Phase II Study of Docetaxel and Capecitabine in Advanced Squamous Cell Carcinoma of the Head and Neck

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ABSTRACT

Title: Phase II Study of Docetaxel and Capecitabine in Advanced Squamous Cell Carcinoma of the Head and Neck

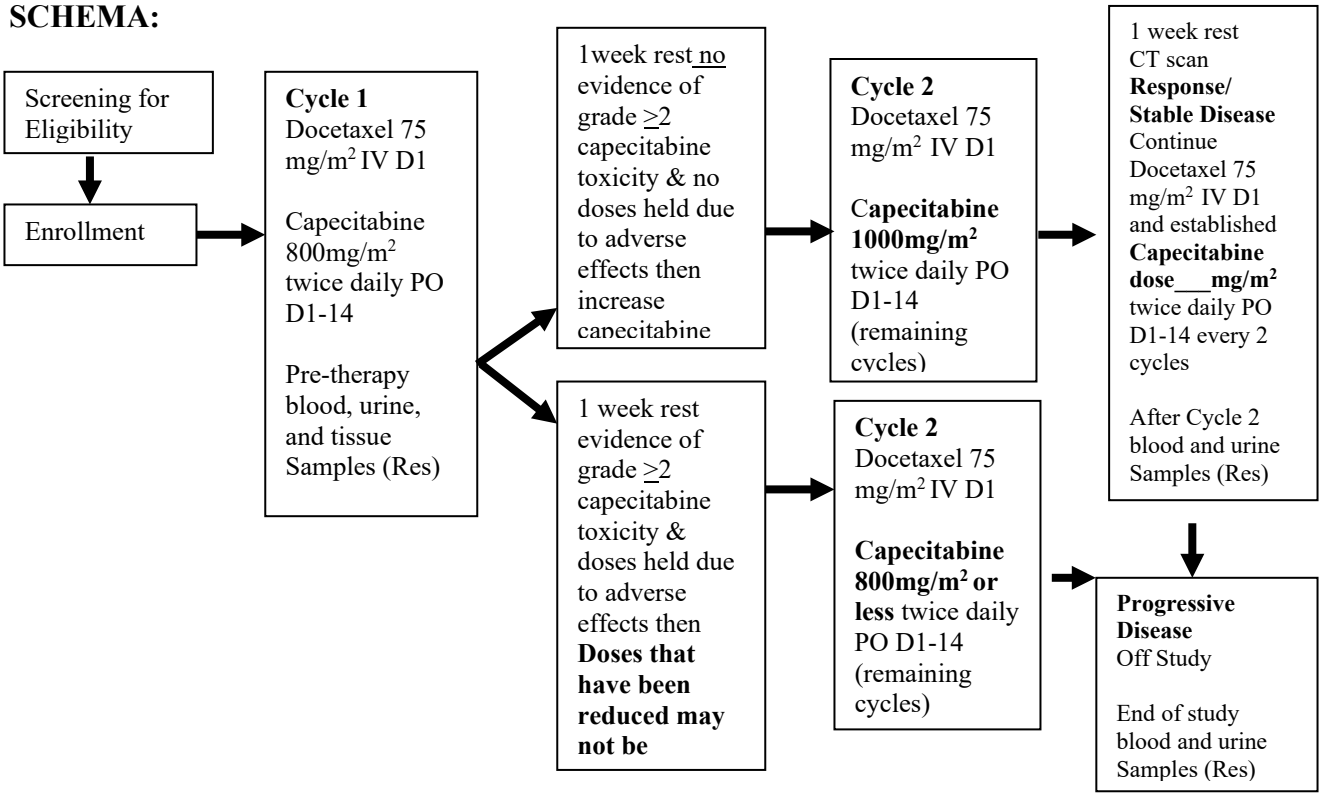
Objectives: To assess the safety and efficacy of the combination of docetaxel and capecitabine in subjects with advanced squamous cell carcinoma of the head and neck who are not candidates for surgery or radiation therapy.

Eligibility: Subjects with histologically proven squamous cell carcinoma of the head and neck with measurable disease that is either recurrent after attempted cure with surgery and/or radiation therapy or newly diagnosed disease with distant metastases or incurable at diagnosis are eligible. Subjects must not have received prior cytotoxic chemotherapy for metastatic squamous cell carcinoma of the head and neck. Subjects who have received chemotherapy as part of a multi-modality curative approach for head and neck cancer will be eligible as long as they have not received either medication (or 5-FU) as part of that regimen. Subjects who have received single agent immune checkpoint inhibitors for metastatic head and neck squamous cell cancer will be eligible.

Intervention: Subjects will receive study treatment with docetaxel 75 mg/m^2 IV on day 1 in combination with oral capecitabine 800mg/m^2 twice daily, from days 1-14 of a 3-week cycle. If there is no evidence of grade 2 or greater toxicity with capecitabine and if the doses of capecitabine are not held due to adverse effects after the first cycle, then the dose of capecitabine will be increased to 1000 mg/m^2 twice daily for the remaining cycles. Treatment will be continued till progression or toxicity.

Evaluation: Subjects will be evaluated every two cycles with imaging studies and clinical evaluation. Subjects with progressive disease will come off study. Subjects with stable or responding disease will continue on study with another evaluation at the end of every two cycles till progression.

SCHEMA:



1.0 Objectives

1. To evaluate in a Phase II study the efficacy (the radiographic assessment of disease status after 2 cycles of therapy) of a combination of docetaxel and capecitabine in subjects with advanced squamous cell carcinoma of the head and neck who are not candidates for surgery or radiation therapy.
2. To evaluate the safety and toxicities of docetaxel and capecitabine in subjects with advanced squamous cell carcinoma of the head and neck.
3. To descriptively examine the effects of the combination of docetaxel and capecitabine on the quality of life of subjects with advanced squamous cell carcinoma of the head and neck.

2.0 Introduction

Cancer of the head and neck refers to a collection of cancers, predominantly squamous cell carcinoma, arising from a variety of sites namely, the oral cavity, (lips, buccal mucosa, anterior tongue, floor of the mouth, hard palate, upper gingiva, and lower gingival), pharynx, larynx, nasal cavity and the paranasal sinuses (maxillary, ethmoid, sphenoid, and frontal sinuses) and major (paired parotids, submandibular, and sublingual) and minor salivary glands. There are approximately 600,000 cases of squamous cell carcinoma of the head and neck (SCCHN) diagnosed annually worldwide, of which approximately 52,000 cases are in the United States. It is estimated that in 2012 there will be 52,610 new cases of squamous cell carcinoma of the

head and neck and 11,500 deaths from the disease[1]. Despite advances in diagnosis and treatment, there have been only small improvements 5-year survival rate for these cancers[2].

Patients who present with advanced stage, unresectable disease have a 5-year survival rate of 30% as compared to 60-98% 5-year survival rates in patients who present with early stage disease[3]. With the recent advances in the management of locally advanced SCCHN, due to better loco-regional control, the proportion of patients with distant metastases appears to be increasing as compared to those with loco-regional relapse, i.e. reverse-failure pattern[4,5]. The risk of distant metastases appears to be in patients with a large primary (T4) and more advanced lymph node disease (N2-3)[5]. Also, while standard therapy for early stage head and neck cancer has been surgery or radiation therapy with curative intent, the prognosis with this approach is quite poor in patients with unresectable primary disease, with <30% patients being cured. The majority of patients will die of local or regionally persistent or recurrent disease[6] and re-resection and/or re-irradiation may not be suitable options. Also, nearly two thirds of patients present with advanced (stage III and IV) disease[7], and therefore are at a higher risk of developing metastatic disease.

The goal of treatment of metastatic or recurrent SCCHN is mainly palliative. Therapy usually involves a platinum based regimen. Cisplatin or carboplatin have been combined with 5-FU to achieve response rates of 20-30% with overall survival of about 5-7 months[8]. Addition of the epidermal growth factor receptor antibody, cetuximab appears to improve the survival to about 10 months[9]. While these data appear promising in the context of metastatic disease, the main problems with platinum based therapy are related to their toxicity. The major toxicities associated with cisplatin include neurotoxicity, nephrotoxicity, and nausea and vomiting, while carboplatin causes myelosuppression. Hence, studies evaluating newer, safer, therapeutic strategies are needed to improve outcomes in this group of patients.

The Keynote-048 study compared survival and disease progression in patients on pembrolizumab monotherapy or pembrolizumab with chemotherapy [EXTREME regimen - platinum and 5-fluorouracil (5-FU)] in previously untreated recurrent or metastatic HNSCC patients [29]. Data presented recently showed pembrolizumab monotherapy improved overall survival (OS) by 39% (p=0.0007) in patients whose tumors expressed PD-L1 (combined proportion score ≥1) compared to chemotherapy. The median OS was 12.3 months vs. 10.3 months with chemotherapy. However response rates with single agent pembrolizumab was less than 20%. When the combination of pembrolizumab with chemotherapy was studied the response rates were only 42% compared to 38% with chemotherapy. Hence, despite the approval of pembrolizumab in the first-line setting, newer regimens need to be investigated. (Ref: 29. Rischin D, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, Psyrri A, Baste N, Neupane PC, Bratland A, Fuereder T, Hughes BGM, Mesia R, Ngamphaiboon N, Rordorf T, Ishak WZW, Zhang Y, Jin F, Gumuscu B, Burtness B. Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). J Clin Oncol 2019;37:15_suppl, 6000.)

Docetaxel: Docetaxel is a taxane that is approved for a variety of solid tumors including lung, breast and head and neck cancer either alone or in combination with platinum agents. As a single agent, it has been shown to be effective against squamous cell carcinoma of the head and neck xenografts[10,11]. It was also active in cell lines relatively resistant to cisplatin, thereby

indicating an absence of cross-resistance[10]. Docetaxel appears to be more cytotoxic in the majority of human primary tumor specimens than paclitaxel[12].

Docetaxel has been studied in various phase II clinical trials in patients with squamous cell cancer of the head and neck and has shown single agent activity ranging from 27-45%[13-16]. Three of these studies used docetaxel 100 mg/m^2 as a one-hour infusion repeated every three weeks[13-15]. In these studies, the main toxicity was neutropenia, but neutropenic fever was not common. In addition, patients developed alopecia, fatigue, anorexia, stomatitis, diarrhea, peripheral neuropathy, and fluid retention. A fourth study used docetaxel at a lower dose of 60 mg/m2 every three weeks, but the response rate obtained was similar to the above studies with acceptable toxicity[16].

5-Fluorouracil (5-FU) in head and neck cancer: 5-FU is routinely used as a radiation sensitizer in the management of head and neck cancer. There have been a few studies evaluating its efficacy as a single agent in the treatment of advanced head and neck cancer. In a randomized phase III study conducted 249 patients with recurrent head and neck cancer were randomized to one of three treatments: cisplatin 100 mg/m^2 on day 1, 5-FU 1gm/m^2 daily from days 1-4, or a combination of cisplatin and 5-FU in the same doses every 3 weeks. They found that when given as a single agent 5-FU had a response rate of 13%. The median survival with 5-FU was similar to that obtained with either cisplatin alone or the combination[17].

Capecitabine: Capecitabine is an orally active cytotoxic prodrug of 5-fluorouracil (5-FU). After oral administration, capecitabine crosses the gastrointestinal barrier intact and is rapidly and almost completely absorbed[18,19]. It is subsequently converted into 5-FU in a three-stage mechanism involving several enzymes. In the first step, it is metabolized into 5'-deoxy-5-fluorocytidine (dFCR) by hepatic carboxylesterase. 5'dFCR is then deaminated into 5'dFUrd by cytidine deaminase mainly localized in liver and tumor tissues. Finally, 5'dFUrd is transformed into 5-FU under the action of thymidine phosphorylase, an enzyme with higher activity in tumor than in normal tissues. Higher levels 5-FU are thus produced within tumors with minimal exposure of healthy tissue to 5-FU[20,21].

This suggests that at least theoretically capecitabine would have a greater activity and lesser systemic toxicity by being concentrated more in the tumor tissues as compared to healthy tissues[22]. In a pharmacokinetic study on 19 patients with colorectal cancers who were undergoing elective resection of either a primary lesion or liver metastases Schuller et al. found a higher concentration of 5-FU in the tumors (both primary and metastatic) than in adjacent healthy tissues[23].

Capecitabine has been studied as a single agent in patients with metastatic head and neck cancer. In a phase II trial of 40 patients who had failed platinum based therapy, capecitabine had a response rate of approximately 24% and the median survival was 7.3 months[24]. Capecitabine appears to be effective in combination with cisplatin as well. In a phase I study Pivot et al treated 21 patients with locally recurrent or metastatic head and neck carcinoma with cisplatin and capecitabine. They had a 14% CR rate and a response rate of 33%[25].

Combination of docetaxel and capecitabine: Preclinical studies in human cancer xenograft models have shown that docetaxel or paclitaxel further up-regulate thymidine phosphorylase in tumor tissues[26]. Co-administration of docetaxel or paclitaxel with capecitabine resulted in synergistic tumor cell killing in a xenograft model[26]. In a trial in women with metastatic breast

cancer, O'Shaughnessy et al., combined docetaxel every three weeks with capecitabine days 1 -14, and reported significantly improved time to progression and survival when compared to treatment with docetaxel alone[27]; however the synergistic effect between docetaxel and capecitabine does not seem to be entirely related to the enhancement of thymidine phosphorylase activity.

A study in human cancer xenograft models evaluated different schedules for the combination of docetaxel and capecitabine in both docetaxel sensitive and less-docetaxel sensitive xenografts[28]. The combination was evaluated in the docetaxel-sensitive MX-1 and MAXF401 human mammary, A755 murine mammary, and the less-docetaxel-sensitive WiDr human colon xenograft. Although synergy was demonstrated in all xenografts, in the breast tumor models, docetaxel administered on day 8 in combination with capecitabine daily for 14 days (days 1 to 14) every 3 weeks had higher antitumor activity than when administered on days 1 or 15. In contrast, in the colon cancer xenograft, docetaxel administered on day 1 demonstrated higher antitumor activity as compared with other days of administration. There was no significant upregulation of thymidine phosphorylase in the MAXF401 and A755 models, and only slight upregulation (1.9-fold) was seen in the MX-1 models, whereas there was significant upregulation (4.8-fold) on WiDr, the only model in which the day-1 combination was superior. Thus for certain tumors, modulation of docetaxel by capecitabine may be more important than capecitabine modulation by docetaxel[29].

The combination of docetaxel and capecitabine has been studied in other solid tumors with reasonable efficacy and toxicity. In a randomized phase III study in pre-treated metastatic breast cancer, the capecitabine (1250 mg/m^2)-docetaxel (75 mg/m^2) combination was found to have a response rate of 32%[30]. However 27% of patients discontinued treatment due to adverse events. In contrast in a prostate cancer study of weekly docetaxel (35 mg/m^2) and a lower dose of capecitabine (650 mg/m^2), the response rate was 68.2% and 87% of patients completed 4 cycles of therapy[31]. The combination of weekly docetaxel and capecitabine was found to have an overall survival that was similar to that seen with the cisplatin-5-FU regimen[32]. Current evidence suggests that if the two agents are to be used in combination, docetaxel should be started at a higher dose while capecitabine should be started at a dose lower than its maximum tolerated dose and if adverse events develop, the dose of docetaxel should be decreased[33].

Since both docetaxel and 5-FU are active agents in squamous cell carcinoma of the head and neck, we will evaluate the efficacy of the combination of docetaxel given every three weeks and capecitabine (prodrug for 5-FU) and determine if the synergy seen in other tumors is present in advanced squamous cell carcinoma of the head and neck.

3.0 Eligibility Criteria

Inclusion criteria:

1. Histologically proven squamous cell carcinoma of the head and neck with measurable disease that is either recurrent after attempted cure with surgery and/or radiation therapy or newly diagnosed disease with distant metastases or incurable at diagnosis.
2. Performance Status: Karnofsky score ≥70 or ECOG 0-2 (See Appendix A).

3. Age 19 years or older (the age of consent in Nebraska); Age 18 years or older (applicable to States where the age of majority is 18).

4. No prior cytotoxic chemotherapy for metastatic squamous cell carcinoma of the head and neck. Subjects who have received chemotherapy as part of a multi-modality curative approach for head and neck cancer will be eligible as long as they have not received either docetaxel or capecitabine (or 5-FU) as part of that regimen. Patients who have received single agent immune checkpoint inhibitors for metastatic disease will be eligible.

5. Adequate pre-treatment bone marrow reserve (WBC count $\geq$3,500/mm^3, platelet count $\geq$100,000/mm^3).

6. Adequate renal function (serum creatinine less than 1.5 times the upper limits of normal).

7. Adequate hepatic function (serum AST and ALT less than 1.5 times the upper limits of normal, serum alkaline phosphatase less than 2.5 times the upper limits of normal, serum total bilirubin is less than or equal to the upper limits of normal).

8. PT or INR, and PTT $\leq$ 1.5 x upper limit of normal unless subject is receiving anticoagulants. If the subject is on anticoagulation therapy, levels should be within therapeutic range.

9. Women of reproductive potential must be non-pregnant and non-nursing and must agree to employ 2 effective methods of birth control throughout the study and for up to 6 months following treatment.

10. Women of child-bearing potential must have a negative pregnancy test within 7 days of initiating study. *(No childbearing potential is defined as age 55 years or older and no menses for two years or any age with surgical removal of the uterus and/or both ovaries)*.

11. The subject must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.

Exclusion criteria:

1. Prior cytotoxic chemotherapy for metastatic squamous cell carcinoma of the head and neck. Subjects who have received chemotherapy as part of a multi-modality curative approach for head and neck cancer will be eligible as long as they have not received either docetaxel or capecitabine (or 5-FU) as part of that regimen.

2. Patients who have received chemotherapy in combination with immunotherapy for metastatic disease.

3. Allergy to either of the study medications or 5-fluorouracil.

4. Simultaneous participation in other therapeutic clinical trials will not be allowed.

5. Because of potential drug interactions between allopurinol/cimetidine/antivirals and 5-FU, if a subject is receiving any of these drugs they must be discontinued prior to starting this protocol.

6. Prior malignancy, except for adequately treated basal cell or squamous cell carcinoma of the skin, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels (GnRH analogs or androgen receptor blockers acceptable); or other cancers from which the subject has been disease-free for at least five years.
7. Uncontrolled intercurrent illnesses including, but not limited to symptomatic congestive heart failure, severe oxygen dependent chronic obstructive pulmonary disease, unstable angina or uncontrolled cardiac arrhythmia that could jeopardize the subject's ability to receive the chemotherapy described in the protocol safely.
8. Pregnant and nursing women are excluded from this study because the chemotherapy agents have the potential for teratogenic or abortifacient effects.
9. Inability to co-operate with the study visit schedule and other requirements of the protocol.
10. Any other clinically significant medical disease or condition, laboratory abnormality or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

NOTE:

All questions regarding eligibility for **all potential subjects** should be directed to the UNMC Fred & Pamela Buffet Cancer Center Project Coordinator.

UNMC and Participating/Collaborating Sites should use the Eligibility Checklist (See Appendix B) as source documentation. It should be reviewed, signed, and dated prior to registration by the treating physician. The eligibility checklist must be accompanied by all other source documents that verifies the subject's eligibility (i.e., dictation, pathology, radiology, laboratory, etc.).

4.0 Registration Procedures

4.1 Recruitment

Subjects, who are referred to Nebraska Medicine / UNMC; Faith Regional Carson Cancer Center, Norfolk, NE or other IRB approved participating/collaborating sites, with histologically proven squamous cell carcinoma of the head and neck with measurable disease that is either recurrent after attempted cure with surgery and radiation therapy or newly diagnosed disease with distant metastases, may be eligible for this trial.

Screening eligibility, based on standard clinical care, will be performed by the treating physician at the time of encounter. On initial presentation, a history and physical examination are performed, laboratory data obtained and Performance Status is assessed. Imaging studies obtained include a high-resolution multi-detector computed tomography (CT) of the neck and chest. Additional radiologic/imaging evaluations for staging will be performed as clinically indicated and is at the discretion of the treating physician.

The subject's primary Oncologist will make the decision as to eligibility of the candidate based on the eligibility criteria listed above, prior to offering consent (See Section 3.0).

If the subject is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the subject after thorough review of the study is completed with the physician and his/her designee.

Some Insurance carrier's may decline to cover the costs of usual medical care if the subject is participating in a clinical trial. The subject will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The subject can then decide if they wish to participate.

4.2 Eligibility Verification/Registration

Before subjects are registered to the study, an Eligibility Checklist (See Appendix B) must be completed to verify the subject meets the eligibility criteria. Informed consent must be obtained by following procedures defined in section 12.6 entitled Process of Informed Consent. Subjects will be registered through the Sponsor Principal Investigator by contacting the UNMC Fred & Pamela Buffett Cancer Center Research Project Coordinator.

All Study personnel from UNMC and non-UNMC IRB approved sites will contact the UNMC Project Coordinator if a subject appears to meet the eligibility criteria. They will scan/email the completed Eligibility Checklist (See Appendix B) to the UNMC Project Coordinator. The Eligibility Checklist will be maintained in a study file. If the UNMC Project Coordinator confirms that the subject meets criteria and target accrual has not been met, approval for the subject will be given. A confirmation of Registration will be forwarded by the UNMC Project Coordinator.

Registration**:**
Study site personnel will provide the UNMC Project Coordinator with the following information:

- Demographics scan cover sheet (located in the Study Manual)
- Copy of the signed and dated consent form
- Signed Eligibility Checklist
- Source documents with assigned subject I.D. (if known on each page or subject identification) to support eligibility (i.e., Medical/Surgical Hx, labs, pathology reports, scans, etc.).

Registration Date: Eligibility verification and notification of assigned subject number (by UNMC) will be known as the Registration date.

Date of Enrollment: This is defined as the date of the start of study treatment / first protocol related intervention.

4.3 Instructions for Subjects Who Do Not Start Assigned Protocol Treatment

If a subject does not receive any assigned protocol treatment after consenting, baseline and follow-up data will still need to be collected and must be submitted according to the instructions in the protocol. The reason he/she did not receive any treatment and the date and type of the first non-protocol treatment that the subject receives must also be reported.

5.0 Research Design

This is a Phase II, Open Label, Non-Randomized trial for patients with recurrent or metastatic squamous cell carcinoma of the head and neck. All subjects will receive the same dose of the combination chemotherapy drugs docetaxel and capecitabine.

5.1 Pre-treatment Evaluations- *Standard of Care (SOC)*

No tests or procedures are conducted solely for the purposes of research to determine subject eligibility.

*WITHIN **FOUR WEEKS***

- History and physical
- CBC with differential, Platelet count
- Comprehensive Metabolic Panel (CMET) – electrolytes (sodium, potassium, chloride, bicarbonate, creatinine, BUN, AST, ALT, T. protein, albumin, bilirubin, alkaline phosphatase, calcium, glucose)
- PT, PTT, INR
- Serum/urine pregnancy test (if applicable)
- Height and weight
- Performance Status Assessment using Karnofsky Score
- Quality of Life (QOL) Assessment
- Vital signs, including blood pressure
- High-resolution multi-detector computed tomography (CT) of the neck and chest
- The need for further radiologic evaluations for staging, as clinically indicated, is at the discretion of the treating physician.
- Provide pathology report for review of confirmation of diagnosis.

Research Samples will be collected at baseline, after cycle 2 and at the end of treatment. (See protocol section 5.6 for details).

5.2 Drug Administration / Treatment Plan

5.2.1 Body Surface Area Calculations

Dosage calculations will be based on the subject's body surface area, at baseline. Actual height and weight should be used in determining body surface area. (See Appendix C). Dose adjustments at the beginning of each cycle do not need to be made unless there has been a >10% weight gain/loss.

5.2.2 Premedication

All subjects will receive premedication for nausea and vomiting with appropriate anti-emetic regimens based on recommendations made by the NCCN Guidelines (SOC), pre and post medications as prescribed by the treating physician. (See http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf).

Subjects will receive dexamethasone 4 mg twice a day orally on the day before, the day of and the day after docetaxel to help decrease the edema associated with docetaxel.

5.2.3 Systemic Therapy (Medicare Qualifying research related combination chemotherapy)

- Docetaxel 75 mg/m^2 IV in normal saline IV over one hour on day 1; cycled every 21 days (3 weeks) for all cycles.
- Capecitabine 800mg/m^2 orally twice daily on days 1-14 of a 3 week cycle for the initial cycle (Cycle 1).

If there is no evidence of grade 2 or greater toxicity with capecitabine and if the doses of capecitabine are not held due to adverse effects after the first cycle, THEN for Subsequent Cycles (Cycle 2 and remaining cycles) the dose of capecitabine will be increased to 1000 mg/m^2 orally twice daily on days 1-14 of a 3 week cycle for the remaining cycles.

To provide a means of ensuring oral route of medication adherence to patients while participating in this clinical trial, standard procedure for "Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)" will be followed (See Appendix D).

5.2.4 Criteria for holding and resuming treatment

As per Section 5.4 dose modifications instruction.

5.2.5 Evaluations during therapy *(SOC)*

Every 3 weeks during chemotherapy:

- Subjects will be clinically evaluated by an oncologist for toxicities
- CBC w/ differential, platelet count
- Comprehensive metabolic panel (CMET) – electrolytes (sodium, potassium, chloride, bicarbonate, creatinine, BUN, AST, ALT, T. protein, albumin, bilirubin, alkaline phosphatase, calcium, glucose)
- Weight
- Performance Status Assessment
- QOL Assessment
- Vital signs, including blood pressure

Every 6 weeks during chemotherapy:

- High-resolution multi-detector computed tomography (CT) of the neck and chest.
- The need for further radiologic evaluations for staging, as clinically indicated, and is at the discretion of the treating physician.

Data will be collected on dose delays/reductions, hospitalizations, treatment discontinuation, deaths and toxicities.

5.3 Clinical Endpoint/Radiographic Assessment of disease status

A dedicated CT Response assessment will be done after every 2 cycles per standard of care and at the completion of the study. Subjects with stable or responsive disease will continue on therapy until progression.

Follow-up (SOC): All patients will be clinically evaluated by an oncologist at the completion of the study and then followed for survival.

Post Trial Assessments:

- Subjects who go off study treatment at any time during the trial will be followed for 30 days after the last day of treatment or until other disease-related treatment begins. For all subjects, drug-related Serious Adverse Events (SAEs) and Adverse Events (AEs) will be followed until resolution, baseline or ≤ grade 1 levels.

- Subjects who responded or maintained stable disease during the study will be followed for date of disease progression and/or death. Subjects may refuse to participate in the post-trial assessments.

5.4 Dose modifications

5.4.1 General instructions for dose modifications

- Adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology, Criteria for Adverse Events (NCI-CTCAE), version 4.0 (See Appendix E), which can be accessed at the following URL: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
- All doses should be based on the AE requiring the greatest modification.
- Doses may be delayed, missed or reduced based on subject tolerance. Missed doses will not be made up at the end of the cycle.
- Doses that have been reduced may not be escalated.
- Proceeding with study therapy after grade 4 events, other than neutropenia/granulocytopenia and thrombocytopenia is at the discretion of the treating physician.

5.4.2 Docetaxel Dose Modifications

5.4.2.1 Hematologic Toxicity

Potential hematologic toxicities of docetaxel that are most common would be -Neutropenia, anemia. Since severe myelosuppression is uncommon with capecitabine therapy, the dose of capecitabine will not be decreased for hematologic toxicity occurring in the prior cycle if full doses of docetaxel were given.

Docetaxel will be held for an ANC <1,500/μL and/or platelet count <100,000/μL. For subsequent cycles, if there is a delay of more than 1 week because of low blood counts, the dose of docetaxel will be reduced by 25% for subsequent courses. In the event of a delay of more than 4 weeks, the subject will be taken off study.

In the event of febrile neutropenia, the dose of docetaxel will be reduced by 25% and filgrastim will be administered for subsequent courses. If febrile neutropenia occurs despite filgrastim, the dose of docetaxel will be reduced by another 25% for subsequent courses.

5.4.2.2 Non-Hematologic Toxicity

Dose Modifications for Abnormal Liver Function

Subjects who develop abnormal liver function tests for any reason while on the study will have the following dose reductions (See Table 1):

Table 1: Docetaxel Dosing based on Alk Phos and AST/ALT

		AST or ALT			
		≤ ULN	>1x but ≤1.5x	>1.5x but ≤5x	>5x ULN
Alkaline Phosphatase	≤ ULN	Full Dose	Full Dose	Full Dose	Hold*
	>1x but ≤ 2.5x	Full Dose	Full Dose	Reduced by 25%	Hold*
	>2.5x but ≤ 5x	Full Dose	Reduced by 25%	Hold*	Hold*
	>5x ULN	Hold*	Hold*	Hold*	Hold*

*Hold until recovered (maximum 21 days) then re-treat at a reduced dose. "Recovered" is defined as meeting the study baseline eligibility criteria.

Both AST and ALT should be drawn. The more abnormal of the two values (AST or ALT) should be used in determining the dose.

Docetaxel should not be administered to subjects with serum total bilirubin >ULN. If serum total bilirubin is >ULN on treatment day, hold docetaxel until serum total bilirubin is ≤ ULN (maximum 21 days), then re-treat at a 25% reduced dose.

Both chemotherapy drugs will be held for grade 3 or 4 neurotoxicity and may be restarted on resolution to less than a grade 1 (unless recovery is >2 weeks for which subject will be removed from study). The dose of docetaxel will be decreased by 25% at resumption. Docetaxel will be discontinued if grade 3 or 4 neurotoxicity recurs after a dose reduction and capecitabine will be continued as a single agent.

Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

There are no dose reductions for fluid retention.

5.4.3 Capecitabine Dose Modifications

5.4.3.1 Hematologic Toxicity

Since severe myelosuppression is uncommon with capecitabine therapy, the dose of capecitabine will not be decreased for hematologic toxicity occurring in the prior cycle if full doses of docetaxel were given.

5.4.3.2 Non-Hematologic Toxicity

Certain toxicities, such as diarrhea, abdominal pain, constipation, palmar-plantar erythrodysesthesia (hand-foot syndrome), etc., are typically associated with capecitabine therapy. Therefore, the dose of capecitabine will be preferentially reduced for such toxicities (See Table 2). Again, both chemotherapy drugs will be held for grade 3 or 4 neurotoxicity and may be restarted on resolution to less than a grade 1 (unless recovery is >2 weeks for which subject will be removed from study). The dose of docetaxel will be decreased by 25% at resumption. Docetaxel will be discontinued if grade 3 or 4 neurotoxicity recurs after a dose reduction, and capecitabine will be continued as a single agent.

Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

There are no dose reductions for fluid retention.

For grade 2 diarrhea, stomatitis or hand-foot syndrome, capecitabine will be held until the event returns to a grade 0 or 1 and then resumed at the same dose. If these symptoms persist until the start of the next cycle, the cycle will be delayed until it is resolved to a grade 0 or 1 and then continued at 100% of the original dosing.

For grade 3 diarrhea, stomatitis or hand-foot syndrome, capecitabine will be resumed with a 25% dose reduction once the diarrhea/hand-foot syndrome has resolved to a grade 0 or 1. Docetaxel will be continued at the same dose.

On any subsequent development of grade 2 or higher diarrhea, stomatitis or hand-foot syndrome, therapy will be held until symptoms resolved to grade 0 or 1 and then the doses of both agents will be reduced by 25%. In the event of a delay of more than 4 weeks, the subject will be taken off study.

Table 2: Capecitabine Dosing for diarrhea, stomatitis or hand-foot syndrome

	Within same cycle	At start of next cycle	Any subsequent development of Grade 2 or higher
GRADE 2 diarrhea/stomatitis/hand-foot syndrome	Hold* then resumed at 100%	Delay cycle** then resumed at 100%	Hold* then Reduce both docetaxel and capecitabine by 25%
GRADE 3 diarrhea/stomatitis/hand-foot syndrome	Hold* then Reduce by 25%	Delay cycle** then reduced by 25%	Hold* then Reduce both docetaxel and capecitabine by 25%

*Hold until returned to grade 0 or 1.

**Delay cycle until returned to grade 0 or 1. If delay is more than 4 weeks, the subject is taken off study.

5.5 Supportive Care

5.5.1 Requirement for venous access

Central venous access is not required for protocol participation, but may minimize the risk of venous irritation associated with docetaxel therapy. A previously placed central venous access device will be employed if it is functioning properly (free infusion of saline, unimpeded blood return, good condition of external appliance, no recent history of device infection or thrombosis). Should the subject require central venous access, an implanted port central venous access device (i.e. a Medi-Port® or Port-a-Cath®) or a peripherally inserted central catheter (PICC) will be placed. Other aspects of catheter/port management will be in accordance with nursing clinic central venous port procedures.

5.5.2 Diarrhea

Loperamide should not be taken prophylactically. Subjects will be instructed to begin taking loperamide after the (1) first poorly formed or loose stool, (2) first episode of 5 or

more bowel movements, OR (3) 2 "watery" stools in one day (20). Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea THEN 2 mg after each loose stool (do not exceed 8 tablets in 24 hours or 16 mg total).

Subjects must notify the research team as to when they initiated loperamide therapy. If diarrhea persists despite loperamide therapy, then the subject should be evaluated for the need for IV fluid and electrolyte replacement.

Subjects may take alternative medications as prescribed by the treating physician.

5.5.3 Palmar-Plantar Erythrodysesthesia (hand-foot syndrome)

The use of pyridoxine (vitamin B6) may ameliorate the palmar-plantar erythro-dysesthesia associated with certain chemotherapeutic agents including fluorouracil. Therefore, a therapeutic trial of pyridoxine 50 to 150 mg po tid daily for six weeks should be tried at the first symptoms of hand-foot syndrome.

5.5.4 Stomatitis/Mucositis

Mild symptoms will be treated with topical antiseptic and analgesic agents. Both viscous lidocaine and diphenhydramine have local anesthetic properties, while the aluminum hydroxide component of Maalox has a beneficial drying property. Subjects with severe pain require systemic narcotic analgesics. Topical anti-fungal agents will be added as clinically indicated. More severe symptoms will require all of the above, as well as stronger analgesic agents and admission to hospital for IV fluid and electrolyte replacement if dehydrated. GELCLAIR bioadherent oral gel is a topical agent that can provide pain relief for 5-7 hours after administration. Subjects with ulcers on the lips may benefit from a topical lip balm such as Abreva (10% docosanol).

A rinse with baking soda and salt is an inexpensive and convenient remedy: mix 2 teaspoons salt and 2 teaspoon baking soda in 1 cup warm water; swish and spit; repeat 4 times daily.

Sample prescription mouthwash formulas: take 5 cc of the formula, swish for 30 seconds then spit out; repeat 4 to 6 times daily (may swallow if there is esophageal involvement)

1) Tetracycline suspension	500 mg/20 mL
Diphenhydramine	50 mg/20 mL
Nystatin	50,000 U/5 mL
Maalox	30 mL
Sterile Water, USP	105 mL
2) 2% viscous lidocaine	30 mL
Diphenhydramine elixir	60 mL (12.5 mg/5 mL)
Maalox	90 mL

5.5.5 Treatment of Fever and Neutropenia

Subjects developing a fever of 100.5 degrees F or higher will have a CBC with WBC differential obtained along with a history and physical examination to look for signs of infection.

If the ANC is less than 1000/μL, a specific treatment plan as prescribed by the treating physician or the sites Institutional Guidelines will be followed.

Fever and neutropenia occurring during a treatment cycle may require interruption of chemotherapy. The subject may resume chemotherapy at the start of the next scheduled cycle, if therapy for infection has been completed and the subject meets other criteria for starting a new cycle.

5.5.6 Management of Docetaxel Acute Hypersensitivity

Severity of Symptoms	Treatment Guidelines
(Grade 1)-<u>Mild</u> symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	• consider decreasing the rate of infusion until recovery from symptoms; stay at bedside and monitor subject • then, complete docetaxel infusion at the initial planned rate
(Grade 2)- <u>Moderate</u> symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	• interrupt docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor subject until resolution of symptoms • resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the subject, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, *(i.e.. infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, then finally, resume at the initial planned rate)* • depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment and the rate of infusion should be decreased initially and then increased back to initial planned rate, *(i.e. infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, and finally, administer at the initial planned rate)*
(Grade 3)- <u>Severe</u> symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	• immediately discontinue docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor subject until resolution of symptoms • the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
(Grade 4)- <u>Life-threatening</u> symptoms: Anaphylaxis	• NO FURTHER docetaxel DRUG THERAPY
(Grade 5)- Death related to AE	

5.5.7 Fluid Retention

Subjects developing new onset edema, progression of existing edema or another sign of fluid retention are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below:

- Triamterene/hydrochlorothiazide one capsule oral daily up to three times a day.
- Furosemide 40 mg oral daily if edema progresses despite Triamterene/hydrochlorothiazide therapy. Potassium supplementation should be given as needed.
- If after a two-week trial, furosemide 40 mg oral daily is ineffective, the subject may be treated with furosemide 20 mg oral daily plus metolazone 2.5 mg oral daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the subject, the overall tumor response and the medical judgment of the Investigator will determine if it is in the subject's best interest to continue or discontinue treatment.

5.5.8 Hyperlacrimation

The following guidelines may be taken for subjects experiencing clinically significant hyperlacrimation:

- Withhold docetaxel treatment until resolution.
- Frequent instillation of artificial tears.
- Steroid ophthalmic solution starting the day before docetaxel administration in subjects *without* a history of herpetic eye disease.
- Ophthalmologist consult.

5.6 Correlative Studies Related to the Research

Research Samples will be collected at baseline, after cycle 2 and at the end of treatment (See Appendix I for instructions). Samples will include:

- Blood Samples-30 mL including two – 10ml EDTA lavender top tubes and one – 10ml red top tube
- Urine Sample - 10 mL.

Samples should be sent overnight at room temperature, Monday through Thursday only to Dr. David L. Kelly's Lab, **Attn: Amy Wells, MS.** Do not send the day before a Holiday.

5.7 Potential Drug Interactions

5.7.1 Allopurinol

Oxypurinol, a metabolite of allopurinol can potentially interfere with 5-FU anabolism via OPRT'ase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a subject is receiving 5-FU (including 5-FU prodrugs such as capecitabine), it is recommended that the need for taking allopurinol be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen and another agent substituted for it.

5.7.2 Warfarin

Bleeding associated with prolonged prothrombin time (PT) has been noted in several subjects receiving 5-FU and concomitant warfarin. These observations suggest a possible interaction leading to prolonged PT. Therefore, it is recommended that all subjects receiving 5-FU (including 5-FU prodrugs such as capecitabine) and concomitant warfarin at therapeutic doses be closely monitored for changes in prothrombin time.

5.7.3 Cimetidine

Because cimetidine can decrease the clearance of capecitabine/5-FU, subjects should not enter on this study until the cimetidine is discontinued. Ranitidine or another class of anti-ulcer agents can be substituted for cimetidine, if necessary.

5.7.4 Sorivudine and Brivudine

A metabolite of the above two investigational antiviral agents, 5-bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Subjects should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine. If a subject has received prior sorivudine or brivudine, then at least four weeks must elapse before the subject receives capecitabine therapy.

5.8 Criteria for Removal from Study

- Progression of Disease
- If at any time the constraints of this protocol are detrimental to the subject's well-being or if the subject is unable to comply with the requirements of the protocol, the subject will be removed from protocol therapy.
- Undue toxicity that would make continued treatment detrimental to the subject's safety.
- Development of intercurrent medical problems that would make continued protocol therapy detrimental to the subject's safety. *If a non-treatment related intercurrent illness is expected to be of limited nature, then treatment may be delayed for more than 2 weeks. In this case, the patient would need to be re-evaluated before resuming protocol therapy.*
- The subject chooses to discontinue treatment or follow-up.

The reason(s) for withdrawing the subject from the treatment portion of the study will be documented in the case report form. Where possible and feasible, subjects who received at least one dose of study drugs should be subjected to the procedures scheduled at the end of the study and should be submitted to the follow up to assess disease progression.

If available, the following information will be recorded in the case report form: (1) date of disease relapse, (2) date of death, (3) cause of death and (4) autopsy report.

6.0 Measurement of effect

6.1 Tumor Response in Subjects with Measurable Disease

CTEP's RECIST Version 1.1 Guidelines will be followed. A quick reference to the RECIST Guidelines can be downloaded at the following URL:

https://ctep.cancer.gov/protocolDevelopment/default.htm

Measurable disease is defined as lesions that can be accurately measured in at least 1 dimension in which the longest diameter to be recorded is 20 mm or larger with conventional techniques or 10 mm or larger with spiral CT scan. Measurable disease is defined by the

presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/ histology.

Non-measurable disease is defined as all other lesions, including small lesions in which the longest diameter is less than 20 mm with conventional techniques or less than 10 mm with spiral CT scan and disease that is not detectable or not readily quantifiable with conventional techniques. Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques and cystic lesions.

All measurements should be recorded in metric notation by use of 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 treatment.

6.1.1 Baseline documentation of "Target" & "Non-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), recorded and measured at baseline.
Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. Such lesions in a previously irradiated area might be considered measurable if there has been a documented increase in the size of the lesion since completion of the radiation.

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.

6.1.2 Response criteria

Evaluation of target lesions (taking into account the measurement of the longest diameter only for all target lesions), response criteria are defined as:

- **Complete Response (CR)**: the disappearance of <u>all</u> target lesions
- **Partial Response (PR)**: at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter

- **Progressive Disease (PD)**: at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions
- **Stable Disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started

6.2 Progression-Free Survival:

Progression-free survival will be defined as from the first date of therapy until the first notation of clinical progression, relapse or death from any cause. For subjects who are still progression-free at the time of the study analysis or are lost to follow-up, progression-free survival will be censored at the last recorded date that the subject was known to be progression-free.

6.3 Time to Treatment Failure:

The time to treatment failure will be defined as from the first date of therapy until the date the subject is removed from study for any reason.

6.4 Survival:

Survival will be defined as from the first date of therapy until the date of death from any cause. For subjects who are still alive at the time of the study analysis or are lost to follow-up, survival will be censored at the last recorded date that the subject was known to be alive.

6.5 Toxicity criteria

The NCI Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0 will be used to grade toxicity and is available at the following internet site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.0 Study Parameters

Required studies	Time (weeks)															
	Screen-ing (4 wks)	1	2	3	4	5	6	7	8	9	10	11	12	13[1]	14[1]	15[1]
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Recurring Cycles		
History and physical	X	X			X			X			X			X		
Weight & Karnofsky PS	X	X			X			X			X			X		
Toxicity notation	X				X			X			X			X		
QOL[5] Assessment	X				X			X			X			X		
Laboratory studies																
CBC w/ diff, plt	X				X			X			X			X		
CMET[3]	X				X			X			X			X		
PT, PTT/INR [4]	X															
Research Blood and Urine	X							X						X end of study only		
Diagnostic biopsy only[8]	X															
Imaging studies																
CT scan of the neck and chest[6]	X							X[2]						X[2]		
Chemotherapy																
Docetaxel, IV day 1		X			X			X			X			X		
Capecitabine, PO BID days 1-14[7]		X	X		X	X		X	X		X	X		X	X	

[1] Every subsequent cycle until discontinuation from study.

[2] Every two (2) cycles, even with delays, until discontinuation from study.

[3] Comprehensive metabolic panel (CMET) – electrolytes (sodium, potassium, chloride, bicarbonate, creatinine, BUN, AST, ALT, Total protein, albumin, bilirubin, alkaline phosphatase, calcium, glucose)

[4] As necessary. Subjects on concomitant warfarin at therapeutic doses should be closely monitored for changes in prothrombin time.

[5]Quality of Life (QOL) Assessment will be performed using European Organisation for Research and Treatment of Cancer QLQ Core 30 (EORTC QLQ-C30, See Appendix G) and QLQ Core Head & Neck 35 (QLQ-H&N35, See Appendix H)

[6] The need for further radiologic evaluations for staging, as clinically indicated, and is at the discretion of the treating physician.

[7] Missed doses should not be made up.

[8] Diagnostic Biopsy Pathology Report can be used to confirm diagnosis.

8.0 Drug Formulation and Procurement

Docetaxel (Taxotere®): Aventis Pharmaceuticals

Form: Docetaxel for injection.

Dilution: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Preparation: Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Just prior to use allow the docetaxel to reach room temperature for 5 minutes. Add the contents of the diluent vial to the active drug and mix by gently rotating the vial for 15 seconds. Allow the vial to stand for 5 minutes at room temperature and check that the solution is homogenous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel with overfill.

Storage and stability: Docetaxel infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour IV administration).

Method of administration: Docetaxel will be administered as a 1-hr infusion, via an infusion control device (pump).

Precautions: Severe hypersensitivity reactions characterized by hypotension, bronchospasms, or minor reactions characterized by generalized rash/erythema may occur and can be minimized by use of premedications.

Availability & Drug Ordering: Docetaxel is commercially available from Aventis Pharmaceuticals.

Significant clinical toxicities:
Cardiovascular: Fluid retention, including peripheral edema, pleural effusions, and ascites.
Dermatologic: Alopecia, nail disorder (banding, onycholysis, hypo- or hyperpigmentation)
Gastrointestinal: Mucositis/stomatitis, nausea and vomiting, diarrhea.
Hematologic: Myelosuppression, neutropenia, thrombocytopenia, anemia.
Hepatic: Elevated transaminase levels.
Neuromuscular & skeletal: Myalgia, neurosensory changes (paresthesia, dysesthesia, pain), motor neuropathy (including weakness).
Miscellaneous: Hypersensitivity reactions - angioedema, rash, flushing, fever, hypotension.

Capecitabine (Xeloda®)(Ro 09-1978): Roche Pharmaceuticals

Product description: Capecitabine is supplied as a biconvex, oblong film coated tablets for oral administration as follows: 150 mg – light peach color, engraved with XELODA on one side and 150 on the other; 500 mg – peach color, engraved with XELODA on one side and 500 on the other.

Route of administration: Oral. The total daily dose will be taken in two divided doses in the morning and evening about 12 hours apart. The medication should be taken within 30 minutes after taking a meal with at least 200 mL of water. If the dose is missed, it should be skipped altogether. The patient should NOT double the next dose. If the treatment is interrupted due

to toxicity, the missed doses should not be replaced or restored. The total daily dose in mg/m^2 will be rounded down to the nearest tablet size. If the dosing calls for an uneven number of pills, the larger dose will be given in the evening.

Stability: Capecitabine tablets are stable when the bottle is kept tightly closed and stored between 15° and 30°C (59° and 86°F). An expiration date is on the bottle.

Incompatibilities: potentially Allopurinol and Cimetidine

Drug Interactions: Patients who are on warfarin should have their INR closely monitored while taking capecitabine. They should not receive the investigational antiviral drugs brivudine or sorivudine.

Contraindications: Patients with an unusual, life-threatening clinical toxicity with 5-FU.

Availability & Drug Ordering: Capecitabine is commercially available from Roche Pharmaceuticals (Roche Laboratories, 340 Kingsland St., Nutley, NJ 07110-1199).

Significant clinical toxicities:
Cardiovascular: Edema, venous thrombosis, chest pain.
Central nervous system: Tiredness, weakness, fatigue, fever, pain, headache, dizziness, insomnia.
Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome), the palms of the hands and the soles of the feet may tingle or become numb, painful, swollen or red. A rash may occur, and the skin may be dry and itchy (dermatitis).
Gastrointestinal: Diarrhea, mild to moderate nausea, vomiting, sores in the mouth and throat stomatitis, abdominal pain, constipation loss or appetite or decreased appetite, and excessive water loss from the body.
Hematologic: Lymphopenia, anemia, neutropenia, thrombocytopenia.
Hepatic: Increased bilirubin.
Neuromuscular & skeletal: Paresthesia, back pain, neuropathy.
Ocular: Eye irritation.
Respiratory: Dyspnea.

9.0 Toxicity Reporting Guidelines

The chemotherapeutic agents used in the protocol are commercially available agents with well-characterized toxicity profiles.

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional IRB and FDA Guidelines for the Toxicity Reporting.

All subjects will be closely followed for toxicity/adverse events (AEs). Adverse events will be assessed by reports from subjects to their physician/Investigator and by physical examinations using the CTCAE Version 4.0. All AEs and SAEs will be followed from the time of informed consent until resolution, baseline, or ≤ grade 1 levels.

AEs considered by the Investigator as not related or probably not related to the treatment will not be followed beyond 4 weeks (30 days) after the final dose of study drug is administered. Concomitant medications will be collected up to 4 weeks (30 days) after the final dose of study drug is administered to facilitate AE attribution assessment.

Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the University of Nebraska Medical Center Fred & Pamela Buffett Cancer Center Data Safety Monitoring Committee (DSMC).

9.1 Adverse Experience Definitions

Adverse Event:
An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (i.e., the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria and/or if the Investigator considers them to be adverse events.

Unexpected Adverse Event:
An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the labeled event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event:
A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

- Results in death
- Is a serious threat to life, health, safety, or welfare of subject[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity[2]

- Is a congenital anomaly or birth defect
- Another serious important medical event[3]
- Any medical event in an investigational drug study that requires treatment to prevent one of the outcomes listed above
- The rights, safety, or welfare of subjects is seriously jeopardized.

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.2 Adverse Event Reporting and Definitions Per the University of Nebraska Medical Center Institutional Review Board (UNMC IRB) and the University of Nebraska Medical Center Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC)

9.2.1 IRB REPORTING

All internal serious adverse events (SAEs) must be reported to the University of Nebraska Medical Center Institutional Review Board (UNMC IRB) promptly, per Institutional Policy and in no case later than two (2) business days following PI notification that the event occurred. *If* the PI determines that conditions A, and B are met:

a. The AE is unexpected, *AND*

b. The AE is related to, or possibly related to, the drug biologic, device, or other research intervention.

All *unexpected*, internal, fatal AEs must be reported promptly to the local IRB per Institutional Policy, but no later than *24 hours* following PI notification that the event occurred. If documentation is still pending, the IRB office must be notified by a telephone call or e-mail.

All *expected*, internal, fatal AEs (i.e., due to progressive disease or which reflect a risk currently found in the consent form) must be reported to the local IRB per Institutional Policy no later than ten (10) business days following PI notification that the event occurred.

9.2.2 Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) Reporting

All grade 3 or greater toxicities (expected and unexpected, regardless of attribution) will be reported to the DSMC.

All AE's and SAE's irrespective of attribution, when occurring after the start of the study drug, will need to be reported to the DSMC.

Attribution of AE: The Investigator will assign a causal relationship for all reportable AE's according to the NCI Common Toxicity Criteria. The likelihood of relationship of the AE to the study drugs will be determined by the Investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious (AE related to underlying or concurrent illness).

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment (AE has no temporal relationship to the study drug and/or a more likely etiology exists).

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes (AE has strong temporal relationship to study drug, alternative etiology is equal or less likely).

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms (AE has strong temporal relationship to the study drug or recurs on re-challenge, another etiology is unlikely or significantly less likely).

Definitely related: There occurrence and timing of the AE are clearly attributable to the study treatment.

Severity Grade of AE. The severity of events reported on the AE case report form will be determined by the principal investigator according the NCI Common Toxicity Criteria (CTC version 4.0).

AEs will be collected from the time the subject starts the study drugs and ending 30 days following the final chemotherapy. All AEs will be followed until resolution, baseline, or ≤ grade 1 levels. Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

AEs judged by the Investigator as not related or probably not related to the study drugs will NOT be followed beyond the 30 days after the final chemotherapy.

ALL internal/external Adverse Events (AEs) will be reported to the UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) using the DSMC approved forms. The DSMC will also review the protocol on at least a quarterly basis. A copy of the Policy and Procedures for this section may be reviewed at: http://www.unmc.edu/cancercenter/clinical/prms.html.

9.2.3 FOOD AND DRUG ADMINISTRATION (FDA) REPORTING

It is the responsibility of the UNMC Sponsor-Investigator, Apar Ganti, M.D., to submit to the FDA Post-marketing Safety Reports in accordance with 21 CFR 314.80.

SAEs not meeting Post-marketing 15-day "Alert" will not be made available to FDA by the sponsor-investigator pursuant to 21 CFR 314.80 (c)(1)(i).

All sites will utilize the FDA MedWatch Form (See Appendix F) for the reporting of serious adverse events (SAEs) and follow up information to those events. The form can be found at the following URL: http://www.fda.gov/Safety/MedWatch/default.htm

It is the responsibility of ALL sites to submit the completed MedWatch Form, SAE PI Assessment Form and SAE (located in your Study Manual) to the UNMC Project Coordinator within 24 hours of his/her knowledge of the SAE:

The SAE information will be routed to the UNMC PI who will further evaluate the SAE. The SAE will be submitted to FDA if the PI determines 21 CFR 314.80 (c) criteria are met.

SAE reporting instructions are reiterated and further outlined in the Participating Site Study Manual.

9.3 Auditing

The UNMC Fred & Pamela Buffett Cancer Center Protocol Review & Monitoring System (PRMS) Office Audit Committee defines a *Participating/Collaborating Site* as: a hospital clinic, or other provider of medical services who has agreed to participate in a therapeutic trial that has been designed and developed by a University of Nebraska Medical Center/Nebraska Medicine Investigator and is Sponsored by UNMC.

For participating/collaborating site(s) that are NCI Designated Cancer Centers, the protocol specific finding of the site's Audit Committee will be submitted to the UNMC Audit Committee for review on a schedule to be determined by the UNMC Audit Committee.

For participating/collaborating site(s) that are not NCI Designated Cancer Centers, the Audit process will be established by the UNMC Audit Committee on a site-by-site basis.

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo Audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

A copy of the Policy and Procedures for this section may be reviewed at: http://www.unmc.edu/cancercenter/clinical/prms.html.

9.4 Monitoring

9.4.1 Communication

Various methods will be implemented by the Sponsor to exchange information with participating/collaborating sites. Methods of communication will include:

- Site Initiation/Orientation

- Regular Teleconferences, including group wide progress within the agenda
- Investigator meetings, as feasible (remote or TBA, possibly in conjunction with larger meetings)
- Email distributions/reports, as needed.

9.4.2 Ongoing safety monitoring for all the subjects in this study:

All Participating/Collaborating sites are required to execute a Data Compliance Policy Agreement. UNMC will monitor the data of sites in adherence to applicable research regulations, the protocol and the Policy Agreement. De-identified source documents, which support data entered, must be provided to the Sponsor by mail, fax or electronic means for centralized compliance monitoring.

9.4.3 Data and Safety Monitoring Plan

The UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Plan is designed to ensure the safety of participants in clinical trials conducted by the UNMC Fred & Pamela Buffett Cancer Center members and to comply with National Cancer Institute (NCI) and National Institutes of Health (NIH) requirements. This protocol will comply with all Monitoring Policies and Procedures outlined in the Monitoring Plan.

Under the Guidelines of the Monitoring Plan, the:

- UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) is responsible for initial scientific review of protocols requiring informed consent; reviews all changes or amendments to previously reviewed protocols and reviews study progress at least annually. The SRC is also responsible for the ongoing annual scientific review of UNMC Fred & Pamela Buffett Cancer Center protocols.
- UNMC Fred & Pamela Buffett Cancer Center Data and Safety and Safety Monitoring Committee (DSMC) is responsible for the ongoing monitoring of Investigator Initiated intervention trials to ensure subject safety (i.e., adverse events).
- UNMC Fred & Pamela Buffett Cancer Center Audit Committee is responsible for ensuring protocol compliance.

The Data and Safety Monitoring Plan also includes adherence to Data Safety Monitoring Preparation and Reporting. The study PI, Research and Data Coordinator reviews all Serious Adverse Events occurring on all Investigator Initiated intervention trials on an ongoing basis per the SOP. In addition, the DSMC reviews all safety data of all subjects enrolled on these trials every 3 months and may convene for a special session when necessary. CTCAE v4.0 will be used to determine grading of adverse events.

A copy of the Policy and Procedures for this section may be reviewed at: http://www.unmc.edu/cancercenter/clinical/prms.html.

10.0 Statistical considerations including stopping criteria

The intent to treat analysis will be conducted for all eligible subjects (See Section 10.5 Evaluable Subject).

10.1 Primary Endpoint

The primary endpoint for this study is the overall response rate (complete or partial response rate, defined in section 6.1.2) as defined by the RECIST Version 1.1 criteria at 15 weeks of a chemotherapy regimen involving docetaxel and capecitabine as front line therapy for subjects with advanced squamous cell carcinoma of the head and neck who are not candidates for surgery or radiation therapy.

10.2 Secondary endpoints

- Progression-Free Survival
- Survival
- Incidence and severity of adverse events
- Quality of Life of subjects will be assessed using the European Organisation for Research and Treatment of Cancer QLQ Questionnaire-Core 30 (QLQ-C30) and QLQ-Head and Neck 35 (QLQ-H&N35) module

10.3 Sample Size

1st Stage = 18 evaluable subjects
(interim analysis)
2nd Stage = 25 evaluable subjects
For a total of = 43 evaluable subjects

Rationale for sample size parameters:
The combination of docetaxel and capecitabine has been studied in other solid tumors with reasonable efficacy and toxicity. In a randomized phase III study in pre-treated metastatic breast cancer, the capecitabine (1250 mg/m^2)-docetaxel (75 mg/m^2) combination was found to have a response rate of 32%[30]. However 27% of subjects discontinued treatment due to adverse events.

Sample size justification:
This Phase II study will utilize a Simon[35] optimal two-stage design and will be employed for this study, with 18 evaluable subjects accrued in the first stage. If 2 evaluable subjects or fewer achieve a complete or partial response (defined in section 6.1.2) at week 15 then the study will be terminated. If 3 or more evaluable subjects have achieved a complete or partial response, then 25 additional subjects will be accrued in the second stage, for a total of 43 evaluable subjects. When accrual to the second stage is complete, if 7 or fewer evaluable subjects have achieved a response then we will conclude that the docetaxel and capecitabine combination does not give a response rate of at least 25%. This optimal two-stage design is to test the null hypothesis that the complete or partial response is <= 0.10 vs. the alternative that complete or partial response rate is ≥ 0.25 at the significance level of 0.05 and with power of 0.80.

Currently, the three drug combination of platinum, 5-fluorouracil and cetuximab has a response rate of approximately 36%, while the doublet of platinum and fluorouracil has a response rate of approximately 20%[9]. We plan to study the experimental combination of docetaxel and capecitabine further only if it has a response rate of at least 25%.

10.4 Stopping Rules

An interim analysis to include monitoring of the complete or partial response rate at week 14 as in Phase II oncology trials as follows:

If 2 or fewer in the first 18 evaluable subjects experience complete or partial response (defined in section 6.1.2) at week 14, then STOP; otherwise continue to 43 evaluable subjects and declare the overall response rate acceptable if at least 8 complete or partial responses are observed.(29)

The Principal Investigator at the University of Nebraska Medical Center will inform all sites when the study has enrolled 18 evaluable subjects. At that time, enrollment will stop pending receipt of the interim analysis of the first 18 evaluable patients. UNMC will require UNMC SRC/IRB/DSMB review of the interim analysis and SRC/IRB/DSMB approval to continue enrollment.

To evaluate the adverse events profiles associated with the treatment, the maximum grade for each type of adverse event will be recorded for each patient and frequency tables will be reviewed to determine the overall patterns. The number and severity of grade ≥ 4 adverse events will be tabulated and summarized per the DSMC plan. If it is ever determined during a DSMC review that an unacceptable incidence of grade 4 neutropenia or other grade 4 non-hematologic toxicities has occurred, the study will be stopped.

Sequential boundaries will be used to monitor toxicity rate, defined as the proportion of patients who are withdrawn from the study due to treatment-related side effects, as determined by the treating physician. The accrual will be halted if excessive numbers of toxicities are seen, that is, if the number of toxicities is equal to or exceeds b_n out of n patients with follow-up (See table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most [probability of early stopping] when the rate of toxicity is equal to the acceptable rate of 0.30.

The trial will be stopped if the number of toxicities is equal to or exceeds b_n out of n patients with completed follow-up.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Boundary, b_n	-	-	-	4	5	5	6	6	7	7	7	8	8	9	9	10	10	10

Reference: Ivanova, A., Qaqish, B.F., and Schell, M.J. (2005). Continuous toxicity monitoring in phase II trials in oncology. Biometrics 61: 540-545.

Subjects may be withdrawn from the study by the Investigator for the following reasons:

- any adverse event or toxicity which compromises the subject's ability to participate
- disease progression
- discontinuation of study drugs for any reason
- major violation of the study protocol
- suspected pregnancy
- any intercurrent illness or condition which in the opinion of the Investigator would necessitate withdrawal from the study

Additionally, the subject may decide to withdraw from the study and will be offered consultation with the Investigator to discuss consequences and benefits of such withdrawal.

Subjects, who discontinue treatment for any reason, will be followed for toxicity, relapse, and death as per any standard subject.

10.5 Evaluable Subject

Every subject who fulfills all aspects of subject eligibility who receives at least 2 complete courses of chemotherapy will be evaluable for the response endpoint.

Subjects with a global deterioration of health status requiring permanent discontinuation of study treatment (taken off study) without objective evidence of disease progression will be counted as progressive disease. Every effort should be made to document the objective progression even after discontinuation of treatment. Deaths will be counted as treatment failure.

Every subject who fulfills all aspects of subject eligibility who receives a partial or complete course of chemotherapy will be evaluable for toxicity. Any exclusion, for any reason, must be specified by the responsible Investigator on the flow sheets.

10.6 Analysis of Primary Endpoints

The primary efficacy endpoint is the complete or partial response rate at week 14. The best response within the first 14 weeks will determine the primary endpoint. The response rates and 95% confidence intervals will be calculated.

10.7 Analysis of Secondary Endpoints

Partial response rates will be descriptively summarized using percentages and 95% confidence intervals.

The Kaplan-Meier method will be used to estimate time to event distributions for progression-free survival (defined in section 6.2) and survival (defined in section 6.4).

Adverse events will be summarized using subject level incidence rates so that a subject contributes once to any adverse event. The number and percentage of subjects with any adverse event will be summarized for each course. Serious adverse events will be analyzed similarly.

Quality of life endpoints will be descriptive summarized using means and 95% confidence intervals. The European Organisation for Research and Treatment of Cancer QLQ Questionnaire-Core 30 (QLQ-C30) and QLQ-Head and Neck 35 (QLQ-H&N35) module will be used for these assessments.

11.0 Records to be kept

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms in the eCRF. Source

documents which support data entered must be maintained for centralized compliance monitoring. Serious adverse events, when noted, will be recorded on site via the standard Serious Adverse Event (SAE) Form.

11.1 Quality assurance

Complete records must be maintained on each subject treated on the protocol. These records should include primary documentation (i.e., lab results, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The subject met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (i.e., dated notes about doses given and reasons for any dose modifications).
- Toxicity was assessed according to protocol (i.e., laboratory reports, etc.).
- Response was assessed according to protocol (i.e., x-ray, scan, lab reports, dated notes on measurements and clinical assessment, as appropriate)

11.2 Advarra Electronic Data Capturing (EDC) System

Data will be stored electronically for this study in the Forte EDC system contained on the Advarra secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Advarra logo.

Advarra EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect subject confidentiality. Authorized users log into Advarra through a secure connection and must provide a valid username, password, and database ID.

12.0 Human Subjects Protection Issues and Subject Consent Process

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Subjects are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Pathology material will be reviewed, and the diagnosis confirmed by the University Nebraska Medical Center Pathology Department, as outlined in the protocol.

12.4 Recruitment and Informed Consent

Subjects with advanced squamous cell carcinoma of the head and neck who are not candidates for surgery or radiation therapy will be available for recruitment. These subjects will be informed of the nature of this study, and will be asked to participate on a voluntary basis after

informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed on the title page.

12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent

If the subject chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there are any indications that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld

No information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects

It is anticipated that the use of the protocol chemotherapy in this subject population represents a reasonable treatment option. There are risks associated with chemotherapy, but the risk to benefit ratio is considered acceptable for subjects with advanced squamous cell carcinoma of the head and neck.

12.10 Potential Benefits to Society

Information obtained from this study may help other subjects by contributing to the knowledge of the biology of advanced squamous cell carcinoma of the head and neck and to understand the potential clinical benefit of this regimen.

12.11 Potential Risks

The use of cytototoxic chemotherapy are associated with numerous potential risks. Combined chemotherapy is considered a valid treatment option for subjects with advanced squamous cell carcinoma of the head and neck. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment.

12.12 Therapeutic Alternatives

If subjects choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include other chemotherapy drugs, palliative radiation, best supportive care, or a combination of these approaches. The treatment recommendations may or may not be similar to treatment as described in this protocol.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy, we anticipate that subjects who receive the treatment phase of the protocol will do no worse than expected with standard therapy, and may experience an improved outcome. The risk is considered to be acceptable in the setting of cancer.

12.14 Consent Form Documents

The consent document used in this study will include the adult consent document.

13.0 References

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14.0 Data Forms

Please refer to the Study Site Manual for the forms.

APPENDIX A - Karnofsky Scale for Performance Status

Scale (%)	Description
100	Normal; no complaints
90	Able to carry on normal activities; minor signs or symptoms of disease
80	Normal activity with effort
70	Cares for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance but able to care for most of needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated though death not imminent
20	Very sick. Hospitalization necessary. Active supportive treatment necessary
10	Moribund
0	Dead

Reference: Karnofsky DA, et al. Cancer 1:634-656, 1948.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Reference: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

APPENDIX B - ELIGIBILITY CHECKLIST

Date Completed (ddMMMyyyy):	IRB# 762-14 - Phase II Study of Docetaxel and Capecitabine in Advanced Squamous Cell Carcinoma of the Head and Neck PI: Apar Kishor Ganti, MD	Checklist #: Version 6.1 Dated: 16Oct2019
Institution:		
Subject ID:	Subject Initials:	Waiver #:

INCLUSION CRITERIA: Response should be YES	YES	NO	N/A
1. Histologically proven squamous cell carcinoma of the head and neck with measurable disease that is either recurrent after attempted cure with surgery and/or radiation therapy or newly diagnosed disease with distant metastases or incurable at diagnosis.	☐	☐	☐
2. Performance Status: Karnofsky score ≥70 or ECOG 0-2 (See Appendix A). **Enter PS**:	☐	☐	☐
3. Age 19 years or older (the age of consent in Nebraska); Age 18 years or older applicable to States where the age of majority is 18. **Enter Age**:	☐	☐	☐
4. No prior cytotoxic chemotherapy for metastatic squamous cell carcinoma of the head and neck. Subjects who have received chemotherapy as part of a multi-modality curative approach for head and neck cancer will be eligible as long as they have not received either docetaxel or capecitabine (or 5-FU) as part of that regimen. Patients who have received single agent immune checkpoint inhibitors for metastatic disease will be eligible.	☐	☐	☐
5. Adequate pre-treatment bone marrow reserve; WBC count ≥3,500/mm^3, platelet count ≥100,000/mm^3). **Enter WBC**: **Enter Platelet count**:	☐	☐	☐
6. Adequate renal function; serum creatinine less than 1.5 times the upper limits of normal. **Enter creatinine**:	☐	☐	☐
7. Adequate hepatic function: serum AST and ALT less than 1.5 times the upper limits of normal, serum alkaline phosphatase less than 2.5 times the upper limits of normal, serum total bilirubin is less than or equal to the upper limits of normal. **Enter AST**: **Enter ALT**: **Enter Alk Phos**: **Enter Total Bilirubin**:	☐	☐	☐
8. PT or INR, and PTT ≤ 1.5 x upper limit of normal unless subject is receiving anticoagulants. If the subject is on anticoagulation therapy, levels should be within therapeutic range. **Enter PT or INR**: / **Enter PTT**:	☐	☐	☐
9. Women of reproductive potential must be non-pregnant and non-nursing and must agree to employ 2 effective methods of birth control throughout the study and for up to 6 months following treatment.	☐	☐	☐
10. Women of child-bearing potential must have a negative pregnancy test within 7 days of initiating study. *(No childbearing potential is defined as age 55 years or older and no menses for two years or any age with surgical removal of the uterus and/or both ovaries).* **Enter date**: __/___/____ and **Result**	☐	☐	☐
11. The subject must be aware of the neoplastic nature of his/her disease and willingly provide written informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.	☐	☐	☐

*All of the above must be **yes** to be eligible.*

APPENDIX B - ELIGIBILITY CHECKLIST (Continued)

Date Completed (ddMMMyyyy):	IRB# 762-14 - Phase II Study of Docetaxel and Capecitabine in Advanced Squamous Cell Carcinoma of the Head and Neck PI: Apar Kishor Ganti, MD	Checklist #: Version 6.1 Dated: 16Oct2019
Institution:		
Subject ID:	Subject Initials:	Waiver #:

EXCLUSION CRITERIA: Response should be NO	YES	NO	N/A
1. Prior cytotoxic chemotherapy for metastatic squamous cell carcinoma of the head and neck. Subjects who have received chemotherapy as part of a multi-modality curative approach for head and neck cancer will be eligible as long as they have not received either docetaxel or capecitabine (or 5-FU) as part of that regimen.	☐	☐	☐
2. Patients who have received chemotherapy in combination with immunotherapy for metastatic disease.	☐	☐	☒
3. Allergy to either of the study medications or 5-fluorouracil.	☐	☐	☐
4. Simultaneous participation in other therapeutic clinical trials.	☐	☐	☐
5. Because of potential drug interactions between allopurinol/cimetidine/antivirals and 5-FU, if a subject is receiving any of these drugs they must be discontinued prior to starting this protocol.	☐	☐	☐
6. Prior malignancy, except for adequately treated basal cell or squamous cell carcinoma ofthe skin, or thyroid cancer.; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels (GnRH analogs or androgen receptor blockers acceptable); or other cancers from which the subject has been disease-free for at least five years.	☐	☐	☐
7. Uncontrolled intercurrent illnesses including, but not limited to symptomatic congestive heart failure, severe oxygen dependent chronic obstructive pulmonary disease, unstable angina or uncontrolled cardiac arrhythmia that could jeopardize the subject's ability to receive the chemotherapy described in the protocol safely.	☐	☐	☐
8. Pregnant OR nursing woman.	☐	☐	☐
9. Inability to co-operate with the study visit schedule and other requirements of the protocol.	☐	☐	☐
10. Any other clinically significant medical disease or condition laboratory abnormality or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.	☐	☐	☐

*All of the above must be **no** to be eligible.*

Eligibility:

☐ **Patient satisfies all criteria**

☐ **Patient not formally eligible, but admitted to this study because (state reason):**

☐ **Patient is not eligible for this study.**

ELIGIBILITY reviewed and confirmed.

Investigator Signature _____ **Date**_____

Printed Name of Investigator: _____

APPENDIX C - Body Surface Area Calculation

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m2):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

APPENDIX D - Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)

PURPOSE

To provide a means of ensuring oral, sublingual and/or buccal routes of medication adherence to patients while participating in a clinical trial.

1. A physician's order will be completed by study patients or representative for oral, sublingual and/or buccal administration per IRB approved protocol.
2. To ensure the consistent and safe administration of medications not given under the direct supervision of study staff (at home), there will be a "Medication Information Sheet" and a calendar to document times of drug administration.
3. To record medication adherence Study staff will document results of medication reconciliation and or medication return in the patient's chart.
4. Maintain documentation of medications returned or sent to investigational pharmacy for destruction (if applicable).

PROCEDURE

1. Protocol specific information regarding the individual medication(s) should be listed on the form "Medication Information Sheet" and given to the patient at the start of the study and throughout treatment if necessary to help ensure adherence. (See Form A)

2. Name, dose and route of each medication should be listed under 'How to take your Medication' on the "Medication Information Sheet".

3. Patients will be given a monthly "Medication Calendar". The calendar will have a place for the patient to record the time that the medication(s) were taken. (See Form B for example)

4. The research nurse will review the patient's "Medication Calendar" for adherence to the study regimen for oral medication administration. Adherence will be noted in the patient's chart. Medication reconciliation will be done and if there is medication to be returned/destroyed it will be sent to the Nebraska Medical Center Investigational Pharmacist for return/destruction in accordance to the Nebraska Medical Center Destruction of Investigational product, Policy #4.860.

Medication Information Sheet (Form A)

Patient Name:_____ Study or MRN #: _____

Title of protocol: Phase II Study of Docetaxel and Capecitabine in Advanced Squamous Cell Carcinoma of the Head and Neck

IRB# 762-14

Medication: Capecitabine (Xeloda®) is a chemotherapy pill.

How to take your medication: Capecitabine (Xeloda®) The total daily dose _____mg (___tablets) should be taken by mouth in two divided doses _____mg (___tablets) in the morning and _____mg (___tablets) evening about 12 hours apart every day for 14 days in a row. The total daily dose in mg will be rounded down to the nearest tablet size. If the dosing calls for an uneven number of pills, the larger dose will be given in the evening. Follow your Medication Calendar that is provided to you by the research nurse.

Things to know about your medication:

1. You should take your medication at the same time each day and it should be taken within 30 minutes after taking a meal.
2. Tablets should be swallowed whole with a full glass of water. If the tablets are accidentally opened or damaged, precaution should be taken to avoid inhalation or contact with the skin or mucous membranes.
3. **If you miss a dose of your medication, it should be skipped altogether.** You should NOT double the next dose. If a dose is missed make sure to mark it on your Medication Calendar (Form B).
4. **If the treatment is interrupted due to toxicity, the skipped doses should not be replaced.**
5. Return unused medication to your research nurse for proper procedures for handling and disposal of chemotherapy.

Your research nurse is: _____

Contact information: phone _____

After hours, nights, weekends and holidays please call 402-559-5600 and ask for the Oncologist on call.

PATIENT PILL CALENDAR

IRB #: 762-14 SUBJECT ID#:

	Cycle DATE			Number of Tablets Taken (refer to Medication Adherence Form)		Use this area below to make notes about things you would like to tell the doctor (including unusual symptoms, other medications, etc.).
Day	Month	Day	Year	AM	PM	
1				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
2				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
3				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
4				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
5				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
6				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
7				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
8				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
9				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
10				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
11				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
12				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
13				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
14				____ 500 mg ____ 150 mg	____ 500 mg ____ 150 mg	
Other notes: Take 4 mg dexamethasone twice daily the day before your docetaxel infusion, the day of, and the day after. **DO NOT make up missed doses of Capecitabine.**						

APPENDIX E - NCI Common Toxicity Criteria Version 4.0 (CTCAE) Active Date: May 29, 2009

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Minor editorial updates have been made to CTCAE v4.0, which are represented in v4.03. These edits do not change the meaning of v4.0 content and all previous versions (CTCAE v4.0, v4.01, v4.02) are still valid and referred to as CTCAE v4.0. V4.03 includes clarifications for a select few grading scales and adverse event term definitions. Most of the revisions are associated with grading scales that include a quantitative component. A list of changes is located at :

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

An updated version (4.03) is now in use as of June 14, 2010.

APPENDIX F - FDA MEDWATCH form 3500A

Available on-line at:

https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

http://www.fda.gov/medwatch/SAFETY/3500.pdf

APPENDIX G - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4

Specimen

48.	Has your appearance bothered you?	1	2	3	4

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

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Specimen

APPENDIX I - Schedule of HBM Sample Assessments (for research purposes only)

Sample Collection: Source and Human Biologic Material (HBM) to be used: We will use two- 10 mL EDTA (lavender top tubes) and one- 10 mL (red top tube) for blood sample collection. We will collect 10 mL urine sample from the patient to store for future research purposes including DNA sequencing. (See Protocol Section 5.6 for details).

No therapeutic intervention will be undertaken and the results of these studies will not have any influence on the medical management of the subjects.

Facility	Sample	Contact Person(s) and Shipping Address	Date and Time Points
Laboratory of David L. Kelly, PhD Fred & Pamela Buffett Cancer Center	Blood: (30 mL total) two-10*ml EDTA (lavender top) and one- 10ml (red top)* blood collection Urine: 10 mL urine collection Deliver or ship same day at room temperature	David L. Kelly PhD Tel: (402) 559-9157 Cell: (402) 699-1132 Fax: (402) 559-4651 Email: dkelly@unmc.edu Amy Wells, MS Research Technologist Tel: (402) 559-6015 Email: awells@unmc.edu Shipping address: Attn: Amy Wells, MS University of Nebraska Medical Center 601 S. Saddle Creek Rd. Fred & Pamela Buffett Cancer Center, Room # BCC 5.12.429 Omaha, Nebraska 68106	☐ **Baseline** Blood Sample Date: ___/___/____ ☐ **Baseline** Urine Sample Date: ___/___/____ ☐ **After cycle 2**, Blood Sample Date: ___/___/____ ☐ **After cycle 2**, Urine Sample Date: ___/___/____ ☐ **End of study**, Blood Sample Date: ___/___/____ ☐ **End of study**, Urine Sample Date: ___/___/____

Please contact Amy Wells above to advise of planned shipments and/or the Research Support Nurse Manager at 402-559-5286 to discuss appropriate procedures.

Visit	Specimen Type	Collection amount	Tube	Handling Instructions
Baseline	Whole blood Urine	30 mL 10 mL	• 2 - 10 mL lavender top tubes • 1 10 mL red top tub • Urine cup	**Whole blood** - Store and Ship at 4ºC **Plasma sample** – The samples should be maintained at 2-8°C while handling. Gently invert tube with blood. Centrifuge for 15min at 3,000 rpm at 4°C (no breaks). Transfer plasma to clean tube and store at 2–8°C. Deliver or ship the same day as collection at room temperature.
After 2 cycles	Whole blood Urine	30 mL 10 mL	• 2 - 10 mL lavender top tubes • 1 10 mL red top tub • Urine cup	
End of Study	Whole blood Urine	30 mL 10 mL	• 2 - 10 mL lavender top tubes • 1 10 mL red top tub • Urine cup	