Oncogenic kinase fusions: an evolving arena with innovative clinical opportunities

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ABSTRACT

Cancer biology relies on intrinsic and extrinsic deregulated pathways, involving a plethora of intra-cellular and extra-cellular components. Tyrosine kinases are frequently deregulated genes, whose aberrant expression is often caused by major cytogenetic events (e.g. chromosomal translocations). The resulting tyrosine kinase fusions (TKFs) prompt the activation of oncogenic pathways, determining the biological and clinical features of the associated tumors. First reported half a century ago, oncogenic TKFs are now found in a large series of hematologic and solid tumors. The molecular basis of TKFs has been thoroughly investigated and tailored therapies against recurrent TKFs have recently been developed. This review illustrates the biology of oncogenic TKFs and their role in solid as well as hematological malignancies. We also address the therapeutic implications of TKFs and the many open issues concerning their clinical impact.

INTRODUCTION

The discovery of Philadelphia chromosome (Ph) in Chronic Myeloid Leukemia (CML) [1], the subsequent identification of the genes involved in this translocation [2] and the description of its molecular mechanisms [3, 4] have marked a scientific milestone, which dramatically shaped our understanding of kinase-mediated oncogenesis. Since these findings, many studies have investigated cell transformation via Tyrosine Kinase Fusions (TKFs). A recent appraisal of the literature shows that ~1000 independent studies have been published describing the oncogenic properties of TKFs. Recurrent kinase chimeras are detected in ~2-3% of human tumors and this frequency increases when non-recurrent fusions (4-5%) or cancer-associated abnormal karyotypes (5-7%) are considered [5]. TKFs do not represent the only cancer-associated gene derangement involving Tyrosine Kinases (TKs). During oncogenic transformation, TKs can indeed undergo a number of molecular impairments, including: (i) gene mutations; (ii) gene amplifications; (iii) chromosomal translocations; and (iv) non-fusion rearrangements (e.g. CRLF2 rearrangements in ALL) [6, 7]. All such Tyrosine Kinase (TK)-associated aberrations induce a huge variety of metabolic and signaling derangements, which ultimately lead to neoplastic transformation.

The widespread occurrence of TKFs in human cancers, their ability to synergistically fire multiple signaling pathways and their overall pivotal role in clinical oncology justify the many recent efforts to identify new anti-TKF target therapies. Of note, similar TKF-related pathways have been reported in different tumors; this constitutes the rationale for the use of similar therapies in tumors bearing the same molecular derangements. This approach is well represented by Ph-like leukemias, whose transcriptomes closely resemble those of conventional Ph-positive ALL, even in the absence of BCR-ABL translocations [8, 9]. This model and its corresponding
Patient Derived Tumor Xenografts (PDTX) allow the assessment of therapeutic agents targeting common molecular “hubs” [10]. This perspective is in line with the new “basket trial” era, where patients with different tumor types may be grouped together based on their tumors’ mutational profile.

In this review, the role of TKFs in both hematologic and solid neoplasms will be discussed. Special attention will be devoted to the many open issues concerning the treatment of TKF-bearing neoplasms.

STRUCTURES OF TKFs AND ROLE OF THE N-TERMINUS DOMAINS

Tyrosine kinases are the most common kinases and catalyze the transfer of a phosphate group from ATP to tyrosine residues. On a structural level, TK display a variety of modules dictating their cellular localization, function stability and response to therapy [11]. The enzymatic activity of these proteins relies on their TK domains (TKD), which are targeted by ATP-competitive and irreversible, covalent inhibitors [12]. Other important regions are the SH2 domains, the extracellular domains and remote allosteric sites, which can also be targeted by neutralizing drugs [13].

TKD are highly conserved modules, frequently composed by a N-terminal ATP-binding region and by a regulatory C-terminal domain. Upon activation, a cascade of events occurs, including ATP consumption, kinase dimerization, conformational changes, trans-autophosphorylation and oligo-complex formation. TK regulation is disrupted in oncogenic TKFs, which display constitutive dimerization due to loss of the inhibitory domains and forced oligodimerization of partner peptides [14]. Both inter- and intra-chromosomal rearrangements can lead to TKFs. Most break-points occur within introns and allow the synthesis of chimericomosomal rearrangements carrying the functional kinase domain and its flanking regions (Tables 1 and 2). Translocations involving TK membrane receptors frequently have breakpoints between exons coding for the juxta-membrane region. Though less frequent, the breaks can also split the trans-membrane domain upstream from the GXGXXG-coding exon. If protein products presenting the TK transmembrane domain localize to the cellular membrane, the exclusion of such a domain will localize the TK according to the properties of the translocation partner instead (Figure 1). In both cases, the natural TK ligand-binding site is lost. TKF involving intracytoplasmic kinases are also characterized by the loss of regulatory regions.

Gene fusions typically replace the TK promoter;

Figure 1: Structure and Signaling Transduction Motifs of Tyrosine Kinase Fusions. The constitutive activation of Tyrosine Kinase Fusion oncoproteins are achieved through multiple mechanisms taking advantage of direct or indirect oligodimerization. Seldom no dimerization are required. Fusion partners can also engage per se oncogenic signaling pathways, directly or indirectly modulating Transcription Factors (i.e. NFκB) and their corresponding genes. Kinase activation induces multiple canonical pathways (PI3K/AKT, JAK/STAT, PLCγ/PKC and RAS/ERK), which regulate genes controlling transcription and providing pro-tumorigenic signals. Compensatory pathways and regulatory modalities may act in place (i.e. miRNA regulation).
Therefore TKF expression becomes ectopically regulated by the promoter of the partner gene. Partner genes contribute to the oncogenic potential in a number of ways. In most instances, the partner N-terminus region provides dimerization domains, which recruit molecular adaptors and lead to the constitutive trans-phosphorylation and activation of the kinase. TKF partners can also directly activate oncogenic pathways, as observed in the TFG-NTRK1 and TRAF1-ALK fusions, independently activating the NF-kB pathway [15]. We and others have recently demonstrated that a small subset of systemic (<5%) and cutaneous (~20%) Anaplastic Large Cell Lymphomas (ALCL) bears ROS1 or TYK2 fusions. In such cases, the TKF N-terminus region comprises a transcription factor (NFkB) or a transcriptional repressor (NCOR2) fused to ROS1 and TYK2, respectively [16]. These TKFs clearly illustrate how the chimera may also influence the transcriptional activity of the partner genes, perturbing transcription promotion or repression. This, in turn, may lead to a widespread derangement of several metabolic and signaling pathways, which ultimately concur to neoplastic transformation [15, 16]. The N-terminus can also contribute to the neoplastic phenotype by preventing protein degradation through the recruitment of heat shock proteins (Hsp70, Hsp90) [17]. This may constitute a valid therapeutic target, as observed with Hsp90 inhibitors for the treatment of NPM-ALK ALCL [16, 17] and FLT3-positive leukemias [18]. Fusion partners can further contribute to neoplastic transformation by directing TKF localization. In T-ALL, for example, NUP214 of the NUP214-ABL orchestrates TKF nuclear pore localization, which is required for neoplastic transformation [19]. Similarly, the ectopic localization of NPM-ALK and FOP-FGFR1 contributes to oncogenesis by impacting centrosome deregulation and chromosomal instability. Lastly, fusion partners can act as dominant negative mutants. By decreasing the access to wild-type TPM3, TPM3-ALK fusions induce changes in the cytoskeleton organization and confer a higher metastatic capacity [20].

**TKF IN HUMAN CANCERS**

TKFs are found in many human cancers, although at very different frequencies. Among recurrent translocations, hematologic cancers were first shown to carry rearrangements characterized by TKF expression. Subsequent studies demonstrated that RET [21], TRK [22] or NTRK1 [23] were frequently translocated in a fraction of thyroid carcinomas, as well as other epithelial and soft tissue neoplasms [24, 25]. This list has grown steadily to >300 oncogenic TKF [5] (http://cgap.nci.nih.gov/Chromosomes/Mitelman) (Tables 1 and 2).

**Are TKF drivers or passengers in human oncogenesis?**

There is strong evidence that both TK and TKFs play an oncogenic role in human cancers [26-28]. Nevertheless, TKF-driven transformation requires multiple genomic defects and the contribution of the host microenvironment to drive oncogenesis. This paradigm is well represented by Chronic Eosinophilic Leukemia (CEL), where the sustained expression of FIP1L1-PDGFRα is necessary (but insufficient) to sustain eosinophils proliferation [29]. In humans, CEL also requires the overexpression of IL-5 through a single nucleotide polymorphism of *I L5RA*. The same holds true for systemic mastocytosis (SM), in which the constitutive activation of c-KIT alone is insufficient to induce the neoplastic phenotype and requires the stimulation of stem cell factor (SCF) as well [30].

This view is somehow challenged by seminal studies on other myeloproliferative neoplasms (MPNs), like CML, which may in fact represent monogenic disorders. The implantation of BCR-ABL (p210) retroviral-transduced marrow precursors into recipient mice can indeed cause rapidly progressing MPNs, which closely resemble human CML [31]. Of note, this scenario is hardly achievable in mouse models, where the TKF is ectopically expressed by means of more conventional molecular strategies [32, 33]. Moreover, Foley et al. have recently shown that the expression of BCR-ABL alone from the knock-in allele is unable to induce leukemia [34], suggesting that this TKF is per se insufficient to induce a disease fully recapitulating human CML. This latter hypothesis is consistent with the observation of BCR-ABL-positive hematopoietic cells also in healthy individuals [35], but is challenged by the observation that a fraction of CML patients who have achieved a sustained complete molecular remission (CMR) on imatinib can remain in CMR after drug withdrawal [36]. This latter observation raises the possibility that BCR-ABL signaling may not be the only driving force in some cases of CML. Of note, the concomitant loss of p14 (ARF) [37-39], and the critical role of Bcl-6 [40], miR-29 [41], and Raf1 [42] in CML suggest that the co-occurrence of selective defects and/or the full activation of selective pathways are required to achieve the complete neoplastic phenotype. This is line with the recent observation that IKF1-mutated P-positive high-risk ALL, in which IKF1 and Arf alterations synergistically promote the development of an aggressive lymphoid leukemia, can be effectively treated with retinoid receptor agonists which potentiate the activity of dasatinib in mouse and human BCR-ABL1 ALL [43].

The evidence that normal T-lymphocytes can undergo neoplastic transformation upon ectopic expression of fusion proteins alone (e.g. NPM-ALK) may further challenge the aforementioned paradigm [44]. Further studies are however needed to clarify this issue, as TKF transcripts have also been documented in healthy T-cells.
and in normal hematopoietic cells [35, 45]. Taken together, these observations indicate that TKFs alone are probably unable to drive T-cell neoplastic transformation completely and require secondary chromosomal abnormalities/TK activating mutations [46].

TKF expression levels may also play a role in tumor development. This is the case of ALK-translocated tumors: high NPM-ALK expression is indeed seen in ALCCL, while lower EML4-ALK levels characterize NSCLC. These differences are mainly due to different transcriptional activities of the partner genes. Lastly, the regulation of TKF expression may depend on miRNAs/translational regulation and TKF degradation. Overall, these data provide empirical support to the concept of global neutrality, or near-neutrality (i.e. very weak selection of the mutant clone in the early phases of neoplastic transformation) for TKFs [47].

Are TKFs required for the maintenance of a neoplastic phenotype?

It is generally believed that TKFs contribute to the maintenance of the neoplastic phenotype. This is well exemplified by the therapeutic success of TK inhibitors (TKi) for the treatment of chronic/indolent hematologic disorders (CML and CEL) [48, 49]. The oncogenic contribution of TKF to tumor maintenance can nevertheless vary according to several variables, including: (i) the properties of each fusion; (ii) the cellular context and the tumor microenvironment; (iii) the disease stage and evolution phase [28, 49]; (iv) the degree of oncogenic addiction to the TKF (e.g. ROS1-positive NSCLCs show better response to Crizotinib than ALK-positive NSCLCs) [50]; (v) the presence of concomitant genomic aberrations [30, 51]. In particular, the occurrence of multiple genetic defects may influence the response to therapy. This is the case of genetically complex disorders (e.g. ALL or end-stage solid cancers), which show a very aggressive clinical behavior and only partial responses to TKi [52]. The same holds true for some cases of ALK+ ALCCL. The majority of ALK+ ALCCL patients have a fairly good outcome with conventional chemotherapy treatments. However, rapid and even leukemic progression can occur. These are frequently associated with disrupting events, including TP53 and Blimp1 deletions [53] and c-myc translocation/amplifications. The acquisition of secondary events may indeed be linked to a more aggressive phenotype and can dampen the addiction to ALK signaling [15]. This mechanism has also been reported in CML in blast crisis [54] and in ALK-positive NSCLCs resistant to Crizotinib. In the first case, BCR-ABL induces an IGF1 autocrine loop via Hck and Stat5b, in the latter case, the IGF-IR signaling synergizes with (and overcome) ALK by engaging the adaptor protein IRS-1 [51]. Moreover, restoration of p16 (INKa) or p14 (ARF) into Ph-positive leukemic cells (both CML in blast crisis and ALL) is able to determine cell growth arrest and/or apoptosis suggesting a pathogenic role for these deletions and their co-operating role with BCR-ABL [39].

TKFs in hematopoietic disorders

Among hematologic malignancies, distinct subsets of acute leukemias, MPNs and non-Hodgkin lymphomas harbor specific TKFs (Table 1). The most frequent TKFs involve ABL-1 and PDGFRα/b, but translocations of ARG, JAK2, NTRK3 and SYK have been reported, as well. Not all partner genes provide oligodimerization domains, as in the case of the FIP1L1-PDGFRα fusion, which leads to the activation of the kinase moiety by disruption of its juxtamembrane regulatory motif [55]. Alternatively, the partners do not interact directly, but engage intermediate proteins leading to an indirect dimerization (e.g. CTCL-ALK, NUP214-ABL, FOP-FGFR1).

The t(9;22)(q34;q11) translocation juxtaposes the BCR and ABL1 genes in virtually all cases of CML and in a subset of adult/pediatric ALL. The latter may represent a de novo disease or, as in many adults, the blastic transformation of CML. Of note, adult and (more frequently) pediatric ALL carry other TKFs, which are associated with a Ph-like phenotype [9]. The oncogenic properties of such fusions have been demonstrated in a large variety of in vitro and in vivo systems [9, 56, 57]. The second most common TKFs involve PDGFRα, PDGFRβ and FGFR1. Such TKFs characterize a group of hematological disorders, sharing similar clinico-pathological features, such as peripheral blood eosinophilia, clinical presentation as MPN and/or lymphoid tumors, and, at least for PDGFRα and PDGFRβ fusions, good response to Imatinib. For this reason, the 2008 WHO Classification of hematopoietic and lymphoid tumors has introduced a separate diagnostic category for such disorders, referred to as “Myeloid and Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRα, PDGFRβ or FGFR1” [58].

Among mature T-cell neoplasms, subsets of Peripheral T-cell Lymphomas, not otherwise specified (PTCL, NOS) and Angioimmunoblastic T-cell Lymphomas (AITL) display SYK translocations and ITK-SYK fusion proteins [59-61]. ALK chimeras have been reported in a subset of ALCCL (ALK-positive ALCCL) [59], which are again recognized as a specific entity by the 2008 WHO Classification. Of note, the aberrant expression of ITK-SYK and NPM-ALK fusions in mice can lead to T-cell transformation [61, 62]. In particular, ITK-SYK mediates lymphomagenesis through the N-terminal phosphatidylinositol 3,4,5-trisphosphate-binding pleckstrin homology (PH) domain of ITK and SLP-76. ALK fusions, on the other hand, require the kinase domain and its flanking regions to activate multiple signaling pathways [59, 63]. Novel translocations
| Kinase | Activating Mechanisms | Chromosomal translocation | Entity | Kinase inhibitor | Frequency (%) | Reference |
|--------|-----------------------|---------------------------|--------|-----------------|---------------|-----------|
| ALK    | Fusion to NPM1        | t(2;5)(p23;q35)           | ALCL, DLBCL | Crizotinib | 75-80, N/A    | Morris et al. 1994, Adam et al. 2003 |
|        | Fusion to ALO17        | t(2;17)(p23;q25)          | ALCL    | Crizotinib | <1            | Cools et al. 2002 |
|        | Fusion to TGF          | t(2;3)(p23;q21)           | ALCL    | Crizotinib | 2             | Hernandez et al. 1999 |
|        | Fusion to MSN          | t(2;X)(p32;q11-12)        | ALCL    | Crizotinib | <1            | Tort et al. 2001 |
|        | Fusion to TPM3         | t(1;2)(q25;p23)           | ALCL    | Crizotinib | 12-18         | Lamant et al. 1999 |
|        | Fusion to TPM4         | t(2;19)(p23;p13)          | ALCL    | Crizotinib | <1            | Meech et al. 2001 |
|        | Fusion to ATIC         | inv(2)(p23;q35)           | ALCL    | Crizotinib | 2             | Ma et al. 2000 |
|        | Fusion to MYH9         | t(2;22)(p23;q11.2)        | ALCL    | Crizotinib | <1            | Lamant et al. 2003 |
|        | Fusion to TRAF1        | t(2;9)(p23;q33)           | ALCL    | Crizotinib | <1            | Feldman AL et al. 2013 |
|        | Fusion to CLTC1        | t(2;17)(p23;q23)          | ALCL, DLBCL | Crizotinib | 2, N/A       | Touriol et al. 2000 |
|        | Fusion to SQSTM1       | t(2;5)(p23.1;q35.3)       | DLBCL   | Crizotinib | N/A           | Takeuchi et al. 2010 |
|        | Fusion to SEC31A       | t(2;4)(p24;q21)           | DLBCL   | Crizotinib | N/A           | Bedwell et al. 2007 |
|        | Fusion to RANBP2       | inv(2)(p23;q13)           | AML     | Crizotinib | <1            | Maesako et al. 2014 |
| ABL    | Fusion to BCR          | t(9;22)(q34;q11)          | CML, B-ALL | Imatinib | 85-90, <30   | Klein et al. 1982 |
|        | Fusion to TEL          | t(9;12)(q34;p13)          | AML     | Dasatinib | <1            | Golub et al. 1996 |
|        | Fusion to NUP214       | t(9;9)(q34.1;q34.3)       | T-ALL, T-ALL, Ph-like ALL | Nitolinib | 5            | Graux et al. 2004, Roberts et al 2014 |
|        | Fusion to EML1         | t(9;14)(q34;q32)          | T-ALL   | Nitolinib | <1            | De Keersmaecker et al. 2005 |
|        | Fusion to ZMIZ1        | t(9;10)(q34;q22)          | B-ALL   | N/A | <1            | Soler et al. 2008 |
|        | Fusion to RCSD1        | t(1;9)(q24;q34)           | B-ALL   | Dasatinib | <1            | Mustjoki et al. 2009 |
|        | Fusion to FOXP1        | t(3;9)(p12;q34)           | B-ALL   | N/A | <1            | Ernst T et al. 2011 |
|        | Fusion to SNX2         | t(5;9)(q23;q34)           | B-ALL   | Imatinib | <1            | Ernst T et al. 2011, Masuzawa et al. 2014 |
|        | Fusion to SEPT9        | t(9;17)(q34;q25)          | T-PLL   | N/A | <1            | Suzuki et al. 2014 |
|        | Fusion to multiple partners | t(9;12)(q34;p13) | Ph-like ALL | Dasatinib | <1            | Roberts et al. 2012, Roberts et al. 2014 |
| ARG    | Fusion to TEL          | t(1;12)(q25;p13)          | AML, aCML | Imatinib | <1            | Golub et al. 1995 |
|        | Fusion to FIP1L1       | t(4;12)(q23;p12)          | HES     | Imatinib | 12            | Cools et al. 2003 |
| Fusion to BCR | t(4;22)(q12;q11.2) | CEL, T-ALL,  | Imatinib | <1 | Baxter et al. 2002, Yigit et al. 2015, Cluzeau et al. 2015 |
| Fusion to BCR | t(4;10)(q12;q23.3) | MPN, CML-like MPN w/ eosinophilia | Imatinib | <1 | Chalmer et al. 2014 |
| Fusion to STRN | t(2;14)(p22;q12) | MPN, CML-like MPN w/ eosinophilia | Imatinib | <1 | Curtis et al. 2007 |
| Fusion to STRN | t(4;12)(q23;p12) | MPN, CML-like MPN w/ eosinophilia | Imatinib | <1 | Curtis et al. 2007 |
| Fusion to KIF5B | t(4;12)(q12;p11) | MPN, CML-like MPN w/ eosinophilia | Imatinib | <1 | Score et al. 2006 |
| Fusion to CDK5RAP2 | ins(9;4) (q33;q12q25) | CEL | Imatinib | <1 | Walz et al. 2006 |
| PDGFRb | Fusion to TEL | t(5;12)(q33;p13) | CMML | Imatinib | 4 | Golub et al. 1994 |
| PDGFRb | Fusion to HIP1 | t(5;7)(q33;q11) | CMML | Imatinib | 4 | Ross et al. 1998 |
| PDGFRb | Fusion to Rabaptin5 | t(5;17)(q33;p13) | CMML | Imatinib | <1 | Magnusson et al. 2001 |
| PDGFRb | Fusion to H4(D10S170) | t(5;10)(q33;q11-q21) | aCML | Imatinib | <1 | Kulkarni et al. 2000 |
| PDGFRb | Fusion to CEV14 | t(5;14)(q33;q32) | AML | Imatinib | <1 | Abe et al. 1997 |
| PDGFRb | Fusion to Myomegalin | t(1;5)(q23;q33) | Eosinophilia | Imatinib | <1 | Wilkinson et al. 2003 |
| PDGFRb | Fusion to ATF71P | t(5;12)(q23;p13) | Ph-like ALL | Imatinib | <1 | Kobayashi et al. 2015 |
| PDGFRb | Fusion to EBF1 | t(5;5)(q33.1;q33.3) | Ph-like ALL | Dasatinib | <1 | Roberts et al. 2012, Roberts et al. 2014 |
| FGFR1 | Fusion to multiple partners | t(2;8)(q12;p11) | EMS, AML | None | <1 | Etienne et al. 2007 |
| FGFR1 | Fusion to FOP | t(6;8)(q27;p11) | MPN | None | <1 | Lee et al. 2014 |
| FGFR1 | Fusion to SQSTM1 | t(5;8)(q35;p11) | AML | None | <1 | Nakamura Y et al. 2014 |
| FGFR3 | Fusion to TEL | t(4;12)(p16;p13) | PTCL | Fiin23, NVP-BGJ398 | <1 | Maeda et al. 2005 |
| FGFR3 | Fusion to IGH | t(4;14) (p16; q32) | CLL | Fiin23, NVP-BGJ398 | <1 | Geller et al. 2014 |
| FGFR3 | Fusion to TIF1 | t(7;8)(q34;p11) | MDS, CML-like | Fiin23, NVP-BGJ398 | <1 | Maeda et al. 2005 |
| JAK2 | Fusion to TEL | t(9;12)(p24;p13) | ALL, CML-like | Ruxolitinib | <5 | Lacronique et al. 1997 |
| JAK2 | Fusion to OFD1 | t(X;9)(p22;p24) | ALL | Jak2 inhibitors | <1 | Yano et al. 2015 |
| JAK2 | Fusion to SPAG9 | t(9;17)(p24;q21) | ALL | Jak2 inhibitors | <1 | Kavamura M et al. 2015 |
| JAK2 | Fusion to PAX5 | t(9;9)(p13;p24) | ALL | Jak2 inhibitors | <1 | Nebral K et al. 2009 |
| JAK2 | Fusion to BCR | t(9;22)(p24;q11.2) | aCML | Ruxolitinib | <5 | Griesinger et al. 2005 |
| JAK2 | Fusion to multiple partners | t(9;12)(p24;p13) | Ph-like ALL | Jak2 inhibitors | <1 | Roberts et al. 2012, Roberts et al. 2014 |
| NTRK3 | Fusion to TEL | t(12;15)(p13;q25) | AML | None | <1 | Knezevich et al. 1998 |
involving \( \text{TYK2} \) and \( \text{ROS-1} \) in CD30-positive cutaneous lymphoproliferative disorders [64] and systemic ALK-negative ALCL [16] have been previously described. Interestingly, in addition to \( \text{NPM-1} \), \( \text{NFkB2} \) and \( \text{NCOR2} \) are partners of these new TKFs and contribute to the neoplastic phenotype [16]. Finally, precursor T-cell neoplasms (i.e. T-cell acute lymphoblastic lymphoma [T-ALL]) may also harbor TKFs, which usually involve the \( \text{ABL} \) gene. Some of such translocations are also observed in B-ALL (e.g. ABL-NUP214), while others seem to be specific of T-ALL (ABL-EML1) [65] (Table 1). Interestingly, several lymphoproliferative disorders also display TK oncogenic mutations, further demonstrating the tumorigenic role of deregulated kinase signaling in hematopoietic disorders [66, 67].

TKFs are less frequent in mature non-Hodgkin B-cell neoplasms, with the notable exception of ALK-positive diffuse large B-cell lymphoma, in which the TKFs bear distinct oncogenic and clinico-pathological features [68] (Table 1).

### TKFs in Solid Tumors

In solid tumors, aberrant TK activity results from diverse mechanisms, including: (i) point mutations; (ii) gene amplifications; (iii) gene overexpression; and (iv) chromosomal translocations [51, 69, 70]. Abnormal TK activity can also result from de novo transcription initiation (ATI) sites, which lead to the synthesis of truncated intracellular TKDs (e.g. ALK\textsuperscript{ATI} in melanoma or ERBB\textsuperscript{ATI} in ALCL) [71, 72].

In recent years, a wide array of recurrent translocations has been reported in solid tumors (Table 2) [14, 28]. In a systematic survey of nearly 7000 samples from the Cancer Genome Atlas, Stransky \textit{et al.} have depicted an extremely variegated translocation landscape in solid tumors [5], which can display heterogeneous chromosomal translocations, with specific malignancies (such as sarcomas) being characterized by a high percentage of non-recurrent translocations and/or infrequent but recurrent gene fusions.

| SYK     | Fusion to TEL | t(9;12)(q22;p12) | MDS       | Imatinib | <1 | Kanie \textit{et al.} 2004 |
|---------|---------------|-----------------|-----------|----------|----|---------------------------|
| Fusion to ITK | t(5;9)(q33;q22) | PTCL-NOS, AITL | None      | 17, <1  | Streubel \textit{et al.} 2006, Attygale \textit{et al.} 2013 |
| TRKC    | Fusion to TEL | t(12;15)(p13;q25) | AML and fibrosarcoma | None | <1 | Dobus \textit{et al.} 2001 |
| FLT3    | Fusion to ETV6 | t(12;13)(p13;q12) | HES       | Sunitinib, Midostaurin, Lestaurnitin | <1 | Vu \textit{et al.} 2006 |
| ETV6    | Fusion to TEL | t(4;12)(p16;p13) | PTCL-NOS  | Ruxolitinib | <1 | Yagasaki \textit{et al.} 2001 |
| CSF1R   | Fusion to SSBP2 | t(5;5)(q14;q33) | Ph-like ALL | Dasatinib | <5 | Mullighan \textit{et al.} 2009, Roberts \textit{et al.} 2014 |
| CRLF2   | Fusion to IGH  | t(X;14)(p22;q32)/t(Y;14)(p11;q32) | Ph-like ALL | Jak2 inhibitors | <5 | Mullighan \textit{et al.} 2009, Roberts \textit{et al.} 2014 |
| ROS1    | Fusion to NFKB2 | t(6;10)(q22;q24) | ALCL      | Ros1 inhibitors | <1 | Crescenzo \textit{et al.} 2015 |
| Fusion to NCOR2 | t(6;12)(q22;q24) | ALCL      | Ros1 inhibitors | <1 | Crescenzo \textit{et al.} 2015 |
| TYK2    | Fusion to NFKB2 | t(19;10)(p13;q24) | ALCL      | Tyk2 inhibitors | <1 | Crescenzo \textit{et al.} 2015 |
| Fusion to NPM1 | t(19;5)(p13;q35) | LPDs      | Tyk2 inhibitors | <1 | Velusamy \textit{et al.} 2014 |
| LYN     | Fusion to NCOR | t(8;17)(q13;p11) | ALL       | NA        | <1 | Yano \textit{et al.} 2015 |

**Abbreviation:**
ALCL: anaplastic large cell lymphoma, AML: acute myeloid leukemia, B-ALL: B-cell acute lymphoblastic leukemia; T-ALL: T-cell acute lymphoblastic leukemia, Ph-like ALL: Philadelphia Chromosome like acute lymphoblastic leukemia, CEL: chronic eosinophilic leukemia, CML: chronic myeloid leukemia; aCML: atypical chronic myeloid leukemia, CMML: chronic myelomonocytic leukemia, DLBCL: diffuse large B-cell lymphoma, EMS: 8p11 myeloproliferative syndrome, HES: hyper eosinophilic syndrome, LPDs: lymphoproliferative disorders, MDS: myelodysplastic syndrome, MPN: myeloproliferative neoplasm, PTCL-NOS: peripheral T-cell lymphoma not otherwise specified.
| Kinase | Activating Mechanisms | Chromosomal translocation | Entity | Kinase inhibitor | Frequency (%) | Reference |
|--------|-----------------------|---------------------------|--------|----------------|--------------|----------|
| **ALK** | Fusion to ATIC | inv(2)(p23;q35) | IMT | Crizotinib | < 5 | Debiec-Rychter et al. 2003 |
|        | Fusion to CARS | t(2;11)(p23;p15) | IMT | Crizotinib | <5 | Cools et al. 2002 |
|        | Fusion to CLTC | t(2;17)(p23;q23) | IMT | Crizotinib | <5 | Bridge et al. 2001 |
|        | Fusion to EML4 | inv(2)(p21;q23) | NSCLC | Crizotinib, Ceritinib, Alecitinib | 2-5 | Soda et al. 2007 |
|        | Fusion to FN1 | t(2;11)(q31;p15) | Soft tissue sarcoma | Crizotinib | <5 | Lin et al. 2009 |
|        | Fusion to KIF5B | t(2;10)(p23;p11) | NSCLC | Crizotinib | <1 | Takeuchi et al. 2009 |
|        | Fusion to KLC1 | t(2;14)(p23;q32) | NSCLC | Crizotinib | <5 | Jung et al. 2012 |
|        | Fusion to RANBP2 | t(2;2)(p23;q13) | IMT | Crizotinib | <5 | Ma et al. 2003 |
|        | Fusion to SEC31L1 | t(2;4)(p23;q21) | IMT | Crizotinib | <5 | Panagopoulos et al. 2006 |
|        | Fusion to VCL | t(2;10)(p23;q22) | RCC | Crizotinib | <3 | Debelenko et al. 2011 |
|        | Fusion to SEC31A | t(2;4)(p23;q21) | NSCLC | Crizotinib | <1 | Kim et al. 2015 |
|        | Fusion to STRN | t(2;2)(p23;q22) | Thyroid cancer | Crizotinib | <1 | Pérot et al. 2014, Kelly et al. 2013 |
|        | Fusion to GTF2IRD1 | t(2;7)(p23;q11.23) | Thyroid cancer | Crizotinib | <1 | Stransky et al. 2015 |
|        | Fusion to TFG | t(2;3)(p23;q21) | NSCLC | Crizotinib | 2 | Rikova et al. 2007 |
|        | Fusion to TPM1 | t(2;15)(p23;q22.2) | Bladder cancer | Crizotinib | <1 | Stransky et al. 2015 |
|        | Fusion to TPM3 | t(1;2)(q21;p23) | IMT | Crizotinib | 50 | Lawrence et al. 2000 |
|        | Fusion to TPM4 | t(2;19)(p23;p13) | IMT | Crizotinib | <5 | Lawrence et al. 2000 |
|        | Fusion to PTPN3 | t(2;9)(p23;q31.3) | NSCLC | Crizotinib | <1 | Jung et al. 2012 |
|        | Fusion to A2M | t(2;12)(p23;p13) | FLIT | Crizotinib | <1 | Onoda et al. 2014 |
|        | Fusion to TPR | t(2;1)(p23;q31.1) | NSCLC | Crizotinib | <1 | Choi et al. 2014 |
|        | Fusion to HIP1 | t(2;7)(p23;q11.23) | NSCLC | Crizotinib | <1 | Hong et al. 2014 |
|        | Fusion to SQSTM1 | t(2;5)(p23;q35) | NSCLC | Crizotinib | <1 | Iyevleva et al. 2015 |
|        | Fusion to DCTN1 | t(2;2)(p23;p13) | NSCLC | Crizotinib | <1 | Iyevleva et al. 2015 |
|        | Fusion to SMEK2 | t(2;2)(p23;p16.1) | CRC | Crizotinib | <1 | Stransky et al. 2015 |
|        | Fusion to CAD | inv(2)(p22-21p23) | CRC | Entrectinib | <1 | Lee et al. 2015, Amatu et al. 2015 |
| ROSI   | Fusion to CD74 | t(5;6)(q32;q22) | NSCLC | Crizotinib | <2 | Bergehton et al. 2012 |
|        | Fusion to EZR | inv(6)(q22q25.3) | NSCLC | Crizotinib | <2 | Arai et al. 2013 |
|        | Fusion to GOPC | del(6)(q22q22.3) | NSCLC | Crizotinib | <2 | Rimkunas et al. 2012, Suehara et al. 2012 |
| Fusion to Lrig3 | t(6;12)(q22;q14.1) | NSCLC | Crizotinib | <1 | Gu et al. 2011 |
|----------------|--------------------|-------|-----------|----|----------------|
| Fusion to SDC4 | t(6;20)(q22;q12)   | NSCLC | Crizotinib | <2 | Davies et al. 2012 |
| Fusion to SLC3A2| t(4;6)(q15.2;q22)  | NSCLC | Crizotinib | <2 | Davies et al. 2012|
| Fusion to TPM3 | t(1;6)(q21.2;q22)  | NSCLC | Crizotinib | <2 | Takeuchi et al. 2012|
| Fusion to TFG  | t(6;3)(q22.1;q12.2)| IMT   | Crizotinib | <1 | Yamamoto et al. 2015|

**RET**

| Fusion to CCDC6| inv10(q11;q21) | NSCLC | Cabozantinib, Vandetanib | <2 | Wang et al. 2012 |
|----------------|---------------|-------|--------------------------|----|------------------|
| Fusion to KIF5B| inv(10)(p11;q11)| NSCLC | Cabozantinib, Vandetanib | <2 | Ju et al. 2012 |
| Fusion to NCOA4| inv(10)(q11;q11)| Thyroid cancer | Cabozantinib, Vandetanib | <2 | Rui et al. 2012|
| Fusion to PRKAR1A| t(10;17)(q11.2;q23)| Thyroid cancer | Cabozantinib, Vandetanib | <2 | Rui et al. 2012|

**BRAF**

| Fusion to KIAA1549| t(7;7)(q34;q34)| Brain tumors | BRAF/MEK inhibitors | <1 | Tian et al. 2011 |
|-------------------|---------------|-------------|---------------------|----|------------------|
| Fusion to FAM131B | t(7;7)(q34;q34)| Brain tumors | BRAF/MEK inhibitors | <1 | Cin et al. 2011 |
| Fusion to CEP89   | t(7;19)(q34;q13)| Melanoma | BRAF/MEK inhibitors | <5 | Wiesner et al. 2014|

**FGFR1**

| Fusion to TACC1   | t(8;8) (p11.23;p11.22)| GBM | FGFR inhibitor | <3 | Singh et al. 2012 |
|-------------------|-----------------------|----|---------------|----|------------------|
| Fusion to BAG4    | t(8;8) (p11.23;p11.23)| NSCLC | FGFR inhibitor | <1 | Rui et al. 2014 |

**FGFR2**

| Fusion to BICC1   | t(10;10)(q26;q21.1)| CCA | FGFR inhibitor | <1 | Yi-Mi et al. 2013|
|-------------------|-------------------|-----|---------------|----|------------------|
| Fusion to KIAA1967| t(10;8)(q26;p21.3) | NSCLC | FGFR inhibitor | <1 | Yi-Mi et al. 2013|

**FGFR3**

| Fusion to TACC3   | del4(p16;p16) | GBM | FGFR inhibitor | <3 | Singh et al. 2012, Bao et al. 2014 |
|-------------------|--------------|----|---------------|----|------------------|
|                    |              | Bladder cancer | FGFR inhibitor | <2 | Williams et al. 2013|
|                    |              | NSCLC | FGFR inhibitor | <2 | Rui et al. 2014 |
|                    |              | ESCC | FGFR inhibitor | <1 | Yuan et al. 2014|

**FGFR3**

| Fusion to TACC3   | del4(p16;p16) | GBM | FGFR inhibitor | <3 | Singh et al. 2012, Bao et al. 2014 |
|-------------------|--------------|----|---------------|----|------------------|
|                    |              | Bladder cancer | FGFR inhibitor | <2 | Williams et al. 2013|
|                    |              | NSCLC | FGFR inhibitor | <2 | Rui et al. 2014 |
|                    |              | ESCC | FGFR inhibitor | <1 | Yuan et al. 2014|
| Abbreviation: |  |
|----------------|----------------|
| BC: breast cancer, CCA: cholangiocarcinoma, CFS: congenital fibrosarcoma, CRC: colon-rectal cancer, ESCC: esophageal squamous cell carcinoma, FL-HCC: fibrolamellar hepatocellular carcinoma, FLIT: fetal lung interstitial tumor, GBM: glioblastoma, GIST: gastrointestinal stromal tumor, HGG: high grade glioma, HGSC: high-grade serous ovarian cancer, IMT: inflammatory myofibroblastic tumor, MASC: mammary analogue secretory carcinoma of salivary glands, NPC: nasopharyngeal carcinoma, NSCLC: non-small cell lung cancer |

| Gene/Abbreviation | Fusion to | Chromosome | Cancer Type | Kinase | Inhibitor | Reference |
|-------------------|-----------|-------------|-------------|--------|-----------|-----------|
| **NTRK1**         | TPM3      | t(1;3)(q21;q11) | Thyroid cancer | TRKA | Falconiz | Beimfohr et al. 1999 |
|                    | CRC       |             | Cervical cancer | TRKA | Falconiz | Creancier et al. 2015 |
|                    | HGG       |             | Thyroid cancer | TRKA | Falconiz | Wu et al. 2014 |
| Fusion to TPR      | inv1(q23;q21) | Thyroid cancer | TRKA | Falconiz | Greco et al. 1999 |
| Fusion to MPRIP    | t(1;17)(p11) | NSCLC | TRKA | Falconiz | Vaishanvi et al. 2013 |
| Fusion to CD74     | t(1;5)(q21;q32) | NSCLC | TRKA | Falconiz | Vaishanvi et al. 2013 |
| Fusion to RABGAP1L | t(1;1)(q21;25.1) | CCA | TRKA | Falconiz | Ross et al. 2014 |
| Fusion to SQSTM1   | t(1;5)(q21;q35) | NSCLC | Entrectinib | Falconiz | Farago et al. 2015 |
| Fusion to LMNA     | t(1;1)(q21;q22) | Soft tissue sarcoma | LOXO-101 | Falconiz | Doelebe et al. 2015 |
|                    | CRC       |             | Entrectinib | Falconiz | Sartore-Bianchi et al. 2015 |
| **NTRK2**         | VCL       | t(9;10)(q22.1;q22) | HGG | TRKA | Falconiz | Wu et al. 2014 |
| Fusion to AGBL4    | t(9;1)(q22.1;p33) | HGG | TRKA | Falconiz | Wu et al. 2014 |
| **NTRK3**         | ETV6      | t(12;15)(p13;q25) | Thyroid cancer | TRKA | Falconiz | Ricarte-Filho et al. 2013 |
|                    | IMT       |             | CFS | TRKA | Falconiz | Knezevih et al. 1998 |
| Fusion to ETV6     | t(12;15)(p13;q25) | Thyroid cancer | TRKA | Falconiz | Ricarte-Filho et al. 2013 |
| Fusion to BTBD1    | t(15;15)(p24;q25) | HGG | TRKA | Falconiz | Wu et al. 2014 |
| **AKT2**          | BCAM      | t(19;19)(q13.2;q13.3) | HGSC | AKT2 | Falconiz | Kamani et al. 2015 |
| PRKACA            | DNAJB1    | t(19;19)(p13.1;p13.2) | FL-HCC | PKA | Falconiz | Honeyman et al. 2014 |
| PRKD1             | ARID1A    | t(14;1)(q12;p36) | Salivary gland tumor | PRKD1 | Falconiz | Weinreb et al. 2014 |
| MET               | PTPRZ1    | t(7;7)(q31.2;q31.3) | GBM | MET | Falconiz | Bao et al. 2014 |
| PIK3CA            | TBL1XR1   | t(3;3)(q26.3;26.32) | BC | PIK3CA | Falconiz | Stransky et al. 2015 |
To date, fusions involving 14 different TKs have been described in solid tumors (Table 1). ALK is translocated in several tumors, including lung, colorectal, breast, renal, thyroid carcinomas and soft tissue tumors. Fusion partners include EML4, TFG, KIF5B, KLC1 and STRN [28]. Rare translocations involving SMEK2 (rectal adenocarcinoma) or GTF2IRD1 (thyroid carcinoma) have also been reported.

Next generation sequencing (NGS) analyses have highlighted new patterns of translocations, defining specific subgroups of common solid tumors (BRAF in melanoma; FGFR1, FGFR2, FGFR3 in lung cancer; NTRK in thyroid cancer), and in clinically unmet patients (BRAF and FGFR1 translocations in pediatric low-grade glioma; NTRK1 and NTRK2 in high-grade gliomas, and cholangiocarcinoma, Table 1). Lastly, MET is involved in chromosomal translocations of secondary glioblastomas and papillary renal carcinomas and P3KCA translocations are observed in breast and prostate carcinomas.

The transforming activity of TKF in solid cancers has been extensively characterized through pre-clinical models [73], proving that classical MEK-ERK and PI3K-AKT pathways are critical players in sustaining the transformed phenotype and in mediating resistance to targeted therapies [74]. TKF dependency thus provides a molecular explanation for the “oncogene addiction” of different TKF-driven tumors [75].

Mechanistically, multiple causes of chromosomal translocations have been predicted: (i) exposure to toxic agents (probably the major initiating event); (ii) exposure to ionizing radiation (e.g. in papillary thyroid carcinoma); (iii) oxidative stress and chemotherapeutic agents (e.g. topoisomerase inhibitors).

**DISCOVERY AND DETECTION OF TK FUSIONS**

The oncogenic role of TKFs has prompted huge efforts to improve their detection in cancer patients to better guide patient-directed treatment strategies [76].

Affinity purification coupled with mass spectrometry (AP-MS) is a powerful tool to characterize aberrant gene products and protein-protein interactions (PPIs). AP-MS has been successfully used to discover novel TKFs in NSCLC (ALK and ROS1) [77] and rare TKFs in other tumor histotypes [78]. AP-MS could also define activating mutations linked to TKi-resistant phenotypes [79]. Furthermore, proteomic patterns distinguish normal from pathological tissues and correctly classify primary/metastatic lesions, allowing tailored treatments and a better stratification of NSCLC [80].

The introduction of NGS-based approaches has rapidly enriched the overall knowledge of TKF, giving a better representation of their distribution in human cancers. In hematologic malignancies, NGS studies of Ph-like ALL have detected TKFs in >90% of patients [8]. Technically, both RNAseq and Whole Exome Sequence (WES) made these achievements possible. In some cases an exon capture specific for TK genes followed by massive parallel sequencing was applied [81-84]. Since these analyses can be performed on formalin-fixed paraffin-embedded samples, they can be applied to routine clinical practice. The possibility to test archived material will also allow for the characterization of the clonal evolution of TKF-bearing tumors, with consequent implementation of cancer tailored therapies.

**Clinical diagnostic tests: tumor fingerprints**

Clinically, TKF in human hematological cancers can be detected by an array of techniques. Genomic/conventional cytogenetics (CG) or FISH are commonly used for the detection of BCR-ALB translocations. Negative samples (<5% of cases) frequently carry variant translocations or cryptic rearrangements, which can occasionally be detected by FISH. Both approaches are also used to monitor drug responses and disease evolution. FISH and RT-PCR have shown higher sensitivity at diagnosis and better MRD detection than CG. In particular, qRT-PCR has become the gold standard for the diagnosis of MRD [49]. FuseFISH probe-based approaches for the detection of fusion transcripts have also recently emerged [85], but their usefulness in clinical practice is uncertain.

Resistance to TKi treatments is currently detected by RT-PCR coupled with DNA Sanger sequencing, but new methods have been developed. Massive parallel sequencing is rapidly replacing the above reported strategies, as it can also identify subclonal populations and characterize tumor clonal heterogeneity [86]. Analogous approaches have now been extended to the detection of actionable mutations, copy number variations, and gene rearrangement in clinical cancer specimens.

In solid tumors, TKFs are clinically identified by several techniques, some of which are performed as companion tests to select the best TKi agent. In 2013, the USA and China’s FDA approved FISH- and IHC-based diagnostic tests to identify ALK fusions or ALK protein expression in NSCLC. Similar strategies were proposed to assess ROS1 and RET fusions [87]. Alternatively, a NGS-based detection kit for RET-rearrangements has been used to enroll patients in NSCLC clinical trials [Eisai sponsored trial; NCT01829217]. It is conceivable that screening approaches to detect simultaneously multiple fusions will be implemented in the clinical arena [88].

Since different TKFs can be present in distinct cancer subsets, multi-targeted platforms have emerged as powerful tools to screen diagnostic samples. As multi-gene screening methods are entering into routine diagnostic procedures, new technical and therapeutic questions need to be addressed. Indeed, the greater efficacy of TKi compared to conventional treatments needs to be established for naïve patients carrying targetable fusions.
Similarly, patients treated with multiple rounds of chemotherapeutic regimens need to be evaluated for the compliance to selective TKi, as limited data are available to justify their usage.

**TUMOR-ASSOCIATED TK TRANSLOCATIONS: CURRENT THERAPEUTIC STRATEGIES**

The discovery of recurrent tumor-associated TK translocations has brought new strategies for the treatment of hematologic and non-hematologic tumors. In the last decades, TKi have revolutionized the treatment of CML, Ph-positive B-ALL [89] and NSCLC carrying ALK or ROS-1 gene rearrangements [14, 90].

**TKi-based therapies for the treatment of hematological tumors**

**BCR-ABL1** gene rearrangements are reported in all cases of CML and in about 30% of adult B-ALL. The fusion gene usually results from the t(9;22)(q34;q11.2) translocation, but 5-10% of cases bear variants and/or cryptic translocations [2]. BCR-ABL1 oncogenic properties are due to the constitutive activation of ABL1 TK [91, 92] and the loss of ABL-1 N-terminus regulatory domain.

Clinically, Imatinib has revolutionized the prognosis and outcome of CML, converting a highly lethal hematological neoplasm to a chronic and curable disease [49]. Complete cytogenetic responses (CCyR) are indeed reported in 87% of Imatinib-treated patients, with a progression-free survival (PFS) of 93% [93]. After 2 years of sustained CCyR, the life expectancy for CML patients is comparable to that of the general population [94]. Despite these results, several studies pinpointed a subset of cases with primary/secondary resistance to Imatinib, which can be overcome by new generation TKi (i.e. Nilotinib, Dasatinib and Bosutinib) with improved clinical efficacy [95]. These lines of evidence led the European Leukemia Net to recommend Imatinib, Nilotinib and/or Dasatinib as first line drugs for the treatment of CML. More aggressive therapeutic approaches (e.g. hematopoietic stem cell transplant) are considered only in very selected cases (e.g. refractory/relapsing cases unresponsive to TKi or accelerated/blast phase CML) [49].

In CML patients, resistance to TKi can result from two major mechanisms: (i) occurrence of TKi-resistant BCR-ABL1 mutations; (ii) enhancement of BCR-ABL1-independent pro-survival pathways. BCR-ABL1-dependent resistance has been overcome by third generation TKi that also target the most common ABL1 mutations (e.g. BCR-ABL1 T315I) [96]. The most promising therapeutic agents are the conventional TKi, Ponatinib, and the BCR-ABL1 switch control inhibitor, DCC-2036 [96]. Notably, good results with Ponatinib have been obtained even in accelerated and blast phase CML [97], while the distinct action of DCC-2036 may overcome pre-existing mutations, including T315I [96]. Pemovska et al. have recently re-proposed the utility of Axitinib, an anti-VEGFR molecule approved for renal cell carcinoma, to counteract the resistance phenotype of T315I gatekeeper CML. Indeed, Axitinib tightly binds the T315I mutated kinase and inhibits leukemic cell growth, showing a better toxicity profile than other new-generation drugs, such as Ponatinib [98].

BCR-ABL1-independent resistance is mainly due to the activation of alternative signaling pathways promoting neoplastic cell survival [99]. Such pathways can be either extrinsic (i.e. activated by the marrow microenvironment) or intrinsic (i.e. due to microenvironment-independent mechanisms). Both intrinsic and extrinsic pathways lead to the activation of STAT3, through its phosphorylation at Tyr-705 [100]. Combined inhibition of STAT via BP-5-087, a potent and selective STAT3 SH2 domain inhibitor and BCR-ABL1 leads to synthetic lethality in resistant CML and constitutes a very promising therapeutic approach for refractory/relapsing CML [100]. Another therapeutic opportunity is represented by glitazones, anti-diabetic drugs that down-regulate STAT5 expression by inhibiting the peroxisome proliferator-activated receptor-γ (PPARγ). Recent data show that their use may lead to the complete eradication of leukemic stem pools, thus greatly improving the survival of CML patients in sustained CMR [101].

Unlike what has been observed in CML, the use of single-agent TKi in Ph-positive ALL has not produced sustained clinical responses. This is probably due to the rapid development of TK mutations, which are reported in >80% of adult Ph-positive ALLs at relapse [102]. Ph-positive ALL and CML also greatly differ in terms of genomic backgrounds, which may influence the response to TKi. For instance, INK4-ARF deletions, which often occur in acute Ph-positive ALL with aggressive clinical course, facilitate the emergence of BCR-ABL drug-resistant clones. This molecular event is not observed in indolent CML or in CML in blast crisis [103].

These data provide the rationale for the use of multimodal regimens for the treatment of Ph-positive ALL, based on a combination of intensive chemotherapy and TKi. Very encouraging results have been first obtained in pediatric trials (COG, EShALL and SHOP-2005 trials) [104, 105] and, more recently, in adult patients [106]. In particular, a recent Phase II trial on Imatinib mesylate plus HyperCVAD (Cyclophosphamide, Vincristine, Doxorubicine, Dexamethasone) has reported complete clinical remission in 93% of adults with active Ph-positive ALL, with a 5-year overall survival (OS) of 43%. Notably, allogeneic stem cell transplant (ASCT) after Imatinib and HyperCVAD improved median OS only in patients with residual molecular disease. The role of Dasatinib and Nilotinib for the treatment of pediatric
and adult Ph-positive ALL is still under evaluation, but preliminary results indicate their safety and efficacy when used with high dose chemotherapy and/or ASCT [107]. Encouraging data have also been obtained with Dasatinib and corticosteroid, which proves the potential efficacy of chemo-free protocols [108]. Finally, the association of TKi and bispecific T-cell engaging antibodies (BiTE) or chimeric antigen receptors T-cells (CARTs) represents a promising strategy for the treatment of Ph-positive ALL [109].

**TKI-based therapies for the treatment of solid tumors**

The introduction of TKi for the treatment of ALK-, ROS1- and RET-translocated NSCLC [14, 110, 111] has led to an astonishing improvement of patients’ outcome and survival. More recently, fusions involving NTRK1 and FGFR1/2/3 have been reported (Table 1), thus enlarging the spectrum of promising therapies for NSCLC (i.e. Crizotinib, Ceritinib, Alecitinib for ALK-positive NSCLC; Crizotinib for ROS1-positive NSCLC; Cabozantinib and Vandetanib for RET-negative NSCLC). Crizotinib represents the paradigm of efficient translation of molecular knowledge to the bedside. Initially developed as a c-Met inhibitor, Crizotinib showed clinical activity on advanced ALK-positive NSCLC in both the PROFILE 1001 (phase I) and PROFILE 1014 (phase III) clinical trials. Of note, in such tumors, Crizotinib displayed even greater efficacy than standard chemotherapy [112]. Similar results have been observed in ROS1- or RET-positive NSCLCs, with good responses to Crizotinib in ROS1-positive cases [14] and to Cabozantinib in Crizotinib-refractory cells [113].

The application of TKi has recently expanded to RET-mutated medullary thyroid carcinoma, RTK-translocated NSCLC and other solid tumors (NCT02183870, NCT0194502, NCT01639508). More recently, inhibitors with broad spectrum of activities were tested (RDX-101), providing novel strategies to target different molecular defects (NTRK1/2/3, ROS1 and ALK translocation) shared by wide range of solid tumors (NCT02568267, NCT02097810).

Despite these outstanding results, TKi often lose their efficacy due to the development of treatment-related resistance [114]. Much like hematologic neoplasms, primary and secondary mechanisms determine resistance to TKi in solid tumors. Primary resistance is linked to the tridimensional structures of the protein that confer TKi-resistance [115], whereas secondary resistance mainly consists of gene mutations, bypass mechanisms, and/or gene amplifications overcoming the effect of TKi at therapeutic levels.

As for target mutations, different genetic alterations associated with resistance have been described for ALK-positive NSCLC: i) L1169M within the “gatekeeper” domain (the most frequent); ii) L1152R, associated with EGFR signaling activation; iii) G1202R and S1206Y within the ATP-binding pocket, leading to a decreased Crizotinib affinity [116]. The most frequently reported bypass mechanisms associated with secondary resistance to ALK inhibition are: i) EGFR/KRAS mutations [117] and Tyrosine Kinase Receptor (ERBB, c-MET, etc.) activation triggered by paracrine stimuli [118, 119]; ii) c-KIT amplification, requiring SCF [120], IGF-1R up-regulation [51] and recruitment of P2Y receptors [121]. Other resistance mechanisms include impaired drug influx (OCT-1), increased drug efflux (MDR1), or microenvironment-mediated resistance [122].

Different strategies have been proposed to overcome TKi acquired resistance, including the development of next-generation drugs, such as the ALK-inhibitors LDK378-Ceritinib and AP26113-Brigatinib (for ALK-positive NSCLC resistant to Crizotinib), Lecitinib (for ALK-positive NSCLC carrying the L1169M mutation) and PF06463922 (a dual ALK/ROS1 inhibitor with a good CNS penetration profile) [123]. Additionally, Hsp90 inhibitors (AUY922-Ganetespib) are currently under evaluation in phase I/II clinical trials. Other emerging strategies include the administration of combined therapies to by-pass the “addiction” to single TKFs (e.g., combined inhibition of HER family [Dacomitinib], c-KIT [Dasatinib], src [Saracatinib], MEK [AZD6244], and IGF-1R [Linsitinib]). The re-timing of drug administration should also be considered, as recently demonstrated by the case of a Crizotinib-resistant ALK-positive NSCLC, displaying good response to this TKi after a withdrawal period [124]. Similar results have been obtained in an EGFR-mutated NSCLC, which regained sensitivity to EGFR-inhibitors upon therapy discontinuation [125]. Lastly, immunotherapeutic strategies (i.e. vaccination against over-expressed oncogenic antigens) may represent an effective approach for solid tumors, as recently reported in ALK-positive disorders [59, 126].

A final major roadblock concerning TKi is the poor response of central nervous system (CNS) metastases to therapy. This drawback may be overcome by different strategies: (i) combined therapies with drugs favoring TKi CNS accumulation, as recently attempted through the co-administration of Vandetanib and Everolimus (an immunosuppressive drug also modulating the P-glycoprotein efflux activity) [127]; and (ii) usage of single compound with higher brain penetration, such as Ceritinib compared to Crizotinib.

**FUTURE PERSPECTIVES**

Despite TKi have dramatically changed the clinical management of numerous cancers, many questions have still to be answered. One of the major problems concerning TKi is the high frequency of primary refractoriness/tumor
relapses [128] (Figure 2). Possible solutions for this limitation are: (i) the development of more potent drugs with limited side effects; (ii) the co-administration of TKi and chemotherapeutic agents [129], immune-based protocols [130] and/or bone marrow transplant [131]; and (iii) further research on treatment timing and dosage.

Of note, a growing number of protocols combining chemotherapy and TKi are currently being tested in both TKF-induced hematological and solid tumors [107, 132] [133], and several trials are evaluating the efficacy of new TKi either alone or in combination with more conventional therapies (NCT02269085; NCT02427620; NCT02315768; NCT01606878; NCT02134912; NCT02511184). Preclinical studies have also demonstrated a substantial advantage of combining classical chemotherapy with TKi: Das and colleagues showed a synergistic effect of Crizotinib and Temozolomide in FIG-ROS1-positive glioblastoma patient-derived cells, paving a route to improve clinical outcome [134]. Similarly, Appelmann and colleagues evaluated the possibility of combining Dasatinib, Ruxolitinib and Dexamethasone to prolong remission and avoid major toxicities in a mouse model of Ph-positive ALL [135].

One of the most challenging issues on the combined use of TKi and chemotherapeutics concerns the optimal doses and schedules to use. Toward this end, mathematical models might improve the clinical success, limiting unacceptable side effects and TKi/conventional therapy-resistance [136]. This approach also needs dedicated trials, the cooperative agreement of pharmaceutical companies and new regulations on intellectual and commercial issues. Moreover, we need to develop biological and mathematical models to predict cancer evolution, capable of predicting cancer evolutionary trajectories based on pre-treatment diversity. Lastly, we foresee that these predictions need to be adjusted in each individual patient by integrating longitudinally acquired molecular readouts representative of the global cancer landscape.

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**Figure 2: Mechanisms of Intrinsic and/or Acquired Resistances to Tyrosine Kinase Exposure.** Multiple mechanisms are associated with the emergence of drug resistance. These include: development of secondary mutations in the Kinase Domain (KD) at gatekeeper sites; copy number gains; activation of alternative oncogenic pathways via somatic mutations (i.e. RAS), and compensatory “by-pass” routes by Receptor Tyrosine Kinases signaling (i.e. EGFR, HER-2, HER-3, c-MET). Alternatively, resistance may also be due to either paracrine external signals through the tumor microenvironment, or via autocrine loops. The major drug categories and their therapeutic modalities are indicated.
(i.e. comprehensive genomic data [WES] of multiple sites, liquid biopsies, etc.).

Other questions regarding TKi concern the risks and benefits of second/third generation drugs. Thus, the use of first generation compounds remain a valuable option in many settings, including highly targeted diseases and the management of third world populations. The increasing health costs, the uncontrolled fee schedules in many industrialized countries, the increasing co-payer costs and the accessibility of generic TKi represent very tangible issues which may be solved only via international based supports and regulations. Finally, the need of cutting health system costs poses unprecedented challenges to molecular medicine programs. In fact, the success of such therapies depends on the characterization of individual cancers (both primary and recurrent/metastatic lesions). These analyses have to be performed by a pool of medical centers following certified programs, with consequent huge health costs.

These practical problems are paralleled by a series of scientific and methodological challenges. Although the genomic characterization of each cancer has originally prompted the use of selective compounds, it is now clear that this approach may not be sufficient. Indeed, favorable responses to selective drugs are not strictly linked to defined genetic defects. Thus, functional tests (e.g. comprehensive phosphorylation maps) should be performed together with genomic analyses. As an alternative, in vitro preclinical tests on patient-derived cell lines or PDTX may be introduced (Figure 3).

![Figure 3](image)

**Figure 3: Comprehensive Management of Tyrosine Kinase-driven Cancers.** Molecular and functional characterization of human cancers in combination with drug screening tests on primary patient tumor samples is expected to drive precise target therapies. It is anticipated that tumor samples will be used to generated 2D/3D and well as PDTX models. In vitro models from primary samples or from PDTX will serve to screen large libraries of compounds, whose efficacy will be established using a battery of biological and molecular readouts. The data emerging from these high throughput screenings will be pivotal to test selected molecules in preclinical PDTX-based trials. Extensive molecular and functional readouts will then be obtained from both tumors and host compartments (i.e. plasma/liquid biopsy) to create a detailed profile of in vivo classifiers and biomarkers. These will ultimately serve as surrogates to predict and define response to specific therapies in cancer patients. The development of tumor biorepositories of primary and metastatic lesions, cell lines and PDTX from primary human cancers is predicted to lead to the recognition and understanding of new oncogenic events. It is anticipated that effective targeted therapies will improve clinical responses and ultimately will lead to lower health care costs.
Of note, *in vitro* tests with patient-derived tissue samples may allow personalized pharmacologic interventions without the limits related to the use of immortalized cell lines or other tumor models. Patient-derived cancer models are indeed pivotal for drug discovery, for the characterization of cancer biology and for the assessment of personalized therapies [137-139]. Several cancer PDTX models have been developed, but only handful of them carries TKFs [15, 140-142]; thus, a more systematic effort in generating “ad hoc” models is highly recommended.

We anticipate that *in vitro* primary cell lines will allow for the rapid testing of drug libraries, with subsequent validation in more complex models (e.g. PDTX). It is also desirable that new clinical trials will include parallel co-clinical mouse PDTX-trials, which will establish the efficacy of such models. The molecular stratification of these models will finally provide new cancer classifiers with possible diagnostic/prognostic implications (Figure 3).

The considerable therapeutic progress against TKF-driven tumors may also prove beneficial for the treatment of those translocation-negative neoplasms, which nonetheless carry defects of TKF-related signaling pathways. As previously highlighted, TKFs indeed represent only one of the several mechanisms leading to TK dysfunction, and other TK impairments (i.e. gene mutations/amplifications or non-fusion rearrangements) lead to phenotypes closely resembling those of TKF-driven neoplasms. This is, for instance, the case of subsets of ALK-negative ALCL, carrying JAK1 and STAT3 activating mutations, which induce transcriptional signatures akin to those of ALK-positive ALCL [16]. Moreover, it is now recognized that activating mutations can synergize with TFKs and lead to full neoplastic transformation [8]. This molecular evidence constitutes the rationale for the administration of TKi compounds in specific subsets of both TKF-negative and TFK-positive tumors. Further studies and clinical trials will help clarify this captivating opportunity.

In conclusion, it is desirable that the academic community promotes dedicated programs on TKi and TKF-bearing cancers, also encouraging the support of pharmaceutical companies and the distribution of compounds under compassionate use. This approach, together with the creation of open-access clinical databases, will greatly contribute to the understanding of cancer-related TKFs and to a better management of (TKF-positive and TKF-negative) cancer patients.

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**Authors’ contributors**

FT, MP, PK, BR and GI researched and reviewed the existing literature and editedwrote the manuscript.

**CONFLICTS OF INTERESTS**

We declare no competing interests.

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