Induction therapy with cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (ETPF) in patients with resectable nonmetastatic stage III or IV squamous cell carcinoma of the oropharynx. A GERCOR phase II ECHO-07 study

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To cite this version:

Benoist Chibaudel, Roger Lacave, Marine Lefevre, Patrick Soussan, Martine Antoine, et al.. Induction therapy with cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (ETPF) in patients with resectable nonmetastatic stage III or IV squamous cell carcinoma of the oropharynx. A GERCOR phase II ECHO-07 study. Cancer medicine, 2015, 4 (5), pp.721-731. <10.1002/cam4.408>. <hal-01213456>
Induction therapy with cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (ETPF) in patients with resectable nonmetastatic stage III or IV squamous cell carcinoma of the oropharynx. A GERCOR phase II ECHO-07 study

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Keywords  
Cetuximab, chemotherapy, induction therapy, oropharyngeal cancer, papillomavirus

Abstract

Induction TPF regimen is a standard treatment option for squamous cell carcinoma (SCC) of the oropharynx. The efficacy and safety of adding cetuximab to induction TPF (ETPF) therapy was evaluated. Patients with nonmetastatic resectable stage III/IV SCC of the oropharynx were treated with weekly cetuximab followed the same day by docetaxel and cisplatin and by a continuous infusion of 5-fluorouracil on days 1-5 (every 3 weeks, 3 cycles). The primary endpoint was clinical and radiological complete response (crCR) of primary tumor at 3 months. Secondary endpoints were crCR rates, overall response, pathological CR, progression-free survival, overall survival, and safety. Forty-two patients were enrolled, and 41 received ETPF. The nine planned cetuximab doses and the full three doses of planned chemotherapy were completed in 31 (76%) and 36 (88%) patients, respectively. Twelve (29%) patients required dose reduction. The crCR of primary tumor at the completion of therapy was observed in nine (22%) patients. ETPF was associated with a tumor objective response rate (ORR) of 58%. The most frequent grade 3–4 toxicities were as follows: nonfebrile neutropenia (39%), febrile neutropenia (19%), diarrhea (10%), and stomatitis (12%). Eighteen (44%) patients experienced acne-like skin reactions of any grade. One toxic death occurred secondary to chemotherapy-induced colitis with colonic perforation. This phase II study
This study was presented in part at the ESMO 2012 Meeting, Vienna, Austria (abstract #1036P).

**Introduction**

Cancer of the upper aerodigestive tract, predominantly squamous cell carcinoma (SCC) of the oropharynx, is the fifth most common malignancy and the seventh leading cause of cancer death in France [1]. The majority of diagnosed patients present locally advanced disease invading underlying structures and/or spreading to regional lymph nodes (stages III and IV). The survival rates are relatively poor ranging from 30% to 60% at 5 years [2].

The standard treatment in moderately advanced disease (i.e., resectable) includes surgery with appropriate adjuvant therapy, and chemoradiotherapy in patients with advanced disease (i.e., unresectable) [3]. Induction therapy with cisplatin prior to definitive chemoradiotherapy is still controversial [4, 5].

The most active induction chemotherapy regimen in patients with unresectable SCC of the oropharynx is the combination of 5-fluorouracil (5-FU), docetaxel, and cisplatin (TPF) [6, 7]. However, an improvement in survival comparing induction therapy followed by chemoradiotherapy to direct chemoradiotherapy has not yet been established.

An overexpression of the epidermal growth factor receptor (EGFR) or any of its linked pathways occurs in more than 90% of head and neck SCC [8]. Increased EGFR protein expression or EGFR gene copy number amplification are associated with poor prognosis [8–10], radiation-resistance [11], locoregional treatment failure [10], and increased rates of distant metastases [10, 12]. Monoclonal antibody cetuximab blocks ligand-induced EGFR activation [13] and improves survival when used concurrently in combination with radiotherapy in locoregionally advanced disease [14] and cisplatin/5-FU-based chemoradiotherapy in recurrent/metastatic setting [15].

Human papillomavirus (HPV) type-16 (HPV16) infection has been associated with an increased risk of developing oropharyngeal cancer [16]. In contrary to the HPV-negative tumors (primarily related to tobacco use and alcohol consumption) [17, 18], an increasing incidence and greater responsiveness to radiotherapy of HPV-positive tumors have been reported [19–21]. The potential role of anti-EGFR treatment in HPV16-positive locally advanced oropharyngeal SCC cancer remains questionable [22].

Reports an interesting response rate for ETPF in patients with moderately advanced SCC of the oropharynx. The schedule of ETPF evaluated in this study cannot be recommended at this dosage.

The aim of this study was to evaluate the cetuximab-TPF combination (ETPF) as induction therapy in treatment of patients with locally advanced resectable SCC of the oropharynx.

**Materials and Methods**

**Study design**

ECHO-07 (ClinicalTrials.gov #NCT00665392) was a prospective multicenter single-arm open-label phase II study. The protocol was approved by the National Security Agency for Medicines and Health Products (ANSM, France) and Ethics Committee of Groupe Hospitalier Pitié-Salpêtrière (Paris VI, France). All patients provided written informed consent.

**Patient eligibility criteria**

Eligible patients were 18–75 years with previously untreated, resectable AJCC/UICC TNM (American Joint Committee on Cancer/Union Internationale Contre le Cancer) stage III (T3/T1-2N1-2M0) to IVB (T4/T1-3N3M0) SCC of the oropharynx [23]. Other eligibility criteria included measurable or evaluable disease (Response Evaluation Criteria in Solid Tumors [RECIST] 1.0), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, adequate laboratory parameters (absolute neutrophil count (ANC) ≥1500/mm³, platelet count ≥100,000/mm³, hemoglobin ≥9 g/dL, creatinine <1.5-fold the upper limit of the normal (ULN) value) and no uncontrolled cardiac or other disease.

**Induction chemotherapy**

Treatment consisted of cetuximab by intravenous (IV) infusion over 1–2 h on days 1, 8, and 15 (loading dose of 400 mg/m² on day 1, then 250 mg/m² weekly) followed the same day by docetaxel and cisplatin both given as a 1h IV infusion (at a 75 mg/m² dose) and by 5-FU IV infusion on days 1–5 (at a 750 mg/m² dose per day). Treatment was given every 3 weeks for a maximum of three cycles. Pre- and concomitant medication consisted of IV hydration and infusion of diphenhydramine hydrochloride and dexamethasone. A primary prophylaxis with granulocyte colony stimulating factors (G-CSF) was required.
Response assessments
Baseline assessment including medical history, physical examination, otolaryngology evaluation with nasofibroscopy, laboratory evaluation, histological diagnosis, and computed tomography (CT) scan of the neck and chest was performed within 3 weeks prior to induction therapy initiation. During ETPF treatment, patients were assessed for toxicity before each cycle of chemotherapy. The evaluation of tumor response was assessed at 3 months from inclusion and before local treatment using clinical examination and RECIST 1.0 criteria. After local treatment, patients were evaluated regularly for 3 years.

The primary endpoint was clinical and radiological complete response (crCR) rate of primary tumor. Secondary endpoints were clinical complete response (cCR) rate, radiological complete response (rCR) rate, overall survival (OS), progression-free survival (PFS), pathological complete response (pCR), safety, and biomarkers analysis. OS was defined as the time interval between patient inclusion and death (all causes). Patients for whom death was not recorded were censored at the date of last news. PFS was defined as the time interval from inclusion to the first local, regional and/or distant progressive disease (PD), or death (all causes). Alive patients without PD were censored at the date of last news.

Adverse events (AE) were collected during induction treatment and follow-up visits. Toxicity evaluation was carried out according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v3.0) scale.

Postinduction therapy
Local treatment with surgery or chemoradiotherapy after induction therapy was not part of the study protocol and was performed at investigator’s discretion.

Biomarkers analysis
For each patient, pretreatment formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks or FFPE unstained slides of primary tumor and cryopreserved tumor blocks for molecular analysis of the EGFR pathway components and HPV genotyping were required. The potential predictive value of EGFR-related biomarkers for response to ETPF induction therapy was evaluated by (1) EGFR gene and EGFR ligands encoding genes expression analyses (epidermal growth factor [EGF], transforming growth factor α [TGFα], amphiregulin [AREG], epiregulin [EREG], heparin-binding EGF-like growth factor [HB-EGF], and betacellulin [BTC]) performed by semiquantitative real-time-PCR [24], (2) EGFRvIII gene expression analysis performed according to Sok et al. [25], (3) EGFR-intron 1 polymorphism analysis according to Etienne-Grimaldi et al. [26], and (4) EGFR gene copy-number assessed by fluorescent in situ hybridization (FISH) using an EGFR/CEN-7 FISH DNA/PNA probe (Dako, France). The high-risk HPV16 genotype screen (by PCR) and quantification of HPV16 viral DNA (by RT-PCR) were assessed.

Statistics
Given that a complete response (CR) rate ≤10% was unsatisfactory, a CR rate ≥30% was expected. To test the efficacy and safety of the treatment, 40 evaluable patients were required to reach a power of 90% and at a significance level 5% (a one-sided type I error). Assuming 5% nonevaluable patients, a total of 42 patients had to be enrolled. Analyses were performed on a modified intent-to-treat (mITT) population (patients were considered evaluable for tumor response if they had received at least one dose of ETPF combination). Means (min-max) and standard deviations (SDs) were used to describe continuous variables; categorical variables were expressed in terms of frequencies and percentages together with 95% confidence intervals (CIs). Response rates and corresponding 95% CIs were calculated using a binomial distribution. Survival and median follow-up were estimated using the Kaplan–Meier and reverse Kaplan–Meier methods, respectively. Stratified hazards ratios (HRs) were calculated using the univariate Cox proportional hazard model. Correlational research of EGFR-related biomarkers and HPV status in tumors and blood samples obtained prior and after induction therapy were done for exploratory purpose as planned in the study protocol. Statistical analyses were performed using SAS 9.1 software (SAS Institute Inc, Cary, NC).

Results
Patient characteristics
Between July 2008 and November 2011, 42 patients 42 patients were enrolled from nine centers (Table 1). Median age of patients was 56 years, with 81% males. The majority of patients (79%) were ECOG PS 0, had a primary tumor located in the tonsil area (88%) and a stage III disease (76%).

Induction treatment
Forty-one patients (mITT population) started induction therapy (Fig. 1). One patient did not receive an intended treatment due to investigator decision to replace cisplatin by carboplatin and not to administer cetuximab.
Thirty-one (76%) patients and 36 (88%) patients received all nine planned doses of cetuximab and full three doses of planned chemotherapy, respectively. Dose reduction of cetuximab was required in two (5%) patients and in 10 (24%) patients for chemotherapy. Treatment had to be stopped early in eight (19%) patients, mainly due to limiting toxicity in five patients (diarrhea, febrile neutropenia, neutropenia without fever, diarrhea with febrile neutropenia, and skin toxicity), one toxic death (colonic perforation), one acute pancreatitis, and one consent withdrawal.

Tumor response

After ETPF, crCR of the primary tumor at 3 months was observed in nine (22%) of 41 patients in the mITT population (Table 2). Seventeen (41%) patients achieved cCR and 14 (34%) had rCR. No disease progression occurred during induction therapy. An objective response rate (ORR) of 58% was observed.

PFS and overall survival

After a median follow-up of 23.9 months (95% CI, 15.4–28.6), median PFS was 37.6 months (95% CI, 19.1–NA), and median OS was not achieved. The 2-year estimated PFS and OS rates were 63.6% and 82.4% (standard error 8.2% and 6.6%), respectively (Fig. 2). Of 11 patients with PD, three progressed locally, four progressed in nodal sites, and three had metastatic recurrence.

Safety

The most frequent grade 3–4 toxicities in 41 treated patients were neutropenia (39%), febrile neutropenia (19%), diarrhea (10%), and stomatitis (12%) (Table 3). All febrile neutropenia events occurred on days 8 or 15. Acne-like skin reactions of any grade were observed in 18 (44%) patients. One (2%) toxic death occurred from chemotherapy-induced colitis with colonic perforation.
during the first cycle of induction therapy. Of 18 serious AE (SAE) reported by the investigators, four were considered to be cetuximab- and 13 chemotherapy-related toxicities. None of them was unexpected.

**Biomarkers analysis**

Transcriptional analyses of FFPE from 38 patients were performed. Univariate analysis identified EGFRvIII mutation and EGFR amplification as predictive factors significantly correlated with rCR (Table 4). Of 42 patients tested for HPV16, 17 were HPV16-positive (40%) (Table 5). A crCR was observed in four (24%) and five (20%) patients with HPV-positive and HPV-negative tumor, respectively.

**Surgery**

Neck dissection before postinduction therapy was performed in seven patients who went onto chemoradiation.
and in 22 patients who underwent surgery. Treatment after primary tumor resection was performed in 22 patients (Fig. 1). Complete (R0) tumor resection was achieved in 17 patients.

Chemoradiotherapy

After induction therapy, 36 patients received chemoradiotherapy, either after surgical intervention (19 patients) or without primary tumor resection (17 patients). A concomitant systemic therapy was carried out with cetuximab (18 patients), platinum salt (14 patients), or both (three patients). The median chemoradiation duration was 9.1 weeks (range, 1.0–13.1).

Pathological response

Of 22 patients with both primary tumor resection and neck dissection, nine had a pCR of the primary tumor, and six had a pCR of both the primary and node tumors. Of the seven patients who underwent neck dissection, two had a pCR.
Discussion

The ECHO-07 phase II study shows that addition of cetuximab to the standard TPF induction regimen in patients with locally advanced resectable stage III-IV SCC of the oropharynx produces a crCR of 22%.

The major goals of induction chemotherapy are to downsize the tumor, improve locoregional control, and target distant metastases prior to definitive treatment. TPF-based induction chemotherapy followed by chemoradiotherapy has been shown to improve outcomes (time-to-treatment failure, locoregional control) in patients with advanced SCC of the oropharynx [6, 7, 27]. Despite the potential benefits seen in these initial studies, recent trials, DeCIDE and PARADIGM [4, 5], failed to show a survival advantage with this treatment thus questioning the role of induction chemotherapy.

The ETPF regimen was previously evaluated in 50 patients with unresectable SCC of the oropharynx [28]. In this phase II trial the ORR after four cycles of induction was 78%. In our study, induction ETPF was associated with a radiological tumor response (complete and partial) of 58%, a low incidence of distant metastases (17%), and locoregional recurrence (7%). Given that the tumor response definition differs across studies of patients with SCC of the oropharynx, a comparison of response rates with those given by others [4, 28, 29] would be biased and misleading, therefore not acceptable. The cCR in our study is about twofold higher than crCR (41% vs. 22%). Such situation generates an urgent need to standardize the current clinical endpoints definitions and to evaluate more clinically relevant endpoints (e.g., Health related quality of life measures). Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) program to develop standardized definitions of commonly used endpoints, enabling appropriate comparisons of future trials is currently ongoing [30].

A major concern of TPF induction treatment is a high incidence of treatment-induced toxicity. In this study, febrile neutropenia during ETPF induction was reported in 19% of patients despite a systematic G-CSF support required in the protocol. This rate is higher than that reported by previous studies using TPF induction therapy (5–12%) [5–7, 31], but similar to prior safety profiles when adding cetuximab to TPF [28]. This may be explained by a weekly assessment of hematological toxicities, rather than the addition of cetuximab to TPF regimen. Moreover, removing 5-FU from ETPF leads to a 10% rate of febrile neutropenia [32]. One (2%) treatment-related death occurred during induction therapy secondary to chemotherapy-induced colitis with colonic perforation. Of note, only 22% of SAE were considered to be cetuximab-related. 5-FU is currently a substantial part of this three-drug induction regimen, but its input remains debatable. A chemotherapy doublet induction therapy with taxanes and platinum-salt with cetuximab could be an appropriate approach to improve therapeutic index while decreasing toxicity in patients with SCC of the oropharynx [32–36]. Another approach would be to use 5-FU with a shorter duration of continuous infusion as performed in other cancers [37]. To reduce associated toxicity during ETPF administration, dose modifications of induction regimen might be also considered. The modified TPF regimen was shown to have similar efficacy with standard dose TPF with an acceptable toxicity profile in gastric cancer studies [38, 39].

Table 3. Safety evaluation carried out during induction treatment and follow-up in the modified intent-to-treat population (n = 41).

| Adverse event                        | NCI-CTCAE v3.0 common toxicity criteria |
|--------------------------------------|----------------------------------------|
|                                      | Grade 0 N (%) | Grade 1 N (%) | Grade 2 N (%) | Grade 3 N (%) | Grade 4 N (%) |
| Hematologic toxicity                 |              |              |              |              |              |
| Neutropenia                          | 22 (53.7)    | 0            | 2 (4.9)      | 6 (14.6)     | 10 (24.4)    |
| Anemia                               | 7 (17.1)     | 26 (63.4)    | 7 (17.1)     | 0            | 0            |
| Thrombocytopenia                     | 31 (75.6)    | 9 (21.9)     | 0            | 0            | 0            |
| Febrile neutropenia                  | 32 (78.1)    | 0            | 0            | 8 (19.5)     | 0            |
| Nonhematologic toxicity              |              |              |              |              |              |
| Nausea                               | 25 (61.0)    | 8 (19.5)     | 7 (17.1)     | 1 (2.4)      | 0            |
| Vomiting                             | 28 (68.3)    | 8 (19.5)     | 4 (9.8)      | 1 (2.4)      | 0            |
| Stomatitis                           | 27 (65.8)    | 5 (12.2)     | 4 (9.8)      | 5 (12.2)     | 0            |
| Diarrhea                             | 14 (34.1)    | 12 (29.3)    | 11 (26.8)    | 3 (7.3)      | 1 (2.4)      |
| Neuropathy                           | 37 (90.2)    | 3 (7.3)      | 1 (2.4)      | 0            | 0            |
| Acne-like skin reactions             | 23 (56.1)    | 9 (21.9)     | 7 (17.1)     | 2 (4.9)      | 0            |
| Creatinine                           | 32 (78.1)    | 7 (17.1)     | 2 (4.9)      | 0            | 0            |

NCI-CTC, National Cancer Institute Common Terminology Criteria for Adverse Events.
We explored the potential value of the EGFR and its ligands in predicting clinical response to ETPF treatment. Although most markers correlated positively, only EGFR amplification and EGFRvIII mutation were strongly associated with CR by univariate analysis. Recent data suggested that persistent signaling through c-MET activation in the setting of EGFR inhibition contributes to the limited clinical responses to EGFR targeting in patients with SCC of the oropharynx [40, 41]. Hence, future studies will need to investigate the relevance of cross talk between EGFR and c-MET signaling and define whether cosequential/sequential targeting of these oncogenic pathways may represent more effective therapy in this patient population.

### Table 4. Biomarker levels analysis according to tumor response in the patients for whom pretreatment formalin-fixed, paraffin-embedded tumor tissue block, and cryopreserved tumor blocks were available (n = 38).

| Marker               | Complete (N = 9) | Incomplete (N = 29) | All (N = 38) |
|----------------------|------------------|---------------------|--------------|
| **EGFR**             |                  |                     |              |
| Median (min, max)    | 0.6 [0.1;2]      | 0.7 [0.1;89.6]      | 0.6 [0.1;89.6]|
| Mean (SD)            | 0.8 (0.7)        | 4.1 (17.1)          | 3.3 (14.8)   |
| n                    | 9                | 27                  | 36           |
| **EGF**              |                  |                     |              |
| Median (min, max)    | 0.8 [0.1;3.3]    | 0.7 [0.1;76]        | 0.7 [0.1;76] |
| Mean (SD)            | 1.1 (1.1)        | 3.9 (14.5)          | 3.2 (12.5)   |
| n                    | 9                | 27                  | 36           |
| **TGF-α**            |                  |                     |              |
| Median (min, max)    | 4.2 [1.6;15.4]   | 4.6 [0.6;33]        | 4.4 [0.6;33] |
| Mean (SD)            | 5.3 (4.1)        | 8.2 (8.9)           | 7.5 (8)      |
| n                    | 9                | 27                  | 36           |
| **HB-EGF**           |                  |                     |              |
| Median (min, max)    | 8.8 [0.6;28.9]   | 7.1 [0.7;66.9]      | 7.5 [0.6;66.9]|
| Mean (SD)            | 9.9 (9)          | 15.8 (17.7)         | 14.3 (16)    |
| n                    | 9                | 27                  | 36           |
| **BTC**              |                  |                     |              |
| Median (min, max)    | 3.6 [0.9;8.6]    | 3.1 [0.6;83]        | 3.2 [0.6;83] |
| Mean (SD)            | 3.9 (2.6)        | 6.6 (12.9)          | 5.9 (11.2)   |
| n                    | 9                | 27                  | 36           |
| **AREG**             |                  |                     |              |
| Median (min, max)    | 0.2 [0.3]        | 0.2 [0.92.9]        | 0.2 [0.92.9] |
| Mean (SD)            | 0.7 (1.1)        | 9.8 (24.8)          | 7.5 (21.8)   |
| n                    | 9                | 27                  | 36           |
| **EREG**             |                  |                     |              |
| Median (min, max)    | 0 [0;0.9]        | 0 [0;9.9]           | 0 [0;9.9]    |
| Mean (SD)            | 0.2 (0.3)        | 0.7 (1.9)           | 0.6 (1.7)    |
| n                    | 9                | 27                  | 36           |
| **Allele 1 intron 1 CA repeats** |          |                     |              |
| Median (min, max)    | 16 [16;20]       | 16 [14;20]          | 16 [14;20]   |
| Mean (SD)            | 16.7 (1.4)       | 16.4 (1.4)          | 16.5 (1.4)   |
| n                    | 9                | 27                  | 36           |
| **Allele 2 intron 1 CA repeats** |          |                     |              |
| Median (min, max)    | 17 [16;20]       | 19 [15;22]          | 18 [15;22]   |
| Mean (SD)            | 17.2 (1.4)       | 18.5 (2.2)          | 18.2 (2.1)   |
| n                    | 9                | 27                  | 36           |
| **EGFRvIII mutation** |                  |                     |              |
| No                   | 5 (62.5%)        | 23 (88.5%)          | 28 (82.4%)   |
| Yes                  | 3 (37.5%)        | 3 (11.5%)           | 6 (17.7%)    |
| **EGFR amplification** |                |                     |              |
| No                   | 3 (50%)          | 19 (82.6%)          | 22 (75.9%)   |
| Yes                  | 3 (50%)          | 4 (17.4%)           | 7 (24.1%)    |

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; TGF-α, transforming growth factor α; HB-EGF, heparin-binding EGF-like growth factor; BTC, betacellulin; AREG, amphiregulin; EREG, epiregulin; AREG, amphiregulin; EREG, epiregulin; SD, standard deviation.
HPV-positive patients with SCC of the oropharynx have a more favorable outcome compared with HPV-negative patients, however, this advantage can be obscured in heavy smokers [22]. An increase in distant metastases and tumor recurrence in patients with advanced HPV-positive oropharyngeal cancer who smoked tobacco was observed [42]. Moreover, the risk of cancer progression/death was shown to increase directly as a function of pack-years/total number of years of smoking, regardless of HPV status [18]. These findings suggest that tobacco smoking may worsen treatment response, disease control, and increase risk of developing a second primary cancer. In our study, crCR rate was comparable between HPV-positive patients (24%) and patients with HPV-negative tumors (20%). Only nine (21%) patients were nonsmokers, which indicate that the majority of treated patients were at increased risk for recurrence/death from disease. It will therefore be of great importance to stratify patients for HPV status and tobacco use in future trials to discriminate those who are at high risk for treatment failure.

In conclusion, ECHO-07 study reports an interesting response rate for ETPF in patients with moderately advanced SCC of the oropharynx. The dose levels of the ETPF combination evaluated in this study cannot be recommended. However, signs of clinical activity seen in these patients suggest that its further evaluation as induction therapy with optimal safety profile management is warranted.

Acknowledgments

The authors thank Sylvain Hugonin and Eolia Flandre for technical assistance.

Conflict of Interest

All authors report no conflict of interest. Merck KGaA has reviewed this manuscript but the views and opinions described do not necessarily reflect those of Merck KGaA.

Table 5. Distribution of alcohol and tobacco use according to HPV16 status in the total study population (n = 42).

| Use                          | HPV16-positive (N) | HPV16-negative (N) | All (N) |
|------------------------------|--------------------|--------------------|---------|
| Alcohol only                 | 2                  | 1                  | 3       |
| Tobacco only                 | 5                  | 3                  | 8       |
| Both alcohol and tobacco     | 8                  | 17                 | 25      |
| None                         | 2                  | 4                  | 6       |
| Total                        | 17                 | 25                 | 42      |

HPV16, human papillomavirus type-16.

References

1. Ferlay, J., H. R. Shin, F. Bray, D. Forman, C. Mathers, and D. M. Parkin. 2010. GLOBOCAN 2008 v2.0. Cancer Incidence and Mortality Worldwide: International Agency for Research on cancer (IARC). Available at http://globoCAN.iarc.fr (accessed 8 September 2014).
2. Edge, S., D. Byrd, C. Compton, A. G. Fritz, F. L. Greene, and A. Trotti. 2010. AJCC cancer staging manual. P. 120. In Springer, ed. Stomach. Springer, New York, NY.
3. Pfister, D. G., K. K. Ang, D. M. Briyzel, B. A. Burtness, P. M. Busse, J. J. Caudel, et al. 2013. Head and neck cancers, version 2.2013. Featured updates to the NCCN guidelines. J. Natl. Compr. Canc. Netw. 11:917–923.
4. Haddad, R., A. O’Neill, G. Rabinowits, R. Tishler, F. Khuri, D. Adkins, et al. 2013. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 14:257–264.
5. Cohen, E., T. Karrison, M. Kocherginsky, C. H. Huang, M. Agulnik, B. B. Mittal, et al. 2012. DeCIDE: a phase III randomized trial of docetaxel (D), cisplatin, 5-fluorouracil (F) (TPF) induction chemotherapy (IC) in patients with N2/N3 locally advanced squamous cell carcinoma of the head and neck (SCCHN). J. Clin. Oncol. 30(Suppl. 15):5500.
6. Vermorken, J. B., E. Remenar, C. van Herpen, T. Gorlia, R. Mesia, M. Degardin, et al. 2007. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N. Engl. J. Med. 357:1695–1704.
7. Posner, M. R., D. M. Hershock, C. R. Blajman, E. Mickiewicz, E. Winquist, V. Gorbounova, et al. 2007. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N. Engl. J. Med. 357:1705–1715.
8. Grandis, J. R., and D. J. Tweardy. 1993. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. Cancer Res. 53:3579–3584.
9. Chung, C. H., K. Ely, L. McGavran, M. Varella-Garcia, J. P.Ark, N. Parker, et al. 2006. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. J. Clin. Oncol. 24:4170–4176.
10. Ang, K. K., B. A. Berkey, X. Tu, H. Y. Zhang, R. Katz, E. H. Hammond, et al. 2002. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res. 62:7350–7356.

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11. Sheridan, M. T., T. O’Dwyer, C. B. Seymour, and C. E. Mothersill. 1997. Potential indicators of radiosensitivity in squamous cell carcinoma of the head and neck. Radiat. Oncol. Investig. 5:180–186.

12. Chiang, W. F., S. Y. Liu, C. Y. Yen, C. N. Lin, Y. C. Chen, S. C. Lin, K. W. Chang, et al. 2008. Association of epidermal growth factor receptor (EGFR) gene copy number amplification with neck lymph node metastasis in areca-associated oral carcinomas. Oral Oncol. 44:270–276.

13. Karamouzis, M. V., J. R. Grandis, and A. Argiris. 2007. Therapies directed against epidermal growth factor receptor in aerodigestive carcinomas. JAMA 298:70–82.

14. Bonner, J. A., P. M. Harari, J. Giralt, R. B. Cohen, C. U. Jones, R. K. Sur, et al. 2006. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N. Engl. J. Med. 354:567–578.

15. Vermorken, J. B., R. Mesia, F. Rivera, E. Remenar, A. Kawecki, S. Rottey, C. Tam, S. Perier, P. Soussan, J. L. St Guilz, et al. 2008. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N. Engl. J. Med. 359:1116–1127.

16. Mirghani, H., F. Moreau, M. Lefevre, C. Tam, S. Perier, P. Soussan, J. L. St Guilz, et al. 2011. Human papillomavirus type 16 oropharyngeal cancers in lymph nodes as a marker of metastases. Arch. Otolaryngol. Head Neck Surg. 137:910–914.

17. Li, W., C. H. Thompson, C. J. O’Brien, E. B. McNeil, R. A. Scolyer, Y. E. Cossart, et al. 2003. Human papillomavirus positivity predicts favourable outcome for squamous carcinoma of the tonsil. Int. J. Cancer 106:553–558.

18. Gillison, M. L., Q. Zhang, R. Jordan, W. Xiao, W. H. Westra, A. Trotti, et al. 2012. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J. Clin. Oncol. 30:2102–2111.

19. Chaturvedi, A. K., E. A. Engels, W. F. Anderson, and M. L. Gillison. 2008. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J. Clin. Oncol. 26:612–619.

20. Marur, S., G. D’Souza, W. H. Westra, and A. A. Forastiere. 2010. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol. 11:781–789.

21. St Guilz, J. L., A. C. Jacquard, J. L. Pretet, J. Haesebaert, A. Beby-Defaux, C. Clavel, et al. 2011. Human papillomavirus genotype distribution in oropharynx and oral cavity cancer in France—The EDiTH VI study. J. Clin. Virol. 51:100–104.

22. Ang, K. K., J. Harris, R. Wheeler, R. Weber, D. L. Rosenthal, P. F. Nguyen-Tan, et al. 2010. Human papillomavirus and survival of patients with oropharyngeal cancer. N. Engl. J. Med. 363:24–35.

23. Greene, F. L., D. L. Page, I. D. Fleming, A. Fritz, C. M. Balch, et al. 2002. AJCC cancer staging manual. Pp. 157–164 In Springer, ed. Exocrine pancreas. Springer, New York, NY.

24. Tanaka, Y., S. Miyamoto, S. O. Suzuki, E. Oki, H. Yaki, K. Sonoda, et al. 2005. Clinical significance of heparin-binding epidermal growth factor-like growth factor and a disintegrin and metalloprotease 17 expression in human ovarian cancer. Clin. Cancer Res. 11:4783–4792.

25. Sok, J. C., F. M. Coppelli, S. M. Thomas, M. N. Lango, S. Xi, J. L. Hunt, et al. 2006. Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. Clin. Cancer Res. 12:5064–5073.

26. Etienne-Grimaldi, M. C., S. Pereira, N. Magne, J. L. Formento, M. Francoual, X. Fontana, et al. 2005. Analysis of the dinucleotide repeat polymorphism in the epidermal growth factor receptor (EGFR) gene in head and neck cancer patients. Ann. Oncol. 16:934–941.

27. Hitt, R., J. J. Grau, A. Lopez-Pousa, A. Berrocal, C. Garcia-Giron, A. Iriyoguen, et al. 2014. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann. Oncol. 25:216–225.

28. Mesia, R., S. Vázquez, J. J. Grau, J. A. Garcia-Saenz, C. Bayona, J. C. Galceran, et al. 2009. A single-arm phase II trial to evaluate the combination of cetuximab plus docetaxel, cisplatin, and 5-fluorouracil (TPF) as induction chemotherapy (IC) in patients (pts) with unresectable SCCHN. Int. J. Clin. Oncol. 27(Suppl. 15):6015.

29. Argiris, A., A. Buchanan, B. Brockstein, J. Kolesar, M. Ghebremichael, M. Pins, et al. 2009. Docetaxel and irinotecan in recurrent or metastatic head and neck cancer: a phase 2 trial of the Eastern Cooperative Oncology Group. Cancer 115:4504–4513.

30. Bellera, C. A., M. Pulido, S.ourgou, L. Collette, A. Doussau, A. Kramar, et al. 2013. Protocol of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project: formal consensus method for the development of guidelines for standardised time-to-event endpoints’ definitions in cancer clinical trials. Eur. J. Cancer 49:769–781.

31. Pointreau, Y., P. Garaud, S. Chapet, C. Sire, C. Tuchais, J. Tortochaux, et al. 2009. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J. Natl. Inst. Cancer Inst. 101:498–506.

32. Argiris, A., D. E. Heron, R. P. Smith, S. Kim, M. K. Gibson, S. Y. Lai, et al. 2010. Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and
33. Kies, M. S., F. C. Holsinger, J. J. Lee, W. N. Jr William, B. S. Glisson, H. Y. Lin, et al. 2010. Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. J. Clin. Oncol. 28:8–14.

34. Dietz, A., V. Rudat, J. Dreyhaupt, M. Pritsch, F. Hoppe, R. Hagen, et al. 2009. Induction chemotherapy with paclitaxel and cisplatin followed by radiotherapy for larynx organ preservation in advanced laryngeal and hypopharyngeal cancer offers moderate late toxicity outcome (DeLOS-I-trial). Eur. Arch. Otorhinolaryngol. 266:1291–1300.

35. Guigay, J., J. Fayette, A. Dillies, J. Sire, J. N. Kerger, I. Tsenevet, et al. 2011. Cetuximab, docetaxel, and cisplatin (TPEx) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): first results of phase II trial GORTEC 2008-03. J. Clin. Oncol. 29:5567.

36. Wanebo, H. J., J. Lee, B. A. Burtness, J. A. Ridge, M. Ghebremichael, S. A. Spencer, et al. 2014. Induction cetuximab, paclitaxel, and carboplatin followed by chemoradiation with cetuximab, paclitaxel and carboplatin for stage III/IV head and neck squamous cancer: a phase II ECOG-ACRIN trial (E2303). Ann. Oncol. 25:2036–2041.

37. de Gramont, A., J. F. Bosset, C. Milan, P. Rougier, O. Bouche, P. L. Etienne, et al. 1997. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J. Clin. Oncol. 15:808–815.

38. Arslan, C., F. D. Koseoglu. 2014. Modified docetaxel, cisplatin, and 5-fluorouracil combination regimen in advanced gastric cancer: Toxicity and efficacy results. J. Clin. Oncol. 32 (suppl): Abstract e15036.

39. Ozal, G., M. Dogan, H. Akbulut, B. Yalcin, G. Utkan, Y. Urun, F. Icli. The safety and efficacy of modified-dose docetaxel, cisplatin, and 5-fluorouracil (mDCF) combination in the front-line treatment of advanced gastric cancer. Gastrointestinal Cancers Symposium 2010. Abstract 113.

40. Velpula, K. K., V. R. Dasari, S. Asuthkar, B. Gorantla, and A. J. Tsung. 2012. EGFR and c-Met cross talk in glioblastoma and its regulation by human cord blood stem cells. Transl. Oncol. 5:379–392.

41. Wheeler, D. L., S. Huang, T. J. Kruser, M. M Nechrebecki, E. A. Armstrong, S. Benavente, et al. 2008. Mechanisms of acquired resistance to cetuximab: role of HER (ErbB) family members. Oncogene 27:3944–3956.

42. Maxwell, J. H., B. Kumar, F. Y. Feng, F. P. Worden, J. S. Lee, A. Eisbruch, et al. 2010. Tobacco use in human papillomavirus-positive advanced oropharynx cancer patients related to increased risk of distant metastases and tumor recurrence. Clin. Cancer Res. 16:1226–1235.