A RANDOMIZED PHASE III TRIAL OF OLANZAPINE VERSUS MEGESTROL ACETATE FOR CANCER-ASSOCIATED ANOREXIA

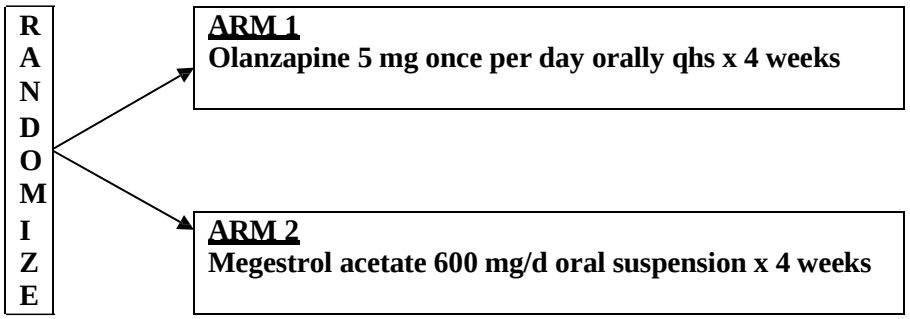
Eligibility Criteria (see Section 3.0)

- Diagnosis of advanced cancer. (See §3.2.1)

Required Initial Laboratory Values
Serum Creatinine: ≤2.0 mg/dL
AST/ALT: ≤3 x upper limit of normal (ULN)
Glucose: ≤140 mg/dL
Granulocytes: > 1000/hpf

- Patient-reported 2-month weight loss of at least 5 pounds (2.3 kilograms) and/or physician-estimated caloric intake of less than 20 calories/kilogram of body weight per day. (See §3.2.2)
- Appetite score of 4 or worse on the "Please rate your appetite…."question (See §3.2.3)
- Not receiving ongoing tube feedings or parenteral nutrition. (See §3.2.4)
- Not currently using adrenal steroids. (See §3.2.5)
- No use of androgens, progesterone analogs, or other appetite stimulants.(See§3.2.6)
- Patient should not have poorly controlled hypertension or congestive heart failure at registration. (See §3.2.7)
- No obstruction of the alimentary canal, malabsorption, or intractable vomiting. (See §3.2.8)
- Not currently using olanzapine for another medical condition or had previously used olanzapine for chronic nausea or for any pre-existing psychotic disorder.(See §3.2.9)
- No impaired decision making capacity (See §3.2.10).
- No presence of a hormone-sensitive tumor (See §3.2.11).
- No previous blood clot. (See §3.2.12)
- No history of poorly controlled diabetes (See §3.2.13).
- No LMD or known brain metastases. (See §3.2.14)
- No history of hypersensitivity to olanzapine or megestrol acetate (See §3.2.15)
- No COVID-19 infection in the past that, in the opinion of the treating physician, had left patients with compromised taste. (See §3.2.16)
- Not pregnant and not nursing. (See §3.2.17)
- Age ≥ 18 years. (See §3.2.18)
- ECOG Performance Status 0, 1 or 2. (See §3.2.19)
- Life expectancy of 3 months or longer. (See §3.2.20)
- No treatment with another antipsychotic agent (See §3.2.22)
- Participants must be able to speak and read English or Spanish (See §3.2.23)

Schema



Treatment will continue for up to 4 weeks, unless the patient declines therapy or has unacceptable adverse events.

whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agents.
- Clinicians should be aware of drug interactions between the agents used in this study and drugs that can prolong the QT interval, that can induce or inhibit CYP1A2, or that can function as an anticholinergic. Clinicians should use their clinical judgment to decide whether the doses and duration of such agents is such that they can be used concurrently with the medications prescribed in this study

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease: Diagnosis of advanced cancer.**

___ **3.2.2 Patient-reported 2-month weight loss of at least 5 pounds (2.3 kilograms) and/or physician-estimated caloric intake of less than 20 calories/kilogram of body weight per day.**

___ **3.2.3 The patient must perceive loss of appetite and/or weight as a problem; and have an appetite score of 4 or worse on the "Please rate your appetite…."question that requires a patient response on a 0-10 numeric rating scale. (See Appendix I)**

___ **3.2.4 Not receiving ongoing tube feedings or parenteral nutrition at the time of registration.**

___ **3.2.5 Not currently using systemic adrenal steroids (with the exception of short-term dexamethasone within 3 days of chemotherapy for control of chemotherapy side effects).**

____ **3.2.6 No use of androgens, progesterone analogs, or other appetite stimulants within the past month.**

____ **3.2.7 Patient should not have poorly controlled hypertension, defined as multiple blood pressure readings with systolic levels above 160 and diastolic levels above 100 or congestive heart failure at registration.**

____ **3.2.8 Patient should not have an obstruction of the alimentary canal, malabsorption, or intractable vomiting** (defined as vomiting more than 3 times per day over the preceding week).

____ **3.2.9 Not currently using olanzapine for another medical condition** or had previously used olanzapine for chronic nausea or for any pre-existing psychotic disorder.

____ **3.2.10 Patients with impaired decision-making capacity from any etiology** (such as with a diagnosis of dementia or memory loss) are not eligible for this study.

____ **3.2.11 No presence of a hormone-sensitive tumor, such as breast, endometrial, or prostate cancer** (this exclusion criterion is intended to circumvent any confounding antineoplastic effects of megestrol acetate).

____ **3.2.12 Patient should not have had a previous blood clot at any time in the past.**

____ **3.2.13 No history of poorly controlled diabetes.**

____ **3.2.14 No symptomatic leptomeningeal disease or known brain metastases as these patients may have difficulty taking oral medications.**

____ **3.2.15 No history of hypersensitivity to olanzapine or megestrol acetate.**

____ **3.2.16 No COVID-19 infection in the past that, in the opinion of the treating physician, had left patients with compromised taste, which has not resolved at the time of registration.**

____ **3.2.17 Not pregnant and not nursing, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.**

Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 14 days prior to registration is required.

____ **3.2.18 Age ≥ 18 years.**

____ **3.2.19 ECOG Performance Status 0, 1 or 2.**

____ **3.2.20 Estimated life expectancy of 3 months or longer.**

____ **3.2.21 Required Initial Laboratory Values:**

Serum Creatinine	≤ 2.0 mg/dL
AST or ALT	≤ 3 x upper limit of normal (ULN)
Glucose	≤ 140 mg/dL
Granulocytes	> 1000/hpf

___ **3.2.22 No treatment with another antipsychotic agent, such as risperidone, quetiapine, clozapine, butyrophenone within 30 days of enrollment.**

___ **3.2.23 In order to complete the mandatory patient-completed measures, participants must be able to speak and/or read English or Spanish.** Sites seeking to enroll Spanish-speaking patients should have access to Spanish speaking staff on site or through the use of a translation service to be able to conduct the informed consent discussion in Spanish, and to conduct the weekly phone calls**.**