

FAST FACTS

RTOG 1216 - RANDOMIZED PHASE II/III TRIAL OF ADJUVANT RADIATION THERAPY WITH CISPLATIN, DOCETAXEL-CETUXIMAB, OR CISPLATIN-ATEZOLIZUMAB IN PATHOLOGIC HIGH-RISK SQUAMOUS CELL CANCER OF THE HEAD AND NECK

Phase III Conditions for Patient Eligibility

1. Pathologically (histologically or cytologically) proven diagnosis of head and neck squamous cell carcinoma (HNSCC) involving the oral cavity (excluding lips), oropharynx (p16 negative), larynx, or hypopharynx.
2. Patients with oropharyngeal cancer must have p16-negative based on central review prior to Step 2 registration (see more details in Section 12.5). All patients with oropharyngeal primary must consent for mandatory tissue submission for central p16 confirmation.
3. Patients must have undergone gross total surgical resection of high-risk oral cavity, oropharynx (p16 negative), larynx, or hypopharynx within 63 days prior to registration. **Note:** Patients may have biopsy under general anesthesia in an operating room followed by definitive ablative cancer surgery representing gross total resection. The gross total resection has to be done within 63 days prior to registration. If, however, patients have ablative resection but shortly recur or are determined to have persisting disease requiring re-resection to achieve gross total resection, then the patient is not eligible.
4. Patients must have at least 1 of the following high-risk pathologic features: extracapsular nodal extension or invasive cancer at the primary tumor resection margin (tumor on ink or tumor in a final separately submitted margin).
5. Pathologic stage III or IV HNSCC (AJCC 7th edition), including no distant metastases, based upon the following minimum diagnostic workup:
 - General history and physical examination by a Radiation Oncologist or Medical Oncologist within 84 days prior to registration;
 - Examination by an ENT or Head & Neck Surgeon prior to surgery; a laryngopharyngoscopy (mirror or fiberoptic or direct procedure), if appropriate, is recommended but not required. Intra-operative examination is acceptable documentation.
 - Pre-op Imaging of the head and neck: A neck CT (with contrast and of diagnostic quality) or PET/CT (with contrast and of diagnostic quality) and/or an MRI of the neck of diagnostic quality (T1 with Gadolinium and T2) within 84 days prior to surgery; **Note:** this imaging data (diagnostic pre-operative scan showing gross disease) is to be submitted in DICOM format via TRIAD. The report is to be uploaded into Rave; see [Section 14.3](#).
 - Chest CT scan (with or without contrast) or PET/CT that includes the chest (with or without contrast) either within 84 days prior to surgery or within 120 days prior to registration; **Note:** If the PET/CT with or without contrast is done within 84 days prior to surgery, it fulfills the chest imaging requirement.
6. Zubrod Performance Status of 0-1 within 14 days prior to registration;
7. Age \geq 18;
8. CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:
 - Leukocytes \geq 2,500 cells/mm³;
 - Absolute neutrophil count (ANC) \geq 1,500 cells/mm³;
 - Platelets \geq 100,000 cells/mm³;

- Hemoglobin \geq 8.0 g/dL (**Note:** The use of transfusion or other intervention to achieve Hgb \geq 8.0 g/dL is acceptable).
9. Adequate hepatic function within 14 days prior to registration, defined as follows:
 - Total bilirubin \leq 1.5 x institutional upper limit of normal (ULN) (however, patients with known Gilbert disease who have serum bilirubin level \leq 3 x institutional ULN may be enrolled);
 - AST or ALT \leq 3 x institutional ULN;
 - Alkaline phosphatase \leq 2.5 x institutional ULN
 10. Adequate renal function, defined as follows:
Creatinine clearance (CrCl) \geq 50 mL/min within 14 days prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:
CrCl male = $[(140 - \text{age}) \times (\text{wt in kg})] / [(\text{Serum Cr mg/dL}) \times (72)]$
 11. Patients with feeding tubes are eligible for the study.
 12. Negative urine or serum pregnancy test within 14 days prior to registration for women of childbearing potential;
 13. All patients must provide study specific informed consent prior to study entry.
 14. Patients positive for human immunodeficiency virus (HIV) are allowed on study, but HIV-positive patients must have:
 - A stable regimen of highly active anti-retroviral therapy (HAART);
 - No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections;
 - A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests.

Phase III Conditions for Patient Ineligibility

1. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days [3 years] with the following exceptions: T1-2, N0, M0 resected differentiated thyroid carcinoma;
Note that noninvasive cancers (For example, carcinoma in situ of the breast, oral cavity, or cervix) are permitted even if diagnosed and treated < 3 years ago;
2. Patients with simultaneous primaries or bilateral tumors are excluded, with the exception of patients with bilateral tonsil cancers or patients with T1-2, N0, M0 resected differentiated thyroid carcinoma, who are eligible.
3. Prior systemic therapy, including cytotoxic chemotherapy, biologic/targeted therapy (such as anti-EGF therapy), or immune therapy for the study cancer. Note that prior chemotherapy for a different cancer is allowable, however, a prior anti-PD-1, anti-PD-L1, or anti-PD-L2 agent is not permitted;
4. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
5. Severe, active co-morbidity, defined as follows:
 - a. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better within 6 months prior to registration
 - b. Transmural myocardial infarction within 6 months prior to registration;
 - c. Severe infections within 4 weeks prior to registration including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia;
 - d. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; Note: Patients receiving prophylactic antibiotics (e.g., for prevention of a

urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible.

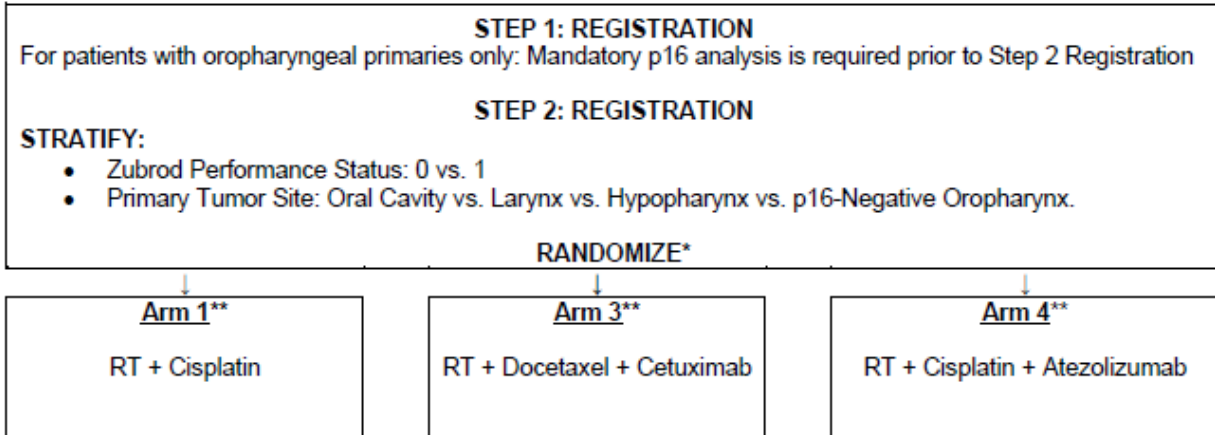
- e. Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- f. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in a prior radiation field (fibrosis) is permitted, provided that field does not overlap with the planned radiation field for the study cancer;
- g. Patients with active tuberculosis (TB) are excluded;
- h. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease;
 - o Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
 - o Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- i. History of allogeneic bone marrow transplantation or solid organ transplantation.
- j. A diagnosis of immunodeficiency:
 - o Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note: HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
- k. Is receiving treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to registration.
 - o Note: Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
 - o Note: The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- l. History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
 - o Patients with a history of autoimmune hypothyroidism who are asymptomatic and/or are on a stable dose of thyroid replacement hormone are eligible.
 - o Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
 - o Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
 - o Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
 - o Rash must cover less than 10% of body surface area (BSA)
 - o Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

- o No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)
- m. Grade 3-4 electrolyte abnormalities (CTCAE, v. 4) within 14 days prior to registration:
 - Serum calcium (ionized or adjusted for albumin) < 7 mg/dL (1.75 mmol/L) or > 12.5 mg/dL (> 3.1 mmol/L) despite intervention to normalize levels;
 - Glucose < 40 mg/dL (< 2.2 mmol/L) or > 250 mg/dL (> 14mmol/L);
 - Magnesium < 0.9 mg/dL (< 0.4 mmol/L) or > 3 mg/dL (> 1.23 mmol/L) despite intervention to normalize levels;
 - Potassium < 3.0 mmol/L or > 6 mmol/L despite intervention to normalize levels;
 - Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.
- n. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception for up to 5 months from last study treatment; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic. Women who are breastfeeding and unwilling to discontinue are also excluded.
- o. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- p. Patients taking bisphosphonate therapy for symptomatic hypercalcemia. Use of bisphosphonate therapy for other non-oncologic reasons (e.g., osteoporosis) is allowed.
- q. Patients requiring treatment with a RANKL inhibitor (e.g. denosumab) for non-oncologic reasons who cannot discontinue it before registration.
- r. Patients with known distant metastatic disease are excluded.
- s. Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.
- t. Major surgical procedure within 28 days prior to registration or anticipation of need for a major surgical procedure during the course of the study. Note: This exclusion criteria does not apply to section 3.2.3.
- u. Administration of a live, attenuated vaccine within 4 weeks prior to registration or anticipation that such a live, attenuated vaccine will be required during the study and for patients receiving atezolizumab, up to 5 months after the last dose of atezolizumab.
 - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks prior to registration or at any time during the study.
- v. Psychiatric illness/social situations that would limit compliance with study requirements.
- w. Prior allergic reaction to any of the study agents (cisplatin, docetaxel, cetuximab, atezolizumab).

RTOG 1216

RANDOMIZED PHASE II/III TRIAL OF ADJUVANT RADIATION THERAPY WITH CISPLATIN, DOCETAXEL-CETUXIMAB, OR CISPLATIN-ATEZOLIZUMAB IN PATHOLOGIC HIGH-RISK SQUAMOUS CELL CANCER OF THE HEAD AND NECK (02-JUN-2021)

PHASE III SCHEMA (20-MAR-2020)



*Randomization to Arm 1, Arm 3, and Arm 4 is 1:1:2. Arm 2 was dropped after phase II.

**See Section 6.0 for radiation therapy and section 7.0 for systemic therapy treatment details.

Required Sample Size: Phase III Component: 480 randomized patients