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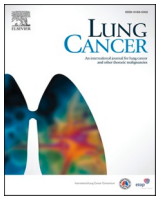

Real-world treatment patterns and survival of patients with *ROS1* rearranged stage IV non-squamous NSCLC in the Netherlands

Deirdre M.H.J. ten Berge [a,b], Ronald A.M. Damhuis [c], Joachim G.J.V. Aerts [b], Anne-Marie C. Dingemans [b,*]

[a] *Dept. of Radiology, ADRZ, 's-Gravenpolderseweg 114, 4462 RA Goes, the Netherlands*
[b] *Dept. of Pulmonary Medicine, Erasmus MC Cancer Institute, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands*
[c] *Dept. of Research and Development, Netherlands Cancer Registry, Netherlands Comprehensive Cancer Organization (IKNL), Godebaldkwartier 419, 3511 DT Utrecht, the Netherlands*

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ABSTRACT

Introduction: Rearrangement of c-ros oncogene 1 (*ROS1*) is a rare gene alteration in patients with stage IV non-squamous non-small cell lung cancer (NSCLC). Molecular testing for *ROS1* is recommended to enable primary treatment with tyrosine kinase inhibitors (TKI). Aim of this study was to describe real-world treatment patterns and survival for patients with *ROS1* in the Netherlands.

Methods: All non-squamous NSCLC stage IV patients, diagnosed 2015–2019, were identified from the population-based Netherlands Cancer Registry (N = 19,871). For patients with *ROS1* rearrangements (*ROS1*+) who received first line TKI, additional information about progression and second-line treatment was retrieved by active follow-up. Overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan-Meier estimators.

Results: A total of 67 patients (0.43%) were diagnosed with a *ROS1*+ NSCLC. Systemic treatment was administered in 75% which was most often TKI (n = 34) followed by chemotherapy (n = 14). Two-year OS for patients receiving upfront TKI versus other systemic treatment was 53% (95% CI 35–68) and 50% (95% CI 25–71), respectively. For patients receiving TKI, median OS was 24.3 months. Survival was inferior in case of brain metastasis (BM) at diagnosis (5.2 months). One in five patients receiving TKI as a first line treatment had BM at diagnosis, of the remaining 22 another 9 developed BM during follow up. PFS was also inferior for patients with BM at diagnosis with a median PFS of 4.3 months versus 9.0 without BM.

Conclusion: In this real-world population of *ROS1*+ NSCLC patients, only half received primary treatment with TKI. Overall survival and PFS during TKI were disappointing, mainly related to brain metastasis. TKI treatment with agents that have intra-cranial activity may be beneficial in this patient population and our results confirm the importance of performing an MRI of the brain as part of the standard diagnostic work up in patients with *ROS1*+ NSCLC.

1. Introduction

Over the past decades oncogenic targets such as, *EGFR, ALK, BRAF, ROS1, MET, RET, NTRK, KRAS* and *HER2* have been identified. These targets harbor specific activating genomic aberrations such as point mutations, fusions and amplifications for which development of targeted therapies have led to substantial improvement of outcomes [1–3]. Although, *ROS1* gene rearrangements occur only in 0,9–2,6% of patients with NSCLC [4–6] the impact of targeted therapy makes it essential to identify these patients.

Targeted therapies directed against *ROS1* rearranged *(ROS1+)* NSCLC were approved by the European Medicine Agency (EMA) in 2016 [7] and the current Dutch guideline advices first line treatment with tyrosine kinase inhibitor (TKI) crizotinib for patients with advanced

Abbreviations: ROS1, c-ros oncogene 1; NSCLC, non-small cell lung cancer; TKI, Targeted therapy; BM, Brain metastasis; OS, overall survival; PFS, progression free survival; EMA, European medicine Approval; NCR, Netherlands Cancer Registry; IKNL, Netherlands Comprehensive Cancer Organization; TNM, TNM classification of malignant tumors; WHO, World health organization; PS, performance score; MEC, medical ethics committee; CCMO, Central Committee on Research involving Human Subjects; BSC, best supportive care.

* Corresponding author.
E-mail address: a.dingemans@erasmusmc.nl (A.-M.C. Dingemans).

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ROS1+ NSCLC [8]. Alternative entrectinib has recently become available in the Netherlands and lorlatinib can be made available off-label for second-line treatment. Treatment with crizotinib gives, based on non-randomized controlled studies, an overall response rate of 65–87%, a median progression free survival (mPFS) of 15–23 months and an median overall survival (mOS) of 33–51 months [9–14] (in most studies not reached), which is relatively long for stage IV NSCLC and outperforms the platinum-base chemotherapy [15].

Characteristics of *ROS1*+ NSCLC patients differ from most NSCLC patients similar to the earlier discovered *ALK*-rearranged NSCLC: patients tend to be younger, never-smokers and tumors more often involve adenocarcinoma histology [5]. Also, patients have a higher incidence of brain metastases (BM), reaching up to 36% of patients at the time of diagnosis [16]. Post crizotinib treatment, the incidence of BM can be as high as in the mid 50% range, indicating BM are a major morbidity for *ROS1*+ NSCLC patients throughout the course of treatment.

Only few real-world data exist about *ROS1*. The aim of this population-based study is to describe the characteristics, treatments, metastatic patterns, PFS and OS of patients identified with *ROS1*+ NSCLC between 2015 and 2019 in clinical daily practice in the Netherlands.

2. Methods

This study is an observational, population-based cohort study from the Netherlands. Population-based data from the Netherlands Cancer Registry (NCR) were used, which is maintained by the Netherlands Comprehensive Cancer Organization (IKNL). The NCR records data on all patients newly diagnosed with cancer in the Netherlands and covers greater than 95% of all cancers diagnosed in the Dutch population of around 17 million inhabitants. A standardized dataset is collected by trained registry personnel from hospital patient records consisting of basic patient and disease characteristics, including histology, the TNM classification of malignant tumors (TNM) stage, World health organization (WHO) Performance Score (PS), site(s) of metastasis, diagnostic brain scans (CT or MRI) and type of first line treatment. As of 2015, common molecular aberrations such as *EGFR, ALK* and *ROS1* are also recorded and PD-L1 TPS is registered as of 2017. Information about molecular testing method is not available in the NCR but a national pathology study evaluated molecular testing in patients with non-squamous NSCLC diagnosed in 2017 and reported that multiplex sequencing techniques were used in more than 75% of cases [17]. The frequency of testing for *ROS1* was estimated around 62% for non-squamous NSCLC and around 22% for squamous NSCLC.

Information on OS is obtained by annual linkage with the population registry. For patients with *ROS1*+ NSCLC who received systemic treatment, additional information about progression and second-line treatment was retrieved by active follow-up. Progression was defined by the treating physician's interpretation and the real world PFS resulting from this was calculated from the start of crizotinib. Due to logistical reasons, information could not be gathered in three of the Dutch hospitals, and the latter cases were excluded from the analysis of PFS. Information about smoking history, comorbidity, treatment response, toxicity and cause of death is not recorded by the registry.

Considering its non-interventional nature, this study does not require approval from an accredited medical ethics committee (MEC) or the Central Committee on Research involving Human Subjects (CCMO) according to Dutch jurisdiction. However, the study has been reviewed and approved by the Privacy Review Board and the Scientific Review Board of the NCR (application number K22.364).

2.1. Statistics

From the NCR, we selected all adult patients with a *ROS1* rearrangement, diagnosed with stage IV non-squamous NSCLC between January 1, 2015 and December 31, 2019. Association between patient characteristics and systemic treatment was evaluated by tabulations and chi-square tests. Summary statistics for continuous variables are represented by median values and 25%-75% interquartile rates. The primary endpoint of this study is OS, calculated from the day of starting systemic treatment or day of diagnosis for patients receiving best supportive care (BSC), until death from any cause, with follow up until February 1, 2022. OS was calculated using Kaplan-Meier statistics and reported as median OS or as two-year OS with 95% CI. Due to the exploratory nature of the analyses, we refrained from significance testing of differences in survival. Due to small numbers, 95% confidence intervals are reported as not reached (NR) when upper confidence bound is missing. For patients who received primary treatment with crizotinib, PFS was analyzed from start of crizotinib up to progression, death or end of follow-up. Both progression and intercurrent death were considered PFS events. Statistical analyses were performed using Stata, version 17.

3. Results

Out of a total of 19,871 patients with stage IV non-squamous NSCLC, diagnosed from 2015 through 2019, 67 patients (0.34%) were diagnosed with a *ROS1*+ NSCLC. Out of which 63 with adenocarcinoma and 4 with large cell carcinoma not otherwise specified. Median time between diagnosis and confirmation of *ROS1*+ NSCLC was 22 days (IQR 15–30).

3.1. Patient and tumor characteristics

The median age was 62 years (IQR 55–72), about one third was 70 years or older [Table 1]. 25% was diagnosed with TNM stage M1A and 75% with stage M1B/C. 66% was diagnosed with cT4 or cN3. Bone and liver metastases were diagnosed in 33% and 16%, respectively. Bone metastasis was more common among women (46%) than among men (17%). 16% of patients (n = 11) had brain metastases (BM) at time of diagnosis. During the diagnostic work up 39% of patients received a diagnostic brain scan (88% MRI).

3.2. First line treatment

Systemic treatment was administered in 50 out of 67 patients (75%) [Table 1]. Use of systemic treatment was less frequent in patients with poorer performance status (p = 0.01). Most patients received crizotinib (n = 34) as a first line treatment, followed by chemotherapy (n = 14), immunotherapy mono (n = 1) or immunotherapy-chemotherapy combination (n = 1), respectively. Median time between diagnosis and start of systemic treatment was 32 days (IQR 27–51).

3.3. Survival

Median follow-up time of censored patients was 39 months, 47/67 patients (70%) had deceased before study closure. Median survival for patients receiving BSC was 2.0 months (95% CI 1.2–2.6) [Fig. 1]. Two-year OS for patients receiving first line treatment with crizotinib versus other systemic treatment was 53% (95% CI 35–68) and 50% (95% CI 25–71), respectively. For patients receiving crizotinib as a first line treatment, median OS was 24.3 months (95% CI 12.1-NR). Median OS in this group was the worst in case of having BM (5.2 months (95% CI 4.3-NR)), followed by liver metastasis (9.9 months (95% CI 4.9-NR)) and bone metastasis (13.0 months (95% CI 4.9–30.2)).

3.4. Progression free survival and second line treatment

For 43 out of 50 patients receiving systemic treatment, information about progression and 2nd line treatment was available. Out of this group, twenty-eight patients were treated with first line crizotinib, and

Table 1
Characteristics of stage IV *ROS1*+ non-squamous NSCLC patients in the Netherlands from 2015 through 2019.

		ROS1 N (%↓)[#]	Systemic treatment N (%→)[#]	P-value
Gender	Male	30 (44.8)	25 (83)	0.14
	Female	37 (55.2)	25 (68)	
Age	18–59	26 (38.8)	22 (85)	0.16
	60–69	20 (29.9)	12 (60)	
	70+	21 (31.3)	16 (76)	
WHO performance status	0	14 (20.9)	13 (93)	0.01
	1	24 (35.8)	19 (79)	
	2+	9 (13.4)	3 (33)	
	X	20 (29.9)	15 (75)	
Clinical M−stage	1A	17 (25.4)	14 (82)	0.40
	1B/C	50 (74.6)	36 (72)	
Number of organs with distant metastasis	1	28 (41.8)	20 (71)	0.54
	2	23 (34.3)	19 (83)	
	3+	16 (23.9)	11 (69)	
Diagnostic brain scan	No	41 (61.2)	31 (76)	0.82
	Yes	26 (38.8)	19 (73)	
Brain metastasis at diagnosis	No	56 (83.6)	44 (79)	0.09
	Yes	11 (16.4)	6 (55)	
Bone metastasis at diagnosis	No	45 (67.2)	34 (76)	0.80
	Yes	22 (32.8)	16 (73)	
Liver metastasis at diagnosis	No	56 (83.6)	43 (77)	0.36
	Yes	11 (16.4)	7 (64)	

ROS1: c-ros oncogene 1, NSCLC: non-small cell lung cancer, N: number of patients.
arrows display direction of percentages.

18 of those received second-line systemic treatment upon progression, including lorlatinib in 13 cases. Median PFS was 8.6 months (95% CI 6.7–12.4). [Fig. 1].

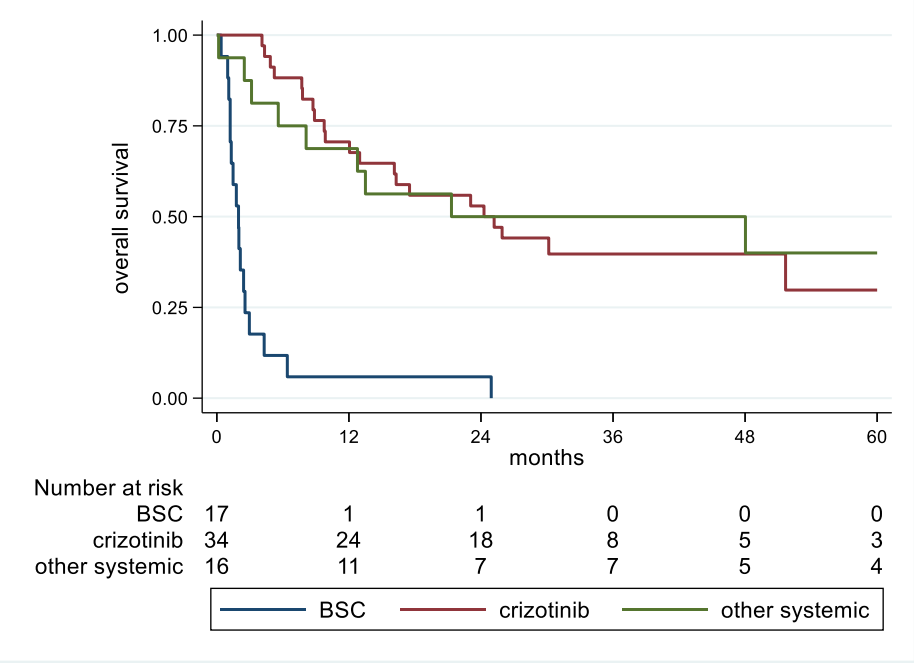
Within the subgroup starting with other systemic treatment, two patients received upfront immunotherapy and thirteen received first-line pemetrexed-platinum combination treatment, and 6 of those received second-line crizotinib at progression.

3.5. Brain metastasis

Six out of the 28 patients that received crizotinib as a first line treatment had BM at diagnosis. During follow up 9 of the remaining 22 (41%) developed BM. PFS was worse for patients with BM at diagnosis [Fig. 2], median PFS 4.3 (95% CI 1.7-NR) versus 9.0 months (95% CI 6.9–20.7) without BM, respectively.

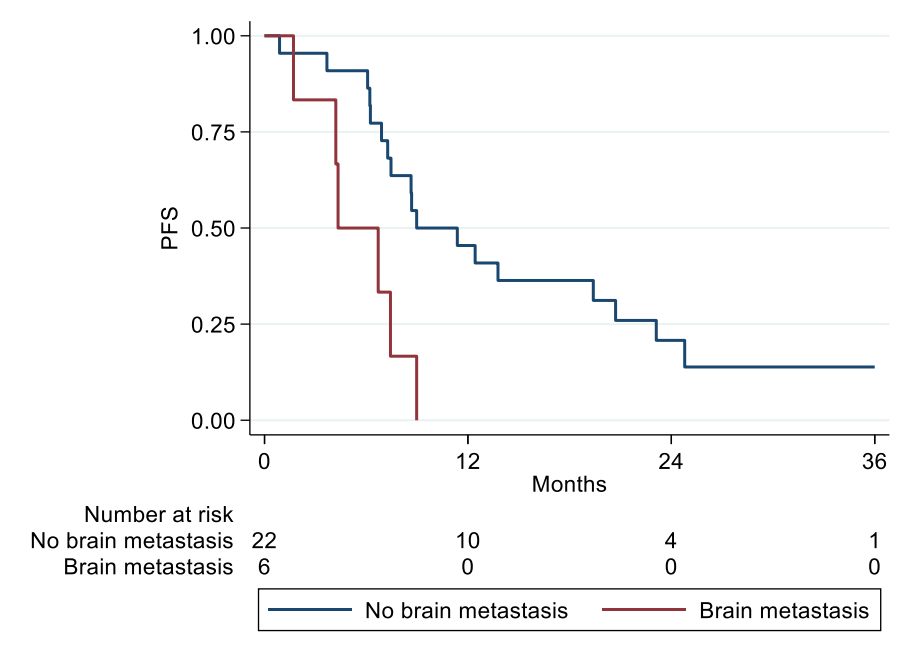
4. Discussion

This study investigates a real-world nation-wide cohort of patients with *ROS1*+ NSCLC and their management in everyday clinical practice in the Netherlands. Out of the 19,871 patients with stage IV non-squamous NSCLC included in this study, 67 patients (0,34%) were



BSC: best supportive care

Fig. 1. Overall survival by type of primary treatment BSC: best supportive care.



ROS1: c-ros oncogene 1, NSCLC: non-small cell lung cancer, PFS: progression free survival

Fig. 2. Progression free survival for patients who received primary treatment with crizotinib for stage IV *ROS1*+ non-squamous NSCLC, stratified by prevalence of brain metastases at diagnosis. ROS1: c-ros oncogene 1, NSCLC: non-small cell lung cancer, PFS: progression free survival.

diagnosed with a *ROS1* rearrangement. Most patients (n = 34) received crizotinib as a first line treatment with a median OS of 24.3 months. Median PFS in the group that received crizotinib as a first line treatment was 8.6 months. Survival was mainly restricted by brain metastasis at diagnosis or their occurrence during treatment. The prevalence of BM at diagnosis was rather low because only 39% of patients received brain imaging during initial diagnostic work-up.

ROS1+ NSCLC is known to be a rare disease, but the 0.34% found in this study is considerably lower than the 0.9–2.6% reported in other series [4–6]. To detect *ROS1* rearrangements, currently, sampling of tumor tissue is necessary. And, although routinely performed during the study period, not all patients are eligible for this invasive procedure of tissue sampling. Furthermore, the procedure presents substantial challenges such as limited tissue availability or intra-tumor and inter-tumor heterogeneity [18,19]. A large pathology study estimated that in 2017 62% of non-squamous stage IV NSCLC tumors were sampled for *ROS1* in the Netherlands [17]. Indicating that there is still room for improvement in the uptake of molecular testing. However, when we would be able to enhance the current testing rate from 62% to 100%, prevalence would still be around 0.55%. A limitation of this study is that we only have information on *ROS1* status at the time of initial cancer diagnosis. This might cause an under estimation of the *ROS1*+ patient group as some patients might have been tested later on. However, our study reflects a real-world European population whereas most other studies involve series from Asia or enriched series, preferentially selecting patients who are young or never-smoker. Also, the patient numbers reported in clinical trials or real-world observational studies are very low [Table 2], suggesting that the prevalence rate might be overestimated.

This population demonstrated a mOS of 24.3 months after starting first line crizotinib falling into the low to mid-range of the other world cohorts. The mPFS of 8.6 months is even lower compared to the other studies, where only the AcSé trial found a shorter PFS. [Table 2] [9,12–14,20–30]. The AcSé trial is a prospective phase II study that reported a PFS and OS that were much shorter than others studies at 6 months and 17 months, respectively [20]. This was attributed to a heavily pre-treated study population with higher frequency of Eastern Cooperative Oncology Group (ECOG) performance status 2, compared to other studies. It is likely that the relatively large differences found between studies are mostly due to the rarity of the disease and heterogenicity of the study populations accordingly. Aggressive tumors are less likely to reach second line treatment options and most other studies are probably enriched with, for example, more female, young, non-smoking patients with less BM. Also study protocols differ, the Canadian study for example is less comparable because both mPFS and mOS were measured from the time of diagnosis instead of the start of therapy, with patients receiving crizotinib at a median of 58 days (IQR: 29–359) post-diagnosis [30]. In our study we used real world PFS as it was based on clinician interpretation making it less comparable to most clinical trials that use objective measurements of computed tomography scans with RECIST criteria. It is true that real world and clinical trial progression are inherently different. In addition to likely differences in scan frequency, objective and blinded progression assessments are not performed in the real world as they are in a clinical trial setting [27]. The data do however, present a clearer insight in current clinical practice. Compared to our data, other studies mostly included patients that received crizotinib as a $\geq$ 2nd line treatment. Although, the mPFS and mOS of the only other first line treatment study were much longer, 23.0 and 60.0 months respectively [26]. Unfortunately, the optimal sequence of treatment options cannot be determined in observational studies. Notable is the similar two-year OS for patients receiving first line treatment with crizotinib versus other systemic treatment is this study, of 53% (95% CI 35–68) and 50% (95% CI 25–71), respectively. There are no studies that directly compare between chemotherapy and TKI regimens. In a one-center retrospective study, differences between patients who had received crizotinib as first-line treatment (30 patients) and platinum-pemetrexed (47 patients) were shown[11]. Clinical characteristics were similar between both groups. Responses were higher in the crizotinib group, with an ORR of 86.7% compared with a 44.7%, and mPFS of 18.4 and 8.6 months, respectively. At the data cutoff, mOS in the crizotinib group was not reached and, in the platinum-pemetrexed group was 28.4 months. Interestingly, 37 patients received the other therapy at progression and showed no difference in OS if they had received upfront

Table 2
Review of studies reporting median progression free survival and median overall survival for crizotinib treated *ROS1* + NSCLC.

Study	Study type	Region	N	mPFS in months [95% CI]	mOS in months [95% CI]	line
PROFILE 1001 (as reported by Shaw et al., 2019)	Phase I (NCT00585195)	USA	53	19.3 [15.2–39.1]	51.5 [29.3–NR]	1st /2nd or later
OxOnc (as reported by Wu et al., 2018)	Phase II (NCT01945021)	Asia	127	15.8 [12.9–24.0]	32.5 [32.5–NR]	1st/2nd or later
EUCROSS (as reported by Michels et al., 2019)	Phase II (NCT02183870)	Europe	34	20.0 [10.1–NR]	Not reached (data immature) [17.7–NR]	1st/2nd or later
AcSé (as reported by Moro-Silbot et al., 2019)	Phase II (NCT02034981)	Europe	36	5.5 [4.2–9.1]	17.2 [6.8–32.8]	1st/2nd or later
METROS (as reported by Landi et al., 2019)	Phase II (NCT02499614)	Europe	26	22.8 [15.2–30.3]	40.0	2nd or later
Li et al., 2018	Real-World Evidence (China)	Asia	36	12.6 [IQR: 7.7–19.3]	32.7 [IQR: 18.8–NR]	1st/2nd or later
Liu et al., 2019	Real-World Evidence (China)	Asia	35	11.0 [7.8–14.2]	41 [22.5–59.5]	1st/2nd or later
Masuda et al., 2019	Real-World Evidence (Japan)	Asia	13	10 [5.1–27.0]	28.7 [6.7–NR]	1st/2nd or later
Park et al., 2018	Real-World Evidence (Korea)	Asia	15	13.1 [4.4–NR]	15.1 [5.4–NR]	1st/2nd or later
Zheng et al., 2020	Real-World Evidence (China)	Asia	56	23.0 [22.4–33.6]	60.0 [40.7–79.3]	1st
Doebele et al., 2019	Real-World Evidence (USA Flatiron Health Dataset)	USA	65	8.8 [8.2–9.9] (time to treatment discontinuation)	18.5 [15.1–19.9]	2nd or later
Gainor et al., 2017	Real-World Evidence (USA)	USA	30	11.0	30 [12–NR]	1st/2nd
Patil et al., 2018	Real-World Evidence (USA)	USA	19	11.0 [8.0–23.0]	–	1st/2nd
Gibson et al., 2022	Real-World Evidence (Canada)	Canada	21	10.6	33.1	1st/2nd
Mazieres et al., 2015	Real-World Evidence (Europe: EUROS1)	Europe	31	9.1	–	1st/2nd or later
Ten Berge et al.	Real-World Evidence (Netherlands)	Europe	34	8.6 [6.7–12.4] (based on 28 cases)	24.3	1st

ROS1: c-ros oncogene 1, NSCLC: non-small cell lung cancer, N: number of patients, mPFS: median progression free survival, mOS: median overall survival, NR: not reached.

crizotinib (7 patients, median OS 38.6 months) or upfront platinum-pemetrexed (30 patients, median OS 32.8 months).

Despite that the size of our *ROS1*+ NSCLC cohort was comparable to those in most other studies, our sample size was not large enough to permit multivariable analyzes and because of the heterogeneity of treatment patterns, we refrained from detailed subgroup analyses. A major limitation of our study is the absence of information on treatment response.

In our cohort 21% of the patients had BM at diagnosis and another 41% developed BM during the course of their disease. *ROS1*+ NSCLC is known to have an incidence of CNS metastases reaching between 18% and 36% at the time of diagnosis [16,29]. Those with brain metastases at crizotinib initiation had a significant decreased time to progression compared to the others, a pattern also observed within Phase II clinical trial studies [13,14]. It was also the primary site of progression in our study. Despite crizotinib's notable benefit in the management of *ROS1*+ NSCLCs, its poor brain penetration makes the central nervous system the primary site of progression [6]. Therefore, approval and reimbursement of novel *ROS1*-targeting molecules with better cerebral penetration, such as entrectinib, lorlatinib and repotrectinib, seems essential [31]. Both ceritinib and lorlatinib are not approved by the EMA and despite the recent uptake of entrectinib and repotrectinib into the European Society for Medical Oncology (ESMO) guidelines, to date crizotinib remains the most advised and prescribed first-line reference therapy for metastatic *ROS1*+ NSCLCs [6,32]. The recently updated guideline now recommend to consider imaging of the central nervous system at diagnosis for all patients with metastatic disease and imaging is now required for patients with neurological symptoms or signs [32].

The frequent omission of brain imaging before and during TKI hampers proper understanding of the development of BM in patients with *ROS1*+ NSCLC. Patients with subclinical BM may benefit from early access to novel CNS-penetrant TKIs. Given the major impact of BM on the well-being of patients, our results confirm the importance of performing an MRI of the brain as part of the standard diagnostic work up in patients with *ROS1*+ NSCLC. As the disease is rare, the impact on medical expenses on population level is expected to be low with potential great benefit on research and patient level.

CRediT authorship contribution statement

Deirdre M.H.J. ten Berge: Investigation, Methodology, Writing – original draft. **Ronald A.M. Damhuis:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Joachim G.J.V. Aerts:** Writing – review & editing, Supervision. **Anne-Marie C. Dingemans:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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