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

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Objective: Overexpression of epidermal growth factor receptor (EGFR) in many cancers makes it an attractive therapeutic target. This study evaluated the clinical utility of nimotuzumab, a monoclonal anti-EGFR antibody, used concurrently with radiotherapy (RT) and chemoradiotherapy (CRT) in squamous cell carcinoma of the head and neck (SCCHN).

Methods: This open-label study randomized 92 treatment-naïve patients (1:1) with advanced SCCHN into chemoradiation (CRT ± nimotuzumab) or radiation (RT ± nimotuzumab) group by investigator’s discretion; these were further randomized into CRT + nimotuzumab or CRT and RT + nimotuzumab or RT groups, respectively. Treatment included 6 cycles each of cisplatin (50 mg/week), nimotuzumab (200 mg/week), and RT (total dose, 60–66 Gy). Response (tumor size reduction) was assessed at Month 6 post-treatment and survival, at Month 60.

Results: Forty and 36 patients in the chemoradiation and radiation groups, respectively (intent-to-treat population) were evaluated. Overall response at Month 6 post-treatment was 100% with CRT + nimotuzumab, 70% with CRT, 76% with RT + nimotuzumab, and 37% with RT. At Month 60, overall survival was 57% with CRT + nimotuzumab, 26% with CRT (P = 0.03), 39% with RT + nimotuzumab, and 26% with RT (P > 0.05). Median overall survival was not reached for CRT + nimotuzumab; it was 21.94 months for CRT (P = 0.0078), 14.36 months for RT + nimotuzumab, and 12.78 months for RT (P = 0.45). Risk of death was 64% lower with CRT + nimotuzumab than with CRT (95%CI: 0.37, 1.56), and 24% lower with RT + nimotuzumab than with RT (95%CI: 0.16, 0.79). Thus nimotuzumab was safe and well tolerated with few mild to moderate self-limiting adverse events.

Conclusion: Concurrent use of nimotuzumab with CRT/RT is safe and provides long-term survival benefit.

Introduction

Head and neck cancers (HNCs) constitute approximately 5% of all cancers globally [1], with about 0.7 million new cases being diagnosed annually in India [2]. Of the 0.3 million annual cancer-related deaths in India, nearly 33% arise from tobacco-related HNCs [2]. Radiotherapy (RT) is the standard-of-care for the initial stages of HNC, while RT plus chemotherapy, particularly cisplatin, is used for non-resectable and locally advanced cases of squamous cell carcinoma of the head and neck (SCCHN) [3]. Though advantageous, combination therapies are associated with an increased risk of toxicity, with the average survival of patients being as low as 12 months, depending on various prognostic factors [3–7]. This warrants the discovery of novel treatment strategies to improve the overall survival outcome of SCCHN.

At the forefront of research are therapies involving molecular targets such as epidermal growth factor receptor (EGFR), a topic extensively researched over the last decade. EGFR overexpression has been observed in various cancers, including gliomas [8], sarcomas [9], and HNCs [10]. Its consequent downstream signaling could influence tumorigenesis and may even serve as a marker for identifying high-risk populations [11]. EGFR overexpression is also associated with poor prognosis in HNC and is implicated in...
the development of resistance to radiotherapy [12] and therapeutic drugs [13]. Thus, EGFR overexpression is an attractive target for cancer therapy.

The most commonly employed EGFR antagonists include antibodies (IMC-C225, also called cetuximab), small tyrosine kinase inhibitors (gefitinib, erlotinib), and pharmacological inhibitors of downstream mediators of the EGFR signaling pathway (tyrosinotins). These agents have shown encouraging results when used concurrently with conventional therapy [14–18]. Of particular interest is the development of EGFR-specific monoclonal antibodies that can inhibit the EGFR-mediated growth-signaling pathway, particularly in EGFR-dense cancer cells, leading to tumor cell death. The cetuximab plus RT or chemotherapy combination has shown better locoregional tumor control and survival compared to standard therapy in locally advanced SCCHN [5]. Pfister et al. studied cetuximab plus RT or chemoradiotherapy (CRT) and found the combination to be effective, though significant drug-related toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5]. The promising clinical efficacy of anti-EGFR antibodies on the one hand and their toxicities prompted early trial discontinuation [5].

Nimotuzumab is a humanized monoclonal antibody constructed by transplanting the conserved active domain of a murine antibody (anti-EGFR R3) to a human framework, using complementarity-determining region grafting [19]. It binds to the EGFR extracellular domain and inhibits receptor-ligand binding. The efficacy of nimotuzumab has been previously demonstrated in SCCHN patients. A placebo-controlled, double-blind, randomized clinical trial was conducted in 106 patients suffering from advanced SCCHN. A statistically significant correlation was observed between EGFR expression and survival in nimotuzumab-treated patients [20]. A striking outcome of nimotuzumab administration was the almost complete absence of severe adverse events (AEs) [20–22]. Unlike most anti-EGFR drugs, nimotuzumab caused minimal skin rash [22]. The current study evaluated the safety and efficacy of nimotuzumab, a radio-sensitizer, administered along with CRT or RT in patients with inoperable, locally advanced SCCHN by assessing the immediate response and long-term survival.

Methods

Study design

This open-label, randomized, phase IIb study was performed at 3 centers in India; approved by the respective institutional review boards or ethical committees (Trial registry: h-R3/SCCHN/001/IND); and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and Declaration of Helsinki (1996). Informed consent was obtained from all patients before study initiation. Initial safety and efficacy evaluation was conducted at 6 months post-treatment, and the final extended follow-up at 60 months post-treatment (Fig. 1A). The protocol amendment for the extended follow-up was approved by the respective institutional review boards or ethical committees.

Screening was performed at Visit 1, and randomization was conducted within 2 weeks of screening (Visit 2) (Fig. 1A). Six treatment cycles were administered, from Visit 2 through Visit 7 (6 weeks post-randomization). Follow-up visits (visits 8–11) occurred at 6-week intervals for 6 months following Visit 7. After Visit 11, magnetic resonance imaging (MRI)/computed tomography (CT) scans were carried out biannually during the follow-up phase of 54 months.

Patient eligibility

Patients aged 18–70 years with histologically proven stage III or IVA (T1–T4a, N0–N2) SCCHN who were suitable for concurrent CRT/RT, had a Karnofsky performance status of ≥60% with a life expectancy of >6 months, and adequate hematological function (white blood cell [WBC] count, >4000/µL; absolute neutrophil count [ANC], >1500/µL; platelets, >100,000/µL; total bilirubin, ≤1.2 mg/dL; aspartate aminotransferase [AST] and alanine aminotransferase [ALT], ≤2.5 times the normal limit [37 and 40 U/L, respectively]; serum creatinine, <1.4 mg/dL) were included. Patients for whom surgery was contraindicated owing to prohibitive morbidity or compromised quality of life were also included.

Exclusion criteria included nasopharyngeal carcinoma, history of malignancy other than nonmelanoma skin cancer or carcinoma-in situ of the cervix, evidence of distant metastases or concurrent secondary malignancy or T4b lesion, chemotherapy within 3 months before enrollment, prior RT to the head and neck, prior immunotherapy, increased risk of lethal infections and pharmacokinetic interactions with nimotuzumab, or history of allergy with similar biological compounds. Pregnant/lactating females and patients on other investigational drugs/devices were also excluded.

Interventions

Eligible patients were grouped based on the investigator’s discretion into Group I (chemoradiation group – patients suitable for chemotherapy) and Group II (radiation group – patients unsuitable for chemotherapy). Each group was further randomized in a 1:1 fashion—Group I into CRT + nimotuzumab or CRT and Group II into RT + nimotuzumab or RT (Fig. 1B). Every week, from Monday to Friday, 60–66 Gy of ionizing radiation was administered by conventional fractionation (2 Gy/fraction/day) for 6–6.5 weeks. The spinal cord was shielded to ensure a maximum of 45 Gy exposure. The radiation dose used in our study was similar to those previously used [23,24].

Nimotuzumab was administered on Thursdays (chemoradiation group) or Mondays (radiation group) by diluting 4 vials (50 mg each) in 250 mL of 0.9% saline to obtain a 200 mg suspension. The suspension was infused intravenously as a single dose over 1 h using an indwelling cannula placed in the forearm or the ante-cubital vein. A total of 6 doses (1 per week) were administered.

Cisplatin was administered on Mondays for 6 weeks as a continuous intravenous infusion over 2 h by diluting 50 mg in 1 L saline. This dose is similar to that used in previously published pivotal studies [25]. Chemotherapy was preceded by hydration with 1–2 L of fluid infused over 8–12 h. Nimotuzumab was administered 3 days after cisplatin in order to identify AEs related to either intervention separately.

Assessments

Baseline measurements included recording of medical history; physical and local examinations; head and neck MRI; chest radiography; abdominal ultrasonography; primary site biopsy; fine needle aspiration cytology (FNAC) of the neck nodes where relevant; histopathological examination; Multiple Gated Acquisition Scan (MUGA); oral and throat swabs for bacterial and fungal culture and sensitivity; blood samples for hematological, biochemical, and serological estimations; and complete urine analysis.

At baseline, measurable lesions—a maximum of 5 lesions per organ and 10 lesions in total—were identified as target lesions; these were selected based on their size (lesions with the longest diameter [LD]) and suitability for accurate repeated measurements. Lesions with at least 1 dimension measuring ≥20 mm by
conventional techniques or \( P \geq 10 \text{ mm} \) by spiral CT were considered as measureable lesions. The sum of the LDs of all target lesions was calculated and reported as baseline sum LD, which was used as the reference for tumor response. MRI was conducted at the screening visit and subsequently at visits 9 (12 weeks after Visit 7) and 11 (24 weeks after Visit 7) to assess treatment response in terms of tumor size. During Visit 8 and Visit 10, tumor assessment was done clinically. Subjects who received all 6 doses of nimotuzumab and had at least 1 MRI were considered evaluable. Follow-up for survival was performed every 2 months up to 60 months.

Response and progression were evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) [26]. Toxicity assessments were performed at all visits according to the common toxicity criteria of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).

**Primary endpoint**

The primary endpoint included response rates for outcomes [complete response (CR), partial response (PR), progression of disease (PD), and stable disease (SD)] at Month 6, based on MRI data. CR was defined as disappearance of all target lesions; PR, as \( P \geq 30\% \) reduction in the sum LD of target lesions compared to the baseline sum LD; objective response rate (ORR), as the sum of CR and PR; and PD, as \( P \geq 20\% \) increase in tumor size compared to the nadir size. These endpoints were based on previously published pivotal trials [27] and are well accepted in oncology studies [28]. The disease was considered stable if neither a sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD was noted. Safety was assessed based on the incidence, severity, and relationship to study drug of the AEs and serious adverse events (SAEs).
Secondary endpoints

Secondary endpoints included assessment of progression-free survival (PFS) and overall survival. PFS was defined as the duration from start of treatment to progression of the disease/last scheduled visit.

Tertiary endpoints

Tertiary endpoints included evaluation of EGFR expression using immunohistochemical staining. Low-to-moderate EGFR expression was defined as 26–90% positive tumor cells; high EGFR expression, as >90% positive tumor cells [29].

Statistical analysis

The tested one-sided null hypothesis was the absence of difference in safety or efficacy when nimotuzumab is used as an adjuvant with standard therapy (CRT and RT or RT alone). According to the George W. Snedecor and William G. Cochran method [30], the sample size was 17 patients per arm, calculated by assuming \( P < 0.05 \) (5%), \( \beta < 0.2 \) (20%), power = 0.80 (80%), and a confidence interval (CI) of 95%.

For efficacy, intent-to-treat (ITT) analysis was performed following the last-observation-carried-forward (LOCF) principle. Data were evaluated using a Chi-square test and Fisher’s exact probability test, as appropriate. Median overall survival along with 95% CI, mean, and the standard error for the respective arms was estimated by the Kaplan–Meier method. The \( P \) value for comparison of survival distribution was obtained using the log-rank test. Hazard ratio (HR) along with 95% CI was determined by fitting the Cox proportional regression model. A \( P \) value of <0.05 was considered significant.

Results

Patient characteristics

Between September 2004 and July 2005, 113 patients were screened; 92 treatment-naive patients were enrolled and assigned into respective randomization groups. The chemoradiation group included 46 patients; 23 received CRT + nimotuzumab and 23 received CRT; 20 patients were evaluable and 3 patients were non-evaluable in each arm. Similarly, in the radiation group, 23 patients received RT + nimotuzumab and 23 received RT (Fig. 1B); 17 and 19 patients were evaluable, and 6 and 4 patients were non-evaluable in the RT + nimotuzumab and RT arms, respectively. All 4 arms had similar baseline and demographic characteristics (Table 1). The mean age ranged from 49.9 to 58.7 years. About 70% had regionally advanced tumors (N2 and N3), and close to 90% had stage IV disease.

Primary endpoint

ORR was significantly higher in the CRT + nimotuzumab arm than in the CRT arm (20/20, 100% vs. 14/20, 70%; \( P = 0.020 \)). Likewise, in the radiation group, ORR was significantly higher in the RT + nimotuzumab arm than in the RT arm (13/17, 76.47% vs. 7/19, 36.84%; \( P = 0.023 \)) (Table 2). PD was 0% (0/20), 30% (6/20), 23.5% (4/17), and 57.5% (11/19) in the CRT + nimotuzumab, CRT, RT + nimotuzumab, and RT arms, respectively. In the RT arm, 5.26% (1/19) patients showed SD as compared to 0% in other arms.

Secondary endpoints

The 5-year overall survival was significantly higher in the CRT + nimotuzumab arm than in the CRT arm (57% [95% CI: 34.49, 76.81] vs. 26% [95% CI: 10.23, 48.41]; \( P = 0.03 \)), and was 39% (95% CI: 19.71, 61.46) in the RT + nimotuzumab arm versus 26% (95% CI: 10.23, 48.41; \( P > 0.05 \)) in the RT arm. The median 5-year overall survival was yet to be met in the CRT + nimotuzumab arm, whereas it was 21.94 months in the CRT arm (\( P = 0.0078 \)); the addition of nimotuzumab to CRT caused a 64% reduction in death risk (HR = 0.36, 95% CI: 0.37, 1.56). The median 5-year overall survival in the RT + nimotuzumab arm was 14.36 months and was higher than the 12.78 months noted in the RT arm; the difference was not statistically significant (\( P = 0.45 \)), and the addition of nimotuzumab to RT caused a 24% reduction in death risk (HR = 0.76, 95% CI: 0.16, 0.79) (Fig. 2A).

At the 5-year follow-up, when the overall survival of patients receiving CRT + nimotuzumab and RT + nimotuzumab (\( n = 46 \)) was compared to that of patients who did not receive nimotuzumab (\( n = 46 \)), the former demonstrated a significantly better survival (49.38 vs. 16.36 months; \( HR = 0.52, 95\% CI: 0.30, 0.89; P = 0.012 \)) and a 48% reduction in death risk (Fig. 2B).

The 5-year PFS was 47.83% (95% CI: 27.41, 68.24) in the CRT + nimotuzumab arm, 26.09% (95% CI: 8.14, 44.03) in the CRT arm, 39.13% (95% CI: 19.19, 59.08) in the RT + nimotuzumab arm, and 26.09% (95% CI: 8.14, 44.03) in the RT arm. The median 5-year PFS was 54.24 months in the CRT + nimotuzumab arm and was significantly higher than the 14.95 months observed in the CRT arm (\( P = 0.036 \)). The median 5-year PFS was 14.29 and 9.76 months in the RT + nimotuzumab and RT arms, respectively (\( P = 0.41 \)).

EGFR expression

In the CRT + nimotuzumab arm, 21.7% and 43.5% patients, respectively, had low-to-moderate and high EGFR expression; the corresponding percentages in the CRT arm were 52.1% and 39.1%. Similarly, in the RT + nimotuzumab arm, 34.7% and 30.4% patients, respectively, had low-to-moderate and high EGFR expression as compared to 52.1% and 30.4%, respectively, in the RT arm. No correlation was found between EGFR expression and response at Month 6 post-treatment or survival at Month 60 post-treatment, although the numbers were too small to draw conclusions.

Safety analysis

Table 3 shows grade 3 events across all study arms. The nimotuzumab-related AEs in the chemoradiation group included asthenia (grade 1/2), dizziness, hematuria (microscopic), vomiting, and loose stools. The AEs were mild-to-moderate in severity, self-limiting, reversible, and probably or possibly related to nimotuzumab, except grade 1/2 rash and chills that were considered as certainly related to nimotuzumab. The common nimotuzumab-related AEs in the radiation group were fever, chills, pruritus, urticaria/rash, headache, hypertension, and fluctuation in blood pressure. Infusion of nimotuzumab neither interfered with chemotherapy nor increased RT-related morbidities. No death was attributed to the study drug. Skin rash occurred in 2 patients in the RT + nimotuzumab arm and 1 patient in the RT arm. No long-term drug-related toxicity was seen during the median follow-up of 65.7 months.

One patient in the RT + nimotuzumab arm had an SAE of anaphylactic reaction with skin rash, which was treated with symptomatic therapy; this patient was withdrawn from the trial. First-dose-infusion reaction was observed in 3 patients who recovered without any sequelae and could withstand subsequent infusions of nimotuzumab. At the 2-year analysis, there were a total of 4,
Table 1
Demographic and baseline data.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chemoradiation group</th>
<th>Radiation group</th>
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<tr>
<td></td>
<td>CRT + nimotuzumab (n = 23)</td>
<td>CRT (n = 23)</td>
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<tr>
<td>Age (years) Mean (SD)</td>
<td>49.87 (10.57)</td>
<td>53.65 (9.03)</td>
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<tr>
<td>Median (range)</td>
<td>50 (27–65)</td>
<td>55 (30–68)</td>
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<td>Gender (%)</td>
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<tr>
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<td>Female</td>
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<td>KPS n (%)</td>
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<td>70</td>
<td>5 (21.74)</td>
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<td>80</td>
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<td>90</td>
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<td>8 (34.78)</td>
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<td>Primary tumor site (%)</td>
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<td>(n = 20)</td>
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<td>Tobacco chewing, n (%)</td>
<td>Occasionally</td>
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<td>1 (4.76)</td>
<td>1 (5.26)</td>
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<tr>
<td>Tobacco smoking, n (%)</td>
<td>Occasionally</td>
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<tr>
<td>Heavily</td>
<td>1 (4.35)</td>
<td>4 (21.5)</td>
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<td>(n = 11)</td>
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<td>Alcohol, n (%)</td>
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Abbreviations: CRT, chemoradiotherapy; KPS, Karnofsky performance status; RT, radiotherapy.
to CRT had clinical merits. The ORR at 6 months was 100% for the combination, with a 5-year overall survival of 57%. The CRT + nimotuzumab combination offered an overall survival benefit and was well tolerated without an increase in treatment-related toxicities.

Bonner et al. reported an ORR of 74% and an overall survival of 45.6% at 5 years using cetuximab, which is in agreement with our data with nimotuzumab and RT [15,27]. In these studies, patients having locoregionally advanced HNC were treated with either RT or RT + cetuximab, and the ORR was assessed as a sum of CR and PR. Although cetuximab prolonged the PFS, certain severe side effects such as rash were reported.

Interestingly, patients who received concurrent nimotuzumab in the current study showed a statistically significant improvement in the 5-year overall survival as compared to patients who did not receive nimotuzumab, which is in agreement with results reported previously [20]. These results strongly suggest that nimotuzumab contributes to improving locoregional control and helps prolong survival when used along with RT or CRT.

EGFR overexpression is known to cause radioresistance in cells [12], since EGFR and downstream Akt signaling are known key players in mediating cell survival following irradiation [31,32]. It is therefore possible that the anti-EGFR agents have a dual mode of action. First, they inhibit the EGFR-signaling pathway and reduce the rate of cellular proliferation, and second, they negate the EGFR-mediated radioresistance and sensitize malignant cells to concomitant RT. Wang et al. showed that pre-treatment of cells with EGFR inhibitors increased radiation-induced apoptosis by more than 3-fold [31]. These data suggest that RT and EGFR inhibitors may act additively or, maybe, even synergistically in promoting tumor cell death. Similarly, EGFR antagonists may augment the tumor response to chemotherapy since EGFR overexpression is also known to cause resistance to chemotherapeutic agents [33]. In our study, addition of nimotuzumab to conventional therapy resulted in prolonged survival, which is in agreement with these findings.

Furthermore, ionizing radiation generates free radicals that create a state of intracellular oxidative stress. It has been shown that free radicals such as H2O2 trigger Akt signaling via an EGFR-dependent pathway and that elevated Akt activity confers protection against oxidative stress-induced apoptosis [34]. Thus, the use of EGFR inhibitors may enhance tumor cell killing by limiting the free radical-induced Akt-mediated cell survival following irradiation.

The exceptional safety profile of nimotuzumab, as shown in our study, has been previously reported [20,22]. While other EGFR monoclonal antibodies show a high incidence of skin toxicities (60–80%) [35], in our study, skin rash was observed in approximately 6.5% of the patients. The enhanced safety can be attributed to the fact that unlike other anti-EGFR antibodies, nimotuzumab requires bivalent binding for stable attachment, leading to selective binding to cells expressing moderate to high EGFR levels. When EGFR density is low, such as in normal tissues, nimotuzumab monovalent interaction is transient, thus sparing healthy tissues and avoiding severe toxicities [36].
Our study has a few limitations such as an unconventional trial design and imbalance in the baseline characteristics for stage of disease and histopathology between the nimotuzumab and control groups. However, in comparison to trials with other monoclonal antibodies that required treatment discontinuations due to hypersensitivity reactions, grade 3 or 4 toxicities, dose reductions, or trial terminations [3], our study showed nimotuzumab as a safe and well-tolerated drug.

Conclusion

Our findings support the use of nimotuzumab with CRT/RT as a viable therapeutic option in patients with inoperable, locally advanced SCCNH. Well-designed, late-stage clinical trials are, however, needed to further validate these findings.

Conflict of interest statement

None declared.

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