COG-ARST1921: A Safety, Pharmacokinetic and Efficacy Study of a Gamma-Secretase Inhibitor, Nirogacestat (PF-03084014; IND# 146375), in Children and Adolescents with Progressive, Surgically Unresectable Desmoid Tumors

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.

___1. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than ten (10) calendar days after the date of study enrollment. Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___2. Fertility Preservation
As nirogacestat may cause primary ovarian insufficiency in female patients and have an unknown effect on male patients, all patients and parents/legal guardians should be counseled about and consider fertility preservation options before starting treatment.

___3. **Patient Eligibility Criteria**

Laboratory Studies
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.

Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Disease/Staging Imaging
Disease/Staging Imaging studies, if applicable, must be obtained within 4 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

Inclusion Criteria

___4. Age
Patients must be > 12 months and < 18 years of age at the time of enrollment.

___5. BSA
Patients must have a body surface area of > 0.3 m^2 at the time of enrollment.

___6. Diagnosis
Existing or recurrent desmoid tumor that is deemed not amenable to surgery without significant morbidity and progressed by ≥ 10% as assessed by RECIST v1.1 within the 6-month period prior to study enrollment.
- Patients must have had histologic verification of the desmoid tumor.
- Patients must have measurable disease by RECIST v1.1 criteria.
- Patient must have received at least one prior course of systemic therapy for desmoid tumor.

___7. Performance Level
Patients must have a Lansky (for patients ≤ 16 years of age) or Karnofsky (for patients > 16 years of age) performance status score of ≥ 50. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be

considered ambulatory for the purpose of assessing performance score. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

___8. Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, surgery or radiotherapy prior to entering this study. **Patients may not be using or anticipate using these treatments after the observed progression (inclusion criteria 3.2.3) or within the time period stated below.**

a. Cytotoxic chemotherapy: Must not have received within 2 weeks of entry onto this study (4 weeks if prior nitrosourea).
b. Small molecule tyrosine kinase inhibitors (e.g., sorafenib, pazopanib, imatinib), rapalogs (e.g., temsirolimus, everolimus, sirolimus) or anti-estrogen therapy (e.g., tamoxifen): May not have received within 28 days prior to the first dose of study treatment.
c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.
d. Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent.
e. Local regional tumor directed therapy, including, but not limited to small port radiation therapy (RT), radiofrequency ablation, cryotherapy, surgery: At least 2 weeks since these therapies and all toxicity must have resolved to Grade ≤ 1. If prior craniospinal RT or if ≥ 50% radiation of pelvis then ≥ 6 months must have elapsed. If other substantial BM radiation, then ≥ 6 weeks must have elapsed.
f. Stem Cell Transplant (SCT): No evidence of active graft vs. host disease. For allogeneic SCT, ≥ 6 months must have elapsed.
g. No prior γ-secretase, Notch or β-catenin inhibitor
h. Investigational Drugs: Must not have received investigational drug within 4 weeks of study entry, and all toxicities related to prior therapy must be resolved to Grade ≤ 1 or baseline.

___9. Concomitant Medication Restrictions

a. Steroids: Patients who are receiving dexamethasone must be on a stable or tapering dose for at least 2 weeks prior to study entry. Use of steroids for non-tumor indications (e.g., asthma or severe allergic reaction) is permitted.
b. Growth factor(s): Must not have received within 1 week of entry onto this study.
c. Patients who are currently receiving drugs that are strong inducers or moderate to strong inhibitors of CYP3A4 are not eligible. Strong inducers or moderate to strong inhibitors of CYP3A4 are not allowed from 14 days prior to enrollment to the end of protocol therapy. See Appendix III for a list of agents. Note: CYP3A4 inducing anti-epileptic drugs on a stable dose, are allowed.
d. Must not be receiving non-steroidal anti-inflammatory drugs (NSAIDs) as treatment for desmoid tumor after the observed progression (inclusion criteria 3.2.3) and patient agrees to not use NSAIDs while on study. **Occasional use (defined as ≤ 3 times per week) for treatment of pain is permitted.**

Please see Section 4.1 for the concomitant therapy restrictions for patients during treatment.

Organ Function Requirements

___10. Adequate Bone Marrow Function Defined As:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/µL
- Platelet count ≥ 100,000/µL (transfusion independent)
- Hemoglobin ≥ 9.0 g/dL (may receive RBC transfusions)

___11. Adequate renal function defined as:
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

___12. Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age (unless secondary to previously diagnosed Gilbert's syndrome), and
- SGPT (ALT) ≤ 135 U/L*

**Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*

___13. Adequate cardiac function defined as:
- QTc interval < 470 ms
- No history of congenital or acquired prolonged QTc syndrome
- No history of clinically significant cardiac arrhythmias, congestive heart failure, stroke or myocardial infarction within 6 months prior to study entry

___14. Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix VIII.

REQUIRED PRO/QOL QUESTIONNAIRES
See Section 14.4.1

REQUIRED CENTRAL IMAGING REVIEW
See Section 15

EXCLUSION CRITERIA:

___1. Active or chronic infection within 7 days prior to study entry.
___2. Patients with gastrointestinal conditions that might predispose for drug intolerability or poor drug absorption (e.g., inability to take oral medication, prior surgical procedures affecting absorption (e.g., gastric bypass), malabsorption syndrome, and active peptic ulcer disease).
___3. Patients with ulcerative colitis, inflammatory bowel disease, or a partial or complete small bowel obstruction.
___4. Known active infection with hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
___5. Patients with a prior history of malignancy, with the exceptions of desmoid tumor(s) and non-melanoma skin cancer, who are not in remission for more than 3 years.
___6. Patients who are unable to swallow tablets. Tablets must not be crushed or chewed. Administration of nirogacestat via gastrostomy tube or nasogastric tube is not allowed.
___7. Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study.
___8. Sexually active female patients of reproductive potential who have not agreed to use 1 method of highly effective contraceptive (including copper-containing intrauterine device, condom with spermicidal foam/gel/film/cream/suppository, bilateral tubal ligation, established use of inserted, injected or implanted hormonal method of contraception, abstinence, or male sterilization) for the duration of their study participation and for at least 6 months after last dose of nirogacestat. A second form of contraception (i.e. barrier method) is required for patients who are using hormonal contraception as nirogacestat may reduce the efficacy of hormonal contraceptives.
___9. Sexually active male patients of reproductive potential who have not agreed to use a condom and their female partner who have not agreed to use one of the highly effective methods of contraception mentioned above during treatment and for at least 90 days after the last dose of nirogacestat.
___10. <u>Pregnancy and Breastfeeding</u>

- Female patients who are breastfeeding.
- Female patients who are pregnant. These patients are excluded because there is no available information regarding the effects of nirogacestat on the developing human fetus and inhibition of γ-secretase is known to be teratogenic.
- Female patients of childbearing potential unless a negative pregnancy test result has been obtained.

REQUIRED OBSERVATIONS:

Required Observations - Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. History, physical exam, height (only Day 1), weight. For females, the medical history should also include, if applicable, a detailed menstrual history including onset of menarche, the date of the last menstrual cycle and any history of amenorrhea, menstrual irregularities, or symptoms of primary ovarian insufficiency (e.g., hot flashes). Any history of infertility in male participants should also be recorded, if applicable. For all patients, any hormone replacement or suppressive therapy should be documented (see Section 4.1.1.3 for examples). If a fertility preservation procedure (e.g. sperm or oocyte cryopreservation) is performed prior to study entry that should be noted.
b. Vital signs (temperature, heart rate, respiratory rate, blood pressure)
c. Performance score
d. CBC with differential and platelets
e. Electrolytes, BUN, creatinine, Ca^{2}+, PO_4, Mg^{2}+
f. AST, ALT, albumin, total bilirubin (if elevated obtain direct bilirubin)
g. Blood hormone levels (before treatment initiation; submit to central lab). See Appendix VI.
    - Males: Total testosterone, FSH, and LH. Note: Testosterone should be drawn in the morning.
    - Females: FSH, LH, estradiol, AMH, prolactin (Day 1 only), and TSH (Day 1 only). If TSH abnormal, test free T4 level.
h. Urinalysis
i. ECHO
j. 12-lead ECG: Pre-dose ECG must be obtained on Day 1. Post-dose ECG must be obtained 1 to 4 hours after the first dose of nirogacestat.
k. X-ray tibial growth plate. See Section 15.2.
l. Pregnancy test: Female patients of childbearing potential require a negative pregnancy test prior to the start of each cycle of therapy.
m. Blood for pharmacokinetics. See Section 14.1.1.
n. Archival tumor tissue (required if available). See Section 13.0 and 14.0.
o. Blood for genotyping (optional). See Section 14.1.2.
p. Blood for lymphocyte subsets: CD3 (Total T cells), CD3+CD4+(T helper cells), CD3+CD8+(T cytotoxic cells), CD4:CD8 ratio, CD3+HLA-DR+ (Activated T cells) percentages and absolute counts.
q. Blood for immunoglobulin subsets (D, G, and M)
r. PRO/QOL questionnaires
s. Blood for banking (optional). See Section 14.2.1.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

See Section 13 for retrospective central pathology review requirements.

BIOLOGY REQUIREMENTS:

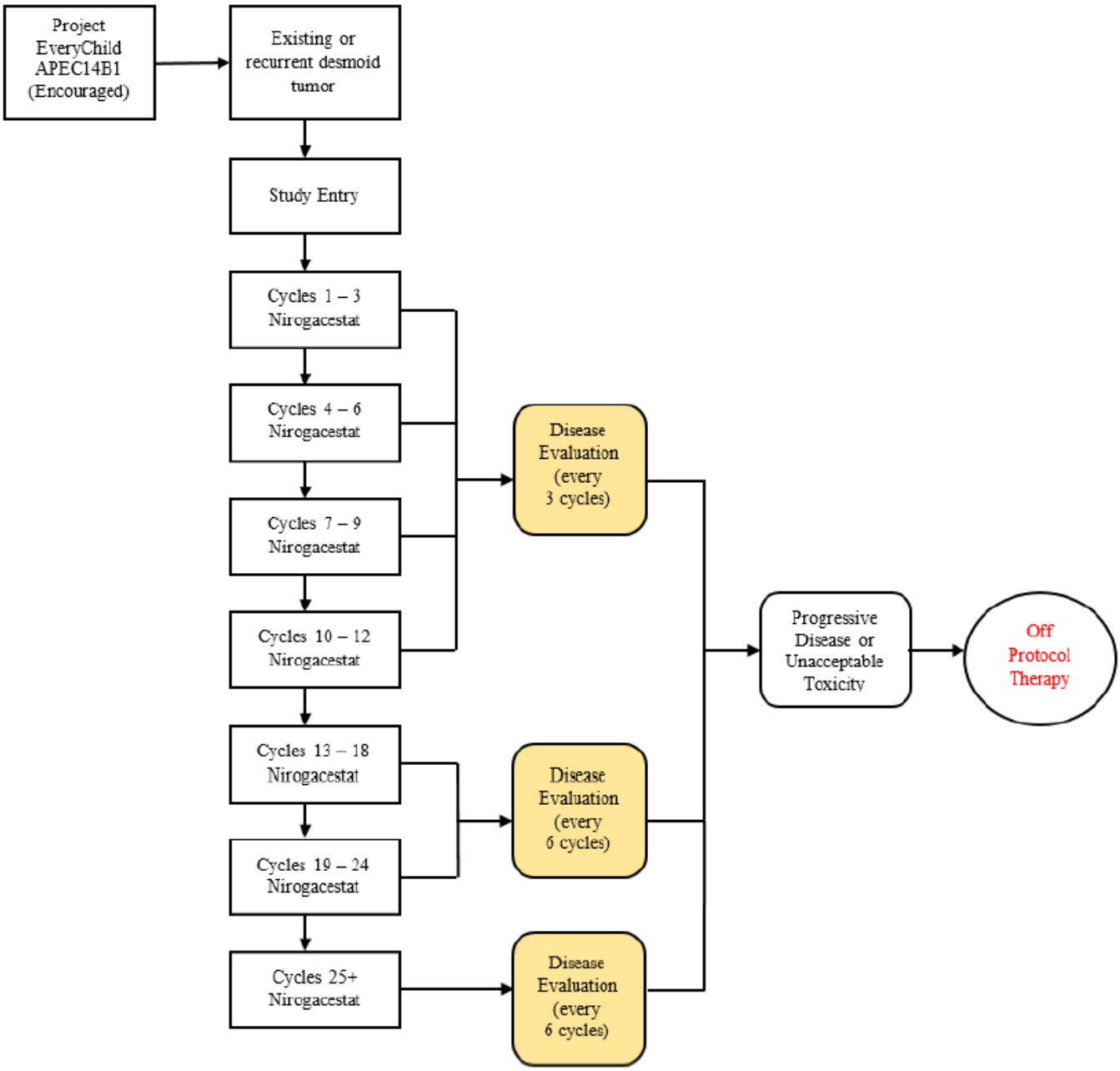
Pharmacokinetic studies will be required in all patients. See Section 14.

Tumor tissue samples for comprehensive genomic analysis of tumor tissue - See Section 14.1.2.1

Optional Biology Studies – See Section 14.2

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA



This is an open-label single arm study of single-agent nirogacestat administered at 90 mg/m^2/dose (maximum per dose 150 mg) twice a day on a continuous dosing schedule (one cycle = 28 days). Dosing will be based on body surface area (BSA) and rounded to the nearest 10 mg using a dosing nomogram (see Section 4.2.3). Patients may receive subsequent cycles of therapy in the absence of progressive disease or unacceptable toxicity.