RTOG 0522: A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin vs. Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] For Stage III and IV Head and Neck Carcinomas

**FAST FACTS**

**ELIGIBILITY CRITERIA**

1. Pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx.
2. Selected stage III or IV disease (T2N2-3M0, T3-4 any N M0) Note: patients with T1, and N, or T2N1 tumors are not eligible.
4. Patient must be ≥ 18 years of age.
5. Patients must have the following laboratory values (obtained within 2 wks. prior to registration):
   - ANC ≥ 1800 cells/mm³
   - Platelets > 100,000 cells/mm³
   - Hemoglobin ≥ 8.0 g/dl (The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
   - Bilirubin ≤ 1.5 mg/dl (for patients with Gilbert’s disease as the sole cause of elevated Bilirubin, please contact the PI, Dr. Ang)
   - AST or ALT ≤ 2x ULN
   - Serum Creatinine ≤ 1.5 mg/dl
   - Creatinine Clearance ≥ 50 ml/min
6. Pregnancy test within two weeks prior to registration for women of childbearing potential.
7. Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment).
8. Patients participating in 0522 also are eligible for and are strongly encouraged to participate in RTOG 0514, the Head and Neck tissue banking protocol.

**INELIGIBILITY CRITERIA**

1. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.
2. Patients with simultaneous primaries or bilateral tumors are excluded.
3. Gross total excision of the primary tumor; however, partial removal of the tumor to alleviate an impending airway obstruction does not make the patient ineligible.
4. Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.
5. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.
6. Primary site of tumor of oral cavity, nasopharynx, sinuses, or salivary glands.
7. Initial surgical treatment, excluding diagnostic biopsy of the primary site or nodal sampling of neck disease; radical or modified neck dissection is NOT permitted.
8. Severe, active co-morbidity, defined as follows:
   - Current uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction
   - Left Ventricular Ejection Fraction < 45%
   - Transmural myocardial infarction within the last 6 months
   - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
   - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at time of registration
• HIV based upon current CDC definition (Note: HIV testing is not required for entry in this study. The need to exclude patients with AIDS is necessary because the treatments involved may be significantly immunosuppressive.
• Any uncontrolled condition, which in the opinion of the investigator, would interfere in the safe and timely completion of study procedures.

9. Electrolyte Abnormalities – See section 3.2.6.8
10. Pregnant or lactating women or women of childbearing potential and men who are sexually active and not willing /able to use medically acceptable forms of contraception.
11. Prior allergic reaction to the study drug(s) involved in this protocol.
12. Prior therapy that specifically and directly targets the EGFR pathway.
13. Prior severe infusion reaction to a monoclonal antibody.

PRE-STUDY PARAMETERS
1. H&P; Ht/Wt (including assessment of wt. & wt. Loss in past 6 months).
2. Examination by medical oncologist.
3. Chest x-ray (or chest CT scar or PET/CT scan).
4. CT scan or MRI of head and neck (of the primary tumor and neck nodes) or PET/CT scan.
5. Toxicity evaluation (including mucosal assessment).
6. LEF determined by ECHO and/or MUGA.
7. CXR or thoracic CT; CT/MRI of tumor/primary site (within six wks prior to registration).
8. CBC/Diff/Platelets; Electrolytes, Mg++; Bilirubin/AST/or ALT/Serum Creatinine; Creatinine clearance; Serum calcium or corrected serum calcium; (within two wks. prior to registration; Electrolytes: sodium, potassium, bicarbonate, chloride, BUN, glucose, and phosphorus.
9. Pregnancy test for women of childbearing potential, within 2 wks. prior to registration.
10. Tissue/blood for TRP (primary tumor tissue and peripheral blood, taken before the initiation of treatment).
11. These evaluations/interventions are not required but are highly recommended: PET/CT scan; dental evaluation and if applicable, prophylaxis within 12 weeks prior to treatment; serum albumin; baseline audiogram; nutritional evaluation for prophylactic gastrostomy (PEG) tube placement.
12. QOL Assessments – PSS-HN/EQ-5D/FACT-H&N (If the patient consents to participate in the quality of life component of the study, the PSS-HN & EQ-5D will be administered pretreatment, during one of the last 2 wks. of treatment, at 3 & 12 months from start of treatment, then annually for years 2-5; FACT-HN will be administered pre-treatment, and annually in years 1 and 5.

TREATMENT

Arms 1 and 2: Cisplatin (with concurrent RT)
• Patients will receive cisplatin, 100mg/m², administered on days 1 and 22 of the treatment course. 
  Note: Patients on Arm 2 will begin cisplatin and RT the week after the initial dose of cetuximab.
• High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens should be followed.
• Patients must receive vigorous hydration and diuresis.

Arm 2: Cetuximab (with concurrent RT and Cisplatin)
• Initial Dose: Patients on Arm 2 will receive an initial dose of cetuximab (C225), 400 mg/m², intravenously over 120 minutes. No chemotherapy or radiation will be given this day, and the 400 mg/m² initial dose of cetuximab will precede the first 250 mg/m² dose of cetuximab and the first radiation treatment by at least 5 days. The infusion rate of cetuximab must never exceed 5 mL/min.
• Weeks 1-7 (concurrent with RT and cisplatin): Patients on Arm 2 will receive cetuximab, 250 mg/m², intravenously over 60 minutes prior to radiation therapy and cisplatin. The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week on Monday or Tuesday for a total of 7 doses (patients must receive cetuximab for a total of 8 weeks, including the initial dose).
Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients’ first infusion reactions have been reported following subsequent doses (a severe reaction occurred in one patient following the 8th dose). The infusion reaction may occur during the infusion or be delayed until any time after the infusion.

All patients will be pre-medicated with diphenhydramine hydrochloride, 50 mg, (or an equivalent antihistamine) by IV 30-60 minutes prior to the first dose of cetuximab in an effort to prevent an infusion reaction.