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Quality of Life in Patients With p16+ Oropharyngeal Cancer Receiving Accelerated Radiation Therapy With Either Cisplatin or Cetuximab in the NRG/RTOG 1016 Randomized Controlled Trial.

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Quality of life in patients with p16+ oropharyngeal cancer receiving accelerated radiotherapy with either cisplatin or cetuximab in the NRG/RTOG 1016 randomized controlled trial

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Abstract

Background: NRG/RTOG 1016 was a phase III randomized non-inferiority de-escalation trial comparing cetuximab vs cisplatin, concurrent with accelerated radiation (RT) 70 Gy/6 weeks, in p16+ oropharyngeal cancer (OPC). Quality of life (QOL) was a secondary endpoint.

Methods: Eligible/consenting patients among the first 400 entered completed the EORTC QLQ-C30/H&N35 at baseline, end of treatment, 3, 6, and 12 months post-treatment, to provide 90% power to detect an effect size of 0.5 in the between-arm change in QOL scores from baseline to 6 months. We report completion, responsiveness, and patterns over time across domains between arms, considering a difference of > 10 points as clinically significant.

Results: Consent to the QOL substudy was 91%, with analyzable data in 375 patients. No significant differences in patient/tumor characteristics were found by QOL participation status. Completion at the 5 timepoints did not differ by arm (IMRT+cisplatin/cetuximab) and was: 92/94%, 74/77%, 76/81%, 76/81%, and 73/74%. No significant difference was observed between arms for the 6-month change from baseline on any domain. At the end of treatment, all domains showed statistically and clinically significant mean worsening across both arms except Emotional Functioning, Dyspnea, Financial Difficulties, Diarrhea, and Teeth. By 6 months, drops > 10 points remained for: Senses, Social Eating, Opening Mouth, Dry Mouth, Sticky Saliva; and at 12 months for Senses, Trouble with Social Eating, Opening Mouth, Dry Mouth, Sticky Saliva, Pain Killers, and Weight Gain. Pain Killer reduced at both 6 and 12 months.

Conclusion: Although replacing concurrent IMRT+cisplatin with IMRT+cetuximab did not improve global health status or swallowing at 6 months, this study supports the responsiveness of the EORTC QLQ-C30/H&N35 to the effects of IMRT+systemic therapy for OPC. Dry Mouth, Sticky Saliva, and Senses showed large, significant, and persistent impairment, whereas domains related to eating (Swallowing, Appetite, Nutritional Supplements, Social Eating, and Weight Loss) did not show sustained significant impairment in this study.

Introduction

Beginning in the first decade of the second millennium, our understanding of the biology of head and neck cancer (HNC) was revolutionized by the recognition of Human Papillomavirus (HPV) as a driver in certain oropharyngeal cancers (OPC). The recognition that this subset constituted a distinct disease entity with differing etiology, prognosis and

treatment response[1] was followed by interest in risk-stratified treatment.[2, 3] Just prior, another transformative change, the introduction of intensity-modulated radiation therapy (IMRT), had provided the ability to improve sparing of critical structures, improving quality of life (QOL) +/− functional outcomes.[4,5,6] The combination of these two advances led to a focus on de-escalation of treatment for low-risk patients which continues to this day. NRG/RTOG 1016 was the first large randomized trial to investigate de-intensification in p16+ OPC. The EGFR-inhibitor cetuximab was chosen as the experimental systemic therapy on the basis of a previous trial which had shown improved survival for concurrent use of this drug with radiotherapy (RT), versus RT alone, without increased negative impact on QOL.[7]

NRG/RTOG 1016 parent trial

This randomized phase III trial of IMRT plus cetuximab versus cisplatin chemoradiotherapy in p16+ oropharynx cancer was launched by the Radiation Therapy Oncology Group (RTOG; now NRG Oncology) in 2011 and closed to accrual in 2014, completing accrual well ahead of schedule. Powered for non-inferiority in overall survival (OS), it included important secondary endpoints related to acute toxicity, patient-reported swallowing function, and overall, head and neck cancer-specific, health-related QOL. The overarching goal of this and subsequent de-escalation studies is to identify an equally or more effective treatment strategy that can reduce toxicity and improve long-term QOL and survivorship experience in the subgroup of oropharyngeal cancer patients identified as having a good prognosis with conventional, cisplatin-based IMRT.

Eligible patients were adults with biopsy-proven p16-positive squamous cell carcinoma of the oropharynx, AJCC 7th edition[1] T1–2, N2a-3 or T3–4, N0–3, with Zubrod PS 0–1 and adequate organ function parameters. p16 positivity by ISH was used as a surrogate for HPV-associated OPC.[9] Ethics approval was obtained from institutional review boards of participating institutions. All patients provided informed consent.

All patients received accelerated IMRT, 70 Gy/35 fractions/6 weeks. Randomization used randomly permuted blocks and stratification by T-category (T1–2 vs T3–4), N-category (N0–2a vs N2b-3) and smoking (≤10 vs >10 pack-years). The standard arm received cisplatin 100 mg/m^2 days 1 and 22 of RT (IMRT+cisp), whereas the experimental arm received a loading dose of 400 mg/m^2 of cetuximab at 5–7 days prior to RT, then 250 mg/m^2 weekly for 7 doses (IMRT+cetux).

At the third planned interim analysis, IMRT+cetux did not meet the non-inferiority criterion for OS (HR[IMRT+cetux/IMRT+cisp]=1.45, one-sided 95% CI=1.94), and the study was closed on the advice of the NRG Oncology Data Monitoring Committee.[10] IMRT+cisp remains the standard of care for eligible patients with p16+ OPC.

Methods and Materials

Patients in this QOL Substudy

The first 419 patients recruited for the overall trial were offered enrollment in this QOL substudy.

Patient-Reported Outcome Instruments

In the design of this study, there was significant focus on the early QOL experience of patients within 6 months of treatment completion. Based on a prior trial using cetuximab[11] and its being the most commonly used HNC-specific QOL instrument, the EORTC QLQ-C30/H&N35 suite of cancer-specific QOL instruments was chosen for proven responsiveness over the shorter-term time frame.[12,13] The instrument was administered and scored according to developers' guidelines.[14] Clinically meaningful difference (CMD) was estimated as 10 points based on prior anchor-based evaluation.[15]

EORTC QLQ-C30

The QLQ-C30 v. 3.0 is a 30-item questionnaire including 5 functional subscales (role, physical, cognitive, emotional, and social functioning), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), 6 single-item symptom questions (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and 2 questions assessing overall QOL (global health status, GHS). Higher scores indicate a higher level of functioning (better) or higher level of symptoms (worse).

EORTC QLQ-H&N35

The QLQ-H&N35 is a 35-question supplementary module administered with the QLQ-C30. Seven multi-item symptom scales include pain, swallowing, senses problems, speech problems, trouble with social eating, trouble with social contact, and less sexuality. Eleven single-item symptom questions include teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, and weight gain. Higher scores indicate worse level of symptoms.

Assessment Schedule

All patient-reported outcome measures (PROMs) were collected electronically in clinic prior to physician visits at baseline (pretreatment), end of treatment, and 3, 6, and 12 months post-treatment.

Endpoints and Sample Size

The patient-reported outcome (PRO) objectives were to compare short-term (6 months, primary) and longer-term (12 months, secondary) overall QOL, as measured by the EORTC QLQ-C30 global health status (GHS), and to compare short-term and longer-term swallowing QOL, as measured by the QLQ-H&N35 swallowing domain, between treatment arms. An additional secondary QOL objective was to describe patterns of QOL domains across time.

The primary endpoints of this substudy were to compare changes in the QLQ-C30 GHS and QLQ-H&N35 swallowing domains from baseline to 6 months post-treatment between arms. The primary hypothesis was that IMRT+cetux would show a more favourable change in GHS and swallowing at 6 months post-treatment compared with IMRT+cisp. With a one-sided alpha of 0.05 and 90% power, a t-test for two independent groups required 246 analyzable patients (123/arm) at 6 months to detect an effect size of 0.375 in a QOL

subscale. Based on a 35% attrition rate at 6 months, the study was designed to enroll 400 patients for the PRO/QOL substudy.

Patients Included vs. Excluded in the QOL Substudy

Distributions of patient and tumor characteristics for eligible and treated patients included in the QOL analysis were compared with those excluded using descriptive statistics. Logistic regression models were fit to assess potential patient and tumor characteristics associated with the inclusion status. QOL completion status was summarized using the QLQ-C30 global health status domain completion rate; “useable” is defined as having answered both global health status questions.

Statistical Analyses

All QLQ-C30 and H&N35 domains were summarized using descriptive statistics (mean and standard deviation [SD]), both cross-sectionally and longitudinally, as changes from the pretreatment value for each time point by arm. For the primary PRO/QOL endpoints that compared changes in the QLQ-C30 GHS and QLQ-H&N35 swallowing domains from baseline to 6 months post-treatment between arms, a two-sample independent t-test was performed according to the protocol-specified analysis plan (0.05 one-sided alpha). No multiplicity adjustment was specified for these two domains in the protocol. A Wilcoxon rank sum test was also performed as a supplementary analysis. In post hoc, non-protocol-specified analyses, change from baseline to 6 months post-treatment between arms was compared using a Wilcoxon rank-sum test (two-sided p-value) for the remaining QLQ-C30 and H&N35 domains.

For the QLQ-C30 GHS and QLQ-H&N35 swallowing domains, multivariable linear mixed-effects models (LMMs) with all time points (discrete), treatment arm, and their interaction were also used to compare scores over time between arms (0.05 two-sided alpha). Models also included key baseline patient and tumor characteristics as covariates: age, gender, race, smoking history, tumor site, T and N stage, Zubrod performance status, fatigue, and feeding tube presence. The covariance structures were chosen using the Bayesian information criterion (BIC). These analyses assume a missing-at-random mechanism for missing data.

Similar linear mixed-effects models with an unstructured covariance matrix were used to assess changes in scores over time for all the remaining QLQ-C30 and H&N35 domains. Based on these models, between-arm differences over time were assessed by testing the treatment-by-time interaction (0.05 two-sided alpha). The Benjamini, Hochberg, and Yekutieli method[16], was employed to control the false discovery rate, which refers to the proportion of false discoveries among the rejected hypotheses, due to multiple testing across several domains in the previous analyses. The same multiplicity adjustment method was used for Wilcoxon tests comparing mean change scores from baseline to 6 months post-treatment between arms across all remaining domains of both instruments, as previously discussed. For domains with no significant interactions, differences in mean scores from the baseline to all time points were tested to assess patients’ return to baseline. Mean changes over time after adjusting for treatment arm and the additional covariates mentioned

above were assessed using appropriate contrasts based on the LMMs. These analyses used Dunnett's method to adjust for multiple tests across time points within each domain.[17]

A difference of more than 10 points in either direction in any domain was considered clinically meaningful for all analyses.[15]

In a protocol-specified analysis, the percent worsening in GHS score was described as worsened or not worsened, and as worsened, stable, or improved. Worsened was defined as a score decrease of >10 points, stable as a score between −10 and 10 points, and improved as an increase of >10 points from baseline. Differences between arms were compared using Fisher's exact test (0.05 two-sided) at each time point with no multiplicity adjustment. Worsened status (worsened/not worsened) was modeled using a longitudinal model for binary outcomes based on the general estimating equation (GEE) approach. The regression structure of the log odds ratio (OR) was chosen using the quasi-likelihood under the independence model criterion (QIC).

In a further post-hoc, exploratory analysis, Spearman correlation coefficients were used to assess the association between all QLQ-C30 and H&N35 domains after pooling arms and time points. This assessment could provide support for the internal validity of the instrument in this subpopulation of patients with head and neck cancer.

Results

Study Participation and Patient Characteristics

Of 792 eligible and treated patients in RTOG 1016, 419 patients were offered participation in the QOL substudy (recruitment ended in February 2013), and 381 (91%) consented. Ultimately, 375 (47.3% of eligible and treated patients) were included in the QOL analysis after excluding six patients for protocol violations (Figure S1).

Based on bivariate analyses, no apparent differences were found in the distribution of patient and tumor characteristics between the QOL inclusion groups. However, a multivariable logistic regression model suggested that patients who were not married or had unknown marital status had higher odds of being excluded from the QOL substudy (OR=1.37 [95% confidence interval (CI) 1.00, 1.87] for not married/in a domestic partnership; OR=1.89 [95% CI 1.04, 3.46] for unknown status—compared to married/domestic partnership; p=0.03). Older patients also showed higher odds of being excluded from the QOL substudy (OR=1.02 [95% CI 1.0, 1.3], p=0.069).

Table 1 shows the characteristics of 375 patients eligible for QOL analysis. The median age was 57, 89.6% were male, and 94.7% were white. Participants had excellent performance status (Zubrod 0 in 76.8%), but 29.1% would be classified as intermediate risk of death (36.8% had >10 pack-years smoking history, 11.2% had T4 disease, and 91.2% had N2–3 disease as per AJCC 7th edition).[2]

Instrument Completion Rates

QOL completion rates, based on the GHS, are displayed in Table 2. Baseline assessments were completed for 91.7% of patients on IMRT+cisp and 94.0% on IMRT+cetux. After excluding patients who died or withdrew consent prior to the 6-month time point, 76.4% on IMRT+cisp and 80.7% on IMRT+cetux completed assessments at 6 months. No notable differences between the arms were seen in the reasons assessments were not completed or the pattern of complete assessments (data not shown).

Comparison of QOL Changes from Baseline to 6- and 12-Months Post-Treatment

In both treatment arms, scores were lowest at the end of treatment and then increased, indicating worse quality of life at the conclusion of RT, followed by gradual improvement (Figure 1A). The mean GHS scores at baseline and 6 months post-treatment, by treatment arm, are shown in Table 3. At 6 months post-treatment, there was no significant difference in mean change from baseline in GHS scores between treatment arms (IMRT+cisp:−0.57 [95% CI −4.88, 3.74], IMRT+cetux: −0.90 (95% CI [−4.95, 3.15]); p=0.5438). At 1 year post-treatment, no significant difference in mean GHS change scores from baseline between arms was observed either (IMRT+cisp: 3.15 [95% CI −1.10, 7.40], IMRT+cetux=2.59 (95% CI [−1.29, 6.47]; p=0.7827 from LMM) (Figure 1B). Similar trends were seen for role functioning (Figures 1C and 1D).

Swallowing symptoms deteriorated (higher scores) at the end of treatment and steadily improved (scores decreased) thereafter in both treatment arms (Figure 2A). At 6 months post-treatment, the mean change from baseline in swallowing scores between treatment arms did not differ significantly (IMRT+cisp: 8.65 [95% CI 4.53, 12.77], IMRT+cetux: 10.13 [95% CI 6.88, 13.38]; p=0.7108; Table 3). At 1 year post-treatment, no differences in change in swallowing scores were observed either (IMRT+cisp: 2.52 [95% CI −1.04, 6.09], IMRT+cetux: 7.61 [95% CI 4.34, 10.89], p=0.0760 from LMM; Figure 2B). Appetite loss tracked similarly (Figures 2C and 2D).

The mean and 95% CI score changes from baseline to 6 months post-treatment by treatment arm for all EORTC QLQ-C30 and H&N35 domains are shown in Figure S2. These analyses did not suggest any patient-experience benefit of cetuximab over cisplatin at 6 months post-treatment (unadjusted Wilcoxon's $p \geq 0.054$ and multiplicity-adjusted $p \geq 0.949$ across all QLQ-C30 and QLQ-H&N35 domains).

Between-Arm Differences Over Time

Tables S1 through S33 summarize (mean and SD) for all QLQ-C30 and H&N35 domains, both cross-sectionally and longitudinally, as changes from baseline for each time point by arm.

Analyses based on multivariable LMMs, without multiplicity adjustment across domains, suggested that treatment-by-time interaction was significant for H&N35 dry mouth (p=0.0226). Mean change scores from baseline in dry mouth scores were higher (worse symptoms) for IMRT+cetux (mean change=58.40 [SD=32.93]) at the end of treatment compared with IMRT+cisp (43.85 [SD=40.03]; Figures 3A and 3B). After adjusting

for multiplicity, none of the domains showed a significant treatment-by-arm interaction (adjusted p-values across all domains were ≥ 0.524).

Temporal Trends Within Domains

Since the treatment-by-time interaction was not significant in any domain after multiplicity adjustment, changes from baseline to each time point across treatment arms were assessed within each domain using appropriate LMM-based contrasts (Figures S3–S5). Results suggested that all EORTC QLQ-C30 and H&N35 domains except emotional functioning, dyspnea, diarrhea, financial difficulties, teeth, and weight gain showed a significant and clinically relevant change (> 10 points) from baseline to the end of treatment (example for Senses shown in Figures 3C and 3D). Mean scores changed significantly and meaningfully from baseline in the domains of sensory changes, dry mouth, sticky saliva (Figures S6A and S6B), all indicating worsening symptoms, while pain killers showed improvement/less use (Figures S7A and S7B) at or beyond 6 months.

“Response”-Based GHS Analysis

Table S34 shows the distribution of worsened, stable, and improved GHS scores, as defined in the protocol, at each time point by treatment arm. At the 6-month time point, 22.5% of patients had worsened (score decrease of >10 points) GHS scores, 52.7% had stable scores (scores between −10 and 10), and 24.8% improved (score increase of >10 points) in both arms. There were no significant differences between treatment arms at any time point (p ≥ 0.232 across all time points). Moreover, a longitudinal model (GEE, fully parameterized clusters regression structure) with binary worsened/non-worsened response showed no significant difference between treatment arms over time (treatment-by-time interaction p=0.73).

Correlation Analysis Between Instrument Subscales

The relationships between subscales within the EORTC QLQ-C30 and H&N35 were examined using Spearman correlation coefficients after pooling data across treatment arms and time points (Figures S8 and S9) in a post-hoc analysis. Strong positive correlations (>0.6) were found between GHS and physical, role, and social functioning (0.62, 0.66, and 0.65, respectively); the functional scales also showed strong cross-correlations. Fatigue correlated positively with pain (0.65) and negatively with GHS and role, social, and physical functioning subscales (−0.70, −0.69, −0.75, and −0.76, respectively). On H&N35, high correlations were seen involving pain, senses, social contact, social eating, speech, swallowing, dry mouth, and sticky saliva.

Discussion

As a large, multicenter trial with relatively high completion rates, QOL data from RTOG 1016 refutes the patient experience benefits that were expected by substituting cetuximab for cisplatin (given with radiotherapy) in p16+ oropharyngeal cancer. The primary hypothesis that IMRT+cetux would show a more favourable change in QLQ-C30 GHS and QLQ-H&N35 swallowing at 6 months post-treatment compared with IMRT+cisp was not upheld. Neither the protocol-specified two-sample independent t-test, nor supplementary analyses

using a Wilcoxon rank sum test showed such a benefit. Additional multivariable LMM analysis did not alter this finding. Indeed, no significant difference was observed between arms for the 6-month change from baseline on any domain.

Consistent with literature experience of concurrent IMRT+drug experience in OPC, most QOL domains worsened through treatment, and certain domains showed persistent impairment. By 6 months, clinically meaningful drops > 10 points remained for: Senses, Social Eating, Opening Mouth, Dry Mouth, Sticky Saliva; and at 12 months for Senses, Trouble with Social Eating, Opening Mouth, Dry Mouth, Sticky Saliva, Pain Killers, and Weight Gain. These findings are consistent with both literature and clinical experience, in which many survivors grateful for successful treatment nonetheless struggle with taste changes, dry mouth and eating/swallowing challenges long-term. These findings underline the importance of continuing to study strategies to minimize QOL impairments whilst effectively controlling OPC.

The rapid accrual of RTOG 1016 demonstrates the appeal to patients and investigators of approaches designed to improve long-term experience for cancer survivors. This and other HNC trials conducted in the modern era have shown the willingness of patients to complete patient-reported outcome measures (PROMs), and the feasibility of achieving high completion rates in an appropriately resourced and monitored clinical trial setting.[18,19,20]

Eligibility for this study overlapped both low- and intermediate-risk categories for OPC. All patients were p16+, but some had smoking pack-years >10 and multiple nodes or a node >6 cm, the combination of which indicates intermediate risk of death. Extremely low-risk patients (T1–2, N0–1) were excluded. Nevertheless, the 5-year OS of 85% in the standard IMRT+cisplatin arm confirms that most p16+ OPC patients have an excellent prognosis. The cumulative incidence of such cancers is predicted to rise from about 12/100,000 in 2020 to 14/100,000 by 2035, with only modest impact from existing HPV vaccines (mainly reducing incidence in younger patients).[21] Consequently, we continue to expect many long-term survivors in future, underlining the continued importance of seeking safe de-escalation strategies and continuing to measure QOL and functional outcomes in current and future trials.

This research experience has led to questions about the most appropriate endpoints to evaluate patient-centred experience improvement in HNC de-escalation trials. It may be that overall health-related QOL is too general to register changes that are more focal, such as the implications of dry mouth or hearing loss.[22] Additionally, the well-recognized phenomenon of response shift,[23] which may be thought of as healthy adaptation, also influences overall QOL; survivors of cancer re-evaluate their priorities and may report excellent QOL whilst simultaneously acknowledging a “new normal”. Nonetheless, measuring data directly from the patient is critical, given that third-party measures provided by clinicians significantly under-rate the degree of problems experienced by patients.[24] The focus has shifted to instruments designed for more specific symptoms or functional deficits, such as dysphagia-specific QOL; however, as demonstrated in this trial, which symptom should be targeted will be specific to the cancer subsite, stage, and treatments being compared in a specific trial. With full-dose IMRT and concurrent systemic therapy, the OPC patients in our study

showed sustained impairments related mainly to dry mouth, sticky saliva, and sensory changes, suggesting that similar studies may wish to target these issues. In a contrasting example of an intervention with a “matching” PROM, a recently published study of dysphagia-optimized IMRT using the MDADI instrument was able to show a meaningfully better dysphagia-related QOL at 1 year for patients who received a lower dose of radiation (49.7 vs 57.2 Gy) to the superior and middle pharyngeal constrictors.[25]

The EORTC QLQ-C30/H&N35 has been the most commonly-used HNC-specific QOL instrument in the literature.[26] A more recent version of the HNC module is now available, HN-43.[27,28] This study adds to the body of evidence on the content and construct validity of the instrument, its continued relevance for patients with HPV-related cancers, as well as its responsiveness to changes related to combined RT and systemic therapy in OPC.

This analysis has several limitations. The study population in this trial was overwhelmingly male (90%) and white (93%). It has been recognized that cancer clinical trials, often led from and conducted in high-profile, university-based cancer centers, may be less accessible to the diverse individual[29] and that racialized Americans have been underrepresented in clinical trials.[30] Population-based data in the USA suggests that currently, men make up about 84% of p16+ cancers[31] and white individuals also account for about 84%.[32] Non-disease-specific variables identified as associated with QOL in HNC include younger age, medical comorbidity, lower socioeconomic status, and unemployment.[33] Thus, these results may not be representative of the overall population of North Americans with p16+ OPC. In addition, the purpose and design of the research was not focused on instrument validation, and thus this work can only support, but not fully demonstrate, construct validity of the chosen QOL instruments. Moreover, variability in contouring of tumours and organs at risk, as well as in radiotherapy planning techniques, can influence QOL and functional outcomes and is magnified in multi-center trials. Current and future research is increasing efforts to attract and support more diverse and representative participants to clinical trials; technical improvements in radiotherapy also continue.

Conclusions

Cetuximab is not an effective substitute for cisplatin in patients with p16-positive oropharyngeal cancer, as concurrent systemic therapy with modern IMRT, even for patients who prioritize QOL. Although acute toxicity (T-score) and swallowing at 1 year were modestly better, overall QOL and late toxicity were not impacted and survival was inferior. Efforts to de-escalate therapy for good prognosis HNC patients, including p16+ OPC, continue. This study supports the responsiveness of the EORTC QLQ-C30/H&N35 to the effects of concurrent systemic therapy with IMRT. This analysis suggests that sensory changes, dry mouth, sticky saliva, and pain killers exhibit measurable longer-term impairment after standard IMRT+cisplatin and may be among the most fruitful to target in future de-escalation trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement for this Work:

All deidentified participant data and data dictionary from this paper will be available upon request within 6 months of publication in accordance with NRG data sharing policy, which can be found at https://www.NRGoncology.org/Resources/Ancillary-Projects-Data-Sharing-Application

APPENDIX

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Beaumont NCORP

Cancer Research Consortium of West Michigan

Cape Radiation Oncology

Carle Foundation Hospital

Carolinas Medical Center/Levine Cancer Institute

Case Western Reserve/University Hospital Seidman Cancer Center

City of Hope

Colorado Cancer Research Program (CCRP)

Cooper Health System University Hospital

Dana-Farber Cancer Institute (DCFI with BWH)

Dartmouth-Hitchcock Medical Center/Norris Cotton Cancer Center

Delaware Christiana Care Community Clinical Oncology Program

Emory University

Flower Hospital

Fox Chase Cancer Center

Georgia NCORP

Intermountain Medical Center

James Graham Brown Cancer Center, University of Louisville

John H Stroger Jr Hospital of Cook County

Kaiser Permanente

Kansas City Clinical Oncology Program

London Health Sciences Centre/Western University

Loyola University Medical Center

Maine Medical Center

Mayo Clinic

McGill University Health Centre

MD Anderson Cancer Center

MD Anderson Cancer Center Orlando

Medical College of Wisconsin

Mercy Cancer Center - Sacramento

Metro-Minnesota Community Clinical Oncology Program

Michigan Cancer Research Consortium

Moffitt Cancer Center and Research Institute

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Northeast Radiation Oncology Center

NorthShore University Health System

Northwest NCORP

Northwestern University

Ohio State University

Ozark Health Ventures LLC Cancer Research for the Ozarks

Pacific Cancer Research Consortium

Piedmont Hospital

Reading Hospital

Roger Williams Medical Center

Sacred Heart Hospital

Saint Helena Hospital

Sentara Norfolk General Hospital

Southeast Clinical Oncology Research (SCOR) Consortium NCORP

Stanford University

Summa Health System

Sutter Cancer Research Consortium

The Cancer Institute of New Jersey

Toledo CCOP

Tom Baker Cancer Centre

University of Alabama at Birmingham Medical Center

University of California, Davis

University of California, San Diego (UCSD)

University of California, San Francisco (UCSF)

University of Cincinnati

University of Colorado

University of Florida

University of Iowa Hospitals and Clinics

University of Kansas Comprehensive Cancer Center

University of Kentucky

University of Miami

University of Mississippi Medical Center

University of Nebraska Medical Center

University of New Mexico Cancer Center/New Mexico Cancer Care Alliance

University of Oklahoma Health Sciences Center

University of Rochester

University of Utah/Huntsman Cancer Institute

University of Wisconsin Hospital and Clinics

Vanderbilt University/Ingram Cancer Center

Washington University School of Medicine

WellSpan Health-York Hospital

Wisconsin NCORP

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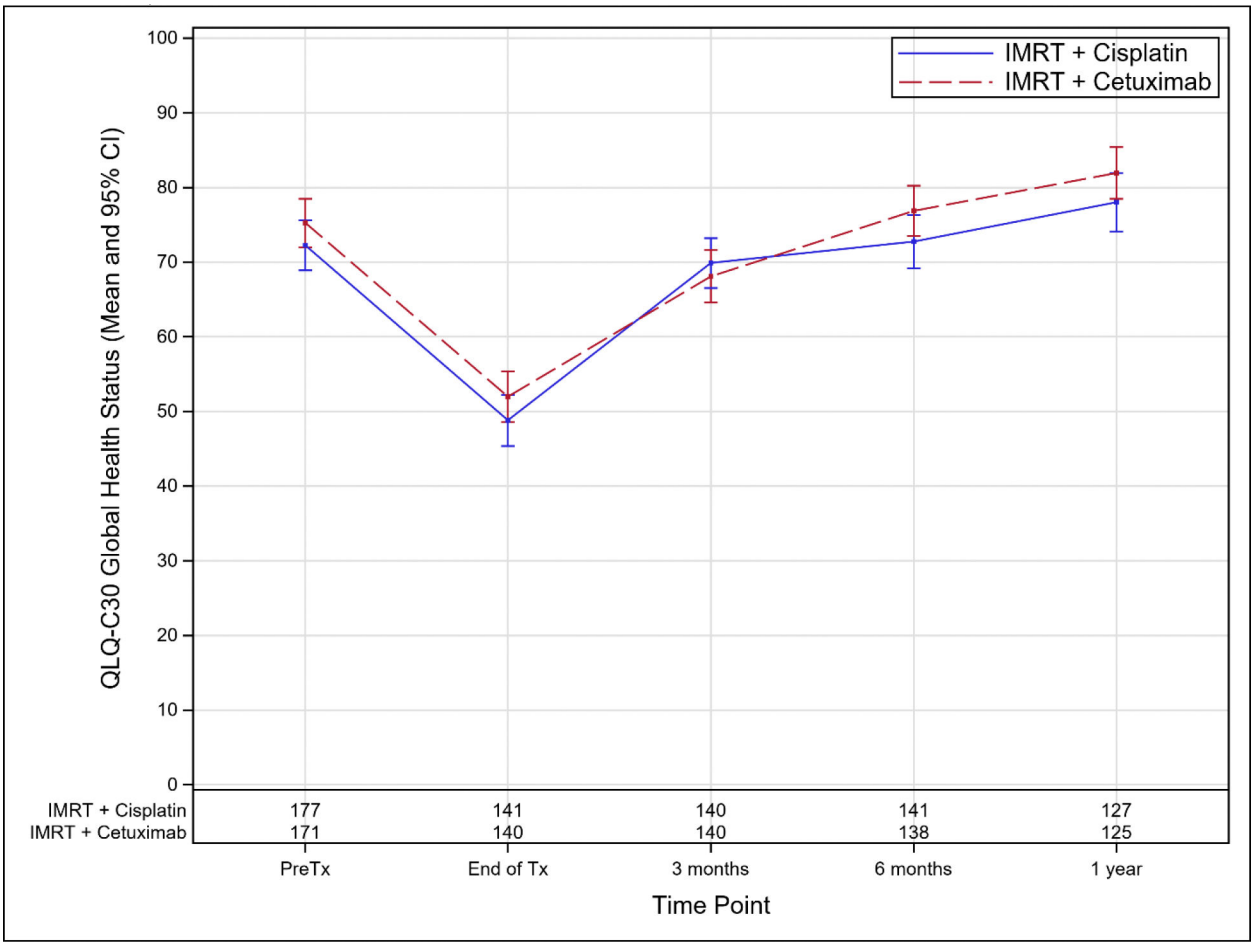

Figure 1A: EORTC QLQ-C30 Global Health Status Scores
(line going up means better global health status)

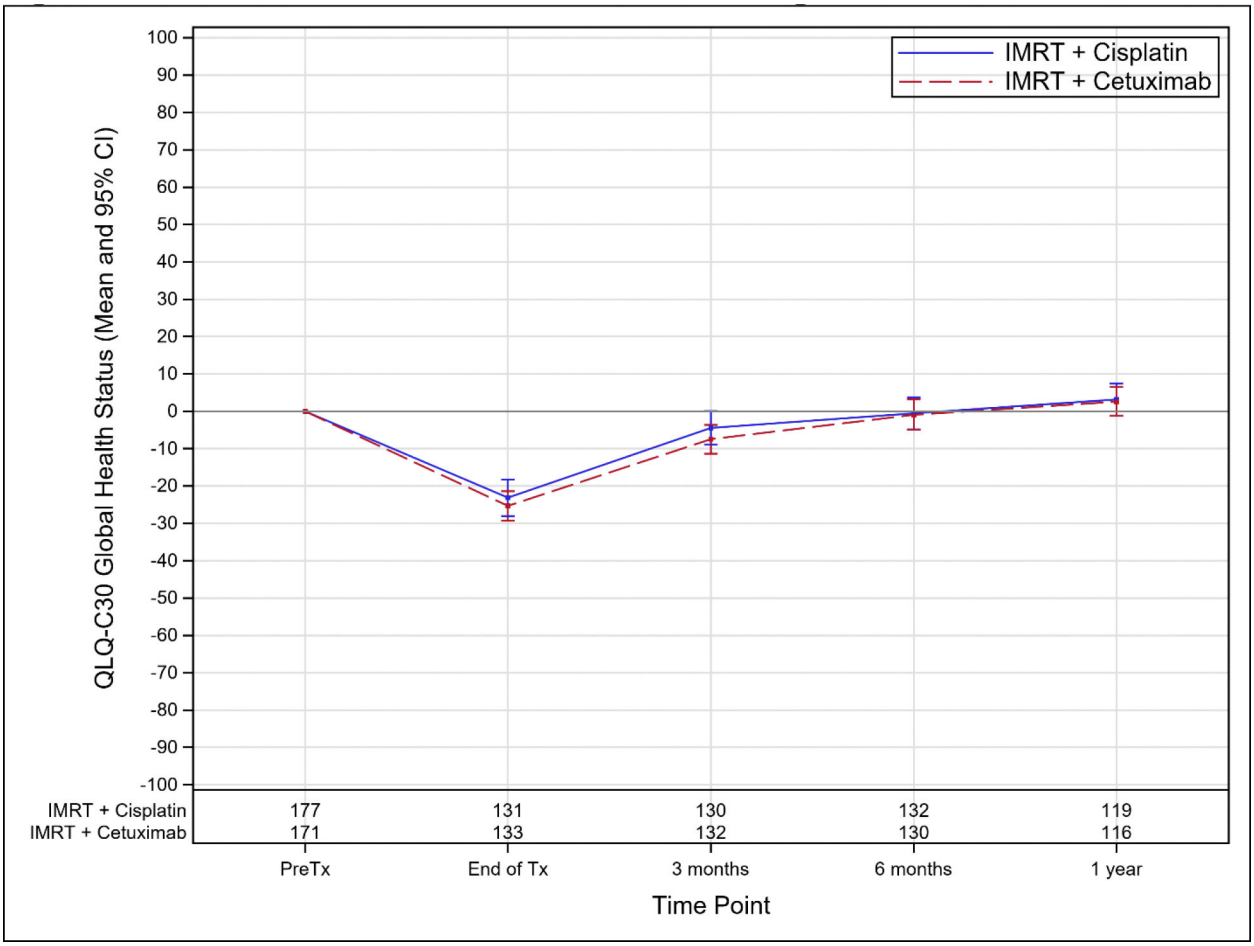

Figure 1B: EORTC QLQ-C30 Global Health Status Change from Baseline

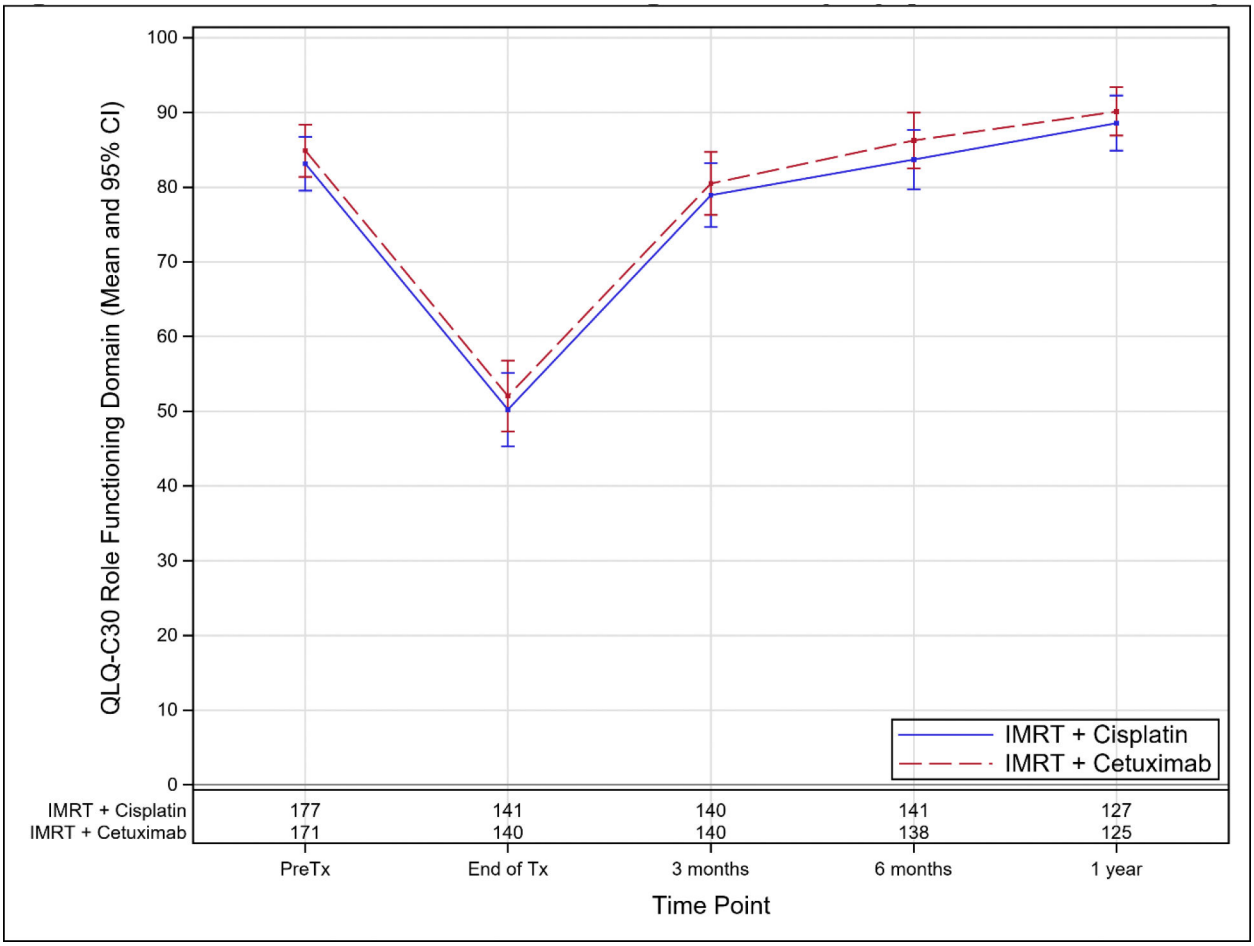

Figure 1C: EORTC QLQ-C30 Role Functioning Scores
(line going up means better functioning)

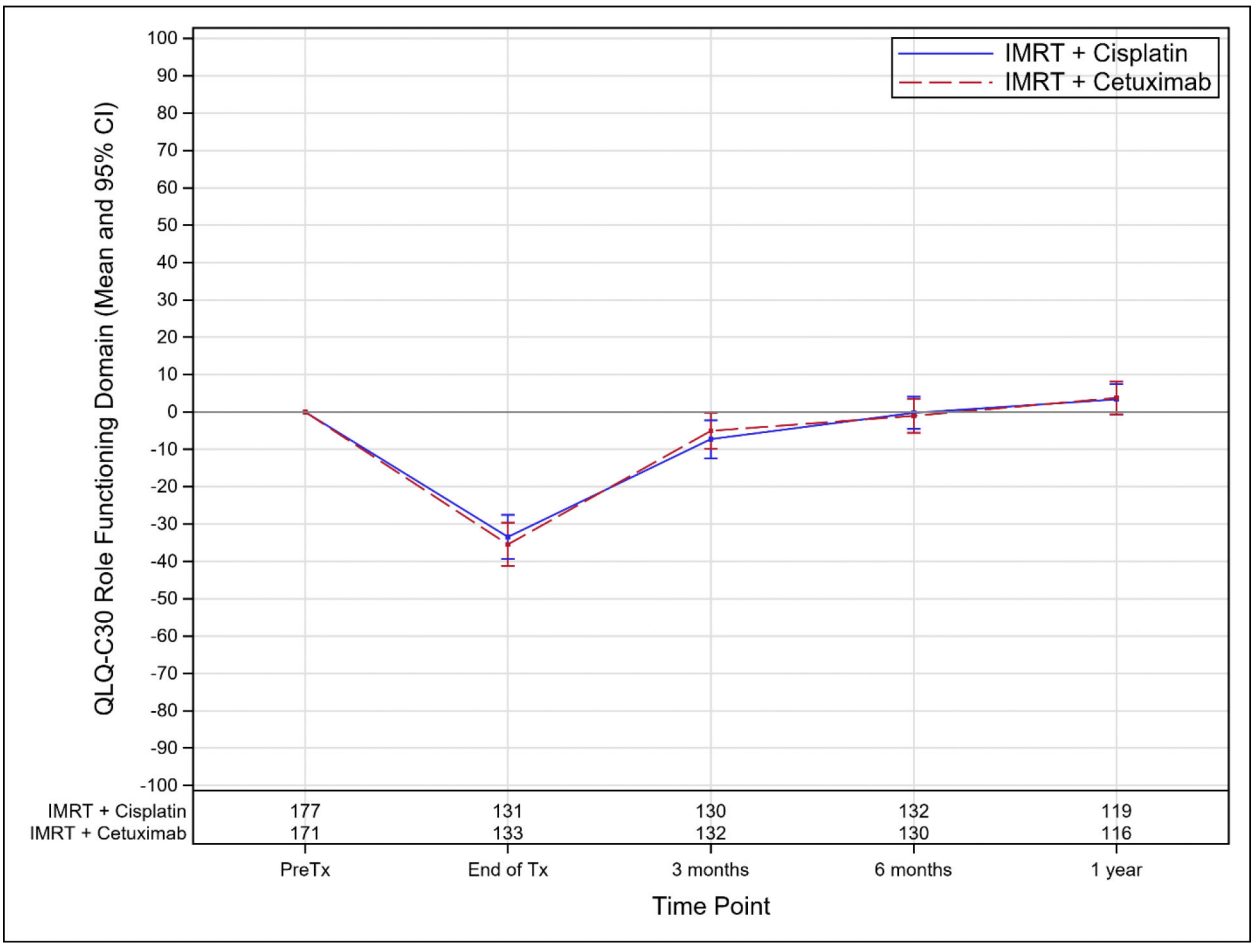

Figure 1D: EORTC QLQ-C30 Role Functioning Change from Baseline

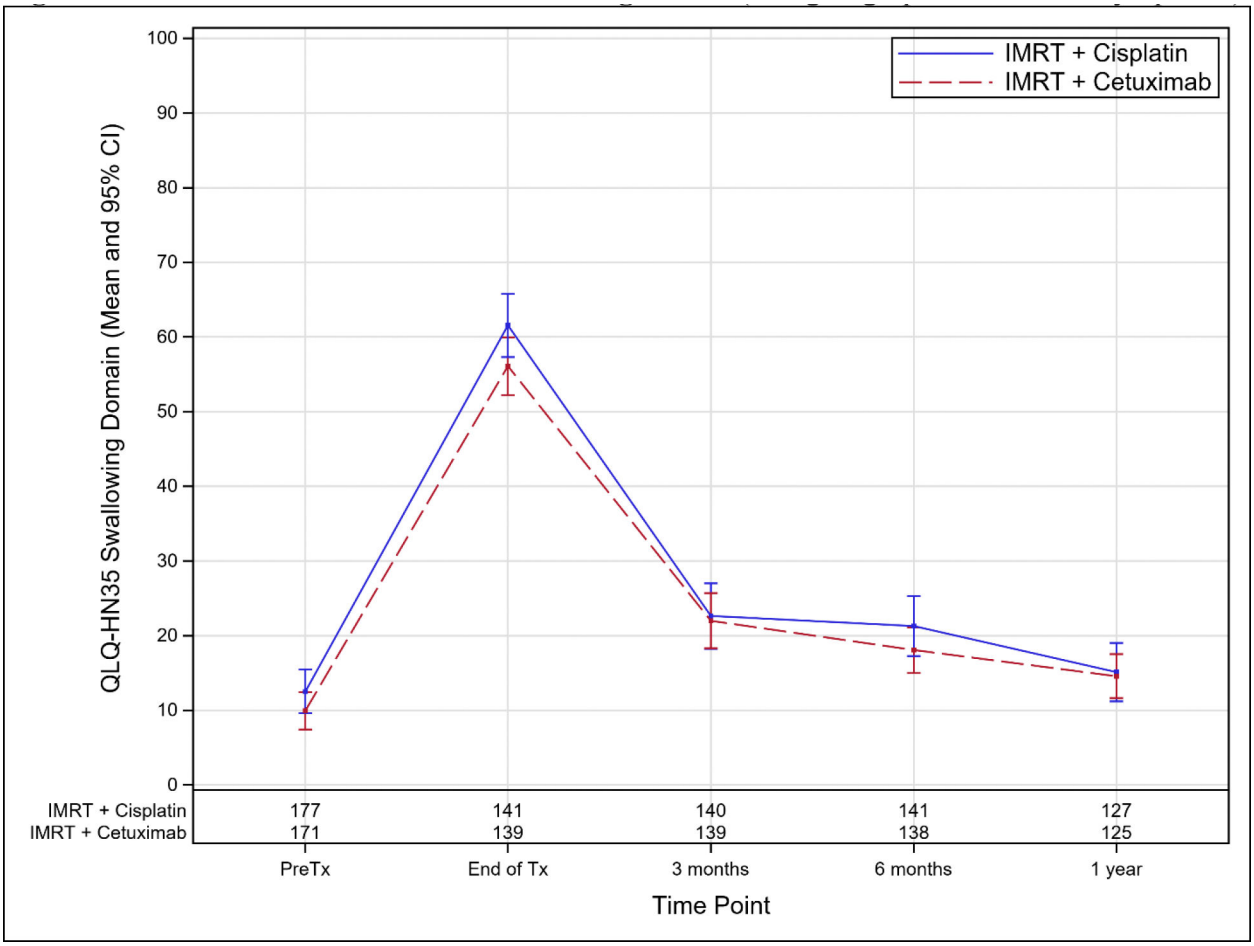

Figure 2A: EORTC QLQ-H&N35 Swallowing Scores
(line going up means worse symptoms)

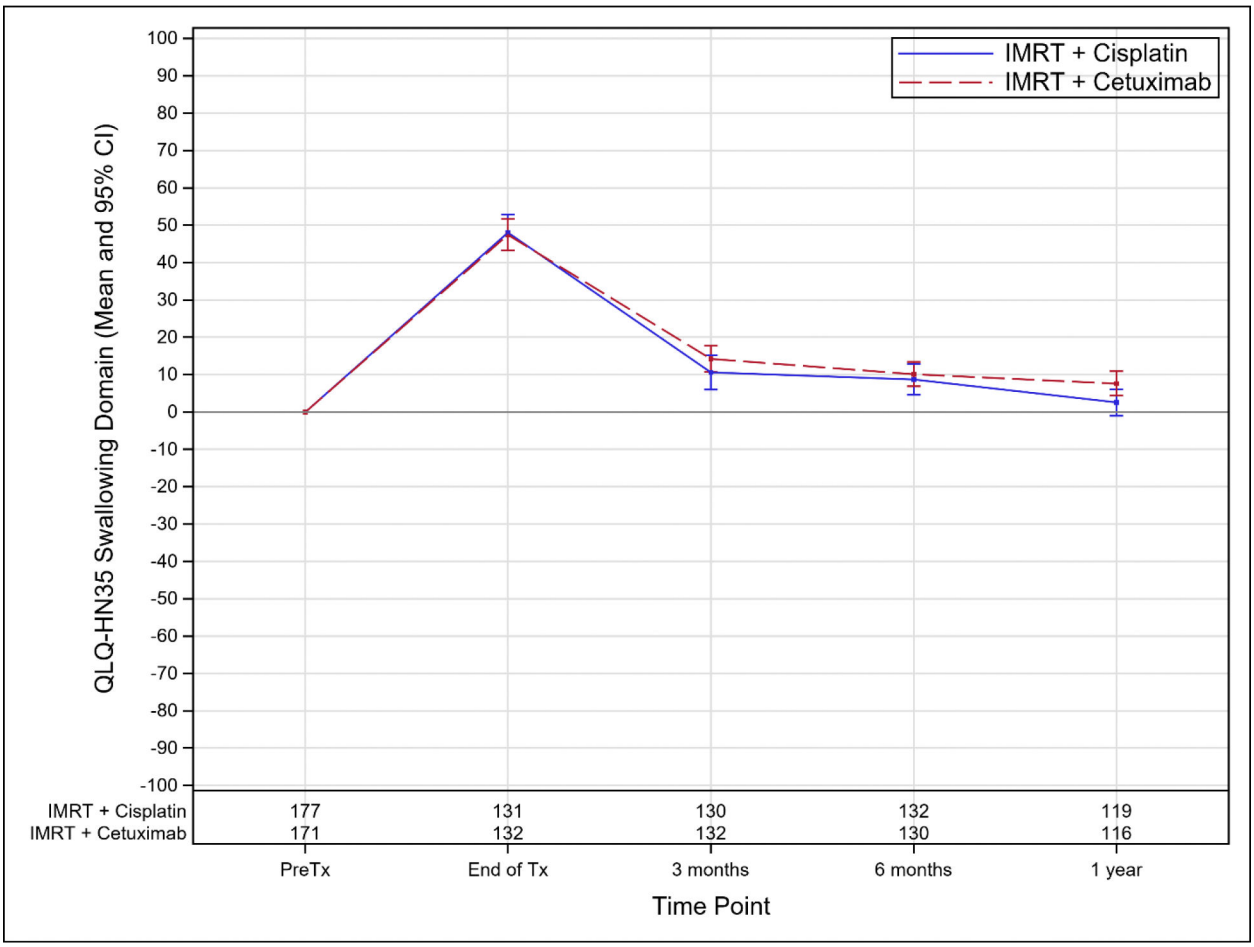

Figure 2B: EORTC QLQ-H&N35 Swallowing Change from Baseline

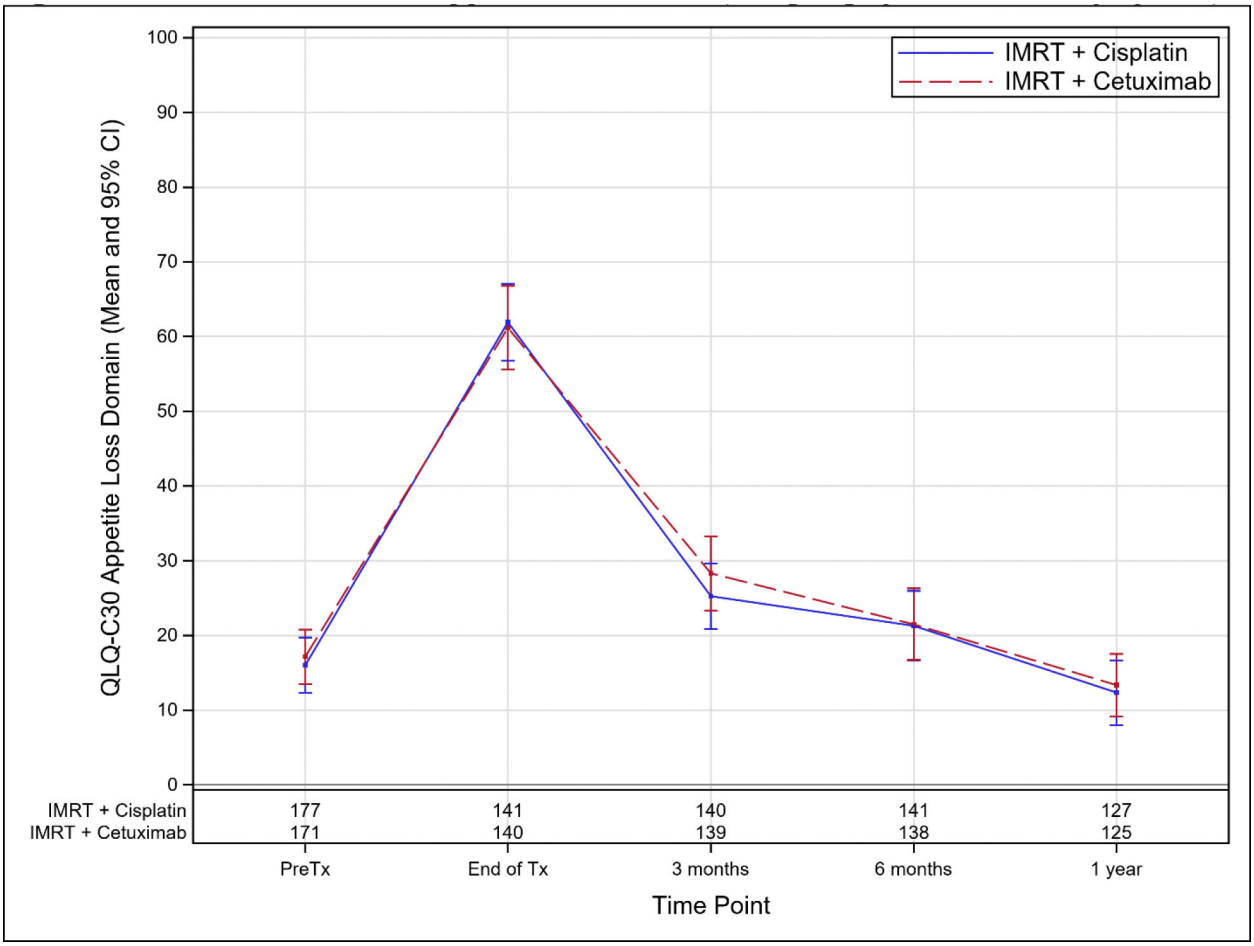

Figure 2C: EORTC QLQ-C30 Appetite Loss Scores
(line going up means worse symptoms)

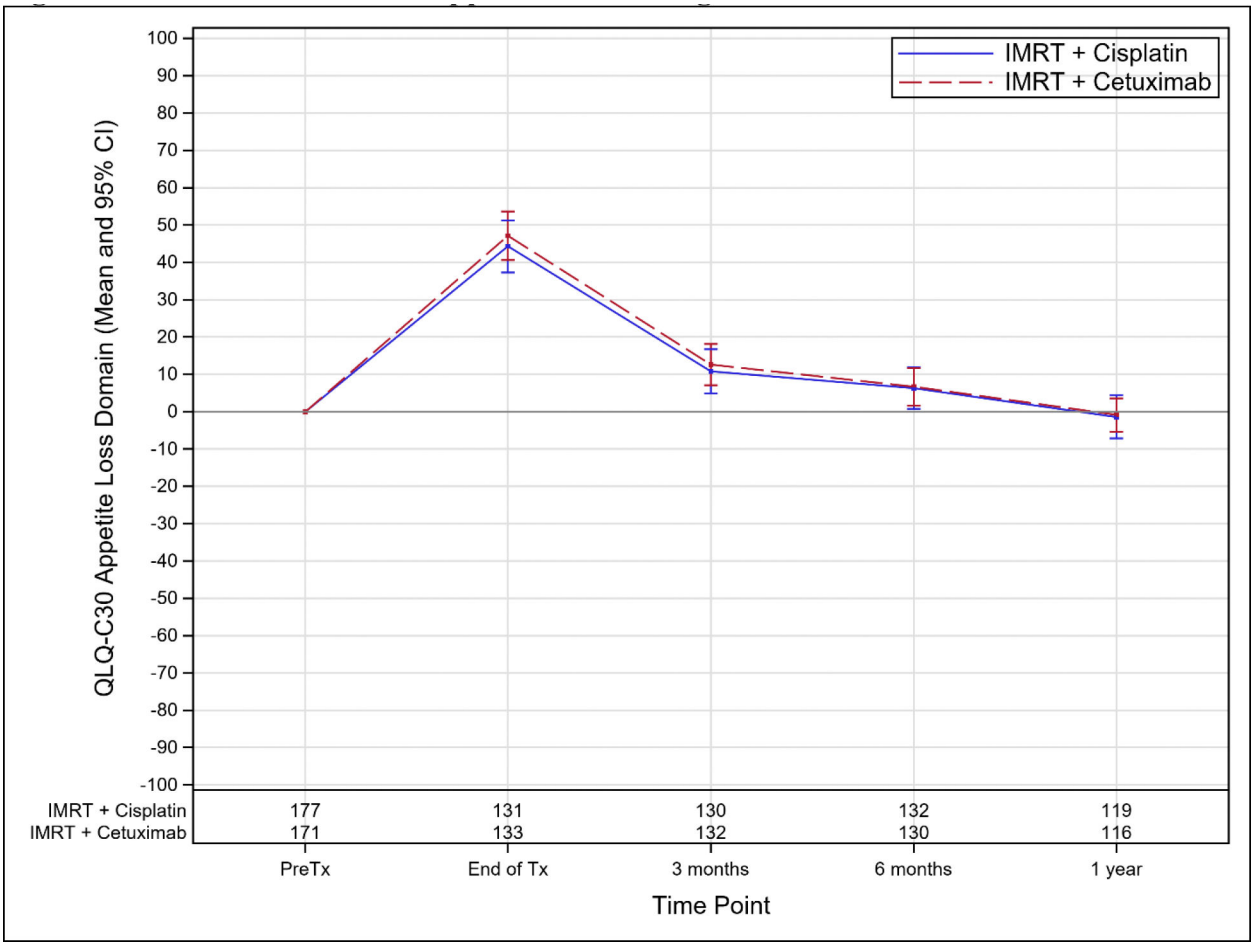

Figure 2D: EORTC QLQ-C30 Appetite Loss Change from Baseline

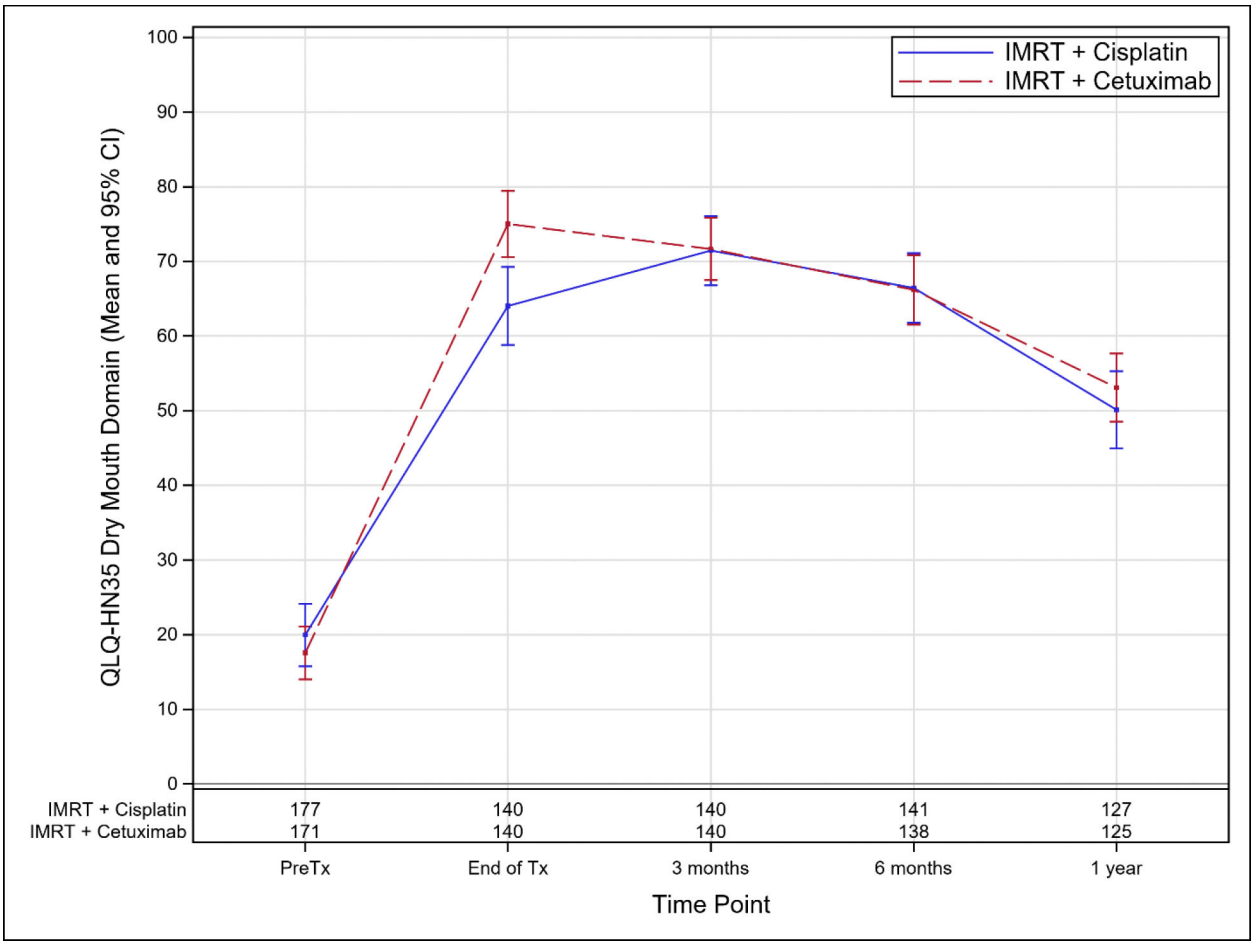

Figure 3A: EORTC QLQ-H&N35 Dry Mouth Scores
(line going up means worse symptoms)

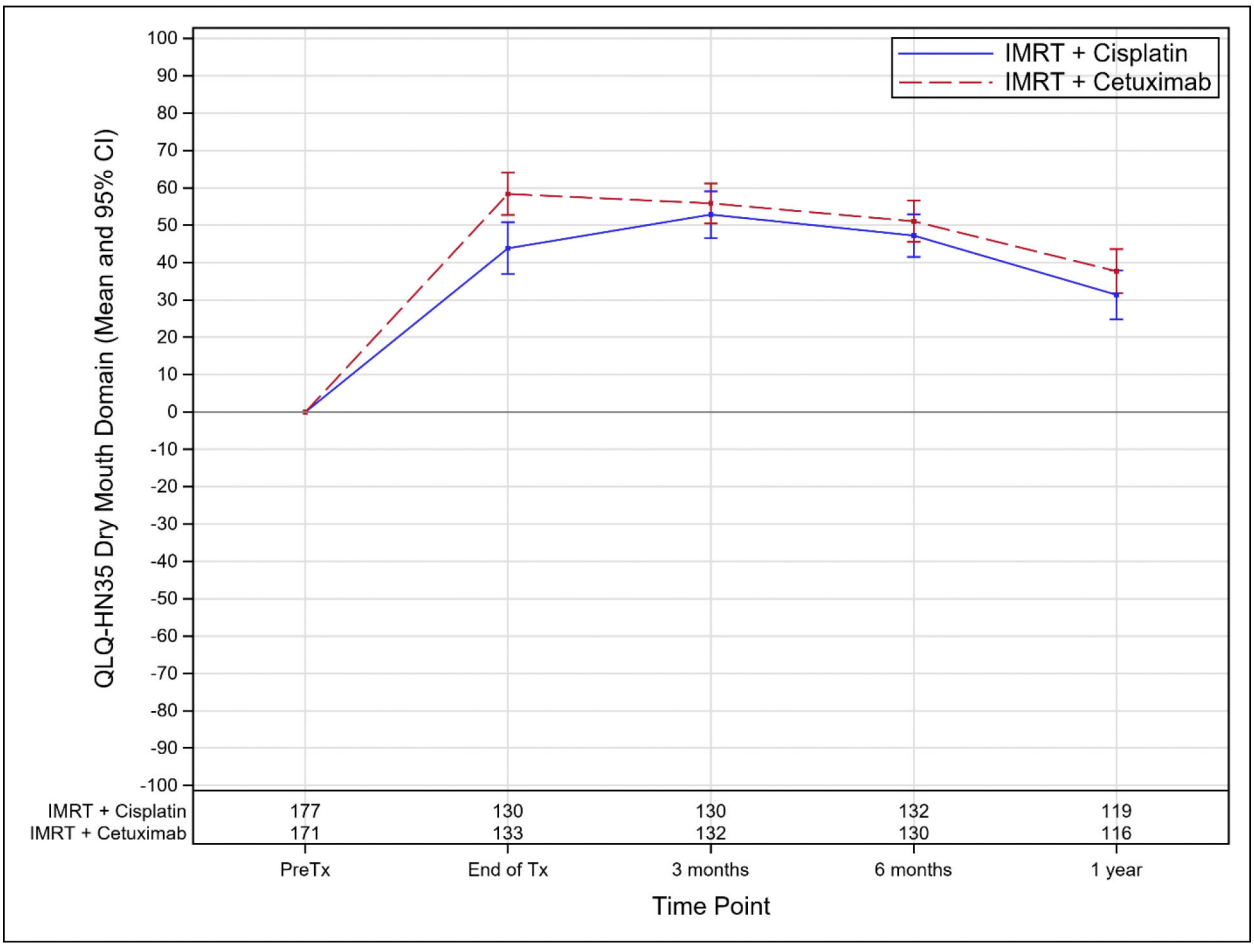

Figure 3B: EORTC QLQ-H&N35 Dry Mouth Change from Baseline

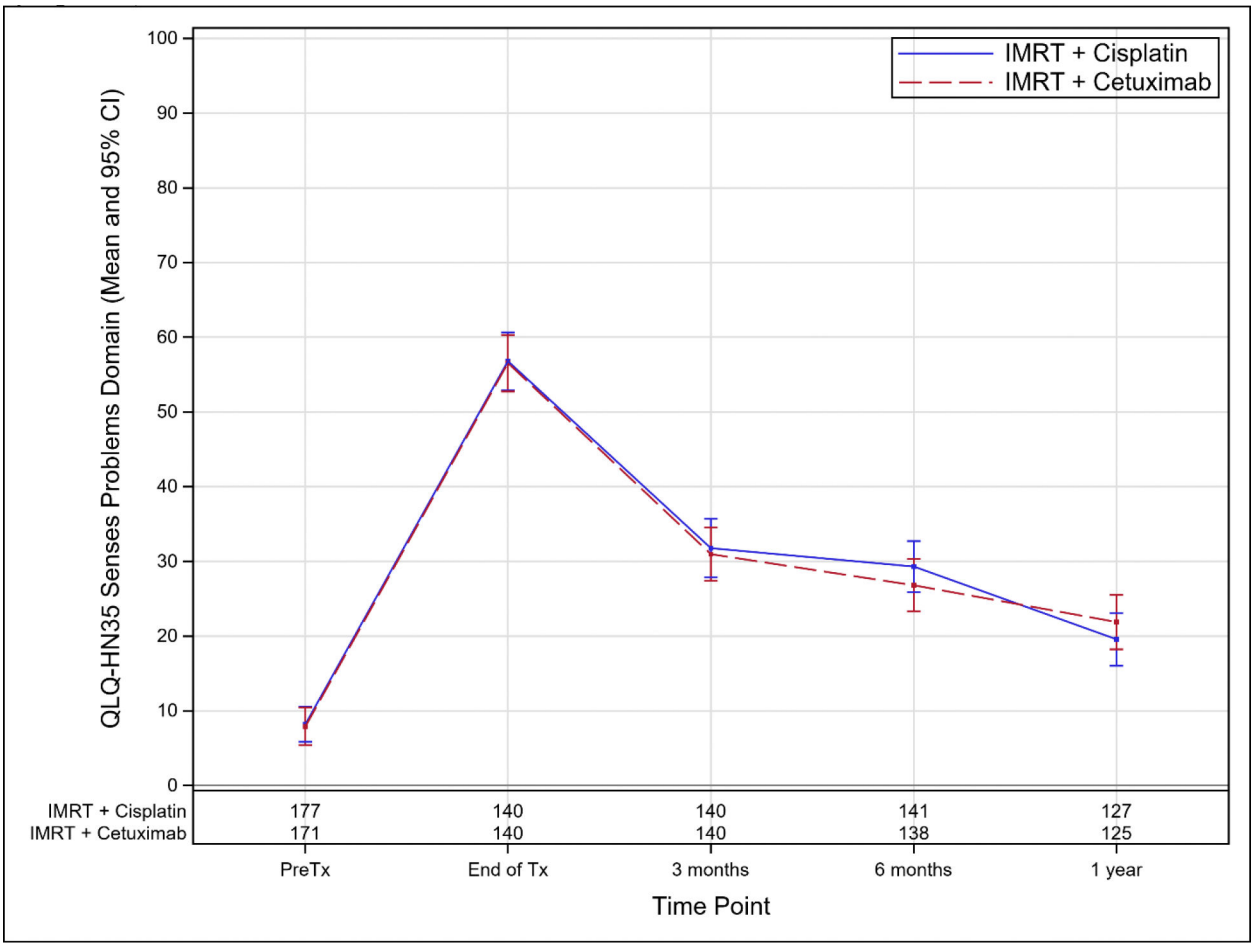

Figure 3C: EORTC QLQ-H&N35 Senses Problems Scores
(line going up means worse symptoms)

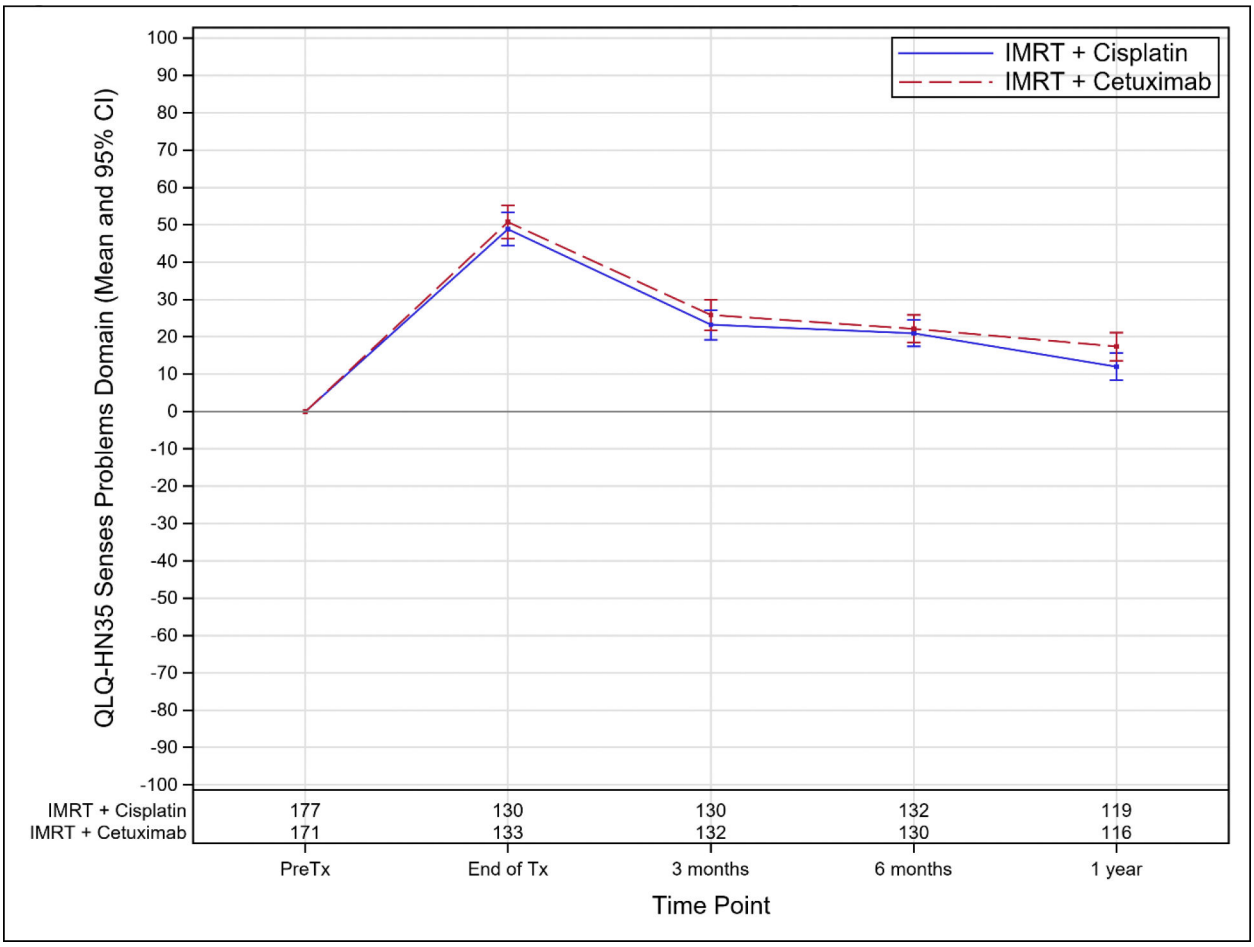

Figure 3D: EORTC QLQ-H&N35 Senses Problems Change from Baseline

Table 1.

Patient and Tumor Characteristics

Patient or Tumor Characteristic	IMRT + Cisplatin (n=193)	IMRT + Cetuximab (n=182)	Total (n=375)
Age (years)			
Median	57	58	57
Min - Max	33 – 83	33 – 80	33 – 83
Q1 - Q3	51 – 63	51 – 63	51 – 63
≤ 49	35 (18.1%)	38 (20.9%)	73 (19.5%)
50 – 59	82 (42.5%)	71 (39.0%)	153 (40.8%)
60 – 69	62 (32.1%)	63 (34.6%)	125 (33.3%)
≥ 70	14 (7.3%)	10 (5.5%)	24 (6.4%)
Gender			
Male	176 (91.2%)	160 (87.9%)	336 (89.6%)
Female	17 (8.8%)	22 (12.1%)	39 (10.4%)
Race			
American Indian/Alaska Native	0 (0.0%)	2 (1.1%)	2 (0.5%)
Asian	0 (0.0%)	1 (0.5%)	1 (0.3%)
Black or African American	5 (2.6%)	8 (4.4%)	13 (3.5%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (0.5%)	1 (0.3%)
White	186 (96.4%)	169 (92.9%)	355 (94.7%)
Unknown or not reported	2 (1.0%)	1 (0.5%)	3 (0.8%)
Ethnicity			
Hispanic or Latino	6 (3.1%)	8 (4.4%)	14 (3.7%)
Not Hispanic or Latino	183 (94.8%)	167 (91.8%)	350 (93.3%)
Unknown	4 (2.1%)	7 (3.8%)	11 (2.9%)
Zubrod performance status			
0	142 (73.6%)	146 (80.2%)	288 (76.8%)
1	51 (26.4%)	36 (19.8%)	87 (23.2%)
Smoking history			
0 pack-years	88 (45.6%)	91 (50.0%)	179 (47.7%)
> 0 - ≤ 10 pack-years	36 (18.7%)	22 (12.1%)	58 (15.5%)
> 10 pack-years	69 (35.8%)	69 (37.9%)	138 (36.8%)
Primary site			
Tonsillar fossa, tonsil	98 (50.8%)	88 (48.4%)	186 (49.6%)
Base of tongue	82 (42.5%)	87 (47.8%)	169 (45.1%)
Oropharynx, NOS	6 (3.1%)	4 (2.2%)	10 (2.7%)
Pharyngeal oropharynx	4 (2.1%)	3 (1.6%)	7 (1.9%)
Soft palate	3 (1.6%)	0 (0.0%)	3 (0.8%)

Patient or Tumor Characteristic	IMRT + Cisplatin (n=193)	IMRT + Cetuximab (n=182)	Total (n=375)
p16 status (central review)			
p16-positive	193 (100.0%)	182 (100.0%)	375 (100.0%)
p16 status (local testing)			
p16-negative	1 (0.5%)	0 (0.0%)	1 (0.3%)
p16-positive	181 (93.8%)	172 (94.5%)	353 (94.1%)
Tested but unknown	0 (0.0%)	1 (0.5%)	1 (0.3%)
Not tested	11 (5.7%)	9 (4.9%)	20 (5.3%)
T stage			
T1	46 (23.8%)	44 (24.2%)	90 (24.0%)
T2	76 (39.4%)	71 (39.0%)	147 (39.2%)
T3	51 (26.4%)	45 (24.7%)	96 (25.6%)
T4	20 (10.4%)	22 (12.1%)	42 (11.2%)
N stage			
N0	7 (3.6%)	6 (3.3%)	13 (3.5%)
N1	10 (5.2%)	10 (5.5%)	20 (5.3%)
N2a	26 (13.5%)	33 (18.1%)	59 (15.7%)
N2b	101 (52.3%)	90 (49.5%)	191 (50.9%)
N2c	41 (21.2%)	36 (19.8%)	77 (20.5%)
N3	8 (4.1%)	7 (3.8%)	15 (4.0%)
Stage			
III	13 (6.7%)	13 (7.1%)	26 (6.9%)
IV	180 (93.3%)	169 (92.9%)	349 (93.1%)

Q1, first quartile; Q3, third quartile.

Table 2.

QOL Completion Rates*

Time point	IMRT + Cisplatin	IMRT + Cetuximab
Baseline (pre-treatment)	177/193 (91.7%)	171/182 (94.0%)
End of treatment (−2 to +4 weeks)	141/191 (73.8%)	140/182 (76.9%)
3 months post-treatment (−4 to +6 weeks)	140/184 (76.1%)	140/173 (80.9%)
6 months post-treatment (−6 to +8 weeks)	139/182 (76.4%)	138/171 (80.7%)
1 year post-treatment (± 3 months)	127/175 (72.6%)	125/168 (74.4%)

*Based on both Global Health Status questions of the EORTC QLQ-C30 answered in window. Excludes patients who died or withdrew consent prior to time point (also known as variable denominator completion rates).

Table 3.

EORTC QLQ-C30/H&N35 Mean Domain Raw Score Changes from Baseline to 6 Months by Assigned Treatment

Domain	Assigned treatment	Mean (SD)		Mean diff. (95% CI)		
		Baseline	6 months	Within-arm*	Between-arm**	p***
QLQ-C30 Global Health Status	IMRT + Cisplatin	72.27 (22.67)	72.75 (21.41)	−0.57 (−4.88, 3.74)	−0.33 (−6.22, 5.56)	0.5438/0.6350/0.5326
	IMRT + Cetuximab	75.24 (21.34)	76.87 (20.04)	−0.90 (−4.95, 3.15)		
QLQ-HN35 Swallowing	IMRT + Cisplatin	12.52 (19.91)	21.28 (24.14)	8.65 (4.53, 12.77)	1.48 (−3.76, 6.71)	0.7108/0.8671/0.5651
	IMRT + Cetuximab	9.94 (16.58)	18.06 (17.97)	10.13 (6.88, 13.38)		

SD, standard deviation; diff, difference; CI, confidence interval.

*Within-arm mean difference between time points (6 months - baseline).

**Between-arm mean difference (IMRT + Cetuximab − IMRT + Cisplatin) of 6-month change from baseline.

***One-sided p-value for between-arm difference based on t-test/Wilcoxon rank sum test/LMM contrast.

For Global Health Status, higher scores mean better QOL, so a positive change from baseline indicates improvement. For Swallowing, higher scores mean worse QOL, so a positive change from baseline indicates worsening.

The multivariable LMM included age, gender, race, smoking history, tumor site, T and N stage, Zubrod performance status, fatigue, and feeding tube. A compound symmetry and unstructured covariance matrix was used for both domains.

For Global Health Status, higher scores mean better QOL, so a positive change from baseline indicates improvement. For Swallowing, higher scores mean worse QOL, so a positive change from baseline indicates worsening.