NRG-GY016
SCHEMA

Recurrent or persistent clear cell carcinoma of the ovary

MK-3475 (Pembrolizumab) 200 mg IV q 3 weeks and epacadostat 100 mg po BID (Cycle = 21 days) until disease progression or adverse effects prohibit further treatment.

Cycle = 21 days
Accrual Goal: 23

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Statistics and Data Management Center (via the contact list on the NRG web site). For radiation therapy-related eligibility questions, please contact RTQA (via the contact list on the NRG web site). *[Insert appropriate center/person and location of contact information]*

3.1 Patient Selection Guidelines

Although the guidelines provided below in 3.1.1 and 3.1.2 are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other 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.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Submission of formalin-fixed, paraffin embedded tumor tissue is required for all patients. Investigators should check with their site Pathology Department regarding release of biospecimens before approaching patients about participation in the trial. (See details of X submissions in Sections 9 and 10.)

3.2 Eligibility Criteria

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

3.2.1 Primary tumors must be at least 50% clear cell histomorphology in order to be eligible or have a histologically documented recurrence with at least 50% clear cell histomorphology. Recurrence should be biopsy proven as per standard of care unless the tumor is located in an area deemed unsafe to biopsy. Histologic confirmation of the original primary tumor is required via the pathology report.

The percentage of clear cell histomorphology must be documented in the pathology report or in an addendum to the original report. If slides of the primary tumor are not available for review due to disposal of slides by the histology laboratory (typically 10 years after diagnosis), a biopsy of the recurrent or persistent tumor is required to confirm at least 50% clear cell histomorphology, as long as tumor is located in an area deemed safe to biopsy. The percentage of clear cell involvement must be documented in the pathology report or in an addendum to the original report.

3.2.2 All patents must have measurable disease, and at least one "target lesion" to be used to assess response as defined by RECIST 1.1. 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, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.2.3 Appropriate stage for study entry based on the following diagnostic workup:

- History/physical examination within 28 days prior to registration;
- Imaging of target lesions within 28 days prior to registration;
- Further protocol-specific assessments
  - Recovery from adverse effects of recent surgery, radiotherapy or chemotherapy
  - Any other prior therapy directed at the malignant tumor including chemotherapy,

and biologic/targeted agents must be discontinued at least 4 weeks prior to registration. Any hormonal therapy directed at the malignant tumor must be discontinued at least 2 weeks prior to registration.
    - Any prior radiation therapy must be completed at least 4 weeks prior to registration, and progression must be outside the radiation field.
    - At least 4 weeks must have elapsed since any major surgery prior to registration.

3.2.4 Age ≥ 18

3.2.5 The trial is open only to women with recurrent or progressive clear cell carcinoma of the ovary

3.2.6 Patients must have an ECOG Performance Status of 0 or 1 within 28 days prior to registration;

3.2.7 Patients must have had one prior platinum-based chemotherapy for management of primary disease. Patients are allowed to receive, but are not required to receive, up to two additional cytotoxic regimens for management of recurrent or persistent disease.

3.2.8 Adequate hematologic function within 14 days prior to registration defined as follows:

- ANC ≥ 1,500/ul
- Platelets ≥ 100,000/ul
- Hgb ≥ 8.0g/dL (Note: the use of transfusion of other intervention to achieve a Hgb ≥ 8.0 g/dL is acceptable)

3.2.9 Adequate renal function within 14 days prior to registration defined as follows:

- Creatinine ≤ 1.5 x institutional upper limit of normal (ULN) or CrCl ≥ 60mL/min using Cockcroft-Gault formula

3.2.10 Adequate hepatic function within 14 days prior to registration defined as follows:

- Bilirubin ≤ 2.5 x ULN
- ALT and AST ≤ 2.5 x ULN

3.2.11 Normal thyroid function testing (TSH) within 14 days prior to registration

3.2.12 Negative pregnancy test in women of childbearing potential

3.2.13 Women of childbearing potential who are sexually active should be willing and able to use medically acceptable forms of contraception for the course of the study through 120 days after the last dose of MK-3475 (pembrolizumab). Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile, who have had a hysterectomy and/or bilateral oophorectomy) do not require contraception.

3.2.14 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.3 Ineligibility Criteria

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

3.3.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years

3.3.2 Patients who have had prior therapy with MK-3475 (pembrolizumab) or epacadostat or with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathways.

3.3.3 History of severe hypersensitivity reaction to any monoclonal antibody.

3.3.4 Patients with active auto-immune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjogren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.3.5 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure and unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3.6 Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures which are not controlled with non-enzyme inducing anticonvulsants, and/or epidural disease, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months prior to the first date of study treatment.
Those with brain metastases are permitted as long as they have been treated with brain radiation therapy and have been documented stability 4 weeks following completion of brain radiation therapy.

3.3.7 In order for patients with human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) to be eligible, they must be on a stable highly active antiretroviral therapy (HAART) regimen with no drug-drug interaction with UGT1A9, have CD4+ counts > 350, with no detectable viral load on quantitative PCR, and no opportunistic infection.

3.3.8 Patients with treated hepatitis viral infections (Hepatitis B and C) are eligible if they have completed definitive treatment at least 6 months prior, have no detectable viral load on quantitative PCR, and LFTs meet eligibility requirements.

3.3.9 Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration.

3.3.10 Therapy with monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitor (SSRIs) within the last 4 weeks or history of Serotonin Syndrome. Concomitant use of monoamine oxidase inhibitors with epacadostat (INCB024360) is prohibited.

3.3.11 Patients who have had evidence of active or acute diverticulitis, intra-abdominal abscess, abdominal/pelvic fistula, gastrointestinal perforation, GI obstruction and/or who require parenteral hydration and/or nutrition.

3.3.12 Epacadostat (INCB024360) is a substrate of CYP3A4, CYP1A2, CYP2C19, UGT1A9, P-gp, and BCRP. Use caution when administered with strong inhibitors/inducers of these isoenzymes and transporter proteins. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. Appendix V (Patient Drug Information Handout and Wallet Card) should be provided to patients.

3.3.13 History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval >480 milliseconds is excluded (corrected by Fridericia). In the event that a single QTc is >480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is <480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 msec), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be <340 milliseconds if JTc is used in place of QTc. Subjects with left bundle branch block are excluded.

3.3.14 Patients who are pregnant or nursing.