Anaplastic lymphoma kinase fusions: Roles in cancer and therapeutic perspectives (Review)

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Abstract. Receptor tyrosine kinase (RTK) anaplastic lymphoma kinase (ALK) serves a crucial role in brain development. *ALK* is located on the short arm of chromosome 2 (2p23) and exchange of chromosomal segments with other genes, including nucleophosmin (*NPM*), echinoderm microtubule-associated protein-like 4 (*EML4*) and *Trk*-fused gene (*TFG*), readily occurs. Such chromosomal translocation results in the formation of chimeric *X-ALK* fusion oncoproteins, which possess potential oncogenic functions due to constitutive activation of ALK kinase. These proteins contribute to the pathogenesis of various hematological malignancies and solid tumors, including lymphoma, lung cancer, inflammatory myofibroblastic tumors (IMTs), Spitz tumors, renal carcinoma, thyroid cancer, digestive tract cancer, breast cancer, leukemia and ovarian carcinoma. Targeting of ALK fusion oncoproteins exclusively, or in combination with ALK kinase inhibitors including crizotinib, is the most common therapeutic strategy. As is often the case for small-molecule tyrosine kinase inhibitors (TKIs), drug resistance eventually develops via an adaptive secondary mutation in the *ALK* fusion oncogene, or through engagement of alternative signaling mechanisms. The updated mechanisms of a variety of *ALK* fusions in tumorigenesis, proliferation and metastasis, in addition to targeted therapies are discussed below.

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1. Introduction

Located on chromosome 2p23, receptor tyrosine kinase (RTK) anaplastic lymphoma kinase (ALK) is physiologically expressed in fetal neural cells. Phosphorylated and activated ALK controls the basic mechanisms of cell proliferation, survival and differentiation during development of the nervous system (1). In 1994 ALK t(2;5) chromosomal translocation was reported in anaplastic large cell lymphoma (ALCL) (2). This translocation induced formation of the nucleophosmin (NPM)-ALK chimeric protein (3). Over the ensuing two decades, *ALK* fusion oncogenes have been associated with the development of diverse tumor types of different lineages, including, but not limited to, lymphoma, lung cancer, inflammatory myofibroblastic tumors (IMTs), Spitz tumors, renal carcinoma, thyroid cancer, digestive tract cancer, breast cancer, leukemia and ovarian carcinoma. During this period, the discovery of *EML4-ALK* in non-small cell lung cancer (NSCLC) was a major development that led to significant diagnostic and therapeutic advances (4).

In general, *ALK* fusions arise from fusion of the 3' end of the *ALK* gene (exons 20-29) with the 5'portion of a different gene (5). To date, numerous X-ALK fusion oncoproteins have been identified in various tumor types of different lineages. Although targeting *ALK* fusions markedly promotes tumor shrinkage due to acquisition of activating mutations, genomic rearrangement or copy number amplification of *ALK*, a subset of patients inevitably acquire resistance to ALK inhibitors. The functional roles of a variety of *ALK* fusions in neoplasms and targeted therapy advances are summarized below.

2. *ALK* rearrangement

In the majority of cancer types, *ALK* is activated via chromosomal rearrangement. The breakpoint of *ALK* often occurs at intron 19, which results in dissociation of the 3' end of exons 20-29 from 5' end sequences, including the gene

promoter, regulatory elements and coding sequences corresponding to the extracellular and transmembrane domains of *ALK*. The other breakpoint affects a diverse group of genes that contribute to the fusion oncogene, including a different gene promoter and a series of 5' exons of variable lengths and properties, which predominantly share the ability to self-associate. Additionally, clinical data indicate that different fusion partners affect treatment responses in patients with lung cancer (6). The resulting fusion oncoproteins (X-ALK) are chimeric, self-associating polypeptides with a variety of N-terminal domains and a common, constitutively active C-terminal tyrosine kinase domain (Fig. 1) (5).

In 1994, Morris *et al* (2), first demonstrated *NPM-ALK* expression in ALCL. Subsequently, a variety of fusion partners have been found (Table I), including the following: α-2-macroglobulin (*A2M*); 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (*ATIC*); carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (*CAD*); cysteinyl-tRNA synthetase (*CARS*); clathrin heavy chain (*CLTC*); dynactin (*DCTN1*); echinoderm microtubule-associated protein like-4 (*EML4*); fibronectin 1 (*FN1*); huntingtin-interacting protein 1 (*HIP1*); kinesin family member 5B (*KIF5B*); kinesin light chain 1 (*KLC1*); moesin (*MSN*); non-muscle myosin heavy chain 9 (*MYH9*); PTPRF interacting protein, binding protein 1 (*PPFIBP1*); RAN binding protein 2 (*RANBP2*); ring finger protein 213 (*RNF213*); SEC31 homolog A (*SEC31A*); spectrin beta non-erythrocytic 1 (*SPTBN1*); sequestosome 1 (*SQSTM1*); striatin (*STRN*); TRK-fused gene (*TFG*); tropomyosin 3 (*TPM3*); tropomyosin 4 (*TPM4*); translocated promoter region (*TPR*); TNF receptor-associated factor 1 (*TRAF1*); and vinculin (*VCL*).

The precise mechanisms of *ALK* gene rearrangement remain unclear. Widely considered a key source of genomic rearrangement, non-homologous end-joining may be divided into 3 steps: i) Generation of double-stranded DNA breaks; ii) ligation of DNA; and iii) gene rearrangement (7,8). Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) are widely used in clinical settings to detect *ALK* rearrangements (9-11). However, FISH and IHC exhibit low specificity in the recognition of fusion partners, which may be identified by reverse transcription polymerase chain reaction (RT-PCR) or rapid amplification of cDNA ends (RACE)-coupled PCR sequencing (10,12).

3. Roles of ALK fusion oncoproteins in cancer pathogenesis

Lymphoma. Lymphomas comprise a group of blood cancer types that develop from lymphocytes and are classified as either Hodgkin's lymphoma (HL, 10%) or non-Hodgkin's (NHL, 90%) lymphoma. Based on the normal function of lymphocytes, NHL may be further divided into three subtypes: i) B cell NHL; ii) T cell NHL; and iii) natural killer cell NHL. Compared with HL, NHL patients have a poor prognosis, and the five-year survival rate is ~69% (13,14).

According to certain studies, *ALK* rearrangements are common in ALCL, which is a type of T cell NHL (15). Statistically, a total of ~90% of ALCLs in children and teenagers, and 50% of ALCLs in adults are ALK-fusion-positive (16-18). The most frequent *ALK* fusion partner is *NPM*, as the ALK-NPM fusion protein is observed in ~70-80% of all ALCL cases. A total of ~25% cases of ALCL exhibit the *TPM3-ALK* rearrangement, whereas other rearrangements, including *TFG-ALK*, *ATIC-ALK* and *CLTC1-ALK*, are rare (Table I). Notably, the prognoses of patients with ALK-fusion-positive ALCL are substantially improved compared with those of patients with ALK-fusion-negative ALCL (the five-year survival rate is 70-80% for ALK-fusion-positive patients compared with 15-45% for ALK-fusion-negative patients) (19,20).

Expression of X-ALK was thought to be restricted to *ALK*-fusion-positive ALCLs; however, in 1997, Delsol *et al* (21), first demonstrated aberrant expression of NPM-ALK in diffuse large B cell lymphoma (DLBCL). ALK-fusion-positive DLBCL is usually a nodal disease that affects 34~55 years old males, presents at advanced clinical stages and has a poor prognosis (22). The most common *ALK* rearrangement in DLBCL is t(2;17)(p23;q23), which corresponds to the *CLTC-ALK* fusion; a minority are *NPM-ALK* rearrangements (23). Rare cases that harbor *SEC31A-ALK* and *SQSTM1-ALK* fusions have also been described (24-27).

Lung cancer. Lung cancer is the most prevalent type of cancer and the leading cause of mortality among all malignancies. Despite tremendous progress in the diagnosis and treatment of lung cancer, prognosis for these patients remains poor, with only 15% surviving more than 5 years after initial diagnosis (28). NSCLC accounts for ~80-85% of these cases of lung cancer, whereas the remainder involve small cell lung cancer and lung carcinoid tumors (29).

The *EML4-ALK* fusion was first observed in 5 out of 75 (6.7%) Japanese patients with NSCLC; notably, these patients did not harbor epidermal growth factor receptor (*EGFR*) or *KRAS* mutations (4). Multiple studies have determined the frequency of the *EML4-ALK* translocation in NSCLC patients, which ranges from 2 to 7% in individual studies, with an average frequency of ~5% (30-37). During the past decade, over 11 different variants of *EML4-ALK* have been identified in a variety of tumors, including NSCLC, digestive tract and breast cancer. The most common variant among *EML4-ALK* fusions is variant 1 (33%), followed by variant 3 (29%) and variant 2 (10%) (12,38). Furthermore, other *ALK* fusion partners have been identified in NSCLC, including *KLC*, *TFG*, *KLC*, and *KIF5B* (39-41). *ALK*-rearranged NSCLC is frequently observed in young patients, in addition to never or former light smokers. Morphologically, acinar, tubulopapillary, cribriform and solid patterns are the most common histological subtypes, and >10% of tumor cells display a distinctive signet ring morphology with abundant intracellular mucin (42). In addition, the oncogenic potential of *X-ALK* has been confirmed in lung cancer models, including patient-derived cell lines and transgenic mouse models. Several studies have identified the *X-ALK* gene in a number of NSCLC patients harboring *EGFR* mutations (38,43-46). The majority of these patients are insensitive to the ALK inhibitor crizotinib, but exhibit a partial response to the EGFR inhibitor erlotinib. Therefore, they may not further benefit from coordinated treatment with ALK and EGFR inhibitors compared with either intervention alone.

IMTs. IMT is a type of mesenchymal neoplasm composed of a mixture of several inflammatory cells, which primarily occurs in children (47,48). IMTs are generally benign or

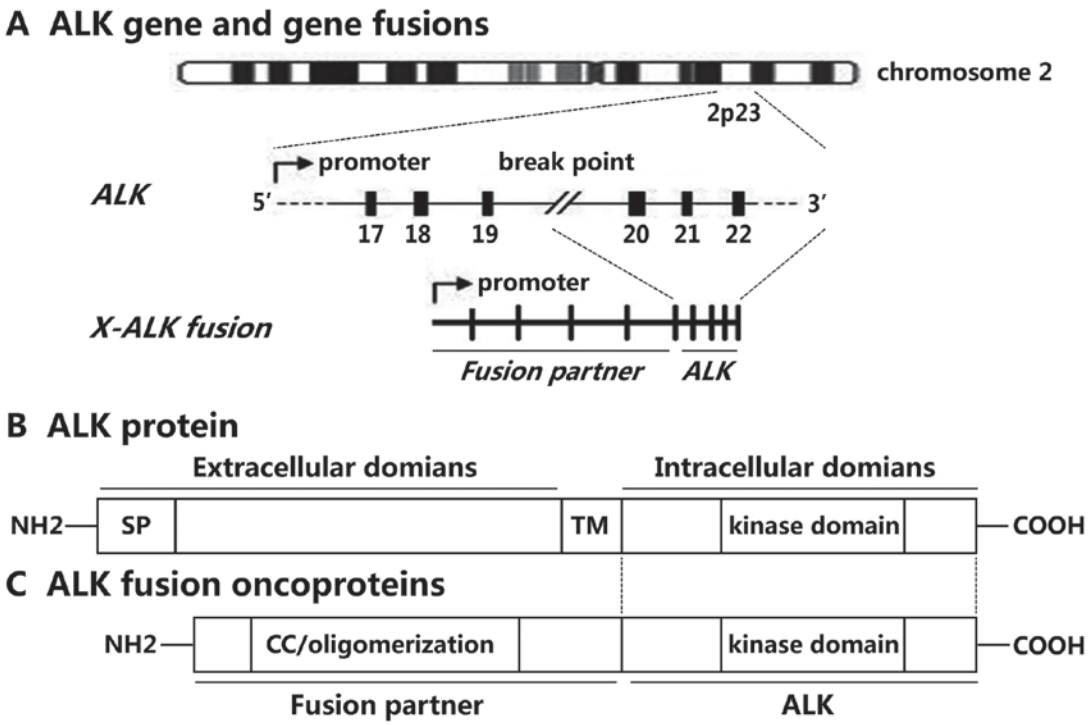

Figure 1. Schematic structure of the (A) *ALK* gene, (B) ALK protein and (C) an ALK oncoprotein, illustrating a prototypical oncogenic rearrangement (5). SP, signal peptide; TM, transmembrane domain; CC, coiled coil domain; ALK, anaplastic lymphoma kinase.

low-grade malignant tumors, and patients usually only require surgical treatment (49,50). According to certain statistics, ~50% of IMTs are ALK-fusion-positive, and two of the most common fusion partners are *TPM3* and *TPM4* (51). Similar to ALCL, various *ALK* fusion partners have been identified in IMTs, including *PPF1BP1*, *PCTN1*, *RANBP2*, *EML4*, *CLTC*, *CARS*, *ATIC*, *SEC31A* and *FN1* (Table I). Additionally, a study suggested that patients with ALK-fusion-positive IMT may exhibit a more favorable prognosis compared with those with ALK-fusion-negative IMT (52).

Spitz tumors. Spitz tumors are a type of melanocytic neoplasm that tend to occur in younger people (2-35 years old). Spitz tumors may be divided into three subtypes: i) Benign Spitz nevus; ii) atypical Spitz tumor; and iii) Spitz malignant melanoma (53). In 2014, *DCTN1-ALK* and *TPM3-ALK* were identified in Spitz tumors (53,54). Follow-up studies have demonstrated that activation of the X-ALK oncoprotein serves an important role in the pathogenesis of Spitz tumors (55).

Renal carcinoma. Renal carcinoma, a type of tumor that originates from cells in the kidney, accounts for <2% of all cancer types. Renal carcinoma may be divided into two main subtypes: i) renal cell carcinoma (RCC) with a poor prognosis; and ii) transitional cell carcinoma (accounting for 5-10% of cases) (56). Due to the difficulty of early diagnosis in renal carcinomas, their pathogenesis is not completely known. *ALK* fusions have been documented in a small percentage of RCCs (<1%) (57,58). Based on clinical settings, RCCs with *ALK* translocation are divided into two categories: i) RCCs with *VCL-ALK*, composed of sickle cells; and ii) other fusions, which are not associated with sickle cell composition (59,60). In addition to *ALK* rearrangements, up to 10% of RCC cases show a low level of *ALK* copy number gains (58). The therapeutic relevance of these findings in RCC is yet to be established.

Thyroid cancer. Thyroid cancer is a common type of endocrine tumor that is classified as either benign thyroid adenoma or a thyroid malignancy (61). Based on the cells that comprise these tumors, thyroid malignancies can be further divided into four subtypes: i) papillary (PTC; 80-85%); ii) follicular (10-15%); iii) medullary (3%); and iv) anaplastic thyroid cancer (ATC; 2%). Among these four types of tumor, the degree of malignance of ATC is high, and its prognosis is poor, with a median patient survival of only 5 months (62-64). In 2015, translocations involving *ALK* were detected by Chou *et al* (65), in 2.2% of PTC patients. Several other *ALK* fusion genes have been reported in thyroid cancer, including *EML4-ALK*, *TFG-ALK* and *STRN-ALK* (Table I).

Digestive tract cancer. Digestive tract cancer refers to neoplasms of the digestive system, including cancer of the mouth, esophagus, stomach and intestines. Epidemiological studies have indicated that the frequency of different digestive tract cancer types differs widely in different countries. A recent study illustrated that several factors determine the prognosis of patients with digestive tract cancer, including the location of the tumor, clinical stage and the type of cancer cell (66). In 2006, the TPM4-ALK fusion was first reported in esophageal squamous cell carcinomas (67). Subsequently, other fusion partners have been described in digestive tract cancer, including *EML4*, *CAD* and *SPTBN1* (68-70).

Other neoplasms. Surveys in which a variety of techniques have been applied to a large series of tumors have revealed differentially convincing evidence of *ALK* rearrangement in

Table I. ALK fusion proteins described in diverse tumors.

Gene fusion	Chromosomal aberration	Partner protein	Tumor type	Frequency, %	(Refs.)
NPM-ALK	t(2;5)(p23;q35)	Nucleophosmin	Lymphoma	45	(3,22)
MSN-ALK	t(X;2)(q11-12;p23)	Moesin	Lymphoma	<1	(106)
MYH9-ALK	t(2;22)(p23;q11)	Non-muscle myosin heavy chain 9	Lymphoma	<1	(107)
RNF213-ALK	t(2;17)(p23;q25)	Ring finger protein 213	Lymphoma	<1	(108)
TRAF1-ALK	t(2;9)(p23;q33.2)	Tumor necrosis factor receptor-associated factor 1	Lymphoma	N/A	(109)
ATIC-ALK	inv(2)(p23q35)	5-aminoimidazole-4-carboxamideRibonucleotide formyltransferase	Lymphoma	2	(110)
			IMT	<1	(39)
CLTC-ALK	t(2;17)(p23;q23)	Clathrin heavy chain	Lymphoma	<1	(23,108)
			IMT	13	(111)
SQSTM1-ALK	t(2;5)(p23.1;q35.3)	Sequestosome 1	Lymphoma	<1	(26)
			Lung cancer	<1	(112)
TFG-ALK	t(2;3)(p23;q21)	Tyrosine kinase receptor-fused gene	Lymphoma	<1	(113)
			Lung cancer	<1	(39)
			Thyroid cancer	2	(63)
TPM4-ALK	t(2;19)(p23;p13)	Tropomyosin 4	Lymphoma	3	(114,115)
			IMT	17	(67)
			Digestive tract cancer	2	
TPM3-ALK	t(1;2)(q21;p23)	Tropomyosin 3	Lymphoma	9	(115,116)
			IMT	21	(39)
			Renal carcinoma	<1	(53,54)
			Spitz tumor	6	
A2M-ALK	t(2;12)(p23;p13)	α-2-macroglobulin	Lung cancer	<1	(117)
HIP1-ALK	t(2;7)(p23;q11.23)	Huntingtin-interacting protein 1	Lung cancer	N/A	(118,119)
KIF5B-ALK	t(2;10)(p23;p11)	Kinesin family member 5B	Lung cancer	<1	(40)
KLC1-ALK	t(2;14)(p23;q32.1)	Kinesin light chain 1	Lung cancer	N/A	(41)
TPR-ALK	t(1;2)(q31.1;p23)	Translocated promoter region	Lung cancer	N/A	(120)
EML4-ALK	inv(2)(p21p23)	Echinoderm microtubule-associated protein like-4	Lung cancer	5	(4)
			IMT	<1	(50)
			Thyroid cancer	2	(121)
			Renal carcinoma	<1	(39)
			Digestive tract cancer	N/A	(71)
			Breast cancer	<1	(71)
DCTN1-ALK	inv(2)(p13p23)	Dynactin	Lung cancer	<1	(112,122)
			IMT	<1	(123)
			Thyroid cancer	<1	(53,54)
			Spitz tumor	4	
CARS-ALK	t(2;11;2)(p23;p15;q31)	Cysteinyl-tRNA synthetase	IMT	<1	(108)
PPFIBP1-ALK	t(2;12)(p23;p11)	Protein tyrosine phosphatase, receptor type F-interacting protein, binding protein 1	IMT	<1	(124)
SEC31A-ALK	t(2;4)(p23;q21)	SEC31 homolog A	IMT	<1	(125)
FN1-ALK	inv(2)(p23q34)	Fibronectin 1	IMT	<1	(126)
			Ovarian sarcoma	<1	(73)
RANBP2-ALK	inv(2)(p23q11-13)	RAN binding protein 2	IMT	3	(127)
			Leukemia	<1	(72)

Table I. Continued.

Gene fusion	Chromosomal aberration	Partner protein	Tumor type	Frequency, %	(Refs.)
STRN-ALK	t(2)(p23;p22.2)	Striatin	Thyroid cancer Renal carcinoma	<1 N/A	(63,128)
VCL-ALK	t(2;10)(p23;q22)	Vinculin	Renal carcinoma	<1	(59)
CAD-ALK	inv(2)(p23;p22)	Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase	Digestive tract cancer	<1	(69)
SPTBN1-ALK	t(2)(p16.2;p23)	Spectrin β non-erythrocytic 1	Digestive tract cancer	<1	(70)

Not all *ALK* fusions identified worldwide are included; clear statistics are not available for several ALK fusions found in tumors. IMT, inflammatory myofibroblastic tumor; N/A, data unavailable.

rare cases of breast carcinoma (fusions in 5 out of 209 cases assessed by RT-PCR) (71), leukemia (fusions in 3 out of 1,708 cases assessed by RT-PCR) (72) and ovarian carcinoma (3 out of 69 tumors expressed ALK) (73). Although these reports are technically sound, for the most part, the relevance of these findings remains to be clarified through functional studies in pertinent models.

4. Therapeutic implications

ALK is a compelling therapeutic target, as it is a critical oncogenic driver in diverse tumor types of different lineages. However, its expression and functions are limited in normal tissues. Indeed, Bilsland *et al* (74) confirmed that *ALK* double-knockout mice exhibited no significant phenotypic differences, a normal life span, no structurally detectable defects and minor behavioral abnormalities, which advocates a wide non-toxic therapeutic window of ALK-specific inhibition. Various therapeutic methods for tumor treatment are currently in development, including direct targeting of activated ALK with small-molecule inhibitors or immunotherapeutic agents and modulation of downstream signaling intermediates in cancer types with *ALK* rearrangement. In addition, the X-ALK fusion oncoprotein predominantly activates the RAS/MAPK cell proliferation pathway, in addition to the PI3K/AKT/mTOR and JAK/STAT cell survival pathways. Therefore, an understanding of these downstream effectors has prompted the development of novel therapeutic strategies, some of which are being tested in preclinical/clinical trials.

Multiple structurally distinct ALK drugs are being developed based on a deep understanding of the structure of ALK (Table II), three of which are currently in clinical use for the treatment of *ALK*-fusion-positive lung cancer, including crizotinib, ceritinib and alectinib. Crizotinib, an oral ALK TKI, has been extensively studied in preclinical and clinical settings. Early phase I studies (PROFILE 1001) have indicted notable activity of crizotinib, with satisfactory tolerability in patients with *ALK*-fusion-positive NSCLC (75,76). Two-phase III studies further demonstrated the superiority of crizotinib to standard chemotherapy in patients with advanced NSCLC with *X-ALK*. One of these studies (PROFILE 1007) illustrated that crizotinib treatment significantly prolonged progression-free survival (PFS), which was the primary end point, compared with chemotherapy with either pemetrexed or docetaxel (7.7 vs. 3.0 months, respectively) (77). Another study (PROFILE 1014) compared crizotinib with carboplatin or cisplatin plus pemetrexed in 343 patients with advanced *X-ALK* NSCLC, and clarified the significance of crizotinib as a first-line treatment for these tumors (78). Furthermore, crizotinib displayed excellent activity in IMT and ALCL cases harboring *X-ALK* fusions (79).

Despite the excellent efficacy of crizotinib in the setting of NSCLC with *ALK* translocation, almost all patients developed resistance to crizotinib, but the exact molecular mechanism underlying this phenomenon is yet to be confirmed. The known mechanisms that confer intrinsic or acquired resistance to crizotinib are as follows: i) secondary mutations in the *ALK* kinase domain (L1152R, C1156Y, I1171T, F1174C/L/V, L1196M, G1202R, S1206Y, E1210K and G1269A/S); ii) *ALK* gene amplification; and iii) activation of alternative ALK-independent survival pathways, including the EGF signaling pathway, the IGF signaling pathway, the RAS/SRC signaling pathway, and the AKT/mammalian target of rapamycin (mTOR) signaling pathway (80-87). Synergistic and/or complementary treatment strategies to overcome resistance are being investigated. Second-generation ALK TKIs, such as ceritinib and alectinib, have been demonstrated to be effective not only in crizotinib-sensitive patients, but also in those who are resistant to crizotinib. Furthermore, other therapeutic options to overcome drug resistance have been proposed, e.g., the use of heat shock protein 90 (HSP90) inhibitors, which can indirectly inhibit ALK fusion (88,89).

Currently, multiple ALK TKIs, including ceritinib, alectinib, lorlatinib, entrectinib, brigatinib, CEP-28122, TSR-011, X-396 and ASP3026, are being investigated as potential therapies for cancer types characterized by *ALK* rearrangement (Table II). Ceritinib, a highly potent and selective TKI, was approved by the Food and Drug Administration (FDA) as a second-line treatment for patients with *X-ALK* NSCLC, and following unsuccessful treatment with crizotinib. A total of 114 patients with *ALK*-fusion-positive NSCLC were enrolled in a global multi-institutional phase I trial, among whom 70%

Table II. Novel drugs for use in therapies targeting *ALK* rearrangement tumors.

Drug	Molecular target	Tumor	Phase	(Refs.)
Crizotinib	*NPM-ALK*, *EMLA-ALK*, *RANBP2-ALK*	Lung cancer IMT	Approved by FDA Phase II/III ongoing	(75-78) (129,130)
Ceritinib	*EML4-ALK*	Lung cancer Thyroid cancer	Approved by FDA Phase II/III ongoing	(90) (79)
Alectinib	*EML4-ALK*	Lung cancer	Approved by FDA	(131,132)
Lorlatinib	*NPM-ALK*, *EML4-ALK*	Lung cancer Lymphoma	Phase I/II ongoing Phase I/II ongoing	(133,134) (135)
Entrectinib	*EML4-ALK*, *CAD-ALK*	Lung cancer Digestive tract cancer	Phase I/II ongoing Phase I/II ongoing	(98) (69)
Brigatinib	*NPM-ALK*, *EML4-ALK*	Lung cancer	Phase I/II ongoing	(136,137)
CEP-28122	*NPM-ALK*	Lung cancer Lymphoma	Preclinical study Preclinical study	(138)
TSR-011	*EML4-ALK*	Lung cancer	Phase I/II ongoing	(139)
X-396	*EML4-ALK*	Lung cancer	Phase I/II ongoing	(98)
ASP3026	*NPM-ALK*, *EML4-ALK*	Lung cancer Lymphoma	Phase I ended Phase I ended	(134,140) (96)
Retaspimycin (HSP90 inhibitor)	*EML4-ALK*	Lung cancer	Preclinical study	(88,89)
Tanespimycin (HSP90 inhibitor)	*NPM-ALK*, *EML4-ALK*, *TPR-ALK*, *RANBP2-ALK*	Lung cancer Lymphoma IMT	Preclinical study Preclinical study Preclinical study	(141) (100) (84)

Only clinically available drugs are listed; the development of ASP3026 was discontinued due to strategic adjustment of the company. IMT, inflammatory myofibroblastic tumor; HSP90, heat shock protein 90; ALK, anaplastic lymphoma kinase; FDA, Food and Drug Administration.

were crizotinib-sensitive and 30% were crizotinib-resistant. All patients received at least 400 mg of crizotinib per day, and the overall response rate (ORR) was 59% (90). Alectinib is a TKI used clinically that exhibits minimal inhibitory activity against kinases other than ALK and RET (91,92). Furthermore, *in vitro* and *in vivo* studies have demonstrated that alectinib effectively inhibits ALK with or without the gatekeeper mutation L1196M (92). A separate clinical study was conducted to investigate the safety and activity of alectinib in TKI-naive patients with *X-ALK* NSCLC, with an ORR of 48% (93). Lorlatinib, which is structurally similar to crizotinib, has been demonstrated to be active against identified crizotinib-resistant ALK mutations, such as the most common mutation seen clinically (G1202R) (94). In 2014, Brigatinib received breakthrough therapy designation from the FDA and a nationwide phase III clinical study in which brigatinib was compared with crizotinib in patients with *X-ALK* NSCLC was recently initiated (95). Furthermore, the antitumor activities of at least 5 other novel ALK inhibitors, including entrectinib, CEP-28122, TSR-011, X-396 and ASP3026, have been shown *in vitro*, and these agents are currently under clinical investigation (96-98). In addition to targeting ALK directly, several pharmacological strategies allow its indirect targeting. Specifically, HSP90 inhibitors, including retaspimycin and tanespimycin, have displayed certain clinical efficacy in the treatment of patients with ALK rearrangements (84,99,100).

5. Conclusion

ALK fusions are remarkably versatile oncoproteins that may drive a variety of tumors of different lineages, including, but not limited to, lymphoma, lung cancer, IMTs, Spitz tumors, renal carcinoma, thyroid cancer, digestive tract cancer, breast cancer, leukemia and ovarian carcinoma. Furthermore, a profusion of *ALK* fusion partners has been consistently identified in *ALK*-translocated cancer types, which are unique neoplasms that can be effectively targeted by several clinically available TKIs, including crizotinib, ceritinib and alectinib. By using alternative methods of tumor detection, novel *ALK* translocations may be discovered in upcoming years, which may reveal novel aspects of ALK biology. Substantial efforts are focused on therapeutic considerations and novel approaches to target ALK, including rationally designed tyrosine kinase inhibitors, the study of resistance mechanisms, the design of dual-blockade therapeutic strategies that target downstream signaling intermediates, and immunotherapy against activated receptor tyrosine kinases.

In addition to disease-causing gene mutations, genome-level alterations, including chromosomal imbalances and instability, clonal chromosomal aberrations (CCAs, also known as recurrent karyotypic alterations) and non-clonal chromosome aberrations (NCCAs), also serve a significant role in carcinogenesis and the development of malignant tumors. Since cancer-specific aneuploidy

catalyzes karyotypic variation, the degree of aneuploidy predicts the clinical risk of tumor progression. Increasing evidence has indicated the complexity of cancer, which cannot be explained by somatic mutation theory. To address this complexity, additional ad hoc explanations have been postulated, and carcinogenesis is thought to represent a problem of tissue organization on the basis of tissue organization field theory (101-103). According to recent studies, chromosomal aberration-mediated genome evolution is responsible for all major transitions in cancer evolution, including phenotypic plasticity, metastasis and drug resistance (104,105). It is believed that the genome serves as the evolutionary platform that links gene/epigene interaction and multiple levels of omics, which can be driven by genome-level alteration rather than individual hallmarks as gene mutation or epigenetic alteration. Conclusively, ongoing research with the aim of characterizing the clinicopathological and biological consequences of *ALK* rearrangement may allow us to better understand the genome-mediated evolutionary mechanism of cancer.

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Authors' contributions

ZFC and WBO drafted the manuscript. ZFC, QG, MXF, NN and YTP were responsible for the collection of the relevant literature. WBO designed the outline and revised the manuscript. All authors have read and approved the final manuscript.

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Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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