

Activity of EGFR Tyrosine Kinase Inhibitors in NSCLC With Refractory Leptomeningeal Metastases

Citation for published version (APA):

Flippot, R., Biondani, P., Auclin, E., Xiao, D., Hendriks, L., Le Rhun, E., Leduc, C., Beau-Faller, M., Gervais, R., Remon, J., Adam, J., Planchard, D., Lavaud, P., Naltet, C., Caramella, C., Le Pechoux, C., Lacroix, L., Gazzah, A., Mezquita, L., & Besse, B. (2019). Activity of EGFR Tyrosine Kinase Inhibitors in NSCLC With Refractory Leptomeningeal Metastases. *Journal of Thoracic Oncology*, 14(8), 1400-1407. <https://doi.org/10.1016/j.jtho.2019.05.007>

Document status and date:

Published: 01/08/2019

DOI:

[10.1016/j.jtho.2019.05.007](https://doi.org/10.1016/j.jtho.2019.05.007)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 05 Jan. 2021

Activity of EGFR Tyrosine Kinase Inhibitors in NSCLC With Refractory Leptomeningeal Metastases



Ronan Flippot, MD, MSc,^a Pamela Biondani, MD,^b Edouard Auclin, MD,^c Dingyu Xiao, MD,^d Lizza Hendriks, MD, PhD,^{a,e} Emilie Le Rhun, MD,^{f,g,h,i} Charlotte Leduc, MD,^j Michèle Beau-Faller, MD, PhD,^k Radj Gervais, MD,^d Jordi Remon, MD,^a Julien Adam, MD, PhD,^l David Planchard, MD, PhD,^a Pernelle Lavaud, MD,^a Charles Naltet, MD,^a Caroline Caramella, MD,^m Cécile Le Pechoux, MD,ⁿ Ludovic Lacroix, PharmD, PhD,^o Anas Gazzah, MD,^a Laura Mezquita, MD, PhD,^a Benjamin Besse, MD, PhD^{a,p,*}

^aDepartment of Medical Oncology, Gustave Roussy, Villejuif, France

^bDepartment of Medical Oncology, Paul Brousse Hospital, Villejuif, France

^cDepartment of Gastroenterology and Digestive Oncology, Hôpital Européen Georges Pompidou, Paris, France

^dDepartment of Medical Oncology, Centre François Baclesse, Caen, France

^eDepartment of Pulmonary Diseases, GROW - School for Oncology and Developmental Biology, Maastricht UMC+, Maastricht, Netherlands

^fUniversity of Lille, Lille, France

^gNeuro-oncology, General and Stereotaxic Neurosurgery Department, Lille University Hospital, Lille, France

^hBreast Cancer Department, Oscar Lambret Center, Lille, France

ⁱDepartment of Neurology & Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland

^jDepartment of Pneumology, Strasbourg University Hospital, Strasbourg, France

^kDepartment of Molecular Biology, Strasbourg University Hospital, Strasbourg, France

^lDepartment of Pathology, Gustave Roussy, Villejuif, France

^mDepartment of Radiology, Gustave Roussy, Villejuif, France

ⁿDepartment of Radiotherapy, Gustave Roussy, Villejuif, France

^oDepartment of Molecular Biology, Gustave Roussy, Villejuif, France

^pParis-Sud University, Orsay, France

Received 6 April 2019; revised 30 April 2019; accepted 1 May 2019
Available online - 18 May 2019

ABSTRACT

Introduction: Leptomeningeal metastases (LMs) are associated with dismal prognosis in NSCLC. Optimal management remains unknown in patients with *EGFR*-

mutated NSCLC after initial tyrosine kinase inhibitor (TKI) failure.

Methods: We conducted a multicenter retrospective study including patients with *EGFR*-mutated NSCLC and LM. TKI

*Corresponding author.

Disclosure: Dr. Flippot has received personal fees from Pfizer. Dr. Hendriks has received grants from Roche, Boehringer Ingelheim; and has received personal fees from Bristol-Myers Squibb, Roche, Quadria, and Boehringer Ingelheim; and has received nonfinancial support from Astra Zeneca. Dr. Le Rhun has received grants from Amgen and Mundi Pharma; and has received personal fees from Mundi Pharma, AbbVie, Daiichi Sankyo, and Novartis. Dr. Remon has received grants from Ose Immunotherapeutics; and has received personal fees from Osi Immunotherapeutics, MSD, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Astra Zeneca, and Roche. Dr. Adam has received grants from MSD, Sanofi, and Pierre Fabre; and has received personal fees from Astra Zeneca, Bristol-Myers Squibb, MSD, and Roche. Dr. Planchard has received personal fees from Astra Zeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Celgene, Novartis, Roche, and Pfizer. Dr. Lavaud has received personal fees from Pfizer. Dr. Caramella has received personal fees from Bristol-Myers Squibb

and Pfizer. Dr. Pechoux has received personal fees from Astra Zeneca. Dr. Mezquita has received grants from Roche; and has received personal fees from Bristol-Myers Squibb, TecnoPharma, Roche, Astra Zeneca, and Chugai. Dr. Besse has received grants from AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, Bristol-Myers Squibb, Celgene, Lilly, GlaxoSmithKline, Ignyta, Ipsen, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, and Tiziana Pharma. The remaining authors declare no conflict of interest.

Address for correspondence: Benjamin Besse, MD, PhD, Gustave Roussy, Paris Sud University, 114 rue Edouard Vaillant, 94800 Villejuif, France. E-mail: benjamin.besse@gustaveroussy.fr

© 2019 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2019.05.007>

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 (range: 0–9) systemic therapies. Median overall survival from LM diagnosis was 6.1 months (95% confidence interval [CI]: 4.2–7.6 months). Among 87 patients with TKI failure, patients rechallenged with TKI ($n = 50$) had a median LM overall survival of 7.6 months (95% CI: 5.7–10.9) compared to 4.2 months (95% CI: 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 of 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 first- and second-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.

© 2019 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

Keywords: NSCLC; *EGFR*; Tyrosine kinase inhibitor; Leptomeningeal metastases

Introduction

Lung cancer is the leading cause of death from cancer worldwide.¹ Targeted molecular therapies provided significant improvements in outcomes of patients presenting with somatic *EGFR* mutations, found in up to 15% of NSCLC cases in the western world.² Although underdiagnosed, leptomeningeal metastases (LM) will arise in ~10% of patients with *EGFR*-mutated NSCLC, leading to dismal outcomes: survival in this population does not exceed 1 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 (CSF) 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 erlotinib, whereas higher-dose regimens have shown potential to rescue subsets of patients refractory to standard dose therapy.⁷⁻⁹

High-dose osimertinib (160 mg) has been studied in a phase I study and provided clinical stability or improvement at 12 weeks in 23 of 32 (72%) patients.¹⁰ 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 LM.¹¹ Nowadays, several *EGFR*-TKIs are available in *EGFR*-mutant NSCLC, and optimal therapeutic sequence in this population remains unknown. As LMs often develop during systemic TKI therapy, exploring the activity of subsequent TKI therapy after initial TKI failure is essential.

Herein, we report 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.

Material and Methods

Patients

We included consecutive patients with *EGFR*-mutated NSCLC and LM across five 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 CSF (European Association of Neuro-Oncology [EANO]-European Society for Medical Oncology [ESMO]-confirmed LM), or by concordant clinical and radiologic assessments including at least brain magnetic resonance imaging (MRI) (EANO-ESMO-probable LM).¹² In case of EANO-ESMO-probable LM, MRI was to be performed before any lumbar puncture to avoid nonspecific leptomeningeal enhancement. TKI failure was defined as: (1) diagnosis of LM during systemic therapy with TKI or (2) 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 (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 neurologic 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 intervals (95% CIs). 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 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.

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 (range: 0.1 to 38.6 months). Most patients were female (68%), never-smokers (74%), and had stage IV disease at diagnosis (85%). *EGFR* mutations were determined by gene panel sequencing or polymerase chain reaction–based assays and were predominantly L858R substitutions (45%) or exon 19 deletions (28%). Rare activating *EGFR* mutations were found in 14% of patients, whereas 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 (range 0–106 months). LM was diagnosed after systemic therapy consisting in TKI in 52 of 92 (56%) patients, chemotherapy in 32 of 92 (35%), or before any systemic therapy for stage IV disease in 8 of 92 (9%) patients. Overall, patients received a median number of two systemic therapies (range: 0–9) before diagnosis of LM. Concurrent brain metastases were reported in 61 of 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), whereas the remaining 37% had typical symptoms and imaging (EANO-ESMO–probable LM). At LM onset, 85 of 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 1).

Table 1. Baseline Characteristics of the Study Population

Baseline Characteristics	N = 92
Median age, (range) y	60 (26-79)
Sex	
Male	29 (32)
Female	63 (68)
Smoking	
Smoker	22 (24)
Nonsmoker	68 (74)
Unknown	2 (2)
Stage at diagnosis	
I	3 (3)
II	1 (1)
III	6 (7)
IV	78 (85)
Unknown	4 (4)
Median number of metastatic sites at diagnosis, (range)	1 (0-5)
<i>EGFR</i> mutation	
Exon 21 L858R	41 (45)
Exon 19 del	26 (28)
Other	13 (14)
Unknown	12 (13)
Median time to LM onset, (range), mo	18.5 (0-106)
LM diagnosis	
Cytology confirmed	58 (63)
Imaging and symptoms	34 (37)
Symptoms related to LM	85 (92)
Concurrent brain metastases	61 (66)
Radiation therapy for brain metastases	
Radiation therapy	29 (32)
Including: WBRT	18 (20)
SRS	8 (9)
WBRT + SRS	3 (3)
No. of systemic treatments before LM diagnosis, median (range)	2 (0-9)

Values are shown as n (%) or median (range).
LM, leptomeningeal metastases.

Overall Survival From LM Diagnosis

Among the entire study population, LM OS was 6.1 months (95% CI: 4.2–7.6), and the 12-month LM OS rate was 27% (95% CI: 18%–37%) (Fig. 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 of 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, Eastern Cooperative Oncology Group performance status, previous lines of therapy, and context of

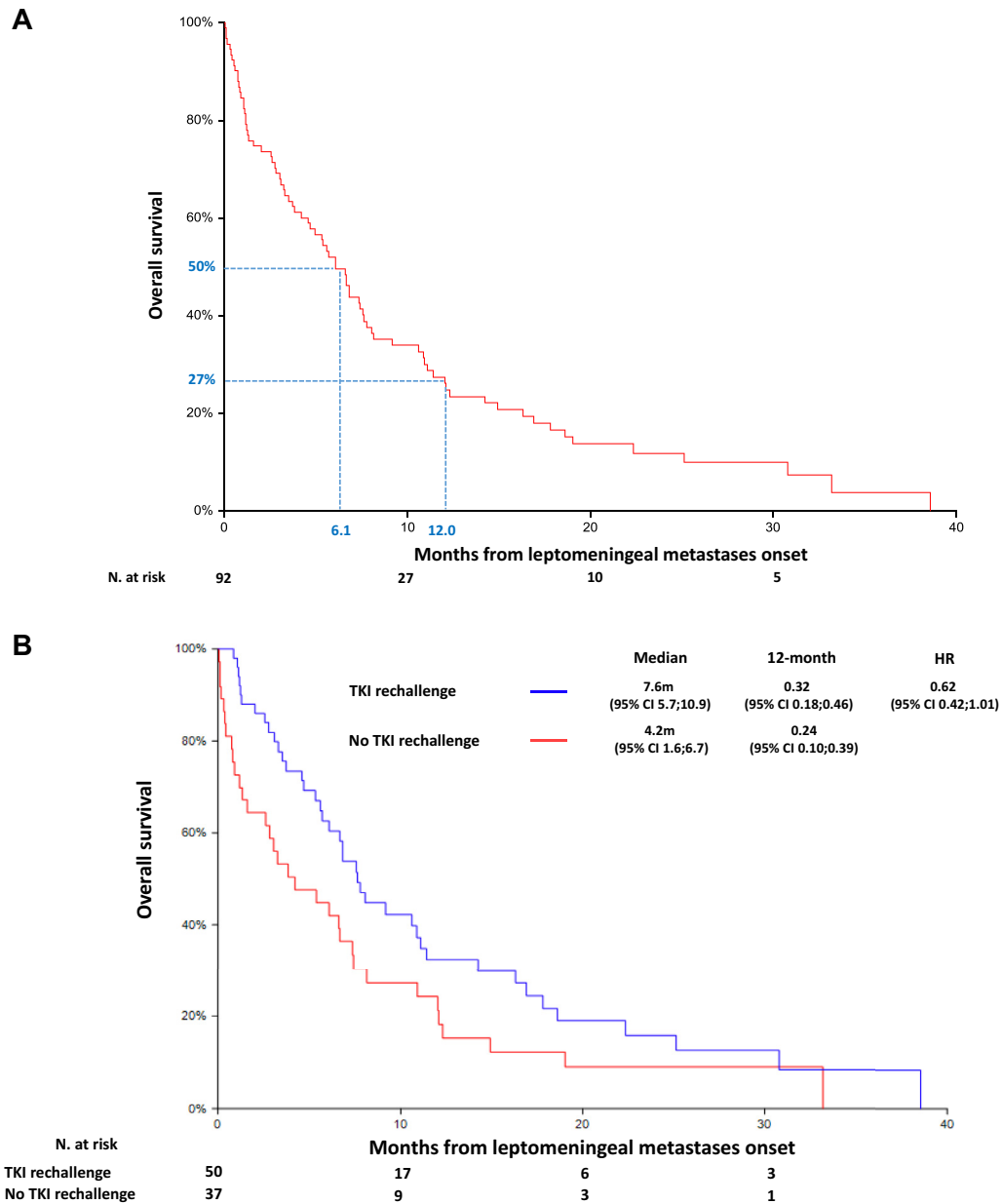


Figure 1. Overall survival in the study population. (A) Overall survival from leptomeningeal metastases diagnosis. (B) Overall survival according to systemic therapy for refractory leptomeningeal metastases.

TKI failure, with an adjusted HR for death of 0.42 (95% CI: 0.24–0.75) (Supplementary Table 2). Respective 12-month OS rates in both groups were 32% (95% CI: 18%–46%) and 24% (95% CI: 10%–39%) (Fig. 1B).

Therapeutic Strategies and Outcomes From TKI Rechallenge

Among 50 patients rechallenged with TKI, 44 (88%) were refractory to first- or second-generation TKI, including erlotinib (19), 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 (60%) had TKI switch, whereas 40% were treated with the same TKI but with more intensive regimens, including either dose intensification aiming at increasing CNS diffusion (34%) or combination therapies (6%) (Supplementary Table 3). Patients were treated with a median number of two systemic therapies after initial TKI failure (range: 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

Table 2. Therapeutic Sequence in Patients With TKI Rechallenge at Initial TKI Failure (n = 50)

Treatment	n (%)
Regimen switch	
Erlotinib	22 (44)
From first- / second-generation TKI	20 (40)
From third-generation TKI	2 (4)
Afatinib/gefitinib	4 (8)
From first- / second-generation TKI	4 (8)
Osimertinib	4 (8)
From first-/second-generation TKI	4 (8)
Regimen adaptation	
Increased dose intensity	17 (34)
From first-/second-generation TKI	13 (26)
From third-generation TKI	4 (8)
Combinations	3 (6)
From first-/second-generation TKI	3 (6)
Median no. of systemic therapies after TKI failure (range)	2 (1-5)
Intrathecal therapy for refractory LM	8 (16)

Values are n (%) unless otherwise stated. TKI, tyrosine kinase inhibitor; LM, leptomeningeal metastases.

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 4).

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%) (Fig. 2 and Supplementary Fig. 1). 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 (95% CI: 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 of 50 (44%) patients, including 20 patients who had received prior afatinib or gefitinib, and two who had received prior third-generation TKI. Clinical response was observed in 6 of 22 (27%) and clinical benefit in 12 of 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 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 3). Among those, 6 of 17 (35%) had clinical response and 10 of 17 (59%) clinical benefit. At 6 months, 24% were treatment failure-free (95% CI: 3%–44%). Four patients

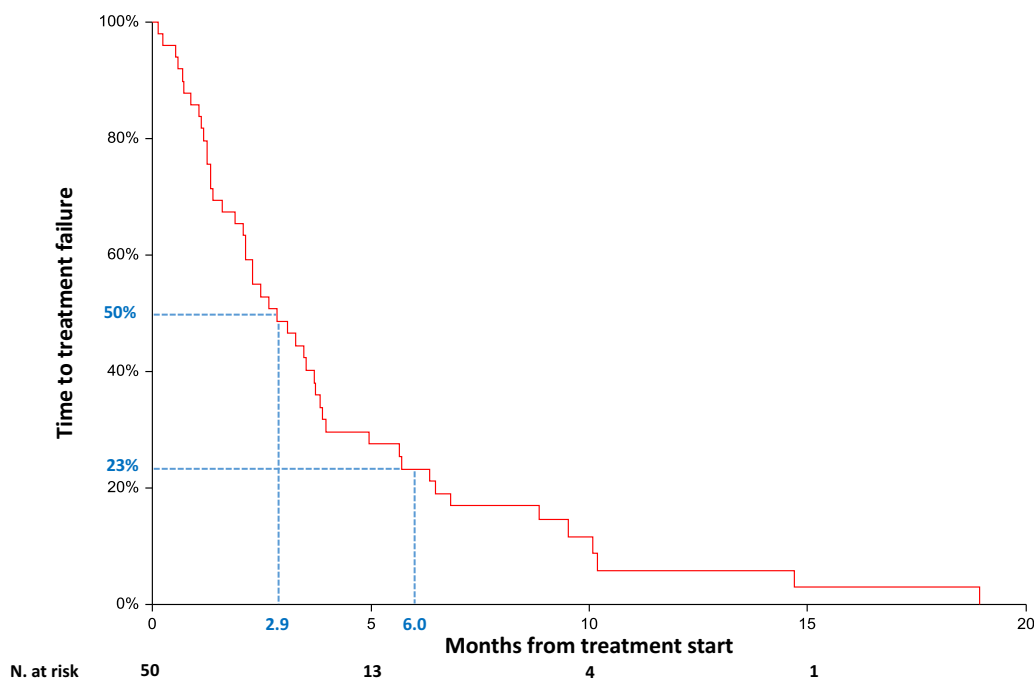


Figure 2. Time-to-treatment failure of patients treated for refractory leptomeningeal metastases.

Table 3. Clinical Response and Time to Treatment Failure According to Therapy for Refractory LM

Variable	Regimen Switch		Regimen Adaptation			Patients Rechallenged with TKIs n = 50
	Erlotinib n = 22	Afatinib / Gefitinib n = 4	Osimertinib n = 4	Increased Dose intensity n = 17	Combinations n = 3	
Clinical response	6 (27)	1 (25)	1 (25)	6 (35)	0	14 (28)
Stable disease	6 (27)	1 (25)	3 (75)	4 (24)	2 (67)	16 (32)
Progressive disease	9 (41)	2 (50)	0	7 (41)	1 (33)	19 (38)
Unknown	1 (5)	0	0	0	0	1 (2)
Median TTF, months (95% CI)	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 (95% CI)	24% (95% CI: 6%-42%)	0	67% (95% CI: 13%-100%)	24% (95% CI: 5%-44%)	0	23% (95% CI: 11%-35%)

Values shown are n (%) unless otherwise stated. TTF, time to treatment failure; LM, leptomeningeal metastases; CI, confidence interval.

with known *T790M* mutations had increased dose intensity from osimertinib-based regimen, leading to clinical benefit for all of them, including three partial responses and one 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 160 mg due to grade 3 adverse events including rash and diarrhea.

Four patients switched to osimertinib after first- or second-generation TKI, among whom three had evidence of *T790M* mutation at initial TKI failure. All derived clinical benefit with three having stable diseases and one having clinical response, with prolonged median TTF of 10.1 months. All but one of four patients was 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 first- or second-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 5).

Discussion

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

High response rates and prolonged TTF were observed 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 LMs may be related to limited CNS diffusion.^{13,14} Erlotinib has better brain-blood-barrier penetration than afatinib or gefitinib, and dose-intensification strategies have been proven to improve CNS diffusion of TKIs.^{5,13,15} 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

CNS disease, as higher-dose therapies may not rescue extracranial resistance after TKI failure.¹⁷

Although 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 1 year after TKI rechallenge. This is in line with recent reports on intracranial activity of osimertinib for both brain and LMs.^{6,10,18,19} Osimertinib may be highly active by targeting diseases which acquire *T790M* mutations, as well as through high CNS 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 patients who are *T790M*-negative 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 LM biology might help elaborate better therapeutic strategies for these patients. LMs might have different molecular alterations compared to solid brain metastases. In particular, LMs have been found to be enriched in *EGFR*, *MET* proto-oncogene, receptor tyrosine kinase (*MET*), and tumor protein p53 (*TP53*) mutations, whereas they rarely harbor *KRAS* alterations compared to other solid metastases from NSCLC.²⁰⁻²² Tailoring therapy to molecular alterations found in the CSF has been reported to be feasible while providing clinical benefit in subsets of patients.²² In this context, the use of CSF as liquid biopsy specimens may facilitate translational research programs and help to personalize subsequent treatment.²¹

The choice of clinical endpoints in our study shows the difficulties encountered when assessing response of LMs. MRI evaluation leads to false-negative assessments in up to 30% of patients at diagnosis, whereas 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 LMs, considering the high proportion of patients who experience neurologic symptoms and the fact that therapeutic decisions were guided by clinical outcomes in our cohort. The Response Assessment in Neuro-Oncology and EANO-ESMO working groups established frameworks relying on neurologic evaluation, MRI of the CNS, and cytology of the CSF to assess LM diagnosis and follow-up, which may help improve clinical management and drug development in this particular population.^{12,24}

In conclusion, our study shows that a strategy using various lines of EGFR TKIs leads to a significant OS benefit in patients with LMs. 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 LMs 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.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2019.05.007>.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Cheng T-YD, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The international epidemiology of lung cancer: latest trends, disparities, and tumor characteristics. *J Thorac Oncol*. 2016;11:1653-1671.
3. Li Y-S, Jiang B-Y, Yang J-J, et al. Leptomeningeal metastases in patients with NSCLC with EGFR mutations. *J Thorac Oncol*. 2016;11:1962-1969.
4. Kuiper JL, Hendriks LE, van der Wekken AJ, et al. Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: a retrospective cohort analysis. *Lung Cancer*. 2015;89:255-261.
5. Clarke JL, Pao W, Wu N, Miller VA, Lassman AB. High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. *J Neurooncol*. 2010;99:283-286.
6. Ballard P, Yates JWT, Yang Z, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. *Clin Cancer Res*. 2016;22:5130-5140.
7. Nosaki K, Shiraishi Y, Hirai F, et al. Phase II study of erlotinib in advanced non-small cell lung cancer patients with leptomeningeal metastasis. *J Clin Oncol*. 2016;34(suppl 15):e20596-e20596.
8. Kawamura T, Hata A, Takeshita J, et al. High-dose erlotinib for refractory leptomeningeal metastases after failure of standard-dose EGFR-TKIs. *Cancer Chemother Pharmacol*. 2015;75:1261-1266.
9. Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol*. 2011;13:1364-1369.
10. Yang JC-H, Cho BC, Kim D-W, et al. Osimertinib for patients (pts) with leptomeningeal metastases (LM) from EGFR-mutant non-small cell lung cancer (NSCLC):

- updated results from the BLOOM study. *J Clin Oncol.* 2017;35(suppl 15), 2020-2020.
11. Ahn M-J, Kim D-W, Cho BC, et al. Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): a phase 1, open-label, dose-escalation and dose-expansion study. *Lancet Respir Med.* 2017;5:891-902.
 12. Le Rhun E, Weller M, Brandsma D, et al. EANO-ESMO clinical practice guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol.* 2017;28(suppl 4): iv84-iv99.
 13. Togashi Y, Masago K, Masuda S, et al. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. *Cancer Chemother Pharmacol.* 2012;70:399-405.
 14. Hoffknecht P, Tufman A, Wehler T, et al. Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol.* 2015;10: 156-163.
 15. Deng Y, Feng W, Wu J, et al. The concentration of erlotinib in the cerebrospinal fluid of patients with brain metastasis from non-small-cell lung cancer. *Mol Clin Oncol.* 2014;2:116-120.
 16. Smit EF, Gervais R, Zhou C, et al. Efficacy and safety results from CurrentS, a double-blind, randomized, phase III study of second-line erlotinib (150 mg versus 300 mg) in current smokers with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2014;32(suppl 15): 8046-8046.
 17. Kuiper JL, Heideman DA, Thunnissen E, van Wijk AW, Postmus PE, Smit EF. High-dose, weekly erlotinib is not an effective treatment in EGFR-mutated non-small cell lung cancer-patients with acquired extracranial progressive disease on standard dose erlotinib. *Eur J Cancer.* 2014;50:1399-1401.
 18. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol.* 2018;36:3290-3297.
 19. Vishwanathan K, Varrone A, Varnas K, et al. Abstract CT013: osimertinib displays high brain exposure in healthy subjects with intact blood-brain barrier: a microdose positron emission tomography (PET) study with ¹¹C-labelled osimertinib. *Cancer Res.* 2018;78(suppl 13). CT013-CT013.
 20. Li Y, Liu B, Connolly ID, et al. Recurrently mutated genes differ between leptomeningeal and solid lung cancer brain metastases. *J Thorac Oncol.* 2018;13: 1022-1027.
 21. Ying S, Ke H, Ding Y, et al. Unique genomic profiles obtained from cerebrospinal fluid cell-free DNA of non-small cell lung cancer patients with leptomeningeal metastases. *Cancer Biol Ther.* 2019;20:562-570.
 22. Jiang B-Y, Li Y, Chuai S, et al. NGS to reveal heterogeneity between cerebrospinal fluid and plasma ctDNA among non-small cell lung cancer patients with leptomeningeal carcinomatosis. *J Clin Oncol.* 2017;35(suppl 15):9022-9022.
 23. Remon J, Le Rhun E, Besse B. Leptomeningeal carcinomatosis in non-small cell lung cancer patients: a continuing challenge in the personalized treatment era. *Cancer Treat Rev.* 2017;53:128-137.
 24. Chamberlain M, Junck L, Brandsma D, et al. Leptomeningeal metastases: a RANO proposal for response criteria. *Neuro Oncol.* 2017;19:484-492.