

Phase I/II Study of Abemaciclib + Ramucirumab in Metastatic Esophageal/Gastroesophageal Junction Carcinomas

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PROTOCOL SIGNATURE PAGE

Study Title: Phase I/II Study of Abemaciclib + Ramucirumab in Metastatic Esophageal/
Gastroesophageal Junction Carcinomas

Protocol Number: 2.1

IRB Number: 020-055

I have read this protocol and agree to adhere to the requirements outlined within. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed regarding the requirements of this protocol. I will also ensure that this study is conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory agencies and their requirements.

Clinical Investigator (Printed Name)

Clinical Investigator (Signature)

Date

PROTOCOL AMENDMENT HISTORY TABLE

Protocol #/Version Date	Section (section with page #)	Language Added/Revised/Deleted	Rationale
2.1, 26Sep2022	Participating Institutions, Pg. 1	Revised name of the investigator at the participating institution, Alleghany Health Network Pittsburgh PA, from Blair Job, MD to Moses Raj, MD.	Change in investigator.
2.1, 26Sep2022	6.1 Recruitment, Pg. 32	Added nomenclature process for assigning subject numbers and listed site numbers in the protocol.	To establish links for data entry and analysis.
2.1, 26Sep2022	14.1 Screening, Pg. 64; Table 13, Pg. 74	Revised PET/CT scan option at screening, a PET scan may also be performed (not required). Subjects are required to have only a CT scan at screening.	To align with standard of care treatment.
2.1, 26Sep2022	14.1 Screening, Pg. 64; Table 13, Pgs. 74-75	Revised urinalysis requirement to be done within 2-4 weeks prior to strat of therapy and at Cycle 1 Day 1.	Revised to demonstrate subjects meet inclusion criteria at screening and Day 1 of treatment.
2.1, 26Sep2022	14.1 Screening, Pg. 64; Table 13, Pgs. 74-75	Removed amylase and lipase lab tests.	These lab tests are not required to assess safety.
3.0, 04Oct2023	Table of Contents, Pgs. 8-9, and throughout Protocol	Revised section numbers in the Table of Contents and throughout the Protocol.	To align with protocol revisions requiring section renumbering.
3.0, 04Oct2023	Synopsis, Pg. 11	Revised "Main Site" to "Coordinating Site".	To align with wording throughout the protocol.
3.0, 04Oct2023	6.1 Recruitment, Pg. 32	Revised participant number description to include main site IRB protocol number, site initials, and the sequential number at the time of consent.	To more accurately reflect the description of the participant number.
3.0, 04Oct2023	7.1 Recruiting, Pgs. 37-38; 8.0 Concomitant Treatments, Pg. 53; Table 18, Pg. 77; 23.2.2 Case Report Form Procedures, Pg. 93	Deleted OpenClinica. Added REDCap.	To accurately reflect the database used for data.
3.0, 04Oct2023	7.1 Registration and Informed consent process, Pg. 38	Revised "consenting" to "consent". Revised "once consent is obtained" to "After signed consent".	Grammatical correction.

3.0, 04Oct2023	13.0 Data Safety Review Committee (DSRC), Pgs. 61-62	Deleted section "Data Safety Review Committee (DSRC)".	To align with regulatory requirements and standard study conduct.
3.0, 04Oct2023	17.1 Data Management, Table 18, Pg. 77	Deleted "registration tab". Added "'Eligibility Criteria' eCRF".	To align with data field established in REDCap.
3.0, 04Oct2023	17.1 Data management, Pg. 78	Deleted "Data monitoring of this protocol will occur as indicated in section 13" and "done through the Safety Review Committee (SRC) at". Added "conducted during teleconferences of investigators and study staff from the sites which are scheduled by BSWUMC CORC Department as outlined in section 19.0."	To align with regulatory requirements and standard study conduct.
3.0, 04Oct2023	17.1 Data management, Pg. 78	Deleted "Clinical Oncology Research Coordination". Added "(CORC)" or "CORC" in areas following the first referenced. Revised monitor to monitored.	Grammatical correction.
3.0, 04Oct2023	19.0 Monitoring Meetings, Pg. 79	Deleted "bi-weekly" and "both". Added "Routine" and "Frequency of teleconferences will be based on subject enrollment and will be held no less than once every other month". Deleted "Dr. Ronan Kelly". Added "the Lead PI".	To align with standard study conduct.
3.0, 04Oct2023	21.0 Coordinating Center, Pg. 90	Added "The coordinating site will collect and manage the study data using the BSWRI REDCap platform. Following data collection and analysis, this data will be removed from REDCap and archived on a limited access shared drive for 2 years after closure of the study, after which the data will be destroyed."	To clarify data management and retention timeline.

ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CMP	Complete metabolic profile
CO ₂	Carbon dioxide
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CR	Complete response
CRF	Case report form
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
gm	Gram
HgB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ID	Identification
ITT	Intent to treat
IV	Intravenous
mg	milligram
mL	milliliter
MRI	Magnetic resonance imaging
NE	Not evaluable
PI	Principal Investigator
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
ULN	Upper limits of normal
WLN	Within normal limits

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SYNOPSIS

Protocol Title:	Phase I/II Study of Abemaciclib + Ramucirumab in Metastatic Esophageal/Gastroesophageal Junction Carcinomas
Study Phase:	I/II
Research Hypothesis:	CDK4/6 and Cyclin D1 are significantly expressed in approximately 80% of esophageal and gastroesophageal junction tumors suggesting that CDK4/6 inhibition may be a successful strategy in these chemotherapy and immunotherapy resistant diseases.
Study Objectives:	Primary Objective: To describe the safety profile of Abemaciclib + Ramucirumab as assessed according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). Secondary Objectives: 1) To assess response rate, progression free and overall survival; 2) To determine the rate of stable disease at 3 months post targeted therapy; 3) Correlative studies - changes in the expression of selected serum/tissue genomic markers of interest.
Treatment Plan & Study Design:	Subjects with previously treated metastatic esophageal or gastroesophageal junction adenocarcinomas are eligible for this study. Subjects will be treated with combination Abemaciclib plus Ramucirumab.  <pre> graph LR A["Stage IV E/GEJ cancer previously treated with chemotherapy in first line setting"] -- "30 Pts" --> B["Abemaciclib + Ramucirumab"] </pre> Primary objective: - Safety and Feasibility Secondary objectives: - Response Rate, Progression Free Survival, Overall Survival
Investigational Product(s):	Abemaciclib, an FDA-approved drug for the treatment of patients with breast cancer. It is not currently approved for the treatment of metastatic esophageal/gastroesophageal junction carcinomas Ramucirumab, is an FDA-approved drug for the treatment of patients with advanced gastric or gastro-esophageal junction adenocarcinoma
Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):	Abemaciclib 150mg dose administered orally twice daily every day plus Ramucirumab dose 8mg/kg iv every 2 weeks until evidence of disease Progression or unresolved toxicity.
Number of Subjects	30

Study Population:	Subjects must meet all eligibility criteria. The key inclusion and exclusion criteria are as follows: Key Inclusion Criteria: • All subjects must have metastatic esophageal or gastroesophageal junction carcinomas (adenocarcinoma only) • ECOG performance status of 0 or 1 • Tumor tissue must be available for correlative studies - Either a formalin fixed paraffin block or a minimum of ten 5-micron tissue section's (slides) of tumor biopsy sample must be available for biomarker evaluation. • Patients must have received at least one prior line of standard systemic therapy for recurrent or Stage IV disease, and that patients with HER2 overexpression have received an anti-HER2 drug. Key Exclusion Criteria: • Squamous cell carcinomas • Mixed histology with small cell components Refer to section 6.2 for detailed inclusion and exclusion criteria
Lead PI and Coordinating site Principal Investigator:	Ronan Kelly, MD (Lead PI and Baylor Scott and White University Medical Center - PI)
Sub Site Principal investigator/s:	Vincent Lam-Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Moses Raj -Allegheny Health Network Pittsburgh PA
Study Sites:	Coordinating Site: Baylor Charles A. Sammons Cancer Center, Dallas, Tx Sub Site: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Sub Site: Allegheny Health Net Work
Duration of Study:	2 years
Efficacy Assessments	Overall response rate (ORR), rate of stable disease (SD) at 3 months, progression free survival (PFS), overall survival (OS), changes in the expression of selected serum/tissue genomic markers of interest
Safety Assessment	Toxicity
Statistical Considerations:	Sample Size Justification A total of 30 subjects will be enrolled. The primary goal is to describe the safety profile of Abemaciclib in combination with Ramucirumab among all enrolled subjects. If grade 3 or higher treatment-related adverse events occur in 20 subjects, the upper bound of 95% Wilson confidence interval for the adverse event rate would be below 81% (16.7% - 47.9%). Table 1 lists confidence intervals for some potential results.

Table 1: The number of subjects with grade 3 or higher adverse events and their corresponding confidence intervals

Number of Subjects with Grade 3 or Higher Adverse Event	95% Confidence Interval of Grade 3 or Higher Adverse Event
18	(42.3%, 75.4%)
19	(45.5%, 78.1%)
20	(48.8%, 80.8%)
21	(52.1%, 83.3%)
22	(55.5%, 85.8%)

If 11 subjects achieved an objective response by RECIST1.1 criteria, the upper bound of 95% Wilson confidence interval of ORR would be higher than 20% (16.7% - 47.9%). Table 2 lists confidence intervals for some potential results.

Table 2: The number of subjects who achieved objective response and their corresponding confidence intervals

Number of Subjects Who Achieved Objective Response	95% Confidence Interval of Subjects Who Achieve Objective Response
9	(16.7%, 47.9%)
10	(19.2%, 51.2%)
11	(21.9%, 54.5%)
12	(24.6%, 57.7%)
13	(27.4%, 60.8%)

Analysis plan

The safety analysis will be performed in all treated subjects. Adverse event data will be listed individually and graded according to the National Cancer Institute Common Terminology Criteria, version 4.03. Summary statistics will include counts and proportions as well as rates with 95% confidence intervals. Toxicities will be reported as a tabulated table by type and grade.

Objective response rate is defined as the percentage of subjects who achieve an objective response by RECIST1.1 criteria (i.e. Complete response or Partial Response) to Abemaciclib in combination with Ramucirumab. We will estimate the objective response rate, along with the Wilson 95% confidence interval, for the population of subjects.

Overall survival will be defined as the time from study enrollment to death. This will be summarized using a Kaplan-Meier curve. Progression-free survival will be measured from the time of randomization to radiographic tumor progression or death, and summarized using a Kaplan-Meier curve.

Stopping guidance

The proportion of subjects with grade 4 or higher treatment-related adverse events will be monitored continuously throughout the trial using a Bayesian stopping guideline. A Beta (1, 19) prior, representing a toxicity rate of 5%, slightly lower than the expected rate of 6%, was used in the development of our guidelines. The therapy will be re-evaluated if the posterior probability that the toxicity rate exceeds 10% is greater than 75%. Table 3 summarizes the stopping boundaries starting with the initial cohort of 3 subjects through the maximum sample size of 30 subjects.

Table 3: The number of unacceptable toxicities needed to trigger stopping guidelines throughout the course of the study

Number of subjects	Number Needed to trigger re-evaluation
3-6	3
7-15	4
16-23	5
24-30	6

The probability of triggering the stopping guidelines was assessed for a range of possible toxicity rates using simulations with 5000 replicates (Table 4). The probability of stopping to re-evaluate was 1% if the true proportion with an unacceptable toxicity was 5%. In comparison, the probability of stopping early was 99.6% if the true proportion with an unacceptable toxicity was 40%.

Table 4. Probability of triggering a re-evaluation for a range of values for the true underlying toxicity rate.

True probability of grade 3 or higher adverse events	Probability of triggering stopping guideline	Average sample size
1%	<1%	30
5%	1%	30
10%	11.8%	29
20%	63.3%	21
40%	99.6%	10

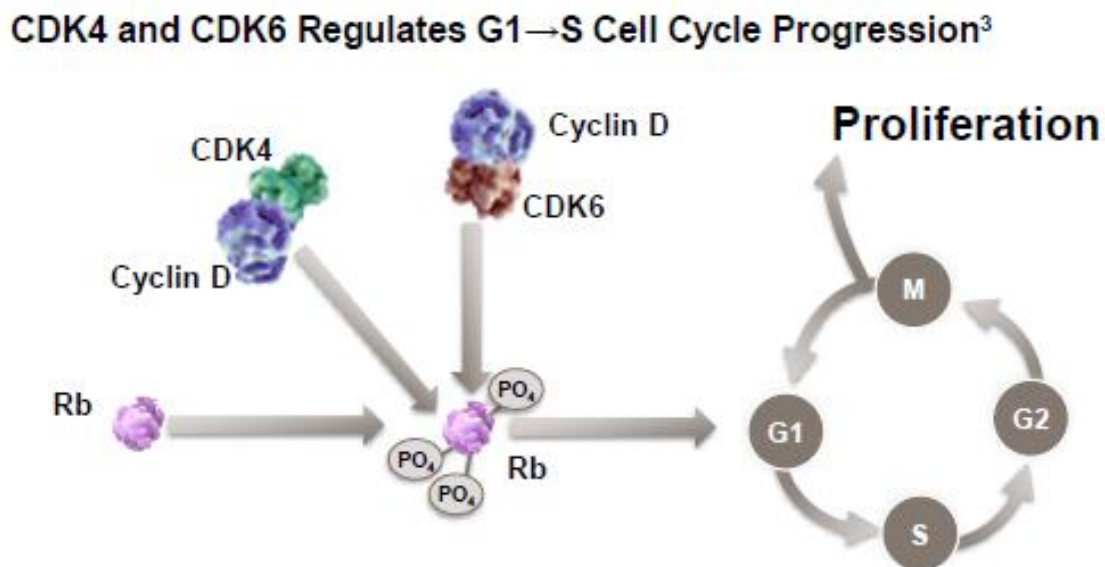
PART I – CLINICAL TRIAL PROTOCOL

1.0 Introduction

1.1 Study Rationale/Background

Cyclin dependent kinases (CDKs) are serine/threonine kinases that are responsible for phosphorylating the intracellular proteins that coordinate cell-cycle progression[1]. Cyclin D1 and CDK4/6 play an integral role in cell-cycle progression by phosphorylating and inactivating the retinoblastoma protein which acts as a tumor suppressor restraining G1-to S-phase progression[1, 2]. Cyclin D1 increases upon signaling from a number of pathways including the human epidermal growth factor receptor (EGFR) pathway which is known to be overexpressed in esophageal cancer. As cyclin D1 accumulates they associate with CDK4/6 and they result in phosphorylation of Rb protein. When unphosphorylated, Rb prevents advance from G1 to S by repressing the E2F family of transcription factors by blocking their transactivation domains and recruiting histone deacetylase. The Cyclin D/CDK4/6 complex initiates phosphorylation of Rb which results in a conformational change that inhibits histone deacetylase binding and permits subsequent hyperphosphorylation by cyclin E-CDK2 which results in E2Fs being released and a transcriptional program that allows S-phase entry to be initiated[1, 2].

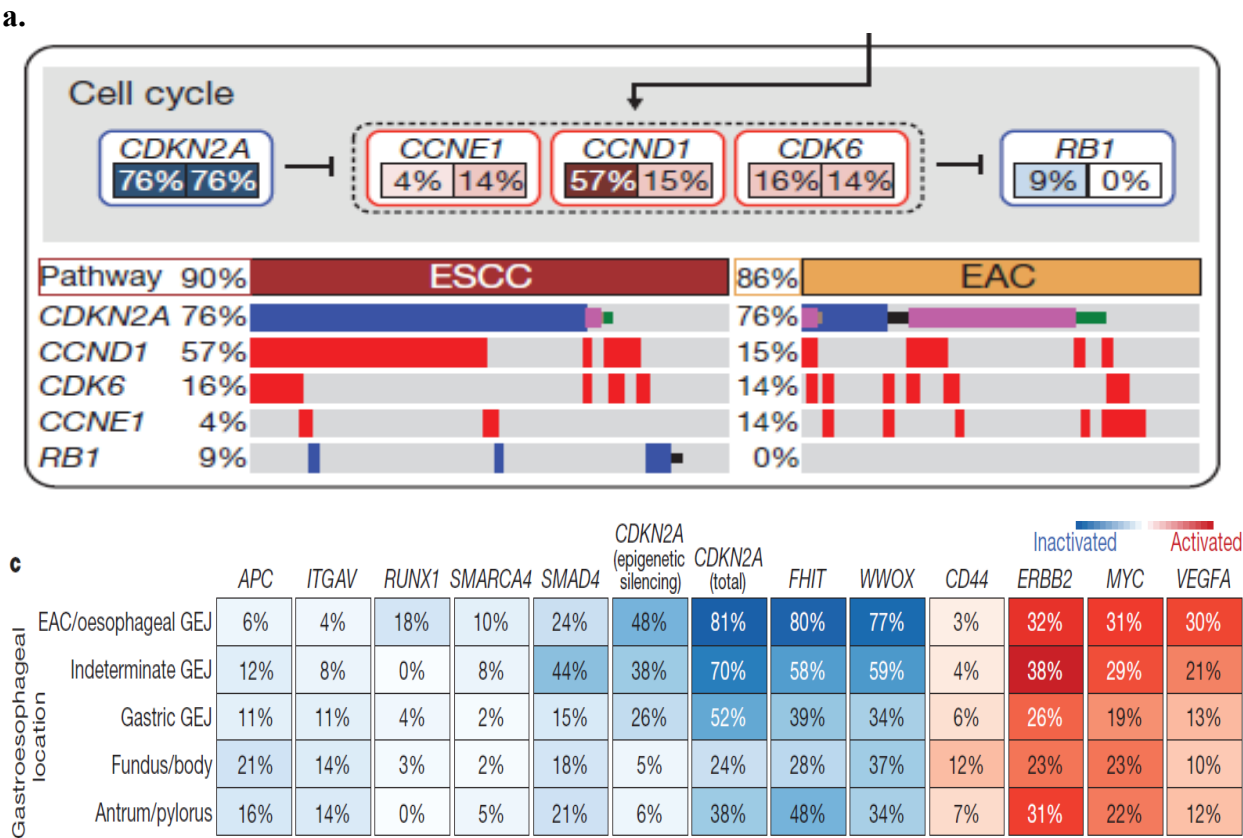
Figure 1



The balance between mitogenic signaling and inhibitory signaling in G0/G1, is reflected by cyclin D levels and cyclin D-CDK4/6 activity. Once Rb is hyperphosphorylated the cell is committed to completing the cell cycle and on the most part is unresponsive to external stimuli. As this commitment occurs late in G1phase it is likely that inhibitors of CDK4-6-cyclin D1 may be of the greatest therapeutic benefit of all cell cycle inhibitors in development. Specific tumors like esophageal cancer are known to have significant cyclin D1 amplification and CDK4 copy number gain alterations. The recently published TCGA molecular analysis of esophageal/gastroesophageal junction (E/GEJ) carcinomas has highlighted significant dysregulation of *CDKN2A*, the gene coding for the tumor suppressor *p16*, through deletion or epigenetic silencing in up to 81% of cases and the associated significant upregulation of the CDK4/6-Cyclin D- axis[3]. This clearly represents a viable new target in gastroesophageal tumors, which, with the exception of Trastuzumab and Ramucirumab have seen limited therapeutic advances in recent years.

Figure 2

(a) *CDKN2A* epigenetic silencing for EAC and ESCCs and (c) frequency of alterations in selected genes along the anatomic axis with tumor suppressor inactivation in blue and oncogene activation in red (Integrated genomic characterization of esophageal carcinoma, TCGA, Nature 2017)[3].



Abemaciclib is a highly specific ATP-competitive CDK4/6 inhibitor that induces reversible G1-phase cell-cycle arrest in retinoblastoma-positive tumor models. Abemaciclib demonstrates IC50s of 2 nmol/L and 10 nmo/L for CDK4 and CDK6, respectively (Abemaciclib Investigator Brochure). In a phase I study in advanced solid tumors, the twice-daily regimen of 200mg was selected as a result of the sustained inhibition of pRb in pharmacodynamic correlatives and improved tolerability. One hundred and ninety-two patients were treated in tumor specific cohorts. All grade toxicities were mostly grade 1 and grade 2 and included diarrhea (63%), nausea (45%), and fatigue (41%). Rates of myelosuppression were lower with Abemaciclib than with other CDK4-6 inhibitors which may allow for longer continuous administration.

In conclusion, CDK4/6 inhibitors are an extremely promising cell-cycle therapeutics which represents an exciting area of clinical research in esophageal and gastroesophageal cancers which are relatively chemotherapy resistant and have modest responses to single agent PD-1 inhibition as witnessed by the negative press releases for two recent phase III trials, Keynote 061 and Javelin 300 for pembrolizumab and avelumab respectively.

Preclinical Data:

Drs Zaidi/Jobe/Kosovec and colleagues at AHN in collaboration with Dr Kelly at Johns Hopkins have demonstrated that single agent Abemaciclib has potent antitumor efficacy both *in vitro* and *in vivo* in EAC with direct pathway inhibition[4]. Significant activity was seen in the OE33 (p=0.048) and FLO1 (p=0.043), esophageal cancer cell lines while western blot revealed downregulation of Cyclin D, phospho-pRb, E2F1, and Cyclin A2[4]. *In vivo* experiments, utilizing the Levrat model of end-to-side esophagojejunostomy performed on Sprague-Dawley rats demonstrated that 78.9% of animals given Abemaciclib demonstrated >20% tumor volume decrease (placebo 0%)[4]. Mean tumor volume change in the treatment arm was -65.5% (placebo +133.5%), and prevalence changed by -37.5% (placebo +16.7%)[4]. Post treatment comparison between placebo and abemaciclib of qRT-PCR gene expression demonstrated downregulation of pathway correlates, including CDK4 (p=0.023), CDK6 (p=0.068), E2F1 (p=0.005), Rb1 (p=0.067), Cyclin D (p=0.031), and Cyclin A (p=0.039) (See figures 3 to 8 below)[4]. Eli Lilly has internal data on the safety of combining Ramucirumab with Abemaciclib from a phase I study performed in patients with a variety of solid tumors (see clinical data).

Figure 3

A. CDK4/6 pathway. Tumor suppressor p16 normally inhibits Cyclin D-CDK4/6 complex, resulting in the release of E2F transcription factor and commitment to S-phase of the cell cycle. **B. in vivo study design.** Modified Levrat surgery was performed on Sprague-Dawley rats to induce EAC. After 36 weeks, all animals received a baseline MRI scan and endoscopic biopsy and were randomized to control and treatment arms. At 40 weeks post-surgery, all rats received a final MRI and were euthanized. The entire esophagus was harvested 1cm distal to the anastomosis for histological and downstream molecular correlate analysis (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic option for a deadly disease. Oncotarget 2017)[4]

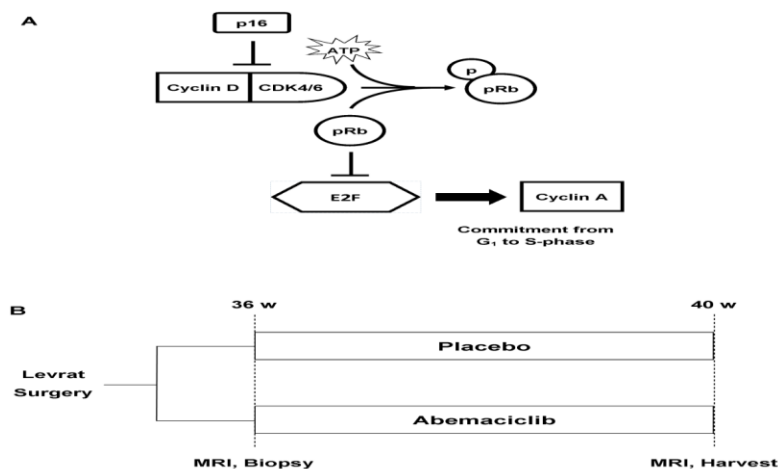


Figure 4

Apoptosis. EAC cell lines OE19, OE33, and FLO1 were utilized to evaluate the effects of abemaciclib on apoptosis through flow cytometry analysis using Annexin-V and Calcein to stratify early and late apoptotic effects. With treatment, total apoptosis increased across all three cell lines by 123.9%, 103.7%, 145.5%, respectively. Early apoptosis also increased by 172.7%, 229.7%, 108.7%, respectively. (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic option for a deadly disease. Oncotarget 2017)[4].

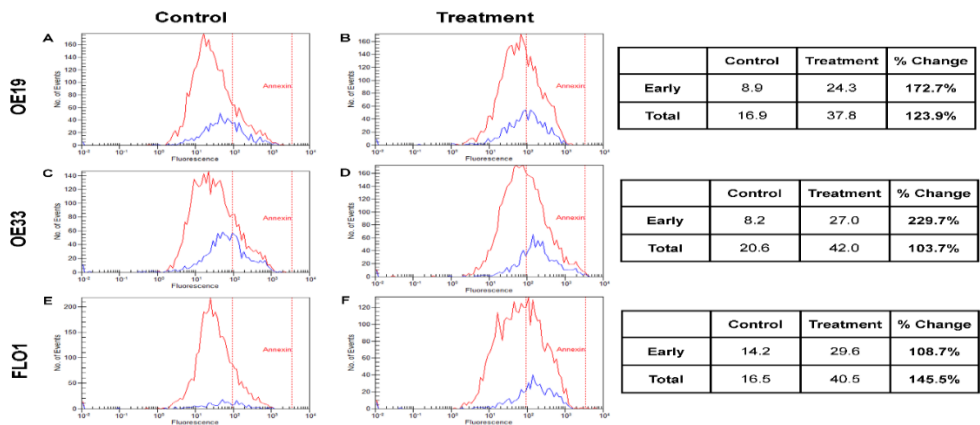


Figure 5

(A) Proliferation. Esophageal adenocarcinoma cell lines OE19, OE33, and FLO1 were utilized for proliferation analysis by BrdU ELISA using an ED50 of 10μM, 6μM, and 14μM, respectively. Proliferation significantly decreased in both OE33 and FLO1 after treatment with abemaciclib. (B) Western blot. Protein expression analysis revealed downregulation of Cyclin D1, E2F1, p-pRb, and Cyclin A2 across all cell lines due to treatment with abemaciclib (+) when compared to untreated (-). (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic option for a deadly disease. Oncotarget 2017)[4].

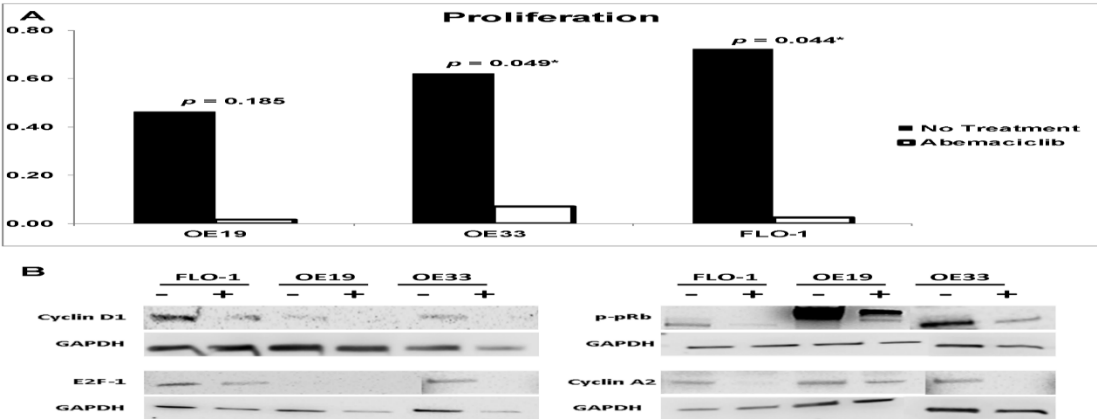


Figure 6

(A) Tumor prevalence change by MRI analysis. On comparison of pre and post-treatment MRI between Placebo and Treatment groups, animals receiving abemaciclib demonstrated a decrease in tumor prevalence by 37.5%; whereas control animals displayed an increase in prevalence by 16.7% (p<0.01). (B,C) MRI Tumor Response. Pre (B) and post (C) treatment MRI scans of a single animal demonstrating complete response on imaging after treatment with abemaciclib. Red arrow indicates tumor area. (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic option for a deadly disease. Oncotarget 2017)[4].

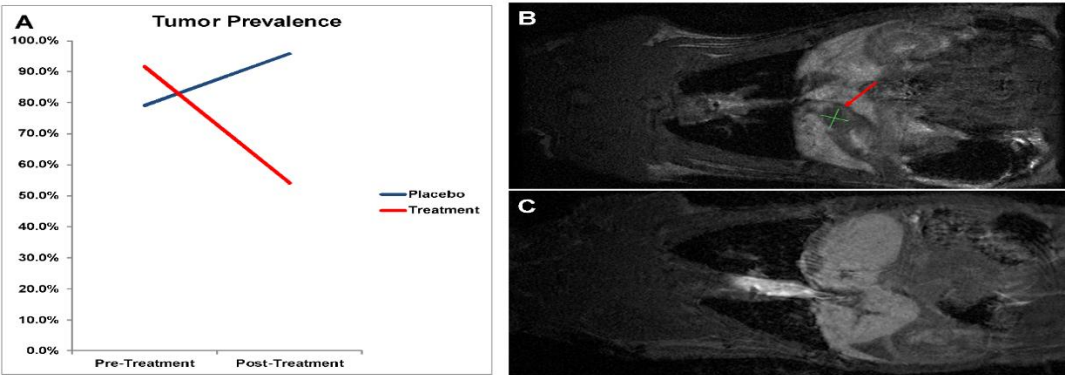


Figure 7

A. Percentage of animals with change in tumor volume. On comparison of pre and post-treatment MRIs, 78.9% of placebo animals demonstrated an increase in tumor volume, and 21.1% had stable disease. Following treatment with abemaciclib, 81.8% of animals demonstrated a decrease in tumor volume, and 18.2% had stable disease. RECIST criteria of <20% increase or <30% decrease in volume were classified as stable. **B. Mean percent change in tumor volume.** Following treatment, animals in the placebo arm demonstrated a mean increase in tumor volume of 133.5%. Conversely, animals treated with abemaciclib revealed a mean decrease in tumor volume by 65.5% ($p<0.01$). (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic option for a deadly disease. Oncotarget 2017)[4].

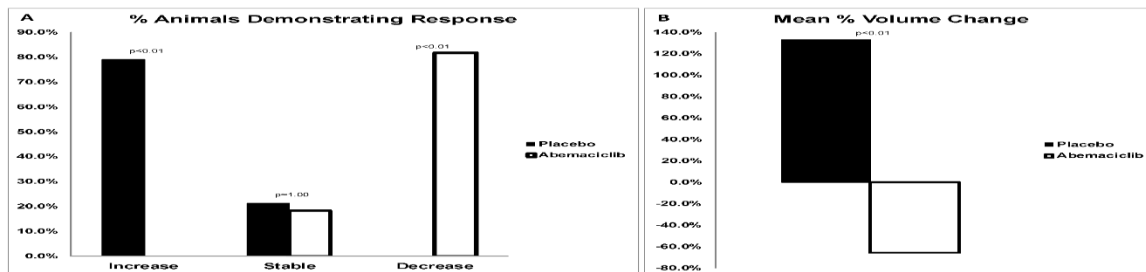
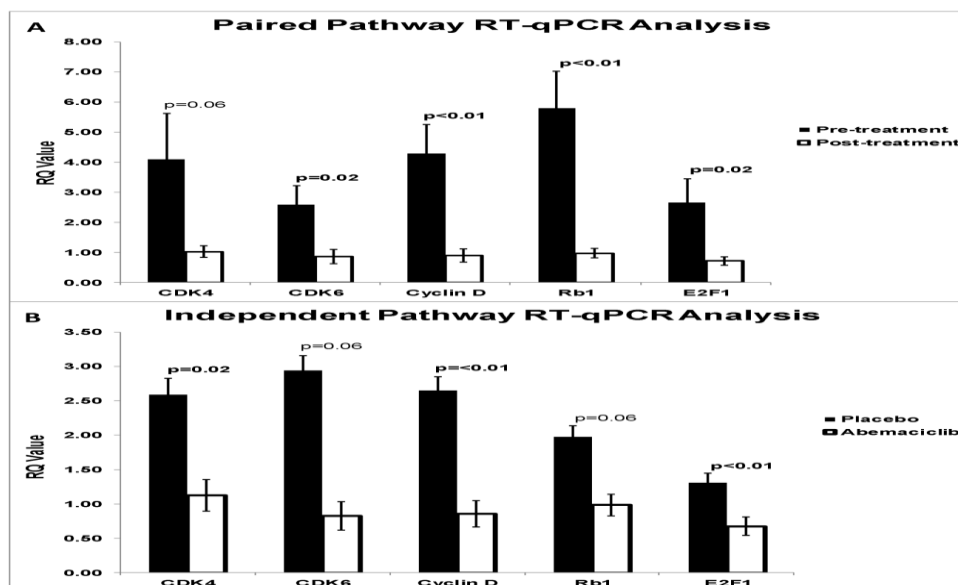


Figure 8

(A) qRT-PCR pre versus post treatment pathway analysis. Pre-treatment biopsy samples were compared with harvested samples post-abemaciclib administration. Paired analysis demonstrated downregulation of CDK4 ($p=0.057$), CDK6 ($p=0.017$), Cyclin D ($p<0.01$), Rb1 ($p<0.01$), and E2F1 ($p=0.025$). **(B) qRT-PCR placebo versus abemaciclib pathway analysis.** Endpoint placebo and abemaciclib treated samples were compared. Independent analysis demonstrated downregulation of CDK4 ($p=0.016$), CDK6 ($p=0.064$), Cyclin D ($p<0.01$), Rb1 ($p=0.56$), and E2F1 ($p<0.01$). (Kosovec J et al. CDK4/6 dual inhibitor abemaciclib demonstrates compelling preclinical activity against esophageal adenocarcinoma: a novel therapeutic option for a deadly disease. Oncotarget 2017)[4].



Clinical Data:

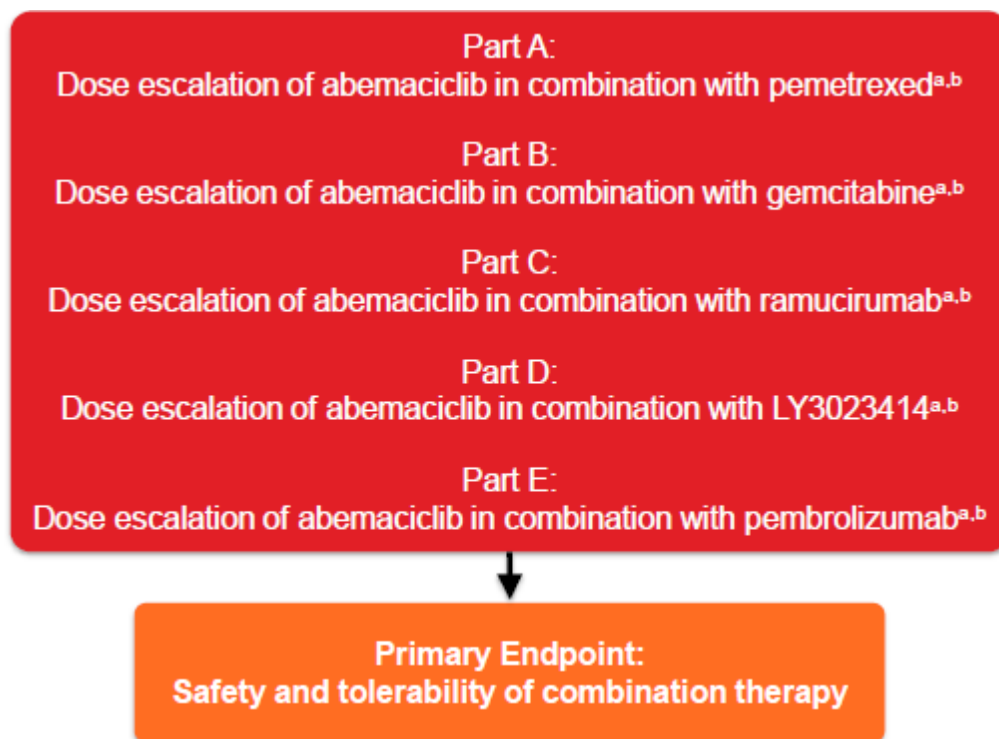
Prior to the recent publication of the Monarch 3 breast cancer phase III trial[5], validated safety data for 572 patients treated with abemaciclib across multiple studies JPBA, JPBB, JPBC, JPBH, JPBJ, and JPBN were available (Abemaciclib Investigator Brochure). Cumulatively, the most common adverse events ($\geq 10\%$) possibly related to study drug for patients receiving abemaciclib either as a single agent, with endocrine therapy, with a targeted agent, or with chemotherapy are diarrhea (73.3%), fatigue (48.6%), nausea (48.3%), neutropenia (32.9%), vomiting (25.3%), decreased appetite (25.2%), thrombocytopenia (22.9%), anemia (22.4%), leukopenia (20.3%), abdominal pain (18.2%), and blood creatinine increased (14.0%). Treatment-emergent CTCAE laboratory toxicities that were reported in $\geq 25\%$ of patients included creatinine increased (92.7%), WBC decreased (75.7%), neutrophil count decreased (62.6%), anemia (60.7%), lymphocyte count decreased (49.7%), and platelet count decreased (43.0%) (Abemaciclib Investigator Brochure). The majority of deaths reported for patients in the studies with available safety data were due to study disease.

SAEs that were possibly related to study drug and experienced by more than 5 patients out of 146 patients treated with abemaciclib either on completed studies or ongoing studies as of Oct 2015 included diarrhea (17 patients), anemia (13 patients), neutropenia (12 patients), dehydration (11 patients), acute kidney injury and nausea (10 patients each), pneumonia (8 patients), pulmonary embolism (7 patients), febrile neutropenia (6 patients), and vomiting (5 patients) (Abemaciclib Investigator Brochure). Validated safety data for 65 healthy subjects in the completed abemaciclib Phase 1 studies JPBD, JPBF, JPBG, and JPBS are also available. Cumulatively in healthy subjects, the most common ($\geq 5\%$) AEs that were possibly related to study drug were headache (14%), nausea (11%), diarrhea (8%), and vomiting (8%). One healthy subject had an SAE of syncope possibly related to study drug. No deaths or discontinuations due to AEs were reported in these studies.

The MONARCH 3 trial was recently published in the Journal of Clinical Oncology in November 2017[5]. This is a double-blind, randomized phase III study of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor in 493 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Patients received abemaciclib or placebo (150 mg twice-daily continuous schedule) plus either 1 mg anastrozole or 2.5 mg letrozole, daily. The primary objective was investigator-assessed progression-free survival.

Secondary objectives included response evaluation and safety. Median progression-free survival was significantly prolonged in the abemaciclib arm (hazard ratio, 0.54; 95% CI, 0.41 to 0.72; $P = .000021$; median: not reached in the abemaciclib arm, 14.7 months in the placebo arm)[5]. In patients with measurable disease, the objective response rate was 59% in the abemaciclib arm and 44% in the placebo arm ($P = .004$)[5]. In the abemaciclib arm, diarrhea was the most frequent adverse effect (81.3%) but was mainly grade 1 (44.6%)[5]. Comparing abemaciclib and placebo, the most frequent grade 3 or 4 adverse events were neutropenia (21.1% v 1.2%), diarrhea (9.5% v 1.2%), and leukopenia (7.6% v 0.6%)[5]. The author's conclusions were that Abemaciclib plus a nonsteroidal aromatase inhibitor was effective as initial therapy, significantly improving progression-free survival and objective response rate and demonstrating a tolerable safety profile in women with HR-positive, HER2-negative advanced breast cancer[5]. As a result of this study and the earlier Monarch 2 trial, this combination is now FDA approved and is currently being prescribed for women throughout the US.

The JPBJ study was a phase 1B study of Abemaciclib in combination with multiple single agents in stage IV non-small cell lung cancer[6-8]. Arm C evaluated the combination of abemaciclib plus ramucirumab.



Abemaciclib combined with ramucirumab had an acceptable toxicity profile[6-8] with safety findings consistent with those of the single agent abemaciclib or ramucirumab. The maximum tolerated dose of abemaciclib was established at 200mg Q12H for combination with ramucirumab. The disease control rate for the combination was 39% with 3 confirmed partial responses being observed: one in Cohort B and two in cohort C. The range of abemaciclib exposures achieved when combined with ramucirumab is consistent with that observed in single-agent studies and there is no evidence of an effect of abemaciclib on the PK of ramucirumab. Abemaciclib steady-state exposures achieved in this study were associated with inhibition of Rb phosphorylation and G1 cell cycle arrest in xenograft models.

Safety Data:

As per the clinical trial section of this protocol the phase IB JPBJ study evaluated the safety and efficacy of Abemaciclib in combination with multiple single agents in stage IV non-small cell lung cancer. Arm C evaluated the combination of abemaciclib plus ramucirumab. To date there have been no new safety concerns reported with this drug combination. Common toxicities and their management are listed in section 6.0.

1.2 Research Hypothesis

CDK4/6 and Cyclin D1 are significantly expressed in approximately 80% of esophageal and gastroesophageal junction tumors suggesting that CDK4/6 inhibition may be a successful strategy in these chemotherapy and immunotherapy resistant diseases.

2.0 Product Development Background

2.1 Mechanism of Action

Abemaciclib:

Abemaciclib represents a selective and potent small molecule CDK4 and CDK6 dual inhibitor with broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. Abemaciclib is now FDA approved as either a single agent or combined with either Fulvestrant or an Aromatase Inhibitor for the management of metastatic breast cancer.

Ramucirumab:

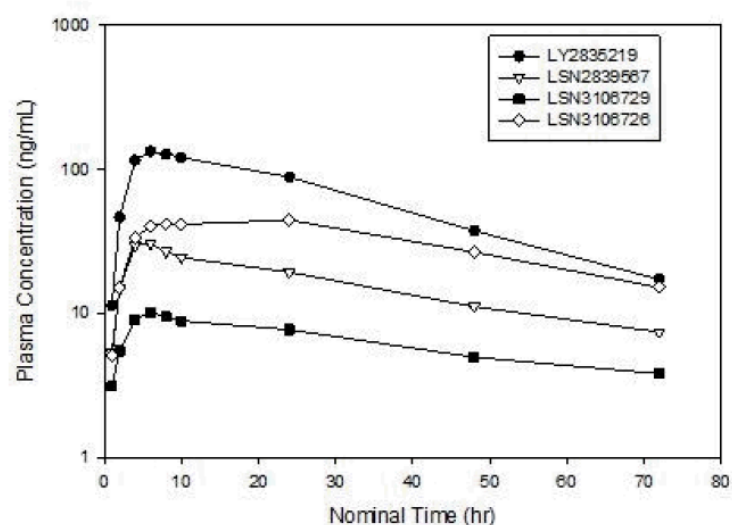
Ramucirumab (Cyramza®) is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream intracellular signaling components, including Erk1/Erk2, neutralizing ligand induced proliferation and migration of human endothelial cells. Ramucirumab has been studied and/or continues to be investigated in ongoing clinical studies for multiple indications and has been FDA approved for the management of metastatic esophagogastric cancer for a number of years either as a single agent or combined with paclitaxel. As of 31 December 2016, ramucirumab or placebo has been administered either as a single agent or in combination with various antineoplastic agents to approximately 9414 patients with different oncologic conditions in Phase 1/1b, Phase 2, and Phase 3 clinical trials. Based upon actual exposure data from completed and ongoing clinical trials (including blinded trials), an estimated 5582 patients have received ramucirumab with 1152 patients receiving single-agent ramucirumab and 4430 patients receiving ramucirumab in combination with antineoplastic agents (Ramucirumab investigators brochure). Ramucirumab has also been provided for use in expanded access programs globally (I4T-MC-JVCP [JVCP]) and in France (I4T-MC-JVCS [JVCS]), with clinical data being collected in a database designed for expanded access trials.

Ramucirumab has shown clinical efficacy and safety in patients with esophagogastric cancer in 2 randomized Phase III trials: The REGARD trial [9] (ramucirumab monotherapy with best supportive care [BSC]) and the RAINBOW trial [10] (ramucirumab in combination with paclitaxel). Ramucirumab has also shown efficacy and safety in non-small cell lung cancer (NSCLC) in the REVEL trial [11] (ramucirumab in combination with docetaxel) and colorectal cancer in the RAISE trial [12] (ramucirumab in combination with irinotecan, 5-fluorouracil, and folinic acid [FOLFIRI]). Ramucirumab has been studied as a single agent as well as in combination with a variety of chemotherapy agents, including docetaxel; paclitaxel; FOLFIRI; 5-fluorouracil/folinic acid and oxaliplatin (FOLFOX4, FOLFOX-6, and modified FOLFOX-6 [mFOLFOX-6]); dacarbazine, paclitaxel plus carboplatin; pemetrexed/gemcitabine + platinum based chemotherapy; eribulin; mitoxantrone + prednisone; and capecitabine. In addition, ongoing studies continue to evaluate ramucirumab in combination with other antineoplastic agents.

2.2 Summary of Clinical Pharmacology

2.2.1 Abemaciclib

The PK profile of abemaciclib was studied using data available from a total of 222 patients enrolled in Study JPBA (Abemaciclib investigators brochure). A general overview of abemaciclib PK based on several studies in healthy subjects and cancer patients is presented below with additional information available in the Investigators Brochure. The mean concentration time profiles for abemaciclib and metabolites at a dose of 200 mg in cancer patients in Study JPBA are depicted in below.



In the dose range of 50 to 275 mg, abemaciclib absorption is slow, with a T_{max} ranging from 4 to 6 hours, and AUC and C_{max} generally increased in a dose-proportional manner after a single dose and also with multiple twice daily doses. With repeated twice daily administration of 200 mg, which was identified as the maximum tolerated dose (MTD) in Study JPBA, abemaciclib accumulated with a geometric mean accumulation ratio of 2.5 (67% CV). At steady state after repeated oral Q12H dosing of 200 mg, the mean minimum plasma concentration at steady state ($C_{min,ss}$) and maximum observed plasma concentration at steady state ($C_{max,ss}$) were 197 and 298 ng/mL, respectively. The mean area under the steady state plasma concentration-time curve over a dosing interval ($AUC_{0-\tau,ss}$) and area under the steady state plasma concentration-time curve over 24 hours ($AUC_{0-24,ss}$) were approximately 3000 and 5520 ng.hr/mL, respectively. The mean absolute bioavailability (Study I3Y-MC-JPBS [JPBS]) of abemaciclib after a single oral dose of 200 mg is 45%. A food-effect study (I3Y-MC-JPBG [JPBG]) involving administration of abemaciclib as a 50% w/w capsule to healthy volunteers with a high-fat

meal indicated that the C_{max} was increased 24% while the AUC remained unchanged, when compared to the fasted state. Preliminary results from a study (I3Y-MC-JPBU [JPBU]) of the effect of a high-fat meal using the proposed commercial formulation (25% w/w capsule) show an increase of approximately 30% in AUC and C_{max} in the presence of food. A high fat meal did not change the inter individual variability in PK. Although the change in AUC and C_{max} in Study JPBU was statistically significant, it was small relative to the variability in exposure in the cancer patient population, and therefore not considered to be clinically relevant. Based on currently available data, abemaciclib can be taken without regard to meals. New protocols no longer contain requirements regarding food restrictions.

Abemaciclib was highly bound to plasma proteins in humans (mean bound fraction was approximately 96% to 98%) and the binding was independent of concentration from 152 ng/mL to 5066 ng/mL. Abemaciclib binds to both serum albumin and alpha-1-acid glycoprotein. The active metabolites were approximately 89% to 94% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (V_{ss}/F) for abemaciclib is approximately 1300 L (96% CV). In vitro and in vivo studies indicate that metabolism is the main route of elimination for abemaciclib. It is metabolized to several oxidative metabolites primarily by cytochrome P450 (CYP) 3A, with formation of LSN2839567 (M2) representing the major elimination pathway. Following oral administration of a single 150 mg dose of [14C] abemaciclib to healthy subjects, abemaciclib was the major drug-derived entity in plasma (34%), with the metabolites LSN3106726 (M20), LSN2839567 (M2), and LSN3106729 (M18) accounting for approximately 26%, 13%, and 5%, respectively. Abemaciclib was extensively metabolized, with 7% of the dose recovered in the feces as unchanged drug. In vitro, the major metabolites LSN3106726 and LSN2839567 are active with similar potency as abemaciclib. The active metabolites were eliminated via biliary excretion directly and/or further metabolized and eliminated via biliary excretion. The elimination half-life of LSN2839567 and LSN3106726 in cancer patients at a dose of 200 mg was 36 hours and 32 hours, respectively. Across a dose range of 50 to 200 mg, the elimination half-life and metabolite-to-parent drug ratio remained stable with dose for LSN2839567 and LSN3106726, suggesting that metabolism of abemaciclib does not change with dose. The geometric mean apparent oral clearance (CL/F) of abemaciclib was 38.3 L/h (105% CV), and the mean (range) plasma elimination half-life for abemaciclib in patients at a dose of 200 mg was 21 (12-63) hours. The mean t_{1/2} ranged from 17 to 38 hours with no consistent trends related to dose, suggesting no dose-dependent change in CL. After a single oral dose of [14C]-abemaciclib in 6 healthy subjects,

approximately 81% of the dose was excreted in the feces and 3.4% excreted in urine. The majority (52%) of the dose excreted in feces constituted metabolites indicating that abemaciclib is highly metabolized.

Given the high variability in cancer patients, abemaciclib PK appears comparable in cancer patients (Study JPBA) and healthy subjects (Study JPBG) after a single 200-mg dose. The median (range) tmax was 6 hours (2-72) and 8 hours (6-12) in cancer patients and healthy subjects, respectively. Abemaciclib apparent clearance was 38.3 L/h (105% CV) in cancer patients and 47 L/h (65% CV) in healthy subjects. The apparent volume of distribution was 1300 L (96% CV) and 1870 L (55% CV) in cancer patients and healthy subjects, respectively. The mean terminal elimination half-life for abemaciclib was 21 hours in cancer patients and 26 hours in healthy subjects.

Abemaciclib has been studied in combination with fulvestrant, anastrozole, letrozole, tamoxifen, exemestane, everolimus, trastuzumab, pemetrexed, gemcitabine, PI3K/mTOR inhibitor (LY3023414), Pembrolizumab, necitumumab, ERK1/2 Inhibitor (LY3214996), and ramucirumab (Kim et al. 2015; Tolaney et al. 2015). No clinically significant pharmacokinetic drug interaction has been observed with these agents.

2.2.2 Ramucirumab

Clinical PK data derived from the modified assay are available from 6 Phase III clinical studies (REGARD, RAINBOW, ROSE, REVEL, REACH, and RAISE) and 7 Phase 1 and Phase 2 clinical studies (I4T-IE-JVBW [IMCL CP12-1026], I4T-IE-JVBX [IMCL CP12-1028], I4T-IEJVBY [IMCL CP12-1029], I4T-IE-JVCA [IMCL CP12-1032], I4T-IE-JVCC [IMCL CP12-0713], I4T-IE-JVBJ [IMCL CP12-0708], and I4T-MC-JVBT [IMCL CP12-0918]). Trough concentrations (or minimum concentrations [Cmin]) were collected in 2 Phase 3 studies (REGARD and RAINBOW) in patients with gastric cancer. Following the selected clinical dose regimen, 8 mg/kg every 2 weeks, observed Cmin values were similar between REGARD and RAINBOW (Table 1). The geometric mean observed trough values were approximately 50 ng/mL and approximately 60 to 70 ng/mL before the fourth and seventh doses, respectively.

Table 1

Summary of Observed Ramucirumab Trough Concentration for patients with Advanced

Gastric Cancer Following Administration of 8 mg/kg of Ramucirumab Every 2 weeks as an I.V. Infusion over Approximately 1 Hour Alone (REGARD) or in Combination with Paclitaxel (RAINBOW)				
Trough^a Serum Concentration (µg/mL)				
Dose Number	4		7	
	REGARD	RAINBOW	REGARD	RAINBOW
n _{pk}	53	203	34	142
Geo Mean	49.5	45.0	74.4	62.8
Geo CV%	81	50	58	47
Abbreviations: CSR = clinical study report; CV% = percentage coefficient of variation; Geo = geometric; I.V. = Intravenous; n _{pk} = number of pharmacokinetic observations included in calculation. a = Trough concentrations were obtained prior to doses 4 and 7. They also represent C _{min} following doses 3 and 6.				
Sources: JVBE CSR Table JVBE.11.5.11; JVBD CSR Table JVBD.11.14				

Pharmacokinetic data from the 11 studies involving 1639 patients were also pooled together for a population pharmacokinetic (PopPK) analysis. In these studies, ramucirumab was administered as a 1-hour I.V. infusion, at either 8 mg/kg once every 2 weeks on a 14- or 28-day cycle, or 10 mg/kg every 3 weeks on a 21-day cycle. The studies included patients with varying cancer indications: gastric cancer (24.4% of patients), NSCLC (26.8%), breast cancer (0.7%), CRC (26.8%), HCC (19.0%), and other non-recorded tumor types (2.3%). The geometric mean (percent coefficient of variation [CV%]) of PopPK model-derived estimates of ramucirumab clearance (CL), volume of distribution at steady state (V_{ss}) and terminal half-life (t_{1/2}) were 0.0147 L/h (30.0%), 5.4 L (15.0%), and 14 days (20.0%), respectively. The PK were found to be similar in patients with gastric cancer, NSCLC, and CRC. These parameter estimates were consistent with those observed with other human monoclonal IgG1 (Keizer et al.2010) antibodies. Results from the PopPK analyses indicate that the PK of ramucirumab following 8- and 10-mg/kg dose administrations were dose linear and time independent. In addition, covariate analysis indicated that ramucirumab PK was not affected by body weight (range, 29.8 to 139 kg), sex, age (range, 19 to 87 years), serum albumin (range, 15 to 64.8 g/L), race (White and Asian), hepatic status (as assessed by alanine aminotransferase [range, 1 to 750 IU/L], aspartate transaminase [range, 1 to 1703 IU/L], alkaline phosphatase [range, 25 to 3163 IU/L], and total bilirubin [range, 1.2 to 182 mol/L]), and renal function (as assessed by Cockcroft-Gault creatinine clearance [range, 15.5 to 682 mL/min]).

2.3 Safety Summary

2.3.1 Abemaciclib

Validated safety data for 572 patients treated with abemaciclib in Studies JPBA, JPBB, JPBC, JPBH, JPBJ, and JPBN are available (Abemaciclib investigators brochure). Cumulatively, the most common TEAEs ($\geq 10\%$) possibly related to study drug for patients receiving abemaciclib either as a single agent, with endocrine therapy, with a targeted agent, or with chemotherapy are diarrhea (73.3%), fatigue (48.6%), nausea (48.3%), neutropenia (32.9%), vomiting (25.3%), decreased appetite (25.2%), thrombocytopenia (22.9%), anemia (22.4%), leukopenia (20.3%), abdominal pain (18.2%), and blood creatinine increased (14.0%). Treatment-emergent CTCAE laboratory toxicities that were reported in $\geq 25\%$ of patients included creatinine increased (92.7%), WBC decreased (75.7%), neutrophil count decreased (62.6%), anemia (60.7%), lymphocyte count decreased (49.7%), and platelet count decreased (43.0%). The majority of deaths reported for patients in the studies with available safety data were due to study disease. As of 14 October 2015, 146 patients in ongoing and completed cancer patient studies experienced 222 SAEs that were reported as possibly related to study drug. SAEs that were possibly related to study drug and experienced by more than 5 patients included diarrhea (17 patients), anemia (13 patients), neutropenia (12 patients), dehydration (11 patients), acute kidney injury and nausea (10 patients each), pneumonia (8 patients), pulmonary embolism (7 patients), febrile neutropenia (6 patients), and vomiting (5 patients). Validated safety data for 65 healthy subjects in the completed abemaciclib Phase 1 studies JPBD, JPBF, JPBG, and JPBS are also available. Cumulatively in healthy subjects, the most common ($\geq 5\%$) AEs that were possibly related to study drug were headache (14%), nausea (11%), diarrhea (8%), and vomiting (8%). One healthy subject had an SAE of syncope possibly related to study drug. No deaths or discontinuations due to AEs were reported in these studies. SAEs that were possibly related to study drug and were experienced by 2 or more patients are summarized in the following table (Table 2).

Table 2

Event Preferred Term	Number of patients
Diarrhea	17
Anaemia	13
Neutropenia ^a	12
Dehydration	11
Acute kidney injury	10

Nausea	10
Pneumonia ^b	8
Pulmonary embolism	7
Febrile neutropenia	6
Vomiting	5
Abdominal pain ^c	4
Confusional State	4
Pneumonitis	4
Sepsis	4
Alanine aminotransferase increased	3
Asthenia	3
Blood creatinine increased	3
Dyspnea	3
Hyponatraemia	3
Pyrexia	3
Renal Failure	3
Septic shock	3
Thrombocytopenia	3
Aspartate aminotransferase increased	2
Atrial fibrillation	2
Blood bilirubin increased	2
Colitis	2
Decreased appetite	2
Deep vein thrombosis	2
Drug-Induced liver injury	2
Fatigue	2
General physical health deterioration	2
Hypokalaemia	2
Lung infection	2
Rectal haemorrhage	2
White blood cell count decreased	2
Neutropenia = events of neutropenia and neutrophil count decreased. Pneumonia = events of pneumonia, lobular pneumonia, and pneumonia fungal. Abdominal pain = events of abdominal pain and abdominal pain upper. Studies that are included in the LSS listing are JPBA, JPBB, JPBE, JPBH, JPBJ, JPBK, JPBL, JPBM, JPBN, and JPBO. No serious adverse events related to study drug were experienced by patients in studies JPBC and JPBX.	

2.3.2 Ramucirumab

Completed Phase 3 Studies in Esophagogastric cancer include the Regard and Rainbow trials [9, 10]. In the Regard trial a total of 355 patients were randomized (ramucirumab, n=238; placebo, n=117). The most common Grade ≥ 3 treatment-emergent adverse event (TEAE) occurring at a higher rate on the ramucirumab arm compared with the placebo arm was hypertension (composite term incidence: 7.6% vs. 2.6% for Grade 3); no Grade ≥ 4 hypertension was observed. No individual Grade ≥ 3 TEAE was

observed in more than 10% of patients. The Rainbow trial evaluated Ramucirumab plus Paclitaxel. A total of 665 patients were randomized (ramucirumab plus paclitaxel, n=330; placebo plus paclitaxel, n=335). By Preferred Term, Grade ≥ 3 TEAEs occurring in at least 10% of patients and at a higher incidence in the ramucirumab plus paclitaxel arm than the placebo plus paclitaxel arm, respectively, were fatigue (consolidated term; 11.9% vs. 5.5%), neutropenia (consolidated term; 40.7% vs. 18.8%), leukopenia (consolidated term; 17.4% vs. 6.7%), and hypertension (AESI incidence; 14.1% vs. 2.4%). While, a higher incidence of neutropenia (any grade and Grade ≥ 3) was observed in the ramucirumab plus paclitaxel arm, the incidence of neutropenic infectious complications including febrile neutropenia was low and similar in both treatment arms. Although there was a higher incidence of Grade ≥ 3 TEAEs in the ramucirumab plus paclitaxel arm compared to the placebo plus paclitaxel arm, the percentage of patients who experienced at least 1 treatment-emergent serious adverse event (TE-SAE) or TEAE leading to death was similar in both treatment arms.

2.3.3 Potential Risk Associated with Ramucirumab in Combination with Abemaciclib

Abemaciclib combined with ramucirumab had an acceptable toxicity profile in studies to date. A Phase 1b study of abemaciclib in combination with multiple single agents in stage IV NSCLC. Poster presented at the American Society of Clinical Oncology Annual Meeting; 2015 May 29-Jun 2; Chicago, IL. Abstract 8047) with safety findings consistent with those of the single agent abemaciclib or ramucirumab. The maximum tolerated dose of abemaciclib was established at 200mg Q12H for combination with ramucirumab. The disease control rate for the combination was 39% with 3 confirmed partial responses being observed: one in Cohort B and two in cohort C. The range of abemaciclib exposures achieved when combined with ramucirumab is consistent with that observed in single-agent studies and there is no evidence of an effect of abemaciclib on the PK of ramucirumab. Abemaciclib steady-state exposures achieved in this study were associated with inhibition of Rb phosphorylation and G1 cell cycle arrest in xenograft models.

3.0 Overall Risk/Benefit Assessment

Subjects with stage IV E/GEJ/G cancer represent a great unmet need with expected survival of less than 12 months. Single agent Ramucirumab or Ramucirumab combined with paclitaxel is standard of care treatment but many patients cannot tolerate chemotherapy. To ensure an ongoing favorable risk/benefit

assessment for subjects enrolled in this study and to monitor for safety, subjects will be seen every two weeks in the medical oncology clinic during the course of treatment.

4.0 Trial Objectives

Primary Objective:

- To describe the safety profile of Abemaciclib + Ramucirumab as assessed according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

Secondary Objectives:

- To assess objective response rate, progression free and overall survival
- To determine the rate of stable disease at 3 months post targeted therapy
- Additional correlative studies to be defined.

5.0 Study Design

This is a multicenter, open label, phase I/II safety study that will be conducted at Baylor Scott and White University Medical Center (BSWUMC), Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC) and Allegheny Health Network (AHN). Study will enroll 30 subjects with metastatic esophageal and gastroesophageal junction adenocarcinomas post first line systemic chemotherapy. Subjects will be treated with oral abemaciclib 150 mg po daily bid given with ramucirumab 8mg/kg every 2 weeks until evidence of disease progression or unacceptable toxicities.



Primary objective:
- Safety and Feasibility

Secondary objectives:
- Response Rate, Progression Free Survival, Overall Survival

6.0 Selection Of subjects

6.1 Recruitment

Subjects will be recruited through the oncology clinics at BSWUMC, SKCCC, and at the AHN. Thirty subjects will be enrolled over a period of 24 months. Each enrolled subject will be assigned a participant number that comprises of the main site IRB protocol number, site initials, and the sequential number, at the time of consent:

- Baylor Site Number is 020-055-BSWH
 - *First subject number will be 020-055-BSWH-001 (sequential subject number)*
- Johns Hopkins SKCC Site Number is 020-055-JHU
 - *First subject number will be 020-055-JHU-001 (sequential subject number)*
- Allegheny Health Network Site Number is 020-055-AHN (sequential subject number)
 - *020-055-AHN-001 (sequential subject number)*

6.2 Eligibility Criteria

6.2.1 Inclusion Criteria

A subject will be eligible for inclusion in this study if he or she meets all of the following criteria:

- Men and women aged ≥ 18 years old.
- Histologically proven adenocarcinoma of esophagus or gastro-esophageal junction (core biopsy required if possible)
- Either a formalin fixed paraffin block or a minimum of ten 5-micron tissue section's (slides) of fresh or archival tumor biopsy sample must be available for biomarker evaluation.
- Recurrent disease or Stage IV disease as per AJCC staging 8.0
- ECOG performance status 0-1
- Patients must have received at least one prior line of standard systemic therapy for recurrent or Stage IV disease, and that patients with HER2 overexpression have received an anti-HER2 drug.
- Subjects who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤ 1) from the acute effects of chemotherapy except for residual

alopecia or Grade 2 peripheral neuropathy prior to randomization. A washout period of at least 21 days is required between last chemotherapy dose and randomization (provided the subject did not receive radiotherapy).

- Subjects who received adjuvant radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization.
- The subject is able to swallow oral medications. A palliative esophageal stent is allowed
- The subject has adequate organ function for all of the following criteria, as defined in Table 3 below.

Table 3: Laboratory Value Guidance to Establish Adequate Organ Function

System	Laboratory Value
Hematologic	
ANC	$\geq 1.5 \times 10^9/\text{L}$
Platelets	$\geq 100 \times 10^9/\text{L}$
Hemoglobin	$\geq 8 \text{ g/dL}$
	Subjects may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.
Hepatic	
Total bilirubin	$\leq 1.5 \times \text{institutional ULN}$ Subjects with Gilbert's syndrome with a total bilirubin ≤ 2.0 times institutional ULN and direct bilirubin within normal limits are permitted.
ALT and AST	$\leq 3 \times \text{institutional ULN}$; the ULN or 5.0 times the ULN in the setting of liver metastases.
Renal	
Serum creatinine	$\leq 1.5 \times \text{institutional ULN}$

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal.

- Prothrombin time (PT) such that international normalized ratio (INR) is ≤ 1.5 (or an in-range INR, usually between 2 and 3, if a subject is on a stable dose of therapeutic warfarin) and a (PTT) ($\text{PTT/aPTT} < 1.5 \times$ institutional upper limits of normal [ULN]). Subjects on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH). If receiving warfarin, the subject must have an $\text{INR} \leq 3.0$. For heparin and LMWH there should be no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).
- The subject has adequate renal function as defined by a serum creatinine ≤ 1.5 times the institutional ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute (that is, if serum creatinine is > 1.5 times the institutional ULN, a 24-hour urine collection to calculate creatinine clearance must be performed).
- The subject's urinary protein is $\leq 1+$ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is $\geq 2+$, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in this protocol).
- Adequate cardiac function as defined by: no evidence of PR prolongation or AV block on baseline electrocardiogram (ECG).
- The effects of abemaciclib and ramucirumab, on the developing human fetus are unknown. For this reason women of childbearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for 5 months after the last dose of abemaciclib plus ramucirumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. A female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib. Sexually active fertile men must use effective barrier birth control if their partners are WOCBP for 7 months after the last dose of abemaciclib plus ramucirumab. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within two weeks of registration.

- Subject understands the study regimen, its requirements, risks and discomforts and is able and willing to sign the informed consent form. Voluntary signed and dated IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines must be obtained before the performance of any protocol related procedures that are not part of normal subject care. Subjects must be competent to report AEs, understand the drug dosing schedule and use of medications to control AEs.

6.2.2 Exclusion Criteria

A subject will be ineligible for inclusion in this study if he or she meets any of the following criteria:

- Subjects who have received a prior CDK4/6 inhibitor or a prior VEGF inhibitor
- The subject has 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, severe renal impairment (estimated creatinine clearance < 30ml/min) or preexisting Crohn's disease or ulcerative colitis, a history of major surgical resection involving the stomach or small bowel, or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea].
- Females who are pregnant or lactating.
- The subject has active systemic infection such as bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment.
- The subject has a 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.
- The subject has experienced any Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.
- The subject has a history of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous

thrombosis are not considered “significant”) during the 3 months prior to first dose of protocol therapy.

- The subject has:
 - cirrhosis at a level of Child-Pugh B (or worse) or
 - cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
- The subject has experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy.
- The subject has uncontrolled or poorly controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.
- The subject has a prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.
- The subject has a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy.
- The subject has undergone major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to the first dose of protocol therapy. The subject has elective or planned major surgery to be performed during the course of the clinical trial.
- The subject is receiving chronic antiplatelet therapy with dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
- Subjects with previous malignancies (except non-melanoma skin cancers, in situ bladder, gastric, breast, colon or cervical cancers/dysplasia) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
- Subjects with known brain metastasis are excluded from this study.
- Known positive history or positive test for Human Immunodeficiency Virus or Acquired Immunodeficiency Syndrome (AIDS).
- History of allergy to study drug components.
- Women who are pregnant or nursing.

- Men with female partners (WOCBP) that are not willing to use contraception
- Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug or radiation hazardous or obscure the interpretation of toxicity or adverse events.
- Prisoners or subjects who are involuntarily incarcerated or compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness.

Subjects must meet all inclusion criteria and none of the exclusion criteria. Eligibility Waivers will not be granted.

6.2.3 Inclusion of Genders and Minorities

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age, gender or race in the clinical trial outlined. This trial is open to the accrual of men and women who meet the inclusion/exclusion criteria outlined.

7.0 Investigational Plan

7.1 Registration Procedures

Recruiting:

Investigators will identify and recruit subjects within their practice and/or from referrals for participation in the study. subject

Eligibility is confirmed as defined in section 6.2 and consent will be obtained by following procedures defined in section entitled registration and informed consent process.

- Once all screening activities are complete, the eligibility packet must be sent to the Project Manager for review and approval prior to Cycle 1 Day 1.

Subjects who sign a consent form, but do not initiate protocol treatment for any reason (i.e., screen failures), will be replaced and will not count towards the overall accrual goal. The study staff will update the status of the subject in the EDC (research study database) as a screen failure. The reason for removal from study prior to starting study treatment will be required in REDCap. The Coordinating Center (BSWUMC) should be notified by phone/email as soon as possible.

Registration and Informed consent process:

Before protocol specific procedures are carried out, the investigator or designated study staff (i.e. study coordinator) will explain full details of the protocol and study procedures as well as the risks involved to subject before enrollment in the study. Subjects will be informed that they are free to withdraw from the study at any time. Once reviewed and all questions are addressed, the designated study staff member obtaining consent and the subject must sign the IRB approved consent form for the participant to be in the study. The investigator is ultimately responsible for the subject regardless of who administers and obtains the signed/dated study consent. Written documentation of full, noncontingent IRB approval must be on file before a subject can be consented/enrolled and /or undergo any study related procedures.

After signed consent is obtained, subjects will undergo screening to determine eligibility.

If the subject is determined to be eligible based on the screening procedures, the primary clinical research coordinator or designee at sub sites will complete registration of the subjects through BSWUMC as well as enter their information in to the electronic database, REDCap.

Registration Process:

To register a subject, the following documents should be completed by the designated study staff at the participating sites and emailed to Ronan.Kelly@BSWHealth.org and CorcSolidTumor@BSWHealth.org for review and approval:

- Signed subject consent form
- Eligibility Checklist
- Source documentation for eligibility questions:
 - Diagnostic pathology report(s)
 - CT CAP or PET/CT scan report
 - Laboratory reports including:
 - Complete blood count (CBC) with differential (including absolute lymphocyte count) and direct platelet count.
 - Chemistry: Albumin, SGOT (AST), SGPT (ALT), Bilirubin (total) (Direct only if clinically indicated), Calcium, Creatinine, Glucose, Total protein, Urea

- nitrogen, (Uric Acid only if clinically indicated), Electrolytes (including sodium, potassium, chloride and bicarbonate).
- Baseline thyroid immune safety assay: Thyroid Stimulating Hormone (TSH). Abnormal endocrine results should be followed up per standard of care, and may require an endocrine consult and additional testing.
- Pulmonary function report and additional pulmonary testing if required according to eligibility criteria
- Other documents, if requested.

Study treatment cannot begin until approval is obtained from the Project Manager at BSWUMC.

Upon receipt of the required study documents, BSWUMC will conduct an interim review of all documents.

If the eligibility checklist is not complete or source documents are missing, the participant will not be approved, and the participating site will be notified and required to send completed eligibility documents within 5 business days.

If the external site eligibility packet is complete and the subject is confirmed eligible, the BSWUMC Project Manager/Project Coordinator will complete the registration process by:

- Complete the eligibility confirmation field (eligible or not eligible) on the subject eligibility form.
- Register the subject on the treatment portion of the study with the Baylor Scott and White Clinical Oncology Research Coordination Department.
- Fax or e-mail the subject's eligibility status (eligible or not eligible) to the participating site
- Call or e-mail the study staff at the participating site and confirm registration eligible start date for treatment.

7.2 Study Treatment Administration

All subjects will receive Abemaciclib 150 mg po bid daily and Ramucirumab 8mg/kg iv every 2 weeks in a 28-day treatment cycle until evidence of disease progression or toxicity. See Table 4 for details on the dosing schedule.

Table 4: Schedule of drug administration after completion of SBRT (8Gy x 3)

Drug Name	Cycle 1	Cycle 2 and beyond
Abemaciclib	Week 1	Continuing 150mg every day orally bid (dose reduction allowed if necessary) until disease progression or toxicity requiring discontinuation
Ramucirumab	Week 1	Week 3 and continuing every 2 weeks until disease progression or toxicity requiring discontinuation

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to recalculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up to the nearest milligram per institutional standard.

When study drugs (Abemaciclib and Ramucirumab) are to be administered on the same day, subject should take their morning dose of Abemaciclib at the normal time, and Ramucirumab can be infused thereafter, at a time convenient for the subject and physician. Subject will then take their nightly dose of Abemaciclib at their regular time.

The start and stop time of the study therapy infusions and any interruptions or infusion rate reductions should be documented in the drug administration section of CRF.

7.2.1 Premedications

Premedication Regimen for Abemaciclib:

There are no recommended premedications for Abemaciclib administration. Supportive care can be used at the discretion of the investigator

Premedication Regimen for Ramucirumab:

Pre-medications as per institutional standards are recommended for Ramucirumab. Subjects should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, subjects should be managed according to section 7.2.3 below.

7.2.2 Dose Modifications (delay/reductions) of Abemaciclib

Table 5: Dose reductions for Abemaciclib

Initial Abemaciclib Dose	First Dose Reduction To:	Second Dose Reduction To:
150mg po bid	100mg po bid	50mg po bid

Hematologic Toxicities:

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Of these, neutropenia is considered an important identified risk. Subjects should be monitored closely for signs of infection, anemia, and bleeding. Dose adjustment may be considered for hematologic toxicity $\geq$ Grade 3. If G3 toxicity occurs, suspend dose until toxicity resolves to G2; dose reduction is not required. If recurrent G3 or G4, suspend dose until toxicity resolves to $\leq$ G2. Resume at next lower dose. If subject requires 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 $\leq$ G2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor. Hematologic toxicities must resolve to baseline or at least Grade 2 prior the start of each cycle. Blood cell growth factors are only to be used in a manner consistent with ASCO guidelines (Smith et al. 2006; Smith et al. 2015). Fever or infection in the presence of severe neutropenia should be managed promptly with broad-spectrum antibacterial therapy, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. Anemia and thrombocytopenia should be treated supportively and, if necessary, with red cell or platelet transfusions.

Table 6: Dose Modification and Management — Hematologic Toxicities

Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to $\leq$ Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to $\leq$ Grade 2. Resume at next lower dose.
Subject 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 $\leq$ 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.

Gastrointestinal Toxicities:

Gastrointestinal toxicities including diarrhea, nausea, and vomiting have been observed in patients treated with abemaciclib, and causality has been established. Subjects should be monitored closely for gastrointestinal side effects. Subjects with these symptoms should be evaluated promptly, treated supportively, and monitored closely for sequelae such as dehydration. Because diarrhea possibly related to abemaciclib has been manageable with standard antidiarrheal agents such as loperamide, early treatment of diarrhea is recommended. Subjects should be instructed to initiate anti-diarrheal therapy and notify the investigator at the first sign of loose stool. Investigators should assess the response of the anti-diarrheal therapy within 24 hours of notification. If the diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1. Dose reduction may be considered if diarrhea persists despite maximal medical therapy with anti-diarrheal agents.

Guidelines for Diarrhea Management:

Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Eli Lilly has reported that early identification and intervention for the management of diarrhea has been helpful to patients.

At enrollment, subjects 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 subject should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Subjects 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 7** for additional information for diarrhea management and dose modification.

Table 7: Dose Modification and Management- Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide.	
CTCAE Grade	Abemaciclib Dose Modifications
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to $\leq$ Grade 1, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to $\leq$ Grade 1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	

Dose level reductions should be made in 50 mg increments. For example, if the starting dose of abemaciclib is 150 mg q12 hours, dose reduction 1 would be 100 mg q12 hours, dose reduction 2 would be 50 mg q12 hours.

General Guidance for 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 month of abemaciclib, and remains elevated but stable throughout the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C. 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. There is no information for dosage adjustments in patients with severe renal insufficiency or concomitant disease, or who are undergoing dialysis.

General Guidance for Interstitial lung disease (ILD)/Pneumonitis events

Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported. Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask subjects to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, dyspnea, cough or interstitial infiltrates on radiologic exams. These symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high-resolution computer tomography (HRCT), bronchoalveolar lavage (BAL), and biopsy as clinically indicated. (see also Table 8: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

Table 8: Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

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	Discontinue abemaciclib.

General Guidance for Hepatic Monitoring:

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation can occur with the use of abemaciclib. No dosage adjustments are required for subjects with mild or moderate hepatic

impairment, but a dose reduction may be required for subjects with severe hepatic impairment (as defined by Child-Pugh criteria).

Table 9: Dose Modification and Management — Increased ALT

Monitor ALT prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 ($>ULN-3.0 \times ULN$) Grade 2 ($>3.0-5.0 \times ULN$)	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 ($>5.0-20.0 \times ULN$) 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.	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 ($>5.0 \times ULN$) with total bilirubin $>2 \times ULN$, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 ($>20.0 \times ULN$)	Discontinue abemaciclib.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study subject experiences elevated ALT $5 \times ULN$ and elevated TBL $2 \times ULN$, or ALT $8 \times ULN$, liver tests, including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. To ensure subject safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown below in the below

Table 10: Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality

Hepatic Hematology	Haptoglobin
Hemoglobin	
Hematocrit	Hepatic Coagulation
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	Hepatic Serologies^a
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	Anti-nuclear antibody
AST	Anti-actin antibody
GGT	Anti-smooth muscle antibody
CPK	

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.

General Guidance for Non-hematologic Toxicities (excluding diarrhea and increased ALT) Monitoring:

Non-hematologic toxicities excluding diarrhea:

- 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 11: Dose Modification and Management — Non-hematologic Toxicities Excluding Diarrhea and ALT Increased

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	

General Guidance for Concomitant Therapy:

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.

CYP3A inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution should be administered when coadministering moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors.

- If coadministration with a strong CYP3A inhibitor is unavoidable, abemaciclib dose should be reduced to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily.
- In subjects who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily.
- Subjects should avoid grapefruit or grapefruit juice.
- If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

General Guidance for use of Radiotherapy in Combination with Abemaciclib:

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with coadministering abemaciclib with radiotherapy.

General Guidance for Women of Child Bearing Potential and/or Use of Contraceptive Methods:

Abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for abemaciclib. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Additionally, there are no available data on effects of breastfeeding. Advise a nursing woman to discontinue breastfeeding during treatment with abemaciclib.

- A female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.
- Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a subject 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.

7.2.3 Dose Modification (delay/reduction) criteria for Ramucirumab

Doses of Ramucirumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

Infusion-Related Reactions:

Treatment with histamine H1 antagonist (eg, diphenhydramine) I.V. prior to administration of ramucirumab is recommended. If a subject experiences a Grade 1 or 2 IRR, premedication must be given for all subsequent infusions. Reduce the ramucirumab infusion rate by 50% for the duration of the

infusion and all subsequent infusions if the subject experiences a Grade 1 or 2 IRR (per National Cancer Institute Common Terminology Criteria for Adverse Events). If a subject has a second Grade 1 or 2 IRR, administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medications: diphenhydramine hydrochloride I.V., acetaminophen, and dexamethasone. Subjects with grade 3 or 4 infusion-related reactions must not receive further treatment with Ramucirumab.

Hypertension:

Monitor blood pressure (BP) during treatment with ramucirumab and treat as clinically indicated. Temporarily suspend ramucirumab for severe hypertension until controlled with medical management. Permanently discontinue ramucirumab if medically significant hypertension cannot be controlled with antihypertensive therapy.

Proteinuria:

Monitor for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein level is $\geq 2+$, perform a 24-hour urine collection. Temporarily discontinue ramucirumab administration if the urine protein level is ≥ 2 g/24 hours. Resume treatment at a reduced dose level once the urine protein level returns to < 2 g/24 hours. A second dose reduction is recommended if a urine protein level ≥ 2 g/24 hours reoccurs. Permanently discontinue ramucirumab therapy if the urine protein level is > 3 g/24 hours or in the setting of nephrotic syndrome.

Table 12: Ramucirumab Dose Reductions for Proteinuria

Initial Ramucirumab Dose	First Dose Reduction to:	Second Dose Reduction to:
8mg/kg	6mg/kg	5mg/kg
10mg/kg	8mg/kg	6mg/kg

Thromboembolic Events:

Arterial Thromboembolic Events

Serious ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials. Permanently discontinue ramucirumab in subjects who experience a severe ATE.

Venous Thromboembolic Events

Venous thromboembolic events are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. Venous thromboembolic events have been reported from clinical studies investigating ramucirumab, particularly in the context of metastatic disease or in regions adjacent to implanted venous access devices. Most VTEs lack early warning signs; therefore, awareness and prompt treatment is important, especially in those subjects with risk factors and/or previous history of VTEs (Chen and Cleck 2009; Suter and Ewer 2013). Ramucirumab therapy should be discontinued in the event of any Grade 3/4 VTE that is considered by the investigator to be life threatening, or symptomatic and not adequately treated by anticoagulation therapy. In some study protocols, at the investigator's discretion, ramucirumab therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the subject is receiving therapeutic anticoagulation therapy.

Bleeding/Hemorrhage:

Ramucirumab is an antiangiogenic therapy and may increase the risk of severe bleeding. Severe GI hemorrhage was reported in patients with gastric cancer treated with ramucirumab in combination with paclitaxel, and in patients with CRC treated with ramucirumab in combination with FOLFIRI. Permanently discontinue ramucirumab in subjects who experience Grade 3 or 4 bleeding.

Gastrointestinal Perforation:

Ramucirumab is an antiangiogenic therapy and may increase the risk of GI perforations. Cases of GI perforation have been reported in patients treated with ramucirumab. Permanently discontinue ramucirumab in subjects who experience GI perforations.

Reversible Posterior Leukoencephalopathy Syndrome:

Reversible posterior leukoencephalopathy syndrome (RPLS) is a clinical and radiologic syndrome typically consisting of reversible cortical neurological dysfunction and brain-imaging findings of subcortical edema involving the posterior circulation, particularly the occipital lobes (Hinchey et al. 1996). The symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits (Hinchey et al. 1996; Garg 2001; Lee et al. 2008). Magnetic resonance imaging (MRI) represents the most reliable method for diagnosis (Lee et al. 2008). Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported (Hinchey et al. 1996; Tajima et al. 1999; Garg 2001; Lee et al. 2008). Across the clinical program, 2 cases of RPLS have been reported. Both cases (1 in each treatment arm) occurred in the completed double-blind, randomized, placebo-controlled Phase 3 Study I4T-MC-JVBB (IMCL CP12-0920) evaluating FOLFIRI in combination with ramucirumab versus FOLFIRI in combination with placebo for patients with mCRC. Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of BP, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures (Stott et al. 2005). If the diagnosis of RPLS is confirmed, ramucirumab DP should be permanently discontinued.

Congestive Heart Failure in Patients Who Received Ramucirumab DP in Combination With Mitoxantrone or Following Prior Anthracycline Therapy:

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies. While the mechanism of action is currently unknown, based on the safety data received to date it is likely that treatment with ramucirumab enhances the cardiotoxicity associated with mitoxantrone and has the potential to enhance cardiotoxicity of other agents within the anthracycline/anthracendione class of chemotherapy medications. Subjects with risk factors should be closely monitored for signs and symptoms of CHF. Caution should be exercised when treating subjects with clinically significant cardiovascular disease, such as pre-existing coronary artery disease or CHF. Subjects with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly

controlled cardiac arrhythmia should not be enrolled in clinical trials with ramucirumab. Ramucirumab should be discontinued in the event of any Grade 3-4 events consistent with CHF.

Fistula Formation:

Gastrointestinal and non-GI fistula formation have been associated with some other antiangiogenic agents, including bevacizumab and sunitinib (Kamba et al. 2007). Some fistulas can be resolved with surgery procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009). Ramucirumab treatment should be discontinued in subjects who develop fistulas.

Impaired Wound Healing:

The impact of ramucirumab has not been evaluated in patients with serious or non-healing wounds. In a study conducted in animals, ramucirumab did not impair wound healing. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld prior to scheduled surgery. The decision to resume ramucirumab following surgical intervention should be based on clinical judgment of adequate wound healing.

If a subject develops wound healing complications during therapy, discontinue ramucirumab until the wound is fully healed.

Liver Failure, Other Significant Liver Injury in Patients with Child-Pugh Class B Cirrhosis, or Cirrhosis (Any Degree) and a History of Hepatic Encephalopathy or Clinically Meaningful Ascites:

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Subjects with cirrhosis at a level of Child-Pugh Class B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis should not be enrolled in clinical trials with ramucirumab. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis. Ramucirumab should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. Refer to the appropriate section of each study protocol for detailed information regarding subject eligibility and criteria for discontinuation.

Ramucirumab Discontinuation:

A subject will have Ramucirumab permanently discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 2 weeks. Subjects with grade 4 hypertension must not receive further treatment with Ramucirumab. Subjects with grade 3 or 4 infusion-related reactions must not receive further treatment with Ramucirumab. Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation or fistula formation. If Posterior Reversible Encephalopathy Syndrome (PRES) is diagnosed, Ramucirumab must be permanently discontinued. All cases of PRES must be reported via the SAE mechanism. Any subject who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from ramucirumab therapy.

Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.

8.0 Concomitant Treatments

All therapies considered necessary for the well-being of the subject may be given at the discretion of the investigator. All concomitant medications (conmed) will be reported on the source documentation. All baseline con-meds will be collected in the REDCap/case report form (CRF).

Prohibited or restricted treatments:

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy or standard or investigational agents for treatment of GC/GEJ).

- 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 any inducer of CYP3A and/or strong, moderate or weak inhibitors of CYP3A should be avoided or substituted if necessary.

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

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

Permitted treatment:

Subjects are permitted to use aspirin up to 325mg daily and anticoagulation as per standard of care.

9.0 Duration of Treatment

9.1 Discontinuation of Subjects following Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Toxicity as specified in Section 7.2.2 & 7.2.3
- Disease progression assessed by RECIST 1.1 criteria, unless the subject meets criteria for treatment beyond progression.

- In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur, if local regulations allow.
- Venous thromboembolic events (VTEs) are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. VTEs have been reported from clinical studies investigating Ramucirumab, particularly in the context of metastatic disease or in regions adjacent to implanted venous access devices. Most VTEs lack early warning signs; therefore, awareness and prompt treatment is important, especially in those subjects with risk factors and/or previous history of VTEs (Chen and Cleck 2009; Suter and Ewer 2013). Ramucirumab therapy should be discontinued in the event of any Grade 3/4 VTE that is considered by the investigator to be life threatening, or symptomatic and not adequately treated by anticoagulation therapy. At the investigator's discretion, Ramucirumab therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the subject is receiving therapeutic anticoagulation therapy.

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures as outlined in Study Assessment and Procedures- Table 13. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, if possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures

and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

9.2 Post-Study Drug Follow up

In this study, safety is the primary endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. All subjects must be followed for safety for at least 100 days after the last dose of study therapy. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required until death or the conclusion of the study. Survival visits are every 2 months for the first year and thereafter follow standard NCCN guidelines.

9.3 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. The investigator and representatives will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

10.0 Investigational Products (Abemaciclib, and Ramucirumab) Pharmaceutical and Drug Information

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational products should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational product is Abemaciclib for oral administration. Ramucirumab is FDA approved as a single agent or in combination with paclitaxel in advanced esophagogastric cancers.

10.1 Abemaciclib

Description:

Abemaciclib is a kinase inhibitor for oral administration. It is a white to yellow powder with the empirical formula C₂₇H₃₂F₂N₈ and a molecular weight 506.59. The chemical name for abemaciclib is 2-Pyrimidinamine, N-[5-[(4-ethyl-1-piperazinyl) methyl]-2-pyridinyl]-5-fluoro-4-[4 fluoro-2-methyl-1-(1-methylethyl)-1H-benzimidazol-6-yl]

Dose: The dose of Abemaciclib on this study is 150 mg q12h.

Product Name, Unit Formula, and Strength:

Abemaciclib tablets are provided as immediate-release oval beige 50 mg tablets.

Inactive ingredients are as follows: Excipients—microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide. Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

Route of administration: Oral on days 1 through 28 of a 28-day cycle.

Recommended Storage and Use Conditions:

Abemaciclib is stored at room temperature; reference the product label for required storage range.

Safe Handling and Administration of Ramucirumab:

Abemaciclib must be taken at approximately the same times every day and to swallow whole (do not chew, crush, or split them prior to swallowing)

Short Title: Abemaciclib + Ramucirumab for GE junction Ca

Abemaciclib may be taken with or without food

If subject vomits or misses a dose, advice must be given to take the next prescribed dose at the usual time

Subjects must be instructed to read FDA-approved patient information.

10.2 Physical/Chemical and Pharmaceutical Properties and Formulation of Ramucirumab and Dose and Schedule of Drugs

Physical/Chemical Properties:

Ramucirumab is an anti-VEGF Receptor 2 recombinant human monoclonal antibody of the IgG1 subclass.

(IgG1) subclass. It is composed of 4 polypeptide chains, 2 identical heavy (γ) chains consisting of 446 amino acids each, and 2 identical light (κ) chains consisting of 214 amino acids each. The antibody contains 1 conserved N-linked glycosylation site at each heavy chain, in the Fc region

Description:

The ramucirumab active ingredient is prepared as an aqueous solution at a pH of approximately 6.0 at a concentration of 12 mg/mL to 20 mg/mL. The monomeric purity of ramucirumab is $\geq 96.0\%$ by size exclusion chromatography.

pI: The pI range is 8.6 to 9.4.

Dose:

The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks administered as an I.V. infusion over approximately 60 minutes (maximum infusion rate 25 mg/minute).

Product Name, Unit Formula, and Strength:

Ramucirumab DP is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10mM histidine, 75mM sodium chloride, 133mM glycine, and 0.01% polysorbate 80. Ramucirumab DP is a clear to slightly opalescent and colorless to slightly yellow liquid without visible particles. The pH is

6.0. The osmolality is 285 mmol/kg. All excipients used for the manufacture of ramucirumab DP are of pharmacopeial grade. No animal-derived components are known to be used in the manufacture of ramucirumab DP excipients. Refer to Section 4.1.3 of the Investigator Brochure for active ingredient description.

Recommended Storage and Use Conditions:

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial.

DO NOT FREEZE OR SHAKE the infusion solution. Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).

Ramucirumab DP is supplied in single-use, 50-mL nominal volume, United States Pharmacopeia (USP) Type I glass vials. Each vial contains 500 mg of ramucirumab at a concentration of 10 mg/mL in a sterile, preservative-free solution. Each vial is stoppered with a chlorobutyl elastomer stopper laminated with FluroTec® (West Pharmaceutical Services, Inc., Exton, PA), and secured with an aluminum 2-piece flip-top seal.

Safe Handling and Administration of Ramucirumab:

1. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.
2. Each vial is intended for single use only. Inspect the content of the vials for particulate matter and discoloration prior to dilution. If particulate matter or discolorations are identified, discard the vial.
3. Calculate the dose and volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/mL solution of ramucirumab. Dilute ramucirumab as required to achieve a final volume of 250 mL. Only use sterile sodium chloride (0.9%) solution for injection as a diluent.

In case of prefilled I.V. infusion container usage:

Based on the calculated volume of ramucirumab, remove the corresponding volume of sterile sodium chloride (0.9%) solution for injection from the prefilled 250 mL I.V. container. Aseptically transfer the calculated volume of ramucirumab to the I.V. container. The final total

volume in the container should be 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

In case of empty I.V. infusion container usage:

Aseptically transfer the calculated volume of ramucirumab into an empty I.V. container. Add a sufficient quantity of sterile sodium chloride (0.9%) solution for injection to the container to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medication

4. Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.
5. Discard any unused portion of ramucirumab left in a vial, as the product contains no preservatives.
6. Administer via infusion pump. A separate infusion line must be used for the infusion and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

11.0 Study Drug Supply and Treatment Compliance

Abemaciclib and Ramucirumab will be supplied by Eli Lilly Pharmaceuticals. The staff at the treating center (BSWUMC, SKCCC, and AHN) will arrange drug supply through Eli Lilly for treatment. Clinical site pharmacy must maintain accountability logs for Abemaciclib and Ramucirumab with the required information (e.g., lot number and expiration date, and subject ID number and dispensing date) for the study. Abemaciclib will be dispensed at the beginning of each cycle. Ramucirumab will be dispensed on the day of administration.

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

12.0 Destruction of Study Drug

The investigator will ensure that arrangements are made for the disposal of study drug according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented.

For further information related to Ramucirumab and Abemaciclib preparation and dosing, please refer to the pharmacy manual.

13.0 STUDY ASSESSEMENTS

13.1 Screening

Eligible subjects as per section 6.2.1 and 6.2.3 will be consented to participate in the study and receive abemaciclib plus ramucirumab.

Prior to entry into the study, the following assessments as per “**Table 13 - Study Assessment and Procedures**” will be performed to determine if the subject is eligible to continue in the study

1. A signed subject informed consent with HIPAA language must be obtained
2. It has been confirmed that the subject meets all inclusion criteria and none of the exclusion criteria
3. A medical history will be obtained to capture relevant underlying conditions within 4 weeks (28 days) prior to the start of therapy.
4. A complete physical examination to assess signs and symptoms of subject’s disease (including vital signs, height, and body weight (BMI), ECOG performance status) must be obtained within 4 weeks (28 days) prior to start of therapy.
5. Electrocardiogram (ECG) to check activity of the heart (including arrhythmia, myocardial ischemia/infarct etc.) must be obtained within 4 weeks prior to the start of therapy
6. A complete blood count (CBC) with differential and platelet count within 2 - 4 weeks prior to start of therapy. CBC must also be done prior to dosing on Cycle 1 Day 1

7. Complete metabolic profile (CMP) including serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN] or serum urea level creatinine, total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium), LDH, Fasting and glucose, must be performed within 2 - 4weeks prior to start of therapy. CBC must also be done prior to dosing on Cycle 1 Day 1
8. Hepatitis B (HBsAg, HBcAb) & C (HBC-Ab) testing within 4 weeks prior to the start of therapy
9. Prothrombin time (PT)/international normalized ration (INR) and partial thromboplastin time (PTT) within 2 weeks (14 days) prior to start of therapy
10. Urinalysis within 2 – 4 weeks prior to start of therapy and at Cycle 1 Day 1
11. TSH, Free T3 and T4 within 4 weeks prior to the start of therapy
12. Radiological assessment of tumor: A CT scan (Chest, Abdomen & Pelvis) must be performed within 4 weeks of start of therapy. A PET scan may also be performed (not required)
13. Females of childbearing potential must have a serum (β -HCG) pregnancy test performed within 4 weeks prior to start of therapy. A urine or serum pregnancy test must also be done within 24 hours prior to initial administration of study drug.
14. Assessment of concomitant medications must be obtained within 4 weeks prior to start of therapy
15. Any serious AEs will be collected as soon as the informed consent form is signed.
16. Subjects will be required to have fresh tumor biopsy of the primary tumor or one of the metastatic sites for exploratory biomarker analyses. Excisional biopsies, or at least 4 core needle biopsies ($\leq$ 21-gauge diameter) are required. Archival sample could be used if fresh biopsy is not possible. If the tissue obtained is insufficient, biopsy should be repeated if possible. Biomarker analysis will be performed at the laboratory of Drs. Victor Velculescu and Valsamo Anagnostou. See section 15.1.3 for additional details.

If a required observation or procedure is missed, documentation is required on the Protocol Deviation Form, and on the eCRF, to explain the reason for this protocol deviation.

13.2 Assessments During Treatment

The following evaluations will be performed during therapy on each cycle (1 cycle =28 days) as specified in the schedule of events: **Table 13 - Study Assessment and Procedures.**

- 1) A brief medical history, to capture events that have occurred since the last cycle, will be performed every 2 weeks (Day 1 and 14.) while subjects are on the study. Toxicity assessment should be captured in adverse event (AE) section of the case report form (CRF). Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4
- 2) Physical examinations (including vitals signs, ECOG PS) are to be performed every 2 weeks (Day 1 and 14.) as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, changes will be reported on the appropriate non-serious or serious adverse event section of CRF.
- 3) CBC with differential and platelet count: Day 1 and 14 (within 3 calendar days prior to dosing)
- 4) CMP: Day 1 and 14 (within 3 calendar days prior to dosing)
CMP will include ALT, AST, total bilirubin, alkaline phosphatase, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, and fasting glucose.
- 5) Serum or urine pregnancy test: Every 4 weeks (± 1 week) during treatment, and 4-10 weeks post treatment for WOCBP.
- 6) Assessment of concomitant medications: D1 and 14 of each cycle
- 7) Imaging: In this safety/feasibility study there will be no additional imaging performed outside of standard of care. Subjects will be followed with CT scans every 2 months for a year as a part of standard of care. After one year, investigators will follow standard NCCN guidelines for imaging as part of standard of care follow up. The methods used for pre-study assessments (CT Scan) should be used throughout the study. If possible, the same equipment should be used each time. PET/CT is not a requirement for follow-ups and may be used as clinically indicated at the discretion of investigators.

8) Blood samples for correlative analysis will be collected as per Section 15.

9) Urinalysis should be done on every Day 1 of each cycle.

Dosing delays due to toxicity will be permitted for subjects enrolled on this study and will follow the guidelines in section 7.2.2 for potential abemaciclib and ramucirumab toxicities and treatment. Prior to re-initiation of therapy any treatment-related toxicity should have resolved to $\leq$ grade 1.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician.

13.3 END OF TREATMENT ASSESSMENTS (OFF TREATMENT ASSESSMENTS)

End of Treatment (EOT) assessments also be called as “Off Treatment Assessments” will be performed within 30 days when subject finishes treatment because of PD, or toxicity, or in cases of physician decision to remove the subject from the study or where subject withdraws consent. No separate visit for EOT or off treatment is required if the visit coincides with last day of subject visit to the clinic for treatment or routine-follow-up.

The following evaluations will be performed at EOT as specified in the schedule of events: **Table 13 - Study Assessment and Procedures.**

- 1) A brief medical history to capture events that have occurred since the last cycle; Toxicity assessment should be captured in adverse event (AE) section of the case report form (CRF). Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4
- 2) Physical examination (including vitals signs, ECOG PS). If there are any new or worsening clinically significant changes since the last exam, changes will be reported on the appropriate non-serious or serious adverse event section of CRF.
- 3) CBC with differential and platelet count

- 4) CMP (including ALT, AST, total bilirubin, alkaline phosphatase, BUN or serum urea level, creatinine, Ca, Na, K, Cl, LDH, and glucose).
- 5) Serum or urine pregnancy test
- 6) Assessment of concomitant medications
- 7) Blood samples for correlative analysis will be collected as per Section 15.
- 8) Urinalysis should be done on every Day 1 of each cycle

*Significant clinical or diagnostic changes from pre-study (screening/baseline) evaluations, during treatment or when subject goes off treatment from the study will be recorded in source document and CRF/REDCap. If a required observation/procedure is missed, documentation is required in the source records, and recorded on the Protocol Deviation form/CRF's, to explain the reason for this protocol deviation.

13.4 Follow-up Assessments

The follow-up assessments will be performed as per routine care once every 3 months for up to 1 year and/or until disease progression whichever is the earliest.

Assessment noted below as performed will be collected and documented on the CRF. **Assessments are also detailed in Table 13 - Study Assessment and Procedures.**

- 1) Adverse events will continue to be assessed (Per Section 14) and subsequent cancer therapy will be reviewed at each follow up clinic visit.
- 2) Physical examination (including vitals signs, ECOG PS) will be performed as per standard of care at each follow-up visits.
- 3) Laboratory tests including CBC and a comprehensive metabolic panel will be performed as per standard of care at each follow up clinic visit.
- 4) Imaging: Subjects may continue having CT scans or MRI to stage the tumor every 2 months for up to 1 year from baseline during the follow-up. These assessments are part of standard of care. After one year, investigators will follow standard NCCN guidelines for imaging as part of standard of care follow up until disease progression or death.

14.0 SAFETY EVALUATIONS

Any adverse events (AE) observed by the investigator/study team or reported by the subject, regardless of severity and whether or not ascribed to the study product, will be followed by investigator, recorded in the appropriate section of the subject's CRF throughout the trial. In addition, Laboratory data will be obtained according to the schedule of assessments and any abnormal results, which are deemed “clinically significant” by the treating physician, will also be monitored & documented in the CRF. Laboratory data will include:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (ie, anemia versus low hemoglobin value).

AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The events, and the relationship of each event to treatment, will be assessed by the Treating Physician and recorded on the CRF (paper or electronic) for AE or SAE. Additional information (such as treatment required, therapy interruption or modification and eventual outcome) will also be recorded on the CRF.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Adverse events (AE/SAE) will be recorded from the time of consent throughout the study, and for up to 100 days following the last study treatment or until all study drug related toxicities resolve/return to baseline/ deemed irreversible, whichever occurs first. The investigator will record any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. Non-serious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. In the event that a subject does not continue his or her treatment at the trial site, every attempt will be made to

collect ongoing information either by direct contact or through communication with the subjects outside physician(s).

Subjects who die or withdraw consent are considered off study and no further information will be collected.

Definitions and additional reporting instructions are provided in Part II of this protocol.

15.0 Samples for Correlative Analyses

Required samples for biomarker and pharmacogenetics research to be collected from all subjects in this study are the following:

- Peripheral blood: buffy coat, plasma and serum (mandatory)
- Tumor tissue (mandatory)

Samples will be procured and stored, and analysis will be performed for markers relevant to pathways associated with metastatic esophageal/gastroesophageal junction carcinomas, the mechanism of action of abemaciclib, ramucirumab, and/or angiogenesis, cancer-related conditions, and may also be used for related research methods and may include, but are not limited to, VEGF Receptor 2 and CDK 4/ CDK 6/ Cyclin D1 axis.

The biomarker data generated will be exploratory in nature. Investigators will not provide biomarker research results to subjects, their family members, any insurance company, an employer, general physician, or any other third party, unless required to do so by law. The subject's samples will not be used for any purpose other than those described in the study protocol. Any leftover study blood and tissue samples will be stored at Johns Hopkins Sidney Kimmel Cancer Center for future research studies. These samples may be released for use in future studies after approval by the principal investigator and other regulatory bodies, as appropriate. Subjects will be asked to consent to the future use of samples in the consent document.

Specific procedures for obtaining/processing specimens are outlined in detail in the laboratory manual.

15.1 Peripheral Blood Sample for Plasma Collection

Plasma specimens for circulating cell-free tumor DNA (ctDNA) analysis will be collected prior to Ramucirumab dosing at Cycle 1 Day 1, Cycle 2 Day 1, and at End of Treatment or Disease Progression, and at any time of Infusion Related Reaction. ctDNA will be isolated and analyzed via targeted next-generation sequencing. We will correlate dynamic changes in the mutant allele fraction of driver genes, cell-free DNA tumor load and aneuploidy in the ctDNA with response to CDK4/6 and VEGFR2 inhibition to detect early molecular signs of relapse.

Potential pharmacodynamics and/or circulating markers of interest may include, but are not limited to, CDKN2A, CDK4, CDK6, E2F1, Rb1, Cyclin D, Cyclin A, FOXM1, VEGF-A, placental growth factor, VEGF-C, VEGF D, soluble vascular endothelial growth factor receptor 1 (sVEGFR-1), sVEGFR-2, and sVEGFR-3.

15.2 Whole Blood Sample for genomic DNA Collection

There is growing evidence that genetic variation may impact a subject's response to therapy. Variable response to therapy may be due to genetic polymorphisms that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, blood samples will be collected, and DNA will be extracted from buffy coat for subsequent pharmacogenetic analysis prior to each ramucirumab dosing at Cycle 1 Day 1, Cycle 2 Day 1, and at End of Treatment or Disease Progression, and at any time of Infusion Related Reaction..

In the event of an unexpected AE or the observation of an unusual response, the samples may also be genotyped and analysis may be performed to evaluate genetic association with response to abemaciclib and/or ramucirumab. These investigations may include focused candidate gene studies or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease, cancer-related conditions, and drug under study in the context of this clinical program.

15.3 Tumor Tissue Analyses

Subjects enrolled on this study will be required to have fresh pretreatment tumor biopsy of the primary tumor or one of the metastatic sites for exploratory analyses as and when possible (archival tumor tissue may be accepted). Excisional biopsies, or at least 4 core needle biopsies (≤ 21 -gauge diameter) are recommended; fine needle aspirates will not be adequate. Tumor samples are going to be formalin fixed

and paraffin embedded as per the study lab manual. Archived formalin fixed paraffin embedded (FFPE) specimens from the original diagnostic tumor biopsy may be utilized. In cases where FFPE blocks cannot be shared with JHU, a minimum of 20 5-micron tissue sections will be requested from all archival tumor samples for each individual. If pretreatment biopsy is not successful in obtaining tumor tissue, archival tumor tissue from the time of diagnosis may be used. Pathology notes accompanying archival tissue are required (de-identified and translated). Re-biopsy may be required for pre-treatment tumor samples with insufficient tumor content if safe and feasible. Genomic analyses will be performed by whole-exome sequencing in tumor samples and matched normal tissue to assess the genomic landscape of response to CDK4/6 inhibition as well evaluate the emergence of resistance genomic alterations; these analyses will be performed using described methods [13, 14]. Pertinent findings may be confirmed by a targeted sequencing approach. Sequence genomic alterations as well as copy number changes will be evaluated with particular focus on the cyclin and cyclin-dependent kinase gene families and related pathways. In addition, gene expression, and/or immunohistochemistry may be performed on these tissue samples to identify potential biomarkers of response to abemaciclib and/or ramucirumab. Markers studied may include, but are not limited to, VEGF Receptor 2 and CDK 4/ CDK 6/ Cyclin D1 pathways.

15.4 Collection Procedures for Translational Research

Plasma samples for biomarker research, whole blood samples processed as serum for DNA, and tumor tissue samples will be collected from participating sites and will be stored at Baylor Scott and White University Medical Center using standard workflows.

The samples will be coded with the subject number and stored for up to a maximum 15 years after the last subject visit for the study. The samples and any data generated from them can only be linked back to the subject by investigator or site key study personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment. Subjects will not receive results of these investigations except where required by local law. Samples will be destroyed according to a process consistent with local regulation. Stored samples will retain the subject identifier (for example, the trial subject number) and will not be stored indefinitely.

Supplies required for the collection and shipment of the subjects' stored samples will be supplied by the coordinating center (BSWUMC). Sample handling, processing and shipment to the coordinating site will occur per instructions provided to the study site.

15.5 Samples for Immunology and pharmacokinetic (PK) Studies

In the event of an Infusion-related reaction, blood samples will be collected for both immunogenicity and PK analysis (to determine abemaciclib and ramucirumab concentrations) as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event. To interpret the results of immunogenicity, a sample to measure the concentration of abemaciclib and ramucirumab in the blood is also collected at the same time point.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of the abemaciclib or ramucirumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of abemaciclib or ramucirumab.

Samples may be stored for a maximum of 15 years following last subject visit for the trial to enable further analysis of immune responses to abemaciclib and ramucirumab. The duration allows the sponsor to respond to regulatory requests related to abemaciclib or ramucirumab.

15.6 Additional Information

The laboratory investigators will be blinded to the subject identifiers and clinical data while generating the research data; additionally, the reported results will not disclose any unique subject identifiers.

Note: The correlative sample collection schedules outlined above are based on an ideal subject. The sample schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.).

Table 13 - Study Assessments and Procedures

Table 13: Screening procedural outline		
Procedure	Screening Visit (window 4 weeks except for tests/procedures specified in notes)	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History*	X	
Safety Assessments		
Physical Examination	X	

Smoking History	X	
Con-medication Review	X	
Vital Signs and O2 Saturation	X	O2 saturation by pulse oximetry should be $\geq 92\%$ both at rest and while walking, off supplemental oxygen (oximetry should be done prior to dosing). Vital signs (blood pressure [BP], heart rate and temperature) will also be obtained within 72 hours prior to first dose.
Assessment of Signs and Symptoms	X	
Complete Blood Count with differential and platelet count	X	Within 2 – 4 weeks prior to start of therapy (C1D1)
Complete Metabolic profile	X	Within 2 – 4 weeks prior to start of therapy (C1D1). Includes, creatinine, glucose, total protein, blood urea nitrogen [BUN] or serum urea level creatinine, total carbon dioxide [CO2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT] and electrolytes (total calcium, chloride, potassium, sodium), LDH, and Fasting glucose
Hepatitis B (HBsAg, HBcAb) & C (HBC Ab) testing	X	
PT/INR/PTT	X	Within 2 – 4 weeks prior to start of therapy (C1D1)
Urinalysis	X	Within 2 – 4 weeks prior to start of therapy (C1D1)
TSH, Free T3 and T4	X	
ECG	X	ECG
Pregnancy Test	X	This is only for WOCBP. Serum or Urine pregnancy test is required to be conducted within 2 – 4 weeks prior to start of therapy (C1D1)
Physical exams (including ECOG status, Height and Weight)	X	

CT Scan w/contrast (Chest, Abdomen & Pelvis)	X	A PET/CT may be done if required
Archived Tumor or Repeat Research Tumor Core Biopsy	X	This is mandatory for study entry. Sample should be received prior to first dose of nivolumab. Submit a copy of the original pathology report along with the sample.
Con-meds	X	
*Must include radiologic or clinical stage at diagnosis.		

Procedure	Cycle 1 and beyond until PD or toxicity		End of Treatment	Follow up for recurrence-free and overall survival
	Day 1 (± 3 days)	Day 14 (± 3 days)	Day (± 30 days). Procedures does not have to be repeated if EOT falls on Day1 or Day 14.	Once every 3 months as per SOC
Physical Exam	X	X	X	X
Vital Signs	X	X	X	X
ECOG PS	X	X	X	X
CBC with Diff	X	X	X	X
Chemistry	X	X	X	X
Urinalysis	X		X	
TSH, T3 and T4	As clinically indicated			
Pregnancy Test (WOCBP Only)	every 4 weeks (+/- 1 week) during treatment		4-10 weeks post treatment	
Ramucirumab	X	X		
Abemaciclib	X	X (continued daily)		
WB & Plasma collection for pharmacogenetic studies & ctDNA (section 15.1 & 15.2)	X		X	
Serum & plasma collection for Immunology & PK (section 15.5)	At any time of infusion related reaction			
PET Scan	If clinically indicated per standard of care			
CT Scan w/contrast (Chest, Abdomen & Pelvis)	Q 8 weeks as per SOC for 1 year followed by NCCN guidelines timeline per SOC until PD or death			
Con Meds	X	X	X	X
Symptom/ Toxicity Assessment	X	X	X (for 100 days or till resolution whichever comes earlier)	X
Follow Up				X
Review of Medical Records, Telephone Contact for Recurrence-Free and Overall Survival				Up to 1 year

16.0 Statistical Considerations

Sample Size Justification:

A total of 30 subjects will be enrolled. The primary goal is to describe the safety profile of Abemaciclib in combination with Ramucirumab among all enrolled subjects. If grade 3 or higher treatment-related adverse events occur in 20 subjects, the upper bound of 95% Wilson confidence interval of the adverse event rate would be below 81% (16.7% - 47.9%). Table 14 lists confidence intervals for some potential results.

Table 14: The number of subjects with grade 3 or higher adverse events and their corresponding confidence intervals

Number of Subjects with Grade 3 or Higher Adverse Event	95% Confidence Interval of Grade 3 or Higher Adverse Event
18	(42.3%, 75.4%)
19	(45.5%, 78.1%)
20	(48.8%, 80.8%)
21	(52.1%, 83.3%)
22	(55.5%, 85.8%)

If 11 subjects achieved an objective response by RECIST1.1 criteria, the upper bound of 95% Wilson confidence interval of ORR would be higher than 20% (16.7% - 47.9%). Table 15 lists confidence intervals for some potential results.

Table 15: The number of subjects who achieved objective response and their corresponding confidence intervals

Number of Subjects Who Achieved Objective Response	95% Confidence Interval of Subjects Who Achieved Objective Response
9	(16.7%, 47.9%)
10	(19.2%, 51.2%)
11	(21.9%, 54.5%)
12	(24.6%, 57.7%)
13	(27.4%, 60.8%)

Analysis plan

The safety analysis will be performed in all treated subjects. Adverse event data will be listed individually and graded according to the National Cancer Institute Common Terminology Criteria,

version 4.03. Summary statistics will include counts and proportions as well as rates with 95% confidence intervals. Toxicities will be reported as a tabulated table by type and grade.

Objective response rate is defined as the percentage of subjects who achieve an objective response by RECIST1.1 criteria (i.e. Complete response or Partial Response) to Abemaciclib in combination with Ramucirumab. We will estimate the objective response rate, along with the Wilson 95% confidence interval, for the population of subjects.

Overall survival will be defined as the time from study enrollment to death. This will be summarized using a Kaplan-Meier curve.

Progression-free survival will be measured from the time of randomization to radiographic tumor progression or death and summarized using a Kaplan-Meier curve.

Stopping guidance

The proportion of subjects with grade 4 or higher treatment-related adverse events will be monitored continuously throughout the trial using a Bayesian stopping guideline. A Beta (1, 19) prior, representing a toxicity rate of 5%, slightly lower than the expected rate of 6%, was used in the development of our guidelines. The therapy will be re-evaluated if the posterior probability that the toxicity rate exceeds 10% is greater than 75%. Table 16 summarizes the stopping boundaries starting with the initial cohort of 3 subjects through the maximum sample size of 30 subjects.

Table 16: The number of unacceptable toxicities needed to trigger stopping guidelines throughout the course of the study

Number of subjects	Number Needed to trigger re-evaluation
3-6	3
7-15	4
16-23	5
24-30	6

The probability of triggering the stopping guidelines was assessed for a range of possible toxicity rates using simulations with 5000 replicates (Table 17). The probability of stopping to re-evaluate was 1% if

the true proportion with an unacceptable toxicity was 5%. In comparison, the probability of stopping early was 99.6% if the true proportion with an unacceptable toxicity was 40%.

Table 17. Probability of triggering a re-evaluation for a range of values for the true underlying toxicity rate.

True probability of grade 3 or higher adverse events	Probability of triggering stopping guideline	Average sample size
1%	<1%	30
5%	1%	30
10%	11.8%	29
20%	63.3%	21
40%	99.6%	10

17.0 Data and Safety Monitoring

17.1 Data Management

Eligible subjects will be registered onto the study by the study coordinator or designee at the participating sites. All sub sites should follow the registration process as detailed in “**Registration and Informed Consenting**” under **Section 7.1** (also included in the Table – 18 below).

Table 18 - Data Management Process:

At the time of registration	To complete the registration process, the Coordinating Center will	Ongoing data submission
Sub sites to Coordinating Center: ○ Registration Form ○ Informed Consent Form (signed by the subject) ○ Eligibility Checklist Source documents related to eligibility and randomization	Coordinating Center to Sub sites: ○ Complete the eligibility confirmation field (eligible or not eligible) in the 'Eligibility Criteria' eCRF in REDCap. ○ Register the subject on the treatment portion of the study with the Baylor Scott and White University Medical Center Clinical Oncology Research Coordination Department ○ Fax or e-mail the subject eligibility status (eligible or not eligible) to the participating site ○ Call or e-mail the research nurse or data manager at the participating site and confirm registration eligible start date for treatment.	Sub sites to Coordinating Center: On Treatment: ○ REDCap Data entry should be completed within 5 days of study visit. Within 2 weeks after final dose of study medication ○ Email/Fax: On study case report forms ○ Email/Fax: Pertinent source documents During Follow Up: ○ REDCap Data entry should be completed within 5 days of study visit. ○ Email/Fax: On study case report forms ○ Email/Fax: Pertinent source documents REDCap can be used during registration, treatment and follow-up in lieu of Email/Fax for CRF completion and source document upload.

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

This is a high complexity trial under the Baylor Scott and White Research Institute (BSWRI) Guidelines for Level of Clinical Site Monitoring. The PI is responsible for internally monitoring the study and establishing additional external data & safety monitoring oversight, as required. The PI will also monitor the progress of the trial, review safety reports, and confirm that the safety outcomes and response assessments favor continuation of the study.

The protocol will be monitored internally by BSWUMC Clinical Oncology Research Coordination (CORC) Department, by the Principal Investigator and by the BSWRI in accordance with established guidelines. Trial monitoring and reporting will be conducted during teleconferences of investigators and study staff from the sites which are scheduled by BSWUMC CORC Department as outlined in section 19.0. The BSWUMC CORC Department and BSWRI will be responsible for data monitored at AHN and JHU.

18.0 Multicenter Guidelines

Protocol Chair

- The Protocol Chair is responsible for performing the following tasks:
- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the Protocol
- Taking responsibility for the overall conduct of the study at all participating Institution's and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first subject registration at that site and maintaining copies of IRB approvals from each site.
- Managing central subject registration.

- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center via CRMS.
- Registering all subjects with the Coordinating Center by submitting subject registration form and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

19.0 Monitoring Meetings

Routine teleconferences of all investigators, research nurses and other study staff involved in the study will take place, starting once sites have enrolled a subject. Frequency of teleconferences will be based on subject enrollment and will be held no less than once every other month. The following study team members involved with the conduct of the trial will be included as appropriate: study coordinators, data managers, research nurses, investigator and sub-investigators, collaborators (if applicable), BSWRI monitor(s) and statistician. Sites with 0 accrual will not be required to participate on the safety calls.

During these meetings matters related to the following will be discussed: enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), validity and integrity of the data, toxicities, acquisition of serum samples and transfer to lab, and progress of data for objectives.

Evaluation of safety will be monitored continuously through day 100 following the last dose of Abemaciclib plus Ramucirumab. The evaluations will be conducted under the direction of the Lead PI and the study statistician; additional information may be found in the statistical section, 16.0.

PART II - PROCEDURES

20.0 Adverse Events

20.1 General

As with any medical product there are anticipated and unanticipated adverse events. However, throughout the course of the proposed study, all efforts will be made to remain alert to possible adverse experiences or untoward findings. If adverse experiences occur, the first concern will be the safety and welfare of the subject, and appropriate medical intervention will be made.

All AEs, regardless of severity, will be followed up by the Investigator until resolution is satisfactory. All adverse events experienced by subjects will be collected from the time of consent, throughout the study and until the final assessment (100 days after the last dose of abemaciclib + ramucirumab) as outlined in the Study Calendar (Table 13). Subjects continuing to experience toxicity after discontinuation of the study drug may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Any adverse event experienced during additional treatment that the investigator feels is related to study treatment will be captured.

20.2 Definitions

20.2.1 Adverse Event (AE)

Defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product. The adverse event does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form will be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

All AEs must be documented in the source documents. Documentation should include onset and resolution, severity/grade, relationship to study drugs, and outcome of the event.

20.2.2 Serious Adverse Event (SAE)

A serious AE (SAE) is any untoward medical occurrence that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not include an adverse experience which hypothetically might have caused death if it were more severe.

- Insubject hospitalization or causes prolongation of existing hospitalization

Note: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 24 hours.

OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study, per protocol for a planned medical or surgical procedure).

OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfil the criteria of ‘medically important’ and as such may be reportable as a serious adverse event dependent on clinical judgement. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event 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 [i.e. 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 that do not result in hospitalization; or development of drug dependency or drug abuse.
- Potential drug induced liver injury (DILI) is also considered an important medical event. Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

- 1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

- 2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

- 3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

20.2.3 Unexpected adverse event

An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected". The Safety Information Section of the abemaciclib and ramucirumab IB's should also be referenced.

20.2.4 Expected (known) adverse event

An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

20.2.5 Major Deviation

A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

20.2.6 Minor Deviation

A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

20.2.7 Relationship

The relationship of all adverse events and serious adverse events to study medication will be assessed by an investigator and assigned as follows:

Definitely Related: An adverse event which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, for which no alternative cause is present.

Probably Related: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, has a high index of suspicion for relationship, follows a known pattern of response, and for which device drug or procedure relationship cannot be ruled out.

Possibly Related: An adverse event, which has a timely relationship to the administration of the investigational drug/agent and cannot be determined to be caused by an alternative product or event.

Unlikely: An adverse event which does not have a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, does not reappear or worsen after re-administration of the investigational drug/agent (if applicable), and for which there is evidence that it is related to a cause other than the investigational drug/agent.

Unrelated: An adverse event for which, there is no evidence that it is related to the investigational device, drug, or the procedures; may be sequelae to the underlying diagnosis, disease progression, etc.

20.2.8 Intensity (Severity) of the Adverse Event

The intensity (severity) of adverse events should be graded according to NCI-CTC version 4.0 criteria.

The severity and grading will be defined as below:

- 0 = No AE or within normal limits
- 1 = Mild AE; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- 2 = Moderate AE; minimal, local or non-invasive intervention indicated; may have interfered with the research subject's daily activities, but did not require discontinuation from the study; resolved with treatment
- 3 = Severe or medically significant but not immediately life threatening; required professional medical attention including hospitalization or prolonged hospitalization and may result in discontinuation from the study; resulted in severe limitations on the research subject and their ability to carry on normal activities; may be associated with sequelae.

4 = Life-threatening consequences; urgent intervention indicated; permanent and/or significant persistent disability or in left untreated would in most likelihood have resulted in the subject's death.

4 = Fatal, otherwise death related to AE

20.2.9 Adverse Events Reporting

Only those specified per section 14 are to be recorded in the CRF. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other diagnostic information. The diagnosis should be documented as the AE/SAE and not the individual signs /symptoms. Toxicities will be graded as detailed in section 20.2.8.

Pre-existing conditions will be recorded at baseline on the Medical History Form. If a pre-existing condition does not change, it does not have to be reported as an AE on subsequent cycles. If a pre-existing condition worsens while subject is on treatment (during study participation), it will be reported as an AE/SAE at the time of identification.

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

20.2.10 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, where doubt exists regarding its status of seriousness must be collected, including those thought to be associated with protocol-specified procedures. SAEs will be reported to IRBs, ethics committees or other third parties, as per standard operating procedure (SOP) of participating institutions within 24 hours of becoming aware of the event.

All SAEs must be documented on the Serious Adverse Event Report Form and on the adverse event CRF page. The event term used on the SAE report should match the term in the CRF. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the as soon as it is available. For unexpected fatal, life-threatening, or other unexpected SAEs, follow-up information must be reported per participating institutions SOP.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, and Institutional Review Board policy.

- In addition to the obligations set forth above, Investigator and Institution agree to provide Eli Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly.
- To notify Eli Lilly, sub-investigators, and the IRB of any problems involving risk to Study subjects and report new safety information to IRBs in accordance with applicable requirements
- To notify Eli Lilly within 15 business days of Investigator and/or Institution receiving notification of any “serious” adverse event experienced by a subject participating in the Study and receiving Study Drug. For purposes of this requirement, “serious” means: (1) death; (2) in-subject hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Eli Lilly using a MedWatch Form or other form acceptable to Eli Lilly. Investigator and Institution further agree to make available promptly to Eli Lilly such records as may be necessary and pertinent for Eli Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.
- In accordance with local regulations, Eli Lilly will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these

criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Event reporting Table - Table 19 and Table 20 below summarizes the event reporting requirements.

Participating institutional sites will be responsible for reporting any event meeting local reporting requirements to their institutional IRB and/or other research oversight committees as indicated per **Table 19**. All IRB approvals will be retained in Regulatory files for review by BSWRI monitors.

Table 19 - Participating Institutional Sites Event Reporting Table

Event Type	Reporting Timeframe	Form in Open Clinica to Use	Report to
Any event meeting the definition of serious adverse events (includes fatal events, anticipated or unanticipated, and whether or not related to the study; events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol)	Within 24 hr. of notification	SAE Report Form/Med Watch 3500 A or similar form SAE Form	For Affiliate Sites: To Baylor Scott and White Research Institute NEWSTUDYSTARTUP@BSWHealth.org and CORCREGULATORYTEAM@BSWHealth.org (If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day) for the coordinating site IRB, FDA and Lilly submission. To Local institutional IRB or other entities per institutional policies and guidelines For Baylor Scott and White Research Institute: Study coordinators and/or Regulatory specialist should Report to Institutional Review Board as indicated in Table 20. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, follow-up SAE reporting should be done.
Any death in a subject receiving study drugs regardless of cause through the 1 year follow-up	Within 24 hr. of notification		
Pregnancy	Within 24 hr. of notification		
Major deviations as defined in section 20.2.5	Within 24 hr. of notification	Deviation Report Form	

Minor deviations as defined in section 20.2.6	Per Institutional Policy	Complete as per local IRB deviation form	For Affiliate Sites: Minor deviations are reported to the Baylor Scott and White Research Institute by the study regulatory specialist annually at the time of continuing review. Report to local institutional IRB or other entities per institutional policies and guidelines. For Baylor Scott and White Research Institute: Minor deviations are reported to the IRB by the study's regulatory specialist annually at the time of continuing review.
Adverse events which results in no change to protocol, ICF or risk to subjects (does not fall in to SAE)	Per Institutional Policy		For Affiliate Sites: Report to local institutional IRB or other entities per institutional policies and guidelines. Adverse events will be captured in the eCRF and information will be emailed/faxed to BSWRI NEWSTUDYSTARTUP@BSWHealth.org and CORCREGULATORYTEAM@BSWHealth.org for FDA/IRB annual report submission.

As the study sponsor, the Baylor Scott and White Research Institute has the following expedited reporting responsibilities, as indicated in **Table 20, for events reported in Table 19**

Table 20 – Coordinating Center Event Reporting Table

Agency Reporting to	Criteria for reporting			Submission system/address or email
BSWRI IRB (for BSWRI subjects only)	SAE unexpected and probably or definitely related – refer to the IRB website for complete details	Within 3 days	Email IRB within 3 days; Report through IRIS	BRI_IRB@BSWHealth.org / IRIS
	Major Deviations that occur at BSWRI as defined in Table 19	Within 10 days	Report through IRIS IRB	
	Adverse events which results in no change to protocol, ICF or risk to subjects (does not fall in to SAE)	Annually	Report through IRIS IRB	
BSWRI IRB (for reports received from participating sites as per table 19)	As per table 19	To follow BSWRI Policy for reporting		

FDA	Unexpected and fatal (includes death) or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	Baylor Scott and White SAE reporting form /Med Watch 3500 A or similar form SAE Form	Submit to FDA as instructed by the FDA on approval letter with a copy emailed or Faxed to Eli Lilly at MAILINDATA GSMTINDY@LILLY.COM (through secure email) or Fax to 866-644-1697
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure	no later than 15 Calendar-Days		
Eli Lilly	All SAEs (BSWRI and participating institutions) reported to the FDA (includes initial and follow up reports)	Within 15 days	Med Watch (completed by participating institution or BSWRI Study coordinator)	MAILINDATA GSMTINDY@LILLY.COM (through secure email) or Fax to 866-644-1697

20.2.11 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (ie, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the IRB of this event and complete and forward a Pregnancy Surveillance Form to Coordinating Center BSWRI within 24 hours and in accordance with SAE reporting procedures described in **Section 20.2.10**

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form in the similar manner and submitted.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

20.2. 12 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 20.2.10 for reporting details).

21.0 Coordinating Center (BSWUMC Clinical Oncology Research Department) Responsibility

The Coordinating Center is the central location for the collection and maintenance of documentation of serious adverse events and is responsible for submitting serious adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all serious adverse event reports for each participating site. Serious adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

BSWRI regulatory specialist will sent MedWatch SAE to the FDA as per the instruction on the FDA IND approval letter. The coordinating site will collect and manage the study data using the BSWRI REDCap platform. Following data collection and analysis, this data will be removed from REDCap and archived on a limited access shared drive for 2 years after study closure, after which the data will be destroyed.

The Coordinating center shall fax or e-mail the SAEs to Eli Lilly as indicated per Table 19 and 20. Eli Lilly will provide the SAE coversheet to use when reporting.

22.0 Participating Sites Responsibility

Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the Coordinating Center as per Table 19:

Adverse event reports are to be emailed (use fax as a back-up) to the Coordinating Center at BSWRI. Follow-up reports are faxed, mailed, or sent electronically to the Coordinating Center as necessary.

The principal investigators at participating institutions will notify the appropriate regulatory agencies of any event due to any cause during the course of this investigation as per the Table 19 and 20. These include the BSWRI Data and Safety Monitoring Committee, and BSWRI (BSWRI-IRB) of Baylor Scott and White University Medical Center.

SAEs should be reported on MedWatch Form 3500A or similar form. It MUST include the institutional **AND** Eli Lilly study ID [per study Agreement]. AEs can be reported in a tabular format annually as indicated in Table 19 and 20.

23.0 PROTOCOL AND DATA DEVELOPMENT

23.1 Ethical Considerations

23.1.1 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or Eli Lilly should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates. The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

23.1.2 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Council on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), Declaration of Helsinki and applicable local requirements. The study will be conducted in compliance with the protocol. All potential serious breaches must be reported to the Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study. Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

23.1.3 Compliance with protocol

The Principal Investigator is responsible for the coordination and development of all protocol amendments. No alterations or changes in this protocol will be permitted without written approval from the Principal Investigator and the IRB unless the amendment is necessary to reduce immediate risk to trial participants...

23.1.4 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate. The principal investigator will provide an appropriate informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Subjects will be given ample time to read the consent. Subject will be informed in simple terms and all questions answered about the objectives, procedures, and risks of study

participation both verbally and in writing in accordance with current regulations. A signed, dated, approved written informed consent form will be obtained prior to any study-specific procedure is performed

23.1.5 Disclosure and Confidentiality of Records

The investigator agrees to keep all information in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents (protocols, investigators brochure, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Data generated by this study will be considered confidential by the investigator. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law.

23.1.6 Changes in Study Personnel

If there is a change of any personnel listed, a new form reflecting the change must be completed and sent to IRB including, when applicable, any new staff member's signed curriculum vitae, medical license (as appropriate), and signed financial disclosure statement.

23. 2. Study Records

23.2.1 Documentation

Confidentiality of all subjects will be maintained throughout the study taking into account the requirement for access to subjects' medical records for the purpose of source data verification by monitors, auditors, and inspectors. Subjects' will be identified only by a number, initials, and birth date in data collected and reports generated.

A log of all subjects evaluated for this protocol must be maintained. Subjects excluded from admission will be provided with a clear explanation of the specific reasons why they have been excluded from the study. Subjects who are included will be assigned a subject identification number.

23.2.2 Case Report Form Procedures

Data will be recorded using a hybrid data collection approach with hard copy and electronic study data base (REDCap). Coexistent diseases and AEs will be coded using Medical Dictionary for Regulatory Activities. Concomitant medications entered into the database will be coded using the World Health

Organization Drug Dictionary, which classifies according to therapeutic/pharmacological class. Data collected will undergo quality control and consistency checks. If necessary, data queries will be raised, and the database updated until all queries are resolved. Study monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required correction or additions in a Good Clinical Practice (GCP)-compliant manner.

Data items from the source documents are entered into the study database using appropriate methodology to ensure that the electronic CRFs are accurately represented. The site's laboratory will analyze the clinical chemistry and hematology samples. Baseline values and clinically significant changes from baseline value during subsequent visits per protocol will be included in the electronic CRF. If possible, subjects will be followed for survival after the completion or removal from the study.

Standardized study data base (electronic CRFs) will be supplied to the investigator. The CRFs are to be completed by the investigator or authorized delegate. CRFs must be completed within 15 calendar days of the end of each cycle and within 30 calendar days following completion of study therapy. The investigator at participating sites must review CRF data entries for accuracy and completeness. The investigator will maintain adequate source documents to support the CRF entry. Any corrections should be performed by a method that allows an audit trail of the changes. This should include the identification of the person making the correction and the date the change was made.

23.2.3 Archiving and Record Retention

All documents concerning the trial including correspondence, regulatory documents, source documents, subject medical files, completed CRFs, and data query resolutions will be retained by the investigator for at least 7 years.

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Appendix A: TNM Staging of esophageal Cancer (7th Edition)

ESOPHAGUS STAGING FORM			
CLINICAL <i>Extent of disease before any treatment</i>	STAGE CATEGORY DEFINITIONS		PATHOLOGIC <i>Extent of disease through completion of definitive surgery</i>
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____	LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
☐ TX ☐ T0 ☐ Tis ☐ T1 ☐ T1a ☐ T1b ☐ T2 ☐ T3 ☐ T4 ☐ T4a ☐ T4b	PRIMARY TUMOR (T) Primary tumor cannot be assessed No evidence of primary tumor High-grade dysplasia * Tumor invades lamina propria, muscularis mucosae, or submucosa Tumor invades lamina propria or muscularis mucosae Tumor invades submucosa Tumor invades muscularis propria Tumor invades adventitia Tumor invades adjacent structures Resectable tumor invading pleura, pericardium, or diaphragm Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc. *High-grade dysplasia includes all non-invasive neoplastic epithelium that was formerly called carcinoma <i>in situ</i> , a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.		☐ TX ☐ T0 ☐ Tis ☐ T1 ☐ T1a ☐ T1b ☐ T2 ☐ T3 ☐ T4 ☐ T4a ☐ T4b
☐ NX ☐ N0 ☐ N1 ☐ N2 ☐ N3	REGIONAL LYMPH NODES (N) Regional lymph nodes cannot be assessed No regional lymph node metastasis Regional lymph node metastases involving 1 to 2 nodes Regional lymph node metastases involving 3 to 6 nodes Regional lymph node metastases involving 7 or more nodes		☐ NX ☐ N0 ☐ N1 ☐ N2 ☐ N3
☐ M0 ☐ M1	DISTANT METASTASIS (M) No distant metastasis (no pathologic M0; use clinical M to complete stage group) Distant metastasis		☐ M1

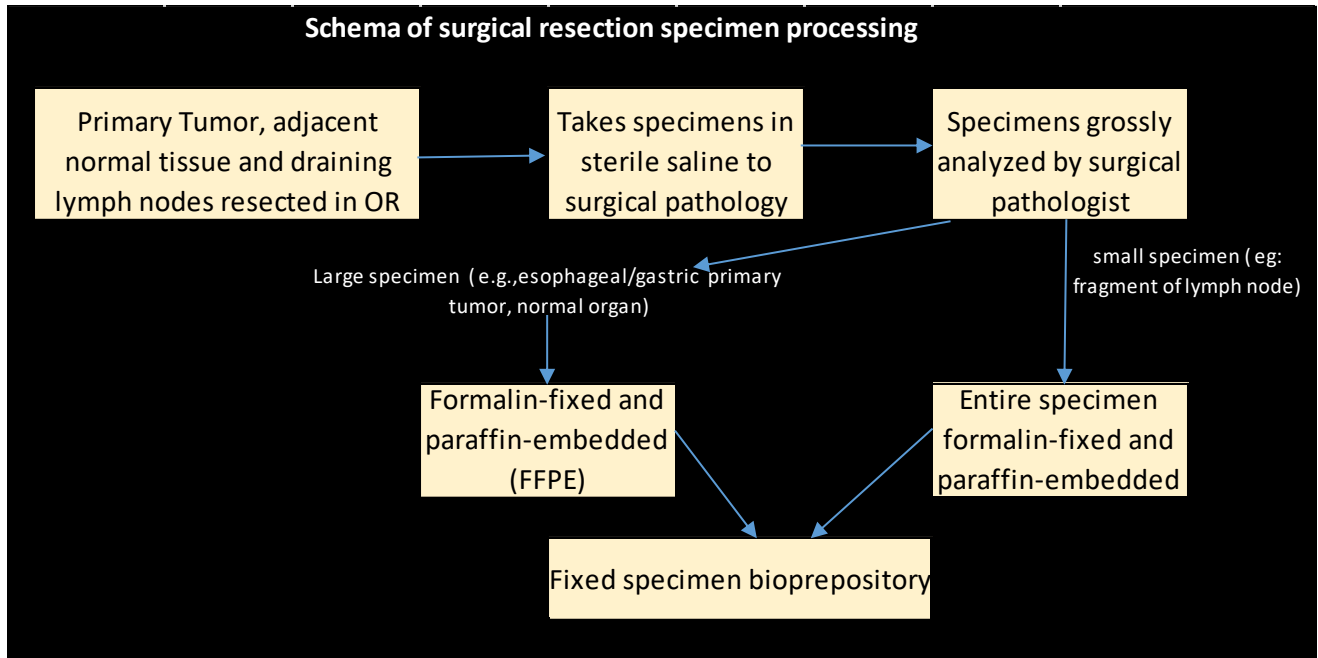
Table 2 AJCC 7 th edition stage groupings									
Stage	Adenocarcinoma				Squamous cell carcinoma				
	T	N	M	Grade	T	N	M	G	Location
0	is	0	0	1	is	0	0	1	Any
IA	1	0	0	1-2	1	0	0	1	Any
IB	1	0	0	3	1	0	0	2-3	Any
	2	0	0	1-2	2-3	0	0	1	Lower
IIA	2	0	0	3	2-3	0	0	1	Upper, middle
					2-3	0	0	2-3	Lower
IIB	3	0	0	Any	2-3	0	0	2-3	Upper, middle
	1-2	1	0	Any	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	1-2	2	0	Any	Any
	3	1	0	Any	3	1	0	Any	Any
	4a	0	0	Any	4a	0	0	Any	Any
IIIB	3	2	0	Any	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	4a	1-2	0	Any	Any
	4b	Any	0	Any	4b	Any	0	Any	Any
	Any	3	0	Any	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any	Any	1	Any	Any

Cancer location definitions: upper thoracic, 20-25 cm from incisors; middle thoracic, 25-30 cm from incisors; lower thoracic, 30-40 cm from incisors.

Appendix B: ECOG Performance Status Scale

Score	Definition
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed less than 50% of day
3	Symptomatic, in bed more than 50% of day, but not bedridden
4	Bedridden

Appendix C: Guidelines for Tissue Banking Process - Esophageal/Gastric Cancer



Note: Only tissue that is absolutely not needed for clinical diagnosis or staging should be collected for tissue banking. If in doubt about this, do NOT submit specimens for banking.

General contraindications to tissue banking

DON'T bank tissue from these specimen types or situations:

- small tumors and other cases where all or most of the lesional tissue is needed for diagnosis
- surgical margins of resection specimens where tumor and benign areas cannot be clearly delineated grossly grossly visible areas of primarily necrosis, hemorrhage, or fat
- specimens which are known to have been delayed significantly more than 30 minutes past their procurement time in the OR
- tissue previously freeze-thawed, or frozen slowly (e.g. in the cryostat or -80 freezer)
- areas of deepest invasion, tumor/normal interface, tumor/capsule interface, extranodal extension of tumor, and other key landmarks needed for surgical pathology evaluation and/or tumor staging
- chemotherapy- or radiation-treated tumors

- diagnostic biopsies where most or all tissue must be submitted for pathology evaluation. Most lymph node, GI, bone marrow, and liver biopsies fall in this category
- tissue clearly marked as intended for a special study such as immunofluorescence