at baseline, after nab-paclitaxel, at EOT and 90 days after surgery, in tables as mean and StD and (if necessary for publication) graphically as boxplots. Number and percentage of patients choosing the worst two item categories will be reported for each of 5 subscales per arm for both randomizations, at every time point.

QoL analysis will be based on the evaluable subset for safety. Number of evaluable questionnaires will be reported per time point.



### **9.10 Analyses of the HER2+ substudy**

Objectives of the HER2+ substudy will be analyzed using the same methods as the main study.

### **9.11 Analyses of the DTC substudy**

DTC presence at baseline will be presented in a frequency table per denosumab arm and overall for all patients evaluated in the DTC substudy.

In the patients DTC positive at baseline the eradication after NACT will be presented per denosumab arm and overall and compared between arms with the exact test of Fisher. pCR rates will be presented in the patients DTC positive at baseline according to the eradication after NACT and compared with the exact test of Fisher.

## **10. LIST OF PLANNED TABLES, FIGURES, LISTINGS, AND APPENDICES**

All listed tables and graphs will be created for each of the two randomizations, if applicable and not stated otherwise.

### **10.1 Patient disposition**

- Tables: Flow of patients (3 tables – per each randomization and in 4 treatment groups)
- List: Screened but not randomized patients
- List: Randomized patients who did not start therapy and are not included into the safety set
- List: Violations of inclusion/exclusion criteria
- List: Other randomization irregularities
- List: Patients who did not receive surgery
- List: Patients excluded from per protocol analysis
- Tables: Completeness of follow-up (with time-to-event outcome analysis)
- Figure: Scatterplot of follow-up duration (with time-to-event outcome analysis)
- Figure: Shifted inverse Kaplan-Meier curve of expected vs real follow-up
- Tables: Status at the last follow-up (with time-to-event outcome analysis)

## 10.2 Baseline and subject characteristics

- Tables. Subject and baseline characteristics, part I (continuous parameters), 3 tables – for each randomization and in 4 groups according to both randomizations
- Tables. Subject and baseline characteristics, part II (categorical and ordinal parameters), 3 tables – for each randomization and in 4 groups according to both randomizations
- Tables: Cardiac assessment at baseline
- Tables: Findings in ECG at baseline
- List: Other findings in ECG at baseline, specification
- Tables: Findings in echocardiogram at baseline
- List: Other findings in echocardiogram at baseline, specification
- Tables: LVEF at baseline
- Tables: General medical history at baseline
- Tables: Relevant concomitant medication at baseline

## 10.3 Primary efficacy

- Tables: pCR (ypT0 ypN0), primary endpoint
- Table: Logistic regression pCR (ypT0 ypN0), primary endpoint, adjusted for stratification factors
- Table: Univariate logistic regressions pCR (ypT0 ypN0), primary endpoint
- Table: Multivariate logistic regression pCR (ypT0 ypN0), primary endpoint
- Table: Multivariate logistic regression pCR (ypT0 ypN0), primary endpoint, with interaction between chemotherapy and denosumab arms
- Figure: Forest plot of multivariate logistic regression pCR (ypT0 ypN0), primary endpoint

- Tables: pCR (ypT0 ypN0), primary endpoint, in subgroups, cross-table
- Tables: pCR (ypT0 ypN0), primary endpoint, in subgroups, logistic regressions
- Figures: Forest plot pCR (ypT0 ypN0), primary endpoint, in subgroups
- Tables: pCR (ypT0 ypN0), primary endpoint, per protocol analysis
- Tables: pCR (ypT0 ypN0), primary endpoint, in subgroups according to *gBRCA* mutation status, cross-table
- Tables: pCR (ypT0 ypN0), primary endpoint, in subgroups according to *gBRCA* mutation status, logistic regressions
- Tables: pCR (ypT0 ypN0), primary endpoint, in subgroups according to RANK, cross-table
- Tables: pCR (ypT0 ypN0), primary endpoint, in subgroups according to RANK, logistic regressions
- Figure: STEPP analysis of pCR according to nab-paclitaxel RTD
- Figure: STEPP analysis of pCR according to nab-paclitaxel RTDI

#### 10.4 Secondary short-term efficacy

- Tables: Secondary pCR definitions ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT<sub>(any)</sub> ypN0
- Table: Logistic regression ypT0/is ypN0 (secondary endpoint) adjusted for stratification factors
- Table: Univariate logistic regressions ypT0/is ypN0 (secondary endpoint)
- Table: Multivariate logistic regression ypT0/is ypN0 (secondary endpoint)
- Figure: Forest plot of multivariate logistic regression ypT0/is ypN0 (secondary endpoint)
- Tables: ypT0/is ypN0 (secondary endpoint) in subgroups, cross-table
- Tables: ypT0/is ypN0 (secondary endpoint) in subgroups, logistic regressions

- Figures: Forest plot ypT0/is ypN0 (secondary endpoint) in subgroups
- Tables: Breast conservation rate
- Tables: Axillary surgery
- Tables: Clinical (imaging) response of the breast after 2 cycles of treatment
- Tables: Clinical (imaging) response of the breast before surgery
- Tables: Response of axillary nodes by sonography and palpation
- Tables: Response of axillary nodes by histology
- Tables: Clinical/imaging response after 2 cycles of treatment vs pCR (5 tables – overall and for each treatment arm for each randomization)
- Tables: Mammographic density score, frequencies
- Tables: Mammographic density score, continuous

#### **10.5 Secondary efficacy, time-to-event outcomes**

- Tables: first IDFS event
- Figures: Kaplan-Meier graph for IDFS
- Tables: IDFS rates
- Table: Univariate Cox regressions IDFS
- Table: Multivariate Cox regression IDFS
- Figure: Forest plot of multivariate Cox regression IDFS
- Tables: Subgroup analysis of IDFS
- Figures: Forest plot of IDFS subgroup analysis
- Tables: first EFS event
- Figures: Kaplan-Meier graph for EFS

- Tables: EFS rates
- Tables: LRRFI events and competing events
- Figures: CIF graph for LRRFI
- Tables: LRRFI - cumulative incidence
- Tables: first DDFS event
- Figures: Kaplan-Meier graph for DDFS
- Tables: DDFS rates
- Table: Univariate Cox regressions DDFS
- Table: Multivariate Cox regression DDFS
- Figure: Forest plot of multivariate Cox regression DDFS
- Tables: Subgroup analysis of DDFS
- Figures: Forest plot of DDFS subgroup analysis
- Figures: Kaplan-Meier graph for OS
- Tables: OS rates
- Table: Univariate Cox regressions OS
- Table: Multivariate Cox regression OS
- Figure: Forest plot of multivariate Cox regression OS
- Tables: Subgroup analysis of OS
- Figures: Forest plot of OS subgroup analysis

## **10.6 Safety**

- Tables: Brief summary of adverse events, all patients
- Tables: Brief summary of adverse events, patients with no treatment additional to

backbone (HER2-/HR+)

- Tables: Brief summary of adverse events, patients treated with carboplatin (TNBC)
- Tables: Brief summary of adverse events, patients treated with trastuzumab biosimilar (ABP980) and pertuzumab (HER2+)
- List: Deaths under therapy
- Tables: Pre-defined AEs any grade and grade 3-4, per patient, all patients
- Tables: Pre-defined AEs any grade and grade 3-4, HER2-/HR+ patients
- Tables: Pre-defined AEs any grade and grade 3-4, TNBC patients
- Tables: Pre-defined AEs any grade and grade 3-4, HER2+ patients
- Tables: Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, per patient, all patients
- Tables: Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, HER2-/HR+ patients
- Tables: Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, TNBC patients
- Tables: Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, HER2+ patients
- Tables: Pre-defined AEs any grade and grade 3-4 under EC, per patient, all patients
- Tables: Pre-defined AEs any grade and grade 3-4 under EC, HER2-/HR+ patients
- Tables: Pre-defined AEs any grade and grade 3-4 under EC, TNBC patients
- Tables: Pre-defined AEs any grade and grade 3-4 under EC, HER2+ patients
- Tables: Other AEs any grade and grade 3-4, per patient, all patients
- Tables: AEs all grades, any patient
- Tables: Brief summary of treatment related adverse events, all patients
- Tables: Treatment-related AEs any grade and grade 3-4, per patient, all patients

- Tables: Treatment-related AEs all grades, per patient, all patients
- Tables: SAEs summary table, all patients
- Tables: SAEs summary table, HER2-/HR+ patients
- Tables: SAEs summary table, TNBC patients
- Tables: SAEs summary table, HER2+ patients
- List: SAEs line-listing
- List: AEs leading to treatment discontinuations
- Tables: LVEF decreased, all patients
- Tables: LVEF decreased, HER2-/HR+ patients
- Tables: LVEF decreased, TNBC patients
- Tables: LVEF decreased, HER2+ patients

## **10.7 Compliance**

### **10.7.1 Discontinuations**

- Tables: Discontinuations of chemotherapy, all patients
- Tables: Discontinuations of chemotherapy, HER2-/HR+ patients
- Tables: Discontinuations of chemotherapy, TNBC patients
- Tables: Discontinuations of chemotherapy, HER2+ patients
- Table: Discontinuations of denosumab, only patients who started denosumab

### **10.7.2 Treatment completeness**

- Tables: Number weeks nab-paclitaxel, all patients, frequencies
- Tables: Number weeks nab-paclitaxel, HER2-/HR+ patients, frequencies
- Tables: Number weeks nab-paclitaxel, TNBC patients, frequencies

- Tables: Number weeks nab-paclitaxel, HER2+ patients, frequencies
- Tables: Number weeks nab-paclitaxel, all patients, continuous
- Tables: Number weeks nab-paclitaxel, HER2-/HR+ patients, continuous
- Tables: Number weeks nab-paclitaxel, TNBC patients, continuous
- Tables: Number weeks nab-paclitaxel, HER2+ patients, continuous
- Tables: Number weeks carboplatin, TNBC patients, frequencies
- Tables: Number weeks carboplatin, TNBC patients, continuous
- Tables: Number cycles EC, all patients, frequencies
- Tables: Number cycles EC, HER2-/HR+ patients, frequencies
- Tables: Number cycles EC, TNBC patients, frequencies
- Table: Number cycles EC, HER2+ patients, frequencies
- Tables: Number cycles EC, all patients, continuous
- Tables: Number cycles EC, HER2-/HR+ patients, continuous
- Tables: Number cycles EC, TNBC patients, continuous
- Tables: Number cycles EC, HER2+ patients, continuous
- Table: Number injections denosumab, all patients, frequencies
- Table: Number injections denosumab, HER2-/HR+ patients, frequencies
- Table: Number injections denosumab, TNBC patients, frequencies
- Table Number injections denosumab, HER2+ patients, frequencies
- Table: Number injections denosumab, all patients, continuous
- Table: Number injections denosumab, HER2-/HR+ patients, continuous
- Table: Number injections denosumab, TNBC patients, continuous



- Table Number injections denosumab, HER2+ patients, continuous

### 10.7.3 Dose delays

- Tables: Any dose delay with reasons, all patients
- Tables: Any dose delay with reasons, HER2-/HR+ patients
- Table: Any dose delay with reasons, TNBC patients
- Table: Any dose delay with reasons, HER2+ patients
- Tables: Dose delay nab-paclitaxel with reasons, all patients
- Tables: Dose delay nab-paclitaxel with reasons, HER2-/HR+ patients
- Tables: Dose delay nab-paclitaxel with reasons, TNBC patients
- Tables: Dose delay nab-paclitaxel with reasons, HER2+ patients
- Tables: Dose delay carboplatin with reasons, TNBC patients
- Tables: Dose delay EC with reasons, all patients
- Tables: Dose delay EC with reasons, HER2-/HR+ patients
- Tables: Dose delay EC with reasons, TNBC patients
- Tables: Dose delay EC with reasons, HER2+ patients
- Table: Dose delay denosumab with reasons, all patients
- Table: Dose delay denosumab with reasons, HER2-/HR+ patients
- Table: Dose delay denosumab with reasons, TNBC patients
- Table: Dose delay denosumab with reasons, HER2+ patients

### 10.7.4 Dose reductions

- Tables: Any chemotherapy dose reduction with reasons, all patients
- Tables: Any chemotherapy dose reduction with reasons, HER2-/HR+ patients

- Tables: Any chemotherapy dose reduction with reasons, TNBC patients
- Tables: Any chemotherapy dose reduction with reasons, HER2+ patients
- Tables: Dose reduction nab-paclitaxel with reasons, all patients
- Tables: Dose reduction nab-paclitaxel with reasons, HER2-/HR+ patients
- Tables: Dose reduction nab-paclitaxel with reasons, TNBC patients
- Tables: Dose reduction nab-paclitaxel with reasons, HER2+ patients
- Tables: Dose reduction carboplatin with reasons, TNBC patients
- Tables: Dose reduction EC with reasons, all patients
- Tables: Dose reduction EC with reasons, HER2-/HR+ patients
- Tables: Dose reduction EC with reasons, TNBC patients
- Tables: Dose reduction EC with reasons, HER2+ patients

#### **10.7.5 Treatment interruptions**

- Tables: Any skipped chemotherapy infusion, with reasons, all patients
- Tables: Any skipped chemotherapy infusion, with reasons, HER2-/HR+ patients
- Tables: Any skipped chemotherapy infusion, with reasons, TNBC patients
- Tables: Any skipped chemotherapy infusion, with reasons, HER2+patients
- Tables: Skipped infusion nab-paclitaxel, with reasons, all patients
- Tables: Skipped infusion nab-paclitaxel, with reasons, HER2-/HR+ patients
- Tables: Skipped infusion nab-paclitaxel, with reasons, TNBC patients
- Tables: Skipped infusion nab-paclitaxel, with reasons, HER2+patients
- Tables: Skipped infusion carboplatin, with reasons, TNBC patients
- Tables: Skipped infusion EC, with reasons, all patients

This table will be presented only overall, since few skipped EC infusions are expected

- Table: Skipped injections denosumab with reasons, all patients
- Table: Skipped injections denosumab with reasons, HER2-/HR+ patients
- Table: Skipped injections denosumab with reasons, TNBC patients
- Table: Skipped injections denosumab with reasons, HER2+ patients
- Table: pause in d 1, 8 nab-paclitaxel schedule not respected

#### **10.7.6 Bar charts of compliance**

- Figures: Bar charts of nab-paclitaxel compliance, one chart for each chemotherapy arm
- Figures: Bar charts of carboplatin compliance (triple-negative patients), for each chemotherapy arm
- Figures: Bar chart of EC compliance, for each chemotherapy arm

#### **10.7.7 RTD and RTDI**

- Tables: Relative total dose of chemotherapy, all patients
- Tables: Relative total dose of chemotherapy, HER2-/HR+ patients
- Tables: Relative total dose of chemotherapy, TNBC patients
- Tables: Relative total dose of chemotherapy, HER2+ patients
- Tables: Relative total dose intensity of chemotherapy, all patients
- Tables: Relative total dose intensity of chemotherapy, HER2-/HR+ patients
- Tables: Relative total dose intensity of chemotherapy, TNBC patients
- Tables: Relative total dose intensity of chemotherapy, HER2+ patients
- Tables: Relative total dose and relative total dose intensity of nab-paclitaxel, based on weekly schedule, all patients

## 10.8 QoL (FACT-Taxane)

- Tables: FACT-Taxane scores according to the time point
- Figures: Boxplots of FACT-Taxane scores according to the time point (optional, if necessary for publication; no shell provided; boxplots in treatment groups repeated for all relevant time points)
- Tables: Patients choosing the worst two item categories according to the time point

## 10.9 HER2+ substudy

Some of the tables listed here are the same as are listed for the Her2+ subgroup for the main study; they will be included in the statistical report twice – with the results of the main study and for the HER2+ substudy, to keep all relevant results together.

### 10.9.1 Efficacy

- Table: pCR (ypT0 ypN0) in HER2+ patients, by nab-paclitaxel arm (and overall)
- Table: pCR (ypT0 ypN0) in HER2+ patients, by denosumab arm
- Table: pCR (ypT0 ypN0) in HER2+ patients in subgroups by HR status, crosstable, denosumab arm
- Table: pCR (ypT0 ypN0) in HER2+ patients in subgroups by HR status, crosstable, nab-paclitaxel arm
- Tables: pCR ypT0/Tis ypN0, ypT0 ypN0/+, ypT0/Tis ypN0/+, ypT(any) ypN0 in HER2+ patients, both randomizations
- Tables: Breast conservation in HER2+ patients, both randomizations
- Tables: Axillary surgery in HER2+ patients, both randomizations
- Tables: Clinical (imaging) response of breast after 2 cycles in HER2+ patients, both randomizations
- Tables: Clinical (imaging) response of breast before surgery in HER2+ patients, both randomizations
- Tables: Response of axillary nodes by sonography and palpation in HER2+ patients, both

randomizations

- Tables: Response of axillary nodes by histology in HER2+ patients, both randomizations
- Figures: iDFS in HER2+ patients, both randomizations
- Tables: iDFS rates in HER2+ patients, both randomizations
- Figures: EFS in HER2+ patients, both randomizations
- Tables: EFS rates in HER2+ patients, both randomizations
- Figures: DDFS in HER2+ patients, both randomizations
- Tables: DDFS rates in HER2+ patients, both randomizations
- Figures: LRRFI in HER2+ patients (CIF curves), both randomizations
- Tables: LRRFI rates in HER2+ patients, both randomizations
- Figures: OS in HER2+ patients, both randomizations
- Tables: OS rates in HER2+ patients, both randomizations

#### **10.9.2 Safety and compliance**

- Tables: Brief summary of adverse events, patients treated with trastuzumab biosimilar (ABP980) and pertuzumab (HER2+)
- List: Deaths under therapy, HER2-positive patients
- Tables: AEs any grade and grade 3-4, HER2+ patients
- Tables: AEs all grades, any patient, HER2+ patients
- Tables: Brief summary of treatment related adverse events, HER2+ patients
- Tables: Treatment-related AEs any grade and grade 3-4, per patient, HER2+ patients
- Tables: Treatment-related AEs all grades, per patient, HER2+ patients
- Tables: SAEs summary table, HER2+ patients

- List: SAEs line-listing, HER2+ patients
- List: AEs leading to treatment discontinuations, HER2+ patients
- Tables: LVEF decreased, HER2+ patients
- Tables: AEs any grade and high grade reported under EC in HER2+ patients
- Tables: Discontinuations of all treatments, HER2+ patients
- Tables: Discontinuations of anti-HER2 treatment before chemotherapy; HER2-positive patients only
- Tables: Number of anti-HER2 treatment infusions, HER2-positive patients only, frequencies
- Tables: Number of anti-HER2 treatment infusions, HER2-positive patients only, continuous
- Tables: Number weeks nab-paclitaxel, HER2+ patients, frequencies
- Tables: Number weeks nab-paclitaxel, HER2+ patients, frequencies
- Table: Number cycles EC, HER2+ patients, frequencies
- Table: Number cycles EC, HER2+ patients, continuous
- Table: Number injections denosumab, HER2+ patients, frequencies
- Table: Number injections denosumab, HER2+ patients, continuous
- Table: Any dose delay with reasons, HER2+ patients
- Tables: Dose delay nab-paclitaxel with reasons, HER2+ patients
- Tables: Dose delay EC with reasons, HER2+ patients
- Table: Dose delay denosumab with reasons, HER2+ patients
- Table: Dose delay trastuzumab biosimilar ABP980 and/or pertuzumab, with reasons, HER2+ patients

- Tables: Any chemotherapy dose reduction with reasons, HER2+ patients
- Tables: Dose reduction nab-paclitaxel with reasons, HER2+ patients
- Tables: Dose reduction EC with reasons, HER2+ patients
- Table: Dose reduction denosumab with reasons, HER2+ patients
- Tables: Any skipped chemotherapy infusion, with reasons, HER2+patients
- Tables: Skipped infusion nab-paclitaxel, with reasons, HER2+patients
- Tables: Skipped injection denosumab, with reasons, HER2+patients
- Table: Skipped infusion trastuzumab biosimilar ABP980 and/or pertuzumab, with reasons, HER2+ patients

#### **10.10 DTC substudy**

- Table. Subject and baseline characteristics of patients included in the DTC substudy, part I (continuous parameters), per denosumab randomization arm
- Table. Subject and baseline characteristics of patients included in the DTC substudy,, part II (categorical and ordinal parameters), per denosumab randomization arm
- Table: DTC at baseline and eradication of DTC after chemotherapy
- Tables: DTC at baseline vs pCR (overall and per biological subtype; also for each denosumab randomization arm separately, all patients and per biological subtype)
- Table: Eradication of DTC after chemotherapy vs pCR (overall and per biological subtype; also for each denosumab randomization arm separately, all patients)

### **11. PRIORITIZATION OF ANALYSES**

The topline results on pCR, discontinuations and SAEs will be reported at SABCS 2019.

Final analysis of all short-term endpoints (including QoL 90 days after surgery) is planned for Q2/2020.

Final analysis of time-to-event endpoints will be performed at a later time point when the follow-up is mature.

## 12. LITERATURE CITATIONS / REFERENCES

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12. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up, *The Lancet*, Vol. 359 April 13, 2002
13. Pearson S & Clopper C. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 26:404-13, 1934
14. GBG Laboratory Value Guideline, Version 8
15. FACT-Taxane Scoring Guidelines Version 4



### 13. DATA NOT COVERED BY THIS PLAN

Substudies on urinary miRNA sampling and pharmacogenetic as well as additional correlative science objectives will be analyzed separately, according to the separate SAPs.

### 14. APPENDIX TABLES/FIGURES/LISTINGS SHELLS

#### 14.1 Patient disposition

**Table 1 Flow of patients, denosumab arm**

<i>Patient status</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>
Number of patients screened			XX
Number of patients randomized	XX	XX	XX
- of them HER2-/HR+	XX	XX	XX
- of them TNBC	XX	XX	XX
- of them HER2+	XX	XX	XX
Number of patients started treatment	XX	XX	XX
- of them HER2-/HR+	XX	XX	XX
- of them TNBC	XX	XX	XX
- of them HER2+	XX	XX	XX
Number of patients treated not according to randomization	XX	XX	XX
Completed both nab-paclitaxel and EC treatment	XX (XX)	XX (XX)	XX (XX)
Completed nab-paclitaxel treatment	XX (XX)	XX (XX)	XX (XX)
Discontinued nab-paclitaxel treatment	XX (XX)	XX (XX)	XX (XX)
- local progressive disease	XX (XX)	XX (XX)	XX (XX)
- distant metastases/secondary malignancy	XX (XX)	XX (XX)	XX (XX)
- death	XX (XX)	XX (XX)	XX (XX)
- AE	XX (XX)	XX (XX)	XX (XX)
- investigator's decision	XX (XX)	XX (XX)	XX (XX)
- patient's wish	XX (XX)	XX (XX)	XX (XX)

<i>Patient status</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>
Started EC (after completion or discontinuation of nab-paclitaxel)	XX (XX)	XX (XX)	XX (XX)
Completed EC treatment	XX (XX)	XX (XX)	XX (XX)
Discontinued EC treatment	XX (XX)	XX (XX)	XX (XX)
- local progressive disease	XX (XX)	XX (XX)	XX (XX)
- distant metastases/secondary malignancy	XX (XX)	XX (XX)	XX (XX)
- death	XX (XX)	XX (XX)	XX (XX)
- AE	XX (XX)	XX (XX)	XX (XX)
- investigator's decision	XX (XX)	XX (XX)	XX (XX)
- patient's wish	XX (XX)	XX (XX)	XX (XX)
Received surgery	XX (XX)	XX (XX)	XX (XX)
No surgery	XX (XX)	XX (XX)	XX (XX)

**Table 2 Flow of patients, nab-paclitaxel arm**

Shell similar to Table 1.

**Table 3 Flow of patients, in 4 groups**

Shell similar to Table 1 but with 4 columns according to both randomizations: nPac weekly with D, nPac weekly without D, nPac d 1, 8 with D, nPac d 1, 8 without D.

**Table 4 Screened but not randomized patients**

<i>Patient number</i>	<i>Reason for screening failure</i>
XXXXp	.....

**Table 5 Randomized patients who did not start therapy (they are not included into the safety set)**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Reason for not starting therapy</i>
XXXX		X	X .....

**Table 6 Violations of inclusion and exclusion criteria**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Violation</i>
XXXX		X	X .....

**Table 7 Other randomization irregularities**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Irregularity</i>
XXXX		X	X .....

**Table 8 Patients who did not receive surgery**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Reason for not receiving surgery</i>
XXXX		X	X .....

**Table 9 Patients excluded from per protocol analysis**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Reason for being not included into per protocol analysis</i>
XXXX		X	X .....

If more than 20 patients are excluded from per protocol set, a summary table per category will be created additionally to the list.

**Table 10 Follow-up completeness, denosumab arm**

	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
Median FU, months	XX	XX	XX
Median expected FU, months	XX	XX	XX
Completeness, %	XX	XX	XX

**Table 11 Follow-up completeness, nab-paclitaxel arm**

Shell similar to Table 10.

**Figure 4 Scatterplot of follow-up duration**

No shell, standard scatterplot as described in [12].

**Figure 5 Shifted inverse Kaplan-Meier curve of expected vs real follow-up duration**

No shell, standard Kaplan-Meier curve.

**Table 12 Status at the last follow-up, denosumab arm**

<i>Patient status</i>	<i>With D N(%)</i>	<i>Without D N(%)</i>	<i>Overall N(%)</i>
-----------------------	--------------------	-----------------------	---------------------

Alive and tumor-free	XX (XX)	XX (XX)	XX (XX)
Alive after event	XX (XX)	XX (XX)	XX (XX)
Dead	XX (XX)	XX (XX)	XX (XX)

**Table 13 Status at the last follow-up, nab-paclitaxel arm**

Shell similar to Figure 5.

## 14.2 Baseline and subject characteristics

**Table 14 Subject and baseline characteristics, part I (continuous parameters), denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
Age, years	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	
Height, cm	Mean	XXX	XXX	XXX	.XXX
	StD	XX	XX	XX	
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	
Weight, kg	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	
BMI	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	
Tumor size by palpation, mm	Mean	XXX	XXX	XXX	.XXX
	StD	XX	XX	XX	
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	
Tumor size by sonography, mm	Mean	XXX	XXX	XXX	.XXX

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
Ki67, %	StD	XX	XX	XX	
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	
	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
Stromal TILs, %	Missing, N	X	X	X	
	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	

**Table 15 Subject and baseline characteristics, part I (continuous parameters), nab-paclitaxel arm**

Shell similar to Table 14.

**Table 16 Subject and baseline characteristics, part I (continuous parameters), in 4 groups**

Shell similar to Table 14 but with 4 columns according to treatment.

**Table 17 Subject and baseline characteristics, part II (categorical and ordinal parameters), denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Age, years	<30	XX (XX)	XX (XX)	XX (XX)	.XXX
	30-<40	XX (XX)	XX (XX)	XX (XX)	
	40-<50	XX (XX)	XX (XX)	XX (XX)	
	50-<60	XX (XX)	XX (XX)	XX (XX)	
	60-<70	XX (XX)	XX (XX)	XX (XX)	
	70+	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
Gender	female	XX (XX)	XX (XX)	XX (XX)	.XXX
	male	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
BMI, kg/m <sup>2</sup>	<18.5	XX (XX)	XX (XX)	XX (XX)	.XXX

<i>Parameter</i>	<i>Category</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Menopausal status	18.5-<25	XX (XX)	XX (XX)	XX (XX)	.XXX
	25-<30	XX (XX)	XX (XX)	XX (XX)	
	≥30	XX (XX)	XX (XX)	XX (XX)	
	premenopausal	XX (XX)	XX (XX)	XX (XX)	
	postmenopausal	XX (XX)	XX (XX)	XX (XX)	
	n.a. (male patient)	XX (XX)	XX (XX)	XX (XX)	
Karnofsky index	missing	X	X	X	.XXX
	80%	XX (XX)	XX (XX)	XX (XX)	
	90%	XX (XX)	XX (XX)	XX (XX)	
	100%	XX (XX)	XX (XX)	XX (XX)	
Tumor site	missing	X	X	X	.XXX
	unilateral	XX (XX)	XX (XX)	XX (XX)	
	bilateral	XX (XX)	XX (XX)	XX (XX)	
Tumor, by palpation	missing	X	X	X	.XXX
	unifocal	XX (XX)	XX (XX)	XX (XX)	
	multifocal	XX (XX)	XX (XX)	XX (XX)	
	multicentric	XX (XX)	XX (XX)	XX (XX)	
Tumor, by sonography	missing	X	X	X	.XXX
	unifocal	XX (XX)	XX (XX)	XX (XX)	
	multifocal	XX (XX)	XX (XX)	XX (XX)	
	multicentric	XX (XX)	XX (XX)	XX (XX)	
cT by palpation	missing	X	X	X	.XXX
	cT1	XX (XX)	XX (XX)	XX (XX)	
	cT2	XX (XX)	XX (XX)	XX (XX)	
	cT3	XX (XX)	XX (XX)	XX (XX)	
	cT4a-c	XX (XX)	XX (XX)	XX (XX)	
	cT4d	XX (XX)	XX (XX)	XX (XX)	
cT by sonography	missing	X	X	X	.XXX
	cT1	XX (XX)	XX (XX)	XX (XX)	
	cT2	XX (XX)	XX (XX)	XX (XX)	
	cT3	XX (XX)	XX (XX)	XX (XX)	
	cT4a-c	XX (XX)	XX (XX)	XX (XX)	
	cT4d	XX (XX)	XX (XX)	XX (XX)	
cT	missing	X	X	X	.XXX
	cT1-3	XX (XX)	XX (XX)	XX (XX)	
	cT4a-c	XX (XX)	XX (XX)	XX (XX)	
	cT4d	XX (XX)	XX (XX)	XX (XX)	

<i>Parameter</i>	<i>Category</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
cN by palpation	missing	X	X	X	
	cN0	XX (XX)	XX (XX)	XX (XX)	.XXX
	cN1	XX (XX)	XX (XX)	XX (XX)	
	cN2	XX (XX)	XX (XX)	XX (XX)	
	cN3	XX (XX)	XX (XX)	XX (XX)	
cN by sonography	missing	X	X	X	
	cN0	XX (XX)	XX (XX)	XX (XX)	.XXX
	cN1	XX (XX)	XX (XX)	XX (XX)	
	cN2	XX (XX)	XX (XX)	XX (XX)	
	cN3	XX (XX)	XX (XX)	XX (XX)	
Core- or fine needle biopsy of lymph node	not performed	XX (XX)	XX (XX)	XX (XX)	.XXX
	negative	XX (XX)	XX (XX)	XX (XX)	
	positive	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
	cN combined*	cN0	XX (XX)	XX (XX)	XX (XX)
cN+		XX (XX)	XX (XX)	XX (XX)	
missing		X	X	X	
SNB at baseline (not recommended)	none	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
	negative	XX ( XX)	XX ( XX)	XX ( XX)	
	positive	XX ( XX)	XX ( XX)	XX ( XX)	
	no sentinel node detected	XX ( XX)	XX ( XX)	XX ( XX)	
	missing	X	X	X	
ER/PgR, local assessment	both ER, PgR negative	XX (XX)	XX (XX)	XX (XX)	.XXX
	ER and/or PgR positive	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
ER/PgR, central pathology	both ER, PgR negative	XX (XX)	XX (XX)	XX (XX)	.XXX
	ER and/or PgR positive	XX (XX)	XX (XX)	XX (XX)	
HER2, local assessment	negative	XX (XX)	XX (XX)	XX (XX)	.XXX
	positive	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
HER2, central pathology	negative	XX (XX)	XX (XX)	XX (XX)	.XXX
	positive	XX (XX)	XX (XX)	XX (XX)	

<i>Parameter</i>	<i>Category</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Breast cancer subtype (stratification)	HER2-/HR+	XX (XX)	XX (XX)	XX (XX)	.XXX
	TNBC	XX (XX)	XX (XX)	XX (XX)	
	HER2+	XX (XX)	XX (XX)	XX (XX)	
Grading	G1	XX (XX)	XX (XX)	XX (XX)	.XXX
	G2	XX (XX)	XX (XX)	XX (XX)	
	G3	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
Histological tumor type	NST	XX (XX)	XX (XX)	XX (XX)	.XXX
	lobular invasive or mixed lobular	XX (XX)	XX (XX)	XX (XX)	
	other	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
Ki67 (stratification)	<=20%	XX (XX)	XX (XX)	XX (XX)	.XXX
	>20%	XX (XX)	XX (XX)	XX (XX)	
LPBC (stratification)	no (<=50% stromal TILs)	XX (XX)	XX (XX)	XX (XX)	.XXX
	yes (>50% stromal TILs)	XX (XX)	XX (XX)	XX (XX)	
Planned EC schedule (stratification)	2-weekly	XX (XX)	XX (XX)	XX (XX)	.XXX
	3-weekly	XX (XX)	XX (XX)	XX (XX)	
Family risk	no	XX (XX)	XX (XX)	XX (XX)	.XXX
	yes	XX (XX)	XX (XX)	XX (XX)	
gBRCA	mt	XX (XX)	XX (XX)	XX (XX)	.XXX
	wt	XX (XX)	XX (XX)	XX (XX)	
	unknown	XX (XX)	XX (XX)	XX (XX)	

\*as defined in 4.1.2

**Table 18 Subject and baseline characteristics, part II (categorical and ordinal parameters), nab-paclitaxel arm**



Shell similar to Table 17.

**Table 19 Subject and baseline characteristics, part II (categorical and ordinal parameters), in 4 groups**

Shell similar to Table 17 but with 4 columns according to treatment.

**Table 20 Cardiac assessment at baseline, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
<i>ECG abnormal</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>no</i>	XX ( XX)	XX ( XX)	XX ( XX)	
<i>yes</i>	XX ( XX)	XX ( XX)	XX ( XX)	
<i>missing</i>	XX ( XX)	XX ( XX)	XX ( XX)	
<i>Echocardiogram abnormal</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>no</i>	XX ( XX)	XX ( XX)	XX ( XX)	
<i>no</i>	XX ( XX)	XX ( XX)	XX ( XX)	
<i>missing</i>	XX ( XX)	XX ( XX)	XX ( XX)	

**Table 21 Cardiac assessment at baseline, nab-paclitaxel arm**

Shell similar to Table 20.

**Table 22 Findings in ECG at baseline, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
<i>Previous myocardial infarction (Heart attack)</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Evidence of myocardial infarction</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Coronary heart disease</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Cardiac arrhythmia</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Angina pectoris</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Other</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX

**Table 23 Findings in ECG at baseline, nab-paclitaxel arm**

Shell similar to Table 22.

**Table 24 Other findings in ECG at baseline, specification**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Finding in ECG</i>
XXXX	X	X	.....

**Table 25 Findings in echocardiogram at baseline, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
<i>Valvular heart disease</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Heart failure</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX
<i>Other</i>	XX ( XX)	XX ( XX)	XX ( XX)	.XXX

**Table 26 Findings in echocardiogram at baseline, nab-paclitaxel arm**

Shell similar to Table 25.

**Table 27 Other findings in echocardiogram at baseline, specification**

<i>Patient number</i>	<i>Arm 1<sup>st</sup> randomization</i>	<i>Arm 2<sup>nd</sup> randomization</i>	<i>Finding in echocardiogram</i>
XXXX	X	X	.....

**Table 28 LVEF at baseline, denosumab arm**

<i>LFEF, %</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
<i>Mean</i>	XX	XX	XX	.XXX
<i>Median</i>	XX	XX	XX	
<i>Min, max</i>	XX, XX	XX, XX	XX, XX	
<i>Missing, N</i>	X	X	X	

**Table 29 LVEF at baseline, nab-paclitaxel arm**

Shell similar to Table 28.

**Table 30 General medical history at baseline, denosumab arm**

<i>SOC</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
SOC XXX	XX (XX)	XX (XX)	XX (XX)	
SOC XXX	XX (XX)	XX (XX)	XX (XX)	
...	XX (XX)	XX (XX)	XX (XX)	

**Table 31 General medical history at baseline, nab-paclitaxel arm**

Shell similar to Table 30.

**Table 32 Relevant co-medication at baseline, denosumab arm**

<i>Co-medication</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
None	XX (XX)	XX (XX)	XX (XX)	

<i>Co-medication</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
ACE inhibitors	XX (XX)	XX (XX)	XX (XX)	
Anti-depressant drugs	XX (XX)	XX (XX)	XX (XX)	
B-blocker	XX (XX)	XX (XX)	XX (XX)	
Bisphosphonates	XX (XX)	XX (XX)	XX (XX)	
Calcium channel blocker	XX (XX)	XX (XX)	XX (XX)	
Corticosteroids	XX (XX)	XX (XX)	XX (XX)	
Diuretics: thiazide or furosemide	XX (XX)	XX (XX)	XX (XX)	
Insulin	XX (XX)	XX (XX)	XX (XX)	
Heparin, coumarine derivatives or anti Xa inhibitors	XX (XX)	XX (XX)	XX (XX)	
Hormone replacement therapy	XX (XX)	XX (XX)	XX (XX)	
Low dose aspirin or clopidogrel	XX (XX)	XX (XX)	XX (XX)	
NSAID (except low dose aspirine or clopidogrel)	XX (XX)	XX (XX)	XX (XX)	
Oral antidiabetics	XX (XX)	XX (XX)	XX (XX)	
Thyroid hormones	XX (XX)	XX (XX)	XX (XX)	
Other	XX (XX)	XX (XX)	XX (XX)	
Missing concomitant medication	X	X	X	
no concomitant medications	XX (XX)	XX (XX)	XX (XX)	.XXX
1 concomitant medication	XX (XX)	XX (XX)	XX (XX)	
2 or moreconcomitant medications	XX (XX)	XX (XX)	XX (XX)	
missing	X	X	X	

**Table 33 Relevant co-medication at baseline, nab-paclitaxel arm**

Shell similar to Table 32.

### 14.3 Primary efficacy

**Table 34 pCR (ypT0 ypN0), primary endpoint, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value*</i>	<i>p-value unstratified</i>
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		

\*stratified test, primary analysis

**Table 35 pCR (ypT0 ypN0), primary endpoint, chemotherapy arm**

Shell similar to Table 34.

**Table 36 pCR (ypT0 ypN0), primary endpoint, logistic regression adjusted for stratification factors**

<i>Parameter</i>	<i>Category</i>	<i>OR</i>	<i>90% CI</i>	<i>95% CI</i>	<i>p-value</i>
Arm denosumab	With D				
	Without D	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Arm chemotherapy	nPac weekly				
	nPac day 1, 8	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Breast cancer subtype	HER2-/HR+				.XXX
	TNBC	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
	HER2+	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
LPBC	no				
	yes	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
EC schedule	2-weekly				
	3-weekly	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX

**Table 37 pCR (ypT0 ypN0), primary endpoint, univariate logistic regressions**

<i>Parameter</i>	<i>Category</i>	<i>OR</i>	<i>90% CI</i>	<i>95% CI</i>	<i>p-value</i>
Arm denosumab	With D				
	Without D	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Arm chemotherapy	nP weekly				
	nP day 1, 8	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Breast cancer subtype	HER2-/HR+				.XXX
	TNBC	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
	HER2+	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
LPBC	no				
	yes	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
EC schedule	2-weekly				
	3-weekly	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Age, years	<40				
	>=40	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Tumor size, mm	≤25				
	>25	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
cT	cT1-3				
	cT4	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
cN	cN0				
	cN+	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX
Grading	G1-2				
	G3	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX

**Table 38 pCR (ypT0 ypN0), primary endpoint, multivariate logistic regression**

Shell similar to Table 37.

**Table 39 pCR (ypT0 ypN0), primary endpoint, multivariate logistic regression, with interaction between denosumab and chemotherapy arm**

Shell similar to Table 37, with additional row for the interaction.

**Figure 6 pCR (ypT0 ypN0), primary endpoint, multivariate logistic regression, forest plot**

Standard forest-plot figure.

**Table 40 pCR (ypT0 ypN0), primary endpoint, in subgroups, cross-tables, denosumab arm**

<i>Subgroup</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value*</i>	<i>p-value unstratified</i>
HER2-/HR+					
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		
TNBC					
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		
HER2+					
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		
No LPBC					
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		

LPBC	pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
	No pCR	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
EC 2-weekly	pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
	No pCR	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
EC 3-weekly	pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
	No pCR	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
nPac weekly	pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
	No pCR	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
nPac d1, 8	pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
	No pCR	X (X)	X (X)	X (X)		

90% CI	(X%, X%)	(X%, X%)	
Difference with 90% CI			X% (X%, X%)
95% CI	(X%, X%)	(X%, X%)	
Difference with 95% CI			X% (X%, X%)

\*stratified test

**Table 41 pCR (ypT0 ypN0), primary endpoint, in subgroups, cross-tables, chemotherapy arm**

Shell similar to Table 40.



**Table 42 pCR (ypT0 ypN0), primary endpoint, in subgroups, logistic regression, denosumab arm**

<i>Subgroup</i>	<i>OR no D vs D</i>	<i>95% CI</i>	<i>p-value</i>	<i>p-value interaction</i>
HER2-/HR+	X.XX	(X.XX, X.XX)	.XXX	.XXX
TNBC	X.XX	(X.XX, X.XX)	.XXX	
HER2+	X.XX	(X.XX, X.XX)	.XXX	
LPBC no	X.XX	(X.XX, X.XX)	.XXX	.XXX
LPBC yes	X.XX	(X.XX, X.XX)	.XXX	
EC 2-weekly	X.XX	(X.XX, X.XX)	.XXX	.XXX
EC 3-weekly	X.XX	(X.XX, X.XX)	.XXX	
nPac weekly	X.XX	(X.XX, X.XX)	.XXX	.XXX
nPac d 1, 8	X.XX	(X.XX, X.XX)	.XXX	

**Table 43 pCR (ypT0 ypN0), primary endpoint, in subgroups, logistic regression, chemotherapy arm**

Shell similar to Table 42

**Figure 7 pCR (ypT0 ypN0), primary endpoint, in subgroups, logistic regression, denosumab arm, forest plot**

Standard forest-plot figure.

**Figure 8 pCR (ypT0 ypN0), primary endpoint, in subgroups, logistic regression, chemotherapy arm, forest plot**

Standard forest-plot figure.

**Table 44 pCR (ypT0 ypN0), primary endpoint, per protocol analysis, denosumab arm**

Same shell as Table 34.

**Table 45 pCR (ypT0 ypN0), primary endpoint, per protocol analysis, chemotherapy arm**

Shell similar to Table 34.

**Table 46 pCR (ypT0 ypN0), primary endpoint, in subgroups according to germline BRCA mutation status, cross-tables, denosumab arm**

<i>Subgroup</i>	<i>With D (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value*</i>	<i>p-value**</i>
<b>gBRCA 1 or 2 mutation</b>					
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		
<b>No gBRCA mutation or unknown</b>					
pCR (ypT0, ypN0)	X (X)	X (X)	X (X)	.XX	.XX
No pCR	X (X)	X (X)	X (X)		
90% CI	(X%, X%)	(X%, X%)			
Difference with 90% CI			X% (X%, X%)		
95% CI	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		

\*stratified

\*\*unstratified

**Table 47 pCR (ypT0 ypN0), primary endpoint, in subgroups according to gBRCA mutation status, cross-tables, chemotherapy arm**

Shell similar to Table 46.

**Table 48 pCR (ypT0 ypN0), primary endpoint, in subgroups according to gBRCA mutation status, logistic regressions, denosumab arm**

<i>Subgroup</i>	<i>OR no D vs D</i>	<i>90% CI</i>	<i>95% CI</i>	<i>p-value</i>	<i>p-value interaction</i>
<i>gBRCA 1 or 2 mutation</i>	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX	.XXX
<i>No gBRCA mutation</i>	X.XX	(X.XX, X.XX)	(X.XX, X.XX)	.XXX	

**Table 49 pCR (ypT0 ypN0), primary endpoint, in subgroups according to gBRCA mutation status, logistic regressions, chemotherapy arm**

Shell similar to Table 48.

**Table 50 pCR (ypT0 ypN0), primary endpoint, in subgroups according to RANK, cross-tables, denosumab arm**

Shell similar to Table 46.

**Table 51 pCR (ypT0 ypN0), primary endpoint, in subgroups according to RANK, cross-tables, chemotherapy arm**

Shell similar to Table 46.

**Table 52 pCR (ypT0 ypN0), primary endpoint, in subgroups according to RANK mutation status, logistic regressions, denosumab arm**

Shell similar to Table 48.

**Table 53 pCR (ypT0 ypN0), primary endpoint, in subgroups according to RANK mutation status, logistic regressions, chemotherapy arm**

Shell similar to Table 48.

**Figure 9 STEPP analysis of pCR (ypT0 ypN0), primary endpoint, according to nab-paclitaxel RTD**

Standard STEPP figure.

**Figure 10 STEPP analysis of pCR (ypT0 ypN0), primary endpoint, according to nab-paclitaxel RTDI**

Standard STEPP figure.

14.4 Secondary efficacy, short-term

Table 54 Secondary pCR definitions ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT0(any) ypN0, denosumab arm

		<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value*</i>	<i>p-value unstratified</i>
ypT0/is, ypN0	no	X (X)	X (X)	X (X)	.XX	.XX
	yes	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
ypT0, ypN0/+	no	X (X)	X (X)	X (X)	.XX	.XX
	yes	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
ypT0/is, ypN0/+	no	X (X)	X (X)	X (X)	.XX	.XX
	yes	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		
ypT(any), ypN0	no	X (X)	X (X)	X (X)	.XX	.XX
	yes	X (X)	X (X)	X (X)		
	90% CI	(X%, X%)	(X%, X%)			
	Difference with 90% CI			X% (X%, X%)		
	95% CI	(X%, X%)	(X%, X%)			
	Difference with 95% CI			X% (X%, X%)		

\*stratified

**Table 55 Secondary pCR definitions ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT0(any) ypN0, chemotherapy arm**

Shell similar to Table 54.

**Table 56 pCR (ypT0/is ypN0) (secondary endpoint), logistic regression adjusted for stratification factors**

Shell similar to Table 36.

**Table 57 Univariate logistic regressions ypT0/is ypN0 (secondary endpoint)**

Shell similar to Table 37.

**Table 58 Multivariate logistic regression ypT0/is ypN0 (secondary endpoint)**

Shell similar to Table 37.

**Figure 11 Forest plot of multivariate logistic regression ypT0/is ypN0 (secondary endpoint)**

Standard forest plot figure

**Table 59 pCR (ypT0/is ypN0, secondary endpoint) in subgroups, cross-tables, denosumab arm**

Shell similar to Table 40.

**Table 60 pCR (ypT0/is ypN0, secondary endpoint) in subgroups, cross-tables, chemotherapy arm**

Shell similar to Table 40.

**Table 61 pCR (ypT0/is ypN0, secondary endpoint) in subgroups, logistic regression, denosumab arm**

Shell similar to Table 42.

**Table 62 pCR (ypT0/is ypN0, secondary endpoint) in subgroups, logistic regression, chemotherapy arm**

Shell similar to Table 42.

**Figure 12 pCR (ypT0/is ypN0, secondary endpoint) in subgroups, logistic regression, denosumab arm, forest plot**

Standard forest-plot figure.

**Figure 13 pCR (ypT0/is ypN0, secondary endpoint) in subgroups, logistic regression, chemotherapy arm, forest plot**

Standard forest-plot figure.

**Table 63 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to gBRCA mutation status, denosumab arm, cross tables**

Shell similar to Table 46.

**Table 64 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to gBRCA mutation status, chemotherapy arm, cross tables**

Shell similar to Table 46.

**Table 65 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to gBRCA mutation status, denosumab arm, logistic regressions**

Shell similar to Table 48.

**Table 66 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to gBRCA mutation status, chemotherapy arm, logistic regressions**

Shell similar to Table 48.

**Table 67 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to RANK, denosumab arm, cross tables**

Shell similar to Table 46.

**Table 68 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to RANK, chemotherapy arm, cross tables**

Shell similar to Table 46.

**Table 69 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to RANK, denosumab arm, logistic regressions**

Shell similar to Table 48.

**Table 70 pCR (ypT0/is ypN0, secondary endpoint) in subgroups according to RANK, chemotherapy arm, logistic regressions**

Shell similar to Table 48.

**Table 71 Breast conservation, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>	<i>p-value unstratified</i>
BCS	X (X)	X (X)	X (X)	.XX	.XX
Mastectomy	X (X)	X (X)	X (X)		
95% CI for BCS	(X%, X%)	(X%, X%)	(X%, X%)		
Difference with 95% CI			X% (X%, X%)		
No surgery performed	X	X	X		
Missing surgery information	X	X	X		

**Table 72 Breast conservation, chemotherapy arm**

Shell similar to Table 71

**Table 73 Axillary surgery, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value*</i>
<i>Axillary surgery</i>				
SNB only (before or after chemotherapy)	X (X)	X (X)	X (X)	.XX
- only before chemotherapy	X (X)	X (X)	X (X)	
- only after chemotherapy	X (X)	X (X)	X (X)	
- before and after chemotherapy	X (X)	X (X)	X (X)	
Axilla dissection with or without prior SNB	X (X)	X (X)	X (X)	
- without prior SNB	X (X)	X (X)	X (X)	
- with prior SNB	X (X)	X (X)	X (X)	

<i>Axillary surgery</i>	<i>Without D</i>		<i>Overall N (%)</i>	<i>p-value*</i>
	<i>With D N (%)</i>	<i>N (%)</i>		
95% CI for SNB only	(X%, X%)	(X%, X%)		
Difference with 95% CI			X% (X%, X%)	
Missing axilla surgery type	X	X	X	
No axilla surgery	X	X	X	

\*comparing rate of SNB only

**Table 74 Axillary surgery, chemotherapy arm**

Shell similar to Table 73

**Table 75 Clinical (imaging) response of the breast after 2 cycles of treatment, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value*</i>	<i>p-value**</i>
CR	X (X)	X (X)	X (X)		
PR	X (X)	X (X)	X (X)		
ORR (CR or PR)	X (X)	X (X)	X (X)	.XX	.XX
95% CI for ORR	(X%, X%)	(X%, X%)			
Difference with 95% CI			X% (X%, X%)		
NC	X (X)	X (X)	X (X)		
PD	X (X)	X (X)	X (X)		
Not evaluable/missing	X (X)	X (X)	X (X)		

\* comparing ORes-rate in treatment groups, stratified

\*\*unstratified

**Table 76 Clinical (imaging) response of the breast after 2 cycles of treatment, chemotherapy arm**

Shell similar to Table 75.

**Table 77 Clinical (imaging) response of the breast before surgery, denosumab arm**

Same shell as Table 75.

**Table 78 Clinical (imaging) response of the breast before surgery, chemotherapy arm**

Shell similar to Table 75.



**Table 79 Response of axillary nodes by palpation/sonography, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
cN+ at baseline	XXX	XXX	XXX	
Converted to cN0 by palpation/sonography before surgery	X (X)	X (X)	X (X)	.XX
missing	X	X	X	

**Table 80 Response of axillary nodes by palpation/sonography, chemotherapy arm**

Shell similar to Table 79.

**Table 81 Response of axillary nodes by histology**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
cN+ at baseline	XXX	XXX	XXX	
Converted to ypN0 at surgery	X (X)	X (X)	X (X)	.XX
No axillary surgery	X	X	X	

**Table 82 Clinical (imaging) response rate after 2 cycles of treatment vs. pCR, overall**

	<i>CR after 6 weeks</i>	<i>PR after 6 weeks</i>	<i>NC after 6 weeks</i>	<i>PD after 6 weeks</i>	<i>Not evaluable/missing (NE) after 6 weeks</i>
pCR	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX
No pCR	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX

**Table 83 Clinical (imaging) response rate after 2 cycles of treatment vs. pCR, denosumab arm**

Same shell as Table 82.

**Table 84 Clinical (imaging) response rate 2 cycles weeks of treatment vs. pCR, no denosumab arm**

Same shell as Table 82.

**Table 85 Clinical (imaging) response rate after 2 cycles of treatment vs. pCR, nab-paclitaxel weekly arm**

Same shell as Table 82.

**Table 86 Clinical (imaging) response rate 2 cycles weeks of treatment vs. pCR, nab-paclitaxel d 1, 8 arm**

Same shell as Table 82.

**Table 87 Mammographic density score, frequencies**

<i>Timepoint</i>	<i>MD score</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
At baseline					
	1	XX (XX)	XX (XX)	XX (XX)	
	2	XX (XX)	XX (XX)	XX (XX)	
	3	XX (XX)	XX (XX)	XX (XX)	
	4	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
At surgery					
	1	XX (XX)	XX (XX)	XX (XX)	
	2	XX (XX)	XX (XX)	XX (XX)	
	3	XX (XX)	XX (XX)	XX (XX)	
	4	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	
Change					
	-3	XX (XX)	XX (XX)	XX (XX)	X.XX
	-2	XX (XX)	XX (XX)	XX (XX)	
	-1	XX (XX)	XX (XX)	XX (XX)	
	0	XX (XX)	XX (XX)	XX (XX)	
	1	XX (XX)	XX (XX)	XX (XX)	
	2	XX (XX)	XX (XX)	XX (XX)	
	3	XX (XX)	XX (XX)	XX (XX)	
	missing	X	X	X	

**Table 88 Mammographic density score, continuous**

<i>Timepoint</i>	<i>Statistic</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
At baseline					
	Mean	XX	XX	XX	
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	
At surgery					
	Mean	XX	XX	XX	
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	
Change					
	Mean	XX	XX	XX	X.XX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	

## 14.5 Secondary efficacy, long-term

**Table 89 First IDFS event, denosumab arm**

	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
Locoregional relapse	XXX	XXX	XXX
Contralateral BC	XXX	XXX	XXX
Distant relapse	XXX	XXX	XXX
Secondary malignancy	XXX	XXX	XXX
Death	XXX	XXX	XXX

**Table 90 First IDFS event, chemotherapy arm**

Shell similar to Table 89.

**Figure 14 IDFS, Kaplan-Meier curves, denosumab arm**

Standard Kaplan-Meier figure.

**Figure 15 IDFS, Kaplan-Meier curves, chemotherapy arm**

Standard Kaplan-Meier figure.

**Table 91 IDFS rates, denosumab arm**

	<i>With D</i>	<i>Without D</i>
Estimated 3 year IDFS (95% CI)	XX% (XX%, XX%)	XX% (XX%, Xx%)
Estimated 4 year IDFS (95% CI)	XX% (XX%, XX%)	XX% (XX%, XX%)
Estimated 5 year IDFS (95% CI)	XX% (XX%, XX%)	XX% (XX%, XX%)
HR (95% CI)		X.XX (X.XX, X.XX)
(Stratified) log-rank p-value		X.XX

**Table 92 IDFS rates, chemotherapy arm**

Shell similar to Table 91.

**Table 93 IDFS, univariate Cox regressions**

<i>Parameter</i>	<i>Category</i>	<i>HR</i>	<i>95% CI</i>	<i>p-value</i>
Arm denosumab	With D			
	Without D	X.XX	(X.XX, X.XX)	.XXX
Arm chemotherapy	nPac weekly			
	nPac d 1, 8	X.XX	(X.XX, X.XX)	.XXX
Breast cancer subtype	HER2-/HR+			.XXX
	TNBC	X.XX	(X.XX, X.XX)	.XXX
	HER2+	X.XX	(X.XX, X.XX)	.XXX
LPBC	no			
	yes	X.XX	(X.XX, X.XX)	.XXX
EC schedule	2-weekly			

<i>Parameter</i>	<i>Category</i>	<i>HR</i>	<i>95% CI</i>	<i>p-value</i>
Age, years	3-weekly	X.XX	(X.XX, X.XX)	.XXX
	<40			
Tumor size, mm	>=40	X.XX	(X.XX, X.XX)	.XXX
	<=25			
cT	>25	X.XX	(X.XX, X.XX)	.XXX
	cT1-3			
cN	cT4	X.XX	(X.XX, X.XX)	.XXX
	cN0			
Grading	cN+	X.XX	(X.XX, X.XX)	.XXX
	G1-2			
pCR (ypT0/is ypN0)	G3	X.XX	(X.XX, X.XX)	.XXX
	no			
	yes	X.XX	(X.XX, X.XX)	.XXX

**Table 94 IDFS, multivariate Cox regression**

Shell similar to Table 93.

**Figure 16 IDFS, multivariate Cox regression, forest plot**

Standard forest-plot figure.

**Table 95 IDFS in subgroups, Cox regressions, denosumab arm**

<i>Subgroup</i>	<i>HR no D vs D</i>	<i>95% CI</i>	<i>p-value</i>	<i>p-value interaction</i>
HER2-/HR+	X.XX	(X.XX, X.XX)	.XXX	.XXX
TNBC	X.XX	(X.XX, X.XX)	.XXX	
HER2+	X.XX	(X.XX, X.XX)	.XXX	
LPBC no	X.XX	(X.XX, X.XX)	.XXX	.XXX
LPBC yes	X.XX	(X.XX, X.XX)	.XXX	
EC 2-weekly	X.XX	(X.XX, X.XX)	.XXX	.XXX
EC 3-weekly	X.XX	(X.XX, X.XX)	.XXX	

**Table 96 IDFS in subgroups, Cox regressions, chemotherapy arm**

Shell similar to Table 95.

**Figure 17 IDFS in subgroups, Cox regression, denosumab arm, forest plot**

Standard forest-plot figure.

**Figure 18 IDFS in subgroups, Cox regression, chemotherapy arm, forest plot**

Standard forest-plot figure.

**Table 97 First EFS event, denosumab arm**

	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
Progression under therapy rendering patient inoperable	XXX	XXX	XXX
Locoregional relapse	XXX	XXX	XXX
Contralateral BC	XXX	XXX	XXX
Distant relapse	XXX	XXX	XXX
Secondary malignancy	XXX	XXX	XXX
Death	XXX	XXX	XXX

**Table 98 First EFS event, chemotherapy arm**

Shell similar to Table 97.

**Figure 19 EFS, Kaplan-Meier curves, denosumab arm**

Standard Kaplan-Meier figure.

**Figure 20 EFS, Kaplan-Meier curves, chemotherapy arm**

Standard Kaplan-Meier figure.

**Table 99 EFS rates, denosumab arm**

Shell similar to Table 91.

**Table 100 EFS rates, chemotherapy arm**

Shell similar to Table 91.

**Table 101 LRRFI events and competing events, denosumab arm**

	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
Events:	XXX	XXX	XXX
- Locoregional relapse	XXX	XXX	XXX
- Contralateral BC	XXX	XXX	XXX
Competing events:	XXX	XXX	XXX
- Distant relapse	XXX	XXX	XXX
- Secondary malignancy	XXX	XXX	XXX
- Death	XXX	XXX	XXX

**Table 102 LRRFI events and competing events, chemotherapy arm**

Shell similar to Table 101.

**Figure 21 LRRFI, CIF curves, denosumab arm**

Standard CIF figure.

**Figure 22 LRRFI, CIF curves, chemotherapy arm**

Standard CIF figure.

**Table 103 LRRFI - cumulative incidence, denosumab arm**

	<i>With D</i>	<i>Without D</i>
Estimated 3 year cumulative incidence (95% CI)	XX% (XX%, XX%)	XX% (XX%, Xx%)
Estimated 4 year cumulative incidence (95% CI)	XX% (XX%, XX%)	XX% (XX%, XX%)
Estimated 5 year cumulative incidence (95% CI)	XX% (XX%, XX%)	XX% (XX%, XX%)
HR (95% CI)		X.XX (X.XX, X.XX)
(Stratified) Gray p-value		X.XX

**Table 104 LRRFI, chemotherapy arm**

Shell similar to Table 103.

**Table 105 First DDFS event, denosumab arm**

	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
Distant relapse	XXX	XXX	XXX
Secondary malignancy	XXX	XXX	XXX
Death	XXX	XXX	XXX

**Table 106 First DDFS event, chemotherapy arm**

Shell similar to Table 105.

**Figure 23 DDFS, Kaplan-Meier curves, denosumab arm**

Standard Kaplan-Meier figure.

**Figure 24 DDFS, Kaplan-Meier curves, chemotherapy arm**

Standard Kaplan-Meier figure.

**Table 107 DDFS rates, denosumab arm**

Shell similar to Table 91.

**Table 108 DDFS rates, chemotherapy arm**

Shell similar to Table 91.

**Table 109 DDFS, univariate Cox regressions**

Shell similar to Table 93.

**Table 110 DDFS, multivariate Cox regression**

Shell similar to Table 93.

**Figure 25 DDFS, multivariate Cox regression, forest plot**

Standard forest-plot figure.

**Table 111 DDFS in subgroups, Cox regressions, denosumab arm**

Shell similar to Table 95.

**Table 112 DDFS in subgroups, Cox regressions, chemotherapy arm**

Shell similar to Table 95.

**Figure 26 DDFS in subgroups, Cox regression, denosumab arm, forest plot**

Standard forest-plot figure.

**Figure 27 DDFS in subgroups, Cox regression, chemotherapy arm, forest plot**

Standard forest-plot figure.

**Figure 28 OS, Kaplan-Meier curves, denosumab arm**

Standard Kaplan-Meier figure.

**Figure 29 OS, Kaplan-Meier curves, chemotherapy arm**

Standard Kaplan-Meier figure.

**Table 113 OS, denosumab arm**

Shell similar to Table 91.

**Table 114 OS, chemotherapy arm**

Shell similar to Table 91.

**Table 115 OS, univariate Cox regressions**

Shell similar to Table 93.

**Table 116 OS, multivariate Cox regression**

Shell similar to Table 93.

### Figure 30 OS, multivariate Cox regression, forest plot

Standard forest-plot figure.

### Table 117 OS in subgroups, Cox regressions, denosumab arm

Shell similar to Table 95.

### Table 118 OS in subgroups, Cox regressions, chemotherapy arm

Shell similar to Table 95.

### Figure 31 OS in subgroups, Cox regression, denosumab arm, forest plot

Standard forest-plot figure.

### Figure 32 OS in subgroups, Cox regression, chemotherapy arm, forest plot

Standard forest-plot figure.

## 14.6 Safety

**Table 119 Brief summary of adverse events, all patients, denosumab arm**

AE	With D N (%)	Without D N (%)	Overall N (%)	p-value
Any AE, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any AE, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any hematological AE, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any hematological AE, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any non-hematological AE, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any non-hematological AE, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any SAE	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	
Any AESI	XX (XX)	XX (XX)	XX (XX)	X.XX
95% CI	(XX, XX)	(XX, XX)	(XX, XX)	



**Table 120 Brief summary of adverse events, all patients, chemotherapy arm**

Shell similar to Table 119.

**Table 121 Brief summary of adverse events, HER2-/HR+ patients, denosumab arm**

Same shell as Table 119.

**Table 122 Brief summary of adverse events, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 119.

**Table 123 Brief summary of adverse events, TNBC patients, denosumab arm**

Same shell as Table 119.

**Table 124 Brief summary of adverse events, TNBC patients, chemotherapy arm**

Shell similar to Table 119.

**Table 125 Brief summary of adverse events, HER2-positive patients**

Same shell as Table 119.

**Table 126 Brief summary of adverse events, HER2-positive patients**

Shell similar to Table 119.

**Table 127 Deaths under therapy**

<i>Patient No</i>	<i>Arm denosumab</i>	<i>Arm chemotherapy</i>	<i>Subtype</i>	<i>Cycle</i>	<i>Death cause</i>
XXXX	XXX	XXX	XXX	X	.....
...	...	...	...	...	.....

**Table 128 Pre-defined AEs any grade and grade 3-4, all patients, denosumab arm**

<i>AE</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Anemia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Anemia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Leukopenia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Leukopenia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Neutropenia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Neutropenia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX

<i>AE</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
missing	X	X	X	
Febrile neutropenia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Thrombopenia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Thrombopenia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Increased bilirubin, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Increased bilirubin, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Increased AP, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Increased AP, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Increased ASAT, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Increased ASAT, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Increased ALAT, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Increased ALAT, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Increased creatinine, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Increased creatinine, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Fatigue, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Fatigue, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Headache, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Headache, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Nausea, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Nausea, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Anorexia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Anorexia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Vomiting, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Vomiting, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Diarrhea, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX

<i>AE</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Diarrhea, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Hypertension, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Hypertension, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Peripheral sensory neuropathy, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Peripheral sensory neuropathy, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Arthralgia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Arthralgia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Myalgia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Myalgia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Epistaxis, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Epistaxis, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Dyspnea, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Dyspnea, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Alopecia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
PPE, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
PPE, grade 3-4	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Thromboembolic event, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Thromboembolic event, grade 3-4	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Fever without neutropenia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Fever without neutropenia, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Missing	X	X	X	
≥10% decrease in LVEF from baseline and <50%*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Osteonecrosis of the jaw, any grade*	XX (XX)	XX (XX)	XX (XX)	X.XX
Osteonecrosis of the jaw, high grade*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Hypocalcemia, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX

<i>AE</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Hypocalcemia, high grade*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Anaphylaxis, grade 3-4*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Any AE affecting cranial nerves*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Macular edema*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Atypical fracture of the femur*	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Infusion related reaction, any grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
Infusion related reaction, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Allergic reaction, any grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
Allergic reaction, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Heart failure, any NYHA class**	XX (XX)	XX (XX)	XX (XX)	X.XX
Heart failure, NYHA class 3-4**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Pneumonitis, any grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
Pneumonitis, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Cough, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Cough, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Other pulmonary toxicity, any grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
Other pulmonary toxicity, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Pneumonia, any grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
Pneumonia, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Other infection, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Other infection, high grade**	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
Other AEs, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Other AEs, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	

\*AE of special interest for denosumab

\*\*AE of special interest for HER2-positive patients treated with ABP 980

**Table 129 Pre-defined AEs any grade and grade 3-4, all patients, chemotherapy arm**

Shell similar to Table 128.

**Table 130 Pre-defined AEs any grade and grade 3-4, HER2-/HR+ patients, denosumab arm**

Same shell as Table 128.

**Table 131 Pre-defined AEs any grade and grade 3-4, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 128.

**Table 132 Pre-defined AEs any grade and grade 3-4, TNBC patients, denosumab arm**

Same shell as Table 128.

**Table 133 Pre-defined AEs any grade and grade 3-4, TNBC patients, chemotherapy arm**

Shell similar to Table 128.

**Table 134 Pre-defined AEs any grade and grade 3-4, HER2 + patients, denosumab arm**

Same shell as Table 128.

**Table 135 Pre-defined AEs any grade and grade 3-4, HER2 + patients, chemotherapy arm**

Shell similar to Table 128.

**Table 136 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, all patients, denosumab arm**

Same shell as Table 128.

**Table 137 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, all patients, chemotherapy arm**

Shell similar to Table 128.

**Table 138 Pre-defined AEs any grade and grade 3-4, HER2-/HR+ patients under nab-paclitaxel, denosumab arm**

Same shell as Table 128.

**Table 139 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 128.

**Table 140 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, TNBC patients, denosumab arm**

Same shell as Table 128.

**Table 141 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, TNBC patients, chemotherapy arm**

Shell similar to Table 128.

**Table 142 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, HER2 + patients, denosumab arm**

Same shell as Table 128.

**Table 143 Pre-defined AEs any grade and grade 3-4 under nab-paclitaxel, HER2 + patients, chemotherapy arm**

Shell similar to Table 128.

**Table 144 Pre-defined AEs any grade and grade 3-4 under EC, all patients, denosumab arm**

Same shell as Table 128.

**Table 145 Pre-defined AEs any grade and grade 3-4 under EC, all patients, chemotherapy arm**

Shell similar to Table 128.

**Table 146 Pre-defined AEs any grade and grade 3-4, HER2-/HR+ patients under EC, denosumab arm**

Same shell as Table 128.

**Table 147 Pre-defined AEs any grade and grade 3-4 under EC, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 128.

**Table 148 Pre-defined AEs any grade and grade 3-4 under EC, TNBC patients, denosumab arm**

Same shell as Table 128.

**Table 149 Pre-defined AEs any grade and grade 3-4 under EC, TNBC patients, chemotherapy arm**

Shell similar to Table 128.

**Table 150 Pre-defined AEs any grade and grade 3-4 under EC, HER2 + patients, denosumab arm**

Same shell as Table 128.

**Table 151 Pre-defined AEs any grade and grade 3-4 under EC, HER2 + patients, chemotherapy arm**

Shell similar to Table 128.

**Table 152 Other AEs, specification, any grade and grade 3-4, all patients, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Event 1, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Event 1, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Event 2, any grade	XX (XX)	XX (XX)	XX (XX)	X.XX
Event 2, high grade	XX (XX)	XX (XX)	XX (XX)	X.XX
...				

**Table 153 Other AEs any grade and grade 3-4, all patients, chemotherapy arm**

Shell similar to Table 152.

**Table 154 AEs all grades, all patients, denosumab arm**

<i>AE</i>	<i>Grade</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>
Anemia	1	XX (XX)	XX (XX)	XX (XX)
	2	XX (XX)	XX (XX)	XX (XX)
	3	XX (XX)	XX (XX)	XX (XX)
	4	XX (XX)	XX (XX)	XX (XX)
	missing	X	X	X
....				
Other AE**	1	XX (XX)	XX (XX)	XX (XX)
	2	XX (XX)	XX (XX)	XX (XX)
	3	XX (XX)	XX (XX)	XX (XX)
	4	XX (XX)	XX (XX)	XX (XX)

For the list of AE see the shell for the main AE table (Table 128).

**Table 155 AEs all grades, all patients, chemotherapy arm**

Shell similar to Table 154.

**Table 156 Brief summary of treatment-related adverse events, all patients, denosumab arm**

Same shell as Table 119.

**Table 157 Brief summary of treatment-related adverse events, all patients, chemotherapy arm**

Shell similar to Table 119.

**Table 158 Treatment-related AEs any grade and grade 3-4, all patients, denosumab arm**

Same shell as Table 128.

**Table 159 Treatment-related AEs any grade and grade 3-4, all patients, chemotherapy arm**

Shell similar to Table 128.

**Table 160 Treatment-related AEs all grades, all patients, denosumab arm**

Same shell as Table 154.

**Table 161 Treatment-related AEs all grades, all patients, chemotherapy arm**

Shell similar to Table 154.

**Table 162 SAEs summary table, all patients, denosumab arm**

<i>SAE</i>	<i>With D N</i>	<i>Without D N</i>	<i>Overall N</i>
Term 1	XX	XX	XX
Term 2	XX	XX	XX
Subtotal SOC 1 infections and infestations	XX	XX	XX
....			
Total	XX	XX	XX
At least one SAE per patient	XX (XX%)	XX (XX%)	XX (XX%)

**Table 163 SAEs summary table, all patients, chemotherapy arm**

Shell similar to Table 162.

**Table 164 SAEs summary table, HER2-/HR+, denosumab arm**

Same shell as Table 162.



**Table 165 SAEs summary table, HER2-/HR+, chemotherapy arm**

Shell similar to Table 162.

**Table 166 SAEs summary table, TNBC, denosumab arm**

Same shell as Table 162.

**Table 167 SAEs summary table, TNBC, chemotherapy arm**

Shell similar to Table 162.

**Table 168 SAEs summary table, HER2 +, denosumab arm**

Same shell as Table 162.

**Table 169 SAEs summary table, HER2 +, chemotherapy arm**

Shell similar to Table 162.

**Table 170 SAEs line-listing**

<i>SOC</i>	<i>Patient Nr</i>	<i>Site Nr</i>	<i>Age</i>	<i>Event</i>	<i>CTC-grade</i>	<i>Date serious</i>	<i>Date reported</i>	<i>Outcome</i>	<i>Date of death, if fatal</i>	<i>Drug/event relationship</i>	<i>Arm denosumab</i>	<i>Arm chemotherapy</i>	<i>Arm Subtype</i>	<i>Cycle</i>
XX	XXX	XXX	XX	XXXXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXXX	XX/XX/XXXX	XX	XX		XX	X
...														

**Table 171 AEs leading to treatment discontinuations**

<i>Pat ID</i>	<i>Denosumab arm</i>	<i>Chemotherapy arm</i>	<i>Biological subtype*</i>	<i>Cycle</i>	<i>AE</i>
XX	XXX		XXX	XX	XXXXXXXX
XX	XXX		XXX	XX	XXXXXXXX
..	..		..	..	.....

\*Treatment by biological subtype, patients treated with capecitabine by mistake will be included in TNBC group.

**Table 172 LVEF decreased, all patients, denosumab arm**

	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
LVEF decreased by 10% since baseline in any assessment	XX (XX)	XX (XX)	XX (XX)	X.XX
40%-<50%	XX (XX)	XX (XX)	XX (XX)	X.XX
30%-<40%	XX (XX)	XX (XX)	XX (XX)	X.XX
<30%	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
LVEF after 2 cycles decreased by 10% since baseline	XX (XX)	XX (XX)	XX (XX)	X.XX
40%-<50%	XX (XX)	XX (XX)	XX (XX)	X.XX
30%-<40%	XX (XX)	XX (XX)	XX (XX)	X.XX
<30%	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	
LVEF before surgery decreased by 10% since baseline	XX (XX)	XX (XX)	XX (XX)	X.XX
40%-<50%	XX (XX)	XX (XX)	XX (XX)	X.XX
30%-<40%	XX (XX)	XX (XX)	XX (XX)	X.XX
<30%	XX (XX)	XX (XX)	XX (XX)	X.XX
missing	X	X	X	

**Table 173 LVEF decreased, all patients, chemotherapy arm**

Shell similar to Table 172.

**Table 174 LVEF decreased, HER2-/HR+ patients, denosumab arm**

Same shell as Table 172.

**Table 175 LVEF decreased, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 172.

**Table 176 LVEF decreased, TNBC patients, denosumab arm**

Same shell as Table 172.

**Table 177 LVEF decreased, TNBC patients, chemotherapy arm**

Shell similar to Table 172.

**Table 178 LVEF decreased, HER2+ patients, denosumab arm**

Same shell as Table 172.

**Table 179 LVEF decreased, HER2R+ patients, chemotherapy arm**

Shell similar to Table 172.

## 14.7 Compliance

### 14.7.1 Discontinuations

**Table 180 Discontinuations of chemotherapy, all patients, denosumab arm**

<i>Patient status</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Completed both nab-paclitaxel and EC treatment	XX (XX)	XX (XX)	XX (XX)	.XX
Completed nab-paclitaxel treatment	XX (XX)	XX (XX)	XX (XX)	.XX
Discontinued nab-paclitaxel treatment	XX (XX)	XX (XX)	XX (XX)	
- local progressive disease	XX (XX)	XX (XX)	XX (XX)	
- distant metastases/secondary malignancy	XX (XX)	XX (XX)	XX (XX)	
- death	XX (XX)	XX (XX)	XX (XX)	
- AE	XX (XX)	XX (XX)	XX (XX)	
- hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	
- other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- AE not related to study medication	XX (XX)	XX (XX)	XX (XX)	
- investigator's decision	XX (XX)	XX (XX)	XX (XX)	
- patient's wish	XX (XX)	XX (XX)	XX (XX)	
Started EC (after completion or discontinuation of nab-paclitaxel)	XX (XX)	XX (XX)	XX (XX)	
Completed EC treatment	XX (XX)	XX (XX)	XX (XX)	.XX
Discontinued EC treatment	XX (XX)	XX (XX)	XX (XX)	
- local progressive disease	XX (XX)	XX (XX)	XX (XX)	
- distant metastases/secondary malignancy	XX (XX)	XX (XX)	XX (XX)	
- death	XX (XX)	XX (XX)	XX (XX)	

<i>Patient status</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
- AE	XX (XX)	XX (XX)	XX (XX)	
- hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	
- other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- AE not related to study medication	XX (XX)	XX (XX)	XX (XX)	
- investigator's decision	XX (XX)	XX (XX)	XX (XX)	
- patient's wish	XX (XX)	XX (XX)	XX (XX)	

**Table 181 Discontinuations of chemotherapy, all patients, chemotherapy arm**

Shell similar to Table 180.

**Table 182 Discontinuations of chemotherapy, HER2-/HR+ patients, denosumab arm**

Shell similar to Table 180.

**Table 183 Discontinuations of chemotherapy, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 180.

**Table 184 Discontinuations of chemotherapy, TNBC patients, denosumab arm**

Shell similar to Table 180.

**Table 185 Discontinuations of chemotherapy, TNBC patients, chemotherapy arm**

Shell similar to Table 180.

**Table 186 Discontinuations of chemotherapy, HER2+ patients, denosumab arm**

Shell similar to Table 180.

**Table 187 Discontinuations of chemotherapy, HER2+ patients, chemotherapy arm**

Shell similar to Table 180.

**Table 188 Discontinuations of denosumab, only patients who started denosumab**

<i>Patient status</i>	<i>nPac weekly N (%)</i>	<i>nPac d 1, 8 N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Completed denosumab treatment	XX (XX)	XX (XX)	XX (XX)	.XX
Discontinued denosumab treatment	XX (XX)	XX (XX)	XX (XX)	
- local progressive disease	XX (XX)	XX (XX)	XX (XX)	
- distant metastases/secondary malignancy	XX (XX)	XX (XX)	XX (XX)	

<i>Patient status</i>	<i>nPac weekly N (%)</i>	<i>nPac d 1, 8 N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
- death	XX (XX)	XX (XX)	XX (XX)	
- AE	XX (XX)	XX (XX)	XX (XX)	
- hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	
- dental event	XX (XX)	XX (XX)	XX (XX)	
- other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- AE not related to study medication	XX (XX)	XX (XX)	XX (XX)	
- investigator's decision	XX (XX)	XX (XX)	XX (XX)	
- patient's wish	XX (XX)	XX (XX)	XX (XX)	

#### 14.7.2 Treatment completion

**Table 189 Number weeks (infusions) nab-paclitaxel, all patients, frequencies, denosumab arm**

<i>Number weeks nab- paclitaxel</i>	<i>With D N(%)</i>	<i>Without D N(%)</i>	<i>Overall N(%)</i>	<i>p-value</i>
1 week	XX (XX%)	XX (XX%)	XX (XX%)	.XXX
2 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
3 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
4 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
5 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
6 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
7 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
8 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
9 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
10 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
11 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
12 weeks	XX (XX%)	XX (XX%)	XX (XX%)	

**Table 190 Number weeks nab-paclitaxel, all patients, frequencies, chemotherapy arm**

Shell similar to Table 189 but without p-value since the number of weeks nab-paclitaxel is different in the chemotherapy arm by design.

**Table 191 Number weeks nab-paclitaxel, all patients, frequencies, denosumab arm, HER2-/HR+ patients**

Same shell as Table 189.

**Table 192 Number weeks nab-paclitaxel, all patients, frequencies, denosumab arm, HER2-/HR+ patients**

Same shell as Table 190.

**Table 193 Number weeks nab-paclitaxel, all patients, frequencies, denosumab arm, TNBC patients**

Same shell as Table 189.

**Table 194 Number weeks nab-paclitaxel, all patients, frequencies, denosumab arm, TNBC patients**

Same shell as Table 190.

**Table 195 Number weeks nab-paclitaxel, all patients, frequencies, denosumab arm, HER2 + patients**

Same shell as Table 189.

**Table 196 Number weeks nab-paclitaxel, all patients, frequencies, denosumab arm, HER2 + patients**

Same shell as Table 190.

**Table 197 Number weeks nab-paclitaxel, all patients, continuous, denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
Weeks nab-paclitaxel	Mean	XXX	XXX	XXX	.XXX
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	

**Table 198 Number weeks nab-paclitaxel, all patients, continuous, chemotherapy arm**

Shell similar to Table 197 but without p-value since the number of weeks nab-paclitaxel is different in the chemotherapy arm by design.

**Table 199 Number weeks nab-paclitaxel, HER2-/HR+ patients, continuous, denosumab arm**

Same shell as Table 197.

**Table 200 Number weeks nab-paclitaxel, HER2-/HR+ patients, continuous, chemotherapy arm**

Same shell as Table 198.

**Table 201 Number weeks nab-paclitaxel, TNBC patients, continuous, denosumab arm**

Same shell as Table 197.

**Table 202 Number weeks nab-paclitaxel, TNBC patients, continuous, chemotherapy arm**

Same shell as Table 198.

**Table 203 Number weeks nab-paclitaxel, HER2+ patients, continuous, denosumab arm**

Same shell as Table 197.

**Table 204 Number weeks nab-paclitaxel, HER2+ patients, continuous, chemotherapy arm**

Same shell as Table 198.

**Table 205 Number weeks carboplatin, TNBC patients, frequencies, denosumab arm**

<i>Number weeks carboplatin</i>	<i>With D N(%)</i>	<i>Without D N(%)</i>	<i>Overall N(%)</i>	<i>p-value</i>
1 week	XX (XX%)	XX (XX%)	XX (XX%)	.XXX
2 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
3 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
4 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
5 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
6 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
7 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
8 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
9 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
10 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
11 weeks	XX (XX%)	XX (XX%)	XX (XX%)	
12 weeks	XX (XX%)	XX (XX%)	XX (XX%)	

**Table 206 Number weeks carboplatin, TNBC patients, frequencies, chemotherapy arm**

Shell similar to Table 205.

**Table 207 Number weeks carboplatin, TNBC patients, continuous, denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
Weeks Carboplatin	Mean	XXX	XXX	XXX	.XXX
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	



**Table 208 Number weeks carboplatin, TNBC patients, continuous, chemotherapy arm**

Shell similar to Table 207.

**Table 209 Number EC infusions, all patients, frequencies, denosumab arm**

<i>Number cycles EC</i>	<i>With D N(%)</i>	<i>Without D N(%)</i>	<i>Overall N(%)</i>	<i>p-value</i>
1 cycle	XX (XX%)	XX (XX%)	XX (XX%)	.XXX
2 cycles	XX (XX%)	XX (XX%)	XX (XX%)	
3 cycles	XX (XX%)	XX (XX%)	XX (XX%)	
4 cycles	XX (XX%)	XX (XX%)	XX (XX%)	

**Table 210 Number EC infusions, all patients, frequencies, chemotherapy arm**

Shell similar to Table 209.

**Table 211 Number EC infusions, HER2-/HR+ patients, frequencies, denosumab arm**

Same shell as Table 209.

**Table 212 Number EC infusions, HER2-/HR+ patients, frequencies, chemotherapy arm**

Shell similar to Table 209.

**Table 213 Number EC infusions, TNBC patients, frequencies, denosumab arm**

Same shell as Table 209.

**Table 214 Number EC infusions, TNBC patients, frequencies, chemotherapy arm**

Shell similar to Table 209.

**Table 215 Number EC infusions, HER2+ patients, frequencies, denosumab arm**

Same shell as Table 209.

**Table 216 Number EC infusions, HER2+ patients, frequencies, chemotherapy arm**

Shell similar to Table 209.

**Table 217 Number cycles EC, all patients, continuous, denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
Weeks Carboplatin	Mean	XXX	XXX	XXX	.XXX
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	

**Table 218 Number cycles EC, all patients, continuous, chemotherapy arm**

Shell similar to Table 217.

**Table 219 Number cycles EC, HER2-/HR+ patients, continuous, denosumab arm**

Same shell as Table 217.

**Table 220 Number cycles EC, HER2-/HR+ patients, continuous, chemotherapy arm**

Shell similar to Table 217.

**Table 221 Number cycles EC, TNBC patients, continuous, denosumab arm**

Same shell as Table 217.

**Table 222 Number cycles EC, TNBC patients, continuous, chemotherapy arm**

Shell similar to Table 217.

**Table 223 Number cycles EC, HER2+ patients, continuous, denosumab arm**

Same shell as Table 217.

**Table 224 Number cycles EC, HER2+ patients, continuous, chemotherapy arm**

Shell similar to Table 217.

**Table 225 Number injections denosumab, all patients, frequencies**

<i>Number injections D</i>	<i>nPac weekly N(%)</i>	<i>nPac day 1, 8 N(%)</i>	<i>Overall N(%)</i>	<i>p-value</i>
1 injection	XX (XX%)	XX (XX%)	XX (XX%)	.XXX
2 injections	XX (XX%)	XX (XX%)	XX (XX%)	
3 injections	XX (XX%)	XX (XX%)	XX (XX%)	
4 injections	XX (XX%)	XX (XX%)	XX (XX%)	
5 injections	XX (XX%)	XX (XX%)	XX (XX%)	
6 injections	XX (XX%)	XX (XX%)	XX (XX%)	

**Table 226 Number injections denosumab, HER2-/HR+ patients, frequencies**

Shell similar to Table 225.

**Table 227 Number injections denosumab, TNBC patients, frequencies**

Shell similar to Table 225.

**Table 228 Number injections denosumab, HER2+ patients, frequencies**

Shell similar to Table 225.

**Table 229 Number injections denosumab, all patients, continuous**

<i>Parameter</i>	<i>Category</i>	<i>nPac weekly</i>	<i>nPact day 1, 8</i>	<i>Overall</i>	<i>p-value</i>
Number injections denosumab	Mean	XXX	XXX	XXX	.XXX
	Median	XXX	XXX	XXX	
	Min, Max	XXX, XXX	XXX, XXX	XXX, XXX	
	Missing, N	X	X	X	

**Table 230 Number injections denosumab, HER2-/HR+ patients, continuous**

Shell similar to Table 229.

**Table 231 Number injections denosumab, TNBC patients, continuous**

Shell similar to Table 229.

**Table 232 Number injections denosumab, HER2+ patients, continuous**

Shell similar to Table 229.

### 14.7.3 Dose delays

**Table 233 Any dose delay with reasons, all patients, denosumab arm**

<i>Delay</i>	<i>With D</i>	<i>Without D</i>	<i>Overall N (%)</i>	<i>p-value</i>
	<i>N (%)</i>	<i>N (%)</i>		
due to any reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to organizational reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX

<i>Delay</i>	<i>With D</i>	<i>Without D</i>	<i>Overall N (%)</i>	<i>p-value</i>
	<i>N (%)</i>	<i>N (%)</i>		
due to cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to AE not related to the study medication	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to unknown reason	XX (XX)	XX (XX)	XX (XX)	X.XX

**Table 234 Any dose delay with reasons, all patients, chemotherapy arm**

Shell similar to Table 233.

**Table 235 Any dose delay with reasons, HER2-/HR+ patients, denosumab arm**

Same shell as Table 233.

**Table 236 Any dose delay with reasons, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 233.

**Table 237 Any dose delay with reasons, TNBC patients, denosumab arm**

Same shell as Table 233.

**Table 238 Any dose delay with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 233.

**Table 239 Any dose delay with reasons, HER2+ patients, denosumab arm**

Same shell as Table 233.

**Table 240 Any dose delay with reasons, HER2+ patients, chemotherapy arm**

Shell similar to Table 233.

**Table 241 Dose delay of nab-paclitaxel with reasons, all patients, denosumab arm**

Same shell as Table 233.

**Table 242 Dose delay of nab-paclitaxel with reasons, all patients, chemotherapy arm**

Shell similar to Table 233.

**Table 243 Dose delay of nab-paclitaxel with reasons, HER2-/HR+ patients, denosumab arm**

Same shell as Table 233.

**Table 244 Dose delay of nab-paclitaxel with reasons, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 233.

**Table 245 Dose delay of nab-paclitaxel with reasons, TNBC patients, denosumab arm**

Same shell as Table 233.

**Table 246 Dose delay of nab-paclitaxel with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 233.

**Table 247 Dose delay of nab-paclitaxel with reasons, HER2+ patients, denosumab arm**

Same shell as Table 233.

**Table 248 Dose delay of nab-paclitaxel with reasons, HER2+ patients, chemotherapy arm**

Shell similar to Table 233.

**Table 249 Dose delay of carboplatin with reasons, TNBC patients, denosumab arm**

Same shell as Table 233.

**Table 250 Dose delay of carboplatin with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 233.

**Table 251 Dose delay of EC with reasons, all patients, denosumab arm**

Same shell as Table 233.

**Table 252 Dose delay of EC with reasons, all patients, chemotherapy arm**

Shell similar to Table 233.

**Table 253 Dose delay of EC with reasons, HER2-/HR+ patients, denosumab arm**

Same shell as Table 233.

**Table 254 Dose delay of EC with reasons, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 233.

**Table 255 Dose delay of EC with reasons, TNBC patients, denosumab arm**

Same shell as Table 233.

**Table 256 Dose delay of EC with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 233.

**Table 257 Dose delay of EC with reasons, HER2+ patients, denosumab arm**

Same shell as Table 233.

**Table 258 Dose delay of EC with reasons, HER2+ patients, chemotherapy arm**

Shell similar to Table 233.

**Table 259 Dose delay denosumab with reasons, all patients**

<i>Delay</i>	<i>nPac weekly N (%)</i>	<i>nPac d 1, 8 N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
due to any reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to organizational reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to AE not related to the study medication	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to unknown reason	XX (XX)	XX (XX)	XX (XX)	X.XX

**Table 260 Dose delay denosumab with reasons, HER2-/HR+ patients**

Same shell as Table 259.

**Table 261 Dose delay denosumab with reasons, TNBC patients**

Same shell as Table 259.

**Table 262 Dose delay denosumab with reasons, HER2+ patients**

Same shell as Table 259.

#### **14.7.4 Chemotherapy dose reductions**

**Table 263 Any chemotherapy dose reduction with reasons, all patients, denosumab arm**

<i>Reduction</i>	<i>Without D</i>		<i>Overall N (%)</i>	<i>p-value</i>
	<i>With D N (%)</i>	<i>N (%)</i>		
due to any reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX

<i>Reduction</i>	<i>Without D</i>		<i>Overall N (%)</i>	<i>p-value</i>
	<i>With D N (%)</i>	<i>N (%)</i>		
due to AE not related to the study medication	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to unknown reason	XX (XX)	XX (XX)	XX (XX)	X.XX

**Table 264 Any chemotherapy dose reduction with reasons, all patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 265 Any chemotherapy dose reduction with reasons, HER2-/HR+ patients, denosumab arm**  
Same shell as Table 263.

**Table 266 Any chemotherapy dose reduction with reasons, HER2-/HR+ patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 267 Any chemotherapy dose reduction with reasons, TNBC patients, denosumab arm**  
Same shell as Table 263.

**Table 268 Any chemotherapy dose reduction with reasons, TNBC patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 269 Any chemotherapy dose reduction with reasons, HER2+ patients, denosumab arm**  
Same shell as Table 263.

**Table 270 Any chemotherapy dose reduction with reasons, HER2+ patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 271 Nab-paclitaxel dose reduction with reasons, all patients, denosumab arm**  
Same shell as Table 263.

**Table 272 Nab-paclitaxel dose reduction with reasons, all patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 273 Nab-paclitaxel dose reduction with reasons, HER2-/HR+ patients, denosumab arm**  
Same shell as Table 263.

**Table 274 Nab-paclitaxel dose reduction with reasons, HER2-/HR+ patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 275 Nab-paclitaxel dose reduction with reasons, TNBC patients, denosumab arm**  
Same shell as Table 263.

**Table 276 Nab-paclitaxel dose reduction with reasons, TNBC patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 277 Nab-paclitaxel dose reduction with reasons, HER2+ patients, denosumab arm**  
Same shell as Table 263.

**Table 278 Nab-paclitaxel dose reduction with reasons, HER2+ patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 279 Carboplatin dose reduction with reasons, TNBC patients, denosumab arm**  
Same shell as Table 263.

**Table 280 Carboplatin dose reduction with reasons, TNBC patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 281 EC dose reduction with reasons, all patients, denosumab arm**  
Same shell as Table 263.

**Table 282 EC dose reduction with reasons, all patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 283 EC dose reduction with reasons, HER2-/HR+ patients, denosumab arm**  
Same shell as Table 263.

**Table 284 EC dose reduction with reasons, HER2-/HR+ patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 285 EC dose reduction with reasons, TNBC patients, denosumab arm**  
Same shell as Table 263.

**Table 286 EC dose reduction with reasons, TNBC patients, chemotherapy arm**  
Shell similar to Table 263.

**Table 287 EC dose reduction with reasons, HER2+ patients, denosumab arm**  
Same shell as Table 263.

**Table 288 EC dose reduction with reasons, HER2+ patients, chemotherapy arm**  
Shell similar to Table 263.

#### 14.7.5 Treatment interruptions

**Table 289 Any skipped chemotherapy infusion, with reasons, all patients, denosumab arm**

Infusion n.d.	Withd D	Without D	Overall N (%)	p-value
	N (%)	N (%)		



<i>Infusion n.d.</i>	<i>Withd D</i> <i>N (%)</i>	<i>Without D</i> <i>N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
due to any reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	X.XX
due to AE not related to the study medication	XX (XX)	XX (XX)	XX (XX)	X.XX
due to other reason	XX (XX)	XX (XX)	XX (XX)	X.XX
due to unknown reason	XX (XX)	XX (XX)	XX (XX)	X.XX

**Table 290 Any skipped chemotherapy infusion, with reasons, all patients, chemotherapy arm**

Shell similar to Table 289.

**Table 291 Any skipped chemotherapy infusion, with reasons, HER2-/HR+ patients, denosumab arm**

Same shell as Table 289.

**Table 292 Any skipped chemotherapy infusion, with reasons, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 289.

**Table 293 Any skipped chemotherapy infusion, with reasons, TNBC patients, denosumab arm**

Same shell as Table 289.

**Table 294 Any skipped chemotherapy infusion, with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 289.

**Table 295 Any skipped chemotherapy infusion, with reasons, HER2+ patients, denosumab arm**

Same shell as Table 289.

**Table 296 Any skipped chemotherapy infusion, with reasons, HER2+ patients, chemotherapy arm**

Shell similar to Table 289.

**Table 297 Skipped infusion nab-paclitaxel, with reasons, all patients, denosumab arm**

Same shell as Table 289.

**Table 298 Skipped infusion nab-paclitaxel, with reasons, all patients, chemotherapy arm**

Shell similar to Table 289.

**Table 299 Skipped infusion nab-paclitaxel, with reasons, HER2-/HR+ patients, denosumab arm**

Same shell as Table 289.

**Table 300 Skipped infusion nab-paclitaxel, with reasons, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 289.

**Table 301 Skipped infusion nab-paclitaxel, with reasons, TNBC patients, denosumab arm**

Same shell as Table 289.

**Table 302 Skipped infusion nab-paclitaxel, with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 289.

**Table 303 Skipped infusion nab-paclitaxel, with reasons, HER2+ patients, denosumab arm**

Same shell as Table 289.

**Table 304 Skipped infusion nab-paclitaxel, with reasons, HER2+ patients, chemotherapy arm**

Shell similar to Table 289.

**Table 305 Skipped infusion carboplatin with reasons, TNBC patients, denosumab arm**

Same shell as Table 289.

**Table 306 Skipped infusion carboplatin, with reasons, TNBC patients, chemotherapy arm**

Shell similar to Table 289.

**Table 307 Skipped infusion EC, with reasons, all patients, denosumab arm**

Same shell as Table 289.

**Table 308 Skipped infusion EC, with reasons, all patients, chemotherapy arm**

Shell similar to Table 289.

**Table 309 Skipped injection denosumab, with reasons, all patients**

Shell similar to Table 289.

**Table 310 Skipped injection denosumab, with reasons, HER2-/HR+ patients**

Shell similar to Table 289.

**Table 311 Skipped injection denosumab, with reasons, TNBC patients**

Shell similar to Table 289.

**Table 312 Skipped injection denosumab, with reasons, HER2+ patients**

Shell similar to Table 289.

**Table 313 Pause in day 1, 8 nab-paclitaxel arm not respected**

<i>Pause not respected</i>	<i>Withd D</i>	<i>Without D</i>	<i>Overall N (%)</i>	<i>p-value</i>
	<i>N (%)</i>	<i>N (%)</i>		
Any number of times	XX (XX)	XX (XX)	XX (XX)	X.XX
Once	XX (XX)	XX (XX)	XX (XX)	
Twice	XX (XX)	XX (XX)	XX (XX)	
In 3 cycles	XX (XX)	XX (XX)	XX (XX)	
In all 4 cycles	XX (XX)	XX (XX)	XX (XX)	

#### 14.7.6 Bar charts of chemotherapy compliance

Figure 33 Bar chart of nab-paclitaxel compliance, weekly arm

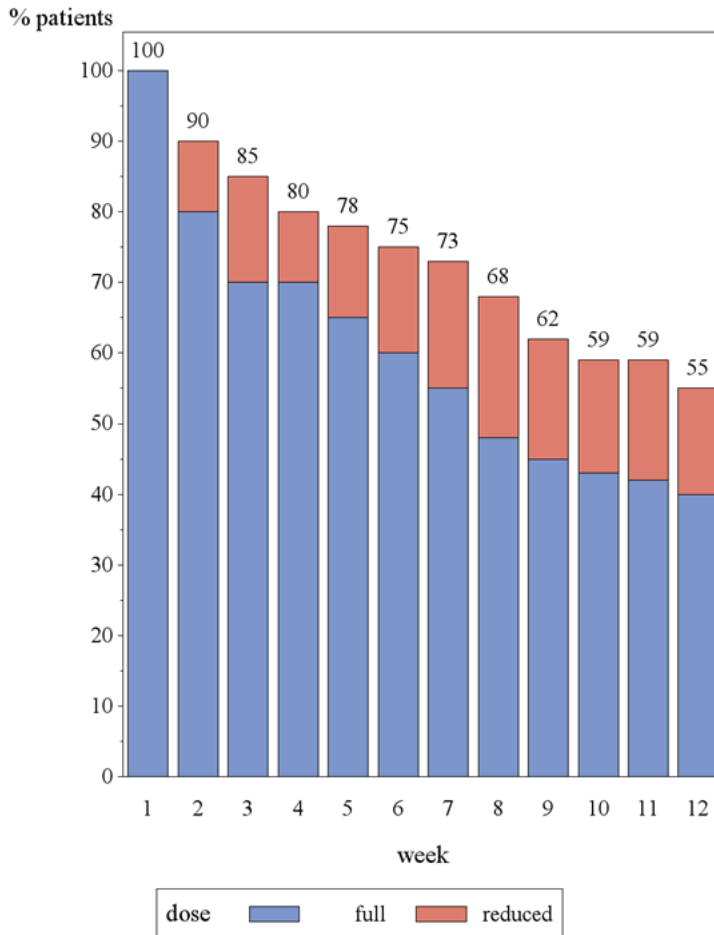


Figure 34 Bar chart of nab-paclitaxel compliance, day 1, 8 arm

Shell similar to Figure 33.

Figure 35 Bar chart of carboplatin compliance, TNBC patients, weekly nab-paclitaxel arm

Shell similar to Figure 33.

Figure 36 Bar chart of carboplatin compliance, TNBC patients, nab-paclitaxel day 1, 8 arm

Shell similar to Figure 33.

Figure 37 Bar chart of EC compliance, weekly nab-paclitaxel arm

Shell similar to Figure 33.

Figure 38 Bar chart of EC compliance, nab-paclitaxel day 1, 8 arm

Shell similar to Figure 33.

#### 14.7.7RTD and RTDI

**Table 314 Relative total dose of chemotherapy, all patients, denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
RTD overall, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	
RTD nP±Cb, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X.	X	X	
RTD EC, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N		X		

**Table 315 Relative total dose of chemotherapy, all patients, chemotherapy arm**

Shell similar to Table 314.

**Table 316 Relative total dose of chemotherapy, HER2-/HR+ patients, denosumab arm**

Same shell as Table 314.

**Table 317 Relative total dose of chemotherapy, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 314.

**Table 318 Relative total dose of chemotherapy, TNBC patients, denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
RTD overall, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X	X	X	

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
RTD nP±carbo, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X.	X	X	
RTD nP, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X.	X	X	
RTD Cb, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N	X.	X	X	
RTD EC, %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N		X		

**Table 319 Relative total dose of chemotherapy, TNBC patients, chemotherapy arm**

Shell similar to Table 318.

**Table 320 Relative total dose of chemotherapy, HER2+ patients, denosumab arm**

Same shell as Table 314.

**Table 321 Relative total dose of chemotherapy, HER2+ patients, chemotherapy arm**

Shell similar to Table 314.

**Table 322 Relative total dose intensity of chemotherapy, all patients, denosumab arm**

Shell similar to Table 314.

**Table 323 Relative total dose intensity of chemotherapy, all patients, chemotherapy arm**

Shell similar to Table 314.

**Table 324 Relative total dose intensity of chemotherapy, HER2-/HR+ patients, denosumab arm**

Shell similar to Table 314.

**Table 325 Relative total dose intensity of chemotherapy, HER2-/HR+ patients, chemotherapy arm**

Shell similar to Table 314.

**Table 326 Relative total dose intensity of chemotherapy, TNBC patients, denosumab arm**

Shell similar to Table 318.

**Table 327 Relative total dose intensity of chemotherapy, TNBC patients, chemotherapy arm**

Shell similar to Table 318.

**Table 328 Relative total dose intensity of chemotherapy, HER2+ patients, denosumab arm**

Shell similar to Table 314.

**Table 329 Relative total dose intensity of chemotherapy, HER2+ patients, chemotherapy arm**

Shell similar to Table 314.

**Table 330 RTD and RTDI of nab-paclitaxel based on weekly schedule, all patients, denosumab arm**

<i>Parameter</i>	<i>Category</i>	<i>With D</i>	<i>Without D</i>	<i>Overall</i>	<i>p-value</i>
RTD nP (based on weekly schedule), %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N		X		
RTDI nP (based on weekly schedule), %	Mean	XX	XX	XX	.XXX
	StD	XX	XX	XX	
	Median	XX	XX	XX	
	Min, Max	XX, XX	XX, XX	XX, XX	
	Missing, N		X		

**Table 331 RTD and RTDI of nab-paclitaxel based on weekly schedule, all patients, chemotherapy arm**

<i>Parameter</i>	<i>Category</i>	<i>nP weekly</i>	<i>nP d1, 8</i>	<i>Overall</i>
RTD nP (based on weekly schedule), %	Mean	XX	XX	XX
	StD	XX	XX	XX
	Median	XX	XX	XX
	Min, Max	XX, XX	XX, XX	XX, XX
	Missing, N		X	
RTDI nP (based on weekly schedule), %	Mean	XX	XX	XX
	StD	XX	XX	XX
	Median	XX	XX	XX
	Min, Max	XX, XX	XX, XX	XX, XX
	Missing, N		X	

(no p-value, arms are different by design)

#### 14.8 QoL

**Table 332 FACT-Taxane scores according to the time point, denosumab arm**

	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
Baseline			
PhWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SFWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
EWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AC mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane TOI mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-G total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
After nab-paclitaxel			
PhWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SFWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
EWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AC mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane TOI mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-G total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
EOT			
PhWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)



	<i>With D</i>	<i>Without D</i>	<i>Overall</i>
SFWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
EWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AC mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane TOI mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-G total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
90 days after surgery			
PhWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SFWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
EWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FWB mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AC mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane TOI mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-G total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FACT-Taxane total score mean (StD)	xx (xx.x)	xx (xx.x)	xx (xx.x)

**Table 333 FACT-Taxane scores according to the time point, denosumab arm**

Shell similar to Table 332.

**Table 334 Patients choosing the worst two item categories according to the time point, denosumab arm**

<i>Patients choosing the worst two item categories per subscale</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>
Baseline			
PhWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
SFWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
EWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
FWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
AC	xx (x.x%)	xx (x.x%)	xx (x.x%)
After nab-paclitaxel			
PhWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
SFWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
EWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
FWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
AC	xx (x.x%)	xx (x.x%)	xx (x.x%)
EOT			
PhWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
SFWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
EWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
FWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
AC	xx (x.x%)	xx (x.x%)	xx (x.x%)
90 days after surgery			
PhWB	xx (x.x%)	xx (x.x%)	xx (x.x%)

<i>Patients choosing the worst two item categories per subscale</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>
SFWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
EWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
FWB	xx (x.x%)	xx (x.x%)	xx (x.x%)
AC	xx (x.x%)	xx (x.x%)	xx (x.x%)

**Table 335 Patients choosing the worst two item categories according to the time point, chemotherapy arm**

Shell similar to Table 334.

#### 14.9 HER2+ substudy

Most tables will be similar to the tables of the main study.

**Table 336 Discontinuations of anti-HER2 treatment before chemotherapy; HER2-positive patients only, denosumab arm**

<i>Patient status</i>	<i>With D N (%)</i>	<i>Without D N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
Discontinued both ABP 980 and pertuzumab before chemotherapy	XX (XX)	XX (XX)	XX (XX)	.XXX
- AE	XX (XX)	XX (XX)	XX (XX)	
- hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	
- other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- AE not related to study medication	XX (XX)	XX (XX)	XX (XX)	
- Investigator's decision	XX (XX)	XX (XX)	XX (XX)	
- Patient's wish	XX (XX)	XX (XX)	XX (XX)	
Discontinued ABP 980 but not pertuzumab before chemotherapy	XX (XX)	XX (XX)	XX (XX)	.XXX
- AE	XX (XX)	XX (XX)	XX (XX)	
- hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	
- other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- AE not related to study medication	XX (XX)	XX (XX)	XX (XX)	
- Investigator's decision	XX (XX)	XX (XX)	XX (XX)	
- Patient's wish	XX (XX)	XX (XX)	XX (XX)	

<i>Patient status</i>	<i>With D</i>	<i>Without D</i>	<i>Overall N (%)</i>	<i>p-value</i>
	<i>N (%)</i>	<i>N (%)</i>		
Discontinued pertuzumab but not ABP 980 before chemotherapy	XX (XX)	XX (XX)	XX (XX)	.XXX
- AE	XX (XX)	XX (XX)	XX (XX)	
- hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- cardiac toxicity	XX (XX)	XX (XX)	XX (XX)	
- other non-hematological toxicity	XX (XX)	XX (XX)	XX (XX)	
- AE not related to study medication	XX (XX)	XX (XX)	XX (XX)	
- Investigator's decision	XX (XX)	XX (XX)	XX (XX)	
- Patient's wish	XX (XX)	XX (XX)	XX (XX)	

#### 14.10 DTC substudy

**Table 337 Subject and baseline characteristics of patients included in the DTC substudy, part I (continuous parameters)**

Shell similar to Table 14.

**Table 338 Subject and baseline characteristics of patients included in the DTC substudy, part II (categorical and ordinal parameters)**

Shell similar to Table 17.

**Table 339 DTC at baseline and eradication of DTC after chemotherapy**

	<i>With D</i>	<i>Without D</i>	<i>Overall N (%)</i>	<i>p-value</i>
	<i>N (%)</i>	<i>N (%)</i>		
Patients with DTC at baseline assessed	XXX	XXX	XXX	
DTC negative	XX (XX)	XX (XX)	XX (XX)	
DTC positive	XX (XX)	XX (XX)	XX (XX)	
Patients DTC positive at baseline with DTC after chemotherapy assessed	XXX	XXX	XXX	
DTC negative	XX (XX)	XX (XX)	XX (XX)	.XX
DTC positive	XX (XX)	XX (XX)	XX (XX)	

**Table 340 pCR (ypT0 ypN0) according to the DTC at baseline**

	<i>DTC negative at baseline N (%)</i>	<i>DTC positive at baseline N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
pCR (ypT0, ypN0)	XX (XX)	XX (XX)	XX (XX)	.XX
No pCR	XX (XX)	XX (XX)	XX (XX)	

This table will be presented overall and per denosumab treatment arm, overall and per biological subtype.

**Table 341 pCR (ypT0 ypN0) according to the eradication of DTC**

	<i>DTC negative after NACT N (%)</i>	<i>DTC positive after NACT N (%)</i>	<i>Overall N (%)</i>	<i>p-value</i>
pCR (ypT0, ypN0)	XX (XX)	XX (XX)	XX (XX)	.XX
No pCR	XX (XX)	XX (XX)	XX (XX)	

This table will be presented overall (all patients and per biological subtype) and per denosumab treatment arm.