INTERNATIONAL BREAST CANCER STUDY GROUP

TREND (TRIAL 41-13)

TRial on the Endocrine activity of Neoadjuvant Degarelix:

Statistical Analysis Plan (SAP)

October 2017

Version	Author	Date	Status
1.0	Kathryn P Gray, PhD	10/2017	Final

1 STUDY OVERVIEW

1.1 SYNOPSIS

The TREND randomized phase II trial evaluates neoadjuvant endocrine therapy (degarelix [GnRH antagonist] versus triptorelin [GnRH agonist]) in combination with letrozole as treatment for premenopausal women diagnosed with endocrine-responsive cancer. A 1:1 randomization allocation (degarelix+ letozole vs triptorelin +letozole) is used. The primary objective is to compare the endocrine activity of neoadjuvant degarelix and triptorelin in premenopausal patients receiving letrozole for primary endocrine-responsive breast cancer. The endocrine activity is measured by time to optimal ovarian function suppression, with the hypothesis that degarelix will achieve faster ovarian suppression than triptorelin.

The study was activated on 28 March 2013 and the first patient was enrolled on 24 February 2014, with the delay due to changes in trial activation rules in Italy during that time.

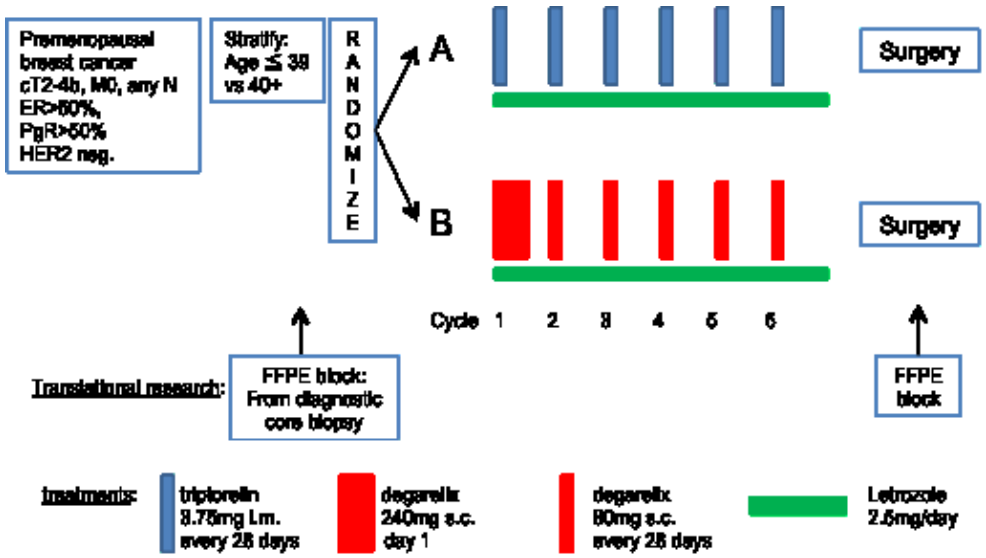
The trial activated in seven participating centers in Italy: Bologna, Genoa, Milan, Pavia, Prato, Rimini, and Varese.

1.2 TRIAL DESIGN

TREND (TRIAL 41-13) OVERVIEW

Title	**TRial on the Endocrine activity of Neoadjuvant Degarelix (TREND):** A randomized phase II trial evaluating the endocrine activity and efficacy of neoadjuvant degarelix versus triptorelin in premenopausal patients receiving letrozole for primary endocrine responsive breast cancer
Patient Population	Premenopausal patients with histologically confirmed primary breast cancer and with primary tumor which is ER+ and PgR+ (>50%) and HER2-negative or not amplified
Entry	Patients must be entered before initiating any treatment for primary invasive breast cancer. Patients cannot have received GnRH analogue, SERM or AI within 12 months prior to randomization, and cannot have used hormonal treatment in the two months prior to randomization. Premenopausal status must be determined by estradiol (E2) above 54 pg/mL (or above 198 pmol/L), measured in a local laboratory within 14 days prior to randomization.
Activation Date	28 March 2013 (first patient entered 24 February 2014)
Target Accrual	50
Closure Date	12 January 2017 (Last patient enrolled 10 January 2017)
Final Accrual	51

Schema:



Stratification Factors:

Age: ≤39 versus 40+ (years).

Treatment Schedules:

Arm A: Triptorelin 3.75 mg administered intramuscularly (i.m.) on day 1 of every cycle* + letrozole 2.5 mg/day orally for 6 cycles

Arm B: Degarelix 240 mg given as two subcutaneous injections (s.c.) of 120 mg on day 1 of cycle* 1, followed by 80 mg sc on day 1 of cycles 2 to 6 + letrozole 2.5 mg/day orally for 6 cycles

*one cycle is 28 days

Blood Sampling Schedule:

Blood will be sampled at the following times to determine estradiol (E2) levels in a central laboratory:

- Baseline: day 1 of the first treatment cycle before the administration of the first dose of degarelix or triptorelin
- 24 and 72 hours thereafter
- 7 days and 14 days after the first injection
- Day 1 of cycles 2 to 6 before the administration of degarelix or triptorelin**.**

1.3 STATISTICAL DESIGN AND SAMPLE SIZE

50 patients will be randomized using 1:1 allocation and stratified based on age (≤39 vs. ≥40 years). to

- 25 patients to treatment with triptorelin plus letozole; and
- 25 patients to treatment with degarelix plus letozole.

The sample size was determined in consideration of the trial primary objectives. Specifically, the primary endpoint of time to optimal ovarian function suppression will be assessed in the two treatment arms and is defined as time from the first injection of degarelix or triptorelin to the first centrally assessed E2 ≤2.72 pg/mL or ≤10 pmol/L during the 6 cycles of neoadjuvant treatment. The blood samples are taken at day 1 of the first treatment cycle before the administration of the first dose of degarelix or triptorelin (baseline), and thereafter at 24 and 72 hours, 7 days and 14 days after the first injection, and on day 1 of cycles 2 to 6 before the administration of degarelix or triptorelin.

The following table provides the assumption on the cumulative percent of patients who are anticipated to reach optimal ovarian function suppression (E2 level ≤2.72 pg/mL or ≤10 pmol/L) during the 6 cycles of neoadjuvant treatment.

	Cumulative percent (%) of patients with E2 ≤2.72 pg/mL or ≤10 pmol/L				
Treatment arms	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks
Triptorelin+Letrozole (control: arm A)	30	60	75	90	100
Degarelix+Letrozole (experiment: arm B)	60	95	100	100	100

With 23 patients in each treatment arm and based on the assumption in the table above, the study has 90% power to detect a difference in time to optimal ovarian function suppression (E2 ≤2.72 pg/mL or ≤10 pmol/L) between the two treatment arms, using a two-sample log-rank test at a two-sided significance level of 0.05. Calculations were performed using nQuery Advisor® (logrank test of survival in two groups, simulation with percentages specified in above table).

To allow for missing data, the study enrolls 25 patients to each treatment arm for a total of 50 patients.

1.4 TRIAL CONDUCT

1.4.1 Protocol Versions/Amendments

The trial was activated with protocol version 1.0 on dated 28 March 2013, and first patient enrolled on 24 February 2014. Final patient enrolled in January 2017 with final enrollment of N=51.

There is no amendment.

1.4.2

IBCSG Data and Safety Monitoring Committee (DSMC) conducts regularly scheduled semi-annual reviews of interim clinical and safety data for trial 41-13 (TREND)

The DSMC conducted reviews on April 24, 2014 and subsequently around every 6 month, concluded the trial to continue as planned.

2 OVERVIEW OF ANALYSIS PLANS

Analysis Steps:

- Identify patients who are enrolled into two arms and check the treatment status.
- Define primary endpoint using data from the relevant CRFs and centrally assessed E2 values at timepoints.
- Define (baseline clinical) covariates for model adjustment and calculate age stratification factor (at randomization)
- Use the method described below for analyses.

2.1 ANALYSIS POPULATIONS

ITT population: All randomized patients without regard to adherence with treatment assigned.

The safety population: All patients who received at least one dose of trial treatment were included in assessments of safety and tolerability

Surgery population: All patients who received surgery at the end of neoadjuvant therapies.

PRS population: All patients who received at least one dose of trial treatment and had at least one FACT-ES assessment were included in the analysis.

2.2 ANALYSIS PLANS

2.2.1 Primary Objective

To compare the endocrine activity of neoadjuvant degarelix and triptorelin in premenopausal patients receiving letrozole. The endocrine activity is measured by time to optimal ovarian function suppression.

2.2.2 Secondary Objectives

To evaluate:

- Node-negative disease at surgery
- Breast-conserving surgery (BCS) rate
- The Preoperative Endocrine Prognostic Index (PEPI) score determined after completion of neoadjuvant therapy or at the time of surgery
- Ki67 proliferation marker changes
- Best overall (disease) response
- Safety and tolerability as documented according to NCI CTCAE version v4.0
- Patient-reported symptoms (PRS) outcomes

2.2.3 Primary Endpoint

Time to optimal ovarian function suppression (TTOFS): time from the first injection of degarelix or triptorelin to the first assessment of centrally assessed 17-β-estradiol (E2) level in the range of optimal ovarian function suppression (E2≤2.72 pg/mL or ≤10 pmol/L) during the 6 cycles of neoadjuvant treatments. Time for patients who do not reach the targeted E2 level will be censored at the last E2 assessment date.

2.2.4 Secondary Endpoints

1. Node-negative disease at surgery: The number of lymph nodes assessed at surgery minus the number of positives nodes identified, equal to zero.
2. Breast-conserving surgery (BCS): Whether or not patient undergoes BCS (per Surgery form). If patient does not undergo surgery within the trial then patient is to be excluded from the surgery outcome summary (analysis is based on surgery population)
3. Change in Ki67 expression level: the percent change in Ki67 expression from pre-treatment diagnostic (baseline) biopsy to surgery, calculated as (surgery-baseline)/baseline*100.
4. The Preoperative Endocrine Prognostic Index (PEPI, range 0-12) score at time of surgery: By integrating central pathology review (CPR) results of pathological features and biomarkers with risk points (table below), the PEPI is the sum of the risk points with a 0 score representing the best prognostic feature, as previously determined to be associated with recurrence-free survival (RFS):

		RFS	
Pathology, biomarker status		HR	Adverse Points
Tumor size:			
T1/2			0
T3/4		2.8	3
Nodal status			
Negative			0
Positive		3.2	3
Ki67 level			
0 – 2.7%	(0 – 1 [a])		0
>2.7 – 7.3%	(1 – 2 [a])	1.3	1

>7.3 – 19.7%	(2 – 3 [a])	1.7	1
>19.7 – 53.1%	(3 – 4 [a])	2.2	2
>53.1%	(>4 [a])	2.9	3
ER status, Allred score			
0 – 2		2.8	3
3 – 8			0

[a]The natural logarithm interval corresponding to the per cent Ki67 values on the original percentage scale

5. Best overall response: based on WHO tumor measurement and response criteria [1], measured from the start of treatment across all time points until disease progression or the end of 6 cycles of neoadjuvant therapies, whichever comes first. Response was determined by the IBCSG Head of Medical Affairs. An internal review (IR) form was created to record the final determination on best overall response. Confirmation of partial or complete response by an additional scan was not required in this trial.

   Best overall response was assessed based on changes in tumor size from baseline to the assessments after 3 and after 6 cycles (denoted as day 1 of cycle 4 and prior to surgery respectively) as measured physically by caliper or ruler and as measured by breast tumor imaging (i.e., bilateral mammography and breast ultrasound).

   - Complete Response (CR): The disappearance of all known disease;
   - Partial Response (PR): A 50% or more decrease in total tumor size (i.e. the product of the lesion's maximal diameter (MD) and the corresponding largest perpendicular diameter (LPD) of lesion) which have been measured to determine the effect of the therapy. In addition, there can be no appearance of new lesions or progression of any lesion;
   - Stable Disease (SD): Neither a 50% decrease in total tumor size (i.e. the product of the lesion's two diameters, MD*LPD of lesion) nor a 25% increase in the size of one or more measurable lesions has been determined;
   - Progressive Disease (PD): An increase of at least 25% in total tumor size relative to the smallest size measured during the trial and/or appearance of one or more new lesions.
6. Safety and tolerability: Adverse events (AE) were collected using CTCAE v4.0.
   a. Each targeted AE will be classified according to the maximum grade of the event while on trial treatment (grade 0,1,2,3,4,5; where 0=no report).
   b. Other grade 3-5 AEs will be classified according to the maximum grade of any reported other AE.
7. Patient-reported symptoms (PRS) outcomes (see Section 2.2.6)

2.2.5 Analysis of the primary endpoint

The primary endpoint (TTOFS) was compared between the two treatment arms using a stratified two-sample log-rank test, with a α=0.05 type I error, using stratification factors of age <=39 vs. 40+ as defined for randomization. The test statistic and p-value were taken from the stratified Cox proportional hazards (PH) model (reported as score test). Hazard ratios (degarelix+letrozole /triptorelin+letrozole, so that HR>1 indicates increased hazard of event with degarelix+letrozole

and HR<1 indicates decreased hazard of an event with degarelix+letrozole) were estimated from a stratified Cox PH model, with two-sided Wald 95% confidence intervals (CIs). Recall, here an event is a good thing, so we expect HR>1.

Cox proportional hazards model were also used to assess the difference in time to optimal ovarian function suppression between the treatment arms adjusting for selected covariates including baseline E2 level, body mass index (BMI), smoking history, and recent oral contraceptive usage.

The distribution of the primary endpoint was summarized using the method of Kaplan-Meier with reporting of median TTOFS as well as cumulative probability of time to OFS (1- event-free probability). The standard errors used Greenwood's formula and the pointwise 95% CIs were obtained using complementary log(-log(endpoint)) transformation methodology.

Two-sided 95% confidence interval (CI) for the difference in proportion of patients who achieved optimal OFS (defined as E2 level ≤2.72 pg/mL or ≤10 pmol/L) between the two treatment arms at the end of the 1st, 2nd and 4th cycle were to be provided. *(Not performed due to all (except one data-point at end of cycle2) were at OFS by the end of cycle 1, not meaningful*).

Spider plots displayed the E2 data over scheduled sampling time. Boxplots illustrated the distribution of E2, FSH and LH at the scheduled sampling times.

2.2.6 Analyses of secondary endpoints

- Node negative disease at surgery: The percentage of patients with node-negative disease at surgery will be descriptively summarized by treatment arm. Two sided 90% CI for the difference in percentage of patients with node-negative disease between treatment arms will be reported.
- Breast-conserving surgery (BCS):
    - Details of the surgical procedure performed overall and according to treatment arms.
    - The percent of patients in each treatment arm who had a breast-conserving surgery were presented, and the difference between the treatment arms were assessed using a two-sided exact 90% CI.
    - Rate of conversion (patient identified as candidates/planned for BCS or mastectomy per data on RA-form vs surgery performed on C-form): Cross-tabulation of surgery status between "planned" vs 'performed' and the percent in conversion overall and according to treatment arms were presented.
- Change in Ki67 (Surgery population, unless otherwise noted)
    - Ki67 expressions at baseline (pre-treatment, based on ITT population) and at surgery were descriptively summarized (median, IQR and mean) according to treatment arms.
    - The change in Ki67 expression from baseline (pre-treatment) to surgery was summarized for each treatment arm and two-sided 90% CI for the change were calculated and explored using a paired sample Wilcoxon signed-rank test.

- The percentage changes in Ki67 expression between the treatment arms from baseline to surgery were assessed using a two-sided 90% CI and explored using a two-sample Wilcoxon rank sum test.
- Boxplots were used to illustrate the marker distribution at baseline and surgery timepoints.
- Spider plots were used to show the individual paired Ki67 data from baseline to surgery.

- The preoperative endocrine prognostic index (PEPI) score at time of surgery

  Patients in surgery population will be included in the assessment. Descriptive statistics are used to summarize the PEPI score by treatment arm. Two-sided 90% CI for the difference in the PEPI scores between the two arms maybe constructed. (*NOT DONE, given only one pt had PEPI score of 0*)
- Objective response was defined as CR/PR vs. Others (SD/PD/NE), where NE stands for non-evaluable:

  - Best overall response, overall and by treatment arm, were provided with Ns and proportions.
  - Objective response (CR/PR as best overall response) rate was summarized as N (%) with 90% CI, overall and by treatment arm, as well as the absolute percent difference of objective responses between arms were reported with exact binominal 90%CI.
  - Clinical responses at the end of cycle 3 and 6, including complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were descriptively summarized by treatment arms.

- Safety and tolerability

  Tolerability was evaluated in each treatment arm separately, using the safety population. For each patient, the targeted AEs recorded over time were summarized for each AE type as the maximum grade reported for that AE (without regard to reported relation to study treatments). The frequencies and percentages of patients experiencing each targeted AE were reported according to maximum grade, separately by treatment arm.. Two-sided 90% exact confidence interval (CI) for the difference in proportion of patients with each type of grade 3 or higher targeted AE between the treatment arms were assessed.

  - The maximum grade of all targeted AEs are summarized by treatment arm, and the number and percentage of patients experiencing at least one grade 3 or higher targeted AE will be reported (with CI) according to treatment arm.
  - Targeted adverse events (AEs) and other (non-targeted) grade 3 or higher AEs occurring during study were collected using CTCAE v4.0 on the AE Form. The AE Forms were submitted at the end of every cycle (27 days) and 30 days after surgery. All patients submitted AE data during 6 cycles of treatment period when available.
  - AEs are reported as maximum grade. The maximum grade consolidates the reports of a given type of AE for a patient over time by taking the maximum

(worst grade) across time (i.e., a patient appears only once for a given type of AE). Patients with reports of multiple AEs of different types are reported multiple times under the relevant AE categories. Maximum grade 0 indicates that the AE type was been reported.

- Patient-reported symptoms (PRS) analysis

Longitudinal assessments collected PRS outcome at *baseline* (prior to randomization), at *day 1 of cycle 2 (day29)*, at *day 1 of cycle 4 (day 85)* of triptorelin or degarelix administration and prior to surgery.

The PRS were assessed using the Functional Assessment of Cancer Therapy Endocrine Subscale (FACT-ES: for endocrine symptom) comprising 19 items (each has score range from 0 to 4) with a possible maximum total score (denoted as ESS) of 76. Functional Assessment of Chronic Illness Therapy (FACIT) guidelines will be used for scoring and interpretation of the FACT-ES total score.

The primary endpoint was FACT-ES total score (or ESS). Note that the FACT-ES items are negatively framed, thus scores were reversed for analysis so that high scores equate to a good quality of life (QOL) [Lesley et al]

In order to better describe the specific type of QOL measures, as exploratory analysis, four subscales/groups of FACT-ES were also summarized, namely,

- Vasomotor symptoms (VS, score 0-12): hot flashes, cold sweats, night sweat (note: sleeping difficult was an item not collected in our dataset)
- Neuropsychological symptoms (NS, score 0-16): light-headed/dizzy, headache, mood swings, feeling irritable (lack of energy, nervous were not collected in our study)
- GI symptoms (GIS, score 0-16): Vomiting, Gained weight, Diarrhea, bloated feeling (nausea no data)
- Gynecologic symptoms (GYNS. score 0-28): vaginal discharge, vaginal irritation, vaginal bleeding, vaginal dryness, discomfort intercourse, lost interest in sex, breast tenderness

To provide clinically useful information regarding treatment side effects, patient responses to each ES question are labeled as ‘‘clinically significant’’ if they scored 3 or 4 (corresponding to ‘‘quite a bit’’ or ‘‘very much’’ a problem, respectively, on the questionnaire) and as ‘‘not clinically significant’’ for scores of 0, 1, or 2 (‘‘not at all’’, ‘‘a little bit’’, or ‘‘somewhat’’ a problem, respectively). The questionnaire is completed before any subsequent procedures or treatment and refers to the past 7 days.

All patients who received at least one dose of study treatment and with at least one FACT-ES assessment were included in the analysis (PRS population=ITT population).

The differences in FACT-ES scores (ESS) measurements between the two treatment arms over time were assessed using a mixed-effect model (SAS proc mixed, note a change from GEE model stated in the protocol, due to the small sample size and for simplicity). The ESS

scores as well as the 4 subscales and individual FACT-ES items were modeled as a function of time and treatment arm to investigate the time pattern of FACT-ES scores and differences controlling for the stratification factor of age (dichotomized ≤39 vs 40+ years). The covariance structure used *autoregressive* (type =AR(1) assuming between observations on the same patient are not equal but decrease toward zero with increasing lag). All available data were included in the model.

This model described the effects of two neoadjuvant treatments (degarelix+letrozole or triptorelin+letrozole) on FACT-ES for the observation period. The analysis will be exploratory, given the limited sample size (maximum 25 patients per treatment arm). The power of the repeated measure test is likely to be low except if treatment differences are substantial.

Means scores at each timepoint for each treatment arm, and for the difference between the treatment arms, were estimated from the models and reported with 90% CIs.

2.3 CORRELATIVE OBJECTIVES/ANALYSIS

A tumor block from the diagnostic core biopsy and one from final surgery will be collected and banked for central review and future translational research at the IBCSG Tissue Bank hosted by the European Institute of Oncology in Milan, Italy (Prof. G. Viale).

No specific correlative/translational analysis is planned.

3 ADDITIONAL ANALYSIS COMPONENTS AND PRESENTATION

3.1 FOLLOW-UP

The database cutoff is September 5, 2017

Stratification: patients are stratified by age at randomization ((≤39 vs. > 39 years)

Dynamic institution balancing will be used in order to balance randomized assignments within institutions.

3.2 INTERIM ANALYSIS/DATA MONITORING

Interim analyses for primary efficacy were not planned.

Adverse event reports are to be submitted within 28 days of each clinic visit. All relevant adverse events will be reviewed by the DSMC every 6 months (twice a year). The DSMC will make recommendation to the study management team if it notes any concerns regarding patient safety or if further action needs to be taken based on the safety monitoring review results. Formal assessment of targeted adverse events will also be included in statistical analysis for secondary objectives as detailed in section 2.2.6.

3.3 ENROLLMENT, ELIGIBILITY, FOLLOW-UP COMPLIANCE

This section summarizes registration, enrollment, eligibility according to internal review, exclusions from the ITT population, CRF submission status and follow-up compliance.

3.3.1 Enrollment overview will include:

- Tables
    - Enrollment period
    - Numbers of patients registered and randomized, over time, by participating centers, by stratification factors
- Figures
    - Numbers of patients registered and randomized (two lines; y-axis) over time (x-axis)

3.3.2 CONSORT diagram, the following data will be summarized:

- Number of patients registered.
    - Reasons registered patients were not randomized
- Number of patients randomized to each treatment group
- Patients excluded from ITT population (do not initiate treatment and WC for all participation), according to treatment group
- Treatment status: initiation vs. non-initiation of assigned trial treatment
- Follow-up status: complete per protocol (or on treatment) vs. WC/LFU

3.3.3 Stratification factors will be overviewed (for the randomized population):

- Tables:
    - Distribution of stratification factor, overall and by treatment assignment
    - Cross-tabulation of stratification factor, as randomized vs as corrected

3.3.4 Eligibility status will be summarized (for the randomized population):

- Tables
    - Distribution of eligibility status, overall and by treatment assignment
    - Tabulation of reasons ineligible
    - Listing of ineligible patients (patid, center id, mo/yr randomized, strat factors, treatment assignment, reason); sorted by reason

3.3.5 Follow-up compliance will be summarized

- Tables
    - CRF submission status
    - Trial status (e.g., completed per protocol, WC/LFU, in follow-up per protocol, continuing treatment per protocol)
    - Blood sample status (expected vs actual)

3.4 PATIENT DEMOGRAPHICS AND BASELINE DISEASE AND PRIOR TREATMENT

Characteristics of the ITT population will be summarized overall and according to treatment assignment..Continuous variables are summarized descriptively (e.g., mean, SD, minimum, maximum, and interquartiles(IQR)). Categorical variables are summarized as N (%); for variables with unavailable (missing, unknown, not done) values, the default approach is to list the number of unknowns as a category but calculate percentages excluding these unknowns from the denominator.

- Stratification factors (as analyzed)
- Patient:
    - Age at randomization
    - BMI at randomization
    - ECOG Performance status at randomization
    - Smoking status/history
    - Oral contraceptive use
    - Centrally assessed baseline E2 levels)
    - Baseline AE/symptoms, comorbidity history
- Pre-treatment Disease characteristics:
    - Tumor size or tumor lesion (via WHO criteria): product of maximum diameter (MD) and largest perpendicular diameter (LPD) of target lesions at baseline), multiple assessments (clinical, mammography, ultrasound)
    - Grade (centrally assess via core biopsy)
    - Histologic type (ductal, lobular, not determinable)
    - ER, PgR status, Allred score, and Her2 status of core biopsy
    - Clinical Nodal status
    - Ki67 label index (%)
    - Baseline CEA, CA15-3: CEA (carcinoembryonic antigen) and CA15-3 (breast cancer associated antigen)
- Prior Treatment (Hform):
    - Type of prior endocrine therapies: SERM, AI and GnRH/LHRH agonist (eligibility exclusions for any endocrine Rx taken within 12 months or oral contraceptive use within 2 months of rando), mainly to confirm not taken it.
- Tables
    - Characteristics, overall ITT population and by treatment assignment

3.5 TREATMENT

Trial treatments are to start within 14 days of randomization and can be started at any time during the menstrual cycle. The neoadjuvant trial treatments will be administered in 4-week (28-day) cycles for a total of 6 cycles or be stopped in the following cases, and the patient should undergo surgical intervention:

- If ovarian function suppression is not achieved within 56 days after start of treatment according to local laboratory limits
- In the case of an adverse event grade ≥ 3, judged by the Investigator to be at least possibly related to study drugs.

Definitive surgery should be performed within 2 to 3 weeks after the last administration of triptorelin or degarelix.

3.5.1.1 Protocol-assigned treatment

- Number of cycles of study therapy (letrozole, triptorelin or degarelix)
- Reasons for stopping therapy

Specifically,

Triptorelin or degarelix, the following information will be calculated for each patient:

- number injections administered
- Number of skipped doses
- Duration of exposure, from first injection to last injection +28 days
- Time from randomization to cessation (last injection +28 days);
- Reason stopped triptorelin or degarelix

Letrozole, the following information will be calculated for each patient:

- Duration of exposure, from date first dose to date last dose + 1 day
- Number of times dose interruption/delay or modification within that exposure period
- Reason stopped letrozole

Also to summarize:

- Time(days) lapse between blood sample (for measuring E2 levels) and last triptorelin or degarelix injection

Tables and Figures

- Descriptive statistics (median, IQR, min, max) of triptorelin or degarelix cycles exposure duration
- Descriptive statistics (median, IQR, min, max) of letrozole, dose interruption/delay, exposure duration

3.6 PRIMARY ANALYSIS

Analysis of TTOFS as described in 2.2.5

Description of E2 and FSH/LH levels over the 6 month period.

Tables

- Serum sample status (expected vs actual drawn)
- List of patients with missing samples/results and reasons
- Sampling (blood draw) time vs OFS injection time (off schedule)

- Descriptive summaries (median, geometric mean with 95%CI, % change (reduction) of markers from baseline to timepoints for each marker

Figures:

- Scatting plots of E2, FSH, LH data over time
- Distribution of E2, FSH, LH using Boxplot

3.7 POST-TREATMENT SURGERY & PATHOLOGY

Centrally pathology assessment based on surgical specimens included histology type, tumor size, Ki67 level, ER status, ER Allred score, PgR status, PgR Allred score, Her2 status as measured by IHC or FISH, vessel invastion, LN status, and PEPI score (defined as in section 2.3.2)

Table of CPR pathological characteristics, overall and according to treatment assignments.

- Ki67 and ER Allred score data: baseline, post neoadjuvant/surgery data and percent change from baseline will be summarized, difference with 90%CI
- Node negative disease at surgery: percent of patients with node-negative disease is summarized overall, by treatment arms, difference between arms using exact binominal 90% CI

3.8 BREAST CONSERVAING SURGERY (BCS) RATE

- Table of surgery received by treatment arms, difference in BCS rate between arms, 90%CI.
- Table of BCS conversion from planned or (candidate) at baseline to actual received

3.9 PRS SUMMARIES (SEE SECTION 2.2.6)

4 SUBSTUDY / CORRELATIVE

NA

5 DEFINITIONS / ACRONYMS / ABBREVIATIONS

6 REFERENCES

World Health Organization (WHO) criteria: WHO Handbook for Reporting Results of Cancer Treatment. Offset Publication, Geneva, Switzerland, 1979

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