**NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx**

A. Trotti,1 J. Harris,2 M. Gillison,3 A. Eisbruch,4 P.M. Harari,5 D.J. Adelstein,6 E.M. Sturgis,7 J.M. Galvin,8 S. Koyfman,9 D. Blakaj,10 M.A. Razaq,11 A.D. Colevas,12,13 J.J. Beitler,14 C.U. Jones,15

N.E. Dunlap,16 S.A. Seaward,17 S.A. Spencer,18 J.A. Ridge,19 J. Phan,20 and Q.T. Le21;

*1Mofffitt Cancer Center and Research Institute, Tampa, FL, 2RTOG, Philadelphia, PA, 3MD Anderson Cancer Center, Houston, TX, 4Department of Radiation Oncology, University of Michigan, Ann Arbor,*

*MI, 5Department of Human Oncology, University of Wisconsin, Madison, WI, 6Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, 7The University of Texas MD Anderson Cancer Center, Houston, TX, 8IROC, Philadelphia, PA, 9Department of*

*Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, 10Ohio state university, Columbus, OH, 11University of Oklahoma, Oklahoma City, OK, 12Stanford, Palo Alto, CA, 13Stanford University, Palo Alto, CA, 14Emory, Atlanta, GA, 15Sutter Medical Group and Cancer Center, Sacramento, CA, 16University of Louisville Hospital, Department of Radiation Oncology, Louisville, KY, 17Kaiser Permanente, Vallejo, CA, 18University of Alabama at Birmingham, Birmingham, AL, 19Fox Chase Cancer Center, Philadelphia, PA, 20Dept. of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, 21Stanford Cancer Institute, Stanford, CA*

**Purpose/Objective(s):** To determine whether radiation with cetuximab has non-inferior overall survival compared to radiation with cisplatin in patients with locoregionally advanced human papillomavirus (HPV)- related oropharynx cancer.

**Materials/Methods:** Eligible patients were randomized (1:1) to 70 Gy in 6 weeks accelerated (6 fractions/week) with 2 cycles of cisplatin 100mg/m2 every 3 weeks, versus the same radiation with weekly cetuximab. All patients had central laboratory confirmation of HPV status by p16

immunohistochemistry and were stratified by T-stage, N-stage, Zubrod performance status, and smoking history. At final analysis, non-inferiority would be concluded if the overall survival hazard ratio (cetuximab/cisplatin) upper confidence bound was ≤1.45.

**Results:** From 6/11 to 7/14, 849 patients were randomized, of whom 805 were analyzed. 90% were male with median age of 58. The overall survival hazard ratio was 1.45 (95%CI 1.03-2.05). Estimated 5-year survival rates were 84.6% (80.6-88.6) with cisplatin versus 77.9% (73.4-82.5) with cetuximab. Progression-free survival was significantly worse with cetuximab compared to cisplatin [hazard ratio 1.72 (1.29-2.29); one-sided log-rank p=0.0001] with 5-year estimates of 78.4% (73.8-83.0) with cisplatin and 67.3% (62.4-72.2) with cetuximab. Estimated 5-year local-regional failure/distant metastases rates were 9.9%/8.6% with cisplatin and 17.3%/11.7% with cetuximab. Acute grade 3-4/5 adverse events were 82%/0.8% and 77%/ 1.3% with cisplatin and cetuximab, respectively. The distribution of grade 3-4 adverse events varied by treatment with anemia, hearing loss, nausea,

vomiting, neutropenia, and kidney injury more common with cisplatin, and rash being more common with cetuximab. Long-term severe dysphagia was 4% for the cisplatin arm and 6% for the cetuximab arm. Extensive quality of life measures were collected and will be reported separately.

**Conclusion:** This study failed to establish the non-inferiority of radiation/cetuximab for patients with locoregionally advanced HPV-related oropharynx cancer . Radiation/cetuximab resulted in inferior overall and progression-free survival. Radiation with concurrent cisplatin remains the standard of care in these patients.