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LETTER TO THE EDITOR

Comprehensive characterization of a novel, oncogenic and targetable SEPTIN6::ABL2 fusion in T-ALL

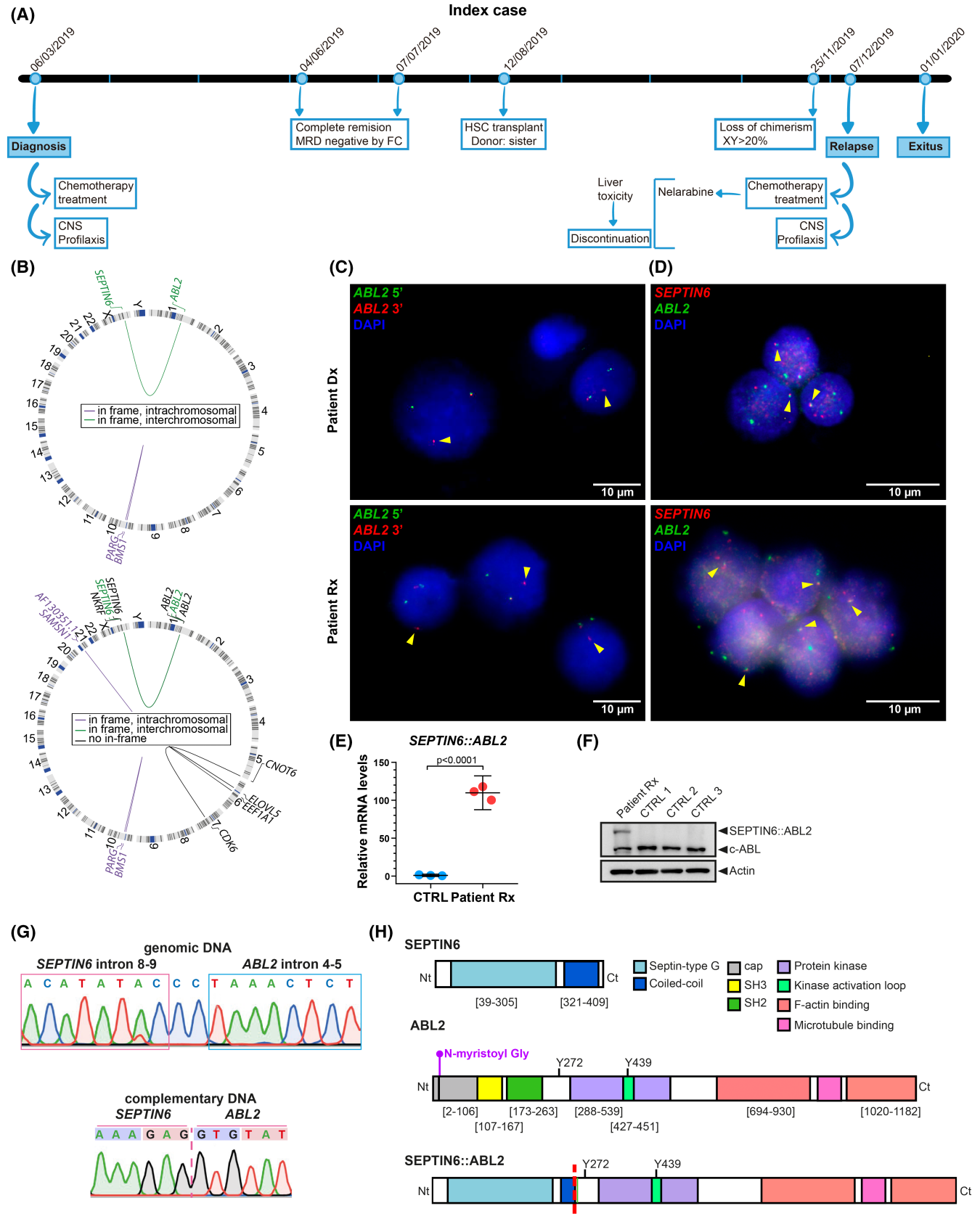
T-cell acute lymphoblastic leukaemia (T-ALL) arises from the malignant transformation of T-cell progenitors.[1,2] Current standard-of-care treatment for T-ALL consists of high-dose multi-agent chemotherapy followed by haematopoietic stem cell transplantation (HSCT) in standard-high risk patients.[3] Despite reasonable rates of initial complete responses (CR), patients who relapse or do not respond to first-line treatments show a dismal outcome with cure rates below 10% and limited therapeutic options.[2] Actually, since the approval of nelarabine in 2005 no pharmacological inhibitors have been approved for relapsed/refractory T-ALL patients.[4] Therefore, there is an urgent need to identify the molecular alterations that are present in such patients and that promote leukemogenesis in order to implement personalized-therapies with higher efficacy and fewer adverse effects.[5]

Here, we identify and comprehensively characterize a novel, oncogenic and targetable *SEPTIN6*::*ABL2* fusion in a 16-year-old boy with T-ALL (Figure 1A). We evaluated the mutational profile of the patient in matched tumour samples at diagnosis (Patient Dx) and relapse (Patient Rx) by paired-end 2 × 150 bp exome sequencing analysis. We observed no mutations in previously reported T-ALL oncogenes or tumour suppressor genes (TSG)[6] in Patient Dx and only two frameshift mutations affecting the TSG *PTPRC*[7] in Patient Rx (Figure S1). We next analysed copy-number-variations and identified a trisomy 17 and a homozygous deletion in *CDKN2A* (Figure S1), which were confirmed by FISH and MLPA respectively (Figure S1). Trisomy 17 is not considered a cancer-driver event *per se*[8] while *CDKN2A* is a TSG frequently altered in T-ALL,[9] suggesting the presence of additional genetic alterations that may explain the aggressiveness of this tumour.

Chromosomal rearrangements are relevant events in haematological malignancies,[10] so we performed paired-end 2 × 100 bp RNA-Seq to assess for the presence of fusion transcripts and detected two fusions in Patient Dx and seven fusions in Patient Rx (Figure 1B and Table S1). Among them, only the *SEPTIN6*::*ABL2* fusion involved coding genes from different chromosomes and maintained the reading frame. To confirm the presence of this novel fusion, we first verify the *ABL2* rearrangement, using a commercially available break-apart probe for *ABL2* (Figure 1C), and subsequently demonstrate the co-localization between *ABL2* and *SEPTIN6*, using a newly developed double-fusion probe for *SEPTIN6*::*ABL2* (Figure 1D). Notably, *SEPTIN6*::*ABL2* was present at both diagnosis and relapse with a frequency of 75% and 91%, respectively ($n = 200$ analysed nuclei), indicating that the treatments administered to the patient were not effective in completely eradicating the tumour cells bearing this particular alteration. The expression of *SEPTIN6*::*ABL2* fusion was also confirmed at the mRNA and protein levels in the tumour cells at relapse (Figure 1E,F).

RNA-Seq data coupled to multiplex PCRs and Sanger sequencing allowed us to identify the fusion breakpoint between *SEPTIN6* intron 8–9 and *ABL2* intron 4–5, which remained intact except for the presence of two additional cytosines (Figure 1G). RT-PCR and Sanger sequencing further revealed the complete coding sequence of *SEPTIN6*::*ABL2* (Figure 1G and Figure S2). Since this fusion involves the amino-terminal region of SEPTIN6 and the carboxy-terminal region of ABL2, it lacks the autoinhibitory domains of ABL2, resulting in complete loss of the myristoyl glycine and the SH3 domain and in partial loss of the SH2 domain, while the kinase domain of ABL2 remains intact and, therefore, its catalytic ability (Figure 1H). To assess whether the SEPTIN6::ABL2 fusion could exhibit aberrant tyrosine-kinase activity and contribute to leukemogenesis, we cloned the *SEPTIN6*::*ABL2* cDNA into a lentiviral vector and analysed its ability to promote cell growth and viability. M07e cells transduced with *SEPTIN6*::*ABL2* showed significantly higher levels of cell growth and viability compared to cells transduced with the empty-vector or with $ABL2^{WT}$ in the absence of cytokines (Figure 2A). Furthermore, such effects correlated with an increase in the levels of phosphorylated-tyrosines (Figure 2B), indicating that SEPTIN6::ABL2 displays enhanced kinase activity in comparison with $ABL2^{WT}$ and postulating this fusion as a new oncogene. The oncogenic role of SEPTIN6::ABL2 was further confirmed in Ba/F3 cells (Figure 2C,D). To the best of our knowledge, this is the first fusion gene involving *SEPTIN6* or *ABL2* that has been directly identified in the tumour sample from a T-ALL patient and subsequently characterized as oncogenic.

Since the patient did not achieve a durable response with conventional chemotherapeutic treatments and ABL2



functions as a tyrosine-kinase protein, we tested whether tyrosine-kinase inhibitors (TKIs) are effective against the oncogenic activity of SEPTIN6::ABL2. We analysed the effects of imatinib on the growth of Ba/F3 cells expressing SEPTIN6::ABL2 (Ba/F3-SA), using K562 and Jurkat cell lines as positive and negative controls respectively. Imatinib

FIGURE 1 Identification of a novel *SEPTIN6*::*ABL2* fusion. (A) Medical history of index case. CNS, central nervous system; MRD, minimal residual disease; FC, Flow Cytometry; HSC, haematopoietic stem cell transplantation. (B) CIRCOS plot illustrating transcript fusions affecting coding regions in the patient tumour sample at diagnosis (top) and relapse (bottom). (C) FISH analysis of interphase cells in the patient at diagnosis (Patient Dx) and relapse (Patient Rx), using an *ABL2* break-apart probe; 3′ end of *ABL2* (yellow arrowhead) is involved in *SEPTIN6*::*ABL2* fusion. (D) FISH analysis of interphase cells in Patient Dx and Patient Rx using a *SEPTIN6*::*ABL2* double-fusion probe; *SEPTIN6*::*ABL2* fusion is indicated with a yellow arrowhead. FISH images are representative examples of at least three independent experiments. Expression levels of *SEPTIN6*::*ABL2* in Patient Rx and control-thymocytes (CTRL) at the transcript level determined by RT-qPCR (E) and protein levels determined by Western Blot (F). The graphics in (E) show the mean with 95% confidence interval after three independent experiments. Statistical significance was set at $p < 0.05$. (G) Electropherograms showing the fusion point between *SEPTIN6* and *ABL2* in Patient Rx at genome (top) and transcript level (bottom). (H) Protein domains of SEPTIN6::ABL2 fusion. Predicted domain structure of SEPTIN6::ABL2 fusion protein (bottom), in comparison with its wildtype counterparts; Nt, amino-terminal end; Ct, carboxy-terminal end; numbers in brackets indicate amino acids. All images are representative examples of at least three independent experiments.

robustly and selectively inhibited cell growth of Ba/F3-SA and K562 cells, but not of Jurkat cells (Figure 2E), indicating that SEPTIN6::ABL2 is sensitive to imatinib. These results were validated using two additional TKIs, nilotinib and dasatinib (Figure 2E). To determine whether the observed reduction in cell growth was a consequence of cell cycle deregulation, we analysed the cell cycle profile in the presence of imatinib, nilotinib and dasatinib and we observed a cell cycle arrest at G1 (Figure 2F,G and Figure S3). Next, we analysed cell viability and observed that TKIs also induced an increase in apoptosis (Figure 2H,I). Our results indicate that SEPTIN6::ABL2 promotes cell growth, survival and G1/S transition, inducing oncogenic hallmarks that can be reversed with TKIs.

Here, we identify a novel *SEPTIN6*::*ABL2* fusion in a T-ALL patient. Although gene translocations are common events in T-ALL,[10] only a fraction generate fusion proteins, with *NUP214*::*ABL1* being the most representative example in T-ALL.[11] However, the frequency of fusion proteins may be underestimated, as most are the result of cryptic rearrangements not easily detected by exome sequencing or gene expression profiling. This is particularly relevant for *ABL2* since, unlike *ABL1*, break-apart probes for *ABL2* are not routinely used in the clinical diagnosis of T-ALL patients. While the *ETV6*::*ABL2* fusion has been reported in a cell line with mixed T-lymphoid/myeloid immunophenotype,[12] *SEPTIN6*::*ABL2* represents the first fusion involving *ABL2* that has been directly identified in a T-ALL patient at diagnosis and relapse. Notably, its increased frequency at relapse suggests that current treatments were not effective enough in eradicating the tumour cells bearing this particular alteration. Additionally, the patient did not show molecular alterations in proto-oncogenes belonging to the NOTCH1, JAK/STAT, PI3K/AKT and MAPK/ERK signalling pathways, highlighting the oncogenic potential of the *SEPTIN6*::*ABL2* fusion in leukemogenesis. We observed that SEPTIN6::ABL2 promotes the growth and viability of different haematopoietic cell lines, unveiling the role of *ABL2* as a proto-oncogene in T-ALL and emphasizing the heterogeneous landscape of this haematological malignancy.[6] The high efficacy of TKIs in inhibiting the growth of cells expressing *SEPTIN6*::*ABL2* by arresting cell cycle and inducing apoptosis offers a targeted therapeutic opportunity for leukaemia patients with this alteration. Although such inhibitors are not routinely used in T-ALL, previous reports showing their efficacy for T-ALL patients with the *NUP214*::*ABL1* fusion,[13,14] together with the results presented in this study, postulate TKIs as a potential treatment for a subgroup of T-ALL patients. Overall, our study provides a comprehensive characterization of the novel and oncogenic *SEPTIN6*::*ABL2* fusion as a potential therapeutic target in T-ALL (Figure 2J).

AUTHOR CONTRIBUTIONS

Antonio Lahera, Laura Vela-Martín, José Fernández-Piqueras and María Villa-Morales conceived and designed the initial hypothesis and the working plan. Antonio Lahera and Laura Vela-Martín prepared cell lines for in vitro research, conducted cell growth and viability experiments, performed Flow Cytometry and Western Blot assays. Pilar López-Nieva validated the *SEPTIN6*::*ABL2* fusion breakpoint at cDNA and gDNA levels. Rocío N. Salgado, Sandra Rodríguez-Perales and Raúl Torres-Ruiz conducted cytogenetic analyses and FISH. Antonio Lahera, Laura Vela-Martín and María Villa-Morales cloned the *SEPTIN6*::*ABL2* coding sequence into an expression vector. José L. López-Lorenzo, Javier Cornago and Pilar Llamas provided clinical care and collected human samples. Pablo Fernández-Navarro assisted with statistical analysis, interpretation of bioinformatics data and graphical representation of results. Rocío N. Salgado, Rebeca Sánchez-Domínguez, José C. Segovia, Isabel Sastre and María Á. Cobos-Fernández performed clinical laboratory tests and human sample processing. Antonio Lahera, Laura Vela-Martín, Pilar López-Nieva, Pablo Fernández-Navarro, José Fernández-Piqueras and María Villa-Morales analysed RNA-Seq and WES data. Isabel Sastre and María Á. Cobos-Fernández provided technical assistance and helped with qRT-PCR validations. Pablo Menéndez and Javier Santos made critical intellectual contributions throughout the project. Javier Santos, José Fernández-Piqueras and María Villa-Morales obtained funding. José Fernández-Piqueras and María Villa-Morales supervised the project. Antonio Lahera, Laura Vela-Martín, José Fernández-Piqueras and María Villa-Morales wrote the original draft, which was reviewed and edited by all authors prior to submission. All authors approved the final version of the manuscript.

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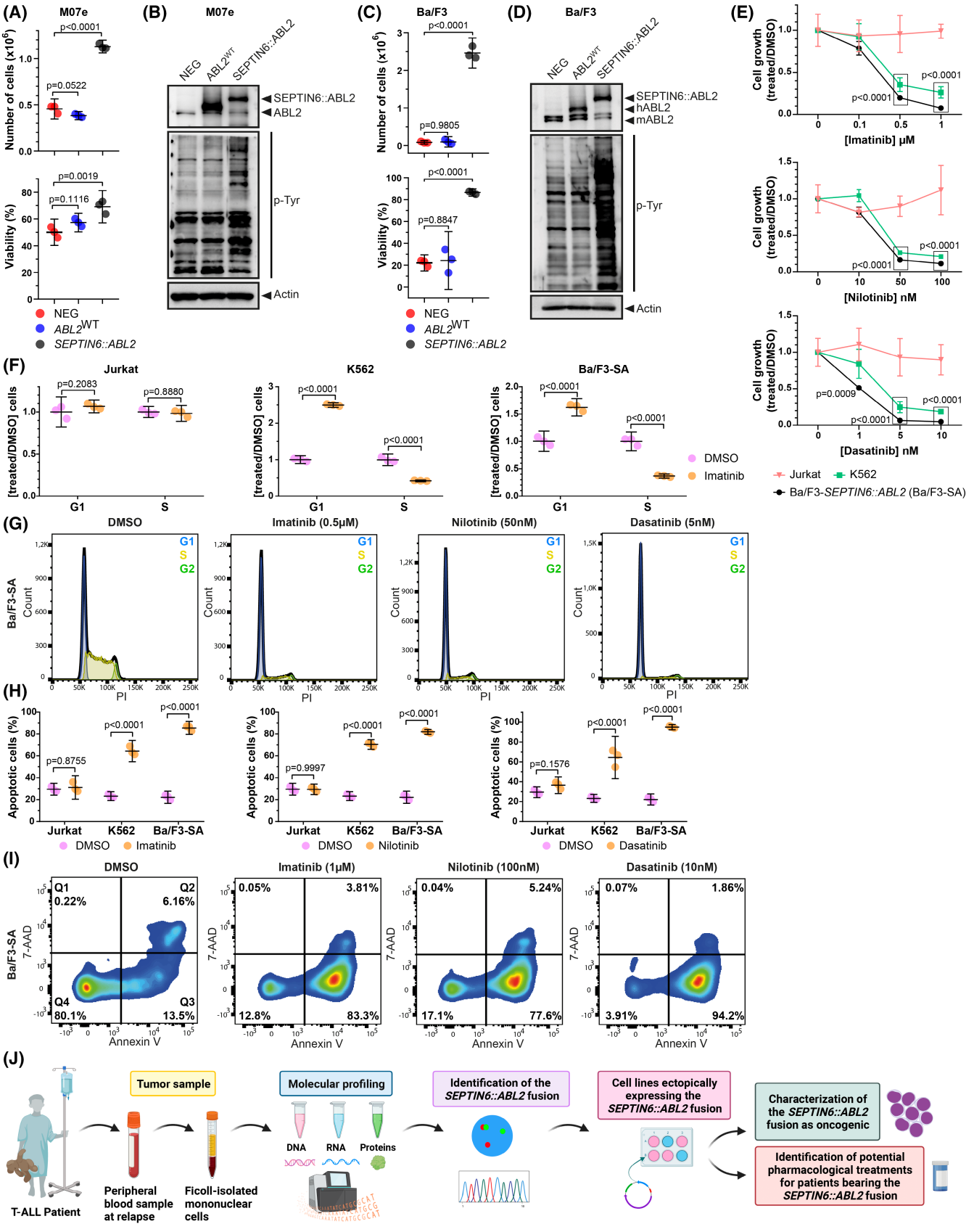

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FIGURE 2 Characterization of SEPTIN6::ABL2 fusion as oncogenic and treatment with tyrosine kinase inhibitors. (A) Cell growth (top) and viability (bottom) analyses of M07e cells untransduced (NEG), transduced with *ABL2*^{WT} or with *SEPTIN6*::*ABL2* in the absence of GM-CSF for 72 h. (B) Western Blot (WB) for ABL2 and pTYR in M07e cells untransduced (NEG), transduced with *ABL2*^{WT} or with *SEPTIN6*::*ABL2*. (C) Cell growth (top) and viability (bottom) analyses of Ba/F3 cells untransduced (NEG), transduced with *ABL2*^{WT} or with *SEPTIN6*::*ABL2* in the absence of interleukin-3 for 72 h. The graphics in (A, C) show the mean with 95% confidence interval after three independent experiments. Multiple comparisons were made in (A, C) with respect to NEG. Statistical significance was set at $p < 0.05$. (D) Western Blot (WB) for ABL2 (m, mouse; h, human) and pTYR in Ba/F3 cells untransduced (NEG), transduced with *ABL2*^{WT} or with *SEPTIN6*::*ABL2*. (E) Cell growth analysis of Jurkat, K562 and Ba/F3 cells transduced with *SEPTIN6*::*ABL2* (Ba/F3-SA) treated with Imatinib (0.1, 0.5 or 1 μM; left), Nilotinib (10, 50, 100 nM; middle) and Dasatinib (1, 5, 10 nM; right) and referred to DMSO-treated cells. K562 cells were used as a positive control while Jurkat cells were used as a negative control since these cell lines have been previously reported as sensitive and resistant to TKIs respectively. The graphics in (E) show the mean with s.d. after three independent experiments. Multiple comparisons were made in (E) with respect to DMSO-treated cells. Statistical significance was set at $p < 0.05$. For the sake of simplicity, only significant *p*-values are shown in (E). (F) Cell cycle analysis of Jurkat (left), K562 (middle) and Ba/F3-SA (right) cells treated with Imatinib (0.5 μM) and referred to DMSO-treated cells. (G) Representative images for Ba/F3-SA cells are depicted. (H) Annexin-V/7-AAD analysis showing the percentage of apoptotic (Q2 + Q3) Ba/F3-SA cells treated with DMSO or Imatinib (1 μM, left), Nilotinib (100 nM, middle) and Dasatinib (10 nM, right). Jurkat and K562 (BCR::ABL1^{+}) cell lines were used as negative and positive control respectively. The graphics in (F, H) show the mean with 95% confidence interval after three independent experiments. Multiple comparisons were made in (F, H) with respect to DMSO-treated cells. Statistical significance was set at $p < 0.05$. (I) Representative images for Ba/F3-SA cells are depicted. Q1: necrosis, Q2: late apoptosis, Q3: early apoptosis and Q4: alive cells. (J) Schematic representation of the approach followed in the present work to study the SEPTIN6::ABL2 fusion. For experimental assays, M07e and Ba/F3 cells were washed three times with 1X PBS and cultured in medium free of cytokines and growth factors. All images are representative examples of at least three independent experiments. Schematic representations were created with BioRender.com.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Clinical data and raw genomic and transcriptomic data from index case will be available upon reasonable request to the corresponding authors.

ETHICS STATEMENT

Institutional review board approval was obtained for this study (CEI-70-1260).

PATIENT CONSENT STATEMENT

The participants provided written informed consent in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

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