



# A case of T-prolymphocytic leukemia harboring *RAS* mutation

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Received: 31 December 2025 / Accepted: 30 March 2026  
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## Abstract

The text reports the clinical case of a 61-year-old woman with a long history of generalized pruritus who was eventually diagnosed with T-cell prolymphocytic leukemia (T-PLL), a rare and aggressive T-cell lymphoproliferative disorder. At presentation, the patient had fever, skin lesions, lymphocytosis, thrombocytopenia, coagulation abnormalities, and marked splenomegaly without lymphadenopathy. Morphological, immunophenotypic, and histological analyses of peripheral blood and bone marrow revealed diffuse infiltration by mature T lymphocytes with strong *TCL1* expression, and T-cell receptor gene rearrangement confirmed clonality, supporting the diagnosis of T-PLL. The patient initially received bendamustine chemotherapy, which failed to induce a response. Second-line treatment with the anti-CD52 monoclonal antibody alemtuzumab was subsequently initiated, but the disease proved refractory, with persistent bone marrow involvement, worsening cytopenias, disease progression, and clinical deterioration. As a result, alemtuzumab was discontinued and the patient was transitioned to palliative care. A particularly notable finding was the detection, by next-generation sequencing, of a pathogenic *KRAS* G12A mutation, which has not previously been reported in T-PLL. This mutation was identified incidentally using a myeloid-targeted NGS panel. The finding broadens the known mutational spectrum of T-PLL and suggests that activation of the *RAS* signaling pathway may represent an alternative oncogenic mechanism beyond the canonical *TCL1* and *JAK–STAT* pathways. We suggest that investigating for *KRAS* mutations in additional T-PLL cases may be beneficial to explore this pathogenetic pathway and could open new avenues for future targeted therapeutic strategies.

**Keywords** T-prolymphocytic leukemia (T-PLL) · Alemtuzumab · *KRAS* · Bendamustine

## Introduction

T-PLL is a rare (2 per million per year) T-cell lymphoproliferative disorder characterized by a poor prognosis and an aggressive behavior [1]. The clinical presentation includes B-symptoms, hepato-splenomegaly, and usually marked lymphocytosis [2]. Here we present a case-report of a patient with T-PLL harboring a particular mutation that conferred further dismal outcome.

## Case presentation

In October 2024, a 61-year-old woman presented to the emergency department of our hospital with fever, generalized pruritus, and cutaneous lesions. She had a history of more than one year of pruritus, but several dermatological consultations were inconspicuous. Blood tests showed normal hemoglobin levels (11 g/dL), leukocytosis ( $13.0 \times 10^9/L$ )

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with lymphocytosis (absolute lymphocyte count of  $9.0 \times 10^9/L$ ), and thrombocytopenia ( $39 \times 10^9/L$ ). Elevated levels of serum lactate dehydrogenase (LDH, 500 U/L) and of bilirubin (BT (3.73MG/DL, BD 1.29 mg, BI 1.29) were detected. Uric acid and creatinine were within normal ranges. Coagulation tests showed: INR 2.1, fibrinogen 96 mg/dl, antithrombin III 50.6%, D-dimer 3.64 mg/dl.

A contrast-enhanced abdominal CT scan revealed splenomegaly (20 cm in maximum diameter) without lymphadenopathy. Examination of the peripheral blood smear showed monotonous, small- to medium-sized lymphoid cells (Supplemental Fig. 1). Peripheral blood flow cytometry analysis indicated an expanded population of lymphocytes, which accounted for 76% of viable WBC, with pathologic, mature T-cell immunophenotype.

Histopathological examination of the bone marrow biopsy revealed a diffuse infiltration by a monotonous lymphoid population positive for CD3, CD5, CD7, TCL1, CD4, and PD1, and negative for CD8, CD30, ALK1, TIA1, and TdT that accounted for 40% of the total cellularity. The residual hematopoietic cells showed normal maturation. These findings were consistent with involvement by a peripheral T-cell lymphoma, in which the strong expression of TCL1 suggested the diagnosis of T-cell prolymphocytic leukemia (T-PLL). Molecular clonality studies performed on peripheral blood showed a monoclonal rearrangement of the T-cell receptor gamma gene (TRG). Cytogenetics failed at diagnosis, and *TP53* was wild-type by sequencing. A skin biopsy to the right shoulder where the patient complained an itchy dyschromic lesion, showed a completely cleaved intradermal nevus and skin with epidermal hyperplasia.

The patient underwent a PET scan, which showed an enlarged spleen with a finely heterogeneous FDG distribution, maintaining a physiological hepato-splenic uptake ratio, and no evident focal areas of abnormal uptake. A mild and diffuse radiotracer uptake was also observed in the bone marrow.

She started chemotherapy consisting of four cycles of bendamustine. Disease reassessment at the end of the four chemotherapy cycles, performed with a contrast-enhanced CT scan, showed persistence of hepatosplenomegaly, lymphocytosis, and generalized pruritus. Blood tests revealed white blood cell (WBC) count of  $6.8 \times 10^9/L$ , with an absolute lymphocyte count of  $5.73 \times 10^9/L$ , a hemoglobin level of 7.3 g/dL, and a platelet count of  $26 \times 10^9/L$ . Serum lactate dehydrogenase (LDH) was elevated at 1000 U/L.

Following confirmation of persistent T-PLL on bone marrow biopsy, second-line therapy with (MoAb anti-CD52) alemtuzumab was initiated with progressively increasing doses, according to the following schedule: Day-1 3 mg, D-2 10 mg, D-3 30 mg, but further weekly doses of alemtuzumab were reduced at a dose of 15 mg due to thrombocytopenia.

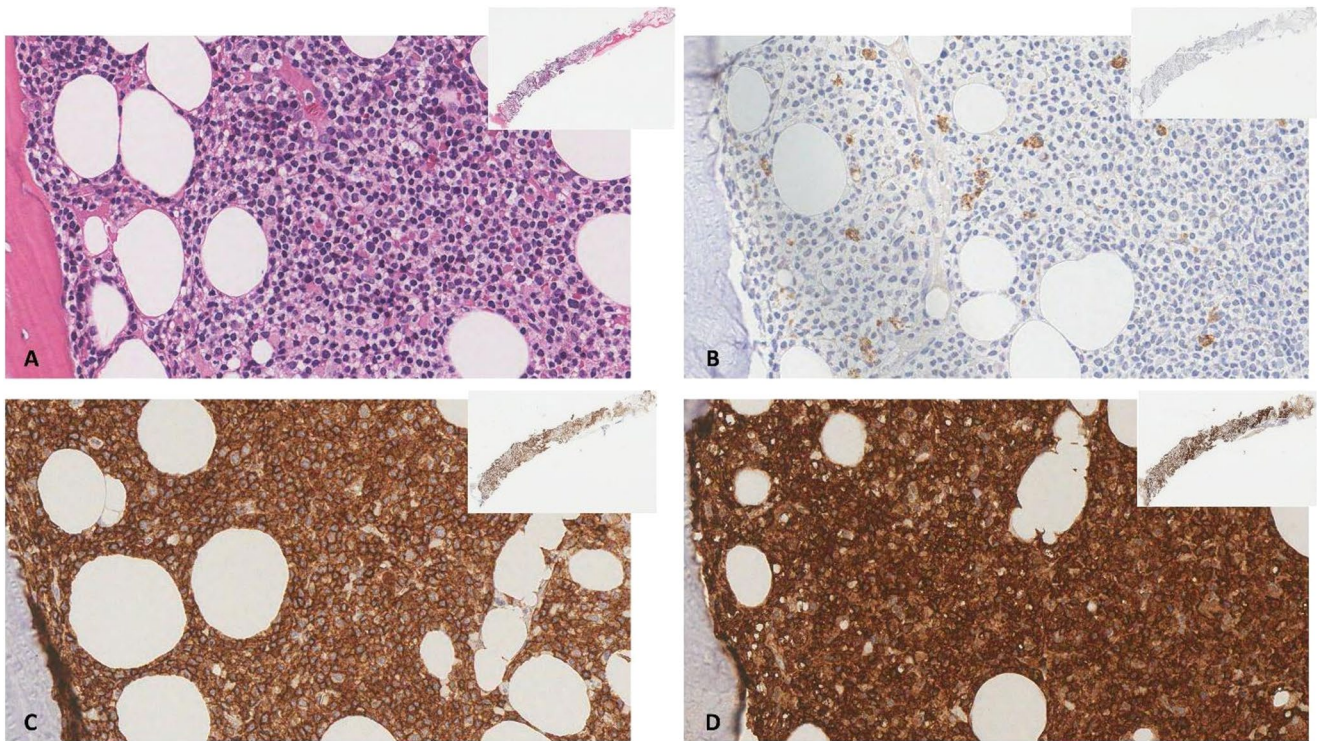
Following the first cycle of therapy (1 month), the patient underwent a bone marrow aspiration showed heterogeneous cellularity averaging 60% and are the site of diffuse infiltration by a lymphoproliferative disease composed of medium-sized elements with a T-cell phenotype: CD3+, CD5+, CD7+, CD2+, with a proportion of CD4+ cells greater than CD8+, TCL1+, TdT-, CD1a-, LMO2-, CD34-, MPO-, CD25-, CD23-, CD10+/-, BCL6+/-, PD1+/-, BCL2+/- (weak), cyclin D1+, CD56-, TIA1-, GrzB-, ALK1-, CD79a-, CD20-, PAX5-, CD30-, EBER-, p53- (strong nuclear positivity in 4–5% of cells). The proliferative index (Ki67) was 20–30%. Occasional CD138+ plasma cells (2–5% of marrow cellularity), polytypic, were also present. The residual hematopoietic population was below 5%. Diffuse reticular fibrosis with focal formation of collagen bundles (MF-2) was present. The histological features observed indicated bone marrow involvement by peripheral T-cell lymphoma, consistent with the diagnosis of T-PLL.

Flow cytometry analysis confirmed persistence of 26.67% lymphocytes with the following immunophenotypic profile: CD10+ (8%), CD7+ (93%), CD5+ (93%), CD2+ (93%), CD3+ (93.29%), cytoplasmic CD3+ (98%), CD4+ (79%), and CD8+ (15%). The bone marrow biopsy (Fig. 1) showed 60% cellularity, with evidence of diffuse infiltration by small-to-medium-sized T-cells CD3+, CD5+, CD7+, CD2+, TCL1+, PD1+/-, with a predominance of CD4+ over CD8+ and p53 strong nuclear positivity in 4–5% of the cells. The cells were negative for TdT, CD1a, LMO2, CD34. The residual hematopoietic population was <5%. Cytogenetic analysis of bone marrow blood revealed a complex karyotype no further characterized due to the small number of cells (Fig. 2). Next-generation sequencing (NGS) (targeted myeloid solution panel, 30 genes, Sophia Genetics) identified *KRAS* pathogenetic mutation c.35G>C (variant allele frequency (VAF) 38%).

In light of disease progression documented by bone marrow examination, the reappearance of lymphocytosis ( $10,000/mm^3$ ), lack of response to alemtuzumab, the development of pulmonary consolidation, and worsening of general clinical condition, it was decided to discontinue treatment with alemtuzumab. The patient was placed on palliative therapy.

## Discussion

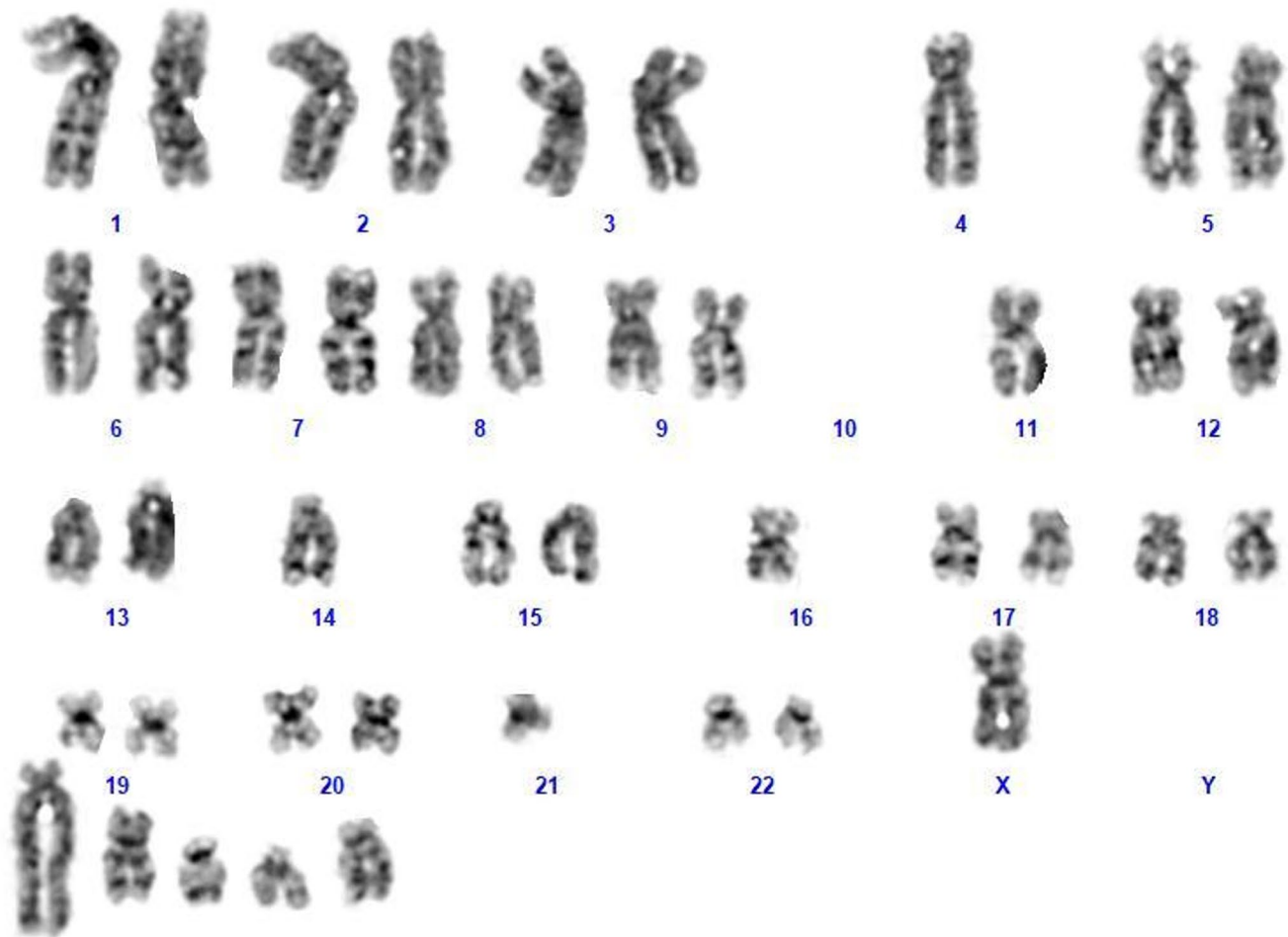
The WHO 5th edition recognizes T-PLL with appropriate phenotype, T-cell monoclonality and the presence of genetic aberrations, including structural variants with breakpoints affecting the *TCL1A* or *MTCP1* locus or expression of TCL1 [3]. In particular, the rearrangements involving



**Fig. 1** Bone marrow diffusely infiltrated by small-to-medium sized cells (A, original magnification (o.m.) x 400, insert o.m. x5), negative for MPO (B, o.m. x400, insert o.m. x5) but expressing CD3 (C, o.m. x 400, insert o.m. x5) and TCL1A (D, o.m. x 400, insert o.m. x5)

TCL1 (T-cell leukemia/lymphoma1) family genes TCL1A, MTCP1 (mature T-cell proliferation), or TCL1B (alias TCL1/MTCP1-like 1 [TML1]), are relatively specific for T-PLL and are present in more than 90% of cases, either as *inv(14)(q11q32)* or *t(14;14)(q11;q32)* (involving TCL1A or TCL1B), or *t(X;14)(q28;q11)* (involving MTCP1; mature T-cell proliferation). Unfortunately, in our case cytogenetic analysis was unable to identify these rearrangements due to the small number of cells, but TCL1a protein expression was identified by immunohistochemistry with a strong staining in the bone marrow lymphoid infiltrate [2]. The mutational landscape of T-PLL has been explored by several studies and alterations of the *JAK-STAT* pathway have been identified as the most frequent ones (75% of T-PLL) [4, 5]. Our patient showed a pathogenetic mutation of *KRAS*. To our knowledge this is the first report of *KRAS* mutation in T-PLL. We employed an NGS panel for myeloid neoplasms instead of a lymphoid-dedicated panel. Indeed, *RAS* mutations can be detected in AML and other myeloproliferative neoplasms [6–8]. In AML the presence of *RAS* mutations has also been implicated in resistance to targeted therapies, including FLT3 and IDH1/2 inhibitors [9, 10]. Moreover, *KRAS* mutations have been reported in other T-cell lymphomas, such as T-follicular helper (TFH)-derived peripheral T-cell lymphoma (PTCL) samples [11].

The identification of *KRAS* mutation in this patient could broaden the mutational spectrum of T-PLL. It could a hypothesis generating finding, that suggests that *RAS* pathway activation might represent an alternative oncogenic mechanism beyond the canonical *TCL1* and *JAK-STAT* pathways. Interestingly, in other solid neoplasms, like non-small cell lung cancer, can harbor *KRAS* mutations, and there are approved drugs targeting these genomic lesions [9]. Indeed, currently approved *KRAS* inhibitors, such as sotorasib and adagrasib, are selective for the *KRAS* G12C mutation (c.34G > T), but not for G12A or other non-G12C variants [12–15]. For tumors harboring *KRAS* G12A mutations, like our T-PLL case, management remains reliant on standard cytotoxic chemotherapy, immunotherapy, or other targeted agents based on tumor histology and molecular profile, but not on *KRAS*-specific inhibition [16]. Unfortunately, the poor conditions of our patient prevented us from associating alemtuzumab with chemotherapy (fludarabine, mitoxantrone, cyclophosphamide (FMC) or cladribine) [17, 18]. Conversely, the biology of our case was particularly unfavorable, since at least a transient response to alemtuzumab is generally seen in T-PLL [19]. In this single case, it is difficult to establish the sole biologic role of *KRAS* mutation, since other biological features could contribute (e.g., TCL1 expression [20]).



**Fig. 2** G-banding analysis demonstrated the presence of a complex karyotype with 43 chromosomes including five unidentified markers chromosomes due to the small number of cells (bone marrow sample)

## Conclusion

In conclusion, this case emphasizes the opportunity of identifying *KRAS* in other patients with T-PLL. Since *KRAS* mutations directly impact the MAP-Kinase signaling pathway and have been previously identified in various PTCL subtypes, its presence in T-PLL may indicate an additional, albeit less frequent, pathogenetic driver within this aggressive malignancy. New therapeutic approaches are emerging for T-PLL, involving drugs that target autophagy, nuclear export, and inhibitor of apoptosis proteins (IAPs; birinapan) [21]. In this scenario, targeting *KRAS* might represent another option to be explored in the future.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00277-026-06986-2>.

**Author contributions** All authors have read and approved the final version of the manuscript and have contributed significantly to its content.

**Funding** Open access funding provided by Università degli Studi di

Roma La Sapienza within the CRUI-CARE Agreement..

**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethical statement** This work was done in accordance to Helsinki declaration. All information was anonymized.

**Consent to publish** Written consent was given by relatives.

**Competing interests** The authors declare no competing interests.

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## References

- Gutierrez M, Bladek P, Goksu B et al (2023) T-Cell prolymphocytic leukemia: diagnosis, pathogenesis, and treatment. *Int J Mol Sci* 24:12106. <https://doi.org/10.3390/ijms241512106>
- Staber PB, Herling M, Bellido M et al (2019) Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. *Blood* 134:1132–1143. <https://doi.org/10.1182/blood.2019000402>
- Alaggio R, Amador C, Anagnostopoulos I et al (2022) The 5th edition of the world health organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia* 36:1720–1748. <https://doi.org/10.1038/s41375-022-01620-2>
- Kiel MJ, Velusamy T, Rolland D et al (2014) Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. *Blood* 124:1460–1472. <https://doi.org/10.1182/blood-2014-03-559542>
- Mikhaylenko N, Wahnschaffe L, Herling M et al (2022) Computational gene expression analysis reveals distinct molecular subgroups of T-cell prolymphocytic leukemia. *PLoS ONE* 17:e0274463. <https://doi.org/10.1371/journal.pone.0274463>
- Carr RM, Vorobyev D, Lasho T et al (2021) RAS mutations drive proliferative chronic myelomonocytic leukemia via a KMT2A-PLK1 axis. *Nat Commun* 12:2901. <https://doi.org/10.1038/s41467-021-23186-w>
- Zhang F, Liu Y, Zhu Y et al (2025) Molecular, clinical, and prognostic implications of RAS pathway alterations in adult acute myeloid leukemia. *Leuk Lymphoma* 66:753–763. <https://doi.org/10.1080/10428194.2024.2441855>
- Vallois D, Dobay MPD, Morin RD et al (2016) Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell–derived lymphomas. *Blood* 128:1490–1502. <https://doi.org/10.1182/blood-2016-02-698977>
- Jones L, Rukhlenko O, Dias T et al (2025) A structure-based modelling approach identifies effective drug combinations for RAS-mutant acute myeloid leukemia bioRxiv [Preprint]. <https://doi.org/10.1101/2025.04.29.651188>
- Herling M, Patel KA, Teitell MA et al (2008) High TCL1 expression and intact T-cell receptor signaling define a hyperproliferative subset of T-cell prolymphocytic leukemia. *Blood* 111:328–337
- Perrone S, Tresoldi C, Rigamonti S, Molica M, Zhdanovskaya N, Cicconi L (2025) How to read a next-generation sequencing report for aml and mds? what hematologists need to know. *J Clin Med* 14(24):8681. <https://doi.org/10.3390/jcm14248681>
- Reck M, Carbone DP, Garassino M, Barlesi F (2021) Targeting KRAS in non-small-cell lung cancer: recent progress and new approaches. *Ann Oncol* 32:1101–1110. <https://doi.org/10.1016/j.annonc.2021.06.001>
- Kasper S, Sebastian M (2025) The Pharmacologic inhibition of KRAS mutants as a treatment for cancer: therapeutic principles and clinical results. *Deutsches Ärzteblatt international*. <https://doi.org/10.3238/arztebl.m2025.0002>
- Hallin J, Bowcut V, Calinisan A et al (2022) Anti-tumor efficacy of a potent and selective non-covalent KRASG12D inhibitor. *Nat Med* 28:2171–2182. <https://doi.org/10.1038/s41591-022-02007-7>
- Hitchen N, Williams S, Desai J (2025) Recent advances in therapeutic targeting of the KRAS pathway in cancer. *Pharmacol Ther* 273:108889. <https://doi.org/10.1016/j.pharmthera.2025.108889>
- Kirschner T, Müller MP, Rauh D, Targeting KRAS, Diversity (2024) Covalent modulation of G12X and beyond in cancer therapy. *J Med Chem* 67(8):6044–6051
- Arani N, Rausch CR, Geppner A et al (2025) Cladribine and venetoclax combined with alemtuzumab in patients with relapsed/refractory T-cell prolymphocytic leukemia. *Leuk Lymphoma* 1–5. <https://doi.org/10.1080/10428194.2025.2566318>
- Hopfinger G, Busch R, Pflug N et al (2013) Sequential chemioimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia. *Cancer* 119:2258–2267. <https://doi.org/10.1002/cncr.27972>
- An N, Bian K, Li C (2025) Alemtuzumab for haematological malignancies. *Ann Hematol* 104:2593–2603. <https://doi.org/10.1007/s00277-025-06344-8>
- Perrone S, Ottone T, Zhdanovskaya N, Molica M (2023) How acute myeloid leukemia (AML) escapes from FMS-related tyrosine kinase 3 (FLT3) inhibitors? Still an overrated complication. *Cancer Drug Resist* 6:223–238. <https://doi.org/10.20517/cdr.2022.130>
- Pohly MF, Putzker K, Scheinost S et al (2025) IAP dependency of T-cell prolymphocytic leukemia identified by high-throughput drug screening. *Blood* 145:2336–2352. <https://doi.org/10.1182/blood.2024027171>

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