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Tyrosine kinases in nodal peripheral T-cell lymphomas

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Nodal peripheral T-cell lymphomas (PTCL) are uncommon and heterogeneous tumors characterized by a dismal prognosis. Targeted therapy has been proposed. However, reliable targets are mostly represented by a few surface antigens (e.g., CD52 and CD30), chemokine receptors (e.g., CCR4), and epigenetic gene expression regulation. In the last two decades, however, several studies have supported the idea that tyrosine kinase (TK) deregulation might be relevant for both the pathogenesis and treatment of PTCL. Indeed, they can be expressed or activated as a consequence of their involvement in genetic lesions, such as translocations, or by ligand overexpression. The most striking example is ALK in anaplastic large-cell lymphomas (ALCL). ALK activity is necessary to support cell proliferation and survival, and its inhibition leads to cell death. Notably, STAT3 was found to be the main downstream ALK effector. Other TKs are consistently expressed and active in PTCLs, such as PDGFRA, and members of the T-cell receptor signaling family, such as SYK. Notably, as in the case of ALK, STAT proteins have emerged as key downstream factors for most of the involved TK.

KEYWORDS

peripheral T-cell lymphoma, anaplastic large cell lymphoma, follicular T-cell lymphoma, PDGFRA = PDGFR alpha, JAK/STAT (janus kinase/signal transducer and activator of transcription), tyrosine kinase inhibitors (TKI), ALK (anaplastic lymphoma kinase), ITK/SYK rearrangement

1 Introduction

Since the approval of imatinib mesylate (Glivec or Gleevec) for treating Philadelphia chromosome-positive leukemias in 2000 (1), tyrosine kinases have become increasingly attractive therapeutic targets in human cancer (1–4). Therefore, they have been largely investigated in terms of expression and function, and several recurrent mutations have been identified in different cancer types, including solid and hematological malignancies (2, 5).

As far as the latter is concerned, several targets have been identified and characterized, leading to the development and approval of many different tyrosine kinases inhibitors (TKI) (6, 7). The most widely targeted TKs include ABL1, KIT, FLT3, BTK, JAK family members, and PDGFRs (6, 7). Interestingly, lymphomas despite being the most common hematological

tumors, have benefitted from TKI, probably less than leukemias, for some years. More recently, BTK inhibitors have become the standard treatment for B-cell malignancies such as mantle cell lymphoma and chronic lymphocytic leukemia (8, 9). In contrast, T-cell lymphomas/leukemias have so far been partially neglected; the only exception represented by anaplastic large cell lymphoma (ALCL) ALK+ (10).

In this article, the Authors review the most recent and relevant data on TK expression in PTCL, focusing on the commonest nodal subtypes, i.e. PTCL/NOS, T-follicular helper (TFH) related PTCLs, and ALCL.

2 ALK signaling in anaplastic large cell lymphoma

In the latest edition of the WHO classification, ALCL is divided into four main categories: ALK+, ALK-, primary cutaneous, and breast implant-associated (11). ALK+ ALCL is defined as the presence of genetic rearrangement of the anaplastic lymphoma kinase (ALK) gene. ALK encodes the 210 kDa tyrosine kinase (TK) receptor (CD247), which belongs to the insulin growth factor receptor (IR) superfamily, and its genomic locus is located at the chromosomal band 2p23 (10, 12–14).

Physiologically, ALK is highly expressed in the nervous system during embryogenesis but not in adults (15). Its precise role remains unknown, but some evidence suggests its involvement in neuronal differentiation (10). ALK protein activation is induced by ligands, activation mutations, and fusion proteins, leading to a decrease in apoptosis (16).

In cancer, virtually all genomic breakpoints leading to ALK chimeras are located within the intron between exons 19 and 20 (NM_004304.3), leading to the fusion of the intracytoplasmic domain of ALK (exons 20–29) with different partners, which provide dimerization domains (10, 17, 18).

The most common translocation in ALK+ ALCL is t (2, 5)(p23; q25), which causes the expression of an NPM1–ALK fusion protein (Table 1 and Figure 1) (14). NPM1 is a multifunctional protein that acts as a molecular chaperone in the transport of pre-ribosomal particles from the nucleus to the cytoplasm, although it also plays a critical role in DNA repair, transcription, and genomic stability (19). The N-terminal domain of NPM1, within the ALK chimera, provides a dimerization domain essential for autophosphorylation, allowing constitutive activation of the kinase and firing of downstream signaling (17, 20, 21). Functional studies have indicated several NPM1–ALK interacting molecules mediate cellular proliferation (PLC-γ, S-SRC), cell growth (RAS, S-SRC), anti-apoptotic effects (PI3P), and cell migration (S-SRC) (10, 17; Figure 2). The oncogenic activity of ALK fusion proteins is largely mediated by STAT3 in ALCL, and STAT3 activation is required for neoplastic phenotype maintenance (22). NPM1–ALK can directly phosphorylate STAT3 or activate JAK3, which in turn can contribute to STAT3 activation (17). STAT3 phosphorylation induces expression of BCL2, BCLXL, survivin, and MCL1 proteins, resulting in anti-apoptotic effects. STAT3-mediated signaling also determines uncontrolled proliferation by interacting with CCND3 and MYC (17).

Clinically, ALK+ ALCL shows an overall better prognosis than ALK- cases; however, careful attention must be paid to concomitant prognostic factors, such as patient age, since in age-matched series, the difference is not as striking (18).

In contrast, remarkably, ALK is a suitable therapeutic target. Experimentally, in preclinical models, ALK knockdown led to cell cycle arrest, followed by massive apoptosis *in vitro* and/or *in vivo* (23). Similar results were observed for small molecules. Crizotinib (Xalkori), a multitarget TKI targeting ALK, ROS1, and MET, has been approved for treating relapsed refractory ALCL in children and young adults (24–28). Approval was obtained based on a high overall response rate (88%), complete response rate (81%), and duration of response, with 67% of patients not undergoing stem cell transplantation reaching at least 6 months of CR. Cases of long-lasting remission at 28 months and 31 months have also been reported. The effect was relatively rapid, as the median time to the first response was 3.9 weeks (28). Long term results confirmed the efficacy of the drug with relevant continuous complete remission rates and overall good tolerability (29). Interestingly, deletion of PTPN1 and PTPN2 phosphatases was related to the genesis of crizotinib resistance by upregulating SHP2 (30). Consistently, combined blockage of ALK and SHP2 potentiated the efficacy of crizotinib in ALCL cells (30). Similarly, combinations of crizotinib with CHOP chemotherapy, decitabine and trametinib, or with second-generation ALK inhibitors often completely suppressed the emergence of resistant cells and were more effective than single drugs in the long-

TABLE 1 Commonest chromosomal translocations involving *ALK* gene in ALCL.

Fusion protein	Chromosomal abnormality	Frequency in ALCL	Cellular localization
NPM–ALK	t(2;5)(p23;q35)	75%	N/C
TPM3–ALK	t(1;2)(q25;p23)	18%	C
ATIC–ALK	inv (2)(p23;q35)	2%	C
CLTC–ALK	t(2;17)(p23;q23)	2%	C
RNF213–ALK	t(2;17)(p23;q25)	1%	C
TFG–ALK	t(2;3)(p23;q21)	1%	C
MSN–ALK	t(2;X)(p23;q11–12)	<1%	CM
TPM4–ALK	t(2;19)(p23;p13)	<1%	C
MYH9–ALK	t(2;22)(p23;q11.2)	<1%	C

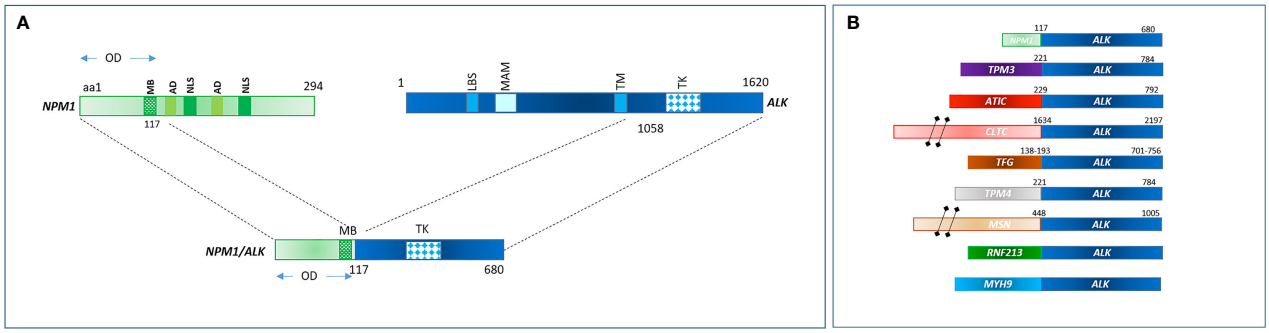

FIGURE 1
(A) *NPM1-ALK* rearrangement in ALCL as consequence of t(2;5)(p23;q35). **(B)** Commonest fusion genes involving ALK in ALCL.

term control of lymphoma cells expansion, by inducing deeper inhibition of oncogenic signaling and higher rates of apoptosis (31).

Second generation ALK inhibitors also appeared very interesting. Alectinib showed favorable clinical activity and was well tolerated in patients with ALK-positive ALCL who had progressed on standard chemotherapy (32). In a phase II clinical trial it induced objective responses in 8/10 patients, with 6 complete remissions (32). The 1-year progression-free survival, event-free survival, and overall survival rates were 58.3%, 70.0%, and 70.0%, respectively (32).

3 JAK/STAT signaling in PTCLs

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway are critical for blood formation and immune response (33). It includes over 30 transmembrane proteins that recognize specific cytokines, many of which transmit antiapoptotic, proliferative, and differentiation signals (33). Several cancers, including blood malignancies, have been associated with the constitutive activation of STAT family members, which normally require JAK-mediated tyrosine phosphorylation for transcriptional activation.

JAK/STAT signaling plays a prominent role in adult T-cell leukemia and lymphoma because of the effects of HTLV1 lymphomagenesis (34), T-large granular leukemia (35), T-lymphoblastic leukemia/lymphoma (35), cutaneous lymphomas (36, 37), and various nodal and extranodal TCLS (38). Notably, STAT3 is the main downstream effector of ALK in ALCL (22).

As far as nodal PTCLs are concerned, gene expression analyses first provided evidence for activation of the JAK/STAT pathway and the downstream nuclear factor kB (NF-kB) (39, 40), which was further confirmed by immunohistochemical detection of nuclear-phosphorylated STAT proteins (38). It is noteworthy that experimental retroviral-insertion mutagenesis performed on oligoclonal mature T-cells demonstrated the transforming potential of JAK1 in this setting through JAK/STAT pathway activation (41).

Several studies have consistently demonstrated the presence of recurrent mutations targeting the JAK/STAT pathways in various PTCLs, including NK/T-cell, nodal, and intestinal forms (42–44). However, it should be noted that the frequency of such mutations is relatively low (below 10%) in nodal PTCLs, mostly affecting JAK1, STAT3, and CCR4. In contrast, evidence of pathway activation is supported by nuclear staining of p-STAT3, p-STAT5, and p-STAT6 in at least 25–30% of cases (38, 44). Therefore, other activation mechanisms have been investigated. Common STAT activation mechanisms in PTCLs include the overexpression of TKs rather than ALK, such as LCK (45) or PDGRs (38, 46), microenvironment-mediated cytokine expression and interleukin-2 receptor engagement (47), and MTMR2 overexpression (48).

Interestingly, the activation of JAK/STAT and downstream NF-kB might represent a suitable therapeutic target in PTCLs. A recent phase I/II study tested ruxolitinib in cutaneous and nodal T-cell lymphomas. Cases were divided into three different cohorts based on the presence of activating mutations in JAK1, JAK2, JAK3, STAT3, or STAT5B (cohort1) or evidence of STAT3 activation by IHC in the absence of mutations (cohort 2). Patients enrolled in cohort 3 lacked both activation mutations and detection of nuclear p-STAT3. The overall clinical benefit rate (CBR) was defined as the combination of complete response (CR), partial response (PR), and stable disease lasting at least six months. Among the PTCL patients (n = 45), CBR was 53%, 45%, and 13% in cohorts 1, 2, and 3, respectively (P = .02). This indicated that the pre-treatment selection of patients could be very useful for effective direct treatment. Eight patients had a CBR > 12 months. Notably, the expression of phosphorylated S6, a marker of PI3 kinase or mitogen-activated protein kinase activation, was associated with clinical responses (P = .05) (49).

4 Platelet-derived growth factor receptors in PTCLs

Platelet-derived growth factor (PDGF) receptors (PDGFRs) belong to the family of receptor tyrosine kinases (RTKs). There are two isoforms of PDGF receptors, PDGFRα and PDGFRβ, which are encoded by two different genes: *PDGFRA* and *PDGFRB*. Five different ligands (PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC, and PDGF-DD) can bind to receptors, inducing their dimerization and functional activation (50). Phospholipase Cγ (PLCγ), phosphatidylinositol- 3-kinase (PI3K), SRC family kinases, and STATs) are the main PDGFR signaling downstream components (46). MAP kinases and other adaptor molecules are also recruited to PDGFR, which regulates multiple pathways (50)(Figure 3).

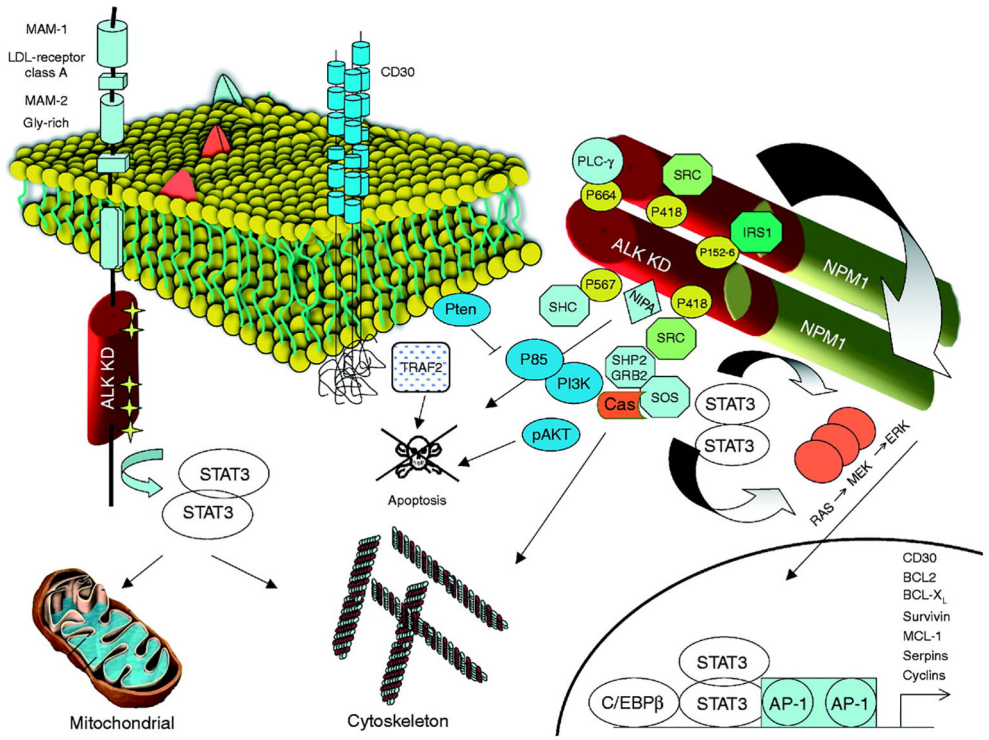

FIGURE 2
ALK and its signaling transduction pathways. Mutated ALK-R and ALK fusion proteins can elicit multiple signaling pathways, which are responsible for cell transformation and for the maintenance of the neoplastic phenotype. The kinase activation, in both mutated ALK and ALK chimeras, is associated with the docking of several adaptors, which in turn fire several signaling pathways. A critical oncogenic player is represented by the JAK/STAT3 pathway, which provides essential survival signals and modulates the cellular metabolism regulating the mitochondrial oxidation chain. STAT3 is activated by ALK either directly or through JAKs. Reproduced from Journal of Molecular Endocrinology 47, 1; 10.1530/JME-11-0004.

PDGFRA was found to be consistently overexpressed in PTCL/NOS in terms of both mRNA and protein expression, based on gene expression profiling and tissue microarray analysis (51). Subsequently, PDGFRA activation was shown to be necessary for PTCL cell proliferation and survival, as exposure to imatinib mesylate led to cell cycle arrest and apoptosis *ex vivo* and *in vivo* (52). Interestingly, unlike other malignancies, PDGFRA activation is not due to somatic mutations or other genetic events. Rather, it has been shown that autocrine stimulation through PDGF ligands could activate the receptor *ex vivo* and *in vivo* (38). Without ligand availability, PTCL cells showed PDGFRA dephosphorylation and consistent inactivation of downstream STATs (38). PDGFRA expression was also been detected in TFH-related PTCL angioimmunoblastic type (AITL) (53), cutaneous lymphomas, and anaplastic large cell lymphoma (38). Consistent with these findings, an *in vivo* study was conducted to demonstrate the relevance of PDGFRs activation in maintaining PTCL cell vitality (54). Simultaneously, different studies have provided clinical evidence of the potential effectiveness of TKI in PTCLs (38, 54).

Based on this data, clinical trials have been conducted to test different TKIs. Dasatinib, a multi-target TKI, was shown to increase the efficacy of chemotherapy, particularly the CHOEP scheme, both *in vitro* and *in vivo* (55). When dasatinib was used in the relapsed/refractory setting, the overall response rate among 10 PTCL patients was approximately 50%; however, 2 patients with PTCL/NOS carrying *LRRK2* mutations achieved stable and durable complete remission (56). Despite the limited number of patients, sorafenib showed intriguing efficacy, inducing CR in 3/3 PTCL patients (2 AITL) (57).

5 Targeting TK downstream the T-cell receptor

The engagement of immunoreceptors results in a bright proliferative and metabolic response in T-cells. This response is largely mediated by the NF-kB signaling pathway (40). Indeed, in T-cell lymphomas, ITK and GATA3 are involved, and not only does the T-cell receptor (TCR) supports proliferation and survival but also directly maintains chemotherapy resistance (58). Several TK participating in the TCR complex or mediating downstream signals have been reported to be either activated by somatic mutations and/or chromosomal translocations or simply overexpressed in PTCLs.

The most commonly affected lesion appears to be TK SYK. Feldman et al. reported in 2008 that SYK was consistently overexpressed in PTCL (59), and SYK inhibition led to PTCL cell apoptosis in an experimental model (60). However, since then, the actual role of wild-type SYK in PTCLs has not been demonstrated. In contrast, SYK is involved in the most common translocation observed in TFH-related PTCLs, specifically in the follicular variant, t (5, 9)(q33;q22), leading to the fusion gene *ITK-SYK* (61). The ITK-SYK fusion protein acts as a constitutively active SYK tyrosine kinase with oncogenic properties *in vitro* and *in vivo* by mimicking a constitutively active TCR signal. The conditional expression of ITK/SYK recapitulated the development of PTCL in a mouse model for the first time *in vivo* (62). Further evidence has shown that the transforming potential of t (5, 9)(q33;q22) is mediated by IL2RG/JAK3/STA3-STAT5 activation and is associated with CD69 expression (63, 64). Notably, although AITL can present with ITK gains (65), ITK/

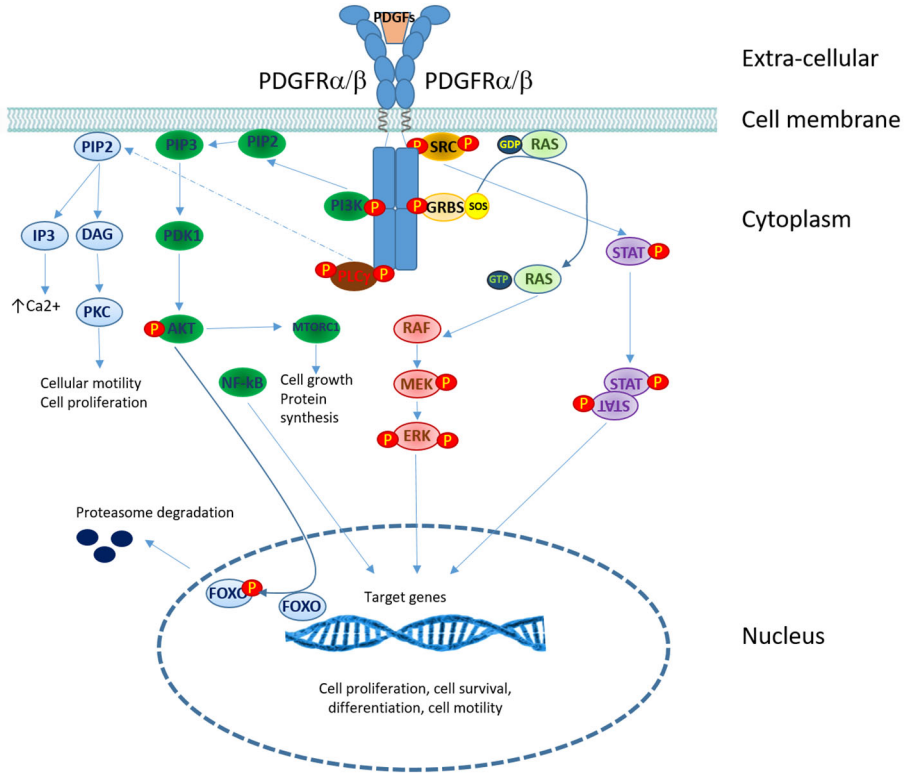

FIGURE 3
PDGFRs signaling in T-cell lymphomas. Overview of signaling pathways downstream of PDGF receptors. PDGF binding induces receptor dimerization and trans-phosphorylation. The recruitment of signaling and adaptor molecules to the phosphorylated receptor triggers several signaling cascades: phospholipase C γ (PLCγ), phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein (MAP) kinases and signal transducers and activators of transcription (STATs). (P, phosphorylation site).

SYK fusion is highly specific to follicular PTCL and is only exceptionally observed in AITL (66). Unfortunately, despite the rationale, the clinical use of ibrutinib, a Bruton tyrosine kinase inhibitor effective on ITK signaling, showed limited efficacy in PTCL in a pivotal trial (67).

Another TK associated with the TCR complex, which can be involved in chromosomal translocations, is FYN. FYN-TRAF3IP2 rearrangement was recently described in PTCL/NOS and is associated with NF-κB activation (68, 69). More rarely, LCK can hijack TCR signaling through KHDRBS1-LCK rearrangement (69).

6 Other tyrosine kinases in PTCLs

A few other TKs may have a relevant role in PTCL pathogenesis and may be good candidates as therapeutic targets.

Protein kinase C (PKC) is critical for T lymphocyte activation and proliferation. Different isoforms, including zeta, theta, and iota, are overexpressed in PTCLs (52, 70). They may promote cell survival through higher nitric oxide synthase (NOS) activity, which may represent a suitable target (71). Recently, Debackere et al. described t (1, 5)(p34;q21.3) and t (15, 16)(q26.1;q22.1) with ITK-FER and RLTPR-FES rearrangements, both acting through STAT3 phosphorylation (72).

Vascular endothelial growth factor receptor (VEGFR) is consistently overexpressed in AITL (53). Autocrine stimulation has been proposed as not being affected by genetic lesions of any type but being co-expressed with VEGF by neoplastic cells (1, 52, 53). However, no formal demonstration of this has been provided.

KIT is weakly expressed in approximately 30% of PTCL/NOS cases, presenting somatic mutations in exon 11 in only 5% of cases (72). Finally, B-lymphoid tyrosine kinase (BLK) expression in nodal PTCL should be evaluated, as it is commonly found in CTCL, and dasatinib showed some degree of effectiveness in such instances (73).

7 Conclusions and perspectives

Tyrosine kinases are often involved in the molecular pathogenesis of PTCL and are either activated by genetic events (somatic mutations and translocations) or simply overexpressed and activated by receptor engagement. Therefore, despite the existence of autocrine stimulation, the microenvironment plays a significant role.

So far, with few exceptions, TKIs have not yet shown prominent clinical activity. However, the strong biological rationale and the remarkable (though still anecdotic) experience in a few patients (Piccaluga (1, 52, 53); laimer; Umakanthan; gibson) suggest that this strategy should be better investigated. Furthermore, since TK signaling activates multiple downstream molecules, such as PI3K/AKT, JAK/STAT3-STAT5, mTOR, and SRC, it is reasonable to speculate that several small molecules targeting key effectors within these pathways should be investigated in PTCL patients. Additionally, given the

enormous redundancy of signal transduction pathways in a given PTCL case, it is conceivable that using disease/patient-specific cocktails will be more effective in successfully knocking down multiple players among different pathways. Therefore, targeting STAT, EGFR, SRC, and MEK may also be considered. Finally, novel immunological strategies, including checkpoint inhibitors and epigenetic modifiers combined with TKI and chemotherapy, might be considered to enhance anti-tumor responses and eventually achieve complete eradication of lymphomatous cells.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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