REVIEW ARTICLE

A Catalog of 5’ Fusion Partners in ROS1-Positive NSCLC Circa 2020

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ABSTRACT

ROS1 fusion–positive (ROS1+NSCLC) was discovered in 2007, the same year as the discovery of ALK-positive (ALK+) NSCLC but has trailed ALK+NSCLC in terms of development. There seems to be a differential response to ROS1 inhibitors, which depend on fusion partners (CD74, SLC34A2, or SDC4); thus, knowledge of the fusion partners in ROS1+NSCLC is important. To date (end of February 2020), we have identified 24 unique 5’ fusion partners of ROS1 in ROS1+NSCLC from published literature and congress proceedings. Thus, we published this catalog for easy reference.

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Keywords: ROS1 fusion partner; Next-generation sequencing; ROS1-positive NSCLC

Introduction

ROS1 fusion–positive (ROS1+) NSCLC was discovered in 2007, the same year as ALK fusion–positive (ALK+) NSCLC.1 It constitutes about 2.9% of all adenocarcinomas of the lung.2 The development of ROS1 TKIs has followed the development of ALK TKIs; but to date, there are only two U.S. Food and Drug Administration–approved ROS1 TKIs (crizotinib and entrectinib).3,4 Neel et al.5 reported that different ROS1 fusion partners determine the subcellular localization of the ROS1 fusion variant and the subsequent oncogenic potency of that ROS1 fusion variant. In addition, Li et al.6 suggested that ROS1 fusion partners (CD74-ROS1 versus non–CD74-ROS1) have a differential response to crizotinib, and, more importantly, have a predilection for central nervous system metastasis. Thus, it is important to have a catalog of fusion partners of ROS1 in ROS1+NSCLC.

Methods and Results

We extensively searched publications in PubMed, conference abstracts and presentations, and the cBioPortal for Cancer Genomics website to identify novel ROS1 fusion partners (including noncoding RNAs). We included only 5’ fusion partners that retained the 3’-ROS1 kinase domain. Overall, a total of 24 distinct ROS1 fusion partners were identified in the literature by the end of February 2020 (Table 1). We did not include one case report, in which the ROS1 fusion variant arose as a resistance mechanism to EGFR TKI, but the fusion partner to ROS1 was a 3’ fusion partner (ROS1-ADGRG6). In that ROS1 fusion variant, the ROS1-ADGRG6 fusion

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Table 1. Catalog of Fusion Partners in ROS1-Positive NSCLC

| No. | Fusion Partner | Year Published in Print/Presented | Chromosomal Location | Fusion Breakpoint | Tumor Source | Method of Detection | Variant Frequency in Tumor (%) | References |
|-----|----------------|----------------------------------|----------------------|-------------------|--------------|---------------------|-------------------------------|------------|
| 1   | CD74           | 2007                             | 5q33.1               | (C6, R34)         | FFPE         | 5' RACE RT-PCR      | NR                            |+/NR       |
| 2   | SLC34A2        | 2007                             | 4p15.2               | (S4, R34)         | HCC78 cell line | 5' RACE RT-PCR      | NR                            |+/NR       |
| 3   | EZR            | 2012                             | 6q25.3               | (E10, R34)        | FFPE         | 5' RACE RT-PCR      | NR                            |+/NR       |
| 4   | LRG3           | 2012                             | 12q14.1              | (L16, R35)        | FFPE         | 5' RACE RT-PCR      | NR                            |+/NR       |
| 5   | SDC4           | 2012                             | 20q13.12             | (S2, R32)         | FFPE         | 5' RACE RT-PCR      | NR                            |+/NR       |
| 6   | TPM3           | 2012                             | 1q21.3               | (T8, R35)         | FFPE         | 5' RACE RT-PCR      | NR                            |+/NR       |
| 7   | GOPC (FIG)     | 2012                             | 6q22.1               | NR                | FFPE         | RT-PCR              | NR                            |+/+        |
| 8   | KDREL2         | 2012                             | 7p22.1               | NR                | PPPE         | DNA NGS             | NR                            |NR/NR       |
| 9   | CCDC6          | 2012                             | 10q21.2              | (C6, R34)         | PPPE         | DNA NGS             | NR                            |NR/NR       |
| 10  | LIMA1          | 2012                             | 12q13.12             | NR                | FFPE         | Targeted RNA sequencing | NR                            |+/+        |
| 11  | MSN            | 2012                             | Xq12                 | (M9, R34)         | FFPE         | Targeted RNA sequencing | NR                            |+/+        |
| 12  | CLTC           | 2014                             | 17q23.1              | (C31, R35)        | FFPE         | RNA sequencing      | NR                            |NR/NR      |
| 13  | TMEM106B       | 2015                             | 7p21.3               | (T3, R35)         | FFPE         | DNA NGS             | NR                            |NR/NR       |
| 14  | TPDS2L1        | 2016                             | 6q22.31              | (T3, R33)         | FFPE         | DNA NGS             | NR                            |NR/NR       |
| 15  | SLCE6A17       | 2017                             | 1p13.3               | NR                | FFPE         | NGS                 | NR                            |NR/NR       |
| 16  | CEP72          | 2018                             | 5p15.33              | (C11, R23)        | FFPE         | DNA NGS             | NR                            |NR/NR       |
| 17  | ZCCHC8         | 2018                             | 12q24.31             | NR                | FFPE         | NGS                 | NR                            |NR/NR       |
| 18  | SLMAP          | 2018                             | 3p14.3               | (S7, R35)         | FFPE         | NGS                 | NR                            |NR/NR       |
| 19  | MYOSC          | 2018                             | 15q21.2              | (M2, R35)         | FFPE         | NGS                 | NR                            |NR/NR       |
| 20  | TFG            | 2018                             | 3q12.2               | NR                | FFPE         | NGS                 | 19.3                          |NR/NR       |
| 21  | WNK1           | 2019                             | 12p13.33             | (W25, R34)        | FFPE         | NGS                 | NR                            |NR/NR       |

(continued)
| Year | Chromosomal Breakpoint | Fusion Partner | Response to crizotinib | Method of Detection | Tumor Source | Frequency in Tumor (%) | References |
|------|------------------------|----------------|-----------------------|--------------------|-------------|----------------------|------------|
| 2019 | 7q36.1                 | NR             | NR                    | Plasma             | NGS         | NR/NR                | Dagogo-Jack et al.32 |
| 2019 | 3                      | NR             | NR                    | Plasma             | NGS         | NR/NR                | Dagogo-Jack et al.32 |
| 2020 | 8p12 (R1, R32)         | Response to crizotinib | FFPE                | 23.7               | NR/NR      | Zhang et al.33       |

*Both fusions were detected and treated in the crizotinib phase 2 trial. The ROS1 fusion identified in the 2 reports was likely the same identical fusion variant. One report described the technique of its identification while the other report reported its response to crizotinib in the expand crizotinib phase 1 trial.

**Discussion**

The number of ROS1 fusion partners identified in ROS1+ NSCLC as of February 2020 is approximately 24, which is lower than that reported for ALK+ and RET+ NSCLC.10,11 It is quite surprising, given the fact that ROS1+ NSCLC was discovered in 2007, whereas RET+ NSCLC was discovered only in 2012, although RET fusions have been identified in other solid tumors, especially in thyroid cancer. The ROS1 gene is located on chromosome 6q22.1 and only two fusion partners are located near ROS1 (GOPC, TPD52L1), and one fusion partner, ERZ, is located on 6q25.3. Unlike ALK+ and RET+ NSCLC, only one intergenic rearrangement has been reported in ROS1+ NSCLC (Table 2).

Another unique feature of ROS1+ NSCLC is the high incidence of venous thromboembolic events.12-14 Given the potential role of fusion partners in affecting different oncogenic potencies on the ROS1 fusion variant,5 the potential differential response to crizotinib, and the predilection for central nervous system metastasis,7 identifying ROS1 fusion partners is essential to further advance the science and management of ROS1+ NSCLC. Although five fusion partners (CD74, SLC34A2, SDC4, ERZ, TPM3) made up most of the ROS1+ patients with NSCLC who were enrolled in the entrectinib trials, 23% of the patients diagnosed with ROS1+ NSCLC had unknown fusion partners.4 Thus, it is important for future prospective studies of ROS1 TKIs to identify the fusion partners as much as possible, so that future translational studies can be performed from hypotheses generated from the subgroup analysis of these trials.
Conclusions

1. **ROS1+ NSCLC** is a heterogeneous disease with at least 24 distinct fusion partners identified in the literature up until February 2020; but fewer fusion partners were identified compared with **ALK+** and **RET+ NSCLC**.

2. It is likely that many more fusion partners and intergenic rearrangements will be identified with the ever-increasing adoption of targeted RNA sequencing and whole transcriptome sequencing owing to the increasing demands of identifying rare, actionable fusions, such as **NTRK** and **NRG1** fusions.

3. We recommend clinicians worldwide to continue to report these novel fusions/intergenic rearrangements, with information on exon breakpoints/ fusions, response to ROS1 TKI and allele frequency, and, if possible, whether the tumor is **ROS1**-positive on fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC).

4. In this **ROS1** fusion partner catalog, most of the **ROS1+ NSCLC** did not undergo any FISH or IHC testing. Currently, the companion diagnostic test for **ROS1** rearrangement approved by the U.S. Food and Drug Administration is next-generation sequencing (Oncomine Dx Target test, PMA numberP160045). But given that FISH and IHC are still routinely used to detect **ROS1** fusion, we continue to encourage clinicians when they report novel 5’ **ROS1** fusion partners to describe the FISH or IHC results if they had been performed.

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**Table 2. List of Chromosomal Location of Intergenic Translocations With Potential **ROS1** Fusion Partners***

| No. | Year Published in Print/Presented | Chromosomal Location | Potential Fusion Partner Gene | **RET** Exon Fusion | Response to ALK TKI At the Time of Publication | Method of Detection | Variant Frequency in Tumor | FISH/IHC | Reference
|-----|----------------------------------|----------------------|-------------------------------|-------------------|-----------------------------------------------|-------------------|-------------------------|---------|-------------------|
| 1   | 2019                             | 6q22.1               | **DCBLD1**                    | R35               | NR                                            | FFPE              | DNA NGS                 | NR/ NR  | Xu et al. 34       |

*DCBLD1 intergenic rearrangement - **ROS1** was identified as a potential resistance RTK fusion to osimertinib in an EGFR+ patient with NSCLC (Del 19, T790M) in addition to RP11-56SP22.6-NTRK1 fusion.

FFPE, formalin-fixed paraffin embedded; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NR, not reported; TKI, tyrosine kinase inhibitor.

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