

**CTSU E1305: A Phase III Randomized Trial of Chemotherapy with or without Bevacizumab In Patients with Recurrent Or Metastatic Head and Neck Cancer**

*Fast Facts*

1. Patients must have histologically or cytologically confirmed Squamous Cell Cancer of the Head and Neck (SCCHN), from any primary site, including unknown primary cancers of the head and neck. Patient must not have nasopharyngeal carcinoma of histologic types WHO 2 or 3 or squamous cell carcinoma that originated in the skin.
2. Patients must have SCCHN that is either (a) recurrent, judged incurable by surgery or radiation or (b) metastatic.  
**NOTE:** Patients who refuse radical resection for recurrent disease are eligible  
**NOTE:** A second primary squamous cell carcinoma of the head and neck is allowed if eligibility is based on a recurrent or metastatic first primary squamous cell carcinoma of the head and neck.
3. No prior chemotherapy or biologic/molecular targeted therapy for recurrent or metastatic SCCHN.
  - a. Patients may have received one regimen of induction, concomitant chemoradiotherapy and/or adjuvant chemotherapy as part of initial potential curative therapy but **must not have received prior chemotherapy for recurrent or metastatic disease.**
  - b. A minimum of 4 months is required between last dose of chemotherapy or chemoradiotherapy and study treatment. In addition patients must be progression free for at least 6 months after completion of chemotherapy or chemoradiotherapy or radiation plus cetuximab given with a curative intent. (Cetuximab therapy: 6 months is required between last dose of chemotherapy or chemoradiotherapy and study treatment if part of concurrent regimen, 8 weeks if part of adjuvant regimen post radiation).
  - c. Patients having progression after 2 cycles of induction chemotherapy are not eligible for the study.
4. No prior bevacizumab is allowed.
5. A maximum of one prior radiotherapy regimen, curative or palliative, to the head and neck is allowed. If the radiation is combined with chemotherapy and/or cetuximab, a period of 4 months must elapse between the end of radiotherapy and study treatment. If the radiation is given alone, a minimum of 8 weeks must elapse between the end of radiotherapy and registration. A minimum of 3 weeks must elapse between prior radiation to other areas and registration.
6. Patients must not be receiving any other investigational agent while on the study.
7. ECOG performance status of 0-1
8. Patients must have recovered to grade 1 or better from the effects of any prior surgery, chemotherapy, or radiation therapy, and should be > 4 weeks post surgery.
9. Patients must have measurable disease based on RECIST (see Sec. 6.0). Baseline measurements and evaluations of all sites of disease must be obtained ≤4 weeks prior to randomization. Disease in previously irradiated sites is considered measurable if there has been unequivocal disease progression or biopsy-proven residual carcinoma following radiation therapy.  
 Persistent disease after radiotherapy must be biopsy proven at least 8 weeks after completion of radiation therapy. (Radiographic findings are acceptable providing that clear cut measurements can be made).
10. Baseline parameters: ≤ 2 weeks prior to randomization
  - ANC ≥ 1,500/mm<sup>3</sup>
  - Hgb ≥ 8.0 g/dL
  - Platelet count ≥ 100,000/mm<sup>3</sup>
  - Creatinine clearance of ≥ 60 ml/min.
 Creatinine clearance will be estimated using the Cockcroft-Gault formula for creatinine clearance:
  - Total bilirubin within normal limits (must be obtained ≤ 2 weeks prior to randomization):
  - AST or ALT and Alkaline Phosphatase must be within the range allowing for eligibility, as determined by the table below.
  - Alkaline phosphatase, SGOT (AST) and SGPT (ALT) values must be obtained ≤ 2 weeks prior to randomization

	AST or ALT*			
ALK PHOS	≤ ULN	> 1x but ≤ 1.5x	> 1.5x but ≤ 5x	> 5x ULN
≤ ULN	Eligible	Eligible	Eligible	Ineligible
> 1x but ≤ 2.5x	Eligible	Eligible	Ineligible	Ineligible

> 2.5x but ≤ 5x	Eligible	Ineligible	Ineligible	Ineligible
> 5x ULN	Ineligible	Ineligible	Ineligible	Ineligible

\*AST/ALT level is based upon more abnormal of the two.

11. Urine protein should be screened by urine analysis for Urine Protein Creatinine (UPC) ratio ≤ 2 weeks prior to randomization. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level must be <1000 mg for patient to be eligible.

NOTE: UPC ratio of spot urine is an estimation of the 24 urine protein excretion - a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm.

12. No known brain metastases.

13. Patients who meet the following criteria will be excluded due to the possibility of increased risk for tumor bleeding with bevacizumab therapy:

- a) tumors that invade major vessels (e.g. the carotid) as shown unequivocally by imaging studies (i.e. tumor crosses fat boundary),
- b) central (i.e. within 2 cm from the hilum) lung metastases that are cavitory as shown unequivocally by imaging studies,
- c) any prior history of bleeding related to the current head and neck cancer,
- d) history of gross hemoptysis (bright red blood of ½ teaspoon or more per episode of coughing) ≤ 3 months prior to enrollment.

14. No history of coagulopathy or hemorrhagic disorders.

15. Patients should not have a history of thrombosis (e.g. pulmonary embolism or deep venous thrombosis) currently requiring therapeutic anticoagulation (prophylactic use of warfarin 1 mg per day is allowed) and INR should be < 1.5 at registration.

16. Patients must not be receiving chronic daily treatment with aspirin (> 325 mg/day) or non-steroidal anti-inflammatory agents (NSAID's) known to inhibit platelet function. The use of anti-platelet agents (e.g. dipyridamole (Persatine), ticlopidine (Ticlid), clopidogrel (Plavix)) is allowed only if patient is not receiving aspirin or NSAID's known to inhibit platelet function.

17. No hypercalcemia related to head and neck cancer.

18. Patients with a prior history of squamous cell or basal carcinoma of the skin or *in situ* cervical cancer must have been curatively treated. Patients with a history of other prior malignancy must have been treated with curative intent and must have remained disease free for 5 years post diagnosis.

19. No current peripheral neuropathy ≥ grade 2 at time of randomization.

20. Patients must not have any co-existing condition that would preclude full compliance with the study.

21. No prior history of severe hypersensitivity reaction to Docetaxel or other drugs formulated with polysorbate 80.

22. All patients must have blood pressure ≤ 150/90 ≤ 2 weeks prior to randomization. Patients with history of hypertension must be well-controlled upon study entry (≤150/90) on a stable regimen of anti-hypertensive therapy.

23. No major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment, or anticipation of need for major surgical procedure during the course of the study. No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration. No serious non-healing wound, ulcer, or bone fracture.

24. No unstable angina or myocardial infarction within the previous 6 months; no symptomatic congestive heart failure, New York Heart Association (NYHA) Grade II or greater (see Appendix IX); no history of aortic dissection or presence of aneurysm > 6 cm (or at high risk for rupture); no serious cardiac arrhythmia requiring medication (history of chronic atrial fibrillation or other atrial arrhythmia with controlled rate on medication is allowed); no clinically significant peripheral vascular disease manifested by intermittent claudication or need for vascular intervention; no history of aortic dissection; no history of any CNS cerebrovascular ischemia or stroke within the last 6 months; no active serious infection.

25. Patients should not have prior history of a serious human anti-human antibody (HAHA) reaction. Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies are not eligible.

26. Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of bevacizumab in patients <18 years of age, children are excluded from this study.

27. Women must not be pregnant or breast feeding because chemotherapy may be harmful to the fetus or the nursing infant. Pregnant women are excluded from this study because chemotherapy and/or bevacizumab have the potential for teratogenic or abortifacient effects. Women of child-bearing potential and men must agree to total abstinence or to use adequate hormonal or barrier method of birth control prior to study entry and for the

duration of study participation. Should a woman become pregnant or suspect she is pregnant while in this study, she should inform her treating physician immediately.

28. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.
29. HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible drug interactions with study drugs. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

#### Pre-Study Parameter

1. History and physical including vital signs, height, weight, performance status
2. CBC with differential, CMP, Magnesium, urine protein Creatinine, PT/PTT (if clinically indicated), pregnancy test (for women of child-bearing potential)
3. CT chest, CT/MRI neck, tumor measurements, EKG

#### Treatment

##### Arm A

Agent	Dose	Route	Days	Frequency
Cisplatin-doublet <sup>^</sup>	See below			q 21 days

##### Arm B

Agent	Dose	Route	Days	Frequency
Cisplatin-doublet <sup>^</sup>	See below			q 21 days
Bevacizumab	15 mg/kg	IV	Day 1	q 21 days

<sup>^</sup> Physician choice of chemotherapy regimen:

- 1) Docetaxel 75 mg/m<sup>2</sup> IV on day 1, followed by cisplatin 75 mg/ m<sup>2</sup> IV on day 1 every 21 days
- 2) Cisplatin 100 mg/ m<sup>2</sup> IV on day 1, 5-FU 1000mg/ m<sup>2</sup>/day continuous infusion x 4 days, every 21 days

Treatment continues until progression, unacceptable toxicity or patient request. At the discretion of the physician, chemotherapy may be discontinued after 6 cycles if there is maximum response. For patients on Arm B, Bevacizumab will continue until progression.