Introduction

RET fusion–positive (RET+) NSCLC was discovered in early 2012, 1-4 5 years after the discovery of ALK and ROS1 fusion–positive NSCLC. There have been prospective studies investigating multikinase inhibitors (MKIs) such as vandetanib, cabozantinib, lenvatinib, sorafenib, and RXDX-105, which revealed modest clinical activity. 5-9 More importantly, differential responses were observed on the basis of the specific fusion partner KIF5B versus non–KIF5B in RET+ NSCLC. The KIF5B–RET variant in NSCLC seems to be more resistant to MKIs than the other dominant CCDC6–RET fusion variant. 6,9 Two highly potent and selective RET tyrosine kinase inhibitors (TKIs), selpercatinib (LIBRETTO-001, NCT03157128) and pralsetinib (ARROW, NCT03037385), 10,11 are undergoing clinical trials for RET+ and RET-mutated tumors. In addition, RET fusion is one of the major receptor tyrosine kinase fusions identified as a resistance mechanism to EGFR TKIs. 12 We undertook this review to catalog the fusion partners identified in literature up to April 2020 for easy reference.

Methods and Results

We searched PubMed publications and conference or congress abstracts and presentations extensively to identify novel RET fusion partners (including noncoding RNAs). We also communicated with authors who had presented posters to obtain lists of novel fusion partners. We included only fusion partners that retained the 3’ RET kinase domain. Overall, a total of 48 distinct RET fusion partners have been identified in literature as of
| No. | Fusion Partner | Year Presented/ Published in Print Numbers | Chromosomal Location | Fusion Breakpoint | Response to RET TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC | References |
|-----|----------------|--------------------------------------------|----------------------|-------------------|-----------------------------------------------|-------------|-------------------|--------------------------------|---------|------------|
| 1   | KIF5B          | 2012                                       | 10p11.22             | (K15, R12) (K16, R12) (K23, R12) | Not treated with RET TKI                        | FFPE        | RNA sequencing     | NR                             | NR/NR  | Ju et al.  |
| 2   | KIF5B          | 2012                                       | 10p11.22             | (K15, R12) (K16, R12) (K23, R12) (K24, R8) | Not treated with RET TKI                        | FFPE        | RT-PCR, Sanger sequencing | NR                             | NR/+   | Kohno et al.  |
| 3   | KIF5B          | 2012                                       | 10p11.22             | (K15, R12) (K16, R12) (K23, R12) (K24, R11) | Not treated with RET TKI                        | FFPE        | RT-PCR, Sanger sequencing | NR                             | NR/NR  | Takeuchi et al.  |
| 4   | CCDC6          | 2012                                       | 10q21.2              | (K15, R12) (K22, R12) | Not treated with RET TKI                        | FFPE        | RT-PCR, Sanger sequencing | NR                             | NR/NR  | Takeuchi et al.  |
| 5   | CCDC6          | 2012                                       | 10q21.2              | (C1, R12) | Not treated with RET TKI                        | Cell line   | RT-PCR            | NR                             | NR/NR  | Matsubara et al.  |
| 6   | NCOA4          | 2012                                       | 10q11.22             | (N6, R12) | Not treated with RET TKI                        | FFPE        | RT-PCR            | NR                             | +/+     | Wang et al.  |
| 7   | TRIM33         | 2013                                       | 1p13.2               | (T14, R12) | Not treated with RET TKI                        | FFPE        | NGS               | NR                             | +/NR    | Drilon et al.  |
| 8   | RUFY2          | 2014                                       | 10q21.3              | (R9, R12) | Not treated with RET TKI                        | FFPE        | Targeted RNA sequencing | NR                             | +/NR    | Zheng et al.  |
| 9   | CUX1           | 2014                                       | 7q22.1               | (C10, R12) | Not treated with RET TKI                        | FFPE        | Anchored multiple PCR, NGS | NR                             | +/NR    | Lira et al.  |
| 10  | KIAA1468/ (RELCH) | 2014                                      | 18q21.33             | (K10, R12) | Not treated with RET TKI                        | FFPE        | RT-PCT            | NR                             | NR/NR  | Nakaoku et al.  |
| 11  | KIAA1468/ (RELCH) | 2019                                      | 18q21.33             | NR               | Treated with selpercatinib                       | FFPE or plasma | NGS               | NR                             | NR/NR  | Drilon et al.  |
| 12  | RELCH          | 2020                                       | 18q21.33             | (R10, R12) | Not treated with RET TKI                        | FFPE        | NGS               | NR                             | +/NR    | Jiang et al.  |
| 13  | MPRIP          | 2016                                       | 17p11.2              | (M19, R12) | Not treated with RET TKI                        | FFPE        | Targeted RNA sequencing | NR                             | NR/NR  | Fang et al.  |
| 14  | CLIP1          | 2016                                       | 12q24.31             | NR               | PR to cabozantinib                               | FFPE        | NGS               | NR                             | NR/NR  | Drilon et al.  |
| 15  | ERC1           | 2016                                       | 12p13.33             | NR               | SD to cabozantinib                               | FFPE        | NGS               | NR                             | NR/NR  | Drilon et al.  |
| 16  | KIAA1217       | 2016                                       | 10p12.2-p12.1        | (K11, R10) | Not treated with RET TKI                        | FFPE        | NGS               | NR                             | +/NR    | Lee et al.  |
| 17  | MYO5C          | 2016                                       | 15q21.2              | (M25, R12) | SD to vandetanib                                | FFPE        | NGS               | NR                             | +/NR    | Lee et al.  |

(continued)
| No. | Fusion Partner | Year Presented/Published in Print with Page Numbers | Chromosomal Location | Fusion Breakpoint | Response to RET TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC | References |
|----|----------------|--------------------------------------------------|---------------------|------------------|-----------------------------------------------|-------------|-------------------|--------------------------|---------|------------|
| 13 | EPHA5          | 2017                                             | 4q13.1-q13.2        | NR               | Response to RET TKI                           | FFPE        | NGS               | NR                       | NR/NR               | Gautschi et al. [24] |
| 14 | PICALM         | 2017                                             | 11q14.2             | NR               | Not treated with RET TKI                      | FFPE        | NGS               | NR                       | NR/NR               | Gautschi et al. [24] |
| 15 | FRMDA4 (KIAA1294) | 2017                                             | 10p13               | (F12, R12)       | Not treated with RET TKI                      | FFPE        | NGS               | NR                       | +/NR                | Velcheti et al. [25] |
| 16 | RASSF4         | 2017                                             | 10q11.21            | (R3, R12)        | Not treated with RET TKI                      | FFPE        | NGS               | NR                       | NR/NR               | Zehir et al. [26]   |
| 17 | KIF13A         | 2018                                             | 6p22.3              | (K18, R12)       | Not treated with RET TKI                      | FFPE        | NGS               | NR                       | NR/NR               | Zhang et al. [27]   |
| 18 | WAC            | 2018                                             | 10p12.1-p11.2       | (W3, R12)        | Not treated with RET TKI                      | FFPE        | NGS               | NR                       | NR/NR               | Velcheti et al. [28] |
| 19 | TBC1D32 (C6orf170) | 2019                                             | 6q22.31             | (T9, R12)        | Not treated with RET TKI                      | FFPE        | NGS               | NR                       | NR/NR               | Peng et al. [29]    |
| 20 | EML4           | 2019                                             | 2p21                | NR               | PR to RXDX-105                                | FFPE        | NGS               | NR                       | NR/NR               | Drilon et al. [9]   |
| 21 | PARD3          | 2019                                             | 10p11.22-11.21      | NR               | PR to RXDX-105                                | FFPE        | NGS               | NR                       | NR/NR               | Drilon et al. [9]   |
| 22 | ARHGAP12       | 2019                                             | 10p11.22            | NR               | Treated with selpercatinib                    | FFPE or plasma | NGS               | NR                       | NR/NR               | Drilon et al. [20] |
| 23 | CCDC88C        | 2019                                             | 14q32.11-32.12      | NR               | Treated with selpercatinib                    | FFPE or plasma | NGS               | NR                       | NR/NR               | Drilon et al. [20] |
| 24 | DOCK1b         | 2019                                             | 10q26.2             | NR               | Treated with selpercatinib                    | FFPE or plasma | NGS               | NR                       | NR/NR               | Drilon et al. [20] |
| 25 | RBPMSb         | 2019                                             | 8p12                | NR               | Treated with selpercatinib                    | FFPE or plasma | NGS               | NR                       | NR/NR               | Drilon et al. [20] |
| 26 | PRKAR1A        | 2019                                             | 17q24.2             | NR               | Treated with selpercatinib                    | FFPE or plasma | NGS               | NR                       | NR/NR               | Drilon et al. [20] |
| 27 | ADD3           | 2019                                             | 10q25.1-q25.2       | (A1, R12)        | Not treated with selpercatinib               | FFPE or plasma | NGS               | NR                       | NR/NR               | Zhang et al. [31]   |
| 28 | ANKS1B         | 2019                                             | 12q23.1             | (A1, R12)        | Not treated with selpercatinib               | FFPE or plasma | NGS               | NR                       | NR/NR               | Zhang et al. [31]   |
| 29 | CCDC186        | 2019                                             | 10q25.3             | (C10, R12)       | SD to combination of cabozantinib and osimertinib | FFPE or plasma | NGS               | NR                       | NR/NR               | Zhang et al. [31]   |
| 30 | CCNYL2b        | 2019                                             | 10q11.21            | (C6, R16)        | SD to combination of cabozantinib and osimertinib | FFPE or plasma | NGS               | NR                       | NR/NR               | Zhang et al. [31]   |
| 31 | PCM1           | 2019                                             | 8p22                | (P29, R12)       | Not treated with selpercatinib               | FFPE or plasma | NGS               | NR                       | NR/NR               | Zhang et al. [31]   |
| 32 | PRKG1          | 2019                                             | 10q11.23-21.1       | (P7, R12)        | Not treated with selpercatinib               | FFPE or plasma | NGS               | NR                       | NR/NR               | Zhang et al. [31]   |
| No. | Fusion Partner | Year Presented/Published With Page Numbers | Chromosomal Location | Fusion Breakpoint | Response to RET TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC | References |
|-----|----------------|--------------------------------------------|----------------------|------------------|-----------------------------------------------|-------------|-------------------|-----------------------------|---------|------------|
| 33  | PTPRK          | 2019 6q22.33 (P3, R12)                     | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Zhang et al. 31            |
| 34  | SIRT1          | 2019 10q21.3 (S8, R12)                     | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Zhang et al. 31            |
| 35  | SORBS1         | 2019 10q24.1 (S8, R12)                     | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Zhang et al. 31            |
| 36  | TSSK4          | 2019 14q1 (T1, R12)                        | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Zhang et al. 31            |
| 37  | TRIM24         | 2019 7q33-q34 NR                           | Treated with selpercatinib | FFPE or plasma | NGS                                           | NR          | NR/NR            | Drilon et al. 20           |
| 38  | CDC3           | 2019 7q33-q34 NR                           | NR                   | Plasma           | NGS                                           | NR          | NR/NR            | Rich et al. 32             |
| 39  | CTNNA3         | 2019 10p13 NR                              | NR                   | FFPE             | NGS                                           | NR          | NR/NR            | Liu et al. 30              |
| 40  | DYDC1          | 2019 10q23.1 NR                            | NR                   | FFPE             | NGS                                           | NR          | NR/NR            | Liu et al. 30              |
| 41  | EML6           | 2019 10q23.1 NR                            | NR                   | FFPE             | NGS                                           | NR          | NR/NR            | Liu et al. 30              |
| 42  | PRKQ           | 2019 10q15.1 NR                            | NR                   | FFPE             | NGS                                           | NR          | NR/NR            | Liu et al. 30              |
| 43  | PRPF18         | 2019 10q13 NR                              | NR                   | FFPE             | NGS                                           | NR          | NR/NR            | Liu et al. 30              |
| 44  | LSM14A         | 2020 19q13.11 (L9, R20)                    | NR                   | FFPE             | NGS                                           | NR          | +/NR             | Lv et al. 33                |
| 45  | GPRC5B         | 2020 16p12.3 NR                            | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Lu et al. 34                |
| 46  | GPR139         | 2020 16p12.3 NR                            | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Lu et al. 34                |
| 47  | ANK3           | 2020 10q21.2 NR                            | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Lu et al. 34                |
| 48  | EPC1           | 2020 10p11.22 NR                           | NR                   | FFPE or plasma   | NGS                                           | NR          | NR/NR            | Lu et al. 34                |

*aKIAA1468 is the same as RELCH.
*DOCK1-RET and RBPS5-RET occurred in the same tumor.
*CCNYL2-RET as resistance to osimertinib (EGFR L858R).
*TRIM24-RET as resistance to EGFR del 19.
*GPRC5B and GPR139 were detected as dual fusions in one case.
*EPC1 was detected as dual fusions in one case with the other fusion partner being KIF5B.

FFPE: formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NR: not reported; PR: partial response; RT-PCR, reverse transcriptase polymerase chain reaction; SD: stable disease; TKI, tyrosine kinase inhibitor.
| No. | Year Presented/Published in Print | Chromosomal Location | Potential Fusion Partner Gene | RET Exon Fusion | Response to RET TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC | References |
|-----|---------------------------------|----------------------|------------------------------|-----------------|-----------------------------------------------|-------------|-------------------|-----------------------------|--------|-----------|
| 1   | 2019                            | 10p14-p13            | CDC123<sup>a</sup>           | R12             | Treated with capmatinib, unknown response     | FFPE        | NGS               | NR                          | NR/NR | Xu et al.  
| 2   | 2019                            | 10q11.21             | ALOX5                        | R11             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 3   | 2019                            | 10q21.2              | ANK3                         | R11             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 4   | 2019                            | 10q25.2              | DUSP5                        | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 5   | 2019                            | 10p13                | FAM188A (MINDY3)             | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 6   | 2019                            | 10p15.1              | IL2RA                        | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 7   | 2019                            | 10q23.31             | LOC101926942 (LINC02653)     | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 8   | 2019                            | 10p12.1              | LOC105376468                 | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 9   | 2019                            | 10q11.21             | LOC105378269                 | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 10  | 2019                            | 5p12                 | MRPS30                       | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 11  | 2019                            | 10p11.22             | NRP1                         | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 12  | 2019                            | 16q23.2              | PRCA-T47 (ARLNC1)           | R11             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 13  | 2019                            | 10p13                | PTER                         | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 14  | 2019                            | 10q21.1              | UBE2D1                       | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 15  | 2019                            | 19p12                | ZNF43                        | R12             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  
| 16  | 2019                            | 10p11.23             | ZNF438                       | R11             | NR                                            | FFPE or plasma | NGS               | NR                          | NR/NR | Zhang et al.  

<sup>a</sup>RET fusion as potential resistance to osimertinib for EGFR (del 19, T790M, C797G/S).

FFPE: formalin-fixed paraffin-embedded; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NR, not reported; TKI, tyrosine kinase inhibitor.
April 2020 (Table 1). The RET gene is located on chromosomal 10q11.21. A total of 11 fusion partners are located on the long arm of chromosome 10 (10q), and three of the fusion partners are located around 10q11.1. Given the discovery of RET+/ NSCLC occurred about 5 years after that of ALK+/ and ROS1+/ NSCLC, many of these novel RET fusion variants have not been treated with either MKIs or highly selective RET TKIs. Multiple intergenic rearrangements, mostly to exon 12 of RET, have also been identified and listed separately in Table 2.31,35 To date, none of these intergenic RET rearrangements have been reported to respond to RET TKIs; thus, the significance of these intergenic rearrangements remains to be determined, including whether functional fusion RNAs can be transcribed from these intergenic rearrangements.

Discussion

The number of RET fusion partners identified in RET+/ NSCLC as of April 2020 is about 48, which is fewer than the number of ALK fusion partners identified. Again, we expect that more fusion partners in RET+/ NSCLC will be identified with the continual use of next-generation sequencing (NGS), including whole-transcriptome sequencing as the diagnostic platform migrates to exhaustively identify all the actionable driver mutations in NSCLC, particularly RET fusions, given the impending approval of selpercatinib and pralsetinib. Furthermore, not all the fusion partners identified in other tumor types such as thyroid cancer have been identified in RET+/ NSCLC.26 Currently, only the KIF5B fusion partner in KIF5B-RET has been reported to confer poor response to MKIs,6,7 because the kinesin domain of KIF5B interacts with the kinase domain of RET to create a signaling hub rendering resistance to RET inhibition alone.38 With this catalog of 5’ fusion partners in RET+/ NSCLC, we hope to increase awareness of the various fusion partners in RET+/ NSCLC and stimulate further translational research.

Concluding Perspectives

1. RET+/ NSCLC is a heterogeneous disease with at least 48 distinct fusion partners identified in the literature as of April 2020.

2. With the anticipated approval of selpercatinib and pralsetinib for RET+/ NSCLC, many more fusion partners and intergenic rearrangements will likely be identified with the ever-increasing adoption of targeted RNA sequencing and whole-transcriptome sequencing because of the need to identify rare actionable fusions such as NTRK and NRG1 fusions in general, and also RET fusions in particular.

3. RET fusions are also common receptor tyrosine kinase fusions identified as acquired resistance to EGFR TKIs. Two novel fusion partners (CCNYL2 and TRIM24) were identified as resistance mechanisms to EGFR TKI in EGFR+/ NSCLC.

4. The functional significance of intergenic rearrangements remains to be determined. In one study, intergenic rearrangements accounted for 7.7% of the RET fusions identified. However, it is yet to be determined whether these intergenic rearrangements are transcribed into functional RET RNA fusions.

5. We recommend that clinicians from all over the world continue to report these novel fusions and intergenic rearrangements with information on the following: (1) exon or fusion breakpoints; (2) response to RET TKIs; (3) allele frequency; and (4) whether the tumor is RET-positive on fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC), if possible. Although RET TKIs are being developed after ALK and ROS1 TKIs, RET detection by IHC and FISH has not gone through health agency regulations given that NGS is the primary companion diagnostic platform used to detect RET fusions; thus, not much is known about the sensitivity and specificity as well as the positive and negative predictive values of these two testing modalities. We do realize that the uptake and utility of IHC and FISH for RET detection may be limited when NGS is likely the first approved companion diagnostic platform for RET fusions and increasing uptake to identify even rarer actionable driver alterations such as NRG fusions.

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