Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online August 24, 2015

DOI: 10.1634/theoncologist.2015-0208

Title: A Randomized, Multicenter, Phase II Study of Cetuximab With Docetaxel and Cisplatin as Induction Chemotherapy in Unresectable, Locally Advanced Head and Neck Cancer

Authors: Keun-Wook Lee,[a,*] Youngil Koh,[d,g,*] Sung-Bae Kim,[h] Sang-Won Shin,[k] Jin-Hyoung Kang,[m] Hong-Gyun Wu,[e] Myung-Whun Sung,[f] Bhumsuk Keam,[d,g] Dong-Wan Kim,[d,g] Tae Min Kim,[d,g] Kwang Hyun Kim,[f] Tack-Kyun Kwon,[f] J. Hun Hah,[f] In-Ah Kim,[b] Soon-Hyun Ahn,[c] Dok Hyun Yoon,[h] Sang-Wook Lee,[i] Sang Yoon Kim,[j] Soon Yuhl Nam,[j] Kwang-Yoon Jung,[l] Seung-Kuk Baek,[l] Sook Hee Hong,[m] Se-Hoon Lee,[d,g] Dae Seog Heo[d,g]

Departments of [a]Internal Medicine, [b]Radiation Oncology, and [c]Otorhinolaryngology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea; Departments of [d]Internal Medicine, [e]Radiation Oncology, and [f]Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital, and [g]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; Departments of [h]Oncology, [i]Radiation Oncology, and [j]Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; Departments of [k]Internal Medicine and [l]Otorhinolaryngology-Head and Neck Surgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [m]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
*Contributed equally.

ClinicalTrials.gov Identifier: NCT00623558

Sponsor(s): None (Investigator-initiated trial)

Principal Investigator: Dae Seog Heo

IRB Approved: Yes

Disclosures

Se-Hoon Lee: Merck KGaA (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Lessons Learned

- Addition of cetuximab may affect tolerability and, in turn, affect eventual outcomes.
- The incidence of prior human papillomavirus infection has emerged as an important variable that can confound trials enrolling patients with oropharyngeal cancer.

Author Summary: Abstract and Brief Discussion

Background

We investigated the efficacy of cetuximab when added to induction chemotherapy followed by concurrent chemo-radiotherapy (CCRT) in patients with locally advanced head and neck squamous cell carcinoma.

Methods
Patients were randomized to receive three cycles of docetaxel and cisplatin (TP regimen) with or without cetuximab (TP plus cetuximab [CTP] vs. TP) as induction chemotherapy. Patients in the CTP arm received CCRT with cetuximab and cisplatin, whereas patients in the TP arm received cisplatin alone. The primary endpoint was the objective response rate (ORR) after induction chemotherapy.

Results
Overall, 92 patients were enrolled. The ORRs for induction chemotherapy in the CTP and TP arms were not different (81% vs. 82%). Adding cetuximab lowered the completion rate of induction chemotherapy and CCRT and resulted in more frequent dose reductions of the induction chemotherapy, although this did not reach statistical significance. In the CTP and TP arms, respectively, the 3-year progression-free survival (PFS) rates were 70% and 56% ($p = .359$), and the overall survival (OS) rates were 88% and 74% ($p = .313$). When limited to patients who completed induction chemotherapy, 3-year PFS rates of 78% and 59% ($p = .085$) and OS rates of 94% and 73% ($p = .045$) were observed in the CTP and TP arms, respectively.

Conclusion
Adding cetuximab to sequential treatment did not increase the treatment efficacy and resulted in greater toxicity. In the intent-to-treat population, neither PFS nor OS was improved by the addition of cetuximab to sequential treatment; however, a suggestion of improved survival outcomes was observed in patients completing cetuximab-containing induction chemotherapy.

Discussion
The epidermal growth factor receptor (EGFR) is highly overexpressed in head and neck squamous cell carcinoma (SCCHN). The addition of the EGFR inhibitor cetuximab to radiotherapy has been found to improve survival outcomes in locally advanced SCCHN (LA-SCCHN), and combining cetuximab with cytotoxic agents prolongs survival in metastatic SCCHN. Based on these additive effects of cetuximab for both radiotherapy and chemotherapy, we hypothesized that the addition of cetuximab to both induction chemotherapy and concurrent chemoradiotherapy (CCRT) phases would improve treatment outcomes. The current study represents the first randomized trial to test the effect of cetuximab integration into both the induction and CCRT phases in LA-SCCHN.

In our study, although not statistically significant, cetuximab addition to sequential treatment seemed to decrease a patient's ability to tolerate treatment. Adding cetuximab lowered the completion rate of induction chemotherapy (docetaxel plus cisplatin) and CCRT and caused more frequent dose reductions of induction chemotherapy (Table 1). Although there was no significant difference in the frequency of severe (grade $\geq$3) adverse events, overall adverse events occurred more frequently in the CTP arm. The objective response rate (the primary endpoint), progression-free survival, and overall survival were not improved by cetuximab addition in the intent-to-treat population (Table 1). Nonetheless, we found that the addition of cetuximab seemed to more favorably affect patients who completed the planned 3 cycles of induction chemotherapy (3-year PFS 78% vs. 59% [$p = .085$] and 3-year OS 94% vs. 73% [$p = .045$] in the CTP vs. TP arms).

The shortcomings of our study are as follows. Because the importance of human papillomavirus tests in oropharyngeal cancer was little known when this study was initiated and the planned sample size was small, stratification according to primary tumor site or other additional clinical variables could not be performed in the randomization process. Instead, considering possible differences in clinical practice patterns at the various participating institutions, we stratified patients only according to institution; therefore, the sex distribution was unequal between the arms ($p = .044$), and the proportion of oropharyngeal disease was slightly higher in the CTP arm than in the TP arm, although this was not statistically significant. Consequently, we cannot exclude the possibility that these unexpectedly uneven patient distributions contributed to the favorable survival outcomes in patients who completed cetuximab-containing induction chemotherapy.

In conclusion, although the addition of cetuximab to sequential treatment of LA-SCCHN may somewhat decrease patient compliance, it was tolerable overall. The primary endpoint of this study was not met, but the survival data observed in patients who completed the planned cetuximab-containing induction chemotherapy suggest that further investigation of cetuximab addition in this setting is warranted.

Trial Information

Disease	Head and Neck Cancers
Stage of disease / treatment	Neoadjuvant
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Randomized
Primary Endpoint	Overall Response Rate
Secondary Endpoint	Progression-Free Survival
Secondary Endpoint	Overall Survival
Secondary Endpoint	Toxicity
Secondary Endpoint	Completion rates of induction chemotherapy and concurrent chemoradiotherapy (CCRT)

Additional Details of Endpoints or Study Design

This open-label randomized phase II study was conducted at five institutions in the Republic of Korea, in accordance with the Declaration of Helsinki. All patients provided written informed consent. Merck KGaA (Darmstadt, Germany, http://www.emdgroup.com), provided the cetuximab supply and administrative support for this study. The study protocol was approved by each hospital's institutional review board.

Adult patients (aged ≥18 years) with measurable, previously untreated, and histologically proven LA-SCCHN were eligible. Patients with undifferentiated carcinoma were also eligible. The disease was required to be one of the following: (a) unresectable LA-SCCHN due to tumor fixation, skull base involvement, or lymph node fixation; (b) LA-SCCHN with low surgical curability due to advanced disease (T3–4) or regional lymph node extension (N2–3, except for T1N2); or (c) LA-SCCHN in which surgery was expected to be associated with severe organ damage, rendering the patient a candidate for organ preservation with CCRT. Primary tumor locations included the oral cavity, oropharynx, hypopharynx, and larynx. Disease was staged according to the criteria of the American Joint Committee on Cancer (version 6.0). Additional eligibility criteria were performance status (PS) between 0 and 1 based on the Eastern Cooperative Oncology Group criteria and adequate bone marrow, renal, and hepatic function. Exclusion criteria included diagnosis of other cancer within 5 years, peripheral neuropathy or hearing disorder of grade ≥2 by National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), or a comorbidity contraindicating administration of systemic chemotherapy and/or radiotherapy.

Patients were randomized 1:1 to receive 3 cycles of docetaxel and cisplatin every 3 weeks with or without cetuximab (CTP vs. TP) as induction chemotherapy. Computer-generated randomization was used, and patients were stratified according to participating institutions.

As induction chemotherapy, patients in the TP arm received 3 cycles of docetaxel (75 mg/m^2, day 1) and cisplatin (75 mg/m^2, day 1) every 3 weeks. If no disease progression was observed, patients received CCRT with a weekly dose of cisplatin (30 mg/m^2) alone. CCRT was initiated 4–8 weeks after the last administration of the induction chemotherapy. Patients in the CTP arm received the same induction chemotherapy (TP, 3 cycles) with the addition of cetuximab (400 mg/m^2 [loading dose] on day 1 of the first TP cycle and then 250 mg/m^2 weekly). Thereafter, patients received CCRT with weekly administration of both cisplatin (30 mg/m^2) and cetuximab (250 mg/m^2). During the induction phase, prophylactic granulocyte-colony stimulating factor (G-CSF) use was allowed only if grade 4 neutropenia persisting ≥7 days or neutropenic fever had developed during the previous cycle of chemotherapy. The initial protocol did not allow for docetaxel dose reduction after the first development of grade 4 neutropenia or neutropenic fever. Docetaxel dose reduction (to 60 mg/m^2) was allowed on the second development of grade 4 neutropenia persisting ≥7 days or neutropenic fever despite previous use of prophylactic G-CSF. After protocol revision in February 2010, for any case in which grade 4 neutropenia persisting ≥7 days or neutropenic fever had developed, both docetaxel dose reduction (to 60 mg/m^2) and secondary G-CSF prophylaxis were implemented in the next cycle. Radiotherapy was planned to be administered by either conventional fractionation (1.8–2.0 Gy/day, 5 days per week, total dose 66–70 Gy) or accelerated hyperfractionation (twice a day with a 6-hour interfraction interval, 5 days per week, total dose 66–74 Gy).

The primary endpoint was the objective response rate (ORR) after induction chemotherapy. Secondary endpoints included completion rates of induction chemotherapy and CCRT, progression-free survival (PFS), overall survival (OS), and toxicities. The locoregional control rate, defined as the proportion of patients who did not experience locoregional disease progression, was also calculated. Responses were classified as complete response, partial response, stable disease, or progressive disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) [1]. PFS was defined as the period from the starting date of induction chemotherapy to disease progression or death from any cause. OS was calculated from the starting date of induction chemotherapy to death from any cause.

Sample size was calculated with the assumption that the ORR would be ≥70% with CTP induction chemotherapy and 50% with TP. Using Fleming's one-stage design with a statistical power of 80% at the 5% level of significance, 41 patients in each arm were needed to verify the superiority of CTP to TP. Assuming a dropout rate of 10%, 46 patients per arm were necessary. Statistical analyses on categorical variables in tables were performed using Pearson's chi-square test. The Kaplan-Meier method was used to calculate PFS and OS. Comparisons between groups were made using log-rank tests. All statistical tests were two-sided with significance defined as $p < .05$. All analyses were performed using SPSS for Windows (IBM Corp., Armonk, NY, http://www.ibm.com). The trial is registered with ClinicalTrials.gov (NCT00623558).

Investigator's Analysis	Correlative endpoints not met but clinical activity observed

Drug Information TP arm

Drug 1 **Generic/Working name**	Docetaxel
Drug class	Microtubule-targeting agent
Schedule of Administration	As induction chemotherapy, patients in the TP arm received 3 cycles of docetaxel (75 mg/m^2, day 1) every 3 weeks.
Drug 2 **Generic/Working name**	Cisplatin
Drug class	Platinum compound
Schedule of Administration	As induction chemotherapy, patients in the TP arm received 3 cycles of cisplatin (75 mg/m^2, day 1) every 3 weeks. If no disease progression was observed, patients received CCRT with a weekly dose of cisplatin (30 mg/m^2). CCRT was initiated 4–8 weeks after the last administration of the induction chemotherapy.

Drug Information CTP arm

Drug 1 **Generic/Working name**	Cetuximab
Drug class	EGFR
Schedule of Administration	Patients in the CTP arm received the same induction chemotherapy (TP, 3 cycles) with the addition of cetuximab (400 mg/m^2 [loading dose] on day 1 of the first TP cycle and then 250 mg/m^2 weekly) during induction chemotherapy and CCRT.
Drug 2 **Generic/Working name**	Docetaxel
Drug class	Microtubule-targeting agent
Schedule of Administration	As induction chemotherapy, patients in the CTP arm received 3 cycles of docetaxel (75 mg/m^2, day 1) every 3 weeks.
Drug 3 **Generic/Working name**	Cisplatin
Drug class	Platinum compound
Schedule of Administration	As induction chemotherapy, patients in the CTP arm received cisplatin (75 mg/m^2, day 1) every 3 weeks. If no disease progression was observed, patients received CCRT with a weekly dose of cisplatin (30 mg/m^2) and cetuximab (250 mg/m^2). CCRT was initiated 4–8 weeks after the last administration of the induction chemotherapy.

Patient Characteristics

Number of patients, male	82
Number of patients, female	10
Stage	stage III or IV
Age	Median (range): Not Collected
Number of prior systemic therapies	Median (range): 0
Performance Status: ECOG	**0** — 38 **1** — 54
Cancer Types or Histologic Subtypes	Oropharynx cancer, 41 Oral cavity cancer, 14 Larynx cancer, 13 Hypopharynx cancer, 24 Squamous cell carcinoma, 90 Undifferentiated carcinoma, 2

Primary Assessment Method

TP arm: Total Patient Population

Number of patients enrolled	44
Number of patients evaluable for toxicity	44
Number of patients evaluated for efficacy	44
Evaluation method	Other
Response assessment CR	$n = 4$
Response assessment PR	$n = 32$
Response assessment SD	$n = 7$
Response assessment PD	$n = 1$
Response assessment OTHER	$n = 0$

CTP arm: Total Patient Population

Number of patients enrolled	48
Number of patients evaluable for toxicity	48
Number of patients evaluated for efficacy	45
Evaluation method	Other
Response assessment CR	$n = 4$
Response assessment PR	$n = 35$
Response assessment SD	$n = 6$
Response assessment PD	$n = 0$
Response assessment OTHER	$n = 3$

Adverse Events TP arm

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Neutrophils/granulocytes (ANC/AGC)	75%	2%	2%	9%	11%	0%	25%
Hemoglobin	86%	0%	14%	0%	0%	0%	14%
Fatigue (asthenia, lethargy, malaise)	57%	21%	18%	5%	0%	0%	43%
Anorexia	50%	25%	16%	9%	0%	0%	50%
Nausea	68%	18%	14%	0%	0%	0%	32%
Vomiting	82%	7%	11%	0%	0%	0%	18%
Mucositis/stomatitis (functional/symptomatic)	93%	2%	5%	0%	0%	0%	7%
Diarrhea	73%	9%	11%	7%	0%	0%	27%
Pain - abdominal pain	93%	2%	0%	5%	0%	0%	7%
Dermatology/Skin - Skin toxicity	89%	7%	5%	0%	0%	0%	11%

Adverse Events Legend
Adverse events during induction chemotherapy in the TP arm
*No Change from Baseline/No Adverse Event

Adverse Events CTP arm

Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Neutrophils/granulocytes (ANC/AGC)	58%	0%	6%	21%	15%	0%	42%
Hemoglobin	94%	0%	2%	4%	0%	0%	6%
Fatigue (asthenia, lethargy, malaise)	54%	23%	17%	6%	0%	0%	46%
Anorexia	50%	27%	16%	6%	0%	0%	50%

Nausea	58%	29%	12%	0%	0%	0%	42%
Vomiting	85%	10%	4%	0%	0%	0%	15%
Mucositis/stomatitis (functional/symptomatic)	60%	17%	15%	8%	0%	0%	40%
Diarrhea	38%	40%	15%	8%	0%	0%	63%
Pain - abdominal pain	85%	4%	8%	2%	0%	0%	15%
Dermatology/Skin - Skin toxicity	25%	25%	44%	6%	0%	0%	75%

Adverse Events Legend
Adverse events during induction chemotherapy in the CTP arm
*No Change from Baseline/No Adverse Event

Serious Adverse Events CTP arm

Name	Grade	Attribution
Unexplained early death	5	Possible
Septic shock	4	Probable

Adverse Events Legend
Adverse events during induction chemotherapy in the CTP arm

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Correlative endpoints not met but clinical activity observed

Discussion

To improve treatment outcomes in locally advanced head and neck squamous cell carcinoma (LA-SCCHN), chemotherapy has been integrated into various multimodal approaches. Although large clinical trials [2, 3] and meta-analyses [4] have established the role of concurrent chemoradiotherapy (CCRT) in LA-SCCHN, the role of induction chemotherapy followed by CCRT (sequential treatment) has not yet been clearly verified. The TAX 323 and 324 trials showed the superiority of the TPF regimen (docetaxel, cisplatin, and 5-fluorouracil) to the PF regimen (cisplatin and 5-fluorouracil) during induction chemotherapy [5–7]; however, two recent phase III trials (DeCIDE [8] and PARADIGM [9]) suggested that sequential treatment using TPF is not superior to CCRT alone. In contrast, an Italian phase III trial showed the superiority of induction TPF followed by CCRT (or cetuximab and radiotherapy) to CCRT (or cetuximab and radiotherapy) alone [10].

Considering the unclear benefit of induction chemotherapy using cytotoxic agents only, the addition of a targeted agent to induction chemotherapy (and/or to CCRT) may be a reasonable alternative approach in LA-SCCHN. Because EGFR is highly overexpressed in SCCHN [11, 12], anti-EGFR agents have been vigorously investigated [13–16]. The addition of cetuximab to radiotherapy has been found to improve survival outcomes in LA-SCCHN [13], and combining cetuximab with cytotoxic agents prolongs survival in metastatic SCCHN [14]. Argiris et al. conducted a single-arm phase II study in LA-SCCHN patients using a regimen very similar to that of our study [17]; however, the study did not have a control arm, hence the "additive effect" of cetuximab to sequential treatment could not be estimated [17]. We conducted this study with the hypothesis that cetuximab addition to both induction and CCRT phases would improve treatment outcomes.

In this study, 92 patients were enrolled between March 2008 and January 2012 (Table 2; Fig. 1). The data cutoff was May 2013. Patient characteristics are presented in Table 2. Regarding sex distribution, the TP (docetaxel and cisplatin) arm had a lower male-to-female ratio than the TP plus cetuximab (CTP) arm ($p = .044$); however, there were no statistical differences in other clinical characteristics between the two arms. Treatment compliance and outcomes are summarized in Table 1 and Figure 1. Overall, 40 of 48 patients (83%) in the CTP arm and 40 of 44 (91%) in the TP arm completed the planned induction chemotherapy; the reasons for incomplete induction chemotherapy are presented in Figure 1. The objective response rates (ORRs) to induction chemotherapy in the CTP and TP arms were 81% and 82%, respectively ($p = .530$). CCRT was initiated in 35 patients in both the CTP and TP arms; 19 patients received intensity-modulated radiotherapy (7 with TP and 12 with CTP). Protocol completion rates (including both induction and CCRT phases) were 67% (CTP) and 77% (TP). The ORRs after CCRT were 94% (22 complete responses [CRs] and 11 partial responses [PRs] in 35 patients with CTP) and 94% (25 CRs and 8 PRs in 35 patients with TP). Adverse events are shown in Table 3. Although there was no significant difference in the frequency of severe (grade $\geq$3) adverse events, overall adverse events seemed to occur more frequently in the CTP arm. Consequently, we found that cetuximab addition to sequential treatment is feasible but decreases tolerability of patients somewhat.

The overall efficacy parameters including the primary endpoint of this study (ORR) were not improved with the addition of cetuximab to sequential treatment (intent-to-treat population). Median progression-free survival (PFS) and overall survival (OS) were not reached in either arm, with a median follow-up time of 33 months. There were 2 distant and 8 locoregional failures in the CTP arm and 2 distant and 13 locoregional failures in the TP arm. When intent-to-treat analysis was performed, the CTP arm showed PFS and OS rates of 70% and 88% at 3 years, whereas the TP arm showed PFS and OS rates of 56% and 74% ($p = .359$ for PFS and $p = .313$ for OS, respectively) (Fig. 2A, 2B). We unexpectedly observed that cetuximab addition more favorably affected patients who completed the planned three cycles of induction chemotherapy. When limited to patients who completed the planned induction chemotherapy, 3-year PFS rates of 78% and 59% ($p = .085$) and 3-year OS rates of 94% and 73% ($p = .045$) were observed in the CTP and TP arms, respectively (Fig. 2C, 2D). The main differences in PFS and OS between the two arms appeared to be among patients with nonoropharyngeal disease (Table 1), but the numbers are too small to show a significant difference.

Our study has some limitations. In this study, patients were stratified only according to institution in the randomization process. Consequently, the proportion of oropharyngeal disease was slightly higher in the CTP arm than in the TP arm, although this was not statistically significant. The sex distribution was unequal between the arms ($p = .044$). One might assume that these unequal patient distributions contributed to the favorable survival outcomes in the CTP arm. In addition, because the importance of human papillomavirus (HPV) in oropharyngeal cancer was little known when this study was initiated, information on the HPV status of oropharyngeal cancer in our study is lacking. Because HPV-positive and -negative SCCHNs are different diseases [18], there is a chance that cetuximab addition may result in different outcomes in these two entities. As shown in Table 1, however, the improved survival outcomes in the CTP arm seem to derive from patients with nonoropharyngeal disease; both the CTP and TP arms showed almost the same survival curves in oropharyngeal disease. Consequently, we hypothesize that CTP induction therapy would be particularly efficacious in nonoropharyngeal disease. Sex is not usually a stratification factor in randomized trials in SCCHN. Although we cannot estimate exactly how this uneven sex distribution affected the survival results between arms, we could effectively exclude the possibility of its playing a major role because there were no differences in PFS or OS between male and female patients in our subgroup analyses (data not shown). In future clinical trials, clinical variables such as primary tumor site and HPV status should be incorporated as stratification factors in the randomization process.

In conclusion, the addition of cetuximab to sequential treatment for LA-SCCHN somewhat decreased patient compliance and did not improve treatment efficacy; however, we unexpectedly observed promising survival outcomes in patients who completed the planned cetuximab-containing induction chemotherapy. Further investigation of cetuximab addition in this setting is warranted.

Acknowledgments

Merck KGaA, Darmstadt, Germany, provided the cetuximab supply and administrative support for this study. This study was partly supported by grants from the Innovative Research Institute for Cell Therapy, Republic of Korea (A062260) and the Korea Healthcare Technology Research and Development Project, Ministry of Health and Welfare, Republic of Korea (A102065).

References

1. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
2. Forastiere AA, Goepfert H, Maor M et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–2098.
3. Adelstein DJ, Li Y, Adams GL et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92–98.
4. Pignon JP, le Maître A, Maillard E et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
5. Lorch JH, Goloubeva O, Haddad RI et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: Long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol 2011; 12:153–159.
6. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357: 1705–1715.
7. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357:1695–1704.
8. Cohen EE, Karrison TG, Kocherginsky M et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol 2014;32:2735–2743.

9. Haddad R, O'Neill A, Rabinowits G et al. 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 2013;14:257–264.
10. Ghi MG, Paccagnella A, Ferrari D et al. Concomitant chemoradiation (CRT) or cetuximab/RT (CET/RT) versus induction docetaxel/cisplatin/5-fluorouracil (TPF) followed by CRT or CET/RT in patients with locally advanced squamous cell carcinoma of head and neck (LASCCHN). A randomized phase III factorial study (NCT01086826). J Clin Oncol 2014;32(suppl):6004a.
11. Grandis JR, Tweardy DJ. 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 1993;53:3579–3584.
12. Dassonville O, Formento JL, Francoual M et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. J Clin Oncol 1993;11:1873–1878.
13. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–578.
14. Vermorken JB, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–1127.
15. Lefebvre JL, Pointreau Y, Rolland F et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: The TREMPLIN randomized phase II study. J Clin Oncol 2013;31:853–859.
16. Buiret G, Combe C, Favrel V et al. A retrospective, multicenter study of the tolerance of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil followed by radiotherapy with concomitant cetuximab in 46 cases of squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2010;77:430–437.
17. Argiris A, Heron DE, Smith RP et al. Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. J Clin Oncol 2010;28:5294–5300.
18. Zandberg DP, Bhargava R, Badin S et al. The role of human papillomavirus in nongenital cancers. CA Cancer J Clin 2013;63:57–81.

Figures and Tables

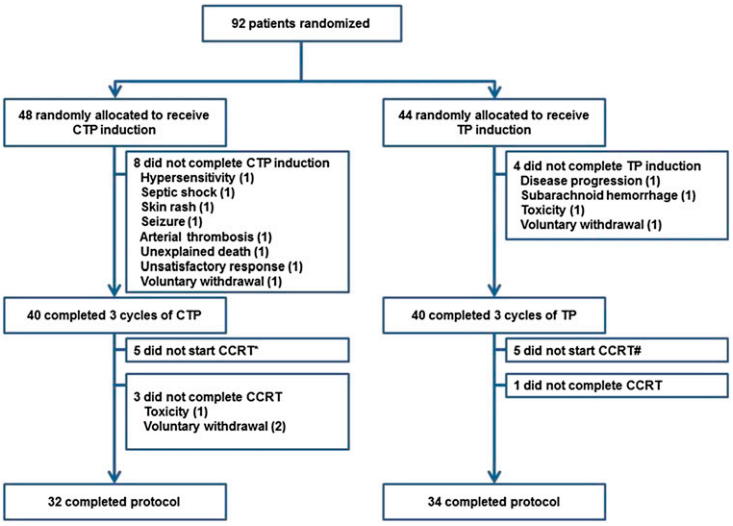

Figure 1. Trial profile. ∗, Five patients in the CTP arm did not receive CCRT due to withdrawal of consent ($n = 2$), unsatisfactory response ($n = 1$), disease progression ($n = 1$), and patient refusal ($n = 1$). #, Five patients in the TP arm did not receive CCRT because of withdrawal of consent ($n = 2$), disease progression ($n = 1$), and patient refusal ($n = 2$).

Abbreviations: CCRT, concurrent chemoradiotherapy; CTP, cetuximab, docetaxel, and cisplatin; TP, docetaxel and cisplatin.

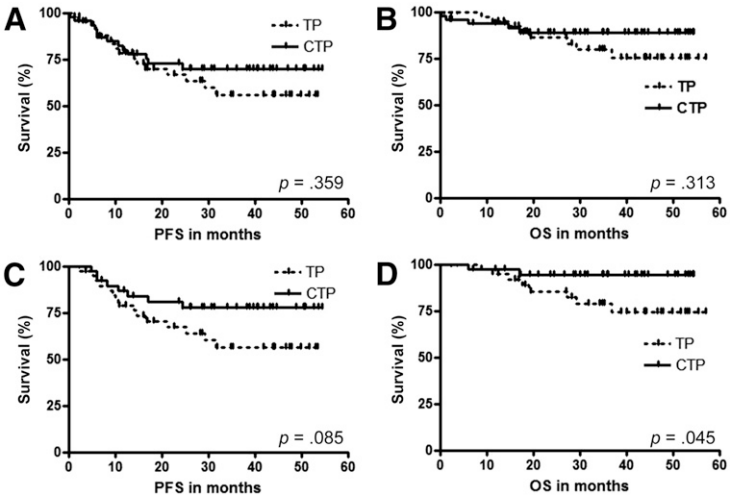

Figure 2. Progression-free survival and overall survival of patients in all patients (intent-to-treat analysis) **(A, B)** and in patients who completed three cycles of induction chemotherapy **(C, D)**.

Abbreviations: CTP, cetuximab, docetaxel, and cisplatin; OS, overall survival; PFS, progression-free survival; TP, docetaxel and cisplatin.

Table 1. Treatment compliance and outcomes

Variable	CTP arm ($n = 48$)	TP arm ($n = 44$)	p value
Completion of induction chemotherapy (*n*)			.360
Yes	40	40	
No	8	4	
Induction completion rate (%)	83	91	
Dose reduction in induction chemotherapy[a] (*n*)			.001
Yes	22	6	
No	26	38	
Dose reduction in docetaxel or cisplatin (*n*)			.170
Yes	12	6	
No	36	38	
Response to induction chemotherapy[b] (*n*)			.530[c]
CR	4	4	
PR	35	32	
SD	6	7	
PD	0	1	
Objective response rate[d] (%)	81	82	
Completion of induction and CCRT (*n*)			.259
Yes	32	34	
No	16	10	
Protocol completion rate (%)	67	77	
Response to CCRT (*n*)			.506[c]
CR	22	25	
PR	11	8	
SD	0	0	
PD	1	1	
CR rate (%)	46	57	
3-years PFS rate (%)			
Total	70	56	.359
Oropharynx	87	84	.975
Nonoropharynx	53	37	.499
3-years OS rate (%)			
Total	88	74	.313
Oropharynx	92	91	.737
Nonoropharynx	86	61	.248

[a]Dose reduction in any compound among docetaxel, cisplatin, and cetuximab.
[b]Three patients in the CTP arm were not evaluable for response due to unexplained early death ($n = 1$), septic shock ($n = 1$), and hypersensitivity reaction after the first cetuximab dose ($n = 1$); all patients were evaluable for response in the TP arm.
[c]*p* value based on binary comparison: whether or not a patient achieved objective response.
[d]Overall response rate was defined as the proportion of patients achieving CR or PR.
Abbreviations: CCRT, concurrent chemoradiotherapy; CR, complete response; CTP, cetuximab, docetaxel, and cisplatin; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TP, docetaxel and cisplatin.

Table 2. Patient characteristics

Variable	CTP arm ($n = 48$)	TP arm ($n = 44$)	p value
Age (years)			
Median (range)	58 (40–73)	61 (29–73)	.560
Sex, *n* (%)			.044
Male	46 (96)	36 (82)	
Female	2 (4)	8 (18)	
ECOG PS, *n* (%)			.401
0	22 (46)	16 (36)	
1	26 (54)	28 (64)	
T stage, *n* (%)			.375
T1	5 (10)	2 (5)	
T2	22 (46)	17 (39)	
T3	7 (15)	12 (27)	
T4	14 (29)	13 (29)	
N stage, *n* (%)			.638
N0	1 (2)	1 (2)	
N1	8 (17)	7 (16)	
N2	35 (73)	35 (80)	
N3	4 (8)	1 (2)	
Stage, *n* (%)			.511
III	4 (8)	6 (14)	
IV	44 (92)	38 (86)	
Histology, *n*			.495
Squamous	46	44	
Undifferentiated	2	0	
Primary disease site, *n* (%)			.130[a]
Oropharynx	25 (52)	16 (36)	
Oral cavity	4 (8)	10 (23)	
Larynx	9 (19)	4 (9)	
Hypopharynx	10 (21)	14 (32)	

[a]*p* value based on binary comparison: whether or not a patient had oropharyngeal disease.

Abbreviations: CTP, cetuximab, docetaxel, and cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; TP, docetaxel and cisplatin.

Table 3. Adverse events during induction chemotherapy and concurrent chemoradiotherapy

	Induction phase[a]				CCRT phase[b]			
	CTP ($n = 48$)[c]		TP ($n = 44$)		CTP ($n = 35$)		TP ($n = 35$)	
Adverse event	**All**	**Grade 3–4**	**All**	**Grade 3–4**	**All**	**Grade 3–4**	**All**	**Grade 3–4**
Abdominal pain	7 (15)	1 (2)	3 (7)	2 (5)	0	0	2 (6)	0
Anorexia	24 (50)	3 (6)	22 (50)	4 (9)	17 (49)	6 (17)	24 (69)	4 (11)
AST/ALT elevation	1 (2)	0	3 (7)	3 (7)	1 (3)	1 (3)	0	0
Diarrhea	30 (63)	4 (8)	12 (27)	3 (7)	0	0	0	0
Fatigue	22 (46)	3 (6)	19 (43)	2 (5)	5 (14)	0	1 (3)	0
Odynophagia	4 (8)	0	2 (5)	0	25 (71)	7 (20)	23 (66)	4 (11)
Dysphagia	0	0	2 (5)	0	9 (26)	3 (9)	9 (26)	2 (6)
Nausea	20 (42)	0	14 (32)	0	7 (20)	0	14 (40)	2 (6)
Vomiting	7 (15)	0	8 (18)	0	4 (11)	0	5 (14)	0
Febrile neutropenia	7 (15)	7 (15)	4 (9)	4 (9)	3 (9)	3 (9)	0	0
Neutropenia	20 (42)	17 (35)	11 (25)	9 (20)	9 (26)	7 (20)	7 (20)	6 (17)
Infection	5 (10)	1 (2)	2 (5)	1 (2)	5 (14)	1 (3)	8 (23)	1 (3)
Anemia	3 (6)	2 (4)	6 (14)	0	4 (11)	1 (3)	7 (20)	2 (6)
Thrombocytopenia	0	0	1 (2)	1 (2)	4 (11)	1 (3)	1 (3)	0
Infusion reaction	5 (10)	1 (2)	0	0	0	0	1 (3)	0
Mucositis	19 (40)	4 (8)	3 (7)	0	16 (46)	9 (26)	11 (31)	3 (9)
Skin toxicity	36 (75)	3 (6)	5 (11)	0	22 (63)	4 (11)	14 (40)	1 (3)
Thromboembolism	1 (2)	1 (2)	0	0	0	0	1 (3)	1 (3)
Hyponatremia	0	0	1 (2)	1 (2)	0	0	0	0
Hypokalemia	1 (2)	1 (2)	1 (2)	1 (2)	0	0	1 (3)	1 (3)

Data are shown as number (percentage).

[a]During induction chemotherapy, diarrhea (63% vs. 27%), mucositis (40% vs. 7%), and skin toxicity (75% vs. 11%) developed more frequently in the CTP arm than in the TP arm ($p < .05$); however, the frequencies of grade ≥3 toxicities were not statistically different, although the frequencies of some adverse events (neutropenia, febrile neutropenia, mucositis, and skin toxicity) were numerically higher in the CTP arm.

[b]During the CCRT phase, although not statistically significant, grade ≥3 toxicities were more likely to develop in the CTP arm than in the TP arm: febrile neutropenia (9% vs. 0%), anorexia (17% vs. 11%), odynophagia (20% vs. 11%), mucositis (26% vs. 9%), and skin toxicity (11% vs. 3%).

[c]One patient in the CTP arm died on the 21st day after the start of induction chemotherapy from an unexplained cause; his family refused diagnostic workup or supportive care after his clinical deterioration. Another patient in the CTP arm experienced neutropenic septic shock after induction chemotherapy and was transferred to another hospital for supportive care without disease evaluation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCRT, concurrent chemoradiotherapy; CTP, cetuximab, docetaxel, and cisplatin; TP, docetaxal and cisplatin.