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CTEP Submission Date: May 10, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: William Nava, Protocol Coordinator (E-mail: wnava@swog.org)

RE: **S1107**, "Parallel (Randomized) Phase II Evaluation of ARQ 197 and ARQ 197 in Combination with Erlotinib in Papillary Renal Cell Carcinoma." Study Chairs: Drs. P.W. Twardowski and P.N. Lara, Jr.

REVISION #4

Study Chair: Przemyslaw W. Twardowski, M.D.
Phone number: 626/256-4673 ext. 68218
E-mail: ptwardowski@coh.org

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  (√) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

REVISION #4

The revision has been prepared in response to the Request for Rapid Amendments (RRA) for ARQ 197 (tivantinib) received on April 11, 2016 from Dr. John Wright (wright@ctep.nci.nhi.gov), Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nhi.gov).

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The above-referenced study has been updated as follows:

1. The Version Date of the protocol has been updated.

2. **Page 10-11, Section 3.1b**: The ARQ 197 adverse effects section has been replaced with a CTEP modified risk information Comprehensive Adverse Events and Potential Risks (CAEPR) Version 2.2, February 19, 2016. This section has been updated as follows:

   - The SPEER grades have been updated.

   - Added New Risk:
     - Reported but With Insufficient Evidence for Attribution: Acute coronary syndrome; Allergic rhinitis; Atrial fibrillation; Conduction disorder; Fall; Hypomagnesemia; Hypophosphatemia; Hypoxia; Intracranial hemorrhage; Myocardial infarction; Paroxysmal atrial tachycardia; Pneumonitis; Pneumothorax; Portal vein thrombosis

   - Increase in Risk Attribution:
     - Changed to Likely from Less Likely: Fatigue
     - Change to Less Likely from Reported but With Insufficient Evidence for Attribution: Alopecia

The model consent form has been revised as follows:

1. The Version Date has been updated.

2. **Page 6, Risk Section**:

   - A new section for 'Common, Some may be serious' has been added to include Tiredness.
   - Hair loss has been added to the 'Occasional, Some May Be Serious' section.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated August 20, 2012

SWOG

PARALLEL (RANDOMIZED) PHASE II EVALUATION OF ARQ 197 AND ARQ 197 IN COMBINATION WITH ERLOTINIB IN PAPILLARY RENAL CELL CARCINOMA

NCT #01688973

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Supplied by CTEP:

ARQ 197 (Tivantinib) (NSC-750832) (IND-112603)
Erlotinib (OSI-774, Tarceva)
(NSC-718781) (IND-63383)

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SWOG/SWOG

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

ALLIANCE/Alliance for Clinical Trials in Oncology

NCIC-CTG/NCIC Clinical Trials Group

NRG/NRG Oncology

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

For patient eligibility questions contact the SWOG Data Operations Center by phone or email:

Phone: 206/652-2267
E-mail: guquestion@crab.org

For treatment or toxicity related questions contact the Study PI of the Coordinating Group (Dr. Przemyslaw W. Twardowski at 626/256-4673 ext. 68213).

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line: 888-823-5923
E-mail: ctsucontact@westat.com

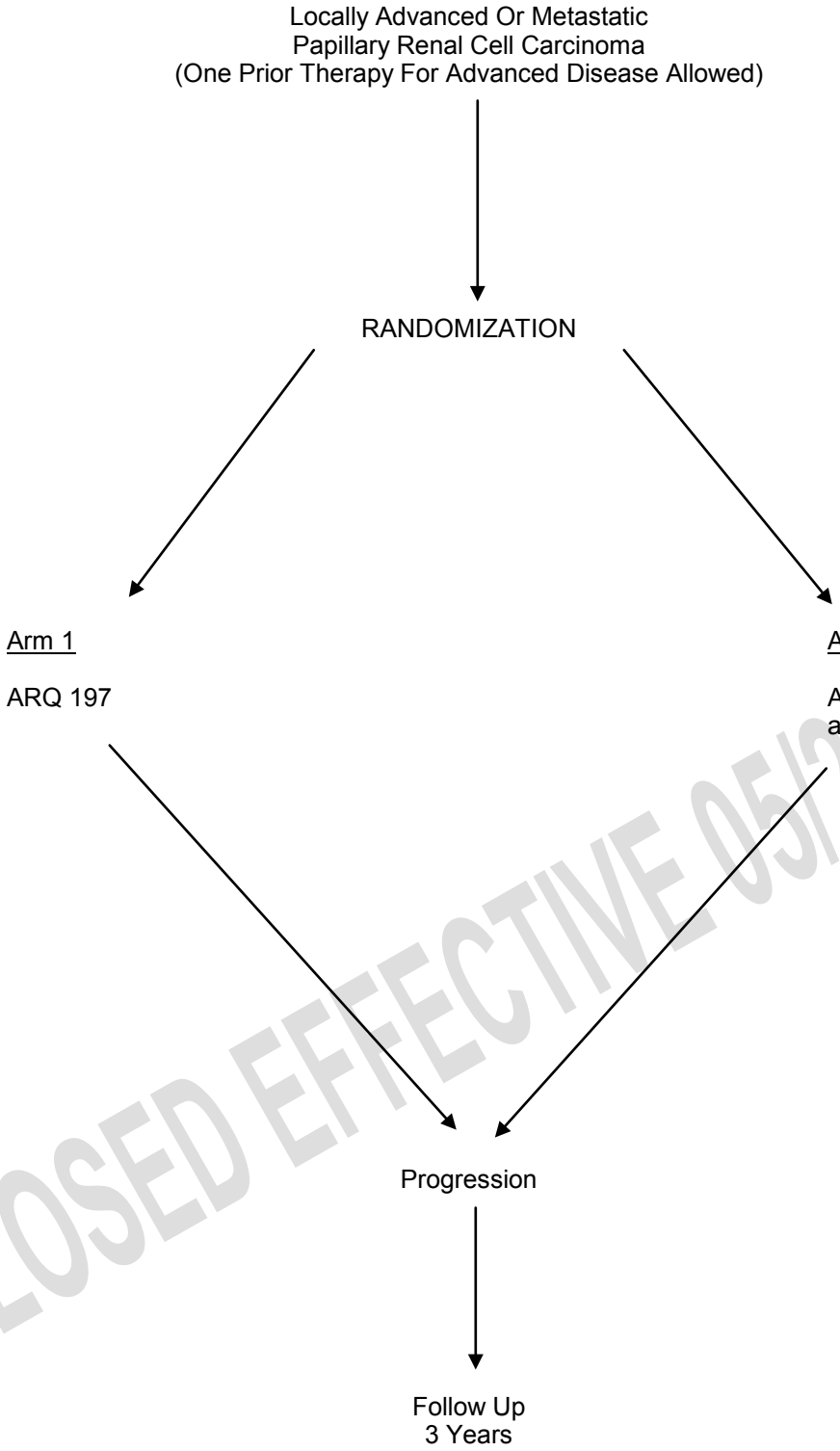
All calls and correspondence will be triaged to the appropriate CTSU representative.

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website:

https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy

The CTSU website is located at https://www.ctsu.org

SCHEMA



1.0 OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to assess the response rate (confirmed complete and partial response) of patients with locally advanced or metastatic papillary renal cell carcinoma treated with either ARQ 197 or ARQ 197 combined with erlotinib.

1.2 Secondary Objectives

a. To assess the progression free survival (PFS) of patients with locally advanced or metastatic papillary renal cell carcinoma treated with either ARQ 197 or ARQ 197 combined with erlotinib.

b. To assess the safety and tolerability of ARQ 197 therapy and ARQ 197 combined with erlotinib.

c. To descriptively assess the role of prior treatment on outcome.

1.3 Translational Medicine Objectives

To bank tissue specimens for future use and once funding is obtained to evaluate the expression of tissue correlative biomarkers such as c-MET and EGFR, and to perform exploratory correlation with clinical outcomes.

2.0 BACKGROUND

Clinical trials for advanced kidney cancer have focused primarily on the most common histologic type - clear cell carcinoma (cRCC) which on the molecular level is characterized by derangements of VHL-HIF-VEGF pathway. Papillary carcinoma (pRCC) is the second most common histologic subset of kidney cancer and accounts for 15% of cases. Among non-clear cell histology pRCC constitutes about 50% of cases. pRCC is associated with different molecular characteristics than cRCC. C-Met proto-oncogene mutations have been identified in patients with familial and sporadic cases of pRCC and implicated in its pathophysiology. *(1, 2)* In preclinical models c-Met inhibitors showed activity against several hereditary papillary renal cell carcinoma-related mutations and tumor xenografts. *(3)* While the treatment of advanced cRCC has undergone dramatic changes with the introduction of receptor tyrosine kinase (rTKI) and m-TOR inhibitors, management of pRCC and other non-clear cell histologies remains undefined. There have been no published clinical trials specifically evaluating the effects of these new compounds in pRCC, but the analysis of clinical trials that allowed treatment of various RCC histologies provides some insight into their efficacy in pRCC. In an expanded access trial of sunitinib in RCC, 276 patients (11.8% of total) with non-clear cell histologies were identified. A majority of them had prior cytokine therapy. Unfortunately this trial did not differentiate between the different non-clear cell subtypes, but based on prevalence it is likely that pRCC constituted a significant fraction of these patients. A response rate of 5.4% and median PFS of 6.7 months were noted. *(4)* A small Phase II trial of sunitinib in patients with non-clear cell RCC enrolled 26 patients (including 13 patients with pRCC). There were no objective responses and median PFS was 48 days. *(5)* Choueiri reported on the efficacy of sunitinib and sorafenib in metastatic non-clear cell RCC. *(6)* This retrospective analysis identified 53 patients who had been treated with either sunitinib or sorafenib at five different cancer centers in the USA and France. The number of patients with pRCC was 41, of which 23 had received prior systemic therapy (non-VEGF targeted). Of the 41 patients with pRCC, 13 were treated with sunitinib. Response rate was 15% and median PFS was 7.6 months. In a subset analysis patients with pRCC treated with sunitinib had the longest median PFS of 11.9 months (compared to 5.1 months if treated with sorafenib p<0.001). The m-TOR inhibitor temsirolimus was evaluated in previously untreated patients with metastatic RCC who had

unfavorable clinical characteristics. *(7)* This study included a significant number of patients with non-clear cell histology. In a subset analysis that included 55 patients withpRCC, median PFS was 7 months. These outcomes in patients with non-clear RCC compare with the RR of 39% and median PFS of 11 months reported in a pivotal Phase III trial of patients with cRCC treated with sunitinib. *(8)* Dual c-MET/VEGFR-2 inhibitor foretinib demonstrated 13.5% response rate and median PFS of 9.3 months. Responses were significantly more common in patients with germline mutations. *(9)* Overall the analysis of available data suggests that clinical benefit of targeted agents, although present in pRCC, is inferior to the one observed in clear cell histology.

Preclinical data indicates that absence of VHL mutations (VHL mutations are typically not seen in pRCC) is associated with greater activity of epidermal growth factor receptor (EGFR) inhibitors in RCC. *(10)* Based on that observation, the oral EGFR inhibitor erlotinib has been evaluated in a Phase II trial of patients with metastatic pRCC in SWOG. *(11)* Patients with histologically confirmed advanced or metastatic pRCC received erlotinib at 150 mg po q day until disease progression. Thirty nine patients were evaluable for response. With a median follow-up of 12.8 months; four patients had confirmed PR for RR of 10%. Median overall survival was 26.9 months. Probability of freedom from treatment failure at 6 months was 29%. There was one Grade 5 adverse event (AE) of pneumonitis and one Grade 4 thrombotic event. As expected only two patients (2/35) demonstrated mutations in vHL gene confirming that pRCC is typically associated with wild-type vHL. All but one specimen stained positive for EGFR (17/18) but no association was observed between EGFR score or staining intensity with clinical outcome. This suggests that mutational status, receptor amplification or differential intracellular signaling mechanisms may play a more significant role in predicting clinical benefit from EGFR-directed therapies. These findings were consistent with those of EGFR therapy in other diseases. Overall results of this study demonstrated activity of erlotinib in patients with pRCC and in the absence of an obvious superior alternative support further evaluation of erlotinib either alone or in combination with therapies targeting other relevant pathways in patients with pRCC.

ARQ 197 is a selective inhibitor of the c-Met receptor tyrosine kinase. ARQ 197 has been evaluated in a Phase I study in patients with advanced solid tumors who failed standard therapy. *(12)* Thirty eight patients were enrolled. The most frequent treatment-related side effects were fatigue (24%), diarrhea (21%) and constipation (21%). Grade 3 or greater events possibly or probably related to ARQ 197 included elevations of ALP (3%), ALT (3%), AST (3%). No DLT was observed. Two patients achieved partial response and 19 had stable disease. Recent evidence suggests that c-Met signaling promotes resistance to EGFR inhibition by stimulating ERBB3 (HER3)-dependent PI3K activation and dual EGFR and c-Met inhibition has been proposed as a strategy to overcome resistance to EGFR-inhibition. A Phase I dose escalation trial of ARQ 197 and erlotinib in patients with advanced solid tumors has been conducted. Erlotinib was given at 150 mg daily and ARQ 197 was escalated from 120 mg BID to 360 mg BID. Twenty-five patients were treated and minor tumor regressions were seen in four out of ten evaluable patients. Pharmacokinetic data revealed no evidence of drug-drug interaction. Two patients experienced serious adverse events including neutropenia and sinus bradycardia but no DLTs were reported. Continuous therapy with erlotinib and ARQ 197 appeared to be well tolerated and a Phase II combination dose (RP2D) of ARQ 197 of 360 mg BID and erlotinib of 150 mg daily was recommended. *(13)*

The combination of two tyrosine kinase inhibitors (TKIs), erlotinib and ARQ-197, which respectively target EGFR and MET was tested in the ACHN renal papillary cancer cell line. This cell line harbors a base substitution in the MET gene at T1010I, which appears to confer a growth advantage compared to wild-type expression. Dose response curves were conducted to determine the activity of each agent. The ACHN cell line expresses high protein levels of both EGFR and MET, which are both active under normal culturing conditions. ACHN cells were responsive to either agent individually, particularly to ARQ-197 with a 50% inhibitory concentration (IC50) of ~0.8uM. Median Effect analysis was conducted to determine the interaction of the agents. At all dose levels tested, the combined treatment outperformed either individual agent, and was additive to synergistic at the effective doses tested. Erlotinib treatment

of ACHN cells at a 2uM dose (24h) resulted in reduced phosphorylation of EGFR, concomitant with increase a small in MET activity. At this dose, erlotinib had negligible impact on phosphorylation of downstream signal transduction factors AKT and ERK. ARQ-197 resulted in diminished activity and protein levels of MET accompanied by reduction of both AKT and ERK phosphorylation. Additionally, ARQ-197 ablated p-EGFR, although not to the extent observed by erlotinib. The combination of the two agents further reduced both pAKT and pERK compared to ARQ-197 alone, and synergized with erlotinib to inhibit EGFR phosphorylation. *(Personal Written Communication, January 201, PC Mack, Ph.D., PN Lara, Jr., M.D., UC Davis Cancer Center)*

Based on erlotinib activity data in pRCC and preclinical studies indicating activity of c-Met inhibitors in pRCC and important interplay between EGFR and c-Met pathways we propose to conduct a randomized Phase II trial of ARQ 197 alone and in combination with erlotinib. *(3, 14)* Specifically, ARQ 197 represents a new compound that warrants testing in pRCC. If promising, this compound would have enhanced activity when combined with other active and theoretically synergistic compounds such as erlotinib, and if ARQ 197 proves inactive as a single agent, it could help potentiate erlotinib. As the combination study would be of interest regardless of the outcome of the single agent ARQ 197 study, these studies will be run in parallel. This has the effect of accelerating our understanding of the role of ARQ 197 in pRCC. The hypothesis is that both ARQ 197 and the combination of ARQ 197 and erlotinib will demonstrate promising activity against pRCC with an acceptable toxicity profile.

Inclusion of Minorities:

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	Females	Males	Total
Hispanic or Latino	3	6	9
Not Hispanic or Latino	24	45	69
Total Ethnic	27	51	78
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	1	1	2
Black or African American	4	7	11
Native Hawaiian or other Pacific Islander	0	0	0
White	22	42	64
Racial Category: Total of all Subjects*	27	51	78

3.0 DRUG INFORMATION

Investigator's Brochures:

For information regarding Investigator's Brochures, please refer to SWOG Policy #15.

For this study, ARQ 197 and erlotinib are being provided under an IND held by the National Cancer Institute. The Investigator's Brochures may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 ARQ 197 (DS-5178) (NSC-750832) (IND-112603)

a. DESCRIPTION

Chemical Name or Amino Acid Sequence: (3R,4R)-3-(5,6-dihydro-4*H*-pyrrolo [3,2,1-*ij*]quinolin-1-yl)-4-(1*H*-indol-3-yl)pyrrolidine-2,5-dione

Other Names: DS-5178

Classification: c-Met inhibitor

CAS Registry Number: 905854-02-06

Molecular Formula: $C_{23}H_{19}N_3O_2$ **M.W.:** 369.43

Mode of Action: c-Met inhibitor ARQ 197 binds to the c-Met protein and disrupts c-Met signal transduction pathways, which may induce apoptosis in tumor cells overexpressing c-Met protein or expressing constitutively activated c-Met protein.

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks list (CAEPR) for ARQ 197 (Tivantinib, NSC 750832)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 579 patients.* Below is the CAEPR for ARQ 197 (tivantinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, February 19, 2016[1]

Adverse Events with Possible Relationship to ARQ 197 (tivantinib) (CTCAE 4.0 Term) [n= 756]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
	Sinus bradycardia		
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Palmar-plantar erythrodysesthesia syndrome	
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

Adverse events reported on ARQ 197 (tivantinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ARQ 197 (tivantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Lymph node pain

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Conduction disorder; Myocardial infarction; Paroxysmal atrial tachycardia
EYE DISORDERS - Dry eye; Eye disorders - Other (blindness unilateral)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Constipation; Dry mouth; Duodenal ulcer; Dyspepsia; Flatulence; Gastrointestinal disorders - Other (eructation [belching]); Gastrointestinal disorders - Other (peritoneal hemorrhage); Mucositis oral; Oral pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Gait disturbance; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis; Hepatic failure; Portal vein thrombosis
INFECTIONS AND INFESTATIONS - Infection[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (pancytopenia); Platelet count decreased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Headache; Intracranial hemorrhage; Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Seizure; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (hydronephrosis); Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Bronchospasm; Cough; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis; Pneumothorax; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin fissures); Skin hyperpigmentation
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event
Note: ARQ 197 (tivantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Potential Drug Interactions: ARQ 197 is metabolized via a drug metabolizing enzyme system associated with cytochrome P450 (CYP2C19 and CYP3A4). Interactions with drugs metabolized via the same enzyme system are possible. Drugs which inhibit CYP2C19 and CYP3A4 may markedly increase the plasma concentration of ARQ 197.

c. PHARMACOLOGY

How Supplied: Daiichi Sankyo supplies and CTEP's Pharmaceutical Management Branch distributes ARQ 197 in 120 mg tablets in 50 mL high-density polyethylene bottles with polypropylene caps. ARQ 197 tablets are red orange film coated and round with a diameter of 9.2 mm. Inert ingredients include lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, purified water, and magnesium stearate. The film coating contains purified water, hypromellose, titanium dioxide, talc and ferric oxide. Each bottle contains 100 tablets.

Storage and Stability: Refer to the label for specific storage conditions. Shelf-life surveillance of the intact bottles is on-going.

Administration: Oral. Administer ARQ 197 tablets with food, and advise patients to take tablets with water and swallow them whole.

d. SUPPLIER

ARQ 197 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. ARQ 197 is provided to the NCI under a Collaborative Agreement between ArQule, Inc., Daiichi Sankyo, Inc. and the DCTD, NCI.

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug may be requested by submitting agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time by emailing PMBAfterHours@mail.nih.gov anytime.

3.2 Erlotinib (NSC-718781; IND-63383)

a. DESCRIPTION

Chemical Name: N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride

Other Names: Erlotinib hydrochloride, Tarceva™, OSI-774

Classification: Tyrosine kinase Inhibitor (EGFR)

Molecular Formula: $C_{22}H_{23}N_3O_4$ **M.W.:** 393.4 (free base)
429.9 (hydrochloride salt)

Mode of Action: Direct inhibition of EGFR tyrosine kinase

b. TOXICOLOGY

Reported Adverse Events and Potential Risks:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for OSI-774 (erlotinib, NSC 718781)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited, Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3,622 patients.* Below is the CAEPR for OSI-774 (erlotinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July 24, 2013[1]

Adverse Events with Possible Relationship to OSI-774 (erlotinib) (CTCAE 4.0 Term) [n= 3622]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
	Dry eye		***Dry eye (Gr 2)***
	Eye disorders - Other (eyelash in-growth and/or thickening)		
		Eye disorders - Other (corneal perforation)	
		Keratitis	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Gastrointestinal hemorrhage[2]		
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection[4]		***Skin infection[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 3)***

Adverse Events with Possible Relationship to OSI-774 (erlotinib) (CTCAE 4.0 Term) [n= 3622]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
	Pneumonitis		***Pneumonitis (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Nail loss		***Nail loss (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3] Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4] Includes infection of the skin (folliculitis or cellulitis) as complications of rash.

Also reported on OSI-774 (erlotinib) trials but with the relationship to OSI-774 (erlotinib) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation
EYE DISORDERS - Blurred vision; Eye disorders - Other (orbital cellulitis); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Duodenal ulcer; Dysphagia; Esophagitis; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (pneumatosis intestinalis); Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs
HEPATOBILIARY DISORDERS - Cholecystitis
INVESTIGATIONS - Creatinine increased; INR increased (in patients taking Coumadin); Lymphocyte count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Dizziness; Ischemia cerebrovascular; Peripheral sensory neuropathy
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pharyngolaryngeal pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria
VASCULAR DISORDERS - Thromboembolic event

Note: OSI-774 (erlotinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: OSI-774 (erlotinib)-induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

Note: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of OSI-774 (erlotinib) in patients with baseline hepatic impairment.

Warning: Treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with erlotinib. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range.

Warning: Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of erlotinib, particularly in patients with baseline hepatic impairment. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended. In the setting of worsening liver function tests, dose interruption and/or dose

reduction with frequent liver function test monitoring should be considered. Erlotinib dosing should be interrupted or discontinued if total bilirubin is > 3 x ULN and/or transaminases are > 5 x ULN in the setting of normal pretreatment values.

Warning: Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (e.g., pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration.

Gastrointestinal Perforation: Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. Some cases had a fatal outcome. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease, are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

Bullous and Exfoliative Skin Disorders: Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

Ocular Disorders: Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal perforation/ulceration. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Potential Drug Interactions: Erlotinib is both protein bound (92% to 95%) and metabolized by CYP3A4. Therefore, a potential for drug-drug interactions exists when erlotinib is co-administered with drugs that are highly protein-bound or CYP3A4 inhibitors or inducers.

There is a potential interaction between erlotinib and warfarin. Patients have experienced elevated INRs and bleeding with this combination of drugs. Patients on warfarin and erlotinib should have more frequent INR/PT determinations (e.g., weekly for the first month and weekly for a minimum of 2 weeks following discontinuation erlotinib).

Proton Pump Inhibitor: Erlotinib's solubility decreases as the pH increases. Co-administration of omeprazole with erlotinib will decrease the AUC and C_{max} by 46% and 61%, respectively.

H2-antagonist: Avoid concomitant use of erlotinib with gastric acid reducing agents if possible. When ranitidine 300 mg is given with erlotinib, erlotinib AUC and Cmax decrease by 33% and 54%, respectively. Increasing the dose of erlotinib will not compensate the loss of exposure. However, if an H2-antagonist receptor is needed, take erlotinib at least 2 hours before or 10 hours following the H2-antagonist administration. Dosing such, erlotinib loss of exposure is minimized to AUC of 15% and Cmax of 17%.

Patient Care Implications: If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

Patients should wear sun screen protection, hat, and long sleeves to avoid sun as it can exacerbate skin rash.

Patients should be advised to stop smoking while taking erlotinib. Smoking induces CYP1A2 enzymes and alters erlotinib exposure by 64%

Pregnancy and Lactation: No information on pregnancy and lactation in humans is available yet.

c. PHARMACOLOGY

Total clearance of erlotinib is similar to hepatic blood flow in dogs and rats. At intravenous doses > 1 mg/kg the clearance decreases and the plasma drug exposure increases supra-proportionately in rats and dogs. In vitro, the agent is slowly oxidized by liver microsomes. Erlotinib is extensively metabolized in rats and dogs with only a small amount excreted unchanged in urine, bile and feces. In a rat model designed to study pulmonary first pass extraction, erlotinib had a pulmonary extraction of approximately 48%. In vitro studies have shown that the agent is metabolized by CYP1A1, which is expressed in lung tissue. Several circulating metabolites have been identified in mouse, rat and dog and subsequently synthesized and demonstrated to be potent as EGFR inhibitors. Only one, OSI-420, a hydroxylated metabolite, was a major metabolite in systemic circulation with a metabolite: parent ratio of 1:4 in plasma from rats or dogs given oral doses. This compound is as potent as erlotinib in the in vivo tumor xenograft model.

The enzymes responsible for formation of the major metabolite in humans were identified as cytochromes P450 3A4 and 3A5 (expressed in liver) and 1A1 (expressed in lung). Studies on the inhibition potential of erlotinib and its major metabolite, OSI-420, on the main human cytochrome P450 isoenzymes revealed a relatively strong inhibition of CYP 3A4 by erlotinib (Ki 8 μM) and a weak inhibition of CYPs 1A2 and 3A4 by OSI-420 (Ki 20 μM). Further studies to evaluate the mechanism of inhibition are ongoing.

Oral bio-availability was found to be 77% in rats and 88% in dogs. Plasma protein binding is 92 - 95% in humans, rats, monkeys and mice, and was 85% in dogs.

How Supplied: Erlotinib is supplied as 25 mg, 100 mg, and 150 mg white film-coated tablets. In addition to the active ingredient, erlotinib, the tablets contain lactose, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate. Tablets are unmarked and unscored. The 25 mg tablets [1/4 inch diameter, 3 mm deep (formerly non-film coated)], 100 mg tablets (11/32 inch diameter, 5 mm deep), and 150 mg tablets (13/32 inch diameter, 5.1 mm deep) are supplied 30 tablets/bottle.

Storage and Stability: Store in accordance with the package labeling. Shelf life surveillance studies of the intact bottle are on-going. Current data indicates erlotinib is stable for at least 3 years at room temperature.

Administration: Erlotinib is administered orally. Tablets should be taken once daily preferably in the morning with up to 200 mL of water one hour before or two hours after food.

d. SUPPLIER

Erlotinib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Erlotinib is provided to the NCI under a Clinical Trails Agreement between OSI Pharmaceuticals and the NCI Division of Cancer Treatment and Diagnosis (DCTD).

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug may be requested by submitting agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time by emailing PMBAfterHours@mail.nih.gov anytime.

4.0 STAGING CRITERIA

This section is not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1107** Prestudy Form and submit via MediData Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. If Day 14, 21, 28, 42 or 56 falls on a weekend or holiday, the limit may be extended to the next working day.

SWOG Patient No. _____

Patient's Initial (L,F,M). _____

5.1 Disease Related Criteria

_____ a. Patients must have histologically or cytologically confirmed papillary histology renal cell carcinoma which is metastatic, or locally advanced and unresectable. Mixed histologies will be allowed provided that they contain ≥ 50% of the papillary component.

_____ b. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (see Section 10.0). X-rays, scans or physical examinations used for tumor measurement must have been completed within 28 days prior to registration. X-rays, scans or physical examinations for non-measurable disease must have been completed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

_____ c. Patients with metastatic disease who have a resectable primary tumor and are deemed a surgical candidate may have undergone resection. At least 28 days must have elapsed since surgery and patient must have recovered from any adverse effects of surgery.

_____ d. Patients with a history of brain metastases who are asymptomatic and have not received steroid therapy in the 14 days prior to registration are eligible. Anti-seizure medications are allowed provided they are non-enzyme inducing (e.g. topiramate, levatiracetam, gabapentin).

5.2 Prior Therapy Criteria

_____ a. Patients may have received up to one prior systemic therapy for advanced or metastatic renal cell carcinoma. Patients must not have received a MET inhibitor or erlotinib as prior therapy. At least 21 days must have elapsed since completion of prior systemic therapy, 42 days for nitrosoureas or mitomycin C. Patients must have recovered from all associated toxicities at the time of registration.

_____ b. Patients may have received prior radiation therapy, but must have measurable disease outside the radiation port. At least 21 days must have elapsed since completion of prior radiation therapy. Patients must have recovered from all associated toxicities at the time of registration.

_____ c. Patients must not be receiving or planning to receive any other investigational agents.

SWOG Patient No. _____

Patient's Initial (L,F,M). _____

5.3 Clinical/Laboratory Criteria

_____ a. Patients must have a complete physical examination and medical history within 28 days prior to registration.

_____ b. Patients must have a Zubrod performance status of 0 - 2 (see Section 10.4).

_____ c. Patients must have adequate hematologic function as documented by a WBC ≥ 2,000/mcL, an ANC ≥ 1,000/mcL, and a platelet count ≥ 75,000/mcL. These tests must be obtained within 14 days prior to registration.

_____ d. Patients must have adequate hepatic function as evidenced by serum bilirubin ≤ 1.5 x institutional upper limits of normal (ULN). Serum transaminase (SGOT/AST and SGPT/ALT) must be ≤ 1.5 x the institutional ULN unless the liver is involved with the tumor, in which case serum transaminase (SGOT/SGPT) must be ≤ 5 x the institutional ULN. These tests must be obtained within 14 days prior to registration.

_____ e. Serum creatinine must be ≤ 2 x the institutional ULN and obtained within 14 days prior to registration.

_____ f. Sodium, potassium and calcium must be obtained within 14 days prior to registration.

_____ g. Patients with a known history of the following corneal diseases are not eligible: dry eye syndrome, Sjogren's syndrome, keratoconjunctivitis sicca, exposure keratopathy, Fuch's dystrophy or other active disorders of cornea.

_____ h. Patients known to be HIV-positive and receiving combination anti-retroviral therapy are not eligible due to possible pharmacokinetic interactions with erlotinib and ARQ 197.

_____ i. Patients must be able to take oral medications. Patients must not have gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease. Patients with intractable nausea or vomiting are not eligible.

_____ j. Patients must not be pregnant or nursing because ARQ 197 and erlotinib have the potential for teratogenic or abortifacient effects. There is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ARQ 197 or erlotinib. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

SWOG Patient No. _____

Patient's Initial (L,F,M). _____

5.3 Clinical/Laboratory Criteria (contd.)

_____ k. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

5.4 Specimen Submission Criteria

_____ a. Patients must be offered the opportunity to participate in specimen banking for future translational medicine studies (see Section 15.0).

5.5 Regulatory Criteria

_____ a. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm *(15)* with stratification based on:

Prior systemic therapy for advanced or metastatic disease (none vs 1).

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Przemyslaw Twardowski at 626/256-4673 ext. 68218 or Dr. Primo N. Lara, Jr. at 916/734-3771. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38)

7.1 Treatment Schedule

Patients will be randomized to either Arm 1: ARQ 197 or Arm 2: ARQ 197 and erlotinib.

a. Treatment schedule for Arm 1: ARQ 197

AGENT	DOSE	ROUTE	DAYS	INTERVAL	DURATION
ARQ 197*	360 mg (3 tablets) 720 mg total daily dose	By mouth	1-28	Twice daily (about 12 hours apart)	Until disease progression

b. Treatment schedule for Arm 2: ARQ 197+ erlotinib

AGENT	DOSE	ROUTE	DAYS	INTERVAL	DURATION
ARQ 197*	360 mg (3 tablets) 720 mg total daily dose	By mouth	1-28	Twice daily (about 12 hours apart)	Until disease progression
Erlotinib**	150 mg (1 tablet)	By mouth	1-28	Daily	Until disease progression

* ARQ-197 is supplied as tablets for oral administration. Patients should take ARQ 197 twice daily (about 12 hours apart), with food.

** Erlotinib tablets should be taken in the morning with up to 200 mL of water on an empty stomach (one hour before or two hours after eating).

NOTE: A cycle of therapy is defined as twenty-eight days. There will be no pause between cycles. Patients will be evaluated for response/progression every two treatment cycles and will continue on therapy until progression or other reason for removal from treatment (see Section 7.6).

7.2 Administration through G-tube

Administration of the study medications through a G-tube is not allowed.

7.3 Concomitant Medications

The use of supportive care medications is allowed according to institutional standards.

7.4 Drug Compliance

Drug compliance will be recorded by patients on the Intake Calendar (see Appendix 18.2). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.5 Reporting Cycle-Specific Toxicity and Dose Information

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirement for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4c, the **S1107** Treatment Form, and the **S1107** Adverse Event Form). A cycle is defined as 28 days.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity.

c. All protocol treatment is held for any reason > 3 weeks.

d. The patient may withdraw from the study at any time for any reason.

e. Physician discretion.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow Up Period

All patients will be followed for a maximum of three years.

8.0 DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are seen for any given single agent, administer dose based on greatest reduction required for any single toxicity observed.

c. Reductions apply to the treatment given in the preceding cycle and are based on toxicities observed since the prior dose.

d. Once dose is reduced, patients will continue at new dose. No dose re-escalations are allowed.

e. If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

f. Use of G-CSF and erythropoietin for patients being treated on this study is at the discretion of the treating physician. If used, it must be documented in the "Notes" section of the **S1107** Treatment Form.

8.3 Patient Evaluations

Patients will be evaluated every two weeks for the first eight weeks and then once every four weeks to determine toxicities and the appropriate dose modification (decrease, hold, or discontinue). If all protocol treatment is delayed more than three weeks, patients will be removed from protocol treatment.

8.4 Radiation Therapy for Palliation

If patients require radiation therapy for palliation in the absence of progressive disease please contact the primary Study Chair, Dr. Przemyslaw Twardowski M.D. 626-256-4673 ext 68218.

8.5 ARQ 197 Dose Modification

If ARQ 197 is held, erlotinib will also be held for patients on Arm 2 and resumed at the same time treatment with ARQ 197 is resumed. There will be no dose reduction of erlotinib if the toxicity was thought to be related to ARQ 197.

a. Hematologic toxicities:

Absolute neutrophil count (ANC) ($x10^6$/L)		Platelets ($x10^6$/L)	ARQ 197
≥ 1,000	and	≥ 75,000	100% dose
< 1,000	or	< 75,000	*Hold until ANC ≥ 1,000 and platelets ≥ 75,000 and reduce to the next lower dose level

* Treatment may be held up to 21 days and can be resumed at the next lower dose level once ANC is ≥ $1000x10^6$/L and platelet count is ≥ 75,000 $x10^6$/L. Patients who cannot tolerate ARQ 197 at 120 mg BID will be removed from the protocol. No dose re-escalation is allowed.

b. Non-hematologic toxicities:

The following modifications should be followed in the event of ARQ 197 related-non-hematologic toxicity.

Toxicity Grade(NCI CTCAE v4.0)	Percent of full dose of ARQ 197l
0-2	100%
3	Hold*
4	Hold*

* Treatment may be held up to 21 days Any patient who experiences Grade 3 or greater non-hematologic toxicity which resolves to Grade 0 or 1 may be treated at a next lower dose level of ARQ 197 for subsequent doses. Patients who cannot tolerate ARQ 197 at 120 mg BID will be removed from the protocol. No dose re-escalation is allowed.

c. ARQ 197 Dose Level Reductions

Starting Dose	First Reduction	Second Reduction
360 mg BID	240 mg BID	120 mg BID

NOTE: Any patient who fails to tolerate treatment of 120 mg BID will be withdrawn from protocol treatment. If a treatment is delayed more than 21 days for the resolution of ARQ 197-related toxicities to Grade 0 or 1 patient will be removed from the protocol.

8.6 Erlotinib Dose Modification[a]

Toxicity (NCI CTCAE v4.0)	Dose Modification
Diarrhea	
Grade 1	None. Initiate therapy with loperamide.(8.7a)
Grade 2	Hold erlotinib. Initiate loperamide until resolution to Grade 0-1. Resume therapy at the same dose.
Grade 3[b] or 4[b]	Hold erlotinib. Initiate therapy with loperamide and appropriate supportive care until resolution to Grade 0 or 1 and then restart at 1 dose level lower
Rash	
Grade 1	None
Grade 2	None. *Initiate treatment (8.7b).* If rash persists and is intolerable or worsens over 10 – 14 days, then reduce by 1 dose level.
Grade 3	Reduce by 1 dose level. If rash persists or worsens over 10 – 14 days, then interrupt erlotinib until resolution to Grade 0, 1 or 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue erlotinib.
Interstitial Lung Disease	
Any Grade	If ILD is suspected, erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities Attributable to Erlotinib	
Grade 1 or 2	None
Grade 3 or 4 [b, c]	Interrupt erlotinib until resolution to Grade 0 or 1 and then restart 1 dose level lower.
Other Toxicities (hematologic and non-hematologic) attributable to ARQ 197	
Grade 1 or 2	None
Grade 3 or 4	Hold erlotinib until ARQ 197 is resumed. If toxicity was deemed related to ARQ 197 no dose reduction of erlotinib is indicated

(a) Doses that have been reduced should not be re-escalated. Any patient who fails to tolerate treatment at 50 mg/day will discontinue erlotinib and continue on single agent ARQ 197.

(b) If the event does not resolve to Grade 0 or 1 within 21 days, erlotinib will be discontinued and patient will continue on a single agent ARQ 197

(c) Only if ≥ 2 Grade level change from baseline

Erlotinib Dose Level Reductions

Starting Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

NOTE: Any patient who fails to tolerate erlotinib at 50 mg/day will continue on single agent ARQ 197. If a treatment is delayed more than 21 days for the resolution of erlotinib-related toxicities to Grade 0 or 1, discontinue erlotinib and continue ARQ 197 alone.

8.7 Suggested management of toxicities

a. Diarrhea. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea resolves for 12 hours In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to intensively treat the dehydration. Since there have been rare reports of hypokalemia and/or acute renal failure (including fatalities), secondary to severe dehydration, renal function and serum electrolytes (including potassium) should be monitored in this setting.

b. Rash/skin toxicity. Patients should be informed that skin toxicity is to be expected during treatment with erlotinib. Skin toxicity may take the form of dry skin, rash, acneiform eruption, or hair or nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib. Creams and ointments are recommended because they have a greater ability to retain moisture than lotions. Examples of suitable emollient creams include: Neutrogena® Norwegian formula, SARNA® Ultra, Vanicream™, Aveeno® (fragrance-free formulation), and Eucerin® cream. Other over-the-counter aqueous creams or emulsifying ointments may also provide symptomatic benefit. Lotions should be avoided because they often contain alcohol, which will dry the skin. Patients should also be encouraged to use a titanium dioxide or zinc oxide-based sunscreen product applied to sun-exposed areas twice per day.

   Patients who develop skin toxicity and are symptomatic should be treated with topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with the topical therapy. A topical immodulating cream such as Elidel could also be considered. For more severe rash, oral corticosteroids may be beneficial. Patients who fail to respond to these measures may have the dose of erlotinib interrupted or reduced.

   Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.

   Bullous, blistering and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Interrupt or discontinue erlotinib treatment if the patient develops severe bullous, blistering, or exfoliating conditions.

c. Ocular Disorders. Corneal perforation or ulceration has been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal ulceration/perforation. Interrupt or discontinue erlotinib therapy if patients present with acute/worsening ocular disorders such as eye pain.

8.8 Dose Modification Contacts

For treatment or dose modification related questions, please contact Dr. Przemyslaw Twardowski at 626/256-4673 ext. 68218 or Dr. Primo N. Lara, Jr. at 916/734-3771.

8.9 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair, the NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

Ω √

		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	
REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 3	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Follow-Up
PHYSICAL											
History & Physical Exam	X *		X	X	X	X	X	X	X	X	X
Weight and Performance Status	X		X	X	X	X	X	X	X	X	X
Disease Assessment ≠	X					X		X		X	
Toxicity Notation			X	X	X	X	X	X	X	X	
S1107 Baseline Abnormalities Form	X										
LABORATORY											
CBC/Differential/Platelets	X		X	X	X	X	X	X	X	X	
Bilirubin	X		X	X	X	X	X	X	X	X	
SGOT & SGPT	X		X	X	X	X	X	X	X	X	
Serum Creatinine	X		X	X	X	X	X	X	X	X	
Electrolytes (see Section 5.3f)	X		X	X	X	X	X	X	X	X	
Pregnancy Test (if applicable)	X										
TISSUE SAMPLES											
Archived tissue sample (see Section 15.0)	X										
X-RAYS AND SCANS											
X-rays/Scans as needed for disease measurement ≠	X					X		X		X	X
TREATMENT Δ											
ARM 1											
ARQ 197		X	X	X	X	X	X	X	X	X	
ARM 2											
ARQ 197		X	X	X	X	X	X	X	X	X	
Erlotinib		X	X	X	X	X	X	X	X	X	

Click here for FOOTNOTES

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

FOOTNOTES

* Physical exam and medical history must be completed within 28 days prior to registration (see Section 5.3a).

Δ Continuous oral daily dosing (see Section 7.1).

Ω Protocol treatment and parameters will continue at these intervals until off protocol treatment per Section 7.6. While on protocol treatment, disease assessments will continue every 8 weeks until progression. If patient is removed from protocol treatment prior to disease progression, assessments will be continued on this schedule until disease progression.

√ After disease progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating investigator) every 3 months for the first year and then every 6 months thereafter for up to three years after registration or until death.

≠ Tumor assessment will be done after every second cycle by the same method used at baseline. REMEMBER, RESPONSE SHOULD BE CONFIRMED BY A SECOND DETERMINATION AT LEAST 4 WEEKS AFTER A COMPLETE OR PARTIAL RESPONSE HAS BEEN NOTED.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective status at each disease evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goal

A parallel (randomized) two-stage design will be used for patient accrual. When conducting both studies in parallel, each study acts independently. Eligible patients with advanced pRCC will be enrolled according to two strata: Strata 1 = 1st line therapy, Strata 2 = 2nd Line therapy. Patients will be randomized to either Arm 1 (single agent ARQ 197) or Arm 2 (ARQ 197+ erlotinib), as long as both arms are open as per stopping rules and toxicity considerations. Each arm will be conducted as an independent clinical trial. The primary endpoint, RECIST response (confirmed CR and PR) will be evaluated every two cycles. There will be no crossover from the single agent arm to the double agent arm.

11.2 Analysis of Primary Endpoint

Arm 1: ARQ 197 as a single agent (35 patients):

With no activity of ARQ 197 as a single agent in pRCC, we would expect a response rate of 10%. We would consider ARQ 197 promising for further investigation if the response rate were ≥ 30%. Initially, 20 eligible patients will be accrued to this arm of the study. If 0-1 patients are responders, this would constitute lack of evidence of sufficient activity, and this arm would be closed to accrual. We would expect this to occur 1% of the time if the true probability of response was 30%. If this arm shows adequate activity in the first stage, and toxicity and safety considerations permit, accrual will continue until a total of 35 eligible patients are accrued. If the total number of patients out of 35 who respond is 8+, we would consider this agent promising and worthy of further investigation in pRCC if toxicity and PFS data are also supportive. In this arm, the design has a significance level (probability of falsely declaring that an agent with a 10% response probability is worthy of further investigation) of 2%, and a power (probability of correctly declaring that an agent with a response rate of 30% is worthy of further investigation) of 87%. Thirty five eligible patients are sufficient to estimate the confirmed response to within ±17% (95% confidence interval).

Arm 2: ARQ 197 plus erlotinib (35 patients):

For ARQ 197 as a combination with erlotinib, we have specified the study with the same two-stage design. While the criteria might be considered slightly higher considering the **S0317** data on erlotinib showing responses and prolonged stable disease, raising the bar is considered unwarranted in this case for two main reasons: 1) this study permits pre-treated patients; 2) **S0317**, with only previously untreated patients had 5/52 patients with responses, including unconfirmed responses, and only 29% free from treatment failure at 6 months, suggesting a reasonable probability that erlotinib alone would not pass the first stage in this study. As a result, the same design considerations for Arm 1 apply. The operating characteristics of these rules were described above.

11.3 Analysis of Secondary Endpoints

Safety and Tolerability will be summarized by arm by examining the frequency and severity of toxicities grade by the CTCAE v4.0 (Common Terminology Criteria for Adverse Events), the frequency and extent of required dose modifications, and the frequency and cause of patient withdrawal for reasons other than progression.

Thirty five eligible patients are sufficient to estimate the probability of an adverse event within ±17% (95% confidence interval). Any adverse event occurring with at least a 5% probability is likely to be seen at least once (83% chance).

Assuming an ineligibility rate of approximately 10%, total accrual (eligible + ineligible) to this study is expected to be 78 patients.

Progression-free survival will be estimated by arm. Thirty five eligible patients are sufficient to estimate the 4 month progression-free survival within ±17% (95% confidence interval).

11.4 Analysis of Translational Medicine Endpoints

Correlative analysis will be exploratory in the context of this Phase II trial. There are several different statistical analyses that will be performed on the correlates:

The role of c-MET and EGFR, when available, will be explored through the use of Cox regression, categorical analysis (responders/non-responders versus high expressors, etc.), and graphical presentations.

11.5 Data and Safety Monitoring Committee Oversight

There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review done in conjunction with this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240/276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Cooperative Group Credit

f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

j. Country of Residence

k. ZIP Code

l. Gender (select one):
- Female Gender
- Male Gender

m. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)

- No Means of Payment (No Insurance)
- Other
- Unknown

o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration procedures

a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes, and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

- The study site is listed as "approved" in the CTSU RSS.

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG web site (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

If you need to submit data that are not available for online data submission, these should be submitted via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.
2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1107 Advanced Renal Carcinoma Onstudy Form

Baseline Tumor Assessment Form

S1107 Baseline Abnormalities Form

Radiology reports from all scans performed to assess disease at baseline

Pathology Report

b. WITHIN 28 DAYS OF REGISTRATION:

Submit materials outlined in Section 15.0 to Lab #201.

c. WITHIN 7 DAYS OF COMPLETION OF EACH CYCLE WHILE ON PROTOCOL TREATMENT:

Submit the **S1107** Treatment Form and **S1107** Adverse Event Form documenting required parameters as specified on the Study Calendar.

d. WITHIN 14 DAYS AFTER EVERY DISEASE ASSESSMENT, AFTER EVERY SECOND CYCLE WHILE ON PROTOCOL TREATMENT; IF PATIENT HAS NOT PROGRESSED ONCE OFF PROTOCOL TREATMENT THEN CONTINUE TO SUBMIT EVERY 8 WEEKS UNTIL PROGRESSION:

Submit the Follow-Up Tumor Assessment Form and all Radiology Reports until documented disease progression per Section 10.2d or removal from protocol treatment.

e. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the Off Treatment Notice and final **S1107** Treatment Form and **S1107** Adverse Event Form.

f. AFTER OFF TREATMENT, EVERY 3 MONTHS FOR THE FIRST YEAR AND THEN EVERY 6 MONTHS UNTIL DEATH OR FOR A MAXIMUM OF 3 YEARS:

Submit the Follow-Up Form.

g. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit a Follow Up Tumor Assessment Form, Radiology Report, **S1107** Treatment Form and **S1107** Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and final **S1107** Treatment Form, **S1107** Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimen Banking

Specimens for banking for future use for translational medicine studies are optional for the patient.

a. With patient's consent an archival tumor paraffin block or sixteen 5 micron unstained slides must be submitted prestudy (see Section 9.0):

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage:

(http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S1107** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

Monitoring

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

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for

routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for investigational agents

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in Arms 1 and 2 of this study are ARQ 197 and erlotinib. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the SWOG Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent ARQ 197 or erlotinib in this study

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:

1) Group-specific instructions

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210/614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Intake Calendar

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

Concurrent administration: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Sequential administration: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. Expected events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1 f of the protocol.

An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 **S1107** Intake Calendar

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**

Institution/Affiliate _____ Physician _____

Instructions for the participant:
This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____