NRG ONCOLOGY

NRG-GY016
(ClinicalTrials.gov NCT* #03602586*)

A Phase II Study of MK-3475 (Pembrolizumab) (NSC #776864) + Epacadostat (NSC #766086) in Recurrent Clear Cell Carcinoma of the Ovary.

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI).

Lead Organization: NRG / NRG Oncology

Participating Organizations
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
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Protocol Agent

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NRG-GY016
A Phase II Study of MK-3475 (Pembrolizumab) (NSC #776864) + Epacadostat (NSC #766086) in Recurrent Clear Cell Carcinoma of the Ovary.

CONTACT INFORMATION (11 -JUN-2020)

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	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. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923 or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU members' website located at (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System RSS.

For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

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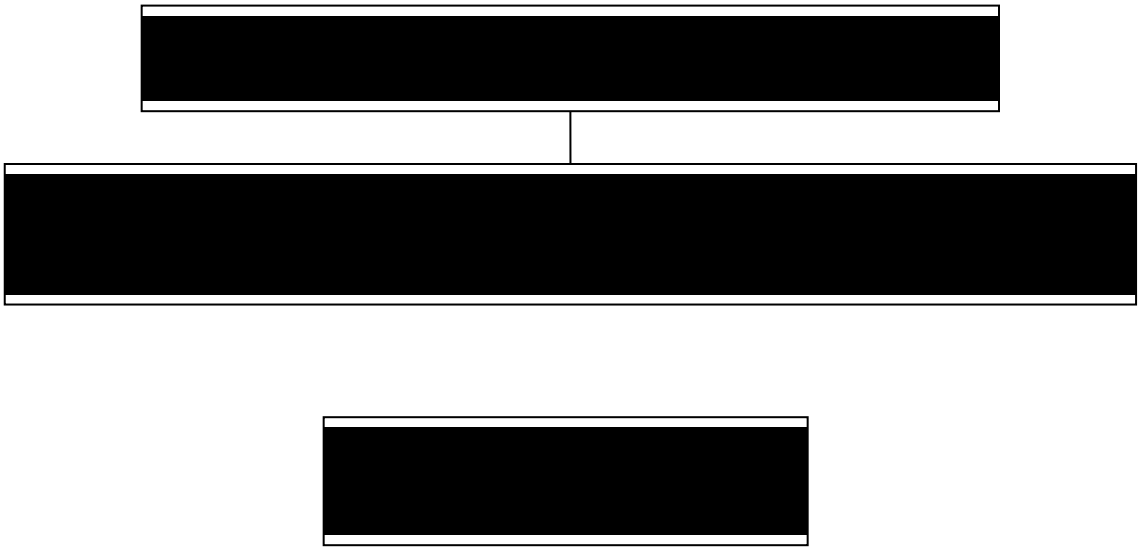

1. OBJECTIVES

1.1 Primary Objective

1.1.1 To assess the objective tumor response (proportion of objective response by RECIST 1.1 criteria) of the combination of MK-3475 (pembrolizumab) and epacadostat in patients with recurrent or persistent clear cell carcinoma of the ovary.

1.2 Secondary Objectives

1.2.1 To determine the nature and degree of toxicity of MK-3475 (pembrolizumab) + epacadostat as assessed by CTCAE in patients with recurrent or persistent clear cell carcinoma of the ovary.

1.2.2 To estimate the progression-free survival (PFS) and overall survival (OS) in patients treated with combination of MK-3475 (pembrolizumab) and epacadostat.

1.3

1.3.1

1.3.2

1.3.3

2. BACKGROUND

2.1 Recurrent Clear Cell Carcinoma of the Ovary

Clear cell carcinoma of the ovary has an estimated prevalence of 3-12% of all epithelial ovarian carcinomas (Anglesio et al., 2011). Clear cell carcinomas of the ovary have a distinct clinical behavior when compared to other epithelial ovarian carcinomas, with a worse prognosis especially in advanced disease (Sugiyama et al., 2000; Jenison et al., 1989; Mackay et al., 2010). The low survival rates in clear cell carcinomas of the ovary may reflect their lack of sensitivity to platinum-based chemotherapy (Sugiyama et al., 2000; Takano et al., 2006). Recurrent or persistent clear cell carcinoma of the ovary is particularly chemoresistant with response rates of <10% (Takano et al., 2008). Not only is this histologic subtype of ovarian cancer disproportionately represented in ovarian cancer clinical trials, the lack of effective therapy leads to clear cell carcinoma having proportionately increased representation for limited options in the recurrent setting. There is an unmet need for therapeutic options in this disease type, given the particularly poor prognosis of this tumor type upon recurrence, the lack of effective treatment, and the rarity of this disease. Future treatment of this disease may rest on novel therapies.

2.2 PD-1 and PD-L1 Targeting

PD-1 receptor is expressed by activated T-cells resulting in reduced cytokine production, cytolytic activity, and lymphocyte proliferation. The activation of PD-1 represents a major mechanism for suppressing anti-cancer T-cell responses (Menderes et al., 2016). These effects are mediated through its ligands PD-L1 and PD-L2. Many types of human tumors, including ovarian cancer, express PD-L1 (Kooi et al., 1996). When PD-L1 binds with PD-1, T-cell activity is attenuated, preventing the immune system from eliminating the tumor at the tissue level (Mellman et al., 2011). Blockade of PD-1 or PD-L1 with monoclonal antibodies can enhance T-cell activity, augmenting the anti-cancer immune response with the potential to produce durable clinical responses (Brahmer et al., 2012; Topalian et al., 2012). PD-L1 expression is associated with poor prognosis in ovarian cancer (Zhang et al., 2003) and PD-L1 also promotes progression of ovarian cancer by inducing host immune-suppression of peripheral cytotoxic CD8+ T cell lymphocytes (Abiko et al., 2013).

2.3 MK-3475 (Pembrolizumab) Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (Dong et al., 2002; Sharpe et al., 2002; Brown et al., 2003; Francisco et al., 2010; Thompson et al., 2007). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Talmadge et al., 2007; Usubutun et al., 1998]. The structure of murine PD-1 has been resolved (Al-Shibli et al., 2008). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3, PKCϴ and the CD3 T-cell signaling cascade (Talmadge et al., 2007; Deschoolmeester et al., 2010; Diez et al., 1998; Galon et al., 2006). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins (Hiraoka et al., 2010; Nobili et al., 2008]. PD-1 was shown to be expressed on activated lymphocytes

including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells (Hodi et al., 2010; Kloor 2009). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (Hillen et al., 2008). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors (Lee et al., 2008; Leffers et al., 2009; Nishimura et al., 2000; Hiraoka et al., 2010). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (Hiraoka et al., 2010). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) (Liotta et al., 2010). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (Pembrolizumab) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 (Pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and patients with metastatic non-small cell lung cancer whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

2.4 MK-3475 (Pembrolizumab) Preclinical and Clinical Study Data

2.4.1 Nonclinical Toxicology

The safety of MK-3475 (pembrolizumab) was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered IV doses of 6, 40 or 200 mg/kg once a week in the 1-month study and once every 2 weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the NOAEL in both studies was ≥200 mg/kg, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

The carcinogenic potential of MK-3475 (pembrolizumab) in long-term animal studies, as well as the genotoxic potential of MK-3475 (pembrolizumab) have not been evaluated as these studies are not required to support treatment of cancer patients.

Animal reproduction studies have not been conducted with MK-3475 (pembrolizumab). The central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of MK-3475 (pembrolizumab) during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

Developmental toxicity studies have not been conducted with MK-3475 (pembrolizumab). There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat dose toxicity studies.

2.4.2 Clinical Efficacy

Many clinical trials have been conducted to evaluate the efficacy of MK-3475 (pembrolizumab) to treat various cancers. MK-3475 (pembrolizumab) has demonstrated robust, substantial, and clinically meaningful benefit in the treatment of melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma (UC), and microsatellite instability-high (MSI-H) tumors based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria and immune-related RECIST (irRECIST) recommendations. For classical Hodgkin lymphoma (cHL), demonstration of clinically meaningful benefit was based on Revised Response Criteria for Malignant Lymphoma (2007) from the International Working Group (IWG).

For the treatment of unresectable or metastatic melanoma, MK-3475 (pembrolizumab) demonstrated superior efficacy over available treatment options (IPI, Investigator's choice chemotherapy) in participants with advanced melanoma who were treatment-naïve, as well as those who progressed on prior therapy, including IPI.

MK-3475 (Pembrolizumab) provided substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. In previously treated participants with PD-L1 TPS ≥1% and disease progression following platinum-containing chemotherapy, MK-3475 (pembrolizumab) provided a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy. For participants with previously untreated metastatic NSCLC whose tumors express high levels of PD-L1, MK-3475 (pembrolizumab) demonstrated significant improvements in PFS and OS over standard of care chemotherapy.

For the treatment of advanced HNSCC in a heavily pretreated population, MK-3475 (pembrolizumab) demonstrated a clinically meaningful response rate and a prolonged duration of response that is substantially distinct from what is expected with standard of care in previously treated participants with HNSCC, and points to the meaningful clinical benefit of MK-3475 (pembrolizumab).

MK-3475 (Pembrolizumab) for the treatment of relapsed or refractory cHL, has demonstrated durable, robust, clinically meaningful responses in this heavily pretreated population that generally included standard front-line therapies, salvage therapies, auto-SCT if eligible with chemo-sensitive disease, other single agent or combination chemotherapy regimens as needed, and with or without brentuximab vedotin (BV).

For the treatment of urothelial carcinoma (UC) in participants who have not received prior chemotherapy and are cisplatin-ineligible, MK-3475 (pembrolizumab) demonstrated a clinically meaningful ORR in participants with locally advanced or metastatic UC. In participants with locally advanced or metastatic UC who have received platinum-containing chemotherapy, treatment with MK-3475 (pembrolizumab) demonstrated a significant improvement in OS and a clinically meaningful benefit in durable responses compared with standard of care therapies.

In participants with MSI-H tumors, MK-3475 (pembrolizumab) provided evidence of clinically meaningful benefit over standard treatments, regardless of tumor histology.

2.4.3 Clinical Safety

MK-3475 (Pembrolizumab) has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related adverse events (AEs) (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%). Furthermore, the frequency of immune-mediated adverse events of special interest (AEOSI) is low, and these events are readily managed in the clinical setting.

MK-3475 (pembrolizumab) is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. MK-3475 (Pembrolizumab) is an immunomodulatory agent, and based on this mechanism of action, immune-mediated AEs are of primary concern. The important identified risks for MK-3475 (pembrolizumab) are of an immune-mediated nature, and included the following in the last IB (v13): pneumonitis; colitis; hepatitis; nephritis; endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism), and Type I diabetes mellitus; uveitis; myositis; Guillain-Barré syndrome; pancreatitis; myocarditis; severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and “solid organ transplant rejection following MK-3475 (pembrolizumab) treatment in donor organ recipients” (risk applicable to post-marketing setting only, as such patients are currently excluded from Merck clinical trials with MK-3475 (pembrolizumab)). The majority of immune-mediated AEs were mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy.

In addition to the immune-related risks noted above, infusion-related reactions are also an important identified risk for MK-3475 (pembrolizumab); however, they are not considered immune-mediated.

Consultation with the appropriate medical specialist should be considered when investigating a possible immune-related adverse event (irAE). These events can occur at times ranging from after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and infrequently require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment, and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers) when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications because the majority of irAEs are reversible with the use of steroids and other immune suppressants.

2.5 Rationale for the Study and Selected Patient Population

In studies evaluating activity of anti-PD-1 or anti-PD-L1 antibodies in ovarian cancer, eligible patients have included all histologic subtypes of ovarian cancer, mainly high grade serous histology (Haminishi et al., 2015; Disis et al., 2015). Notably, in two studies, durable objective responses were seen in patients with ovarian clear cell carcinoma. In a phase II study by Hamanishi et al. (2015), 20 patients with platinum-resistant ovarian cancer were treated with nivolumab, an anti-PD-1 antibody. The disease control rate was 45%. Two patients had a durable complete response (CR), one of whom had clear cell carcinoma with recurrent disease and peritoneal dissemination. After two courses of nivolumab, the peritoneal lesions disappeared and CA-125 decreased to normal range. The patient completed a 1-year trial of nivolumab and continued to experience a CR at time of study publication. In another phase II study by Disis et al. (2015), avelumab, an anti-PD-L1 antibody, was evaluated in recurrent ovarian cancer patients with multiple previous lines of chemotherapy. Among 75 patients, there was an overall response rate of 17.4% and stable disease in 47.8%. Tumor shrinkage by ≥30% was observed in 14.7% of patients, including 2 patients with clear cell histology. These cases are compelling given the general chemo-refractory state of recurrent ovarian clear cell carcinomas. These immune checkpoint inhibitors may have particular benefit for patients with this rare histologic subtype. At this point however, there have been no studies of immunotherapy dedicated to clear cell carcinomas of the ovary.

2.6 Rationale for Combination Therapy with IDO-1 Inhibitor

Although these early studies of immune checkpoint inhibitors in recurrent ovarian cancer have demonstrated promise, the overall response rate with these single agents is approximately 15%. In order to improve these results, strategies incorporating combinations of immunotherapy is needed. Regulatory T cells (Tregs) have an important role in ovarian cancer pathogenesis and outcome (Sato et al., 2005; Wolf et al., 2005). Low ratio of CD8+ T cells to CD4+CD25+FoxP3+ Tregs is associated with poor survival, and therefore Tregs are a potential target to disrupt local immune suppression in ovarian cancer (Preston et al., 2013). In clear cell ovarian cancers specifically, inherited variants in genes encoding Treg related immune molecules are significantly associated

with poorer survival compared to serous cancers (Goode et al., 2013). Moreover, in contrast to high grade serous cancers where the increase of CD8+ T cells is associated with improved survival (HR 0.57, 95%CI 0.49-0.65, p=4.2 x 10^{-16}), in clear cell cancers there is no association between CD8+ T cells and survival (HR 0.92, 95% CI 0.61-1.39, p=0.50), possibly because of the prominent role of Tregs in this subtype (Goode et al., 2017). An agent that can address the high degree of Tregs in the tumor microenvironment in combination with an anti-PD-1 antibody could enhance the immunotherapy effect that has been initially seen in clear cell carcinoma.

Indoleamine 2, 3-dioxygenase 1 (IDO1) is an enzyme that catalyzes oxidative catabolism of the amino acid tryptophan (Trp) to kynurenine (Takikawa et al., 2005). This catabolism of Trp results in the inhibition of antitumor cell–mediated immune responses. Histologic evaluation of most human cancers shows extensive infiltration by inflammatory and immune cells, suggesting that the immune system does recognize and respond to the presence of the malignancy (Galon et al., 2006), but in most cases the immune response is ineffective in inhibiting or eradicating tumor growth. Many tumor cells or the infiltrating immune cells overexpress IDO1, and there have been multiple lines of evidence to suggest that IDO1 is a key regulator in the immunosuppressive mechanisms responsible for tumor escape from immune surveillance (Liu et al., 2009). Therefore, inhibition of this enzyme may provide a unique method to treat malignancies, either alone or in combination with chemotherapeutics or other immune-based therapies.

[redacted]

2.7 Epacadostat Pharmaceutical and Therapeutic Background

Epacadostat (INCB024360) is a potent, selective oral inhibitor of IDO1. Inhibiting IDO1 leads to decreased kynurenine, and downstream downregulation of Tregs, thereby increasing the antitumor immune response. Because IDO1 catabolism of tryptophan (Trp) inhibits T-cell–mediated immune responses and IDO1 expression has been shown to be elevated in many human cancers, IDO1 inhibition may restore an effective antitumor immune response and may provide a method to treat malignant diseases either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies. [redacted]

[redacted]

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2.8 Epacadostat Preclinical and Clinical Study Data

[redacted]

[redacted]

[redacted]

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[redacted]

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2.8.2 Clinical Efficacy

There is no evidence of clinically meaningful antitumor activity for epacadostat monotherapy. Based on preliminary data from ongoing Study INCB 24360-202, epacadostat in combination with MK-3475 (pembrolizumab) demonstrated promising antitumor activity in subjects with advanced melanoma, head and neck squamous cell carcinoma (HNSCC), NSCLC, UC, and renal cell carcinoma (RCC); the response outcomes in triple negative breast carcinoma (TNBC) and ovarian cancer were consistent with those previously reported for MK-3475 (Pembrolizumab**)** monotherapy in PD-L1–positive subjects.

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2.8.3 [redacted]

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2.9 Epacadostat in combination with MK-3475 (Pembrolizumab)

Preliminary results from a phase I/II study of epacadostat in combination with MK-3475 (pembrolizumab), an anti-PD-1 antibody, have been reported in patients with advanced cancers (Gangadhar et al., 2015). In this dose-escalation and dose-expansion study, patients were given MK-3475 (pembrolizumab) 2 mg/kg IV or 200 mg IV every 3 weeks with epacadostat at doses of 25 mg PO BID, 50 mg BID, 100 mg BID. Nineteen patients were evaluable. Overall response rate was 53% with 3 complete responses. The overall disease control rate was 74%, with an especially profound effect in patients with melanoma. The latest updated results have demonstrated that epacadostat in combination with MK-3475 (pembrolizumab) demonstrates promising anti-tumor activity in patients with advanced melanoma, HNSCC, NSCLC, UC, and RCC with ORRs of 33%-56%. The disease control rates (DCRs) were 50-71%.

In Phase 2 of this study, 294 subjects received ≥ 1 dose of study treatment (epacadostat 100 mg BID + MK-3475 (Pembrolizumab) 200 mg Q3W) and were included in the safety analysis. The median (range) epacadostat exposure was 13.6 (1.0+ to 70.7+) weeks.

Treatment-related TEAEs occurred in 67% of Phase 2 subjects and Grade 3/4 treatment-related TEAEs occurred in 18% of Phase 2 subjects. The most common treatment-related TEAEs were fatigue, rash, nausea, and pruritus. The frequency of Grade 3/4 treatment-related TEAEs was low across all tumor types.

Treatment-related TEAEs leading to dose interruptions occurred in 18% of subjects; the most common were rash (3%), fatigue (3%), and lipase increased (3%). Treatment-related TEAEs leading to dose reductions occurred in 5% of subjects; the most common were rash (2%), fatigue (2%), and lipase increased (1%). Treatment-related TEAEs leading to treatment discontinuation occurred in 4% of subjects; the most common were arthralgia and rash (n = 2 each).

There was 1 treatment-related death due to respiratory failure (secondary to aspiration pneumonia; pneumonitis could not be ruled out). TEAEs of special interest and Grade 3/4 TEAEs of special interest occurred in 11% and 4% of subjects, respectively.

The frequency of Grade 3/4 AEs was low and similar across all tumor types.

Based on this data, a phase III study in melanoma comparing MK-3475 (pembrolizumab) + epacadostat versus MK-3475 (pembrolizumab) alone has been activated (clinicaltrials.gov).

Currently, although there is a Phase I/II study of MK-3475 (pembrolizumab) and epacadostat in patients with selected cancers, which includes ovarian neoplasms (clinicaltrials.gov) to date, there have been no clear cell carcinomas included amongst the enrolled ovarian cancer patients due to the rarity of this subtype. [redacted]

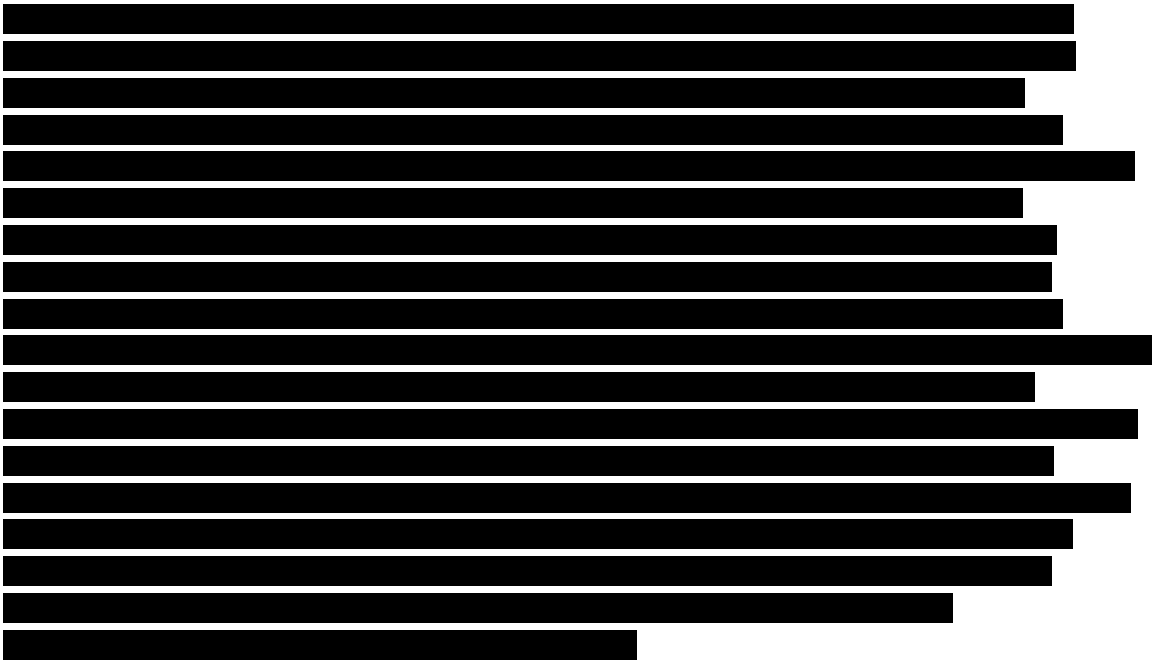
2.10 Rationale for Dose Selection/Regimen: Fixed Dose MK-3475 (Pembrolizumab)

The dose regimen of 200 mg Q3W of MK-3475 (pembrolizumab) is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase I trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent MK-3475 (pembrolizumab). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-

limiting toxicities were observed. This first in human study of MK-3475 (pembrolizumab) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving MK-3475 (pembrolizumab) at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive MK-3475 (pembrolizumab) at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to MK-3475 (pembrolizumab) to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.



2.11 Rationale for Current Trial

Inhibition of the PD-1 receptor is promising with early results demonstrating examples of durable objective responses in patients with clear cell carcinomas of the ovary. However, the immunotherapy studies in ovarian cancer have included all histologic types and there has not been a dedicated study for clear cell carcinomas. It is clear from early studies that a combination approach for immunotherapy is warranted to improve response rates even further. The combination of MK-3475 (pembrolizumab) (anti-PD-1 antibody) and epacadostat (IDO1 inhibitor) has demonstrated promising results in melanoma, such that a phase III trial in melanoma is being conducted with this combination. This combination should be applied to recurrent clear cell carcinomas to determine if the profound effects of PD-1 inhibition can be further enhanced with IDO1 inhibition. For recurrent clear cell ovarian cancer in particular, where historically the response to standard chemotherapy is <10%, an improvement in this outcome is greatly needed.

2.13 Translational Research Background

Recurrent clear cell ovarian cancer (CCOC) has a poor prognosis and limited treatment options. The current protocol tests the combination of the PD-1-blocking monoclonal antibody MK-3475 (pembrolizumab) (PEM) and the IDO-1 inhibitor epacadostat (EPAC) in patients with recurrent CCOC. [redacted]

[redacted]

Regulatory T cells (Tregs) are key peripheral mediators of immunologic self-tolerance and can downmodulate inflammatory responses to self-tissues (Panduro et al., 2016). Ovarian tumors are frequently infiltrated by Tregs, and Tregs are associated with poor prognosis in ovarian cancer (Curiel et al., 2004). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.14 Inclusion of Women and Minorities

NRG Oncology and NRG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin of socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian cancer population treated by participating institutions.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

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 (residual grade 1 toxicity is considered recovered)
- 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 or SSRIs 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.

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

PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Registration (28 calendar days)
History and Physical	≤ 28 days
Vital Signs	≤ 28 days
Performance status	≤ 28 days
Chest imaging (at minimum a chest x-ray, or CT chest)	≤ 28 days
Imaging of target lesion – CT scan or MRI of abdomen and pelvis	≤ 28 days
Electrocardiogram (ECG)	≤ 28 days
Complete blood count with	≤ 14 days

differential •ANC ≥ 1,500/ul • Platelets ≥ 100,000/ul • Hgb ≥ 8.0g/dL	
INR, PTT	≤ 14 days
Creatinine ≤ 1.5 x institutional upper limit of normal (ULN) or CrCl ≥ 60mL/min using Cockcroft-Gault formula	≤ 14 days
•Total Bilirubin ≤ 2.5 x ULN • ALT and AST ≤ 2.5 x ULN	≤ 14 days
Serum glucose	≤ 14 days
TSH	≤ 14 days
CA-125	≤ 14 days
Serum pregnancy test (for women of child-bearing potential)	≤ 14 days

ASSESSMENTS DURING TREATMENTAssessments	Note for Cycle 1***	Prior to Day 1 of each cycle (21 days)	12 weeks after start of treatment	6 weeks (+/- 7 days) for 49 weeks	Every 12 weeks (+/- 7 days) until disease progression or treatment discontinuation
History and Physical		X			
Vital Signs (blood pressure, heart rate, and temperature)		X			
Performance status		X			
Toxicity assessment		X			
Bloodwork – CBC, Creatinine, glucose, Total bilirubin, ALT, AST, TSH		X (≤3 days)			
INR, PTT (if on warfarin)	*	X (≤3 days)			
Serum pregnancy test (if potential for childbearing exists)	**				
CA-125		X (≤3 days)			
Chest imaging (at minimum chest x-ray or CT chest)			X	X	X
Radiographic tumor measurement			X	X	X
Patient diary documenting epacadostat dosing		X			

* Patients who are on warfarin should have INR and PTT repeated on Day 4 and Day 7 of cycle 1.

**Women of childbearing potential should repeat serum pregnancy test at 72 hrs of epacadostat dosing.

***Do not need to repeat routine bloodwork prior to Cycle 1, Day 1 if already completed within 14 days.

ASSESSMENTS IN FOLLOW UP

Assessments (unless consent is withdrawn and patient does not remain on trial)	From end of treatment: q3 mos. x 2 yrs.; q6 mos. x 3 years (either in person or by phone follow-up); then annually, unless otherwise indicated based on symptoms or physical signs suggestive of progressive disease.
History & Physical	X
Performance Status	X
Vital signs (blood pressure, heart rate, and temperature)	X
Routine blood tests	X, as clinically indicated during follow-up after treatment
CT scan or MRI of abdomen and pelvis to measure detectable tumor	*
	For 3 years (either in person or by phone follow-up), unless consent is withdrawn.
Monitor patients for delayed toxicity and survival following disease progression	X

*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).

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Treatment Plan

All patients will receive MK-3475 (pembrolizumab) 200 mg IV q 3 weeks and epacadostat 100 mg orally twice a day continuously until disease progression or adverse effects prohibit further treatment. A cycle equals 21 days.

5.1.1 Patients will be given a Patient Medication Calendar to complete daily for epacadostat (Appendix IV). The Patient Medication Calendar should be reviewed prior to the start of each cycle.

Epacadostat

Route of Administration: Epacadostat will be administered as an oral tablet.

Dose to be Administered: The dose of epacadostat will be 100 mg orally twice a day, in the morning and evening, approximately 12 hours apart.

Dosing Instructions: Oral, may be administered without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next

scheduled dose should be taken at the usual time. If a patient vomits after taking a tablet, the dose should be skipped.

5.1.2 MK-3475 (Pembrolizumab)

Route of Administration: MK-3475 (Pembrolizumab) will be administered as an IV infusion.

Dose to be Administered: The dose of MK-3475 (pembrolizumab) will be 200 mg (fixed dose) IV every 3 weeks.

Dosing Instructions: Patients will receive MK-3475 (pembrolizumab) as an IV infusion over 30 minutes. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of 25-40 minutes is permitted (i.e., infusion time is 25-40 minutes).

Preparation and Administration: See Section 9.1 for specific instructions for the preparation of the MK-3475 (pembrolizumab) infusion fluid and administration of infusion solution.

5.1.3 A patient will be permitted to have an infusion delayed up to 7 days (without this 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 rescheduled). Documentation to justify this decision should be provided, and the Study Chair should be notified.

It will be acceptable for individual infusions to be delivered within a 24-hour window before or after the protocol-defined date. 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 (3 days past due).

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of MK-3475 (pembrolizumab) and 30 days after the last dose of MK-3475 (pembrolizumab) should be recorded. Concomitant medications administered after 30 days after the last dose of MK-3475 (pembrolizumab) should be recorded for serious adverse events (SAEs) and events of clinical interest (ECIs) as defined in Section 7.

Epacadostat (INCB024360) is a substrate of CYP3A4, CYP1A2, CYP2C19, UGT1A9, P-gp, and BRCP. Use caution when administering with strong inhibitors/inducers of these isoenzymes and transporter proteins. Because there is a potential for interaction of epacadostat (INCB024360) with other concomitantly administered drugs. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix V (Patient Drug Information Handout and Wallet Card) should be provided to patients.

Caution should be exercised with concomitant administration of warfarin. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat (INCB024360).

5.2.2 Prohibited Therapies

Patients are prohibited from receiving the following therapies during treatment on this trial:

-
- Immunotherapy not specified in this protocol;
- Chemotherapy not specified in this protocol;
- Radiation therapy not specified in this protocol;
- Investigational agents other than MK-3475 (pembrolizumab) and epacadostat;
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. The use of physiologic doses of corticosteroids (defined as 10 mg prednisone) are acceptable, however site investigators should consult with the Study Chair for any dose higher than 10 mg prednisone.
- Epacadostat (INCB024360) may cause an increase in serotonin levels which has the potential to precipitate serotonin syndrome when administered in combination with monoamine oxidase (MAO) inhibitors or serotonergic agents. Concomitant use of MAO inhibitors or serotonergic agents is prohibited.

Note: The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

Patients who, in the assessment of the treating investigator, require the use of any of the aforementioned treatments for clinical management should be removed from protocol treatment. Patients may receive other medications that the investigator deems to be medically necessary.

See Section 3.3, which describes other medications, which are prohibited in this trial.

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,
- 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.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Adverse Drug Reactions requiring Discontinuation or Delays:

The following adverse drug reactions (ADRs) require permanent treatment discontinuation of MK-3475 (pembrolizumab) and epacadostat:

6.1.1 Any Grade 4 ADRs require permanent treatment discontinuation with MK-3475 (pembrolizumab) and epacadostat except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

6.1.2 Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) do not improve to Grade 0-1 within 8 weeks of last dose.

6.1.3 Unable to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 8 weeks.

6.1.4 Any Grade 3 (severe) treatment-related or immune-mediated adverse reaction occurs.

6.1.5 Patients who experience an unacceptable adverse event strictly due to epacadostat such that the patient requires permanent treatment discontinuation of epacadostat alone, following resolution of toxicity to ≤ grade 1 and permission from the Study Chair or Co-Chair, the patient can continue the use of MK-3475 (pembrolizumab) alone. This should be confirmed with the Study Chair or Co-Chair on an individual basis. The same management guidelines should be followed, and any patient with any further unacceptable adverse events while receiving MK-3475 (pembrolizumab) alone should be taken off study treatment permanently.

Tumor assessments should continue if protocol therapy is discontinued for reasons other than disease progression (see protocol section 4).

6.2 MK-3475 (pembrolizumab) Infusion-Related Reactions

Since MK-3475 (pembrolizumab) contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

For Grade 1 infusion reaction: (Mild transient reaction; infusion interruption not indicated; intervention not indicated)
Remain at bedside and monitor subject until recovery from symptoms. Infusion rate may be slowed. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

For Grade 2 infusion reaction: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment [*e.g.*, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids]; prophylactic medications indicated for ≤ 24 hours).
Stop the MK-3475 (pembrolizumab) infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 500 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further MK-3475 (pembrolizumab) will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and acetaminophen 500 to 1000 mg should be administered at least 30 minutes before additional MK-3475 (pembrolizumab) administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 infusion reaction: Grade 3: (Prolonged [*e*.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae); or **Grade 4:** (Life threatening consequences; urgent intervention indicated).

Immediately discontinue infusion of MK-3475 (pembrolizumab). Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. MK-3475 (Pembrolizumab) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids).

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

Table: Infusion Reaction Treatment Guidelines:

NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 (pembrolizumab) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic)

	premedication should be permanently discontinued from further trial treatment administration.	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing

6.3 Immune-Related Adverse Events (irAEs) General Definition, Monitoring, and Management

For the purposes of this protocol, an immune-related adverse reaction irAE is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an irAEs. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented in CTEP-AERS.

Overall, immune-related AEs commonly start within 3 to 10 weeks from initiation of therapy and are in most cases successfully managed by delaying doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned below. Immune-related AEs generally resolved within days to weeks in the majority of subjects.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-mediated adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-mediated adverse reaction (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-mediated adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

Below are dose delay tables for MK-3475 (pembrolizumab) (depending on assigned

treatment regimen) related to adverse events. Patients may be dose-delayed for evaluation and restarted depending on results.

Investigators should as a rule evaluate suspected adverse effects early, and with any suspicion, erring on the side of caution by withholding drug and instituting appropriate treatment as indicated in the management tables and following event specific guidelines.

There are no dose reductions for MK-3475 (pembrolizumab). If the patient meets retreatment criteria, the full dose of 200 mg will be administered. If patients do not meet retreatment criteria, then the dose of MK-3475 (pembrolizumab) will be HELD and the patient re-evaluated weekly until retreatment criteria are met.

Adverse events (both non-serious and serious) associated with MK-3475 (pembrolizumab) exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. MK-3475 (Pembrolizumab) must be withheld for drug-related toxicities and severe or life-threatening AEs as per the table below.

If MK-3475 (pembrolizumab) and epacadostat are withheld for drug-related toxicities, radiographic tumor measurement and chest imaging should still continue every 6 weeks (+/- 7 days), as outlined in Section 4, Assessments During Treatment. Once MK-3475 (pembrolizumab) and epacadostat are restarted, imaging assessments will resume every 6 weeks from the time the drugs are restarted until week 49.

Although these guidelines are for immune-related AEs attributable to MK-3475 (pembrolizumab), it is also meant to be applied to any suspected immune-related AEs from epacadostat or the combination of epacadostat with other immune-targeted agents.

Table: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	**Hold MK-3475 (pembrolizumab) and epacadostat for NCI CTCAE grade**	**Timing for restarting treatment**	**Discontinue MK-3475 (pembrolizumab) and epacadostat permanently**
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1 and the patient has successfully tapered off of corticosteroids	Toxicity does not resolve within 8 weeks of last dose or inability to taper off corticosteroids within 8 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT or increased bilirubin	2 (ALT/AST >3-5X ULN or total bilirubin >1.5-3X ULN	Toxicity resolves to Grade 0-1 and the patient has tapered off of corticosteroids	Toxicity does not resolve within 8 weeks of last dose.
	3-4	Permanently discontinue	Permanently discontinue

	AST/ALT >5 x ULN or AST/ALT increases ≥50% relative to baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of AST/ALT **or total bilirubin >3 x ULN (Grade 3 or greater)**		
Type I diabetes mellitus (if new onset) or hyperglycemia	T1DM or 3-4	Hold MK-3475 (pembrolizumab) and epacadostat for new onset Type I diabetes mellitus or grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume MK-3475 (pembrolizumab) and epacadostat when patients are clinically and metabolically stable
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 8 weeks of last dose or inability to taper corticosteroids to a dose of prednisone 10 mg or less within 8 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 8 weeks of last dose or inability to taper off corticosteroids within 8 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with MK-3475 (pembrolizumab) and epacadostat can be continued while treatment for the thyroid disorder is instituted	Therapy with MK-3475 (pembrolizumab) and epacadostat can be continued while treatment for the thyroid disorder is instituted.
Infusion reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to grade 0-1	Toxicity does not resolve within 8 weeks of last dose or inability taper off corticosteroid within 8 weeks or if second occurrence of pneumonitis grade ≥ 2

	3-4	Permanently discontinue	Permanently discontinue
Renal failure or nephritis	2	Toxicity resolves to grade 0-1	Toxicity does not resolve within 8 weeks of last dose or inability to taper off corticosteroid within 8 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Myocarditis	1-2	Withhold both epacadostat and MK-3475(pembrolizumab) until Grade 0. May restart at same dose level.	Toxicity does not resolve within 8 weeks of last dose.
	3-4	Permanently discontinue.	Permanently discontinue.
All other drug-related toxicity*	3 or severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 8 weeks of last dose or inability taper off of corticosteroids within 8 weeks.
	4	Permanently discontinue	Permanently discontinue
Note: Permanently discontinue MK-3475 (pembrolizumab) and epacadostat for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. * Patients with intolerable or persistent Grade 2 drug-related AE may hold MK-3475 (pembrolizumab) and epacadostat at physician discretion. Permanently discontinue MK-3475 (pembrolizumab) and epacadostat for persistent Grade 2 adverse reactions for which treatment with study drug has been held, and that do not recover to Grade 0-1 within 8 weeks of the last dose of MK-3475 (pembrolizumab).			

6.4 **Supportive Care Guidelines**

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to MK-3475 (pembrolizumab).

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Pneumonitis:

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis
(DKA)

- For T1DM or Grade 3-4 Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:
Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (TSH and free T4 at the intervals specified, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. No intervention is required for Grade 1 hyperthyroidism or hypothyroidism events.

- Grade 2 hyperthyroidism events:
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- Grade 3-4 hyperthyroidism events:
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

- For Grade 2 events, hold MK-3475 (pembrolizumab) and epacadostat and treat with vigorous hydration and oral corticosteroids. Monitor renal function weekly until returned to baseline values.

Note: if event is considered clinically unrelated or unlikely to be related to MK-3475 (pembrolizumab), and an alternate clinical explanation is likely, probable, or definite in the judgment of the investigator (example, attributable to prerenal azotemia in the setting of nausea, and responding to hydration), then corticosteroids may be omitted and MK-3475 (pembrolizumab) and epacadostat may be administered.

- For Grade 3-4 events, hospitalization is indicated. Treat with vigorous hydration and IV corticosteroids for 24 to 48 hours. Monitor renal function frequently. Consultation with nephrology is recommended.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in the Table below:

TABLE: General Approach to Handling IRAEs

irAE	**Withhold/Discontinue** MK-3475 (pembrolizumab) **and Epacadostat?**	**Supportive Care**
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475 (pembrolizumab) and epacadostat	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3 and Grade 4	Withhold MK-3475 (pembrolizumab) and epacadostat Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 8 weeks of toxicity.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1-2 mg/kg/day prednisone or equivalent. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

6.5 Serotonin Syndrome

Serotonin syndrome has not been reported in any completed or ongoing studies.

There is a potential concern that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome, when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some MAOIs and combinations of serotonergic drugs (Boyer and Shannon 2005). The clinical manifestations of serotonin syndrome range from barely perceptible to lethal. Nonclinical data suggest that serotonin syndrome is unlikely following treatment with either epacadostat alone or in combination with MAOIs such as linezolid (Zhang et al 2016). As of 29 OCT 2017, 2 subjects treated across the epacadostat program have events reported as serotonin syndrome or symptoms of serotonin syndrome; both episodes were confounded, mild in severity, and resolved with dose interruption. Neither report was clinically substantiated to represent a true case of serotonin syndrome by the sponsor. Although the incidence of serotonin syndrome or symptoms of serotonin syndrome is rare, use of MAOIs or SSRIs is prohibited during the study. Subjects should be provided information describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any signs or symptoms is observed (Appendix V).

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

MK-3475 (Pembrolizumab) and Epacadostat are the investigational agents administered in NRG-GY016, and are available under IND sponsored by DCTD, NCI. For MK-3475 (Pembrolizumab) and Epacadostat, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4 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 CTEP and CIP Study Agents

7.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) **(11-JUN-2020)**

for

Epacadostat (INCB024360, NSC 766086)

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 216 patients.* Below is the CAEPR for Epacadostat (INCB024360).

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 2.0, February 9, 2020[1]

Adverse Events with Possible Relationship to Epacadostat (INCB024360) (CTCAE 5.0 Term) [n= 216]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Headache		***Headache (Gr 2)***
	Peripheral sensory neuropathy		***Peripheral sensory neuropathy (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

[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.

[2]INCB024360 can result in severe and potentially fatal immune-mediated adverse events. These include (but are not limited to) autoimmune hepatitis and autoimmune hypophysitis.

Adverse events reported on epacadostat (INCB024360) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that epacadostat (INCB024360) caused the adverse event:

Blood and lymphatic system disorders - Anemia
Gastrointestinal disorders - Abdominal distension; Small intestinal obstruction
General disorders and administration site conditions - General disorders and administration site conditions - Other (hyperthermia)
Infections and infestations - Bacteremia; Lung infection; Sepsis
Investigations - GGT increased
Metabolism and nutrition disorders - Hypernatremia; Hyponatremia
Musculoskeletal and connective tissue disorders - Arthralgia
Nervous system disorders - Dizziness; Dysgeusia
Psychiatric disorders - Insomnia
Renal and urinary disorders - Renal and urinary disorders - Other (renal impairment)
Respiratory, thoracic and mediastinal disorders - Hypoxia; Pneumonitis; Respiratory failure
Skin and subcutaneous tissue disorders - Pruritus
Vascular disorders - Hypertension; Hypotension

Note: Epacadostat (INCB024360) 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.

7.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

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 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

> **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 2.5, December 27, 2019[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[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.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) 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 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 the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

7.4.1 In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP by telephone at 301-897-7497, the NRG Biostatistical/Data Management Center by phone, (number to be provided) and to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.2 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Event Reporting Requirements, a CTEP-AERS-24 Hour Notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by the ING Sponsor for this study (CTEP/DCTD) and NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-230-0159 and NRG Regulatory Affairs at 215-854-0716.
- 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 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.

7.4.3 Expedited Reporting Requirements for Adverse Events

7.4.3.1 **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** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event 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 SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events 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 notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE 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: May 5, 2011

7.4.4 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.4.5 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 reporting via CDUS unless otherwise specified.

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES (11-JUNE-2020

Investigator and Research Associate Registration with CTEP
Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- 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
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all

CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI CTSU.

8.1.1 IRB Approval

For 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 after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). 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 with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) 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 or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB

Certification/Declaration of Exemption Form

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

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-GY016 Site Registration:

Additional 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); and
- Compliance with all protocol-specific requirements (PSRs).
- IRB/REB approved consent.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website:

To access the Regulatory Submission Portal log in 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 at 1-866-651-2878 in order to receive further instruction and support.

Checking Your 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 sites 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.

8.2 Patient Enrollment

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 the 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:

- A valid CTEP-IAM account;
- 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 the 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 IRB number used on the site's IRB approval on their Form FDA 1572 in 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 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.

8.3 Data Submission/Data Reporting

Medidata Rave is a 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:

- A valid and active CTEP-IAM account; and
- 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:

- To hold Rave CRA or Rave CRA (Lab Admin) role must hold 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, must have at 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 Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. 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 link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; 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 display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will 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 at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

8.3.1 Rave-CTEP-AERS Integration

The RAVE Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline 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.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

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. 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.

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 website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides.

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.

8.3.2 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 and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.
The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

9. DRUG INFORMATION

9.1 MK-3475 (Pembrolizumab) (NSC 776864)

Other Names: Pembrolizumab, SCH 900475, KEYTRUDA®

Classification: Anti-PD-1 MAb

Molecular Weight: 148.9-149.5 KDa

CAS Number: 1374853-91-4

Mode of Action: The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. MK-3475 (pembrolizumab) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands.

Description: Pembrolizumab (MK-3475) is a humanized MAb of the IgG4/kappa isotype.

How Supplied: Pembrolizumab (MK-3475) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 100 mg vials containing a sterile, non-pyrogenic, and clear to opalescent aqueous solution (25 mg/mL). Proteinaceous particles may be present. MK-3475 solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

Preparation: Pembrolizumab (MK-3475) solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

If a storage temperature excursion is identified, promptly return MK-3475 to between 2-8°C 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.

Stability: Stability testing of the intact vials is on-going**.**

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 20 hours. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection.

Method of Administration: Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

9.2 Epacadostat (NSC 766086)

Chemical Name: (*Z*)-*N*-(3-Bromo-4-fluorophenyl)-*N′*-hydroxy-4-(2-(sulfamoylamino) ethylamino)-1,2,5-oxadiazole-3-carboximidamide

Other Names: INCB024360

Classification: Indoleamine-2, 3-dioxygenase 1 (IDO1) inhibitor

Molecular Formula: $C_{11}H_{13}BrFN_7O_4S$ **M.W.:** 438.23

Approximate Solubility: The solubility of INCB024360 at 25°C is approximately 0.1 mg/mL in all aqueous medium types studied (water, pH 7.4 buffer, pH 8 buffer, and pH 2.1 buffer.

Mode of Action: The enzyme IDO1 is responsible for the oxidation of tryptophan into kynurenine. The catabolism of tryptophan by IDO1 inhibits T cell-mediated responses. Within the immune system, IDO1 activity is induced in dendritic cells and macrophages localized at sites of inflammation. By inhibiting IDO1 in tumor cells, epacadostat enhances T cell and natural killer cell proliferation and gamma interferon production while reducing regulatory T cell differentiation and dendritic cell apoptosis.

Description: The epacadostat drug substance is a white to off-white powder.

How Supplied: Epacadostat is supplied by Incyte Corporation and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg uncoated tablets (white, round, debossed with the strength "100") The immediate release tablets contain drug substance, lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. Tablets are to be dispensed in the original bottles. Each bottle contains 35 tablets.

Storage: Store at controlled room temperature (15-30°C/59-86°F).

If a storage temperature excursion is identified, promptly return epacadostat to between 15 and 30°C 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.

Stability: Shelf-life stability studies of epacadostat tablets are ongoing.

Route of Administration: Oral administration. May be administered without regard to food.

Potential Drug Interactions: Metabolism of INCB024360 occurs via CYP3A4, CYP1A2, CYP2C19, and UGT1A9 isoenzymes and via glucuronidation. The potential for weak to moderate inhibitors of UGT1A9 to cause clinically significant drug interactions with epacadostat via inhibition of UGT1A9 activity is low. Results suggest that epacadostat is not a CYP inducer in vitro. Epacadostat has low potential to cause clinically significant drug-drug interactions through CYP and UGT inhibition and induction. Use caution when administered with strong inhibitors/inducers of CYP3A4, CYP1A2, CYP2C19, and UGT1A9.
Epacadostat may cause an increase in serotonin levels which has the potential to precipitate serotonin syndrome when administered in combination with monoamine oxidase (MAO) inhibitors or serotonergic agents. Concomitant use of MAO inhibitors or serotonergic agents is prohibited.

Caution should be exercised with concomitant administration of warfarin. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. The dose of warfarin should be reduced when coadministered with epacadostat doses > 100 mg BID.

Epacadostat and its metabolites are moderate inhibitors of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3. The potential for epacadostat to cause clinically relevant drug-drug interactions via uptake transporters is low. Studies suggest that epacadostat is likely a substrate of P-gp and BCRP. Epacadostat is a weak P-gp inhibitor, however the potential for epacadostat to cause drug-drug interactions through P-gp interaction is low at clinically relevant exposures. Epacadostat is not an inhibitor of BCRP. Use caution when administered with strong inhibitors/inducers of P-gp and BCRP.

9.3 **Agent Ordering and Agent Accountability**

9.3.1 Availability of MK-3475 (Pembrolizumab)

MK-3475 (Pembrolizumab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

MK-3475 (Pembrolizumab) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix III).

9.3.2 Availability of Epacadostat

Epacadostat is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Epacadostat is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix III).

9.3.3 Agent Ordering and Agent Accountability

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 investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. 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.

9.3.4 Agent Inventory Records – 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 agent, strength, formulation and ordering investigator on this protocol.

9.3.5 Investigator Brochure Availability
The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP 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.

9.3.6 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 Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/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)

10. BIOSPECIMEN

10.1 Biospecimen Submission Tables

Biospecimens listed below should not be submitted until after patient registration and Bank ID assignment.

10.1.1 Mandatory Specimen Submissions

The patient must give permission to participate in this mandatory study component. Participating sites are required to submit the patient's biospecimens as outlined below.

Please refer to Appendix VI for details.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE TUMOR – Submit *one* of the following (listed in order of preference)		
FFPE Recurrent Primary Tumor (FRP01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]	Archival tumor collected prior to the patient receiving study treatment *(Recurrent or persistent are preferred specimen types - Submit one)*	NRG BB-Columbus within 8 weeks of registration[3]
FFPE Recurrent Metastatic Tumor (FRM01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]		
FFPE Persistent Primary Tumor (FPP01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]		
FFPE Persistent Metastatic Tumor (FPM01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]		
FFPE Primary Tumor (FP01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]	Archival tumor collected prior to the patient receiving any treatment *(Submit one if recurrent or persistent tumor collected prior to study treatment is not submitted.)*	
FFPE Metastatic Tumor (FM01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]		
FFPE Primary Neoadjuvant Tumor (FPT01)[1] 1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]	Archival tumor collected after the patient received neoadjuvant treatment, but prior to the patient receiving study treatment *(Submit one if recurrent or persistent tumor collected prior to study treatment or primary or metastatic tumor collected prior to all*	
FFPE Metastatic Neoadjuvant Tumor (FMT01)[1]		

1st Choice: block 2nd Choice: 10 unstained consecutive slides (charged, 5µm)[2]	*treatment is not submitted.)*	
BLOOD BIOSPECIMENS		
Pre-treatment **Fasting** Plasma (PB01) prepared from 7-10mL of **fasting** blood drawn into purple top (K2EDTA) tube(s)	Prior to study treatment; **patient must be fasting**	NRG BB-Columbus within 6 weeks of registration[3]
C2D1 **Fasting** Plasma (PB02) prepared from 7-10mL of **fasting** blood drawn into purple top (K2EDTA) tube(s)	Cycle 2, day 1, prior to study treatment; **patient must be fasting**	
Final **Fasting** Plasma (PB03) prepared from 7-10mL of **fasting** blood drawn into purple top (K2EDTA) tube(s)	At disease progression or end of treatment; **patient must be fasting**	NRG BB-Columbus within 26 weeks of registration[3]

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

2 If less than the requested numbers of slides are available, please contact BPCBank@nationwidechildrens.org.

3 NRG BB-Columbus / Protocol NRG GY016 Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.3 Banking Biospecimens for Future Research

Details regarding the banking and use of biospecimens for future research can be found in Appendix VI.

11. ASSESSMENT OF EFFECT

11.1 **Definition of Disease Assessments**

Response and progression will be evaluated in this study using the new 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.

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.

11.3 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.

11.4 **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.

CA-125: **CA125 cannot be used to assess response or progression in this study**. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use only in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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.

11.5 **Response Criteria**

Determination of response should take into consideration all target and non-target lesions and, if appropriate, biomarkers.

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.

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).

Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

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).

[redacted]

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks confirmation**

CR	Non-CR/Non-PD	No	PR	≥ 4 wks confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
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.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* '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

11.7 **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 the treatment started, including the baseline measurements.

11.8 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.9 Survival

Survival is defined as the duration of time from start of treatment to time of death or the date of last contact.

12. DATA AND RECORDS

12.1 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 7.2 for information about expedited and routine reporting.

12.2 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Monitoring Method for Protocol NRG-GY016: Complete

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

The primary objective of this study is to assess the anti-tumor activity for women receiving the combination of MK-3475 (pembrolizumab) and epacadostat for recurrent or persistent clear cell carcinoma of the ovary. The primary measure of efficacy is the objective tumor response rate, defined as a complete response or partial response.

This is a single-arm, phase II clinical trial that will use a flexible, two-stage design (Chen et al., 1998). Since it is a single-arm trial, it does not require randomization or stratification. If the trial enters both stages, the total accrual target will be 23 patients but will be allowed to range from 21 to 25, due to the difficulty in accruing precise numbers of patients in a multicenter trial. A hard stop on accrual will occur after accrual completes to the first stage (see Section 13.3.2). The study will re-open to accrual in the event the study advances to the second stage.

The biologic mechanism of the study agent is expected to impede the growth of tumors already present and inhibit the development of new metastases. Therefore, the objective tumor response rate will be used as the primary measure of efficacy.

13.2 Study Endpoints

List of endpoints that correspond to the study objectives, e.g. the endpoint of overall survival for the study objective to evaluate the impact of drug X on overall survival in X population. Include endpoint definitions.

Primary endpoints:

- Complete or partial objective tumor response within 7 months of study entry as assessed by RECIST v. 1.1 criteria

Secondary endpoints:

- Nature and degree of toxicity as assessed using CTCAE version 5
- Progression-free survival
- Overall survival

13.3 Primary Objectives Study Design

13.3.1 Primary Hypothesis and Endpoints

The primary hypothesis of this study tests the proportion of patients with objective complete or partial tumor response (π) evaluated by RECIST v. 1.1 criteria. Based on predicted response rates in similar patient populations, the null hypothesis is that the proportion of patients with objective tumor response will be 15% or less, i.e.:

H_0: $\pi \leq 0.15$.

The alternative hypothesis is the complement of the null parameter space (i.e. H_1: $\pi > 0.15$). The study is powered to detect a 25 percentage point increase in response: $\pi = 0.40$.

13.3.2 How Primary Endpoints Will Be Analyzed

The study will use a flexible two-stage design with early stopping guidelines based on

tumor response rate intended to limit the accrual of patients to ineffective treatments. The first stage of this study will target an accrual of 12 eligible patients, but in practice will permit accrual to range from 10 to 14 patients. A hard stop on accrual will occur after 14 patients have enrolled in the study. If the number responding is less than or equal to 1, then the study will terminate early and the regimen will be declared uninteresting. If there are at least 2 patients with response, the study advances to the second stage and the study re-opens to accrual. If the study advances to the second stage, then the overall study accrual of 23 eligible patients will be targeted, but the actual accrual will be permitted to range from 21 to 25 patients. If the number responding is less than or equal to 5 for a sample size of 21 – 23 patients or less than or equal to 6 for a sample size of 24 – 25 patients, then the regimen will be declared uninteresting to warrant further investigation. All enrolled patients deemed eligible and who initiate study treatment will be included in the analysis of objective response. Exact 95% confidence limits, accounting for interim analysis, will be provided in the final report.

13.3.3 Sample Size and Power Calculations: All supporting assumptions and/or important considerations, such as expected sample size or patient cohorts. Also can include information such as over-accrual and how many patients are planned for enrollment to define power.

A two-stage design was chosen to allow for flexibility in accrual. The target sample size for the first stage is 12 eligible patients but allowed to vary between 10 and 14. A hard stop on accrual will occur after 14 patients have enrolled in the study. The study will re-open to accrual in the even the study advances to the second stage. The target cumulative sample size at the second stage is 23 eligible patients but allowed to vary between 21 and 25. Across all possible accrual combinations and assuming uniform probabilities of accrual across these, the average probability of early termination is 45% under the null, and the average alpha and power are 0.08 and 0.91 respectively. For most accrual combinations, the alpha is <0.10 and the power is >0.90.

Table 1. Operating characteristics of the trial design

True ORR	Probability of early stopping	Average Sample size	Probability of claiming experimental agent is promising
0.15 (null)	**0.45**	**18**	**0.08**
0.25	0.17	21	0.44
0.30	0.09	22	0.65
0.35	0.05	22	0.81
0.40	**0.02**	**23**	**0.91**
0.45	0.01	23	0.96

13.4 Study Monitoring of Primary Objectives

(Interim Analysis)

See Section 13.3.2 for details regarding study monitoring of primary objectives.

Monitoring of the primary objective and impact on stage transition will be summarized in

a formal report provided by the Study Statistician to be reviewed by the protocol monitoring committee. The protocol monitoring team will consist of the Study Chair, the Study Statistician, the Study Co-Chairs, the Data Manager, and any others required. 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 the meeting written by the Study Chair 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.

See Section 13.7.6 for details regarding the Early Phase Trial Oversight Committee.

13.5 Accrual/Study Duration Considerations

Section should include as applicable accrual rate, accrual goal, study/accrual duration, estimated duration for completion of primary endpoints

Protocol Number	**Accrual Start Date**	**Temporary Accrual Closure**	**Final Accrual Date**	**Accrual/Month Rate** (excluding temporary closure period)	**Number of Patients Enrolled**
NRG-GY001	April 1, 2015	Nov. 1, 2015		1.7/month	13
GOG-0283	Feb. 3, 2014	Dec. 19, 2014 – Oct. 6, 2015 Aug. 10, 2016		2.4/month in first 11 months 1.7/month overall	35
GOG-0254	April 19, 2010	Feb. 6 2012 – Oct. 1, 2012	Sept. 30, 2013	1.1/month	35

There have been several trials recruiting patients with clear cell carcinoma of the ovary through NRG Oncology. GOG-0254 was a two-stage, phase II trial of sunitinib that accrued 35 patients over 34 total months. GOG-0283, a Phase II single-agent, open-label trial of dasatinib, accrued Stage I (all comers) with 26 evaluable in 11 months (2.4 patients per month), with 1.7 patients per month overall. NRG-GY001 (cabozantinib) activated April 1, 2015 and enrolled its first stage (n=13) in 7 months. The ovarian clear cell carcinoma community is active and a frequent inquirer for clinical trials. Based on the accrual information above, the present trial is expected to accrue 1.5 patients/month (18 patients/year).

Twelve eligible patients are required for the first stage (allowable range 10-14), with a cumulative target of 23 eligible patients (allowable range 21-25) in the second stage. A hard stop on accrual will occur after 14 patients have enrolled in the study. The study will re-open to accrual in the event the study advances to the second stage.

Approximately eight months are expected to be required for the first stage of accrual, followed by approximately eight months of evaluation of objective tumor response to determine whether to open the second stage; if required, eight months are expected for accrual for the second stage, followed by eight months of evaluation for response. If the study requires two stages, final analysis is expected in approximately three years.

13.6 Dose Level Guidelines

(Escalation or de-escalation): Mandatory for phase I or phase I/II trials

Dose level guidelines are not applicable for this study.

13.7 Secondary [redacted] (including correlative science aims)

If there are secondary [redacted] aims, they must be addressed in the Statistical Considerations section.

13.7.1 Secondary Hypotheses and Endpoints: The expected level of detail for secondary hypotheses will be less than for the primary hypothesis and endpoint.

The secondary endpoints of adverse events, progression-free survival and overall survival will be estimated as described in Section 13.7.2.

13.7.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

CTCAE version 5 will be used to grade and categorize adverse events. 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.

Disease progression will be defined using RECIST v. 1.1 criteria. Progression-free survival (PFS) is defined as the duration of time from the start of study treatment to time of progression or death, whichever occurs first. Overall survival (OS) is defined as the duration of time from the start of study treatment to time of death or the date of last contact. The distributions of PFS and OS will be estimated and graphed using the Kaplan-Meier product limit method.

13.7.3 Interim Analysis for All Other Endpoints (Goals): Include as applicable

No interim analyses are planned for secondary endpoints.

13.7.4 Power Calculations: power can be provided as applicable for selected secondary endpoints, if any. The power is based on the sample size for the primary endpoints.

Power calculations are not needed for the secondary endpoints because only estimation, not testing, will be done for these endpoints.

13.7.5 Expected Sample Size or Patient Cohorts:

Not applicable.

13.7.6 Data and Safety 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 on this protocol will be reviewed by the protocol monitoring team on a quarterly basis (every three months) via conference call. 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 Study Chair 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 Early Phase Trial Oversight Committee will review the study quarterly (every three months) with respect to patient accrual and morbidity. Face-to-face meetings will be held at the semiannual NRG Oncology group meetings and intervening quarterly meetings will be held by conference call. Each quarterly report will be forwarded to the CIRB.

The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the Study Chairperson, Gynecologic Rare Tumor Committee, and NRG Safety Review Committee (SRG) in conjunction with each semi-annual meeting (twice per year). For studies sponsored by CTEP of the National Cancer Institute (NCI), standardized toxicity reports are also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB).

All serious adverse events (SAEs) are reported to the Study Chairperson, Sponsor, Pharmaceutical company, and regulatory agencies as mandated in the protocol. SAE reports are reviewed by the Study Chairperson (or designated co-chairperson)

immediately for consideration of investigator notification of a suspected unexpected serious adverse reaction (SUSAR), protocol amendment, and/or immediate study suspension. All participating institutions will receive notification of the SUSAR from NRG as well as the reason study suspension, if applicable. Upon suspension, accrual cannot be re-activated until review of the study by the SRG. However, patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless otherwise directed.

13.8 [redacted]

[redacted]

[redacted]

[redacted]

13.9 Gender/Ethnicity/Race Distribution

The distribution below is based on the maximum, two-stage sample size of 25 patients.

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	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	1	0	0	0	1
White	20	0	1	0	21
More Than One Race	0	0	0	0	0
Total	24	0	1	0	25

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	0	0	0	0	0

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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: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.

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 – COLLABORATIVE AGREEMENT

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are 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:

Email: 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.

APPENDIX IV – PATIENT PILL CALENDAR

This is a calendar on which you are to record the time and number of tablets you take each day. Complete one form for each cycle (21 days). You should take your scheduled dose of each pill. You can take the pill either with or without food. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Epacadostat

DAY	Date Month	Day	Year	Time pills taken (circle AM/PM		Number of pills taken each day (100 mg)	Comments
1					AM/PM		
2					AM/PM		
3					AM/PM		
4					AM/PM		
5					AM/PM		
6					AM/PM		
7					AM/PM		
8					AM/PM		
9					AM/PM		
10					AM/PM		
11					AM/PM		
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18					AM/PM		
19					AM/PM		
20					AM/PM		
21					AM/PM		

Patient Signature: _____ Date: _____

APPENDIX V: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug epacadostat (INCB024360). This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Epacadostat (INCB024360) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4, CYP1A2, CYP2C19, and UGT1A9. Epacadostat (INCB024360) is metabolized by CYP3A4, CYP1A2, CYP2C19, and UGT1A9 and may be affected by other drugs that inhibit or induce these enzymes.
- The proteins in question are OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp, and BCRP. Epacadostat (INCB024360) is a substrate of P-gp and BCRP and may be affected by other drugs that inhibit or induce these transporters. Epacadostat (INCB024360) is an inhibitor of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, and P-gp and may affect transport of other drugs in and out of cells.
- Epacadostat (INCB024360) may cause an increase in serotonin levels when administered in combination with monoamine oxidase (MAO) inhibitors. Use of MAO inhibitors is prohibited.
- Caution should be exercised with concomitant administration of warfarin and epacadostat (INCB024360). Patients taking these medications should be monitored more frequently.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Epacadostat (INCB024360) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Epacadostat (INCB024360) must be used very carefully with other medicines that need certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors or substrates of CYP 3A4, 1A2, 2C19, UGT1A9, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp, and BCRP. MAO inhibitors are prohibited. Warfarin must be used with caution and closely monitored."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- You may need to be monitored more frequently if you are taking warfarin with epacadostat (INCB024360).
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

12/2017

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **epacadostat (INCB024360).** This clinical trial is sponsored by the NCI**. Epacadostat (INCB024360)** may interact with drugs that are **processed by your liver, or use certain transport proteins in your body**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- **MAO inhibitors are prohibited.**
- **Warfarin must be used with caution and closely monitored.**

Epacadostat (INCB024360) interacts with **CYP 3A4, 1A2, 2C19, UGT1A9, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp, and BCRP**, and must be used very carefully with other medicines that interact with these enzymes and proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors or substrates of CYP 3A4, 1A2, 2C19, UGT1A9, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp, and BCRP**"
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

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