IBCSG 48-14 / BIG 8-13
POSITIVE Trial
Synopsis 25 March 2014
CONFIDENTIAL

1. Protocol Summary and Schema

TITLE	**A study evaluating the pregnancy outcomes and safety of interrupting endocrine therapy for young women with endocrine responsive breast cancer who desire pregnancy (POSITIVE).**
SPONSOR	International Breast Cancer Study Group (IBCSG)
PHARMA PARTNER	None
INDICATION	Premenopausal endocrine responsive early breast cancer
CLINICAL PHASE	Other
POPULATION	Premenopausal women with endocrine responsive early breast cancer who received adjuvant endocrine therapy for 18 to 30 months, are between 18 and 42 years of age at enrollment, and wish to interrupt endocrine therapy to attempt pregnancy.
INTER-VENTION	▪ Endocrine therapy interruption after having completed between ≥ 18 months and ≤ 30 months ▪ 3 months wash-out between treatment interruption and pregnancy attempt ▪ Up to 2 years interruption to allow pregnancy, delivery, breastfeeding or failure to conceive ▪ Endocrine therapy resumption ▪ Completion of full duration of endocrine therapy according to individual risk, institutional policy or patient's preference

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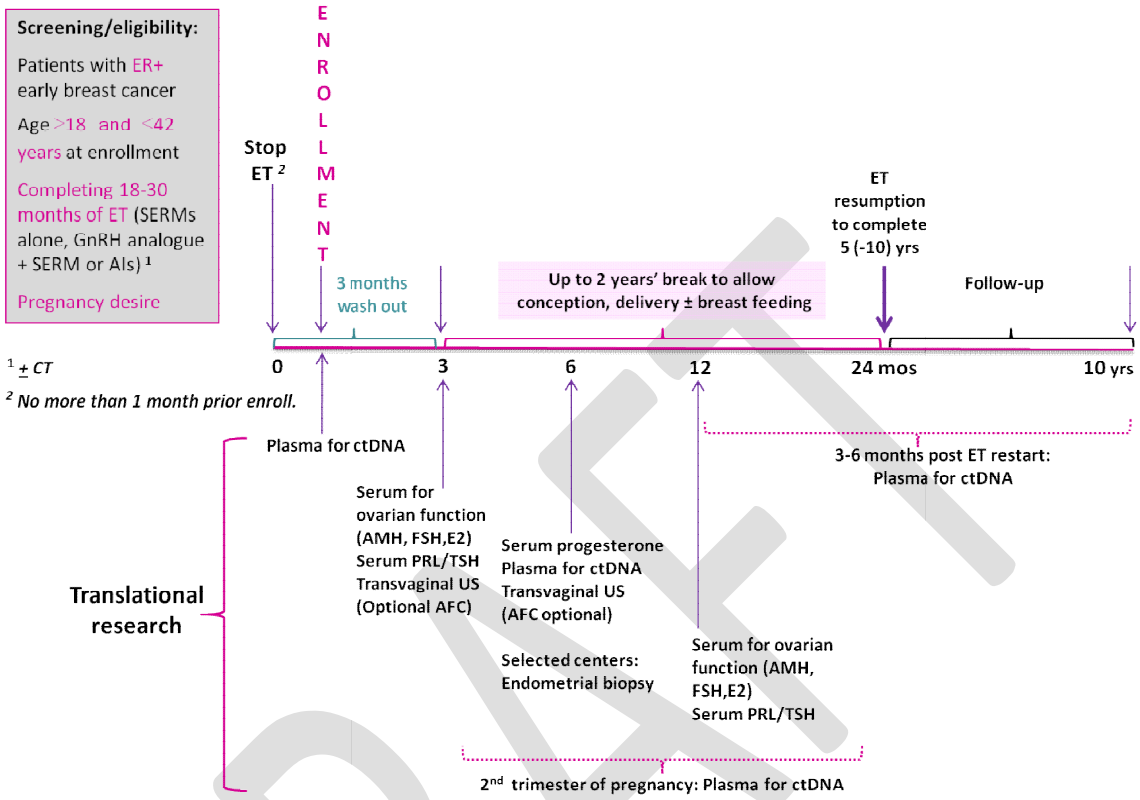
STUDY SCHEMA



RATIONALE

- Recent decades have witnessed a delay in childbearing for a variety of reasons including cultural, educational, and professional. As a consequence, breast cancer in young women often occurs before the completion of reproductive plans.
- Infertility has a significant impact on quality of life, resulting in substantial distress in younger women with breast cancer and influencing treatment decisions in a consistent proportion of patients.
- The best available evidence suggests that pregnancy after breast cancer does not increase a woman's risk of developing a recurrence.
- For women desiring pregnancy after a breast cancer, 5-10 years of endocrine therapy may substantially reduce the chance of conception; however, a shorter duration of endocrine therapy in this population has not been studied in a prospective manner.
- Birth outcome after breast cancer has not been shown to be different from that of the normal population, but increased risks of delivery complications, cesarean section, preterm birth and low birth weight have been reported.
- Endocrine agents are potentially teratogenic: taking into account their median half-life, waiting 3 months after their interruption before

	attempting conception is considered safe. ▪ The limited evidence available on breastfeeding after breast cancer reports successful lactation from the treated breast in approximately 30% of women without detrimental effect on survival. ▪ **No prospective definitive data are available.**
ELIGIBILITY	**Inclusion criteria:** ▪ Age ≥ 18 and ≤ 42 years at enrollment. ▪ Receiving (or stopped within 1 month prior to enrollment) adjuvant endocrine therapy (SERM alone, GnRH analogue plus SERM or AI) for ≥18 months but ≤30 months for early breast cancer. *Note*: Patients who have received neo/adjuvant endocrine treatment within a clinical trial and patients who have received tamoxifen as pharmaco-prevention are eligible. ▪ Patient wishes to become pregnant. *Note*: Patients who have undergone oocyte/embryo/ovarian tissue cryopreservation at breast cancer diagnosis and/or have a previous history of assisted reproductive technology (ART) are eligible. ▪ Breast cancer for which patient is receiving endocrine therapy must have been histologically-proven stage I-III, endocrine-responsive (i.e. estrogen and/or progesterone receptor positive, according to local definition of positive, determined using immunohistochemistry (IHC)), and treated with curative intent. *Note*: Patients with synchronous bilateral invasive breast cancer (diagnosed histologically within 2 months) and patients with BRCA1/2 mutations are eligible. *Note*: Patients could have received neo/adjuvant chemotherapy, or other systemic therapy (e.g., neo/adjuvant HER2-targeted therapy) according to institutional policy and patient's desire. ▪ Patient must be premenopausal at breast cancer diagnosis, as determined locally and documented in patient record. ▪ Patient must be without clinical evidence of loco-regional and distant disease, as evaluated according to institutional assessment standards and documented in the patient record. ▪ Written informed consent (IC) for trial participation must be signed and dated by the patient and the investigator prior to enrollment. ▪ Written consent to biological material submission, indicating the patient has been informed of and agrees to tissue and blood material use, transfer and handling, must be signed and dated by the patient and the investigator prior to any procedures specific for this trial. ▪ The patient has been informed of and agrees to data transfer and handling, in accordance with national data protection guidelines.

	▪ Patient must be accessible for follow-up. **Exclusion criteria:** ▪ Peri- or post-menopausal patients at BC diagnosis, as determined locally. ▪ History of hysterectomy, bilateral oophorectomy or ovarian irradiation. ▪ Patients with current local, loco-regional relapse and/or distant metastatic breast cancer. ▪ Patients with a history of prior (ipsi- and/or contralateral) invasive BC. ▪ Patients with previous or concomitant non-breast invasive malignancy. Exceptions are limited exclusively to patients with the following previous malignancies, if adequately treated: basal or squamous cell carcinoma of the skin, in situ non-breast carcinoma, contra- or ipsilateral in situ breast carcinoma, stage Ia carcinoma of the cervix. ▪ Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety. ▪ Patients with a history of noncompliance to medical treatments and/or considered potentially unreliable. ▪ Patients with psychiatric, addictive, or any disorder that would prevent compliance with protocol requirements.
STUDY OBJECTIVES AND ENDPOINTS	**Primary objective** To assess the risk of breast cancer relapse associated with temporary interruption of endocrine therapy to permit pregnancy. **Secondary objective** To evaluate factors associated with pregnancy success after interruption of endocrine therapy. **Primary endpoint:** ▪ Breast cancer free interval (BCFI) defined as the time from enrollment in the study to the first invasive BC event (local, regional, or distant recurrence or a new invasive contralateral BC). **Secondary endpoints:** ▪ Menstruation recovery and pattern. ▪ Pregnancy (determined by pregnancy test). ▪ Pregnancy outcome: full term pregnancy, caesarean section, abortion, miscarriage, ectopic, stillbirth. ▪ Offspring outcome: preterm birth, birth defects. ▪ Breastfeeding; pattern of breastfeeding (duration, use ipsilateral breast if previous breast conservation, side exclusivity). ▪ Use of assisted reproductive technology (ART).

	▪ Adherence to endocrine treatment assessed by: - Treatment resumption after the ~2 year ET break. - Total duration of at least 5 years of ET. ▪ Distant recurrence-free interval (DRFI), defined as the time from enrollment in the study to the first BC recurrence in a distant site, excluding second (non-breast) primary cancers and contralateral breast cancer.
PSYCHO-ONCOLOGY	A Psycho-oncological companion study on fertility concerns, psychological well-being and decisional conflicts will be conducted in interested centers. This study is described in a separate study protocol.
TRANSLA-TIONAL RESEARCH	The characteristics and number of patients participating into this trial represent a unique opportunity to evaluate different parameters related to fertility, pregnancy and breast cancer biology in young women. **Examinations**: 1. Ovarian function evaluation: ▪ Anti-müllerian hormone (AMH), follicle stimulating hormone (FSH), estradiol (E2), serum progesterone; antral follicular count (AFC) (if possible). Other factors that may affect ovarian function will be also evaluated: thyroid stimulating hormone (TSH) and serum prolactin level (PRL). 2. Uterine evaluation: ▪ Transvaginal ultrasound ▪ In selected centers: endometrial biopsy 4. Circulating tumor DNA (ctDNA). 5. Formalin- fixed, paraffin - embedded (FFPE) tissue block of the primary tumor. **Translational research endpoints:** ▪ Ovarian function and ovarian reserve: anti-müllerian hormone (AMH), follicle stimulating hormone (FSH) and estradiol (E2), antral follicular count (AFC) (if possible). ▪ Serum progesterone. ▪ Serum prolactin (PRL) and thyroid stimulating hormone (TSH). ▪ Endometrial thickness and edema. ▪ Change in plasma levels of circulating tumor DNA (ctDNA). ▪ In selected centers: Biomarkers from endometrial biopsy including but not restricted to integrins (α1, α4, α1vβ3, and others).
STATISTICAL CONSIDE-	The primary objective of this study is to assess the safety of interrupting ET in terms of potential increased risk of BC relapse in endocrine responsive

RATIONS	premenopausal BC patients. For planning purposes, a true risk of BC recurrence of 2% per year is assumed for patients who do not interrupt endocrine treatment based on overall information from the IBCSG SOFT and TEXT trials. This corresponds to a BCFI percent of 94.2% at 3 years and 90.5% at 5 years from enrollment. Prior to the primary analysis of BCFI we will identify potential control group populations to assess the validity of this 2% per year BC recurrence assumption for the patients enrolled in POSITIVE. Three candidate control groups are 1) patients enrolled in the SOFT and TEXT trials, 2) patients enrolled in the ABCSG-12 trial, and 3) data obtained from ASCO's CancerLinQ database. With 500 patients enrolled during 4.0 years and an additional 1.6 years of follow up, there will be approximately 1600 patient-years of follow up and a median follow up of approximately 3 years at the time of the primary analysis, anticipated to occur 5.6 years after enrollment of the first patient. If the true risk of BC recurrence is 2% per year, we anticipate observing 31 BC recurrences at that time. With this number of events, the estimated 3-year BCFI failure percent will be 5.6%, and the 95% confidence interval will be 4.0% to 7.9%. Thus, the planned enrollment will provide a precise (half-width less than 2%) 95% confidence interval for the 3-year BCFI percent. Three interim analyses of BCFI are planned at approximately 270, 600, and 1100 patient-years of follow up; approximately 2.5, 3.5 and 4.5 years after enrollment of the first patient. The probability of early stopping is 0.99 if the BC recurrence rate is 4% per year and 0.04 if it is 2% per year. Long-term follow up and reporting of results every 2 years will continue for 10 years after the last patient enrolled to evaluate any late occurring consequences of ET interruption.
NUMBER OF PATIENTS	The overall accrual goal is 500 patients
STUDY DURATION	▪ Approximately 6 patients per month are expected to be accrued during the first year and 12 patients per month afterwards in this worldwide collaboration. Recruitment is anticipated to be completed in 4.0 years. ▪ First results regarding safety are anticipated within 5.6 years of study activation. ▪ Patients will be followed for at least 10 years after enrollment. Total duration including long-term follow up will be 14 years.