JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Improved Outcome by Adding Concurrent Chemotherapy to Cetuximab and Radiotherapy for Locally Advanced Head and Neck Carcinomas: Results of the GORTEC 2007-01 Phase III Randomized Trial

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Published at jco.org on June 7, 2018.

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0732-183X/18/3699-1/$20.00

ABSTRACT

Purpose
To investigate the effect of adding concurrent chemotherapy (CT) to cetuximab plus radiotherapy (RT; CT-cetux-RT) compared with cetuximab plus RT (cetux-RT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN).

Patients and Methods
In this phase III randomized trial, patients with N0-2b, nonoperated, stage III or IV (nonmetastatic) LA-SCCHN were enrolled. Patients received once-daily RT up to 70 Gy with weekly cetuximab or with weekly cetuximab and concurrent carboplatin and fluorouracil (three cycles). To detect a hazard ratio (HR) of 0.64 for progression-free survival (PFS) with 85% power at a two-sided significance level of $P = .05$, 203 patients needed to be included in each arm.

Results
Four hundred six patients were randomly assigned to either CT-cetux-RT or cetux-RT. Patient and tumor characteristics were well balanced between arms, including p16 status. With a median follow-up of 4.4 years, the HR for PFS favored the CT-cetux-RT arm (HR, 0.73; 95% CI, 0.57 to 0.94; $P = .015$), with 3-year PFS rates of 52.3% and 40.5% and median PFS times of 37.9 and 22.4 months in the CT-cetux-RT and cetux-RT arms, respectively. The HR for locoregional control was 0.54 (95% CI, 0.38 to 0.76; $P < .001$) in favor of CT-cetux-RT. These benefits were observed regardless of p16 status for oropharynx carcinomas. Overall survival (HR, 0.80; $P = .11$) and distant metastases rates (HR, 1.19; $P = .50$) were not significantly different between the two arms. The CT-cetux-RT arm, compared with cetux-RT, had a higher incidence of grade 3 or 4 mucositis (73% *v* 61%, respectively; $P = .014$) and of hospitalizations for toxicity (42% *v* 22%, respectively; $P < .001$).

Conclusion
The addition of concurrent carboplatin and fluorouracil to cetux-RT improved PFS and locoregional control, with a nonsignificant gain in survival. To our knowledge, this is the first evidence of a clinical benefit for treatment intensification using cetux-RT as a backbone in LA-SCCHN.

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.76.2518

Data Supplement
DOI: https://doi.org/10.1200/JCO.2017.76.2518

DOI: https://doi.org/10.1200/JCO.2017.76.2518

INTRODUCTION

Squamous cell carcinomas of the head and neck (SCCHNs) are among the most common cancers and predominately involve the oral cavity, larynx, oropharynx, and/or hypopharynx. These cancers are closely associated with tobacco and alcohol use, but a growing proportion of squamous cell carcinomas (SCCs) of the oropharynx are associated with human papillomavirus (HPV),[1] and HPV-positive tumors have a higher cure rate than HPV-negative tumors.[2,3]

A majority of SCCHNs are locally advanced (LA-SCCHN) with local or distant failure rates between 30% and 65%.[4,5] On the basis of phase III randomized trials, concurrent chemoradiotherapy (CRT) has been established as

a preferred standard of care (SOC) for nonoperated LA-SCCHN,[5-8] with a survival benefit of adding chemotherapy (CT) to radiotherapy (RT) of 6.5% at 5 years and an approximately 13% improvement in locoregional control (LRC).[5] The most common standard CRT regimen is RT plus high-dose cisplatin 100 mg/m^2 every 3 weeks; an alternative CRT category 1 regimen according to the National Comprehensive Cancer Network Guidelines is RT plus carboplatin and fluorouracil (FU).[8-10] Several attempts to challenge concurrent CRT by adding induction CT, by intensifying RT, and/or by using alternative concurrent treatments have failed to demonstrate a benefit compared with CRT alone.[9,11-13] A third category 1 SOC regimen has been established in LA-SCCHN by combining RT and epidermal growth factor receptor targeting with cetuximab monoclonal antibody.[8,14] This SOC is commonly given to patients who are unfit to receive high-dose CT and/or to patients with less advanced disease (intermediate stages and/or HPV-positive disease), and the benefits as a result of the addition of cetuximab seem to be more pronounced with altered fractionated RT.[14] In this context, we explored the effect of combining RT with the systemic agents from two category 1 SOC regimens (carboplatin plus FU and cetuximab). The results showed that adding carboplatin and FU improved the oncologic outcome when using cetuximab plus RT (cetux-RT) as a backbone.

PATIENTS AND METHODS

Study Design

This study was a randomized multicenter phase III trial performed in 31 centers and was approved by our ethics committee (Le Kremlin-Bicêtre, France).

Patients

All patients provided written informed consent. This trial was restricted to patients with limited nodal spread (N0-2a; a few patients with N2b disease were included if the cervical nodes were not detectable clinically but only detectable on neck imaging) and was run in parallel with the Groupe Oncologie Radiothérapie Tête et Cou (GORTEC) 2007-02 randomized trial studying induction CT in patients with bulky nodal spread.

The inclusion criteria were age $\leq$ 70 years; Karnofsky performance score of 80 to 100; and diagnosis of nonmetastatic, nonoperated stage III or IV SCC of the oral cavity, oropharynx, hypopharynx, or larynx. Immunostaining for p16 was centrally performed and considered positive when diffuse, strong, and homogeneous nuclear and cytoplasmic staining was present in $\geq$ 70% of the cells. Patients had to have adequate liver, renal (creatinine clearance $\geq$ 50 mL/min), and cardiac functions and adequate hematologic blood counts, allowing the administration of high-dose FU and carboplatin.

Random Assignment and Masking

Random assignment to either cetux-RT or CT plus cetux-RT (CT-cetux-RT) was done by minimization[15] on centers, T stage (T0-2 *v* T3-4), and N stage (N0 *v* N1-2). To avoid deterministic minimization and assure allocation concealment, the treatment that minimizes the imbalance was assigned a probability of $P = .80$ (ie, < 1.0). Random assignment was done centrally using the software TENAlea (Netherlands Cancer Institute, Amsterdam, the Netherlands). The minimization parameters were implemented by the Biostatistics Department of Institut Gustave-Roussy (Villejuif, France).

Procedures

The addition of cetuximab to RT was similar in both arms, with a loading dose of 400 mg/m^2 at day 7 followed by a weekly dose of 250 mg/m^2 during RT. RT was prescribed at 70 Gy, 2 Gy per fraction, 5 days a week, and intensity-modulated RT was recommended. Doses of 70 and 50 Gy were prescribed to the definitive and prophylactic planning target volumes, respectively. Concurrent CT consisted of three cycles of carboplatin 70 mg/m^2/d on days 1 to 4 and FU 600 mg/m^2/d on days 1 to 4 with continuous infusions.[7]

The initial workup included a medical history, clinical examination, blood tests, head and neck computed tomography scan and/or magnetic resonance imaging, chest computed tomography, and endoscopic examination under general anesthesia. After the completion of treatment, patients were assessed at 3 months with clinical examination and imaging (computed tomography scanning with or without magnetic resonance imaging) and then every 3 months for 2 years and then every 6 months thereafter.

Outcomes

The primary end point was progression-free survival (PFS), which was defined as the time from random assignment to first disease progression (locoregional or distant) or death from any cause. Patients who did not have any of these events were censored at the date of last follow-up contact. A second cancer was not considered as progression.

Secondary end points were toxicity, overall survival (OS), and cumulative incidence of locoregional failure, distant failure, and death without earlier locoregional or distant progression. OS was defined as the time from random assignment to death from any cause. Locoregional failure and distant failure were defined as date of random assignment to failure as first event. National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 were used for toxicity evaluation.

Statistical Analysis

The PFS estimate was based on previous experiences of our cooperative group and especially on the most recent study that included a subgroup of comparable patients (mainly smokers with stage N0-2b disease in the GORTEC 99-02 trial).[9] The estimation of the number of required events was based on the time-to-event end point (PFS) with exponential survival function. To detect a hazard ratio (HR) of 0.64 (this HR value corresponds to an increase in 3-year PFS from 45% to 60%), 180 events in 406 patients are required, with a 85% power, assuming a two-sided type I error of $\alpha = .05$. No interim analysis for efficacy was planned.

PFS and OS were estimated using the Kaplan-Meier method, and the 95% CIs of yearly rates were estimated according to the Rothman method.[16] The PFS analysis was done according to the intent-to-treat principle, and the primary comparison between the two treatment groups was done using the Cox model adjusted for the minimization factors (T stage [two categories: T0-2 *v* T3-4], N stage [two categories: N0 *v* N1-2], and centers [six categories: one for each site that included $\geq$ 30 patients, one category for all sites that included $>$ 10 patients and $<$ 30 patients, and one for sites that included $\leq$ 10 patients]). Presented HR was adjusted for these factors. The same analysis was done for OS. *P* values of unadjusted log-rank tests are also presented.

To estimate the contribution of local progression, distant progression, and death without earlier locoregional or distant progression to PFS, the cumulative incidences of these three types of events were calculated within the competing risks framework.[17] Cumulative incidences were estimated using the method proposed by Koscielny and Thames.[18] Median follow-up was estimated using the reverse Kaplan-Meier method.

To test whether there was any evidence that treatment effect difference could differ according to p16 status, the interaction between treatment effect and patient subgroups was tested (p16 positive *v* p16 negative) in a Cox model containing treatment arm, p16 status, and treatment type $\times$ p16 status interaction and minimization factors. The

P value of the Wald test of the treatment × p16 status interaction is presented.

The rates of complete response, adverse events, early death, hospitalization for toxicity, and feeding tube use were compared between the two arms using the χ^2 test or Fisher's exact test according to the numbers. Analyses were done using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient and Tumor Characteristics

Between January 2008 and March 2014, 406 patients were randomly assigned, with 204 assigned to the CT-cetux-RT arm and 202 assigned to the cetux-RT arm. All patients had a biopsy-proven SCC of the oral cavity, oropharynx, hypopharynx, or larynx. Six patients were not eligible, including three with T2N0 disease, two with N2c nodal disease, and one with a concomitant lung cancer (Fig 1). According to the intent-to-treat principle, these patients were included in the analyses. The distribution of patients according to sex, age, performance status, tumor site, and nodal and tumor stage was well balanced between the two arms (Table 1). The majority of patients had T2-3 tumors (70% and 69% in the CT-cetux-RT and cetux-RT arms, respectively), and the rate of N0 disease was 34% in both arms. More than 60% of patients in both arms had an oropharyngeal carcinoma (OPC), and a majority of patients were p16 negative (79% in both arms). The flowchart of the study is shown in Figure 1.

Compliance to Treatment

Intensity-modulated RT was administered to 39% of patients in the CT-cetux-RT arm and 42% in the cetux-RT arm, with the rest of the patients receiving three-dimensional conformal RT. Regarding compliance to RT, 88% of patients in the CT-cetux-RT arm and 90% in the cetux-RT arm received 35 fractions, with a mean overall treatment time of 51.8 days and 52 days, respectively. In the CT-cetux-RT and cetux-RT arms, the rates of temporary RT interruption ≥ 7 days were 15% and 14%, respectively; the rates of temporary RT interruption ≥ 14 days were 3% and 2.5%, respectively; and the rates of discontinuation of RT were 4% and 3%, respectively. To ensure that there was no imbalance of RT quality between the two arms, the RT records of the first three patients of each center were analyzed and then one third of other enrolled patients per center were also reviewed. Total RT doses, planning target volume for 70 Gy coverage, dose to organs at risk such as spinal cord and brainstem, dose per fraction, overall treatment time, and adequate verification imaging were reviewed by the GORTEC RT quality assurance experts. No difference in any of these items was found between the arms.

The proportion of patients who could receive at least seven injections of cetuximab was 85% in the cetux-RT arm and 73% in the CT-cetux-RT arm ($P = .003$). In the CT-cetux-RT arm, 73% of patients received three cycles of CT as planned. Among the patients who received cycles 1, 2, and 3, 97%, 95%, and 86%, respectively, received 95% to 100% of the theoretical dose.

Adverse Events

The incidence of grade 3 or 4 adverse events was not different between the two arms (91% in each arm; Table 2). However, there were more early deaths (during the treatment and 30 days after its completion) in the CT-cetux-RT arm than in the cetux-RT arm (10 *v* three deaths, respectively; $P = .052$). After removing the early deaths related to cancer progression, the numbers of early deaths were six (3%) and two (1%) in the CT-cetux-RT and cetux-RT arms, respectively ($P = .28$). In addition, in the CT-cetux-RT arm versus the cetux-RT arm, the use of a feeding tube was more frequent (67% *v* 54%, respectively; $P = .01$) and more hospitalizations occurred during treatment (42% *v* 22%, respectively; $P < .001$; Table 2).

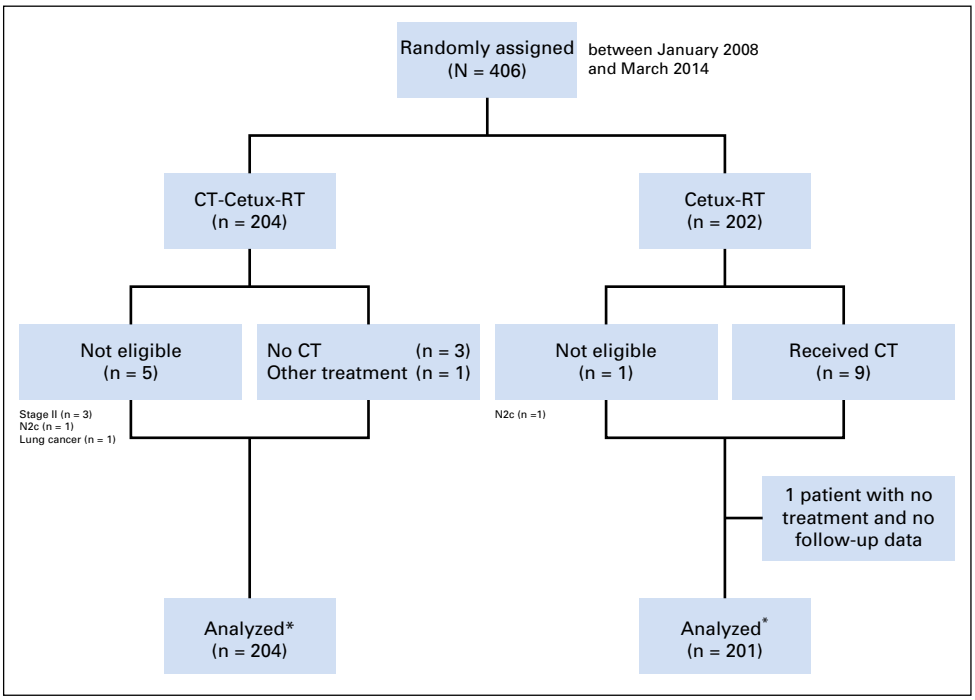

Fig 1. Patient flowchart. Cetux, cetuximab; CT, chemotherapy; RT, radiotherapy. (*) Performed as intent-to-treat analysis (only one patient without any treatment data was excluded).

Table 1. Initial Patient and Tumor Characteristics

Characteristic	CT-Cetux-RT	Cetux-RT	All
Sex, No. (%)			
Male	170 (83)	172 (85)	342 (84)
Female	34 (17)	30 (15)	64 (16)
Mean age, years (range)	57 (36-70)	57 (42-70)	57 (36-70)
Karnofsky performance score, No. (%)			
90-100	166 (81)	162 (80)	328 (81)
80	38 (19)	40 (20)	78 (19)
T stage, No. (%)			
T0-2	44 (21)	43 (21)	87 (21)
T3	99 (49)	97 (48)	196 (28)
T4	61 (29)	62 (30)	123 (30)
N stage, No. (%)			
N0	69 (34)	68 (34)	1237 (34)
N1-2a	91 (45)	92 (46)	183 (45)
N2b (nonpalpable)	43 (21)	41 (20)	84 (21)
N2c	1	1	2
Initial location, No. (%)			
Oropharynx	141 (69)	124 (61)	265 (65)
Oral cavity	24 (12)	23 (11)	47 (12)
Hypopharynx	27 (13)	33 (16)	60 (15)
Larynx	12 (6)	21 (10)	33 (8)
Only nodes	0	1	1

Abbreviations: Cetux, cetuximab; CT, chemotherapy; RT, radiotherapy.

There were more instances of grade ≥ 3 mucositis during treatment in the CT-cetux-RT arm (73% *v* 61% in the cetux-RT arm; $P = .014$) and also more liver enzyme elevations in the CT-cetux-RT arm (33% *v* 18% in the cetux-RT arm; $P < .005$), but these were mostly grade 1 (23% *v* 13% in the cetux-RT arm). With the exception of leukopenia (10% for grade 3 and 2% for grade 4 in the CT-cetux-RT arm), the other types of toxicity were not different between the two arms, including skin toxicity (Table 2).

Oncologic Results

The median follow-up time was 4.4 years for the CT-cetux-RT arm (interquartile range, 3.1 to 5.2 years) and 4.6 years for the cetux-RT arm (interquartile range, 3.4 to 5.2 years). Two hundred eleven deaths and 245 PFS events occurred (Table 3). At 3 years, the PFS rate was 52.3% (95% CI, 45% to 59%) in the CT-cetux-RT arm and 40.5% (95% CI, 34% to 48%) in the cetux-RT arm. The adjusted HR was 0.73 (95% CI, 0.57 to 0.94; $P = .015$) in favor of the CT-cetux-RT arm. The unadjusted log-rank test for PFS demonstrated $P = .017$. The median PFS was 37.9 months (95% CI, 26.1 to 51.6 months) in CT-cetux-RT arm and 22.4 months (95% CI, 14.2 to 30.6 months) in the cetux-RT arm. Similarly, the cumulative incidence of locoregional failure was 21.6% in the CT-cetux-RT arm compared with 38.8% in the cetux-RT arm (HR, 0.54; 95% CI, 0.38 to 0.76; $P < .001$; Figs 2A and 3A). The OS rate at 3 years was improved in the CT-cetux-RT arm compared with cetux-RT arm, but the difference was not statistically different (60.8% [95% CI, 54% to 67%] *v* 54.9% [95% CI, 48% to 62%], respectively; HR, 0.80 [95% CI, 0.61 to 1.05]; $P = .11$; Fig 2B). The unadjusted log-rank test for OS demonstrated $P = .13$. The median OS was 53.4 months (95% CI, 42.5 months to not reached) in the CT-cetux-RT arm and 44.5 months (95% CI, 34.5 to 52.5 months) in the cetux-RT arm. No difference was observed between the two arms regarding the rate of distant metastases, considered as a first event (HR, 1.19; 95% CI, 0.72 to 1.97; $P = .50$; Fig 3B), and also regarding the cumulative incidence of deaths without cancer progression (HR, 1.11; 95% CI, 0.64 to 1.95; $P = .71$; Fig 3C).

Oncologic Results by p16 Status

p16 status was assessable by immunohistochemistry in 236 patients with OPC (89%; 121 patients in the CT-cetux-RT arm and 115 patients in the cetux-RT arm). p16-positive immunostaining was found in 21% of the tumors in each arm. Of the 49 patients exhibiting p16-positive tumors, the majority (29 patients, 59%) were smokers, with no difference between the two arms. A significant improvement in PFS was found in patients with p16-positive compared with p16-negative OPC ($P < .001$). The addition of concurrent CT to cetux-RT markedly improved PFS and LRC in patients with OPC regardless of their p16 status. Indeed, a significantly improved PFS was observed in favor of the CT-cetux-RT arm in patients with p16-negative OPC (HR, 0.63; 95% CI, 0.44 to 0.91) as well as in those with p16-positive OPC (HR, 0.23; 95% CI, 0.07 to 0.73), and the interaction between p16 status and treatment modality was not significant ($P = .13$). For LRC, a similar benefit was found for both p16-negative and p16-positive OPC favoring the CT-cetux-RT arm, with HRs of 0.33 (95% CI, 0.19 to 0.56) and 0.16 (95% CI, 0.02 to 1.36), respectively.

DISCUSSION

This phase III randomized trial was restricted to patients with limited nodal spread and run in parallel with the GORTEC 2007-02

Table 2. Adverse Events During Treatment

	No. of Patients (%)					
	CT-Cetux-RT			Cetux-RT		
Adverse Event	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Radiodermatitis	194 (97)	108 (54)	18 (9)	190 (96)	107 (54)	10 (5)
Skin reaction outside RT field	24 (12)	8 (4)	0 (0)	25 (13)	8 (4)	0 (0)
Mucositis	198 (99)	128 (64)	17 (9)	188 (97)	113 (58)	5 (3)
WBC count	94 (47)	20 (10)	4 (2)	0 (0)	0 (0)	0 (0)
Renal function	11 (6)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Liver enzyme increase	66 (33)	9 (4)	0 (0)	35 (18)	3 (1)	0 (0)

Abbreviations: Cetux, cetuximab; CT, chemotherapy; RT, radiotherapy.

Table 3. Events

Event	CT-Cetux-RT	Cetux-RT	All
Death	97	114	211
Progression or death (PFS)	112	133	245
Type of first event in PFS			
Locoregional progression	51	82	133
Distant progression (with or without locoregional progression)	34	28	62
Death as first event	27	23	50

Abbreviations: Cetux, cetuximab; CT, chemotherapy; PFS, progression-free survival; RT, radiotherapy.

trial that was restricted to patients with bulky cervical nodes. In addition to limited nodal spread, the majority of our patients (more than two thirds) had T2-3 tumors, and it was not known what the benefit would be of adding CT to the SOC cetux-RT regimen in this particular selection of patients with intermediate risk. The primary end point was met with a significant improvement of PFS with intensified treatment. However, the observed HR for the 3-year PFS of 0.73 was higher than the HR of 0.64 originally targeted in the protocol. This HR corresponds to a difference in PFS at 3 years of 11.8% (from 40.5% to 52.3%), instead of the 15% initially targeted (from 45% to 60%). This is a result of a greater than expected event rate along with an accrual period longer than planned, and this could minimize the clinical significance of the observed benefit. A major benefit was also observed for LRC, along with a nonsignificant benefit in survival (Fig 2B). The intensified treatment was feasible, although it seemed to be clearly more toxic than cetux-RT alone. Indeed, there was more treatment-related death, more mucositis, more liver and hematologic toxicity, more use of feeding tubes, and more hospitalizations during treatment. All these adverse effects can be expected with the addition of concurrent high-dose CT, and the magnitude of the benefit has to be put in perspective with this increased toxicity.

In contrast with our study, another trial studying treatment intensification by adding cetuximab to CRT failed to show an improvement in the outcome of patients with LA-SCCHN[11] (Radiation Therapy Oncology Group [RTOG] 0522). This trial showed that treatment intensification did not improve outcomes and was more toxic.[11] However, this study had some differences when compared with our study that make cross-study comparisons difficult or perhaps inappropriate. Indeed, our SOC was cetux-RT and not cisplatin-RT, as in the RTOG 0522 study.[11] The RTOG study also used altered fractionated RT, whereas we used once-daily fractionated RT. However, a retrospective review of the trial by Bonner et al,[14] in which cetuximab-RT was superior to RT, showed more benefit of cetuximab with altered fractionated RT compared with once-daily RT. Our choice of the cetux-RT as reference treatment could be debated, but it is a category 1 recommendation according to the National Comprehensive Cancer Network[8] that is not inappropriate for patients mostly with T2-3 disease and all with limited nodal spread. However, an important question that will not be answered by our trial is whether similar benefit could be obtained without cetuximab in the CT-cetux-RT arm. A direct comparison of CRT to cetux-RT has been conducted by the RTOG in patients with HPV-positive LA-SCCHN, but the results are not yet available. Another difference with the RTOG 0522 trial was the use of carboplatin plus FU instead of cisplatin concurrent with RT. Carboplatin plus FU concurrent with RT is also recommended as a category 1 SOC in LA-SCCHN and has been previously validated in several randomized trials.[6,8-10] It cannot be ruled out that a potential synergy of FU with cetuximab could contribute differently to the observed outcome, as compared with cetuximab and cisplatin. Indeed, the combination of FU and cetuximab can be synergistic in experimental models[19-21] and has also been successful in clinical trials.[22,23] Finally, there was another difference with the RTOG 0522 trial,[11] which was the much higher rate of p16-positive OPC in the RTOG trial, whereas our trial included mostly tobacco- and alcohol-related cancers. In addition, most of our patients with p16-positive OPC were smokers. This is in agreement with the current scenario of OPC in North America with a high proportion of p16-positive cancers,[24,25] but is also in agreement with some recent European data showing an approximate 20% rate of p16-positive tumors in Spanish patients with OPC[3] but also with data from the United Kingdom showing no relative increase in p16 positivity.[26] These differences in p16 status suggest that the comparison between our trial and the RTOG 0522 trial is complicated, although this is mitigated by the fact that the benefit favoring the treatment intensification was observed in our study regardless of p16 status.

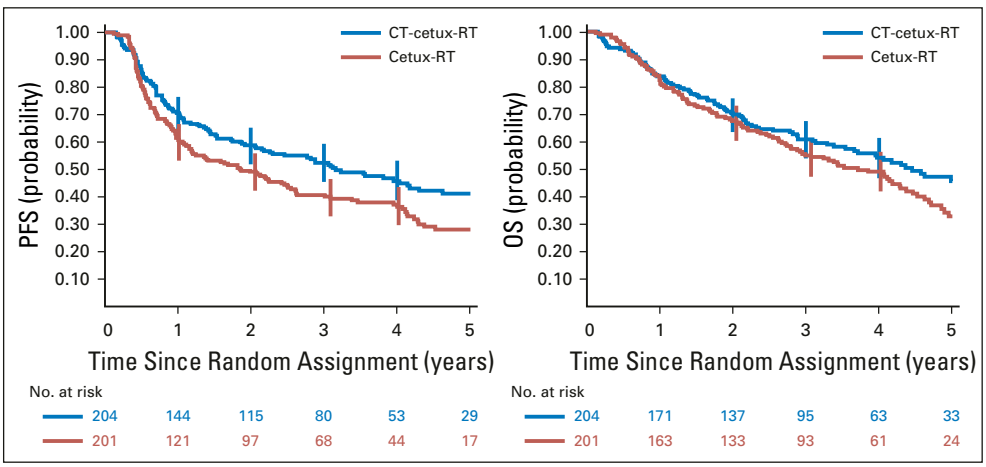

Fig 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS). Vertical bars denote 95% CIs of the PFS and OS rates. Cetux, cetuximab; CT, chemotherapy; RT, radiotherapy.

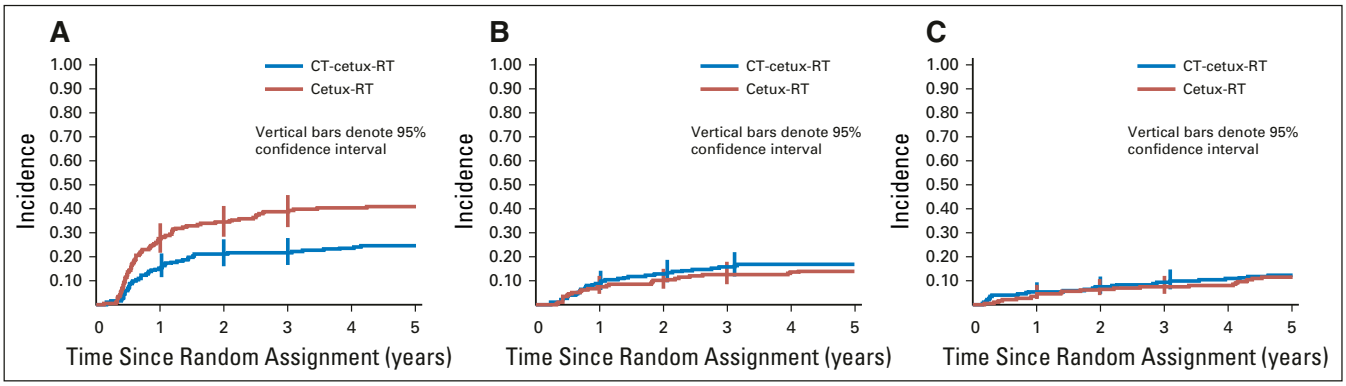

Fig 3. Cumulative incidence of (A) locoregional progression, (B) distant progression, and (C) death without earlier locoregional or distant progression. Vertical bars denote 95% CI. Cetux, cetuximab; CT, chemotherapy; RT, radiotherapy.

Finally, Considering the current SOC in LA-SCCHN, this trial answers an important scientific question, but it could have a limited clinical impact, essentially for patients not eligible for high-dose cisplatin (impaired renal or hearing functions) and for whom carboplatin plus FU combined with cetux-RT can still be used. In conclusion, the addition of concurrent carboplatin and FU to cetux-RT improved PFS and LRC in patients with intermediate-risk LA-SCCHN.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Merck Serono (France), an affiliate of Merck KGaA (Darmstadt, Germany).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improved Outcome by Adding Concurrent Chemotherapy to Cetuximab and Radiotherapy for Locally Advanced Head and Neck Carcinomas: Results of the GORTEC 2007-01 Phase III Randomized Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Acknowledgment

We thank Sarah Jorge-Lourenco for her help in preparing the article.

Appendix

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