Lung Cancer 130 (2019) 201–207

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

CNS metastasis in *ROS1*+ NSCLC: An urgent call to action, to understand, and to overcome

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ARTICLE INFO

Keywords:
ROS1 lung cancer
CNS metastasis
ROS1 fusion variants

ABSTRACT

The incidence of CNS metastasis at the time of diagnosis of and during the natural disease history of advanced *ROS1*+ NSCLC is largely unknown. It is generally believed that the incidence of CNS metastasis is lower in *ROS1*+ NSCLC than *ALK*+ NSCLC as ROS1 fusions are regarded as a less powerful driver mutation than ALK fusions in *ALK*+ NSCLC based on the longer progression-free survival of *ROS1*+ NSCLC patients than *ALK*+ NSCLC patients treated with crizotinib. Here we reviewed the incidence of CNS metastasis from prospective clinical trials and retrospective case series from primarily single institution. The incidence of CNS metastasis in *ROS1*+ NSCLC patients at the time of diagnosis ranged from 20% to mid 30% while the incidence of CNS metastasis can be as high as in the mid 50% range post-crizotinib indicating CNS metastasis is indeed a major morbidity for *ROS1*+ NSCLC patients throughout the course of treatment. To date 22 fusion partners in *ROS1*+ NSCLC have been reported in the literature and one report has indicated CD74-ROS1 fusion variant increased the predilection for CNS metastasis than non-CD74-ROS1 fusion variants. We reviewed reported intra-cranial activity of all preclinical and clinical development stage ROS1 TKIs and pemetrexed-based chemotherapy in *ROS1*+ NSCLC patients. While several ROS1 TKIs (i.e. entrectinib, cabozantinib, lorlatinib, repotrectinib) have reported intra-cranial response rates, there is no literature reporting on the intra-cranial activity of pemetrexed-based chemotherapy in *ROS1*+ NSCLC patients. In summary, better understanding the high incidence of CNS metastasis in *ROS1*+ NSCLC patients, how certain ROS1 fusion variant may increase the incidence of CNS metastasis, and any intra-cranial efficacy data of pemetrexed in *ROS1*+ NSCLC are all urgently needed.

1. Introduction

With the discovery of anaplastic lymphoma kinase (ALK) rearrangement (*ALK*+) in non-small cell lung cancer (NSCLC) in 2007 [1,2], and the successful development and approval of 5 structurally different ALK tyrosine kinase inhibitors (TKIs) in the US [3,4], *ALK*+ NSCLC has become the prototypic model for drug development in targeted therapy. Additionally, it is now recognized that receptor tyrosine kinase (RTK) rearrangement/fusion is a class of actionable de novo driver mutation in NSCLC and other solid malignancies [5,6] and more recently as one category of acquired resistance mechanism to epidermal growth factor receptor (EGFR) TKIs [7]. As the prototypic RTK fusion positive disease model, the treatment of *ALK*+ NSCLC has alerted medical oncologists to the high prevalence and incidence of central nervous system (CNS) metastases even during the first-line treatment with ALK TKI [8–11]. However, despite being discovered in the same year (2007) as *ALK*+ NSCLC [2], much less is known about the incidence and treatment of CNS metastasis in *ROS1*-rearranged NSCLC patients likely due to lower overall incidence of *ROS1*-rearranged (*ROS1*+) NSCLC [12,13] and later development of ROS1 TKI with crizotinib as the only approved *ROS1*+ NSCLC eight years after the discovery of *ROS1* + NSCLC [14]. Here we review the literature on the molecular biology and epidemiology of *ROS1*+ NSCLC, summarize the incidence of CNS metastasis in *ROS1*+ NSCLC and treatment outcome of CNS metastasis with ROS1 TKI and pemetrexed-based chemotherapy.

2. *ROS1*-rearranged (*ROS1*+) NSCLC

ROS1 (c-ros-oncogene) is one of 58 human RTKs and the lone member of its own subfamily [15]. ROS1 and ALK shares extensive amino acid homology especially in the kinase domain [16] and is phylogenetically related to ALK [17]. Thus, most of the current

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https://doi.org/10.1016/j.lungcan.2019.02.025
Received 28 November 2018; Received in revised form 11 February 2019; Accepted 21 February 2019

Table 1
List of ROS1 fusion variants published in the literature.

Number	ROS1 fusion variant	Reference*
1	CD74-ROS1	Rikova [2]
2	SLC34A2-ROS1	Rikova [2]
3	ERZ-ROS1	Takeuchi [21]
4	SDC4-ROS1	Takeuchi [21]
5	TPM3-ROS1	Takeuchi [21]
6	LRIG3-ROS1	Takeuchi [21]
7	GOPC (FIG)-ROS1	Rimkunas [22], Suehara [23]
8	KDERL2-ROS1	Govindan [24]
9	CCDC6-ROS1	Seo [25]
10	LIMA1-ROS1	Shaw [26]; Zheng [27]
11	MSN-ROS1	Shaw [26]; Zheng [27]
12	CLTC-ROS1	TGCA [28]
13	TMEMB106B-ROS1	Ou [29]
14	TPD52L1-ROS1	Zhu [30]
15	CEP72-ROS1	Zhu [31]
16	ZCCHC8-ROS1	Park [32], Hicks [33], Zhu [34]
17	SLMAP-ROS1	Park [32]
18	MYO5C-ROS1	Park [32]
19	TFG-ROS1	Park [32]
20	CD79-ROS1	Park [32]
21	MLL3 (KMT2C)-ROS1	Dagogo-Jack [35]
22	CTD-2021J15.1 (LINC00973)-ROS1	Dagogo-Jack [35]

CCDC6, coiled coil domain containing 6 gene;
CD74, CD 74 molecule gene;
CD79, CD79 molecule gene;
CLTC, Clathrin heavy chain gene;
CTD-2021J15.1, (LINC00973, long intergenic non-protein coding RNA 973).
EZR, ezrin gene;
GOPC, Golgi-associated PDZ and coiled-coil motif-containing protein gene;
KDEL R2, KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2 gene;
LIMA1, LIM domain and actin binding 1 gene;
LRIG3, leucine-rich repeats and immunoglobulin-like domains 3 gene;
MLL3 (KMT2C, lysine methyltransferase 2C).
MSN, moesin gene;
MYO5C, myosin VC gene;
SDC4, syndecan 4 gene;
SLC34A2, solute carrier family 34 member 2 gene;
SLMAP, sarcolemma associated protein gene;
TFG, TRK-fused gene;
TPM3, tropomyosin 3 gene;
TMEM106B, Transmembrane 106B protein gene; ZCCHC8, zinc finger CCHC-type containing 8 gene;
* Only reference which is the first to report the particular ROS1 fusion is cited. In some cases, several references are cited when they appeared around the same time in pubmed.

approved or clinical stage ALK TKI have demonstrated pre-clinical or clinical activity against ROS1 with the exception of alectinib [18].

2.1. Discovery of ROS1-rearranged and molecular biology of NSCLC

Transforming activity of ROS1 (known as *mcf3* then) was first identified in 1984 [19] and the first *ROS1* rearrangement (FIG-ROS) rearrangement was identified in a glioblastoma cell line [20]. It is not until 2007 that *ROS1* rearrangement in NSCLC was reported by the Cell Signalling Technology group in the same year (2007) as *ALK* rearrangement in NSCLC [2] where global survey for tyrosine kinase activity in NSCLC tumors and cell lines identified CD74-ROS1 and SLC34A2-ROS1 fusion variants in NSCLC [2]. To date, 22 different ROS1 fusion variants have been reported in NSCLC (Table 1) [20–35]. In contrast to *ALK*+ NSCLC where EML4-ALK is the dominant ALK fusion variant accounting for close to 95% of ALK + NSCLC [36], the most common CD74-ROS1 variant in *ROS1*+ NSCLC accounting for less than 50% of the ROS1 fusion variants [37]. However, it is likely that not all the ROS1 fusion variants described in other solid malignances such as inflammatory fibroblastic tumor (IMT) (YWHAE-ROS1) [38], anaplastic large cell lymphoma (NFkB2-ROS1, NCOR-ROS1) [39], and in pigmented spindle cell nevus/Spitz nevus (CLIP1-ROS1, ERC1-ROS1, HLA-A-ROS1, KIAA1598-ROS1, PWWP2A-ROS1) [40] have been reported in *ROS1*+ NSCLC.

Importantly *ROS1* rearrangement is generally the lone or sole driver mutation in the tumor type [41]. Thus, understanding the biology of the various ROS1 fusion variants will be important in the next decade of the development of therapy against *ROS1*+ NSCLC. Using the prototypic *ALK*+ NSCLC as a model, the difference in breakpoints of EML4 generates EML4-ALK fusion proteins with varying degree of stability [42,43] and sensitivity to crizotinib [43–46]. Indeed, the progression-free survival (PFS) among *ALK*+ NSCLC patients with different EML4-ALK fusion variants differed significantly when treated with crizotinib [43–45]. As such there is a difference in the spectrum of acquired resistance mutations observed arising from different ELM4-ALK fusion variants when treated with first- or second-generation ALK TKI with the more re-calcitrant solvent front mutation G1202R arising from the less ALK TKI sensitive EML4-ALK variant 3 resulting in a significant difference in PFS when lorlatinib is used after crizotinib [46]. One hypothesis is that different selection pressure on the EML4-ALK fusion variants exists due to the difference in its intrinsic sensitivities to various ALK TKIs. Finally, Christine Lovly and her colleagues extended the importance of identifying the fusion partners in the pre-clinical setting by demonstrating differential sensitivities to crizotinib and other second- and third-generation ALK TKIs according to the different fusion partners to ALK [47].

2.2. Epidemiology of ROS1-rearranged NSCLC

In most of the literature the incidence of *ROS1*+ NSCLC is cited to be 1–2% of NSCLC [48]. Two meta-analyses have demonstrated the incidence of *ROS1*+ NSCLC is about 2.4% (95% confidence interval [CI]; 1.8%–3.1%) [12] to 2.9% [13] among adenocarcinomas and 0.2% [12] to 0.6% [13] in non-adenocarcinomas. The incidence of *ROS1*+ NSCLC in adenocarcinomas is 2.6% (95%CI: 1.7–3.5) among Asians and 2.1% (95%CI: 1.0–3.1) among Caucasians [12]. Additionally, *ROS1*+ NSCLC was more commonly found in females (Odd Ratio [OR] = 1.54, 1.02–2.34) although the female predominance is only significant in Caucasian (OR = 1.99; 95%CI: 1.14–3.48) but not in Asian population (OR = 1.33, 95%CI: 0.78–2.27) [12]. *ROS1*+ NSCLC is more common among never-smokers (OR = 3.27, 95%CI: 1.44–7.45) but interestingly the prevalence is much higher among never-smoking Caucasians (OR = 11.98, 95%CI: 5.02–28.56) than among Asians (OR = 2.15, 95%CI: 0.86–5.38) [12]. Additionally, survey of the 860 metastatic adenocarcinomas of the lung from Memorial Sloan Kettering Cancer Center database revealed the incidence of *ROS1* rearrangement is 2.6% very similar to the meta-analyses [49].

3. Central nervous system (CNS) metastasis in *ROS1*+ NSCLC

Given the high prevalence of CNS metastasis in *ALK*+ NSCLC gleamed from randomized phase 3 trials [8–11,50] and that crizotinib with its poor CSF penetration [51,52] is the sole approved ROS1 TKI, it is rather surprising that there are relatively few published literature on CNS metastasis in *ROS1*+ NSCLC. Several aspects of CNS metastasis in *ROS1*+ NSCLC remain largely unknown: the incidence at diagnosis of advanced stage, the cumulative incidence of CNS metastasis as patients progress on multiple lines of therapy, and the response of CNS metastasis to ROS1 TKIs and chemotherapy in particular pemetrexed-based.

3.1. Molecular biology of CNS metastasis in ROS1+ NSCLC

Recently, the role of fusion partner seems to be important in determining the predilection for CNS metastasis [53]. In a study from Shanghai Chest Hospital, among 19 CD74-ROS1 patients, 31.6% had CNS metastases compare to no (0%) CNS metastasis among the 17 non-

CD74-ROS1 patients (p = 0.02). This translated to a numerically higher ORR among the non-CD74-ROS1 fusions (94.1%) versus CD74-ROS1 fusion (73.7%, p = 0.18) when treated with crizotinib. The median PFS (17.6 months versus 12.6 months; p = 0.048) and OS (44.5 months versus 24.3 months; p = 0.036) were also significantly longer among non-CD74-ROS1 patients. By multivariate analysis, the presence of CNS metastasis before crizotinib treatment was an independent factor for poorer OS (HR = 8.973, 95% CI: 1.723–46.720, p = 0.010). Worrisomely, during crizotinib treatment and the follow up period, the proportion of CNS progression was numerically higher (33.3%) among non-CD74-ROS1 patients compared to CD74-ROS1 patients (21.4%, p = 0.64) indicating potentially even with an initial lower predilection for CNS metastasis at baseline development of CNS metastasis can catch up during crizotinib treatment whose CNS penetration property is low [51,52]. This is the first and only report that suggested particular ROS1 fusion variant may increase CNS predilection and thus should be treated as hypothesis generating that needed to be collaborated by other observational studies. A very recent report indicated three most common ROS1 fusion partners have different subcellular locations. Both SLC34A2-ROS1 and SDC4-ROS1 localize to the endosomes and maximally activate MAPK pathway while CD74-ROS1 locazlies to endoplasmic reticulum and MAPK signaling is impaired. Maximally activated MAPK pathway results in more aggressive tumor [54]. Importantly, it remained to be determined if differential activation of MAPK pathway will result in difference in incidence of CNS metastasis.

3.2. Incidences of CNS metastasis from prospective clinical trials

The first publication of clinical efficacy of TKI in *ROS1*+ NSCLC thus validating *ROS1* rearrangement to be a driver mutation was published in 2014 [26]. The study enrolled 53 *ROS1*+ NSCLC patients and was one of the expansion cohorts of the original phase 1 trial of crizotinib that was designed in 2006. At the time of the design of the trial, the potential high incidence of CNS metastasis in RTK-fusion driven NSCLC was clearly not appreciated. Thus, the incidence of CNS metastasis was not captured centrally (no mandatory requirement for brain imaging at the time of study entry) and the incidence of brain metastasis was not reported [26]. Subsequently the largest prospective trial (00–1201) of any ROS1 TKI (crizotinib in this trial) which was conducted primarily in East Asians (China including Taiwan, Japan, South Korea) did report the incidence of CNS metastases at baseline and on followed up (Table 2) [55]. The incidence of CNS metastasis was 18.1% at study entry by independent review. It was not reported whether the incidence of CNS metastasis increases with increased line of therapy. Furthermore, whether a particular ROS1 fusion variant had a higher predilection for CNS metastasis was not reported although all the *ROS1*+ NSCLC patients were identified by reverse transcription-polymerase chain reaction (RT-PCR) which could detect 7 ROS1 fusion variants [56].

Other phase 2 studies of crizotinib in *ROS1*+ NSCLC including EUCROSS conducted in Europe (Germany, Spain, Switzerland) [57] and AcSé conducted in France [58] did report the incidence of CNS metastasis (Table 2). The Italian Study (METROS) has not yet reported the results the efficacy of cirzotinib in *ROS1*+ NSCLC patients. Several other ROS1 TKIs: ceritinib [59], entrectinib [60–62], lorlatinib [63,64], repotrectinib [65], and DS6051b [66] all reported incidence of CNS metastasis (Table 2).

Overall, the incidence of brain metastasis from prospective trials of ROS1 TKIs ranged from 20% to slightly above 40% in TKI-naïve patients and ranged from 30% to up to mid 50% in TKI-pretreated patients indicating effective treatment approach that targets CNS metastasis in *ROS1*+ NSCLC patients is urgently needed. However, we are aware there is a selection bias on the part of both clinical investigators and even patients to preferentially seek out and enroll ROS1 patients with CNS metastasis into ROS1 TKIs that have intra-cranial activity. Therefore, these second line or beyond ROS1 TKI single arm trials may artificially inflate the incidence of brain metastasis as part of the natural history of *ROS1*+ NSCLC. Nevertheless, this also reflects a huge unmet need of ROS1 TKIs with potent intra-cranial activity in the second-line setting and beyond.

3.3. Incidences of CNS metastasis from retrospective studies

There are many retrospective studies in the literature investigating the clinic, pathological, and histological characteristics of *ROS1*+ NSCLC patients but only a few have reported the incidence of brain metastasis [32,53,67,69–71] (Table 2). In one of largest retrospective analysis of *ROS1*+ NSCLC patients treated by various ROS1 TKIs and pemetrexed-base chemotherapy, incidence of CNS metastasis at baseline was 22.3% and increased to 45.6% during the duration of follow up [32]. Of note among the 80 patients who did not have CNS metastasis at the time of diagnosis, 24 (30%) developed new CNS metastasis [32]. Another major retrospective analysis of *ROS1*+ NSCLC patients was published by the Massachusetts General Hospital that included comparison to *ALK*+ NSCLC patients [67]. The incidence of CNS metastasis in *ROS1*+ NSCLC patients at the initial metastatic diagnosis (19.4%) was significantly lower than the incidence of CNS metastasis in *ALK*+ NSCLC patients (39.1%) (p = 0.033) (Table 2). Furthermore, the cumulative incidence of brain metastasis in *ROS1*+ NSCLC (22%) was significantly lower than *ALK*+ NSCLC (56%, p = 0.001) among *ROS1*+ and *ALK*+ NSCLC patients without CNS metastasis at the time of diagnosis. When compared to *ALK*+ and *RET*+ NSCLC, the cumulative incidence of CNS metastasis was lowest among *ROS1*+ NSCLC patients, followed by *RET*+ NSCLC patients and then *ALK*+ NSCLC patients [68]. However, similar single institution retrospective analysis from University of Colorado reported contradictory findings [69]. The incidence of brain metastasis at the time of diagnosis was similar between *ROS1*+ (36%) and *ALK*+ NSCLC patients (34%). CNS metastasis was the sole and the most common site of relapse among *ROS1*+ NSCLC patients. Limitations of this study are small number of patients and potential referral bias given the incidence of CNS metastasis was similar across all NSCLC with targetable driver mutations (ROS1, ALK, EGFR, BRAF, KRAS) [69]. Finally, earlier and smaller series of *ROS1*+ NSCLC patients reported lower incidence of CNS metastasis [70,71]. Although known to exist, the incidence of leptomeningeal carcinomatosis in *ROS1*+ NSCLC patients has not been reported in the literature.

4. Treatment of CNS metastasis in ROS1+ NSCLC

4.1. Efficacy of first-generation ROS1 TKI against CNS metastasis in *ROS1*+ NSCLC

4.1.1. Crizotinib

From the largest study of crizotinib in *ROS1*+ NSCLC (OO-12-01, N = 127), the ORR in patients with CNS metastasis (73.9%, 95%CI: 51.6–89.8) was similar to patients without CNS metastasis (71.2%, 95%CI: 61.4–79.6). However median PFS was shorter in patients with brain metastasis (N = 23; 10.2 months, 95%CI: 5.6–13.1 months) than patients without baseline brain metastasis (N = 104; 18.8 months, 95%CI: 13.1 – NR) indicating CNS metastasis is a poor prognostic factor in *ROS1*+ NSCLC patients [55]. However, no separate analysis of intracranial-overall response rate (IC-ORR) or analysis of the first site of disease progression especially among patients with CNS metastasis have been reported [55]. The ORR of crizotinib in *ROS1*+ NSCLC was similar regardless of prior lines of chemotherapy. As described above, the pivotal trial of crizotinib in *ROS1*+ NSCLC did not capture CNS metastasis in the database [26].

4.1.2. Entrectinib

Entrectinib is an ALK/ROS1/pan-NTRK inhibitor that is currently being developed as a ROS1 and NTRK inhibitor [72]. In the 2018 STARTRK-1/-2 update, among the 23 patients with baseline CNS

Table 2
List of incidences of CNS metastasis of ROS1 + NSCLC in the published literature (Prospective trials and retrospective analysis).

Study [references]	ROS1 TKI	Prospective Study Total Number of patients	Number and percentage of brain metastasis
		Phase 1 portion	
STARK-1 [60]	Entrectinib	13	2/13 (15.4%)
Lorlatinib Phase 1 [63]	Lorlatinib	12	6/12 (50%) to 7/12 (58.35)*
DS-6051b Japan Phase 1 [66]	DS-6051b	15	5 (33.3%)-baseline
TRIDENT-1 Phase 1 [65]	Repotrectinib	30	16/30 (53.3%)-study entry 5/10 (50%)-TKI-naïve 11/20 (55%)-TKI-refractory
		Phase 2	
PROFILE1001 [26]	Crizotinib	53	NA
OO-1201 [55]	Crzotinib	127	23 (18.1%)-baseline
EUCROSS [57]	Crizotinib	34	NA
AcSé [58]	Crizotinib	37	8 (21.6%)
Ceritinib Pan-Korean Study [59]	Ceritinib	32	8 (25%)-baseline 1/2 (50%)-crizotinib-refractory 7/30 (23.3%)-ROS1 TKI-naive
STARTRK-2 [61]	Entrectinib	32	11 (34.2%)
STARTRK-1/2 (2018 update) [62]	Entrectinib	53	23 (43.4%)
Lorlatinib Phase 2 [64]	Lorlatinib	47	25/47 (53.2%)-study entry 6/13 (46%)-Crizotinib-naïve 19/34 (56%)-Crizotinib pre-exposed
		Retrospective	
EUROS1 [70]	Crizotinib	31	1 (3.2%)
Samsung/Yonsei Hospitals, Seoul, South Korea [32]	Multiple ROS1 TKIs	103	23 (22.3%)-baseline 47 (45.6%)-duration of follow up 30% (24/80) of patients without baseline CNS mets developed CNS mets
Massachusetts General Hospital, Boston, MA, USA [67]	Crizotinib	39	19.4%-baseline 22%-cumulative incidence in patients without brain mets initially 34%-cumulative incidence at years after initial metastatic disease diagnosis
Shanghai Chest Hospital, Shanghai, China [53]	Crizotinib	36	6 (16.7%)-baseline 11 (30.6%)-duration of follow up
University of Colorado, Aurora, CO, USA [69]	Crizotinib	33	12 (36.4%)-at initial stage IV diagnosis
Tata Memorial Hospital, Mumbai, India [71]	Criozotinib	11	0 (0.0)-baseline

00-1201: Oxford Oncology-1201 trial; NA-not available.
* One patient was false positive ALK but whether the patient has CNS metastasis is not reported.

metastasis at the time of study entry, 20 had measurable disease. The ORR among patients with baseline CNS metastasis was 73.9% (51.6–89.8) which is similar to the ORR among patients without baseline CNS metastasis (80%, 95%CI: 61.4–92.3). Specifically, the confirmed IC-ORR was 55% (95%CI: 32–77) with an intracranial duration of response (DoR) of 12.9 months. The median DoR for patients with baseline CNS metastasis on entrectinib was 12.6 months (95%CI: 6.5 – NE) compared to 24.6 months of DoR among patients without baseline CNS metastasis (95%CI: 11.4–34.8). The median PFS for patients with baseline CNS metastasis on entrectinib treatment was 13.6 months (4.5 – NE) compared to 26.3 months (95%CI 15.7–36.6) for patients without CNS metastasis [60]. These results raised the question that even with good CNS activity, CNS metastasis is such a poor prognostic factor and that ROS1 TKI with better CNS penetration is required. Understanding this observation will also have implication whether it is ethnical to randomize patients to pemetrexed-based chemotherapy [62].

4.1.3. Ceritinib

In the small phase 2 study of *ROS1* + NSCLC patients, 8 patients had baseline CNS metastasis (measurable, non-measurable and non-evaluable). The IC-ORR among these 8 patients was 25% [59].

4.1.4. Cabozantinib

Cabozantinib is multi-targeted kinase inhibitor including being a ROS1 inhibitor. Activity of cabozantinib has been reported in one patient who developed a solvent front D2033 N mutation on progression on crizotinib [73]. Although the patient had developed CNS metastasis on crizotinib and treated with whole brain radiation with continuation of crizotinib beyond progression, it is not known whether cabozantinib had demonstrated intra-cranial activity. Recently intra-cranial activity of cabozantinib has been reported in 3 *ROS1* + NSCLC patients who had achieved intra-cranially control after progression on crizotinib and ceritinib [74].

4.1.5. Brigatinib

Only 3 ROS1 patients were enrolled onto the phase 1 trial of brigatinib hence there is very limited clinical efficacy data on brigatinib as a ROS1 inhibitor [75]. Brigatinib is being investigated in a food-food interaction study that also enrolls *ROS1* + in addition to *ALK* + solid tumors. (ClinicalTrials.gov Identifier: NCT03420742).

4.1.6. Ensartinib

Ensartinib (X-396) is a second generation ALK/ROS1 TKI that has shown preliminary activity in *ALK* + NSCLC patients [76]. Preclinical enzymatic studies also indicated ensartinib is also a ROS1 inhibitor with an IC_{50} against GOPC-ROS1 of 0.98 nM [77]. Ensartinib is the TKI in the ALK/ROS1 arm of the Pediatric Match trial in the US (ClinicalTrials.gov Identifier: NCT03213652). However clinical efficacy of ensartinib against *ROS1* + NSCLC patients has not been reported.

4.2. Efficacy of second generation ROS1 TKI against CNS metastasis in ROS1 + NSCLC

4.2.1. Lorlatinib

Lorlatinib is a next generation ALK/ROS1 inhibitor [78]. The clinical efficacy of lorlatinib in both crizotinib-naïve and crizotinib-refractory *ROS1* + NSCLC patients was recently presented [64]. Among

the 19 crizotinib-pretreated patients with baseline CNS metastasis (measurable or non-measurable), the confirmed IC-ORR was 53% (95%CI: 29–76) with a median DoR not reached (95%CI: 5 months – NR). This is similar to the IC-ORR of 66.7% (95%CI: 22–96) among the 6 crizotinib-naïve *ROS1*+ NSCLC patients. The median DoR intra-cranially among the 19 crizotinib-refractory patients on lorlatinib has not been reached (95%CI: 5 – NR) [64].

4.2.2. Repotrectinib (TPX-0005)

Repotrectinib is a next generation compound that potently targets ROS1/NTRK/ALK but also the solvent front mutations arising from first generation TKIs [79]. Additionally, it has demonstrated CNS activity against ROS1 (and NTRK) [79]. In an update of the on-going phase 1 study, among the TKI-naïve patients with measurable disease (N = 3) the confirmed IC-ORR was 100% [65]. The IC-ORR among all 5 TKI-naïve ROS1+ NSCLC patients was 60%. Among the TKI-refractory patients with measurable CNS metastasis (N = 4), the IC-ORR was 25%. Among all TKI-refractory patients with CNS metastasis, the confirmed IC-ORR was 9.1% at the very preliminary stage [65].

4.2.3. DS-6051b

DS-6051b is a potent ROS1/pan-NTRK inhibitor developed by Daiichi Sankyo, Inc. with an enzymatic IC_{50} against ROS1, NTRK1, NTRK2, and NTRK3 of 0.207 nM, 0.622 nM, 2.28 nM, and 0.980 nM respectively [80]. Additionally, it has potent inhibitory activity against both the gate keeper ROS1 L2026 M mutation and solvent-front ROS1 G2032R mutation with low GI_{50} against Ba/F3 cells bearing ETV6-ROS1 constructs with these mutations (GI_{50} = 4 nM against ETV6-ROS1 WT, GI_{50} = 14 nM against ETV6-ROS1 L2026 M; GI_{50} = 64 nM against ETV6-ROS1 G2032R) [80]. In comparison the GI_{50} for crizotinib against ETV6-ROS1 WT, EV6-ROS1 L2026 M, ETV6-ROS1 G20232R were 25 nM, 147 nM, and > 500 nM in the same set of preclinical data [80]. Of the 15 *ROS1*+ NSCLC patients enrolled in a Japanese phase 1 study, 5 had CNS metastasis. Response image of 1 *ROS1*+ NSCLC patient with CNS metastasis was shown but the treatment efficacy of the other 4 patients were not reported [66].

4.3. Efficacy of pemetrexed-based chemotherapy

Individual case reports and retrospective case series have shown that pemetrexed-based chemotherapy has high ORR and duration of disease control in *ROS1*+ NSCLC patients [32,81–86]. The largest retrospective case series of pemetrexed in *ROS1*+ NSCLC was from South Korea where 103 *ROS1*+ NSCLC patients were analyzed including 90 *ROS1*+ NSCLC patients treated with platinum/pemetrexed followed by pemetrexed maintenance, 58 *ROS1*+ NSCLC patients treated with various ROS1 TKIs, and39 patients received both pemetrexed and ROS1 TKIs [32]. It seems that the ORR, PFS, and OS all numerically favor TKI over pemetrexed. The ORR with ROS1 TKI was 70.7% compared to 53.3% with pemetrexed-based chemotherapy. The median PFS with ROS1 TKI was 12.7 months (95%CI: 8.1–21.8) while the median PFS was 8.0 months with pemetrexed-base chemotherapy (95%CI: 6.4–11.7). The OS of patients who received a ROS1 TKI was 64.9 months (95%CI: 26.3 – NR) while patients who did not receive a ROS1 TKI was 20.7 months (95%CI: 8.4–54.3). More importantly, the median OS of patients who received pemetrexed but did not receive ROS1 TKI was only 20.3 months (95%CI: 8.0 – NR) compared to 60.1 months of OS (95%CI: 25.6 – NR) for patients who received both pemetrexed and ROS1 TKI. The efficacy data of pemetrexed on crizotinib- or TKI-refractory *ROS1*+ NSCLC patients are unknown.

Among 23 patients with baseline CNS metastasis and another 24 patients who developed new CNS metastasis during the period of analysis, the IC-ORR of pemetrexed in CNS metastasis was not abstracted. Additionally, while the median time to CNS metastasis was 12 months it is unknown if there is a difference between patients treated with pemetrexed-based chemotherapy versus ROS1 TKIs [32].

Another large-scale retrospective analysis of 51 Chinese *ROS1*+ NSCLC patients indicated crizotinib achieved a higher ORR, DOR, and longer median PFS than pemetrexed-based chemotherapy. However, the retrospective analysis did not report the incidence of CNS metastasis nor the efficacy if any on pemetrexed-based therapy post-crizotinib [85].

In an earlier and smaller retrospective analysis of European *ROS1*+ NSCLC patients (EUROS1), similar efficacy of pemetrexed-based chemotherapy was reported. On the EUROS1 study, 24 *ROS1*+ NSCLC patients received pemetrexed-based chemotherapy at any time during their treatment history and the ORR was 57.7% and median PFS of 7.2 months (95%CI: 4.8–9.6) [70]. Again, the efficacy data of pemetrexedpost-crizotinib progression was not reported and only one patient had CNS metastasis in the EUROS1 study. Both European and Korean retrospective analyses implicated brain metastasis is more common for patients on TKIs compared to pemetrexed-based chemotherapy likely due to progression extra-cranially as the first site of progression (hence censoring) occurring in pemetrexed-treated patients as first progression. This indicated with superior extracranial efficacy the selection pressure for relapse/progression is in the CNS metastasis.

5. Summary

1. Despite the exhaustive review of the literature, the incidence of CNS metastasis in *ROS1*+ NSCLC can only be best estimated from single-arm, phase 2 clinical trials or single institution retrospective studies.
2. Generally it can be concluded that the incidence of CNS metastasis at the time of diagnosis rangeds from 20% to mid 30%. Additionally, approximately about 30% of patients who had no baseline CNS metastasis are expected to develop CNS metastasis during treatment with crizotinib. The incidence of CNS metastasis ranged from mid 30% to mid 55% among patients who had progressed on crizotinib.
3. *ROS1*+ NSCLC is a heterogeneous group of NSCLC with at least 22 different fusion partners identified. A provocative report indicated CD-74 ROS1 fusion variant has increased predilection for CNS metastasis and lower ORR and shorted PFS and OS in response to crizotinib treatment when compared to non-CD74-ROS1 fusion variants.
4. Crizotinib is the only ROS1 TKI approved by the US Food and Drug Administration (FDA) in 2016. The high incidence of CNS metastasis in *ROS1*+ NSCLC patients especially those who progressed from crizotinib represents an urgent unmet medical need. There are encouraging CNS activity from several ROS1 TKIs while the intracranial clinical activity of pemetrexed-based chemotherapy is nil in the literature. Clinical developemnt of next generation ROS1 TKIs that can overcome CNS metastasis and various resistance *ROS1* mutations is urgently needed.

6. Action item

Analysis of longitudinal electronic medical records of large health networks such as FLATIRON which currently abstracts data from 39 academic practices and 261 community practices [87] has provided patient characteristics and treatment outcome of rare driver mutations in NSCLC [87] and has been utilized by the US FDA to assess unmet treatment need after approval of immunotherapy [88]. The presence of or lack of CNS activity of pemetrexed-based chemotherapy is critically needed to assess planning for future clinical trials for next generation ROS1 TKIs. The FLATIRON database represents an opportunity to shed light on the prevalence of CNS metastasis during various stages of *ROS1*+ NSCLC treatment and provide guideposts on treatment outcome of various modalities for clinical trial planning purposes.

Conflict of interest

SHI Ou has received consulting fee from Pfizer, Takeda/ARIAD,

Roche/Genentech, Astra Zeneca, Boehringer Ingelheim, X-covery, Spectrum pharmaceuticals.

SHI Ou has received speaker honorarium from Pfizer, Roche/Genentech, Foundation Medicine Inc, Astra Zeneca, Merck, and Takeda/ARIAD.

SHI Ou is a member of the scientific advisory board of Turning Point (TP) Therapeutics, Inc. and has stock ownership in TP Therapeutics, Inc. TP Therapeutics, Inc is developing repotrectinib for *ROS1*+ and *NTRK*+ patients.

VW Zhu has received consulting fee from Biocept, Takeda/ARIAD, Astra Zeneca, and TP Therapeutics.

VW Zhu has received speaker honorarium from Roche/Genentech, Foundation Medicine Inc, Astra Zeneca, and Takeda/ARIAD.

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