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Treatment and survival of patients with *EGFR*-mutated non-small cell lung cancer and leptomeningeal metastasis: A retrospective cohort analysis

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ABSTRACT

Objectives: Development of leptomeningeal metastasis (LM) in non-small cell lung cancer (NSCLC)-patients is associated with a poor prognosis. It has been suggested that LM-patients with epidermal growth factor receptor mutated (*EGFR*+) NSCLC have a superior prognosis compared to *EGFR*-wild type NSCLC. Studies in *EGFR*+ NSCLC-patients with LM are scarce. We retrospectively evaluated a multi-institutional cohort of *EGFR*+ NSCLC-patients for LM to assess clinical outcome in relation to patient characteristics and treatment modalities.
Material and methods: Medical records of advanced-stage *EGFR*+ NSCLC-patients (diagnosed between August 2000 and June 2014) from 11 Dutch hospitals were evaluated for LM as diagnosed by MRI and/or cytopathological liquor analysis. Data on patient characteristics, treatment and outcome were collected.
Results: Thirty-two of 356 (9.0%) advanced-stage *EGFR*+ NSCLC-patients (median follow-up 21.0 months), were diagnosed with LM between 2006 and 2014. LM was diagnosed by MRI (59.4%), liquor analysis (9.4%) or by both MRI and liquor analysis (31.3%). Median survival after LM-diagnosis was 3.1 months (95% CI: 0.0–7.3). Six- and 12-month survival rates were 43.8% and 18.8%, respectively. Patients with performance status (PS) 0–1 at time of diagnosis of LM had a significantly higher chance to be alive after 6 months and had a significantly longer survival after diagnosis of LM compared to patients with PS $\geq$ 2. Age, treatment with high-dose EGFR-TKI, radiotherapy and whether LM was the only site of progressive disease did not influence survival after LM-diagnosis.
Conclusion: Although median survival after LM-diagnosis in *EGFR*-mutated NSCLC-patients was poor, a substantial part of the patients had a prolonged survival of more than 6 months. PS of 0–1 at time of

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; CI, confidence intervals; CSF, cerebrospinal fluid; DCR, disease control rate; EGFR, epidermal growth factor receptor; LM, leptomeningeal metastasis; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; TKI, tyrosine kinase inhibitor.

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diagnosis of LM was associated with prolonged survival. No other patient- or treatment-related characteristics were identified. Further research is warranted to identify treatment strategies that improve survival in *EGFR*+ NSCLC-patients with LM.

1. Introduction

Neoplastic meningitis, or leptomeningeal metastasis (LM), is the result of spread of malignant cells to the subarachnoid space within the compartment of the cerebrospinal fluid (CSF) [1]. It occurs in many types of cancer, including non-small cell lung cancer (NSCLC). LM is associated with poor prognosis and rapid deterioration of performance status [1]. Radiotherapy, surgery and intrathecal chemotherapy all have been described as treatment options for NSCLC-patients with LM. However, the efficacy of these treatments for LM-patients is unclear and there is no consensus which (combination) provides the optimal therapeutic strategy [2,3]. Treatment should be discussed in a multidisciplinary team involved in the treatment of this complication of cancer.

It has been reported that central nervous system (CNS) metastases (including LM) are more often diagnosed in epidermal growth factor receptor (*EGFR)*-mutated (*EGFR*+) NSCLC-patients [4]. This may be due to the prolonged survival of *EGFR*+ NSCLC-patients and/or the poor penetration of first generation tyrosine kinase inhibitors (TKIs) across the blood–brain barrier (BBB) into the CSF [5]. Several studies have reported on LM in NSCLC-patients. However, in most studies, *EGFR*-mutation status was not provided or only in a small subset ($N = 6$–23) of patients [2,3,6–15].

Small series suggest that EGFR-TKI naïve *EGFR*+ patients who received EGFR-TKI treatment after diagnosis of LM may experience a better survival than patients who do not receive EGFR-TKI treatment after diagnosis of LM [3,6,15]. However, since LM is usually a late event, most *EGFR*+ NSCLC-patients have already been treated with EGFR-TKIs prior to diagnosis of LM. In addition to the previous mentioned treatment modalities for LM, high-dose EGFR-TKIs and switch of EGFR-TKI-treatment have been described as treatment option for *EGFR*+ NSCLC-patients with LM [7,14,16,17].

Altogether, data on LM in *EGFR*+ NSCLC are scarce. We therefore retrospectively evaluated a multi-institutional cohort of *EGFR*+ NSCLC-patients for diagnosis of LM. The purpose of this study was to describe diagnosis of LM and treatment modalities and survival after diagnosis of LM, in *EGFR*+ NSCLC-patients.

2. Materials and methods

Medical records of *EGFR*+ NSCLC-patients from 11 Dutch hospitals (4 academic and 7 non-academic) who were diagnosed with advanced-stage (stage IIIB or IV) NSCLC between August 2000 and June 2014 were retrospectively reviewed for diagnosis of LM. A diagnosis of LM was defined as focal or diffuse enhancement of leptomeninges, nerve roots or ependymal surface diagnosed by magnetic resonance imaging (MRI) and/or a cytopathological diagnosis of malignant cells in the CSF. Detection of atypical and/or suspicious cells in the liquor did not qualify for the diagnosis of LM. All patients were tested for the presence of *EGFR*-mutations in their tumour as standard of care. An *EGFR*-mutation was defined as any mutation detected in exon 18, 19, 20 and/or 21 of the *EGFR*-gene. Data on demographics, clinical and tumour-related features, treatments and clinical outcomes were extracted from the medical records. The medical ethical committee of the VU University Medical Center approved the protocol.

Follow-up was extended through October 2014 and was calculated from first diagnosis of advanced-stage NSCLC until death or last day of follow-up. Objective response rate (ORR) of extracranial lesions on standard-dose EGFR-TKI treatment was calculated as the proportion of patients with complete or partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [18]. Disease control rate (DCR) on standard-dose EGFR-TKI treatment was calculated as the proportion of patients with an objective response or stable disease for at least 6 weeks according to RECIST 1.1 [18]. Progression-free survival (PFS) on standard-dose EGFR-TKI treatment was calculated as the time from first day of EGFR-TKI treatment until progression of disease or death. Overall survival (OS) was calculated from first diagnosis of advanced-stage NSCLC until date of death or patients were censored at last follow-up. Survival after diagnosis of LM was calculated as the time from date of diagnosis of LM until date of death or patients were censored at last follow-up.

Comparison of categorical variables was performed with Pearson's χ^2 test. Comparison of continuous variables was performed with independent *T*-test. Survival analyses were performed according to the Kaplan–Meier method and tested for significance with the log-rank test. Two-sided *P* values ≤ 0.05 were considered significant and confidence intervals (CI) were calculated at a 95% confidence level. Statistical analyses were performed using SPSS for Windows (version 20; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. *Leptomeningeal metastases in* EGFR+ *NSCLC-patients*

Medical records of 356 advanced-stage NSCLC-patients with an *EGFR*-mutation were screened for diagnosis of LM. Median follow-up of these patients was 21.0 months (range 0.2–144.9). Two patients were lost to follow-up after 24.5 and 44.5 months. LM was diagnosed in 9.0% of the patients (32 patients). Patient and tumour characteristics are provided in Table 1.

In 19 patients (59.4%) LM was diagnosed by MRI, in three patients (9.4%) by CSF cytology and in 10 patients (31.3%) by both MRI and CSF cytology (Table 2). In one patient, LM was detected on MRI but CSF analysis was negative twice for malignant cells. In three patients in whom LM was detected by CSF cytology, there was no confirmation of LM by MRI; in one patient only a CT-scan was performed and in two patients LM could not be detected on MRI.

In six patients, mutation analysis was performed on the liquor specimen. In all six patients the identical *EGFR* driver mutation was detected in the CSF as detected in the diagnostic biopsy from a systemic lesion (four patients with an exon 19 deletion, one patient with an exon 21 L858R and one patient with an exon 20 insertion). In one patient with an exon 19 deletion who was progressive while on EGFR-TKI treatment, the T790M mutation was detected in both a rebiopsy from an extracranial lesion as well as in the liquor.

3.2. *Characteristics of* EGFR+ *NSCLC-patients with leptomeningeal metastases*

LM was diagnosed between November 2006 and March 2014. The majority of *EGFR*+ NSCLC-patients with LM was female (56.2%)

Table 1
Patient characteristics.

Patient characteristics	*EGFR*+ NSCLC-patients without LM (*N* = 324)		*EGFR*+ NSCLC-patients with LM (*N* = 32)		*P*
Median age[a] (years)	61.0 (range 30.0–90.7)		54.0 (range 29.2–78.6)		0.014
Median overall survival[b] (months)	25.4 (95% CI: 22.3–28.5)		19.9 (95% CI 11.6–28.2)		0.476
Patient characteristics	*EGFR*+ NSCLC-patients without LM (*N* = 324)		*EGFR*+ NSCLC-patients with LM (*N* = 32)		*P*
	Frequency	(Percentage)	Frequency	(Percentage)	
Gender					
Male	98	(30.2%)	14	(43.8%)	0.117
Female	226	(69.8%)	18	(56.2%)	
Smoking					
Current smoker	31	(9.6%)	2	(6.2%)	0.925
Former smoker	117	(36.1%)	12	(37.5%)	
Never-smoker	152	(46.9%)	16	(50.0%)	
Unknown	24	(7.4%)	2	(6.2%)	
Performance status (PS)[a]					
PS 0	126	(38.9%)	16	(50.0%)	0.511
PS 1	139	(42.9%)	10	(31.3%)	
PS 2	23	(7.1%)	1	(3.1%)	
PS 3	8	(2.5%)	2	(6.3%)	
PS 4	2	(0.6%)	0	(0.0%)	
Unknown	26	(8.0%)	3	(9.4%)	
Histology					
Adenocarcinoma	297	(91.7%)	32	(100%)	0.577
Adenosquamous carcinoma	1	(0.3%)	0	(0.0%)	
Squamous cell carcinoma	1	(0.3%)	0	(0.0%)	
Large-cell lung cancer	23	(7.0%)	0	(0.0%)	
Non-small cell neuro-endocrine carcinoma	2	(0.6%)	0	(0.0%)	
Mutation					
EGFR-exon 18	9	(2.8%)	1	(3.1%)	0.730
EGFR-exon 18 + 20	12	(3.7%)	1	(3.1%)	
EGFR-exon 18 + 21	2	(0.6%)	0	(0.0%)	
EGFR-exon 19	169	(52.2%)	17[c]	(53.1%)	
EGFR-exon 19 + 21	2	(0.6%)	0	(0.0%)	
EGFR exon 20[d]	42	(13.0%)	1	(3.1%)	
EGFR-exon 20 + 21	3	(0.9%)	0	(0.0%)	
EGFR-exon 21	85	(26.2%)	12[e]	(37.5%)	

Abbreviations: LM, leptomeningeal metastases; EGFR, epidermal growth factor receptor.
[a] At time of 1st diagnosis of advanced-stage NSCLC.
[b] From date of diagnosis of stage IV untill date of death or last day of follow-up.
[c] All exon 19 deletions.
[d] All non-T790M mutations.
[e] All exon 21 L858R mutations.

and most patients were never- (50.0%) or former smokers (37.5%), alike *EGFR*+ NSCLC-patients without LM (Table 1). At time of first diagnosis of advanced-stage NSCLC, median age was 54.0 years (range 29.2–78.6), being significantly younger than *EGFR*+ NSCLC-patients without LM (61.0 (range 30.0–90.7), $P = 0.014$). Median time from diagnosis of advanced-stage NSCLC until diagnosis of LM was 13.6 months (95% CI: 7.7–19.5, range 0.0–61.4) (Table 2). ECOG performance status (PS) at time of diagnosis of LM was PS 1 in 15 patients (46.9%), PS 2 in ten patients (31.3%) and PS 3 in seven patients (21.9%). Twenty-six patients (81.3%) presented with symptoms of cerebral LM, five patients (15.6%) with symptoms of thoracic and/or lumbar LM and one patient (3.1%) with symptoms of both cerebral and thoracic LM. In 15 patients (46.9%) LM was the only site of progression; in these patients all extra-CNS lesions were controlled at time of diagnosis of LM. In 17 patients (53.1%) LM was diagnosed while extra-CNS lesions were progressive as well. Among patients with cerebral LM, the most frequent presenting symptom was headache (48.1%), followed by confusion (33.3%), weakness in limbs (29.6%), nausea/vomiting (29.6%) and dizziness (25.9%). Diplopia occurred in three patients (11.1%) and seizure in one patient (3.7%). All six patients with thoracic or lumbar LM presented with back pain. One of these patients also presented with a cauda equina syndrome. Apart from LM, parenchymal brain metastases were detected in 71.9% of the patients at some time point in the course of their disease (Table 2).

3.3. *Previous EGFR-TKI treatment in* EGFR-*mutated NSCLC-patients with leptomeningeal metastases*

Treatments and outcome of individual *EGFR*-mutated NSCLC-patients who developed LM are provided in Fig. 1. Patients received a median of 2 systemic lines of treatment prior to diagnosis of LM (range 0–3). Twenty-seven patients (84.4%) were treated with at least one line of EGFR-TKI treatment prior to diagnosis of LM, three patients (9.4%) received only cytotoxic chemotherapy as systemic treatment prior to diagnosis of LM and in two patients (6.3%) LM-diagnosis coincided with first diagnosis of NSCLC. As first EGFR-TKI treatment prior to diagnosis of LM, 17 patients (63.0%) received erlotinib and ten patients (37.0%) received gefitinib. In two patients there was no documented progression on EGFR-TKI treatment prior to diagnosis of LM, as these patients underwent a pneumectomy after treatment with erlotinib. The remaining 25 patients had developed progression on EGFR-TKI treatment and median PFS was 10.1 months (95% CI: 8.9–11.2). Median PFS on EGFR-TKI treatment of these patients was not significantly different compared to *EGFR*+ patients who were treated with EGFR-TKI ($N = 239$) who did not develop LM (9.8 months (95% CI: 8.3–11.3), $P = 0.885$).

Six patients (24.0%) were diagnosed with LM at time of first progression on EGFR-TKI treatment and 19 patients (76.0%) had developed progression on EGFR-TKI treatment prior to diagnosis of

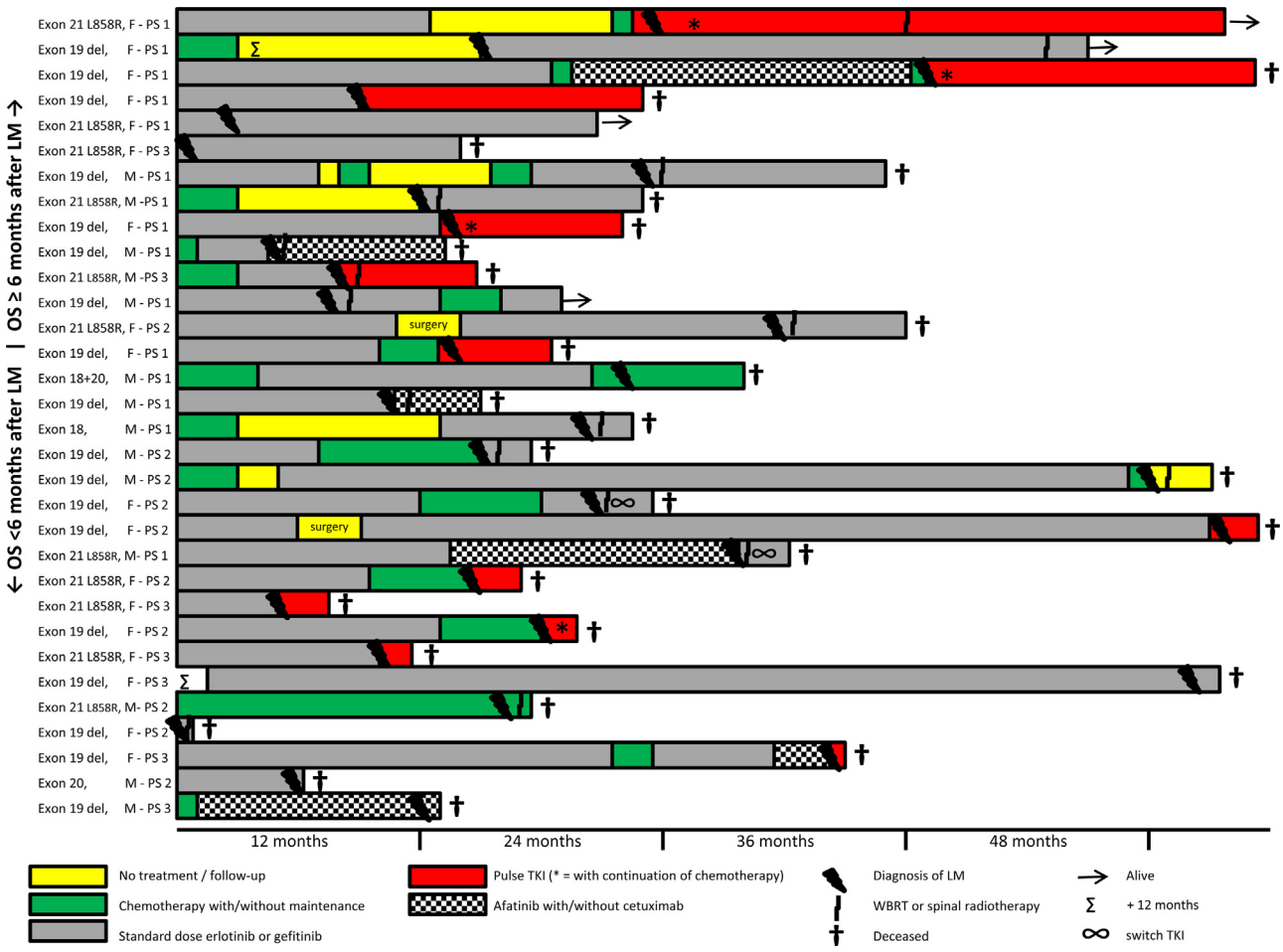

Fig. 1. Treatment of individual *EGFR*+ NSCLC-patients with LM.

LM. Among 27 patients who received EGFR-TKI treatment prior to diagnosis of LM, the ORR was 92.6% and DCR was 100.0%. In patients who did not develop LM, the ORR was 72.1% ($P = 0.021$) and DCR was 88.9% ($P = 0.069$).

Table 2
Leptomeningeal metastasis.

	Patients ($N = 32$)	
Median time from advanced-stage NSCLC until diagnosis of LM (months)	13.6 months (95% CI: 7.7–19.5)	
	Patients ($N = 32$)	
	No. of patients	(Percentage)
Anatomical location of LM		
Cerebral	26	(81.3%)
Thoracic/lumbar	5	(15.6%)
Thoracic/lumbar + cerebral	1	(3.1%)
Diagnosis of LM		
MRI	19	(59.4%)
Cytopathology	3	(9.4%)
MRI + cytopathology	10	(31.3%)
Detection of parenchymal brain metasases		
Concurrently with diagnosis of LM	16	(50.0%)
Prior to diagnosis of LM	6	(18.8%)
After diagnosis of LM	1	(3.1%)
None	9	(28.1%)

Abbreviations: NSCLC, non-small cell lung cancer; LM, leptomeningeal metastases; MRI. magnetic resonance imaging.

3.4. *Treatment of* EGFR-*mutated NSCLC-patients with leptomeningeal metastases*

At the time of diagnosis of LM most patients (62.5%) were on (re-)treatment with an EGFR-TKI (Table 3). After LM had been diagnosed, six different types of systemic treatment regimens were applied: continuation of current EGFR-TKI treatment ($N = 9$), continuation of current chemotherapy ($N = 2$), start of EGFR-TKI treatment ($N = 4$), switch of EGFR-TKI treatment ($N = 4$), high-dose EGFR-TKI treatment ($N = 8$) and high-dose EGFR-TKI treatment in combination with chemotherapy ($N = 4$) (Fig. 1, Table 3). Fourteen patients were treated with radiotherapy; eleven with WBRT and three with thoracic and/or lumbar RT (Fig. 1).

3.5. *Survival and response of* EGFR-*mutated NSCLC-patients with leptomeningeal metastases*

At the time of analysis of this cohort of *EGFR*+ NSCLC-patients with LM, 28 patients (87.5%) had died and median follow-up was 20.0 months (range 0.8–67.2).

Median survival after diagnosis of LM was 3.1 months (95% CI: 0.0–7.3, range 0.2–29.9) (Fig. 2). One-year survival rate was 18.8% (six patients) and 6-month survival was 43.8% (14 patients) after diagnosis of LM. Patients with PS 0–1 at time of diagnosis of LM ($N = 15$) had a significantly longer survival after diagnosis of LM compared to patients with PS ≥ 2 ($N = 17$) (11.0 months (95% CI: 7.7–14.3) and 2.1 months (95% CI: 1.4–2.8) respectively, $P = 0.000$). Patients in whom LM was the only site of disease progression ($N = 15$) had a longer median survival compared to patients

Table 3
Treatment prior to and after diagnosis of LM.

	Patients ($N=32$)	
	No. of patients	(Percentage)
Treatment at time when LM was diagnosed		
EGFR-TKI	20	(62.5%)
CT	7	(21.9%)
EGFR-TKI + CT	1	(3.1%)
No current treatment[a]	4	(12.5%)
Systemic treatment started after diagnosis of LM		
Stop treatment	1	(3.1%)
Continuation of EGFR-TKI	9	(28.1%)
Continuation of CT	2	(6.3%)
Start EGFR-TKI	4	(12.5%)
High-dose EGFR-TKI[b]	8	(25.0%)
High-dose EGFR-TKI + CT[c]	4	(12.5%)
EGFR-TKI switch[d]	4	(12.5%)
Radiotherapy started at time of diagnosis of LM		
WBRT	11	(34.4%)
Radiotherapy (thoracic/lumbal)	3	(9.4%)
None	18	(56.3%)

Abbreviations: LM, leptomeningeal metastases; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CT, chemotherapy; WBRT, whole brain radiotherapy.

[a] Two patient had finished previous chemotherapy.

[b] Two patients were treated with erlotinib 600 mg every 4 days, 6 patients were treated with erlotinib 1500 mg once weekly.

[c] All patients received erlotinib 1500 mg once weekly.

[d] TKI-switch: in 1 patient gefitinib → erlotinib, in 1 patient afatinib → gefitinib and in 2 patients gefitinib → afatinib.

in whom there was evidence of synchronous extra-CNS progression of disease ($N=17$); 6.5 months (95% CI: 0.9–12.1) versus 2.6 months (95% CI: 1.9–3.3) respectively, but this difference was not statistically significant ($P=0.499$).

Patients who were treated with high-dose EGFR-TKI treatment after diagnosis of LM ($N=12$) did not survive longer than patients who were not ($N=20$); median 2.4 months (95% CI: 0.0–8.3) versus 3.1 months (95% CI: 0.0–7.3) respectively ($P=0.863$). There was no difference between patients who received radiotherapy ($N=14$) and patients who did not ($N=18$); median 3.1 months (95% CI: 0.0–6.6) versus 2.4 months (95% CI: 0.0–9.7), respectively ($P=0.359$). There was a trend for a longer survival after LM-diagnosis in patients who were <60 years old at time of LM-diagnosis ($N=18$) compared to patients who were >60 years old ($N=14$); median 5.7 months (95% CI: 1.6–9.7) and 2.4 months (95% CI: 0.6–4.2), respectively ($P=0.064$).

Survival after diagnosis of LM was not statistically significantly different in patients in whom LM was the only site of progression who were treated with pulsatile EGFR-TKI treatment compared to patients who were not; 5.6 months (95% CI: 0.00–11.8) and 6.5 months (95% CI: 0.00–17.1), respectively ($P=0.737$).

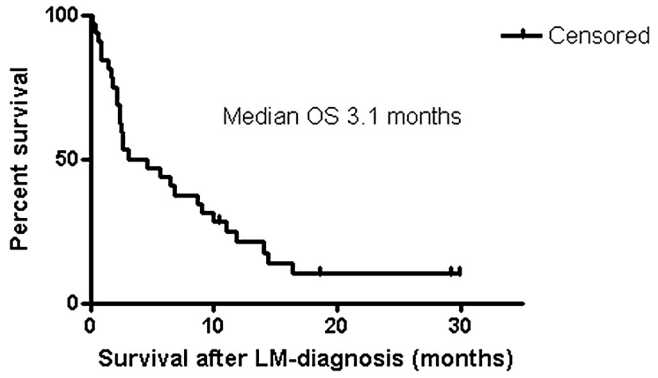

Fig. 2. Survival of *EGFR*+ NSCLC-patients after diagnosis of LM.

Patients with PS of 0–1 at time of diagnosis of LM had a significantly higher chance to be alive after 6 months compared to patients with PS ≥ 2 ($P=0.002$). Gender, smoking status, type of *EGFR*-mutation, treatment with high-dose EGFR-TKIs, treatment with radiotherapy and whether extra-CNS lesions were controlled were not related to 6-month survival (Supplement Table 1).

Fourteen patients were radiologically evaluated after treatment for LM had been initiated; in 10 patients (31.3%) there was a radiological response of LM, in 3 patients (9.4%) there was no radiological response and no radiological progression of LM and in 1 patient (3.1%) LM was progressive at re-evaluation. In the remaining 18 patients (56.3%), no radiological follow-up was performed. Five patients had not been treated with an EGFR-TKI prior to diagnosis of LM; four started EGFR-TKI treatment in standard dose after diagnosis of LM. Three of these patients had a prolonged survival of 11.0, 14.4 and 29.9 months after diagnosis of LM (Fig. 1). Two of these patients were evaluated for response of LM and both experienced a radiological response.

4. Discussion

In this cohort of *EGFR*+ NSCLC-patients LM was detected in 9.0%, comparable to the previously reported rate of LM in *EGFR*-wild type NSCLC-patients [19]. To the best of our knowledge, this report describes the largest group of *EGFR*+ NSCLC-patients with LM. The median survival after diagnosis of LM was a disappointing 3.1 months, which is similar to unselected NSCLC-patients with LM [2,3]. Interestingly, a considerable part of the patients had a longer than expected survival with 43.8% and 18.8% still being alive 6 months and one year after diagnosis of LM, respectively. Patients with PS of 0–1 at time of diagnosis of LM had a higher chance to be alive after 6 months and had longer median survival after diagnosis of LM.

Only one other study that included more than twenty *EGFR*+ patients with LM has been published ($N=23$), however all of these patients were treated for the first time with EGFR-TKIs after diagnosis of LM, which does not represent current practice [15]. Another study of Lee et al. [8] compared erlotinib with gefitinib for control of LM in 25 NSCLC-patients. It was suggested that erlotinib had a better LM control rate, however 16 patients were EGFR-TKI naïve at diagnosis of LM and only 17 patients had a confirmed *EGFR*-mutation. Although several treatment strategies for LM in *EGFR*+ NSCLC have been described, it is at present unclear which is the best treatment to be preferred. In the present study no superior treatment could be identified either, although due to the small sample size and retrospective design no firm conclusions can be drawn. High-dose EGFR-TKI treatment (erlotinib 1500 mg once weekly, or erlotinib 600 mg every 3–4 days) is a strategy that has been described for *EGFR*+ NSCLC-patients with CNS-metastases [7]. Due to the BBB, the concentration of available EGFR-TKIs is considerably lower in the intra-CNS compartment as compared to systemic concentrations [20]. Clarke et al. demonstrated that once the systemic concentration of EGFR-TKIs is high enough, therapeutic concentrations can be achieved in the CSF [21]. Toxicity of this 'pulsatile' treatment strategy is generally acceptable [7,22,23]. At present, only a few reports have described this treatment strategy for *EGFR*+ NSCLC-patients with LM, with both positive and negative results [7,24,25]. In this retrospective study survival did not seem to improve by treatment with high-dose EGFR-TKIs as compared to other treatment strategies. To answer this question, a randomized controlled trial is urgently needed.

Afatinib is a second generation EGFR-TKI and irreversible blocker of the ErbB receptor tyrosine kinase family. In a recent study that evaluated patients who progressed on standard dose erlotinib or gefitinib, 66% had CNS disease control with afatinib

[26]. However, there was no discrimination between patients with brain metastases or LM in this study. In our study, three patients were treated with afatinib (and cetuximab) after diagnosis of LM. One of these patients had been on afatinib treatment prior to LM-diagnosis and survived for 0.2 months after LM-diagnosis. Survival of the other two patients was 4.6 and 8.7 months (Fig. 1). Data regarding the efficacy of the third generation EGFR-TKIs, AZD9291 and CO-1686, on CNS metastases are very scarce [27,28]. Further investigation on the efficacy of these agents in *EGFR*+ NSCLC-patients with LM is warranted.

Radiotherapy is another treatment modality that is commonly applied after diagnosis of LM. However, evidence for the efficacy of radiotherapy in NSCLC-patients with LM is limited [3]. It has been suggested that this may be caused by the fact that only one compartment of the CNS is irradiated, while LM is a disorder that affects all compartments of the CNS [29]. In this study we did not detect a difference in survival in patients who were or were not irradiated. Yet, due to the retrospective setting and small sample size, definite conclusions cannot be drawn. It is plausible that patients with a 'good' performance score are better candidates for an 'aggressive' treatment (i.e. high-dose EGFR-TKI treatment) and clinicians are more likely to advocate radiotherapy for patients who are in a poor clinical condition. As radiotherapy increases the BBB permeability and high-dose EGFR-TKI provides a better penetration of TKI into the brain [21] a sequential combination of radiotherapy and high-dose EGFR-TKI could be an interesting treatment option for patients with LM. However, immediate toxicity of radiotherapy should be taken into account in this often-symptomatic patient population with a limited survival.

Intrathecal chemotherapy has been described as treatment option for NSCLC-patients with LM [2]. However, this treatment strategy could not be incorporated in the analyses of this study, since none of the patients received this treatment. In the Netherlands, as in other European countries, this treatment is not routinely applied in NSCLC-patients, as the evidence is rather limited [30,31].

It has been stated that classic EGFR-TKI resistance mechanisms, i.e. the T790M-mutation, develop under selective pressure of EGFR-TKI treatment. Given the fact that the BBB inhibits penetration of EGFR-TKIs into the CNS, these mechanisms of resistance would normally not be detected in tumour cells from the CNS [7,13]. Interestingly, in this study, in one patient in whom mutation analysis was performed on malignant cells present in the CNS, the T790M mutation was detected.

Age above 60 years old was identified as a negative prognostic factor by Gwak et al. in a study of unselected NSCLC-patients [2]. Also in the present study, patients younger than 60 had a trend to a better survival after diagnosis of LM. Patients in whom LM was the only site of progressive disease had longer survival compared with patients in whom there was also extracranial progression at time of LM-diagnosis, although this difference was not statistically significant. This is similar to NSCLC-patients with BM and uncontrolled extracranial disease (so called sync-oligometastasis [32]) who have a worse prognosis compared to patients with controlled extracranial disease [33,34].

Strength of this study is that all patients were pathologically confirmed to carry an *EGFR*-mutation in their primary tumours. Also, the disease control rate of 100% to first EGFR-TKI treatment suggests that no patients with primary EGFR-TKI resistance were included.

However, some limitations should be taken into account when interpreting the results of this study. First, the retrospective design and small sample size preclude strong conclusions. Second, due to its non-invasive character, MRI is the technique of choice to diagnose LM. However, the false-negative rate of MRI for detecting LM is approximately 30% [35]. In this study, LM was diagnosed by MRI in most patients. The same is true for cytopathological evaluation of CSF; it has a low sensitivity (50–60%) compared to autopsy-proven LM [36]. This may be caused by a low number of recognizable malignant cells in the liquor or by compartmentalization. Ideally, a negative lumbar puncture should be repeated at least twice to be able to exclude LM [37]. Finally, in the non-LM group, more patients with an *EGFR* exon 20 mutation were included compared to the LM-group, which might have caused bias.

In conclusion, in this cohort of *EGFR*+ NSCLC-patients LM was diagnosed in 9.0% of the patients. This study describes the largest cohort of *EGFR*+ NSCLC-patients with LM. Survival after diagnosis of LM was disappointing (3.1 months) and is comparable to *EGFR* wild type NSCLC-patients with LM. Nevertheless, 43.8% and 18.8% of the patients survived for at least 6 months and 1 year, respectively. Patients with PS 0–1 at time of diagnosis of LM had a better prognosis. Treatments associated with a superior survival after diagnosis of LM could not be identified. Further research is warranted to identify treatment strategies that improve survival in these patients.

Conflicts of interest

A.M.C. Dingemans received consultancy fees from Roche, Eli Lilly, Boehringer Ingelheim, Novartis and Pfizer. H.J.M. Groen received fees for participation in review activities from Roche and consultancy fees from Roche, MSD, GSK, Eli Lilly and Pfizer. F.H. Krouwels received consultancy fees from Boehringer and payment for lectures from GSK, Boehringer and Novartis. A.J. van der Wekken received money through his institution for board membership from Pfizer, Boehringer Ingelheim and Eli Lilly and for lectures from Roche, Astra Zeneca and Pfizer. E.M. Speel received money for board membership from Pfizer, Amgen and Roche and payment for lectures from Pfizer. The other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.05.023

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