Catalog of 5’ Fusion Partners in ALK-positive NSCLC Circa 2020

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Received 4 February 2020; accepted 5 February 2020
Available online - 19 February 2020

ABSTRACT

Since the discovery of anaplastic lymphoma kinase fusion-positive (ALK+) NSCLC in 2007, the methods to detect ALK+ NSCLC have evolved and expanded from fluorescence in situ hybridization and immunohistochemistry to next-generation DNA sequencing, targeted RNA sequencing, and whole transcriptome sequencing. As such, the deep sequencing methods have resulted in the expansion of distinct fusion partners identified in ALK+ NSCLC to 90 (one variant PLEKHM2-ALK is found in small cell lung cancer but included in this catalog) by the end of January 2020; about 65 of them (since 2018) and most of the recent novel fusion partners were reported from China. Thirty-four of the distinct fusion partners are located on the short arm of chromosome 2; 28 of these 34 fusion partners are located on 2p21-25, in which ALK is located on 2p23.2-p23.1. Many of these new ALK+ NSCLC fusion variants have responded to ALK tyrosine kinase inhibitors (TKIs). Several of these novel ALK fusion variants were identified as being resistant to EGFR TKIs or as dual 3’ALK fusions. In addition, at least 28 intergenic ALK rearrangements have also been reported, with three of them reported as responding to crizotinib. This review aims to serve as a central source of reference for clinicians and scientists. We aim to update and improve the list going forward.

Keywords: ALK fusion partners; Next-generation sequencing; ALK+ NSCLC; Whole transcriptome sequencing

Introduction

Since the discovery of anaplastic lymphoma kinase fusion-positive (ALK+) NSCLC (EML4-ALK, TPF-ALK) in 2007, there has been a rapid development of ALK tyrosine kinase inhibitors (TKIs) to treat ALK+ NSCLC with five ALK TKIs approved in the United States (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib) by 2018. At the same time, the detection of ALK+ NSCLC has expanded and shifted from the original methods of fluorescence in situ hybridization and immunohistochemistry (IHC) to next-generation sequencing (NGS), targeted RNA sequencing, and even whole transcriptome sequencing being offered by commercial sequencing companies. Targeted RNA sequencing and whole transcriptome sequencing have been used to supplement...
| No. | Fusion Partner | Year Published in Print/Presented | Chromosomal Location | Fusion Breakpoint | Response to ALK TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC | References |
|-----|----------------|---------------------------------|---------------------|------------------|-----------------------------------------------|-------------|-------------------|-------------------------|----------|------------|
| 1   | EML4           | 2007                            | 2p21                | (E13, A21)       | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Soda, 2007 |
|     |                | 2007                            | 2p21                | (E20, A21)       | Not treated with ALK TKI                     | Cell line/Tumor | 5’RACE PCR DNA sequencing | NR          | ND/ND    | Rikova, 2007 |
| 2   | TFG            | 2007                            | 3q12.2              | (T3, A20)        | Not treated with ALK TKI                     | Tumor       | 5’RACE PCR DNA sequencing | PCR/Sanger sequencing | NR      | ND/ND    | Soda, 2007 |
|     |                | 2007                            | 3q12.2              | NR               | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Rikova, 2007 |
| 3   | KIF5B          | 2009                            | 10p11.22            | (K24, A20)       | Not treated with ALK TKI                     | Tumor       | RACE PCR DNA sequencing | NR          | ND/ND    | Takeuchi, 2009 |
|     |                | 2011                            | 10p11.22            | (K15, A20)       | Not treated with ALK TKI                     | Tumor       | RACE PCR DNA sequencing | NR          | ND/ND    | Won, 2011 |
|     |                | 2012                            | 10p11.22            | (K17, A20)       | Not treated with ALK TKI                     | Tumor       | RACE PCR DNA sequencing | NR          | ND/ND    | Takeuchi, 2012 |
| 4   | KLC1           | 2012                            | 14q32.33            | (K9, A20)        | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Togashi, 2012 |
| 5   | STRN           | 2013                            | 7q11.23             | (H2, A20)        | Not treated with ALK TKI                     | Tumor       | RACE PCR DNA sequencing | NR          | ND/ND    | Majewski, 2013 |
|     |                | 2017                            | 7q11.23             | (H21, A20)       | Not treated with ALK TKI                     | Tumor       | RNA sequencing         | NR          | ND/ND    | Yang, 2017 |
|     |                | 2019                            | 7q11.23             | (H30, A20)       | Not treated with ALK TKI                     | Tumor       | DNA NGS               | NR/ND       | ND/ND    | Nakanishi, 2017 |
| 6   | HIP1           | 2014                            | 1q31.1              | (T15, A20)       | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ouyang, 2014 |
|     |                | 2015                            | 1q31.1              | (T15, A20)       | Not treated with ALK TKI                     | Tumor       | RACE PCR DNA sequencing | NR          | ND/ND    | Ouyang, 2015 |
|     |                | 2016                            | 1q31.1              | (T15, A20)       | Not treated with ALK TKI                     | Tumor       | DNA NGS               | NR/ND       | ND/ND    | Ouyang, 2016 |
| 7   | TPR            | 2016                            | 17q23.1             | (C31, A20)       | Unknown setting not treated with ALK TKI     | Tumor       | Targeted RNA sequencing | NR          | ND/ND    | Ali, 2016 |
| 8   | BIRC6          | 2016                            | 17q24.2             | (P5, A20)        | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 9   | DCTN1          | 2016                            | 2p21                | (P1, A20)        | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 10  | SQSTM1         | 2016                            | 5q35.3              | (S5, A20)        | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 11  | SOCS5          | 2016                            | 2p21                | NR               | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 12  | SEC31A         | 2016                            | 4q21.22             | (S21, A20)       | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 13  | CRTC           | 2017                            | 17q24.2             | (P5, A20)        | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 14  | PPM1B          | 2017                            | 2p21                | (P1, A20)        | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 15  | EIF2AK3        | 2017                            | 2p11.2              | (E2, A20)        | PR to crizotinib                            | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Ali, 2016 |
| 16  | CRIM1          | 2017                            | 2p22.2              | NR               | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Tan, 2016 |
| 17  | CEBPZ          | 2017                            | 2p22.2              | (C2, A20)        | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Li, 2017 |
|     | CEBPZ          | 2019                            | 2p22.2              | NR               | Not treated with ALK TKI                     | Tumor       | PCR/Sanger sequencing | NR          | ND/ND    | Xu, 2019 |
| 18  | PICALM         | 2017                            | 11q14.2             | (P19, A20)       | Not treated with ALK TKI                     | Tumor       | Targeted RNA sequencing | NR          | ND/ND    | Li, 2017 |
| 19  | CLIP1          | 2017                            | 12q24.31            | (C22, A20)       | PR to crizotinib                            | Tumor       | Targeted RNA sequencing | NR          | ND/ND    | Vendrell, 2017 |

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|-----|----------------|----------------------------------|----------------------|------------------|-----------------------------------------------|-------------|-------------------|-----------------------------|----------------------|
| 21  | BCL11A         | 2017 2p16.1 (B4, A20)            | PR to crizotinib     | DNA and RNA NGS  | NR 54.2% (PPFE) 14.9% (plasma) | Tumor and plasma | DNA NGS            | ND/ND                      | Tian, 2017           |
|     | BCL11Ac        | 2019 2p16.1 (B2, A18)            |                       |                  |                  |             |                   | ND/ND                      | Qin 2019             |
| 22  | GCC2           | 2017 2q12.3 (G12, A20)          | NR Adjunct setting, not treated with ALK TKI | Tumor RT-PCR, NGS | NR ++/+     | Tumor and plasma | RT-PCR, sanger sequencing | Noh, 2017            |
|     |                | 2018 2q12.3 (G18, A20)          | PR to crizotinib and then ceritinib | Tumor RT-PCR, NGS | NR ++/+     | Tumor and plasma | RT-PCR, sanger sequencing | Vendrell, 2017       |
| 23  | LMO7           | 2017 13q22.2 (L15, A20)         | NR                   | Tumor Targeted RNA sequencing | NR         | Tumor and plasma | RT-PCR, sanger sequencing | Noh, 2017            |
| 24  | PHACTR1        | 2017 6p24.1 (P7, A20)           | No with crizotinib, SD with pemetrexed | Tumor NGS       | ~7.5%/-/- | Tumor and plasma | RT-PCR, sanger sequencing | Jiang, 2018          |
| 25  | CMTR1          | 2018 6p21.2 (C2, A20)           | PR to alectinib      | Tumor NGS        | NR ++/+     | Tumor and plasma | RT-PCR, sanger sequencing | Du, 2018             |
| 26  | VIT            | 2018 2p22.2 (V7, A20)           | Extracranial PR but intracranial progression to crizotinib | Tumor NGS       | 23.7%/ND  | Tumor and plasma | RT-PCR, sanger sequencing | Yin, 2018            |
| 27  | DYSF           | 2018 2p13.2 (P15, A20)          | Extracranial PR but intracranial progression to crizotinib | Tumor NGS       | 15.2%/ND  | Tumor and plasma | RT-PCR, sanger sequencing | Yin, 2018            |
| 28  | ITGAV          | 2018 2q32.1 (P15, A20)          | Extracranial PR but intracranial progression to crizotinib | Tumor NGS       | 11%/ND    | Tumor and plasma | RT-PCR, sanger sequencing | Zhang, 2018          |
| 29  | PLEKHA9        | 2018 11p15.2-p15.1 (P26, A19)   | PR to alectinib + osimertinib | Plasma NGS      | ND/ND      | Plasma and RNA NGS | RT-PCR, sanger sequencing | Schrock, 2018        |
| 30  | CUX1           | 2018 7q22.1 (C8, A20)           | PR to crizotinib     | Tumor NGS        | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Zhang, 2018          |
| 31  | VKORC1L1       | 2018 7q11.21 (V1, A20)          | PR with crizotinib and alectinib | Plasma NGS      | ND/ND      | Plasma and RNA NGS | RT-PCR, sanger sequencing | Zhu, 2018            |
| 32  | FBX036         | 2018 2q36.3 (P15, A19)          | PR to crizotinib     | Tumor NGS        | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Xu, 2018             |
| 33  | SPTBN1         | 2018 2p16.2 (P1, A20)           | PR to crizotinib     | Tumor NGS        | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Ramalingam, 2018     |
| 34  | EML6           | 2018 2p16.1 (E1, A20)           | PR to crizotinib     | Tumor NGS        | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Lin, 2018            |
| 35  | FBX011         | 2018 2p16.3 (F1, A20)           | PR to crizotinib     | Tumor NGS        | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Lin, 2018            |
| 36  | CLIP4          | 2018 2p23.2 (C7, A20)           | PR to crizotinib     | Tumor NGS        | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Zhao, 2018           |
| 37  | CAMKMT         | 2018 2p21 (C3, A20)             | Not treated with ALK TKI | Tumor NGS       | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Hu, 2019             |
| 38  | NOCA1          | 2018 2p23.3 (P32, A20)          | PR to crizotinib, PFS > 18 months | Tumor NGS       | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Cao, 2019            |
| 39  | MYT1L          | 2019 2p25.3 (M14, A20)          | PR on crizotinib, PD on ceritinib and alectinib | Tumor NGS       | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Tsou, 2019           |
| 40  | SRBD1          | 2019 2p21 (S20, A20)            | Not treated with ALK TKI | Tumor NGS       | 2.6%/ND   | Tumor and plasma | RT-PCR, sanger sequencing | Hou, 2019            |
| 41  | SRD5A2         | 2019 2p23.1 (S1, A20)           | Not treated with ALK TKI | Tumor NGS       | ND/ND      | Tumor and plasma | RT-PCR, sanger sequencing | Zhao, 2019           |

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| No. | Fusion Partner | Year Published in Print/Presented | Chromosomal Location | Fusion Breakpoint | Response to ALK TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC | References |
|-----|----------------|----------------------------------|----------------------|-------------------|-----------------------------------------------|-------------|---------------------|----------------------------|--------|------------|
| 42  | NYAP2 (KIAA 1486) | 2019 | 2q36.3 | (N3, A20) | NR | Tumor | NGS | NR | ND/- | Zhao, 2019 |
| 43  | MPPIP         | 2019 | 17p11.2 | (M21, A20) | PR to crizotinib | Tumor | RNA sequencing | NR | +/+ | Fan, 2019 |
| 44  | ADAM17        | 2019 | 2p25.1 | (A4, A20) | PR to alectinib | Plasma | DNA NGS | 3.68% | NR/NR | Supplee, 2019 |
| 45  | ALK           | 2019 | 2p23.2-p23.1 | (A6, A20) | NR | Plasma | DNA NGS | 26.63% | NR/NR | Supplee, 2019 |
| 46  | LPIN1         | 2019 | 2p25.1 | NR | Response to crizotinib + erlotinib | Tumor | NR | NR | NR/NR | Supplee 2019 |
| 47  | WDPCP         | 2019 | 2p15 | (W17, A20) | PR to crizotinib | Tumor | DNA NGS | 52.6% | +/+ | He, 2019 |
| 48  | CEPP5         | 2019 | 10q23.3 | (C3, A20) | NR | Tumor | DNA NGS | NR | NR/NR | Couëtoux du Tertr, 2019 |
| 49  | ERC1          | 2019 | 12p13.33 | (E15, A20) | NR | Tumor | DNA NGS | NR | NR/NR | Couëtoux du Tertr, 2019 |
|     | 2019 | 12p13.33 | NR | NR | Tumor / plasma | DNA NGS | NR | NR/NR | Zhou, 2019 |
| 50  | SLC16A7       | 2019 | 12q14.1 | (S1, A20) | PR to crizotinib | Tumor | DNA NGS | NR | NR/NR | Couëtoux du Tertr, 2019 |
| 51  | TNIP2         | 2019 | 4p16.3 | (T5, A20) | PR to crizotinib | Tumor / plasma | DNA NGS | 0.1% (plasma) | ND/+ | Feng, 2019 |
|     |               | 2019 | 4p16.3 | (T5, A20) | PR to crizotinib | Tumor / plasma | DNA NGS | 3.3% (tumor) | ND/+ | Feng, 2019 |
| 52  | ATAD2B        | 2019 | 2p24.1-p23.3 | (A1, A20) | Treated with crizotinib | Tumor | DNA NGS | NR | ND/+ | Bai, 2019 |
| 53  | SLMAP         | 2019 | 3p14.3 | (S12, A20) | Unknown, adjuvant treatment with crizotinib | Tumor | Anchored Multiplex RNA sequencing | NR | ++/+ | Paga, 2019 |
| 54  | FBN1          | 2019 | 15q21.1 | NR | NR | Tumor / plasma | DNA NGS | NR | NR/NR | Zhou, 2019 |
| 55  | SWAP70        | 2019 | 11p15.4 | NR | NR | Tumor / plasma | DNA NGS | NR | NR/NR | Zhou, 2019 |
| 56  | TCF12         | 2019 | 15q21.3 | NR | NR | Tumor / plasma | DNA NGS | NR | NR/NR | Zhou, 2019 |
| 57  | TRIM66        | 2019 | 11p15.4 | NR | NR | Tumor / plasma | DNA NGS | NR | NR/NR | Zhou, 2019 |
| 58  | WNK3          | 2019 | Xp11.22 | NR | NR | Tumor / plasma | DNA NGS | NR | NR/NR | Zhou, 2019 |
| 59  | AKAP8L        | 2019 | 19p13.12 | NR | ensartinib | Tumor / plasma | DNA NGS | NR | NR/NR | Horn, 2019 |
| 60  | SPECC1L       | 2019 | 22q11.23 | (S9, A20) | Not treated with ALK TKI | Tumor | DNA NGS | NR | NR/NR | Pan, 2019 |
| 61  | PRKCB         | 2019 | 16p12.2-p12.1 | (P2, A19) | PR to crizotinib, disappearance of PRKCB-ALK fusion variant | Tumor and plasma | NGS | 2.6% (tumor) | NR/NR | Luo, 2019 |
|     |               |       |       |       |       |       |       | 0.8% (plasma) |       |       | |

References:

- Zhao, 2019
- Fan, 2019
- Supplee, 2019
- Supplee, 2019
- He, 2019
- Couëtoux du Tertr, 2019
- Zhou, 2019
- Feng, 2019
- Bai, 2019
- Paga, 2019
- Zhou, 2019
- Zhou, 2019
- Zhou, 2019
- Zhou, 2019
- Horn, 2019
- Pan, 2019
- Luo, 2019

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|-----|----------------|----------------------------------|----------------------|-------------------|-----------------------------------------------|-------------|-------------------|--------------------------|---------|------------|
| 62  | CDK15          | 2019                             | 2q33.1               | (C10, A19)        | NR                                            | Tumor       | DNA NGS           | NR/NR                  | NR/NR  | Wen, 2019  |
| 63  | LCLAT1         | 2019                             | 2p23.1               | NR                | NR                                            | Tumor       | DNA NGS           | NR/NR                  | NR/NR  | Wen, 2019  |
| 64  | YAP1           | 2019                             | 11q22.1              | NR                | NR                                            | Tumor       | DNANGS           | NR/NR                  | NR/NR  | Wen, 2019  |
| 65  | PLEKHM2 (SCLC) | 2020                             | 1p36.21              | (P7, A20)         | SD to crizotinib and brigatinib              | Tumor       | NGS               | ND/+                   | ND/NR  | Li, 2020   |
| 66  | DCHS1          | 2020                             | 11p15.4              | NR                | PR or SD to ensartinib                       | Tumor       | NGS               | NR/NR                  | NR/NR  | Yang, 2020 |
| 67  | PPFIBP1        | 2020                             | 12p11.23-11.22       | NR                | PR or SD to ensartinib                       | Tumor       | NGS               | NR/NR                  | NR/NR  | Yang, 2020 |
| 68  | ATP13A4        | 2020                             | 3q29                 | (A9, A19)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 69  | C12orf75       | 2020                             | 12q23.3              | (C1, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 70  | EPAS1          | 2020                             | 2p21                 | (E1, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 71  | FAM179A (TOGARAM2) | 2020                   | 2p23.2              | (F1, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 72  | FUT8           | 2020                             | 14q23.3              | (F3, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 73  | LMD1           | 2020                             | 3p21.31              | (L2, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 74  | LINC00327      | 2020                             | 13q12.12             | (L2, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 75  | LOC349160      | 2020                             | 7q33                 | (L1, A20)         | SD to crizotinib                             | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 76  | LYPD1          | 2020                             | 2q21.2               | (L3, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 77  | RBBM20         | 2020                             | 10q25.2              | (R1, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 78  | TACR1          | 2020                             | 2p12                 | (T1, A20)         | PR to crizotinib                             | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 79  | TANC1          | 2020                             | 2q4.2                | (T3, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 80  | TTC27          | 2020                             | 2p22.3               | (T12, A20)        | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 81  | TUBBB          | 2020                             | 6p21.33              | (T3, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 82  | SMPD4          | 2020                             | 2q21.1               | (S1, A20)         | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 83  | SORCS1         | 2020                             | 10q25.1              | (S10, A20)        | NR                                            | Tumor       | NGS               | NR/NR                  | NR/NR  | Tian, 2020 |
| 84  | LINC00211      | 2020                             | 2p22.2               | (L2, A20)         | PR with crizotinib and alectinib, SD with lorlatinib | CSF        | NGS               | 33.2%                  | ND/+   | Li, 2020   |
| 85  | SOS1           | 2020                             | 2p22.1               | (S2, A20)         | PR to crizotinib                             | FFPE       | NGS               | ND/ND                  | ND/ND  | Chen, 2020 |
| 86  | C9orf3         | 2020                             | 9q22.32              | (C12, A20)        | NR                                            | FFPE       | NGS               | 22.6%                  | ND/+   | Zhang, 2020|
| 87  | CYBRD1         | 2020                             | 2q31.1               | (C21, A20)        | NR                                            | FFPE       | NGS               | 12.5%                  | ND/NR  | Zhang, 2020|
| 88  | MTAP            | 2020                             | 2p21                 | (M6, A20)         | SD with crizotinib, no response to alectinib  | FFPE       | NGS               | 15.3%                  | ND/NR  | Zhang, 2020|
| 89  | THADA          | 2020                             | 2p21                 | (T25, A20)        | SD to crizotinib, PR to ceritinib             | Plasma     | NGS               | 0.3%                   | ND/NR  | Zhang, 2020|

(continued)
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|---------------|----------------------------------|----------------------|------------------|---------------------------------------------|-------------|---------------------|---------------------------|----------|---------------------|
| TSPYL6        | 2020                             | 2p16.2                | (T6, A20)        | PR to crizotinib, SD to alectinib           | FFPE        | NGS                 | 8.5%                      | ND/NR   | Zhang, 2020        |
| WDR37         | 2020                             | 10p15.3               | (W6, A20)        | PR to crizotinib                           | FFPE        | NGS                 | 30.2%                     | ND/NR   | Zhang, 2020        |
| PLEKHH2       | 2020                             | 2p21                  | (P6, A20)        | PR to alectinib                            | FFPE        | Targeted RNA sequencing | NR           | ND/NR   | M. Nagasaka, written communication, 2020 |

aThe earliest detected ALK fusion partners were not treated with crizotinib at the time of publication; but all of them have been shown to respond to ALK TKIs. The column entry is for the later discovery of ALK fusion partners.

The first report(s) are cited except when response information from ALK TKIs are from later reports on some of the rare fusion partners, or if the fusion is identified as a resistance mechanism to EGFR TKI.

bALK fusions identified as resistance to EGFR TKIs.

cDual fusion with EML4-ALK (E18, A20).

dDual fusions (EML6 and FBX011) together.

eDual fusion (ERC1 and SLC16A7) together.

fDual fusion with EML4-ALK (E6, A20).

gDual fusion with EML4-ALK (E7, A18).

+, positive; -, negative; ALK, anaplastic lymphoma kinase; CF, cerebrospinal fluid; FISH, fluorescence in situ hybridization; FFPE, formalin-fixed paraffin embedded; FNA, fine-needle aspiration; IHC, immunohistochemistry; ND, not done; NGS, next-generation sequencing; NR, not reported; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; ADAM17, ADAM metallopeptidase domain 17; AKAPB1, A-kinase anchoring protein 8 like; ATAD2B, ATPase family AAA domain containing 2B; ATP13A4, ATPase 13A4; BCL11A, BAF chromatin remodeling complex subunit; BIRC6, baculoviral IAP repeat containing 6; C12orf75, chromosome 12 open reading frame 75; CAMKMT, calmodulin-lysine N-methyltransferase; CDK15, cyclin dependent kinase 15; CEBPZ, c-Myb; CCAAT enhancer binding protein zeta; CLIP1, CAP-Gly domain containing linker protein family member; CLIP4, CAP-Gly domain containing linker protein family member 4; CMTR1, cap methyltransferase 1; CRIM1, cysteine rich transmembrane BMP regulator 1; CUX1, cut like homeobox 1; CYB5R1D1, cytochrome b reductase 1; DACH1, dachous cadherin-related; DCTN1, dynactin subunit 1; DYSF, dysferlin; ERC1, ELKS/RAB6-interacting/CAST family member 1; FAM179A, family with sequence similarity 179 member A; FBX011, F-box protein 11; FABP1, f-box protein 36; FUT8, fucosyltransferase 8; GCC2, GCP and coiled-coil domain containing 2; HIP1, huntingtin interacting protein; ITPG, integrin subunit alpha V; KLC1, kinesin light chain 1; LINC00211, long intergenic non-protein coding RNA 211; LINC00327, long intergenic non-protein coding RNA 327; LMO7, LIM domain 7; LOC349160, uncharacterized LOC349160; LPIN1, lipin 1; LYPD1, LYPD6/PLAUR domain containing 1; NCOA1, nuclear receptor coactivator 1; PLEKHA7, pleckstrin homology, MyTH4 and FERM domain containing 2; PLK2, pleckstrin homology and RUN domain containing 2; PPFIBP1, Liprin-beta-1/PPF1A; PRKAR1A, protein kinase CAMP-dependent type 1 regulatory subunit alpha; PRKCB, protein kinase C beta; RBM20, RNA binding motif protein 20; SEC31A, SEC31 homolog A; TACR1, tachykinin receptor 1; TAC1, tetranectinpeptide repeat, ankyrin repeat and coiled-coil containing 1; TCF12, transcription factor 12; TFG, trafficking from ER to golgi regulator; THADA, THADA (thyroid adenoma associated) armadillo repeat containing; TNIP2, TNFAIP3 interacting protein 2; TOGARAM2, TOG array regulator of axonemal microtubules 2; TRAP, translocated promoter region, nuclear basket protein; TRIM66, tripartite motif containing 66; TSPYL6, TSPY like 6; TACC1, tetratricopeptide repeat domain 27; TUBB, tubulin beta class 1; VANKL, vitamin K epoxide reductase complex subunit 1 like 1; WDR37, WD repeat domain 37; WDPCP, WD repeat containing planar cell polarity effector; WNK3, WNK lysine deficient protein kinase 3; YAP1, Yes associated transcriptional regulator.
Table 2. List of Chromosomal Locations of Intergenic Translocations With Potential Fusion Partners

| No. | Year | Chromosomal Location | Potential Fusion Partner Gene | Response to ALK TKI at the Time of Publication | Tumor Source | Method of Detection | Variant Frequency in Tumor | FISH/IHC References |
|-----|------|----------------------|-------------------------------|-----------------------------------------------|--------------|---------------------|--------------------------|-----------------------|
| 1   | 2019 | 12q23.3              | *RIC8B*                       | NR                                            | Tumor        | NGS                 | NR                       | ND/NR                 | Zhao, 2019 [44]     |
| 2   | 2019 | 2p21                 | *LOC388942* (LINCO1913)       | NR                                            | Tumor        | NGS                 | NR                       | ND/NR                 | Zhao, 2019 [44]     |
|     | 2020 | 2p21                 | *LOC388942* (LINCO1913)       | NR                                            | Tumor        | NGS                 | NR                       | ND/NR                 | Tian, 2020 [59]    |
| 3   | 2019 | 2p21                 | *LOC388942* (LINC01913)       | NR                                            | Tumor        | NGS                 | NR                       | ND/NR                 | Tian, 2020 [59]    |
| 4   | 2019 | 2p23.3               | *CENPA*                       | PR to crizotinib                              | Tumor        | NGS                 | +/+                      | Fei, 2019 [53]       |
| 5   | 2019 | 2p16.11              | *CDH2*                        | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 6   | 2019 | 2p16.2               | *MIR4431*                     | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 7   | 2020 | 2p12.11              | *MIR548AD*                    | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 8   | 2020 | 2p23.3               | *CENPA*                       | PR to crizotinib                              | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 9   | 2020 | 2q11.3               | *CHRNA7*                      | PR to crizotinib                              | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 10  | 2020 | 2q14.3               | *CNTNAP5*                     | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 11  | 2020 | 2p21                 | *CENPA*                       | PR to crizotinib                              | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 12  | 2020 | 2p13.2               | *COX7A2L*                     | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 13  | 2020 | 2p23.3               | *CDH2*                        | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 14  | 2020 | 2p12.11              | *CENPA*                       | PR to crizotinib                              | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 15  | 2020 | 2q22.3               | *LRP1B*                       | NR                                            | Tumor        | NGS                 | NR                       | Zhao, 2019 [44]      |
| 16  | 2020 | 2p22.3               | *MEMO1*                       | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 17  | 2020 | 2p22.3               | *CELF4*                       | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 18  | 2020 | 2p22.3               | *CENPA*                       | PR to crizotinib                              | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 19  | 2020 | 2q22.1-q22.2         | *CELF4*                       | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 20  | 2020 | 2q11.2               | *PDCL3*                       | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 21  | 2020 | 2p22.2               | *QPCRT*                       | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 22  | 2020 | 2p23.3               | *RAB10*                       | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 23  | 2020 | 2p22.1               | *SLC8A1*                      | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 24  | 2020 | 2q32.3               | *STK17B*                      | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 25  | 2020 | 6q24.1-q24.2         | *VTA1*                        | NR                                            | Tumor        | NGS                 | NR                       | Tian, 2020 [59]      |
| 26  | 2020 | 19q13.42             | *CDC42EP3*                    | No response to crizotinib and alectinib       | Plasma       | NGS                 | 13.0%                    | ND/+                  | Zhang, 2020 [60]   |
| 27  | 2020 | 3p22.1               | *RPSA*                        | NR                                            | Tumor        | NGS                 | 7.9%                     | ND/+                  | Zhang, 2020 [60]   |
| 28  | 2020 | 2p23.3               | *UBXN2A*                      | NR                                            | Tumor        | NGS                 | 25.4%                    | ND/NR                 | Zhang, 2020 [60]   |

*Together with EML4-ALK (E6, A20) and breakpoint is 3′UTR of CDC43EP3 to exon 20 of ALK. +, positive. ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; ND, not done; NGS, next-generation sequencing; NR, not reported; PR, partial response; SD, stable disease; CENPA, centromere protein A; CDC42EP3, CDC42 effector protein 3; CDH2, cadherin 2; CELF4, CUGBP Elav-like family member 4; CNTNAP5, contactin associated protein family member 5; COX7A2L, cytochrome c oxidase subunit 7A2 like; DPYSLS, dihydropyrimidinase like 5; DYF, dysferlin; FSHR, follicle stimulating hormone receptor; GJB6, gap junction protein beta 6; LINCO1210, long intergenic non-protein coding RNA 1210; LINCO1913, long intergenic non-protein coding RNA 1913; LRPS1, LDL receptor related protein 18; MEMO1, mediator of cell motility 1; MIR4431, microRNA 4431; MIR548AD, microRNA 548ad; MGST2, microsomal glutathione S-transferase 2; PDCL3, phosducin like 3; PRPF31, pre-mRNA processing factor 31; QPCRT, glutaminyl-peptide cyclotransferase; RAB10, RAB10, member RAS oncogene family; RIC8B, RIC8 guanine nucleotide exchange factor B; RPSA, ribosomal protein SA; SLC8A1, solute carrier family 8 member A1; STK17B, serine/threonine kinase 17b; UBXN2A, UBX domain protein 2A; VTA1, vesicle trafficking 1.
DNA NGS to detect even rare actionable driver mutations such as NTRK and NRG1. Although EML4-ALK (with multiple fusion breakpoints in EML4) remains the major fusion variant in ALK+ NSCLC (accounting for approximately 95% of ALK fusion variants), multiple case reports have reported novel ALK fusion partners in ALK+ NSCLC. In this article, we have compiled a list of the ALK fusion partners including intergenic rearrangements identified in the literature for easy reference.

Methods and Results
We searched PubMed publications, conference/congress abstracts, and presentations extensively to identify novel ALK fusion partners (including noncoding RNAs). We included only those fusion partners that retained the 3’ALK kinase domain. Reciprocal/nonreciprocal ALK translocations involving 5-ALK gene rearrangements (most frequently ALK exons 1-19 fused to a 3’-truncated gene [ALK-XX]) were not listed although these nonfunctional 5’-ALK fusion variants are usually listed as ALK fusion variants in the literature. Overall, a total of 90 distinct ALK fusion partners (including noncoding RNAs) have been identified in the literature (by the end of January 2020) (Table 1).

Many of these novel ALK fusion variants have been reported to respond to ALK TKIs or shown to be ALK IHC positive. Twenty-five intergenic rearrangements to exon 20 of ALK have also been identified and listed separately in Table 2. Three of these intergenic ALK rearrangements have been shown to respond to crizotinib, but the significance of these intergenic rearrangements remains to be determined, including whether functional fusion RNAs are translated from these intergenic rearrangements.

Discussion
With the increasing adoption of NGS for molecular profiling of NSCLC, especially in China, the pace at which new fusion partners are being identified and reported has rapidly increased since 2018. In particular, from 2018 onwards, approximately 65 of the 90 fusion partners reported in the literature (calculated at the time page numbers were assigned for this publication) were almost exclusively identified from China, indicating the widespread use of NGS there. Dual in-frame 3’-ALK fusion variants with different 5’ fusion partners are now being recognized; however, whether the relative contribution of each of the dual ALK fusion variant to oncogenesis depends on the allele frequency of each fusion variant remains to be elucidated. We identified at least 28 intergenic 3’-ALK rearrangements. Whether these translate to a functional (and truncated)? ALK RNA fusion transcript and whether these intergenic rearrangements are related to the isolated 3’-ALK fusion signals remain to be determined.

The concluding perspectives are as follows:
1. ALK+ NSCLC is a heterogeneous disease with at least 90 distinct fusion partners identified in the literature by January 2020;
2. It is likely that many more fusion partners and intergenic rearrangements will continue to be identified with the ever-increasing adoption of targeted RNA sequencing and whole transcriptome sequencing owing to the need to identify rare actionable fusions such as NTRK and NRG1 fusions;
3. The role of individual 3’-ALK fusion variant in a dual 3’-ALK fusion variants will need to be elucidated; and
4. The functional significance of intergenic rearrangements remains to be determined.

We recommend that clinicians from around the world to continue to report these novel fusions or intergenic rearrangements with information on the exon or fusion breakpoints, response to ALK TKIs, allele frequency, and if possible, whether the tumor is ALK fluorescence in situ hybridization and IHC positive.

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