Effect of Cetuximab on Mucositis and Dysphagia in SCCHN

Title: Association of HPV and p16 status with mucositis and dysphagia for head and neck cancer patients treated with radiotherapy with or without cetuximab: assessment from a phase 3 registration trial

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**Research in Context**

*Evidence before this study*

Although a number of studies have demonstrated that inclusion of a radiosensitizer increases the effectiveness of radiotherapy (RT) for the treatment of locally-advanced head and neck squamous cell carcinoma (LA-SCCHN), evidence has also shown that the addition of chemotherapy as a radiosensitizer to RT (CRT) increases the incidence of severe mucositis. In contrast, the use of cetuximab as a radiosensitizer does not increase the incidence of severe mucositis compared with RT alone. However, an in-depth analysis of the role of human papillomavirus (HPV) status in the incidence and kinetics of radiation-induced mucositis and dysphagia in patients treated with cetuximab as a radiosensitizer has not previously been performed.

*Added value of this study*

This study confirms that, regardless of HPV status (as determined by the presence of p16), the incidence and kinetics of severe, radiation-associated mucositis and dysphagia were not changed when cetuximab was added to RT. This is especially relevant given the current focus on the reduction of the number of acute toxicities when HPV-positive oropharyngeal cancer (OPC) is treated and validates the effectiveness and tolerability of cetuximab compared with other radiosensitizers for the treatment of LA-SCCHN.

*Implications of all the available evidence*

With the global recognition of the need for less toxic regimens for the treatment of HPV-positive OPC, consideration of alternative RT regimens and selection of advantageous radiosensitizers will be an important component of care going forward. Given its established efficacy and the current tolerability findings, cetuximab emerges as an ideal component of treatment for OPC; it is effective and tolerable regardless of p16 status and does not affect the incidence or kinetics of mucositis and dysphagia compared with treatment with RT alone.
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**Abstract**

**Background:** Mucositis and dysphagia are common adverse effects of radiotherapy (RT) treatment of locally advanced squamous cell cancer of the head and neck (LA-SCCHN). Chemotherapy added to RT increases survival rates but causes worse mucositis and dysphagia. The aim of this analysis was to assess the impact of p16 status on mucositis, dysphagia, and feeding tube use in LA-SCCHN among patients treated with RT ± cetuximab in the phase 3 IMCL-9815 trial.

**Methods:** Patients received RT plus weekly cetuximab or RT alone. Subgroup analyses were conducted on patients with p16-positive (n = 75) or p16-negative (n = 106) oropharyngeal squamous cell carcinoma (OPC), as determined by immunohistochemical analysis. The onset and duration of mucositis and dysphagia by treatment arm and p16 status were displayed using Kaplan-Meier curves and log-rank test. $P$ values for the incidence of mucositis and dysphagia were calculated using the Fisher exact test. Feeding tube use was assessed as the percent of patients reporting use.

**Findings:** The baseline characteristics of patients treated with RT ± cetuximab were similar in both the p16-positive and p16-negative OPC subgroups. Patients within the p16-positive OPC subgroup had higher Karnofsky scores and were more likely to have stage T1–3 cancer and be from the United States. Regardless of p16 status, there was no difference in the onset or duration of grade 3/4 mucositis or dysphagia in patients receiving RT plus cetuximab compared with those receiving RT alone. In the overall population, and the p16-positive and p16-negative OPC subpopulations, feeding tube use was not different for patients receiving RT plus cetuximab compared with RT alone.

**Interpretation:** Regardless of p16 status, the addition of cetuximab to RT did not alter the incidence, time to onset, severity, or duration of mucositis and dysphagia and did not impact the frequency of feeding tube use.

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Introduction

Radiotherapy (RT) for locally advanced head and neck squamous cell carcinoma (LA-SCCHN) can induce mucositis, pain, dysphagia, and diminished quality of life.\(^1\)\(^,\)\(^2\) Severe mucositis contributes to the need for narcotic analgesics, intravenous fluids, and gastrostomy feeding and may lead to unplanned RT interruptions, thereby compromising outcomes.\(^3\)\(^,\)\(^4\) Concurrent chemotherapy improves survival rates for patients with SCCHN compared with RT alone, but often at the expense of increased mucositis and dysphagia. In contrast, the phase 3 IMCL-9815 trial, which investigated addition of the anti–epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab to RT, showed that cetuximab did not appear to worsen these toxicities when added to RT.

These findings and the recent availability of p16 analyses of the IMCL-9815 study prompted us to reevaluate these toxicities by characterizing onset, duration, and incidence in both p16-positive and p16-negative oropharyngeal cancer (OPC). Analysis of the IMCL-9815 trial recently showed that patients with either p16-positive or p16-negative OPC benefitted from the addition of cetuximab to RT.\(^5\) An interaction analysis did not indicate that there was an association between p16 status and the efficacy of cetuximab.\(^5\) We believe that it is important to further examine the toxicity profiles of the p16-positive and p16-negative groups. Our rationale for this belief is further underscored by the vast differences in prognosis between p16-positive and p16-negative OPC: for patients with p16-positive disease, their long life expectancy highlights the need for efficacious therapies that incur fewer long-term adverse effects (eg, feeding tube use); in contrast, for patients with poorer-prognosis p16-negative disease, their increased fragility necessitates the avoidance of potentially severe adverse effects (eg, mucositis).
This study is the first to examine the rate of onset and duration of radiation-induced mucositis and dysphagia for patients receiving RT alone or RT and cetuximab. Additionally, the role of p16 status was evaluated in the incidence, onset, and duration of mucositis and dysphagia, as well as feeding tube use, in patients with OPC receiving RT plus cetuximab compared with those receiving RT alone in the IMCL-9815 trial.

**Methods**

**Study design**

The design of the phase 3, randomized IMCL-9815 cetuximab registration trial has previously been reported in detail. Patients with LA-SCCHN were randomized to receive cetuximab plus RT once daily (2.0 Gy/fraction; 5 fractions/week for 7 weeks), twice daily (1.2 Gy/fraction; 10 fractions/week for 6.0–6.5 weeks), or concomitant boost (72 Gy in 6 weeks, using twice-daily fractionation for the final 2.4 weeks) or RT alone. The trial protocol was approved by the ethics committees of all participating centers. The primary endpoint of the study was the duration of locoregional control. Secondary endpoints included overall survival, progression-free survival, and response rate. Quality of life and incidence of adverse events were also evaluated. In this retrospective subgroup analysis, feeding tube use and the incidence of mucositis and dysphagia were evaluated in the overall safety population (n = 181), as well as subpopulations of patients with p16-positive and p16-negative OPC subgroups; by definition (see below), for evaluation of the onset and duration of mucositis and dysphagia, only those patients in the overall safety population who received at least one dose of RT were included (n = 180).

**Safety assessment**

Toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) criteria. Assessments of acute toxicity were carried out during weekly RT and through the eighth week after treatment. Late
radiation effects were assessed thereafter using RTOG toxicity scales. Mucositis was defined as
aphthous stomatitis, gingivitis, glossitis, mouth ulceration, mucous membrane disorder, stomatitis, or
ulcerative stomatitis. The onset of mucositis and dysphagia was calculated from the date of first RT until
the first day of mucositis/dysphagia. Duration was calculated from day of first onset until resolution to
grade 0 or end date. Feeding tube use was derived from a subset of the European Organisation for
Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Head and Neck Cancer (QLQ–H&N35) questionnaire. Scoring was carried out as defined by the EORTC scoring manual. All scores were
derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after a linear
transformation. Data for feeding tube use were reported as the percent of patients with a feeding tube
placed; in our study, feeding tubes were inserted on a patient-needed basis (preemptive use was not
pre-specified in the protocol, nor was it forbidden).

**p16 assessment**

The effect of human papillomavirus (HPV) status on the incidence, onset, and duration of mucositis and
dysphagia in patients with OPC was evaluated by determining the presence of p16 as a surrogate marker
of HPV in the 181 evaluable patients that comprised the safety population (figure 1). p16 protein
expression status was evaluated by means of immunohistochemical analysis using the CINtec histology
kit (Ventana Medical Systems Inc, Tucson, AZ, USA). Positive p16 expression was defined as strong and
diffuse nuclear and cytoplasmic staining in ≥ 70% of the tumor cells.9

**Statistical analysis**

The Fisher exact test was used to evaluate differences in baseline characteristics between treatment
arms and to calculate *P* values for the incidence of mucositis and dysphagia. The onset and duration of
Results

Baseline characteristics and study populations

The baseline characteristics of the patients in the intent-to-treat population (N = 424), the OPC population (n = 253), and the p16-evaluable population (n = 182) are presented in Table 1. Characteristics of the total OPC and p16-evaluable OPC populations were similar. Patients with p16-positive OPC had higher Karnofsky scores and were more likely to have stage T1–3 cancer and be from the United States. Patients with p16-positive OPC were more likely to have received concomitant-boost RT. Treatment arms were well balanced with respect to RT regimen. Baseline characteristics of patients receiving RT plus cetuximab or RT alone were well balanced within the p16-positive (n = 75) and p16-negative (n = 106) OPC subsets (table 1).

The majority of the findings presented in the current analysis were derived from the safety data set; this includes analysis of the overall safety population and the p16 subgroups (figure 1). Of the 420 patients in the safety population, 208 were randomized to receive RT plus cetuximab and 212 received RT alone (table 2).

Mucositis and dysphagia in the safety population

There was no difference in the incidence of all-grade or grade 3/4 mucositis and dysphagia in patients treated with RT plus cetuximab or RT alone (table 2). Because the treatment arms were well balanced with respect to RT regimen, RT regimens were pooled to assess the onset and duration of mucositis and
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dysphagia. There was no difference in the onset or duration of grade 3/4 mucositis in patients receiving RT plus cetuximab or RT alone (figure 2A and 2B). Similarly, the onset and duration of grade 3/4 dysphagia were not significantly different in patients who received RT plus cetuximab or RT alone (figure 2C and 2D). These findings remained consistent when all grades of mucositis and dysphagia were considered (supplementary table 1). When all RT regimens were considered, the addition of cetuximab did not significantly impact the onset or duration of all-grade or grade 3/4 mucositis and dysphagia (supplementary tables 1 and 2).

In contrast, the type of RT regimen had an effect on the incidence of mucositis and dysphagia. Patients who received altered-fractionation RT experienced significantly more events compared with patients who received once-daily RT, regardless of whether or not cetuximab was included in the regimen (table 3). However, with the exception of a significantly later onset of dysphagia in patients who received twice-daily RT compared with those who received twice-daily RT plus cetuximab, there was no significant effect of the addition of cetuximab on the onset or duration of all-grade or grade 3/4 mucositis and dysphagia in patients receiving once-daily, twice-daily, or concomitant-boost RT regimens (supplementary tables 1 and 2).

*p16 subset analysis of mucositis and dysphagia*

In the p16-positive and p16-negative OPC populations, the incidence of all-grade and grade 3/4 mucositis and dysphagia was not significantly different between treatments arms (table 2). Within the p16-positive population, the addition of cetuximab showed a trend toward more cases of grade 3/4 mucositis, all-grade dysphagia, and grade 3/4 dysphagia compared with treatment with RT alone. In the p16-negative population, there was a trend toward more cases of grade 3/4 mucositis but fewer cases of grade 3/4 dysphagia in the RT plus cetuximab arm. These trends did not reach significance (table 2).
In both with p16-positive or p16-negative tumors, the time to onset and duration of grade 3/4 mucositis was not altered by the addition of cetuximab to RT (figure 3). When all grades of mucositis were considered, there was a nonsignificant trend toward a later onset of mucositis in p16-negative patients who received RT alone (supplementary table 3). The duration of all grades of mucositis in p16-negative patients who received RT plus cetuximab appeared to be numerically longer compared with that of patients who received RT alone (supplementary table 3). Although not significant, there was a numerical increase in the duration of all grades of dysphagia in patients with p16-negative disease who received cetuximab plus RT (supplementary table 3).

Overall, the incidence, time to onset, and duration of all-grade and grade 3/4 mucositis did not appear to be different in patients with p16-positive tumors vs those with p16-negative tumors (table 2, figures 3 and 4, and supplementary table 3). Patients with p16-positive OPC had a numerically higher incidence of grade 3/4 mucositis and dysphagia compared with those with p16-negative OPC (table 2), and the onset of dysphagia in patients with p16-negative occurred later compared with patients with p16-positive disease in both treatment arms (supplementary table 3).

Feeding tube use

The use of feeding tubes as assessed by responses to the EORTC QLQ-H&N35 questionnaire during and following RT was evaluated in the overall population and the p16-positive and p16-negative OPC subgroups. In the overall population, there was no difference between feeding tube use at 2 months after RT for patients receiving RT plus cetuximab (n = 175) compared with RT alone (n = 159) (figure 5). This remained consistent 12 months after RT. In both the p16-positive and p16-negative subgroups, the rate of placement of feeding tubes at 2 and 12 months after RT was similar for patients who received RT
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in combination with cetuximab or RT alone (figure 5B and 5C). Compared with patients with p16-positive OPC, the reported use of feeding tubes at 12 months appeared to be numerically greater in patients with p16-negative OPC (figure 5B and 5C).

Discussion

Although some investigations of single-institution experiences have suggested that the addition of cetuximab to RT may result in increased rates of grade ≥ 3 mucositis, compared with radiation alone,\textsuperscript{10-12} this is the only prospectively randomized trial of these treatments, and these results demonstrated no treatment-related differences in rates of this toxicity. Additionally, this is the first report showing that the addition of cetuximab did not alter the rate of onset or duration of grade ≥ 3 mucositis or dysphagia. Our results have been supported by other single-institution studies.\textsuperscript{13,14} Other reviews have suggested that mucosal toxicities occur less frequently with cetuximab and RT treatment compared with cisplatin and RT treatment.\textsuperscript{15} The studies that have suggested increased rates of mucositis for the addition of cetuximab to RT have generally been small studies (14–34 patients) and their processes for treatment selection were not well defined. The finding that the incidence, onset, and duration of grade ≥ 3 mucositis and dysphagia were comparable for RT ± cetuximab is important information for physicians who are selecting treatments and consulting with patients regarding potential side effects. Furthermore, this study included a retrospective analysis of HPV status and revealed that rates of mucositis and dysphagia were not increased with the addition of cetuximab to RT in either the HPV-positive or HPV-negative population.

We found that for patients enrolled in the prospective IMCL-9815 trial for LA-SCCHN, the addition of cetuximab to RT did not alter the incidence, time to onset, severity, or duration of mucositis and dysphagia, specifically including grade 3 dysphagia defined as requiring gastrostomy feeding tubes. We
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recently published the efficacy analysis showing that both the p16-positive and p16-negative subgroups had higher locoregional control and overall survival with the addition of cetuximab, although the difference is much greater for the p16-positive group.

Patients in this study were treated with standard-fractionation, altered-fractionation, concomitant-boost, or hyperfractionation RT. It is well known that altered-fractionation RT can increase the severity of mucositis. However, in both the standard- and altered-fractionation groups, the severity of mucositis peaked during the last week of treatment. At 12 weeks following the start of treatment, fewer than 10% of patients in both groups had grade 3/4 mucositis; by week 16, almost all patients had healed. The majority of patients in our study received concomitant-boost radiotherapy. Although both altered-fractionation RT regimens resulted in a slightly higher incidence of mucositis and dysphagia, the onset and duration of these events did not appear to be affected by RT regimen in the overall or the p16-evaluable OPC populations.

Additionally it is important to note that this trial was conducted in the era of three-dimensional conformal RT and not the more current standard of intensity-modulated radiotherapy (IMRT) for SCCHN. Studies comparing three-dimensional conformal RT and IMRT have shown that IMRT does not reduce the peak incidence of mucositis but may decrease its volume and allow for dose reduction to the pharyngeal constrictors. Therefore, the use of a systemic agent such as cetuximab that does not appear to enhance radiation-induced mucositis remains highly relevant in the IMRT era.

In the overall safety population and p16-evaluable subgroups, we found no significant difference in the rate of feeding tube use during the first year after RT in patients receiving RT plus cetuximab or RT alone. However, there appeared to be a numerically greater incidence of feeding tube usage in patients
with p16-negative disease at 12 months after RT. This may be due to underlying differences in patient demographics, including tumor status, performance status, and US/non-US origin. Furthermore, HPV-negative patients were more likely to have greater tobacco exposure and more comorbidities than their HPV-positive counterparts, which may have contributed to the need for feeding tubes. Although no background characteristics could be confirmed as predictors of feeding tube use in the present trial, this is an interesting hypothesis that could be explored in larger, ongoing studies. Indeed, a limitation of our study is the relatively modest number of patients with feeding tube information available beyond 8 weeks post-RT and we cannot exclude the possibility that this patient subgroup is not representative of the entire study patient population at risk; nevertheless, our data do not suggest a difference in feeding tube use between treatment arms.

Given our prior finding that patients with p16-positive or p16-negative OPC benefitted from the addition of cetuximab to RT, the current study suggests that cetuximab did not increase mucositis and dysphagia rates in either of these populations. Some observed minor differences in the incidence and kinetics of mucositis and dysphagia in the p16-positive and p16-negative populations may be attributable to the differences between smoking-related and HPV-related disease. The data from this study suggest that cetuximab does not increase acute toxicities in HPV-positive patients while still benefiting overall outcome. However, small sample size is a limitation of these analyses, and our findings should be regarded as hypothesis generating.

Several ongoing and recently completed trials are investigating the treatment of HPV-positive OPC with RT and cetuximab. The RTOG recently enrolled 987 patients to RTOG 1016, a phase 3 randomized study to compare the treatment of HPV-positive OPC with RT in combination with either cisplatin or
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cetuximab. The results of this study, which examines treatment efficacy, treatment-related toxicity, and quality of life, are eagerly anticipated. The Eastern Cooperative Oncology Group has completed a phase 2 study (ECOG 1308), in which patients with HPV-positive OPC received three cycles of induction chemotherapy (ICT) consisting of cisplatin, paclitaxel, and cetuximab. Patients who demonstrated a complete response to ICT received a reduced dose of RT with weekly cetuximab. Those who did not achieve a complete response underwent standard RT with weekly cetuximab. Early findings from this study demonstrated a 2-year overall survival rate of 95% in patients who received reduced-dose RT plus cetuximab, which increased to 97% when only patients with fewer than 10 pack-years of smoking were considered. This study suggests that the combination of low-dose RT with cetuximab following ICT may be a worthy alternative regimen for further study.

Cetuximab is a valuable addition to the SCCHN treatment paradigm. Over the last decade, HPV status has emerged as a significant factor in disease etiology and treatment outcome. The current study suggests that regardless of p16 status, when added to RT, cetuximab does not appear to increase the incidence, onset, or duration of severe mucositis and dysphagia. Furthermore, the addition of cetuximab to RT does not appear to increase the use of feeding tubes during the first year following RT. Given the growing incidence of OPC affecting younger, healthier patients—who have a high expected cure rate—compared with those with tobacco-driven cancers, it is important to find the most effective therapeutic regimen that produces the lowest rates of acute mucositis and dysphagia because these acute toxicities are associated with an increased risk for long-term dysphagia, aspiration, and feeding tube requirement. The results of this study support the use of cetuximab for both p16-positive and p16-negative patients with OPC. The maturing RTOG 1016 trial will give further prospective comparison on the efficacy and toxicity profile for cetuximab vs cisplatin for the p16-positive population.
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Author Contributions

Conception and design: JAB, JG, JS, and DIR
Collection and assembly of data: JAB, JL, and JS
Data analysis and interpretation: All authors
Manuscript writing: JAB, JG, PMH, JB, SS, DB, DR, JL, JS, and DIR (KKA is deceased)
Final approval of manuscript: JAB, JG, PMH, JB, SS, DB, DR, JL, JS, and DIR (KKA is deceased)

Declaration of Interests

JAB: Honorarium from Merck Serono, Eli Lilly, and Bristol-Myers Squibb
JG: No conflicts
PMH: No conflicts
JB: Consulting for Merck; advisory boards for Eli Lilly
SS: No conflicts
DB: No conflicts
DR: No conflicts
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Table 1: Baseline characteristics of patients with OPC

| Parameter                      | OPC*        | p16-positive** | p16-negative** |
|--------------------------------|-------------|----------------|----------------|
|                                | All n=253   | RT + cetuximab n=41 | RT n=34        | RT + cetuximab n=43 | RT n=64 |
|                                | n=182 (%)   | (%)             | (%)            | (%)             | (%)     |
| Sex                            | Male        | 81 (%)          | 83 (%)         | 77 (%)          |
| Age                            | <65 years   | 77 (%)          | 75 (%)         | 74 (%)          | 81 (%)  | 67 (%)  |
| Site of primary tumor          | Oropharynx  | 100 (%)         | 100 (%)        | 100 (%)         | 100 (%) |
| Karnofsky score                | >80         | 73 (%)          | 76 (%)         | 90 (%)          | 82 (%)  | 65 (%)  | 70 (%)  |
| Nodal stage                    | N0          | 11 (%)          | 7 (%)          | 14 (%)          | 17 (%)  |
| Tumor stage                    | T1-3        | 72 (%)          | 71 (%)         | 83 (%)          | 88 (%)  | 51 (%)  | 69 (%)  |
| EGFR expression: % positive cells | ≤50%        | 46 (%)          | 71 (%)         | 51 (%)          | 55 (%)  |
|                                | >50%        | 32 (%)          | 27 (%)         | 49 (%)          | 44 (%)  |
|                                | Unknown     | 22 (%)          | 2 (%)          | 0 (%)           | 2 (%)   |
| Radiation fractionation        | Concomitant boost | 58 (%)          | 78 (%)         | 56 (%)          | 59 (%)  |

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|                | Once-daily | 23 | 21 | 2 | 9 | 35 | 30 |
|----------------|------------|----|----|---|---|----|----|
| Twice-daily    |            | 17 | 13 | 17 | 21 | 9  | 9  |
| Region         | United States | 64 | 64 | 95 | 91 | 47 | 41 |

EGFR = epidermal growth factor receptor. OPC = oropharyngeal. RT = radiotherapy. *Demography analysis was performed on the intent-to-treat population. †Fisher exact test did not reveal a significant difference between treatment arms.

Table 2: Incidence of adverse events by treatment arm in the overall safety population

| Adverse Event | Grade       | Overall Safety Population*† | OPC † | p16-positive (n = 74) | p16-negative (n = 106) |
|---------------|-------------|----------------------------|-------|-----------------------|------------------------|
|               |             | RT + cetuximab n=208 (%) | RT n=212 (%) | RT + cetuximab n=40 (%) | RT n=34 (%) | RT + cetuximab n=43 (%) | RT n=63 (%) |
| Mucositis     | All Grades  | 93                          | 94     | 100                   | 100                   | 98           | 95           |
|               | Grades 3-4  | 56                          | 52     | 78                    | 71                    | 65           | 56           |
| Dysphagia     | All Grades  | 65                          | 63     | 80                    | 76                    | 51           | 57           |
|               | Grades 3-4  | 26                          | 30     | 45                    | 38                    | 16           | 24           |

OPC = oropharyngeal carcinoma. RT = radiotherapy. *Rates of mucositis and dysphagia within the overall safety population were previously published in reference 6. †Fisher exact test determined that there was no $P < .05$ when treatment arms were compared.
### Table 3: Rates of mucositis and dysphagia in the overall safety population by RT regimen

| Adverse Event | Grade | RT + cetuximab | RT |
|---------------|-------|-----------------|----|
|               |       | Once-Daily Fractionation | Altered Fractionation* | P value† | Once-Daily Fractionation | Altered Fractionation* | P value† |
|               |       | (n = 55) (%) | (n = 155) (%) | | (n = 50) (%) | (n = 157) (%) | |
| Mucositis     | All Grades | 81.8 | 94.9 | 0.009 | 96 | 97.4 | 0.635 |
|               | Grades 3-4 | 25.5 | 65 | <0.001 | 22 | 63.8 | <0.001 |
| Dysphagia     | All Grades | 50.9 | 68.8 | 0.022 | 58 | 67.7 | 0.233 |
|               | Grades 3-4 | 16.3 | 28.6 | 0.075 | 16 | 35.4 | 0.013 |

RT = radiotherapy. *Twice-daily or concomitant-boost RT. †Fisher exact test was used to determine the P value.
Figures

Figure 1: Selection of patients for p16 subgroup analysis

OPC = oropharyngeal carcinoma. RT = radiotherapy.
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Figure 2: Kaplan-Meier estimates of onset and duration of grade 3/4 mucositis and dysphagia in the applicable safety population

A

B
Onset (A and C) and duration (B and D) of grade 3/4 mucositis (A and B) and dysphagia (C and D) in the applicable safety population (by definition, only those patients in the overall safety population who received at least one dose of RT were included). All radiotherapy (RT) regimens were combined.
Figure 3: Kaplan-Meier estimates of onset and duration of grade 3/4 mucositis in the applicable p16-evaluable OPC subgroups

A

B
Onset (A and B) and duration (C and D) of grade 3/4 mucositis in the p16-positive (A and C) and p16-negative (B and D) oropharyngeal carcinoma (OPC) subgroups (by definition, only those patients in the overall safety population who received at least one dose of RT were included). All radiotherapy (RT) regimens were combined.
Figure 4: Kaplan-Meier estimates of onset and duration of grade 3/4 dysphagia in the applicable p16-evaluable OPC subgroups
Onset (A and B) and duration (C and D) of grade 3/4 dysphagia in the p16-positive (A and C) and p16-negative (B and D) oropharyngeal carcinoma (OPC) subgroups (by definition, only those patients in the overall safety population who received at least one dose of RT were included). All radiotherapy (RT) regimens were combined.
Figure 5: Feeding tube use in the overall safety population and p16-evaluable OPC populations

A

B
Frequency of patient-reported use of a feeding tube before, during, and 1 year following radiotherapy (RT) treatment in the overall safety population (A) and p16-positive (B) and p16-negative oropharyngeal carcinoma (OPC) subgroups (C). F/U = follow-up.
Supplementary Tables

Supplementary Table 1: Onset and duration of all grades of mucositis and dysphagia by RT type in the applicable safety population

| All Grades | Parameter              | RT Regimen       | Statistics | RT + cetuximab | RT   |
|------------|------------------------|------------------|------------|----------------|------|
| Mucositis  | Onset (weeks)          | Overall          | N value    | 205            | 212  |
|            |                        |                  | Median     | 2.1            | 2.3  |
|            |                        |                  | Log Rank Test | 0.10          |      |
|            |                        | Once Daily       | N value    | 49             | 54   |
|            |                        |                  | Median     | 2.1            | 2.4  |
|            |                        |                  | Log Rank Test | 0.219         |      |
|            |                        | Twice Daily      | N value    | 37             | 36   |
|            |                        |                  | Median     | 2.1            | 2.1  |
|            |                        |                  | Log Rank Test | 0.390         |      |
|            |                        | Concomitant      | N value    | 117            | 120  |
|            | Boost                  |                  | Median     | 2.0            | 2.1  |
|            |                        |                  | Log Rank Test | 0.100         |      |
| Duration   | Onset (months)         | Overall          | N value    | 194            | 199  |
|            |                        |                  | Median     | 2.7            | 2.3  |
|            |                        |                  | Log Rank Test | 0.174         |      |
|            |                        | Once Daily       | N value    | 45             | 48   |
|            |                        |                  | Median     | 2.6            | 2.3  |
|            |                        |                  | Log Rank Test | 0.430         |      |
| Dysphagia       | Onset (weeks) | Overall       | Twice Daily | Concomitant Boost |
|----------------|---------------|---------------|-------------|------------------|
|                |               |               | N value     | N value          |
|                |               |               | 37          | 38               |
|                |               |               | 36          | 37               |
|                |               |               | Median      | Median           |
|                |               |               | 2.4         | 2.4              |
|                |               |               | 2.3         | 3.4              |
|                |               |               | Log Rank Test | Log Rank Test |
|                |               |               | 0.981       | 0.016            |
|                |               | Overall       | N value     | N value          |
|                |               |               | 205         | 117              |
|                |               |               | 212         | 115              |
|                |               |               | Median      | Median           |
|                |               |               | 3.6         | 3.4              |
|                |               |               | 3.6         | 3.4              |
|                |               |               | Log Rank Test | Log Rank Test |
|                |               |               | 0.786       | 0.786            |
|                |               | Once Daily    | N value     | N value          |
|                |               |               | 50          | 117              |
|                |               |               | 55          | 120              |
|                |               |               | Median      | Median           |
|                |               |               | 5.1         | 3.4              |
|                |               |               | 6.1         | 2.7              |
|                |               |               | Log Rank Test | Log Rank Test |
|                |               |               | 0.958       | 0.786            |
|                |               | Twice Daily   | N value     | N value          |
|                |               |               | 38          | 135              |
|                |               |               | 37          | 134              |
|                |               |               | Median      | Median           |
|                |               |               | 2.4         | 2.1              |
|                |               |               | 3.4         | 2.3              |
|                |               |               | Log Rank Test | Log Rank Test |
|                |               |               | 0.016       | 0.532            |
|                |               | Once Daily    | N value     | N value          |
|                |               |               | 28          | 117              |
|                |               |               | 29          | 120              |
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|                | Median |       |       |
|----------------|--------|-------|-------|
|                |        | 1.7   | 2.1   |
| Log Rank Test  |        | 0.531 |

Twice Daily

|                | N value |       |       |
|----------------|---------|-------|-------|
|                |         | 30    | 21    |
| Median         |         | 2.6   | 3.1   |
| Log Rank Test  |         | 0.785 |

Concomitant Boost

|                | N value |       |       |
|----------------|---------|-------|-------|
|                |         | 77    | 28    |
| Median         |         | 2.6   | 2.3   |
| Log Rank Test  |         | 0.532 |

By definition, only those patients in the overall safety population who received at least one dose of radiotherapy (RT) were included.
## Supplementary Table 2: Onset and duration of grade 3/4 mucositis and dysphagia by RT type in the applicable safety population

| All Grades | Parameter          | RT Regimen   | Statistics | RT plus cetuximab | RT |
|------------|--------------------|--------------|------------|-------------------|----|
| Mucositis  | Onset (weeks)      | Once Daily   | N value    | 50                | 55 |
|            |                    |              | Median     | 10.1              | -- |
|            |                    |              | Log Rank Test | 0.324          |    |
|            |                    | Twice Daily  | N value    | 38                | 37 |
|            |                    |              | Median     | 6.1               | 6.3|
|            |                    |              | Log Rank Test | 0.947          |    |
|            |                    | Concomitant Boost | N value | 117              | 120|
|            |                    |              | Median     | 5.1               | 5.6|
|            |                    |              | Log Rank Test | 0.066          |    |
|            | Duration (months)  | Once Daily   | N value    | 50                | 55 |
|            |                    |              | Median     | --                | 13.1|
|            |                    |              | Log Rank Test | 0.602          |    |
|            |                    | Twice Daily  | N value    | 38                | 37 |
|            |                    |              | Median     | --                | -- |
|            |                    |              | Log Rank Test | 0.462          |    |
|            |                    | Concomitant Boost | N value | 81              | 79 |
|            |                    |              | Median     | 2.1               | 2.0|
|            |                    |              | Log Rank Test | 0.129          |    |
| Dysphagia  | Onset (weeks)      | Once Daily   | N value    | 50                | 55 |


| Duration (months) | Once Daily | Twiced Daily | Concomitant Boost |
|------------------|------------|--------------|------------------|
| N value | 9 | 38 | 117 |
| Log Rank Test | 0.975 | 0.602 | 0.478 |
| Median | 1.4 | -- | 14.1 |
| | 2.8 | -- | 8.6 |
| | | | |
| N value | 14 | 31 | 117 |
| Log Rank Test | 0.467 | 0.872 | 0.462 |
| Median | 2.5 | 2.2 | 14.1 |
| | 3.0 | 2.1 | 8.6 |

By definition, only those patients in the overall safety population who received at least one dose of radiotherapy (RT) were included. --, not calculated based on the event number being too small.
### Supplementary Table 3: Onset and duration of all grades of mucositis and dysphagia by RT type in the applicable p16-evaluable OPC populations

| All Grades | p16-status | RT plus cetuximab | RT |
|------------|------------|-------------------|----|
| Mucositis  | Onset (weeks) | N value | 40 | 34 |
| p16+       | Median     |       | 1.9 | 1.8 |
|            | Log Rank Test |      | 0.265 | |
| p16-       | N value     | 43 | 63 |
|            | Median     |       | 1.4 | 2.3 |
|            | Log Rank Test |      | 0.150 | |
| Duration (months) | p16+ | N value | 40 | 34 |
|            | Median     |       | 2.8 | 2.8 |
|            | Log Rank Test |      | 0.937 | |
| p16-       | N value     | 42 | 60 |
|            | Median     |       | 2.8 | 2.3 |
|            | Log Rank Test |      | 0.174 | |
| Dysphagia  | Onset (weeks) | p16+ | N value | 40 | 34 |
|            | Median     |       | 3.3 | 2.4 |
|            | Log Rank Test |      | 0.541 | |
|            | p16- | N value | 43 | 63 |
|            | Median     |       | 5.1 | 5.1 |
|            | Log Rank Test |      | 0.489 | |
| Duration (months) | p16+ | N value | 32 | 24 |
|            | Median     |       | 2.6 | 2.9 |
By definition, only those patients in the overall safety population who received at least one dose of radiotherapy (RT) were included.