Original Article

A Randomized Phase 3 Trial Comparing Nimotuzumab Plus Cisplatin Chemoradiotherapy Versus Cisplatin Chemoradiotherapy Alone in Locally Advanced Head and Neck Cancer

Vijay Maruti Patil, MD[1]; Vanita Noronha, MD[1]; Amit Joshi, MD[1]; Jaiprakash Agarwal, MD[2]; Sarbani Ghosh-Laskar, MD [2]; Ashwini Budrukkar, MD[2]; Vedang Murthy, MD[2]; Tejpal Gupta, MD [2]; Manoj Mahimkar, MD[3]; Shashikant Juvekar, MD[4]; Supreeta Arya, MD[4]; Abhishek Mahajan, MD[4]; Archi Agarwal, MD[5]; Nilendu Purandare, MD[5]; Venkatesh Rangarajan, MD[5]; Arun Balaji, MASLP[6]; Sameer Vasant Chaudhari, MD[7]; Shripad Banavali, MD[1]; Sadhana Kannan, MD[8]; Atanu Bhattacharjee, PhD[9]; Anil K. D'Cruz, MS[10]; Pankaj Chaturvedi, MS [10]; Prathamesh S. Pai, MS[10]; Devendra Chaukar, MS[10]; Gouri Pantvaidya, MS[10]; Deepa Nair, MS[10]; Sudhir Nair, MS[10]; Anuja Deshmukh, MS[10]; Shivakumar Thiagarajan, MS[10]; Vijayalakshmi Mathrudev, MBA[1]; Aparna Manjrekar, PGDCR[1]; Sachin Dhumal, MSc[1]; Kamesh Maske, PGDCR[1]; Arti Sanjay Bhelekar, MSc[1]; Kavita Nawale, MBA[1]; Arun Chandrasekharan, MD[1]; Nikhil Pande, MD[1]; Alok Goel, MD[1]; Vikas Talreja, MD[1]; Vijai Simha, MD[1]; Sujay Srinivas, MD[1]; Rohit Swami, MD[1]; Dilip Harindran Vallathol, MD[1]; Hollis Dsouza, MD[1]; Sameer Shrirangwar, MD[1]; Siddharth Turkar, MD[1]; George Abraham, MD[1]; Aditi Harsh Thanky, MD[1]; Usha Patel, MSc[3]; Manish Kumar Pandey, MSc[3]; and Kumar Prabhash, MD [1]

BACKGROUND: Because the addition of nimotuzumab to chemoradiation in patients with locally advanced head and neck cancer improved outcomes in a phase 2 study, the authors conducted a phase 3 study to confirm these findings. **METHODS:** This open-label, investigator-initiated, phase 3, randomized trial was conducted from 2012 to 2018. Adult patients with locally advanced head and neck cancer who were fit for radical chemoradiation were randomized 1:1 to receive either radical radiotherapy (66-70 grays) with concurrent weekly cisplatin (30 mg/m^2) (CRT) or the same schedule of CRT with weekly nimotuzumab (200 mg) (NCRT). The primary endpoint was progression-free survival (PFS); key secondary endpoints were disease-free survival (DFS), duration of locoregional control (LRC), and overall survival (OS). An intent-to-treat analysis also was performed. **RESULTS:** In total, 536 patients were allocated equally to both treatment arms. The median follow-up was 39.13 months. The addition of nimotuzumab improved PFS (hazard ratio [HR], 0.69; 95% CI, 0.53-0.89; $P = .004$), LRC (HR, 0.67; 95% CI, 0.50-0.89; $P = .006$), and DFS (HR, 0.71; 95% CI, 0.55-0.92; $P = .008$) and had a trend toward improved OS (HR, 0.84; 95% CI, 0.65-1.08; $P = .163$). Grade 3 through 5 adverse events were similar between the 2 arms, except for a higher incidence of mucositis in the NCRT arm (66.7% vs 55.8%; $P = .01$). **CONCLUSIONS:** The addition of nimotuzumab to concurrent weekly CRT improves PFS, LRC, and DFS. This combination provides a novel alternative therapeutic option to a 3-weekly schedule of 100 mg/m^2 cisplatin in patients with locally advanced head and neck cancer who are treated with radical-intent CRT. ***Cancer* 2019;125:3184-3197**. © *2019 American Cancer Society*.

KEYWORDS: Chemoradiation, epidermal growth factor receptor (EGFR), head and neck cancer, nimotuzumab.

INTRODUCTION

Locally advanced head and neck squamous cell carcinoma (LAHNSCC) is treated using a multimodality approach.[1,2] Radical chemoradiation is the nonsurgical approach of choice and is associated with improved survival and better organ-preservation rates compared with radical radiation.[3-5] However, the outcomes with radical chemoradiation

Corresponding author: Kumar Prabhash, MD, Department of Medical Oncology, Tata Memorial Hospital, 1108, 11th Floor, HBB, Parel, Mumbai, India 400012; kumarprabhashtmh@gmail.com

[1]Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute (HBNI), Mumbai, India; [2]Department of Radiation Oncology, Tata Memorial Hospital, HBNI, Mumbai, India; [3]Mahimkar Laboratory, Advanced Center for Treatment, Research, and Education in Cancer, Navi Mumbai, India; [4]Department of Radiology, Tata Memorial Hospital, HBNI, Mumbai, India; [5]Department of Nuclear Medicine, Tata Memorial Hospital, HBNI, Mumbai, India; [6]Department of Speech and Therapy, Tata Memorial Hospital, HBNI, Mumbai, India; [7]Biocon Ltd, Bengaluru, India; [8]Department of Biostatistics, Advanced Center for Treatment, Research, and Education in Cancer, Navi Mumbai, India; [9]Department of Epidemiology, Advanced Center for Treatment, Research, and Education in Cancer, Navi Mumbai, India; [10]Department of Head and Neck Surgery, Tata Memorial Hospital, HBNI, Mumbai, India.

The first two authors contributed equally to this article.

This study was presented in part at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; June 1-5, 2018; Chicago, Illinois.

We thank Biocon Ltd and the Tata Memorial Center Research Administration Council for funding this study.

The funding agency had no role in the design or conduct of the study, the collection, management, analysis, or interpretation of the data, the preparation, review, or approval of the article, or the decision to submit the article for publication.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32179, **Received:** January 20, 2019; **Revised:** March 2, 2019; **Accepted:** March 22, 2019, **Published online** May 31, 2019 in Wiley Online Library (wileyonlinelibrary.com)

are modest, with a 3-year overall survival (OS) rate of approximately 50%.[6] Efforts to improve these outcomes have included the use of neoadjuvant chemotherapy,[7] altered fractionation radiation schedules,[8] adding a second chemosensitizer,[3] or adding epidermal growth factor receptor (EGFR)-targeted antibodies[9,10] and have met with limited success.

Among EGFR-targeting antibodies, nimotuzumab (h-R3) is a humanized immunoglobulin G1 isotype monoclonal antibody directed against the extracellular domain of EGFR.[11,12] A phase 2 randomized study in LAHNSCC showed that nimotuzumab plus cisplatin chemoradiation led to better response rate and progression-free survival (PFS) compared with cisplatin chemoradiation alone.[13] On the basis of these results (which were unpublished at that time), we conducted a phase 3 randomized study comparing outcomes between patients who received nimotuzumab plus radical chemoradiation and those who received radical chemoradiation alone.

MATERIALS AND METHODS

Trial Design, Setting, and Conduct

This was an open-label, investigator-initiated study conducted at Tata Memorial Center (TMC), Mumbai, India. Adult patients with newly diagnosed, treatment-naive, nonmetastatic, stage III or IV LAHNSCC arising in the oropharynx, larynx, hypopharynx, or oral cavity were eligible. The other eligibility criteria were a Karnofsky performance status ≥70 and adequate hematologic, renal, and hepatic function. Patients with tumors originating in the nasopharynx, salivary gland, or nasal cavity and those who had received immunotherapy or prior radiotherapy to the head and neck region were excluded. The study protocol was approved by the Institutional Ethics Committee and was registered with the Clinical Trial Registry of India (trial registration identifier CTRI/2014/09/004980). It was conducted according to the Declaration of Helsinki and good clinical practice guidelines, and it was monitored by the TMC Data Safety and Monitoring Committee.

Study Procedures

Before randomization, patients underwent a comprehensive head and neck examination, blood tests (complete hemogram, renal function, and liver function), imaging of the head and neck region (either contrast-enhanced computed tomography or magnetic resonance imaging), chest radiogram, electrocardiogram, and pure tone audiometry. Patients were staged according to the American Joint Committee on Cancer-Union for International Cancer Control staging system (seventh edition). Patients with a lymph node status ≥N2 underwent whole-body positron emission tomography-computed tomography to rule out distant metastasis. Human papillomavirus (HPV) status was examined in the tissue biopsy using immunohistochemistry for p16.[14] All patients had nutritional, speech, swallowing, and dental assessments, and deficiencies noted were managed accordingly. Stratified block, central randomization for 5 factors was performed by an independent statistician, and patients were randomized 1:1 to either the cisplatin-radiation arm (CRT) or the nimotuzumab plus cisplatin-radiation arm (NCRT). These factors were site of malignancy (oropharynx vs others), stage (stage III vs IV), age (≤60 vs >60 years), radiation technique (conventional vs others), and treatment center.

High-dose, curative radiotherapy was administered in both arms over 6.5 to 7 weeks. Irradiation was planned using a standard 2-dimensional technique, a 3-dimensional conformal technique, or intensity-modulated radiotherapy with megavoltage radiation. Gross tumor and lymph node disease received 70 grays (Gy), in 2 Gy per fraction, 5 days per week. Uninvolved nodal regions of the neck were treated to a dose of 46 to 50 Gy. Other altered fractionation schedules were permitted if the biologic equivalent dose for tumor control was similar to 70 Gy at 2 Gy per fraction. Quality assurance was done before commencement and during radiation treatment; plans and doses were cross-checked and confirmed by the radiation oncology study members (for protocol, see supporting information [Clinical Therapy Protocol, Appendix IV]).

In both arms, cisplatin was dosed at 30 mg/m^2 weekly during radiation along with supportive medication. Nimotuzumab was administered weekly in the NCRT arm intravenously as a 200-mg flat dose in 250 mL normal saline over 60 minutes without premedication. Patients underwent a comprehensive clinical examination and positron emission tomography-computed tomography 8 weeks after the completion of chemoradiation. If residual or recurrent disease was resectable, these patients were offered surgical resection. Wherever feasible, residual, progressive, or recurrent disease was pathologically confirmed. Patients who were not willing to undergo surgery or who had unresectable disease were offered palliative chemotherapy.

Study Endpoints

PFS was the primary outcome and was defined as duration from the date of randomization to the date of progression (according to Response Evaluation Criteria in Solid

Tumors [RECIST], version 1.1[15]). Secondary outcomes were locoregional control (LRC), disease-free survival (DFS), OS, treatment compliance, adverse events, and quality of life. Duration of LRC was defined as the time between the date of randomization and the date of locoregional failure. DFS was defined as the period after treatment completion when the patient experienced complete remission. For patients who achieved complete remission after therapy, DFS was calculated from the date of response assessment to the date of recurrence (either locoregional or distant). For patients with residual disease who underwent salvage surgery, DFS was calculated from date of salvage surgery to the date of recurrence. In all other patients, DFS was considered zero. OS was calculated as the time from the date of randomization to the date of death. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Sample Size

A 2-year PFS rate of 60% in the CRT arm was assumed.[16,17] With an α of 5%, power of 80%, and a dropout rate of 10%, we required 536 patients in the study to demonstrate an absolute increase in PFS by 12%. An interim analysis without an α spending function for monitoring early efficacy was planned after 4 years. However, it was never performed because the study recruited slowly.

Statistical Methods

The statistical software packages R (version 3.1.2; R Foundation for Statistical Computing) and SPSS (version 20; SPSS Inc) were used for analysis. Outcomes were analyzed using the intention-to-treat method. Median follow-up was calculated using the reverse Kaplan-Meier method. Descriptive statistics were performed for baseline characteristics, treatment compliance, locoregional response, and adverse events. These were compared between the 2 groups using either the chi-square test or the Fisher test. PFS, DFS, LRC, and OS were estimated using the Kaplan-Meier method. The Brookmeyer and Crowley method was used for the construction of 95% CIs, and time-to-event curves were compared using the log rank test. A Cox proportional hazard model with the Efron method of tie handling was used for calculating the hazard rate with 95% CIs. The proportional hazard model assumptions were checked using Schoenfeld residuals. A P value $\leq .05$ was considered as significant.

A post hoc sensitivity analysis was performed using 2 methods. The first method was a competing risk analysis for PFS, DFS, and LRC, and the second method was a repeat analysis using a composite endpoint (inclusive of death) for PFS (progression or death), LRC (locoregional progression or death), and DFS (progression or death) to confirm the robustness of the results. A multivariate analysis was performed for PFS, DFS, LRC, and OS with known prognostic factors (age, site of malignancy, stage, Eastern Cooperative Oncology Group performance status, and radiation technique) using Cox regression analysis. Because HPV status is an important prognostic factor in oropharyngeal cancers, we performed a post hoc subgroup analysis to address the effect of the interaction between nimotuzumab and HPV status on outcomes.

RESULTS

Baseline Characteristics

Between 2012 and 2018, 536 patients were randomized equally between both arms (268 in each). The median duration of follow-up was 39.13 months (39.5 months in the CRT arm vs 39.0 months in the NCRT arm). The Consolidated Standards for Reporting Trials flow diagram in Figure 1 provides the details of enrollment, allocation of intervention, follow-up, and data analysis. Baseline patient and tumor characteristics were balanced between the arms (Table 1).

Adverse Events

All adverse events occurred with similar frequency in the 2 arms except mucositis and thrombocytopenia (Table 2). Hospitalization because of toxicities was higher in the NCRT arm (58 patients; 21.6%) versus the CRT arm (41 patients; 15.3%; $P = .058$). Nasogastric tubes were placed in 97 patients (36.2%) in CRT arm versus 102 patients (38.1%) in the NCRT arm ($P = .655$).

Treatment

The details of radiation and chemotherapy compliance are shown in Table 3. A cumulative cisplatin dose $\geq$200 mg/m^2 was administered to 211 patients (78.7%) in the CRT arm and to 208 patients (77.6%) in the NCRT arm ($P = .754$).

Outcomes

Progression-free survival

Two hundred thirty-five patients experienced disease progression, including 134 in the CRT arm and 101 in the NCRT arm. The sites of progression in the CRT arm were locoregional in 105 patients (39.2%), distant in 24 patients (9%), and both in 5 patients (1.9%). The

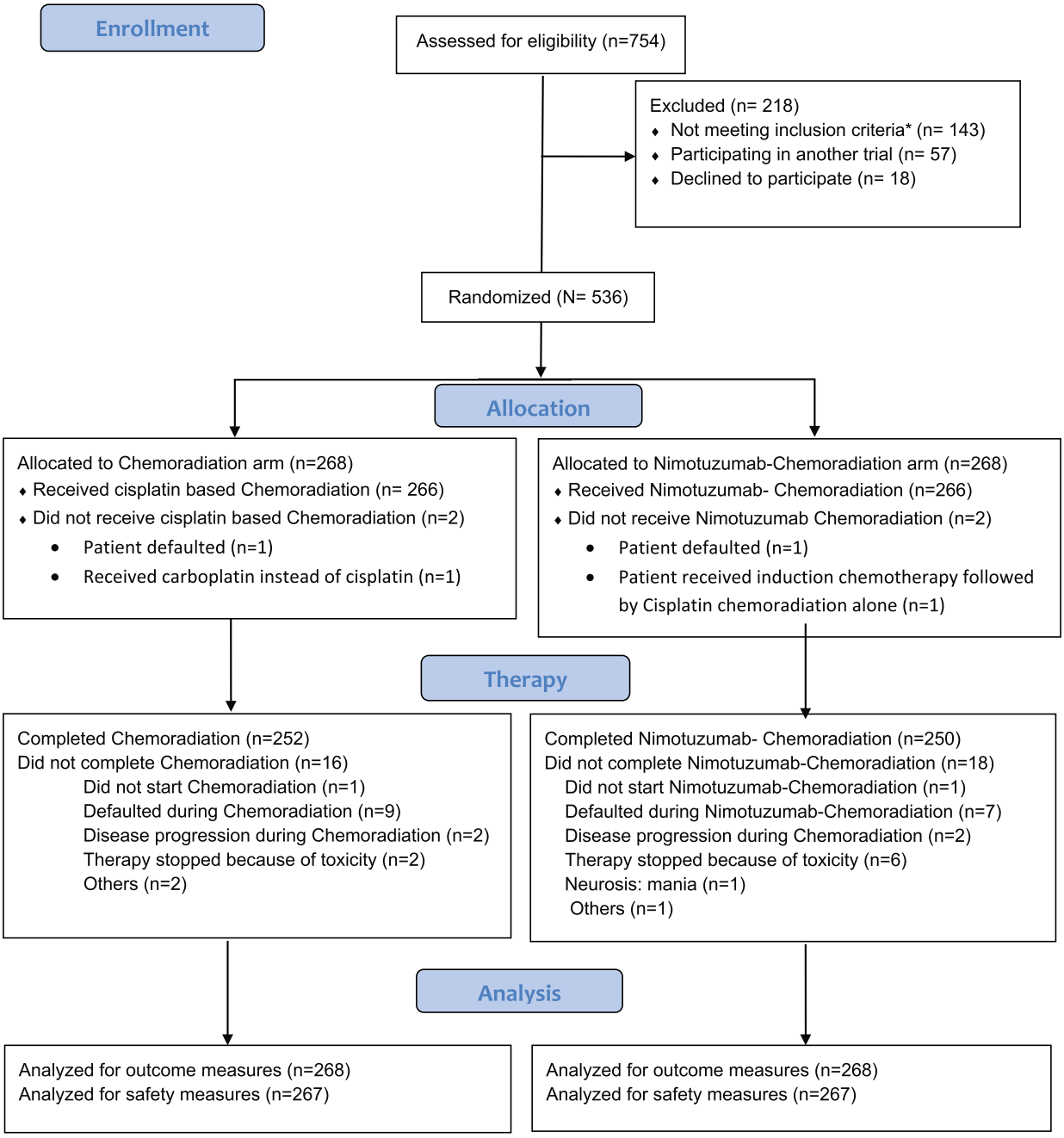

Figure 1. This is a Consolidated Standards for Reporting Trials (CONSORT) diagram of the nimotuzumab plus cisplatin-radiation versus cisplatin-radiation trial showing the flow of patients from enrollment, allocation of intervention, follow-up, and data analysis. (*) Reasons included prior chemotherapy administered (n = 74), prior radiation administered (n = 26), renal dysfunction (n = 16), failed audiometry (n = 4), extensive or metastatic disease (n = 10), recurrent disease (n = 3), second primary (n = 3), poor performance status (n = 4) and comorbidities (n = 3).

corresponding sites of progression in the NCRT arm were locoregional in 70 patients (26.1%), distant in 20 patients (7.5%), and both in 11 patients (4.1%).

The PFS was significantly longer for patients who received NCRT (hazard ratio, 0.69; 95% CI, 0.53-0.89; $P = .004$) (Fig. 2). The 2-year PFS was 50.1% (95% CI, 43.7-56.2) in the CRT arm and 61.8% (95% CI, 55.2-67.7) in the NCRT arm. The addition of nimotuzumab led to a consistent benefit across all subgroups (Fig. 2). The results of the sensitivity analysis using competing risk analysis ($P = .003$; Gray test) and the composite endpoint of progression or death (hazard ratio,

TABLE 1. Baseline Characteristics

Variable	No. of Patients (%)		P
	CRT Arm, n = 268	NCRT Arm, n = 268	
Age, y			
Median [range]	54 [26-77]	55 [20-73]	
<60	191 (71.3)	186 (69.4)	
≥60	77 (28.7)	82 (30.6)	.636[a]
Sex			
Men	231 (86.2)	226 (84.3)	.542
Women	37 (13.8)	42 (15.7)	
ECOG PS			
0-1	267 (99.6)	267 (99.6)	1.00
2	1 (0.4)	1 (0.4)	
Substance use			
Smokeless tobacco	121 (45.2)	120 (44.8)	1.00
Tobacco smoke, beedi	138 (51.5)	133 (49.6)	.729
Tobacco smoke, cigarette	54 (20.2)	49 (18.3)	.661
Alcohol	72 (26.9)	60 (22.4)	.270
Site of malignancy			
Oropharynx	135 (50.4)	134 (50)	.119
Hypopharynx	47 (17.5)	62 (23.1)	
Larynx	83 (31)	72 (26.9)	
Oral cavity	3 (1.1)	0 (0.0)	
Tumor classification[b]			
T1-T2	56 (20.9)	41 (15.3)	.113
T3-T4	212 (79.1)	227 (84.7)	
Lymph node category[b]			
N0-N1	131 (48.9)	122 (45.5)	.488
N2-N3	137 (51.1)	146 (54.5)	
TNM stage grouping[b]			
III	87 (32.5)	80 (29.9)	.753
IVA	172 (64.2)	177 (66.0)	
IVB	9 (3.4)	11 (4.1)	
Extracapsular extension[c]			
Yes	58 (21.6)	57 (21.2)	1.00
No	210 (78.4)	211 (78.7)	
Histologic grade			
1-2	195 (72.8)	197 (73.5)	.922
3	73 (27.2)	71 (26.5)	
HPV status[d]			
Positive	14 (10.4)	10 (7.5)	.517
Negative	91 (67.4)	96 (71.6)	
Equivocal	—	1 (0.7)	

Abbreviations: CRT, cisplatin chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; NCRT, nimotuzumab and cisplatin chemoradiotherapy; TNM, tumor, lymph node, metastasis.
[a]*P* value provided is for the comparison between age <60 years versus age ≥60 years between the 2 arms.
[b]Staging was clinical staging according to the American Joint Committee on Cancer-Union for International Cancer Control TNM staging system, seventh edition.
[c]Extracapsular extension was either clinically or radiologically detected.
[d]HPV status was detected by p16 immunohistochemistry staining and is reported according to the College of American Pathologists criteria for patients with oropharyngeal cancer. Samples for which testing was possible in patients with oropharyngeal cancer included 105 in the CRT arm and 107 in the NCRT arm.

0.79; 95% CI, 0.62-0.99; $P = .045$) also confirmed the above-mentioned results. On post hoc analysis, the benefit of nimotuzumab was observed even in patients who received a cumulative dose of cisplatin ≥200 mg/m^2 (hazard ratio, 0.73; 95% CI, 0.54-0.98; $P = .036$). The impact of various prognostic factors on PFS is shown in the Supporting Information (see Supporting Table 1). Nonoropharyngeal site of primary malignancy ($P = .08$) and stage III disease ($P = .001$) were associated with improved PFS (see Supporting Table 1).

Disease-free survival

The addition of nimotuzumab decreased the hazard of disease recurrence by 29% (hazard ratio, 0.71; 95% CI, 0.55-0.92; $P = .008$). The 2-year DFS was higher in the NCRT arm (60.2%; 95% CI 53.6%-66.3%) compared with the CRT arm (48.5%; 95% CI, 42.1%-54.7%) (Fig. 3). The results of the sensitivity analysis using competing risk analysis ($P = .004$; Gray test) and the composite endpoint of progression or death (hazard ratio, 0.82; 95% CI, 0.65-1.03; $P = 0.092$) also were in concordance with the above-mentioned results. The

TABLE 2. Adverse Events Between the 2 Treatment Arms[a]

	No. of Patients (%)				
	CRT Arm		NCRT Arm		*P*
Variable	All Grades	Grade 3-5	All Grades	Grade 3-5	Grade 3-5
Hematologic adverse events					
Anemia	211 (80.5)	4 (1.5)	229 (86.1)	3 (1.1)	.689
Neutropenia	45 (17.2)	9 (3.4)	45 (16.9)	6 (2.3)	.415
Febrile neutropenia	—	5 (1.9)	—	4 (1.5)	.737
Thrombocytopenia	64 (24.4)	4 (1.5)	46 (17.3)	3 (1.1)	.689
Biochemical adverse events					
Increased serum creatinine	26 (9.9)	0 (0.0)	24 (9.0)	2 (0.8)	.16
Increased AST	48 (18.3)	3 (1.1)	41 (15.4)	2 (0.8)	.641
Increased ALT	75 (28.6)	3 (1.1)	85 (32.0)	4 (1.5)	.719
Electrolyte disturbance					
Hyponatremia	236 (90.1)	82 (31.3)	237 (89.1)	89 (33.5)	.596
Hypokalemia	10 (3.8)	3 (1.1)	16 (6.0)	2 (0.8)	.641
Hypomagnesemia	79 (30.2)	—	89 (33.5)	—	—
Local radiation adverse events					
Mucositis	252 (96.9)	145 (55.8)	256 (97)	176 (66.7)	.01
Radiation dermatitis	238 (91.5)	76 (29.2)	234 (88.6)	73 (27.7)	.689
Odynophagia	252 (96.9)	98 (37.7)	257 (97.3)	109 (41.3)	.4
Dysphagia	226 (86.9)	75 (28.8)	229 (86.7)	80 (30.3)	.715
Gastrointestinal adverse events					
Nausea	124 (47.7)	2 (0.8)	127 (48.1)	4 (1.5)	.422
Vomiting	78 (30.0)	4 (1.5)	77 (29.2)	3 (1.1)	.689
Weight loss	133 (51.2)	2 (0.8)	160 (60.6)	3 (1.1)	.666
Other adverse events					
Maculopapular rash	6 (2.3)	—	19 (17.2)	—	—
Stroke	—	—	4 (1.5)	2 (0.8)	.16
Tinnitus	3 (1.2)	—	3 (1.1)	—	—
Long-term side effects, >90 d					
Xerostomia	186 (97.4)	4 (2.1)	181 (95.8)	8 (4.2)	.233
Dysgeusia	151 (79.1)	—	143 (75.7)	—	—
Subcutaneous fibrosis	183 (95.8)	48 (25.1)	178 (94.2)	55 (29.1)	.384
Decreased shoulder range of motion	7 (3.7)	—	7 (3.7)	2 (1.1)	.154
Dysphagia	79 (41.4)	6 (3.1)	79 (41.8)	12 (6.3)	.141
Impaired hearing caused by SNHL	33 (17.3)	9 (4.7)	31 (16.4)	11 (5.8)	.629

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRT, cisplatin chemoradiotherapy; NCRT, nimotuzumab and cisplatin chemoradiotherapy; SNHL, sensorineural hearing loss.

[a]In the data for acute adverse events, *nonlaboratory parameters* were available for 260 patients (97.1%) in the CRT arm and 264 (98.6%) in the NCRT arm, whereas *laboratory parameters* were available for 266 patients (99.3%) in both arms. Chronic toxicity data were captured for 191 patients (71.3%) in the CRT arm and 189 (70.5%) in the NCRT arm.

benefit was across all subgroups (see Supporting Fig. 1), inclusive of the patients who received a cumulative cisplatin dose ≥200 mg/m^2 (P = .024; hazard ratio, 0.71; 95% CI, 0.53-0.96). The impact of various prognostic factors on DFS is provided in the supporting information (see Supporting Table 1).

Locoregional control

The increment in PFS from the addition of nimotuzumab was largely because of a decrease in locoregional failures (P = .006) (Fig. 3). The 2-year LRC rate was significantly better in the NCRT arm (67.5%; 95% CI, 60.9%-73.3%)than in the CRT arm (57.6%; 95% CI, 50.9%-63.6%). The addition of nimotuzumab led to a 33% reduction (hazard ratio, 0.67; 95% CI, 0.50-0.89; P = .006) in the risk of locoregional failure, and the reduction was consistent across all subgroups (Fig. 3), inclusive of the patients who received a cumulative cisplatin dose ≥200 mg/m^2 (P = .016; hazard ratio, 0.66; 95% CI, 0.48-0.93). The results of the sensitivity analysis using competing risk analysis (P = .006; Gray test) and the composite endpoint of locoregional failure or death (hazard ratio, 0.79; 95% CI, 0.62-0.99; P = .049) also confirmed the above-mentioned results. The impact of various prognostic factors on LRC is shown in the supporting information (see Supporting Table 1). Nonoropharyngeal site of primary malignancy (P = .003), stage III disease (P = .024), and intensity-modulated radiation technique (P = .043) were associated with improved LRC.

TABLE 3. Treatment Delivery Details

Variable	No. of Patients (%)		P
	CRT Arm, n = 268	NCRT Arm, n = 268	
Radiotherapy details			
Radiotherapy dose: Median [IQR], Gy	70 [70-70]	70 [70-70]	.713[a]
100% of planned radiotherapy dose completed	252 (94.0)	250 (93.3)	.723
Dose <100%	16 (6.0)	18 (6.7)	
Reasons for dose <100%			
Never started radiation	1 (0.4)	1 (0.4)	—
Default	9 (3.3)	7 (2.6)	
Toxicity	2 (0.7)	6 (2.2)	
Progression	2 (0.7)	2 (0.7)	
Others	2 (0.7)	1 (0.4)	
Neurosis/mania	—	1 (0.4)	
Technique			
Conventional	229 (85.4)	238 (88.8)	.240[b]
Intensity modulated	38 (14.2)	29 (10.8)	
Radiotherapy	—	—	
Not received	1 (0.4)	1 (0.4)	
Time to complete radiation: Median [IQR], d	51 [49-54]	51 [49-54]	.630[a]
Radiation completion time >63 d	7 (2.6)	5 (1.9)	.559
Patients with gaps >2 d	72 (26.9)	80 (29.9)	.443
Cumulative duration of gap; Median [IQR], d	5 [3-9]	5 [3-8]	.824[a]
Cause of gaps >2 d			
Logistics	58 (21.6)	62 (23.1)	—
Toxicity	10 (3.7)	12 (4.5)	
Default	4 (1.5)	5 (1.9)	
Contagious infection, Varicella	—	1 (0.4)	
Toxicity leading to gaps ≥2 d[c]			
Febrile neutropenia	5 (1.9)	3 (1.1)	
Mucositis	2 (0.7)	3 (1.1)	—
Dermatitis	1 (0.4)	2 (0.7)	
Hyponatremia	1 (0.4)	3 (1.1)	
Non-neutropenic fever	—	1 (0.4)	
Dengue	1 (0.4)	—	
Chemotherapy details			
Cisplatin			
No. of cycles: Median [IQR]	7 [7-7]	7 [7-7]	.389[a]
No. of cycles completed			
≥7	219 (81.7)	226 (84.3)	.421[d]
6	20 (7.5)	23 (8.6)	
5	12 (4.5)	4 (1.5)	
<5	17 (6.3)	15 (5.6)	
Reason for receipt of <7 cycles			
Patient defaulted/refused	11 (4.1)	5 (1.9)	
Toxicity	34 (12.7)	35 (13.1)	—
Progression	1 (0.4)	1 (0.4)	
Logistics, radiation was completed	3 (1.1)	—	
Neurosis/mania	—	1 (0.4)	
Patients who had a delay ≥3 d	87 (32.5)	82 (30.6)	.642
Delay in chemotherapy: Median [IQR], d	3 [1-7]	3 [1-7]	.990
Patients who had dose reductions	21 (7.8)	26 (9.7)	.445
Dose reduction: Median [IQR], %	40 [10-40]	40 [40-40]	.081
Patients who received ≥200 mg/m^2	211 (78.7)	208 (77.6)	.754
Nimotuzumab			
No. of cycles: Median [IQR]	Not applicable	7 [7-7]	—
No. of cycles completed	Not applicable		—
≥7		226 (84.3)	
6		23 (8.6)	
5		4 (1.5)	
<5		15 (5.6)	
Patients who had dose reductions	Not applicable	—	—

Abbreviations: CRT, cisplatin chemoradiotherapy; d, days; Gy, grays; IQR, interquartile range; NCRT, nimotuzumab and cisplatin chemoradiotherapy.
[a]Median values were compared using the Kruskal-Wallis test.
[b]*P* value provided is for a comparison between the completion of intensity-modulated radiotherapy versus conventional radiotherapy.
[c]Some patients had multiple adverse events, which led to interruptions; however, the toxicities shown are those that were considered by the investigator to be the most significant.
[d]*P* value provided is for a comparison between the completion of ≥7 cycles versus ≤6 cycles.

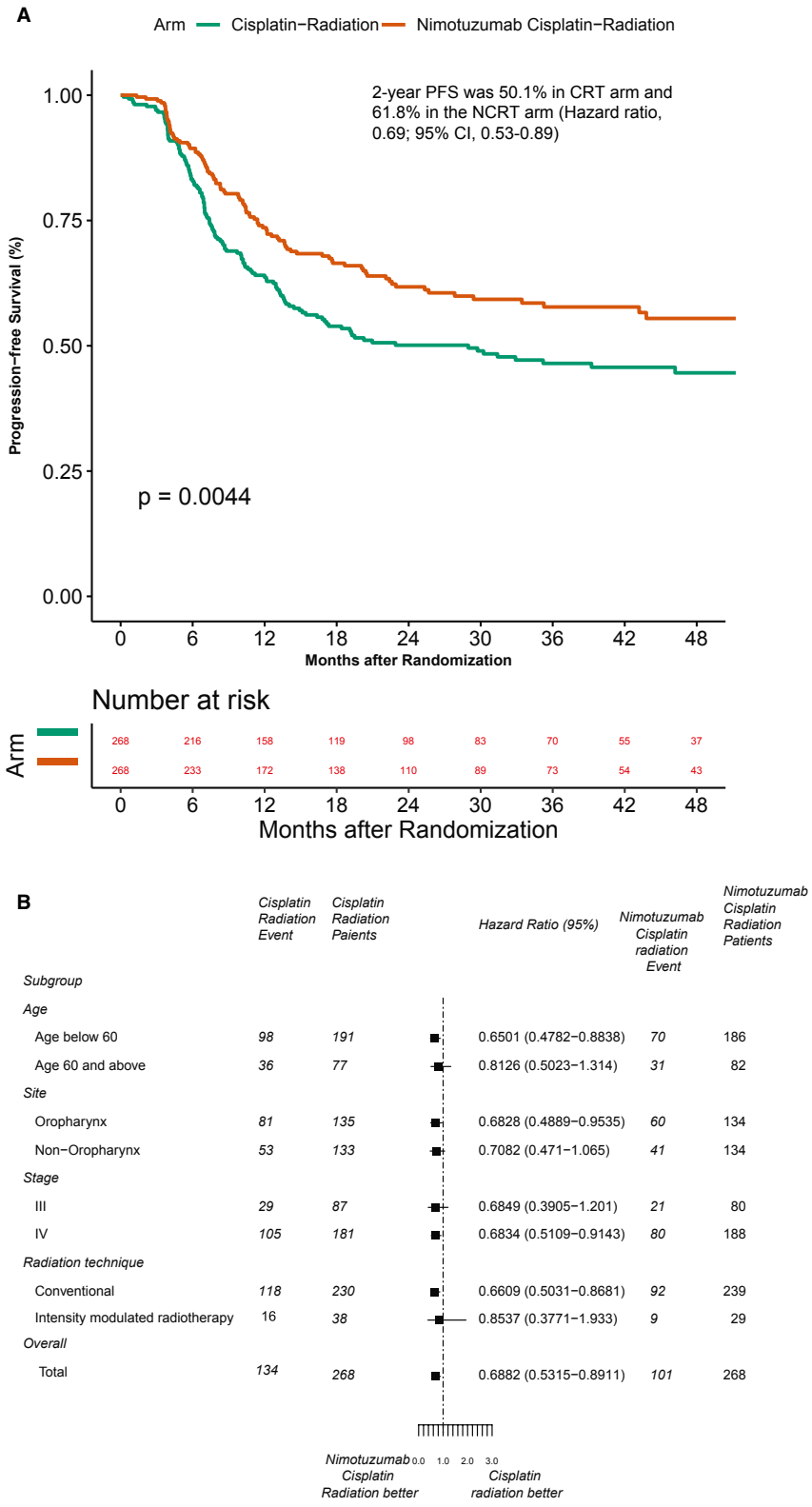

Figure 2. (A) Kaplan-Meier estimates of progression-free survival (PFS) are illustrated for patients treated in the weekly cisplatin-radiation arm (CRT) versus the weekly nimotuzumab plus cisplatin-radiation (NCRT) arm. PFS was significantly longer among patients in the nimotuzumab plus cisplatin-radiation arm. (B) This forest plot depicts the effect of treatment on various subgroups used for stratification.

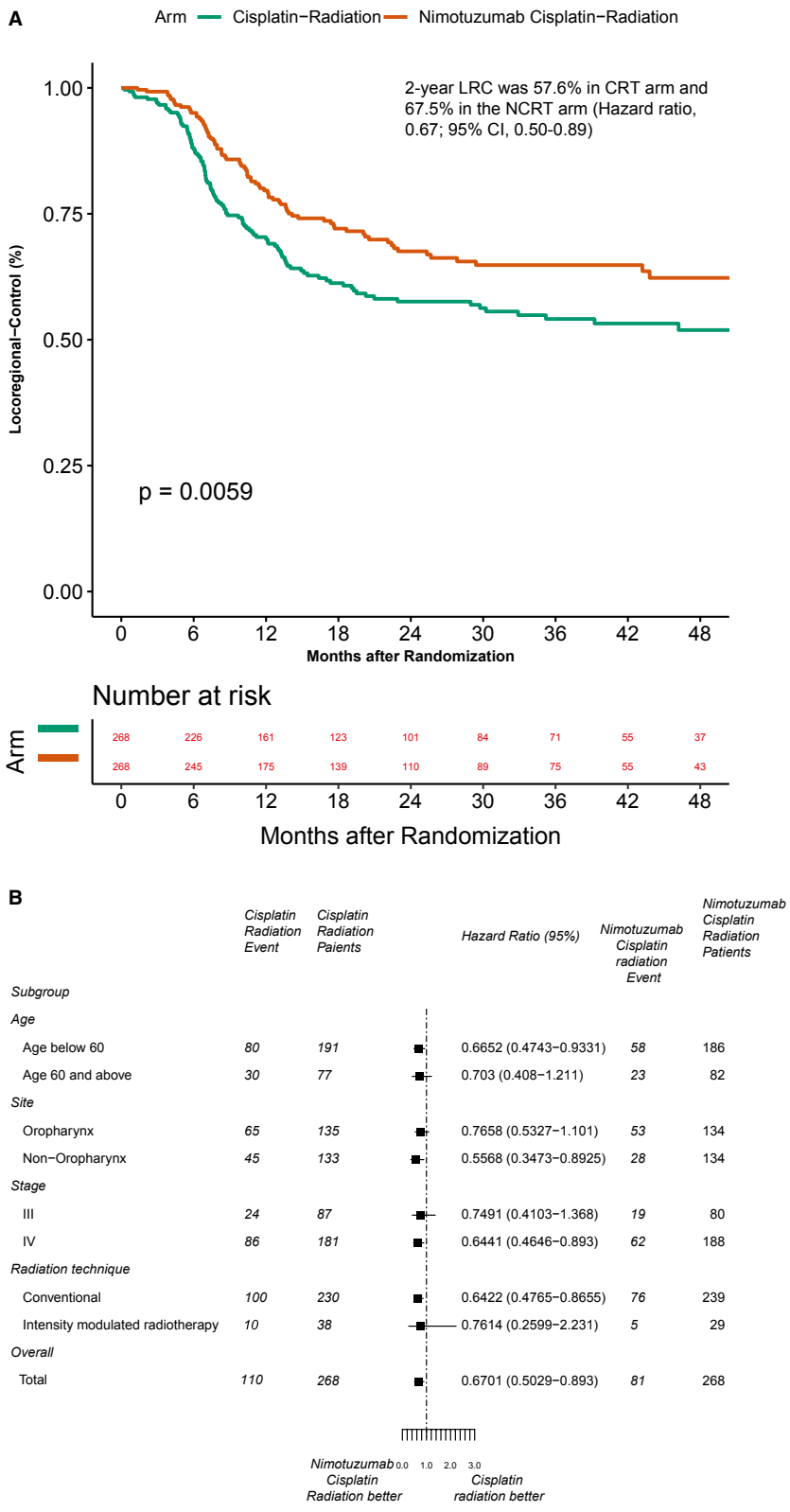

Figure 3. (A) Kaplan-Meier estimates of the duration of locoregional control (LRC) are illustrated for patients treated in the weekly cisplatin-radiation (CRT) arm versus the weekly nimotuzumab plus cisplatin-radiation (NCRT) arm. (B) This forest plot depicts the effect of treatment on various subgroups used for stratification.

TABLE 4. Details of Cause of Death Across Both Arms

Variable	No. of Patients (%)	
	CRT Arm, n = 268	NCRT Arm, n = 268
Alive	140 (52.2)	155 (57.8)
Death from disease	100 (37.3)	81 (30.2)
Death from second primary in head and neck region	3 (1.1)	1 (0.4)
Death from second primary in non-head and neck region	2 (0.7)	5 (1.9)
Death from toxicity within 90 d after completion of therapy	4 (1.5)	7 (2.6)
Death from to toxicity >90 d after completion of therapy	3 (1.1)	5 (1.9)
Death from tuberculosis	1 (0.4)	1 (0.4)
Death from liver disease	1 (0.4)	—
Death from unknown cause	14 (5.2)	13 (4.9)

Abbreviations: CRT, cisplatin chemoradiotherapy; NCRT, nimotuzumab and cisplatin chemoradiotherapy.

Overall survival

There were 128 deaths in the CRT arm and 113 in the NCRT arm (hazard ratio, 0.84; 95% CI, 0.65-1.08; $P = .163$). The 2-year OS was 63.8% (95% CI, 57.3%-69.6%) and 57.7% (95% CI, 51.3%-63.6%) in the NCRT and CRT arms, respectively. Details of causes of deaths in each arm are shown in Table 4. The impact of nimotuzumab on various subgroups is depicted in Figure 4; and, for patients who received a cumulative cisplatin dose ≥200 mg/m^2, the impact was similar to that in the overall results (hazard ratio, 0.84; 95% CI, 0.62-1.13; $P = .237$). The impact of various prognostic factors on OS is shown in the supporting information (see Supporting Table 1). Among the tested factors, the presence of stage III disease ($P = .001$) was associated with improved OS.

Salvage Surgery for Residual Disease

Objective responses postchemoradiation were evaluable in 239 patients (89.2%) in the CRT arm and 233 patients (86.9%) in the NCRT arm ($P = .424$). The overall response rate among evaluable patients was 89.1% (n = 213) in the CRT arm versus 89.3% (n = 208) in the NCRT arm. A complete response post-treatment completion was documented in 62.7% of patients in the CRT arm (n = 168) and in 61.6% of patients (n = 165) in the NCRT arm. Salvage surgery for residual disease was planned in the multidisciplinary clinic for 72 patients, including 34 in the CRT am and 38 in the NCRT arm. Of the 34 patients in the CRT arm, 22 underwent salvage surgery, 5 progressed before salvage surgery, and 7 patients refused surgery. The 22 salvage surgeries performed were neck lymph node dissection in 16 patients, local excision in 2 patients, and both local excision and neck lymph node dissection in 4 patients. Of the 38 patients in the NCRT arm, 26 underwent salvage surgery, 5 progressed before salvage surgery, and 7 patients refused surgery. The 26 salvage surgeries performed were neck lymph node dissection in 13 patients, local excision in 1 patient, and both local excision and neck lymph node dissection in 12 patients.

HPV Status and Outcomes

The HPV status of oropharyngeal cancers is shown in Table 1. There was a significant interaction between HPV status and treatment outcomes (see Supporting Table 2). The hazard ratio for PFS in p16-negative oropharyngeal cancers was 0.54 (95% CI, 0.36-0.79), whereas hazard ratio for p16-positive cancers was 2.6 (95% CI, 0.57-11.9). The 2-year PFS was 31.5% (95% CI, 21.5%-42.0%) in the CRT arm and 57.2% (95% CI, 45.8%-67.1%) in the NCRT arm in patients with p16-negative oropharyngeal cancers ($P = .001$). A similar higher magnitude of benefit was observed with regard to DFS (hazard ratio, 0.55; 95% CI, 0.37-0.82; $P = .006$), LRC (hazard ratio, 0.61; 95% CI, 0.4-0.94; $P = .024$), and OS (hazard ratio, 0.63; 95% CI, 0.43-0.92; $P = .018$). The 2-year OS was 39% (95% CI, 28.3%-49.6%) in the CRT arm and 57.6% (95% CI, 46.3%-67.4%) in the NCRT arm in patients with p16-negative oropharyngeal cancers.

DISCUSSION

In this first phase 3 study with nimotuzumab, we found that its addition to cisplatin prolonged PFS compared with cisplatin alone in patients with LAHNSCC who received radical chemoradiation. The addition of nimotuzumab improved 2-year PFS and decreased the hazard of progression by 31%. Similar benefits also were observed in the time to LRC and DFS. The improvement in OS was not significant. However, OS was not the primary endpoint of the study, and data currently are immature for this comparison.

Studies have shown that EGFR antibodies did not improve outcomes when added to cisplatin in patients

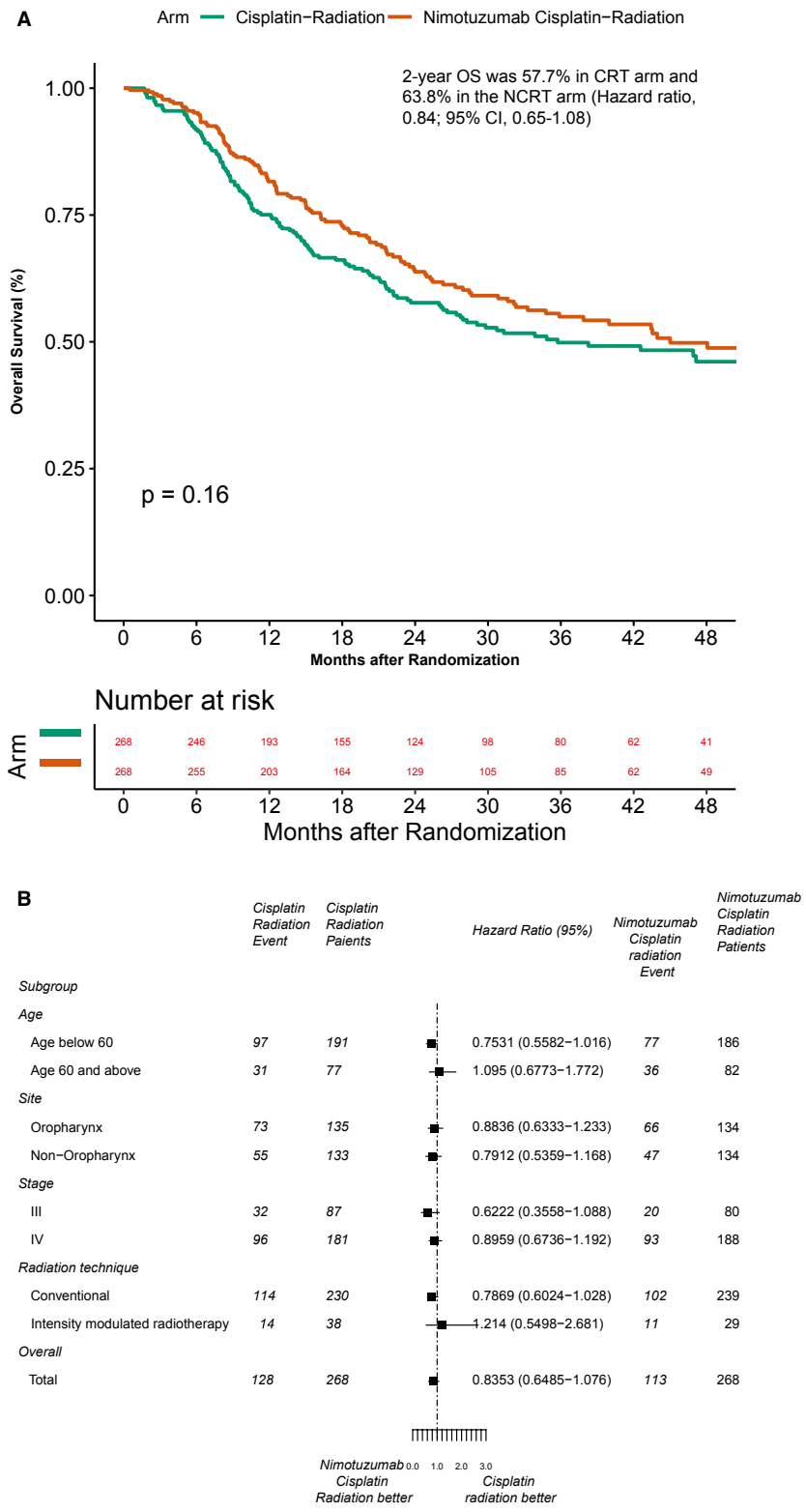

Figure 4. (A) Kaplan-Meier estimates of overall survival (OS) are illustrated for patients treated in the weekly cisplatin-radiation (CRT) arm versus the weekly nimotuzumab plus cisplatin-radiation (NCRT) arm. (B) This forest plot depicts the effect of treatment on various subgroups used for stratification.

with LAHNSCC who received chemoradiation.[9,10] The results of our study need to be interpreted in continuity with the results from Radiation Therapy Oncology Group (RTOG) 0522. In that study, subgroup analysis revealed that the addition of cetuximab led to a trend toward improved outcomes in young patients, those with HPV-negative tumors of the oropharynx or hypopharynx, and the T4 subgroup. However, the proportion of these patients in RTOG 0522 was in the minority. Seventy percent of patients in that study had primary tumors in the oropharynx, and only 27% of these were HPV-negative. The hypopharynx as a site of primary malignancy was present in 6.9% of patients. Compared with those findings, in our study, these characteristics were present in the majority of patients (Table 1). Our post hoc subgroup analysis in p16-negative patients further strengthened this assumption. The use of nimotuzumab in this cohort of patients led to a decrease in the risk of progression by nearly 50%, which translated into a decrease in the risk of death by 37%. Hence we believe that our results echo the findings of the RTOG 0522 subgroup analysis and the recently reported GORTEC (the French Head and Neck Radiation Oncology Group) study,[18] suggesting that younger patients and those with adverse prognostic features typically benefit from the nimotuzumab-weekly cisplatin concurrent combination (lighter CRT). Second, in the RTOG 0522 study, concurrent cetuximab with cisplatin led to more adverse events, which, in turn, led to more toxicity-related radiation interruptions (26.9% vs 15.1%, respectively).[9] Radiation interruptions and delays during concurrent chemoradiation are known adverse prognostic factors.[19] Third, nimotuzumab is molecularly and biologically different from cetuximab[20] and panitumumab.[21] Drugs with similar mechanisms of action are known to have differential impacts.[22] Nimotuzumab inhibits both ligand-dependent and ligand-independent signaling of the EGFR pathway.[23]

The control arm in our study demonstrated a 3-year PFS of 45.8%, which appears to be lower than the rates in other similar randomized studies from North America (which has a predominant HPV-positive population) but similar to the rates in HPV-negative cohorts in the literature.[9,24-27] Furthermore, our patients had a high proportion of hypopharyngeal primaries, high rates of tobacco use (86.5%), and almost one-fifth had gross perinodal extension, all of which are recognized adverse prognostic features.[28-31]

National Comprehensive Cancer Network guidelines recommend 3-weekly or weekly cisplatin as standard treatment options.[32] We used weekly cisplatin in this study, and it is used worldwide, especially in head and neck cancer-endemic regions (>85% of centers), at doses from 30 to 40 mg/m^2.[33-37] This use as routine practice is reflected in Asian guidelines,[38] Indian Council of Medical Research (ICMR) guidelines,[39] the evidence-based guidelines of TMC,[40] and in multiple randomized studies from this region.[33,34,36] We reported a benefit of 3-weekly cisplatin over weekly cisplatin. However, this benefit was predominantly applicable in the adjuvant setting and for oral cavity cancer and is not applicable to the patients in the current study.[41]

A cumulative cisplatin dose of 200 mg/m^2 provides adequate antitumor effects.[41] In the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) analysis, among the variety of monocisplatin schedules combined with radiation, negative results were obtained only in a single study, which used a cumulative cisplatin dose of 140 mg/m^2, a dose much below the desired level of 200 mg/m^2.[3,42] Similar findings were echoed in a meta-analysis reported by Ghi et al,[43] who found no difference in the hazard rate of death between groups of patients who received cumulative doses of cisplatin ≤300 mg/m^2. However, the hazard rate was markedly increased when the cumulative dose of cisplatin was <150 mg/m^2 compared with cisplatin doses between 200 and 225 mg/m^2.[43] The proportion of patients who received cumulative dose of cisplatin ≥200 mg/m^2 in the current study was 78.7% in the CRT arm and 77.6% in the NCRT arm (Table 3). The corresponding rate in the RTOG studies and in other major studies ranged between 62.5% and 88.5%.[5,9,44,45] Furthermore, a post hoc analysis confirmed that the benefit seen with nimotuzumab also was observed in patients who received cisplatin ≥200 mg/m^2.

Adverse event rates were similar between the 2 arms except for a higher incidence of grade ≥3 mucositis, which was seen with the addition of nimotuzumab. However, this did not hamper the treatment delivery. The lack of EGFR-specific side effects is courtesy of its lower affinity for EGFR receptor and hence a higher specificity for tumor binding because as it has a higher density of EGFR receptor than skin and other normal organs.[46,47]

There are certain limitations in this study. This was a single-center study, and the accrual took 6 years. However, no major changes have occurred over the last decade in chemoradiation for head and neck cancers. The stratification was not according to HPV status. The incidence is low in the Indian population (range,

15.0%-22.8%).[48] However, HPV status was similar between both the arms, which ensured the statistical integrity of the analysis. There were disproportionately higher numbers of hypopharyngeal cancers (which carry a poor prognosis) in the NCRT arm, but this does not affect the study conclusions. The dose of 100 mg/m^2 3 weekly was not used as a standard, hence the additional impact of nimotuzumab with this dose remains unknown.

The radiation schedules and techniques in this study were standard; therefore, these results are generalizable, especially in centers where weekly cisplatin radiosensitization is used.[49] The follow-up for OS is immature, hence the data for OS need to be interpreted with caution.

Conclusion

The addition of nimotuzumab to concurrent weekly cisplatin and chemoradiotherapy improves PFS, LRC, and DFS. Three-weekly cisplatin with radiotherapy remains the preferred option of treatment, and this combination provides a novel alternative therapeutic option when weekly cisplatin is used.

FUNDING SUPPORT

This study was funded by Biocon Ltd, Science and Engineering Research Board grant EMR/2015/001591, and by the Tata Memorial Center Research Administration Council.

CONFLICT OF INTEREST DISCLOSURES

Sameer Vasant Chaudhari is an employee of Biocon Ltd and reports personal fees and nonfinancial support from the company outside the submitted work. Vanita Noronha reports grants from Dr. Reddy's Laboratories Inc, Amgen, and Sanofi Aventis outside the submitted work. Kumar Prabhash reports support through an institutional grant from Biocon Ltd during the conduct of the study and support through institutional grants from Dr. Reddy's Laboratories Inc, Fresenius Kabi India Pvt Ltd, Alkem Laboratories, Natco Pharma Ltd, BDR Pharmaceutics Intl Pvt Ltd, and Roche Holding AG outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Vijay Maruti Patil: Planning, conduct, conducted the statistical analysis (had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis), reporting, and guarantor. **Vanita Noronha:** Planning, conduct, reporting, and guarantor. **Amit Joshi:** Planning, conduct, and reporting. **Jaiprakash Agarwal:** Conduct and reporting. **Sarbani Ghosh-Laskar:** Conduct and reporting. **Ashwini Budrukkar:** Conduct and reporting. **Vedang Murthy:** Conduct and reporting. **Tejpal Gupta:** Conduct and reporting. **Manoj Mahimkar:** Conduct and reporting. **Shashikant Juvekar:** Conduct and reporting. **Supreeta Arya:** Conduct and reporting. **Abhishek Mahajan:** Conduct and reporting. **Archi Agarwal:** Conduct and reporting. **Nilendu Purandare:** Conduct and reporting. **Venkatesh Rangarajan:** Conduct and reporting. **Arun Balaji:** Conduct and reporting. **Sameer Vasant Chaudhari:** Planning and reporting. **Shripad Banavali:** Conduct and reporting. **Sadhana Kannan:** Conduct and reporting. **Atanu Bhattacharjee:** Conduct, conducted the statistical analysis, and reporting. **Anil K. D'Cruz:** Conduct and reporting. **Pankaj Chaturvedi**: Conduct and reporting. **Prathamesh S. Pai:** Conduct and reporting. **Devendra Chaukar:** Conduct and reporting. **Gouri Pantvaidya:** Conduct and reporting. **Deepa Nair:** Conduct and reporting. **Sudhir Nair:** Conduct and reporting. **Anuja Deshmukh:** Conduct and reporting. **Shivakumar Thiagarajan:** Conduct and reporting. **Vijayalakshmi Mathrudev:** Conduct and reporting. **Aparna Manjrekar:** Conduct and reporting. **Sachin Dhumal:** Conduct and reporting. **Kamesh Maske:** Conduct and reporting. **Arti Sanjay Bhelekar:** Conduct and reporting. **Kavita Nawale:** Conduct and reporting. **Arun Chandrasekharan:** Conduct and reporting. **Nikhil Pande:** Conduct and reporting. **Alok Goel:** Conduct and reporting. **Vikas Talreja:** Conduct and reporting. **Vijai Simha:** Conduct and reporting. **Sujay Srinivas:** Conduct and reporting. **Rohit Swami:** Conduct and reporting. **Dilip Harindran Vallathol:** Conduct and reporting. **Hollis Dsouza:** Conduct and reporting. **Sameer Shrirangwar:** Conduct and reporting. **Siddharth Turkar:** Conduct and reporting. **George Abraham:** Conduct and reporting. **Aditi Harsh Thanky:** Conduct and reporting. **Usha Patel:** Conduct and reporting. **Manish Kumar Pandey:** Conduct and reporting. **Kumar Prabhash:** Planning, conduct, conducted the statistical analysis (had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis), reporting, guarantor, and administrative support.

REFERENCES

1. Pfister DG, Ang KK, Brizel DM, et al. Head and neck cancers, version 2.2013. Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2013;11:917-923.
2. Gregoire V, Lefebvre JL, Licitra L, Felip E; EHNS–ESMO–ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v184-v186.
3. Pignon JP, le Maitre A, Maillard E, Bourhis J; MACH-NC Collaborative Group. 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.
4. Blanchard P, Baujat B, Holostenco V, et al. Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol*. 2011;100:33-40.
5. 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.
6. Ghi MG, Paccagnella A, Ferrari D, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. *Ann Oncol*. 2017;28:2206-2212.
7. Pignon JP, Baujat B, Bourhis J. [Individual patient data meta-analyses in head and neck carcinoma: what have we learnt?] *Cancer Radiother*. 2005;9:31-36.
8. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol*. 2014;32:3858-3866.
9. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. 2014;32:2940-2950.
10. Mesia R, Henke M, Fortin A, et al. Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol*. 2015;16:208-220.
11. Mateo C, Moreno E, Amour K, Lombardero J, Harris W, Pdrez R. Humanization of a mouse monoclonal antibody that blocks the epidermal growth factor receptor: recovery of antagonistic activity. *Immunotechnology*. 1997;3:71-81.
12. Ramakrishnan MS, Eswaraiah A, Crombet T, et al. Nimotuzumab, a promising therapeutic monoclonal for treatment of tumors of epithelial origin. *MAbs*. 2009;1:41-48.
13. Reddy BK, Lokesh V, Vidyasagar MS, et al. Nimotuzumab provides survival benefit to patients with inoperable advanced squamous cell

carcinoma of the head and neck: a randomized, open-label, phase IIb, 5-year study in Indian patients. *Oral Oncol*. 2014;50:498-505.
14. Bhosale PG, Pandey M, Desai RS, et al. Low prevalence of transcriptionally active human papilloma virus in Indian patients with HNSCC and leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;122:609-618.e7.
15. 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.
16. Kubota A, Furukawa M, Komatsu M. [Concurrent chemoradiotherapy for head and neck squamous cell carcinoma with indication of total laryngectomy]. *Nihon Jibiinkoka Gakkai Kaiho*. 2004;107: 1004-1010.
17. Kubota A, Furukawa M, Fujita Y, Yagi H. [Concurrent chemoradiotherapy for resectable locoregionally advanced squamous cell carcinoma of the head and neck—analysis of factors associated with toxicity and efficacy]. *Nihon Jibiinkoka Gakkai Kaiho*. 2010;113: 101-109.
18. Tao Y, Auperin A, Sire C, et al. 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. *J Clin Oncol*. 2018;36:3084-3090. doi:10.1200/JCO.2017.76.2518
19. Ferreira BC, Sa-Couto P, Lopes MC, Khouri L. Compliance to radiation therapy of head and neck cancer patients and impact on treatment outcome. *Clin Transl Oncol*. 2016;18:677-684.
20. Garrido G, Tikhomirov IA, Rabasa A, et al. Bivalent binding by intermediate affinity of nimotuzumab: a contribution to explain antibody clinical profile. *Cancer Biol Ther*. 2011;11:373-382.
21. Tikhomirov I, Hidalgo G, Yang E, Sherman I, Rodriguez R. Bivalent binding properties of epidermal growth factor receptor targeted monoclonal antibodies: factors contributing to differences in observed clinical profiles [abstract]. *Clin Cancer Res*. 2008;14(15 suppl):A36.
22. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol*. 2013;31:4067-4075.
23. Berger C, Krengel U, Stang E, Moreno E, Madshus IH. Nimotuzumab and cetuximab block ligand-independent EGF receptor signaling efficiently at different concentrations. *J Immunother*. 2011;34: 550-555.
24. 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.
25. 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.
26. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. 2010;11:21-28.
27. Rischin D, Peters LJ, O'Sullivan B, et al. Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group. *J Clin Oncol*. 2010;28:2989-2995.
28. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010; 363:24-35.
29. Dunne AA, Muller HH, Eisele DW, Kessel K, Moll R, Werner JA. Meta-analysis of the prognostic significance of perinodal spread in head and neck squamous cell carcinomas (HNSCC) patients. *Eur J Cancer*. 2006;42:1863-1868.
30. Giraldi L, Leoncini E, Pastorino R, et al. Alcohol and cigarette consumption predict mortality in patients with head and neck cancer: a pooled analysis within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. *Ann Oncol*. 2017;28:2843-2851.
31. Abrahao R, Anantharaman D, Gaborieau V, et al. The influence of smoking, age and stage at diagnosis on the survival after larynx, hypopharynx and oral cavity cancers in Europe: the ARCAGE study. *Int J Cancer*. 2018;143:32-44. doi:10.1002/ijc.31294
32. Pfister DG, Spencer S, Brizel DM, et al. Head and Neck Cancers, Version 1.2015. *J Natl Compr Canc Netw*. 2015;13:847-855; quiz 856.
33. Ghosh-Laskar S, Kalyani N, Gupta T, et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: results of a prospective randomized trial. *Head Neck*. 2016;38: 202-207.
34. Sharma A, Mohanti BK, Thakar A, Bahadur S, Bhasker S. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. *Ann Oncol*. 2010;21:2272-2277.
35. Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in locoregionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. *Head Neck Oncol*. 2009;1:17.
36. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol*. 2002;20:2038-2044.
37. Iqbal MS, Chaw C, Kovarik J, et al. Primary concurrent chemoradiation in head and neck cancers with weekly cisplatin chemotherapy: analysis of compliance, toxicity and survival. *Int Arch Otorhinolaryngol*. 2017;21:171-177.
38. D'Cruz A, Lin T, Anand AK, et al. Consensus recommendations for management of head and neck cancer in Asian countries: a review of international guidelines. *Oral Oncol*. 2013;49:872-877.
39. Indian Council of Medical Research. Consensus Document for Management of Larynx and Hypopharynx Cancers. New Delhi, India: Indian Council of Medical Research; 2017. Available at: https://www.icmr.nic.in/sites/default/files/guidelines/Larynx%20and%20Hypopharynx%20Cancers_0.pdf. Accessed May 5, 2019.
40. D'Cruz AK, Chaukar D, Gupta T, eds. Evidence Based Management of Cancers in India (Two Parts). Part A: Guidelines for Head and Neck Cancers. Mumbai, India: Tata Memorial Hospital; 2012. Available at: https://tmc.gov.in/tmh/PDF/Head%20and%20Neck.pdf. Accessed May 5, 2019.
41. Ang KK. Concurrent radiation chemotherapy for locally advanced head and neck carcinoma: are we addressing burning subjects? *J Clin Oncol*. 2004;22:4657-4659.
42. Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *Int J Radiat Oncol Biol Phys*. 2011;81:719-725.
43. Ghi MG, Paccagnella A, Floriani I, Garavaglia D. Concomitant chemoradiation in locally advanced head and neck squamous cell carcinoma: A literature-based meta-analysis on the platinum concomitant chemotherapy [abstract]. *J Clin Oncol*. 2011;29(15 suppl):5534.
44. 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.
45. Ang K, Zhang Q, Wheeler RH, et al. A phase III trial (RTOG 0129) of two radiation-cisplatin regimens for head and neck carcinomas (HNC): impact of radiation and cisplatin intensity on outcome [abstract]. *J Clin Oncol*. 2010;28(15 suppl):5507.
46. Allan DG. Nimotuzumab: evidence of clinical benefit without rash. *Oncologist*. 2005;10:760-761.
47. Crombet T, Osorio M, Cruz T, et al. Use of the humanized antiepidermal growth factor receptor monoclonal antibody h-R3 in combination with radiotherapy in the treatment of locally advanced head and neck cancer patients. *J Clin Oncol*. 2004;22:1646-1654.
48. Murthy V, Calcuttawala A, Chadha K, et al. Human papillomavirus in head and neck cancer in India: current status and consensus recommendations. *South Asian J Cancer*. 2017;6:93-98.
49. Goyal G, Patil VM, Noronha V, et al. Once-a-week versus once-every-3-weeks cisplatin in patients receiving chemoradiation for locally advanced head-and-neck cancer: a survey of practice in India. *Cancer Res Stat Treat*. 2018;1:63-67.