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### Multimodality approach towards individualized non-small cell lung cancer treatment

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**Publication date**  
2014

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#### **Citation for published version (APA):**

Schaake, E. E. (2014). *Multimodality approach towards individualized non-small cell lung cancer treatment*. [Thesis, externally prepared, Universiteit van Amsterdam].

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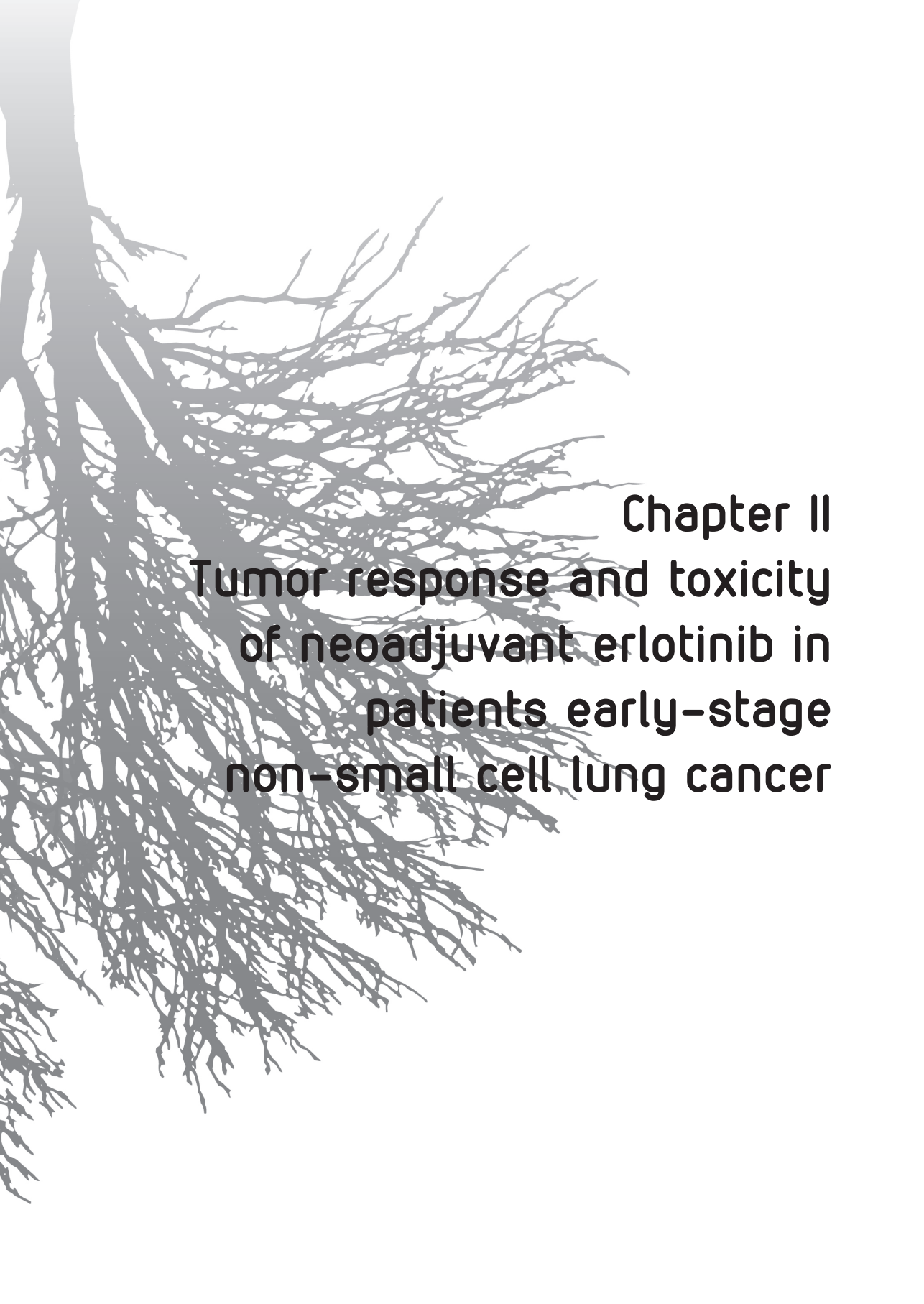
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Journal of Clinical Oncology,  
August 2012

A grayscale silhouette of a tree branch, likely a pine or spruce, extending from the left side of the frame towards the center. The branch is composed of many smaller, thinner twigs, creating a complex, web-like pattern. The background is plain white.

**Chapter II**  
**Tumor response and toxicity**  
**of neoadjuvant erlotinib in**  
**patients early-stage**  
**non-small cell lung cancer**

**ABSTRACT**

*Background* | The development of ‘targeted therapy’ has induced new options to improve treatment outcome in selected patients. The objective of this prospective study was to investigate the safety of preoperative erlotinib treatment and the (in vivo) response in patients with early stage resectable non-small cell lung cancer (NSCLC).

*Patients and Methods* | This study was designed as an open-label phase II trial, performed in four hospitals in the Netherlands, according to a Simon’s minimax 2-stage procedure. Initially, operable patients with early-stage NSCLC (n=15) were entered from an “enriched” population (never-smoker, female gender, non-squamous histology or Asian ethnicity), thereafter unselected patients were included to a total of n=60. Patients received preoperative erlotinib 150 mg once daily for 3 weeks. Response to treatment was evaluated using [18F]-FDG-PET/CT and CT scans during treatment and histological examination of the resection specimen. Primary endpoints were toxicity and pathologic response.

*Results* | Sixty patients were included. Seven patients stopped treatment prematurely (12%). Skin toxicity was present in 37 patients (62%), diarrhea in 21 patients (35%). PET evaluation revealed metabolic response (>25% SUV decrease) in 16 patients (27%), CT evaluation using RECIST showed response in 3 (5%). At surgery, no unexpected complications occurred. Pathologic examination showed >50% necrosis in 14 patients (23%), of which 3 (5%) had >95% tumor necrosis. The response rate in the enriched population was 34% (10/29 pts).

*Conclusion* | According to predefined criteria, neoadjuvant erlotinib has low toxicity and sufficient activity to deserve further testing in future studies in an enriched population.

## INTRODUCTION

A minority of patients with non-small cell lung cancer (NSCLC) present with localized disease (1). Treatment for early stage disease in fit patients is focused on curative surgery. Unfortunately, 5-year survival varies from 36 to 73% after resection with curative intent (2;3). Disease recurrence will become apparent in at least 40% of these patients, often by distant metastases suggesting that early stage NSCLC is frequently a micrometastatic disease at diagnosis (4;5). For this reason adjuvant cisplatin-based therapy is advised for patients with a completely resected NSCLC with hilar metastases (6;7). The overall survival effect of these adjuvant therapies is modest with an estimated benefit of 4-8% at 5 years (8-10). Chemotherapy may be used in a neoadjuvant setting, but the magnitude of the effect is as limited as in the adjuvant setting (11).

The development of “targeted therapy” has induced a new era of clinical research with promising results. Possibilities to improve survival in patients with NSCLC include combinations of standard therapy combined with a more individualized treatment approach based on serum- and tissue markers (12-14).

The Epidermal Growth Factor Receptor (EGFR) is over-expressed or may harbor activating mutations in several solid tumors including NSCLC. Inhibition of this receptor can decelerate tumor growth and induce objective responses in a subset of patients, depending on either clinical characteristics or molecular parameters (15;16). Erlotinib is a small-molecule EGFR tyrosine kinase inhibitor (EGFR-TKI). It blocks the tyrosine kinase domain of EGFR, thereby inhibiting downstream signaling pathways involved in tumor cell proliferation, angiogenesis, invasion and metastasis and prevention of apoptosis. It can be orally administered and has a relatively mild toxicity profile. It has shown to be effective in patients with advanced NSCLC and is approved by the FDA and EMEA for treatment of patients with advanced (chemotherapy-refractory) NSCLC (17). The objective of this study was to evaluate the efficacy of a short course of preoperative erlotinib in patients with early stage NSCLC, eligible for surgical resection. This report presents the results of toxicity and radiologic, metabolic and pathologic response.

## PATIENTS AND METHODS

### *Study design*

This study was designed as an open-label, non-comparative phase II study performed in four hospitals in The Netherlands (The Netherlands Cancer Institute-Antoni van Leeuwenhoek hospital (NKI-AVL), Amsterdam; Kennemer Gasthuis, Haarlem; HAGA Hospital, The Hague, and the University Medical Center Maastricht. The study was approved by each local independent ethics committee and was designed in accordance with GCP guidelines.

First, 15 patients with resectable NSCLC from a selected (“enriched”) population ( $\geq 2$  of the following features: female, adenocarcinoma, non-smoker, Asian) were enrolled. After evaluation of treatment in these patients by the safety committee, another 45 unselected patients were included (see statistical consideration). All 60 patients received, prior to resection, neoadjuvant erlotinib daily during an intended course of three weeks. Written informed consent was obtained from each patient before the start of study treatment. The primary endpoint was pathological response. Secondary endpoints were toxicity, radiological and metabolic response; progression free survival (PFS) and overall survival (OS).

### *Eligibility*

Patients with newly diagnosed resectable NSCLC, i.e. clinical T1-3 N0-1, were allowed to enter the study. In addition, patients with separate tumor nodule in a different ipsilateral lobe (T4) or patients with a controlled solitary (brain) metastasis were considered for inclusion. All patients were evaluated in a multidisciplinary meeting prior to study entry. The diagnosis had to be histologically proven or highly probable ( $> 95\%$ ) based on medical history, chest X-ray, spiral CT-scan, bronchoscopy and [18F]-FDG-Positron Emission Tomography (PET/CT scan). Patients had to be fit for surgery with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and to be neither pregnant nor breast feeding. Further exclusion criteria were continuation of smoking (18), ophthalmologic abnormalities (causing dry eyes), unwillingness or inability to wear glasses instead of contact lenses during treatment, or prior malignancy treated with HER1/EGFR inhibitors.

### *Treatment schedule*

Preoperative treatment consisted of one tablet of 150 mg erlotinib daily for a period of 3 weeks, and was stopped 72 hours prior to surgery. This duration of treatment was chosen to fit within the “preoperative window”. Patients were examined every 10 days for adverse events (Common Toxicity Criteria v3.0). In case of toxicity that was not controllable by medication, by optimal supportive care, or not tolerated by the patient, the daily dose of erlotinib was decreased in steps of 50 mg or discontinued. CT as well as FDG-PET/CT scans were performed at 21 days from the start of erlotinib treatment. Surgical resection was scheduled in the fourth week after start of treatment and involved a radical resection of the tumor, preferably by lobectomy, and regional lymph node dissection (with sampling of at least three hilar and three mediastinal lymph node stations).

Tumor specimens and imaging data were sent to the NKI-AVL for central review and analyses. CT scans and FDG-PET/CT scans performed after treatment with erlotinib were compared to baseline scans. All CT scans were interpreted by the same radiologist (H.T.). Radiological tumor response was assessed following RECIST measurement criteria 1.1(19) yet after 21 days of treatment. FDG-PET/CT imaging was performed using

a hybrid system (GeminiTF, Philips, Eindhoven, the Netherlands) 60 minutes after tracer injection and was evaluated by one nuclear physician (R.V.O.). PET/CT imaging was only evaluative when scans were acquired with the same scanner, acquisition protocol and reconstruction software, and with similar intervals from tracer injection to scanning. Metabolic response was assessed following the EORTC criteria for tumor response (20). FDG tumor uptake was quantified using SUVmax (maximum activity concentration of FDG divided by the injected dose and corrected for the body weight of the patient). For the determination of the SUVmax, the maximum FDG-uptake was searched within the volume of the primary tumor. These regions of interest (ROI) were manually drawn. The resection specimens were scored for residual vital tumor and the presence of morphological signs of therapy-induced regression such as foam cell reaction, giant cell reaction, cholesterol clefts and fibrotic alterations (Junker classification (21)). Before initiation of this study, 35 resection specimens of NSCLC patients were evaluated for histological patterns of spontaneous and treatment-induced tumor regression. In treatment naive patients, specimens (n=23) showed a mean percentage of necrosis of 22% (95%-CI 15-29%, range 0-50%), specimens after neoadjuvant chemo(radio)therapy (n=12) showed a mean necrosis percentage of 55% (95%-CI 38-72%, range 20-100%). For reporting in this study, a cut off of 50% necrosis (with morphological signs of therapy-induced regression) was used for pathological response.

Of the formalin-fixed resection samples, areas with macroscopically (most) viable tumor tissue were paraffin-embedded and serial sections were stained with haematoxylin and eosin. Mutation testing was performed centrally at the certified laboratory of the NKI-AVL. EGFR and KRAS mutation status were determined in the postoperative material by isolating DNA from formalin-fixed paraffin-embedded tumor samples. For EGFR mutation analysis, exons 18–21 were PCR amplified using exon-specific primers (exon 18-21). For KRAS mutation, analyses of codon 12 and 13 were carried out with forward and reverse primer.

#### *Statistical considerations*

A Simon's minimax 2-stage procedure was applied, to provide 80% power to declare the treatment sufficiently active if the pathological response rate was 30% or more, and 5% probability ( $\alpha=0.05$ ) to wrongly declared it active when the response rate (pCR+pPR) was 10% or less ( $p_0=0.10$ ,  $p_1=0.30$ ) (22). First, 15 patients from an "enriched" population were entered into the study and the response was evaluated. As determined in advance, the threshold was at least two responses to continue the study. At this point, eligibility criteria were broadened to allow inclusion of an unselected population of eligible NSCLC patients. If five or less responses would be observed within the expected total 25 patients of the enriched population (15 from the first step and 10 additional), it would be concluded that this treatment has insufficient activity to deserve further testing in future studies.

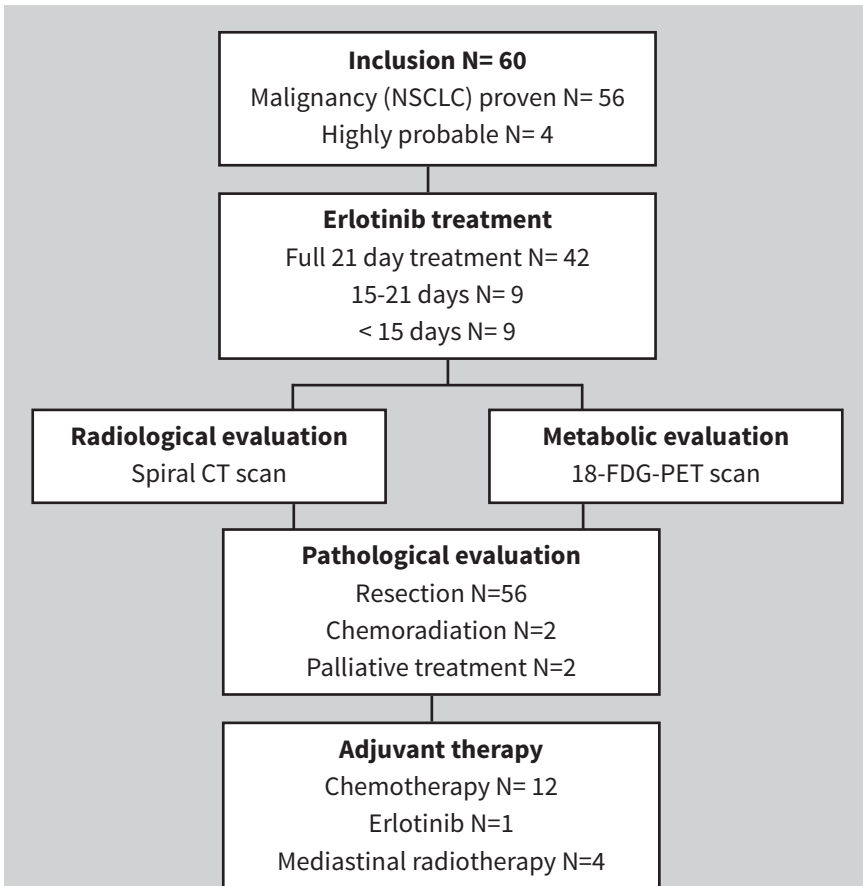


Figure 1. Patient flow diagram

## RESULTS

From December 2006 until November 2010, 60 patients with NSCLC (or highly probable NSCLC) eligible for surgical resection were enrolled in this multicenter study (Figure 1). In 56 patients, preoperative biopsy showed malignancy matching NSCLC (93%). Twenty-nine patients fulfilled the criteria of the enriched population, and the other 31 patients did not meet these criteria (non-enriched population). Median age was 64 years (range 37 – 74 years). Clinical and histological data for all patients are listed in Table 1. Median follow-up, until December 2011, was 30 months (range 3-58 months).

### *Treatment toxicity and feasibility*

Forty-two patients completed 21 days of erlotinib treatment using 150mg/day. In seven patients, surgery was planned before day 21; these patients used erlotinib 15-18 days. In four patients the dose was reduced to 100mg/day and seven patients stopped erlotinib prematurely due to toxicity (after 8 - 15 days). In most patients, no

Table 1. Patient and tumor characteristics.

Characteristics	Total population		Enriched population		Unselected population	
	n= 60	% or range	n=29	% or range	n=31	% or range
<b>Gender M/F</b>	26/34	43-57	3/26	11-89	23/8	72-28
<b>Median age at diagnose</b>	64	36-76	59	36-73	64	50-76
<b>Smoking status</b>						
Never	14	23	14	48	0	0
former	27	45	8	28	19	61
current	19	32	7	24	12	39
<b>Clinical Stage: pre treatment</b>						
IA	18	30	13	45	5	16
IB	18	30	7	24	11	36
IIA	7	12	3	10	4	13
IIB	9	15	3	10	6	19
IIIA	5	8	2	7	3	10
IV	3	5	1	3	2	6
<b>Histology</b>						
Large cell	5	8	1	3	4	13
Squamouscell	12	20	0	0	12	39
Adenoca	38	63	26	90	12	39
Bronchio alveolar Ca	1	2	0	0	1	3
LCNEC	1	2	0	0	1	3
Other	3	5	2	7	1	3
<b>Pathological stage</b>						
No tumor	1	2	0	0	1	3
IA	18	30	10	35	8	26
IB	14	24	7	25	7	23
IIA	4	6	2	7	2	6
IIB	4	6	2	7	2	6
IIIA	12	20	4	14	8	26
IV	4	6	1	2	3	9
Other than NSCLC	3	5	3	10	0	0
<b>Mutation status</b>						
<b>EGFR mutation</b>	7	12	5	17	2	6
Exon 19/Exon 21	4/2		4/1		0/1	
Exon 20	1		0		1	
No EGFR mutation	47	78	21	72	26	84
Not assesed	6	10	3	10	3	10
<b>K-ras mutation</b>	12	20	6	21	6	19
Codon 12/codon 13	12		6		6	
No K-ras mutation	42	70	20	69	22	71
Not assesed	6	10	3	10	3	10

*Table 2. Toxicity according to the CTC 3.0 criteria for all patients treated with erlotinib (n=60).*

<b>Toxicity</b>	<b>grade 1</b>	<b>grade 2</b>	<b>grade 3</b>	<b>grade 4</b>	<b>Total</b>
Rash	13	19	5	0	<b>37</b>
Dry skin	9	4	0	0	<b>13</b>
Pruritus	2	5	0	0	<b>7</b>
Diarrhea	13	6	2	0	<b>21</b>
Nausea/ vomiting	4	0	0	0	<b>4</b>
Mucositis	1	3	0	0	<b>4</b>
Fatigue	6	0	1	0	<b>7</b>
Anorexia	1	1	0	0	<b>2</b>
Dry eyes	0	8	0	0	<b>8</b>
Blurry vision	1	0	0	0	<b>1</b>
Infection/pneumonitis	0	2	1	0	<b>3</b>

unexpected toxicity was seen. Skin rash and diarrhea were common but often mild (Table 2). Side effects dissolved within seven days after treatment in all patients but one, who showed an acneiform skin rash up to three weeks after the end of treatment. Median time between the last day of erlotinib and surgery was 3 days (range 1-20 days). Fifty-six patients underwent a lobectomy or segment resection, no pneumonectomy was performed. Four patients turned out to have unresectable disease due to local tumor invasion (n=2) or malignant pleural effusion (n=1, pleural nodules in retrospect noticeable on baseline CT-scan), or N2 disease on the repeat PET scan (n=1, proven by mediastinoscopy). They received chemoradiation or chemotherapy. Median duration of hospital stay was nine days (range 5 – 17 days), including one day (range 0 – 7 days) at the intensive care unit. No unexpected per- or postoperative complications were seen. Postoperative complications were pneumonia (n=1), anemia requiring blood transfusion (n=2), persisting air leak (n=1), and urinary retention (n=2). No re-interventions were necessary, and there were no postoperative deaths.

Histology showed NSCLC in 56 patients, LCNEC (carcinoid) in one patient, a pulmonary metastasis of breast cancer in one patient, a B-cell non-Hodgkin lymphoma in another patient and in one patient no vital tumor cells were found in the suspected lesion.

## **RESPONSE EVALUATION**

Figure 2a and 2b provide an overview of radiological, metabolic and pathological responses per patient. Radiological partial response (PR), measured by CT after three weeks of erlotinib treatment, was seen in 3/60 patients (5%), all in the enriched population. Metabolic partial response, measured by PET scan was present in 16/60

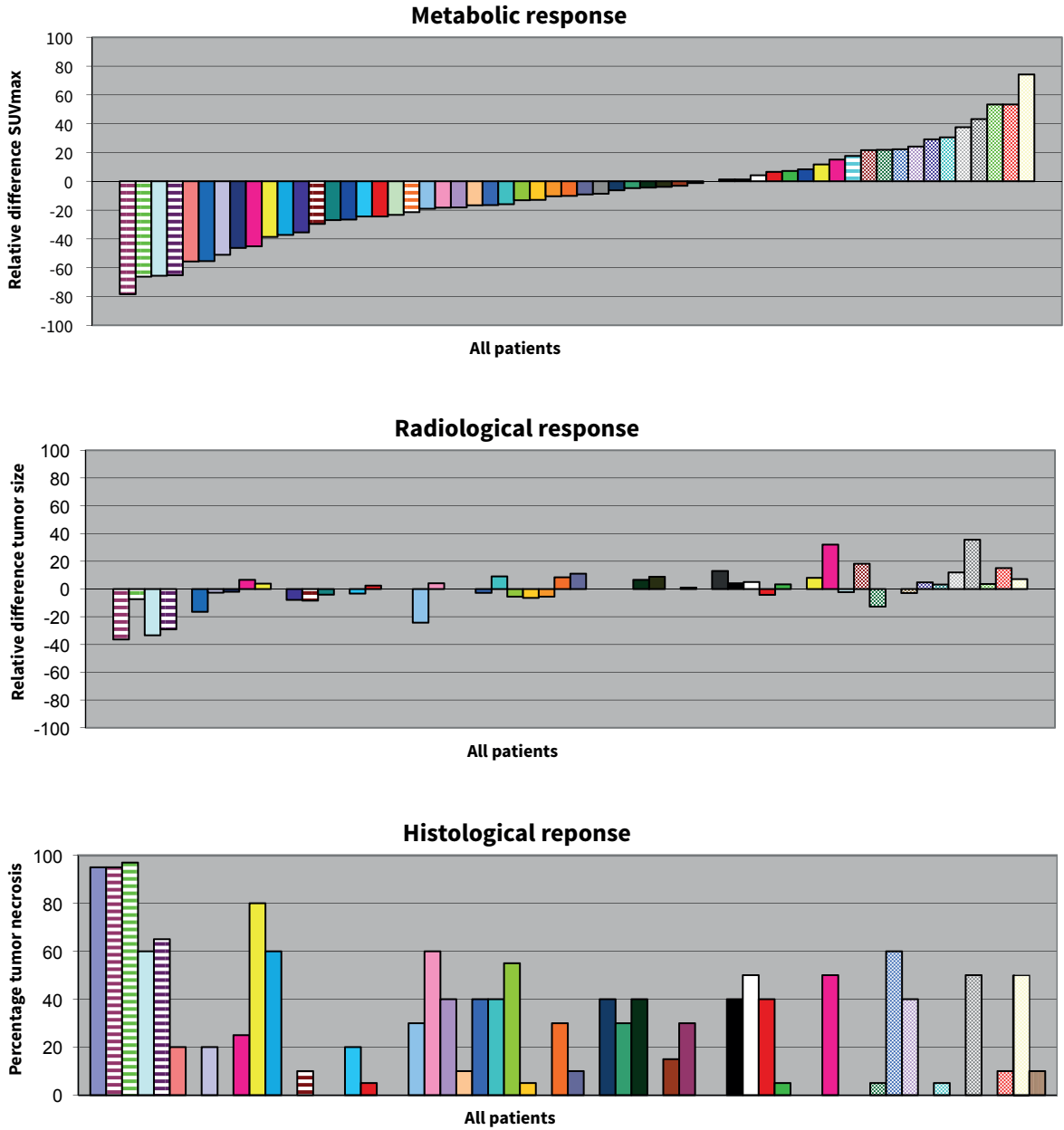


Figure 2a. Shows the individual response: each coloured bar indicates the response of an individual patient showing a) SUVmax after 3 weeks of erlotinib as compared to baseline SUVmax [%], b) Tumor diameter after 3 weeks of erlotinib as compared to baseline CT [%], c) Relative amount of tumor necrosis [%] in resection specimen (4 tumors indicated by x were unresectable). The striped bars indicate patients with EGFR mutated tumor.

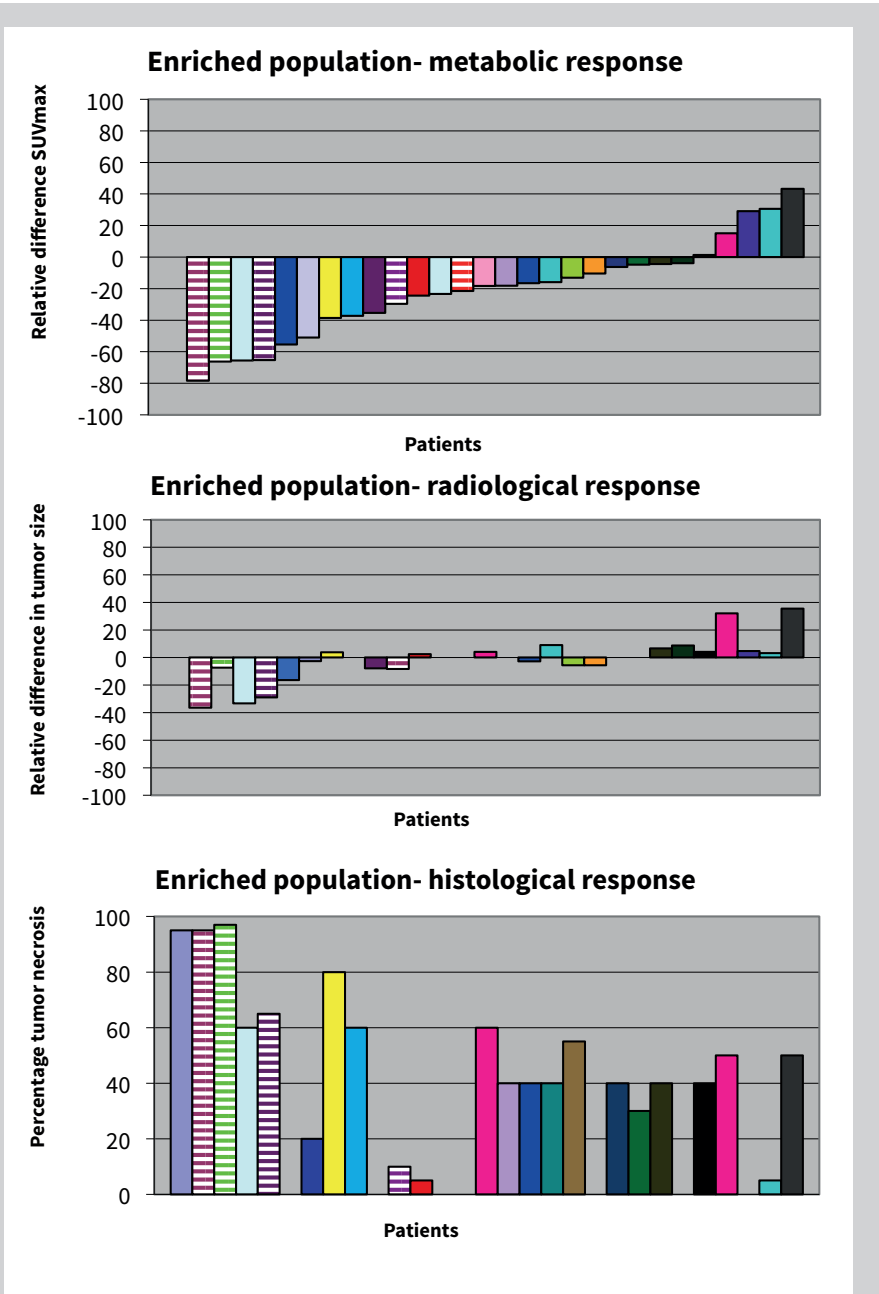


Figure 2b. Shows the individual response in the enriched population: each coloured bar indicates the response of an individual patient showing a) SUVmax after 3 weeks of erlotinib as compared to baseline SUVmax [%], b) Tumor diameter after 3 weeks of erlotinib as compared to baseline CT [%], c) Relative amount of tumor necrosis in resection specimen [%]. The striped bars indicate patients with an EGFR mutated tumor.

Table 3. Tumor response A) according to study design. B) according to mutation status.

A Tumor response according to study design (n=60)						
	Total population		Enriched population		Unselected population	
	n= 60	% or range	n=29	% or range	n=31	% or range
<b>Median Erlotinib treatment (days)</b>	20		20		19	
	days	3-28	3- 28		8-26	
<b>Median Follow- Up (months)</b>	30	3-58	36	5-58	24	3-52
<b>Median change SUV max (n=59)</b>	-10%	-78 to 76%	-20%	-78 to 43%	0.7%	-56 to 76%
<b>Metabolic response EORTC criteria</b>						
<b>PR</b>	16	27	10	34	6	20
<b>SD</b>	36	61	16	55	20	66
<b>PD</b>	7	12	3	10	4	13
<b>Median change millimeters in Tumor size (n=59)</b>	0.7	-10 to 16	0.5	-10 to 16	0.9	-8 to 10
<b>Radiologic response RECIST criteria</b>						
<b>PR</b>	3	5	3	10	0	0
<b>SD</b>	54	92	24	83	30	100
<b>PD</b>	2	3	2	7	0	0
<b>Pathological evaluation (n=56)</b>						
<b>Median % necrosis</b>	29%	0- 97%	40%	0-97%	18%	0-60%
<b>&gt; 50% necrosis</b>	14	23	11	38	3	10
<b>&lt; 50% necrosis</b>	42	70	18	62	24	77
<b>No resection</b>	4	7	0	0	4	13
B Tumor response according to mutation status (n=54)						
	EGFR mutated		K-ras mutated		Double wildtype	
	n= 7	% or range	n= 12	% or range	n= 35	% or range
<b>Median Erlotinib treatment (days)</b>	21	13 - 27	19	11 - 26	19	8 - 28
<b>Median Follow- Up (months)</b>	35	7-54	26	3-45	29	7-58
<b>Median change SUV max</b>	-40%	-78 to 17%	-7%	-45 to 24%	-3%	-66 to 74%
<b>Metabolic response EORTC criteria</b>						
<b>PR</b>	4	57	2	17	8	23
<b>SD</b>	2	28	10	83	20	57
<b>PD</b>	0	0	0	0	7	20
<b>Median change millimeters in Tumor size</b>	-5	-8 to 1	2	-2 to 16	0	-10 to11
<b>Radiologic response RECIST criteria</b>						
<b>PR</b>	2	28	0	0	1	3
<b>SD</b>	4	57	11	92	33	94
<b>PD</b>	0	0	1	8	1	3
<b>Pathological evaluation</b>						
<b>Median % necrosis</b>	46%	0 to 97%	29%	0 to 60%	26%	0 to 95%
<b>&gt; 50% necrosis</b>	3	43	3	25	8	23
<b>&lt; 50% necrosis</b>	4	57	9	75	24	69
<b>No resection</b>	0	0	0	0	3	8

patients (27%), of which 10/29 in the enriched population (34%). Two patients were not evaluable due to marginally elevated FDG uptake in a proven adenocarcinoma (n=1) and refusal of repeated imaging (n=1). Histopathologic examination of the resection specimen revealed > 50% tumor necrosis or fibrosis accompanied by morphological signs of therapy-induced regression in 14/60 patients (23%) of which 11/29 in the enriched population (38%). Response data are summarized in Table 3. In some other patients, considerable amounts of necrosis and fibrosis were observed, however without evidence of regression signs and therefore not classifiable as therapy-induced necrosis. In patients with (near) complete tumor regression, additional pathological staining methods (e.g. pankeratin immunostain) were used to differentiate complete from near complete pathological response. Pathologic response was scored as > 95% necrosis in three patients (5%), all in the enriched population. These patients had proven malignancy prior to treatment. In one additional patient no vital tumor cells were found after resection, but no pre-treatment diagnosis was obtained, excluding this patient for pathological evaluation. Specimens of 11 patients showed pPR with morphological signs of therapy-induced regression or necrosis of 50- 90% of the tumor mass.

#### *Mutation status*

Table 4 shows an overview of all three response evaluations according to mutation status. EGFR mutations were found in 7/56 NSCLC patients (13%; 5 adenocarcinoma, 2 large cell carcinoma), KRAS mutations were found in 12 patients (21%; 9 adenocarcinomas, 2 large cell carcinoma and 1 BAC). Of the EGFR mutants, 5 patients were from the enriched population. Six KRAS mutant tumors were found in each population. The specific mutation types are listed in Table 1. In six patients, mutation analyses were not performed (no resection, no vital tumor mass or other histology). Four patients with an EGFR mutation had a metabolic response; necrosis > 50% was seen in three. Two patients (exon 19 mutation, exon 20) did not show any type of response. One patient with EGFR mutation did not complete erlotinib treatment and refused further repeat PET-CT and CT scans, 10% necrosis was found after resection. One patient with a KRAS mutation had a metabolic response and >50% tumor necrosis. The tumor size did not change on CT.

#### *Follow up*

Fourteen patients received adjuvant chemotherapy, one patient adjuvant erlotinib (3 months) and 4 patients received mediastinal radiotherapy. Kaplan-Meier curves in Figure 3 show a 2- year PFS of 77% and OS of 82%, 10 patients died due to disease progression (median 13 months, range 5-24), one patient died from sepsis after an abdominal infection 13 months after surgery.

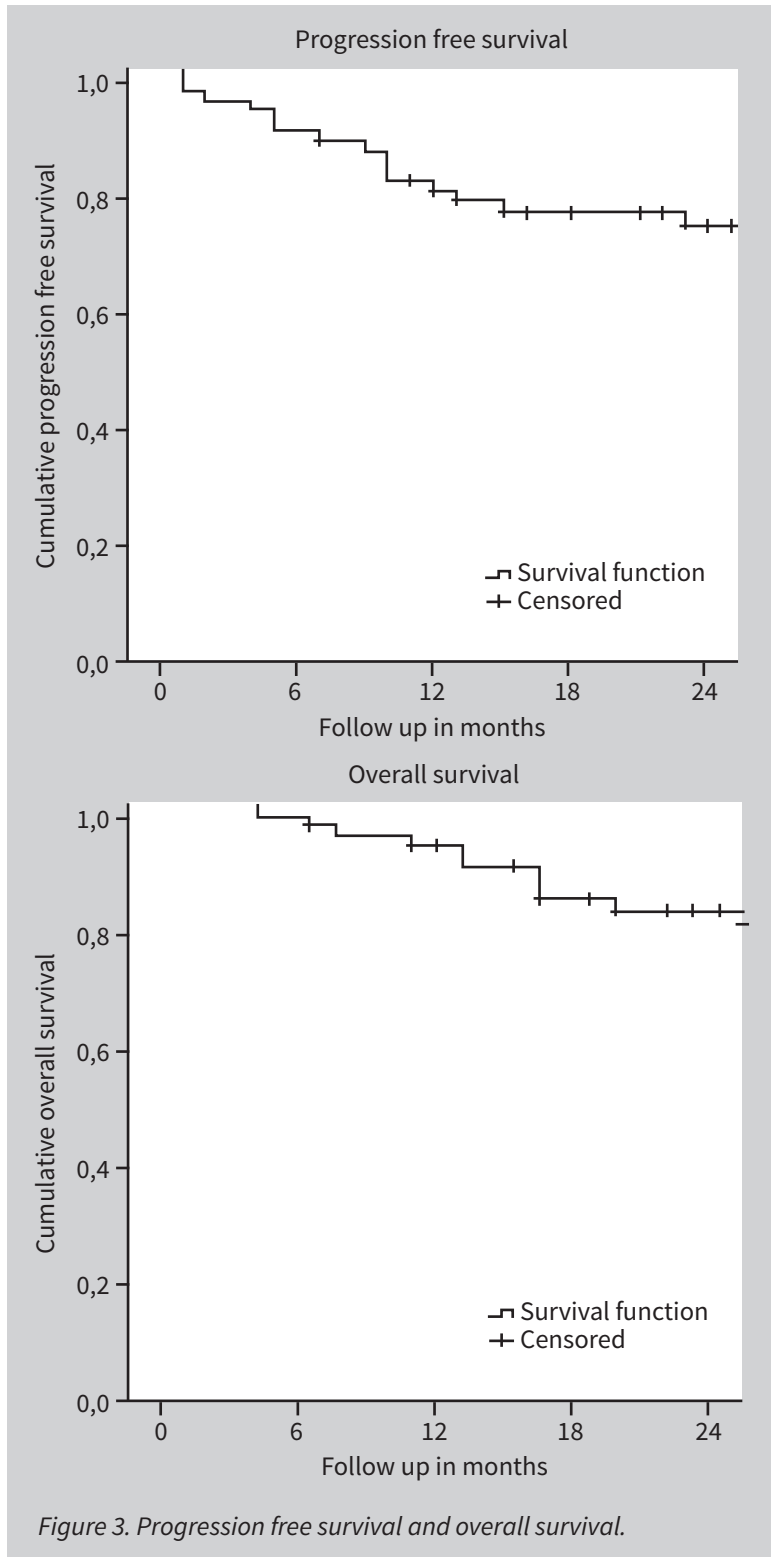


Figure 3. Progression free survival and overall survival.

## DISCUSSION

Administration of preoperative erlotinib was safe. In this setting of “preoperative window” treatment, seven patients (12%) stopped erlotinib prematurely due to subjective unacceptable toxicity. In the enriched population (n=29), tumors of 10 patients showed > 50% necrosis. The most remarkable finding was the occurrence of > 95% tumor necrosis within 3 weeks of treatment in three patients (5% of total, 10% of enriched population). Therefore we conclude that this treatment has sufficient activity to deserve further testing in future studies.

Toxicity in general was mild, although in seven patients mostly skin rash was reason for patients to stop treatment. In the neoadjuvant study setting, the threshold to discontinue treatment may be lower compared to patients with advanced disease for whom a TKI is first or second-line standard treatment. Other limitations of this study are the lack of an untreated control group and preoperative histology in all patients. It remains difficult to ascertain whether the degree of necrosis and fibrosis reflects extensive tumor heterogeneity and spontaneous necrosis or treatment effect. The difficulty of obtaining (representative) tumor tissue prior to treatment also reveals the limitation of patient selection for EGFR-TKI treatment based on mutation analysis only. For radiological and metabolic measurements, imaging was performed on the same scanner using the same image acquisition and reconstruction protocols for each patient.

Metabolic response evaluation showed marked SUV decreases in 16 patients within 3 weeks of treatment. As shown, metabolic response did not exactly correspond to histopathologic regression of the tumor or radiological response. Three factors may explain this discrepancy: the sampling of the tumor for histopathologic evaluation, problems in differentiation of spontaneous and treatment induced necrosis and the lack of a standard to qualify regression to TKI therapy.

All these factors might lead to over- as well as under estimation of response to TKI treatment. By pathological response evaluation, the amount of necrosis and regression was evaluated on tumor samples from vital parts of the lesion. Central necrosis or degradation of the tumor can occur spontaneously in many NSCLC's and cannot be used for evaluation of therapy. Although reports on histopathologic effects of neoadjuvant treatment are scarce, quality and quantity of pathological response have been described based on necrosis, fibrosis and regression criteria (21). This classification was derived from tumor tissue of patients treated with neoadjuvant chemotherapy or (chemo-) radiation, most probably causing different tissue responses than to TKI's. Furthermore, these responses were described after 2-3 months of treatment instead of after 3 weeks of treatment. Response to erlotinib can be expected to develop within several weeks, although it is not sure to what extent, and tissue reactions as apoptosis are difficult to quantify. Also unknown is, how metabolic activity

reflects various tissue reactions, as senescence, fibrosis formation, and inflammatory reactions (23). These processes may even lead to increased PET- uptake.

Radiological response (by CT) was observed in only 5% of patients (or 10% in the enriched population). RECIST measurements were used, but are suboptimal for radiological response evaluation of 3 week treatment with an EGFR-TKI. Apoptosis, transition of necrosis to fibrosis, lymphocytic and granulomatous reactions may not be translated into early decrease in tumor volume (24). Tumor volume reduction is not expected to occur within days, but in weeks to months (25). This issue of RECIST not being the best response indicator during targeted treatment has been discussed extensively for Gastro Intestinal Stromal Tumors (GIST) (26). In our study, even near complete response at pathologic examination was not predicted by preoperative CT evaluation. A study on the effect of neoadjuvant 4-week treatment with gefitinib in NSCLC (mainly adenocarcinoma) patients by Lara-Guerra et al reported partial response in 11% of 36 patients (27). Histological features in these (radiological) responders were a decrease in tumor cellularity and proliferation (Ki-67 index) (28).

Although our data show that defining response in the setting of targeted therapy for early stage NSCLC is challenging, change in metabolic activity, measured by FDG-PET/CT may be a better tool to monitor EGFR-TKI therapy. There is an ongoing discussion on prediction of response and survival in NSCLC patients receiving neoadjuvant therapy (29;30), however early during treatment, metabolic response evaluation is more helpful than CT to identify response to EGFR-TKI's (31;32).

Only six metabolic responses and no complete pathological responses were observed in the group of patients without clinical enrichment criteria. This study was started in 2006 when selection based on clinical characteristics was common. In such enriched populations (females, non-smokers, Asian origin and adenocarcinoma), responder rates of 30-40% can be observed (16). Currently, patients with advanced NSCLC are being selected for first-line TKI treatment based on mutation status.

In this study, including mainly patients with early NSCLC, we found EGFR mutations in 13% (3/7 being responders). This indicates that selection based on mutation analysis may be associated with considerable under-treatment, as an undefined group of patients without an evident mutation benefits from erlotinib treatment as well. Therefore, selection of patients and response evaluation remain important issues for future research in this field. More specific, patient selection could be improved either by in-vivo monitoring of response by early PET or by in-vitro prediction of response using measurements of inhibitory effects at the kinase level in tumor material of individual patients (33).

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