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RTOG 1016 long-term update and smoking analysis

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Background

RTOG 1016 was a noninferiority phase 3 trial that compared overall survival (OS) for patients with HPV-positive oropharyngeal cancer (OPC) randomized to cisplatin (n=406) or cetuximab (n=399) with intensity-modulated radiotherapy (IMRT). After a median follow-up of 4.5 years, IMRT with cetuximab did not meet noninferiority for OS. Given high survival rates for this population, long-term disease-control outcomes and late adverse events are of considerable interest.

Methods

Patients with AJCC 7th edition T1-2N2-3 or T3-4N0-3 p16-positive OPC were stratified by T stage, N stage, Zubrod performance status and smoking history ($\leq$ or $>$ 10 pack-years) and completed a mandatory life-time tobacco use questionnaire at enrollment. Secondary endpoints included progression-free survival (PFS) and acute and late (≤ 180 vs. > 180 days after IMRT) adverse events. Hazard ratios (HR) were estimated by Cox models.

Results

With median follow-up of 10.2 years, cetuximab with IMRT did not meet noninferiority for OS (HR 1.18; one-sided 95% upper confidence interval [CI] 1.46; 10-year OS, 68.7/66.5%). PFS remained significantly higher for cisplatin with IMRT (63.9/59.1%; HR 1.30; 95%CI 1.03, 1.63). Treatment-related late grade 3-4 adverse events were 25/20% overall and 6/8% for dysphagia; for any-grade hearing impairment, 33/17%; tinnitus, 31/13%; dysgeusia, 62/59%; dry mouth, 86/86%; chronic kidney disease, 1/0%; and peripheral sensory neuropathy, 15/8%. Among 805 patients, 45% were never or never regular (daily for ≥ 1 month) cigarette smokers, 45% former, and 10% current. Regular users reported a median of 20 (IQR 8-37) pack-years. Only 38% of patients had >10 pack-years. In univariate analysis, current cigarette smoking (HR 2.00; 95%CI 1.42, 2.80), smoking in the last 10 years (HR 2.11; 95%CI 1.64, 2.71) and >10 pack-years (HR 1.67; 95%CI 1.30, 2.14) were associated with increased hazard of death. Hazard increased per pack-year (HR 1.008; 95%CI 1.004, 1.012) and year of use (HR 1.017; 95%CI 1.010, 1.024).

Conclusions

For patients with HPV-positive OPC, cetuximab with IMRT did not meet non-inferiority with longer follow-up and was associated with significantly worse PFS. Hearing-related toxicities were more frequent in the cisplatin arm. Current smoking at diagnosis was associated with worse survival.

Clinical trial identification

NCT01302834.

Legal entity responsible for the study

NRG Oncology.

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Disclosure

M. Gillison: Financial Interests, Personal, Speaker, Consultant, Advisor: Day One, GSK, Takeda, LLX Solutions, Eisai Medical Research, Sensei, EMD Sereno, Debiopharm, Onclive, Istari Oncology, iTeos Therapeutics, Coherus Biosciences, Caladrius Biosciences, Exelixis Inc., Shattucks Labs, Surface Oncology, Suzhou Liangyihi Network Technology, Boxer Capital, Pfizer, Brightly Network, Guidepoint, Bicara Therapeutics, Aptitude Health, Axion Healthcare, Adaptimmune Limited, Ispen Biopharmaceuticals; Financial Interests, Personal and Institutional, Other, Consulting and Research Funding: BioNTech AG, Kura Oncology, Seagen, BMS, AbbVie, Merck, Genentech; Financial Interests, Personal and Institutional, Other, Consulting and Research Funding: Gilead Sciences Inc.; Financial Interests, Personal, Other, Consulting and Research Funding: Merus B.V.; Financial Interests, Personal, Other, Editorial Role: American Society of Clinical Oncology; Financial Interests, Personal and Institutional, Research Funding: NRG, Roche; Financial Interests, Personal and Institutional, Other, Consulting and research funding: INVAX. J. Caudell: Financial Interests, Institutional, Research Grant: Varian Medical Systems; Financial Interests, Personal, Royalties: UpToDate. J.L. Geiger: Financial Interests, Institutional, Local PI: Merck, EMD Serono, Astellas, Janssen, Merus, Regeneron; Financial Interests, Institutional, Advisory Board: Merck, Astellas, Janssen; Financial Interests, Institutional, Other, Educational materials (non-branded): Aveo Oncology. M.F. Gensheimer: Financial Interests, Personal, Stocks/Shares: Amgen, Roche; Financial Interests, Institutional, Research Funding: Varian Medical Systems, XRad Therapeutics. N. Dunlap: Financial Interests, Personal, Invited Speaker: AstraZeneca. Q. Le: Financial Interests, Personal, Other, Travel: RTOG Foundation; Financial Interests, Personal, Member of Board of Directors: RTOG Foundation. S.S. Yom: Financial Interests, Institutional, Research Grant: Bristol Myers Squibb International, Merck; Financial Interests, Institutional, Local PI: EMD Serono; Financial Interests, Personal, Steering Committee Member: Johnson and Johnson; Non-Financial Interests, Member of Board of Directors: RTOG Foundation; Non-Financial Interests, Leadership Role: NRG Oncology. All other authors have declared no conflicts of interest.

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