Editorial

Targeting *ROS1* rearrangements in non-small cell lung cancer with crizotinib and other kinase inhibitors

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The discovery of molecular subtypes of non-small cell lung cancer (NSCLC) with oncogenic driver mutations and translocations/rearrangements has led to successful development of targeted therapies and improvement in outcomes of advanced lung cancer patients. The frequency of these different subtypes and their clinical impact are illustrated in *Figure 1A* (1). Of these, drugs have already been approved by regulatory agencies for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 receptor tyrosine kinase (ROS1), and B-RAF proto-oncogene serine/threonine kinase (BRAF) targeted treatments. There are ongoing clinical trials for development of targeted therapies against other activated "driver oncogenes" in NSCLC, including MET proto-oncogene receptor tyrosine kinase (MET), ret proto-oncogene (RET), Erb-B2 receptor tyrosine kinase 2 (ERBB2), and neurotrophic receptor tyrosine kinase 1 (NTRK) among others.

ROS1 rearrangements were first reported in NSCLC in 2007 (2). Since then, *ROS1* rearranged NSCLC has been described as a distinct molecular type in approximately 1–2% of patients with NSCLC (2,3). It was the third clinically actionable subtype after *EGFR*-mutated and *ALK*-rearranged NSCLC to receive United States Food and Drug Administration (FDA) approval for a targeted therapy, the tyrosine kinase inhibitor (TKI) crizotinib.

The *ROS1* locus is located on chromosome 6 and encodes for an orphan tyrosine kinase receptor, i.e., with no known ligand and biologic function in humans (4). *ROS1* rearrangements/translocations lead to fusions of an intact ROS1 tyrosine kinase domain with partner genes, which are usually present on another chromosome (*Figure 1B*) (5,6). They can be detected in clinical samples via fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse transcription polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS) (2). So far, 14 different fusion partner genes have been identified in lung cancer patients, including *CD74*, *SLC34A2*, Syndecan 4 gene (*SDC4*), ezrin gene (*EZR*), fused in glioblastoma gene (*FIG*), tropomyosin 3 gene (*TPM3*), leucine-rich repeats and immunoglobulin-like domains 3 gene (*LRIG3*), KDEL endoplasmic reticulum protein retention receptor 2 gene (*KDELR2*), coiled-coil domain containing 6 gene (*CCDC6*), moesin gene (*MSN*), transmembrane protein 106B gene (*TMEM106B*), tumor protein D52 like 1 gene (*TPD52L1*), clathrin heavy chain gene (*CLTC*), and LIM domain and acting binding 1 gene (*LIMA1*) (2,5). Of these, the *CD74-ROS1* fusion has been reported as the most common rearrangement in NSCLC. These fusion events lead to constitutive activation of the ROS1 kinase that drives cellular transformation and promotes survival and proliferation through downstream signaling via SHP-1/SHP-2, JAK/STAT, PI3K/AKT/MTOR and MAPK/ERK pathways (2,4,5,7).

With the discovery that lung cancers with *ROS1* rearrangements are dependent on the driver oncogene, there was a natural interest in developing ROS1-targeted TKIs as a tailored treatment option for these patients. Given that *ROS1*-rearranged cancers form an undeniably small subset of patients with NSCLC, larger comparative trials are likely not going to be feasible. A number of phase I/II studies have been successfully performed however, demonstrating the utility of targeting this driver mutation and leading to a growing list of treatment options for this disease (*Tables 1,2*).

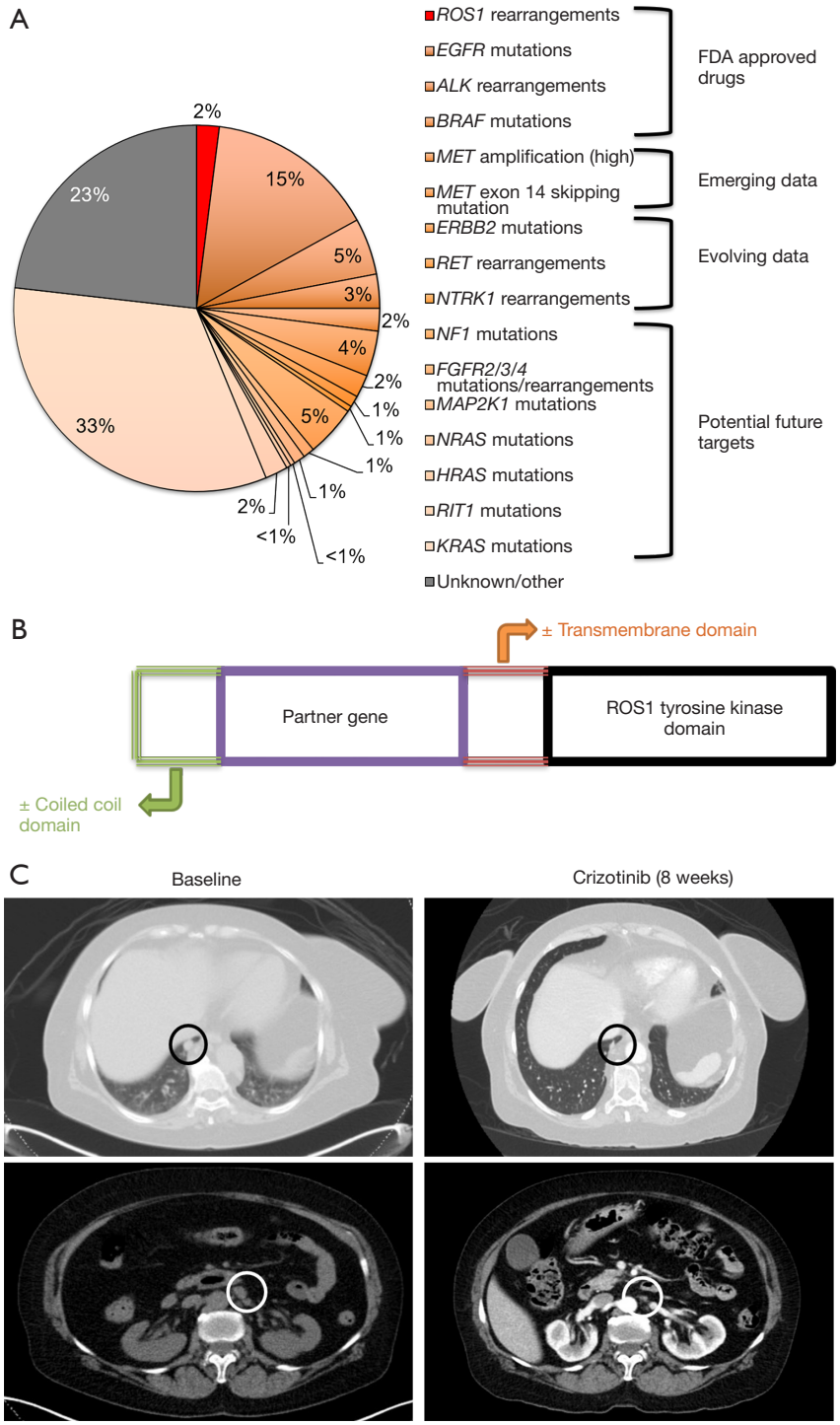

Figure 1 *ROS1* rearrangements in context. (A) Frequency of molecular subtypes of non-small cell lung cancer of adenocarcinoma histology with a focus on *ROS1* rearrangements; (B) representation of ROS1 partner fusion proteins. All constructors retain the ROS1 tyrosine kinase domain. ROS1 transmembrane and coiled-coil domains are variably present or absent in different fusions; (C) representative pre- and post-treatment images at 8 weeks in a patient with advanced lung cancer with a *ROS1* rearrangement treated with first line crizotinib 250 mg twice daily. Black circles indicate thoracic tumor burden; whole white circles indicate mesenteric lymphadenopathy.

ROS1 and ALK tyrosine kinase domains share significant homology, including bindings sites for adenosine triphosphate (ATP) and crizotinib (3,8). Although, *ROS1* rearrangements and *ALK* rearrangements are mutually exclusive (3,5,17), they share similar clinicopathological features (3,6). Both are generally seen in younger patients with light or never smoking history and have a preponderance for adenocarcinoma histology. However, their patterns of metastatic spread were recently found to be different (18). *ROS1*-rearranged NSCLC was described to have significantly lower rates of extra-thoracic and intracranial metastases at the time of diagnosis, as well as lower cumulative incidence of intracranial metastases. A subsequent single institution retrospective study has, however, questioned these findings by describing similar rates of intracranial metastases at diagnosis among patients with *ALK*- and *ROS1*-rearranged lung cancers (19).

Given the considerable clinicopathological overlap and shared homology between the ROS1 and ALK tyrosine kinases, it should come as no surprise that crizotinib—a multitargeted MET/ALK/ROS1 inhibitor—was shown to have considerable clinical efficacy in *ROS1*-rearranged lung cancers. The global phase 1 study (PROFILE 1001) was amended to include *ROS1*-rearranged lung cancer in the expansion cohort, with a brisk overall response rate (ORR) of 72%, disease control rate (DCR) of 90%, and median progression-free survival (PFS) of 19.2 months, much as had been seen with *ALK*-rearranged tumors (8). On the basis of these striking results, crizotinib was granted full approval in the spring of 2016 by the FDA for treatment of advanced *ROS1*-rearranged lung cancer and remains to date the only approved treatment for this molecularly defined subset. Two subsequent studies from Europe have demonstrated PFS about half of that originally described for crizotinib in PROFILE 1001, in the 9-10-month range (9,10). However, it should be noted that for both of these studies, the number of patients evaluated was low (<30), and the EUROS1 study was retrospective (*Table 1*). Later iterations of TKIs—ceritinib (12) and entrectinib (13)—have both shown to be potent inhibitors in *ALK*-rearranged NSCLC and have also been shown to have overlap activity with *ROS1*-rearranged disease. Although phase I/II studies have suggested disease activity in crizotinib naïve cases (ORR >70% and PFS ~19 months), their activity seems to be considerably less so in the setting of crizotinib drug resistance. In comparison, lorlatinib—a highly potent, central nervous system (CNS)-penetrant, and selective ALK and ROS1 TKI—was shown in a multicenter phase 1 trial to be active in crizotinib-resistant disease. Amongst the cohort of 12 patients with *ROS1*-rearranged tumors and including seven crizotinib pretreated patients, an objective response was achieved by 6 (50%) (14). Clinical activity seen with other TKIs in *ROS1*-rearranged NSCLC has also been described (*Tables 1,2*) (15,16).

Although patients with *ROS1*-rearranged NSCLC have been shown to have variable rates of brain metastases at baseline as compared with *ALK*-rearranged disease, the brain remains a common and clinically relevant site of disease progression (18,19). A recent study found crizotinib resistance mutations in 64% of non-intracranial specimens compared to 0% in three intracranial specimens (18). Lack of *ROS1* resistance mutations in the CNS points to pharmacokinetic barriers as the underlying mode of drug failure, as crizotinib is known to have limited blood-brain barrier penetrance (20). TKIs that can penetrate the blood-brain barrier may provide more durable disease responses. Ceritinib, entrectinib, and lorlatinib—all have better CNS penetration and demonstrable CNS activity (*Tables 1,2*). Although interpretation must be made with caution due to small numbers, they may soon supersede crizotinib by virtue of better prevention and control of recalcitrant CNS disease.

Data on the safety and tolerability of crizotinib in *ROS1*-rearranged cohorts does not differ considerably from larger cohorts using this agent for *ALK*-rearranged disease. There were no treatment-related Common Terminology Criteria for Adverse Events (CTCAE) grade 4 or 5 events reported by Shaw *et al*. (8). The most common adverse events included mild visual impairment (described as transient dark-light adaptation adjustments) seen in >80%, peripheral edema (>30%), and gastrointestinal side effects including nausea, vomiting, diarrhea, and constipation, which were all mostly grade 1 and seen in up to a third of the total cohort (8). Cross-trial comparisons suggest more frequent gastrointestinal toxicities with ceritinib (50–70%), leading to dose reductions and adjustments (12,21). Entrectinib and lorlatinib, on the other hand, seem to have a lower incidence of nausea, diarrhea, and constipation (10–20%)—although it is notable that lorlatinib was associated with an almost 40% incidence of peripheral neuropathy and cognitive adverse events that have not been noted in other studies of TKIs in this setting (13,14).

Wu *et al.* have further expanded the armamentarium of evidence in this domain with the recent publication of the first prospective phase II international, single-arm, open-label study of crizotinib in East Asian patients with *ROS1*-rearranged advanced NSCLC (11). This trial studied 127 patients from China, Japan, South Korea, and Taiwan with locally advanced or metastatic NSCLC patients who had received 3 or fewer prior lines of systemic therapy; those with prior exposure to a ROS1- or ALK-directed therapy were excluded. *ROS1* rearrangement status was assessed by

Table 1 Summary of clinical trials of targeted therapies in *ROS1*-rearranged lung cancer and summary of crizotinib resistance mutations

Drug name	Study	Phase	Population	Comparator	ORR, median [95% CI] (%)	PFS, median [95% CI] (months)	OS, median [95% CI] (months)	CNS control	Most common toxicities (>20%)
Crizotinib	Expansion phase of PROFILE 1001, NCT00585195 (8)	I/II	ROS1+ advanced disease, 86% >1 prior regimen (N=50)	None	72 [58–84]	19.2 [14.4–not reached]	16.4 [13.8–19.8]	–	Visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), fatigue (20%), elevated transaminases (14–22%)
	EUROS1, retrospective multicenter study (9)		ROS1+, stage IV disease. 96% >1 prior regimen (N=31)	None	80 [NR]	9.2 [NR]	–	–	Not reported due to retrospective nature
	ACSé phase II trial, NCT02034981 (10)	II	ROS+, progressing after at least 1 treatment (N=29)	None	63 [41–81]	–	–	–	Visual disorders (62%), peripheral edema (55%), diarrhea (51%), nausea (41%), and elevated transaminases (51%)
	East Asian phase II study, NCT01964157 (11)	II	East Asian, ROS1+, advanced NSCLC (N=127)	None	72 [63–79]	15.9 [12.9–24]	32.5 [32.5–NR]	–	Elevated transaminases (55%), vision disorders (48%), nausea (41%) diarrhea (39%) vomiting (32%), constipation (30%), neutropenia (29%), leukopenia (23%), edema (23%)
Ceritinib	NCT01964157 (12)	II	Advanced ROS1+, NSCLC, heavily pretreated, including 2 with crizotinib prior (N=32), 8 patients with intracranial disease	None	62 [45–77]	9.3 [0–22]	24 [5–43]	Intracranial ORR was 25%, 2/8 evaluable patients	Diarrhea (78%), nausea (59%), vomiting (53%), cough (47%), abdominal pain (41%), musculoskeletal pain (41%), fatigue (22%) and dyspnea (22%), elevated creatinine (41%), elevated LFTs (25–31%)

Table 1 (*continued*)

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Drug name	Study	Phase	Population	Comparator	ORR, median [95% CI] (%)	PFS, median [95% CI] (months)	OS, median [95% CI] (months)	CNS control	Most common toxicities (>20%)
Entrectinib	ALKA-372-001, EudraCT 2012-000148-88 and STARTRK-1, NCT02097810 (13)	I	Advanced solid tumors (including 60% NSCLC) with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions (N =119); 14 patients with ROS1+ NSCLC treated with recommended phase II dose	None	86 [60–96]	19.0 [6.5–not reached]	–	63% (5/8 patients with baseline CNS disease, including 2 responders with ROS1+ disease)	Fatigue/asthenia (24%), dysgeusia (47%), paraesthesias (29%), nausea (24%) and myalgias (19%) (reported for all 119 patients)
Lorlatinib	NCT03052608 (14)	I	ALK+ or ROS1+ advanced NSCLC (N=54); 12 patients with ROS1+ NSCLC, of whom 7 had been treated with crizotinib previously and 5 had baseline CNS disease	None	50 [21–79]	7.0 [1.4–13.9]	–	3/5 (60%) had intracranial objective responses	Hypercholesterolemia (59%), hypertriglyceridemia (33%) peripheral edema (39%), peripheral neuropathy (39%) (reported for all 54 patients)
DS-6051b	Japanese study, NCT02675491 (15)	I	ROS1+ NSCLC (N=15), 4 had received crizotinib prior, 5 baseline CNS disease	None	58.3	NR	–	–	Elevated transaminases (80%), diarrhea (53%), nausea (47%), constipation (33%), decreased appetite (20%), dysgeusia (20%), malaise (20%), vomiting (20%)
Brigatinib	NCT01449461 (16)	I/II	Advanced malignancies; all histologies, except leukemia (N=137), 3 patients with ROS1+ NSCLC enrolled in cohort 4	None	33: 1 crizotinib naïve patient had partial response, 2 crizotinib previously treated patient, stable disease	–	–	–	Nausea (53%), fatigue (43%), diarrhea (41%)

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; CNS, central nervous system; NSCLC, non-small cell lung cancer; NR, not reached; LFT, liver function tests.

Table 2 Summary of crizotinib resistance mutations and drugs with pre-clinical or clinical activity in *ROS1*-rearranged lung cancer

Putative ROS1 kinase domain crizotinib resistance mutations	Drugs with preclinical activity	Drugs with clinical response in case reports
G2032R	Repotrectinib, cabozantinib	Repotrectinib
D2033N	Lorlatinib, repotrectinib, cabozantinib	Cabozantinib
S1986Y/F	Lorlatinib	Lorlatinib
L2026M	Ceritinib, brigatinib, lorlatinib, repotrectinib, cabozantinib	–
L1951R	Cabozantinib	–

validated RT-PCR using the AmoyDx ROS1 Gene Fusions Detection Kit at three regional laboratories. The patient population was similar in its characteristics to previously reported cohorts: most were younger than 65 years old (83.5%), non-smokers (71.7%), and had adenocarcinoma tumor histology (97.6%). Most patients had been exposed to at least 1 prior line of therapy (81.1%). ORR with crizotinib was found to be 71.7% (95% CI: 63.0–79.3%) with complete response in 13.4% patients. Responses were rapid in onset (median time to response of 1.9 months) and durable (median duration of response 19.7 months). Subgroup analysis showed that responses were maintained across all baseline characteristics (sex, age <65 or >65 years, smoking history, and number of prior lines of therapy both less than or more than or equal to 2). Median PFS was 15.9 months (95% CI: 12.9–24.0 months). ORR was similar to high rates seen in the expansion cohort of the PROFILE 1001 trial (8) and preliminary findings of the two European prospective studies (13,22). The PFS reported in this trial was less than reported in the expansion cohort of PROFILE 1001 (19.2 months). Crizotinib was generally well tolerated with no new safety signals identified. The most common adverse events included: elevated liver enzymes, vision disorder, nausea, diarrhea, and vomiting. CTCAE grade 3 and 4 drug-related adverse events were seen in 25.2% patients, with neutropenia and elevated liver enzymes being the most common ones. Patient-reported outcomes were also assessed and showed clinically meaningful improvements in the respiratory symptoms and expected deterioration of bowel habits. Within the limitations of a single-arm phase II study, it confirmed the clinical efficacy of crizotinib in *ROS1*-rearranged lung cancer in this demographic and has led to regulatory approval of crizotinib in China, Japan, South Korea, and Taiwan. Although crizotinib showed response in both first and later-line settings, it would be hard to justify not using it as first line therapy in newly diagnosed patients with *ROS1*-rearranged NSCLC, given brisk and more durable efficacy with more limited toxicity compared to what might be expected with other established forms of palliative systemic therapy, i.e., chemotherapy, in this setting. As acknowledged by the authors themselves, a significant limitation of the study was that response of intracranial disease was not assessed. This is particularly relevant, given more limited CNS penetrance and intracranial efficacy with crizotinib (20).

The experience of on-label use of crizotinib in *ROS1*-rearranged NSCLC patients in our own multidisciplinary clinic has been similar. We report here a case of a 66-year-old woman and life-long never smoker, who initially presented with shortness of breath. She was found to have extensive bilateral pulmonary embolism and incidentally noted to have diffuse supra-and sub-diaphragmatic lymphadenopathy along with a small right lower lobe lung lesion. Magnetic resonance imaging (MRI) of the brain showed no evidence of intracranial metastatic disease. Due to initial suspicion for a lymphoproliferative disorder, excisional lymph node biopsy was performed and revealed a poorly differentiated adenocarcinoma of lung primary with *ROS1* rearrangement positive by FISH (84% cells); comprehensive genomic profiling (Foundation One, Foundation Medicine, Cambridge, MA) confirmed a *CD74-ROS1* fusion gene. The patient was started on palliative crizotinib 250 mg twice daily, with repeat imaging 8 weeks later showing near complete response with massive regression of diffuse adenopathy and the primary right lung nodule (*Figure 1C*). At the time of this report nearly 11 months later, the patient continues to have a sustained response with limited toxicity, save mild fatigue and nausea and without need for dose reduction or interruption.

Although crizotinib has been associated with remarkable and durable clinical responses, resistance is an inevitable reality for patients and occurs through two succinct mechanisms: (I) "on target" mutations in crizotinib binding sites within the ROS1 tyrosine kinase domain, and (II) "off target" mechanisms including activation of bypass signaling pathways (i.e., EGFR, RAS and KIT) and phenotypic changes such as epithelial to mesenchymal transition (18,23).

"On target" crizotinib resistance mutations are thought to occur more frequently in *ROS1*- (approximately 50–60%) compared to *ALK*- (approximately 20–25%) rearranged NSCLCs. However, these mutations have been described to involve a narrower segment of the tyrosine kinase domain in *ROS1*-rearranged NSCLC (2,18). *Table 2* describes the different *ROS1* resistance mutations reported to date (18,23). The most common crizotinib resistance mutation described is *ROS1*-G2032R mutation. Other mutations include solvent front D2033N, S1986Y/F, gatekeeper L2026M, and L1951R. Various drugs have been tested against these resistance mutations using *in vitro* studies. Those with either preclinical activity or case reports of clinical efficacy against those mutations are described in *Tables 1,2* (2,18). Cabozantinib is a multi-targeted TKI that is thought to be effective for the majority of these resistance mutations. However, significant toxicities due to its non-selective mechanism of action have precluded its widespread use in this setting thus far (2). Lorlatinib is a highly potent and CNS-penetrant ALK/ROS1 inhibitor, which has *in vitro* activity against *ROS1* rearrangements with *ROS1*-D2033N, S1986Y/F, and L2026M mutations. Based upon preclinical studies, its efficacy against *ROS1*-G2032R mutation may be limited and requires further investigation (2). Repotrectinib (formerly known as TPX-0005) has shown efficacy against *ROS1*-G2032R mutation (*Table 2*).

Important issues in the clinical management of patients with actionable genomic events such as *ROS1* rearrangements include the optimal sequencing and utility of other treatment modalities, including cytotoxic chemotherapeutic agents and immune checkpoint inhibitors. In small retrospective studies, pemetrexed-based regimens had lower ORR (54–57%) and a shorter PFS of 7–8 months (24) when compared with what has been seen in phase I–II studies with TKIs in this molecularly defined subset of advanced NSCLC. Of note, compared to other oncogenic driver mutations in NSCLC, *ROS1*-rearranged lung cancers may be associated with better responses to chemotherapy.

Phase I–II clinical trials, retrospective reviews and, small case series on patients with crizotinib resistance mutations have provided significant insight and led to improvements in the outcomes of patients with *ROS1*-rearranged NSCLC. Although the infrequency of this driver mutation will likely preclude direct comparisons between agents, the brisk and durable efficacy of ROS1-directed TKIs has led to widespread use of these agents in the upfront management of advanced stage disease in this subset of patients. The role of immune checkpoint inhibitors is still not clear and merits further study, although the experience with immune monotherapy in NSCLC with other actionable oncogenic driver mutations has been disappointing to date. Current efforts include attempting to determine if there is synergistic antitumor activity with combined immunotherapy and targeted therapy (25). Additionally, high rates of CNS progression associated with crizotinib use and the inevitable development of crizotinib resistance mean that significant challenges exist as we try to transform the long-term outcomes of patients with this disease. Similar to the use of osimertinib and alectinib as initial therapy in *EGFR*-mutated and *ALK*-rearranged advanced NSCLC, respectively, it remains a worthy cause to develop advanced generation CNS-penetrant ROS1-directed therapies that will have efficacy against the most common crizotinib resistance mutations and can be propelled into the frontline setting for these patients.

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Footnote

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