

Phase I clinical trial of the anti-EGFR monoclonal antibody nimotuzumab with concurrent external thoracic radiotherapy in Canadian patients diagnosed with stage IIb, III or IV non-small cell lung cancer unsuitable for radical therapy

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Abstract

Purpose Many patients with non-small cell lung cancer (NSCLC) are eligible only for palliative radiation (RT) at presentation. This study was designed to assess the feasibility of adding the anti-EGFR monoclonal antibody nimotuzumab to palliative thoracic RT.

Methods Patients with stage IIB, III or IV NSCLC considered unsuitable for radical radiation or chemo-radiation received nimotuzumab weekly 8× (100, 200 or 400 mg) with radiation (30 or 36 Gy in 3 Gy fractions). If response or disease stability was observed, nimotuzumab was continued every other week starting from week 10 until progression or toxicity.

Results Eighteen patients were enrolled: 6 at 100 mg, 7 at 200 mg, 5 at 400 mg nimotuzumab. Patient characteristics included median age 69 years, 11 males, 17 smokers, 17 Caucasians, stage IIIA/IIIB/IV 2/7/9, 5 Eastern Cooperative Oncology Group performance status (PS) 2; 9 adenocarcinoma. The most commonly reported adverse events were fatigue, anorexia, chills, pain and hypophosphatemia (grades 1 to 2 in most patients). No severe skin or allergic toxicity was noted. No dose-limiting toxicity was encountered. Objective response rate and disease control rate inside the radiation field were 66 and 94.0%, respectively.

Conclusion Nimotuzumab administered concurrently with palliative thoracic radiation is well tolerated at each of the three doses investigated in NSCLC patients unsuitable for radical treatment. The low toxicity and absence of rash make this combination therapeutically attractive for frail patients with other co-morbidities and poor performance status. These results support further testing of this regimen in the phase II setting.

Keywords Nimotuzumab · Non-small cell lung cancer · Monoclonal antibody · Clinical trial · Toxicity

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Introduction

Non-small cell lung cancer (NSCLC) remains a leading cause of cancer deaths [1]. Many NSCLC patients are ineligible for curative-intent treatment at presentation because of advanced stage or poor performance status. For these, palliative thoracic radiation can provide significant symptomatic relief [2]. Nevertheless, prognosis for these patients is poor, and new treatments to improve local and distal disease control in this population are clearly needed [3, 4].

Over-expression of the epidermal growth factor receptor (EGFR) is associated with many malignancies, including NSCLC, and altered EGFR signaling is implicated in cell proliferation, apoptosis resistance, angiogenesis, invasion, and metastasis [5, 6]. EGFR small molecule tyrosine kinase inhibitors (TKI) have demonstrated anti-tumor activity in NSCLC and are now approved as single agents in the first-, second- and third-line setting for advanced disease [5, 7–9]. Similarly, anti-EGFR monoclonal antibodies (mAb) have demonstrated efficacy in the treatment of several cancers in combination with chemotherapy, including NSCLC [10–12]. All these agents are associated with skin toxicity, commonly an acneiform rash, skin dryness and/or nail changes. In the case of the anti-EGFR mAbs, the skin toxicity can be severe, adversely affecting quality of life [13, 14]. A therapeutically effective anti-EGFR mAb that does not cause skin rash is clearly clinically desirable.

Nimotuzumab, an anti-EGFR mAb, was originally isolated as a mouse IgG2a antibody (R3) and humanized by grafting its complementarity-determining regions (CDRs) to a human IgG1 gene [15–17]. It has shown promising phase I activity in head and neck cancers [18] and pediatric primary brain tumors [19, 20]. In several trials, it has shown activity and been well tolerated when used together with radiation [21]. In contrast to other anti-EGFR mAbs, its administration is not associated with a severe acneiform rash. Preclinical data have suggested that nimotuzumab may enhance the anti-tumor activity of ionizing radiation [22] (reviewed in [23]). Clinical experience has demonstrated good tolerability of nimotuzumab at 50–800 mg doses when given as a single agent [24] or in combination with radiation to head and neck [25, 26] and brain tumors in both the adult [18] and pediatric setting [20]. However, the utility of nimotuzumab in the treatment of NSCLC has not been thoroughly investigated either as a single agent or concurrently with radiation. Given the need to improve outcome in NSCLC and the molecular rationale of targeting EGFR in this disease, we set out to assess the feasibility and tolerability of combining nimotuzumab with palliative dose external beam thoracic radiation in NSCLC patients deemed ineligible for radical treatment.

Methodology

Objective and end points

The primary objectives of this study were to evaluate the safety and feasibility of administering nimotuzumab concurrently with palliative external beam thoracic radiation to patients with NSCLC and to select a dose for a subsequent phase II study. Secondary objectives were to determine response rate within the radiation field, overall survival and

define the maximal tolerated dose if encountered in the study.

Study design

This was a lead-in, phase I, multi-institutional, single-agent, open-label study. Approval by the local ethics committee was obtained at each of the participating centers. Patients meeting the eligibility criteria and providing written informed consent were accrued at three Canadian institutions. Patients were treated with an induction phase of weekly nimotuzumab infusions for 8 weeks with palliative radiation given concurrently for the first 2 weeks, followed by a maintenance phase of biweekly nimotuzumab as a single agent.

Eligibility criteria

Patients with histologically or cytologically confirmed NSCLC stage IIB (unsuitable for surgery), III (unsuitable for radical radiation) and IV (when palliative radiation to a thoracic mass was considered the most appropriate treatment), ECOG performance status 0–2, aged >18 were eligible for the study. Patients with previously treated, stable brain metastases were eligible. Exclusion criteria included prior thoracic radiotherapy, previous anti-EGFR-based treatment, progressive and symptomatic brain metastases, any severe uncontrolled medical illness, and pregnancy or breastfeeding.

Dosing

Based on previous clinical trial experience demonstrating excellent tolerability of nimotuzumab in combination with radiation in the treatment of brain and head and neck cancers, three escalating doses of the mAb were investigated in this study: 100, 200 and 400 mg. In the absence of data suggesting increased efficacy at 800 mg, the highest dose selected for this study was 400 mg.

Five patients were accrued per dose. If no more than 1/5 patients experienced a dose-limiting toxicity (DLT), the dose was increased to the next level. If 2/5 patients experienced a DLT, five additional patients were to be recruited to that dose level with dose escalation proceeding if no additional DLTs were registered. If DLTs were observed in three or more patients in any cohort, dose escalation was stopped and that dose was to be designated as the maximum tolerated dose (MTD). A maintenance phase of nimotuzumab infusions was continued in eligible patients. Given the calculated nimotuzumab half-life range of 62.91 h at 50 mg dose to 304.51 h at 400 mg dose [15], a biweekly infusional schedule was selected for the maintenance phase.

Treatment

All patients received standard palliative thoracic RT consisting of 30 or 36 Gy in 10 or 12 daily fractions based on previous phase III studies and institutional preference [27–30] using a Linear Accelerator with a beam energy not exceeding 10 Mv starting on day 1. All patients underwent simulation prior to starting radiation. Doses were calculated assuming a homogeneous patient. Target volumes were chosen as per institutional standard ensuring adequate coverage of gross disease and mindful of sparing lung tissue.

Nimotuzumab (100, 200 or 400 mg) was administered intravenously as a short infusion over 30 min with 250 mL of saline solution weekly for 8 weeks, 2–6 h after RT starting on RT day 1. Patients were monitored after each nimotuzumab dose (4 h after dose 1, 1 h after subsequent administrations). If local control was achieved, or patients showed clinical benefit, nimotuzumab was continued once every 2 weeks for up to 18 months until unacceptable toxicity or disease progression.

Target lesions and non-target lesions

Although incomplete response/stable disease rate outside the radiation field in non-target lesions is of considerable interest, given the importance of local control in determining palliative benefit for this patient population, we evaluated local response to radiotherapy in combination with nimotuzumab. All measurable lesions up to a maximum of five lesions per planned radiation field were identified as target lesions and recorded and measured at baseline. Target lesions were selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions was calculated and reported as the baseline sum LD, which was used as reference to characterize the objective tumor response. Other lesions (or sites of disease) including measurable lesions outside or partially outside the radiation field as well as non-measurable lesions were identified as non-target lesions and recorded at baseline. Measurement of these lesions was performed when possible, and the presence or absence of each noted throughout follow-up.

Toxicity and response

Systemic and local adverse events were graded according to National Cancer Institute Common Toxicity Criteria (v3.0). Evaluation of treatment response (local and systemic) by CT scan was performed in week 9 and then every 2 months according to the Response Evaluation Criteria in Solid Tumors (RECIST) Criteria [31].

Results

Patient demographics

Between March 2006 and November 2007, 18 patients, median age 69 years, were enrolled; 6 at 100 mg; 7 at 200 mg and 5 at 400 mg. Eleven were male, 17 were Caucasian, 17 were smokers (median 42 years), 13 were ECOG PS ≤ 1 . Two patients were in stage IIIA, 7—IIIB, 9—stage IV; 4 patients had squamous cell, 9 had adenocarcinoma, and 5 were classed as NSCLC not otherwise specified (Table 1). Three patients had received previous chemotherapy. Reasons for unsuitability for radical treatment are listed in Table 2.

Safety and compliance

A total of 278 cycles of nimotuzumab were administered to 18 patients; median number of cycles 17 (12 at 100 mg, 17 at 200 mg, 20 at 400 mg). Sixteen patients went on to receive the biweekly maintenance component of nimotuzumab monotherapy. Nimotuzumab was well tolerated at each of the three doses tested. No serious hypersensitivity reactions were seen. The most common adverse events observed ($\geq 15\%$ of patients) were fatigue (36.9%), chills (27.8%), anorexia (27.8%), pain (16.7%) and hypophosphatemia (16.7%). Nine patients (44%) experienced one or more grade 3 or 4 toxicities which included dyspnea, neutropenia and constipation. One case of radiation pneumonitis was diagnosed in the 200 mg cohort. Of these events, 6 (neutropenia, pneumonia, hypophosphatemia, radiation pneumonitis, elevated alkaline phosphatase levels, and weight loss) were felt to be at least partly attributable to nimotuzumab (Table 3). No grade 3/4 esophageal toxicity was observed. No grade 3/4 skin rashes were seen. Three patients experienced grade 1/2 skin rash attributed to nimotuzumab. Grade 1/2 infusion reactions and hypomagnesemia were observed in 1 and 2 patients respectively, also attributed to nimotuzumab.

Efficacy

Seventeen patients were evaluable for response. Two patients came off study due to progression in non-target lesions before 8 weeks, but one was still evaluable for target lesion response. At the point of cutoff, 9 patients had gone on to receive further treatment: 4 received palliative chemotherapy alone, 3 received palliative radiation alone, and 2 received both palliative radiation and palliative chemotherapy.

Evaluation of target lesions within the radiation field at 8 weeks showed 7 PRs (4 at 100, 2 at 200 and 1 at 400 mg), 10 SD (2 at 100, 5 at 200 and 3 at 400 mg) and no PD. Overall disease control rate at 8 weeks was 94%. Continued

Table 1 Patient demographics

		Nimotuzumab 100 mg	Nimotuzumab 200 mg	Nimotuzumab 400 mg	Total
Number of patients		6	7	5	<i>n</i> = 18
Male/female		2/4	5/2	4/1	11/7
Median age		71.25	65.90	65.43	69.29
ECOG	0	–	2 (28.6%)	2 (40.0)	4 (22.2%)
	1	4 (66.7%)	4 (56.1%)	1 (20.0)	9 (50.0%)
	2	2 (33.3%)	1 (14.3%)	2 (40.0)	5 (27.8%)
Smoking history	Non-smokers	–	1 (14.3%)		1
	Smokers	6 (100%)	6 (85.7%)	5 (100%)	17
	Quit smoking	6 (100%)	3 (50%)	5 (100%)	14
Stage	IIB	0	0	0	0
	IIIA	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
	IIIB	3 (50.0%)	3 (42.9%)	1 (20.0%)	7 (38.9%)
	IV	1 (16.7%)	4 (57.1%)	4 (80.0%)	9 (50.0%)
Histologic type	Squamous cell carcinoma	2 (33.3%)	2 (28.6%)	0 (0.0%)	4 (22.2%)
	Adenocarcinoma	1 (16.7%)	3 (42.9%)	5 (100.0%)	9 (50.0%)
	Other non-small cell lung	3 (50.0%)	2 (28.6%)	0 (0.0%)	5 (27.8%)
EGFR status	EGFR by fish				
	Evaluable	1	3	2	6
	Amplified	1	3	0	4
	EGFR by IHC				
	Evaluable	3	4	3	10
	Over-expressed	2	3	3	8
K-ras status	Evaluable	3	4	3	10
	Mutated	0	3	1	4
	Wild type*	3	1	2	6

* No responses were seen in K-ras-mutated patients

Table 2 Reasons for unsuitability of patients for radical treatment

Subject unsuitable to receive curative-intent therapy due to*	Nimotuzumab 100 mg (<i>n</i> = 6)	Nimotuzumab 200 mg (<i>n</i> = 7)	Nimotuzumab 400 mg (<i>n</i> = 5)	Total (<i>n</i> = 18)
Lesion location makes radical RT/CT impossible	1 (16.7)	1 (14.3)	3 (60.0)	5 (27.8)
Multiple medical problems	2 (33.3)	0 (0.0)	0 (0.0)	2 (11.1)
Patient unable to tolerate combined modality	3 (50.0)	2 (28.6)	1 (20.0)	6 (33.3)
Palliative RT requested by patient/family	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)
Poor quality of life with chemo	1 (16.7)	3 (42.9)	0 (0.0)	4 (22.2)
Poor performance status	1 (16.7)	0 (0.0)	1 (20.0)	2 (11.1)
Symptom management by RT required	2 (33.3)	4 (57.1)	1 (20.0)	7 (38.9)
Other	3 (50.0)	2 (28.6)	1 (20.0)	6 (33.3)

* Subjects can have more than one reason for unsuitability

monitoring showed 5 cases described as SDs at 8 weeks converting to PRs, making best overall response 12 PRs (Table 4, Fig. 1).

Non-target, non-irradiated lesions were evaluable in 12 cases: 3 PR (1 at 100, 2 at 200 mg dose), and 9 PD were

seen. In 6 cases, information on non-target lesions is unavailable.

Median progression free survival was 16 weeks (Fig. 2); median overall survival was 60 weeks, and 1 year survival of 52% (Fig. 3).

Table 3 Grade 3 and 4 adverse events by body system, preferred term, and relationship

MedDra body system /preferred term ¹	Relationship to study drug ²	Nimotuzumab 100 mg (<i>n</i> = 6)	Nimotuzumab 200 mg (<i>n</i> = 7)	Nimotuzumab 400 mg (<i>n</i> = 5)	Total (<i>n</i> = 18)
Overall subjects with $\geq$ one adverse event					
	Unrelated	1 (16.7)	2 (28.6)	1 (20.0)	4 (22.2)
	Related	1 (16.7)	2 (28.6)	1 (20.0)	4 (22.2)
Blood and lymphatic system disorders					
Neutropenia	Related	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Gastrointestinal disorders					
Constipation	Unrelated	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)
General disorders and administration site conditions					
Difficulty in walking	Unrelated	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)
Aphasia	Unrelated	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)
Pain	Unrelated	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Infections and infestations					
Pneumonia	Related	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Investigations					
Blood alkaline phosphatase increased	Related	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)
Weight decreased	Related	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)
Metabolism and nutrition disorders					
Hyperglycemia	Unrelated	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)
Hypophosphatemia	Related	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)
Reproductive system and breast disorders					
Breast discomfort	Unrelated	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	Unrelated	1 (16.7)	1 (14.3)	0 (0.0)	2 (11.1)
Hypoxia	Unrelated	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Radiation pneumonitis	Related	0 (0.0)	1 (14.3)	0 (0.0)	1 (5.6)

Included all grade 3 and 4 adverse events except those related to RT only

¹ Subjects who had more than one event assigned to the same preferred term were counted once² If an event occurred more than once for a subject, the occurrence with the strongest relationship to study drug was tabulated**Table 4** Summary of in-field target tumor response

	Nimotuzumab 100 mg		Nimotuzumab 200 mg		Nimotuzumab 400 mg		Total best overall response (<i>n</i> = 18*)
	Week 8 response (<i>n</i> = 6)	Best overall response (<i>n</i> = 6)	Week 8 response (<i>n</i> = 7)	Best overall response (<i>n</i> = 7)	Week 8 response (<i>n</i> = 5*)	Best overall response (<i>n</i> = 5*)	
CR	0	0	0	0	0	0	0
PR	4	5	2	4	1	3	12
SD	2	1	5	3	3	1	5
PD	0	0	0	0	0	0	0

DCR at 8 weeks: 94%

* Two patients off study due to progression in non-target lesions before receiving 8 doses of nimotuzumab (1 of which was evaluable for target lesion assessment)

Molecular correlative studies

Tumor was available for molecular analysis on 10 of 18 patients; of these 10, all were analyzed for EGFR by IHC and for K-ras mutation by sequencing, while 6 were evalu-

able for EGFR by FISH analysis (Table 5). EGFR mutational analysis was not performed. EGFR staining by IHC was positive in 8/10 tumors, 4/6 demonstrated increased EGFR copy number by FISH and 4/10 were positive for K-ras mutations. There was no statistically significant correlation

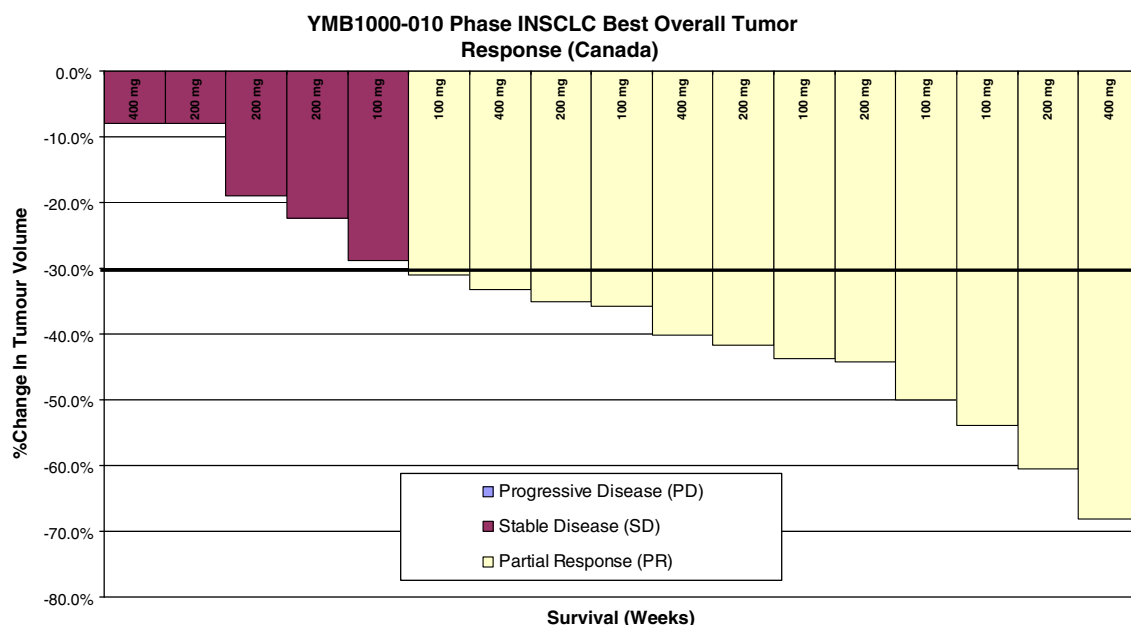
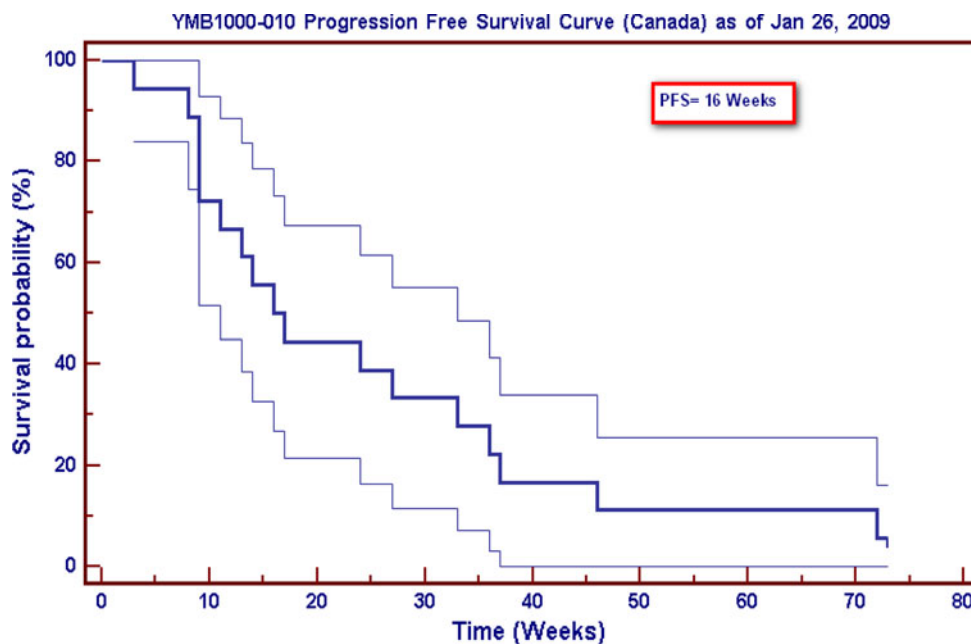


Fig. 1 Best overall in-field tumor response in 17 evaluable patients

Fig. 2 Progression-free survival curve



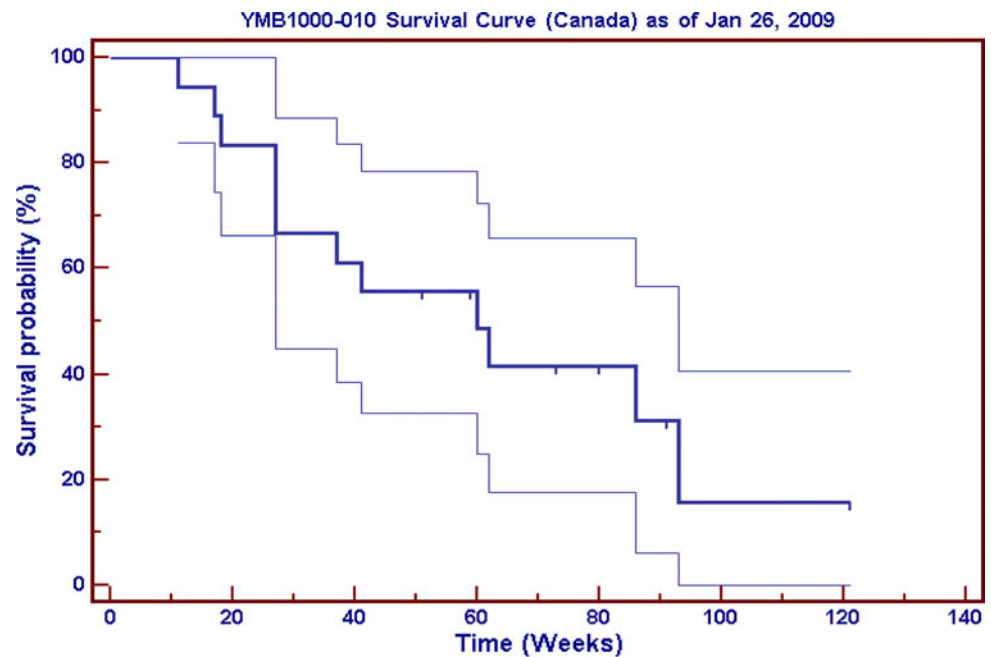
between EGFR expression/copy number or K-ras molecular status and response or outcome.

Discussion

The population included in our study presented the classic challenges posed by NSCLC patients. With a median age of 69 years, the cohort was old, all patients had at least one significant co-morbidity, and 5 patients were described as

ECOG performance status 2 at the start of treatment. Nevertheless, all enrolled patients tolerated the addition of nimotuzumab well and were able to complete the combined modality treatment component.

The disease control rate within the radiation field was high at 94% without inducing additional esophageal toxicity. A median overall survival of 60 weeks and 1 year survival of 52% compare favorably with historical controls. Although the contribution of subsequent treatment to overall survival cannot be precisely assessed, it is encouraging

Fig. 3 Overall survival curve**Table 5** Relationship between tumor response and molecular analysis

Nimotuzumab dose (mg)	Best response (PR, CR, SD, PD)	EGFR IHC	EGFR FISH	Ras mut
100	PR	NP	NP	NP
100	SD	NP	NP	NP
100	PR	+	NP	—
100	SD	+	+	—
100	PR	—	NP	—
100	PR	NP	NP	NP
200	SD	+	NP	+
200	SD	—	+	+
200	SD	+	+	—
200	SD	+	+	+
200	PR	NP	NP	NP
200	PR	NP	NP	NP
200	PR	NP	NP	NP
400	PR	+	NP	—
400	SD	+	—	+
400	PD	+	—	—
400	SD	NP	NP	NP
400	PD	NP	NP	NP

EGFR IHC Epidermal growth factor by immunohistochemistry

EGFR FISH Epidermal growth factor by fluorescent in situ hybridization

NP Not performed

that half the patients were able to go on to receive further treatment. On this basis, the combination of palliative radiation and nimotuzumab in this context seems promising.

This study did not identify the MTD for this therapeutic combination of nimotuzumab and radiation. Although we

show that 400 mg is safe, there is no clear indication from this study that it is more effective than 200 mg in this population. This is not surprising since previous pharmacokinetic studies have suggested that the elimination half-life ($t_{1/2\beta}$), AUC and Cmax for nimotuzumab are comparable at both 200 and 400 mg [15]. Consequently, it is reasonable to suggest that future randomized studies of this combination should be carried out with the 200 mg dosing. Additional data (unavailable at the time of study design) from several studies in a range of tumor types investigating the half-life of nimotuzumab treated with 200 mg [32] imply that a weekly dosing interval may be more appropriate in future than the biweekly regimen used in the maintenance phase of this study.

The absence of grade 3/4 skin toxicity (radiation dermatitis, acneiform rash, nail disruption, conjunctival irritation and hair changes) even at the 400 mg dose was notable. This confirms the experience seen in other clinical trials involving this drug. The reason for the lack of skin toxicity has more recently been attributed to the fact that nimotuzumab's capacity to bind EGFR, in contrast to other anti-EGFR mAbs, is heavily dependent on cell receptor density. It is hypothesized that this is due to an intrinsic difference between monovalent and bivalent binding of nimotuzumab, which is transiently bound monovalently, and strongly bound bivalently to EGFR epitopes [33, 34]. Over-expressing tumor cells may preferentially bind nimotuzumab in comparison with normal epithelial cells, thus creating a potential therapeutic ratio. Should nimotuzumab prove efficacious in subsequent randomized studies, a lack of severe toxicity and the absence of skin rash will be an attractive clinical feature of this agent.

Although molecular determinants of response were investigated in this study, no conclusion can be drawn regarding the presence or absence of EGFR or K-ras mutations and outcome. There was no clear association between response and EGFR expression and gene amplification. K-ras status was evaluable in 10 of 18 patients, and 4 mutant K-ras cases were identified: none of these responded. Although mutated K-ras has been associated with the lack of response to EGFR TKIs in lung cancer [35] and anti-EGFR mAb in metastatic colorectal cancer [36], it is not predictive for response to cetuximab in NSCLC [37], and its role in determining response to radiation is unclear. The lack of association of response with K-ras mutational status is consistent with emerging data in NSCLC [37] and is in line with preclinical studies suggesting that the PI3K-AKT pathway rather than the K-ras pathway is more important in determining response to ionizing radiation [38, 39]. Furthermore, the role of EGFR in determining response to ionizing radiation is less clear and requires further investigation. Additional molecular determinants of response that need further analysis include FcγR polymorphisms that have been implicated in colorectal cancer but whose role in NSCLC remains unknown [40, 41].

In conclusion, this study suggests that adding the anti-EGFR mAb nimotuzumab to palliative external beam radiation is feasible in a population of NSCLC patients. The overall survival of the patient cohort accrued to this study compares favorably with historical controls [2, 3]. Demonstrating the true efficacy of nimotuzumab in NSCLC will require prospective randomized trials. Randomized phase II studies to further explore this approach using nimotuzumab at 200 mg have been initiated in North America and internationally.

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