Twelve-month estrogen levels in premenopausal women with hormone-receptor positive breast cancer receiving adjuvant triptorelin plus exemestane or tamoxifen in the SOFT trial: the SOFT-EST substudy

Bellet et al.

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INTERNATIONAL BREAST CANCER STUDY GROUP

Estrogen Suppression Substudy
SOFT-EST (SOLTI 0801)

Substudy of
SOFT (IBCSG 24-02 / BIG 2-02)

SOFT-EST

Estrogen Suppression Substudy

Investigating estrogen suppression for patients participating in the SOFT trial – Arms B and C

Coordinating Groups: Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos (SOLTI) and International Breast Cancer Study Group (IBCSG)

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Please refer to Section 1 of Appendix VII of the SOFT protocol for group-specific contact information to direct your inquiries about participation/eligibility/treatment for this substudy.

Protocol Signature Page

IBCSG 24-02 / BIG 2-02 / SOLTI 0801 SOFT-EST

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Approved by:
Prof. Richard D. Gelber
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Signature Date

Principal Investigator Protocol Signature Page

SOLTI 0801 Estrogen Suppression Substudy (SOFT-EST) of IBCSG 24-02 / BIG 2-02 / SOFT
Version 1.0 (15 October 2008)

I have read the protocol and agree that it contains all necessary details for conducting this substudy. I will conduct the substudy as outlined in the following protocol and in compliance with GCP. I will provide copies of the protocol **to all physicians responsible to me who participate in this substudy. I will discuss this material with them to assure that they are fully informed** regarding the conduct of the substudy. I agree to keep records on all patient information (Case Report Forms and patient's informed consent statement), and all other information collected during the substudy for a minimum period of 15 years.

Name of Principal Investigator:_____

_____

Signature Date

Substudy Summary and Schema

SOFT Estrogen Suppression Substudy (SOFT-EST)

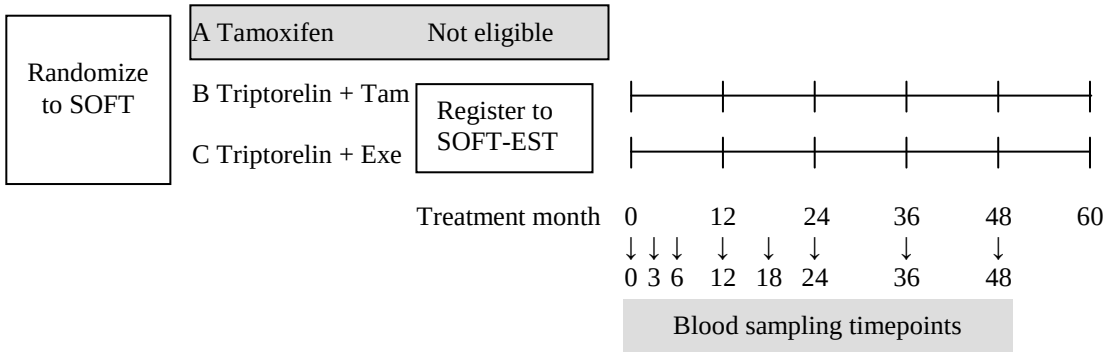
A substudy of the SOFT trial to investigate estrogen suppression for patients participating in arms B and C of the SOFT trial

Patient Population: Premenopausal women with histologically proven, resected breast cancer with ER and/or PgR positive tumors who are enrolled in arms B or C of the SOFT trial, and for whom triptorelin is intended to be used as method of OFS.

Entry: Patients should be enrolled in SOFT-EST immediately after randomization to SOFT. The baseline serum sample must be obtained after randomization but prior to start of protocol therapy, according to the guidelines in the SOFT-EST Samples Management Manual.

Sample size: 120 patients

SOFT-EST schema and blood sampling timepoints



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1. Introduction

The use of gonadotrophin-releasing hormone (GnRH) analogues in advanced breast cancer has proven to be equivalent to ovarian ablation in terms of response rate, time to progression and overall survival[1,2]. Nevertheless, some studies using GnRH analogues in women with either benign (endometriosis) or malignant (breast cancer) disease have shown ovarian function suppression to be incomplete, with slightly higher mean estradiol levels than those observed in physiologic menopause and/or with individual values showing suboptimal castration in a minority of patients[3-8]. Filicori *et al* reported 2 cases of incomplete pituitary-ovarian suppression at 3 months, defined by spotting and estradiol levels in the premenopausal range, among 30 women treated with depot GnRH analogue formulations[7]. In another report, 11 of 119 patients (9%) treated for endometriosis with goserelin for a 6-month period showed persistence of uterine bleeding episodes[8]. Pregnancy has occasionally been reported in women receiving GnRH analogue treatment. Furthermore, most reported series describing endocrine effects of GnRH analogues are flawed due to small sample size[6,7,9], inadequate or at least not-centralised quantification of estradiol levels[10-12] and, most importantly, short follow-up (average of 3-6 months)[4-10]. As a consequence, conclusive data regarding long-term estrogen suppression using GnRH analogues is lacking. The efficacy of GnRH analogues in the long term 1) is relevant in planned lengthy adjuvant treatment, such as in arms B and C of the SOFT trial, which investigate 5 years of triptorelin (GnRH analogue) plus tamoxifen or of triptorelin plus the aromatase inhibitor exemestane, respectively and, 2) is particularly crucial when taken in combination with an aromatase inhibitor (SOFT arm C), since such a compound has a less than optimal effect, and may even have stimulatory activity, in the setting of residual ovarian function [3,13].

1.1. GnRH analogues with or without Tamoxifen in advanced breast cancer

Existing endocrine data regarding GnRH analogues with/without tamoxifen in premenopausal advanced breast cancer patients come from three main studies[9-11]. In one, study groups of 24 and 14 patients with advanced breast cancer, recruited sequentially, were treated with goserelin or goserelin plus tamoxifen, respectively[9]. The authors reported a sustained fall in estradiol levels over a 12-month period in both groups, although individual values were not given. Pooling of the estradiol data showed significantly lower serum estradiol concentrations in the combination group. In another phase III study, 54 and 43 patients received buserelin and buserelin plus tamoxifen, respectively[10]. Amenorrhea developed in 98 and 100% of buserelin and buserelin plus tamoxifen-treated patients. Endocrine data was available in 37 and 34 patients, respectively. The authors reported similar estradiol levels and mean and median values of estradiol into the castrate range during the follow-up. Nevertheless, only 12 and 6 patients had estradiol levels tested at 1 and 2 years, respectively; estradiol testing was not centralised, and again individual peaks of estradiol above postmenopausal level were observed. Finally, a pooled analysis of 193 women with endocrine data from 29 European trials using goserelin was performed[11]. Estradiol levels were measured at 3 months in just 34 patients and the mean levels were in the postmenopausal range. Again, individual variability in estradiol levels was observed, which could be partially explained by the non-centralised analyses.

1.2. GnRH analogues with/without aromatase inhibitors in advanced breast cancer

To date there are limited clinical data regarding GnRH analogues + aromatase inhibitor combination. Forward *et al* [14] treated 16 premenopausal patients with goserelin + anastrozole after goserelin + tamoxifen failure. Median age was 44. All patients included had shown clinical benefit with previous endocrine therapy. The goserelin + anastrozole combination

resulted in 1 PR, 9 SD and 4 PD (2 unassessable patients), a median time to progression of 10 months and a further 76% drop in estradiol levels at 3 months beyond that achieved by treatment with goserelin + tamoxifen. There were no estradiol peaks in the samples from the 12 patients with 12 months of data.

In another study, 22 aromatase inhibitor and GnRH analogue-naive patients were given goserelin + anastrozole[15]. Median age in this subgroup was 43. After one month of treatment a significant fall in estradiol levels was observed (median <10 pg/mL, range 10-52). However, one patient of the 12 still in treatment at 6 months recovered to premenopausal estradiol levels (68 pg/mL). As far as clinical efficacy is concerned, the authors reported 72% clinical benefit rate.

In a third study, Celio *et al* randomised 21 patients to receive triptorelin alone (n=10) or in combination with the aromatase inhibitor formestane (n=11)[6]. The median age was 45 years. The combination achieved a significantly greater reduction in estradiol levels at four weeks (86.9% lower than baseline values using triptorelin alone vs 97.3% using the combination). Three and four patients experienced tumor regression in each group. The geometric mean estradiol levels at 3 months (26.3 pmol/L, 95% CIs:19.7-37) for the 10 patients receiving triptorelin was slightly higher than laboratory cut-off for physiological menopause (<20 pmol/L), while a clear inhibition was observed in the 11 patients receiving triptorelin + formestane (8.9 pmol/L, 95% CIs:3.9-20). No follow-up beyond 12 weeks was reported.

In another study, eleven premenopausal patients were given vorozole over 3 months[4]. All patients had previously received goserelin for at least 2 months. Estrogen levels were obtained and compared with those of a group of 13 postmenopausal patients who also received 3 months of therapy with vorozole. Two-fold higher estrogen levels during vorozole treatment in premenopausal women were seen as compared to the postmenopausal subgroup.

Finally, in a recent study[16], 36 patients received goserelin plus anastrozole as first line endocrine treatment. Median age was 44 years. The clinical benefit rate was 67% and the median time to progression was 7 months. Estradiol levels were reduced by a median of 98%, although neither individual values nor endocrine data beyond 12 months were reported.

1.3. Rationale for present study (SOFT-EST)

In summary, all studies using GnRH analogues + tamoxifen/aromatase inhibitors showed clinical efficacy and effective biochemical suppression for the majority of patients in the advanced breast cancer setting. However, samples sizes were small, long-term follow-up was lacking and the potential existence of a minority of women experiencing less than optimal suppression cannot be ruled out. In fact, anecdotal reports describing suboptimal suppression using GnRH analogues and aromatase inhibitors have been reported[17]. It would be reasonable to hypothesize, therefore, that a small group of patients may exist who are not optimally suppressed. Patients more likely to experience suboptimal suppression are probably those with better ovarian reserve, such as younger, non-smokers and chemotherapy-naïve subjects, or those with regular menses at entry. Obese patients receiving GnRH analogues also might show higher estradiol levels, given the increased peripheral aromatase activity reported in these patients in the menopausal setting.

Therefore a larger study in the adjuvant setting including short and long-term follow-up of serum estrogen levels is warranted in premenopausal patients treated with triptorelin (GnRH analogue), either with tamoxifen or with exemestane. Age, prior chemotherapy, type of

chemotherapy, presence of menses at entry, smoking history and BMI are to be taken into account as potential predictive variables of suboptimal suppression.

In order to avoid flaws seen in prior studies, accurate centralized testing of estrogen levels is indicated. Therefore, gas chromatography-mass spectrometry (GS-MS/MS) will be used, since this method is considered a reference standard for measuring sex hormones at low concentrations[18] and, in the presence of exemestane, does not have the cross-reactivity problems seen with most immunoassays[18]. To perform a complete "estrogen profile" seems advisable: estradiol (E2), as the hallmark of biological activity, estrone (E1) as the major product of aromatase inhibition and estrone sulphate (E1S), as the most stable estrogen fraction measured and the best surrogate-parameter for estrogen suppression *in vivo*. However, the labour-intensive laboratory task and its associated cost limit the sample size and sampling timepoints. Taking into account that suboptimal suppression, if any, is more likely to be observed in the first 24 months, and that the level of suppression in this period is more likely to be clinically relevant, more timepoints will be tested in the first two years. Considering that the issue of an appropriate suppression is, in theory, more clinically relevant in patients receiving GnRH analogue + aromatase inhibitor, more patients in this arm are required and therefore recruitment in a 1:3 ratio (i.e., arm B (triptorelin + tamoxifen): arm C (triptorelin + exemestane)) is planned.

Additional testing related to endocrine function (FSH, LH) may also be performed to elucidate suboptimal estrogen suppression and to validate less complex methods to identify sub-optimally suppressed patients.

2. Objectives

2.1. Primary objectives

2.1.1. To describe estrogen levels (E2, E1 and E1S) at different timepoints during the first 4 years of protocol treatment among patients receiving triptorelin (GnRH analogue) plus either tamoxifen (arm B) or exemestane (arm C).

2.1.2. To assess whether there is a suboptimally estrogen-suppressed subgroup of patients who receive exemestane (arm C).

2.2. Secondary objectives:

2.2.1. To compare levels of estrogens (E2, E1, E1S) at different timepoints between triptorelin + tamoxifen vs. triptorelin + exemestane (arm B vs. C).

2.2.2. To examine potential predictive factors of ineffective estrogen suppression such as: age, chemotherapy (yes/no), type of chemotherapy received, smoking history, BMI and evidence of menses at entry.

2.2.3. To investigate the predictive value of optimal estrogen suppression during the first 6 and 12 months with regard to long term suppression (48-month period).

2.2.4. To compare outcome (disease-free survival) in the suboptimally suppressed group in arm C with that of patients with optimal suppression (exploratory analysis).

2.2.5. To examine related endocrine function (FSH, LH) to further elucidate causes of suboptimal estrogen suppression.

3. Study design

The study has a longitudinal design. Registration to the substudy and baseline sample collection must occur after randomization to the SOFT parent study but prior to commencement of SOFT protocol therapy. A blood sample will be collected at baseline (month 0), 3, 6, 12, 18, 24, 36 and 48 months, coinciding with follow-up visits and with QL assessments on SOFT.

4. Patient Selection

4.1. SOFT-EST participating centers

SOFT-EST will be conducted in selected, mostly European sites (IBCSG, SOLTI, EORTC). All eligible patients randomized to SOFT from these centers should be registered in SOFT-EST.

4.2. Inclusion criteria

4.2.1. Randomized to arm B or C of parent SOFT trial.

4.2.2. Triptorelin (GnRH analogue) is the intended method of OFS.

4.2.3. Written informed consent for SOFT-EST substudy.

5. Patient Registration

Only patients whose intended method of OFS is triptorelin and who have been randomized to arm B or C of the parent SOFT study can be registered in this substudy.

Participating centers are expected to register all patients who enroll in SOFT and who intend triptorelin as the method of OFS and are randomized to an OFS-containing arm (either arm B or C). It is recommended that informed consent for SOFT-EST be obtained at the same time as SOFT if the patient intends to receive triptorelin. If arm B or C is assigned the patient should then be registered for SOFT-EST, and baseline sample should be obtained prior to receiving protocol treatment.

Registration to SOFT-EST should immediately follow randomization to the parent SOFT study, using the IBCSG Registration/Randomization System. The Confirmation of Registration Form (24-SE-A) should be completed prior to registration to confirm eligibility and obtain information on smoking history.

6. Study Parameters and Data Submission

6.1. Assessments

A complete “estrogen profile” will be performed centrally: estradiol (E2), estrone (E1), and estrone sulphate (E1S). Additional testing related to endocrine function (FSH, LH) may also be performed. The results of these assessments will not be available to make treatment decisions during the protocol treatment period.

6.2. Timing of assessments

Assessment timepoints are determined by the interval from date of randomization and coincide with the required clinical follow-up timepoints of the SOFT study.

Substudy Parameters											
Visit	1	2	3	4	5	6	7	8	9	10	11
Year	1	1	1	1	1	2	2	3	3	4	4
Trial month	0	3	6	9	12	18	24	30	36	42	48
Serum sample	x	x	x		x	x	x		x		x
Form 24-SE-SC	x	x	x		x	x	x		x		x

x = mandatory
Note: serum and Form 24-SE-SC must also be submitted at discontinuation (see below)

Samples should be taken in morning fasting condition.

6.3. Required Samples

Baseline sample (month 0): After randomization to the SOFT trial but prior to commencement of SOFT protocol therapy.

Month 3, 6, 12, 18, 24, 36, 48 samples: At the required clinical follow-up visit. If the visit coincides with the 28-day triptorelin injection, then it is preferred that the blood is drawn prior to the injection.

6.4. Additional Samples

For patients who experience vaginal bleeding: One extra sample should be drawn as soon as possible after a patient experiences vaginal bleeding more than 3 months after commencing triptorelin. If the patient goes on to have an oophorectomy, this sample should be collected prior to the oophorectomy.

For patients who discontinue triptorelin and/or receive surgical oophorectomy (see next section).

The Sample Collection Form (24-SE-SC) should be completed and submitted through DataFax at each collection timepoint listed above. This CRF confirms that the required samples were obtained, and can be submitted with the other follow-up CRFs for the SOFT trial.

6.5. Early Discontinuation of SOFT-EST

Sample collection should **not** continue if the patient stops triptorelin for any reason, including a change to an ovarian ablation method or a breast cancer recurrence. Although changes in the GnRH analogue compound are not recommended, if triptorelin is replaced by monthly goserelin for any reason (intolerance or unavailability of triptorelin) the patient should remain in the SOFT-EST substudy, and the appropriate GnRH analogue should be documented in the SOFT CRF (Form 24-OFS). For patients who change their ovarian ablation method to surgical oophorectomy, one additional sample approximately 3 months after the surgery should be obtained and submitted with both the 24-SE-ED and 24-SE-SC forms.

If a patient discontinues the SOFT-EST substudy prior to the last (i.e. 48-month) sample, for any reason different than surgical oophorectomy, an **Early Discontinuation (24-SE-ED) Form** should be completed and submitted via DataFax. An "early discontinuation sample" should be obtained unless blood was recently drawn for the substudy (within 1 month during

the first 6 months of the study and within 3 months for the rest of the study). No further samples will be required after the Early Discontinuation CRF is submitted.

The Data Management Manual for this substudy contains instructions for submitting forms using the DataFax system.

IC Form	Informed Consent Form	Obtain before registration for SOFT-EST and keep with patient records.
Form 24-SE-BMC	Biological Material Consent Form	DataFax after randomization with Form 24-SE-A.
Form 24-SE-A	Confirmation of Registration Form	Fill in before contacting your Randomization Center or entering the IBCSG Registration/Randomization system to register. DataFax completed form for all patients registered.
Form 24-SE-SC	SOFT-EST Sample Collection Form	DataFax at baseline (after randomization to SOFT but prior to commencement of protocol therapy), months 3, 6, 12, 18, 24, 36, and 48. Also submit in the case of vaginal bleeding, surgical oophorectomy or early discontinuation (if occurring at non-required submission time points).
Form 24-SE-ED	SOFT-EST Early Discontinuation Form	Submit once upon early discontinuation of the substudy.

6.6. Sample collection logistics

Blood collection kits containing tubes and labels will be supplied to the participating institutions. These kits must be used for collection, storage and shipment of serum samples. A volume of 20 mL of blood should be drawn and processed to obtain aliquots of serum, according to the Samples Management Manual (SMM). Every aliquot should be labeled as instructed in the SMM and stored at -20ºC until delivery to the central laboratory (Taylor Technology, Inc., USA) for analysis. All samples must be labeled with pre-printed self-adhesive labels, contained in the blood collection kits. The Sample Collection Form (Form 24-SE-SC) should be DataFaxed at the time of the blood draw to inform IBCSG that the collection has been made. All assay results will be assessed centrally and results submitted to IBCSG Data Management Center. A separate SMM will contain the details for sample collection, storage, shipping, etc.

Samples will be anonymized and confidentiality will be maintained during the entire process. The costs of blood collection will be covered by the additional patient fee and shipping will be free of charge.

6.7. Serum banking

Surplus serum will be stored for use in unspecified future research. As part of the informed consent process, patients are asked to indicate whether they agree to donate their sample for such research. The use of the serum for unspecified future research will be under the auspices of the IBCSG Biological Protocols Working Group and any project has to be approved by the IBCSG Ethics Committee.

7. Statistical Considerations

7.1. Study design and objectives

The study will use a longitudinal design with samples drawn over a 48-month period. Only patients enrolled in the parent trial and randomized to arms B (OFS + tamoxifen) or C (OFS + exemestane) and who intend triptorelin as the method of OFS are eligible. The target accrual to the substudy is 120 patients. The main objectives are:

7.1.1. To describe estrogen levels (E2, E1 and E1S) at different timepoints during the first 48 months of protocol treatment among patients receiving triptorelin (GnRH analogue) plus either tamoxifen (arm B) or exemestane (arm C).

7.1.2. To assess whether there is a suboptimally suppressed subgroup of patients who receive exemestane (arm C).

The labor-intensive laboratory task and its associated cost constrain the sample size and number of sampling timepoints. Taking into account that suboptimal suppression, if any, is more likely to be observed in the first 24 months, and that the level of suppression in this period is more likely to be clinically relevant, more timepoints are being tested in the first two years than during later years and sampling at the end of the study (60 month sampling) is considered as less relevant. Considering that the issue of an appropriate suppression is, in theory, more clinically relevant in patients receiving triptorelin + aromatase inhibitor (arm C), a greater effort in this arm is indicated and therefore, a recruitment in a ratio of 1:3 triptorelin + tamoxifen to triptorelin + exemestane (i.e., 30 in arm B: 90 in arm C) is ideal. We therefore anticipate stopping enrollment for patients randomized to arm B earlier than arm C. The IBCSG Statistical Center will monitor the patients enrolled throughout the study to ensure balance between the two arms with respect to patient characteristics.

7.2. Data analyses

7.2.1. Estrogen levels (E2, E1, E1S) will be summarized over time among all patients and by treatment arm using descriptive statistics (mean, SD, median, quartiles). It is anticipated based on the literature that log-transformation of estrogen levels will be required, in which case the geometric mean would be reported.

Using linear mixed modeling of all available data over the 8 timepoints, each estrogen level (with log-transformation) will be modeled as a function of time and treatment arm to investigate the time pattern of estrogen levels and differences in levels between treatment arms. Relationships of specified patient characteristics (age, prior chemotherapy yes/no, type of prior chemotherapy, smoking history, BMI, menses at study entry) with the estrogen levels will also be investigated.

Measures of endocrine function (FSH, LH) would be analyzed similarly.

7.2.2. The proportion of patients who receive exemestane (arm C) experiencing suboptimal suppression and 95% exact binomial confidence interval (CI) will be reported. The pattern of when suboptimal suppression occurred will be described. Patient characteristics hypothesized to be related to suboptimal suppression (age, prior chemotherapy yes/no, type of prior chemotherapy, smoking history, BMI, menses at study entry) will be compared between groups with and without suboptimal suppression using t-tests for continuous variables (or Wilcoxon rank-

sum tests if normality cannot be assumed) or Fisher's exact tests for categorical variables. Because of the expected low rate of suboptimal suppression (10%), multivariable logistic regression modeling will not be feasible. To define suboptimal suppression among patients who receive exemestane (arm C), estradiol levels within the premenopausal range of >20 pmol/L (>5.45 pg/mL) could be considered as a threshold. However, the guidelines of Smith et al. for the use of adjuvant AIs after chemotherapy-induced amenorrhea (13) recommend caution in the situation where estradiol levels, measured using highly sensitive/specific methods such as GC-MS/MS, are >10 pmol/L (>2.72 pg/mL) while on an AI because this indicates that the AI is not exerting its full effectiveness. Thus suboptimal suppression will be defined as: a) clinically overt failure of ovarian suppression (recovery of menses or spotting > 3 months after commencing triptorelin, or pregnancy); or b) E2 levels >10 pmol/L (>2.72 pg/mL) at 2 or more timepoints over at least a 6-month period.

7.2.3. Patients will be classified as suppressed or not during the first 6 months and during the first 12 months. Whether early suppression predicts longer-term estrogen levels will be investigated using linear mixed modeling on the subset of post-12-month estrogen levels.

As an exploratory analysis, disease-free survival will be summarized for groups with and without suboptimal suppression using the Kaplan-Meier method. Because of the expected low rate of suboptimal suppression, this analysis will be descriptive only.

7.3. Sample size considerations

The target accrual to the substudy is 120 patients, ideally 30 in arm B (triptorelin + tamoxifen) and 90 in arm C (triptorelin + exemestane). Taking into account, 1) the actual accrual of European sites, and 2) the proportion of patients randomized to arm B and C that receive triptorelin as method of OFS in Europe (about 90%) a period of 18 months to complete enrollment is expected.

The sample size was selected in consideration of the two primary objectives.

7.3.1. The continuous estrogen levels will be analyzed using longitudinal modeling. The GC-MS/MS assay of Taylor Laboratory has detection limits of 0.625-80 pg/mL for estradiol, 1.56-200 pg/mL for E1 and 3.13-800 pg/mL for E1S (personal communication). In a recent report comparing assay methods for low serum estradiol with the GC-MS/MS as the gold standard[18], among 40 postmenopausal women the median E2 level was 3.8 pg/mL (IQR, 1.1-18.5 pg/mL), and among 374 postmenopausal women the median E2 level was 4.6 pg/mL (IQR, 3.0-6.8 pg/mL) and the mean level was 5.6±3.8 pg/mL. Thus we assume SD=4.0 pg/mL at each timepoint and assume conservatively that the correlation between two timepoints is r=0.5 so that SD of the difference between two timepoints is also 4.0 pg/mL.

For the primary analysis describing estrogen levels over time, among 120 patients there would be 90% power to detect a mean difference between timepoints of 1.2 pg/mL based on a paired Wilcoxon signed rank test (α=0.05 two-sided); in the treatment arms separately, the detectable differences would be 2.5 pg/mL and 1.4 pg/mL in arms B (n=30) and C (n=90), respectively.

For the secondary analysis comparing estrogen levels between treatment arms, there would be 80% power to detect a mean difference of 2.5 pg/mL between treatment arms at any one timepoint based on a two-sample Wilcoxon rank sum test (α=0.05 two-sided).

In a recent study of premenopausal women most of whom received adjuvant chemotherapy followed by randomization to receive adjuvant triptorelin plus either tamoxifen or letrozole, the median serum E2 levels decreased between baseline and 6 months of treatment from 12.4 to 7.95 pg/mL (range, <5 to 43.9 pg/mL) among those treated with triptorelin+ tamoxifen (n=30), and from 14.0 to <5 pg/mL (range, <5 to 24.5 pg/mL) among those treated with triptorelin + letrozole (n=51) based on an ECLIA (Roche) assay with a normal range of 10-40 pg/mL[19]. Thus the detectable differences in this study, which uses a more sensitive assay, are clinically relevant.

7.3.2. We hypothesize that 10% of patients who receive exemestane (arm C) will have suboptimal suppression. With 90 patients on arm C, there is over 95% power to detect a 10% rate of suboptimal suppression as compared with a 1% null rate, using a one-sided binomial test (one-sided α=0.025). If, for example, 9/90 patients on arm C are observed to have suboptimal suppression then the two-sided 95% CI would be (4.7% to 18.2%).

For the secondary objective to examine potential predictive factors of suboptimal suppression, with an expected 10% rate, only 9 cases are expected among 90 patients who receive exemestane (arm C) so multivariable modeling would not be feasible. Adequate power for comparing the groups of patients with suboptimal and optimal suppression in univariate analyses is also limited to large differences. In univariate comparisons of continuous variables there would be 80% power with α=0.05 level two-sided t-tests to detect a mean difference of 1 SD between groups; for binary variables there would be 80% power with α=0.05 level two-sided Fisher's exact tests to detect absolute differences of about 50% between groups (e.g., 11% vs. 61% or 33% vs. 83% of patients with suboptimal vs. optimal suppression having received prior chemotherapy).

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