Protocol Title

Phase II Study of the Combination of Abemaciclib and Pembrolizumab in Locally Advanced Unresectable or Metastatic Gastroesophageal Adenocarcinoma: Big Ten Cancer Research Consortium BTCRC-GI18-149

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 22MAY2019

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

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Site Investigator Title

_____

Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	Phase II Study of the Combination of Abemaciclib and Pembrolizumab in Locally Advanced Unresectable or Metastatic Gastroesophageal Adenocarcinoma: Big Ten Cancer Research Consortium BTCRC-GI18-149
PHASE	Phase II
OBJECTIVES OF THE STUDY	Primary Objective: • Estimate progression-free survival (PFS) of treatment with abemaciclib in combination with pembrolizumab in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. Secondary Objectives: • Estimate progression-free survival (PFS) rate at 6 months in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab. • Estimate disease control rate (DCR) in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab. • Estimate overall survival (OS) in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab. • Estimate objective response rate (ORR) in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab. • Estimate the safety and tolerability of abemaciclib in combination with pembrolizumab in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. Exploratory Objectives: • Correlate PD-L1 expression status with clinical outcomes. • Correlate tumor molecular signature from NGS analysis with clinical outcomes and treatment response. • Collect archival tissue for future studies. • Correlate peripheral blood-based biomarkers that will include, but are not limited to, circulating tumor DNA and circulating immune markers, with clinical outcomes. • Correlate saliva microbiome analysis results with clinical outcomes.
STUDY DESIGN	Phase II, single arm, nonrandomized, open label study of abemaciclib in combination with pembrolizumab in subjects with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma who have progressed or were intolerant to at least 2 lines of prior therapies for advanced disease.

KEY ELIGIBILITY CRITERIA	• Patients age 18 or older. • Histologically confirmed unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. • Measurable disease by RECIST 1.1 is required. • Hematologic parameters: o Absolute neutrophil count ≥ 1500/µl o Hemoglobin ≥ 8 g/dl o Platelet count ≥ 100,000/µl • Renal function: Creatinine < 1.5x ULN or Cockcroft-Gault calculated creatinine clearance ≥ 60 mL/min • Hepatic function o AST and ALT ≤ 3x upper limit of normal (ULN). o Total bilirubin ≤ 1. 5x ULN. Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted. • Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 • Prior therapy o At least two lines of prior systemic therapy for advanced, unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. • Ability to take oral medications • No history of prior therapy with a cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) inhibitors or prior immune checkpoint inhibitors. • No contraindications to immune checkpoint inhibitors.
STATISTICAL CONSIDERATIONS	In the Phase II study, the primary endpoint for sample size justification is progression-free survival (PFS). The null hypothesis that the median PFS is 2 months or less will be tested against the alternative hypothesis that the median PFS is greater than 2 months. A median PFS of at least 4 months will be considered sufficient evidence to consider further clinical investigation of the proposed treatment combination. A sample size of 31 evaluable subjects is required to detect an anticipated increase in the median PFS from 2 months (null hypothesis) to 4 months with 80% power at the one-sided 0.05 significance level. In order to account for non-evaluable subjects (~10%), a total of 34 subjects will be enrolled.
TOTAL NUMBER OF SUBJECTS	N=34
ESTIMATED ENROLLMENT PERIOD	12-18 months
ESTIMATED STUDY DURATION	24 months (18 months for accrual, additional 6 months for primary endpoint follow-up)

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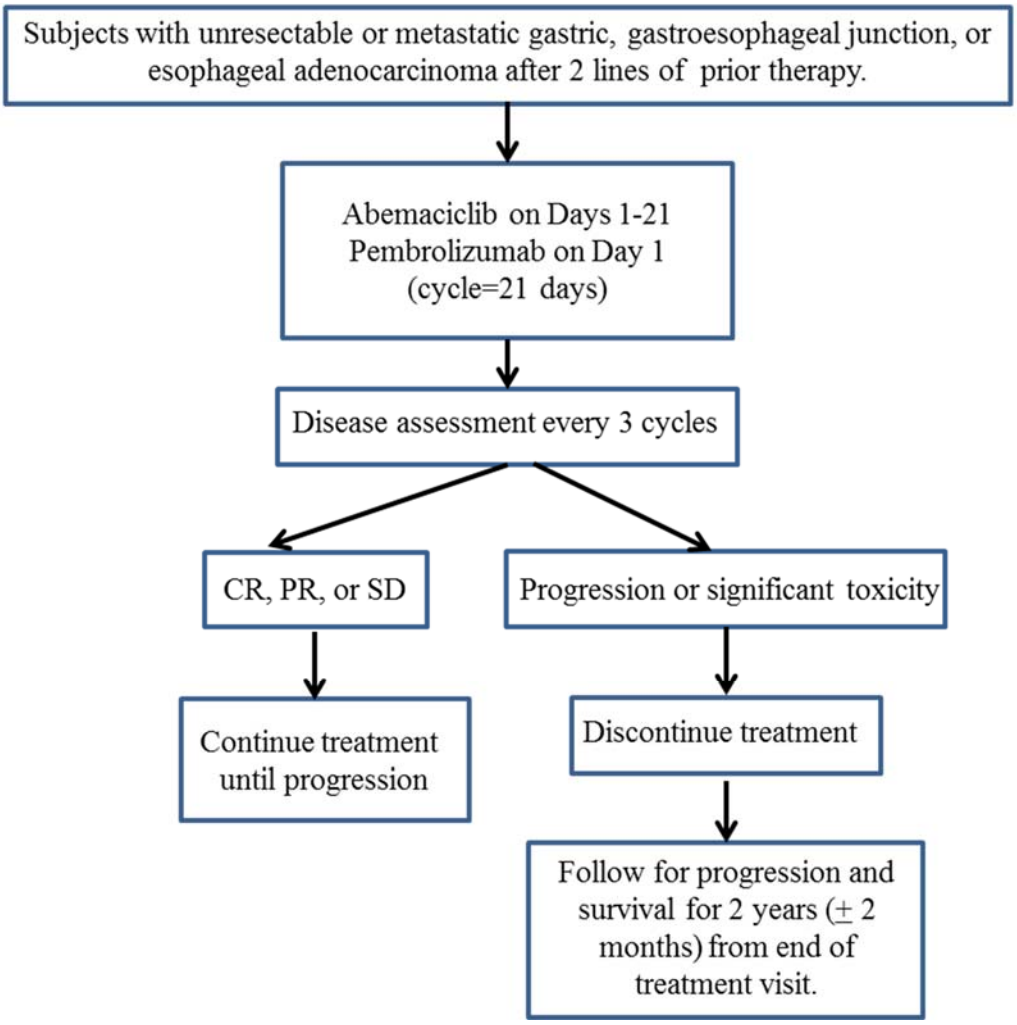
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
cc	Cubic centimeter
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DSMC	Data and Safety Monitoring Committee
EC	Esophageal cancer
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FDA	Food and Drug Administration
GC	Gastric cancer
GEJ	Gastroesophageal junction
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
ICF	Informed consent form
IHC	Immunohistochemistry
irAE	Immune related adverse event
IV	Intravenous
Kg	Kilogram
LFT	Liver function tests
NCI	National Cancer Institute
NGS	Next generation sequencing
ORR	Objective response rate
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
PI	Principal Investigator
PLT	Platelets
PR	Partial response
PRMC	Protocol Review Monitoring Committee
PS	Performance status
SAE	Serious adverse event
SD	Stable disease
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UWCCC	University of Wisconsin Carbone Cancer Center

STUDY SCHEMA



1. BACKGROUND AND RATIONALE

1.1 Disease Background

Esophageal cancer is a major health problem in the world. In Western countries, lower esophagus is the most common site for esophageal cancers, and these tumors frequently involve the gastroesophageal junction (GEJ). There are two major histological subtypes of esophageal cancer: squamous carcinoma and adenocarcinoma. Although the incidence of squamous cell esophageal cancer has been declining, esophageal adenocarcinoma has one of the fastest growing incidence among solid tumors in the Western world. Esophageal adenocarcinoma is more common in males, but over the last few decades its rates among women have been increasing as well[1]. Tobacco and alcohol abuse are major risk factors for esophageal squamous cell carcinoma, while obesity and gastroesophageal reflux disease (GERD) predispose to the development of esophageal adenocarcinoma. The majority of patients are diagnosed with at least stage II disease. Despite aggressive treatments of potentially curative esophageal cancer, about 50% of patients ultimately developed recurrent disease [2]. Recurrent and metastatic esophageal adenocarcinoma is almost universally fatal. Overall survival (OS) for metastatic gastroesophageal adenocarcinoma remains around 12 months with current treatment strategies [3]. Therefore, development of novel treatment strategies is needed to improve prognosis of patients with this disease.

1.2 Immunotherapy in the Treatment of Gastroesophageal Cancers

Programmed death-ligand 1 (PD-L1) is a transmembrane protein that is expressed in about 40% of upper gastrointestinal (UGI) tumors. PD-L1 is one of the ligands for programmed death 1 (PD-1), which is an inhibitory receptor that belongs to the CD28-B7 family. Binding to PD-1 results in down regulation of the T cell immune response allowing PD-L1 positive tumors to evade immune mediated cell death. PDL-1 expression has been shown to be associated with greater depth of muscle invasion, the presence of lymph node metastasis, and overall worse prognosis[4,5]. A number of immunotherapy agents have demonstrated activity against metastatic gastroesophageal cancers. Nivolumab treatment results in longer OS compared to placebo in patients with metastatic gastric and GEJ tumors who have received at least 2 lines of prior therapies [6]. Pembrolizumab treatment resulted in 15.5% objective response rate (ORR) in 259 patients with advanced gastric and gastroesophageal junction cancer that enrolled in a phase 2 Keynote-059 trial [7]. Avelumab has been found to have encouraging results in a similar setting as well, with 15% ORR in subjects with chemotherapy resistant gastroesophageal cancer [8]. Patients who do respond to treatments have durable responses, with median response duration to pembrolizumab of 8.4 months in this advanced setting. However, the majority of patients do not respond to these agents. Hence, novel approaches are needed to increase activity of immune checkpoint inhibitors in patients with esophagogastric malignancies.

1.3 Rationale for Combining Abemaciclib with Pembrolizumab

Combination strategies are key to augmenting activity of immune checkpoint inhibitors against gastroesophageal adenocarcinoma (GEA). CDK4/6 inhibition has been shown to increase anti-tumor immunity in preclinical studies[9,10]. CDK4/6 inhibitors can increase tumor antigen presentation, suppress proliferation of regulatory T cells, and increase infiltration and activation of effector T cells. Moreover, combination of CDK4/6 inhibitors and anti-PD1 agents demonstrated synergistic anti-tumor activity in spheroid cultures and in mouse models[9,10]. This effect was seen in preclinical studies evaluating abemaciclib and pembrolizumab in particular [11]. Moreover, proteins that control cell cycle are frequently altered in GEA, and CDK4 and 6 have been shown to be some of the most frequently upregulated genes in GEA[12,13]. This suggests that targeting genes that regulate cell cycles may have anti-tumor activity in

this disease. In preclinical setting, CDK4/6 inhibitor, abemaciclib, demonstrated promising activity against human esophageal cell lines and a xenograft model [14]. Based on the above data, we hypothesize that the combination of abemaciclib and pembrolizumab will result in clinically relevant activity in patients with advanced GEA.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Estimate progression-free survival (PFS) of treatment with abemaciclib in combination with pembrolizumab in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.

2.1.2 Secondary Objectives

- Estimate PFS rate at 6 months in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab.
- Estimate disease control rate (DCR) in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab.
- Estimate overall survival (OS) in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma treated with abemaciclib in combination with pembrolizumab.
- Estimate the objective response rate (ORR) to abemaciclib in combination with pembrolizumab in subjects with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.
- Estimate the safety and tolerability of abemaciclib in combination with pembrolizumab in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.

2.1.3 Exploratory Objectives

- Correlate PD-L1 expression status with clinical outcomes.
- Correlate tumor molecular profiling results from next generation sequencing (NGS) testing with clinical outcomes and treatment response.
- Correlate peripheral blood-based biomarkers that will include, but are not limited to, circulating tumor DNA and circulating immune markers, with clinical outcomes.
- Correlate saliva microbiome analysis results with clinical outcomes.

2.2 Endpoints

2.2.1 Primary Endpoints

- PFS as determined per RECIST1.1 on treatment with abemaciclib in combination with pembrolizumab in patients with advanced, unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.

2.2.2 Secondary Endpoints

- PFS per irRECIST
- PFS rate at 6 months (RECIST and irRECIST).
- DCR (RECIST and irRECIST), which is defined as percent of patients with stable disease, partial response and complete response after treatment initiation.
- OS as measured from the time of treatment initiation until death.
- ORR as measured as percent of patients who achieved objective response as per RECIST 1.1 and irRECIST while on treatment.
- Safety and tolerability of abemaciclib in combination with pembrolizumab in patients with advanced, unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma, assessed by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.

2.2.3 Correlative Endpoints

- Correlate PD-L1 status with clinical response.
- Correlate tumor molecular signature from NGS analysis with clinical outcomes and treatment response.
- Collect archival tissue for future studies.
- Correlate peripheral blood-based biomarkers that will include, but are not limited to, circulating tumor DNA and circulating immune markers, with clinical outcomes.
- Correlate saliva microbiome analysis results with clinical outcomes.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include women and minorities, the subject population is expected to be no different than that of other advanced solid tumor cancer studies at each participating institution.

Subjects must meet all of the following applicable inclusion criteria to participate in this study:

1. Patients with histologically confirmed metastatic or locally advanced unresectable gastric, gastroesophageal junction or esophageal adenocarcinoma.
2. Be willing and able to provide written informed consent for the trial.
3. Age ≥ 18 years at the time of consent.
4. Prior treatment with at least two lines of systemic therapy for advanced disease. Patients who have received neoadjuvant or adjuvant therapy or definitive chemoradiation and had recurrence during or within 6 months of completion of all treatments may count adjuvant therapy as one chemotherapy line.
5. Presence of measurable disease based on RECIST 1.1 as determined by local site investigator/radiology assessment.
6. ECOG PS 0-1.
7. Patients must have discontinued all previous treatments for cancer (including cytotoxic chemotherapy, molecularly targeted therapy, radiotherapy, and investigational therapy).

8. Patients who received chemotherapy must have recovered (CTCAE Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy. A washout period of at least 21 days is required between last systemic therapy dose and treatment initiation per protocol.
9. A washout period of at least 14 days is required between end of radiotherapy and treatment initiation.
10. The patient is able to swallow oral medications.
11. Demonstrate adequate organ function as defined in Table 1.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L
Platelet count	$\geq 100 \times 10^9$/L
Hemoglobin	≥ 8 g/dL; transfusions to increase the patient's hemoglobin are permitted; however, study treatment must not begin until the day after the transfusion.
Renal	
Calculated creatinine clearance	< 1.5 x upper limit of normal (ULN) or ≥ 50 mL/min using the Cockcroft-Gault formula
Hepatic	
Total bilirubin	≤ 1. 5 × ULN; Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.
Aspartate aminotransferase (AST)	≤ 3 × ULN
Alanine aminotransferase (ALT)	≤ 3 × ULN

12. Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.
13. Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 60 days after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.
14. Men who are not surgically sterile (vasectomy) must agree to use an acceptable method of contraception. Male subjects with female sexual partners who are pregnant, possibly pregnant, or who could become pregnant during the study must agree to use condoms from the first dose of study drug through at least 60 days after the last dose of study drug. Total abstinence for the same time period is an acceptable alternative.
15. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

16. Provided written informed consent and HIPAA authorization for release of personal health information, approved by an Institutional Review Board (IRB). **NOTE**: HIPAA authorization may be included in the informed consent or obtained separately.

3.2 Subject Exclusion Criteria

1. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
2. History of prior therapy with CDK4 or CDK6 inhibitors or prior immune checkpoint inhibitors.
3. Patients with known microsatellite instability will be excluded.
4. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI.
5. Serious preexisting medical condition(s) that would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
6. Symptomatic central nervous system metastasis. Screening of asymptomatic patients is not required for enrollment.
7. Personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
8. Known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include curatively treated basal cell and squamous cell carcinoma of the skin, curatively resected in situ cervical and/or breast cancers, in situ or intramucosal pharyngeal cancer, and Gleason 6 prostate cancer with PSA <10.
9. Patients who have received a live vaccine within 30 days of planned start of pembrolizumab. Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.
10. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
11. Active infection requiring systemic therapy.
12. Patients who are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 60 days after the last dose of pembrolizumab or abemaciclib. (NOTE: breast milk cannot be stored for future use while the mother is being treated on study.)

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten Cancer Research Consortium (Big Ten CRC) Administrative Headquarters'(AHQ) electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within **5 business days** of registration.

5. TREATMENT PLAN

This is a Phase II non-randomized, single arm, open label study of abemaciclib in combination with pembrolizumab in patients with unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma who have received at least two lines of prior therapy. Treatment will be administered in 21-day cycles. Pembrolizumab will be administered intravenously (IV) at a dose of 200 mg on day 1 of each cycle. Abemaciclib will be taken orally twice a day on each day of the cycle, 150 mg per dose. Treatment will continue until disease progression or development of unacceptable toxicities.

5.1 Pre-medication and Hydration

No pre-medications prior to treatment with pembrolizumab are required. Subjects who develop infusion reactions to pembrolizumab while on treatment may receive pre-medication as detailed in table 3 (section 6.2).

5.2 Drug Administration

Table 2. Abemaciclib + Pembrolizumab Administration

Drug	Dose[1]	Length and route of administration	Frequency of administration[1]	Cycle Length
Abemaciclib	150 mg	PO, BID	Days 1-21	21 days
Pembrolizumab	200 mg	30 min (-5/+10); IV	Day 1	
[1] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).				

Dosing will occur in 21-day cycles. Abemaciclib will be dosed at 150 mg PO (bid) on Days 1-21 of each 21-day cycle. Abemaciclib can be taken with or without food. Patients should be instructed to take their doses of abemaciclib at approximately the same times every day. If the patient vomits or misses a dose of abemaciclib, patient will take the next dose at its scheduled time. Additional abemaciclib will not be taken to account for missed doses. Subjects will swallow abemaciclib tablets whole and not chew, crush, or split tablets before swallowing. Patients will record when they take each dose of abemaciclib in a drug diary

supplied to them before the beginning of a new cycle.

Pembrolizumab will be administered as a 30 minute intravenous infusion at a dose of 200 mg. Given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Initiation of cycles after Cycle 1 must meet the treatment criteria found in section 6.1. Subsequent cycles may begin up to 3 days earlier or later than initially planned to accommodate scheduling issues. Attempts will be made not to interrupt abemaciclib dosing if pembrolizumab infusion is delayed. The timing of each cycle initiation will be determined by pembrolizumab dosing (i.e. abemaciclib doses will not be made up if missed during a 21 day period).

5.3 Concomitant Medications

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient from the beginning of the screening period. All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, and nutritional supplements, will be recorded on the electronic case report form (eCRF) up until the follow up visit after treatment completion. Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial.

5.3.1 Allowed Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare, including antiemetics, may be administered at the discretion of the investigator per institutional standards. Growth factor support is allowed as clinically indicated, but abemaciclib must be suspended for at least 48 hours after the treatment.

5.3.2 Prohibited Concomitant Medications

- Administration of anti-cancer agents other than those specified in the protocol is not allowed during study participation.
- Live vaccine administration is prohibited during study participation.
- The use of immunosuppressive agents is prohibited during study participation, including immunosuppressive doses of systemic corticosteroids.
  - Subjects will be allowed to use topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption).
  - Physiologic replacement doses of systemic corticosteroids are permitted at doses of ≤ 10 mg of daily prednisone (or equivalent).
  - A brief course of corticosteroids for prophylaxis (e.g., for contrast dye allergy or to prevent infusion reaction) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

5.3.3 Other Concomitant Treatments

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites. Therefore, drugs that are strong and moderate inducers of CYP3A and/or strong inhibitors of CYP3A should be avoided or substituted if necessary.

If concomitant use cannot be avoided, abemaciclib dose adjustments may be required:

- Patients who must take CYP3A inhibitors such as clarithromycin, diltiazem, or verapamil should reduce the abemaciclib dose to 100 mg twice daily.
- Patients who must take itraconazole should reduce the abemaciclib dose to 50 mg twice daily.
- Patients who must take ketoconazole should reduce the abemaciclib dose to 50 mg once daily.
- Patients should avoid grapefruit or grapefruit juice.

5.3.4 Concomitant Radiotherapy

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with co-administering abemaciclib with radiotherapy. Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the sponsor-investigator by contacting the Big Ten CRC project manager.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI CTCAE version 5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations. Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of protocol therapy.

For toxicities that are clearly attributed to one of the agents, continuation of the other agent is permitted at the discretion of the treating physician. Toxicities should be managed as outlined in sections 6.2 and 6.3. For grade 3 toxicities that have unclear attribution, both agents should be held while with work up is ongoing. Treatment can be resumed as outlined in the protocol for each agent based on most likely attribution and severity.

6.1 Start of a New Cycle

A new treatment cycle will only be initiated when all of the following conditions are met:

- ANC $\geq 1{,}000 \times 10^9$/L
- platelets $\geq 50 \times 10^9$/L
- non-hematologic treatment related toxicities have improved to ≤ Grade 2 or to the subject's baseline values (except alopecia)

If toxicities are outside the acceptable threshold, the subject should be assessed weekly (phone or clinic) until toxicities are at an acceptable level. If treatment is unable to restart within 6 weeks of the planned treatment date, the subject will be permanently discontinued from study therapy. Both pembrolizumab and abemaciclib should be stopped at that time.

6.2 Management of Pembrolizumab Associated Toxicities.

6.2.1 Management of Allergic Reaction/ Hypersensitivity to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 3.

Table 3. Treatment guidelines for subjects who experience an infusion-related reaction associated with administration of pembrolizumab.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2	**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 subject 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 325-1000 mg po (or equivalent dose of antipyretic). Additional medications are allowed at the discretion of the treating physician, with the exception of corticosteroids.
Grades 3 or 4	**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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration.		

6.2.2 Management of Pembrolizumab Immune-Related Toxicities.

Pembrolizumab treatment may result in toxicities related to the activation of immune system and its off-target effects. These immune-related AEs (irAEs) may be seen after the first dose or as late as weeks after the last dose of pembrolizumab. Dose reduction of pembrolizumab is not allowed. Dose delays or treatment discontinuation may be necessary depending on the grade and timing of the AE. Early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. It is possible that a given toxicity is ultimately found to be related to abemaciclib rather than pembrolizumab. In that case pembrolizumab can be continued as previously, even if abemaciclib needs to be delayed or dose reduced. However, if pembrolizumab has been held at the onset of toxicity, it may not be resumed until AE is at grade ≤1 as detailed in the table 4. Further details regarding toxicity management guidelines for irAEs associated with pembrolizumab are provided in the Table 4 below.

Table 4. Management of Immune-Related Adverse Events.

GASTROINTESTINAL irAEs		
Severity of Diarrhea/ Colitis[1]	**Initial Management**	**Follow-up Management**
Grade 1	• Continue pembrolizumab therapy • Symptomatic treatment (for example, loperamide)	• Close monitoring for worsening symptoms • Educate subject to report worsening of symptoms immediately • If worsens: Treat as Grade 2, 3 or 4
Grade 2	• Hold pembrolizumab therapy • Symptomatic treatment	• If improves to Grade < 1: Resume pembrolizumab therapy • If persists > 5 to 7 days or recurs: Treat as Grade 3 to 4 • Endoscopy evaluation highly recommended for grade ≥ 2, especially since both agents in the study can cause diarrhea.
Grade 3	Hold pembrolizumab for Grade 3.	• 1 to 2 mg/kg/day prednisolone IV or equivalent • If improves: Continue steroids until Grade < 1 and taper over at least 1 month; resume pembrolizumab therapy following steroids taper (for initial Grade 3). • If worsens, persists > 3 to 5 days, or recurs after improvement, treat as grade 4 and add infliximab 5 mg/kg (if no contraindication). **Note**: Infliximab should not be used in cases of perforation or sepsis.
Grade 4	Permanently discontinue pembrolizumab therapy for Grade 4 or recurrent Grade 3.	• Steroids and infliximab as above. • Additional care per institutional standards.

- [1]Both study drugs can cause diarrhea. It is recommended that at the onset of diarrhea, diarrhea is initially treated following abemaciclib associated diarrhea management guidelines as outlined in section 6.3.1. If diarrhea persists despite measures outlined in section 6.3.1 and despite stopping abemaciclib for at least 48 hours, or if it is thought to be more likely to be due to pembrolizumab in an investigator's opinion (for example, it occurred after 3-4 cycles of therapy on stable abemaciclib dose), then it should be treated following guidelines outlined above. NOTE: Abemaciclib should be held for grade 2 diarrhea of any cause that lasts more than 24 hours despite supportive measures. Abemaciclib dose reduction is not mandatory once it is resumed if diarrhea is ultimately found to be an irAE.
- NOTE: For grade 3 diarrhea, both drugs should be held until the cause of diarrhea is determined. Endoscopic evaluation is highly recommended to evaluate for possible irAE.

HEPATIC irAEs		
Severity of Hepatitis/ Liver Tests Abnormalities[2]	**Initial Management**	**Follow-up Management**
Grade 1	Continue pembrolizumab therapy with close monitoring	• Monitor labs at least once weekly. Supportive care as appropriate.
Grade 2	Hold pembrolizumab therapy.	• Monitor labs at least once weekly. Supportive care as appropriate. • If improves to Grade ≤1 in ≤7 days: Resume pembrolizumab therapy. • If improves to Grade ≤1 in > 7 days and is thought to be abemaciclib related, may resume pembrolizumab therapy. At least weekly labs will be required after pembrolizumab resumption. • If persists for > 7 days, patient develops significant clinical symptoms and it is thought to be an irAE or unclear cause. administer corticosteroid 0.5-1mg/kg/d prednisone or equivalent ,. Pembrolizumab may be restarted if LFTs return to grade ≤1 within 7 days of steroid treatment and remain stable off steroids for at least 7 days.
Grade 3 or 4[3]	Permanently discontinue pembrolizumab.	• Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent. • If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine. Laboratories daily or every other day. Corticosteroid taper can be attempted around 4-6 weeks.

- [2]Both agents can cause liver test abnormalities, and it may be challenging to determine which drug is the culprit. For subject safety, both pembrolizumab and abemaciclib should be held for grade 2 or higher liver test abnormalities. If LFTs improve to grade ≤1 within 7 days, both drugs can be restarted with close monitoring of liver tests thereafter (at least once a week). Steroid administration for grade 2 LFT abnormalities that last more than 7 days will be determined by a treating investigator and will be indicated if hepatotoxicity is more likely irAE rather than abemaciclib related (for example, it occurred after a few cycles on a stable dose of abemaciclib).
- NOTE: LFTs abnormalities related to abemaciclib are more likely to occur early during treatment, which is why LFTs are monitored twice per cycle during the first 3 cycles.
- [3]NOTE: Pembrolizumab can be restarted after grade 3 LFT elevation if LFTs return to grade ≤1 within 7 days and/or are thought to be abemaciclib related in the opinion of a treating investigator (i.e. occurred early in the course of treatment).

PULMONARY irAEs		
Grade of Pneumonitis	**Initial Management**	**Follow-up Management**
Grade 1	• Consider withholding pembrolizumab therapy • Monitor for symptoms at least twice a week	• Repeat imaging in 3-4 weeks. Hold if radiologic evidence of progression. Re-assess at least every 3 weeks. • If worsens: Treat as Grade 2, 3 or 4
Grade 2	Withhold pembrolizumab therapy	• Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks. Consider bronchoscopy with BAL. Consider empirical antibiotics • Re-assess every 1 to 3 days • If improves: When symptoms return to Grade $\leq$ 1, taper steroids over at least 1 month. Resume treatment. • If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	• Permanently discontinue pembrolizumab therapy • Hospitalize	• 1.0 to 2.0 mg/kg/day prednisolone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy and/or lung biopsy. • If improves to Grade $\leq$ 1: Taper steroids over at least 6 weeks • If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

RENAL irAEs		
Grade of Creatinine Increased	**Initial Management**	**Follow-up Management**
Grade 1	Continue pembrolizumab therapy	• Continue renal function monitoring • If worsens: Treat as Grade 2, 3 or 4
Grade 2 to 3	Withhold pembrolizumab therapy	• Increase frequency of monitoring to every 3 days. If worsening or no improvement over 5-7 days, start 1.0 to 2.0 mg/kg/day prednisone or equivalent. Consider renal biopsy. • If returns to Grade $\leq$ 1: taper steroids over at least 1 month, and resume pembrolizumab therapy following steroids taper. • If worsens: Treat as Grade 4
Grade 4	Permanently discontinue pembrolizumab therapy	• Monitor creatinine daily • Start 1.0 to 2.0 mg/kg/day prednisone or equivalent. Nephrology consult. Consider renal biopsy. When Cr returns to Grade $\leq$ 1: taper steroids over at least 1 month
CARDIAC irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	• Withhold pembrolizumab therapy • Hospitalize. • In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management • Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. • Guideline based supportive treatment as per cardiology consult.* • Consider myocardial biopsy if recommended per cardiology consult.	• If symptoms improve and immune-mediated etiology is ruled out, re-start pembrolizumab therapy. • If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. Permanently discontinue pembrolizumab.
Immune-mediated myocarditis	• Permanently discontinue pembrolizumab.	• Prednisolone 1 to 2 mg/kg/day or equivalent. Once improving, taper steroids over at least 1 month.

	• Guideline based supportive treatment as appropriate as per cardiology consult.*	• If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)

*Local guidelines, or e.g. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

ENDOCRINE irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Continue pembrolizumab therapy. • Endocrinology consult if needed	• Start thyroid hormone replacement • therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis). • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Withhold pembrolizumab therapy. • Consider hospitalization and endocrinology consult	• Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis). Resume pembrolizumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	**If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH):** • Refer to endocrinologist for dynamic testing as indicated and measurement	• Resume pembrolizumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). • In addition, for hypophysitis with abnormal MRI, resume pembrolizumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. • Continue hormone replacement/suppression therapy as appropriate.

	of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue pembrolizumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold pembrolizumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.	

DERMATOLOGICAL irAEs		
Grade of Rash	**Initial Management**	**Follow-up Management**
Grade 1 to 2	• Continue pembrolizumab therapy • Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: • Withhold pembrolizumab therapy. Consider skin biopsy. Consider 0.5 to 1 mg/kg/day prednisolone or oral equivalent. • Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab therapy following steroids taper. • If worsens: Treat as Grade 3 to 4
Grade 3 to 4	• Withhold pembrolizumab for Grade 3. • Permanently discontinue for Grade 4 or recurrent Grade 3.	• 1 to 2 mg/kg/day prednisolone or equivalent. • Consider skin biopsy. Dermatology consult • If improves to $\leq$ Grade 1: Taper steroids over at least 1 month , resume pembrolizumab therapy following steroids taper (for initial Grade 3)

OTHER irAEs (not described above)		
Grade of other irAEs	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold pembrolizumab therapy pending clinical investigation	• If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting pembrolizumab therapy • If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold pembrolizumab therapy	• For grade 2, monitor closely and start steroids if no improvement over 3-5 days. For grade 3, start steroids immediately. • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Consider specialty consult as appropriate. • If improves to Grade ≤ 1: taper steroids over at least 1 month and resume pembrolizumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue pembrolizumab therapy	• 1.0 to 2.0 mg/kg/day prednisone or equivalent • Specialty consult as appropriate. • If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue pembrolizumab therapy	• 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed • Specialty consult. • If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	• Permanently discontinue pembrolizumab therapy • Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

6.3 Management of Abemaciclib Associated Toxicities

The most common treatment-related events associated with abemaciclib include diarrhea (63.0%), nausea (45.1%), fatigue (40.5%), vomiting (24.9%), white blood cell count decreased (24.9%), platelet count decreased (23.1%), neutrophil count decreased (22.5%), anemia (19.7%), anorexia (17.3%), creatinine increased (11.0%), and weight loss (10.4%). Dose reductions of abemaciclib are allowed to decrease treatment associated toxicities. Doses must be reduced sequentially by one dose level as detailed in Table 5. Mid-cycle dose reductions for abemaciclib may be implemented by informing patients to reduce the number of 50-mg capsules taken for each dose. For patients requiring a dose reduction of abemaciclib, any re-escalation to a prior dose level is permitted only after consultation with the study PI.

Table 5. Abemaciclib Dose Modifications for Adverse Reactions

Dose level	Dose of Abemaciclib
Starting Dose	150 mg (PO), bid
Dose level (-1)	100 mg (PO), bid
Dose level (-2)	50 mg (PO), bid

6.3.1 Management of Abemaciclib Associated Diarrhea.

Clinical trial data indicate that the majority of patients who receive abemaciclib will develop diarrhea. Early identification and intervention for the management of diarrhea is critical for safety and best symptom control. Pembrolizumab can cause diarrhea as well, and it may be challenging to differentiate which drug is the culprit. In recent studies, abemaciclib was found to cause diarrhea early during treatment (69% of patients experienced diarrhea during cycle 1 in MONARCH 3 study), and abemaciclib associated diarrhea was low grade (73% were grade 1 or 2 in MONARCH 3 study)[15]. Per IB, median time to diarrhea onset ranged from 6 to 8 days in the abemaciclib registration studies. At the first onset of diarrhea we recommend following abemaciclib guidelines and treat diarrhea as presumed abemaciclib toxicity. In the event when it is very likely that that diarrhea is a pembrolizumab associated irAE in the opinion of a treating investigator (for example, it occurred after a few cycles of therapy on a stable dose of abemaciclib), pembrolizumab toxicity management guidelines in table 4 should be followed. However, even under these circumstances abemaciclib should be held for any diarrhea of grade 2 that lasts more than 24 hours. Abemaciclib should be not dosed until diarrhea is resolved to ≤ Grade 1.

At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Refer to Table 6 for additional information for diarrhea management and dose modifications

Table 6. Management of Abemaciclib Associated Diarrhea

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤ Grade 1, suspend treatment until resolution. No dose reduction is required.
Grade 2 that persists > 3 days or recurs after resuming the same dose despite maximal supportive measures	• Suspend dose until toxicity resolves to ≤Grade 1. • Resume at *next lower dose*.
Grade 3 or 4 or requires hospitalization	• Suspend dose until toxicity resolves to ≤Grade 1. • Resume at next lower dose.

6.3.2 Increases in Serum Creatinine and Assessment of Renal Insufficiency

Elevation of serum creatinine is observed with abemaciclib and is due to a pharmacological inhibitory effect of abemaciclib on renal tubular transporters without affecting glomerular function. The rise in serum creatinine (mean increase, 0.2 mg/dL) occurs within the first 28 days while on abemaciclib treatment and remains elevated but stable throughout the treatment period. This rise in creatinine is reversible upon treatment discontinuation. Alternative markers (such as BUN, cystatin C level, or cystatin C calculated GFR) which are not based on creatinine may be considered to determine whether renal function is impaired.

6.3.3 General Guidance for Hepatic Monitoring

Elevations in liver enzymes may be seen with abemaciclib use. Liver function tests must be checked prior to abemaciclib therapy, twice per cycle during the first 3 cycles of treatment, and at the beginning of each cycle afterwards. Management of ALT and AST elevation associated with abemaciclib use is detailed in Table 7 below. Of note, both study agents can cause liver tests abnormalities, and it may be challenging to decipher which on is the culprit. Abemaciclib associated liver toxicities tends to occur earlier in the treatment course. In a situation when it is impossible to tell which drug is the culprit, patient should be treated for possible irAE as detailed in table 4. Both drugs should be held for any LFT elevation of grade 2 or above.

Table 7. Management of Abemaciclib Associated ALT and/or AST Elevation.

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 (>ULN-3.0 x ULN)	No dose modification or interruption is required.
Grade 2 (>3.0-5.0 x ULN)	Hold abemaciclib. Check weekly labs. Resume at prior doses when grade ≤1.
Persistent (≥ 21 days) or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	• Suspend dose until toxicity resolves to baseline or Grade 1. • Resume at next lower dose.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

To ensure patient safety, labs detailed in Table 8 should be collected in subjects with documented hepatotoxicity of any grade. These labs should be checked at the onset of elevated liver function tests (LFTs). LFTs should be checked weekly until treatment is restarted per table above.

Table 8. Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

Hepatic Hematology	**Hepatic Chemistry**	**Hepatic Serologies[a]**
Hemoglobin	Total bilirubin	Hepatitis A antibody, total
Hematocrit	Direct bilirubin	Hepatitis A antibody, IgM
RBC	Alkaline phosphatase	Hepatitis B surface antigen
WBC	ALT	Hepatitis B surface antibody
Neutrophils, segmented and bands	AST	Hepatitis B Core antibody
Lymphocytes	GGT	Hepatitis C antibody
Monocytes	CPK	Hepatitis E antibody, IgG
Eosinophils		Hepatitis E antibody, IgM
Basophils		
Platelets	**Hepatic Coagulation**	**Anti-nuclear antibody**
	Prothrombin Time	**Anti-actin antibody**
Haptoglobin	Prothrombin Time, INR	**Anti-smooth muscle antibody**
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.		
[a] Reflex/confirmation dependent on regulatory requirements and/or testing availability.		

6.3.4 Management of Abemaciclib Associated Hematologic Toxicity

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia has been observed in patients receiving abemaciclib. Complete blood count (CBC) must be checked prior to abemaciclib therapy, twice per cycle during the first 3 cycles of treatment, and at the beginning of each cycle starting with cycle 4. CBC should include WBC, ANC, hgb and plts. Patients should be monitored closely for signs of infection, anemia, and bleeding. Table 9 provides general guideline on management of hematologic toxicities.

Table 9. Management of Abemaciclib Associated Hematologic Toxicities

CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤ Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤ Grade 2. Resume at next lower dose.
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

6.3.5 General Guidance for Management of Abemaciclib Associated Non-hematologic Toxicities (excluding diarrhea and increased ALT and/or AST)

- Grade 1 or 2: No dose modification is required.
- Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1: suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
- Grade 3 or 4: suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.

Table 10. Management of Abemaciclib Toxicities (excluding diarrhea and ALT/AST)

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

6.4 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables above, treatment may be delayed ≤ 6 weeks from the expected day of the next treatment for any reason. If treatment is delayed ≤ 6 weeks, subjects will proceed with the next cycle of treatment at the dose level recommended according to the toxicity dose modifications detailed in sections 6.2 and 6.3. If pembrolizumab treatment is held, abemaciclib may be continued with daily dosing as per toxicity management guidelines outlined in section 6.3. Given that abemaciclib is taken on a continuous basis, the beginning of each cycle will be determined by the timing of the pembrolizumab infusion, i.e. if pembrolizumab is delayed by 7 days, the prior cycle will be 28 days if abemaciclib is continued. Held or missed doses of abemaciclib will not be made up if it is stopped before the 21-day cycle completion. If a subject is able to resume/continue only one of the drugs because of prior AEs, he/she may continue on single agent therapy if there is clinical benefit in the opinion of the treating investigator and after the discussion with the study PI.

6.5 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression via RECIST or irRECIST (see section 9 for additional details)
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

- A female subject becomes pregnant. Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.
- If protocol therapy is interrupted for > 6 weeks from the expected day of the next treatment.

6.6 Definition of Evaluable Subject

Evaluable for response: Any subject who receives at least 75% of abemaciclib during the first 2 cycles (i.e. at least 63 of 84 doses of abemaciclib) and 2 doses of pembrolizumab during the first two cycles of treatment will be evaluable for response.

Evaluable for toxicity: Any subject who receives at least one dose of treatment on this protocol should be evaluable for toxicity. Safety will be assessed the National Cancer Institute (NCI) CTCAE version 5.

6.7 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Cycle = 21 days	Screen	Cycle 1[2]		Cycle 2-3[2]		Cycle 4+[2]	Safety follow up[2,3]	Long-term Follow up[4]
	-28 days[1]	D1[2]	D8	D1	D8	D1	30 days post last dose	Q 3 months (±14 days)
REQUIRED ASSESSMENTS								
Informed consent	X							
Patient demographics	X							
Medical history[5]	X							
Diagnosis and Staging[6]	X							
Physical exam, height (screen only), weight	X	X		X		X	X	
Vital signs, ECOG Performance status[7]	X	X	X	X		X	X	
AEs & concomitant medications	X	X	X	X		X	X	
Drug Diary review		X	X	X		X		
LABORATORY ASSESSMENTS								
Complete Blood Cell Count (CBC)[8]	X	X[1]	X	X	X	X	X	
Comprehensive Metabolic Profile (CMP)[8,9]	X	X[1]		X		X	X	
TSH, Free T4[10]	X			X		X		
AST, ALT, Total Bilirubin			X		X			
Cortisol[10]	X			X		X		
Pregnancy test (serum or urine) WOCBP[11]	-7 days							
DISEASE ASSESSMENT[12]								
CT or MRI of chest, abdomen, and pelvis[12]	X					Q3 cycles[12]		X[12]
TREATMENT EXPOSURE								
Abemaciclib		→						
Pembrolizumab		X		X		X		
CORRELATIVE SPECIMEN COLLECTION								
Archival Tissue for PD-L1, NGS or prior results[13]		X						
Saliva for Microbiome[14]		X				pre-C4	X	
Plasma for ctDNA[15]		X				pre-C4	X	
BANKING SPECIMEN COLLECTION								
Unstained Slides (if available)[16]		X						
Whole Blood[17]		X				pre-C4	X	
Serum and Plasma[17]		X				pre-C4	X	
FOLLOW-UP								
Survival status, subsequent therapy								X

Key to Footnotes

[1]If screening (baseline) labs were performed within 7 days of D1 of treatment these do not need to be repeated.
[2]A window of 3 days will be applied to all treatment study visits (with the exception of tumor imaging, see footnote 12).
[3]The **safety follow-up** visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed within 30 days (+/-7 days) after the last dose of treatment. All AEs considered related to study drug(s) will be followed until the AE resolves to ≤ grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.
[4]**Long-term follow up** will occur every 3 months (90 days) starting after safety follow up visit for up to 2 years and may be conducted via telephone. Subjects who have ongoing Grade 4 AE or SAE at the time of discontinuation from treatment, and those who come off treatment prematurely for safety reasons will continue to be followed until the event is resolved or deemed irreversible by the site investigator.
[5]**Medical history** to include demographics, prior treatments, radiation and surgical history, previous PD-L1 testing results, previous NGS testing results.
[6]**Diagnosis and staging** to include pathology report.
[7]**Vital signs** to include blood pressure, heart rate, weight, and height (screening only) and ECOG performance status.
[8]If labs are drawn within the time window allotted, but do not meet criteria for treatment, they can be repeated and can be used for treatment decisions.
[9]**CMP** to include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium.
[10]**Cortisol, TSH and free T4** should be checked during screening and before each odd cycle starting with cycle 3.
[11]For women of childbearing potential: serum βhCG within 7 days prior to treatment initiation if clinically appropriate.
[12]**Tumor response assessment** will consist of evaluation by CT or MRI scans of chest, abdomen and pelvis. Additional imaging scans may be performed as clinically indicated in the opinion of the treating physician. Assessments will be performed at screening, and every 3 cycles starting with cycle 4. Tumor imaging may take place within 7 days prior to the study visit. Tumor imaging to be done at treatment discontinuation due to progression. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated.
[13]If prior PD-L1 and NGS testing was performed, submit results. If prior PD-L1 and NGS testing has not been performed, it should be ordered as standard of care. If testing cannot be performed as standard of care, fixed paraffin-embedded blocks or unstained slides will be requested from tumor specimen in all subjects, if available. See section 8 and CLM.
[14]Saliva samples for microbiome analysis will be collected before Cycle 1 Day 1, Cycle 4 Day 1 and at EOT visit.
[15]Plasma samples for ctDNA analysis will be collected before Cycle 1 Day 1, Cycle 4 Day 1 and at EOT visit.
[16]Fixed paraffin-embedded blocks or unstained slides will be requested from tumor specimen in all subjects (optional).
[17]Whole blood, serum, and plasma samples for circulating biomarkers (to be specified at a later time point) will be collected before Cycle 1 Day 1, Cycle 4 Day 1 and at EOT visit (optional).

7.1 Screening Evaluations

7.1.1 Within 28 days prior to registration for protocol therapy

- Informed Consent
- Medical history to include demographics, prior treatments, radiation and surgical history
- Physical exam
- Vital signs: blood pressure, heart rate, weight and height
- ECOG performance status
- Baseline signs and symptoms
- Concomitant medications
- Complete blood count (CBC): hematocrit, hemoglobin, total white cell count with differential, and platelet count.
- Comprehensive metabolic panel (CMP): albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium.
- Thyroid stimulating hormone (TSH) and free T4.
- Cortisol level
- Within 7 days of Cycle 1 Day 1 serum βhCG pregnancy test for women of childbearing potential (WOCP).
- Disease assessment to include evaluation by CT or MRI scans of chest, abdomen and pelvis. Additional imaging scans may be performed as clinically indicated in the opinion of the treating physician.

7.2 On Treatment Evaluations

Note: Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

7.2.1 Cycle 1 Day 1

- Physical exam
- Vital signs: blood pressure, heart rate, weight
- ECOG performance status
- Adverse event assessment
- Concomitant medications
- Drug diary instructions
- CBC with differential
- CMP
- Abemaciclib Days 1-21, bid
- Pembrolizumab IV Day 1

7.2.2 Cycle 1, Day 8 (±3 days)

- Vital signs: blood pressure, heart rate
- ECOG performance status
- Adverse event assessment
- Concomitant medications

- Drug diary instructions
- CBC with differential
- AST, ALT, total bilirubin

7.2.3 Cycle 2+, Day 1 (±3 days)

- Physical exam
- Vital signs: blood pressure, heart rate, weight
- ECOG performance status
- Adverse event assessment
- Concomitant medications
- Drug diary review
- CBC with differential
- CMP
- TSH, free T4 (on day 1 of odd numbered cycles only, starting with cycle 3)
- Cortisol (on day 1 of odd numbered cycles only, starting with cycle 3)
- Abemaciclib (Days 1-21, bid)
- Pembrolizumab Day 1

7.2.4 Cycle 2 and 3, Day 8 (±3 days)

- CBC with differential
- AST, ALT, total bilirubin

7.2.5 Every 3 Cycles (±7 days) starting with Cycle 4 Day 1

- Disease assessment with CT or MRI scans of chest, abdomen and pelvis. Additional scans may be ordered by the treating physicians as clinically indicated and depending on the known sites of disease.

7.2.6 Safety Follow-up Evaluations:

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of study drug or before the initiation of a new anti-cancer treatment, whichever comes first.

- Physical exam
- Vital signs: blood pressure, heart rate, weight
- ECOG performance status
- Adverse event assessment
- Concomitant medications
- CBC with differential
- CMP

7.2.7 Long Term Follow Up (every 90 days +/- 14 days) from Safety Follow Up Visit

Subjects will be followed for survival and disease progression after completing the end of treatment visit. Survival follow up should continue for 2 years (+/- 2 months) after EOT visit or until death, whichever is sooner. When possible, the following information will be obtained:

- Date of disease progression (if known)
- Anti-cancer therapy received since EOT visit

- Date of death

Follow up may be accomplished via clinic visit, phone call, medical record review, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please refer to the Correlative Laboratory Manual for collection, processing, and shipping details.

8.1 Correlative Studies from Tissue

8.1.1 PD-L1 Immunohistochemistry (IHC)

All subjects would ideally have had standard of care PD-L1 testing using PD-L1 22C3 pharmDx qualitative immunohistochemical assay. Assessment of PD-L1 in gastroesophageal cancer is determined using combined positive score (CPS). CPS represents percentage of all cells in tumor microenvironment that express PD-L1 (tumor cells, lymphocytes, macrophages) relative to all viable tumor cells.

If PD-L1 testing has been performed prior to study enrollment, results should be submitted. If subjects have not had PD-L1 testing done, it should be ordered as standard of care with the 22C3 antibody, if possible. The results will be collected for further correlative evaluations. If PD-L1 results with 22C3 antibody are not available, archival tissue samples should be submitted if available.

8.1.2 Tumor Molecular Profiling via Next Generation Sequencing

All subjects would ideally have had standard of care NGS testing already performed. If NGS testing has been performed prior to study enrollment, results should be submitted. If subjects have not had NGS testing done, it should be ordered as standard of care if possible. The results will be collected for further correlative evaluations. If NGS cannot be performed as standard of care, archival tissue samples should be submitted if available.

8.1.3 Circulating Biomarkers

8.1.3.1 Plasma for Circulating Tumor DNA (ctDNA)

Plasma samples will be collected for ctDNA analysis prior to treatment on Cycle 1 Day 1, prior to treatment on Cycle 4 Day 1 visit, to coincide with restaging scans, and at EOT visit.

8.1.4 Saliva Collection

Saliva samples will be collected for microbiome analysis prior to treatment on Cycle 1 Day 1, prior to treatment on Cycle 4 Day 1 visit, to coincide with restaging scans, and at EOT visit.

8.1.5 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.2 Sample Collection and Banking for Future Unspecified Research

Subject consent will be obtained to collect additional samples for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1, before Cycle 4 Day 1, and at EOT visit.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1, prior to treatment on Cycle 4 Day 1 visit, to coincide with restaging scans, and at EOT visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1, prior to treatment on Cycle 4 Day 1 visit, to coincide with restaging scans, and at EOT visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample if available. Repeat biopsy will not be mandatory if archival tumor tissue is not available.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.3 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's Big Ten CRC sequence number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Overview

Both RECIST 1.1 and irRECIST will be used for disease evaluation. RECIST has some limitations when applied to immunotherapy and oncology. Tumors that initially progress per RECIST may subsequently regress. As such, in cases of radiologic progression per RECIST 1.1 but with clinical stability or benefit, irRECIST criteria will be applied. Subjects may continue on treatment past radiological progression on the first set of restaging scans. Disease status will be re-evaluated with repeat scans 4-9 weeks later compared to new baseline established on treatment.

9.2 Timing of Radiographic Evaluations

All subjects will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to first dose date.

The first on-study imaging assessment should be performed prior to initiation of cycle 4. Subsequent tumor imaging should be performed every 3 cycles (±7 days) or more frequently if clinically indicated and at the time of suspected disease progression.

Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed by a repeat tumor imaging assessment. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 3 cycles after the previous scan), whichever is clinically indicated. Additionally, progressive disease (PD) should also be confirmed a minimum of 4 weeks and up to 9 weeks after the first PD assessment; patients may remain on study treatment while awaiting confirmation provided the patient is clinically stable.

Subjects who discontinue treatments for reasons other than disease progression (clinical or radiographic) will not be required to continue getting imaging per schedule outlined in the protocol.

9.3 Assessment of Response per RECIST

9.3.1 Measurable Disease

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

9.3.2 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.

9.3.3 Non-measurable Lesions

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. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: 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 subject, these are preferred for selection as target lesions.

9.3.4 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, but 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.

9.3.5 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.

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

9.3.7 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
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.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.3.8 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.4 Assessment of Response by Immune-Related RECIST

RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen during treatment with CTLA-4 and PD-1/PD-L1 inhibitors. irRECIST will be used by local site investigators to assess tumor response and progression and make treatment decisions.

irRECIST adaptations compared to RECIST v1.1:

- If repeat imaging shows < 20% increase in tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed, and the next tumor imaging should be conducted according to the protocol schedule of every 3 cycles (± 7 days)
- If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site Investigator should consider all target and non-target lesions, as well as any incremental new lesion(s).

If ANY of the following occur by irRECIST on repeat imaging, PD is confirmed:

- Tumor burden remains ≥ 20% and at least 5-mm absolute increase compared with nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

Table 10: Imaging and Treatment after First Radiologic Evidence of Progressive Disease via irRECIST

Tumor Assessment		Confirmation of Response
irCR	Disappearance of all measurable and non-measurable lesions. Lymph nodes must have reduction in short axis to < 10 mm.	Required
irPR	At least 30% decrease in the sum of diameters of measurable lesions, taking as reference the baseline sum diameters.	Required
irSD	Shrinkage does not qualify for irCR/irPR or increase does not qualify for irPD.	Nor required
irPD	At least 20% increase and absolute increase of at least 5 mm in sum of the diameters of measurable lesions. The appearance of new lesions is not considered PD but are to be included in the sum diameters.	Confirmation required at least 4 weeks after the first irPD assessment provided the patient is considered clinically stable

Abbreviations: irCR=immune-related complete response; irPR=immune-related partial response; irSD=immunerelated
stable disease; irPD=immune-related progressive disease; PD=progressive disease

9.5 Treatment and Assessment After Progression

There is accumulating evidence indicating clinical benefit in a subset of patients treated with immunotherapy despite initial evidence of PD per RECIST. During study treatment, a subject with initial evidence of radiological PD per RECIST may continue on study treatment until repeat imaging is obtained (at least 4 weeks and up to 9 weeks later). Investigator's decision to continue treatment beyond the initial assessment of progression should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. A subject may receive study treatments while waiting for confirmatory imaging if he/she is clinically stable per the following criteria:

- Absence of signs and symptoms indicating clinically significant progression of disease, including worsening of laboratory parameters
- No decline in performance status
- Does not have rapid progression of disease
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases, cord compression)

Whenever possible, patients should not be discontinued until progression is confirmed.

9.6 Definitions for Response Evaluation – RECIST 1.1 and irRECIST

9.6.1 Progression-Free Survival

A measurement from the date of the start of treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. PFS will also be measured as the time of first documentation of disease progression per irRECIST as a secondary endpoint.

9.6.2 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment). 6 months PFS Rate 6 months PFS rate is defined as the proportion of subjects who have experienced no progressive disease at a 6 month time point from time of treatment initiation using RECIST and irRECIST criteria.

9.6.3 Disease Control Rate

The disease control rate is the proportion of all subjects with stable disease (SD) for 16 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment). RECIST and irRECIST criteria will be applied

9.6.4 Overall Survival

Overall survival is defined by the date of the start of treatment to date of death from any cause.

9.7 Safety and Tolerability

Safety and tolerability of abemaciclib in combination with pembrolizumab by NCI CTCAE version 5.

10. DRUG INFORMATION

10.1 Abemaciclib (Other names: VERZENIO™)

Please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or on the manufacturer's website.

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

10.1.1 Supplier/How Supplied

Eli Lilly and Company will supply abemaciclib at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Please refer to the package insert for instructions on preparation of abemaciclib.

10.1.3 Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.1.4 Handling and Disposal

Please refer to the package insert for instructions on proper handling of abemaciclib.

10.1.5 Dispensing

Abemaciclib must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Abemaciclib should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

Most common adverse reactions (incidence ≥20%) were diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, and thrombocytopenia.
Please refer to the package insert for the comprehensive list of adverse events.

10.2 Pembrolizumab (other names: KEYTRUDA®, MK-3475, Anti-PD-1 Antibody MK-3475)

Please refer to the latest version of the prescribing information that can be found at *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*, and/or on the manufacturer's website.

Pembrolizumab is a highly selective humanized monoclonal IgG4 antibody directed against the programmed death-1 (PD-1) receptor on the cell surface. The drug blocks the PD-1 receptor, preventing binding and activation of programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). This mechanism causes the activation of T-cell mediated immune responses against tumor cells.

10.2.1 Supplier/How Supplied

Commercial supplies of pembrolizumab will be used in this study and billed to third party payers or the subject.

- Pembrolizumab for injection is supplied as a white to off-white lyophilized powder: carton containing one 50 mg single-dose vial.
- Pembrolizumab injection is supplied as a clear to slightly opalescent, colorless to slightly yellow solution: carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial.

10.2.2 Preparation

Please refer to the package insert for instructions on preparation of pembrolizumab.

10.2.3 Storage and Stability

Pembrolizumab does not contain a preservative. Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution.

If refrigerated, allow the diluted solution to come to room temperature prior to administration. Discard after 6 hours at room temperature or after 24 hours under refrigeration. Do not freeze.

10.2.4 Handling and Disposal

Please refer to the package insert for full instructions on proper handling of pembrolizumab.

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis. Pembrolizumab should be disposed at the site following procedures for the disposal of anticancer drugs.

10.2.5 Adverse Events

Most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. For more detailed information on adverse reactions, warnings, and precautions please refer to the pembrolizumab package insert.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)

Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form (see SPM) to Big Ten CRC AHQ within **1 business day** of discovery of the event**.** The form will be sent electronically to Big Ten CRC AHQ at safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved, sites must electronically submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at safety@hoosiercancer.org.

Big Ten CRC AHQ Requirements for Reporting SAEs to Eli Lilly and Company

Big Ten CRC AHQ will report SAEs to Eli Lilly and Company within **1 business day** of receipt of the SAE Reporting Form from a site. Follow-up information will be provided to Eli Lilly and Company as it is received from a site.

Big Ten CRC AHQ will fax all SAE reports and any other relevant safety information to Eli Lilly and Company (Attn: Global Patient Safety; FAX 866-644-1697 or 317-453-3402).

Big Ten CRC AHQ will provide follow-up information to Eli Lilly and Company Global Patient Safety as reasonably requested.

Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

The FDA has concluded this protocol is exempt from the requirements of an IND. Big Ten CRC AHQ will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

IND Safety Reports Unrelated to this Trial

Eli Lilly and Company will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a multi-institutional Big Ten CRC single arm, phase II study of the combination of abemaciclib and pembrolizumab in subjects with advanced, unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.

12.2 Endpoints

12.2.1 Primary Endpoints

- PFS is defined as the time of treatment initiation until the criteria for disease progression per RECIST1.1 are met or until the date of a death event (any cause).

12.2.2 Secondary Endpoints

- OS is defined as the time of treatment initiation until death from any cause.
- ORR as measured as percent of patients who achieved objective response per RECIST 1.1 and irRECIST criteria while on treatment
- DCR is defined as percent of patients with stable disease, partial response and complete response after treatment initiation per RECIST 1.1 and irRECIST.
- PFS per irRECIST is defined as the time of treatment initiation until the criteria for disease progression per irRECIST are met or until the date of a death event (any cause).
- PFS rate at 6 months (RECIST and irRECIST) is defined as the percent of patients without a progression (or death event) at month 6 after treatment initiation.
- Safety and tolerability of abemaciclib in combination with pembrolizumab in patients with advanced, unresectable or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma, assessed by NCI CTCAE version 5.

12.3 Sample Size and Accrual

The primary efficacy endpoint is used to determine the sample size for this study. The primary efficacy endpoint is PFS. A median PFS of 2 months has been reported in this patient population in patients treated with pembrolizumab alone. If the addition of abemaciclib results into a median PFS at most 2 months, then the efficacy of the proposed combination therapy will be considered as unacceptably low. Hence, the null hypothesis that the median PFS is 2 months or less will be tested against the alternative hypothesis that the median PFS is greater than 2 months. A median PFS of at least 4 months will be considered sufficient evidence to consider further clinical investigation of the proposed treatment combination. A sample size of 31 evaluable subjects is required to detect an increase in the median PFS from 2 months (null hypothesis) to 4 months with 80% power at the one-sided 0.05 significance level. This calculation is based on the non-parametric Brookmeyer-Crowley method for time to event endpoints[16], assuming that the accrual follows a uniform distribution with an accrual period of 12-18 months and a minimum follow-up period of 6 months for each subject. Analogously, a median PFS of 5 months will be detected with 92% power while a median PFS of only 3 months will be detected with 51% power. In order to account for non-evaluable subjects (~10%), a total of 34 subjects will be enrolled.

12.4 Assessment of Safety

The safety population consists of all eligible study participants who received at least one dose of abemaciclib or pembrolizumab. Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

12.5 Assessment of Efficacy

The efficacy population consists of all evaluable study participants. A study participant is evaluable for efficacy assessment if (1) the subject completes at least one cycle of the abemaciclib (Day 1-21)/pembrolizumab (Day 1) therapy and (2) and completes at least one post-baseline disease assessment.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

PFS will be analyzed using the Kaplan-Meier method. The median PFS will be reported along with the corresponding two-sided 95% confidence interval which will be constructed using the non-parametric Brookmeyer-Crowley method[16].

12.6.2 Analysis Plans for Secondary Objectives

OS will be analyzed using the Kaplan-Meier method. The median OS will be reported along with the corresponding 95% confidence interval which will be constructed using the non-parametric Brookmeyer-Crowley method[16]. ORR, DCR, and PFS rate at 6 months will be summarized in tabular format and reported along with the corresponding two-sided 95% confidence intervals which will be constructed using the Wilson score method. The number and frequencies of toxicities will be summarized in tabular format.

12.6.3 Analysis Plans for Exploratory Objectives

Univariable and multivariable Cox proportional hazard regression analyses will be conducted to evaluate whether PD-L1 status and molecular signatures from NGS analysis predict PFS or OS. Analogously, univariable and multivariable Cox proportional hazard regression analyses will be conducted to evaluate whether PD-L1 status and molecular signatures from NGS analysis predict ORR, DCR or PFS rate at month 6. Age, disease type, stage, performance status and tumor CSP score (0 vs. 1-9 vs. 10+) will be included as covariates in the multivariable analyses. Due to the small sample size, these analyses will be considered exploratory.

12.6.4 Other Planned Analyses

Descriptive statistics will be provided to summarize demographics and baseline characteristics parameters of all study participants. Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each of the parameters.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The University of Wisconsin Carbone Cancer Center's Data Safety Monitoring committee will oversee the conduct of this study.

Big Ten CRC AHQ oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their DSMP

13.2 University of Wisconsin Data Safety Monitoring Committee

The DSMC will review the following:

- Adverse event summary report
- Audit results, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The University of Wisconsin DSMC will review AE data twice a year. Documentation of DSMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with Big Ten CRC AHQ to address the DSMC's concerns.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites will be made periodically during the trial to ensure key aspects of the protocol are followed. On-site for-cause monitoring visits will occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Eli Lilly and Company or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality

control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Eli Lilly and Company, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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