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Clinical and molecular characterization of *TP53*-mutant acute lymphoblastic leukemia in adults

Ethan J. Harris[1], Diren Arda Karaoglu[2], Madina Sukhanova[3], Yasmin Abaza[3], Theodoros Karantanos[4], Ann-Kathrin Eisfeld[5], Clare Anderson[6], Chenyu Lin[6], Yenny A. Moreno Vanegas[7], Talha Badar[7], Alexander Coltoff[8], Todd C. Knepper[9], Neval Ozkaya[10], Hamed Rahmani Youshanlouei[2], Sinan Cetin[2], Anand A. Patel[2], Adam S. DuVall[2], Michael W. Drazer[2], Peng Wang[10], Melissa Tjota[10], Jeremy P. Segal[10], Girish Venkataraman[10], Sandeep Gurbuxani[10], Jason X. Cheng[10], Daniel A. Arber[10], Richard A. Larson[2], Olatoyosi Odenike[2], Jonathan Webster[4], Bijal Shah[9], Wendy Stock[2] and Caner Saygin[2]✉

TP53-mutant acute lymphoblastic leukemia (ALL) in adults is a high-risk subtype with poor outcomes, yet its molecular landscape and clinical implications remain incompletely defined. In this multi-institutional study of 830 adult ALL patients treated at eight academic centers between 2010 and 2024, we demonstrated that *TP53* mutations are independent predictors of inferior overall survival in both B-ALL (median, 1.9 vs 5 years) and T-ALL (1.6 vs 9.5 years), irrespective of age, biologic disease subtype, or therapy. Genomic profiling revealed that >90% of *TP53* mutations were DNA-binding domain missense variants, frequently co-occurring with hypodiploidy in B-ALL and NOTCH1/FBXW7 mutations in T-ALL. Unlike myeloid malignancies, biallelic *TP53* mutations did not worsen outcomes, and variant type (missense vs truncating) did not influence survival. *TP53*-mutant B-ALL exhibited higher CD20 positivity than *TP53*-wild type B-ALL (65% vs 31%) but had inferior responses to conventional chemotherapy. Novel immunotherapies (e.g., inotuzumab/blinatumomab) or venetoclax-containing combination regimens improved remission rates, yet relapses were common, often with CD19/CD20/CD22 loss (triple-negative) or acquisition of new mutations. Allogeneic transplantation in first remission trended toward survival benefit (median, 3.3 vs 2.2 years). These findings underscore *TP53*-mutant ALL as a distinct, chemo-resistant entity necessitating tailored approaches, with antigen escape highlighting challenges of immunotherapy durability.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a curable disease in children and young adults [1]. However, outcomes of B- and T-lineage ALL are inferior in older adults due to the higher frequency of adverse-risk molecular characteristics and more limited ability to utilize intensive pediatric-inspired chemotherapy regimens [1, 2]. Biologically, the majority of adult ALL cases harbor aneuploidy (e.g., low hypodiploidy), high-risk fusions (e.g., *BCR::ABL1*-like signature), or mutations in *TP53* or non-*TP53* myeloid genes [3–5]. We and others have shown that adult *TP53*-mutant ALL may arise from pre-existing *TP53*-mutant clonal hematopoiesis (CH) [4, 6, 7]. In adults, *TP53* mutations are somatic in >90% of patients, which contrasts the high incidence of Li Fraumeni syndrome seen in 45% of pediatric low hypodiploid *TP53*-mutant ALL cases [8]. *TP53* mutations are found in 15–20% of adults with ALL and are associated with poor chemotherapy response and overall survival (OS) [4, 9, 10]. In this large multi-institution cohort study, we aim to decipher the unique molecular landscape of adult *TP53*-mutant ALL, as well as the clinical implications of *TP53* mutations in the context of established molecular disease subtypes.

TP53 encodes the transcription factor p53, which is a tumor suppressor that can be induced in response to DNA damage, cellular stress or oncogenic hyperproliferation [11]. *TP53* is the most frequently mutated gene across all cancers, and *TP53*-mutant myeloid neoplasms have an extremely poor prognosis [12, 13]. In acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), biallelic *TP53* mutations predict higher risk for relapse and death when compared to monoallelic mutations [12, 14]. In addition, 80% of *TP53* mutations across all cancer types are protein-altering missense variants in the DNA-binding domain [15]. While some studies in solid tumors and leukemias suggest an oncogenic gain-of-function (GoF) phenotype associated with these missense variants [16, 17], other mechanistic studies found no evidence to support GoF role for mutant p53 in AML [18]. Instead, mutations reduced p53 tumor-suppressive activity in a

[1]Department of Medicine, University of Chicago, Chicago, IL, USA. [2]Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL, USA. [3]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. [4]Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA. [5]Division of Hematology, The Ohio State University, Columbus, OH, USA. [6]Division of Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA. [7]Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, FL, USA. [8]Division of Hematology and Oncology, Medical University of South Carolina, Charleston, SC, USA. [9]Moffitt Cancer Center, Tampa, FL, USA. [10]Department of Pathology, University of Chicago, Chicago, IL, USA. ✉email: caner.saygin@bsd.uchicago.edu

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dominant-negative manner. Biological and clinical significance of *TP53* allelic state and variant type is not established for ALL.

We studied a large cohort of adult patients with ALL treated at eight academic institutions in the US. Through comprehensive genomic profiling and correlative analyses with real-world outcomes data, we found that *TP53* mutations are independent predictors of poor outcomes in adult ALL when adjusted for age, molecular subtype, allelic state or variant type. The adverse impact of *TP53* mutations is driven by inferior chemotherapy response and high rates of CD19, CD20, or CD22 negative relapses upon treatment with newer antibody-based therapies.

METHODS

Patient cohort

A total of 830 adult patients with ALL (age ≥18 years) treated at 8 academic centers between the years 2010 and 2024 were included in this study. Diagnosis, relapse, and disease status were confirmed and assigned according to the World Health Organization (WHO) criteria [19]. Patients with mixed phenotype acute leukemia were excluded. Complete remission (CR) was defined as no circulating blasts or extramedullary disease, <5% bone marrow blasts, adequate neutrophil and platelet count recovery. Measurable residual disease (MRD) was assessed with multiparameter flow cytometry (sensitivity of 0.01%) assay in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories of collaborating institutions [20]. The study was approved by the Institutional Review Boards of participating sites and conducted in accordance with the Declaration of Helsinki. Informed consent has been obtained from participants.

Molecular profiling

Molecular subtype classification was based on the use of multiple assays, including cytogenetics (karyotype), fluorescence in situ hybridization (FISH), polymerase chain reaction for known fusions, DNA and RNA sequencing, and chromosome microarrays for copy-number abnormalities. These assays were performed as part of routine clinical care in CLIA-certified laboratories. Karyotyping of diagnostic bone marrow aspirate specimens was performed by counting 20 metaphase cells. Ph-like gene signature was determined by FISH for common fusions (*CRLF2*, *JAK2*, *ABL1*, *ABL2*, *CSF1R*, *PDGFR*) and RNA-sequencing. Patient samples from the University of Chicago underwent high-throughput targeted next-generation sequencing (NGS) with the OncoPlus assay (178 genes) [21]. Similarly, diagnostic NGS testing was performed with pan-heme NGS panel at the Northwestern University (204 genes) [22], Hematologic Neoplasm Mutation Panel at The Ohio State University [23], Leukemia NGS panel at Johns Hopkins University (94 genes) [24], Myeloid NGS test at Duke University (75 genes) [25], Comprehensive OncoHeme NGS assay at Mayo Clinic [26], FocusHeme NGS panel at the Medical University of South Carolina (49 genes) and Foundation One Heme Assay at the Moffitt Cancer Center (455 genes) [4]. Genes that are shared between the NGS panels of collaborating sites were used for further analysis. For pathogenic and likely pathogenic variants, an allelic frequency (AF) cutoff of 5% was used.

Statistical analysis

Clinical data for patients were available from medical records. The associations between clinical variables and different classes of mutations were investigated by calculating the odds ratios (OR) with the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The impact of covariates on survival outcomes was investigated with univariable and multivariable Cox regression analyses. OS was defined as the time from diagnosis until death or last follow-up. Recurrence-free survival (RFS) was defined as the time from first CR until disease relapse, death, or last follow-up. OS and RFS estimates were calculated with the Kaplan–Meier method, and differences were compared using the log-rank test. All statistical analyses were performed using R v.4.4.2. The figures were generated with the ggplot2 package in R and GraphPad Prism version 9 (GraphPad Software).

RESULTS

TP53 mutations are independent predictors of adverse outcomes in ALL

We retrospectively studied molecular characteristics and survival outcomes of 830 adult patients with ALL (709 with B-ALL, 121 with T-lineage ALL) treated at the collaborating institutions within the recent era of new ALL therapeutics (2010–2024). Demographic characteristics of the cohort are summarized in Table 1. Patients with B-ALL were classified into six genetic subtypes based on the molecular data available from all participating sites. ALL cases harboring *BCL2* or *MYC* fusions, *KMT2A* rearrangements, low hypodiploidy (≤40 chromosomes), or Ph-like signature (i.e., *BCR::ABL1*-like) had inferior OS and RFS outcomes when compared to B-ALL patients with hyperdiploidy, *BCR::ABL1*, and other genetic alterations (Fig. 1A).

TP53 mutations can be seen across different WHO-defined genetic subtypes of ALL [9]. The frequency of *TP53* mutations was 17% in our adult ALL cohort. We investigated the prognostic impact of *TP53* mutation in the context of previously established predictors of adverse outcomes in ALL. Using multivariable Cox regression analysis, *TP53* mutation was an independent predictor of poor OS in B-ALL when adjusted for age, sex, year of ALL diagnosis and molecular subtype (Fig. 1B). Similarly, *TP53* mutation was associated with inferior OS in T-lineage ALL when adjusted for age, sex, year of ALL diagnosis and ETP-status (Fig. 1C). Comparing *TP53*-mutant vs wild-type (WT) ALL, median OS was significantly shorter in *TP53*-mutant B-ALL (1.9 vs 5 years, $p < 0.001$) and T-lineage ALL (1.6 vs 9.5 years, $p = 0.03$) (Fig. 1D, E). The adverse prognostic impact of *TP53* mutations was seen in both younger (<40 years) and older (≥40 years) patients with B- and T-lineage ALL (Supplementary Fig. 1). Altogether, these data suggest that *TP53* mutations confer adverse prognostic risk for B- and T-ALL patients, independent from traditional high-risk features.

Molecular landscape of *TP53*-mutant ALL

To understand the determinants of poor outcomes in *TP53*-mutant ALL, we first studied the genomic landscape associated with *TP53* mutations. Similar to the distributions observed in AML [18] and MDS [14], pathogenic or likely pathogenic *TP53* variants were concentrated in the DNA-binding domain in >90% of patients with ALL (Fig. 2A). *TP53* mutations were most frequent in patients with hypodiploid B-ALL, but rare in patients with *BCL/MYC, BCR::ABL1, BCR::ABL1*-like or hyperdiploid B-ALL (Fig. 2B, C). We found that 14% of B-ALL and 9% of T-ALL patients had biallelic *TP53* mutations, defined by WHO criteria as multiple mutations or mutation with concurrent deletion of the other allele (Fig. 2D) [27]. As expected, biallelic *TP53* alterations were more frequent in B-ALL patients with hypodiploidy (Fig. 2E). We also investigated the landscape of co-occurring gene mutations and found differences between B- and T-lineage ALL (Fig. 2F). Mutations in *RB1* (13%), *IKZF1* (10%), *NF1* (10%), *TET2* (9%) and *NRAS* (7%) were more frequent in *TP53*-mutant B-ALL (Fig. 2G), while *NOTCH1* (62%), *FBXW7* (31%), *PHF6* (31%), *ASXL1* (23%) and *WT1* (23%) mutations were more frequent in *TP53*-mutant T-ALL (Fig. 2H). *CDKN2A* mutations were common in both B- and T-ALL. Collectively, these data suggest that the majority of *TP53* mutations are missense variants affecting the DNA-binding domain, and *TP53*-mutant B- vs T-lineage ALL may harbor co-mutations in different genes associated with lineage.

Clinical outcomes of *TP53*-mutant B-ALL

To determine the biological and clinical factors associated with *TP53*-mutant B-ALL, we studied the associations between *TP53* status and other demographic and clinicopathological variables. Notably, *TP53* mutations were more common with older age (OR 7.53, 95% confidence interval [CI]: 3.3–18, $p < 0.001$) and therapy-related B-ALL (OR 2.6, 95% CI: 1.6–4.1, $p < 0.001$), but less common in individuals of self-reported Hispanic ancestry (OR 0.4, 95% CI: 0.2–0.9) (Fig. 3A). CD20 positivity was more common in *TP53*-mutant B-ALL blasts when compared to *TP53* WT blasts (65% vs 31%, $p = 0.001$) (Fig. 3B). Other therapeutically targetable surface markers, CD19 and CD22 were expressed in >90% of B-ALL cases at diagnosis. Over-expression of the missense-mutant p53 protein

Table 1. Study cohort.

	B-ALL		T-lineage ALL	
	***TP53*-mutant ($n = 125$)**	***TP53* wild-type ($n = 388$)**	***TP53*-mutant ($n = 14$)**	***TP53* wild-type ($n = 90$)**
Age, years (range)	62 (18–86)	46 (18–88)	42 (20–77)	37 (18–88)
Age groups (years)				
18–39	23 (18)	152 (39)	7 (50)	48 (53)
40–60	31 (25)	128 (33)	5 (36)	26 (29)
>60	71 (57)	108 (28)	2 (14)	16 (18)
Sex, n (%)				
Female	58 (46)	198 (51)	6 (43)	29 (32)
Male	67 (54)	190 (49)	8 (57)	61 (68)
T-lineage subtype				
ETP	NA	NA	1 (7)	24 (27)
Pre-T			13 (93)	66 (73)
Year of diagnosis				
2010–2014	27 (22)	46 (12)	2 (14)	6 (7)
2015–2019	53 (42)	200 (51)	7 (50)	49 (54)
2020–2024	45 (36)	142 (37)	5 (36)	35 (39)
Ethnicity				
White	63 (50)	149 (38)	7 (50)	34 (38)
Hispanic	10 (8)	55 (14)	0	5 (6)
Black	10 (8)	26 (7)	4 (29)	13 (14)
Asian	1 (1)	8 (2)	0	4 (4)
Unknown	41 (33)	150 (39)	3 (21)	34 (38)
First-line therapy				
Hyper-CVAD	34 (27)	104 (27)	5 (36)	15 (17)
Pediatric	31 (25)	131 (34)	6 (43)	55 (61)
Low intensity chemotherapy	28 (22)	89 (23)	1 (7)	4 (4)
Antibody	7 (6)	10 (2)	0	0
Hyper-CVD + venetoclax	5 (4)	9 (2)	0	3 (3)
Unknown	20 (16)	45 (12)	2 (14)	13 (14)
Allogeneic HCT, *n* (%)	21/84 (25)	60/249 (24)	2/8 (25)	14/57 (25)

was detectable with immunohistochemistry in diagnostic bone marrow slides, co-localizing with CD20 positive blasts (Fig. 3C).

Next, we investigated the predictors of worse OS in patients with *TP53*-mutant B-ALL. In univariable Cox regression analysis, older age was associated with inferior outcomes, while patients treated between 2020 and 2024 had better OS than those treated in earlier years (Fig. 4A). *TP53* missense mutations in DNA binding domain may have a novel oncogenic GoF phenotype in different cancers. However, we observed similar OS outcomes between patients harboring missense-mutant *TP53* vs other (e.g., frame-shift, splice site mutations) types of loss-of-function *TP53* variants (Fig. 4B). Biallelic *TP53* mutations are associated with worse outcomes than monoallelic *TP53* mutations in some subtypes of myeloid neoplasms. However, *TP53* allelic state did not predict OS or RFS in patients with B-ALL (Fig. 4C, D). To study the roles of different first-line therapies in *TP53*-mutant B-ALL outcomes, we compared CR with flow MRD-negativity rates in patients treated with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine), pediatric protocols (i.e., CALGB 10403 regimen), hyper-CVD (cyclophosphamide, vincristine, dexamethasone) + venetoclax and novel antibody-based approaches (i.e., A41703 regimen of sequential inotuzumab and blinatumomab) (Fig. 4E). Patients with *TP53*-mutant B-ALL had inferior responses to chemotherapy approaches when compared to patients with *TP53*-WT B-ALL, while responses were similar when newer therapies (venetoclax or antibodies) are introduced into frontline regimens. Finally, we compared outcomes of *TP53*-mutant B-ALL patients stratified based on receipt of allogeneic hematopoietic cell transplantation (HCT) (Fig. 4F). We used a 3-month landmark analysis to include patients who achieved CR after first-line therapy. Allogeneic HCT was associated with longer OS, but the difference did not reach statistical significance (median OS, 3.3 vs 2.2 years, $p = 0.07$).

Altogether, these data indicate higher rates of CD20 positivity in *TP53*-mutant B-ALL, in which the type of *TP53* mutation or its allelic state did not predict OS. These patients may benefit from novel antibody-based therapies or BH3 mimetic combinations in first-line therapy, and a subset may benefit from allogeneic HCT in CR1.

Clonal evolution in relapsed *TP53*-mutant B-ALL

To gain insights into the clonal evolution and acquired mechanisms of resistance, we performed genomic and immunophenotypic analysis of serial diagnosis and relapse samples in *TP53*-mutant B-ALL. *TP53* mutations were present in relapse samples of all patients, further confirming the stability of these variants in founder leukemic clones (Fig. 5A). Next, we studied clonal dynamics in patients who developed new acquired mutations at the time of relapse. In B-ALL1, pre-leukemic *TP53* mutation was

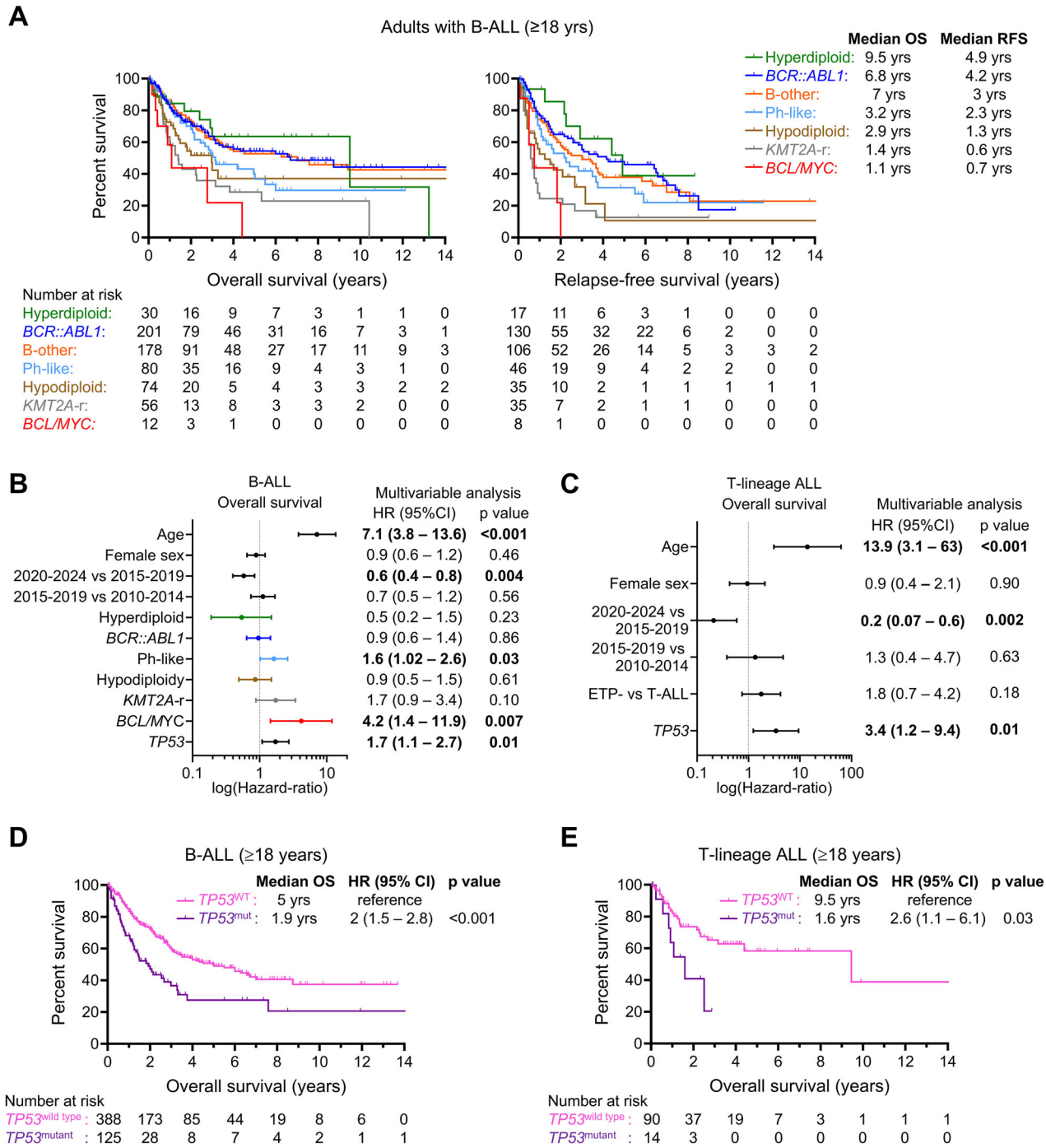

Fig. 1 ***TP53* mutations predict poor outcomes in ALL. A** Overall and relapse-free survival curves for B-ALL patients with different molecular subtypes of disease. Multivariable analysis of overall survival for patients with B-ALL (**B**) and T-lineage ALL (**C**). Survival outcomes of B-ALL (**D**) and T-lineage ALL (**E**) patients stratified based on their *TP53* status. CI confidence interval, HR, hazard ratio, OS overall survival, WT wild type.

detectable at low AF (3%) when the patient was in remission, supporting previous observations that *TP53*-mutant CH is a precursor for B-ALL in adults (Fig. 5B) [4, 6]. *CDKN2A* and *PTPN11* mutations re-emerged at the time of relapse, which was also characterized by the loss of CD19 expression after blinatumomab therapy and new somatic deletion in the *STK11* gene. We observed loss of surface marker expression as a mechanism of immunotherapy resistance in other *TP53*-mutant B-ALL samples. In B-ALL2, first-line treatment with inotuzumab followed by blinatumomab effectively treated *TP53/RB1*-mutant B-ALL, but the disease re-emerged with CD19/CD22-negative relapse (Fig. 5C). CR2 was achieved with rituximab, hyper-CVD, venetoclax combination therapy, but the patient relapsed again with triple-negative (CD19, CD20, CD22) disease and newly acquired *MSH2* mutation resulting in new-onset microsatellite instability (MSI) and high tumor mutation burden in lymphoblasts. Finally, we investigated patterns of relapse after allogeneic HCT. In B-ALL3, relapse post-transplant was associated with an acquired *CCND3* mutation in *TP53, CDKN2A, NF1*-mutant clone (Fig. 5D). Patient achieved CR2 with inotuzumab and blinatumomab combination therapy. In summary, these data indicate that *TP53* mutations are pre-leukemic events in B-ALL and clonal evolution is characterized by

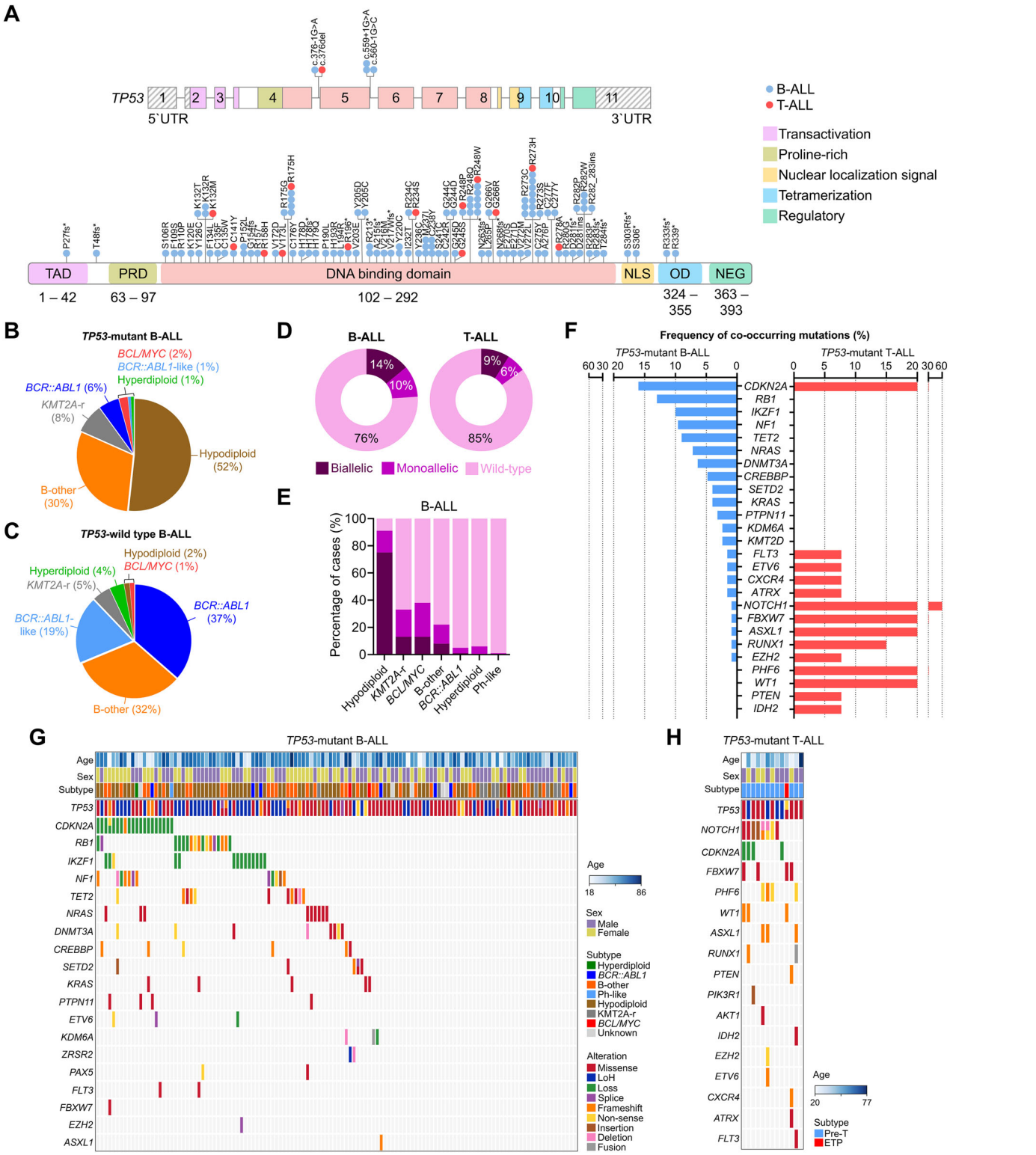

Fig. 2 Molecular characteristics of *TP53*-mutant ALL. A Pathogenic and likely pathogenic *TP53* variants spanning different functional domains of *TP53* gene. Pie charts demonstrate WHO-defined genetic subtypes in *TP53*-mutant (**B**) and wild-type (**C**) B-ALL. Distribution of *TP53* mutations based on allelic state in B- vs T-ALL (**D**) and across genetic subtypes of B-ALL (**E**). **F** Bar graphs comparing the frequencies of mutations that frequently co-occur with *TP53* in B- and T-ALL. Oncoprints summarizing molecular landscape of *TP53*-mutant B-ALL (**G**) and T-ALL (**H**).

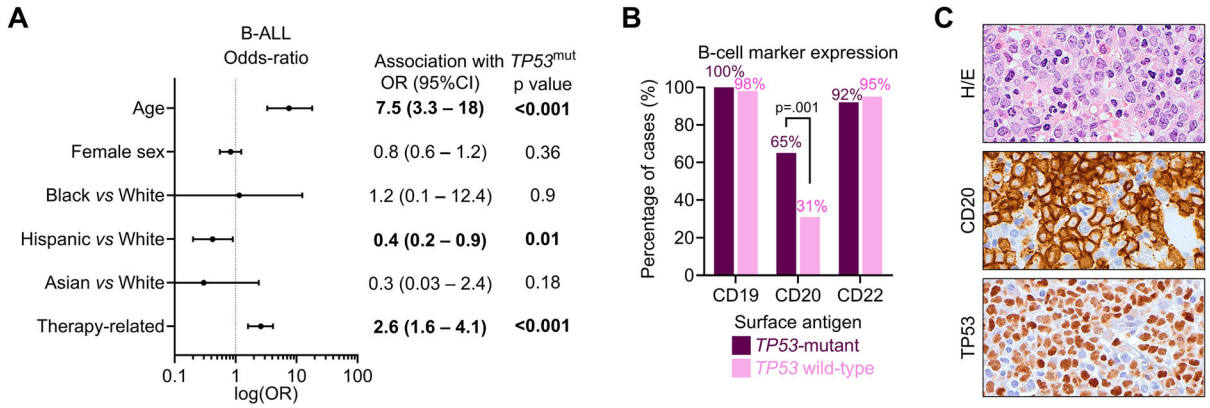

Fig. 3 Clinicopathological variables associated with *TP53*-mutant B-ALL. A Forest plot demonstrates the odds ratios for the associations between clinical variables and *TP53* mutation status in B-ALL. **B** CD19, CD20, and CD22 surface marker expression in *TP53* wild-type vs mutant B-ALL. **C** Representative immunohistochemistry slides showing CD20 and TP53 co-expression in B-ALL.

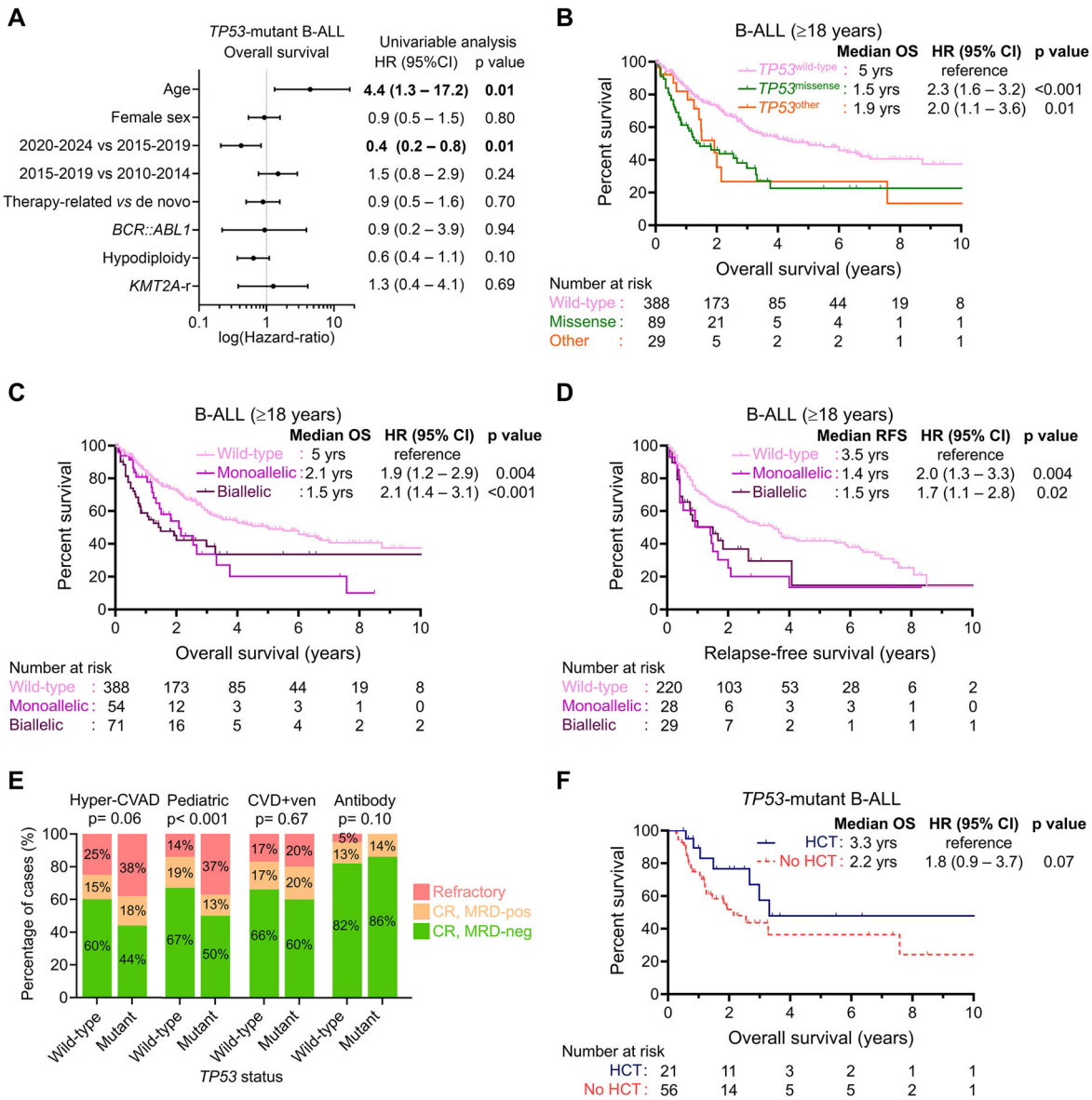

Fig. 4 Clinical outcomes in *TP53*-mutant B-ALL. A Univariable Cox regression analysis for predictors of adverse overall survival. Kaplan-Meier survival curves comparing outcomes of *TP53*-WT vs *TP53*-mutant patients stratified based on *TP53* mutation type (**B**) or allelic state (**C**, **D**). **E** Bar graphs showing complete remission (CR) with flow cytometric measurable residual disease (MRD)-negativity rates between patients with *TP53*-WT vs *TP53*-mutant B-ALL treated with different first-line approaches. **F** Kaplan-Meier overall survival curves comparing outcomes of *TP53*-mutant B-ALL patients stratified based on performance of allogeneic hematopoietic cell transplantation (HCT).

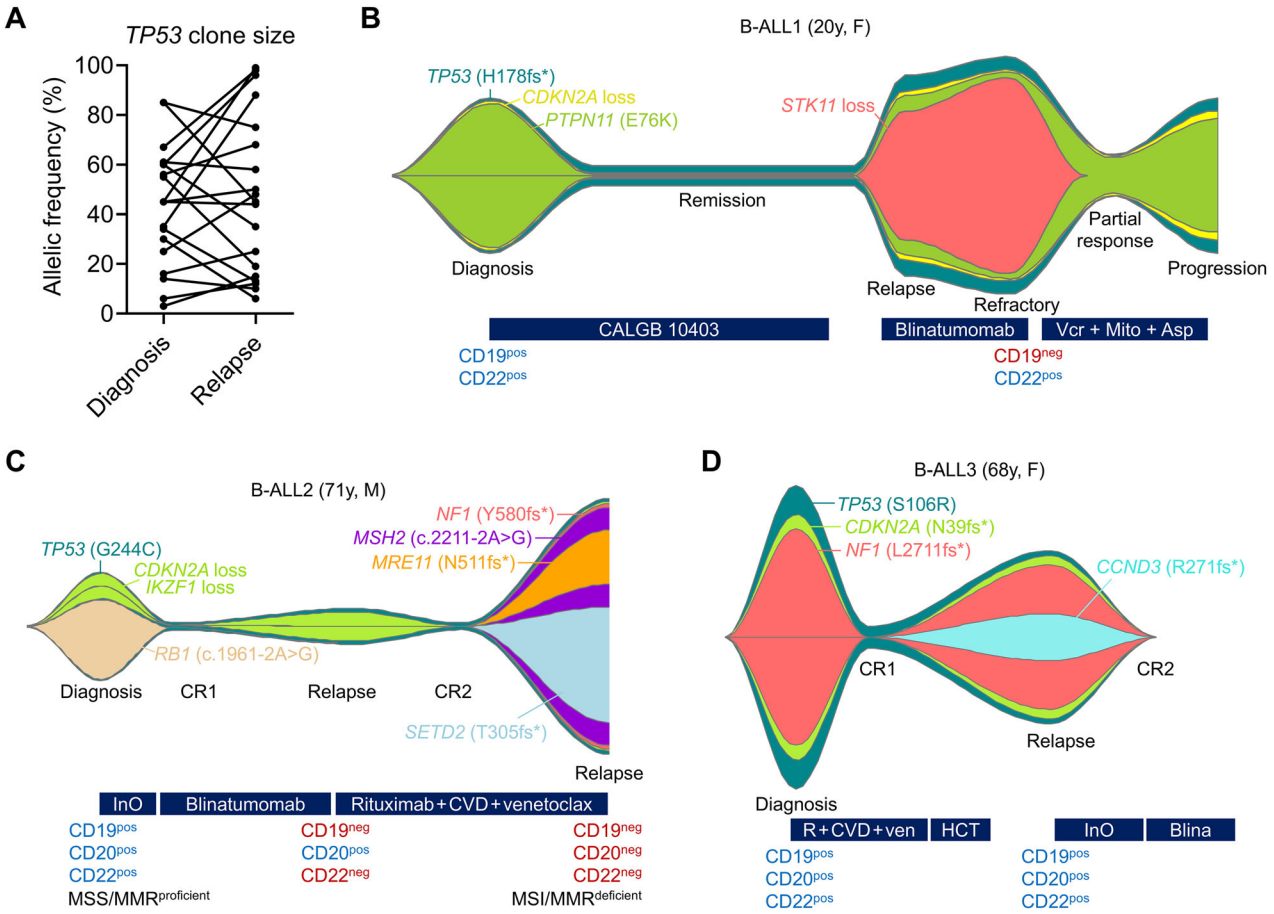

Fig. 5 Clonal dynamics of relapse in *TP53*-mutant B-ALL. A Line graph showing evolution of *TP53* clone size between diagnosis vs relapse in *TP53*-mutant B-ALL. **B**–**D** Fish plots showing evolution of B-ALL clones at the time of relapse, characterized by the acquisition of new mutations (*STK11* loss in B-ALL1, *MSH2* and microsatellite instability [MSI] in B-ALL2, *CCND3* in B-ALL3) and loss of CD19, CD20, or CD22 surface markers under selective pressure of antibody-based targeted therapies.

antigenic loss and emergence of new mutations in genes that are less frequently altered in treatment-naive disease.

DISCUSSION

We established clinical and molecular characteristics of adult *TP53*-mutant ALL by studying a large multi-center cohort of real-world patients. Traditionally, pediatric ALL is more comprehensively studied than adult ALL, and insights obtained from large cohorts of children and young adults with ALL formed the basis for the genetic subtypes established by the WHO and International Consensus Classification [19, 28]. Older adults (age >40 years) were often excluded from adult ALL trials, further exacerbating the gaps in our knowledge on ALL biology, which is very different between children and adults. Several WHO-defined ALL subtypes are either not seen in adults (e.g., *ETV6::RUNX1*) or not routinely assessed in clinical practice with available commercial or in-house assays (e.g., *MEF2D*-rearrangement, *NUTM1*-rearrangement, *ETV6::RUNX1*-like). There exists a discordance between prognostic models proposed by the classification guidelines and what can be feasibly implemented in clinical testing to inform therapeutic decision making for adults with ALL. In this study, we established adverse prognostic impact of high-risk genetic features (i.e., *BCL/MYC* rearrangement, hypodiploidy, *KMT2A*-rearrangement, *BCR::ABL1*-like signature) in the modern era of ALL therapeutics. These subtypes can be readily identified with available sequencing platforms. Given the independent prognostic role of *TP53* mutations in adult ALL, we examined the previously unanswered questions of the significance of *TP53* allelic state, mutation type and allogeneic HCT in predicting outcomes for *TP53*-mutant ALL. While biallelic *TP53* mutations did not portend worse outcomes than monoallelic mutations, a subgroup of patients with *TP53*-mutant ALL may benefit from allogeneic HCT in CR1. This question should be further investigated in future studies examining larger cohorts derived from transplant registries.

TP53-mutant leukemias have a poor prognosis due to their refractoriness to traditional cytotoxic chemotherapy. Importantly, we observed high MRD-negative CR rates when these patients are treated with newer immunotherapy approaches (inotuzumab and blinatumomab) or venetoclax-based combination regimens (hyper-CVD plus venetoclax). However, triple-negative relapses (CD19/CD20/CD22 negative) are common in patients who receive antibody-based therapies. We also observed unique genotypes at the time of relapse, such as acquisition of *MSH2* mutation leading to deficient mismatch repair. MSI-high status has not been observed in large cohorts of AML [29]. Emergence of this phenotype in late stages of *TP53*-mutant lymphoblastic leukemogenesis may indicate a lineage-specific phenomenon with genomic instability.

This study has a few limitations. We performed molecular subclassification based on the genes and fusions that are mutually covered by participating institutions. Some of the recently annotated B-ALL genetic subtypes and most T-ALL genetic subtypes are not covered by these panels, which limited our analyses in T-ALL. However, the clinical and therapeutic significance of these unprofiled genetic alterations (e.g., *NUTM1*, *MEF2D*,

DUX4, *ZEB2*, *CDX2/UBTF*) is not fully established in large cohorts of older adults with ALL. Therefore, we focused on the biological and clinical significance of *TP53* mutations, which have an independent but underappreciated prognostic impact in ALL. As is the case for any retrospective analysis, conclusions related to the role of allogeneic HCT should be interpreted with caution and validated further in larger cohorts.

In conclusion, *TP53*-mutant ALL is a high-risk disease characterized by inferior response to cytotoxic chemotherapy, high-rates of antigen-negative relapse after immunotherapies, and distinct patterns of clonal evolution. Biallelic mutations or missense mutations, which are thought to confer GoF phenotype in other cancers, do not confer higher risk when compared to monoallelic or truncating mutations, respectively. Nevertheless, given the worse outcomes overall, there is an unmet need for new therapeutics in *TP53*-mutant ALL, akin to the significant therapeutic challenge that exists for *TP53*-mutant myeloid neoplasms.

DATA AVAILABILITY

Access to anonymized clinical data might be granted upon request to the corresponding author.

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AUTHOR CONTRIBUTIONS

EH, DAK, and CS analyzed and interpreted the data and prepared the manuscript. MS, YA, TK, A-KE, CA, CL, YAMV, TB, AC, TCK, NO, HRY, SC, AAP, ASD, MWD, PW, MT, JPS, GV, SG, JXC, DA, RAL, OO, JW, BS, and WS contributed patients and data, interpreted data, and wrote and approved the manuscript.

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COMPETING INTERESTS

A-KE's spouse is employed by Karyopharm Therapeutics, she serves on the scientific advisory boards of Syndax, Daiichi Sankyo, and Servier, as well as the DEI AB of Astra Zeneca. CL is on the Advisory Board of Autolus, ADC therapeutics, and consults for Rigel. AC received honoraria from Sobi, PharmaEssentia, and research funding from Merck, Kartos, Oncoverity. AAP received honoraria from AbbVie, Amgen, Astellas, Jazz, Sobi, Syndax; research funding from Pfizer, Servier, Incyte, Sumitomo. MWD has consulting or advisory roles (Argenx, Blueprint Medicines); honoraria for educational writing (American Society of Hematology Self-Assessment Program); honoraria (Novartis). RAL has acted as a consultant or advisor to Ariad/Takeda, CVS/Caremark, Daiichi Sankyo, Epizyme/Ipsen, and Novartis, and has received clinical research support to his institution from Ascentage, Astellas, Biomea Fusion, Cellectis, Daiichi Sankyo, and Novartis, and royalties from UpToDate.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional review boards and ethical committee clearance was obtained (IRB09-130-B and IRB16-0892). All clinical investigations were conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all study participants or their legal guardians.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-025-01350-5.

Correspondence and requests for materials should be addressed to Caner Saygin.

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