

**COG- ALTE2131:
Triptorelin and Protection of Ovarian Reserve in Adolescents and Young Adults with Cancer An NCORP Phase 3
Study**

FAST FACTS

Eligibility Reviewed and Verified By

_____ MD/DO/RN/LPN/CRA Date _____

_____ MD/DO/RN/LPN/CRA Date _____

Consent Version Dated _____

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

___ 1. **Timing**

Patients must be enrolled before study-specific procedures and cancer-directed therapy begins. See Section 3.2.7 for prior therapy exclusions.

All study-specific blood samples for Baseline (see Section 7.2 for details) should be obtained before the start of planned chemotherapy (with the exception of intrathecal therapy and systemic corticosteroids), and for patients randomized to Arm A (the intervention arm), obtained before the study drug (triptorelin) is administered.

Note that if any fertility preservation procedures are planned, study-specific blood samples should ideally be obtained prior to these procedures.

See Section 7.3.2 for guidance on timing of Baseline PROs.

For patients randomized to Arm A the study drug, triptorelin, must be given prior to the start of planned chemotherapy. It may be given as early as 14 days prior to the start of planned chemotherapy or as late as the day chemotherapy is starting. See Section 4 Treatment Plan.

If hormonal stimulation of the ovaries for the purposes of oocyte retrieval is given, triptorelin should be given ≥ 7 days after the oocyte retrieval date if the patient is considered to be at increased risk of ovarian hyperstimulation syndrome.

If ovarian tissue cryopreservation is planned for fertility preservation purposes, there are no restrictions on the timing of triptorelin administration.

___ 2. **Randomization**

Randomization will take place only after a patient is enrolled via OPEN. The treatment will be randomly assigned based on the statistical design of the trial.

___ 3. **Age < 40 years of age at the time of enrollment**

___ 4. **Post-menarchal Menstrual Status**

Patient must be a post-menarchal female and report that their initial menstrual period occurred > 6 months prior to enrollment. (Current menstrual status is not part of the inclusion criteria.)

5. Diagnosis

Newly diagnosed with first cancer, exclusive of breast cancer

Note: Apart from breast carcinoma, other tumor types originating in the breast are permitted (e.g., sarcoma, lymphoma)

6. Treatment Plan

*Planned treatment must include one or more of the following alkylating agents delivered with curative intent: cyclophosphamide, ifosfamide, procarbazine, chlorambucil, carmustine (BCNU), lomustine (CCNU), melphalan, thiotepa, busulfan, nitrogen mustard.

*For patients < 20 years of age at enrollment, the expected alkylator dose must be ≥ 4 g/m² cumulative cyclophosphamide equivalent dose (CED). For patients ≥ 20 years of age at enrollment, any planned alkylator dose is permitted. Eligible patients must receive at least one of the alkylators that contribute to CED.

Equation to calculate cyclophosphamide equivalent dose, CED:

$$\begin{aligned} &1.0 \text{ (cumulative cyclophosphamide dose (mg/m}^2\text{))} + \\ &0.244 \text{ (cumulative ifosfamide dose (mg/m}^2\text{))} + \\ &0.857 \text{ (cumulative procarbazine dose (mg/m}^2\text{))} + \\ &14.286 \text{ (cumulative chlorambucil dose (mg/m}^2\text{))} + \\ &15.0 \text{ (cumulative carmustine dose (mg/m}^2\text{))} + \\ &16.0 \text{ (cumulative lomustine dose (mg/m}^2\text{))} + \\ &40 \text{ (cumulative melphalan dose (mg/m}^2\text{))} + \\ &50 \text{ (cumulative thiotepa dose (mg/m}^2\text{))} + \\ &100 \text{ (cumulative nitrogen mustard dose (mg/m}^2\text{))} + \\ &8.823 \text{ (cumulative busulfan dose (mg/m}^2\text{))} \end{aligned}$$

The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA

1. Planned treatment exclusions

Any planned radiation to the pelvis; or cranial radiation ≥ 30 Gy to the hypothalamus, inclusive of any total body irradiation (TBI).

Planned bilateral oophorectomy.

Note: A participant's desire to pursue alternative fertility preservation procedures (i.e., embryo, oocyte or ovarian tissue cryopreservation) will be allowed (and in fact encouraged).

2. Pre-existing conditions

Congenital syndromes associated with infertility and decreased ovarian reserve at baseline. For example: Turner's Syndrome, Fragile X premutation carriers, Down syndrome, etc.

Pre-existing seizure disorder, congenital long QT syndrome, pseudotumor cerebri; history of pulmonary embolism, venous thrombosis, or myocardial infarction.

____3. Prior Therapy Exclusions

Receipt of long acting (depot) GnRH agonists within 6 months before enrollment. In contrast, subcutaneous GnRH agonist used for oocyte retrieval is not an exclusion; oral and other hormonal contraceptive use is also not an exclusion.

____4. **Note:** Please see Section 4.1 for the concomitant therapy restrictions for patients during the Study treatment period. See Section 4.5 for information about oral and other hormonal contraceptive use during the study treatment period.

____5. Prior receipt of systemic chemotherapy. However, steroids and intrathecal chemotherapy are permitted prior to study enrollment.

____6. Any prior radiation to the pelvis; or cranial radiation ≥ 30 Gy to the hypothalamus, inclusive of any total body irradiation (TBI).

____7. Pregnancy and Lactation

Patients who are pregnant are not eligible. A pregnancy test is required for female patients of childbearing potential.

Lactating females who plan to breastfeed their infants for the duration of triptorelin therapy (24 weeks per dose).

____8. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of triptorelin therapy (24 weeks per dose).

REQUIRED OBSERVATIONS:

1.

	Baseline - prior to cancer therapy
Blood sampling for biomarkers (See Section 7.2)	
AMH (primary endpoint)	X
Other sex hormones: estradiol, FSH, LH	X
<i>DNA (OPTIONAL)</i>	X ¹ _____
Patient reported outcomes (PRO) (See Section 7.3)	
Demographic information	X
Estrogen deprivation symptoms	X
Menstrual history	X
Quality of life	X
Reproductive health concerns	X
Reproductive outcomes	X
Medical record abstraction (See Section 7.4)	
Cancer treatment exposures reporting	
Exogenous hormone use	X
Cancer and vital status	

2. See 7.3 for PRO measures.

3. Ideally patients are asked to complete the assessments at the time of enrollment before knowing their randomization status.

TREATMENT PLAN:

This is an open-label trial with patients randomized 1:1 to (Arm A) IM triptorelin prior to the start of cytotoxic chemotherapy or to (Arm B) cytotoxic chemotherapy without triptorelin. All patients will be followed from randomization through 2 years after the completion of cancer therapy.

TOXICITIES AND DOSAGE MODIFICATIONS:

As the study drug is generally given only once, there are no dose modifications for toxicities. For patients randomized to receive the study drug, a second dose of triptorelin may be given at the discretion of the treating oncologist if alkylator-based chemotherapy lasts beyond the 24 week duration of the original triptorelin dose. For all patients (including controls), participating sites will be asked to document if a subsequent triptorelin or other GnRH α was given and the reason for administration. If there are concerns about toxicity from the initial dose a second dose should not be given.

Contraindications for redosing:

- Anaphylaxis to triptorelin
- Cardiovascular event (myocardial infarction, prolonged QTc, stroke)
- Pituitary apoplexy
- Pseudotumor cerebri
- Seizure
- Pregnancy

SPECIMEN REQUIREMENTS: Also see Specimen Processing Manual

Assay*	Preferred tube	Alternate tubes	Ideal volume (minimum volume)
AMH	Red Top	Tiger Top SST	2-4 mL blood (≥ 0.5 mL serum/plasma)
FSH	Gold SST	Red Top / Orange RST / Lime Green PST / Green top	2-4 mL blood (≥ 0.5 mL serum/plasma)
Estradiol	Red Top	Not applicable	2-4 mL blood (≥ 0.5 mL serum/plasma)
LH	Gold SST	Red Top / Orange RST / Lime Green PST / Green top	2-4 mL blood (≥ 0.5 mL serum/plasma)

**If there are issues with the blood draw and limited blood volume is obtained, please prioritize AMH over other assays. Following AMH, FSH, estradiol, and LH are requested in descending order of priority.*

And: Blood for DNA (if optional consent signed)
2 5ml EDTA tubes

Shipping Instructions: See Specimen Processing Manual