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# **NRG-GY033**: A PHASE II STUDY OF ANDROGEN RECEPTOR (AR) INHIBITION BY DAROLUTAMIDE IN COMBINATION WITH LEUPROLIDE ACETATE AND EXEMESTANE IN RECURRENT ADULT-TYPE OVARIAN GRANULOSA CELL TUMOR

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**Participating Sites**
☒ U.S.
☐ Canada
☐ Approved International Member Sites
☐ Limited Participation

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**Protocol Agents:**

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| Leuprolide Acetate | Commercial | 377526 | | N/A |
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<tr><td>Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal.<br>(Sign in at http://www.ctsu.org, and select Regulatory > Regulatory Submission.)<br><br>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.<br><br>Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
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<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> Contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
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**NRG-GY033**

**SCHEMA**

**Patients with recurrent adult-type Ovarian Granulosa Cell Tumor (AGCT)**



- **Histologically confirmed AGCT**
- **≥1 Prior treatment regimen**
- **Progression on a prior aromatase inhibitor**



**<u>Treatment</u>**

**Darolutamide 600 mg PO twice daily, exemestane 25 mg PO once daily, and leuprolide acetate 7.5 mg IM every four weeks**

## 1. OBJECTIVES

### 1.1 Primary Objective

To determine the objective response rate of darolutamide, leuprolide acetate, and exemestane in recurrent adult-type granulosa cell tumors of the ovary (AGCT).

### 1.2 Secondary Objectives

To determine duration of response of darolutamide, leuprolide acetate, and exemestane in recurrent adult-type granulosa cell tumors of the ovary (AGCT).

To determine progression-free survival of darolutamide, leuprolide acetate, and exemestane when used in recurrent adult-type granulosa cell tumors of ovary (AGCT).

To determine overall survival of darolutamide, leuprolide acetate, and exemestane when used in recurrent adult-type granulosa cell tumors of ovary (AGCT).

To elucidate the toxicities of darolutamide, leuprolide acetate, and exemestane when used in recurrent adult-type granulosa cell tumors of ovary (AGCT).

### 1.3 Exploratory Objectives

To determine biomarkers predictive of response to darolutamide, leuprolide acetate, and exemestane.

## 2. BACKGROUND

Adult-type Granulosa Cells of the Ovary

Granulosa cell tumors (GCT) are a rare subtype of ovarian malignancy accounting for up to 5% of ovarian malignancies overall. Adult-type ovarian granulosa cell tumors (AGCT) make up 95% of GCT and commonly occur in perimenopausal/early postmenopausal women with a median age of 50-54 years old. These tumors are characterized by estrogen excess and can present with associated endometrial hyperplasia or endometrial adenocarcinoma (Jamieson et al., 2012)]. The majority of AGCT are Stage I at diagnosis and 5-year/10-year survival rates are greater than 90% and 84-95%, respectively. Initial treatment typically consists of cytoreductive surgery which can be followed by observation or platinum-based chemotherapy depending on the clinical scenario. Survival outcomes become less favorable with increasing stage (Schumer, 2003). AGCT tend to have an indolent disease course and the median time to recurrence is approximately 4 years but can vary widely with recurrence reported up to 30-40 years after diagnosis lending to need for long-term surveillance (Miller et al, 1997; East et al., 2005). There is an unmet need in the treatment of recurrent AGCT. Approximately 33% of patients will relapse and 50-80% of patients will die from their recurrent disease (Färkkilä et al, 2017).

As AGCT is a rare disease, there is a lack of prospective trials available to guide optimal evidence-based treatment of recurrent disease and there are limited treatment options available. A 2018 Cochrane review examining the effectiveness of different treatment modalities for AGCT had no definitive conclusions due to low-quality evidence and bias in data from current studies (Gurumurthy et al., 2014). National Comprehensive Cancer

Network guidelines recommend carboplatin/paclitaxel as the preferred regimen for recurrence. Other recommended regimens include docetaxel, paclitaxel, paclitaxel/ifosfamide, bleomycin/etoposide/cisplatin (BEP), bevacizumab, aromatase inhibitors, leuprolide acetate, and tamoxifen. This is based on lower-level Category 2A evidence (National Comprehensive Cancer Network, 2021). The recommendations are derived from retrospective and small phase II study data. A phase II GOG trial evaluated BEP for recurrent disease and found that 51% of women with recurrent disease remained progression-free but majority had a non-measurable clinical response and stable disease (Homesly et al., 1999). In a retrospective review of women with AGCT, taxanes demonstrated activity in AGCT and were less toxic than the BEP regimen (Brown et al., 2005). In a phase II NRG trial for recurrent AGCT, single agent paclitaxel led to partial responses in 8/31 patients and only 1 complete response (Burton et al., 2016). Phase II trials have also demonstrated activity of bevacizumab alone and in combination with paclitaxel in recurrent AGCT with acceptable toxicity. 16.7% of patients with recurrent AGCT in the phase II GOG study had a response (partial) to single-agent bevacizumab (Brown et al., 2014). In the ALIENOR-ENGOT-ov7 randomized clinical trial, the objective response rate was 25% with paclitaxel alone and increased to 44% with the addition of bevacizumab (Ray-Coquard et al., 2020). There is also limited experience with immune checkpoint inhibitors in AGCT. A small case series from a phase II basket trial demonstrated stability of disease in 2/5 patients and no objective responses were seen. The tumors did not express PDL1 (How et al., 2021).

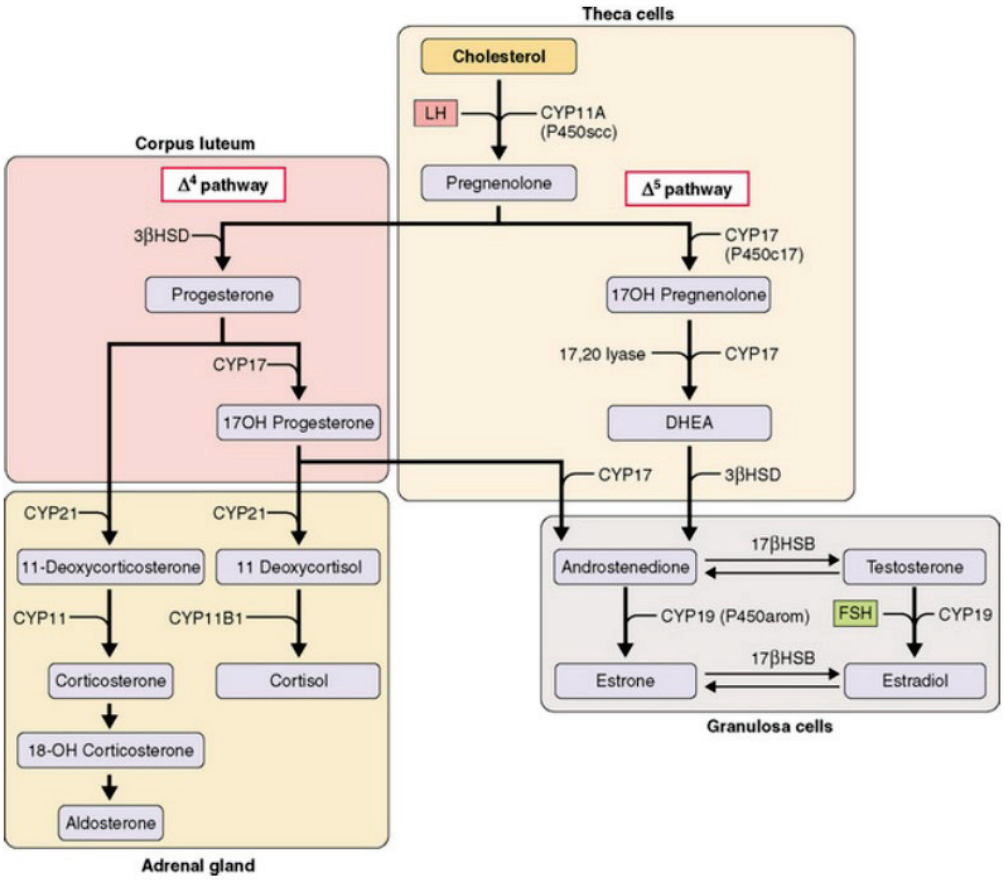
Given the toxicities inherent to chemotherapy and lower response rates, hormonal therapy has been investigated as an option in recurrent disease as these agents are typically well-tolerated and majority of AGCT express estrogen and progesterone receptors. A systematic review did show benefit of hormonal therapy in recurrent AGCT with an overall pooled response rate of 71%. Aromatase inhibitors demonstrated response in 9/9 therapies (Van Meurs et al., 2014). The recently published PARAGON/ANZGOG 0903 trial which looked at anastrozole in recurrent ER and/or PR positive recurrent AGCT showed a clinical benefit rate of 78.9% at 12 weeks. Yet, the overall response rate was 2.6% and 76.3% had stable disease (Banerjee et al., 2021). There remains a need for tolerable therapies that produce measurable response in this rare disease in the recurrent setting.

## 2.1 Steroidogenesis and the FOXL$^{2C134W}$ Mutation

Female steroidogenesis is a highly integrated process. Secretion of the sex steroids (progestins, androgens, estrogens) is predominantly from the adrenal glands and ovaries and there is complex interplay between the adrenal gland, corpus luteum, theca cells, and granulosa cells as demonstrated in figure 1 (Gupta et al., 2013). Steroidogenesis is dysregulated in AGCT, particularly via a FOXL2 somatic missense mutation (C134W) that is present in nearly all tumors. FOXL2 is a transcription factor that is involved in cell proliferation, apoptosis, and steroidogenesis (Leung et al., 2016). The FOXL2$^{C134W}$mutation results in substitution of a tryptophan for a highly conserved cysteine in the fork-head DNA binding region of the protein. This mutation lacks the consistent induction of oncogenes or inactivation of tumor suppressor genes found among other tumor types (Shah et al., 2009). Cells with the mutation have exhibited less apoptotic activity via decreased transcription of death receptors, decreased activation of caspases, BID, BAX, BAK, and cytochrome C

production. TGF-β/activin signaling is enriched leading to increased cell proliferation (Leung et al., 2016). Cluzet et al. utilized a mouse model which showed tumorigenesis was associated with inactivation of p53 and Rb pathways. Increased levels of androgens, estradiol, and anti-Mullerian hormone were noted along with decreased FOXL2 abundance (Cluzet et al., 2020). In examining the steroidogenesis pathway in more detail with the $FOXL2^{C134W}$ mutation, this mutation is thought to disrupt CYP19/aromatase and CYP17 gene transcription. Wildtype FOXL2 is thought to bind to steroidogenic factor-1 (SF-1) to negatively regulate the transcriptional activity of SF-1 which acts on CYP17 and CYP 19. $FOXL2^{C134W}$ stimulates CYP19 transcription leading to elevated estrogen synthesis via direct induction of aromatase. Also, CYP17 (key enzyme involved in androgen production) is no longer repressed leading to increased androgen and estrogen expression (Leung et al., 2016).

**Figure 1. Female steroidogenesis; Gupta MK. Ovarian Hormones: Structure, Biosynthesis, Function, Mechanism of Action, and Laboratory Diagnosis 2013**




## 2.2 FOXL2 and GnRH Receptor Expression

FOXL2 is an important transcription factor and a member of the forkhead-winged-helix family of transcriptions factors. It plays a role in activating *GNRHR* as part of an AP1-SMAD3-SMAD4 complex which encodes the GnRH receptor (Shah et al., 2009; Ellsworth et al., 2003). There have been studies examining this role in the commercially available KGN AGCT cell line. Cheng et al. suggested that wild-type FOXL2 ectopically expressed in KGN

cells may alter GnRH-induced apoptosis by increasing GnRH receptor protein expression and mRNA expression (Leung et al., 2016; Cheng et al., 2013). Benayoun et al. showed increased transactivation capability of $FOXL2^{C134W}$ on luciferase receptors which have the GNRHR activating sequence/FOXL2 promoter sequence in KGN cells (Leung et al., 2016; Benayoun et al., 2010).

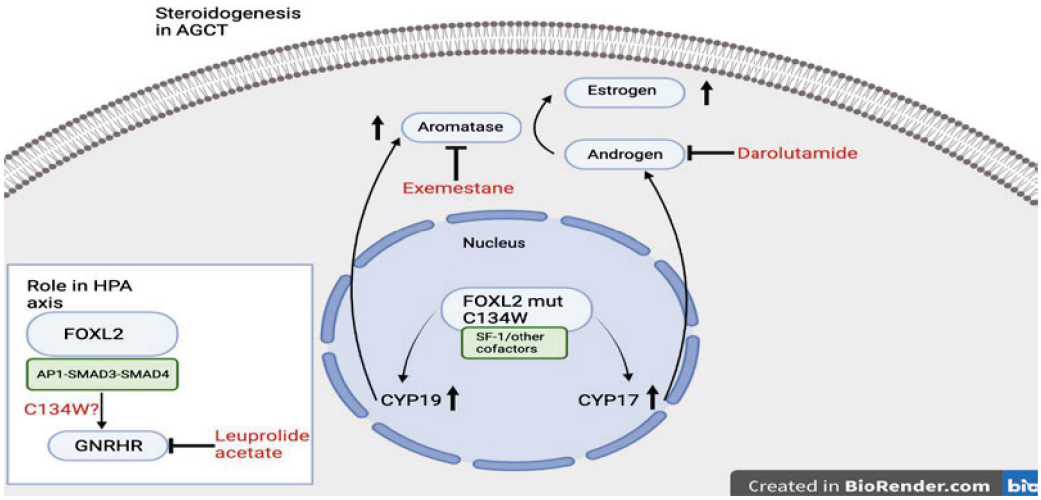
There have been reports of using the GNRH agonist, leuprolide acetate, for persistent or recurrence AGCT. This GnRH agonist initially causes increase of LH and FSH secretion resulting in increased steroidogenesis. Continuous use then causes downregulation of GnRH receptor activity decreasing LH and FSH secretion thus causing decreased levels of gonadal steroids. One study looked at 6 patients, 4 of whom had received prior platinum-based chemotherapy. There were 2 partial responses noted and 3 had stable disease. The treatment was noted to be tolerable with no major side effects (Fishman et al., 1996). A case report of a patient with recurrent AGCT receiving leuprolide acetate also demonstrated a partial response to this therapy (Kim et al., 2009).

### 2.3 Androgen Receptor (AR) Inhibition

The androgen receptor (AR) is part of the Type I class of nuclear hormone transcription factors which includes the estrogen receptor, progesterone receptor, and glucocorticoid receptor (GR). When androgen molecules bind to the androgen receptor, AR homodimerization and translocation to the nucleus results where AR binds to androgen response elements causing activation and transcription of downstream genes (Michmerhuizen et al., 2020). In regard to AR expression in AGCT, Mills et al. evaluated 29 AGCT samples. 59% of samples showed at least focal expression of AR which implies a possible role for anti-androgen agents (Mills et al., 2019).

Data on use of AR inhibition as a potential treatment platform has never been published in the AGCT literature. By examining the pathways involved in granulosa cell development and subsequent aberrations caused by $FOXL2^{C134W}$ mutation as demonstrated in Figures 1 and 2, a novel treatment regimen is proposed for a complete blockade of excess steroidogenesis seen in AGCT. The treatment regimen is darolutamide + exemestane +leuprolide acetate. Darolutamide is a second-generation androgen receptor antagonist. It inhibits AR nuclear translocation. It is currently FDA approved as treatment for nonmetastatic, castration-resistant prostate cancer. This drug has been shown to be well-tolerated in men treated for prostate cancer. Darolutamide is given in conjunction with androgen deprivation therapy (GnRH agonist or antagonist) such as leuprolide acetate 7.5 mg via intramuscular injection every 4 weeks (Fizazi et al., 2019; Rice et al., 2019). As there are no published studies of AR inhibition in AGCT, a level of AR expression at which AR inhibition may be beneficial has not yet been determined.

**Figure 2. Steroidogenesis in AGCT. FOXL2$^{C134W}$ is thought to alter FOXL2-SF-1 transcription of CYP19 and CY17 by causing upregulation of CYP19 and loss of repression of CYP17. Consequently, there is increased hormonal production. FOXL2 also plays a role in activating *GNRHR* as part of an AP1-SMAD3-SMAD4 complex which encodes the GnRH receptor. There have been studies looking into the role FOXL2$^{C134W}$ plays in this pathway. Utilizing exemestane (aromatase inhibitor), darolutamide (androgen receptor antagonist), and leuprolide acetate (GnRH agonist) would allow for complete hormonal blockade in AGCT as noted below.**




## 2.4 Institutional Cohort Data

By coupling darolutamide with a gonadotropin-releasing hormone receptor agonist (leuprolide acetate) and an aromatase inhibitor (exemestane), this multimodal approach would allow for complete hormonal blockade and theoretical tumor response in recurrent AGCT (Figure 2). Published clinical cohort data from our institution supports this concept and to our knowledge, is the only available dataset in which androgen inhibition has been utilized in AGCT. There are no available PDX models for pre-clinical study on the NCI PDX Net to further study the mechanism of this regimen in an *in-vivo* model. Bicalutamide was used in our institutional cohort due to ease of availability. All 7 patients in our cohort had previous disease progression on an aromatase inhibitor and had been heavily pre-treated. Prior to initiating the triple therapy regimen, all patients' disease burden had increased in size on prior treatment. When adding an antiandrogen and leuprolide acetate 7.5 mg IV every 4 weeks with the aromatase inhibitor, clinical benefit was seen. Of the 7 patients, there were 2 patients with partial responses, 4 patients with stable disease, and 1 patient with disease progression as shown in the table below. In addition, progression-free survival of ≥12 months has been noted for subjects within the cohort. The drug combination has been well-tolerated by our patient cohort thus far. One patient elected for treatment break secondary to vasomotor side effects. Further description of subjects is detailed below in Figure 3 (Summey et al., 2022).

**Figure 3.**

Patient Summary. Clinical summary of hormone status, mutation status (if known), radiographic monitoring and outcomes in AGCT patients treated with triplet therapy of bicalutamide, aromatase inhibitor and leuprolide acetate. IHC stains to assess hormone status in patient 1 were performed on two biopsies performed 2.5 years apart and reported in chronological order; all other stains were performed on the most recent biopsy or resection specimen. All patients received bicalutamide and leuprolide acetate but aromatase inhibitors varied, and are listed in the table.

| Subject | Age (y) | Aromatase inhibior | AR+ (%) | ER+ (%) | PR+ (%) | CT exams (months from treatment initiation) | PFS (months) | Response of target lesion | Toxicity on current regimen (CTCAE v5.0) | Prior treatment lines (n) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | Exemestane | >95 | 10<br>50 | 50<br>>95 | 4, 8, 12, 15 | 13 months | Partial response (treatment break due to side effect profile) | Grade 3 hot flashes | 5 |
| 2 | 64 | Exemestane | 95 | 30 | 95 | 8, 12, 15 | > 16 months | Partial response | None | 4 |
| 3 | 73 | Exemestane | 80 | 50 | >50 | 3, 7, 11, 16 | > 20 months | Stable disease | Grade 1 fatigue | 7 |
| 4 | 67 | Exemestane | 50 | 10 | 80 | 3, 11, | > 15 months | Stable disease | Grade 1 arthralgias | 2 |
| 5 | 67 | Letrozole | 95 | 2–3 | 60 | 1, 8 | > 13 months | Stable disease | None | 3 |
| 6 | 36 | Exemestane | 50 | 40 | 70 | 5 | 5 months | Progressive disease | None | 5 |
| 7 | 66 | Anastrozole | 95 | 60 | 85 | 3, 5, 7 | > 9 months | Stable disease | Grade 1 nausea | 2 |

# 3. ELIGIBILITY AND INELIGIBILITY CRITERIA

## 3.1 On Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. Investigators should consider all relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

Physicians should consider the following when evaluating if the patient is appropriate for this protocol:

- Patients must have adequate health that permits completion of the study requirements and required follow up.
- For patients with known HIV, HBV, and/or HCV infection:
    - HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
    - For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
    - Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

In addition:

- The effects of the combination of darolutamide, leuprolide acetate, and exemestane on the developing human fetus are unknown. For this reason, and because androgen receptor inhibitor agents as well as other therapeutic agents used in this trial are known to be teratogenic, participants of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) during study therapy and for 1 month following the completion of study therapy. Should a participant become pregnant or suspect pregnancy while participating in this study, they should inform their treating physician immediately.

**Notes: Per NCI guidelines, exceptions to eligibility criteria are not permitted.** For questions concerning eligibility see protocol cover page.

**NIH Participant Population Inclusion Policy**
NIH policy requires that participants regardless of gender identity and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Participants of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

## 3.2 Eligibility Criteria

***A patient cannot be considered eligible for this study unless ALL of the following conditions are met.***

Submission of tissue is required. Investigators should check with their pathology department regarding release of tissue before approaching patients about participation in the trial (see Section 10 for details).

**3.2.1** Histologically confirmed diagnosis of recurrent adult-type granulosa cell tumor.

**3.2.2** Patient must have measurable disease. Measurable disease is defined in the protocol per RECIST 1.1 criteria. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT or MRI. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

**3.2.3** Patient must have had ≥1 treatment regimen.

**3.2.4** Subject must have progressed on an aromatase inhibitor (letrozole, exemestane, anastrozole) in a prior treatment line.

**3.2.5** Age ≥ 18 years

**3.2.6** ECOG Performance Status of ≤ 2 (see Appendix I).

**3.2.7** Not Pregnant and Not Nursing

**3.2.8** Adequate hematologic function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm$^3$
- Platelets ≥ 100,000 cells/mm$^3$
- Hemoglobin ≥ 8 g/dl **(08-DEC-2023)**

**3.2.9** Adequate renal function defined as follows:

- Creatinine clearance (CrCL) of ≥30 mL/min by the Cockcroft-Gault formula

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{creatinine (mg/dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

**3.2.10** Adequate hepatic function defined as follows:

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
- AST and ALT ≤ 1.5 x institutional ULN

**3.2.11** Adequate cardiac function defined as follows:

- Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better (See Appendix II)

**3.2.12** Comorbid conditions

- No active infection requiring parenteral antibiotics;
- No current evidence of intra-abdominal abscess, abdominal/pelvic fistula (not diverted), gastrointestinal perforation, GI obstruction, and/or need for drainage nasogastric or gastrostomy tube

**3.2.13** The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

### 3.3 Ineligibility Criteria

***Patients with any of the following conditions are NOT eligible for this study.***

**3.3.1** Prior treatment with AR inhibitors

**3.3.2** Known hypersensitivity to the study drugs or their ingredients.

## 4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

### 4.1 PRE-TREATMENT ASSESSMENTS

***Protocol treatment should start within 14 days after registration; pre-registration laboratory assessments performed within 14 days of registration should be used for Cycle 1 Day 1 treatment assessments. Cycle 1 Day 1 labs should be drawn per investigator discretion/institutional standard if pre-registration assessments are performed outside the 14 day timeframe.***

| Assessments | Prior to Registration (calendar days) | Prior to Treatment* (calendar days) (Cycle 1, Day 1) |
|---|---|---|
| History and Physical | ≤ 14 days | ≤ 14 days |
| Concomitant Medications | ≤ 14 days | ≤ 14 days |
| Vital Signs§ | ≤ 14 days | ≤ 14 days |
| Performance Status | ≤ 14 days | ≤ 14 days |
| Toxicity Assessment | ≤ 14 days | ≤ 14 days |
| Complete blood count with differential | ≤ 14 days | ≤ 14 days |
| Comprehensive metabolic panel[1] | ≤ 14 days | ≤ 14 days |
| Inhibin B tumor marker | ≤ 28 days | ≤ 28 days |
| Pregnancy test (in persons of childbearing potential) | ≤ 14 days | |
| Radiographic Tumor Measurement[2] | ≤ 28 days | ≤ 28 days |
| Pathology report detailing ER and PR immunohistochemical staining (if available) | X | |
| Biospecimen Submissions (see Section 10 for details) M=mandatory, O=optional | | |
| Archival FFPE | | M[3] |

*** Prior to Registration Assessments should be used for Cycle 1, Day 1, as long as they are within the stated Cycle 1, Day 1 Window**

§ Vital signs should include Weight, Temperature, BP, Pulse. Any Height recorded in EMR can be used.

[1]Chemistries: sodium, potassium, chloride, CO2, BUN, creatinine, glucose, calcium, protein total, albumin, AST, ALT, alkaline phosphatase, total bilirubin

[2]Radiographic tumor measurements should be obtained via imaging of the chest (CT chest or CXR), and abdomen and pelvis (CT or MRI) to establish the location and extent of disease. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline (and subsequent assessments). Contrast CT is the preferred modality. PET CT is NOT to be used for any disease assessment or reassessment unless there is documentation that PET/CT is of diagnostic quality equal to CT with contrast.
[3]Patient must have an archival FFPE block collected prior to starting study treatment available for submission. Investigators should check with their pathology department regarding release of tissue before approaching patients about participation in the trial (see Section 10 for details).

## 4.2 ASSESSMENTS DURING TREATMENT

| Assessments | Prior to Each Cycle, Day 1 (after Cycle 1, Day 1) | Pre-Cycle 1 only | Timed (Treatment Cycle Independent) |
|---|---|---|---|
| History and Physical | ≤ 3 days | | |
| Concomitant Medications | ≤ 3 days | | |
| Vital Signs[§] | ≤ 3 days | | |
| Performance Status | ≤ 3 days | | |
| Toxicity Assessment | ≤ 3 days | | |
| Complete blood count with differential | ≤ 3 days | | |
| Comprehensive metabolic panel[1] | ≤ 3 days | | |
| Inhibin B tumor marker | ≤ 3 days | | |
| Initiation of darolutamide and exemestane | | X[2] | |
| Radiographic Tumor Measurement | | | X[3] |
| Review of pill diary to assess treatment compliance | X | | |

[§]Vital signs should include Weight, Temperature, BP, Pulse.
[1]Chemistries: sodium, potassium, chloride, CO2, BUN, creatinine, glucose, calcium, protein total, albumin, AST, ALT, alkaline phosphatase, total bilirubin
[2]Darolutmide and exemestane should be initiated 7-14 days prior to leuprolide acetate to avoid tumor flare for Cycle 1 only. Cycle 1, Day 1 will begin when leuprolide acetate is administered.
[3]Radiographic tumor measurement every 12 weeks (+/- 7 days), from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule). All scan dates calculated from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule). Radiographic tumor measurements are obtained until disease progression is confirmed; at the investigator's discretion, they can be repeated any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. A tool is provided to calculate dates of re-imaging. Utilize **same** imaging modality of abdomen and pelvis (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT is NOT to be used for any disease assessment or reassessment.

## 4.3 ASSESSMENTS IN FOLLOW UP

| Assessments | Timed |
|---|---|
| Vital Status | 1 |
| Toxicity Assessment | 2 |
| Radiographic tumor measurement | 3 |

1 Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5-year follow-up period or until study termination, whichever occurs first.
2 Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, see Section 7.
3 In the case that protocol-directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment (until disease progression documented by RECIST 1.1 or until patient initiates a subsequent cancer therapy). Patients who discontinue treatment, electively (e.g. withdrawal of consent) or not, should remain on study until primary endpoint or initiation of other anti-neoplastic intervention. The study team should clarify with the patient if withdrawal of consent is for treatment or for treatment and follow up.

Definition of Disease Assessments
Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

# 5. TREATMENT PLAN/REGIMEN DESCRIPTION

***Protocol treatment should begin within 14 days of registration***. Patients with recurrent histologically confirmed adult-type granulosa cell tumors of the ovary will receive darolutamide along with leuprolide acetate and exemestane for each cycle of therapy (1 cycle=28 days) until disease progression or other prohibiting circumstance.

See General Therapy Guidelines, Appendix III.

## 5.1 Agent based therapy

Exemestane and darolutamide are to be initiated 7 to 14 days **prior** to the start Cycle 1, Day 1 in order to prevent tumor flare. Administration of leuprolide acetate constitutes the start of Cycle 1, Day 1.

### 5.1.1 Darolutamide

Darolutamide 600 mg will be taken orally (PO) twice daily of each 28-day cycle.

**5.1.2** Leuprolide Acetate
Leuprolide acetate 7.5 mg is given as an intramuscular injection (IM) every 28 days.

**5.1.3** Exemestane
Exemestane 25 mg will be taken by mouth (PO) once daily of each 28-day cycle.

## 5.2 General Concomitant Medication and Supportive Care Guidelines

**5.2.1** Concomitant Medication
The study team must be provided information regarding any medication or vaccine the patient is receiving at time of informed consent and/or is receiving during the study period. This information must include reason for use, start/end date of administration, and dose/frequency.

**5.2.2** Drug Interactions

Combined P-gp and Strong or Moderate CYP3A4 Inducer
Concomitant use of darolutamide with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease darolutamide activity. Avoid concomitant use of darolutamide with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors
Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure which may increase the risk of darolutamide adverse reactions. Monitor patients more frequently for darolutamide adverse reactions.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for darolutamide adverse reactions, and consider dose reduction of the BCRP substrate drug.

Darolutamide is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of darolutamide may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs while patients are taking darolutamide.

**5.2.3** Permitted Supportive/Ancillary Care and Concomitant Medications
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

*Herbal and Nutritional Supplement*
The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, the use of general nutritional supplements will be allowed.

Anti-Emetic and Anti-Diarrheal Therapy
If there is not a known or expected drug-drug interaction, the choice and duration of therapy is at the discretion of the Investigator. If there is a known or expected drug-drug interaction, use of therapy must be approved by the study chair.

**5.2.4** Prohibited Therapies

- Other cancer directed therapies
- Systemic ketoconazole
- Abiraterone acetate
- Estrogen or progesterone therapies
- Androgen receptor inhibitors (e.g. bicalutamide, enzalutamide, apalutamide)

**5.2.5** Participation in Other Trials
Patients are not to participate in other therapeutic trials. However, trials that do not add therapeutic agents are allowed (e.g. imaging trials, quality of life, etc).

## 5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression/recurrence,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Death

Note:

- Patient has the right to refuse further treatment, but that does not necessitate withdrawing consent for participation in the study (e.g. follow-up) (See Section 8.2.2 regarding study consent withdrawal). In order to protect the integrity of the study, patients should be encouraged to stay on the study even if they stop protocol treatment.
- See Section 6 to determine if individual treatment components can be stopped independently.
- If all protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

# 6. TREATMENT MODIFICATIONS/MANAGEMENT

## 6.1 Dose Interruption

A participant who experiences a Grade 3 or Grade 4 treatment emergent adverse event (TEAE) that is thought to be related to study drug(s), should interrupt study drug(s) until the TEAE improves to $\leq$ Grade 2 or to baseline status.

Cases of idiosyncratic drug-induced liver injury (DILI) with increases in ALT and/or AST to ≥5 and ≥20 x ULN, including with concomitant bilirubin elevation >2x ULN, have been reported with darolutamide. Liver function tests abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug, should discontinue study drug.

Additional lab tests monitoring is recommended for Grade 2 or higher ALT and/or AST increase (ALT/AST >3 x ULN). Please see the below table:

**Toxicity Study Drug Modifications for ALT and/or AST Increase (08-DEC-2023)**

| Severity Grade | ALT/AST Increase | Further Recommendations |
|---|---|---|
| **Grade 0-1** | Treat on time. Per investigator's decision whether to reduce or interrupt darolutamide[a]. | • If reduced, darolutamide should be reduced to 300 mg orally BID<br>• If interrupted, and ALT and AST return to normal values or to baseline, darolutamide may be restarted at the reduced dose of darolutamide 300 mg orally BID<br>• If, at the reduced dose, there is no increase of ALT or AST in the subsequent two weeks, full dose may be resumed. |
| **Grade 2, 3, or 4** | **If ALT or AST rise to >3 ULN:**<br><br>Per investigator's decision whether to reduce or interrupt the darolutamide for Grade 2[a]<br><br>For Grade 3 or 4, interrupt all study drugs (see below criteria for darolutamide discontinuation).<br><br>Monitor LFT (ALT, AST, total and direct bilirubin, ALP) and INR within 72 hours after the onset and then as frequently as needed according to Investigator's clinical | • If reduced, darolutamide should be reduced to 300 mg orally BID<br>• If interrupted, if ALT and AST return to normal values or to baseline, darolutamide should be restarted at the reduced dose of darolutamide 300 mg orally BID<br>• If, at the reduced dose, ALT or AST values rise again, darolutamide should be permanently discontinued. Monitor LFTs until ALT and/or |

| | | |
|---|---|---|
| | judgment, until ALT and/or AST return to baseline or normal values.<br><br>Participants must be discontinued from all study drugs in case of hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be casually related to study. DILI should be suspected after other causes of liver injury have been excluded. Please see Appendix VII for further guidance.<br><br>Criteria for permanent darolutamide treatment discontinuation (FDA 2009)*:<br><br>• ALT or AST >8 x ULN<br>• ALT or AST >5 x ULN for more than 2 weeks<br>• ALT or AST >3 x ULN and (TBL >2 x ULN or INR >1.5)<br>• ALT or AST >3 x ULN appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)<br>* Per investigator's decision leuprolide acetate and exemestane can be restarted if ALT and AST return to grade 0-1 after darolutamide interruption. | AST return to baseline or normal values. |

a: If there is no recovery after 28 consecutive days treatment with study drug should be permanently discontinued.

## 6.2 Vasomotor Symptoms

If patient experiences grade 2 or higher AE of hot flashes/vasomotor symptoms, medical therapy may be initiated. Example regimen would be initiation of extended-release venlafaxine 37.5 mg once daily. Dose may be increased after 7 days to extended-release venlafaxine 75 mg once daily based on response and tolerability. If hot flashes do not improve, gabapentin 300 mg nightly can be initiated in addition to the extended-release venlafaxine.

## 6.3 Darolutamide Modifications for all Other AEs (except ALT/AST increase)(08-DEC-2023)

Table 6-3 Darolutamide Dose Modifications (except ALT/AST increase)

| Severity Grade | Dose Modifications | Study Treatment Withdrawal |
|---|---|---|
| **Grade 0-2** | Treat on time. Per investigator's decision whether to reduce or interrupt darolutamide[a,b]. | ——— |
| **Grade 3** | Interrupt until Grade 1 or baseline[a]. When the severity is Grade 1 or baseline, restart at a reduced dose of 300mg BID[b,c]. | If Grade ≥3 study drug-related TEAE occurs while the participant is on a dose of 300mg BID (following temporary or permanent dose reduction) the participant must be withdrawn from treatment with darolutamide |
| **Grade 4** | Interrupt until Grade 1 or baseline[a]. When the severity is Grade 1 or baseline, restart at a reduced dose of 300mg BID. | If Grade ≥3 study drug-related TEAE occurs while the participant is on a dose of 300mg BID (following temporary or permanent dose reduction) the participant must be withdrawn from treatment with darolutamide |

a: If there is no recovery after 28 consecutive days, treatment with study drug should be permanently discontinued.
b: When AE returns to baseline or is resolved, re-escalation to 600 mg BID may be considered by the investigator.
c: If following a re-escalation to 600 mg BID a second Grade ≥3 treatment-emergent adverse event occurs, a permanent dose reduction to 300 mg BID is required. A third occurrence of a Grade ≥3 treatment-emergent adverse event related to darolutamide requires permanent discontinuation of treatment with darolutamide.

## 6.4 Dose reduction

If considered necessary for the patient's safety and the AE is attributable to darolutamide, the dose of darolutamide can be reduced to 300 mg twice daily. Any dose reduction needs to be approved by the study chair. If a grade 3 or higher AE attributable to darolutamide recurs after 1 dose reduction despite medical intervention, the patient should permanently discontinue darolutamide (and continue exemestane or leuprolide acetate).

Note: There are no dose reductions for exemestane or leuprolide acetate. Patients who develop intolerance to exemestane therapy may be considered for alternative aromatase inhibitor, specifically, letrozole or anastrozole, at the treating physician's discretion and after review with study chair. If a patient discontinues exemestane and/or leuprolide acetate, they should continue other study agents.

### 6.5 Dosing recommendations (08-DEC-2023)

For patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m2) not receiving hemodialysis, the recommended dose of darolutamide is 300 mg twice daily. For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dose of darolutamide is 300 mg twice daily.

For patients receiving exemestane with a potent CYP 3A4 inducer such as rifampicin or phenytoin, the recommended dose of exemestane is 50 mg once daily after a meal.

## 7. ADVERSE EVENTS REPORTING REQUIREMENTS

### 7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY033 is darolutamide, which is being made available under an IND sponsored by CTEP. For patients receiving darolutamide, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.5.2.1 of the protocol.

Commercial Agents

The commercial agents in NRG-GY033 are leuprolide acetate and exemestane. For patients receiving leuprolide acetate and exemestane, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.5.2.1 of the protocol.

### 7.2 Adverse Events and Serious Adverse Events

**7.2.1** This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

**7.2.2** Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

## 7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Study Agents

**Comprehensive Adverse Events and Potential Risks list (CAEPR)**
**for**
**Darolutamide (BAY 1841788, NSC 815949)**

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the CTEP, NCI Guidelines: Adverse Event Reporting Requirements'' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1118 patients.* Below is the CAEPR for Darolutamide (BAY 1841788).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.1, February 20, 2024**[1]

| **Adverse Events with Possible Relationship to Darolutamide (BAY 1841788) (CTCAE 5.0 Term) [n= 1118]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | |
| GASTROINTESTINAL DISORDERS | | | |
| | Constipation | | |
| | Diarrhea | | |
| | Nausea | | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | |
| | Fatigue | | ***Fatigue (Gr 2)*** |
| HEPATOBILIARY DISORDERS | | | |
| | | Hepatic failure | |
| | | Hepatobiliary disorders - Other (hepatotoxicity) | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | Fall | | |
| INVESTIGATIONS | | | |
| | | Alkaline phosphatase increased | |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 2)*** |

| Adverse Events with Possible Relationship to Darolutamide (BAY 1841788) (CTCAE 5.0 Term) [n= 1118] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| | Blood bilirubin increased | | ***Blood bilirubin increased (Gr 2)*** |
| | Lymphocyte count decreased | | |
| | Neutrophil count decreased | | ***Neutrophil count decreased (Gr 2)*** |
| | Weight loss | | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 2)*** |
| | Back pain | | ***Back pain (Gr 2)*** |
| | Pain in extremity | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | |
| | Headache | | |
| RENAL AND URINARY DISORDERS | | | |
| | Hematuria | | |
| | Urinary frequency | | |
| | Urinary retention | | |
| VASCULAR DISORDERS | | | |
| | Hot flashes | | |
| | Hypertension | | |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Adverse events reported on Darolutamide (BAY 1841788) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Darolutamide (BAY 1841788) caused the adverse event:**

**CARDIAC DISORDERS** - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Sinus bradycardia
**EAR AND LABYRINTH DISORDERS** - Tinnitus
**EYE DISORDERS** - Eye disorders - Other (eyelid edema); Periorbital edema
**GASTROINTESTINAL DISORDERS** - Abdominal distension; Abdominal pain; Cheilitis; Colonic perforation; Dry mouth; Dyspepsia; Flatulence; Gastrointestinal disorders - Other (abnormal feces); Gastrointestinal disorders - Other (incarcerated inguinal hernia); Hemorrhoidal hemorrhage; Ileus; Small intestinal perforation; Vomiting
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Fever; Flu like symptoms; General disorders and administration site conditions - Other (general physical health deterioration); Malaise; Pain
**HEPATOBILIARY DISORDERS** - Hepatobiliary disorders - Other (abnormal hepatic function)
**INFECTIONS AND INFESTATIONS** - Endocarditis infective; Kidney infection; Lung infection; Sepsis; Upper respiratory infection; Urinary tract infection
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising
**INVESTIGATIONS** - Alanine aminotransferase increased; Creatinine increased; Weight gain
**METABOLISM AND NUTRITION DISORDERS** - Anorexia; Dehydration; Hyperglycemia; Hyperkalemia; Hyponatremia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (pain in jaw); Myalgia
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (diffuse large B cell lymphoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (prostate cancer)

**NERVOUS SYSTEM DISORDERS** - Dysgeusia; Ischemia cerebrovascular; Somnolence; Stroke
**PSYCHIATRIC DISORDERS** - Insomnia
**RENAL AND URINARY DISORDERS** - Acute kidney injury; Chronic kidney disease; Dysuria; Urinary incontinence; Urinary tract obstruction
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Breast pain; Gynecomastia; Pelvic pain
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Cough; Dyspnea; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pneumoperitoneum)
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Dry skin; Erythema multiforme; Hyperhidrosis; Photosensitivity; Pruritus; Rash maculo-papular; Skin atrophy
**VASCULAR DISORDERS** - Hypotension; Lymphedema; Thromboembolic event; Vascular disorders - Other (poor peripheral circulation)

**Note**: Darolutamide (BAY 1841788) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

## 7.4 Adverse Events for Commercial Study Agents

Refer to the package insert for detailed pharmacologic and safety information.

## 7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via https://ctepcore.nci.nih.gov/ctepaers/security/login

For studies that utilize the Rave-CTEP-AERS integration, expedited reports are initiated via Rave; see protocol section 12.3.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP for this study by telephone at 301-897-7497 and to NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

### 7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERs 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by CTEP as the IND sponsor for this study and by NRG as needed to complete adverse event review. Deidentified supporting source documentation should be uploaded to the Source Document Portal via the CTEP-AERS integration.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

### 7.5.2 Expedited Reporting Requirements for Adverse Events

#### 7.5.2.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SAEs** that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Grade 1-2 Timeframes | Grade 3-5 Timeframes |
|---|---|
| 24-Hour notification, 10 Calendar Days | 24-Hour notification, 5 Calendar Days |

**NOTE:** Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timeframes are defined as:**

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
**Expedited 24-Hour notifications are required for all SAEs followed by a complete report**

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

**7.5.3** Reporting to the Site IRB/REB

Investigators will report unanticipated problems to NCI CIRB according to the NCI CIRB SOPs.

**7.5.4** Secondary Malignancy:

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**Second Malignancy**:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

## 7.6 Routine Reporting Requirements for Adverse Events

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

**7.6.1** Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

# 8. REGISTRATION AND STUDY ENTRY PROCEDURES

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to

NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

| Documentation Required | IVR | NPIVR | AP | A | AB |
|---|---|---|---|---|---|
| CTEP-IAM Account with ID.me credentials | ✓ | ✓ | ✓ | ✓ | ✓ |
| FDA Form 1572<br>• Practice sites, IRBs, and labs | ✓ | ✓ | | | |
| Financial Disclosure Form | ✓ | ✓ | ✓ | | |
| NCI Biosketch (education, training, employment, certification, licensure, ABMS certification, GCP Training, personal statement, memberships, honors, publications, research support) | ✓ | ✓ | ✓ | | |
| GCP Training Certificated (mandatory file upload) | ✓ | ✓ | ✓ | | |
| Agent Shipment Form (if applicable) | ✓ | | | | |
| CV (optional file upload) | ✓ | ✓ | ✓ | | |
| Annual Re-registration | ✓ | ✓ | ✓ | ✓ | ✓ |

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and

- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

## 8.1 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support System Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

**IRB Approval**

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be to have an approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

**Additional Requirements**
Additional site requirements to obtain an approved site registration status include:
- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

**Downloading Site Registration Documents**

Download the site registration forms for the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster.

To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG* and protocol number *NRG-GY033*.
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

**Submitting Regulatory Documents**
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSUREgHelp@coccg.org to receive further instruction and support.

**Checking Site's Registration Status**
Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

**Delegation of Tasks Log (DTL)**

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

## 8.2 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, informed consent is obtained, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Informed Consent: Patients must be aware of the neoplastic nature of their disease and informed of the procedure(s) to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts prior to signing the informed consent in accordance with institutional and federal guidelines. Current

IRB/REB/REC approval of this protocol and a consent form is required prior to patient consent and registration. The model consent form created for this study adheres to the NCI informed consent template requirements.

### 8.2.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

### 8.2.2 Patient-Initiated Consent Withdrawal from the Study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow up data to be submitted to NRG Oncology), the study applicable form should be completed in Medidata Rave to report the patient's consent withdrawal.
NOTE: This should not be done if the patient has only chosen to stop protocol treatment and is willing to still be followed. (See Section 5.3).

# 9. DRUG INFORMATION

General Patient Care Implications
Patients must use highly effective contraception because the study treatment may be teratogenic. Highly effective contraception is defined as hormonal contraceptives (oral contraceptives, Nuvaring, Depo Provera), intrauterine device, true abstinence, two barrier methods of birth control including condoms with cervical cap or diaphragm, patient has received surgical sterilization.

## 9.1 Investigational Study Agent: Darolutamide (NSC # 815949, IND # [redacted])

**Chemical Name**: N-((S)-1-(3-(3-Chloro-4-cyanophenyl)-1H-pyrazol-1-yl) propan-2-yl)-5-(1-hydroxyethyl)-1H pyrazole-3-carboxamide

**Other Names**: ODM-201, BAY 1841788, NUBEQA

**Classification**: Androgen receptor inhibitor

**Molecular Formula**: $C_{19}H_{19}C_lN_6O_2$ **M.M:** 398.85 g/mol

**Mode of Action:** Darolutamide is an androgen receptor (AR) inhibitor. Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. A major metabolite, keto-darolutamide, exhibited similar in vitro activity to darolutamide. In addition, darolutamide functioned as a progesterone receptor (PR) antagonist in vitro (approximately 1% activity compared to AR). Darolutamide decreased prostate cancer cell proliferation in vitro and tumor volume in mouse xenograft models of prostate cancer.

**9.1.1 Description**: Darolutamide is a white to almost white to off-white powder.

**9.1.2 How Supplied:** Darolutamide is supplied by Bayer and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as film-coated tablets containing 300 mg of darolutamide for oral use. The tablets are blue oval film-coated tablets marked with "OR 300" on one side. Tablets are supplied in 140-count HDPE bottles.

*Inactive ingredients:* lactose monohydrate, calcium hydrogen phosphate anhydrous, croscarmellose sodium, povidone, magnesium stearate

*Film coat/lacquer blue excipient:* hypromellose, lactose monohydrate, titanium dioxide, macrogol 4000, indigocarmine, and ferric oxide red

**9.1.3 Storage:** Store tablets at controlled room temperature between 20°C to 25°C (66°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F).

If a storage temperature excursion is identified, promptly return darolutamide to 20°C to 25°C (68°F to 77°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

**9.1.4 Stability:** Stability studies of the intact bottle are ongoing. It is recommended that darolutamide tablets be dispensed in the original manufacturer's container.

**9.1.5 Route of Administration:** Oral.

**9.1.6 Method of Administration:** Administer darolutamide tablets orally with food. Tablets should be swallowed whole. Do not chew, crush, or split tablets. Missed doses should be taken as soon as the patient remembers prior to the next scheduled dose. Two doses should not be taken together to make up a missed dose.

**9.1.7 Potential Drug Interactions:** Darolutamide is primarily metabolized by CYP3A4, as well as by UGT1A9 and UGT1A1. Darolutamide does not inhibit or induce CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 at clinically relevant concentrations. In vitro, darolutamide did not inhibit or induce UGT1A1, 1A4, 1A6, 1A9, and 2B7 or metabolism of 5-fluorouracil by DPD.

*In vitro*, darolutamide is a substrate of P-gp and BCRP but is not a substrate of OATP1B1, OATP1B3, and OCT1. Avoid concomitant use of combined P-gp and strong or moderate CYP3A4 inducers. Use caution during concomitant use of combined P-gp and strong CYP3A4 inhibitors. Darolutamide is an inhibitor of BCRP, OATP1B1, OAT3, OATP1B3, MATE2K, P-gp, MATE1 in decreasing order of relevance. Avoid concomitant use with BCRP substrates and use caution with OATP1B1 or OATP1B3 substrates if concomitant use cannot be avoided. Concomitant use of darolutamide increased the mean AUC and $C_{max}$ of rosuvastatin (BCRP, OATP1B1 and OATP1B3 substrate) by approximately 5-fold. In vitro darolutamide did not inhibit OAT1, OCT1, OCT2, OATP2B1, NTCP, BSEP or MRP2.

**9.1.8 Patient Care Implications:** All women of child-bearing potential should adhere to the contraceptive guidance detailed in the protocol. Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period.

Male subjects with a female partner of childbearing potential should adhere to the contraceptive guidance detailed in the protocol.

## 9.2 PMB Useful Links and Contacts

- *CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/*
- *NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov*

- *PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm*
- *PMB Agent Inventory Management System (AURORA) application: https://ctepcore.nci.nih.gov/aurora*
- *CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/*
- *CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov*
- *IB Coordinator: IBCoordinator@mail.nih.gov*
- *PMB email: PMBAfterHours@mail.nih.gov*
- *PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)*

## 9.3 Agent Ordering

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites can order study agents in AURORA when a patient is enrolled to treatment.

Submit agent requests through the PMB Agent Inventory Management System (AURORA) application. Access to AURORA requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

### 9.3.1 Investigator Brochure Availability

The current versions of the darolutamide IB will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

### 9.3.2 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page.

Store and maintain separate NCI Investigational Agent Accountability Records for each study participant and ordering investigator on this protocol.

### 9.4 Commercial Agent-Leuprolide Acetate

Please see Section 5.1.2 for administration instructions. Please refer to the current FDA-approved package insert.

#### 9.4.1 Product Description

Leuprolide acetate is commercially available.

#### 9.4.2 Preparation

See the leuprolide acetate package insert for preparation instructions.

#### 9.4.3 Availability/Supply

Leuprolide acetate is obtained by the investigator from commercial supply.

#### 9.4.4 Adverse events

Swelling of body, pain (such as muscles and joints), nausea, vomiting, vaginal discharge, depression, mood swings, difficulty sleeping, flu-like symptoms (fever, chills, body aches, muscle pain), cold symptoms (stuffy nose, sneezing, sore throat), swelling and redness of throat and sinuses which may cause difficulty breathing and swallowing, headache, flushing, tiredness, discomfort at injection site (pain, redness, bruising, itching, swelling).

Please refer to the package insert and the site-specific pharmacy to toxicity and safety information.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.)

### 9.5 Commercial Agent-Exemestane

Please see Section 5.1.3 for administration instructions. Please refer to the current FDA-approved package insert.

#### 9.5.1 Product Description

Exemestane is commercially available.

#### 9.5.2 Preparation

See the exemestane package insert for preparation instructions.

#### 9.5.3 Availability/Supply

Exemestane is obtained by the investigator from commercial supply.

#### 9.5.4 Adverse Events

Hot flashes, flushing, increased sweating, pain, tiredness

Please refer to the package insert and the site-specific pharmacy to toxicity and safety information.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.)

## 10. BIOSPECIMEN COLLECTION AND SUBMISSION

### 10.1 Biospecimen Collection and Submission

A detailed description of biospecimen collection and submission procedures can be found in the Biospecimen Collection and Submission Manual (found on the CTSU protocol page under the Protocol Related Documents tab).

### 10.1.1 Mandatory Biospecimen Collection and Submission

The patient agrees to participate in mandatory biospecimen collection as part of the main trial. Participating sites are required to submit the patient's biospecimens and accompanying documentation as outlined below.

| Biospecimen (Biospecimen Code) | Collection Time Point | Sites Ship Biospecimens to |
|---|---|---|
| **FFPE – Submit *one* of the following (listed in order of preference)** | | |
| Archival FFPE Recurrent Primary (FRP01) or Recurrent Metastatic (FRM01) Tumor[1]<br>Block must be submitted[2] | Prior to study treatment<br><br>Resection preferred; submit biopsy only if resection not available | NRG Oncology Biospecimen Bank-Columbus within 8 weeks of registration[3] |
| Archival FFPE Primary (FP01) or Metastatic (FM01) Tumor[1]<br>Block must be submitted[2] | Prior to all treatment<br><br>Resection preferred; submit biopsy only if resection not available | |

1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG Biospecimen Bank-Columbus.

2 Only blocks will be accepted. Please provide the "Letter to Pathologists" from the Biospecimen Collection and Submission Manual (found on the CTSU protocol page under Protocol Related Documents) to your pathologist.

3 NRG Oncology BB-Columbus / Protocol NRG-GY033, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

### 10.2 Central Review

Not applicable

### 10.3 Integral Biomarker

Not applicable

## 10.4 Integrated Biomarker

**10.4.1** Integrated Biomarker to be Tested
Central androgen receptor (AR) immunohistochemistry (IHC)

*No review required*

**10.4.2** Integrated Biomarker Assay Summary
Formalin-fixed, paraffin-embedded (FFPE) tumor tissue will be used for retrospective AR IHC. Upon NCI approval, the NRG Biospecimen Bank-Columbus will batch ship unstained sections to Dr. Julie Jorns (Medical College of Wisconsin) for central testing.

**10.4.3** Integrated Biomarker Results Reporting
Dr. Jorns will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

## 10.5 Banking Biospecimens for Future Research

Testing of banked biospecimens will not occur until an amendment to this protocol (or a separate correlative science proposal) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

Banked biospecimens will remain in the NRG Biospecimen Bank and made available for approved research projects if the patient has provided permission for the use of their biospecimens for future research. Please refer to the Biospecimen Collection and Submission Manual (found on the CTSU protocol page under the Protocol Related Documents tab) for information regarding patient withdrawal of permission for use of biospecimens.

## 10.6 Exploratory Biomarkers

**10.6.1** Exploratory Biomarkers
Local estrogen receptor (ER) and progesterone receptor (PR) immunohistochemistry (IHC)

*No review required*

**10.6.2** Exploratory Biomarkers Assay Summary
Local ER and PR IHC results will be examined as possible predictive biomarkers of response to darolutamide, leuprolide acetate, and exemestane.

# 11. ASSESSMENT OF DISEASE STATUS

## 11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [Eur J Ca 45:228-247, 2009] Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

## 11.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The

baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

**11.1.2** Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

NRG will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases, e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

## 11.3 Response Criteria

Determination of response should take into consideration all target (See 11.3.1) and non-target lesions (See 11.3.2).

### 11.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters (i.e. the nadir) while on study.

**11.3.2** Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

**11.3.3** Evaluation of Best Overall Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

| Target Lesions | Non-Target Lesions | New Lesions* | Time Point Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | NE | No | PR |
| PR | Non-PD or NE | No | PR |
| SD | Non-PD or NE | No | SD |
| NE | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD** | Yes or No | PD |
| Any | Any | Yes | PD |

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

**Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)**

| Non-Target Lesions | New Lesions* | Time Point Response |
|---|---|---|
| CR | No | CR |
| CR | No | Non-CR/non-PD* |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| NE | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

**11.3.4** Best Overall Confirmed Response

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of results.

| Time Point Response First time point | Time Point Response Subsequent time point | BEST overall confirmed response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR* |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| PR | CR | PR |

| | | |
|---|---|---|
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise, NE |
| NE | NE | NE |

*If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

## 11.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since date of study entry, including the baseline measurements.

### 11.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first, or date of last contact with known progression free status if neither progression nor death has occurred. Patients with no follow-up will be censored 1 day after enrollment.

### 11.6 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact. Patients with no follow-up will be censored 1 day after enrollment.

## 12. DATA AND RECORDS

### 12.1 Data Submission/Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role or Rave SLA must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been

recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

## 12.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.5 and 7.6 for information about expedited and routine reporting.

## 12.3 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules

evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form (i.e., checking the box *Send all AEs for Evaluation* and save the form). Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence, that internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents>*
- *Protocol Related Documents > Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics.*

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

## 12.4 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

### 12.5 Global Reporting/Monitoring

***Demography monitoring***:
Required submission of patient demographic data for this study will be submitted automatically via OPEN.

**Note:** Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

***DMU Complete monitoring:***
Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.htm).

**Note**: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Abstract

This is a single-arm, unblinded, non-randomized Phase 2 study to assess the anti-tumor activity of receiving the combination of darolutamide, leuprolide, and exemestane (DLE) in women with recurrent adult-type granulosa cell tumors of the ovary (AGCT). The primary measure of efficacy is the objective response rate, defined as a complete response (CR) or partial response (PR).

### 13.2 Stratification and Randomization

This trial does not require randomization or stratification.

## 13.3 Patient Cohorts for Analysis

| Population | Description |
|---|---|
| Measurable Disease | The Measurable Disease population includes all patients who<br>1. receive at least 1 dose of the doublet (darolutamide, exemestane)<br>2. have baseline measurable disease per RECIST 1.1<br>3. have at least one tumor assessment, disease progression, or death, whichever occurs first, within 9 months of starting leuprolide acetate.<br>This population will support all analyses related to ORR and response duration. |
| Safety | The Safety population includes all patients who receive at least 1 dose of protocol therapy. All safety analyses will be conducted using the safety population. Safety will be assessed beginning with the initial dose of any treatment. |
| ITT | The ITT population includes all enrolled patients. All enrolled patients will be analyzed, regardless of treatment compliance. This population will be used for demographics and baseline characteristic summaries, participant disposition, and analyses of PFS and OS endpoints. |

## 13.4 Primary Endpoint(s), Sample Size, and Analysis Plan

The primary endpoint is complete or partial confirmed objective tumor response within 9 months of initiating study treatment as assessed by RECIST v. 1.1 criteria.

The primary hypothesis of this study tests the proportion of patients with objective complete or partial tumor response ($\pi$). Based on predicted response rates in similar patient populations, the null hypothesis is that the proportion of patients with objective tumor response will be 20% or less, i.e.:

$$H_0: \pi \leq 0.20.$$

The alternative hypothesis is the complement of the null parameter space (i.e. $H_1: \pi > 0.20$).

### 13.4.1 Sample Size and Power Calculations

The Optimal Simon's two-stage design (Simon, 1989) will be used. In the first stage, 17 patients will be accrued. If there are 3 or fewer responses in these 17 patients for the first stage, the study will be stopped. Otherwise, 20 additional patients will be accrued during the

second stage for a total of 37 patients. The null hypothesis will be rejected if 11 or more responses are observed in 37 patients. This design yields a one-sided Type I error rate of 0.095 and 90% power when the true response rate is 40%.

### 13.4.2 Accrual/Study Duration

The estimated monthly accrual rate is 1 patient per month for the first 6 months and 1.5 patients per month thereafter. It will take approximately 14 months to complete accrual to the first stage. Accrual will be suspended after the 17$^{th}$ patient enrolls in the trial. It is anticipated that it will take 10-12 months to allow for data maturity and review of the stage 1 data.

If it is found that the trial does not meet the criteria to continue to the second stage, the study will permanently close. If it is found that trial meets the criteria to continue to the second stage, the protocol will re-open accrual to the stage 2 patients. Re-opening the trial will require protocol amendment.

If the trial continues to the second stage, it will take a total of 39 months to complete accrual, which includes projected time for stage 1 accrual, accrual suspension, and stage 2 accrual. Complete trial study duration is projected to take 44 months.

### 13.4.3 Analysis Plan

This study uses a two-stage design with early stopping guidelines based on the tumor response rate. The first stage of this study will target an accrual of 17 patients. If the number responding is less than or equal to 3 patients, then the study will terminate early and the regimen will be declared uninteresting. If there are at least 4 patients with a complete or partial response, the study advances to the second stage. If the study advances to the second stage, then the overall study accrual will be 37 patients. If the number responding is less than or equal to 10 patients, then the regimen will be declared uninteresting to warrant further investigation. The objective response rate ORR will be calculated as:

$$\text{ORR} = \frac{Number\ of\ eligible\ patients\ with\ a\ CR\ or\ PR}{Total\ number\ of\ eligible\ patients\ accrued}$$

Exact 95% confidence limits, accounting for interim analysis, will be provided in the final report.

## 13.5 Monitoring/Oversight Committee

### 13.5.1 Data Oversight Committee

NRG Early Phase Oversight Committee-

Study reports focusing on accrual and adverse event data will be prepared regularly and the PI/NRG study team will have regular conference calls to review the accrual/safety data. Information from these calls will be reviewed quarterly by the NRG Oncology Early Phase Oversight Committee (EPOC).

**13.5.2** Data Monitoring

The Data Manager will work with the Study Statistician to keep the data up-to-date on a regular basis.
Accrual and safety data will be reviewed by the protocol monitoring team on a regular basis at the discretion of the NRG EPOC. The protocol monitoring team will consist of the Study Chair, the Study Statistician, the Study Co-Chairs, the Data Manager, and any others required. The Study Statistician will assemble the necessary data and prepare a report for review. The report will include information related to patient accrual, basic patient and tumor characteristics, follow-up information, and adverse events and toxicities.

The protocol monitoring team will consider information in the provided report and the recommendations of the Study Statistician. After review of this information and any other information that may be relevant, the protocol monitoring team should reach a consensus on whether the accrual rate is sufficient to support completion of accrual, whether the rates of adverse events are low enough to be offset by the patient benefit hypothesized for intervention, and whether the number of events is sufficient to proceed to the next phase or sufficient to reach the definitive analysis.

Brief minutes of each meeting written by the Data Manager plus the Study Statistician's report will be forwarded to the NRG Operations Office for archiving. The NRG Operations Office will forward the meeting minutes and the report to the NRG Oncology Internal Early Phase Trial Oversight Committee for review at their regularly scheduled meetings.

The study report will also be reviewed on a bi-annual basis at the NRG Semi-Annual Meetings.

## 13.6 Secondary Endpoints and Analysis Plans

Secondary objectives include:

- To determine duration of response of darolutamide, leuprolide acetate, and exemestane in recurrent adult-type granulosa cell tumors of the ovary (AGCT).

- To determine progression-free survival (PFS) of darolutamide, leuprolide acetate, and exemestane when used in recurrent adult-type granulosa cell tumors of ovary (AGCT).

- To determine overall survival (OS) of darolutamide, leuprolide acetate, and exemestane when used in recurrent adult-type granulosa cell tumors of ovary (AGCT).

- To elucidate the toxicities of darolutamide, leuprolide acetate, and exemestane when used in recurrent adult-type granulosa cell tumors of ovary (AGCT).

Duration of response is defined in Section 13.3. Median duration of response with a corresponding 95% confidence interval will be estimated.

Progression-free survival (PFS) is defined in Section 13.4. Overall survival (OS) is defined in Section 13.5. Both endpoints will be graphed using Kaplan-Meier methods. Median PFS and OS will be estimated with corresponding 95% confidence intervals.

CTCAE version 5 will be used to grade and categorize adverse events. Safety will be assessed beginning with the initial dose of any treatment. Descriptive statistics, including frequencies of maximum grade of adverse events by term and category will be reported. Adverse events categorized as Grade 5 will be individually reported.

## 13.7 Exploratory Endpoints

Exploratory objectives include:

- To determine biomarkers predictive of response to darolutamide, leuprolide acetate, and exemestane.

An analysis plan will be added to protocol via protocol amendment after approval of biomarkers for analysis.

Analysis Plan for Exploratory Objectives **(23-FEB-2026)**
After receipt of FFPE tumor slides for each eligible and consented subject from the NRG Biospecimen Bank, immunohistochemistry (IHC) will be performed at the principal investigator's institution using a College of American Pathologist [CAP]-accredited clinical laboratory. Hormone receptor positivity (including estrogen receptor, progesterone receptor, and androgen receptor) will be assessed via IHC. The percent positivity and median intensity will be assessed for each hormone receptor per subject. IHC results will be correlated with subject response on the study drug regimen. Logistic regression will be used to estimate an odds ratio with 95% confidence limits. IHC results will also be correlated with PFS and OS, using Cox-proportional hazards modeling to estimate hazard ratios with 95% confidence limits. No hypothesis testing is planned.

## 13.8 Gender/Ethnicity/Race Distribution

| **Racial Categories** | **DOMESTIC PLANNED ENROLLMENT REPORT** | | | | |
|---|---|---|---|---|---|
| | **Ethnic Categories** | | | | |
| | Not Hispanic or Latino | | Hispanic or Latino | | Total |
| | Female | Male | Female | Male | |

| | | | | | |
|---|---|---|---|---|---|
| American Indian/Alaska Native | 1 | 0 | 0 | 0 | 1 |
| Asian | 2 | 0 | 0 | 0 | 2 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 | 0 | 1 |
| Black or African American | 3 | 0 | 0 | 0 | 3 |
| White | 28 | 0 | 2 | 0 | 30 |
| More Than One Race | 0 | 0 | 0 | 0 | 0 |
| Total | 35 | 0 | 2 | 0 | 37 |

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## APPENDIX I – PERFORMANCE STATUS CRITERIA

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## APPENDIX II– NYHA CLASSIFICATION

Congestive Heart Failure – New York Heart Association Classification

| Class | Definition |
|---|---|
| **I** | No limitation of physical activity: Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath) |
| **II** | Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath). |
| **III** | Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. |
| **IV** | Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases. |

| Class | Definition |
|---|---|
| **A** | No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity. |
| **B** | Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest. |
| **C** | Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest. |
| **D** | Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest. |

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964: 114.

## APPENDIX III – GENERAL THERAPY GUIDELINES

- For cycle lengths greater than or equal to 21 days, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without being considered a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of cycle lengths greater than or equal to 21 days. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

- Chemotherapy doses are recommended to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

## APPENDIX IV-PATIENT DRUG INTERACTION WALLET CARD

| NIH NATIONAL CANCER INSTITU<br>EMERGENCY INFORMATION | NIH NATIONAL CANCER INSTITU | NIH NATIONAL CANCER INSTITU<br>DRUG INTERACTIONS | NIH NATIONAL CANCER INSTITU |
|---|---|---|---|
| **Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.** | Tell your doctors **before** you **start** or **stop** any medicines.<br>**Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!** | **Carry this card with you at all times**<br>Darolutamide must be used very carefully with other medicines. | |
| **Patient Name:**<br>**Diagnosis:**<br>**Study Doctor:**<br>**Study Doctor Phone #:**<br>**NCI Trial #:** NRG-GY033<br>**Study Drug(S):**<br>Darolutamide<br>Leuprolide Acetate<br>Exemestane | **Use caution and avoid the following drugs if possible:**<br>Use of herbal therapies is not recommended as their safety and potential drug interactions are generally unknown. | Your healthcare providers should be aware of any medicines that are used as other cancer directed therapies, systemic treatment with ketoconazole, estrogen or progesterone therapies, or androgen receptor inhibitors.<br>**Before prescribing new medicines,** your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.<br>Version 05/2023 | |
| **For more information:** 1-800-4-CANCER<br>cancer.gov \| clinicaltrials.gov | **For more information:** 1-800-4-CANCER<br>cancer.gov \| clinicaltrials.gov | **For more information:** 1-800-4-CANCER<br>cancer.gov \| clinicaltrials.gov | **For more information:** 1-800-4-CANCER<br>cancer.gov \| clinicaltrials.gov |

*Fold at dotted lines*:

**APPENDIX V-PRIOR TO CYCLE 1 DAY 1-DAROLUTAMIDE AND EXEMESTANE PATIENT DRUG DIARY**

Today's Date _____ Cycle # _____
Patient Name _____ Patient Study ID _____

1. Complete this form 7-14 prior to the start of Cycle 1, Day1.
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment.
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, take it as soon as you remember. Do not take two doses together to make up for the missed dose. If a dose is missed write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

**DAROLUTAMIDE**
Take _____ (number) _____ mg two times a day.
**Darolutamide must be taken with food.**

**EXEMESTANE**
Take _____ (number) _____ mg tablet once a day.
**Exemestane should be taken after a meal.**
*Enter time taken below under as either AM or PM*

| Day | Date | 300 mg | AM | PM | Day | Date | 25 mg | AM | PM |
|---|---|---|---|---|---|---|---|---|---|
| *1* | 1/1/2023 | 2 | 7:00 | 7:00 | *1* | 1/1/2023 | 1 | 8:00 | - |
| 1 | | | | | 1 | | | | |
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Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date: _____

## APPENDIX VI- DAROLUTAMIDE AND EXEMESTANE PATIENT DRUG DIARY

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

1. Complete one form for each cycle (28 days).
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment.
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, take it as soon as you remember. Do not take two doses together to make up for the missed dose. If a dose is missed write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

**DAROLUTAMIDE**

Take _____ (number) _____ mg two times a day.

**Darolutamide must be taken with food.**

**EXEMESTANE**

Take _____ (number) _____ mg tablet once a day.

**Exemestane should be taken after a meal.**

*Enter time taken below under as either AM or PM*

| Day | Date | 300 mg | AM | PM | Day | Date | 25 mg | AM | PM |
|---|---|---|---|---|---|---|---|---|---|
| *1* | 1/1/2023 | 2 | 7:00 | 7:00 | *1* | 1/1/2023 | 1 | 8:00 | - |
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Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date: _____

## APPENDIX VII- GUIDANCE TO IDENTIFY DRUG INDUCED LIVER INJURY (DILI)

This appendix describes the recommended work up to be followed in order to identify a potential drug induced liver injury (DILI). It is not intended to be a comprehensive guide for the management of elevated liver function tests. During the study the investigator should remain vigilant for increases in liver function tests. The investigator is responsible for determination of the liver function test alterations nature at any point during the study. In cases the Investigator suspects DILI, the Sponsor Medical Representative has to be informed as soon as possible.

DILI is a diagnosis of exclusion. In case of liver enzyme alterations, please consider the following comprehensive work-up and report results in the eCRF (under "unscheduled visits/unscheduled labs" page):

- Please obtain, and report in the eCRF, a detailed, "liver-focused" medical history including liver metastasis/ liver cancer, alcohol-related liver disease, non-alcoholic steatohepatitis, liver cirrhosis, viral hepatitis, ischemic/congestive hepatic injury, vaccination, biliary obstruction, hemochromatosis, pancreatitis, recent systemic infection/sepsis, COVID-19 Infection, autoimmune disease, alcohol abuse or drug abuse and any other clinically relevant information.

- Please investigate and report, in the eCRF, a complete list of concomitant medications, prior chemotherapy or hormonal therapy, antineoplastic drugs, herbal substances, nutritional supplements, complementary and alternative medicines, or exposure to any hepatotoxic agents.

- **Imaging**
  - Abdominal imaging (e.g., Ultrasound, CT, and MRI)
- **Serological tests**
  - Hepatitis A testing: lgM Anti-HAV
  - Hepatitis B testing: anti-HBc lgG, lgM, HBsAg, HBV DNA
  - Hepatitis C testing: anti HCV, HCV RNA (PCR)
  - Hepatitis E testing: anti-HEV (lgG, lgM); HEV RNA
  - Alcoholic hepatitis: carbohydrate-deficient transferrin
  - Anti-Cytomegalovirus (CMV) IgM Antibodies
  - Anti-Epstein Barr Virus (EBV) IgM Antibodies
  - Herpes Simplex IgG, IgM
  - Autoantibody and immunoglobulin testing: ANA, ASMA, ANCA, p-ANCA, AMA
  - Quantitative Ig G, IgM and IgA (optional)
  - Metabolic disease: Alpha-1-antitripsin, ceruloplasmin, iron, ferritin, GGT, LDH, PT, INR, transferrin, transferrin saturation

- **Other tests**
  - PT-INR
  - Serum albumin
  - CK Values
  - Amylase, Lipase

## APPENDIX VIII - CTEP COLLABORATIVE AGREEMENTS LANGUAGE

The agent supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as

appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   E-mail: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.