

SUMMARY OF CHANGES

For Protocol Amendment #7 to:

NCI Protocol #: **9165**

Local Protocol #: **12-1359**

NCI Version Date: 02/01/16 (last NCI approved version)

Protocol Date: **04/19/16** (current version)

#	Section	Page	Change
1.	n/a	n/a	Updated protocol amendment number and protocol version date throughout the document
2.	Protocol History	4	Updated protocol history
3.	Section 7.1	37	Replaced CAPER for ARQ197 (tivantinib) version 2.1, June 17, 2013 with version 2.2, February 19, 2016

NCI Protocol #: 9165 Version 04/19/2016
Local Protocol #: 12-1359

TITLE: A randomized phase II trial of ARQ 197 (tivantinib)/cetuximab versus cetuximab in patients with recurrent/metastatic head and neck cancer.

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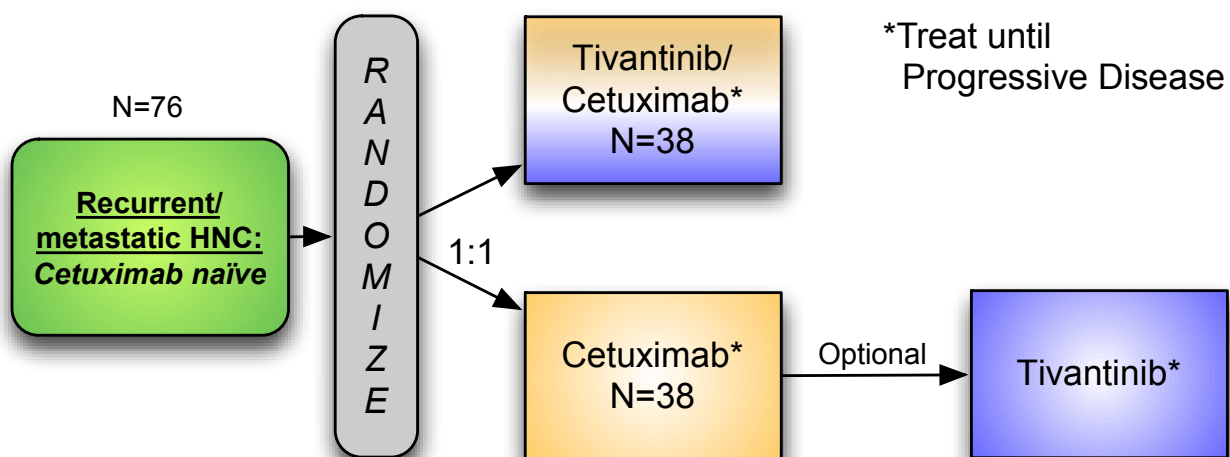
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Contract #	N01-CM-2011-00071
NCI Supplied Agent:	ARQ 197 (tivantinib) (NSC 750832 IND 112603)
Commercial Agents:	Cetuximab (Bristol-Myers/Imclone/Eli Lilly)
Tumor Type:	Head and Neck Cancer, NOS; 10025960

Protocol History

Version Date	Protocol Type / Version #
2/17/12	Version 1.0- Original Submission
4/24/12	Changes submitted in response to NCI consensus review.
5/11/12	Changes submitted in response to NCI follow-up review.
09/20/12	Amendment # 1. Updated Investigators for Mayo and California Consortia and other personnel on Face Page. Added new Appendix F: Patient's Medication Diary
5/28/13	Amendment #2. Updated Site Investigators UCP2C, Mayo and California Consortium. Clarification eligibility criteria in section 3.1. Provided clarification under general guidelines for section 4.2- registration process to indicate that, patients should begin protocol treatment within 14 days after randomization. Clarification on the duration of follow-up in section 5.4. Updated blood processing language, updated key personnel and shipping information in section 9.2- under correlative studies. Schema was amended to include baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy and also that EKG will be evaluated at baseline and later in section 10.0. Provided clarifications on definitions for "evaluable for objective response" and "Evaluable Non-Target Disease Response" in section 11.1. Included clarifications on Sample size/accrual rate, stratification factors, reporting/exclusions and on randomization in the section statistical considerations.. Updated Appendix C for Tissue/Sample collection form.
9/27/13	Amendment #3. Updated CTEP IND agent in Section 2.2. Clarification on exclusion criteria in section 3.2. Provided clarification under agent administration for cetuximab under Section 5.1. Under section 7.1 updated CAPER for ARQ197 with revised CAPER. Updated baseline evaluations under study calendar from 2 weeks to 16 days. Included a new reference.
12/30/13	Amendment #4. Updated site PI at Indiana University and also updated Chicago research personnel. Replaced CAPER for Cetuximab with safety data from FDA-approved package insert. Under Route of administration in Section 8.1, was updated to indicate that it is acceptable "to crush the tablet (ARQ 197) as long as it is taken orally".
04/15/14	Amendment #5. Provided clarification of how ARQ 197 should be taken under subsection 3.1.9. Updated Adverse Event Expedited Reporting System (AdEERS) with CTEP Adverse Event Reporting System (CTEP-AERS) throughout the protocol. Provided clarification about administration via G-tube under section 8.1. Provided clarification in the study calendar under section 10.0.
02/01/16	Amendment #6. Changed the local PI at Indiana University from Wagner to Grethlein.
04/19/16	Amendment #7. Updated CAPER for ARQ197 (tivantinib) version 2.2, February 19, 2016

SCHEMA



Primary Outcome:
Response Rate (RECIST)**

Secondary Outcomes:

- a) Continuous tumor shrinkage**
- b) PFS**
- c) OS**
- d) Outcomes a)-c) will be analyzed in tumors with c-MET copy number >5 and/or high expression (IHC)**

Please note: Patients who fail cetuximab as a single agent have the option to receive ARQ 197 (tivantinib) single agent afterwards..

CT scan assessment of response / tumor measurements (RECIST) will be every 2 cycles (=8 weeks) for all patients.

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1. OBJECTIVES

1.1 Primary Objectives

Response Rate

(We will compare the cetuximab/ARQ 197 (tivantinib) combination with cetuximab single agent activity.

1.2. Secondary Objectives

a) Continuous tumor shrinkage

b) PFS

c) OS

d) Endpoints a), b), and c) above, as well as response rates, will be assessed and compared between treatment arms in the subgroup of patients with high c-MET expression (anticipated to be ~84% of patients (*Seiwert et al, Cancer Research, 2009*), and/or high c-MET copy number (anticipated >10% and largely overlapping with MET IHC (*Seiwert et al, Cancer Research, 2009*)).

e) Single agent activity for ARQ 197 (tivantinib) in patients who have failed cetuximab

2. BACKGROUND

2.1 Study Disease

Head and Neck squamous cell carcinoma (HNSCC) is the 6th most common cause of cancer death worldwide with more than 600,000 cases annual. In the United States, approximately 40,500 new HNSCC cases and 11,000 deaths were expected in 2006. HNSCC results in significant morbidity because major vital functions such as nutrition, respiration and communication are impaired.

Approximately two thirds of patients with HNSCC will present with locoregional disease and despite aggressive local therapy, close to than half will succumb to recurrent and/or metastatic disease. If untreated, the median survival of patients with metastatic disease is dismal and on the order of 4 months (*Ang, Berkey et al. 2002*).

In patients with recurrent or metastatic HNSCC, the only therapeutic options are usually palliative consisting of systemic chemotherapy and the EGFR inhibitor cetuximab (*Vermorken, Mesia et al. 2008*). Median survival is estimated at 10.1 months using a combination of cisplatin/5-FU/cetuximab. Cytotoxic chemotherapy

can have significant toxicities, consisting of bone marrow suppression, nausea/vomiting, rash, hand-foot syndrome, and many others.

2.2 CTEP IND Agent

2.2.1 ARQ 197 (Tivantinib)

Receptor tyrosine kinases (RTKs) have emerged as an important class of molecular targets for anti-cancer therapy. The encouraging results from agents such as imatinib mesylate (Gleevec) against cancers with the constitutively active Bcr-Abl mutation, as well as erlotinib, an inhibitor of mutated and overexpressed EGF receptor kinase, have provided important clinical evidence that molecularly targeted RTK inhibitors are efficacious and can have a significant and broad effect against various cancers. As more RTKs are implicated in the pathophysiology of oncogenesis, the notion has been put forward that the signal transduction pathways that are served by these RTKs become dominant in initiating and maintaining the pro-proliferative and antiapoptotic phenotype of the transformed cell. Indeed, there is growing evidence that dysregulated RTK signaling in cancer cells may result in so-called “oncogene addiction,” providing the opportunity to selectively kill cancer cells by ablating RTK signaling pharmacologically (*Weinstein, 2002*).

The c-Met RTK mediates the signals for a variety of physiological processes that have implications for oncogenesis, including migration, invasion, cell proliferation, and angiogenesis. A wide variety of human cancers exhibit constitutively dysregulated c-Met activity, either through over-expression of the c-Met kinase, activating mutations in c-Met, or increased autocrine or paracrine secretion of the c-Met ligand hepatocyte growth factor/scatter factor (HGF/SF). These alterations have been strongly implicated in tumor progression and metastasis in a variety of cancers, and a high constitutive activation of the c-Met RTK has been correlated with poor clinical prognosis (*Jiang et al., 1999; Birchmeier et al., 2003*).

c-Met can be activated in both a ligand-dependent manner, by the overexpression of c-Met and/or its ligand HGF, or a ligand-independent manner as in the case of activating mutations of c-Met such as those described in sporadic and hereditary papillary renal carcinoma (*Birchmeier et al., 2003*). Activation and autophosphorylation of c-Met results in the binding and phosphorylation of adaptor proteins such as Gab1, Grb2, Shc and c-Cbl, and results in the subsequent activation of signaling pathways, including the PI3K/Akt, FAK, STAT and Ras/MEK/Erk pathways that play various roles in cell survival, proliferation, invasion, and angiogenesis (*Furge et al., 2000; Christensen et al., 2003*). In the melanocyte lineage, c-Met expression is upregulated by microphthalmia-associated transcription factor (MITF), which has been implicated in the oncogenesis of melanoma and other cancers (*Levy et al., 2006; McGill et al., 2006*).

The presence of c-Met in most cancers, and its role in controlling multiple signal transduction pathways involved in tumor growth render this enzyme a logical therapeutic target for human cancer.

ARQ 197 (tivantinib) is a potent RTK inhibitor with high selectivity for the c-Met RTK, as determined by biochemical and cellular assays. A comprehensive review of ARQ 197 (tivantinib) can be found in the ARQ 197 (tivantinib) Investigator's Brochure (2010).

Tivantinib also appears to have anti-tubulin activity, and may act as a cytotoxic. Some investigators believe that the anti-tubulin activity contributes more to tivantinib's anti-cancer activity than the anti- c-Met activity (Michieli et al., 2013)

2.2.2 Nonclinical Pharmacology

In Vitro Efficacy

ARQ 197 (tivantinib) selectively inhibits the *in vitro* biochemical activity of recombinant c-Met with a K_i of approximately 355 nM. The potency of ARQ 197 (tivantinib) inhibition of c-Met activity was independent of ATP concentration, suggesting that the mode of inhibition of ARQ 197 (tivantinib) is of a non-competitive nature. While ARQ 197 (tivantinib) inhibits c-Met kinase activity, it is not a promiscuous kinase inhibitor. When ARQ 197 (tivantinib) was profiled against 230 protein kinases at a nominal concentration of 5 or 10 mcM, ARQ 197 (tivantinib) inhibited only four protein kinases greater than 20% under the conditions of this assay. These data suggest that ARQ 197 (tivantinib) is a highly selective c-Met kinase inhibitor.

In cell-based kinase assays, ARQ 197 (tivantinib) inhibited HGF-induced activation of c-Met (as gauged by autophosphorylation) with an IC_{50} between 0.1 mcM – 0.5 mcM in multiple human cancer cell lines. This suppression was effective for at least eight to twelve hours after withdrawal of ARQ 197 (tivantinib), demonstrating a sustained durability of c-Met inhibition by ARQ 197 (tivantinib). Furthermore, ARQ 197 (tivantinib) decreased phosphorylation of most of the c-Met downstream effectors including FAK, STAT-3, Erk-1 and Erk-2, though not Akt. This indicates that by inhibiting c-Met, ARQ 197 (tivantinib) also induces a decrease in the phosphorylation and activation of many downstream targets in the pathways served by this oncogenic kinase.

ARQ 197 (tivantinib) showed broad-spectrum *in vitro* anticancer activity against human tumor lines, including those derived from breast, pancreas, colon, gastric, and lung. The potency of ARQ 197 (tivantinib) in cancer cells expressing detectable c-Met ranges from 0.1 – 0.6 mcM. By contrast, cells lacking c-Met such as NCI-H661 (human non-small cell lung cancer cells) and NCI-H446 (human small cell lung cancer cells) yielded IC_{50} s approximately 10-fold higher, indicating a correlation between the presence of c-Met and the sensitivity of the cells towards ARQ 197 (tivantinib). The ability of ARQ 197 (tivantinib) to inhibit c-Met phosphorylation correlates with its ability to inhibit growth and induce apoptosis in c-Met expressing cancer cells.

Overexpression of c-Met correlates with tumor cell migration and invasiveness, and invasion assays demonstrated that ARQ 197 (tivantinib) was able to potently inhibit invasion in c-Met expressing tumor cell lines (IC₅₀s of approximately 0.3 to 0.45 mcM), but less so in non-c-Met expressing lines (IC₅₀ = 5.4 mcM). In a wound healing assay, ARQ 197 (tivantinib) also inhibited migration of NCI-H441 cells (human lung adenocarcinoma) in response to HGF, the ligand for the c-Met receptor. Overall, these results indicate that ARQ 197 (tivantinib) has anticancer activity, an effect, which is mediated via its inhibition of c-Met.

Another study assessed a panel of 64 human cancer cell lines encompassing a spectrum of genotypes and tissue origins. The combination of ARQ 197 (tivantinib) and sorafenib showed synergistic cytotoxicity in nine cell lines, including three NSCLC cell lines, two breast cancer cell lines, a melanoma cell line, a renal clear cell carcinoma cell line, a cervical carcinoma cell line, and a squamous cell carcinoma cell line. Additivity was seen with the ARQ 197 (tivantinib)/sorafenib combination across a wide range of 40 human cancer cell lines including, but not limited to, five colon cancer lines, five breast cancer cell lines, four additional NSCLC cell lines, and three hepatocellular carcinomas (HCC).

In Vivo Efficacy

When administered via daily oral dosing, ARQ 197 (tivantinib) was shown to be efficacious against multiple human cancer xenograft models. Beginning at a dose level of 200 mg/kg, tumor growth inhibition was seen in breast (79%), colon (39%), pancreatic (58%), prostate (72%), and gastric (52%) models. Increasing the dose to 300 mg/kg improved tumor inhibition in colon (55%), pancreatic (60%), and prostate (77%) models. ARQ 197 (tivantinib) was well tolerated in these studies with no drug related clinical signs or deaths. There was no significant change in body weight at any of the dose levels tested. Furthermore, the antitumor activity of ARQ 197 (tivantinib) is accompanied by the ablation of c-Met activity, as assessed by the decreased level of phosphorylated c-Met in the dissected xenograft tumor tissue. This suggests a potential mechanism-based clinical biomarker.

In human tumor xenograft models, results of a study conducted with the NCI-H522 NSCLC cell line suggest that antitumor effects of ARQ 197 (tivantinib) and sorafenib were modestly additive and the combination of the two agents was extremely well tolerated, with no body weight gain changes or deaths observed.

2.2.3. Nonclinical Pharmacokinetics

The pharmacokinetics of ARQ 197 (tivantinib) were evaluated and compared in mice, rats, and dogs using different dosing routes, levels, and formulations. In general, exposure to ARQ 197 (tivantinib) increased as the dose was increased. Overall, the corresponding increases in AUC_{0-inf} and C_{max} were generally not dose proportional. The t_{1/2} of ARQ 197 (tivantinib) generally ranged from 1 – 4.5 hours across all studies and all species, though there were a few exceptions. For

instance, rats displayed a highly variable $t_{1/2}$ (1.48 – 37.8 hours), the reason for which is unknown. Bioavailability after single-dosing was somewhat variable between species: 16-35% in rats, 33-60% in dogs, and 21-37% in mice. After multiple dosing in 7-day, 28-day, 8-week, and 26-week studies, there were no consistent changes in C_{max} and AUC values in rat or dog, indicating that there was no marked accumulation of ARQ 197 (tivantinib) after multiple dosing.

Metabolism

Mass balance and tissue distribution studies indicated that primary route of elimination of ARQ 197 (tivantinib) is fecal and that ARQ 197 (tivantinib) generally did not accumulate (after 96 hours) in any of the tissues tested. Data from *in vitro* metabolism studies suggest that ARQ 197 (tivantinib) is relatively stable in human liver microsomes with a $t_{1/2}$ of 29 min. The $t_{1/2}$ of ARQ 197 (tivantinib) in male dog liver microsomes was similar to that of human liver microsomes with a $t_{1/2}$ of 29 min ($t_{1/2}$ in female dog liver microsomes was 20.5 min).

From studies conducted with individual CYP P450 isozymes, ARQ 197 (tivantinib) was rapidly metabolized by CYP2C19 ($t_{1/2}$ = 2.83 min) and moderately metabolized by CYP 3A4 ($t_{1/2}$ = 16.3 min). The $t_{1/2}$ values for the other CYP P450s (1A2, 2C9, 2D6, and 2C8) tested were all greater than 27.4 min. Drugs which affect the activity of CYP2C19 or CYP3A4 may markedly alter the plasma concentration of ARQ 197 (tivantinib). The IC_{50} of ARQ 197 (tivantinib) was evaluated for each CYP 450 isoform (1A2, 2C8, 2C9, 2C19, 2E1 and 3A4), and all were greater than 10 μ M.

2.2.4 Nonclinical Toxicology

Preclinical toxicity for ARQ 197 (tivantinib) was assessed in the rat and beagle dog in single dose studies as well as repeat dose studies of up to 26 weeks in duration. In 28-day repeat-dose studies, clinical pathology signs typically observed at the high dose (45 mg/kg) included lower red cell mass, lower absolute reticulocyte count, and lower absolute neutrophil and monocyte counts for males and females. In addition, females had lower absolute lymphocyte and eosinophil counts. Microscopic findings at high doses included depletion of lymphocytes in the thymus, femur and sternum bone marrow depletion, and hypertrophy and vacuolation in peripherolobular hepatocytes. Importantly, these clinical and anatomic pathology findings were reversed by 2 weeks after cessation of dosing.

Clinical Experience

The pharmacokinetics, metabolism, safety, and efficacy of ARQ 197 (tivantinib) have been investigated in multiple phase 1 and phase 2 clinical trials in cancer patients. Two phase 1 dose escalation trials (ARQ 197-101 and ARQ 197-103) have defined the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for continuous doses of ARQ 197 (tivantinib) as a single agent. Another

phase 1 study (ARQ 197-111) evaluated the MTD and RP2D of ARQ 197 (tivantinib) administered in combination with erlotinib on a continuous schedule. Additional ongoing phase 1 and phase 1/2 trials evaluating ARQ 197 (tivantinib) include ARQ 197-114 (monotherapy in HCC); ARQ 197-116 (combination with sorafenib); and ARQ 197-117 (combination with gemcitabine).

In addition, there have been two completed phase 2 clinical trials. One trial (ARQ 197-204) evaluated the efficacy of ARQ 197 (tivantinib) in patients with MITF-associated tumors, and the other (ARQ 197-209) was a global, randomized, placebo controlled, double-blind phase 2 trial comparing treatment with erlotinib plus ARQ 197 (tivantinib) versus treatment with erlotinib plus placebo in patients with previously treated non-small cell lung cancer (NSCLC). There is also an ongoing phase 2 randomized, placebo-controlled trial (ARQ 197-215) in patients with HCC.

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2010). Safety and efficacy results are summarized below.

Phase 1 Studies

Study **ARQ 197-101** was a phase 1 dose escalation trial of ARQ 197 (tivantinib) in adult patients with locally advanced or metastatic solid tumors. Thirteen dose levels ranged from 10 – 360 mg BID and two dosing schedules (intermittent vs. continuous) were explored. Additional patients were enrolled and treated at the 360 mg BID continuous dose, which was determined to be the RP2D in another Phase 1 clinical trial (ARQ 197-103). The most common drug-related adverse events (AEs; $\geq 5\%$ and ≥ 2 events) seen in this study were fatigue (13.9%), nausea (13.9%), vomiting (10.1%) and diarrhea (6.3%). Serious adverse events (SAEs) reported at a $>3\%$ incidence were disease progression and dehydration (6.3% for each) and anemia, nausea, renal failure acute, and vomiting (3.8% for each). Two patients were discontinued from the study due to dyspnea and deep vein thrombosis. No dose-limiting toxicities (DLTs) were reported at doses below 360 mg BID in this study. The myelosuppression events of neutropenia, leukopenia and thrombocytopenia resolved in 9 days, with treatment continuing thereafter. Vomiting and dehydration resolved in 6 days. A total of 79 patients were evaluable for efficacy analysis per the study protocol. Three (3.8%) of these patients achieved partial responses (PR). Forty (50.6%) patients achieved stable disease (SD).

Study **ARQ 197-103** was a phase 1 dose escalation trial of ARQ 197 (tivantinib) given twice daily continuously in adult patients with advanced solid tumors. The MTD was found to be 360 mg BID. A total of 59 patients were enrolled to this study. The most common ($\geq 5\%$ and ≥ 2 events) drug-related AEs were fatigue (15.7%), nausea (13.7%), vomiting (11.8%), anorexia (7.8%), diarrhea (7.8%), anemia (5.9%), febrile neutropenia (5.9%), and weight loss (5.9%). SAEs reported at a $>5\%$ incidence (more than 1 subject) were febrile neutropenia

(5.9%) and disease progression (9.8%). Among 29 evaluable patients, 17 demonstrated SD as their best response.

Study **ARQ 197-114** is an ongoing safety study of ARQ 197 (tivantinib) in cirrhotic subjects with HCC. ARQ 197 (tivantinib) is administered continuously at a dose level of 360 mg BID. Thus far, a total of 21 patients have been enrolled in this study. The most common drug-related AEs ($\geq 5\%$ and ≥ 2 events) are asthenia (47.6%), neutropenia (42.9%), anemia (42.9%), leukopenia (38.1%), anorexia (38.1%), diarrhea (28.6%), alopecia (19.0%), thrombocytopenia (14.3%), vomiting (14.3%), hepatobiliary disorders (14.3%), hyperbilirubinemia (14.3%), lymphopenia (9.5%), bradycardia (9.5%), dysgeusia (9.5%), and oropharyngeal pain (9.5%). Drug-related SAEs leading to discontinuation from the study include three cases of neutropenia. Of 16 evaluable patients, six have exhibited a decrease in tumor volume by RECIST criteria.

Study **ARQ 197-111** is an ongoing phase 1 dose escalation trial of ARQ 197 (tivantinib) administered in combination with erlotinib in adult patients with advanced solid tumors. One DLT (neutropenia) was reported in a patient receiving an ARQ 197 (tivantinib) dose of 360 mg BID. Based on these data, a dose of 360 mg ARQ 197 (tivantinib) BID in combination with erlotinib 150 mg daily has been identified as the RP2D. The most commonly-reported drug-related AE in this study was bradycardia, with 15 episodes reported in four patients; these events were generally mild and asymptomatic (grade 1), and 14 of these events occurred at the 360 mg BID dose level of ARQ 197 (tivantinib). One drug-related bradycardia event did not resolve. Other common drug-related AEs ($\geq 5\%$ and ≥ 2 events) were fatigue (31.3%), rash (15.6%), diarrhea (21.9%), pruritus (15.6%), muscle spasms (15.6%), anemia (12.5%), nausea (12.5%), dermatitis acneiform (15.6%), anorexia (6.3%), vomiting (6.3%), flatulence (6.3%), dry skin (12.5%), neutropenia (6.3%), and pyrexia (6.3%). As of July 23, 2010, 32 patients were enrolled and evaluable for efficacy. One subject out of 32 (3.1%) achieved an unconfirmed PR. Fourteen (43.8%) patients achieved SD as their best response with a range of follow-up between 8 and 37 weeks.

Phase 2 Studies

Protocol **ARQ 197-204** was a phase 2 study of ARQ 197 (tivantinib) in patients with MITF-associated tumors, including translocation-associated renal cell carcinoma (t-RCC), alveolar soft-part sarcoma (ASPS), and clear-cell sarcoma (CCS). The initially enrolled patients received 120 mg ARQ 197 (tivantinib) BID; patients enrolled after the RP2D was determined (in ARQ 197-103) received 360 mg ARQ 197 (tivantinib) BID. Among 47 patients treated in this study, ARQ 197 (tivantinib) demonstrated a favorable safety profile and was well tolerated at both doses. The most common ($\geq 5\%$ and ≥ 2 events) drug-related AEs were fatigue, pyrexia, nausea, vomiting, diarrhea, retching, anemia, lymphopenia, pain in extremity, anorexia, headache, insomnia, dyspnea, cough, neutrophil count decreased, decreased white blood cell count, increased alanine aminotransferase level, increased aspartate aminotransferase level, decreased hemoglobin level,

sinus bradycardia, and rash. Forty-five patients were evaluable for efficacy. One patient with CCS demonstrated a confirmed PR. Twenty-seven patients demonstrated SD, including 21 with ASPS, three with t-RCC, and three with CCS. Overall, 12 subjects experienced SD for ≥ 24 weeks.

Study **ARQ 197-209** was an ongoing global, randomized, placebo-controlled, double-blind phase 2 trial comparing treatment with erlotinib plus ARQ 197 (tivantinib) versus treatment with erlotinib plus placebo in patients with previously treated NSCLC. The most commonly reported AEs related to the ARQ 197 (tivantinib)-erlotinib combination ($\geq 5\%$ and ≥ 2 events) were rash (63.1%), diarrhea (35.7%), fatigue (33.3%), pruritus (22.6%), and dry skin (20.2%). Thirty-seven deaths were reported to occur within 30 days of the last dose of study drug. According to the investigator assessment, there were 7 PRs and 40 SDs among 73 evaluable patients in the erlotinib plus ARQ 197 (tivantinib) treatment group, for an objective response rate (ORR) of 9.6% and a disease control rate of 64.4%. For the erlotinib plus placebo group, there were 5 PRs and 35 SDs among 72 evaluable subjects, for an ORR of 6.9% and disease control rate of 55.6%.

ARQ 197-215 is an ongoing placebo-controlled study of ARQ 197 (tivantinib) in subjects with HCC. A total of 49 patients have been enrolled in the study. The most common drug-related AEs are neutropenia (16.3%), anemia (12.2%), fatigue (8.2%), asthenia (8.2%), vomiting (6.1%), diarrhea (6.1%), and nausea (6.1%). SAEs which may or may not be related to the study drug include fatigue (3 events), anemia (2), neutropenia (2), and sepsis (2). Two patient deaths (due to sepsis and neutropenic sepsis) have been attributed to study drug.

Myelosuppression

As of July 23, 2010, there were 266 patients enrolled and treated with ARQ 197 (tivantinib) in six ARQ 197 (tivantinib) monotherapy studies. A total of 58 events of myelosuppression (65 anemia, 29 neutropenia, 17 leukopenia, 13 thrombocytopenia, 11 lymphopenia, and 4 febrile neutropenia) were reported. One grade 5 case of pancytopenia case was reported. The greatest incidence of NCI CTCAE grade 3 or 4 events of myelosuppression (anemia and neutropenia) was in subjects with HCC in study ARQ 197-114.

To reduce the risk of severe myelosuppression events, a complete blood count (CBC) should be performed weekly during the first cycle of therapy, and at subsequent time points as designated in the protocols. This testing schedule follows hematology recommendations for monitoring in subjects treated with CYP2C19 or CYP3A4 inhibitors. Subjects who have neutropenia are to be monitored more closely throughout the study and follow dose modifications or delays as specified in the protocols.

Sinus Bradycardia/Bradycardia

Bradycardia has been reported in monotherapy and combination therapy clinical trials of ARQ 197 (tivantinib). Bradycardia was also one of the most frequently reported AEs in a phase 1 trial of ARQ 197 (tivantinib) in combination with erlotinib (Study ARQ 197-111). The majority of these events have been mild and asymptomatic. Therefore, studies will exclude patients with a history of congestive heart failure or other clinically relevant cardiac problems, as defined in section 3.2 (“Exclusion Criteria”). In addition, bradycardic patients with a heart rate ≤ 50 beats per minute should have an ECG done on day 1 of every cycle, or as clinically indicated.

Pharmacokinetics

Approximately 345 subjects with cancer and over 100 healthy subjects participated in phase 1 studies of ARQ 197 (tivantinib). Clinical PK data are available from multiple clinical studies using ARQ 197 (tivantinib) as either the amorphous solid or 1 of 2 crystalline forms designated form A or form B. Overall, following oral administration ARQ 197 (tivantinib) is moderately absorbed with a T_{max} ranging from 2 – 6 hours. In general, ARQ 197 (tivantinib) exposure increases with increases in dose; however, exposure is not dose proportional. There is wide intersubject variability in ARQ 197 (tivantinib) PK. Based on population pharmacokinetic (PopPK) analysis, this variability is partly due to CYP2C19 polymorphism, fed status during ARQ 197 (tivantinib) administration, ARQ 197 (tivantinib) form (amorphous versus crystalline A versus crystalline B), and also possibly ethnicity differences (Caucasian versus Japanese).

In vitro human liver microsome studies indicate involvement of both CYP2C19 and cytochrome P450 3A4 (CYP3A4) in ARQ 197 (tivantinib) metabolism. In humans, ARQ 197 (tivantinib) showed a genotype exposure relationship dictated mainly by CYP2C19 genotype. In healthy subjects, CYP2C19 poor metabolizers (PMs) had much higher exposure than extensive metabolizers (EMs), as reflected by AUC_{0-48} and C_{max} (11-fold and 3-fold higher, respectively) and lower clearance (mean of 2.4 L/h versus mean of 33.9 L/h). However, based on steady state exposure data in cancer subjects the PM exposure (AUC_{0-12}) is only 1.4- to 4-fold greater than EM exposure. Hence, differences in CYP2C19 metabolism will contribute to variability in PK between subjects. In a phase 1 dose-escalation study, 10 of 43 patients were characterized as PMs.

Additional studies comparing the PK of the amorphous form of ARQ 197 (tivantinib) to the crystalline forms A and B of ARQ 197 (tivantinib) showed that the amorphous form of ARQ 197 (tivantinib) resulted in higher exposure (C_{max} , AUC) than either crystalline form A or B. Specifically, C_{max} was approximately 60% to 70% lower for forms A and B, respectively, compared with the amorphous form. Similarly, AUC was 20% to 30% lower for crystalline forms A and B, respectively, relative to the amorphous form.

When ARQ 197 (tivantinib) was administered immediately after a high-fat meal to healthy subjects, the exposure was 3 times greater than the exposure under

fasting conditions, when the agent is administered at least 1 hour before and 2 hours after a meal (fed: AUC_{0-last} 13356 \pm 5385 ng/hr/mL and AUC_{0-inf} 13558 \pm 6397 ng/hr/mL; fasting: AUC_{0-last} 4858 \pm 1793 ng/hr/mL and AUC_{0-inf} 6166 \pm 2393). However, when ARQ 197 (tivantinib) crystalline B was administered 360 mg BID (the phase 3 dose) to cancer subjects (study **ARQ 197-117**), the exposure was similar under fed versus fasting conditions (fed: 12251 ng/hr/mL; fasting: 10453 ng/hr/mL), and comparable in both cases to the exposure in healthy, fed subjects. Additionally, when administered under fed conditions, the variability in ARQ 197 (tivantinib) exposure is generally lower compared with the fasted condition.

Detailed preliminary pharmacokinetic data can be found in the most recent ARQ 197 (tivantinib) Investigator's Brochure (2010).

2.3 Cetuximab

Cetuximab (Erbix[®], C-225) is a chimerized monoclonal IgG₁ subclass antibody with binding affinity to the epidermal growth factor receptor (EGFR) that exceeds the natural ligand epidermal growth factor (EGF). Cetuximab effectively blocks binding of EGF and transforming growth factor alpha (TGF- α) to EGFR and prevents ligand-induced activation, stimulates EGFR internalization, and effectively removes EGFR from the cell surface. Cetuximab is FDA approved for the treatment of head and neck cancers in combination with radiation and in the palliative setting typically with chemotherapy.

Several clinical studies have demonstrated the safety and efficacy of cetuximab in the treatment of HNSCC. Vermorken et al, treated 103 patients with incurable stage III/IV, platinum refractory HNSCC with single agent cetuximab (at 400 mg/m² initial dose and 250 mg/m² weekly subsequently)(*Vermorken, Trigo et al. 2007*). The objective response rate (ORR) in this population was 14%, median time to progression was 2.3 months and median overall survival (OS) was 5.9 months. The treatment was well tolerated.

In another trial 117 patients with metastatic or recurrent HNSCC were randomized between cetuximab plus cisplatin (100 mg/m² every 28 days) or cisplatin plus placebo. The addition of cetuximab to cisplatin improved ORR (26% vs. 10%), median PFS (4.2 months vs. 2.7 months), and median OS (9.2 months vs. 8.0 months) versus control. Cetuximab therapy was associated with increases in the risk of neutropenia, acneform rash, and dyspnea, but the treatment was generally well tolerated.

On the basis of this trial as well as other reports including combinations with chemotherapy and radiation in the pre-clinical and clinical setting two pivotal phase III studies were started. The first phase III trial enrolled 424 patients with locoregionally advanced HNSCC – randomization between cetuximab + radiotherapy (RT) versus radiation alone. Median progression free survival (primary endpoint) in the cetuximab/RT arm was 17.1 months, compared to 12.4 months in the RT alone

arm (= overall survival of 49 months versus 29.3 months. Both arms were reported to comparable RT related toxicities. The primary observed adverse event in this trial attributed to cetuximab was an acneform rash in 17% in the cetuximab/RT group and only 1% in the RT alone arm.

In 2008, results from the landmark phase III EXTREME trial (*Vermorken, Mesia et al. 2008*), comparing cetuximab in combination with either cisplatin plus 5-fluorouracil (5-FU) or carboplatin plus 5-FU with combinations of cisplatin/5-FU or carboplatin/5-FU alone were reported. Results indicated a statistically significant survival benefit associated with adding cetuximab to these regimens.

Based on trials using cetuximab (420 patients receiving cetuximab monotherapy or 354 patients receiving cetuximab + chemotherapy (patients with metastatic colorectal cancer)) cetuximab was well tolerated. The most **serious adverse reactions** associated with cetuximab were: Infusion reaction (3%); Dermatologic toxicity (1%); Interstitial lung disease (0.4%); Fever (5%); Sepsis (3%); Kidney failure (2%); Pulmonary embolus (1%); Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy; Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy. 17 (4%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events. The most common adverse events seen in 420 patients receiving cetuximab monotherapy were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%). The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

Cetuximab is currently Food and Drug Administration (FDA)- approved for use in combination with radiotherapy in the treatment of locally or regionally advanced HNSCC, as well as in the recurrent/ metastatic setting as a single agent, or in combination with cytotoxic chemotherapy.

2.4 Rationale

EGFR is expressed at very high levels in >90% of Head and Neck cancers (HNC; >NSCLC) and treatment with cetuximab (alone or in combination with chemotherapy or radiation) is now considered a standard of care. Nevertheless the response rate to EGFR inhibitors (cetuximab response rate = 13%, 40-50% stable disease) and median progression free survival of 70 days (*Vermorken et al, JCO, 2007*) remain disappointing. While treatment benefit is generally considered to be comparable to cytotoxic therapies with lower toxicity, the potential of EGFR as a therapeutic target in this highly EGFR expressing disease has not been fully exploited. Clinically treatment for recurrent/metastatic disease is either given in combination with chemotherapy (EXTREME) or after initial cytotoxic chemotherapy.

In our translational and preclinical work we demonstrated the following:

Eighty-four percent of the HNC samples showed c-MET overexpression (>NSCLC), and 18 of 20 HNC cell lines (90%) expressed c-MET. HGF overexpression was present in 45% of HNC. c-MET inhibition with SU11274/PF-2341066 abrogated c-MET signaling, cell viability, motility/migration in vitro, and tumor angiogenesis in vivo. Increased c-MET gene copy number was present with >10 copies in 3 of 23 (13%) tumor tissues. A greater-than-additive inhibition of cell growth was observed when combining a c-MET inhibitor with an EGFR inhibitor and synergy was mediated via erbB3 signaling. Finally we identified single nucleotide variants/mutations in the semaphorin (T230M/E168D/N375S), juxtamembrane (T1010I/R988C), and tyrosine kinase (T1275I/V1333I) domains (incidence: 13.5%) although functional contribution of these variants will require further study.

We demonstrated that c-MET is functionally important in HNC with prominent overexpression, and increased gene copy number, in the vast majority of HNC. c-MET inhibition abrogated c-MET functions, including proliferation, migration/motility, and angiogenesis. We concluded that c-MET is a promising, novel target for HNC and combination approaches with EGFR inhibitors should be explored.

The importance of c-MET in general for head and neck cancers and a relationship to EGFR signaling is well supported by corroborative literature: Knowles et al demonstrated the importance of HGF and c-MET for HNC independently (Knowles, et al Clinical Cancer Research 2009). Particular emphasis was put on the tumor fibroblast HGF production. Furthermore recent data from the Univ. of Pittsburgh (California Consortium) show strong synergy of c-MET with EGFR inhibition, and extensive crosstalk between the two receptors (Xu et al, Clinical Cancer Research, 2011).

Both EGFR and c-MET signal downstream via the common signaling adaptor/receptor erbB3, as demonstrated for NSCLC previously and confirmed for HNC (Seiwert et al, Cancer Research 2009). Preclinical co-targeting of EGFR and MET revealed strong synergy in HNC (Seiwert et al, 2009, Cancer Research; Xu et al, 2011, Clinical Cancer Research). Furthermore two phase II randomized studies in NSCLC have yielded positive results suggesting that c-MET inhibition can augment the efficacy of EGFR inhibition and improve PFS in biomarker defined patient populations. EGFR and MET signaling are overlapping and it is well established that one can compensate for the other and joint inhibition provides benefit/synergy. It is crucial to identify the correct biologic subgroup/s that benefit most. Our preclinical work as well as NSCLC lung cancer data suggest that increased c-MET copy number and c-MET expression are the most likely candidate predictive biomarkers also for HNC.

Based on these preclinical findings we now propose to study the EGFR inhibitor cetuximab and the c-MET inhibitor ARQ 197 (tivantinib) in combination.

2.5 Correlative Studies Background

See above for preclinical rationale. Clinically the rationale is largely supported by prior experiences with ARQ 197 (tivantinib) and the c-MET antibody MetMab.

The phase II randomized study of ARQ 197 (tivantinib) in NSCLC identified c-MET copy number as a biomarker of ARQ 197 (tivantinib) benefit ([Sequist, Schiller et al, ESMO, 2010](#)).

The phase II randomized study of MetMab (antibody fragment against the c-MET receptor) demonstrated that benefit of MetMab was limited to tumors with c-MET expression using a standardized and centralized IHC methodology ([Spigel et al, ESMO, 2010](#)).

In this study we will evaluate both c-MET copy number and c-MET expression.

3. PATIENT SELECTION

3.1 Eligibility Criteria

Inclusion Criteria:

- 3.1.1 Histologically / cytologically confirmed diagnosis of squamous cell carcinoma of Head and Neck origin not amenable to curative intent therapy. Both HPV(+) and HPV(-) are eligible, but status has to be known prior to randomization (although not required for consenting). Any type of tissue based HPV assessment is acceptable (e.g. p16 IHC or HPV ISH). If local HPV testing is not available slides can be sent to the University of Chicago for HPV testing. Please note that p16 IHC is generally only considered to be accurate for oropharyngeal tumors.
- 3.1.2 Presence of measurable lesions (as per RECIST 1.1). Generally a ≥ 10 mm tumor lesion (in the longest diameter by CT scan) or a Lymph node ≥ 15 mm (short axis) is considered measurable disease when evaluated by CT scan (with a slice thickness no greater than 5 mm). Please review full RECIST 1.1 criteria ([Eisenhauer EA et al, Eur J Ca, 2009](#)) as well as Section 11 for further details.
- 3.1.3 Availability of tissue (10 tumor containing FFPE slides/sections)
- 3.1.4 ECOG performance status of 0, 1 (see Appendix A).
- 3.1.5 Patients who have received cetuximab or another inhibitor of EGFR in the curative intent treatment setting (e.g. with radiation or during induction chemotherapy (prior to definitive, curative intent therapy)) are eligible for the study.
- 3.1.6 Age ≥ 18 years.

Because no dosing or adverse event data are currently available on the use of ARQ 197 (tivantinib) in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

- 3.1.7 Life expectancy of greater than 8 weeks.
- 3.1.8 Patients must have normal organ and marrow function as defined below:

- hemoglobin	≥ 9.0 g/dL
- leukocytes	$\geq 3,000$ /mcL
- absolute neutrophil count	$\geq 1,500$ /mcL
- platelets	$\geq 100,000$ /mcL
- total bilirubin	≤ 1.5 X institutional upper limit of normal
- AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional upper limit of normal
- serum creatinine	≤ 1.5 X institutional upper limit of normal

OR

– creatinine clearance ≥ 60 mL/min/1.73 m² for patients with creatinine levels above institutional normal.

- 3.1.9 Patients must be able to swallow ARQ 197 (tivantinib) by mouth, unless adequate data about administration by G-tube becomes available. Tablets may be crushed, but must be taken orally.
- 3.1.10 HIV-positive patients with normal immune function (CD4 count >200) are eligible if there are no drug interactions with ARQ 197 (tivantinib) or cetuximab.
- 3.1.11 The effects of ARQ 197 (tivantinib) on the developing human fetus are unknown. For this reason and because tyrosine kinase inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of ARQ 197 (tivantinib) administration.
- 3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- 3.2.1 Patients who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.
- 3.2.2 Nasopharyngeal tumors that show lymphoepithelioma histology
- 3.2.3 Patients who have received more than 2 prior cytotoxic treatments in the palliative treatment setting are ineligible.
- 3.2.4 Patients who have received prior treatment with an EGFR or MET inhibitor in the palliative treatment setting are ineligible
- 3.2.5 Patients with known, active brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of

neurologic and other adverse events. Patients with treated brain metastases stable for ≥ 12 weeks are eligible. Use of corticosteroids (for patients with brain metastasis and other indications for corticosteroid use) is acceptable on a low maintenance or tapering dose schedule.

- 3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AR 197 (tivantinib) or cetuximab.
- 3.2.7 Concurrent life-threatening diseases: Patients with diseases which with reasonable certainty do not limit life expectancy to 12 months or less are eligible. Assessment of such concurrent illnesses should be by the Principal Investigator
- 3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.9 Pregnant women are excluded from this study because ARQ 197 (tivantinib) is a tyrosine kinase inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ARQ 197 (tivantinib), breastfeeding should be discontinued if the mother is treated with ARQ 197 (tivantinib).
- 3.2.10 Concurrent use of warfarin (therapeutic use) is allowed, but requires close monitoring of PT/INR (See Section 5.2)
- 3.2.11 ARQ 197 (tivantinib) is metabolized by CYP2C19, and to a lesser extent CYP3A4. The metabolism and consequently overall pharmacokinetics of ARQ 197 (tivantinib) could be altered by inhibitors and/or inducers or other substrates of CYP2C19 and CYP3A4. While inhibitors/inducers of these cytochrome P450 isoenzymes are not specifically excluded, investigators should be aware that ARQ 197 (tivantinib) exposure may be altered by the concomitant administration of these drugs.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

- 3.2.12 History of congestive heart failure defined as Class II to IV per New York Heart Association (NYHA) classification; active coronary artery disease (CAD); clinically significant bradycardia or other uncontrolled, cardiac

arrhythmia defined as \geq grade 3 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, or uncontrolled hypertension; myocardial infarction occurring within 6 months prior to study entry (myocardial infarction occurring >6 months prior to study entry is permitted).

3.2.13 Patients may not be receiving any other investigational agents

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. Each center will be responsible for ensuring that a representative set of patients (as defined by the Census Bureau) is enrolled.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the University of Chicago by the Study Registrar. All sites should call the Study Registrar, , at **773-834- 3095** or PhaseIIICRA@medicine.bsd.uchicago.edu, to verify agent availability. The UC Phase II Consortium Affiliate Forms are available on the UC P2C website at:

- <https://webres.uccrc.org/login/login>

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies. Eligible patients will be entered on study centrally at the University of Chicago by the study Registrar. All sites should call the study Registrar at **(773) 834 3095** to verify agent availability.

ARQ 197 (tivantinib) may be requested by submitting an agent order through PMB Online Agent Order Processing (OAOP) application. Refer to section Section 8.1.3.1 for more information.

Following registration, the study registrar at the University of Chicago will randomize the patient immediately, and patients should begin protocol treatment within 14 days after randomization. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Registrar should be notified of cancellations as soon as possible.

4.2 Registration Process

All patients must be successfully registered and randomized with the University of Chicago Registrar, prior to the commencement of treatment. The following documents should be completed by the research nurse or data manager and faxed to (773) - 702 4889 or emailed PhaseIICRA@medicine.bsd.uchicago.edu to the Registrar:

- Provider of information
- Treating Physician
- Patient name and hospital ID number
- Patient's zip code of residence
- Date & copy of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- HPV status (can be provided later, but is required for successful randomization)
- Complete **Phase II Consortium Affiliate Clinical Trial Patient Registration Form**
- Source documentation for eligibility and pre-study procedures

The research nurse or data manager at the participating site will then call (773-834-3095) or e-mail PhaseIICRA@medicine.bsd.uchicago.edu to confirm all selection criteria listed in Section 4.0. To complete the registration process, the Coordinator will:

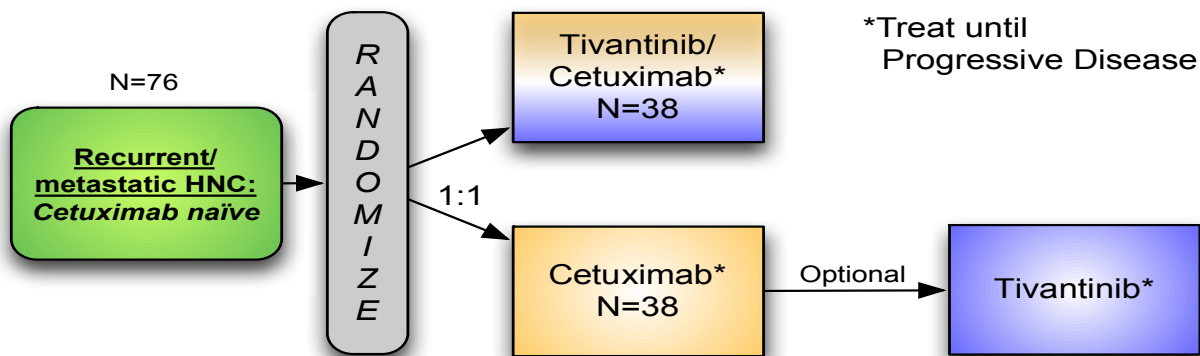
- Assign a patient study number
- Register the patient on the study
- Assign patient to treatment arm based on Randomization (see Section 13)
- Fax or e-mail the patient study number and dose to the participating site
- Provide randomization information regarding treatment arm

Call the research nurse or data manager at the participating site and verbally confirm registration.

5. TREATMENT PLAN

Patients are randomized between two arms (see schema below):

1. cetuximab 500mg/m² iv, every two weeks, PLUS ARQ 197 (tivantinib) 360mg BID, by mouth
2. cetuximab 500mg/m² iv, every two weeks



5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for ARQ 197 (tivantinib) and cetuximab are described in Section 7. Appropriate dose modifications for ARQ 197 (tivantinib) and cetuximab are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 ARQ 197 (tivantinib) administration

- Patients receive ARQ 197 (tivantinib) on an outpatient basis. The starting dose is 360 mg, by mouth, twice daily.
- The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle. A sample medication diary can be requested from the University of Chicago or can be provided by the respective treatment center using a local template.
- ARQ 197 (tivantinib) tablets should be administered orally with meals. A missed or vomited dose (= not taken within 4 hours (i.e. 4 hours before or after) the scheduled time) should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time.

5.1.2 Cetuximab administration

- Cetuximab will be given on an outpatient basis every two weeks intravenously at a dose of 500mg/m² (given over 120 minutes the first time, then over 60 minutes subsequently) (all iv).
- It is acceptable to round the cetuximab dose to the nearest hundred if this is the institutional standard practice.
- Patients will receive cetuximab intravenous infusions via infusion pump or gravity drip. The dose of cetuximab is 500 mg/m² and is administered over 120 or 60 minutes. The dose of cetuximab is dependent upon the patient's baseline body weight in kilograms (mg/kg). If there is a $\geq 20\%$ change in body weight from baseline this dose should be recalculated. Patients should be observed closely during cetuximab infusion and for **60 minutes after the infusion**.

Infusion times may be increased for patients who experience mild allergic reactions, but cannot exceed 4 hours. Prior to infusion, the appropriate volume of cetuximab will be drawn from the vial with a sterile syringe and cetuximab will be transferred from the syringe into a sterile evacuated container. Cetuximab will be filtered through a 0.22- μ m protein-sparing or low- protein binding in-line filter. After infusion, 0.9% normal saline will be used to flush the line.

- Premedication with an H₁ antagonist (diphenhydramine 25-50 mg I.V. or oral) 30 minutes prior to infusion should be given for allergic reaction prophylaxis. 50mg should be administered prior to the first dose of cetuximab in an effort to prevent an infusion reaction.
- Four weeks (28 days) constitutes one cycle of treatment. Treatment continues until one of the criteria in Section 5.3 applies.
- If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, the infusion should be stopped and observation for 15 to 60 minutes (depending upon the reaction severity) instituted. Infusion reactions to cetuximab may be severe and can occur during or after treatment. At the physician's discretion, it may be possible to resume treatment by administering an H₂ blocker approximately 30 minutes before restarting the infusion. The addition of an H₂ blocker such as famotidine 20 mg IV is optional. If famotidine is unavailable, administer ranitidine 50 mg IV (not cimetidine due to the risk for drug interactions). Re-attempting infusion at a slower rate, possibly over one hour is appropriate. Additional treatment of severe allergic reactions is at the discretion of the treating physician and may include corticosteroids as well as other agents.
- As a routine precaution, patients enrolled in this study will be observed closely for any potential adverse events by the medical staff for the duration of the cetuximab infusion and until at least 1 hour after the end of the initial infusion, in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. Patients should be instructed to report any delayed reactions to the investigator immediately.
- Details about dose reductions / resumption of therapy on subsequent treatment days are provided in Section 6.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Prohibited Concomitant Medications

Potential for Drug Interactions

Because there is a potential for interaction of ARQ 197 (tivantinib) with other concomitantly administered drugs through the cytochrome P450 system (see Section

2.2.1), the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix D presents an information sheet for patients to alert them and their caregivers of any medication changes.

Since ARQ 197 (tivantinib) is metabolized by CYP2C19 and CYP3A4, a potential for drug-drug interaction exists when ARQ 197 (tivantinib) is co-administered with drugs that are CYP2C19 inhibitors/inducers or strong CYP3A4 inhibitors. Use of such drugs is permissible, but investigators should use caution and be aware that ARQ 197 (tivantinib) exposure may be altered when concomitantly administering these drugs. No additional laboratory tests are required, but it is expected that side effects as listed in this protocol for tivantinib could potentially be more pronounced.

5.2.1.1 Other Investigational Drug Therapies

Patients may not receive any other investigational drugs while on study drug.

5.2.1.2 Anticancer Therapies

No other anticancer therapies may be administered to patients while they are on study drug. These include but are not limited to chemotherapy, radiotherapy, hormonal therapy (except megestrol acetate as supportive care), immunotherapy, or locoregional therapy.

5.2.1.3 Immunosuppressive therapies

Patients may not receive any immunosuppressive therapies while on study drug.

5.2.2 **Permitted Concomitant Medications**

Standard therapies

Standard therapies for concurrent medical conditions are allowed.

5.2.3. Erythropoietin Stimulating Agents (ESA)

Please follow ASCO or MEDICARE guidelines for the use of ESA in patients diagnosed with cancer, drug labels and the Food and Drug Administration (FDA) alerts dated March 9, 2007; November 8, 2007; March 12, 2008; July 31, 2008; and December 2, 2008. **We generally discourage routine use of ESAs and use should be reserved to patients, who are clinically symptomatic.**

Hematopoietic growth factors

ASCO guidelines should be followed for the use of hematopoietic growth factors, including filgrastim or other colony-stimulating factors.

Antiemetics

Prophylactic and supportive antiemetics may be administered according to common practice.

5.2.4. **Precautions, Warnings, and Other Supportive Care Guidelines**

Myelosuppression

Myelosuppression (anemia, neutropenia, febrile neutropenia, thrombocytopenia, leukopenia, and lymphopenia) has been reported in single agent and combination therapy clinical trials of ARQ 197 (tivantinib). Complete blood count should be performed weekly or every other week. Caution is advised when any CYP2C19 inhibitors and/or strong CYP3A4 inhibitors are used as concomitant therapy. More frequent hematology testing and prophylactic use of hematopoietic growth factors is advised according to ASCO guidelines. The incidence of myelosuppression is higher in patients with HCC. Subjects with HCC or patients who experience neutropenia should be monitored more closely throughout the study and follow dose modifications or delays as specified in the protocols.

Bradycardia

Bradycardia has been reported in single agent and combination therapy clinical trials of ARQ 197 (tivantinib). In general, these events were mild to moderate in severity and asymptomatic, and subjects recovered without additional therapy. ARQ 197 (tivantinib) should be used with caution in patients who have or who are at significant risk of developing bradycardia. Pulse will be evaluated on day 1 of the first cycle and on subsequent visits. Additional EKGs should be performed if clinically indicated, especially if significant abnormalities of the baseline or subsequent EKGs are present.

Other

Treatment of emergent toxicities is at the investigator's discretion.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Pregnancy

Patients treated with cetuximab as a single agent will have the opportunity to receive ARQ 197 (tivantinib) after progressive disease (PD) (*see schema at beginning of protocol*).

5.4 Duration of Follow Up

Patients will be followed for any medical issues for a minimum of **8 weeks (6 months)** is recommended) after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. In addition patients will be followed for **survival 5 years post treatment or until death**, whichever occurs first. Information on progression (as defined in this protocol) or death will be collected even if the patient has been removed from the study previously.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

Patients may be discontinued from trial treatment and assessments at any time, at the discretion of the investigator(s). In addition to the above listed criteria additional specific reasons for discontinuing a patient from this trial are:

- patient lost to follow-up (i.e., dropouts)
- protocol non-compliance

If the reason for withdrawal from the trial is the death of the patient, the two options for categorizing withdrawal are either progressive disease or an adverse event (AE). More than one AE may be documented as a reason for withdrawal. Only one event will be captured as the cause of death. Note that death is an outcome and not an adverse event.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported to NCI primarily for the purposes of serious adverse event (SAE) reporting. However, deaths unequivocally related to progression are not SAEs. All subjects who have new or worsening CTC grade 3 / 4 laboratory values (CTCAE 4.0) at the time of withdrawal must have further tests performed and the results recorded appropriately until the lab values have returned to CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions in the subject's medical records. Laboratory abnormalities should **not** be reported as adverse events unless they meet criteria for a SAE, or the laboratory abnormality causes the subject to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

At withdrawal all on-going study-related toxicities and SAEs must be followed until resolution, unless in the investigator estimates that the condition is unlikely to resolve due to the subject's underlying disease.

After withdrawal from treatment, subjects must be followed up for all existing and

new AEs for 30 days after the last dose of ARQ 197 (tivantinib) and/or cetuximab. All new AEs occurring during that period must be reported to NCI and all study-related toxicities and SAEs must be followed up until resolution if possible.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose Level	Tivantinib Dose
Starting Dose	360 mg, po, twice a day
-1	240 mg, twice a day
-2	120 mg, twice a day

Up to two dose reductions are acceptable. Persistent toxicities in spite of two dose reductions will result in discontinuation of therapy.

Event Name	Non-hematological toxicities	
Grade of Event	Management/Next Dose for ARQ 197 (tivantinib)	Management/Next Dose for Cetuximab
≤ Grade 1	Continue therapy	Continue therapy. See 6.2
Grade 2	Continue therapy	Continue therapy. See 6.2
Grade 3*	If at least possibly related to ARQ 197 (tivantinib) and not amenable to an established, rapidly effective treatment**: hold ARQ 197 (tivantinib) until resolution to ≤Grade 2	If at least possibly related to cetuximab and not amenable to an established, readily effective treatment**: hold cetuximab until resolution to ≤Grade 2. See 6.2
Grade 4*	If at least possibly related to ARQ 197 (tivantinib) and not amenable to an established, rapidly effective treatment**: hold ARQ 197 (tivantinib) until resolution to ≤Grade 2	If at least possibly related to cetuximab and not amenable to an established, readily effective treatment**: hold cetuximab until resolution to ≤Grade 2. See 6.2
* Treating Physician to assess relatedness and impact on patient health		
** E.g. adverse events that are readily addressed with additional therapy typically within 24 hours – e.g. pain medication for increased pain or insulin for increase blood glucose level.		
Patients requiring a delay of >2 weeks should go off protocol therapy. Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: <i>For vomiting</i> : antiemetics. <i>For diarrhea</i> : Loperamide antidiarrheal therapy. Dosage schedule: 4 mg first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Event Name	Hematological Toxicities***
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Grade of Event	Management/Next Dose for ARQ 197 (tivantinib)	Management/Next Dose for Cetuximab
Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
≥ Grade 3 neutropenia recovering within 5 days	Withhold ARQ 197 (tivantinib) If ANC recovers to $\geq 1.5 \times 10^9/L$ ($\geq 1500/mm^3$) within 5 days, resume treatment with ARQ 197 (tivantinib) at the same dose level. For subsequent dose delays resume at one dose level lower.**	Continue therapy if deemed appropriate by the treating physician
≥ Grade 3 neutropenia lasting >5 days or ≥ Grade 3 febrile neutropenia	Withhold ARQ 197 (tivantinib) for up to 14 days.* If ANC recovers to $\geq 1.5 \times 10^9/L$ ($\geq 1500/mm^3$) within 14 days, treatment with ARQ 197 (tivantinib) should resume at a dose that is decreased by one dose level for subsequent cycles.** If ANC does not recover to $\geq 1.5 \times 10^9/L$ ($\geq 1500/mm^3$) within 14 days after interrupting ARQ 197 (tivantinib), discontinue administration of ARQ 197 (tivantinib).	Continue therapy if deemed appropriate by the treating physician
Platelet count $< 50 \times 10^9/L$ ($< 50,000/mm^3$)	Withhold ARQ 197 (tivantinib) for up to 14 days. If platelet count recovers to $\geq 100 \times 10^9/L$ ($\geq 100,000/mm^3$) within 14 days, resume treatment with ARQ 197 (tivantinib) at same dose level.* If a second dose delay is required for the same event, then decrease	Continue therapy if deemed appropriate by the treating physician

	ARQ 197 (tivantinib) dose by one dose level for subsequent cycles**. If platelet count does not recover to $\geq 100 \times 10^9/L$ ($\geq 100,000/mm^3$) within 14 days after interrupting ARQ 197 (tivantinib), discontinue ARQ 197 (tivantinib) administration.	
Grade 4 thrombocytopenia	Discontinue administration of ARQ 197 (tivantinib).	Discontinue treatment
*Patients requiring a delay of >2 weeks should go off protocol therapy.		
**Patients requiring > two dose reductions should go off protocol therapy.		
***Felt to be at least possibly related to ARQ 197 (tivantinib) treatment		
Growth factor support with e.g. G-CSF is acceptable as indicated		

6.1 ARQ 197 (tivantinib)

If using the recommended phase 2 dose (RP2D) of ARQ 197 (tivantinib) (360 mg BID), the following dose reductions for toxicity are suggested, in order: 240 mg BID, and 120 mg BID. See **Table 6-1** for a suggested dose modification plan for common toxicities.

Table 6-1: Recommended dose modification plan for ARQ 197 (tivantinib) for toxicity.

Event Grade (NCI CTC V4.02)	Action
Grade 1 or 2	Continue current dose level.
Grade 3 nonhematologic	If at least possibly related to ARQ 197 (tivantinib) and not amenable to an established, rapidly effective treatment*/**: discontinue ARQ 197 (tivantinib) until resolution to \leq Grade 2 Subsequent administration after discontinuation of ARQ 197 (tivantinib) should be at a dose that is decreased by one dose level for subsequent cycles, unless a second dose reduction is required. A maximum of 2 dose reductions is permitted per subject.
Grade 4 nonhematologic	If at least possibly related to ARQ 197 (tivantinib) and not amenable to an established, rapidly effective treatment*/**: discontinue ARQ 197 (tivantinib) until resolution to \leq Grade 2 Subsequent administration after discontinuation of ARQ 197 (tivantinib) should be at a dose that is decreased by one dose level for subsequent cycles, unless a second dose reduction is required. A maximum of 2 dose reductions is permitted per subject.
\geq Grade 3 neutropenia recovering within 5 days	Withhold ARQ 197 (tivantinib) If ANC recovers to $\geq 1.5 \times 10^9/L$ ($\geq 1500/mm^3$) within 5 days, resume treatment with ARQ 197 (tivantinib) at the same dose level.* If a second dose delay is required for the same event, then decrease ARQ 197 (tivantinib) dose by one dose level for subsequent cycles. For a third or fourth dose delay, decrease ARQ 197 (tivantinib) dose by one dose level. A maximum of 2 dose reductions is permitted per subject.
\geq Grade 3 neutropenia lasting >5 days or \geq Grade 3 febrile neutropenia	Withhold ARQ 197 (tivantinib) for up to 14 days. If ANC recovers to $\geq 1.5 \times 10^9/L$ ($\geq 1500/mm^3$) within 14 days, treatment with ARQ 197 (tivantinib) should resume at a dose that is decreased by one dose level for subsequent cycles. *** If a second or third dose delay is required for the same event, then again decrease ARQ 197 (tivantinib) dose from the current dose by one dose level for subsequent cycles. A maximum of 2 dose reductions is permitted per subject. If ANC does not recover to $\geq 1.5 \times 10^9/L$ ($\geq 1500/mm^3$) within 14 days after interrupting ARQ 197 (tivantinib), discontinue administration of ARQ 197 (tivantinib).
Platelet count $< 50 \times 10^9/L$ ($< 50,000/mm^3$)	Withhold ARQ 197 (tivantinib) for up to 14 days. If platelet count recovers to $\geq 100 \times 10^9/L$ ($\geq 100,000/mm^3$) within 14 days, resume treatment with ARQ 197 (tivantinib) at same dose level.* A maximum of 2 dose delays is permitted per subject. If a second dose delay is required for the same event, then decrease ARQ 197 (tivantinib) dose by one dose level for subsequent cycles. If platelet count does not recover to $\geq 100 \times 10^9/L$ ($\geq 100,000/mm^3$) within 14 days after interrupting ARQ 197 (tivantinib), discontinue ARQ 197 (tivantinib) administration.
Grade 4 thrombocytopenia	Discontinue administration of ARQ 197 (tivantinib).

* Treating Physician to assess relatedness and impact on patient health

** E.g. adverse events that are readily addressed with additional therapy – e.g. pain medication for increased pain, or insulin for elevated blood glucose levels

*** Patients requiring a delay of >2 weeks should go off protocol therapy.

6.2 Cetuximab

Cetuximab related toxicities	
Cetuximab Infusion Reaction	<ul style="list-style-type: none"> • Grade 1 (transient flushing or rash, drug fever <38oC): decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. • Grade 2 (rash, flushing, urticaria, dyspnea, drug fever ≥38oC): stop the cetuximab infusion, administer appropriate therapy, and then restart the cetuximab infusion with a decrease in the infusion rate of 50% and monitor closely for any worsening. • Grade 1 or 2 Infusion Reaction manifesting only as a delayed drug fever (starting after the cetuximab infusion): maintain the cetuximab dose and infusion rate and consider administering acetaminophen or cyclooxygenase-2 inhibitors (at the dose and schedule of the investigator’s discretion) prior to the subsequent cetuximab infusion, if not otherwise contraindicated in the patient. • A grade 3 reaction consists of: symptomatic bronchospasm with or without urticaria, requiring parenteral medication(s); allergy-related edema/angioedema; hypotension. • A grade 4 reaction (anaphylaxis) is a life-threatening event characterized by rapid onset (often within minutes) of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. • Treatment of a Grade 3 or 4 Infusion Reaction: Stop the cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. • Following a grade 3 or 4 infusion reaction, the patient is to receive no further cetuximab treatment. In the event of a grade 1 or 2 infusion reaction, the cetuximab infusion rate should be permanently reduced by 50%. • Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further therapy. Appropriate medical therapies include epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen . Patients should be carefully observed until the complete resolution of all signs and symptoms.
Hypomagnesemia	<p>The incidence of hypomagnesemia (both overall and severe [NCI CTC grades 3 & 4]) is increased in patients receiving chemotherapy and cetuximab as compared with those receiving chemotherapy alone based on controlled clinical trials. Patients receiving cetuximab therapy should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment.</p>
Drug Fever	<p>In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.</p> <p>If a patient experiences isolated drug fever, for the next dose, pre treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours</p>

	<p>after cetuximab infusion. The infusion rate will remain unchanged for future doses.</p> <p>If a patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.</p>
Skin toxicities	<p>Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.</p> <p>If a patient experiences severe acneform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.</p> <p>Management guidelines for treatment of skin toxicities are well established including antibiotics and topical therapies. An overview is provided in Appendix E.</p>

Dose levels for cetuximab are as follows. Dose modifications are typically a result of skin toxicities, but at the discretion of the principal investigator other grade III/IV toxicities may also lead to a dose reduction if felt to be appropriate:

Cetuximab Dose Levels

	Every other week cetuximab dose
Starting dose	500 mg/m²
Dose Level -1	400 mg/m ²
Dose Level -2	250 mg/m ²

There will be no dose level reductions below a dose of 250 mg/m² every other week. An exception can be made if weekly (rather than every other week) dosing is felt to be beneficial, and may be attempted.

Management of Dermatologic Toxicity			
Grade	Cetuximab	Outcome	Cetuximab Dose Modification
Acneform Rash			
1st occurrence	Delay next infusion 1 to 2 weeks (per treating MD)	Improvement	Continue at 250 mg/m ²

		No Improvement	Discontinue cetuximab
2nd occurrence	Delay next infusion 1 to 2 weeks (per treating MD)	Improvement	Reduce Dose Level -1
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay next infusion 1 to 2 weeks (per treating MD)	Improvement	Reduce to Dose Level -2
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

7.1.1 CAEPRs for ARQ 197 (tivantinib) and Cetuximab

7.1.1.1 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/adverse_events.htm for further clarification. *Frequency is provided based on 756 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, 2016¹

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		<i>Anemia (Gr 3)</i>
CARDIAC DISORDERS			

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%)	
	Sinus bradycardia		
GASTROINTESTINAL DISORDERS			
	Diarrhea		<i>Diarrhea (Gr 2)</i>
	Nausea		<i>Nausea (Gr 2)</i>
	Vomiting		<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			<i>Fatigue (Gr 2)</i>
INVESTIGATIONS			
	Lymphocyte count decreased		
	Neutrophil count decreased		<i>Neutrophil count decreased (Gr 4)</i>
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<i>Anorexia (Gr 2)</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Palmar-plantar erythrodysesthesia syndrome	
	Rash maculo-papular		<i>Rash maculo-papular (Gr 2)</i>

¹This 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.

²Infection 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
HEPATOBIILIARY DISORDERS - Bile duct stenosis; Hepatic failure; Portal vein thrombosis
INFECTIONS AND INFESTATIONS - Infection²
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.

7.2 Adverse event list(s) for commercial agent (Cetuximab)

Please also refer to the package insert form the comprehensive list of adverse events.

- Common, very likely (> 10 %)

Acneiform rash, asthenia/malaise, fever, nausea, constipation, diarrhea.

- Less likely (2 to 10 %)

Infusion reaction, kidney failure, sepsis, dehydration.

- Rare (1% or less)

Dermatology toxicity, interstitial lung disease, pulmonary embolus

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the

CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **‘Expectedness’**: AEs can be ‘Unexpected’ or ‘Expected’ (see Section 7.1 above) for expedited reporting purposes only. ‘Expected’ AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).
- **Attribution** of the AE:
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

For protocols with CAEPRs not including a “SPEER” category, protocol-specific exceptions to the CTEP-AERS reporting table can be found in the CAEPR’s “ASAEL” category instead. This protocol-specific exception is limited to Grade 1 and Grade 2 ASAEL events, *i.e.* Grade 3 through Grade 5 ASAEL-listed events are NOT exceptions to CTEP-AERS reporting.

- 7.4.1 Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP Web site (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” which can be downloaded from the CTEP Web site (<http://ctep.cancer.gov>). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- 7.4.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.4.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting

regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

*Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (incl. cysts and polyps) - Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.*

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

<p>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:</p> <ol style="list-style-type: none"> 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). 				
<p>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.</p>				
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		
<p>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</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ “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. 				

¹Serious 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

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.6 Secondary Malignancy

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE 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.

7.7 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents

administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent

8.1.1 ARQ 197 (tivantinib) (NSC 750832)

Chemical Name:

(-)-*trans*-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, Tivantinib

Classification: c-Met inhibitor

CAS Registry Number: 905854-02-06

Molecular Formula: C₂₃H₁₉N₃O₂

M.W.: 369.43

Mode of Action: c-Met inhibitor ARQ 197 (tivantinib) 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.

Description: White/off-white to yellow microcrystalline powder.

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: Store at controlled room temperature (20-25°C) with excursions allowable to 15-30°C).

Stability: Shelf-life surveillance of the intact bottles is ongoing.

Route(s) of Administration: Oral. Administer ARQ 197 (tivantinib) tablets with food, and advise patients to take tablets with water and swallow them by mouth. It is acceptable per the manufacturer (Daiichi Sankyo) to crush the tablet as long as it is taken orally. The tablets are to be crushed and mixed with water immediately prior to taking the dose.

Information about administration via G-tube may become available, but at the time of this protocol version has not been approved by the manufacturer (Daiichi

Sankyo). A note will be sent out should administration per G-tube or other changes to the administration become available, and no protocol amendment will be made.

Method of Administration: tablet

Potential Drug Interactions: ARQ 197 (tivantinib) 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 may markedly increase the plasma concentration of ARQ 197 (tivantinib) . Drugs and substances which inhibit CYP3A4 may increase the plasma concentrations of ARQ 197 (tivantinib). (Refer to:

<http://medicine.iupui.edu/flockhart/table.htm>)

Availability

ARQ 197 (tivantinib) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

ARQ 197 (tivantinib) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 ARQ 197 (tivantinib) Ordering and Agent Accountability

8.1.2.1 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.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<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..

For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

- 8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

8.2 Cetuximab (commercial)

Other names: Erbitux, C225

Mode of action: inhibitor of EGFR tyrosine kinase.

Cetuximab is an FDA approved commercially available drug for head and neck cancer. Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

Supplier/How Supplied

The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

Cetuximab will be obtained commercially and supplied via the respective pharmacy/established channel for each participating center.

Packaging and Labeling

Cetuximab for injection will be obtained commercially in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product.

Handling and Dispensing of Cetuximab

Cetuximab must be dispensed by authorized personnel according to local regulations. Cetuximab should be stored in a secure area according to local regulations.

Storage Requirement/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F).

Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

Preparation and Administration

Cetuximab must not be administered as an IV push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22- micrometer in-line filter. Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. **DO NOT SHAKE OR DILUTE.** Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with cetuximab.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
-
- Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line. Following the cetuximab infusion, a 1-hour observation period is recommended.

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place.

Otherwise, opened vials must be returned to BMS for disposal. For questions regarding cetuximab destruction please contact BMS at 866 339-4267 or 203 677-7017.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product. It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

→ **For additional information please refer to the FDA approved package labeling for cetuximab.**

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies: c-MET copy number / c-MET expression (IHC)

1. Prior experience with c-MET related biomarkers

The phase II randomized study of ARQ 197 (tivantinib) in NSCLC identified c-MET copy number as a strong biomarker of ARQ 197 (tivantinib) benefit ([Sequist, Schiller et al, ESMO, 2010](#)).

The phase II randomized study of MetMab (antibody fragment against the c-MET receptor) demonstrated that benefit of MetMab was limited to tumors with c-MET expression using a standardized and centralized IHC methodology ([Spigel et al, ESMO, 2010](#)).

2. Hypothesis

Targeted agents typically only show activity/benefit in a subgroup of patients. Identification of a predictive biomarker greatly improves the effect size for a subsequent trial and increasingly is considered a requirement for drug approval.

c-MET genetic changes correlate with responsiveness in preclinical models (namely amplification, [Smolen et al, PNAS 2006](#)).

Furthermore protein expression (IHC) may be a valid marker and was shown in a clinical trial in lung cancer to correlate with benefit ([Spigel et al, ESMO 2010](#)). High expression levels are hypothesized to indicate a dependence of the tumor on the respective receptor.

3. Intended use within the proposed study

We intended to retrospectively validate the biomarkers outlined below including those suggested in the above two NSCLC studies in our patient population of HNC patients.

1. **c-MET immunohistochemistry**
2. **c-MET copy number**
3. evaluation for c-MET SNPs/mutations *
4. evaluation of copy number or mutations in c-MET related molecules including those hypothesized to cause resistance to c-MET inhibition*

5. evaluation of signatures of c-MET sensitivity/resistance using DNA and or RNA and or protein*
6. Blood will be used to extract DNA (from white cells). This DNA will be used to compare identified mutations/copy number changes

***Items 3.-5. are optional - pending additional funding from a pending grant submission**

4. Assay method's validity and appropriateness for the study

Candidate Biomarker 1: c-MET IHC

Immunohistochemistry has been shown to have predictive potential in a study of MetMab in NSCLC patients (*Spigel et al. ESMO 2009*). We have extensive experience with c-MET IHC methodology and implement the test using identical methodology (antibody and conditions) to allow comparable results. Briefly we will employ the Ventana CONFIRM c-MET antibody (Catalog Number: 790-4430) using conditions as described in (*Tretiakova et al, J Environ Pathol Toxicol Oncol 2011*)

Candidate Biomarker 2: c-MET copy number

For copy number assessment we will extract tumor DNA from areas of tumor with $\geq 60\%$ tumor content and evaluate MET copy number by quantitative PCR. We may consider c-MET FISH as an alternative and have experience with both methodologies, which in our experience provide comparable results for higher copy number changes (*Seiwert et al, Cancer Research 2009*).

Hypothesis forming additional biomarker analyses:

In addition we will analyze in an exploratory fashion focusing on treatment responders c-MET sequence variations (mutations/SNPs) in the kinase/semaphorin/juxtamembrane domain of the c-MET gene, sequence or copy number variations in c-MET related genes/proteins, expression profiles or signatures e.g. expression of the sole ligand of c-MET (hepatocyte growth factor/HGF), and erbB family members (e.g. amphiregulin, heregulin) (*Seiwert et al, Cancer Research 2009*). These analyses will be descriptive in nature and hypothesis forming. Normal DNA will be obtained from blood in order to assess somatic versus germline changes. Appropriate controls from non-responders may be selected. Analyses of these additional biomarkers as well as the parts of the specific methodologies are depending on additional funding from a pending grant application.

9.2 Laboratory Correlative Studies

9.1.1 Tissue and Blood collection

9.1.1.1 Collection of Specimen

Previously obtained cancer tissue from biopsies or resections will be used or alternatively a new biopsy of the tumor may be performed if clinically justified.

Tissue will be used for c-MET IHC staining. A minimum of 10 slides is required per patient (14 recommended).

Each participating site is to ascertain availability of 17-20 five to ten micrometer thickness unstained slides that can be used for immunohistochemistry. Availability of tumor containing slides is required for participation in the trial. If fewer than 10 slides are available an exception can be considered per the PI (T.Seiwert); please contact him for approval (tseiwert@medicine.bsd.uchicago.edu).

9.1.1.2 Handling of Specimens(s)

- 10-14 slides **5 μ m** thick, cut with a clean blade (use new blade if possible or clean vigorously to avoid RNA/DNA, RNase contamination)

Slides should be usable for immunohisto-chemistry and/or DNA/RNA extraction. Review for presence of tumor is required prior to shipment at the local center.

9.1.1.3 Blood:

9.1.1.3.1 DNA Samples:

DNA Samples (pharmacogenomic sample) need to be drawn in plastic purple top vacutainers and will be used for isolation of normal DNA for validation and comparison of tumor related findings.

-> Two 7-10cc EDTA purple top tubes (plastic), BD#366643 (K2) (use of comparable tubes from the local institution is acceptable)

9.1.1.3.2 Serum Samples (pharmacogenomic sample) need to be drawn in plastic purple top vacutainers and blood for isolation of normal DNA in SST gold tops using the order numbers listed below. Use of other types of tubes needs to be confirmed with the PI/Mary Jo Fekete (see contact info below)

- Two 10cc EDTA purple top tubes (plastic), BD#366643 (K2) (serum)

- One 7.5cc SST gold top (BD#367987) tube (blood).

1. The SST tube(s) must remain at room temperature for 30-60 minutes to clot, please invert tube 5x during this time
2. Spin tube at 1300g for 10 minutes at Room Temperature
3. Aliquot the serum evenly into cryovials (~0.5ml each)
4. Samples should be labeled with institution, protocol number (NCI 9165), patient initials, patient study ID number, and date of draw
5. Store Cryovials at -80C until shipping on dry ice at a later date

Use of other types of vacutainers needs to be confirmed with the PI/ Mary Jo Fekete (see contact info below). Use of red top vacutainers is acceptable in place of gold top vacutainers.

Blood samples can be collected in batches, stored frozen at -80C, and subsequently shipped in batches.

9.1.1.4 Shipping of Specimen(s)

Slides:

Slides are to be packaged in a slide box with appropriate padding and are to be shipped out per courier service (FedEx, UPS, or comparable) to the shipping address below:

Bood (Blood):

DNA Samples (pharmacogenomic sample) need to be drawn in SST/gold top vacutainers / **serum sample** need to be drawn in purple top vacutainer. Both sample types need to be shipped on dry ice (EDTA/SST tops will not be supplied by University of Chicago and the following order numbers should be used: BD # 366643 EDTA (K2) purple top (serum samples), BD # 367987 SST 7.5 mL). The samples may be batched at institution and shipped to the address below. These samples should be shipped on Monday, Tuesday, or Wednesday and **cannot be shipped on Friday**. The shipping address is:

University of Chicago
HTRC, Room P-616
5835 S. Cottage Grove
Chicago, IL 60637
Phone: 773-834-8391
E-mail: tissuebank@bsd.uchicago.edu

Cost of packaging and shipment cost, as well as procurement of shipping materials and courier service shipping supplies are the responsibility of each center and appropriate internal budgeting is mandatory for participation in this trial. A reference sheet outlining summarizing appropriate shipping procedures will be provided to each center.

A sample collection form is provided in **Appendix C**.

On arrival, each sample will be assigned a **Study Number**. All subsequent handling of the tissue samples will be blinded to the investigators performing various tests, except for the clinical pathologists. Only biopsy samples determined by the pathologist to contain tumour will be subjected to immunohistochemical analysis. For all immunohistochemical studies, samples will only be marked with an assigned study number. Patient name, diagnosis and other information will be unknown to the laboratory/clinical investigators involved and will be revealed only after studies are completed for further data analysis and statistics.

9.1.1.5 Site(s) Performing Correlative Study: The University of Chicago

10. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

Baseline evaluations are to be conducted within 16 days prior to start of protocol therapy. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11 and every 2 weeks thereafter	Wk 12	Off Study ^c
ARQ 197 (tivantinib)		A------(given twice daily)-----A												
Cetuximab		B		B		B		B		B		B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X-----X												
Physical exam	X	X		X		X				X		every 4 wks		X
Vital signs	X	X		X		X				X		x		X
Height	X													
Weight	X	X		X		X		X		X		x		X
Performance status	X	X		X		X				X				X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Research Blood draw	X													
Serum chemistry ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG (at baseline then as indicated)	X	X												
Adverse event evaluation		X-----X												X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every 8 weeks.												X
B-HCG	X ^b													
Unstained slides of tumor	X													

A: *ARQ 197 (tivantinib)*: Dose as assigned; *po twice daily*
B: *Cetuximab*: Dose as assigned; *every two weeks*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.
Starting week 5 – MD visits are only required every 4 weeks, unless more frequent visits are medically indicated.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be reevaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-6

weeks following initial documentation of objective response. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (*Eisenhauer EA et al, Eur J Ca, 2009*). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ARQ 197 (tivantinib)/ cetuximab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, and have **received any study drug**, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below (see 13.5.2). (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.).

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have **received any study drug**, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If such lesions show evidence of tumor progression / have known disease they should be included and measurement attempted.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to

characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, 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 be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined 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 (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not

be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought

to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 **Evaluation of Best Overall Response**

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-	No	PR	

	CR/Non-PD/not evaluated			
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration.</i>” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
<p>* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised</p>		

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death of any cause.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

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. Instructions for submitting data using the CDUS can be found on the CTEP web site (<http://ctep.cancer.gov>). **Note:** All adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center or to the Lead Organization on the study quarterly. The date for submission to the Coordinating Center or to the Lead Organization will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.1.1). For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- *The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.*
- *Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.*

12.3 Collaborative Agreements Language

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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

We are targeting two patient populations based on distinct clinical needs:

This trial will enroll patients who are cetuximab naïve (palliative setting). Typically patients will have been treated with cytotoxic chemotherapy in the first line setting and would be considered for cetuximab single agent therapy. Such patients will be randomized between cetuximab and the combination of ARQ 197 (tivantinib) /cetuximab. This patient population would be analogous to the patient population that was used in the two c-MET inhibitor NSCLC studies that met their primary endpoints (ARQ 197 (tivantinib) ([Sequist et al](#))/ MetMab ([Spigel et al](#))).

Patients who have failed treatment with cetuximab as part of the control arm have the option to receive tivantinib as a single agent. This patient population generally has a very poor prognosis and effective therapies are lacking. Patients who have failed EGFR based therapy (in the recurrent / metastatic setting) typically have a progression-free survival of only 1.8 months (based on data from a historical phase II network study cohort – [DeSouza et al, Clinical Cancer Research, 2012](#)). Such patients have either primary or secondary (acquired) EGFR resistance. We hypothesize based on pre-clinical evidence that c-MET signaling (analogous to data for NSCLC) serves as an “exit” pathway and is a key component in mediating EGFR resistance.

Primary Endpoint: Response Rate

We will compare in the cetuximab/ ARQ 197 (tivantinib) combination with single agent activity of cetuximab..

Secondary Endpoints/Analyses:

a) Continuous tumor shrinkage

b) PFS

c) OS

d) Endpoints a), b), and c) above, as well as response rates, will be assessed and compared between treatment arms in the subgroup of patients with high c-MET expression (anticipated to be ~84% of patients ([Seiwert et al, Cancer Research,](#)

2009), and/or high c-MET copy number (anticipated >10% and largely overlapping with MET IHC (*Seiwert et al, Cancer Research, 2009*)).

e) Single agent activity of ARQ 197 (tivantinib) after failure of cetuximab (descriptive)

13.2 Sample Size/Accrual Rate

We expect to jointly enroll 3-6 patients per month for a total of 76 response evaluable patients (38 patients in each arm) over a period of 18-24 months. Patients will then be followed for at least 6 months.

Comparison of combination arm with single agent cetuximab: Response rates in the two arms will be compared using a continuity-corrected chisquare test. A sample size of n=38 patients per arm will provide 80% power to detect a difference of 12% vs. 35% between the cetuximab and combination treatment arms, using a one-sided test at the alpha=0.10 significance level.

Effect Size: We are assuming a comparably large effect size based on the following rationale:

- Preclinical data suggests high expression levels of MET and EGFR (higher than e.g. for NSCLC) as well as strong synergy for combined inhibition (see above).
- The relatively poor response rate for cetuximab alone (10-13%) masks that many more patients (40%) experience SD and oftentimes experience minor tumor shrinkage. By improving inhibition of an EGFR parallel pathway and achieving synergistic tumor inhibition we expect a substantial proportion of SD assessments to convert to responses.
- The response rates for cytotoxic chemotherapies are generally in this range and it is appropriate that an effective targeted therapy (with most head and neck SCCs expressing both relevant targets) would be similarly effective.
- As a secondary outcome measure we will evaluate continuous tumor shrinkage, which will increase power and allow us to detect a smaller difference.
- Furthermore as a secondary outcome we will evaluate PFS. We are not adequately powered to use PFS as a primary outcome given the sample size limitation. Nevertheless a PFS trend/signal comparable to NSCLC data would provide support to consider further evaluation in a follow-up study and the design would be straightforward given the data from this study to pick the optimal treatment and clinical setting.

Early evaluation for toxicity: For safety evaluation we have scheduled an interim safety evaluation after treatment of 3 and 6 patients with the combination of ARQ 197 (tivantinib) /cetuximab. If less than 2 of 6 patients experience severe toxicities / “DLTs”, the trial will continue, although we will continue to monitor adverse events per standard AE evaluation and reporting guidelines.

Early evaluation for futility:

An interim look for futility will be performed at the time when half of the patients (14 per arm) have been randomized and evaluated for response. If the observed response rate in the combination arm is no higher than in the single agent group, early termination will be considered. This will result in a small power loss of < 2% (*Weiland and Therneau, Cont Clin Trials, 1987*).

13.3 Stratification Factors

Patients will be stratified based on HPV status. Any commonly used HPV test is acceptable (e.g. p16 IHC, HPV ISH, etc). If HPV status is not available, slides can be sent to the University of Chicago and HPV testing will be performed. No interim monitoring or efficacy analysis will be done based on this stratification. The goal is primarily to ascertain comparability between the two treatment arms. Please note that p16 IHC is generally only considered accurate if performed in oropharyngeal tumors and retesting in other anatomic sites may be necessary.

13.4 Analysis of Secondary Endpoints

Secondary endpoints will include change in tumor burden (sum of longest diameters of target lesions) from baseline to 8 weeks, PFS, and OS. Early change in tumor burden will be compared between groups using two-sample t-tests. Waterfall plots will be constructed for graphical comparison. In the event that early deaths within 8 weeks or dropouts occur, nonparametric Wilcoxon rank-sum tests will be performed in place of t-tests, with such patients assigned the worst ranking (*Karrison et al, JNCI, 2007*). Kaplan-Meier curves will be generated for PFS and OS and the treatment arms compared via logrank tests. We will also fit logistic and Cox (JRSS, 1972) proportional hazards regression models to examine the effects of laboratory correlates on response, PFS, and OS.

Finally, each of the primary and secondary endpoints will be compared between treatment arms among the subgroup of patients with high c-MET expression and/or high c-MET copy number in an exploratory fashion.

13.5 Reporting and Exclusions

13.5.1 **Evaluation of toxicity** – All patients will be evaluable for toxicity from the time of their first treatment with ARQ 197 (tivantinib)/ Cetuximab. (also see 11.1.1).

13.5.2 **Evaluation of response** – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible unless they are not evaluable as defined under 11.1.1.

Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication (see 11.1.1)) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible, response evaluable patients (see 11.1.1). Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

13.6 Randomization

Patients will be randomized after eligibility and stratification status are known between the two treatment arms (TC and C arms). Randomization is not blinded.

Randomization will use the method of permuted blocks, stratified by HPV status. Randomization will be done at the University of Chicago and investigators are to contact **773-834-3095** or e-mail jzavala@medicine.bsd.uchicago.edu

to find out treatment arm assignment. The trial will randomize sufficient patients in order to obtain 76 evaluable patients.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review. Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug

Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
 - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
 - The Coordinating Center must be designated on the title page.
 - Central registration of patients is required. The procedures for registration must be stated in the protocol.
 - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
 - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
 - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C

Tissue Sample Collection Form
NCI 9165: ARQ 197 (tivantinib)/Cetuximab -- HNC

Clinician/Research Nurse: Please Fill Out	
<u>Tissue Samples</u>	
Patient Name: _____	MRN# (if applicable): _____
Patient Protocol ID #: _____	Date Tissue Obtained: _____
Institution: _____	Attending Physician: _____
Site of Biopsy: _____	Site of Primary Tumor: _____
Did Surgical Pathology review tissue for presence of tumor (please circle)? Yes No	
Number of unstained slides (10-14 slides (5 µm thick),)	
Number of 5 µm slides: _____	
Blood collection (please check):	
Two EDTA tubes (purple top, serum), 2x10ml: ____ (e.g. BD#366643 EDTA (K2)) or similar	One SST tube 7.5ml (gold top): _____ (e.g BD#: 367987 SST, 7.5ml) or similar_ (If volume is <7.5ml provide additional tube/s)__
Date of blood draw: _____	Time of blood draw: _____
Contact Person's Phone Number and email Address at Affiliate:	

Shipment Address:

University of Chicago
HTRC, Room P-616
5835 S. Cottage Grove
Chicago, IL 60637
Phone: 773-834-8391
E-mail: tissuebank@bsd.uchicago.edu

Please notify Mary Jo Fekete with the tracking number once the sample was shipped:

Email: mfekete@bsd.uchicago.edu
Tel: 773-834-4593

Disclaimer: Cost of packaging and shipment cost, as well as procurement of shipping materials and courier service shipping supplies are the responsibility of each center and appropriate internal budgeting is mandatory for participation in this trial. A reference sheet outlining summarizing appropriate shipping procedures will be provided to each center.

APPENDIX D:

INFORMATION ON POSSIBLE INTERACTIONS WITH OTHER AGENTS FOR PATIENTS AND THEIR CAREGIVERS AND NON-STUDY HEALTH CARE TEAM

The patient _____ is enrolled on a clinical trial using the experimental agent ARQ 197 (also known as tivantinib). This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

ARQ 197 (tivantinib) interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet.** These are the things that you and they need to know:

ARQ 197 (tivantinib) interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is/are Cytochrome P450 CYP 2C19 and to a lesser degree CYP 3A4, and ARQ 197 (tivantinib) is broken down by this enzyme in order to be cleared from your system.
- ARQ 197 (tivantinib) must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
 - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of Cytochrome P450, CYP 2C19
- Your prescribers should look at this web site <http://medicine.iupui.edu/clinpharm/ddis/table.asp> or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

and he or she can be contacted at

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent _____ . This clinical trial is sponsored by the NCI.

_____ interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a specific liver enzyme called **CYP_____**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP_____**."
- Before prescribing new medicines, your regular prescribers should go to <http://medicine.iupui.edu/clinpharm/ddis/table.asp> for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

APPENDIX E

Management of Cetuximab induced acneiform rash

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious complications.

Treatment of acneiform rash should be initiated early starting with grade 2. Dose modifications of any future cetuximab infusions are listed in the protocol and should be considered for severe (grade 3/4) acneiform rash.

Rash can be managed by a variety of treatment options to relieve symptoms and improve rash. The recommendations for management are as follows:

—> Grade 1 rash: Mild, Grade 1 rash may not need treatment, but close monitoring is to be initiated to .

—> Grade ≥ 2 rash: May be treated with any of the following:

- Minocycline/doxycycline
- Diphenhydramine
- topical retinoid
- topical clindamycin
- topical silver sulfadiazine

APPENDIX F

PATIENT'S MEDICATION DIARY

Agent: ARQ 197 (Tivantinib)

CTEP-assigned Protocol # _____
Local Protocol # _____

Today's date _____

Patient Name _____ (initials acceptable)

Patient Study ID _____

1. Complete one form for each cycle of treatment.
2. **ARQ 197 (Tivantinib)** should be stored at room temperature.
3. **ARQ 197 (Tivantinib)** tablets should be administered orally with meals. A missed or vomited dose should not be replaced, thus should take the next scheduled dose at the regularly scheduled time.
4. Record the date, the time, and the number of **ARQ 197 (Tivantinib)** capsules taken per day (2 administrations/day).
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of **ARQ 197 (Tivantinib)** when you return for each appointment.

Day	Date	Time of First Dose	Dose taken	Time of Second Dose	Dose taken	Comments
			# of capsule taken		# of capsule taken	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient's Signature: _____

Cycle: _____

Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of capsules taken this Month _____
5. Cycle Number _____
6. Physician/Nurse/Data Manager's Signature _____