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► To cite this version:

Ronan Flippot, Pamela Biondani, Edouard Auclin, Dingyu Xiao, Lizza Hendriks, et al.. Activity of EGFR Tyrosine Kinase Inhibitors in NSCLC With Refractory Leptomeningeal Metastases. *Journal of Thoracic Oncology*, 2019, 14, pp.1400 - 1407. 10.1016/j.jtho.2019.05.007 . hal-03488043

HAL Id: hal-03488043

<https://hal.science/hal-03488043>

Submitted on 20 Dec 2021

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Activity of epidermal growth factor tyrosine kinase inhibitors in non-small cell lung carcinoma with refractory leptomeningeal metastases.

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Word count: 2403

Tables: 3

Figures: 2

Keywords: Non-small cell lung carcinoma; epidermal growth factor receptor; tyrosine kinase inhibitor; leptomeningeal metastases

Abstract

Introduction. Leptomeningeal metastases (LM) are associated with dismal prognosis in non-small cell lung cancer (NSCLC). Optimal management remains unknown in *EGFR*-mutated NSCLC patients after initial tyrosine kinase inhibitor (TKI) failure.

Methods. We conducted a multicenter retrospective study including *EGFR*-mutated NSCLC patients with LM. TKI failure was defined as diagnosis of LM on TKI, or progression of known LM on TKI.

Results. Ninety-two patients were included, median age of 60 years, predominantly female (68%), never-smokers (74%). *EGFR* mutations included *L858R* (45%), exon 19 deletions (28%) or other mutations (14%). Median time to LM diagnosis was 18.5 months after initial diagnosis of advanced NSCLC. LM was diagnosed after a median of 2 (0; 9) systemic therapies. Median (95%CI) overall survival from LM diagnosis (LM OS) was 6.1 months (4.2-7.6). Among 87 patients with TKI failure, patients rechallenged with TKI (N=50) had a median LM OS of 7.6 months (5.7 - 10.9) compared to 4.2 months (1.6 - 6.7) in patients without further therapy. Overall, 60% of patients rechallenged with TKI experienced clinical benefit (clinical response or stable disease > 2 months), and 23% were treatment failure-free at 6 months. Clinical benefit was reported in 11/20 (55%) patients treated with erlotinib after afatinib or gefitinib. Strategies based on increasing dose intensity (N=17) yielded clinical benefit in 59% of patients. All four patients who received osimertinib after 1st/2nd generation TKI experienced clinical benefit.

Conclusions. TKI rechallenge strategies, including dosing intensification, may improve clinical outcomes of patients with LM from *EGFR*-mutated NSCLC after initial TKI failure.

I. Introduction

Lung cancer is the leading cause of death from cancer worldwide¹. Targeted molecular therapies provided significant improvements in outcomes of patients presenting with somatic epidermal growth factor receptor (*EGFR*)-mutations, found in up to 15% of non-small cell lung cancers (NSCLC) in the western world². Although under-diagnosed, leptomeningeal metastases (LM) will arise in ~10% of patients with *EGFR*-mutated NSCLC, leading to dismal outcomes: survival in this population does not exceed a year in the era of *EGFR*-directed tyrosine kinase inhibitors (TKIs)^{3,4}.

Activity of TKIs in *EGFR*-mutated patients with LM has been only described in relatively small retrospective studies and phase I trials. In addition, cerebrospinal fluid penetration may vary for each drug type and dosing^{5,6}. In a retrospective study of 21 patients, 48% had cytologic responses to standard dose erlotinib⁷, while higher-dose regimens have shown potential to rescue subsets of patients refractory to standard dose therapy^{8,9}. High dose osimertinib (160mg) has been studied in a phase I study and provided clinical stability or improvement at 12 weeks in 23/32 (72%) patients¹⁰. Likewise, novel *EGFR* TKIs with high capability to penetrate the blood brain barrier, such as AZD3759, have reported clinical activity in *EGFR*-mutant patients with LM¹¹. Nowadays, several *EGFR*-TKIs are now available in *EGFR*-mutant NSCLC, and optimal therapeutic sequence in this population remains unknown. As LM often develop during systemic TKI therapy, exploring the activity of subsequent TKI therapy after initial TKI failure is essential.

Herein, we conducted a joint international effort to evaluate the activity of *EGFR*-directed TKIs in a large cohort of *EGFR*-mutated NSCLC patients with LM, after first TKI failure.

II. Material and methods

Patients

We included consecutive patients with *EGFR*-mutated NSCLC and LM across 5 European institutions: Gustave Roussy, Villejuif, France; Centre Francois Baclesse, Caen, France; Lille University Hospital, Lille, France, Strasbourg University Hospital, Strasbourg, France, and Maastricht UMC+, Maastricht, Netherlands. We collected clinical characteristics of patients as well as disease-related features including imaging, histology and molecular profiling. Diagnosis of LM was assessed either by cytology of the cerebrospinal fluid (CSF) (EANO-ESMO confirmed LM), or by concordant clinical and radiological assessments including at least brain MRI (EANO-ESMO probable LM)¹². In case of EANO-ESMO probable LM, MRI was to be performed prior to any lumbar puncture, in order to avoid non-specific leptomeningeal enhancement. TKI failure was defined as: i) diagnosis of LM during systemic therapy with TKI or ii) progression of known LM on treatment with TKI. TKI rechallenge was defined as a new line of TKI after TKI failure, including administration of other TKI, or regimen adaptations such as dosing modifications of combination therapies. We analyzed outcomes according to systemic and central nervous system (CNS)-directed treatments.

Statistical analysis

We defined LM overall survival (LM OS) as time from LM diagnosis to death or last follow-up, and TKI OS from TKI rechallenge to death or last follow-up. Time to treatment failure (TTF) was defined as time from TKI rechallenge to treatment discontinuation or death. Patients surviving without treatment failure event were censored at date of last visit. Clinical response was assessed using physician-reported neurological outcomes. Clinical benefit was defined as clinical response or stable disease confirmed at least 2 months after treatment initiation. Survival analyses were performed using Kaplan-Meier estimates, and reported along with their

95% confidence interval (95%CI). A Cox proportional hazards regression model was used to evaluate the association between TKI rechallenge and OS, providing hazard ratio (HR) and 95%CI adjusted for the following characteristics: age; Eastern Cooperative Oncology Group performance status classification (ECOG PS) at the time of TKI failure; number of lines of therapy before TKI failure; context of TKI failure (diagnosis of LM on TKI, or progression of known LM on TKI). Median follow-up was calculated using the reverse Kaplan Meier method. Statistical analyses have been performed using NCSS 12 (NCSS, LLC) and R Studio.

III. Results

Patients

Ninety-two patients with *EGFR*-mutated NSCLC and leptomeningeal dissemination were included, diagnosed with LM between August 2003 and October 2018. Median follow-up was 5.6 months (0.1 to 38.6). Most patients were female (68%), never smoker (74%), and had stage IV disease at diagnosis (85%). *EGFR* mutations were determined by gene panel sequencing or PCR-based assays, and were predominantly L858R substitutions (45%) or exon 19 deletions (28%). Rare activating *EGFR* mutations were found in 14% of patients, while 13% had activating *EGFR* mutations of unspecified subtype. Acquired *T790M* mutations were reported in 15 patients before LM diagnosis.

Median time from initial cancer diagnosis to LM diagnosis was 18.5 months (0; 106). LM was diagnosed after systemic therapy consisting in TKI in 52/92 (56%) patients, chemotherapy in 32/92 (35%), or before any systemic therapy for stage IV disease in 8/92 (9%) patients. Overall, patients received a median number of 2 systemic therapies (0; 9) before diagnosis of LM. Concurrent brain metastases were reported in 61/92 (66%) of patients at LM diagnosis, among whom 29 were treated with radiation therapy (**Table 1**). LM was confirmed by cytology in 63% of patients (EANO-ESMO confirmed LM), while the remaining 37% had typical symptoms and imaging (EANO-ESMO probable LM). At LM onset, 85/92 (92%) patients experienced one or more symptoms related to LM. Most frequent symptoms included headache (26%), cerebellar syndrome (17%), cognitive disorders (21%) and seizures (10%) (**Supplementary Table S1**).

Overall survival from leptomeningeal metastases diagnosis

Among the entire study population, LM OS was 6.1 months (95%CI, 4.2 - 7.6), and 12-month LM OS rate was 27% (95%CI, 18% - 37%) (**Figure 1a**).

TKI failure occurred in 87 patients: 52 who had LM diagnosis during TKI, and 35 who had progression of known LM after TKI. Five additional patients were not treated with TKI at LM onset and did not receive any further treatment. Overall, 50/87 (57%) patients were rechallenged with TKI after TKI failure. Among them, 37 were rechallenged after a diagnosis of LM on TKI, and 13 had known LM that progressed on previous TKI.

LM OS in patients rechallenged with TKI was 7.6 months (95%CI, 5.7 - 10.9) compared to 4.2 months (95%CI, 1.6 - 6.7) in patients without any further therapy at TKI failure. The survival benefit was independent from age, ECOG PS, previous lines of therapy, and context of TKI failure, with an adjusted hazard ratio (HR) for death of 0.42 (95%CI, 0.24 – 0.75) (**Supplementary Table S2**). Respective 12-month OS rates in both groups were 32% (95%CI, 18 % - 46%) and 24% (95%CI, 10% - 39%) (**Figure 1b**).

Therapeutic strategies and outcomes from TKI rechallenge

Among 50 patients rechallenged with TKI, 43 (86%) were refractory to first or second generation TKI, including erlotinib (18), afatinib (5) or gefitinib (20). Six patients (12%) were refractory to third generation TKI, including osimertinib (5) and rociletinib (1). Therapeutic sequences after initial TKI failure are detailed in **Table 2**. Most patients (59%) had TKI switch, while 41% were treated with the same TKI but with more intensive regimens, including either dose intensification aiming at increasing central nervous system diffusion (34%) or combination therapies (6%) (**Supplementary Table S3**). Patients were treated with a median number of 2 systemic therapies after initial TKI failure (1; 5). Eight patients (16%) received additional intrathecal therapy.

Median TKI OS was 6.8 months (95%CI 3.7-8.0) across all 50 rechallenged patients. Patients who were rechallenged following LM diagnosis on TKI had longer TKI OS compared to patients rechallenged after progression of known LM on TKI, with respective median TKI OS of 7.8

months (95%CI 5.7-10.6) and 3.2 months (95%CI 1.8-4.0), adjusted HR for death 0.42 (95%CI 0.19-0.92) (**Supplementary Table S4**).

Median TTF from TKI rechallenge was 2.9 months (95%CI 2.1-3.7), and 6-month treatment failure-free rate was 23% (95%CI 11%-35%) (**Figure 2** and **supplementary Figure S1**). No significant difference in median TTF was observed between patients rechallenged after LM diagnosis on TKI and patients rechallenged after progression of known LM on TKI, with respective TTF of 3.3 months, (95%CI 2.1-3.9) and 2.3 months (1.4-3.1).

Forty-nine patients could be evaluated for response to TKI rechallenge. One patient was lost to follow-up immediately after subsequent TKI initiation and therefore not evaluable for response. Clinical response and clinical benefit occurred in 28% and 60% of patients, respectively. Outcomes of patients by treatment subgroups are detailed in **Table 3**.

Erlotinib was the most frequent TKI used for TKI rechallenge, in 22/50 (44%) patients, including 20 patients who had received prior afatinib or gefitinib, and 2 who had received prior third-generation TKI. Clinical response was observed in 6/22 (27%) and clinical benefit in 12/22 (54%) patients (**Table 3**). Median TTF was 2.7 months (95%CI 1.3-3.7), and 24% of patients were treatment failure-free at 6 months (95%CI 6%-42%). Of the 20 patients who received erlotinib after afatinib or gefitinib failure, 5 (25%) experienced clinical response and 11 (55%) clinical benefit. One clinical response was observed in a patient treated with erlotinib following osimertinib, in a disease without documented T790M mutation.

Seventeen (34%) patients received dose intensified regimens at TKI rechallenge (**Supplementary Table S3**). Among those, 6/17 (35%) had clinical response and 10/17 (59%) clinical benefit. At 6-months, 24% were treatment failure-free (95%CI 3%-44%). Of note, 4 patients with known *T790M* mutations had increased dose-intensity from osimertinib-based regimen, leading to clinical benefit for all of them, including 3 partial responses and 1 stable

disease. Dose modifications were well tolerated. No grade 3/4 toxicities were reported with patients receiving increased dose of first or second generation TKIs. Only two patients discontinued osimertinib 160mg due to grade 3 adverse events including rash and diarrhea.

Four patients switched to osimertinib after first or second generation TKI, among which three had evidence of *T790M* mutation at initial TKI failure. All derived clinical benefit with 3 stable diseases and one clinical response, with prolonged median TTF of 10.1 months. All but one out of four patients were alive at the time of the analysis with a median follow-up of 12,6 months after TKI rechallenge.

Patients treated with afatinib or gefitinib after other 1st or 2nd generation TKI had clinical responses in 25% and clinical benefit in 50%, but a short median TTF at 1.1 months (95%CI 0.1-3.5). No clinical responses were reported in patients treated with combination therapies using the same TKI (N=3).

Seventeen patients received brain radiation therapy for brain metastases and/or LM before TKI rechallenge, including 13 treated by whole brain radiation therapy. No significant difference in disease control or TTF was observed in this subgroup compared to patients who did not receive radiation therapy, regardless of radiation therapy modality. Additional intrathecal therapy (N=8) was not associated with improved clinical benefit nor TTF (**Supplementary Table S5**).

IV. Discussion

This large-scale retrospective study shows that TKI rechallenge provides substantial activity after TKI failure. Notably, we observed prolonged LM OS (7.6 vs 4.2 months) in patients who were rechallenged with a TKI, compared to those who were not.

High response rates and prolonged TTF were seen in patients who received erlotinib after first- or second-generation TKI, or who received high dose erlotinib. These data support the

hypothesis that therapeutic resistance in the context of leptomeningeal metastases may be related to limited central nervous system diffusion^{13,14}. Indeed, erlotinib has better brain-blood-barrier penetration than afatinib or gefitinib^{13,15}, and dose intensification strategies have been proven to improve central nervous system diffusion of TKIs⁵. Prospective studies have confirmed the feasibility of TKI dose increase in clinical practice, notably for erlotinib and osimertinib^{10,16}. Thus, current data support the use of rescue high dose TKI at the time of standard dose TKI failure in *EGFR*-mutant patients with LM. However, this strategy should be considered only in patients with predominant central nervous system disease, as higher-dose therapies may not rescue extracranial resistance after TKI failure¹⁷.

While few patients have been treated with third generation TKI in our cohort, long-term survival has been reported in patients receiving osimertinib including responses that lasted more than a year after TKI rechallenge. This is in line with recent reports on intracranial activity of osimertinib for both brain and leptomeningeal metastases^{6,10,18,19}. Osimertinib may be highly active by targeting diseases which acquire *T790M* mutations, as well as through high central nervous system concentrations in all-comers. In our study, all patients but one who had TKI rechallenge with osimertinib had a documented *T790M* mutation. As a consequence, we cannot generate data on the LM control by osimertinib used upfront in *T790M* negative patients, compared to a sequential strategy. Dedicated studies will be essential to assess the activity of osimertinib in this population as this compound may significantly improve outcomes in this population.

Recent insights into leptomeningeal metastases biology might help elaborate better therapeutic strategies for these patients. Indeed, leptomeningeal metastases might have different molecular alterations compared to solid brain metastases. In particular leptomeningeal metastases have been found to be enriched in *EGFR*, *MET* and *TP53* mutations, while they rarely harbor *KRAS* alterations compared to other solid metastases from NSCLC²⁰⁻²². Tailoring therapy to molecular alterations found in the cerebrospinal fluid has been reported to be feasible while providing

clinical benefit in subsets of patients²². In this context, the use of CSF as liquid biopsies may facilitate translational research programs and help to personalize subsequent treatment²¹.

The choice of clinical endpoints in our study illustrates the difficulties encountered when assessing response of leptomeningeal metastases. Indeed, MRI evaluation leads to false negative assessments in up to 30% of patients at diagnosis, while sensitivity of cytology can be as low as 50%²³. Follow-up is equally difficult with the lack of specific evaluation criteria and high variability. At present, clinical outcomes remain a key variable for the evaluation of leptomeningeal metastases, considering the high proportion of patients who experience neurological symptoms, and the fact that therapeutic decisions were guided by clinical outcomes in our cohort. The RANO and EANO-ESMO working groups established frameworks relying on neurological evaluation, MRI of the central nervous system and cytology of the CSF to assess LM diagnosis and follow-up^{12,24}, which may help improve clinical management and drug development in this particular population.

In conclusion, our study shows that a strategy using various lines of EGFR TKIs leads to a significant OS benefit in patients with leptomeningeal metastases. Regimen switch or strategies using higher dosing may help overcome resistance to TKI in a context of CNS dissemination and improve outcomes. Evaluation of osimertinib in patients with *EGFR*-mutated leptomeningeal metastases regardless of T790M status is warranted and could challenge standard of care in this population. Standardized leptomeningeal assessments and translational research programs are needed to better understand resistance mechanisms and improve current therapeutic strategies.

Conflicts of Interest

RF. Travel: Pfizer

LH. Research funding from Roche, Boehringer Ingelheim (both institution). Advisory board: Boehringer, BMS, (both institution, BMS also self). Travel/conference reimbursement: Roche, BMS (self). Mentorship program with key opinion leaders funded by AstraZeneca. Fees for educational webinars from Quadia (self).

ELR. Research grants from Mundipharma and Amgen. Honoraria for lectures or advisory board participation from Abbvie, Daiichi Sankyo, Mundipharma and Novartis.

LM. Consulting, advisory role: Roche Diagnostics. Lectures and educational activities: Bristol-Myers Squibb, Tecnofarma, Roche, AstraZeneca. Travel, Accommodations, Expenses: Chugai.

BB. Sponsored Research at Gustave Roussy Cancer Center: Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma

JR. Advisory boards: MSD, Boehringer Ingelheim, BMS, AstraZeneca. Travel: OSE Immunotherapeutics, BMS, AstraZeneca, Roche. Speaker: Pfizer.

DP. Consulting or Advisory Role - AstraZeneca; Boehringer Ingelheim; Bristol-Myers Squibb; Celgene; MSD Oncology; Novartis; Pfizer; Roche

JA. Consulting or Advisory Role - AstraZeneca; Bristol-Myers Squibb; Merck Sharp & Dohme; Roche. Research Funding - Merck Sharp & Dohme (Inst); Pierre Fabre (Inst); Sanofi (Inst).

CC. Consulting or Advisory Role - Bristol-Myers Squibb; Pfizer.

CLP. Advisory – AstraZeneca

PL. Travel – Pfizer.

Other authors declare no conflict of interest

Authors contribution

RF. Study design, data collection, data analysis and interpretation. *PB.* study design, data collection, data analysis and interpretation. *DX, ELR, LH, CL, MBF, RG.* Data collection. *JR, JA, DP, CC, CLP, LL, AG.* Study design and data collection. *EA.* data analysis and interpretation. *LM, BB.* Study design, data analysis and interpretation. All authors participated in the redaction of the manuscript and approved the submitted version.

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Figure legends

Figure 1. Overall survival in the study population **a.** Overall survival from leptomeningeal metastases diagnosis **b.** Overall survival according to systemic therapy for refractory leptomeningeal metastases

Figure 2. Time to treatment failure of patients treated for refractory leptomeningeal metastases

Table 1. Baseline characteristics of the study population

Baseline characteristics

N=92 (%)

Median Age, years [min;max]		60 [26;79]
Gender	<i>Male</i>	29 (32)
	<i>Female</i>	63 (68)
Smoking	<i>Smoker</i>	22 (24)
	<i>Non-smoker</i>	68 (74)
	<i>Unknown</i>	2 (2)
Stage at diagnosis	<i>I</i>	3 (3)
	<i>II</i>	1 (1)
	<i>III</i>	6 (7)
	<i>IV</i>	78 (85)
	<i>Unknown</i>	4 (4)
Median number of metastatic sites at diagnosis [min;max]		1 [0;5]
EGFR mutation	<i>Exon 21 L858R</i>	41 (45)
	<i>Exon 19 del</i>	26 (28)
	<i>Other</i>	13 (14)
	<i>Unknown</i>	12 (13)
Median time to LM onset, months [min;max]		18.5 [0;106]
LM diagnosis	<i>Cytology confirmed</i>	58 (63)
	<i>Imaging and symptoms</i>	34 (37)
Symptoms related to LM		85 (92)
Concurrent brain metastases		61 (66)
Radiation therapy for brain metastases	<i>Radiation therapy</i>	29 (32)
	<i>Including: WBRT</i>	18 (20)
	<i>SRS</i>	8 (9)
	<i>WBRT + SRS</i>	3 (3)
Number of systemic treatments before LM diagnosis, median [min;max]		2 [0;9]

LM: leptomeningeal metastases

Table 2. Therapeutic sequence in patients with TKI rechallenge at initial TKI failure

Treatment	N = 50 (%)	
Regimen switch	Erlotinib	22 (44)
	<i>From 1st / 2nd generation TKI</i>	20
	<i>From 3rd generation TKI</i>	2
	Afatinib / Gefitinib	4 (8)
	<i>From 1st / 2nd generation TKI</i>	4
	Osimertinib	4 (8)
<i>From 1st / 2nd generation TKI</i>	4	
Regimen adaptation	Increased dose-intensity	17 (35)
	<i>From 1st / 2nd generation TKI</i>	13
	<i>From 3rd generation TKI</i>	4
	Combinations	3 (6)
<i>From 1st / 2nd generation TKI</i>	3	
Median number of systemic therapies after refractory LM [min;max]		2 [1;5]
Intrathecal therapy for refractory LM		7 (14)

LM: leptomeningeal metastases

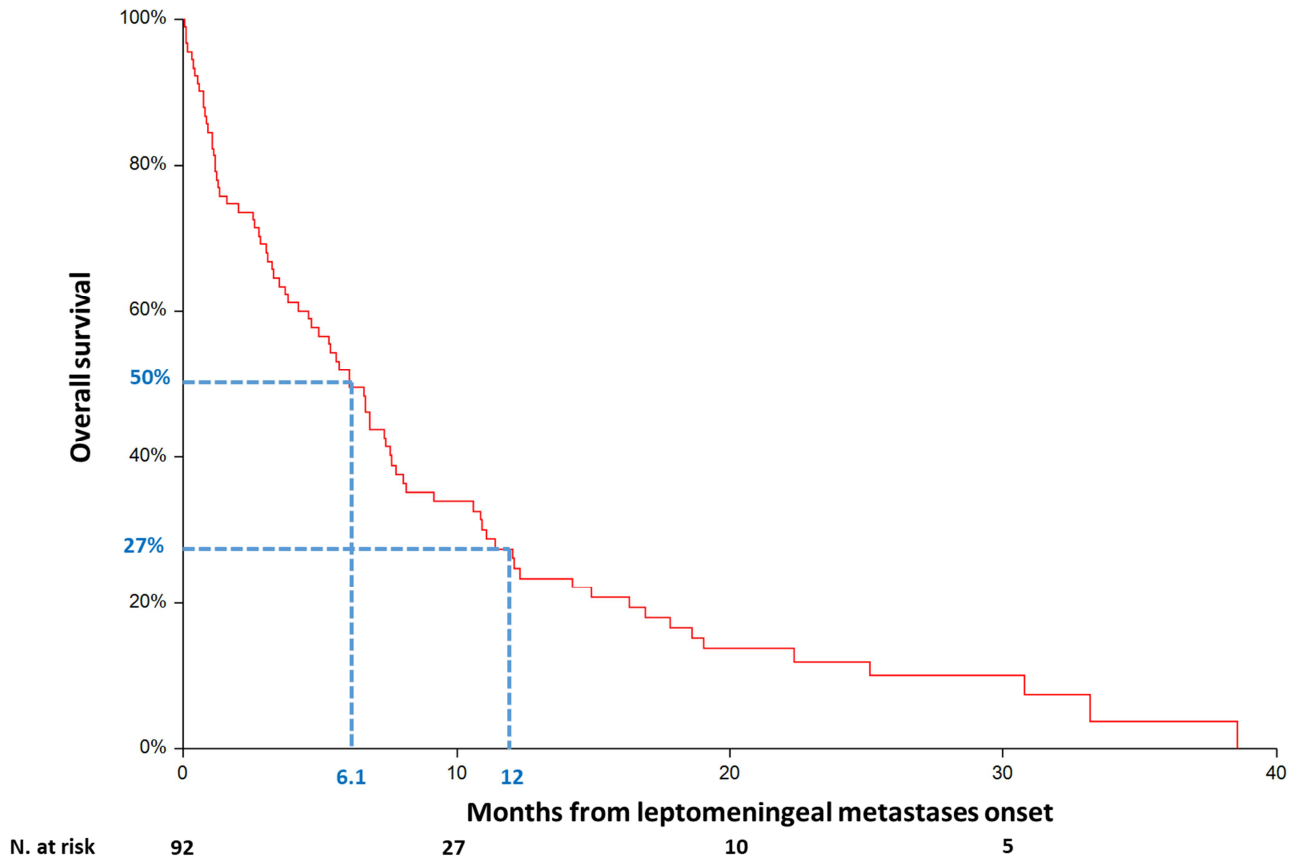
Table 3. Clinical response and time to treatment failure according to therapy for refractory leptomeningeal metastases

Variable	Regimen switch			Regimen adaptation			All patients
	Erlotinib N=22 (%)	Afatinib / Gefitinib N=4 (%)	Osimertinib N=4 (%)	Increased dose- intensity N=17 (%)	Combinations N=3 (%)	N=50 (%)	
Clinical response							
<i>Clinical response</i>	6 (27)	1 (25)	1 (25)	6 (35)	0	14 (28)	
<i>Stable disease</i>	6 (27)	1 (25)	3 (75)	4 (24)	2 (67)	16 (32)	
<i>Progressive disease</i>	9 (41)	2 (50)	0	7 (41)	1 (33)	19 (38)	
<i>Unknown</i>	1 (5)	0	0	0	0	1 (2)	
Median TTF, months	2.7 (95%CI 1.3-3.7)	1.1 (95%CI 0.1-3.5)	10.1 (95%CI 3.8-14.7)	3.3 (95%CI 1.9-5.6)	2.3 (95%CI 1.4-3.7)	2.9 (95%CI 2.1-3.7)	
6-month treatment failure-free rate	24% (95%CI 6%-42%)	0	67% (95%CI 13%-100%)	24% (95%CI 3%-44%)	0	23% (95%CI 11%-35%)	

TTF: Time to treatment failure

Figure 1.

a



b.

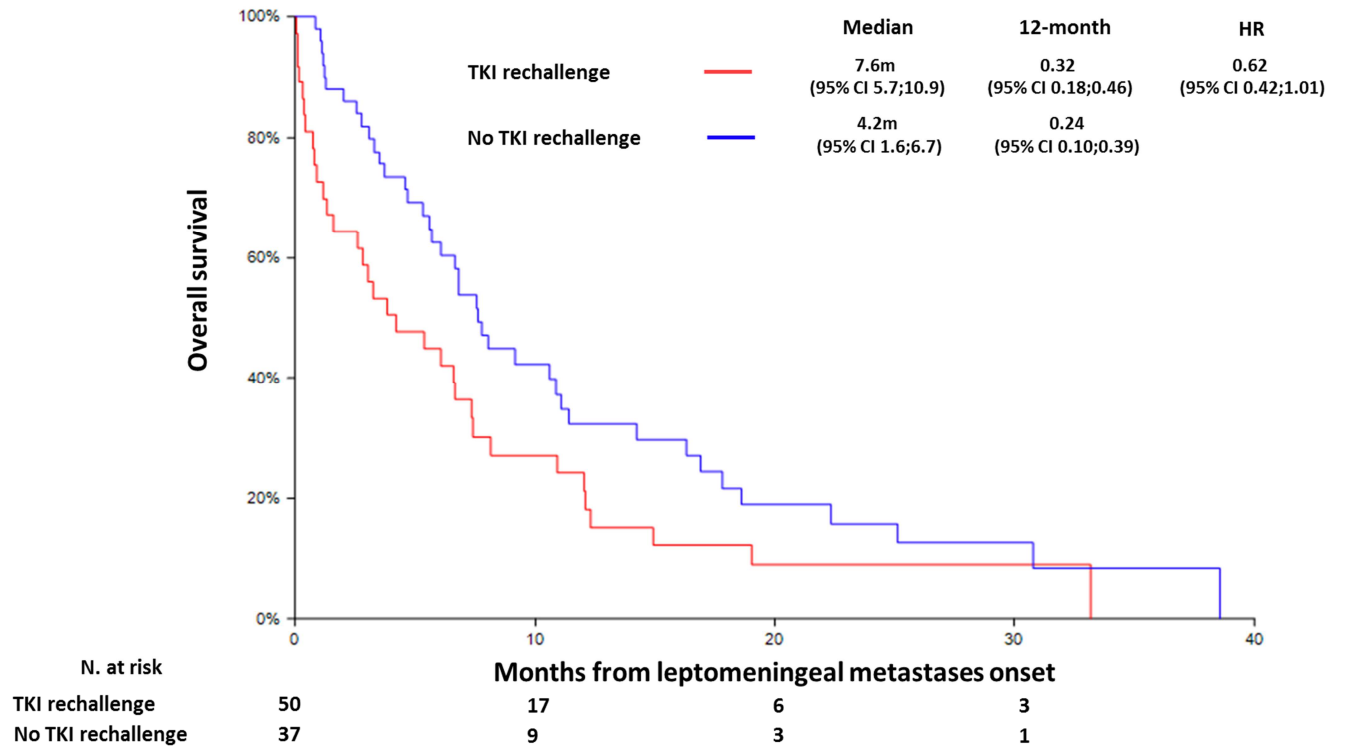


Figure 2.

