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# A phase I study of nimotuzumab in combination with radiotherapy in stages IIB–IV non-small cell lung cancer unsuitable for radical therapy: Korean results

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### ABSTRACT

**Purpose:** This study was undertaken to determine safety and tolerability of nimotuzumab, a humanized anti-epidermal growth factor receptor monoclonal antibody, in combination with radiotherapy in stages IIB–IV non-small cell lung cancer (NSCLC) patients who are unsuitable for radical therapy or chemotherapy.

**Methods:** Nimotuzumab (100 mg, 200 mg and 400 mg) was administered weekly from week 1 to week 8 with palliative radiotherapy (30–36 Gy, 3 Gy/day). If tumor control was achieved, nimotuzumab was continued every 2 weeks until unacceptable toxicity or disease progression. Serial skin biopsies were collected for pharmacodynamic assessment.

**Results:** Fifteen patients were enrolled in the study, with cohorts of five patients assigned in each dose level of nimotuzumab. Patients and disease characteristics included median age 73 years; Eastern Cooperative Oncology Group performance status (PS) 0–1/2 ( $n=3/12$ ); female sex ( $n=2$ ); adenocarcinoma ( $n=5$ ); never-smoker status ( $n=2$ ); and stages IIB/IIIB/IV ( $n=1/8/6$ ). All patients were unable to tolerate radical therapy because of old age or multiple comorbidities. The most commonly reported adverse events were lymphopenia and asthenia (grades 1–2 in most patients). No skin rash or allergic toxicities appeared. Dose-limiting toxicity occurred with pneumonia with grade 4 neutropenia at the 200 mg dose of nimotuzumab. Objective response rate and disease control rate inside the radiation field were 46.7% and 100.0%, respectively.

**Conclusions:** Nimotuzumab in combination with radiotherapy is well-tolerated and feasible. Further clinical investigation of nimotuzumab in NSCLC patients is warranted.

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## 1. Introduction

In NSCLC patients not suitable for radical treatment, the main aim of treatment is palliation. Palliative radiotherapy (RT) remains a therapeutic option, because of its low toxicity [1]. Combined modalities, such as radiotherapy plus targeted agents which result in both radiosensitization and treatment of extra-thoracic metastases, need to be evaluated as additional treatment options.

Epidermal growth factor receptor (EGFR) has emerged as an important therapeutic target in NSCLC, because its activation causes the phosphorylation of multiple downstream cascades,

which promote cell growth, proliferation, invasion, angiogenesis, and metastasis [2]. Two different EGFR inhibition strategies are currently active or under development for NSCLC, namely, tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) [3–5]. These agents have been shown to improve treatment results in patients with metastatic NSCLC and may be alternatives in patients that cannot tolerate conventional chemotherapeutic agents.

Combining radiotherapy with EGRF inhibitors offers an attractive strategy, because radiation rapidly upregulates EGFR expression on cancer cells, and because EGFR expression is correlated with radiation resistance [6,7]. Furthermore, concurrent cetuximab and radiotherapy has been shown to have clinical benefit in head and neck cancer as compared with radiotherapy alone [8].

Nimotuzumab (h-R3) is a humanized anti-EGFR monoclonal antibody that is currently under investigation. Furthermore, nimotuzumab has demonstrated antitumor effects in various tumors in

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preclinical studies, and has been found to enhance the antitumor efficacy of radiation in EGFR-expressing NSCLC cell lines [9,10].

Utilizing this rationale, we conducted a phase I study to evaluate the safety and tolerability of nimotuzumab plus radiotherapy in stages IIB–IV NSCLC patients who were unsuitable for radical treatment.

## 2. Patients and methods

This was a single-center, phase I, open-label, dose-escalating trial of nimotuzumab plus radiotherapy in Korean NSCLC patients. The primary objectives were to determine the safety and feasibility of this combined treatment. The secondary objectives were to determine survival, overall response and local response and disease control rates.

Eligible patients were 18 years of age or older with pathologically confirmed stages IIB–IV NSCLC. Patients were fit palliative radiotherapy but not for radical therapy or systemic combination chemotherapy. Additional eligibility criteria were as follows: an anticipated life expectancy of more than four weeks, normal organ function, and at least one uni-dimensionally measurable lesion. Exclusion criteria included prior thoracic radiotherapy, prior therapy with anti-EGFR drugs, progressive and symptomatic brain metastases, any severe uncontrolled medical illness, and pregnancy or breast-feeding.

Patients received nimotuzumab (h-R3, TheraCIM®) 100 mg, 200 mg, or 400 mg once a week for 8 weeks, which was administered by a short intravenous infusion (30 min) with 250 ml of saline solution. Premedication with antihistamine or steroids was not needed. Weekly doses of nimotuzumab were administered 2–6 h after a radiotherapy session. After 8 weekly doses had been administered, and if tumor control had been achieved, nimotuzumab administration was continued every 2 weeks starting at week 10 and continued for up to 18 months or until disease progression or clinical deterioration. Radiotherapy consisted of standard palliation therapy at doses of 30–36 Gy administered in 10–12 sessions, 5 sessions per week starting on day 1. The target radiotherapy volume included the primary tumor and involved lymph nodes, but not extra-thoracic sites. All patients underwent CT simulation prior to starting radiation. Patients were treated using a linear accelerator with a beam energy not exceeding 10 MV and two opposing anterior-posterior/posterior-anterior fields were used (Fig. 1). This study was undertaken after obtaining approval by a local Human Investigations Ethical Committee and informed consent was obtained from each patient.

Adverse events were evaluated using NCI-CTC, version 3.0. Toxicity assessments were made weekly during the induction period, and then fortnightly. Evaluation of treatment response by CT was performed in the ninth treatment week, and, thereafter, every two months using the Response Evaluation Criteria for Solid Tumors (RECIST). Both local response rate (RR) in the field of radiation and systemic RR were evaluated. Disease control rate (DCR, which includes the complete and partial response, plus stable disease) was also assessed. Response was the best response recorded from the start of the study treatment until end of treatment. Survival analysis was calculated using the Kaplan–Meier estimator.

Dose-limiting toxicities (DLTs) were defined as any grade 3 or grade 4 toxicity (other than grade 3 nausea/vomiting). Maximal tolerated dose (MTD) was defined as the nimotuzumab dose at which three or more of the ten patients experienced DLT. Five patients were treated first at each dose level. If none or only one of the first five patients experienced DLT, dose escalation of nimotuzumab proceeded to the next level. If any DLT occurred in two patients, five additional patients were to be treated at the same dose level, and if DLT was observed again, MTD was considered reached. On the other

**Table 1**  
Patient characteristics.

Characteristic	No. of patients (N = 15)	%
Age, years		
Median	73 (range: 60–87)	
Sex		
Female	2	13.3
Male	13	86.7
ECOG performance status		
0–1	3	19.9
2	12	80.1
Smoking history		
Current smoker	10	66.7
Former smoker <sup>a</sup>	3	20.0
Never smoker	2	13.3
Histology		
Adenocarcinoma	5	33.3
Squamous cell carcinoma	8	53.4
NSCLC, NOS	2	13.3
Stage		
IIB (T2N1)	1	6.6
IIIB	8	53.4
IV	6	40.0
EGFR status <sup>b</sup>		
Mutation	0	0
K-ras status <sup>b</sup>		
Mutated	0	0

Abbreviation: ECOG, Eastern Cooperative Oncology Group; NSCLC, 2NOS, non-small cell lung cancer, not otherwise specified.

<sup>a</sup> Former smokers were defined as persons who stopped smoking more than 1 year previously.

<sup>b</sup> Biomarker analyses were performed in five patients with available paraffin-embedded tumor samples.

hand, if no additional DLT occurred, dose escalation continued up to a maximum of 400 mg.

Pharmacodynamic (PD) analysis was performed after protocol amendment. Skin biopsies from a clinically normal skin area were collected before the first dose of nimotuzumab and after two and eight weeks of treatment. Immunohistochemical analysis of EGFR phosphorylation, receptor signaling (phosphorylated ERK and phosphorylated STAT3), Ki-67 expression, p27<sup>KIP1</sup> and Keratin 1 were performed as described previously [11]. In order to correlate clinical data with biomarkers, we analyzed the EGFR mutation (exons 18–21) and the K-RAS mutation (exon 2). Nucleotide sequences of the kinase domains of EGFR and K-RAS mutations were identified as published [12].

## 3. Results

### 3.1. Patient and characteristics

Between January 2007 and December 2008, a total of 15 patients were enrolled. Patient demographics are listed in Table 1.

### 3.2. Toxicities and tolerability

Treatment with nimotuzumab and radiotherapy was well tolerated. All patients completed planned radiotherapy; eight patients received 30 Gy and seven patients received 36 Gy.

The treatment toxicities encountered during the induction period are shown in Table 2. At 200 mg, one patient developed DLT. This 75-year-old male patient experienced grade 4 pneumonia with neutropenia during the sixth week. After supportive care, his condition was improved without ventilatory support. The causative organism was not isolated and his anti-tumor

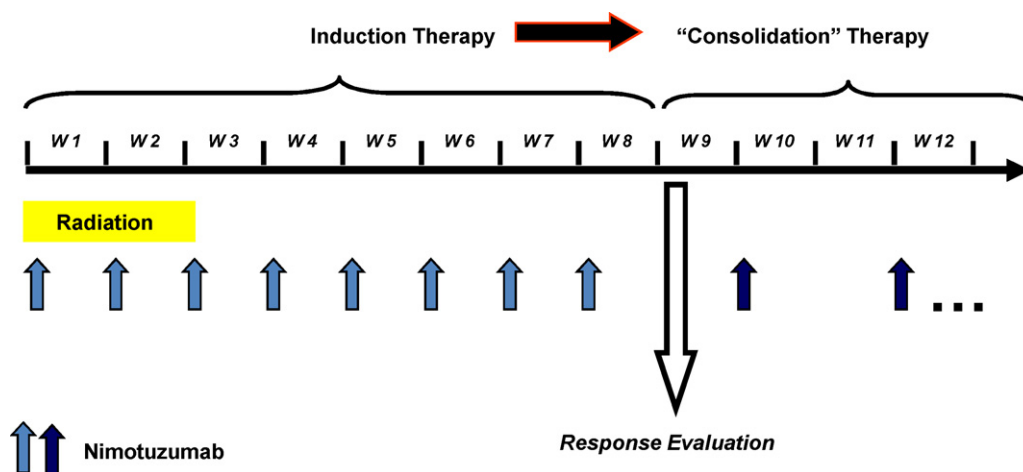


Fig. 1. Treatment schedule.

treatment was stopped. No DLTs occurred in the other patients. The most common adverse events were lymphopenia (86.7%), asthenia (40%), and anorexia (33.3%). Four patients developed radiation pneumonitis, which again resolved with supportive care. No skin rashes or allergic reactions, which are commonly encountered with other EGFR mAbs, appeared. Eight patients received maintenance nimotuzumab therapy, and toxicities during maintenance were mild (Table 3). The median number of nimotuzumab

doses administered during the maintenance phase was 10 (range, 8–24).

3.3. Efficacy

Fifteen patients were evaluated for response. Seven patients achieved partial response and two had stable disease. Six patients [two stage IIIB; four stage IV] had progressive disease due to pro-

Table 2  
Adverse events during induction phase.

Adverse events	100 mg (n = 5)		200 mg (n = 5)		400 mg (n = 5)	
	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3
<b>Hematological</b>						
Lymphopenia	4	2	4	2	5	2
Neutropenia	1	0	0	1 <sup>a</sup>	0	0
Anemia	1	0	1	0	0	0
Thrombocytopenia	3	0	0	0	0	0
<b>Constitutional symptoms</b>						
Asthenia	4	0	0	0	2	0
Insomnia	1	0	0	0	0	0
Fever	1	0	0	0	0	0
<b>Gastrointestinal</b>						
Anorexia	3	0	2	0	0	0
Nausea/vomiting	3	0	1	0	1	0
Diarrhea	2	0	0	0	1	0
Dyspepsia	3	0	1	0	0	0
Stomatitis	0	0	0	0	2	0
Esophagitis	1	0	1	0	2	0
<b>Metabolic/laboratory</b>						
AST elevation	1	0	2	0	1	0
Hypocalcemia	2	0	0	0	2	0
Hypomagnesemia	1	0	0	0	0	0
Hyponatremia	2	0	1	0	0	0
Low bicarbonate	2	0	0	0	0	0
<b>Pulmonary/upper respiratory</b>						
dyspnea	4	0	0	0	0	0
Radiation pneumonitis	1	0	2	0	1	0
<b>Infection</b>						
Pneumonia with neutropenia	0	0	0	1 <sup>a</sup>	0	0
<b>Neurology</b>						
Dizziness	1	0	0	0	1	0
<b>Dermatology/skin</b>						
Flushing	2	0	0	0	0	0
Nail Change	0	0	0	0	1	0
Hand-foot skin reaction	0	0	0	0	1	0

<sup>a</sup> DLT.

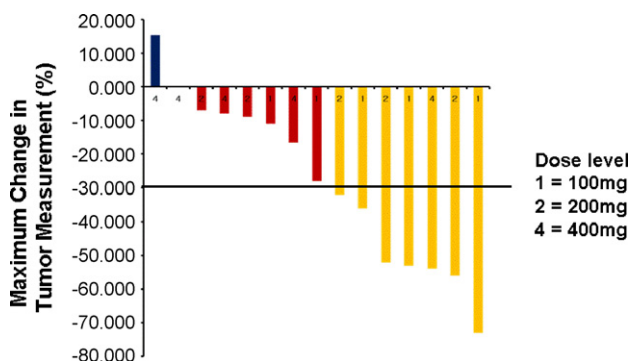
**Table 3**  
Adverse events during maintenance phase.

Adverse events	100 mg (n = 4)		200 mg (n = 2)		400 mg (n = 2)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
<b>Hematological</b>						
Lymphopenia	3	0	2	0	2	0
Thrombocytopenia	1	0	0	0	0	0
<b>Constitutional symptoms</b>						
Asthenia	4	0	2	0	1	0
Insomnia	0	0	1	0	0	0
<b>Gastrointestinal</b>						
Anorexia	4	0	2	0	1	0
Nausea/vomiting	2	0	1	0	0	0
Diarrhea	2	0	0	0	0	0
Dyspepsia	1	0	1	0	0	0
Stomatitis	0	0	0	0	1	0
<b>Metabolic/laboratory</b>						
AST elevation	1	0	0	0	0	0
Hypocalcemia	1	0	0	0	1	0
Low bicarbonate	1	0	0	0	1	0
<b>Neurology</b>						
Dizziness	1	0	1	0	0	0
<b>Dermatology/skin</b>						
Nail change	1	0	0	0	0	0
Hand-foot skin reaction	0	0	0	0	0	0

gression at metastatic sites outside the radiation field or a newly developed metastatic lesion. The effect on local disease activity inside the radiation field was positive, which was supported by a local response rate of 46.7% and disease control rate of 100% (Fig. 2). With a median follow up duration of 9.1 months (95% confidence interval (CI), 6.1–12.1 months), median time to progression and overall survival were 5.4 months (95% CI, 0.9–9.9 months) and 9.8 months (95% CI, 6.5–13.1 months), respectively.

**3.4. Pharmacodynamic analysis**

A skin biopsy was taken from 10 patients in the 200 mg and 400 mg cohorts, and three pretherapy and on-therapy biopsy samples were available for seven patients. Nimotuzumab did not suppress EGFR phosphorylation, receptor signaling, or keratinocyte proliferation (Ki-67). In addition, the expressions of p27<sup>KIP1</sup> and Keratin 1 were not increased, and the characteristic thinning of the stratum corneum and folliculitis induced by other EGFR inhibitors were not observed.



**Fig. 2.** Waterfall pilot of response inside radiation field. Percentage change in tumor size at 9 weeks from baseline in each patient according to RECIST.

**3.5. Biomarker**

Neither the EGFR mutation nor amplification of the K-RAS mutation was detected in the five patients with a paraffin-embedded tumor sample available.

**4. Discussion**

This study demonstrates the tolerability of combining nimotuzumab with thoracic radiotherapy in Korean NSCLC patients. Our patients were considered unsuitable for radical therapy or chemotherapy because of old age, poor PS, or multiple morbidities, and thus, in this study poor risk patients were enrolled. Nevertheless, the toxicity profile of combined nimotuzumab and radiotherapy appeared favorable, and in particular, field complications were mild. Grade 1/2 radiation pneumonitis and esophagitis each occurred in four patients. The tolerability of this combination has already been assessed in previous studies [13,14].

In addition, treatment with nimotuzumab and radiotherapy showed notable antitumor efficacy, in that a 46.7% response rate and 100% disease control rate were achieved inside irradiated regions. Despite the small number of patients recruited and the heterogeneity of disease stages, the results of the nimotuzumab and RT combination were promising enough to be worthy of further investigation.

Although some studies have demonstrated the association of skin toxicities with tumor response of EGFR targeting agents, skin rash can lead to a decreased quality of life and compromise the patient's compliance. In view of the absence of rash, nimotuzumab has distinct clinical benefit, compared with other EGFR targeting agents [15].

After the approval of EGFR-TKIs for salvage treatment in advanced NSCLC, further exploration identified clinical and molecular predictive markers: adenocarcinoma histology, a female gender, a never-smoking status, East Asian ethnicity, and the presence of EGFR mutations [16,17]. Higher frequencies of activating EGFR mutations have been observed in East Asian patients, and this is probably responsible for ethnic differences in responsiveness to

EGFR-TKIs [18]. When conducting new clinical trials on anticancer drugs, possible associations between ethnicity and response should be considered. In this regard, it is noteworthy to have conducted same studies in Korea and Canada in parallel [19].

EGFR mAbs, which target the extracellular domain of the receptor, have effects that differ from those of EGFR TKIs. Therefore, responsiveness to nimotuzumab may be related to level of EGFR expression rather than to EGFR mutation. In addition, K-RAS mutations have been identified as predictors of non-responsiveness to EGFR-targeting agents [20]. In the present study, we could not draw any definitive conclusions on this topic because only five patients underwent biomarker analysis. Further studies are required to determine which of the molecular determinants influence nimotuzumab activity.

In conclusion, nimotuzumab and radiotherapy combination therapy was found to be well tolerated and feasible. Future clinical investigation of nimotuzumab is warranted in NSCLC patients.

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