

# Efficacy and safety of concurrent chemoradiotherapy with or without Nimotuzumab in unresectable locally advanced squamous cell carcinoma of head and neck: Prospective comparative study - ESCORT-N study

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## Abstract

**Background:** Nimotuzumab is an anti-epidermal growth factor receptor monoclonal antibody which can be added to chemoradiotherapy (CRT) to improve efficacy for management of locally advanced squamous cell carcinoma of the head and neck (LASCCHN). We prospectively evaluated the efficacy and safety of nimotuzumab with CRT for LASCCHN and compared with CRT alone. **Materials and Methods:** In this prospective study, 29 LASCCHN (Stage III–IVb) patients received Nimotuzumab plus CRT or CRT alone. Treatment included six cycles of cisplatin (40–50 mg/week) or carboplatin (area under the curve-based), nimotuzumab (200 mg/week), and radiotherapy (60–70 Gy). Tumor response was evaluated as per response evaluation criteria in solid tumors criteria. MoS was estimated using the Kaplan–Meier method. Toxicity and adverse events (AEs) were assessed as per CTCAE v 4.0. **Results:** At 24 weeks after completion of treatment, the tumor response rate (complete response, partial response, stable disease) was 53.3% and 35.7% favoring nimotuzumab arm while progression of disease was 40% and 35.7% in Nimotuzumab plus CRT and CRT groups, respectively. However, the objective response rate was 57% and 30% in favor of nimotuzumab arm. At median follow-up of 45.5 months, MoS was 33 months in Nimotuzumab plus CRT and 27 months in CRT group. The 5-year survival rate was 33.3% in Nimotuzumab plus CRT versus 7.1% in CRT group. Nimotuzumab was observed to be safe with no additional AEs such as hypersensitivity, hypomagnesemia, and allergic reaction was reported. **Conclusion:** Addition of Nimotuzumab to standard CRT showed improved survival rate in unresectable, LASCCHN patients without producing additional toxicity.

**Key words:** Locally advanced head-and-neck carcinoma, monoclonal antibody, nimotuzumab

## Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth leading cancer by incidence worldwide.<sup>[1]</sup> In India, there is rising burden and majority present in locally advanced stages.<sup>[2,3]</sup>

Radiotherapy (RT) is the standard of care for the initial stages, while concurrent chemo-radiotherapy (CRT), particularly cisplatin, is used for unresectable and locally advanced cases of SCCHN.<sup>[4,5]</sup> However, despite superior therapeutic outcomes, they are associated with low survival benefit and increased risk of toxicities.<sup>[6]</sup> This warrants the need to explore novel treatment strategies to improve the overall survival (OS) outcome of SCCHN.

Overexpression of the epidermal growth factor receptor (EGFR) is detected in more than 80% cases of SCCHN and correlates with poor prognosis, locoregional failure, and distant metastases.<sup>[7]</sup> Thus, EGFR-based targeted therapies have attracted attention in the treatment of head-and-neck cancers.

Nimotuzumab (BIOMAb EGFR) is a new humanized anti-EGFR monoclonal antibody (MAb) that binds to the extracellular domain of the EGFR with intermediate affinity and high specificity which results in the blockade of receptor-dependent signal transduction pathways and provides antitumor effects.<sup>[5,8]</sup> The advantage of nimotuzumab over other anti-EGFR MAb is its benign adverse effect profile.<sup>[5,9,10]</sup> The BEST trial demonstrated that addition of nimotuzumab to CRT or RT provided long-term survival benefit in inoperable, locally advanced SCCHN (LASCCHN).<sup>[5]</sup> Recently, there is growing evidence in the literature documenting the efficacy and safety of Nimotuzumab in LASCCHN. Authors in their individual research have documented that the addition of the Nimotuzumab to concurrent CRT have improved therapeutic

outcomes and survival with minimal toxicities.<sup>[11–14]</sup> However, majority studies are restricted with short-term assessment.

This study was carried out to evaluate the efficacy and safety of nimotuzumab with CRT in patients with LASCCHN and compared with CRT alone.

## Materials and Methods

This was an open-labeled, prospective, comparative clinical study carried out in patients with LASCCHN attending radiation oncology unit at a tertiary care hospital in Delhi (India). Approval from the ethical committee was obtained. The study included patients aged 18–70 years with histologically proven stage III or IVA squamous cell carcinoma and were suitable for concurrent CRT, unfit for surgery, Karnofsky performance score (KPS)  $\geq 60\%$  and adequate hematologic, hepatic, and renal functions. We excluded patients aged  $\leq 18$  years, KPS  $\leq 60\%$ , distant metastases or concurrent secondary malignancy and nasopharyngeal malignancy, prior chemotherapy, RT or immunotherapy, history of allergy with similar biological to nimotuzumab compound, inadequate hematologic, renal and hepatic function, uncontrolled infection and any other systemic diseases. Pregnant/lactating females were also excluded from the study.

Two treatment arms (A and B) were defined. Patients were randomized to receive the treatment by simple randomization method.

Arm A-CRT plus nimotuzumab: Chemotherapy (cisplatin - 40–50 mg/m<sup>2</sup> dose, once a week for 6 weeks) + RT (60 Gy to 70 Gy @ 2 Gy/# for 5 days/week over 6–7 weeks) + Nimotuzumab (200 mg/dose, once a week for 6 weeks).

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Arm B: CRT: Chemotherapy (cisplatin - 40–50 mg/m<sup>2</sup> dose, once a week for 6 weeks) + RT (60 Gy to 70 Gy @ 2 Gy/day for 5 days/week over 6–7 weeks).

Follow-up for survival was performed every 3 months up to 60 months.

### Parameters evaluated

The tumor response was evaluated using the response evaluation criteria in solid tumors (RECIST version 1.1). The responses assessed included complete response (CR), partial response (PR), the progression of disease (PD), and stable disease (SD) based on Positron emission tomography – computed tomography (PET-CT/CT) findings. All patients were evaluated using PET-CT scans and metabolic response evaluated. PETCT scan was done 3 monthly for 1 year and then yearly for the next 5 years or earlier in case of clinical suspicion of progression. The objective response rate (ORR) and clinical benefit rate were calculated. OS was calculated from the date of randomization till the date of death or last date of follow-up. Association of OS with various factors, i.e., age, gender, histopathological grade, and chemotherapy was also analyzed. Adverse events (AE's) were assessed and graded by the National Cancer Institute's Common Toxicity Criteria version 4.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 19.0, IBM Corporation, New York). Descriptive statistics was used to express the data. Median OS along with 95% confidence interval (CI) was estimated by the Kaplan–Meier method.

### Results

A total of 29 patients of LASCCHN participated in this study. The median age was 55 years (36–70 years), with majority being males (96.6%). Majority had Stage IV disease and the most common site was oropharynx (75.9%). The baseline characteristics are summarized in Table 1.

Tumor response – At 24 weeks postcompletion of treatment, higher clinical benefit rate (CR + PR + SD) was observed in the Nimotuzumab plus CRT arm, i.e., Arm A than CRT alone arm, i.e., Arm B (53.5% vs. 35.7%). Similarly, the ORR (CR + PR) was higher in Arm A (53.5% vs. 21.4%). PD was observed to be almost equivalent but not statistically significant in both arms (40% vs. 35.7%) [Table 2].

Survival outcome – 5-year survival rate was 33.3% in Arm A versus 7.1% in Arm B. The MoS was 27 months for Arm B and 33 months in Arm A. Although this is not statistically significant, the survival is longer in Arm A [Figures 1 and 2].

Subgroup analysis – On subgroup analysis association of OS in the study groups with respect to age, anatomical site, tumor, histopathology, and chemotherapy was not significant [Table 3].

Safety and toxicity – AE's noted were anemia, mucositis, leukopenia, and dysphagia and were either Grade I/II in both groups. Nimotuzumab was observed to be safer with no added toxicity and did not have any serious adverse effects especially skin rashes or hypomagnesemia [Table 4].

### Discussion

The findings suggest that the addition of nimotuzumab to concurrent chemoradiotherapy (CCRT) improves the survival South Asian Journal of Cancer ♦ Volume 8 ♦ Issue 2 ♦ April-June 2019

**Table 1: Baseline characteristics of locally advanced squamous cell carcinoma of head and neck patients in the treatment groups**

Characteristics	Total (n=29)	CRT plus nimotuzumab (Arm A) (n=15)	CRT (Arm B) (n=14)
Age (years) (%)			
Mean±SD	55.51±7.3	55.0±8.29	56.0±6.5
Median (range)	55 (36-65)	55 (36-65)	56 (44-65)
Gender (%)			
Male	28 (96.6)	15 (100)	13 (92.9)
Female	1 (3.4)	0 (0)	1 (7.1)
Anatomical sub-sites (%)			
Hypopharynx	4 (13.8)	2 (13.3)	2 (14.3)
Larynx	3 (10.3)	0 (0)	3 (21.4)
Oropharynx	22 (75.9)	13 (86.7)	9 (65.3)
TNM stage (%)			
III	9 (31)	3 (20.0)	6 (42.9)
IV-A	19 (65.5)	12 (80.0)	7 (50)
IV-B	1 (3.4)	0 (0)	1 (7.1)
Histo-pathological grade (%)			
MDSCC	16 (55.2)	8 (53.3)	8 (55.2)
PDSKC	5 (17.2)	4 (26.7)	1 (7.1)
SCC	3 (10.3)	1 (6.7)	2 (14.3)
WDSCC	5 (17.2)	2 (13.3)	3 (21.4)
Chemotherapy			
Cisplatin 40 mg	21 (72.4)	11 (73.3)	10 (71.4)
Cisplatin 50 mg	5 (17.2)	2 (13.3)	3 (21.4)
Carboplatin	2 (6.9)	2 (13.3)	0
Capecitabine	1	0	1 (7.1)

SD=Standard deviation, SCC=Squamous cell carcinoma, PDSKC=Poorly differentiated SCC, WDSCC=Well differentiated SCC, MDSCC=Moderately differentiated SCC, CRT=Chemo-radiotherapy

**Table 2: Tumour response in chemo-radiotherapy plus nimotuzumab (Arm A) and chemo-radiotherapy (Arm B) treatment group: Tumour response at 24 weeks in two arms**

	Arm		Total
	Nimotuzumab + CRT	CRT	
N/A			
Count	1	4	5
Percentage within arm	6.7	28.6	17.2
CR			
Count	8	2	10
Percentage within arm	53.3	14.3	34.5
PD			
Count	6	5	11
Percentage within arm	40.0	35.7	37.9
PR			
Count	0	1	1
Percentage within arm	0.0	7.1	3.4
SD			
Count	0	2	2
Percentage within arm	0.0	14.3	6.9
Total			
Count	15	14	29
Percentage within arm	100.0	100.0	100.0

$\chi^2=8.66$ ;  $P=0.076$ . CRT=Chemoradiotherapy, CR=Complete response, PR=Partial response, PD=Progression of disease, SD=Stable disease, CRT=Chemo-radiotherapy

curve than CCRT alone in LASCCHN. LASCCHN pose a clinical challenge to manage despite advances, options and strategies currently available. CCRT remains standard of care

**Table 3: Subgroup analysis of overall survival between the two groups with various factors**

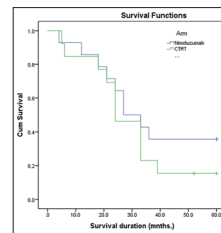
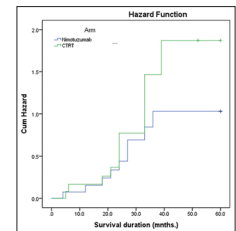
Parameter	CRT plus Nimotuzumab (Arm A=15)		CRT (Arm B=14)	
	n (%)	Mean OS (95% CI)	n (%)	Mean OS (95% CI)
Age				
≤65	13 (86.7)	37.6 (27.3-48.0)	13 (92.9)	28.9 (19.3-38.4)
>65	2 (13.3)	12.0 (12.0-12.0)	1 (7.1)	33 (33-33)
Gender				
Male	15 (100)	35.8 (25.6-46.1)	13 (92.9)	30.1 (20.7-39.5)
Female	0 (0)	- (-)	1 (7.1)	18 (18-18)
Histo-pathological type				
MDSCC	8 (53.3)	30.0 (19.3-40.7)	8 (57.1)	33.4 (19.3-47.5)
PDSCC	4 (26.7)	46.0 (22.2-69.7)	1 (7.1)	24 (24-24)
SCC	1 (6.7)	21.0 (21.0-21.0)	2 (14.3)	19 (0.0-46.4)
WDSCC	2 (13.3)	43.5 (20.6-66.3)	3 (21.4)	28 (18-37.8)
Chemotherapy type				
Cisplatin 40 mg	11 (73.3)	35.2 (21.9-48.4)	10 (71.4)	30.8 (19.5-42.2)
Cisplatin 50 mg	2 (13.3)	31.50 (22.6-40.3)	3 (21.4)	26 (6-45.8)
Carboplatin	2 (13.3)	43.5 (20.6-66.3)	0	-
Capecitabine	0	0	1 (7.1)	24 (24-24)

SCC=Squamous cell carcinoma, PDSCC=Poorly differentiated SCC, WDSCC=Well differentiated SCC, MDSCC=Moderately differentiated SCC, CI=Confidence interval, CRT=Chemo-radiotherapy, OS=Overall survival

**Table 4: Adverse events in chemo-radiotherapy plus nimotuzumab (Arm A) and chemo-radiotherapy (Arm B) treatment group**

Incidence of adverse events	Arm	
	Nimotuzumab (n=15), n (%)	CTRT (n=14), n (%)
Anemia	15 (100.0)	14 (77.8)
Leukopenia	15 (100.0)	13 (72.2)
Skin reaction	15 (100.0)	14 (77.8)
Anorexia	15 (100.0)	14 (77.8)
Hypomagnesemia (<1.8 mg/dl)	0 (0.0)	1 (5.6)
Skin rash	0 (0.0)	0 (0.0)
Dysphagia	15 (100.0)	14 (77.8)
Mucositis	15 (100.0)	14 (77.8)
Salivary gland changes	14 (93.3)	9 (50.0)
Weight loss	14 (93.3)	14 (77.8)
Alopecia	15 (100.0)	14 (77.8)

CTRT=Chemoradiotherapy

**Figure 1: Kaplan-Meier estimates of overall survival in chemo-radiotherapy plus Nimotuzumab (Arm A) and chemo-radiotherapy (Arm B) treatment group****Figure 2: Cumulative hazard for survival outcome in two arms**

in patients with LASCCHN.<sup>[4-6]</sup> The MACH-NC data laid the foundation for CCRT over other strategies. It detected reduction in deaths in favor of CCRT (hazard ratio: 0.81; 95% CI: 0.78–0.86;  $P < 0.0001$ ), and determining absolute survival benefit of 6.5% at 5 years.<sup>[6]</sup> However, they are associated with some increased risk of toxicities.<sup>[6]</sup> This warrants the discovery of novel treatment strategies to improve treatment outcomes without compromising the safety. EGFR represents a promising novel biological target in head-and-neck cancers. The overexpression of the EGFR levels is closely related to cancer cell growth, proliferation, invasion, metastasis, apoptosis, and poor prognosis. Inhibiting EGFR pathway can inhibit tumor cell proliferation, differentiation, tumor angiogenesis, and promote treatment response of chemotherapy and radiation.<sup>[15]</sup>

Nimotuzumab is a humanized anti-EGFR MAb which exerts dual action. First, it binds to the extracellular domain of the EGFR with intermediate affinity and high specificity which results in the blockade of receptor-dependent signal transduction pathways and exerts antitumor effects.<sup>[5,8]</sup> Second, it enhances the tumor radiosensitivity by inhibiting the radiation-induced activation of DNA-PKcs (blocking the PI3K/

AKT pathway).<sup>[16]</sup> BEST trial showed that the addition of nimotuzumab is beneficial in LASCCHN.<sup>[5]</sup> Recently, several authors in their individual research have documented that the addition of Nimotuzumab to CCRT improved tumor response rate and survival outcome with minimal toxicities.<sup>[11-14]</sup> However, majority studies are restricted by short-term assessment. In our study, addition of nimotuzumab to the standard CCRT resulted in improved survival rates than CRT alone in LASCCHN. The survival rate achieved in nimotuzumab plus CRT group at 5-year was 33.3%, while it was 7.1% in CRT group. At a median follow-up of 45.5 months, the median OS was 27 months in CRT group and 33 months in the nimotuzumab group. However, it is not statistically significant. The study also documented higher percentage of ORR and clinical benefit rate in Nimotuzumab plus CRT group than CRT alone. BEST trial documented 5-year OS in the nimotuzumab + CRT group was 57% versus 26% in CRT alone arm. Addition of nimotuzumab to CRT caused a 64% reduction in risk of death. Nimotuzumab was safe and well tolerated in all patients. Bhatnagar and Singh documented overall response rate was 96% in nimotuzumab + CRT arm versus 72% in CRT alone arm. Addition of nimotuzumab was found to be safe without serious adverse effects.<sup>[11]</sup> Somani *et al.* documented that at 6 months posttreatment with nimotuzumab and CRT, the ORR was 80.7%, with 34 patients (59.6%) achieving CR, and 12 (21%) achieving PR, SD in 8 (14%) patients and progressive disease in 3 (5.2%) patients. Nimotuzumab was found to be safe and without

serious adverse effects.<sup>[13]</sup> Subramaniam *et al.* in a retrospective study also documented that addition of nimotuzumab to induction chemotherapy with taxanes, platins, and fluorouracil regimen followed by concurrent Chemoradiotherapy (CRT) in inoperable, LA-SCCN patients resulted in improved tumor response rates and was well tolerated without any added toxicity.<sup>[14]</sup>

In our study, the AE profile observed in Nimotuzumab plus CRT group were similar to that of CRT group. The common AE's observed were Grade I/II which included mucositis, anemia and leukopenia which are similar to previous studies.<sup>[5,11-14]</sup> No Grade IV and V toxicity were observed in Nimotuzumab plus CRT group. No typical anti-EGFR-related toxicity like severe rash or hypomagnesemia or infusion reaction was observed. Nimotuzumab was observed to be safe with no added toxicity in this study. The benign adverse effect profile of Nimotuzumab over other Anti-EGFR drugs can be attributed to the fact that it requires bivalent binding for stable attachment, leading to selective binding to tumor cells expressing moderate-to-high EGFR levels.<sup>[17]</sup> It spares the healthy tissues which have low EGFR levels and thus avoids severe toxicities.<sup>[5,17]</sup>

An important aspect of tumor response is functional and metabolic response and thus PET-CT scan was done for all patients in pretreatment setting and on follow-up's. Seng Chuan Ong *et al.* reviewed the clinical utility of PET-CT in assessing the neck after CCRT for LASCCHN and concluded that 18F-Fluorodeoxyglucose (18F-FDG) PET/CT after CRT has a high negative predictive value (NPV) and specificity for excluding residual locoregional disease. Isles M G *et al.* reviewed the role of PET-CT in follow-up of LASCCHN and concluded that the sensitivity and specificity for detecting residual or recurrent disease was 94% and 82%, respectively. Yao M *et al.* studied the clinical significance of post-RT 18F FDG PET in the management of head-and-neck cancer and reported that the sensitivity, specificity, positive predictive value, and NPV in the neck was 86%, 97%, 71%, and 99%, respectively. Kyzas PA and Evangelou E *et al.* assessed the diagnostic accuracy of 18F-FDG PET in detecting lymph node metastases in patients with head-and-neck squamous cell carcinoma. In 32 studies which included 1236 patients, FDG PET sensitivity was 79% and specificity was 86%.

In summary, the addition of Nimotuzumab to CCRT showed improved survival rate in LASCCHN patients without producing additional toxicity. Although robust multicenter, randomized control trials with larger sample size are needed to validate these results. The study had limitations, the sample size was small, and the study was conducted at a single hospital setting.

## Conclusion

Addition of Nimotuzumab to CCRT showed improved tumor response rate and survival in LASCCHN patients without producing additional toxicity. The important highlights of this study were the safety, efficacy, and benign adverse effect profiles such as skin rash and serum magnesium levels. No incidence of skin rashes and hypomagnesemia was reported

during treatment and follow-up period. PET-CT scan was done for all patients to assess the functional and metabolic response, i.e., pretreatment and posttreatment follow-up (3 monthly for 1 year and then yearly).

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## Conflicts of interest

There are no conflicts of interest.

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