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Precision Medicine in Targeting ROS1- Rearranged Non-small Cell Lung Cancer

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Abstract

Globally, lung cancer is the leading cause of death from cancer among men and women. The overall 5-year survival rate of lung cancer is around 16-19%. The emergence of targeted therapy and immunotherapy have changed the treatment paradigm of advanced NSCLC.

Keywords: NSCLC; ROS1; TKI; Lung cancer; Precision medicine; Immunotherapy

Introduction

The practice of precision medicine is incumbent on optimal tumour sampling, accurate tumour testing, and informed application of results to patient care. The identification of biomarkers and molecular targets has become increasingly important for the management of patients with Non-Small-Cell Lung Cancer (NSCLC) [1]. The management of NSCLC now requires multiple molecular tests, including epidermal growth factor receptor (EGFR) gene, anaplastic lymphoma kinase (ALK), programmed death-ligand 1 (PD-L1) analysis and extended panelling if there is sufficient tissue at baseline to define the optimal treatment strategy. EGFR mutations occur in approximately 10-30% of the NSCLC population globally with an incidence of approximately 10% in the Caucasian population. From an Irish context, in the HSE South 8% (27/334) of patients were found to have sensitizing EGFR mutations [2]. The presence of an EGFR mutation has both prognostic and predictive implications. Figure 1 illustrate the clinical impact of different subtypes of NSCLC.

ROS1-rearranged (ROS1-positive) NSCLC is a subset of NSCLC characterized by dependency on ROS1 signalling and marked sensitivity to ROS1 tyrosine kinase inhibitors. Most recently, *ROS1*, which encodes a receptor tyrosine kinase similar to anaplastic lymphoma kinase (*ALK*) and other insulin receptor family members, has emerged as a new treatment target [1-3]. *ROS1* rearrangements result in constitutive ROS1 kinase activation, leading to dysregulated downstream signaling and cellular transformation [3,4]. Approximately 1% to 2% of patients with NSCLC harbor *ROS1* rearrangements, which is equivalent to 2,000 to 4,500 new cases of *ROS1*-positive NSCLC each year in the United States (US) [2,5,6].

Clinical Characteristics

Patients with ROS1-positive tumours tend to be younger, female, have a history of never or lightly smoking, and with lung adenocarcinoma [2,5].

These findings are based primarily on a study of 1,073 participants, 18 of whom had ROS1-positive NSCLC. The median age of the 18 participants was 49.8 years (range, 32-79 years) [2]. ROS1-positive tumours displayed adenocarcinoma histology, similar to ALK-rearranged NSCLC, although no specific subtype prevailed [2,7]. In contrast with ALK-positive NSCLC, ROS1 rearrangements lacked signet ring cells and had a broad distribution of tumour grades [2,8]. Bergethon and colleagues also noted that more than one-third of tumors were poorly differentiated with high-grade, highly atypical infiltrating cells [2].

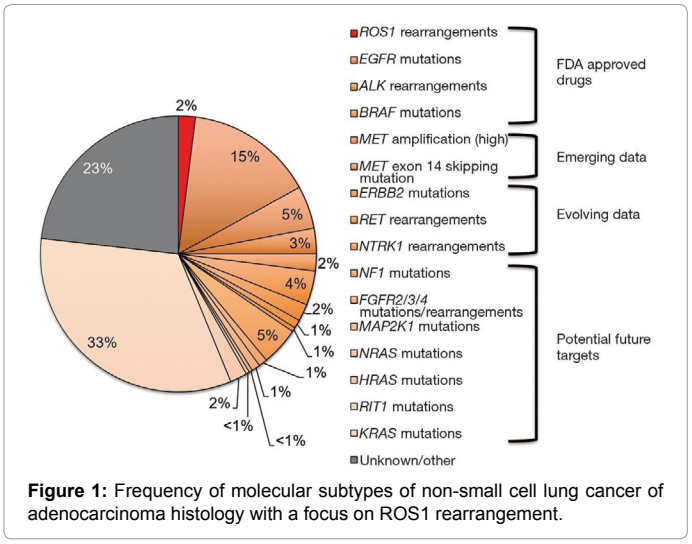

Figure 1: Frequency of molecular subtypes of non-small cell lung cancer of adenocarcinoma histology with a focus on ROS1 rearrangement.

ROS1-positive tumours tend to occur in patients who are considered to have "triple negative" disease, meaning that tumors with ROS1 rearrangements typically do not contain concurrent ALK rearrangements or epidermal growth factor receptor (EGFR) or KRAS mutations [4,5,9]. However, in very rare cases, patients with ROS1-positive lung cancers may harbor more than one oncogenic driver [6].

Testing for ROS1-Positive NSCLC Guidelines

Although *ROS1* rearrangements can result in similar clinicopathologic features as those caused by mutations in other oncogenic drivers, such as *ALK* and *EGFR*, these features should *not* be used to identify candidates for *ROS1* testing [4,5]. Instead, National Comprehensive Cancer Centre (NCCN) guidelines recommend testing for *ROS1* rearrangements in addition to *ALK* rearrangements,

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EGFR mutations, and *BRAF*mutations in patients with advanced nonsquamous NSCLC or NSCLC not otherwise specified (NOS) [1].

Current Testing Methods

The most common *ROS1* fusion partners are *CD74*, *SLC34A2*, *CCDC6*, and *FIG* [1]. Currently, no US Food and Drug Administration (FDA)-approved companion diagnostic tests exist for *ROS1*-rearranged NSCLC [6]. Methods to detect *ROS1* rearrangements include FISH, IHC, RT-PCR, and NGS [4,6].

FISH

Break-apart FISH is considered to be the gold standard for recognizing *ROS1* rearrangements and may be performed on biopsy or cytologic specimens [4,10]. This approach uses two labeled probes of different colors: a green fluorochrome probe labeling the centromeric (3') end of the fusion breakpoint and a red-orange fluorochrome probe labeling the telomeric (5') end [2,4,6]. Similar to those of *ALK* rearrangements, the identification patterns of *ROS1* rearrangements include [4]:

(1) The conventional split pattern with one fusion signal (native *ROS1*) and two separated 3' and 5' signals (*ROS1* rearrangement).

(2) An atypical pattern with one fusion signal and one 3' signal without its corresponding 5' signal.

Tumors are considered *ROS1*-positive if at least 15% of 50 or more neoplastic nuclei exhibit rearranged signals [2,4,10,11].

The limitations of break-apart FISH include the potential difficulty of interpreting test results and an inability to identify the translocation partner of the rearrangement [2,6]. Additionally, false-negatives may occur with rearrangements of *ROS1*and some gene fusion partners, particularly with small intrachromosomal deletion events [4,6]. NCCN guidelines have noted that the *FIG-ROS1* variant may be underdetected by break-apart FISH.

IHC

IHC is currently the most cost-effective approach for detecting *ROS1*-positive NSCLC [4]. Several ROS1 mono- and polyclonal antibodies are commercially available, and at least one exhibits sensitivity close to 100% [4,6]. However, IHC staining is less specific than FISH, and staining results can be operator dependent [4]. IHC staining may be performed on most tissue types, and *ROS1*-positive IHC shows diffuse expression in more than 75% of tumor cells with moderate-to-strong staining intensity [4]. However, intracellular staining patterns vary due to gene fusion partners and the localization of these proteins [4,6,12]. Background staining can make *ROS1* IHC interpretation challenging [6]. Although ROS1 protein is typically absent in normal lung tissue, ROS1 staining has been observed in benign pneumocytes and alveolar macrophages as well as osteoclast-type giant cells in bone metastatic lesions [6,12]. Confirmation of *ROS1* rearrangements with break-apart FISH or NGS is recommended in IHC-positive cases as well as those in which interpretation is uncertain [4,6,12].

RT-PCR

The sensitivity and specificity of RT-PCR for detecting *ROS1* rearrangements is high and facilitates the identification of *ROS1* fusion partners [4]. However, this assay requires the use of fusion-specific primers and therefore cannot be used to identify novel rearrangements [6]. The use of RT-PCR is also limited by the requirement for good-quality RNA, which may be difficult to obtain from smaller tumor samples [4].

NGS

NGS provides rapid, high-throughput sequence data from a sample and provides multiplex testing that enables the simultaneous pooling and sequencing of large numbers of DNA libraries during a single run [13,14]. Both novel and known gene fusions of *ROS1* rearrangements can be detected using this assay [6]. In the future, the identification of these fusion partners may serve as biomarkers that inform decision making and affect clinical outcomes. Current limitations of NGS include higher costs, a need for more tissue during processing, and a relatively longer processing time compared with FISH and IHC [6]. A comparison of these assays is provided in Table 1. It is important to note that a single assay is usually insufficient to confirm the presence of *ROS1* rearrangements [4,6,12]. Often, the use of 2 different methods (eg, IHC followed by FISH or NGS) is required to identify and confirm *ROS1*-positive status [4,6,12].

Current Approved Treatment

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. However, *ROS1*-positive tumours were the third clinically actionable subtype after *EGFR*-mutated and *ALK*-rearranged

Assay	Works Best With	Benefits	Limitations
FISH	Biopsy	Clinical trial gold standard	Difficult to interpret
	Nonbloody cytologic specimens	Less expensive than NGS and RT-PCR	False-negatives may occur with certain gene fusions
	Formalin-fixed paraffin embedded tissue		Translocation partner cannot be identified
IHC	Formalin-fixed paraffin embedded tissue	Inexpensive	Lower specificity than FISH
	Fine-needle aspirates	Faster results than FISH	Difficult to interpret
	Pleural/pericardial effusions	High sensitivity	Results tend to be operator dependent
			False-positives may occur as a result of aberrant ROS1 expression
NGS	Larger tumor specimens	Identifies both known and novel gene fusion partners	Expensive
			Labour intensive
			Requires tissue samples large enough for processing
			Further studies needed to assess and validate different platforms
Derived from Rossi G, Jocollé G, Conti A, et al. Detection of ROS1 rearrangement in non-small cell lung cancer: current and future perspectives. Lung Cancer Targets Ther. 2017;8:45-55; Lin JJ, Shaw AT. Recent advances in targeting ROS1 in lung cancer. J Thorac Oncol. 2017;12(11):1611-1625; Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist. 2013;18(7):865-87			

Table 1: Assays for detecting ROS1 rearrangements.

NSCLC to receive United States Food and Drug Administration (FDA) approval for a targeted therapy, the tyrosine kinase inhibitor (TKI) crizotinib. Treatment with tyrosine kinase inhibitors (TKIs), which target theROS1 kinase domain, is considered the standard of care. TKIs have been shown to have a robust and durable response.

Crizotinib

The American Society of Clinical Oncology (ASCO), NCCN guidelines and HSE National Cancer Control Programme(NCCP) recommend crizotinib as first-line treatment for patients with advanced *ROS1*-positive NSCLC [1,15]. Crizotinib is the first and currently only FDA-approved agent for the treatment of patients with metastatic NSCLC whose tumours contain *ROS1* rearrangements [6,16]. Approval was based on results from the phase 1 PROFILE 1001 study in which an expansion cohort of 50 participants with advanced *ROS1*-rearranged NSCLC experienced an objective response rate (ORR) of 72% with treatment [10]. Within that group, 6% had a complete response, 66% had a partial response, and 18% had stable disease. Median progression-free survival (PFS) was 19.2 months (95% CI, 14.4 to not reached [NR]). Median overall survival (OS), which had not been reached after 12 months, was 85% (95% CI, 72%-93%) at that time. Despite a durable response to treatment, 46% of individuals developed resistance to crizotinib at data cutoff [10].

A larger phase 2 study of 127 East Asian participants with *ROS1*-positive advanced NSCLC found that treatment with crizotinib resulted in an ORR of 71.7% (95% CI, 63.0%-79.3%) [17]. Among treated participants, 13% had a complete response and 58% had a partial response; Wu and colleagues noted that response to treatment did not depend on the number of prior lines of treatment. The disease control rate at week 8 was 88.2% (95% CI, 81.3-93.2). Additionally, median PFS was 15.9 months (95% CI, 12.9-24.0), and median duration of response (DOR) was 19.7 months (95% CI, 14.1 to NR). However, resistance to treatment was observed in 63 individuals (50%) who experienced disease progression at data cutoff [18-21].

The most common adverse effects associated with crizotinib were Visual disturbances, which occurred in a majority (82%) of PROFILE 1001 subjects, typically appeared within the first week of administration and were mild (grade 1) [10,16]. Other notable adverse effects included gastrointestinal issues, edema, renal cysts (which may be complex with cystic invasion occurring beyond the kidney), and transaminitis [16].

Ceritinib

The TKI ceritinib is approved for the treatment of patients with metastatic *ALK*-positive NSCLC and is being explored for participants with advanced *ROS1*-positive NSCLC [22]. In a phase 2 study of ceritinib in 32 Korean participants with *ROS1*-rearranged NSCLC, 30 were crizotinib-naïve and 2 had received previous treatment [23].

Ceritinib is clinically active in crizotinib-naïve *ROS1*-positive NSCLC; however, it has a limited role in the post-crizotinib setting [6,23]. It is not active against the *G2032R*, *D2033N*, *L1951R*, or *S1986Y/F* mutations, although it has been shown to inhibit the *ROS1 L2026M* mutation *in vitro* [6]. Importantly, ceritinib can partially cross the blood-brain barrier and shows some efficacy in patients with brain metastases [24]. The aforementioned Korea-based study also explored treatment response in the 8 individuals with brain metastases (1 crizotinib-treated and 7 crizotinib-naïve) [23]. Disease control was achieved in 5 of the 8 participants (63% [95% CI, 31%-86%]), with 2 participants achieving an objective response that resulted in an intracranial ORR of 25% (95% CI, 7%-59%) [23]. Although the sample size was small and at least 1 individual had previously received radiotherapy to the brain, these efficacy results are consistent with data on ceritinib-treated individuals with *ALK*-positive NSCLC who had brain metastases [24]. The most common adverse effects associated with ceritinib treatment were diarrhea, nausea, and anorexia; 50% of individuals experienced a serious adverse effect with treatment [23]. If off-label ceritinib is initiated in a patient with *ROS1*-positive NSCLC, the preferred dosing regimen is 450 mg orally once daily with food [25].

Entrectinib

Entrectinib is a small-molecule TKI that has been shown to have activity against tumors with *ROS1* rearrangements as well as *ALK* and *NTRK1/2/3* rearrangements [26]. In addition, entrectinib crosses the blood-brain barrier and has clinical activity in the central nervous system (CNS) [6,27]. The FDA has granted a priority review designation for entrectinib for patients with metastatic *ROS1*-positive NSCLC based on an integrated analysis of 3 studies (STARTRK-2, STARTRK-1, and ALKA-372-001) that included data from 53 participants with *ROS1* rearrangements (crizotinib-naïve) [27,28]. Results from the integrated analysis showed that entrectinib shrank tumors in 77.4% of participants with *ROS1*-positive NSCLC. The median DOR was 24.6 months (95% CI, 11.4-34.8), and the median PFS was 19 months (95% CI, 12.2-36.6) [28]. Furthermore, intracranial tumors shrunk in more than one-half of individuals with CNS metastases at baseline (IC ORR, 55%; 95% CI, 31.5-76.9) [28].

Lorlatinib

Lorlatinib, a third-generation TKI, is active against *ROS1* and *ALK* rearrangements [29]. It was rationally designed to penetrate the blood-brain barrier and overcome *ALK*-resistance mutations and was recently approved for the treatment of advanced *ALK*-positive NSCLC in patients whose disease has progressed after a second-generation ALK inhibitor [29,30]. Preclinical studies have shown that lorlatinib retains some potency against the most common *ROS1*-resistance mutation *G2032R* [31]. A phase 2 clinical trial examining lorlatinib in advanced *ALK*- or *ROS1*-positive NSCLC participants (N = 275) found that the *ROS1*-positive cohort (n = 47), which included both crizotinib-naïve and crizotinib-resistant individuals, had an ORR of 36% (95% CI, 23%-52%) [32]. *ROS1*-positive participants with CNS metastases (n = 25) had an intracranial ORR of 56% (95% CI, 35%-76%). Responses to lorlatinib were observed in both the crizotinib-naïve and post-crizotinib groups, but ORR was notably higher in the crizotinib-naïve setting. These findings suggest that lorlatinib activity differs depending on prior crizotinib exposure [33-38]. Of note, a recent molecular analysis suggests that lorlatinib's activity against *ROS1 G2032R* may be limited, as none of the 6 individuals with detectable *ROS1 G2032R* achieved a complete or partial response in the phase 2 study of lorlatinib [39,40].

Conclusion

Crizotinib is currently the only targeted TKI approved for the treatment of advanced *ROS1*-positive NSCLC. Multiple TKIs are being investigated for the treatment of *ROS1*-rearranged NSCLC in both the TKI-naïve and post-TKI setting. There is a continued need to better understand mechanisms of ROS1 resistance and identify therapeutic strategies to best address these mechanisms. Finally, it remains to be seen whether clinical outcomes for patients with advanced *ROS1*-positive NSCLC can be further improved with the optimal sequencing of ROS1-targeted agents.

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