Weekly Docetaxel, Cisplatin, and Cetuximab (TPC) in Palliative Treatment of Patients with SCCHN

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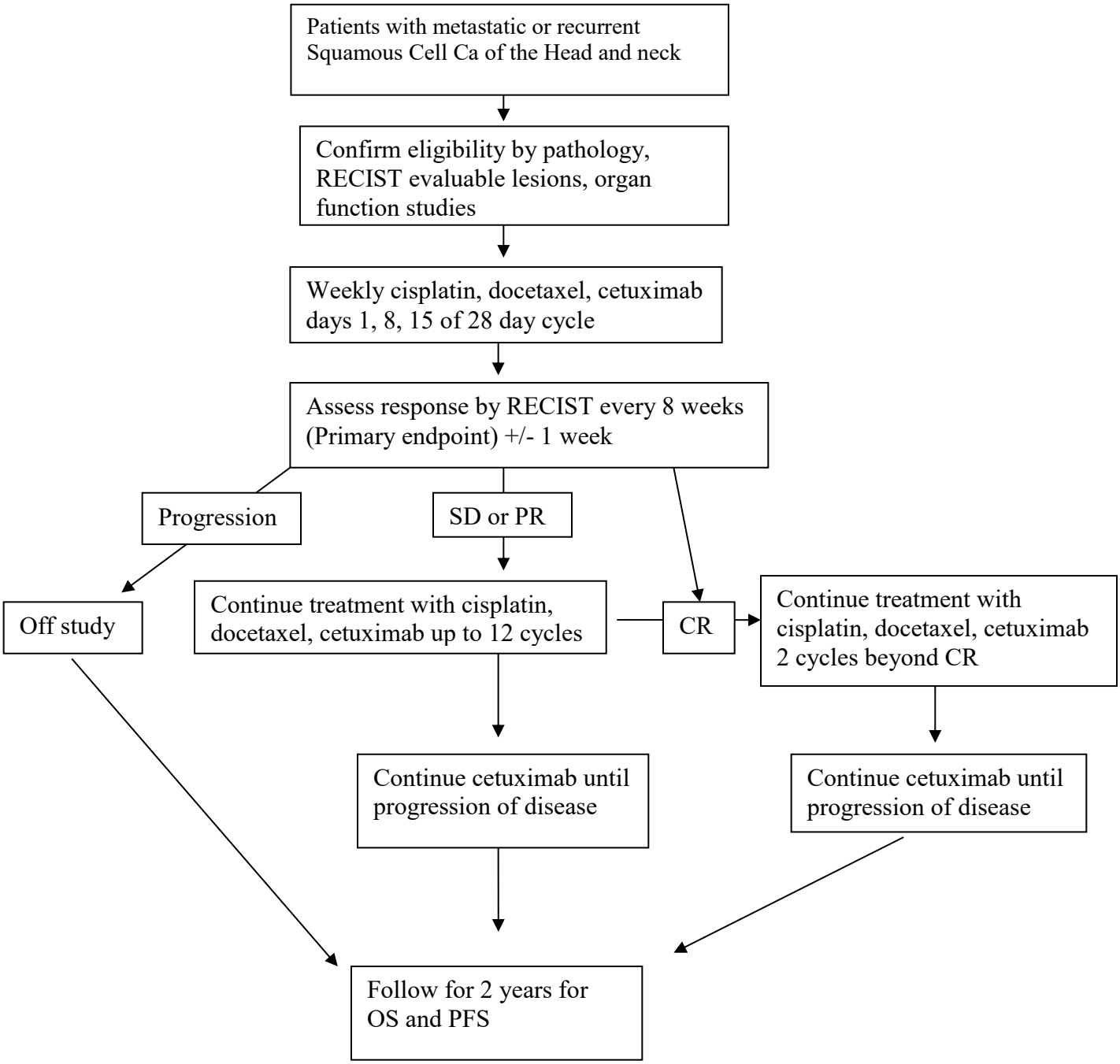
PROTOCOL SYNOPSIS

TITLE	Weekly Cisplatin and Docetaxel with Cetuximab in palliative treatment of patients with SCCHN
STUDY PHASE	Phase 2
INDICATION	Squamous Cell Carcinoma of the Head and Neck (SCCHN)
TREATMENT AGENTS	Cisplatin, Docetaxel, Cetuximab Carboplatin
PRIMARY OBJECTIVE(S)	Response Rate
SECONDARY OBJECTIVE(S)	Progression Free and Overall Survival, Safety
TREATMENT SUMMARY	Docetaxel 30mg/m2/week IV over 30 minutes. Cisplatin 30 mg/m2/week IV over 30 minutes(For certain AEs, Carboplatin to be substituted). CETUXIMAB 400 mg/m2 IV over 2 hours load, then 250 mg/m2 IV over 1 hour weekly. Repeated 3 of every 4 weeks: Patients to receive treatment during scheduled week 1 (Day 1), 2 (Day 8), and 3 (Day 15). Taking a break to recover during the 4th week (Day 21 - 28) of the 28 day cycle. If a dose is held during weeks 1-3, the dose may be given during the 4th week. Continue treatment until evidence of disease progression or unacceptable AE profile.
SAMPLE SIZE	Up to 27 patients in a Simon 2 stage design: 10 patients will be treated in the first stage and up to 17 patients may be treated in the second stage.
STATISTICAL CONSIDERATIONS	To distinguish 25% RR from 50% rr with alpha and beta = 0.1

SCHEMA


Patients with metastatic or recurrent Squamous Cell Ca of the Head and neck
Confirm eligibility by pathology, RECIST evaluable lesions, organ function studies
Weekly cisplatin, docetaxel, cetuximab days 1, 8, 15 of 28 day cycle
Assess response by RECIST every 8 weeks (Primary endpoint) +/- 1 week
Progression
SD or PR
Off study
Continue treatment with cisplatin, docetaxel, cetuximab up to 12 cycles
CR
Continue treatment with cisplatin, docetaxel, cetuximab 2 cycles beyond CR
Continue cetuximab until progression of disease
Continue cetuximab until progression of disease
Follow for 2 years for OS and PFS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

To establish the response rate using RECIST [1] criteria to weekly TPC in patients with metastatic or relapsed squamous cell carcinoma of the head and neck.

1.2. Secondary Objectives

To establish the safety profile, progression free and overall survival of weekly TPC in this patient population.

2. BACKGROUND

2.1 Study Agents

Docetaxel and cetuximab are FDA approved for the treatment of squamous cell carcinoma of the head and neck (SCCHN). Cisplatin and carboplatin, while not FDA approved for SCCHN, have been for several decades used as a standard of care in patients with SCCHN in combination with taxanes and more recently in combination with cetuximab. [2] Please refer to their respective package interests for details concerning pharmacology and expected adverse events.

2.3 Rationale

Rationale/Hypothesis:
Squamous cell carcinoma of the head and neck (SCCHN) region is one of the more chemotherapy sensitive human neoplasms. Response rates approaching 70% have been reported with single agent treatment, and recent reports demonstrate that overall response rates and complete response rates approaching 90% and 60%, respectively are achievable. [3-5] Despite the advances made in the treatment of patients with SCCHN confined to the primary and neck region, many of these patients still relapse and are not candidates for salvage surgery or radiation treatment. Most of these patients die as a result of complications of their cancer. [6-9] Additionally, up to one third of patients present with metastatic disease and are therefore not eligible for multimodality potentially curative treatment. Because patients with recurrent or metastatic disease are generally incurable, the goals of treatment are more limited, and include prolongation of overall survival (OS) or progression-free survival (PFS), palliation of existing symptoms, and prevention of new cancer-related symptoms. Improvement in survival has been the holy grail of treatment in this setting. Platinum- based chemotherapy has been the standard treatment in this setting, based in the fact that platinum based combinations have demonstrated the highest response rates. [10] If overall survival is the benchmark standard, there have been only two trials to date demonstrating superiority of one regimen versus others. Morton et al. compared cisplatin and bleomycin in a 2x2 design, and only the cisplatin arms in aggregate demonstrated a statistically significant survival advantage of 4.3 versus 1.8 months to the CDDP containing arms. [11]

More recently, Vermorken and colleagues demonstrated in a landmark study that the addition of cetuximab to a platinum and 5-FU (PF) backbone was associated with an approximately 3 month improvement in median survival. [2] Unfortunately, because the design of the trial was such that patients in the cetuximab arm received the agent not only with PF but as a maintenance in non-progressors, it is theoretically possible that the survival benefit may be obtained by sequential rather than concurrent dosing. The higher response rate in the cetuximab arm would argue that the concurrent treatment was at least a contributor to the OS advantage; however, it is also worth noting that this trial, dubbed "EXTREME", was notable for significant clinically relevant toxicity in both arms. Over 30% of the patients experienced grade 4 AEs. It is also noteworthy that there were no grade 3 or higher diarrhea or mucositis toxicities reported in this trial, when in ECOG 1395, a 31% high grade stomatiitis rate was

reported for an identical PF regimen, leading one to wonder why so few AEs were reported on the EXTREME study. [12] Additionally, the standard of practice in Belgium is to hospitalize all patients for the administration of PF, whereas in the US, patients are typically treated in outpatient infusion centers. (Jan Vermorken, personal communication ASCO annual meeting 2009)

To further put the EXTREME trial into context, note that Burtness and ECOG colleagues studied cisplatin +/- cetuximab in SCCHN patients in a smaller RCT. [13] Because the trial was much smaller than the Vermorken study, they were not able to demonstrate a statistically significant survival advantage to the addition of cetuximab, but the survival hazard rates in the Burtness and Vermorken trials were similar, suggesting that the benefit from the cetuximab was not largely due to a combination effect with 5-FU. Vermorken and colleagues have also performed a global phase 3 trial of PF +/- panitumumab in patients with recurrent or metastatic SCCHN with a similar design to the EXTREME trial which will answer whether this anti- EGFR MOAB from another IGG class will also improve survival.[14] In this trial, AEs, including stomatitis and mucosal inflammation were substantial as well. Initial reports of this trial, not yet available in the peer reviewed literature, claim that the survival benefit associated with the EXTREME trial using cetuximab were not reproduced using panitumumab.

PF's use as the backbone regimen used for the addition of new agents in the palliative setting is largely driven by the large amount of data of PF in the induction setting, combined with the fact that in some European countries, taxanes remain unapproved for use on patients with head and neck cancer, precluding its use as part of an acceptable backbone regimen in the EORTC trials (Vermorken, personal communication ASCO 2009).

Therefore, the use of PF as the backbone for the addition of cetuximab is largely due to historical and drug availability issues rather than what has been defined as the best therapeutic combination. Another combination shown to be of equal efficacy as PF in this setting is the combination of paclitaxel and cisplatin (PC). A RCT comparing PF versus cisplatin 75 mg/m2 plus paclitaxel 175 mg/m2 q 21 days demonstrated no significant difference in RR or OS, but the high grade AEs in the PF arm were more common than in the PC arm. [12] Granulocytopenia rates were similar but anemia. Infection, vomiting, diarrhea, stomatitis, metabolic disturbances and fatigue were more prominent in the PF arm. Therefore, if access to paclitaxel is not at issue, PC could be considered, based upon therapeutic index, a superior doublet to use in this setting. Similar regimens of docetaxel and cisplatin (TC) have also been studied in this setting, yielding high response rates and similar duration of response as PC. [15] [16] [17]

A major difficulty with the PC and TC regimens administered on a q 21 day schedule is the unpredictability of the hematological AE profile. In many other oncological diseases, the use of weekly treatment regimens has been used to circumvent this problem without the loss of efficacy, and there are data specific to SCCHN which suggest that weekly taxane and cisplatin combinations are very well tolerated and are associated with similar response rates and OS as the q 21d regimens. [18] In the initial treatment setting, platinum plus taxane plus cetuximab regiments have been shown to be highly active, feasible and well tolerated in SCCHN patients but when the platinum and taxanes are given on the q 21 day schedule, toxicity is substantial. [19,20,21] While docetaxel, cisplatin, and cetuximab have been given in the recurrent or metastatic setting, on a q 21 day schedule toxicity has been substantial but response rates as high as 49% in this setting are very high relative to other combinations whose response rates are usually in the 30-40% range in this setting. [22]

2.4 Study Design

This treatment trial is a single arm, unblinded, two staged Simon [23] design to evaluate the RECIST

response rate to weekly TPC in patients with recurrent or metastatic SCCHN.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A for enrollment procedures.

3.1 Inclusion Criteria

3.1.1 Squamous cell carcinoma of head and neck sites, including all pharynx, larynx, oral cavity, skin and para-nasal sinus sites. Patients with a diagnosis of Nasopharyngeal Carcinoma, or SCC of unknown primary presenting in the neck clinically compatible with head and neck mucosal primary sites, are eligible.

3.1.2 Patients who have received prior chemoradiation, radiation, and/ or surgery in the potentially curative setting are eligible as long as 3 months has elapsed since the end of the potentially curative treatment ended.

3.1.4 Patients must be greater than 16 years old.

3.1.5 ECOG Performance Status < 3 at enrollment is required.

3.1.6 Laboratory value requirements at enrollment:
Absolute neutrophil count $\geq$ 1500/mm3
Platelet count $\geq$100K/mm3

AST and ALT < 2.5 x ULN unless liver metastases documented. In this latter case, AST and ALT < 5 x ULN required.
Total Bilirubin < 1.5 x ULN unless the patient has Gilbert's syndrome, in which case T. Bilirubin < 2.5 x ULN required
Serum Creatinine $\leq$ 1.5 mg/dL OR an estimated creatinine clearance from 24 hour urine collection $\geq$ 50 ml/min

3.1.7 Clinical requirements at enrollment:
Peripheral neuropathy < grade 2

Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 No prior palliative chemotherapy

3.2.2 Patients with active infections including known HIV are not eligible. HIV positive patients on HAART with undetectable blood HIV levels are eligible. Patients with a history or serological evidence of exposure to Hepatitis B without active infection are eligible for this study.

3.2.3 Patients with prior grade 3 allergic or infusion reactions to docetaxel, cisplatin or cetuximab are not eligible. A history of well tolerated infusion reactions is NOT an exclusion.

3.2.4 Pregnant women and/or nursing patients will be excluded from the study because of potential harm to the fetus or nursing infant.

3.2.5 Because the primary endpoint of this study is response rate and not survival, patients with a history of other malignancies treated curatively greater than one year prior to enrollment and without evidence of relapse at the time of enrollment are eligible.

3.2.6 Patients with known brain metastasis are eligible only if by CNS imaging there is no evidence of CNS progression at least 30 days following definitive CNS treatment (resection or radiation).

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study treatment. The participant must receive a copy of the signed and dated consent document. A signed and dated copy must be placed into the patient's medical record. The original signed copy of the consent document must be retained in the research file.

3.4 Study Timeline

Primary Completion:
It is estimated that accrual will take 1 year for each of the two stages and another year after each stage has been completed to have the complete response assessment analyzed.

Study Completion:
From first accrual to final response evaluation, 3 years.

4. TREATMENT PLAN

Patients will be treated weekly with cisplatin, docetaxel, and cetuximab according to the specifics designed below. If a dose is held during weeks 1-3, the dose may be given during the 4th week. The next cycle should then begin with Triplet 1 the following week.

STANFORD- NOTE THAT USE OF EPIC BEACON TEMPLATE #2161, ITA HEAD AND NECK DOCETAXEL / CISPLATIN / CETUXIMAB QWEEK(ONC) IS STRONGLY ENCOURAGED.

UC DAVIS- NOTE THAT A UC DAVIS SPECIFIC WRITTEN CHEMOTHERAPY ORDER SET WILL BE CREATED.

AGENT	DOSE	SCHEDULE	CYCLE duration
Docetaxel	30 mg/m^2 over 30 minutes IV	Days 1, 8, 15	28 days
Cisplatin	30 mg/m^2 over 30 minutes IV	Days 1, 8, 15	
Cetuximab	**Loading dose** for cycle 1, day 1 will be administered as 400 mg/m^2 ONLY IV	Days 1, 8, 15*	

	over 120 minutes Then for all subsequent and/or maintenance doses (starting at cycle 1, day 8) will be given as 250 mg/m^2 IV over 60 minutes		
Carboplatin (only if substituting for cisplatin)	AUC** = 2, IV over 30 minutes	Days 1, 8, 15	

*In order to facilitate timely infusion of agents, cetuximab may be administered +/- 8 day of the cisplatin and docetaxel infusions since in some cases the duration of infusion on day 1 cycle 1 may be prohibitively long. In cases where the loading dose of cetuximab was given alone and it has been more than 5 days since the cetuximab was given, cetuximab may be given at the weekly dosing per protocol during the next treatment day, unless treatment must be held due to AE.

In cases where cetuximab treatment has been held for more than 2 scheduled treatment visits [14 days] the patient may be given an additional loading dose of cetuximab. In addition, if the last treatment is >2 weeks (14 days) from last dose, then the cycle shall begin again starting at Triplet 1 to match the loading dose of Cetuximab.

Cycle ONE Clarification:

- Cycle one is to include the loading dose of Cetuximab (alone) and three doses of the triplet (Platinum/Docetaxel/Cetuximab) when the loading dose of cetuximab was given more than 5 days from scheduled triplet #1 dose. [Day 1: Cetuximab Alone … Day 8: Triplet dose # 1]

OR

- Cycle one is to include the loading dose of Cetuximab (alone) and two doses of the triplet (Platinum/Docetaxel/Cetuximab) when the loading dose of cetuximab was given $\leq$ 5 days from scheduled Platinum/Docetaxel dose. [Day 1: Cetuximab Alone … Day 5: Platinum/Docetaxel only (dose #1)]

Calculated using Cockcroft-Gault GFR = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr). Therefore by Calvert formula, **Carboplatin dose (mg) = AUC x (GFR +25)

Duration of treatment: Patients may receive up to 12 cycles of cisplatin and docetaxel treatment. All confirmed complete responders will be treated with cisplatin and/or docetaxel for an additional 2 cycles beyond confirmation of CR. Cetuximab will be continued until progression of disease.

4.1 Premedications and Supportive Care Guidelines

CETUXIMAB

Patients shall receive prior to the first dose of cetuximab:

50 mg of diphenhydramine, PO or IV.

Prior to all doses of subsequent cetuximab, patents shall receive:

25-50 mg of diphenhydramine PO or IV per physician discretion.

CISPLATIN

Patients shall receive prior to each dose of cisplatin:

Ondansetron 24 mg oral or 16 mg IV, or therapeutic equivalent

Dexamethasone 8 mg BID orally or IV x 6 doses beginning approximately 12 hours prior to cisplatin. Note this also is premedication for docetaxel. Per physician discretion, following the first dose of cisplatin and docetaxel, dexamethasone may be reduced to 8 mg BID x 2 doses.

Use of other antiemetics such as aprepitant, metochlopramide, prochlorperazine and lorazepan per physician preference are permitted.

Patients shall receive at least two liters of intravenous saline hydration on days of cisplatin, one liter immediately prior to the cisplatin administration. Use of magnesium supplementation, mannitol for diuresis and additional hydration is per physician preference.

DOCETAXEL

Dexamethasone 8 mg BID orally or IV x 6 doses beginning approximately 12 hours prior to docetaxel. Note this also is premedication for cisplatin. Per physician discretion, following the first dose of cisplatin and docetaxel, dexamethasone may be reduced to 8 mg BID x 2 doses.

CARBOPLATIN

Ondansetron 16 mg oral or 8 mg IV, or therapeutic equivalent.

4.2 Criteria for Removal from Study

Treatment will be stopped and patients will be removed from study for clinical and/or radiological disease progression, unacceptable adverse events, and patients who have withdrawn their consent.

4.3 Alternatives

Standard chemotherapy regimens are available for SCCHN. All procedures noted in Section 9- Study Calendar for this trial are considered Standard of Care, and part of routine ordering at the discretion of the physician.

5. AGENTs INFORMATION

5.1 Agents

Docetaxel, cisplatin, carboplatin and cetuximab are all commercially available agents for use in patients with cancer and are routinely used for the palliative treatment of patients with SCCHN. Please refer to their respective package interests for details concerning pharmacology, preparation, compatibility, administration and expected adverse events.

5.2 Availability

Docetaxel, cisplatin, carboplatin and cetuximab are all commercially available.

5.3 Agent Ordering

N/A. Commercial supplies to be used.

5.4 Agent Accountability

N/A. Commercial supplies to be used and administered according to physician orders.

6. DOSE MODIFICATIONS

All chemotherapy related toxicities should be graded according to the Common Terminology Criteria for Adverse Events Version 4.0. All dose reductions will be based on the most recent lab values and worst overall clinical AE since previous evaluation interval for clinical assessments on the day of treatment.

Dose modification guidelines for chemotherapy and cetuximab are independent. Cetuximab can be continued while docetaxel and cisplatin are held (if criteria for retreatment with cetuximab are met). Similarly, chemotherapy can be continued while cetuximab is held (if criteria for retreatment with chemotherapy are met). If holding of one chemotherapy agent is required, the other chemo-agent can still be administered.

NOTE: No dose re-escalations will be allowed once the reduction has occurred.

Starting dose	Dose level minus one	Dose level minus two
Cisplatin 30 mg/m^2	25 mg/m^2	20 mg/m^2
Docetaxel 30 mg/m^2	25 mg/m^2	20 mg/m^2
Cetuximab 250 mg/m^2	200 mg/m^2	150 mg/m^2
Carboplatin AUC 2	AUC 1.5	AUC 1

Cetuximab dose reduction guidelines:

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe acneiform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended. If a patient experiences severe acneiform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. NO dose reductions below dose level minus two.

Cetuximab Dose modification for rash:

Severe (Grade 4)	Cetuximab dose change	Outcome	Subsequent dosing
1st occurrence	Hold infusion for up to 2 doses (2 weeks)	improvement	No dose change
		No improvement	Discontinue cetuximab
2nd occurrence	Hold infusion for up to 2 doses (2 weeks)	improvement	Reduce one dose level
		No improvement	Discontinue cetuximab
3rd occurrence	Hold infusion for up to 2 doses (2 weeks)	improvement	Reduce one dose level
		No improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Cetuximab infusion reactions

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Severe infusion reactions occurred with the administration of Cetuximab in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

Management of cetuximab infusion reactions

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms. Mild to moderate infusion reactions should be managed by slowing the infusion rate of cetuximab and by continued use of antihistamine medications (e.g., diphenhydramine) in subsequent infusions. If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. Cetuximab should be immediately and permanently discontinued in patients who experience severe (grade 3 or 4) infusion reactions.

GRADE OF Cetuximab infusion reaction	Response
Grade 1 or 2, flushing, rash, feverm dyspnea, urticaria	Stop infusion, administer appropriate therapy, restart at 50% of prior infusion rate.
Grade 3 or 4, brochospasm requiring parenteral medications, angioedema, hypotension, anaphylaxis, stridor	Stop infusion. Permanently discontinue cetuximab. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated

Docetaxel, Cisplatin, and Carboplatin dose reduction guidelines: *Dose reductions are ONLY to be considered for chemotherapy related toxicities.*

(NO dose reductions below dose level minus two permitted)

Toxicity and Grade	Docetaxel modification	Cisplatin and/or Carboplatin modification
ANC Grade 2 (<1500 - 1000/mm^3)	Reduce one level	Reduce one level
ANC Grade 3 or 4 (< 1000/mm^3)	Hold for up to 2 weeks then reduce one level	Hold for up to 2 weeks then reduce one level
PLT Grade 2-4 (<75K/mm^3)	Hold for up to 2 weeks then reduce one level	Hold for up to 2 weeks then reduce one level
T Bili* Grade 2 (> 1.5-3x ULN)	Reduce one level	No Change
T Bili Grade 3-4 (>3 x ULN)	Hold for up to 2 weeks	No Change
Neuropathy or Hearing Loss Grade 2	Hold until < Grade 1 then dose reduce one level for neuropathy, no change for hearing loss	Hold until < Grade 1 then dose reduce one level
Neuropathy or Hearing Loss Grade 3	Hold until < Grade 1 then dose reduce one level for neuropathy, no change for hearing loss	Substitute with carboplatin
Neuropathy or Hearing Loss Grade 4	Discontinue for neuropathy, no change for hearing loss	Substitute with carboplatin

Creatinine: CALCUALTE CREATININE CLEARANCE FOR SERUM Creatinine > 1.3**	No dose modification	Cr Cl $\geq$ 50 ml/min, no change in cisplatin. CrCl < 50 ml. min, substitute carboplatin.
Other non-hematological AEs Grade 3-4	Hold for up to two weeks until < Grade 1 then dose reduce one dose level	Hold for up to two weeks until < Grade 1 then dose reduce one dose level

* Unless Gilbert's syndrome at baseline
** Creatinine clearance estimate by Cockroft-Gault = [(140- age (yrs)) x (actual weight (kg)) / (72 x serum creatinine (mg/dl))] x (0.85 if female).

7. ADVERSE EVENTS

7.1 Potential Adverse Events

Docetaxel, cisplatin, carboplatin and cetuximab are all commercially available.
Please refer to the approved package inserts for these agents to see the complete list of reported AEs. Below is a brief summary of common AEs with these agents:

Cisplatin:
1.Renal: A dose-related, cumulative renal tubular injury can occur; adequate hydration and diuresis usually minimize the risk. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.
2. Neurologic: A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus, occurs in about 30% of patients. Paresthesias, decreased vibratory, position, and touch sensations are less common; particularly at cumulative doses <400 mg/m2.
3. Hematologic: Mild leukopenia and thrombocytopenia occur in 25-30% of patients, but are rarely dose-limiting; anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.
4. Gastrointestinal: Severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea a delayed (72-96 hour) reaction, requiring additional therapy may occur. Anorexia and taste changes may also occur.
5. Hypersensitivity: Allergic reactions are reported in up to 20% of patients Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.
6. Other: Electrolyte wasting (magnesium, potassium and sodium), papilledema, optic neuritis, retrobulbar neuritis are reported

Carboplatin:
1. Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common.
2. Allergic Reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.
3. Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.

4. Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.
5. Hepatic Toxicity: Elevated alkaline phosphatase, total bilirubin, and SGOT have been observed.
6. Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

Docetaxel:
1. Myelosuppression (neutropenia, leukopenia, thrombocytopenia, anemia).
2. Hypersensitivity: Minor symptoms include hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, and tachycardia. More severe reactions include hypotension requiring treatment, dyspnea with bronchospasm, generalized urticaria, and angioedema. The majority (53%) of the reported reactions occurred within 2-3 minutes of initiation of treatment and 78% occurred within the first 10 minutes. Reactions usually occurred with the first and second doses.
3. Cardiovascular: Atrial arrhythmia (sinus bradycardia [usually transient and asymptomatic], sinus tachycardia, and premature beats); significant events include syncope, hypotension, other rhythm abnormalities (including ventricular tachycardia, bigeminy, and complete heart block requiring pacemaker placement), and myocardial infarction. Hypertension, possibly related to concomitant administration of dexamethasone, may also occur.
4. Neurologic: Sensory changes (taste changes); peripheral neuropathy; arthralgia and myalgia (dose-related, more common when colony-stimulating factors are also administered); seizures; mood alterations; neuroencephalopathy; hepatic encephalopathy; motor neuropathy; and autonomic neuropathy (paralytic ileus and symptomatic hypotension).
6. Dermatologic: Alopecia, universal, complete, and often sudden, between days 14-21; injection site reactions (erythema, induration, tenderness, skin discoloration); infiltration (phlebitis, cellulitis, ulceration, and necrosis, rare); radiation recall; and rash.
6. Gastrointestinal: Nausea, vomiting, diarrhea, mucositis, pharyngitis, typhlitis (neutropenic enterocolitis), ischemic colitis, and pancreatitis.
7. Hepatic: Increased SGOT (SAST), SGPT (ALT), bilirubin, alkaline phosphatase; hepatic failure, and hepatic necrosis.
8. Other: Fatigue, headaches, light-headedness, myopathy, elevated serum creatinine, elevated serum triglycerides, and visual abnormalities (sensation of flashing lights, blurred vision).

Cetuximab:
1. Infusion reaction: Characterized by airway obstruction (e.g., bronchospasms, stridor, hoarseness), urticaria, hypotension; infusion reactions occur in about 3% of patients, rarely with fatal outcome (< 1 in 1,000)
2. Pulmonary: Interstitial lung disease (less than 0.5% of cases, usually reported in patients with pre-existing fibrotic lung disease), pulmonary emboli, dyspnea, increased cough
3. Hematologic: Leukopenia, anemia
4. Gastrointestinal: Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain, anorexia, stomatitis, kidney failure,

5. Dermatologic: Rash, acne, dry skin, pruritus, ulceration, alopecia, nail disorder
6. Circulatory: Deep vein thrombosis
7. Neurological: Headache, depression
8. Allergy: Allergic reaction, anaphylactoid reaction
9. Ocular: Conjunctivitis
10. Other: Hypomagnesemia , asthenia, weight loss, dehydration, fatigue.

7.2 Adverse Event Reporting

The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution or until 30 after the last dose of the study treatment.

Any Serious and Non-Serious Adverse Events experience from the following list will be clearly noted in source documentation during each treatment cycle and will be captured on the study specific Case Report Forms (CRFs): Neuropathy, Cetuximab Rash, Hearing Loss, low Absolute Neutrophil Count (ANC), low Platelet Count (PLT), low Hemoglobin (Hgb), and worst Creatinine levels.

SAEs CTCAE v 4.0 Grade 3 and above, and all subsequent follow-up reports will be reported to the CCTO Safety Office regardless of the event's relatedness to the investigation. Following review by the CCTO Safety Officers, any events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of the review, or within 5 working days for deaths or life-threatening experiences.

9. STUDY CALENDAR

Schedules shown in the Study Calendar below represent the first 3 cycles. Subsequent cycles should follow the same pattern. All assessments are Standard of Care (SOC) and routine ordering applies at the physician's discretion.

	Pre-Study[h]	Cycle 1				Cycle 2				Cycle n				Off Study[d]
		Dose 1[f]	Dose 2	Dose 3	Break[g]	Dose 4	Dose 5	Dose 6	Break[g]	Dose n	Dose n2	Dose n3	Break[g]	
Cetuximab, docetaxel, and cisplatin (or carboplatin)[a]		X[f]	X	X		X	X	X		X	X	X		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------												----------X
Physical exam	X	X				X				X				X
Vital signs[b]	X	X	X	X		X	X	X		X	X	X		X
Height	X													
Weight	X	X				X				X				X
Performance status	X													
CBC w/diff, plts	X	X	X	X		X	X	X		X	X	X		X
Serum chemistry[c]	X	X	X	X		X	X	X		X	X	X		X
Adverse event evaluation	X	X				X				X				
Tumor measurements and radiological evaluation	X								X					X[e]

a: Investigational Agent: Dose as assigned; route/schedule.
b: Blood Pressure, Heart Rate (Pulse), Temperature.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
d: Off-study evaluation to be conducted within 30 days of last dose.
e: Off-study evaluation
f: In order to facilitate timely infusion of agents, cetuximab may be administered +/- 8 day of the cisplatin and docetaxel infusions since in some cases the duration of infusion on day 1 cycle 1 may be prohibitively long. In cases where the loading dose of cetuximab was given alone and it has been more than 5 days since the cetuximab was given, cetuximab may be given at the weekly dosing per protocol during the next treatment day, unless treatment must be held due to AE.
g: If a dose is held during weeks 1-3, the dose may be given during the 4th week. The next cycle should then begin with Triplet 1 the following week
h: Pre-study evaluations must be completed within 28 days of treatment initiation, Day 1, with the exception of labs. Labs must be repeated to confirm continued eligibility for day 1 within institution standards for tx initiation.

Cycle 1 Clarification:

Cycle one is to include the loading dose of Cetuximab (alone) and three doses of the triplet (Platinum/Docetaxel/Cetuximab) when the loading dose of cetuximab was given more than 5 days from scheduled triplet #1 dose. [Day 1: Cetuximab Alone … Day 8: Triplet dose # 1] **OR**

Cycle one is to include the loading dose of Cetuximab (alone) and two doses of the triplet (Platinum/Docetaxel/Cetuximab) when the loading dose of cetuximab was given ≤ 5 days from scheduled Platinum/Docetaxel dose. [Day 1: Cetuximab Alone … Day 5: Platinum/Docetaxel only (dose #1)]

10. MEASUREMENT

Antitumor Effect: PRIMARY ENDPOINT IS RECIST DEFINED RESPONSE RATE

For the purposes of this study, patients should be re-evaluated for response every 8 weeks +/- 1 week. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

All measurements will be noted on a tumor measurement log and will have screenshots of relevant imaging or clinical findings available to support measurements.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[1] Changes in the **largest diameter (unidimensional measurement) of the tumor lesions** and the **shortest diameter in the case of malignant lymph nodes** are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with TPC.

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

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

Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-

measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

Methods for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm,

the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

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

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated

Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

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

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

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

Response Review
All response assessments rendered by radiologists or sub-investigators must be confirmed by site PIs.

SECONDARY ENDPOINTS:

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.
Overall survival is defined as time from start of treatment until death from any cause. Patients will be followed for progression on study after treatment completion quarterly with clinic visits or until another treatment is initiated.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute's Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators. Investigators will be expected to obtain IRB approval within 90 days for all amendments.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute's Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). In addition, the DSMC will regularly review serious adverse events

and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan and Study Documentation

Electronic case report forms for specified protocol related information on each trial patient, using the REDCap system, will be created. The Protocol Director and participating site investigators must maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to communicate study data to the lead site. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

Participating Center's PIs will be responsible for maintaining the clinical protocol and subjects' study charts, reporting adverse events, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to their IRB and trials monitoring group(s) as per their facility protocol. A chart with all the relevant research patient information will be maintained for each patient at each institution by the research coordinator and/or responsible PD for that specific institution. Paper copies of the documentation from the medical record which support the data entered into REDCap will be kept in patient specific binders in a secure, locked, and HIPPA compliant environment. Patient charts will be reviewed by Stanford PI and/or Study Coordinator.

Participating Institutions will complete all electronic CRFs in REDCap within 2 weeks of a patients' visit and provide paper source documents supporting the data entered to Stanford for monitoring via secure email to rlira@stanford.edu. Note the subject line of the email is required to first include "secure:" in it. The research coordinator or participating center's investigator will be responsible for database records of patient data and providing them to Stanford. Any electronic data will be kept on a secured server file system.

11.4 Site Communication

When all participating institutions have successfully received IRB approval and have started enrolling patients, teleconferences to discuss participants and study-related matters will be held once per quarter, although call may occur more frequently if necessary. Teleconferences will be coordinated by Research Staff at a participating institution (PIs, Research Coordinators, Nurses, and Co-Investigators if needed will participate). Any issues will patient compliance, database entry, or other items will also be discussed in these calls. Calls will include review by PIs of subject data to assure validity as well as the safety of subjects; and the progress of the trials may also be discussed. At times of study renewals or more frequently if needed, PIs will review safety reports and clinical trial efficacy endpoints and confirm that the safety outcomes favor continuation of the study.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical design and trial size

This treatment trial is a single arm, unblinded, two staged Simon [23]design to evaluate the RECIST response rate to weekly TPC in patients with recurrent or metastatic SCCHN. Patients must have received at least one cycle of weekly TPC in order to be evaluable for response. The assumption is that we wish to distinguish between a response rate of 25% which would be uninteresting and a response rate

of 50% which would merit further testing, based on response rates of trials with similar agents on different schedules.[22] Choosing an alpha type error probability of 0.1 and a beta type error probability of 0.1 would mean that in order to proceed beyond the first stage, at least 3 of 10 patients would have to have responses, and at least 10 of up to 27 patients would have to respond in order declare this regimen of interest. The expected sample size would be 18 patients to see at least 10 responders and the probability of early termination if the true response rate is 25% would be 0.52.

12.2 Descriptive Statistics and Exploratory Data Analysis of secondary endpoints:

Overall survival (OS) (the time from registration to death or date of last contact) and progression free survival (PFS) (patients alive without RECIST progression) are secondary endpoints of the study. Kaplan-Meier estimates of overall and progression-free survival rates will be calculated, along with their corresponding 95% confidence intervals. The median, 12-month and 24-month overall and progression free survival rates will be estimated. AEs attributable to ATO will be collected according the study calendar and tabulated for cumulative evaluation.

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APPENDICES

APPENDIX A: Participant Eligibility Checklist and Registration Process

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and/or the study's Regulatory Binder.

Participant Eligibility Checklist

Inclusion Criteria	
__Yes __No	1. Is the patient willing and able to understand and sign the study specific Informed Consent Form (ICF)?
__Yes __No	2. Is the patient 16 years or older?
__Yes __No	3. Has the patient been diagnosed with Squamous Cell Carcinoma of Head and Neck? Sites include all pharynx, larynx, oral cavity, skin and para-nasal sinus sites. (Patients with a diagnosis of Nasopharyngeal Carcinoma, or SCC of unknown primary presenting in the neck clinically compatible with head and neck mucosal primary sites, are eligible.)
__Yes __No __N/A	4. At least 3 months have elapsed since the end of a potentially curative treatment: prior chemoradiation, radiation, and/ or surgery? (If so, patient is eligible).
__Yes __No	5. Does the patient have an ECOG Performance Status < 3 at the time of enrollment**?**
__Yes __No	6. Does the patient meet the following screening laboratory assessments for enrollment?: - Absolute Neutrophil Counts ≥ 1500 cells/ mm^3 - Platelet count ≥ 100 K/mm^3 - Serum AST and ALT < 2.5 x ULN, if liver metastasis is documented: AST & ALT < 5 xULN - Total Bilirubin < 1.5x upper limit of normal (ULN), unless pt has Gilbert's Syndrome: T.Bilirubin < 2.5 x ULN - Serum Creatinine < 1.5 mg/dL OR estimated creatinine clearance from 24 hour urine collection ≥ 50 ml/min
__Yes __No	7. Does the patient have peripheral neuropathy < grade 2?
Exclusion Criteria	
__Yes __No	1. Has the patient received **prior palliative chemotherapy?**
__Yes __No	2. Does the patient have **active infections including known HIV**? (HIV positive patients on HAART with undetectable blood HIV levels are eligible & patients with a history or serological evidence of exposure to Hepatitis B without active infection are eligible for this study.)
__Yes __No	3. Has the patient had a **prior grade 3** allergic or infusion reactions to docetaxel, cisplatin or cetuximab are not eligible.(A history of well tolerated infusion reactions is NOT an exclusion.)
__Yes __No	4. Does the patient have a history of **other malignancies** treated curatively **LESS** than one year prior to enrollment **and/or** with evidence of relapse at the time of enrollment?
__Yes __No	5. Is the patient female **and** pregnant **or** nursing?
__Yes __No	6. Does the patient have **known** brain metastasis? **NOTE:** patient is eligible **only if** by CNS imaging there is **no evidence** of CNS progression at least 30 days following definitive CNS treatment (resection or radiation).

My signature below confirms that I have reviewed the patient's current and past medical history to confirm they are [Eligible or Not Eligible] in meeting the criteria for study entry:

Principal Investigator/Co-Investigator	Printed Name	Date
Co-Investigator/Other Practitioner	Printed Name	Date
Clinical Research Coordinator/Other Personnel	Printed Name	Date

Registration Process

All participating sites must provide a copy of their IRB approved consent form to the Stanford Protocol Director prior to site initiation and when ICF amendments have been obtained.

To register a patient, the study site will call the Study Coordinator at the Stanford Cancer Institute: XXX-XXX-XXXX , Monday through Friday, between 9:00 a.m. and 3:30 p.m. (Pacific Time). If the Study Coordinator is away, contact the PD (Dr. Colevas) at XXX-XXX-XXXX.

The individual making the phone call will provide the patient's eligibility information, including all necessary source documents supporting information for eligibility confirmation in advance via secure email to rlira@stanford.edu. *Note the subject line of the email is required to first include "secure:" in it.*

If email submission is not available, the documents may be faxed to XXX-XXX-XXXX with a cover sheet:
RE: Request for Registration of TPC Clinical Trial Patient.
Attn: Dr. Colevas/Ruth Lira
Note: Your direct contact information must be included and you are required to send an email to notify site of fax submission, as fax line is not a dedicated line readily checked by research staff.

No subject may begin study treatment prior to registration, and assignment of a subjects' identification number.

Participating sites will have eligibility verified by two personnel at their institution and subsequently verified a third time by Stanford Cancer Institute. All necessary source documents to be sent to Stanford must include:

- Patient Signed and Dated Informed Consent Form
- Participant Eligibility Checklist (verified by two personnel with appropriate signatures and dates)
- Patients' Medical Record information:
    - Prior chemotherapy treatment
    - Prior radiation treatment
    - Prior surgery and pathology reports
    - Laboratory Results confirming eligibility within 1 week of submission
    - Demographics
    - Concurrent Medications
    - Physical Exam
    - Vital Signs (Height, Weight, Blood Pressure, Heart Rate (pulse), and Temperature)
    - Performance Status
    - AE evaluation
    - Radiological Reports completed within 28 days of anticipated Cycle 1 Triplet 1/Loading Dose

At registration, Stanford will sequentially assign eligible subjects an identification number. As confirmation, Stanford will provide the participating investigator with written verification of the subject's registration by email or fax. The maximum allowable time between registration and the first administration of study treatment is 14 days. The subject's identification number will be used on all study specific Case Report Forms (CRFs) and serious adverse event (SAE) forms. Participant information should be entered into OnCore within 7 days by Stanford University and/or the participating institution.

APPENDIX B: **Performance Status Criteria**

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

APPENDICES attached as separate files:

APPENDIX C: ADVERSE EVENT LOG

APPENDIX D: TUMOR MEASUREMENT LOG

APPENDIX E: CLINIC ASSESSMENT FORM

APPENDIX F: SAE COVER SHEET & REPORT FORM

APPENDIX G: HOW TO REPORT SAE