LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 2

LCCC 1717: Phase II single-arm study of the combination of palbociclib and cetuximab in KRAS/NRAS/BRAF wild-type metastatic colorectal cancer

AMENDMENT INCORPORATES (check all that apply):
X Editorial, administrative changes
___ Scientific changes (IRB approval)
X Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:
The protocol was amended to introduce new guidance for continuation of palbociclib treatment in the event of the adverse events, pneumonitis/interstitial lung disease (ILD), as proposed by the drug manufacturer, Pfizer. The guidance was introduced as part of a Dear Investigator Letter from Pfizer, which identified pneumonitis/ILD as new adverse drug events/reaction linked to palbociclib. Additionally, Cetuximab infusions were to occur within a 7 day window (±3 days) weekly per treatment cycle, thus falling on Days 1, 8, 15, and 22 per each cycle. Day 22 of each cycle was incorrectly entered in the protocol as Day 21.

Editorial Changes:
1. Minor edits have been made through the document.

Therapy Changes:
2. [redacted]
3. Section 5.3.1, dose reductions/modification for palbociclib: addition of new guidance for occurrence of the adverse event, pneumonitis/ILD, and assessment of continuation of treatment. In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, palbociclib is stopped immediately and patients to be evaluated. In patients diagnosed with severe ILD or pneumonitis, palbociclib is to be permanently discontinued.
4. Section 7.4, Time and Event Table: the table column headers noting treatment cycle days, were corrected. Day 21 of each treatment cycle was corrected to Day 22.
5. Section 7.4, footnotes 2 and 7: reference to Day 21 of treatment cycles corrected to Day 22.
6. Section 7.6.4: title of header was corrected from D21 of Cycle 1 to D22 of Cycle 1.
7. Section 7.6.8: title of header was corrected from D21 of Cycle 2 to D22 of Cycle 2.
8. Section 7.6.12: title of header was corrected from D21 of Cycle 3-N to D22 of Cycle 3-N.

LINEBERGER COMPREHENSIVE CANCER CENTER
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UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

THE ATTACHED VERSION DATED OCTOBER 10, 2019 INCORPORATES THE ABOVE REVISIONS

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LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 1

LCCC 1717: Phase II single-arm study of the combination of palbociclib and cetuximab in KRAS/NRAS/BRAF wild-type metastatic colorectal cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
____Scientific changes (IRB approval)
____Therapy changes (IRB approval)
_X_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The protocol was amended to clarify the Alpha Gal testing window, clarify the window for cetuximab infusion, update the Time and Events table for consistency, clarify when Cohort B patients are required to complete anti-EGFR therapy, and update the Single Patient/Subject Exceptions with Lineberger Comprehensive Cancer Center Investigator Initiated Trials current policy on eligibility exceptions.

Summary of Changes:

1. Section 7.4, Time and Events Table: to clarify that Alpha Gal testing should be performed within 6 months of Day 1 treatment, a statement was added to Footnote #5.
2. Section 4.0, Patient Eligibility: for consistency the information included in Section 5.1 indicating that Cohort B patients are required to complete their last anti-EGFR therapy 8 weeks prior to initiating treatment in the trial was added to eligibility criteria 4.1.17.
3. Section 7.4, Time and Events Table: for consistency the timeframe for the Long-Term Follow Up visit that is stated Section 7.7.3 as every 90 days (+/- 15 days) has been added as Footnote #8.
4. Section 5.2, Treatment Dosage and Administration: a window was added to clarify that cetuximab infusion administration has a window of +/- 15 minutes.
5. Section 7.3, Correlative Studies: the words "baseline and" have been removed from the second paragraph as the optional biopsy is only requested during treatment.
6. Section 10.5.2, Single Patient/Subject Exceptions: wording was updated to reflect the current policy on eligibility exceptions for Lineberger Comprehensive Cancer Center Investigator Initiated Trials.

THE ATTACHED VERSION DATED SEPTEMBER 5, 2018 INCORPORATES THE ABOVE REVISIONS

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CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC 1717: Phase II single-arm study of the combination of palbociclib and cetuximab in KRAS/NRAS/BRAF wild-type metastatic colorectal cancer

Short Title: Phase II study of palbociclib and cetuximab in KRAS/NRAS/BRAF wild-type metastatic colorectal cancer

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Funding Source: Pfizer
Version date: October 10, 2019

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LCCC 1717: Phase II single-arm study of the combination of palbociclib and cetuximab in KRAS/NRAS/BRAF wild-type metastatic colorectal cancer

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Version date: October 10, 2019

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
Alpha-gal	galactose-alpha-1,3-galactose IgE
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
BRAF	Murine sarcoma viral oncogene homolog B
C1	Cycle 1
CBC	Complete blood count
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CEA	Carcinoembryonic antigen
CMP	Complete metabolic panel
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CT	Computer tomography
ctDNA	Circulating free deoxyribonucleic acid
CYP	Cytochrome P450
D1	Day 1
DCR	Disease control rate (complete or partial response and stable disease)
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
E2F	Eukaryote 2 Transcription Factor
EC50	Concentration associated with 50% maximal effect
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal regulated kinase
FDR	False discovery rate
g/dL	Grams per deciliter
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPPA	Health Insurance Portability Act
IB	Investigator's Brochure
IC50	Concentration associated with 50% inhibition of maximal effect
IDS	Investigational drug service
Ig	Immunoglobulin
IgE	Immunoglobulin E
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMIDs	Immunomodulators
IND	Investigational new drug
INR	International normalized ratio
IV	Intravenous
Kras	Kirsten rat sarcoma (viral oncogene)
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase

mCRC	Metastatic colorectal cancer
Mg	Magnesium
Mm	Millimeter
MSI-H	Microsatellite instability - high
MSS	Microsatellite stable
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NK	Natural killer
NSAIDs	Non-steroidal anti-inflammatory drugs
nM	Nanomolar
N-ras	Neuroblastoma sarcoma viral oncogene homolog
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic or Progressive disease
PET	Positron Emission Tomography
PFS	Progression free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PHI	Personal health information
Phosphor-Rb	Phosphorylated Rb
PI3K	Phosphoinositide 3-kinase
PO	*Per os* (by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	*Quaque die* (once daily)
RAF	Rapidly accelerated fibrosarcoma oncogene
RAS	Rat sarcoma (viral oncogene)
Rb	Retinoblastoma
RBC	Red blood cell
RNA	Ribonucleic acid
RPPA	Reverse phase protein array
SAE	Serious adverse event
SD	Stable disease
SLM	Study laboratory manual
SULT2A1	sulfotransferase enzyme A1
SUSAR	Serious unexpected adverse reaction
TCGA	The cancer genome atlas
TdP	Torsades des pointes
TLS	Tumor lysis syndrome
Tmax	Time to maximum drug concentration
TPF	Tissue procurement facility
ULN	Upper limit of normal
UNC	University of North Carolina
USPI	United States Package insert
VEGFR	Vascular endothelial growth factor receptor
VGPR	Very good partial response

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

We will conduct a multicenter, single-arm, phase II clinical trial of combination therapy with cetuximab and palbociclib in refractory *KRAS*, *NRAS*, and *BRAF* wild-type metastatic colorectal cancer (CRC) patients. Cohort A will include anti-EGFR naïve patients, and Cohort B will include patients previously treated with an anti-EGFR therapy that experienced at least 4 months of disease control (ie, CR, PR or stable disease) with their prior anti-EGFR therapy and received their last anti-EGFR therapy at least 8 weeks prior to the first dose of study drug. Cohort B is limited to the subpopulation of patients previously exposed to anti-EGFR therapy who may benefit from rechallenge with anti-EGFR therapy. The primary endpoint is 4-month disease-control rate upon treatment with the combination of palbociclib and cetuximab in adults with refractory *KRAS*/*NRAS*/*BRAF* wild-type metastatic CRC. We hypothesize that this combination will improve the 4-month disease-control rate in patients with refractory *KRAS*/*NRAS*/*BRAF* wild-type metastatic colorectal cancer (CRC) who are either naïve to EGFR therapy (Cohort A) or eligible for rechallenge (Cohort B). Up to 26 subjects will be enrolled in cohort A and up to 21 subjects will be enrolled in cohort B.

1.2 Colorectal cancer – Current Therapies and Challenges

CRC is the second most common cause of cancer mortality in the United States, causing an estimated 49,190 deaths in 2016. Mortality is primarily driven by the 20% of CRC patients with metastatic disease, who suffer 5-year overall survival of only 12.9% [1]. Patients with mCRC have experienced improvements in median overall survival (OS), from 14.2 months for those diagnosed in 1990-1997 to over 29 months for those diagnosed after 2004 [2]. Much of these improvements are attributable to development of novel therapies. Previously, only fluoropyrimidines were standard options for patients with CRC, but starting in the mid-2000s, increasing numbers of patients were treated with novel chemotherapy agents such as irinotecan, oxaliplatin, and novel biologic drugs such as bevacizumab and the monoclonal antibodies targeting the epidermal growth factor receptor (EGFR); subsequent widespread use of these agents has contributed to improvements in survival. Nevertheless, barring surgical resection of oligometastatic disease, inevitably metastatic cancers develop resistance to therapies, thus resulting in clinical progression and ultimately death. There is a great unmet need to better understand biologic mechanisms of resistance to available therapies and use this knowledge to guide future therapy choices for individual patients with CRC.

While efforts have been extensive to identify molecular markers to guide evidence-based therapy for patients with CRC, the impact of these efforts thus far

on the standard of care for CRC has been limited. Microsatellite instability high (MSI-H) is a molecular fingerprint of a deficient mismatch repair system that is evident in approximately 15% of CRC that has been recognized since the 1990s [3]. The MSI-H phenotype is a unique subset characterized by less aggressive behavior and a favorable prognosis compared to microsatellite stable (MSS) CRC, at least among patients with stage II disease[4]. The prognostic value of MSI-H should be evaluated in all stage II CRC patients regarding chemotherapy as some patients can be spared adjuvant chemotherapy. Evidence for supporting the preferential efficacy of irinotecan in MSI-H tumors is continuing to emerge but remains inconclusive based on disparate results from clinical trials [3, 5, 6].

Currently, available biomarkers for CRC are limited to identifying patients for whom certain treatment is not suited, rather than identifying those who may benefit from treatment [7]. *KRAS* and *NRAS* mutation status provide a basis for patient selection regarding benefit from EGFR targeting antibodies [8] as patients with *KRAS* or *NRAS* mutations, which are detected in approximately 40% of CRCs, do not derive benefit from these treatments. There are no prognostic or predictive molecular markers for bevacizumab-based therapy which is directed against the vascular endothelial growth factor receptor (VEGF-R) pathway; moreover, due to the heterogeneous nature of CRC, a number of patients receive little benefit or no benefit from these targeted agents [7]. Although unique subtypes within CRC have been identified based on a consensus molecular subtyping strategy devised and recently reported by the Colorectal Cancer Subtyping Consortium, [9, 10] critical questions remain regarding the pathogenesis and biology of these tumors, and unfortunately, optimal biomarkers for evidence-based therapeutic approaches remain elusive. Key areas of unmet need include optimizing use of EGFR antibodies for *RAS/RAF* wild-type disease and improving treatment for patients with *RAS* and *RAF* mutations where no proven targeted therapy exists.

1.3 Cetuximab

In 2004, the U.S. Food and Drug Administration approved the first monoclonal antibody targeting the epidermal growth factor receptor (EGFR), cetuximab. Cetuximab significantly improves progression-free and overall survival (PFS and OS) compared to best supportive care in *KRAS* codon 12 and 13 wild-type metastatic CRC patients,[11] and more recent data indicates benefit is limited to those wild-type in *KRAS* and *NRAS* at exons 2, 3, and 4 [12]. Moreover, the presence of a *BRAF* mutation is a marked negative prognostic factor, although there are conflicting reports on whether patients who have *BRAF* mutant CRC benefit from cetuximab [13]. Nevertheless, for the approximately 40% of metastatic CRC patients who have tumors wild-type in *KRAS*, *NRAS*, and *BRAF* [14], and are thus eligible for treatment with anti-EGFR therapy, ultimately disease progression does occur. Thus, novel therapies and combinations are urgently required. Although a wide variety of resistance mechanisms have been

identified, they generally result in aberrant activation of downstream or alternative signaling components through mutation or amplification, resulting in reactivation of ERK signaling and its downstream pathways [15, 16]. The addition of other targeted therapies that synergize with cetuximab will likely mitigate the development of resistance and prolong the duration of benefit with anti-EGFR therapy.

1.4 Palbociclib

The cyclin D-cyclin-dependent kinase (CDK) 4/6-inhibitor or CDK4 (INK)-retinoblastoma (Rb) pathway regulates cellular proliferation by controlling the G1 (pre-DNA synthesis) to S (DNA synthesis) cell cycle checkpoint [17]. This pathway is frequently dysregulated in cancer and aberrant signaling via this checkpoint contributes to cell cycle progression and continued growth. Palbociclib is a highly selective reversible oral inhibitor of CDK 4 and 6 that is being studied for use in the treatment of cancer [18]. Palbociclib inhibits purified CDK4-catalyzed phosphorylation of the retinoblastoma (Rb) protein with an IC50 of less than 20 nM and also tumor growth of several types of human xenograft tumors (SF-295, MDA-MB-435, Colo-205, and others), grown in severely immunocompromised mice. Estimated steady-state plasma concentrations of 1000 ng/mL resulted in 80% to 90% inhibition of phospho-Rb formation and 50% reduction in tumor growth. Reduction in phospho-Rb was rapidly reversible as plasma palbociclib concentrations declined.

Palbociclib has been approved for the treatment of hormone receptor (HR-positive), human epidermal growth factor receptor 2 (HER)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or with fulvestrant in women with disease progression following endocrine therapy (Palbociclib USPI). The recommended dosing regimen is 125 mg administered once daily for 21 consecutive days of a 28-day cycle. Palbociclib in combination with letrozole in postmenopausal women (PALOMA-1 and PALOMA-2) [19, 20], or in combination with fulvestrant in women after progression on endocrine therapy (PALOMA-3) [21] significantly improved PFS and improved clinical benefit response rates. Neutropenia was the most commonly reported any grade and grade $\geq$ 3 adverse event (AE) in these trials (66% of patients in PALOMA-2 and PALOMA-3 had $\geq$ grade 3 neutropenia; median duration 7 days); and was generally manageable with palbociclib dose delays, interruptions or reductions, without the need for growth factor support and without compromising efficacy [17]. The neutropenia was infrequently associated with febrile events (<2%).

As of 31 August 2016, 35 studies evaluating the safety, efficacy, pharmacodynamics and pharmacokinetics of palbociclib as monotherapy or in combination with other cancer drugs have been initiated in healthy volunteers or

in patients with cancer (summarized in table 6.1 of the IB) [18]. Safety information is available and summarized in 15 studies enrolling over 1900 patients with cancer as of 31 August 2016. The most frequently reported palbociclib treatment related AEs (≥ 20% of patients) were fatigue (41.7%), neutropenia (40.8%), diarrhea (25.2%), nausea (24.3%) and anemia (23.3%) (See table 6.2-3 in IB and protocol section 6.1.6) across these trials. Ongoing studies are investigating palbociclib in breast cancer and in other solid tumors.

1.5 Rationale for Cetuximab and Palbociclib Combination Therapy in CRC

There is strong rationale for combining anti-EGFR therapy like cetuximab with CDK4/6 inhibitors like palbociclib. The cell cycle pathway is a key downstream effector pathway of EGFR mitogenic signaling (Figure 1). Activation of EGFR by binding of growth factor ligands results in activation of KRAS and increased signaling in the RAF-MEK-ERK signaling network. ERK activation increases transcription of cyclin D1, which binds to and activates CDK 4/6, which then phosphorylates and inactivates the Rb tumor suppressor, releasing the transcription factor E2F and driving cell cycle progression. Resistance mechanisms to anti-EGFR therapies commonly converge on reactivation of ERK or activation of compensatory growth signaling pathways which consequently reactivate cell cycle progression[16], so combining cell cycle inhibitors with anti-EGFR therapies may synergize. Additionally, nuclear translocation of the EGFR protein has been described as one mechanism of resistance to cetuximab, and nuclear EGFR binds to and activates transcription factors, including E2F1 itself, causing increased cyclin D1 transcription [22]. Conversely, active E2F1 also feeds back to upregulate EGFR and EGFR ligands [23], while EGFR signaling blocks the E2F1-induced pro-apoptotic signals that would otherwise be induced as a protective mechanism [24]. Thus, the combination of anti-EGFR monoclonal antibodies with CDK4/6 inhibitors is a rational combination for further investigation. We also performed analysis of gene expression profiles of anti-EGFR responsive vs resistant CRC tumors and found that anti-EGFR responsive CRCs had significantly greater expression of cell cycle regulation pathways, suggesting that these CRCs have marked cell cycle signaling and that adding CDK4/6 inhibitors to anti-EGFR therapy will further increase benefit (Figure 2). Taken together, these results suggest that the *KRAS* wild-type tumors more likely to have a positive response to cetuximab are likely those with increased evidence of E2F activity. Further inhibition of cell cycle progression may improve the duration of clinical benefit with cetuximab treatment.

Additionally, the overwhelming majority of CRCs have intact Rb expression, which is required for efficacy of CDK4/6 inhibitors, and thus screening for Rb+ tumors is not necessary. *RB1* is wild-type in over 95% of untreated CRCs [14], and studies assaying for mutations in circulating tumor DNA (ctDNA) or in metachronous metastases in CRC patients refractory to prior chemotherapy

regimens failed to identify a substantial rate of acquired mutations in *Rb1* [25, 26], indicating that *Rb1* mutations do not develop in chemorefractory CRC. As such, nearly all CRCs are candidates for potential response to CDK4/6 inhibition. Furthermore, cell cycle pathways are notably active in CRCs, so targeting CDK4/6 is particularly compelling in CRC; PARADIGM pathway analysis of CRCs in The Cancer Genome Atlas (TCGA) demonstrated overexpression of transcriptional targets of Rb and E2F, and of the known CDK4/6 effector FOXM1, compared to normal tissues [14].

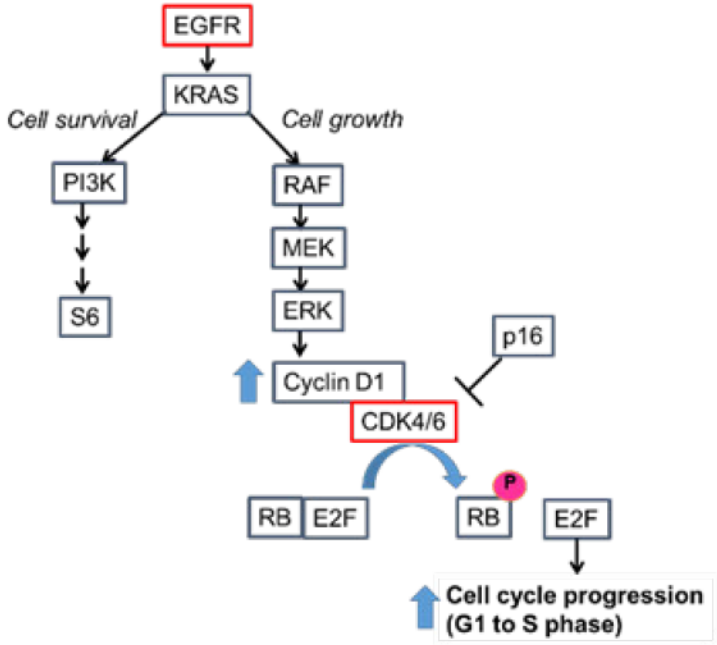
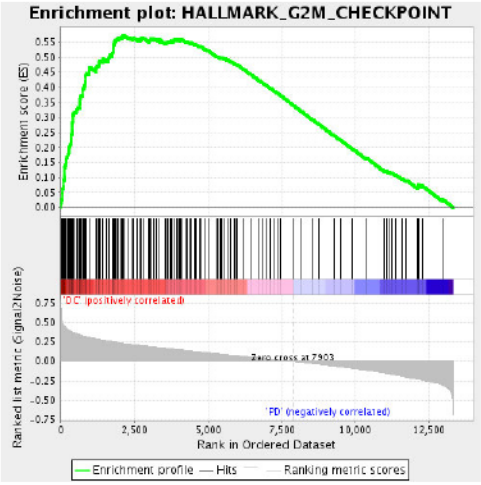


Figure 1: Cell signaling pathways show downstream effect of EGFR on cell cycle pathways.



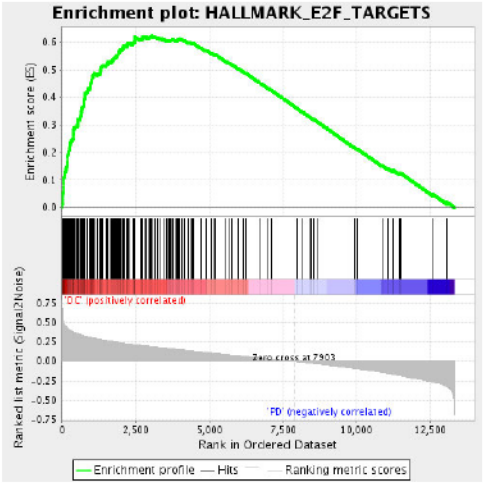


Figure 2: Enrichment plots from gene set enrichment analysis of 39 *KRAS* exon 2-wild type CRC tumors that were either cetuximab resistant or responsive showed cell cycle pathways for the G2M checkpoint and E2F transcription factor targets among the top differentially trending pathways (G2M checkpoint genes with nominal p-value 0.049, FDR q-value 0.38; E2F target genes with nominal p-value 0.065, FDR q-value 0.28).

Notably, the combination of palbociclib and cetuximab has already undergone Phase I investigation to determine a recommended phase II dose. The combination was investigated in a Phase I clinical trial in metastatic head and neck squamous cell carcinoma patients. The recommended phase II dose was palbociclib 125 mg *per os* daily on days 1-21 out of a 28 day cycle, along with cetuximab 400 mg/m^2 IV load on cycle 1 day 1, followed by cetuximab 250 mg/m^2 IV weekly [27]. No dose limiting toxicities (DLTs) occurred during the assessment period, and the only grade 3-4 toxicities reported were hematologic, including leukopenia, neutropenia, thrombocytopenia, and anemia, but without any incidents of febrile neutropenia. Thus, the combination regimen we propose to investigate in LCCC1717 is safe and has a well-defined toxicity profile.

Our proposed Phase II, multicenter trial will evaluate cetuximab and palbociclib combination therapy in refractory KRAS, NRAS, and BRAF wild-type metastatic CRC patients. We will enroll patients into two different cohorts (A or B) based on their prior treatment history. Cohort A will evaluate cetuximab and palbociclib in anti-EGFR naïve patients, and Cohort B will evaluate this regimen in patients previously exposed to anti-EGFR therapy who experienced at least 4 months of disease control on their prior anti-EGFR therapy and completed their last anti-EGFR therapy at least 8 weeks prior to initiating treatment in our trial. As such, Cohort B is limited to the subpopulation of patients previously exposed to anti-EGFR therapy who may benefit from rechallenge with anti-EGFR therapy. Based on retrospective data and an Italian prospective study, patients who derived clinical benefit from their first regimen of anti-EGFR therapy and have sufficient time after discontinuation of their first regimen of anti-EGFR therapy, putatively to allow resistant subclone populations to recede, are more likely to benefit from rechallenge with anti-EGFR therapy [28].

1.6 Correlative Studies

Identifying mechanisms of resistance to targeted therapies, including anti-EGFR therapies, is critical to identifying superior combinations of therapies for the future. Resistance to anti-EGFR therapies is accompanied by increases in circulating tumor DNA harboring KRAS mutations, reflecting expansion of KRAS mutated subclones. We will collect peripheral blood samples serially to facilitate analyses such as mutation analysis and quantitation of circulating free tumor DNA. Additionally, we will collect serum samples for analysis of

circulating thymidine kinase activity, which is a reflection of cell proliferation and has been shown to be a pharmacodynamic biomarker in other trials using CDK4/6 inhibitors. We will also collect archival tissue to have available to assess Consensus Molecular Subtypes by mRNA expression analysis, as these subtypes are associated with differential underlying biology and prognosis and may explain heterogeneity of responses of metastatic CRC to various therapies. We will also include an optional on-treatment biopsy to identify potential biomarkers for anti-EGFR antibodies, which could include integrated genomic analysis with multiplex next generation DNA and RNA sequencing and immunohistochemistry for known pharmacodynamic biomarkers of cell proliferation.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

To estimate the disease control rate at four months (DCR: CR, PR or SD) after a treatment regimen of cetuximab and palbociclib in patients with refractory KRAS/NRAS/BRAF wild-type metastatic CRC in both a cohort of anti-EGFR naïve therapy patients, and a cohort of patients who might benefit from a re-challenge of anti-EGFR therapy.

2.2 Secondary Objectives

2.2.1 To estimate the overall response rate at four months (ORR: CR or PR) after a treatment regimen of cetuximab and palbociclib in patients with refractory KRAS/NRAS/BRAF wild-type metastatic CRC in both a cohort of anti-EGFR naïve therapy patients, and a cohort of patients who might benefit from a re-challenge of anti-EGFR therapy.

2.2.2 To estimate overall survival (OS) after a treatment regimen of cetuximab and palbociclib in patients with refractory KRAS/NRAS/BRAF wild-type metastatic CRC in both a cohort of anti-EGFR naïve therapy patients, and a cohort of patients who might benefit from a re-challenge of anti-EGFR therapy.

2.2.3 To estimate progression free survival (PFS) after a treatment regimen of cetuximab and palbociclib in patients with refractory KRAS/NRAS/BRAF wild-type metastatic CRC in both a cohort of anti-EGFR naïve therapy patients, and a cohort of patients who might benefit from a re-challenge of anti-EGFR therapy.

2.2.4 To evaluate the toxicity and safety profile of the combination of palbociclib and cetuximab in patients with refractory KRAS/NRAS/BRAF wild-type metastatic CRC

2.3 Exploratory Objectives

2.3.1 [redacted]

3.0 Criteria for Evaluation / Study Endpoints

3.1 Primary Endpoint

Four-month disease control rate, defined as complete or partial response or stable disease based on RECIST 1.1 criteria at 4 months after first dose of study drugs.

3.2 Secondary Endpoints

3.2.1 Objective response, defined as complete or partial response based on RECIST 1.1 criteria.

3.2.2 Overall survival (OS), defined as time from first dose of study drug to death from any cause.

3.2.3 Progression-free survival (PFS), defined as time from first dose of study drug to progression or death from any cause.

3.2.4 Toxicity assessed per NCI CTCAE v4.03 starting on day 1 of study treatment.

3.3 Exploratory Endpoints

3.3.1 [redacted]

4.0 PATIENT ELIGIBILITY

In order to participate in this study a subject must meet ALL of the eligibility criteria outlined below.

4.1 Inclusion Criteria

4.1.1 Written informed consent obtained to participate in the study and HIPAA authorization for release of personal health information.

4.1.2 Age ≥ 18 years at the time of consent.

4.1.3 ECOG Performance Status of 0-2

4.1.4 Histologically-confirmed metastatic CRC

4.1.5 Measurable disease according to RECIST v1.1 for solid tumors.

4.1.6 Documented wild-type in KRAS and NRAS (codons 12, 13, 59, 61, 117, and 146) and in BRAF codon 600, based on tumor tissue taken from primary or metastatic site and tested for biomarkers

4.1.7 Previously treated with at least two prior regimens of systemic chemotherapy for metastatic or locally advanced, unresectable disease, including fluoropyrimidines (5-fluorouracil and/or capecitabine), oxaliplatin, and irinotecan.

- A maintenance regimen of 5-fluorouracil or capecitabine, with or without bevacizumab, should not be counted as a separate line of treatment
- For patients who experienced disease recurrence during or within 6 months of completion of adjuvant chemotherapy with fluoropyrimidine and oxaliplatin, only one regimen of systemic chemotherapy for metastatic disease is required

4.1.8 Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained prior to initiating study medications.

System	Laboratory Value
Hematological*	
Hemoglobin (Hgb)	≥ 9 g/dL
Absolute Neutrophil Count (ANC)	≥ 1500/mm^3
Platelets	≥ 100,000/mm^3
Renal*	

Creatinine OR Calculated creatinine clearance	≤1.5 x ULN ≥ 60 mL/min by Cockcroft-Gault formula
Hepatic*	
Bilirubin	≤ 1.0 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≤ 3 × ULN OR ≤ 5 × ULN (if liver metastases present)
Alanine aminotransferase (ALT)	≤ 3 × ULN OR ≤ 5 × ULN (if liver metastases present)

*Note: Hematology and other lab parameters that are ≤ grade 2 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy.

4.1.9 Females of childbearing potential must have a negative serum pregnancy test within 72 hours prior to initiating study medications. **NOTE**: Females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. Documentation of postmenopausal status must be provided.

4.1.10 Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 6 months after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method or an intrauterine device that meets <1% failure rate for protection from pregnancy in the product label.

4.1.11 Male patients with female partners must have had a prior vasectomy or agree to use an adequate method of contraception (i.e., double barrier

method: condom plus spermicidal agent) starting with the first dose of study therapy through 6 months after the last dose of study therapy.

4.1.12 Subjects is willing and able to comply with study procedures based on the judgement of the investigator or protocol designee.

4.1.13 Able to swallow capsules, with no surgical or anatomic condition that will preclude the patient from swallowing and absorbing oral medications.

4.1.14 Has not undergone any major surgical procedures for at least 4 weeks, with full healing of all surgical wounds

4.1.15 At sites in the Southeastern U.S., subject must have negative serum test for galactose-alpha-1,3-galactose IgE See Appendix 12.5 for map (**Note**: positive test result is predictive of immediate-onset anaphylaxis reaction during first exposure to cetuximab, which is prevalent predominantly in limited geographic region of the Southeastern U.S. (Clin Mol Allergy 2012;10:1-11).

4.1.16 For Study Cohort A, has not had prior treatment with cetuximab, panitumumab, or other anti-EGFR therapy.

4.1.17 For Study Cohort B, must have had previous treatment with cetuximab or panitumumab with disease control (defined as complete response, partial response, or stable disease) lasting for ≥ 4 months in duration and completed their last anti-EGFR therapy 8 weeks prior to initiating treatment.

4.2 Exclusion Criteria

4.2.1 Active infection requiring systemic therapy.

4.2.2 Pregnant or breastfeeding (NOTE: breast milk cannot be stored for future use while the mother is being treated on study).

4.2.3 Presence of known, active central nervous system (CNS) metastases.

4.2.4 Treatment with any investigational drug within 28 days prior to initiating study medications.

4.2.5 Prior treatment with drug targeting cyclin-dependent kinase (CDK) family.

4.2.6 Subject is receiving prohibited medications or treatments as listed in section 5.5 of the protocol that cannot be discontinued/replaced by an alternative therapy.

4.2.7 Known hypersensitivity to the components of study drugs or analogs of study drugs.

4.2.8 Has a known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least five years.

4.2.9 Uncontrolled, severe concomitant comorbidity (e.g. uncontrolled hypertension, uncontrolled diabetes mellitus, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection).

4.2.10 History of interstitial lung disease or pneumonitis.

4.2.11 Any other clinically significant heart disease, including angina pectoris, resting bradycardia, left bundle branch block, ventricular tachyarrhythmia, unstable atrial fibrillation, acute myocardial infarction, or heart disease requiring cardiac pacemaker or implantable cardioverter/defibrillator

4.2.12 Known psychiatric or substance abuse disorder that would interfere with the ability of the patient to comply with trial requirements.

4.2.13 History of long-QT syndrome.

4.2.14 Baseline QTcF $\geq$ 470 msec.

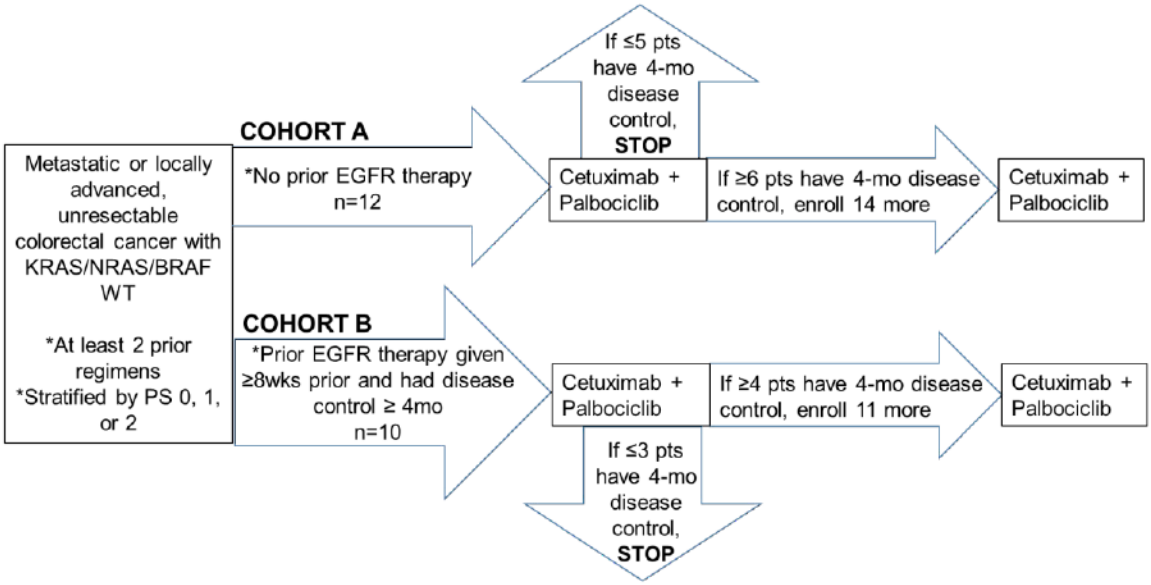
4.2.15 Concomitant use of drugs known to cause QT prolongation as defined in Appendix 12.4 and in section 5.5 (**Note**: Ondansetron at doses $\leq$ 16 mg or less is allowed)

4.2.16 History of any of the following cardiovascular conditions within the past 6 months:

- Class III or IV congestive heart failure as defined by the New York Heart Association Criteria
- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Symptomatic peripheral vascular disease or other clinically significant cardiac disease

5.0 TREATMENT PLAN

5.1 Schema



This is a multicenter Phase II trial of palbociclib and cetuximab combination therapy in KRAS, NRAS, and BRAF wild-type metastatic CRC patients. The trial will initially enroll 22 patients stratified for enrollment into one of two cohorts (A or B) depending on their prior treatment history. Cohort A will evaluate cetuximab and palbociclib in anti-EGFR naïve patients, and Cohort B will evaluate this regimen in patients previously exposed to anti-EGFR therapy who experienced at least 4 months of disease control on their prior anti-EGFR therapy and completed their last anti-EGFR therapy at least 8 weeks prior to initiating treatment in this trial. Cohort A will initially enroll 12 patients. If ≥ 6 out of 12 patients experience disease control lasting ≥ 4 months on palbociclib and cetuximab in this cohort, then enrollment in this arm will continue and an additional 14 patients will be enrolled (n = 26). Cohort B will initially enroll 10 patients with prior exposure to anti-EGFR therapy. If ≥ 4 out of 10 patients experience disease control lasting for at least 4 months on palbociclib and cetuximab in this cohort, then enrollment in this arm will continue and an additional 11 patients will be enrolled (n = 21). Thus, up to 47 evaluable patients could enroll in this study if the combination demonstrates efficacy in both cohorts. Cetuximab will be given per standard of care (400 mg/m^2 IV load on cycle 1 day 1, followed by cetuximab 250 mg/m^2 IV weekly) and palbociclib 125 mg once daily (qd) on days 1-21 of a 28 day cycle, along with cetuximab until disease progression or withdrawal from study therapy for other reasons.

5.2 Treatment Dosage and Administration

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Palbociclib	Take palbociclib with food	125mg	oral	Once daily on Days 1-21, then 7 days off	4 weeks (28 days)
Cetuximab[1,2]	Pretreatment for infusion-related reactions per local standard of care[1] e.g., 50 mg diphenhydramine , H2 blocker (ranitidine or famotidine) and dexamethasone (8-20 mg) See section 5.3.2 for guidance on infusion-related reactions	**Loading dose**: 400 mg/m^2 **Subsequent doses** 250 mg/m^2	IV, administered over 2 hours IV, administered over 1 hour (± 15 minutes)	Once weekly, start with loading dose D1 of wk 1 then subsequent doses given D1 of wk 2 and beyond	

1. In general, a histamine receptor antagonist prior to cetuximab infusion is recommended to prevent hypersensitivity reactions. Corticosteroid premedication may also be given per local guidelines. If hypersensitivity ruled out after the first infusion, premedication(s) may be omitted if permitted per local guidelines.
2. In Southeast only, test for galactose-alpha-1,3-galactose IgE must be performed and must be negative to be eligible for cetuximab therapy.

5.3 Toxicities and Dosing Delays/Dose Modifications

5.3.1 Dose Reductions/Modifications for Palbociclib

Allowed Dose reductions

- Starting dose = 125 mg/day
- First dose reduction = 100 mg/day
- Second dose reduction = 75 mg/day*

  Discontinue palbociclib if further dose reduction is needed.

Dose Modification and Management – Hematologic Toxicities*	
Monitor complete blood counts prior to start of palbociclib and at the beginning of each cycle, as well as on day 15 of the first 2 cycles, and as clinically indicated. For patients who experience a maximum of grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.	
NCI-CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment required
Grade 3	**Day 1 of cycle**: Withhold palbociclib, repeat CBC monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. **Day 15 of first 2 cycles**: If Grade 3 on Day 15, continue palbociclib at current dose to complete cycle and repeat CBC on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery form Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia† with fever ≥38.5^{0}C and/or infection	**At any time**: Withhold palbociclib until recovery to Grade ≤ 2. Resume at *next lower* dose.
Grade 4	**At any time**: Withhold palbociclib until recovery to Grade ≤ 2. Resume at *next lower* dose.

*Table applies to all hematologic AEs except lymphopenia (unless associated with clinical events, eg, opportunistic infections).
† Absolute neutrophil count (ANC): Grade 1 <LLN -1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3, Grade 3 ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3

Dose Modification and Management –Non-hematologic Toxicities	
NCI-CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required
Grade ≥ 3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold palbociclib until symptoms resolve to: • ≤ Grade 1: • ≤ Grade 2: (if not considered safety risk for patient) Resume at the *next lower* dose

Patients to be monitored for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. In patients diagnosed with severe ILD or pneumonitis, palbociclib is to be permanently discontinued.

5.3.2 Dose Modifications/Delays for Cetuximab (Rash)

Severe Acneiform Rash	Cetuximab Dosing	Outcome	Dose modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement No improvement	Continue 250 mg/m^2 Discontinue Cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement No improvement	Reduce to 200 mg/m^2 Discontinue Cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement No improvement	Reduce to 150 mg/m^2 Discontinue Cetuximab
4th occurrence	Discontinue Cetuximab		

5.3.3 Management of infusion-related reactions

Approximately 90% of severe infusion reactions occur with the first infusion of cetuximab. Monitor patients for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Monitor longer to confirm resolution of the event in patients requiring treatment for infusion-related reactions.

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

Continued on next page

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids, • antihistamines, • NSAIDS, • acetaminophen, • narcotics, • oxygen, • pressors, • corticosteroids, • epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	**No subsequent dosing**
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.4 Concomitant Medications/Treatments/Supportive Care Allowed

Patients on the trial are allowed to receive all supportive care therapy needed to alleviate symptoms related to CRC or other medical problems at the investigator's discretion (see prohibited medications in section 5.5 for exceptions). No treatments should be withheld due to a patient's participation in this study. Prophylaxis for infusion-related reactions should be employed per institutional guidelines. A guidance for the management of infusion-related reactions is provided in section 5.3.3 of the protocol. (**Note**: Ondansetron at doses ≤ 16 mg or less is allowed).

5.4.1 Management of Cetuximab Skin Toxicity

Before initiating cetuximab treatment, the following prophylactic measures should be discussed with the patient to help alleviate the risk for skin toxicity.

- Using sunscreens
- Avoiding habits/products that can produce dry skin (eg, hot water, alcohol-based cosmetics
- Enhancing skin hydration (bath oils, etc.)
- Using frequently alcohol-free moisturizing creams
- Using tocopherol oil or gel
- Avoiding tight shoes and
- Avoiding excessive beard growth, shaving with regular shaving razor, sharp multiblade, using pre-shaving cream emollients and moisturizing aftershave, not using alcohol and aftershave or using electric shaver.
- Prophylaxis against skin eruption with minocycline or doxycycline may be used per institutional guidelines.

Management guidelines for skin toxicity (grade ≥ 2) are provided in Appendix 12.1

5.5 Prohibited Medications/Treatments

There are no reported drug-drug interactions with cetuximab. However, palbociclib, is primarily metabolized by CYP3A and sulfotransferase enzyme (SULT2A1). In vivo, palbociclib is a time-dependent inhibitor of CYP3A. The patient handout in Appendix 12.2 should be provided to patients to inform them of drugs to avoid taking while they are receiving study medications.

Prohibit use of strong CYP3A inhibitors ie, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole. Avoid grapefruits and grapefruit juice.
Prohibit concomitant use of strong CYP3A inducers ie, phenytoin, rifampin, enzalutamide, and St John's wort.

Prohibit use of CYP3A substrates with a narrow therapeutic index ie, alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, and tacrolimus).

(A frequently updated P450 drug interaction table is available at: http://medicine.iupui.edu/clinpharm/ddis/)

Warning: QTc prolongation can occur in patients treated with palbociclib and cetuximab. Avoid use of palbociclib with cetuximab in subjects with long QT syndrome. Avoid concomitant use of cetuximab and palbociclib that with agents known to prolong QTc interval or cause torsades de pointes (TdP).

A list of agents known to prolong QTc interval or cause torsades de pointes (TdP) can be found at: https://www.crediblemeds.org. A recently updated list as of July 22, 2017 is provided in Appendix 12.4.

Agents with known risk for QTc prolongation or TdP are exclusionary. Medications with possible risk (PR) or conditional risk (CR) of TdP should be used with caution and if an alternative agent is available, the alternative agent should be used instead. **Ondansetron at doses ≤ 16 mg or less is allowed.**

5.6 Duration of Therapy

Treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment

- Unacceptable adverse event(s)
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Subject completes maximum number of treatment cycles allowed per protocol
- Subject is lost to follow up

It is anticipated that subjects will receive on average 4 to 6 months of study treatment.

5.7 Duration of Follow Up

All patients will be followed for up to 3 years, or until death, whichever occurs first after removal from study treatment for determination of study endpoints. Patients removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the adverse event(s). All patients (including those withdrawn for AEs) should be followed after removal from study treatment as stipulated in the protocol.

5.8 Study Withdrawal

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 5.6 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

If a patient decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The patient should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the patient's study withdrawal should be obtained with an explanation of why the patient is withdrawing from the study.
- If the patient is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

6.0 DRUG INFORMATION

6.1 Palbociclib (Investigational Drug)

6.1.1 Description

Palbociclib is an inhibitor of CDKs 4 and 6. Cyclin D1 and CDK 4/6 are downstream of signaling pathways, which lead to cellular proliferation. In vitro experiments demonstrated that palbociclib blocks cell cycle progression from G1 into S phase and increases cellular senescence and inhibits tumor growth.

Full prescribing information for palbociclib is available at:
http://labeling.pfizer.com/ShowLabeling.aspx?id=2191#section-14

6.1.2 Dosage and Administration

Palbociclib is a 125 mg (100 mg or 75 mg) capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

- Palbociclib should be taken with food.
- Patients should be instructed to take their dose of palbociclib at approximately the same time each day.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.
- Palbociclib capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing).
- Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

6.1.3 Storage and Handling

Palbociclib is supplied in the following strengths

Palbociclib capsules	
Package configuration	**Capsule strength (mg)**
Bottles of 21 capsules	125
Bottles of 21 capsules	100
Bottles of 21 capsules	75

Store at 20 ^{0}C to 25 ^{0}C (68 ^{0}F to 77 ^{0}F); excursions between 15 ^{0}C to 30 ^{0}C (59 ^{0}F to 86 ^{0}F) permitted

6.1.4 Drug Accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from the company sponsor or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial. An accurate and current accounting of the dispensing and return of investigational study drug for each subject will be maintained on an ongoing basis by a member

of the study site staff. The amount of study drug dispensed and returned by the subject will be recorded in the Investigational Drug Accountability Record.

6.1.5 Return and Retention of Study Drug

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy (eg, UNC IDS drug destruction policy). It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that, procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.1.6 Adverse Events Associated with Palbociclib

The AEs provided below are common toxicities associated with palbociclib per March 2017 IB. For additional details, please consult the current IB.

Pooled Adverse Drug Reactions Reported for Patients who received Palbociclib in Randomized Clinical Studies A5481003, A5481008, and A5481023 (N = 872)

System Organ Class Preferred term (PT)[a]	Frequency	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections & Infestations				
Infections	Very common	501 (57.5)	40 (4.6)	8 (0.9)
Blood and lymphatic system disorders				
Neutropenia	Very common	712 (81.7)	497 (57.0)	93 (10.7)
Leukopenia	Very common	420 (48.2)	249 (28.6)	7 (0.8)
Anemia	Very common	247 (28.3)	41 (4.7)	2 (0.2)
Thrombocytopenia	Very common	182 (20.9)	14 (1.6)	4 (0.5)
Febrile neutropenia	uncommon	11 (1.3)	10 (1.1)	1 (0.1)
Eye disorders				
Vision blurred	Common	44 (5.0)	1 (0.1)	0 (0.0)
Lacrimation increased	Common	56 (6.4)	0 (0.0)	0 (0.0)
Dry eye	Common	32 (3.7)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders				
Decreased appetite	Very common	147 (16.9)	8 (0.9)	0 (0.0)
Nervous system disorders				
Dysgeusia	Common	78 (8.9)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	Common	77 (8.8)	0 (0.0)	0 (0.0)
Gastrointestinal disorders				
Stomatitis	Very common	260 (29.8)	7 (0.8)	0 (0.0)
Nausea	Very common	311 (35.7)	5 (0.6)	0 (0.0)
Diarrhea	Very common	230 (26.4)	9 (1.0)	0 (0.0)
Vomiting	Very common	158 (18.1)	5 (0.6)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash	Very common	151 (17.3)	7 (0.8)	0 (0.0)

Alopecia	Very common	232 (26.6)	0 (0.0)	0 (0.0)
Dry skin	Common	88 (10.1)	0 (0.0)	0 (0.0)
General disorders and administration site conditions				
Fatigue	Very common	359 (41.2)	20 (2.3)	2 (0.2)
Asthenia	Common	115 (13.2)	13 (1.5)	1 (0.1)
Pyrexia	Common	113 (13.0)	1 (0.1)	0 (0.0)
Investigations				
AST increased	Very common	88 (10.1)	23 (2.6)	0 (0.0)
ALT increased	common	84 (9.6)	16 (1.8)	1 (0.1)

N/n = number of patients
Frequencies are defined as: very common (≥ 1/10); common (≥1/100); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to N1/1000)
a. Preferred terms according to MedDRA 17.1

Palbociclib use is associated with increased of neutropenia and embryo-fetal toxicity. Patients need to inform their physician promptly of any episodes of fever.

Embryo-fetal toxicity: Palbociclib can cause harm to the fetus. Patients should be advised of potential risk to the fetus and WOCBP must use adequate contraception during treatment and for at least 30 days after the last dose of palbociclib.

6.2 Cetuximab (Erbitux®) (Commercial Drug)

6.2.1 Description

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human EGFR. Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kilodaltons.

Cetuximab is supplied at a concentration of 2 mg/mL as a 100mg/50mL, single use vial or as a 200 mg/100mL, single-use vial as a sterile, injectable liquid containing no preservatives.

Full prescribing information for cetuximab is available at:
http://uspl.lilly.com/erbitux/erbitux.html#Section_2.4

Dosage and Administration:
Cetuximab will be administered on a weekly basis in this trial per the standard dosing regimen described below.

- The recommended initial dose is 400 mg/m^2 administered as a 120-minute IV infusion (maximum infusion rate 10 mg/min)

- The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity

Administer through a low protein biding 0.22-micrometer in-line filter.

Storage and Stability:
Store vials under refrigeration at 2 ^{0}C to 8 ^{0}C (36 ^{0}F to 46 ^{0}F). **Do not freeze**.

Preparations of cetuximab infusion are chemically and physically stable for up to 12 hours at 2 ^{0}C to 8 ^{0}C (36 ^{0}C to 46 ^{0}F and up to 8 hours at controlled room temperature (20 ^{0}C to 25 ^{0}C; 68 ^{0}F to 77 ^{0}F)

Handling and Disposal: Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
http://news.unchealthcare.org/empnews/att/2011/nov/admin0188/.

6.2.2 Adverse Events Associated With Cetuximab

Infusion reactions: serious reactions, requiring medical intervention and immediate and permanent discontinuation of cetuximab included rapid onset of airway obstruction, hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. See section 5.3.3 for management guidelines for infusion-related reactions.

Cardiopulmonary arrest: and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab.

Pulmonary toxicity: Interstitial lung disease, including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in patients with CRC and head and neck cancer.

Dermatologic toxicity: including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (eg, aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, etc.). See sections 5.3.2 for dose modification information. See sections 5.4.1 and Appendix 12.1 for skin toxicity prophylaxis and toxicity management guidelines.

Hypomagnesemia and electrolyte abnormalities: reported incidence in 55% of 365 patients receiving cetuximab for CRC and head and neck cancer, with 6-17% of patients experiencing grade 3 or grade 4 events.

Increased tumor progression, increased mortality or lack of benefit in patients with Ras-Mutant mCRC: Cetuximab is not indicated for use in patients with Ras-mutations of either K-ras, N-ras.

EGFR expression and response: in CRC patients response rate to cetuximab did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

Patient Counseling Information:
Advise patients:

- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems
- Of the potential risks of using cetuximab during pregnancy or nursing and the need to use adequate contraception in both males and females during and for 6 months following the last dose of cetuximab
- That nursing is not recommended during, and for 2 months following the last dose of cetuximab
- To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months following the last dose of cetuximab

For additional details, please refer to the cetuximab package insert.

7.0 EVALUATIONS AND ASSESSMENTS

7.1 Clinical Assessments

Clinical assessments will be performed as outlined in the Time and Events Table in Section 7.4.

7.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and throughout the study as summarized in the Time and Events Table in Section 7.4. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

7.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

7.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history (e.g., tobacco use), and information regarding underlying diseases will be recorded at Screening and a focused medical history on symptoms/toxicity will be performed thereafter.

7.1.4 Physical Examination

A complete physical examination including height (at screening only), weight, performance status per Eastern Cooperative Oncology Group (ECOG) criteria (provided in Appendix 12.3) and **vital signs (i.e.,** temperature, heart rate, blood pressure) will be performed by either the investigator or a sub-investigator who is a physician at Screening and on day 1 of the first and second treatment cycle. An abbreviated physical exam may be performed at all other visits and should include vital signs and ECOG performance status.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

7.1.5 Adverse Events

Events should be assessed per NCI-CTCAE criteria 4.0.3. Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded in the case report form (CRF).

7.1.6 Electrocardiogram

An electrocardiogram should be performed during the screening period (ie, within 4 weeks of instituting study treatment) to ensure that the subject meets eligibility for enrollment.

7.1.7 Disease Assessment (Tumor Measurement)

CRC disease will be assessed by a contrasted computed tomography scan (CT) of the chest, and a contrasted CT or contrasted MRI of the abdomen and pelvis.

Baseline disease assessment should be obtained within 4 weeks of initiating study treatment, and then conducted every 8 weeks (+/- 7 days) thereafter.

7.2 Clinical Laboratory Assessments

7.2.1 Hematology

Blood will be obtained during the study as outlined in section 7.4 and sent to the clinical site hematology lab for assessment of complete blood count (CBC): (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count)

Perform a CBC at screening, on Days 1 and 15 during the first two treatment cycles of combination treatment, on D1 of subsequent cycles (cycle 3 and beyond including the end of treatment visit), and as clinically indicated in subsequent treatment cycles.

Please refer to section 5.3.1 for guidance on how to manage palbociclib-related hematologic toxicity.

7.2.2 Blood Chemistry Profile

Blood will be obtained and sent to the clinical site chemistry lab for determination of a **Complete Metabolic Panel (CMP)**: (Blood urea nitrogen creatinine, sodium, potassium, chloride, bicarbonate, glucose, calcium, albumin, total protein, total bilirubin, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), and alkaline phosphatase) + **Magnesium**

Magnesium and Potassium should be assessed weekly prior to each cetuximab infusion as denoted in the Time and Events table in section 7.4.

Note: On days when CMP is scheduled include Magnesium as part of serum chemistry panel.

After the subject discontinues cetuximab, they must have magnesium and potassium monitored at a minimum as described in Time and Events Table in section 7.4, but with additional lab visits and repletion as clinically indicated per institutional standard.

7.2.3 Other Relevant Tests

7.2.4 Pregnancy Test

A urine or serum pregnancy test will be obtained from WOCBP prior to their participation in the study.

This pregnancy test should be obtained within 72 hours of initiating study combination treatment.

7.2.5 Carcinoembryonic antigen (CEA)

Obtain CEA on D1 of each treatment cycle starting on day 1 of cycle 1, and at the end of treatment visit.

7.2.6 Alpha-gal Test

In Southeast only, test for galactose-alpha-1,3-galactose IgE must be performed and must be negative to be eligible for this study.

7.3 Correlative Studies

We will collect peripheral blood for plasma and serum including two 10-ml tubes of blood for plasma for circulating tumor DNA (such as Na EDTA or Streck tubes) and one 10-ml tube of serum for circulating thymidine kinase activity assay. A limited number of peripheral blood aliquots will be used to collect PMBCs (peripheral mononuclear blood cells) from various time points. These blood samples will be split into cellular and plasma fractions to allow analysis of PMBCs and soluble factors in each sample. Please see the study lab manual for complete details on sample handling procedures.

Additionally, we will plan to test archival tissue and optional on-treatment biopsies for next generation DNA and RNA sequencing. The DNA testing will detect somatic mutations, and specific analysis of germline mutations is not planned. The optional biopsies would be for research purposes and would require consent for these procedures. If insufficient archival tissue is available, the subject can still participate in the clinical trial.

7.4 Time and Events Table

Assessments	Pre-study[1]	Study Treatment (each cycle is 28-days)[2]												End Of Treatment[3]	Day 56 (+/- 7 days) Follow up	Long Term Follow up
		C1 D1	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3-N D1	C3-N D8	C3-N D15	C3-N D22			
Informed Consent	X															
History[8]	X	X		X		X		X		X				X		X
Physical exam	X	X		X		X		X		X				X		
ECOG Performance Status	X	X		X		X		X		X				X		
Electrocardiogram	X															
Tumor measurement[4]	X									X[4]						
Pregnancy test		X														
Alpha-gal test[5]	X															
Hematology	X	X		X		X		X		X				X		
Magnesium & Potassium			X		X		X		X		X	X	X	X[6]	X	
Complete Metabolic Panel + Mg	X	X		X		X		X		X				X		
CEA		X				X				X				X		
Toxicity Assessment[8]	X	X	X	X	X	X		X		X		X		X	X	X
Concomitant Meds	X	X	X	X	X	X		X		X		X		X	X	
Palbociclib		Days 1-21, once daily, PO				Days 1-21, once daily, PO				Days 1-21, once daily, PO						
Patient diary		X				X				X				X		
Cetuximab 400 mg/m^2		X														
Cetuximab 250 mg/m^2 (IV weekly)			X	X	X	X	X	X	X	X	X	X	X			
Request archival	X															
Blood sample for correlatives[7]		X			X	X			X	X[7] c4, 6, 8 etc			X[7] c4, 6, 8, etc	X		
Tumor biopsy[2] (Optional; goal n=5 for each cohort)					X											
Survival analysis[8]																X

Footnotes to Time and Events Table

1. Screening assessments:
    a. Radiological/electrocardiogram/disease assessments and physical exam may be performed within 4 weeks prior to day 1 of treatment.
    b. Other evaluations except for pregnancy test must be performed within 2 weeks prior to Cycle 1 Day 1 (C1D1) of treatment.
    c. Serum or urine β-HCG must be performed **within 72 hours prior** to first dose of study medication for women of child-bearing potential.
    d. Screening labs performed within 72 hours prior to Cycle 1 Day 1 (C1/D1) do not need to be repeated on C1D1

2. A window of +/- 3 days applies to all study visits unless otherwise specified. The optional on-treatment biopsy scheduled for Cycle 1 Day 22 has a window of +/- 7 days.

3. The end of treatment visit should only occur when patients permanently stop study treatment and should be performed within 30 days (+/-7 days) after the last dose of study medication. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator. See section 7.7.3 for long-term follow up plan for this study.

4. Baseline disease assessment should be obtained within 4 weeks of starting study treatment, and then conducted every 8 weeks thereafter (+/- 7 days).

5. Alpha-gal must be negative for any subjects enrolled in Southeastern U.S. sites (See Appendix 12.5). Testing to be performed within 6 months of Day 1 treatment.

6. After a subject discontinues cetuximab, their magnesium and potassium must be monitored for an additional 8 weeks, at a minimum as described in the time and events table, but with additional lab visits and repletion as clinically indicated per institutional standard.

7. Correlative blood draws should occur on day 1 and day 22 of cycles 1 and 2 and then with subsequent even cycles (cycle 4, 6, 8, etc).

8. The Long-term follow up visit will occur every 90 days (+/- 15 days).

7.5 Pre-Study Assessments

1. Consent obtained prior to study assessments
2. Complete medical history and complete physical examination
3. ECOG Performance status
4. Tumor Measurement
5. Electrocardiogram
6. Toxicity Evaluation per NCI CTCAEv4.03 for notation of baseline toxicity
7. Concomitant medications
8. Tumor tissue collection (archival)
9. Laboratory evaluations:
   - Hematology
   - Complete Metabolic Panel (CMP) + Magnesium (Mg)
   - Alpha-gal test (Southeastern US sites)
   - Serum pregnancy test in women of childbearing potential (Note: pregnancy test to be done within 72 hours of day 1 of treatment)

7.6 Treatment Assessments

Study visits should be performed with +/-3 days of the scheduled assessment unless otherwise specified.

7.6.1 D1 of Cycle 1

1. Focused medical history and complete physical examination
2. ECOG Performance status
3. Toxicity Evaluation
4. Concomitant medications
5. Patient diary
6. Laboratory evaluations (do not repeat if performed within last 72 hrs)
   - Hematology
   - Complete Metabolic Panel (CMP) + Magnesium
   - CEA
   - Blood sample for correlatives
7. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.2 D8 of Cycle 1

1. Toxicity Evaluation
2. Concomitant medications
3. Laboratory evaluations)
   - Magnesium (Mg) and potassium
4. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.3 D15 of Cycle 1

1. Focused medical history and physical examination

2. ECOG Performance status
3. Toxicity Evaluation
4. Concomitant medications
5. Laboratory evaluations
   - Hematology
   - Complete Metabolic Panel (CMP) + Magnesium
6. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.4 D22 of Cycle 1

1. Toxicity Evaluation
2. Concomitant medications
3. Tumor biopsy (optional)
4. Laboratory evaluations)
   - Magnesium (Mg) and potassium
   - Blood sample for correlatives
5. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.5 D1 of Cycle 2

1. Focused medical history and complete physical examination
2. ECOG Performance status
3. Toxicity Evaluation
4. Concomitant medications
5. Patient diary
6. Laboratory evaluations)
   - Hematology
   - Complete Metabolic Panel (CMP) + Magnesium
   - CEA
   - Blood sample for correlatives
7. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.6 D8 of Cycle 2

1. Laboratory evaluations)
   - Magnesium and potassium
2. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.7 D15 of Cycle 2

1. Focused medical history and physical examination
2. ECOG Performance status
3. Toxicity Evaluation
4. Concomitant medications
5. Laboratory evaluations

- Hematology
- Complete Metabolic Panel (CMP) + Magnesium

6. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.8 D22 of Cycle 2

1. Laboratory evaluations
   - Magnesium and potassium
   - Blood sample for correlatives
2. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.9 D1 of Cycles 3-N

1. Focused medical history and physical examination
2. ECOG Performance status
3. Tumor measurement (every 8 weeks per footnote #4 of Time & Events table)
4. Toxicity Evaluation
5. Concomitant medications
6. Patient diary
7. Laboratory evaluations)
   - Hematology
   - Complete Metabolic Panel (CMP) + Magnesium
   - CEA
   - Blood sample for correlatives (only on cycles 4, 6, 8, etc)
8. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.10 D8 of Cycles 3-N

1. Laboratory evaluations
   - Magnesium (Mg) and potassium
2. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.11 D15 of Cycles 3-N

1. Toxicity Evaluation
2. Concomitant medications
3. Laboratory evaluations
   - Magnesium and potassium
4. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.6.12 D22 of Cycles 3-N

1. Laboratory evaluations
   - Magnesium and potassium

- Blood sample for correlatives (only on cycle 4, 6, 8, etc)

2. Administer Study Medications (See section 5.2 for details on treatment dosage and administration)

7.7 Post-Treatment/Follow-up Assessments

7.7.1 End of treatment

A subject who is being withdrawn for disease progression or for other reasons (e.g. unacceptable toxicity, etc.) should complete an end of treatment visit.

1. Focused medical history and complete physical examination
2. ECOG Performance status
3. Toxicity Evaluation
4. Concomitant medications
5. Patient diary
6. Laboratory evaluations (do not repeat if performed within last 72 hrs)
   - Hematology
   - Complete Metabolic Panel (CMP) + Magnesium (**If severe hypomagnesemia or hypokalemia is detected at the end of treatment visit, then follow until resolution per institutional standard)
   - CEA
   - Blood sample for correlatives

7.7.2 Day 56 follow-up (+/- 7 days)

1. Toxicity Evaluation
2. Concomitant medications
3. Laboratory evaluations
   - Potassium + Magnesium

7.7.3 Long-term follow up

Subjects should be followed per standard of care after withdrawal from study treatment. Subsequent follow-up visits, defined as every 90 days thereafter (+/- 15 days) for up to 3 years or until death (whichever is first) may be conducted via telephone and/or via clinic visit. These visits will be limited to history of any subsequent cancer treatments, an assessment of any SAEs considered to be possibly or probably related to study treatment until resolution, and survival status.

7.8 Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the Lineberger Comprehensive Cancer Center (LCCC) Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC 1717 Study Laboratory Manual and stored in containers with controlled access. Each sample

will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Information about the patient's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the patient's participation in the clinical study may also be included. This information may be important for understanding how the patient's cancer developed and responded to treatment.

Storage Time:

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the patient to use tissue for other research purposes (e.g., TPF consent form was signed by the patient). In this circumstance, there is no time limit on how long biospecimens may be stored.
    - The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility (e.g., Use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

Compliance Statement

Biospecimen collection for this study will be conducted in full accordance to all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

7.9 Assessment of Safety

Any patient who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv4.0.3.

7.10 Assessment of Efficacy

7.10.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for additional details on RECIST1.1.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

7.10.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression".

7.10.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete response (CR)–Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR)–At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)–At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)–Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

7.10.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)–Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)–Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD)–Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

7.10.5 Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of the study treatment until the end of treatment provided the confirmation criteria are met. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed > 4 weeks after the criteria for response are first met. If a CR/PR cannot be confirmed the original "response" should be considered stable disease. The best overall response will be defined according to the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[2] NE=inevaluable

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical

product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

8.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

8.1.3 Unexpected AE or SAR

An AE or SAR is considered <u>unexpected if</u> the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

8.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

8.3 SAEs or Serious SARs

8.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

8.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the NCCN Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

8.4 Adverse Event Reporting

8.4.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Affiliate sites

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Project Manager using the IRB's web-based reporting system (see section 10.5.3) within 7 days of the Investigator becoming aware of the problem.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 60 of the subject's last dose of study should be recorded as SAEs. The patient is to be discontinued immediately from the study.

For Affiliate sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the UNCCN Project Manager immediately (within 24 hours) via facsimile to 919-966-4300. The UNCCN Project Manager will then report the event to the Funding Source (see requirements below). The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal

outcome) and report the condition of the fetus or newborn to the UCCN Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

8.4.2 Funding Source (e.g. Pfizer) Reporting Requirements:

Reporting of Serious Adverse Events. Within twenty-four (24) hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigators will report to Pfizer by facsimile any Serious Adverse Event ("SAE," as defined below) for which reporting is required under this provision (as described below). Such SAEs are to be reported for (1) Study subjects who are assigned or, in the case of a blinded Study, possibly assigned to receive the Pfizer Product or (2) individuals otherwise exposed to the Pfizer Product as described below. Principal Investigators should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

a. Reporting Forms. Principal Investigators will report SAEs using one of the following forms: (1) a reporting form approved by the local regulatory authority, (2) a CIOMS form, (3) a Pfizer-provided Investigator-Initiated Research Serious Adverse Event Form, or (4) any other form prospectively approved by Pfizer. The Reportable Event Fax Cover Sheet provided by Pfizer must also be included with each SAE submitted.

b. SAE Definition. An SAE is any adverse event, without regard to causality, that is life-threatening (i.e., causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

c. Exposure or Lack of Effect. Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy, exposure to the Pfizer Product during lactation, and occupational exposure to the Pfizer Product are reportable, and lack of effect of the Pfizer Product may also be reportable. These requirements are further explained in the training material provided by Pfizer (see Pfizer-Provided Training, below). As used in this Agreement, the term SAE will be understood to include exposure during pregnancy, exposure during lactation, occupational exposure, and reportable instances of lack of effect.

d. Hy's Law Cases. Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a Study subject develops abnormal values in aspartate aminotransferase ("AST") or alanine aminotransferase ("ALT") or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case. This reporting requirement is further explained in the training material provided by Pfizer (see Pfizer-Provided Training, below). As used in this Agreement, the term SAE will be understood to also include Hy's Law Cases.

e. Exclusions from SAE Reporting Requirements. Specifically excluded from the reporting requirements for SAEs under this provision is any SAE identified in the Protocol as anticipated to occur in the Study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related to the Pfizer Product. Also specifically excluded from the reporting requirements is any SAE judged by the Principal Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

f. SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Pfizer Product through twenty eight (28) calendar days after the last administration of the Pfizer Product, or longer if so specified in the Protocol. In addition, if a Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Pfizer Product, the Principal Investigator should report that SAE to Pfizer if the Principal Investigator suspects a causal relationship between the Pfizer Product and the SAE.

g. Follow-Up Information. Institution will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

h. Regulatory Reporting. Reporting an SAE to Pfizer does not relieve Institution of responsibility for reporting it to appropriate regulatory authorities, if such reporting is required.

i. Pfizer-Provided Training. Pfizer will make available training material that provides information about the SAE reporting requirements for IIR studies. Principal Investigators will review this material and share it with any Study staff engaged in the reporting of SAEs.

8.4.3 Study Sponsor Reporting Requirements:

A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected

adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report." Additionally, upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Notification of Investigators

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any

other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process
If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form should be faxed to the UNCCN Project Manager at 919-966-4300 (or emailed, with address provided at the Start up Meeting (SIM)) along with supporting documentation defining the event and causality. The UNCCN Project Manager will then send the report to the Funding Source. The MedWatch 3500a form can be accessed at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500a, and not form 3500).

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA by the UNCCN Project Manager. If the event is serious, unexpected and considered to be possibly-, probably- or definitely-related to the study treatment, the UCCN Project Manager will inform the Regulatory Associate at UNC, who with the aid of the IND Specialist, will submit the IND Safety Report via IND serial submission to the FDA review division.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified or any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.

The UNCCN Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

Additional Reporting Requirements
The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug.

- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance
Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

8.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design

This will be a prospective, multicenter, phase 2 study containing two separate but parallel cohorts, of a treatment regimen that involves the combination therapy of cetuximab and palbociclib in refractory KRAS, NRAS, and BRAF wild-type metastatic colorectal cancer patients. Cohort A will include anti-EGFR naïve patients, and Cohort B will be of patients previously exposed to anti-EGFR therapy, but who may be able to benefit from a re-challenge with this anti-EGFR therapy. The primary objective of each cohort is the estimate the disease control rate (DCR: CR, PR or SD) at 4 months. Secondary objectives include estimating the overall response rate (ORR: CR or PR) at 4 months, progression free survival (PFS), overall survival (OS) and the toxicity and safety profile in each cohort.

[redacted]

9.2 Sample Size and Accrual

Each cohort will use a Simon two-stage design.

For Cohort A: The disease control rate (DCR: CR+PR+SD) at 4 months on this regimen is expected to be 65%. A Simon two-stage minimax design with an alpha=0.05, and power of 80% will be used. The null and alternative hypothesis DCRs are 40% and 65%, respectively. The null hypothesis of 4-month DCR of 40% is based on data from Kaplan Meier analysis from a previous phase III study [11]. In the first stage, 12 evaluable patients will be enrolled and treated. If 5 or less of these 12 patients are either a CR, PR, or SD at 4 months, the trial will be suspended and the PI will consult with the trial sponsors and the DSMC on whether or not to continue to investigate the treatment regimen further. If 6 or more are either a CR, PR, or SD at 4 months, then another 14 evaluable patients will be accrued for a total of at least 26 evaluable patients. If a total of 15 (or more) of these patients are either a CR, PR, or SD at 4 months, then the treatment regimen for this cohort would be considered of clinical interest and would therefore justify further development.

For Cohort B: The disease control rate (DCR: CR+PR+SD) at 4 months on this regimen is also expected to be 60%. The null and alternative hypothesis DCRs for this cohort are 33% and 60%, respectively. The null hypothesis of 4-month DCR of 33% is based on data from a retrospective analysis of a subgroup of patients rechallenged with cetuximab monotherapy among patients who initially had disease control/response with anti-EGFR therapy, among whom median PFS was 4.90 months [29]. Given that this was a retrospective study with a highly selected group of patients, we believe a reasonable null hypothesis of 4-mo DCR of 0.33 is a reasonable extrapolation. In the first stage, 10 evaluable patients will be enrolled and treated. If 3 or less of these 10 patients are either a CR, PR, or SD at 4

months, the trial will be suspended and the PI will consult with the trial sponsors and the DSMC on whether or not to continue to investigate the treatment regimen for this cohort further. If 4 or more are either a CR, PR, or SD at 4 months, then another 11 evaluable patients will be accrued for a total of at least 21 evaluable patients. If a total of 11 (or more) of these patients are either a CR, PR, or SD at 4 months, then the treatment regimen for this cohort would be considered of clinical interest and would therefore justify further development.

We expect the study accrual for both cohorts to take approximately 14 months.

9.3 Data Analysis Plans

DCRs and ORRs for both cohorts will be reported with their 95% confidence intervals. PFS and OS will be estimated using the Kaplan-Meier method. Toxicity and safety information will be reported in a descriptive manner in the form of frequency tables. Hypothesis generating [redacted], in the form of logistic and Cox regression, designed to investigate potential associations between the outcomes of response rates, such as DCR and ORR, and of PFS and OS, between selected tumor mutations and pharmaco-dynamic biomarkers of interest will be performed when appropriate sample size considerations allow.

10.0 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.3 Registration Procedures

If multicenter study use language below:
All patients must be registered with the LCCC CPO UNCCN at the University of North Carolina before enrollment to study. To register a patient call the UNCCN at 919-966-7359 Monday-Friday 8:30 am – 5:00 pm EST. Fax (919-966-4300) or email (address to be provided at SIM) registration form, signed informed consents and all source documents to confirm eligibility. When sending registration request with eligibility documentation, please allow 24 hours for source to be reviewed.

For Affiliate patients, to register and confirm patient eligibility, please fax registration forms, informed consent, and source documents to 919-966-4300.

10.4 Data Management and Monitoring/Auditing

The CPO UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center compliance committee every six or twelve months, depending on the participation of affiliate sites.

10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

10.5.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

10.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected

- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:

UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Project Manager. The UNCCN Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

10.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the

last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

12.1 Management Guideline for Cetuximab Skin Toxicity

Management of Grade 2 Rash

Skin lesions and symptoms	Eruption with papules (grade 2A) or pustules (grade 2B) covering <50% of body surface, with moderate symptoms, and that does not interfere with daily activities
Cetuximab dose modifications	No
Topical treatment	Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75%–1% cream/gel, twice/day until regression to grade 1 (avoid benzoyl peroxide products). Lesions of the scalp: erythromycin 2% lotion
Systemic treatment	Prevalence of papules (grade 2A): No Prevalence of pustules (grade 2B): Antibiotics: minocycline 100 mg per os once/day, doxycycline 100 mg per os once/day for ≥4 weeks and until the rash is symptomatic

Management of Grade 3 Rash

Skin lesions and symptoms	Eruption with papules (grade 3A) or pustules (grade 3B) covering >50% of body surface; severe symptoms that interfere with daily activities
Cetuximab dose modifications	First occurrence: delay cetuximab infusion for ≤21 days until the skin rash improves to grade ≤ 2. If there is an improvement, continue at 250 mg/m^2. If there is no improvement, discontinue therapy. Second occurrence: delay cetuximab infusion for ≤21 days until the skin rash improves to grade ≤ 2. If there is an improvement, continue at reduced dose of 200 mg/m^2. If there is no improvement, discontinue therapy. Third occurrence: delay cetuximab infusion for ≤21 days until the skin rash improves to grade ≤ 2. If there is improvement, continue at reduced dose of 150 mg/m^2. If there is no improvement, discontinue therapy. Fourth occurrence: discontinue therapy definitively
Topical treatment	Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75–1% cream/gel, twice/day until regression to grade 1 (avoid benzoyl peroxide products). Lesions of the scalp: erythromycin 2% lotion
Systemic treatment	Antibiotics: minocycline 100 mg per os once/day, doxycycline 100 mg per os once/day for ≥4 weeks and until the rash is symptomatic Corticosteroids: methylprednisolone 0.4 mg/kg per os, prednisone 0.5 mg/kg per os, for up to 10 days
Systemic treatment in highly symptomatic/nonresponsive patients	Retinoids: isotretinoin 0.3–0.5 mg/kg per os Corticosteroids: methylprednisolone or dexamethasone i.v. Antihistamines: clorfenamine i.m./i.v. Antibiotics: amoxicillin/clavulanic acid, gentamicin i.v. Intravenous hydration

Reference: Carmine Pinto et al. The Oncologist 2011;16:228-238

Management of Grade 4 Rash

Skin lesions and symptoms	Generalized rash; severe symptoms that require emergency treatment
Cetuximab dose modifications	Discontinue therapy immediately and definitively
Topical treatment	Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75%–1% cream/gel, 2 times daily until regression to grade 1 (avoid benzoyl peroxide products). Lesions of the scalp: erythromycin 2% lotion
Systemic treatment	Retinoids: isotretinoin 0.3–0.5 mg/kg per os
	Corticosteroids: methylprednisolone, dexamethasone i.v.
	Antihistamines: clorfenamine i.m./i.v.
	Antibiotics: amoxicillin/clavulanic acid, gentamicin i.v.
	Intravenous hydration
	Hospitalization

Reference: Carmine Pinto et al. The Oncologist 2011;16:228-238

12.2 Patient Handout: Prohibited Medications

One of the medications you are receiving during this clinical trial is palbociclib. Palbociclib interacts with some drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement). Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**.

- **Palbociclib** is processed by a certain enzyme in the liver called CYP3A4. Drugs that increase the activity of this enzyme are called "inducers", and drugs that decrease the activity of this enzyme are called "inhibitors". **Palbociclib** must be used very carefully with other medicines that are **inducers** or **inhibitors** of CYP3A4. Palbociclib may also interact with other drugs that are processed by the liver.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category

Before you start the study, your study doctor will work with your regular prescriber to switch the following medications if you are taking them:

Avoid strong CYP3A inhibitors ie, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole. Avoid grapefruits and grapefruit juice. If patients must be coadministered a strong CYP3A inhibitor, reduce palbociclib dose to 75 mg once daily. If the strong inhibitor is discontinued, increase palbociclib dose (after 3 to 5 half-lives of the inhibitor) to the dose used prior to initiation of the strong inhibitor.

Avoid strong CYP3A inducers ie, phenytoin, rifampin, enzalutamide, and St John's wort.

Avoid the use of these drugs that are also processed by the liver ie, alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, and tacrolimus).

Avoid the use of drugs known to cause QTc prolongation ie, amiodarone, anagrelide, arsenic trioxide astemizole, azithromycin, bepredil, chloroquine, chloropromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, crizotinib, disopyramide, donepezil, dronedarone, droperidol, erythromycin,

escitolopram, flecainide, fluconoazole, gatifloxacin, grepafloxacin, haloperidol, ibogaine, ibutilide, levofloxacin, levomepromazine, levomethadyl acetate, levosupriride, mesoridzine, methadone, moxifloxacin, ondansetron doses > 16 mg, oxaliplatin, pentamidine, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, thioridazine, and vandetanib,

- Your regular prescribers should look at these websites: https://www.crediblemeds.org http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.
- If you drink grapefruit juice or eat grapefruit, you should avoid these until the study is over.
- Other medicines can be a problem with your study drugs.
    - You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
    - Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

12.3 ECOG Performance Status

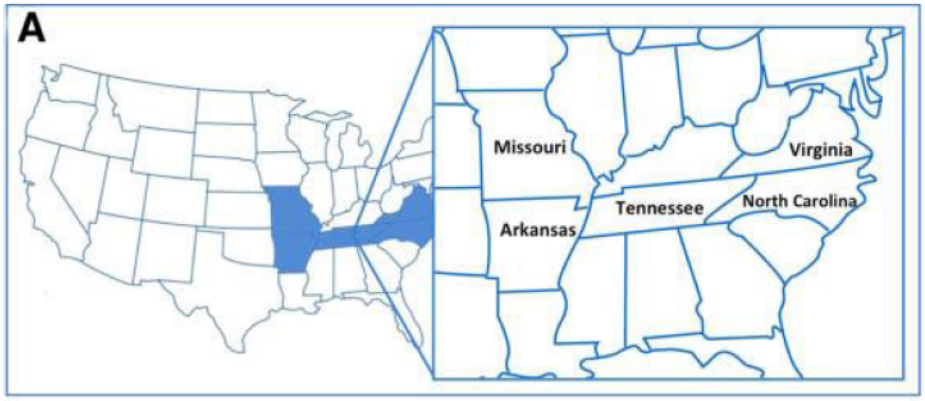
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol* 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.4 List of Drugs that Prolong QT and/or Cause Torsades de Pointes

A list of agents known to prolong QTc interval or cause torsades de pointes can be found at: https://www.crediblemeds.org.

A recently updated list as of July 22, 2017 is attached. **Drugs with known risk (KR) are exclusionary for this study**. Medications with possible risk (PR) or conditional risk (CR) of TdP should be used with caution and if an alternative is available, this alternative agent should be used instead.

12.5 Areas in USA where IgE to Alpha gal is Common



Reference: Clin Mol Allergy 2012;10:1-11.