The kinase inhibitor TKI258 is active against the novel CUX1-FGFR1 fusion detected in a patient with T-lymphoblastic leukemia/lymphoma and t(7;8)(q22;p11)

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ABSTRACT

We report a patient with T-lymphoblastic leukemia/lymphoma and a t(7;8)(q22;p11). *CUX1* was identified as the fusion partner of *FGFR1* by fluorescence *in situ* hybridization and 5' RACE-PCR. We further investigated this novel *FGFR1* fusion using the interleukin-3 (IL-3) dependent Ba/F3 cell line and demonstrated IL-3 independent cell growth of CUX1-FGFR1 expressing cells. TKI258 and PKC412 potently inhibited proliferation of CUX1-FGFR1 transformed Ba/F3 cells. This growth inhibition was shown to be mediated by inhibition of CUX1-FGFR1 kinase activity for TKI258 but not PKC412. In summary, we identified a novel *CUX1-FGFR1* fusion oncogene in a patient with the 8p11 myeloproliferative syndrome and demonstrated its transforming potential in the Ba/F3 cell line. Our *in vitro* data support the further investigation of TKI258 for the treatment of constitutively active FGFR1 fusion proteins.

Key words: myeloid and lymphoid neoplasms with FGFR1 abnormalities (ICD-O 9967/3), 8p11 myeloproliferative syndrome (EMS), T-lymphoblastic leukemia/lymphoma, FGFR1, tyrosine kinase inhibitor, TKI258.

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Introduction

Myeloid and lymphoid neoplasms with FGFR1 abnormalities (ICD-O 9967/3), also called 8p11 myeloproliferative syndrome (EMS) or 8p11 stem cell leukemia/lymphoma syndrome, represent aggressive, atypical stem cell disorders. They are caused by chromosomal translocations that disrupt and constitutively activate FGFR1 (8p11) by fusion to diverse partner genes.[1] To date, ten partner genes have been identified: *BCR, CEP110, CPSF6, FGFR1OP, FGFR1OP2, HERV-K, LRRFIP1, MYO18A, TRIM24* (*TIF1*), *ZMYM2* (*ZNF198*).[2] EMS most commonly presents as a myeloproliferative neoplasm, with progression to acute myeloid leukemia within 1-2 years of diagnosis. At diagnosis, there is a strikingly high incidence of coexisting T- or B-cell lymphoblastic lymphoma/leukemia or mixed phenotype acute leukemia. The only curative treatment at the moment is allogeneic stem cell transplantation.[3]

Rearrangement of the *FGFR1* gene is a defining cytogenetic abnormality in EMS making the FGFR1 receptor tyrosine kinase a promising target for therapy. To date, the tyrosine kinase inhibitors PKC412, SU5402 and PD173074 were shown to potently inhibit the FGFR1 kinase activity.[4,5] Despite promising *in vitro* results, the *in vivo* response in the single patient tested with PKC412 was disappointing and currently none of these compounds is in clinical use.[4]

Another potential drug candidate is TKI258 (CHIR258, Dovitinib). TKI258 is a multitarget receptor tyrosine kinase inhibitor with activity against class III, IV and V receptor tyrosine kinases such as VEGFRs, FGFRs, PDGFRs, FLT3, KIT, and CSF-1R.[6] Previous studies showed that TKI258 had a significant inhibitory activity in a representative panel of tumor xenograft models of acute myeloid leukemia, multiple myeloma, colon and prostate cancer.[6-8] In addition, TKI258 has already been evaluated in a group of patients with advanced solid tumors and is considered to be a new therapeutic agent for the treatment of melanoma and gastrointestinal stromal tumors.[9] Studies performed on ZNF198-FGFR1- or BCR-FGFR1-transformed Ba/F3 cells, KG1 and KG1A AML cell lines (FGFR1OP2-FGFR1) and on primary cells of EMS patients showed that TKI258 inhibited cell proliferation at low nanomolar concentrations.[10] Therefore, the TKI258 inhibitor may provide a new therapeutic option for patients with EMS.

In the present study, a patient with T-lymphoblastic leukemia/lymphoma is reported in whom we identified *CUX1* as a novel fusion partner of *FGFR1*. Our functional

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studies demonstrate that TKI258 has significant and specific activity against CUX1-FGFR1.

Design and Methods

Patient

A 29-year old female patient from Romania requested a second opinion on an outpatient basis. Peripheral blood examination showed anemia (Hb 10.2 g/dl), thrombocytopenia (14×10^9/L) and a leukocyte count of $26{,}280\times10^9$/L (58.9% blasts, 0.7% myelocytes, 4.6% metamyelocytes, 14.6% neutrophils, 0% eosinophils, 1.3% basophils, 14.6% lymphocytes and 5.3% monocytes). The blast immunophenotype indicated a pre-T lymphoblastic leukemia. She refused a repeat bone marrow examination. She died elsewhere of septicemia in aplasia after a first course of high-dose chemotherapy.

Cytogenetics and fluorescence in situ hybridization (FISH)

Cytogenetic and FISH analysis followed standard protocols. For FISH the following FGFR1 and TCRB (7q34) BAC clones were selected: RP11-350N15 (spanning the FGFR1 locus), RP11-1220K2 (located centromeric to TCRB) and RP11-556I13 (located telomeric to TCRB).

Molecular analysis

A peripheral blood sample was obtained from the patient for diagnostic cytogenetic and molecular evaluation. RNA was isolated with TRIzol Reagent (Invitrogen, Merelbeke, Belgium). 5'-RACE PCR was performed using a previously described protocol and primers.[11] The final PCR product was sequenced with the ABI3100 sequencer (Applied Biosystems, Foster City, CA, USA). Fusion of CUX1 to FGFR1 was confirmed by RT-PCR using the primers CUX1-9F1 and FGFR1-9R1. The presence of the reciprocal fusion was evaluated with the primers FGFR1-8F1 and CUX1-14R1. All primer sequences are listed in Table 1.

Construct

The CUX1-FGFR1 fragment was amplified from the patient's peripheral blood cDNA using Platinum Taq DNA Polymerase (Invitrogen, Merelbeke, Belgium) and subsequently cloned into the retroviral pMSCVpuro vector (Clontech, Saint-Germain-en-Laye, France).

Inhibitors

PKC412 (CGP41251/Midostaurin) and TKI258 (CHIR-258/Dovitinib) were purchased from Tocris Bioscience (Bristol, UK) and Selleck Chemicals (Houston, TX, USA), respectively. 10 mM stock solutions of the inhibitors were prepared in dimethyl sulfoxide and were stored at -80°C.

Cell culture

Viral vector production and transduction of Ba/F3 cells was performed as previously described.[12] For the growth curve, 1×10^5 Ba/F3 cells were deprived of IL-3 and viable cells were counted on four consecutive days with a Countess Automated Cell Counter (Invitrogen, Merelbeke, Belgium). For dose-response curves, 1×10^5 *CUX1-FGFR1*-expressing Ba/F3 cells were treated with PKC412 and TKI258. The number of viable cells was determined at the start and after 48 h using the CellTiter AQueous One Solution Cell Proliferation Assay (Promega, Leiden, The Netherlands). In rescue experiments, IL-3 (2 ng/mL) was added to CUX-FGFR1-transduced Ba/F3 cells treated with PKC412 and TKI258 and the cells were incubated for 48 h.

Apoptotic assay

Ba/F3 cells at a density of 5×10^5 were cultured for 48 h in 24-well plates in the presence of PKC412 and TKI258, or vehicle. Induction of apoptosis was evaluated by flow cytometry using Annexin-V-FLUOS Staining Kit according to the manufacturer's protocol (Roche Applied Science, Mannheim, Germany). Samples were acquired with BD FACSCanto System and data were analyzed with BD FACSDiVa software (BD Biosciences, San Jose, CA, USA).

Western Blotting

Four million cells were incubated with inhibitors for 90 min and were lysed after a wash in ice-cold PBS cells. Protein concentrations were determined using the Bio-Rad protein assay (Bio-Rad Laboratories Hercules, CA, USA). Lysates were separated by SDS-PAGE electrophoresis and immunoblotted. Different antibodies were used: anti-FGFR1, anti-STAT5a (Santa Cruz Biotechnology, CA, USA), anti-RPS6K, anti-phospho-FGFR1, anti-phospho-RPS6K, anti-phospho-STAT5 (Cell Signaling Technologies, Danvers, MA, USA) and anti-alpha-tubulin (Sigma-Aldrich, St Louis, MO, USA). Detection was performed by chemiluminescence (Western Lightning-ECL, Perkin Elmer, Waltham, MA, USA) and captured using a FUJI LAS3000mini imaging system.

Results and Discussion

Cytogenetic analysis was performed on a diagnostic blood sample of a patient with precursor T-lymphoblastic leukemia/lymphoma, without apparent myeloproliferation or eosinophilia. A t(7;8)(q22;p11) was found (Figure 1A). Recurrent chromosomal 8p11 rearrangements are the genetic hallmark of EMS and give rise to fusions of the *FGFR1* tyrosine kinase with different partner genes. Therefore, we analyzed the translocation in more detail by FISH using *FGFR1* flanking probes. We could confirm the 8p11 breakpoint and 7q as the partner chromosome (Figure 1B). Using 5'-RACE PCR followed by sequencing, we showed that this translocation leads to the formation of an in-frame fusion transcript between CUX1 exon 11 (7q22) and FGFR1 exon 10 (8p11) (Figure 1D). The *CUX1* and *FGFR1* reference sequences were obtained from the Ensembl release 59 - Aug 2010 (transcripts IDs: *CUX1* - ENST00000292538 and *FGFR1* - ENST00000397091). The presence of this novel CUX1-FGFR1 fusion was further

Table1. Primer sequences used in 5' RACE-PCR, RT-PCR and construct design.

Name	Sequence (5'-3')	Application
FGFR1-12F1	GGAGGCATACTCCACGATGACA	RACE-PCR
FGFR1-10F1	TCTTCACAGCCACTTTGGTCACA	RACE-PCR/Cloning
FGFR1-9F1	AGAAGAACCCCAGAGTTCATGGA	RACE-PCR
CUX1-9F1	GCCGACGAGATTGAAATGAT	RT-PCR
FGFR1-9R1	ATGGCCGAACCAGAAGAAC	RT-PCR
FGFR1-8F1	ATCATCTATTGCACAGGGGCC	RT-PCR
CUX1-14R1	CAGCAACAGCACCTCCAG	RT-PCR
CUX1-1F1-XhoI	CTCGAGACTCTGCCAGGTGGATGTT	Cloning
FGFR1-9F2	ATGCTAGCAGGGGTCTCTGA	Cloning
FGFR1-17R1-MunI	CAATTGAGTCAGCGGCGTTTGAGT	Cloning

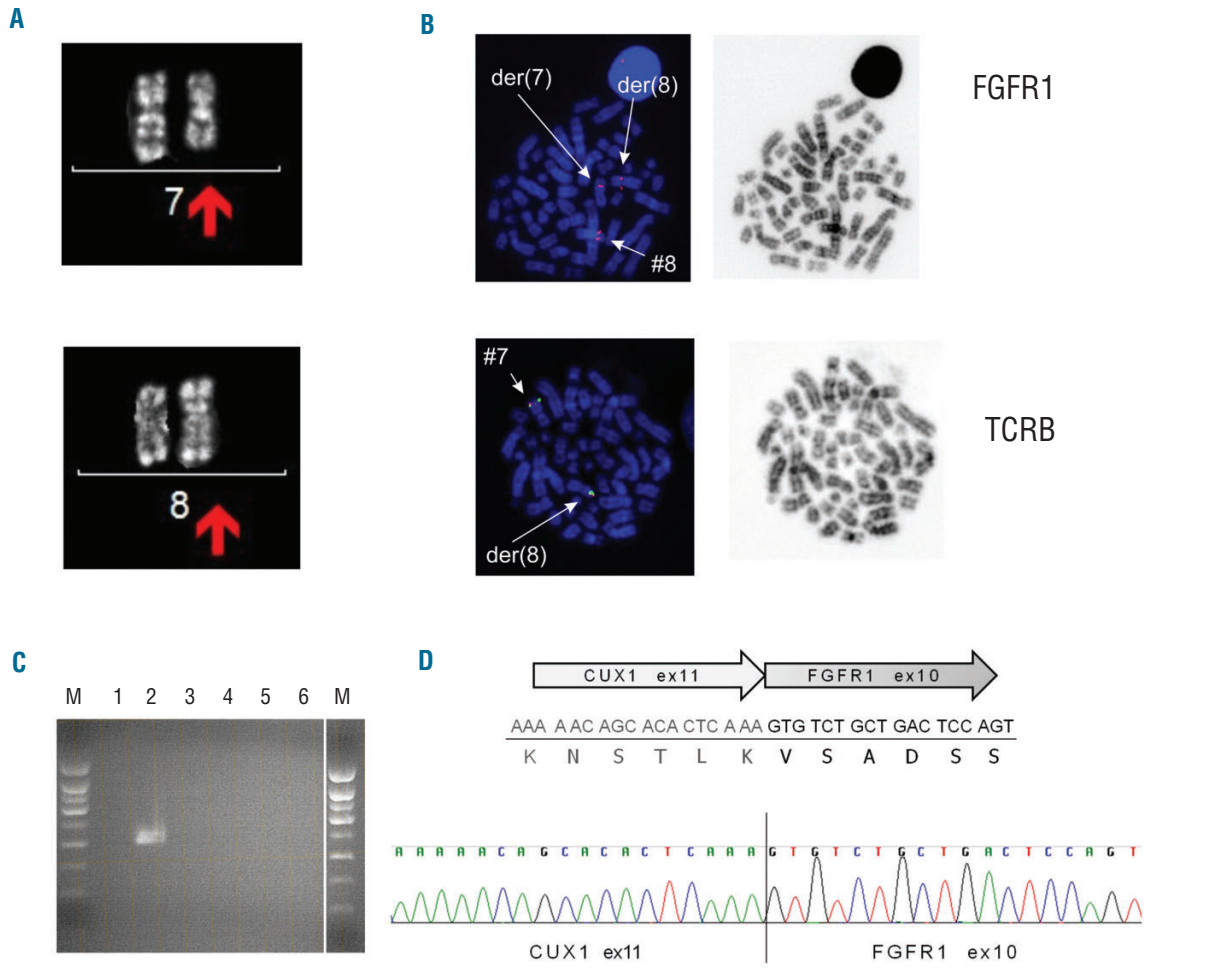

Figure 1. Cytogenetic and molecular identification of *CUX1* as a fusion partner of *FGFR1*. (A) Cytogenetic analysis of patient's peripheral blood cells. The derivative chromosomes 7 and 8 are shown with the arrows. (B) Fluorescence *in situ* hybridization using RP11-350N15 (spectrum orange) spanning the *FGFR1* locus (8p11), and RP11-556I13 (spectrum orange) and RP11-1220K2 (sybr green) flanking *TCRB* (7q34). Hybridization of the *FGFR1* probe shows one normal signal on chromosome 8, one signal on der(7) and one signal on der(8). Hybridization of the *TCRB* probe confirms translocation of the distal part of 7q to 8p. (C) RT-PCR. Lanes 1 and 4: negative control (no cDNA), lanes 2 and 5: cDNA from the reported patient; lanes 3,6: cDNA from a case with CEP110-FGFR1. Forward primer in CUX1 and reverse primer in FGFR1 (Lane 1-3); forward primer in FGFR1 and reverse primer in CUX1 (lane 4-6). Lane M represents 1kb size standard. (D) Schematic representation of the identified fusion transcript. The DNA and protein sequence at the fusion border are presented. An electropherogram with the CUX1-FGFR1 fusion sequence of the PCR product is also shown.

confirmed by RT-PCR and sequencing using primers in both partners (Figure 1C). The reciprocal FGFR1-CUX1 fusion transcript could not be detected in this patient. CUX1 is a homeobox family DNA binding protein which has not previously been described as a fusion partner in hematologic malignancies. Of note, Belloni et al. have reported another translocation t(7;8)(q34;p11) in a patient with the 8p11 myeloproliferative syndrome with a different 7q breakpoint and which led to a fusion between *FGFR1* and *TRIM24* (*TIF1*), transcription intermediary factor 1.[13]

To evaluate the transforming potential of this novel CUX1-FGFR1 fusion, the fusion transcript was cloned and used to transduce Ba/F3 cells. CUX1-FGFR1-expressing Ba/F3 cells displayed IL-3 independent proliferation (Figure 2A). Western blot analysis of these transformed Ba/F3 cells demonstrated constitutive phosphorylation of CUX1-FGFR1 and its downstream effectors STAT5 and ribosomal protein S6 kinase (RPS6K) (*data not shown*). Together these results suggest an oncogenic character of the CUX1-FGFR1 fusion protein.

Next, we tested the sensitivity of CUX1-FGFR1 to PKC412 and TKI258, two multitarget receptor tyrosine kinase inhibitors with reported activity against FGFR1. Treatment of the CUX1-FGFR1-expressing Ba/F3 cells with the kinase inhibitor TKI258 significantly inhibited cell growth with an IC_{50} of 489 nM (Figure 2B). Western blot analysis demonstrated a corresponding decrease in CUX1-FGFR1 phosphorylation with increasing doses of TKI258, while protein expression was unaffected (Figure 2C). A significant inhibition of phosphorylation was already detectable at 50 nM, with complete inhibition at 1 μM. The downstream effectors STAT5 and RPS6K also showed a decreasing phosphorylation with TKI258 concentrations equal to or higher than 500 nM (Figure 2C). Furthermore, using an Annexin-V/propidium iodide-based apoptosis assay, we could show that 48 h exposure to TKI258 induced apoptosis followed by cell death in

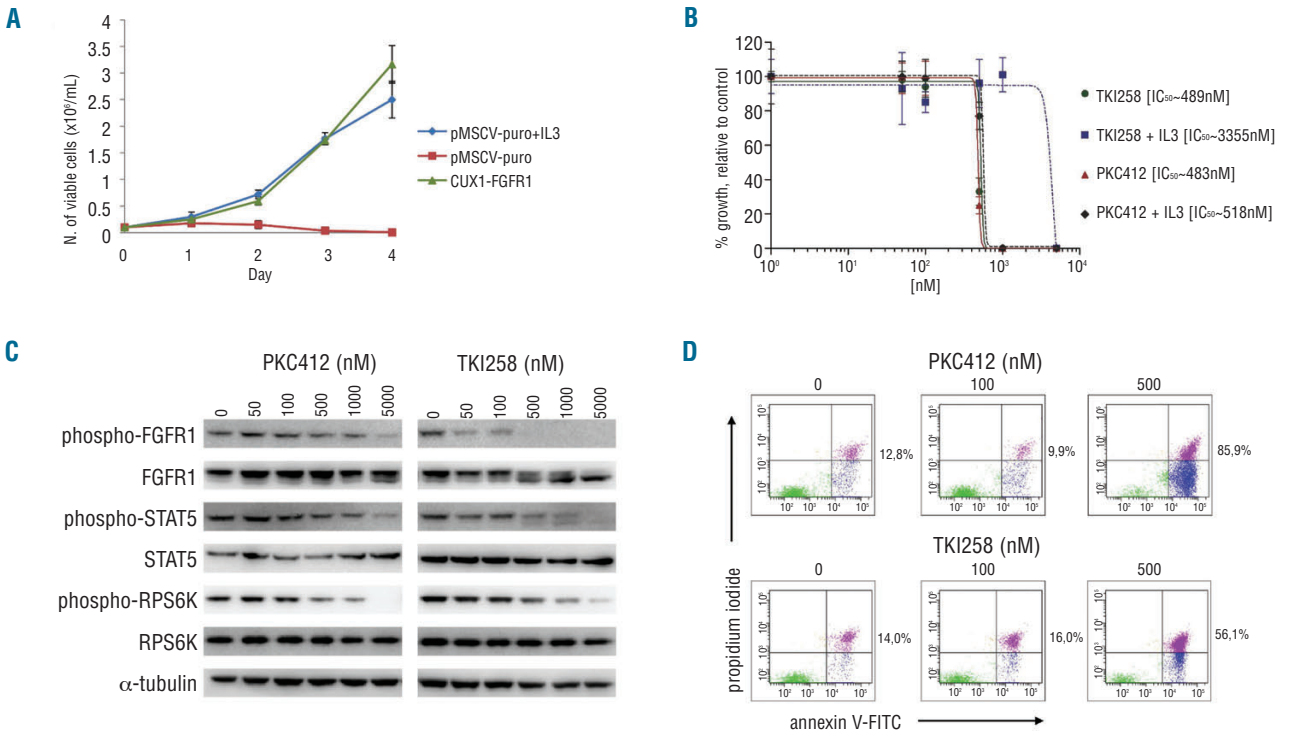

Figure 2. ***In vitro*** **assays on CUX1-FGFR1-expressing Ba/F3 cells. (A) IL-3 deprivation of Ba/F3 cells transduced with CUX1-FGFR1 resulted in transformation to growth factor independent growth. The mean growth ± SEM of 3 separate measurements over four consecutive days is presented. (B) The dose-response curves of CUX1-FGFR1-transduced Ba/F3 cells, treated with TKI258 and PKC412 for 48 h in the absence or presence of IL-3 (2ng/mL) are presented. Points represent the average results of 2 experiments performed in triplicate plotted with the curve-fitting GraphPad Prism 5 software; bars, SD. The calculated IC_{50} for each inhibitor is indicated. (C) Western blot analyses of CUX1-FGFR1-transformed Ba/F3 cells after treatment with PKC412 and TKI258. Phosphorylation of CUX1-FGFR1 and its downstream effectors STAT5 and RPS6K decreased with increasing inhibitor concentrations. Expression of total CUX1-FGFR1, STAT5 and RPS6K remained unaffected. (D) Effect of PKC412 and TKI258 on apoptosis of CUX1-FGFR1-expressing Ba/F3 cells after treatment for 48 h. The percentage of apoptotic plus necrotic CUX1-FGFR1-transduced Ba/F3 cells is indicated.**

CUX1-FGFR1-expressing Ba/F3 cells. Massive apoptosis/necrosis was recorded at 500 nM of TKI258 (Figure 2D).

PKC412 inhibited the cell growth of CUX1-FGFR1-expressing Ba/F3 cells with an IC_{50} of 483 nM and significant induction of apoptosis/necrosis in these cells was also recorded at 500 nM of inhibitor (Figures 2B and D). However, by Western blotting we showed that an effect of PKC412 on the phosphorylation status of CUX1-FGFR1 and its downstream effectors was only obtained at concentrations equal to or higher than 1000 nM. The inhibitory effect on the proliferation of CUX1-FGFR1-expressing cells could be rescued by addition of exogenous IL-3 for TKI258 but not for PKC412 (Figure 2B). This suggests that PKC412 inhibits proliferation in CUX1-FGFR1 transformed Ba/F3 cells by non-specific toxic effects rather than by specific inhibition of the FGFR1- fusion kinase (Figures 2B and C). Non-specific toxic effects of PKC412 at concentrations from 500 nM have also been observed in Ba/F3 transformed with other kinases.[14,15] In contrast, the correlation between inhibition of growth and of phosphorylation by TKI258, and the IL-3 rescue of growth inhibition by TKI258 demonstrate that growth inhibition by TKI is specifically mediated by inhibition of FGFR1 signaling. Taken together, the *in vitro* data presented here suggest that TKI258 is a more potent FGFR1 inhibitor with a wider therapeutic index than PKC412, which could be used for the treatment of the novel CUX1-FGFR1 fusion as well as other constitutively active FGFR1 fusion proteins. This result is consistent with the previous findings by Chase and colleagues.[10]

CUX1 (cut-like homeobox 1) encodes a member of the homeodomain family of DNA binding proteins. This homeobox transcription factor contains one homeobox and three repetitive CUT DNA-binding domains as well as an N-terminal coiled-coil region. CUX1 is expressed as multiple isoforms and is cleaved by proteases such as cathepsin L. In healthy individuals, CUX1 plays a role in embryonic development, cell cycle progression and cell differentiation.[16] An elevated expression of CUX1 has been reported in breast tumors and cancer cell lines, in malignant plasma cells in multiple myeloma and in acute lymphoblastic leukemia, and in pancreatic tumors. A role as an important survival factor downstream of PI3K/AKT has also been suggested.[16,17] In contrast, the 7q22 region where *CUX1* is located was also found to be frequently deleted in uterine leiomyomas, AML and MDS although somatic mutations of *CUX1* have not been demonstrated.[18,19]

In summary, we report a novel translocation t(7;8)(q22;p11) in the WHO disease category of myeloid and lymphoid neoplasms with FGFR1 abnormalities. The t(7;8)(q22;p11) generates an in-frame fusion transcript between CUX1 exon 11 and FGFR1 exon 10. There are no previous reports of *CUX1* as partner gene in cancer

translocations. The N-terminal coiled-coil domain is retained in the fusion and likely mediates dimerization and hence constitutive tyrosine kinase activation, as demonstrated for other oncogenic fusion kinases such as BCR-ABL1 and ETV6-JAK2.[20,21] Some previously identified FGFR1 fusion partners like ZMYM2 and CEP110 are also known to harbor an oligomerization domain. The involvement of exon 10 of *FGFR1* is another typical feature of the 8p11 myeloproliferative syndrome. Furthermore, we demonstrated the transforming character of CUX1-FGFR1 in the Ba/F3 cell system, and established CUX1-FGFR1 as a potential target for therapy. TKI258 specifically inhibited CUX1-FGFR1 phosphorylation and CUX1-FGFR1 driven cell proliferation and survival, in contrast to PKC412, the inhibitory effect of which was not mediated by inhibition of the kinase. Our results encourage further testing of TKI258 in representative patient populations. The outcome of such clinical trials is eagerly awaited since for the moment EMS remains a disorder which cannot be treated.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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