Title
TP53 mutation does not confer a poor outcome in adult patients with acute lymphoblastic leukemia who are treated with frontline hyper-CVAD-based regimens.

Journal
Cancer, 123(19)

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Publication Date
2017-10-01

DOI
10.1002/cncr.30810

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Cancer. 2017 October 01; 123(19): 3717–3724. doi:10.1002/cncr.30810.

TP53 Mutation Does Not Confer a Poor Outcome in Adult ALL Treated with Frontline Hyper-CVAD-based Regimens

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Abstract

BACKGROUND—*TP53* mutations are uncommon in adult acute lymphoblastic leukemia (ALL) and predict poor outcome.

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CONFLICT OF INTEREST DISCLOSURES

Elias Jabbour has received research support from Amgen, Pfizer, Ariad, and Novartis. The remaining authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Rashmi Kanagal-Shamanna: Study design, collection and analysis of the data, writing of the manuscript, and review and approval of the manuscript.**Preetesh Jain:** Study design, collection and analysis of the data, writing of the manuscript, and review and approval of the manuscript. **Koichi Takahashi:** Treatment of the patients and review and approval of the manuscript. **Nicholas J. Short**: Collection and analysis of the data, and review and approval of the manuscript. **Guilin Tang:** Provided cytogenetic data and review and approval of the manuscript. **Ghayas C. Issa:** Collection and analysis of the data, and review and approval of the manuscript. **Farhad Ravandi:** Treatment of the patients and review and approval of the manuscript. **Guillermo Garcia-Manero:** Treatment of the patients and review and approval of the manuscript. **Cameron C. Yin:** Provided cytogenetic data and review and approval of the manuscript. **Rajyalakshmi Luthra:** Provided molecular data interpretation and review and approval of the manuscript. **Keyur P. Patel:** Provided molecular data interpretation and review and approval of the manuscript. **Joseph D. Khoury:** Pathologic interpretation and review and approval of the manuscript. **Guillermo Montalban-Bravo**: Collection and analysis of the data, and review and approval of the manuscript**. Koji Sasaki:** Statistical analysis and review and approval of the manuscript. **Tapan M. Kadia:** Treatment of the patients and review and approval of the manuscript. **Gautam Borthakur:** Treatment of the patients and review and approval of the manuscript. **Marina Konopleva:** Treatment of the patients and review and approval of the manuscript. **Nitin Jain:** Treatment of the patients and review and approval of the manuscript. **Rebecca Garris:** Statistical analysis and review and approval of the manuscript**. Sherry Pierce:** Collection and analysis of the data, and review and approval of the manuscript. **William Wierda:** Treatment of the patients and review and approval of the manuscript. **Zeev Estrov:** Treatment of the patients and review and approval of the manuscript. **Jorge Cortes:** Treatment of the patients and review and approval of the manuscript. **Susan O'Brien:** Treatment of the patients and review and approval of the manuscript. **Hagop Kantarjian:** Study design, collection and analysis of the data, treatment of the patients, writing of the manuscript, and review and approval of the manuscript. **Elias Jabbour:** Study design, collection and analysis of the data, treatment of the patients, writing of the manuscript, and review and approval of the manuscript.

METHODS—We performed *TP53* mutation analysis in 164 newly diagnosed adult ALL patients using a combination of targeted amplicon-based next-generation sequencing and Sanger sequencing.

RESULTS—*TP53* mutations were detected in 25 patients (15%) with a median allelic frequency of 42.2% (range, 5.6-93.8%). Most were single nucleotide variants of missense type and involved the DNA-binding domain. *TP53* mutated (*TP53*^{mut}) ALL was significantly associated with older age, lower median WBC and platelet counts, lower frequency of Philadelphia chromosome and higher frequency of low-hypodiploid karyotype compared to ALL with wild-type *TP53* (*TP53*^{wt}). To evaluate the prognostic effect of *TP53* mutations, we selected 146 B-ALL patients (24 *TP53*^{mut}, 122 *TP53*^{wt}) uniformly treated with frontline hyper-CVAD-based regimens; more than 90% also received a monoclonal antibody. Over a median follow-up duration of 15 months, there was no significant difference in the median overall survival, event-free survival and complete remission duration between *TP53*^{mut} and *TP53*^{wt} ALL patients.

CONCLUSIONS—Hyper-CVAD-based regimens negate the poor prognostic impact of *TP53* mutations in adult B-ALL.

Keywords

TP53; ALL; acute lymphoblastic leukemia; Hyper-CVAD; next-generation sequencing

INTRODUCTION

The *TP53* gene plays a significant role in maintaining genomic stability in response to DNA damage by activating DNA repair programs and triggering cell-cycle arrest.[1,2] *TP53* gene mutations (*TP53*^{mut}), present in over half of human cancers, have been reported to be associated with chemo-refractoriness and higher rates of relapse in pediatric acute lymphoblastic leukemia (ALL), similar to other malignancies.[3-5] Limited studies available on *TP53*^{mut} in newly diagnosed adult ALL report variable mutation frequencies, ranging between 6% and 19%,[6-9] with significant enrichment within B-cell ALL with absent Philadelphia chromosome (Ph).[6,10] These studies suggested that *TP53*^{mut} ALL has inferior overall survival (OS)[6], poor response to induction[7] and higher propensity of relapse[8] compared to wild-type *TP53* (*TP53*^{wt}) ALL. However, most of these studies have analyzed patient cohorts that are heterogeneous with respect to age, treatment, and *MYC* rearrangement.

In this study, we report the clinical characteristics and impact of *TP53* mutations on survival outcomes of adult ALL treated with frontline hyper-CVAD (HCVAD)-based regimens at a single institution.

MATERIALS AND METHODS

Study group

We conducted a retrospective review of all consecutive adults (>18 years) with newly diagnosed ALL treated with HCVAD-based regimens (111 patients were enrolled on clinical trials and 35 were treated off clinical trials) at The University of Texas MD Anderson

Cancer Center between 2012 and 2016 who underwent testing for *TP53* mutation. Burkitt/*MYC*+ ALL were excluded. The study was approved by Institutional Review Board; informed consent was obtained in all patients.

Response and Outcome Definitions

Complete remission (CR) was defined as the (1) <5% blasts in the bone marrow aspirate (2) $>1\times10^9$/L neutrophils and $>100\times10^9$/L platelets in the peripheral blood and (3) no evidence of extramedullary disease. Relapse was defined as the recurrence of ≥5% blasts in bone marrow aspirate or detection of extramedullary disease.

Cytogenetic studies

Conventional cytogenetic studies were performed on pre-treatment BM specimens using standard techniques. Karyotypic results were reported using the 2013 International System for Human Cytogenetic Nomenclature [11]. Karyotypes were classified into cytogenetic categories as described elsewhere[12,13]. Complex karyotype was defined as 5 or more chromosomal abnormalities excluding those patients with an established recurrent translocation or low hypodiploidy/ near triploidy, hyperdiploidy or tetraploidy. Fluorescence *in situ* hybridization (FISH) studies for *TP53* gene deletion was performed on bone marrow (BM) aspirate smears or BM cultured cells using a LSI TP53 /CEP 17 dual color probe (Abbott Molecular, Inc.). BCR-ABL1 rearrangement was tested by FISH using LSI BCR/ABL1 dual color, translocation ES probe (Abbott Molecular, Inc.). A total of 200 interphases were analyzed. Positive cutoff of 4.7% for TP53 deletion and 0% (minor breakapart pattern) or 2% (major breakapart pattern) for BCR/ABL1 rearrangement were established in our cytogenetic laboratory.

Molecular analysis

TP53 mutation analysis was assessed on BM samples by targeted next-generation sequencing (NGS)-based multi-gene profiling[14] (n=124) or Sanger sequencing (SS) (n=40). *TP53* mutation analysis by NGS was performed on 250 ng of genomic DNA extracted from bone marrow samples. Following library preparation, multiplex paired-end sequencing was performed on Illumina Miseq (Illumina, San Diego, CA) using either 28-gene panel that targeted the entire coding region of *TP53* gene (n=96), or 53-gene panel that targeted the hotspot regions within exons 2 through 10 of *TP53* gene (n=28). The median amplicon coverage was 3000x-4000x. Sequencing data were aligned against hg19 human genome as the reference. Integrative Genomics Viewer (IGV) was used for variant visualization; Miseq reporter software was used for variant calling. Variants with more than 5% allelic frequency and a minimum coverage of 250X in both directions were considered. Data from literature, and COSMIC databases were used for interpretation of the somatic nature of the mutant calls. Single nucleotide polymorphisms listed in dbSNP 137 and 138 and 10K genome project were excluded. *TP53* mutation analysis within exons 4 through 9 by SS was performed following polymerase chain reaction (PCR) using standard techniques (sensitivity 10-20%).

Assessment of minimal residual disease

For Ph-positive (Ph+) ALL, minimal residual disease (MRD) assessment was performed using reverse-transcription polymerase chain reaction (RT-PCR).[15] For Ph-negative ALL, MRD was assessed using 6-color multiparametric flow cytometry (MFC) analysis.[16]

Statistical analysis

Comparison between categorical and continuous variables between *TP53*^{mut} and *TP53*^{wt} groups was performed using Fisher exact test and paired t-test respectively. OS was calculated from the time of treatment initiation to death; event-free survival (EFS) was calculated from the time of treatment initiation to disease relapse/ progression/ death. Median OS and EFS were estimated using Kaplan-Meier analysis (GraphPad Prism). Outcome differences between groups were assessed using log-rank test. The associations between survival outcome and different parameters were determined using Cox proportional hazards regression models using SPSS software (version 22). A p-value of ≤0.05 was considered significant.

RESULTS

Patient characteristics

In total, 164 adult ALL patients who underwent treatment with HCVAD regimens with available *TP53* mutation status were identified in our database. These included 97 men and 67 women with a median age of presentation at 53 years (range, 18-81). Majority of patients (n=146, 89%) were of B-cell immunophenotype while only 18 patients were of T-cell immunophenotype. Within B-ALL patient group, complete karyotype and flow immunophenotypic data was available in 139 patients; classification using the 2016 WHO classification showed: 59 (40.4%) patients with B-lymphoblastic leukemia/ lymphoma with t(9;22), 5 patients with t(v;11q23.3), 6 with hyperdiploidy, 13 with hypodiploidy (12 of which met the criteria for low hypodiploid karyotype defined as 30-39 chromosomes), 3 with t(1;19) and 53 B-lymphoblastic leukemia/ lymphoma patients, not otherwise specified. Eleven patients showed early precursor B-ALL immunophenotype, 81 patients showed common B-ALL and 47 patients showed pre-B ALL immunophenotype.

Of the total 164 patients, 25 patients had *TP53* mutation. Twenty-four of 25 *TP53*^{mut} ALL patients (96%) were of B-cell type. The clinical, laboratory and cytogenetic characteristics of *TP53*^{mut} and *TP53*^{wt} ALL subgroups are presented in Table 1. Compared to *TP53*^{wt} ALL patients, *TP53*^{mut} ALL patients were significantly older at presentation (median age 64 versus 47 years; p=0.007), had significantly lower median white blood cell (WBC) count (2.0 versus 5.0K/μL; p=0.009), lower median platelet count (22 versus 40K/μL; p=0.02). Patients with *TP53*^{mut} had lower frequency of Philadelphia chromosome (Ph) (4% versus 42%; p=0.0002), and higher frequency of low hypodiploidy (44% versus 1%; p=0.0001). Distribution of complex karyotype did not differ between the two groups (p=0.3).

TP53 mutation characteristics

A total of 29 *TP53* mutations were identified in 25 of164 patients (15%); 2 patients had 2 concomitant *TP53* mutations each; 1 had 3 *TP53* mutations. These included 28 (97%) point

mutations [25 missense, 3 nonsense] and 1 frame-shift duplication. Twenty-seven (93%) mutations involved the DNA-binding domain (Fig. 1A). All missense mutations were predicted to be non-functional for transcriptional activity and deleterious per SIFT algorithm.[17] Most common amino acid change (13/29) involved substitution of arginine residues. For 22/25 *TP53*^{mut} patients identified by NGS, the median mutant allelic frequency (MAF) was 40.2% (range, 5.6-93.8%). The median MAF normalized to flow cytometry-estimated blast percentage was 97.5%. Fifteen patients had likely homozygous and 6 had heterozygous *TP53* mutations; 1 patient had MAF suggestive of sub-clonal mutation. Six *TP53*^{mut} ALL patients (27%) had concurrent mutations in other genes: 2 with *NRAS*, 1 with *BRAF, NOTCH1, TET2* and *DNMT3A* each. Concurrent gene mutations in *TP53*^{mut} and *TP53*^{wt} groups are depicted in Fig. 1B.

TP53 gene deletion

Within *TP53*^{mut} ALL cohort, we assessed for copy number state of *TP53* gene. Eleven (10 B-ALL and 1 T-ALL) of 25 *TP53*^{mut} ALL patients showed monosomy 17 by karyotype. In the remaining 14 patients without chromosome 17 abnormalities, interphase FISH was successful in 5 patients, 3 of which showed both *TP53* and CEP17 deletions (monosomy 17). In total, 14 *TP53*^{mut} ALL patients had both mutation and deletion, 2 patients had *TP53* mutation without deletion, while copy number state of *TP53* gene could not be inferred in 9 patients.

Survival outcome

To assess the prognostic impact of *TP53*^{mut} in a homogeneous population, we excluded the 18 T-ALL patients. The final cohort for survival analysis included 24 *TP53*^{mut} and 122 *TP53*^{wt} B-ALL. All patients were treated with frontline hyper-CVAD or mini hyper-CVD-based regimens.[18-22] Treatment details and outcomes are presented in Tables 2 and 3. The median follow-up duration was 15 months (range, 0.2 to 41); there was no significant difference in survival rates between *TP53*^{mut} and *TP53*^{wt} patients (Fig. 2A and 2B). For *TP53*^{mut} and *TP53*^{wt} patients, 3-year OS rates were 55% and 59% (p=0.49), and 3-year EFS rates were 53% and 50% (p=0.66), respectively. There was no significant difference in OS or EFS rates between *TP53*^{mut} and *TP53*^{wt} when only Ph-negative BALL patients were assessed (3-year OS rates, 51% and 43%, p=0.6; 3-year EFS rates, 50% and 48%, p=0.68) (Fig. 2 C, D). Of note, the OS and EFS survival curves for *TP53*^{mut} and *TP53*^{wt} ALL showed a tendency to diverge between 10 and 20 months of follow-up. However, no common cause of death was identified in *TP53*^{mut} ALL patients during this time period (sepsis, n=2; post stem cell transplant complications, n=1 and encephalitis, n=1). CR duration was similar in *TP53*^{mut} and *TP53*^{wt} patients (all B-ALL and Ph-negative B-ALL, Fig. 2E and 2F). There was no significant difference in the CR rates (83% in *TP53*^{mut} versus 91% in *TP53*^{wt}, p=0.25) or MRD negativity rates at CR (67% in *TP53*^{mut} versus 59% in *TP53*^{wt}, p=0.48). Although patients with low hypodiploidy had a trend for inferior outcome, there were no statistical significant differences in EFS, OS or CR duration between ALL patients with low-hypodiploid and diploid karyotype (OS, 27.5 months versus undefined, p=0.73; EFS, 18 versus 27.5 months, p=0.82). Similarly, within the *TP53* mutated subgroup, there was no statistically significant differences in EFS or OS between patients with low hypodiploidy (n=11) and diploid karyotype (n=5) (EFS, p=0.79; OS, p=0.62). Furthermore

we assessed outcome by whether patients with *TP53*^{mut} B-ALL had gene deletion (n=13) or not (n=2); *TP53*^{mut} B-ALL patients with *TP53* gene deletion had a worse OS (27.5 months versus unreached; p=0.2) and EFS (18 months versus unreached; p=0.1) compared to *TP53*^{mut} B-ALL patients without gene deletion. This difference was not significant due to limited number of patients. In addition, comparison of OS/EFS between patients with homozygous and heterozygous/sub-clonal *TP53*^{mut} mutations did not show a significant difference, although our study was limited in number. Assessment of OS, EFS and CR duration in *TP53*^{mut} and *TP53*^{wt} patients with all types of ALL (B-cell and T-cell immunophenotype) also showed no significant statistical difference [OS, not reached in both groups, p=0.5; EFS, not reached versus 27.5 months, p=0.7; CR duration, not reached in both groups, p=0.4].

DISCUSSION

The present study shows that *TP53*^{mut} is encountered in about 15% of adults with newly diagnosed ALL with a significant association with low-hypodiploid karyotype. Our data also confirmed previously published findings[6-8] that *TP53* mutations predominantly occur in older B-ALL patients with low frequency of Philadelphia chromosome. However, in contrast with three previous studies that have analyzed the impact of *TP53* mutations in newly diagnosed adult ALL,[6-8] our study did not observe any significant difference in survival and CR duration between *TP53*^{mut} and *TP53*^{wt} B-ALL patients.

Chiaretti et al.[7] evaluated 98 heterogeneously treated adult ALL patients, and showed a poorer response to induction therapy in *TP53*^{mut} ALL. Their *TP53*^{mut} frequency was lower (6%), likely attributable to the lower median age and use of a less-sensitive microarray-based mutation assay compared to deep sequencing. Stengel et al.[6] showed that *TP53*^{mut} ALL had a shorter survival, especially when associated with wild-type *TP53* allele loss. Their cohort included a mixture of adult, childhood and Burkitt/*MYC*+ ALL. Importantly, neither study analyzed the impact of *TP53* mutations in uniformly treated patients, which may have confounded the results. Recently, Salmoiraghi et al.[8] evaluated 171 Ph-negative ALL patients treated on the NILG-ALL 09/2000 clinical trial. *TP53* mutation was independently associated with worse OS and higher cumulative incidence of relapse. However, the incidence of *TP53* mutations (~8%) was lower (in our study, *TP53*^{mut} frequency in Ph-negative ALL was 23%), likely due to lower median age. In all of these studies, it is unclear whether the poor outcomes in *TP53*^{mut} ALL were due to the *TP53* mutations themselves or due to the overlap with low-hypodiploidy, which is an independent predictor of worse overall and relapse-free survival by itself.[12]

In contrast to European studies, our patients were treated with HCVAD-based regimens in combination with newer targeted therapies such as anti-CD20/anti-CD22 monoclonal antibodies and TKIs (in Ph+ ALL).[21,23] Prior studies have shown a survival benefit with the addition of rituximab to standard chemotherapy for adults with CD20+ ALL.[19,24] Similarly, in one study, the addition of inotuzumab ozogamicin to the mini-hyper-CVD regimen in older adults was associated with excellent outcomes that were significantly improved compared to a historical cohort of patients who did not receive inotuzumab ozogamicin.[20] The incorporation of TKIs into regimens for patients with Ph+ ALL has also significant

improved outcomes in this ALL subset.[23] In the present study, 91% of all ALL (87.5% of *TP53*^{mut} ALL) received a monoclonal antibody as part of the induction and consolidation regimen. Our finding that *TP53*^{mut} does not confer a negative prognosis in patients treated predominantly with regimens incorporating monoclonal antibodies suggests that chemoimmunotherapy may be able to overcome the poor prognostic effect of *TP53*^{mut} in B-ALL.

In the present study, neither *TP53* mutation status nor hypodiploid karyotype was associated with adverse outcome. Previously published study from our group showed that low hypodiploidy/near-triploidy was an independent predictor of worse overall and relapse-free survival in Ph-negative ALL.[12] The cohort in the present study is different except for 3 patients, as the selection criteria included patients with known *TP53* mutation status; low hypodiploid karyotype had inferior OS compared to diploid karyotype, but was not statistically different. Our study is limited by small number of patients with *TP53* mutations and relatively shorter follow-up duration. Stengel et al. have shown that the presence of *TP53* mutation and deletion had a significantly negative impact on OS of ALL patients, while *TP53* mutation alone did not.[9] In our study, *TP53*^{mut} B-ALL patients with *TP53* deletion showed a shorter OS and EFS compared to *TP53*^{mut} B-ALL patients without *TP53* gene deletion. However, the findings were not statistically significant due to a small number of *TP53*^{mut} B-ALL patients in our study. Further, due to limited availability of genomic DNA, single nucleotide polymorphism based microarrays could not be performed retrospectively. Hence, copy neutral loss of heterozygosity of *TP53* gene could not be assessed. Comprehensive genomic profiling that includes assessment of gene mutation and deletion on a larger scale is warranted for definitive conclusions. A further limitation of our study is that a subset of *TP53*^{wt} patients tested by SS may indeed have the mutation at low-level or outside of tested exons. However, this is likely to be very few, since the median marrow blast percentage of patients tested by SS was 81%. Furthermore, among 22 *TP53* mutations detected by NGS, only 1 (~5%) was located outside exons 4-9.

In conclusion, we show that *TP53* mutations may not have a significant negative impact on survival in newly diagnosed adult ALL patients after frontline treatment with HCVAD-based regimens. Further studies are underway to expand the cohort and identify the relevance of *TP53* mutations in the era of novel chemoimmunotherapies.

Acknowledgments

FUNDING SOURCES

This study was supported in part by the NIH/NCI under award number P30CA016672 and by the NCI under award number P01CA049639.

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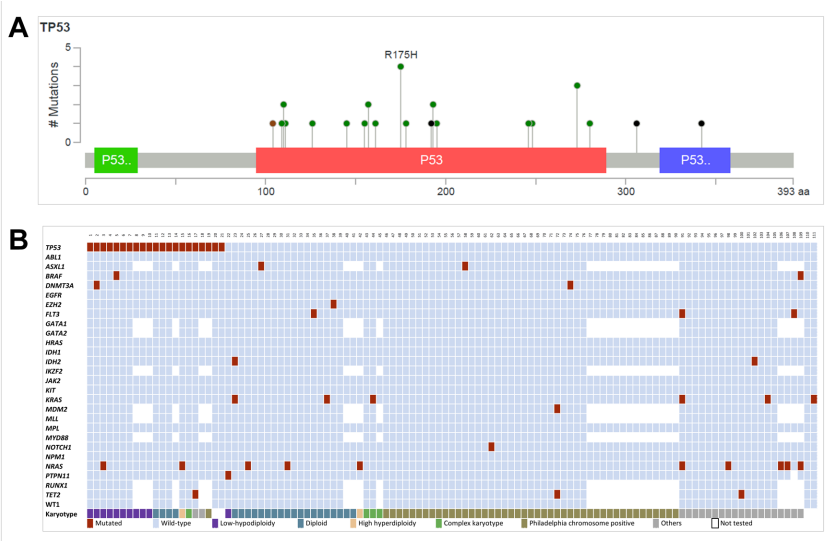

Figure 1.

TP53 mutation in newly diagnosed ALL patients (**A**) Lollipop figure of *TP53* mutations in 25 ALL patients (24 B-ALL and 1 T-ALL). Green dots indicate missense mutations and red dots indicate nonsense mutations [http://www.cbioportal.org/]; the green box over the *TP53* gene represents the transactivation motif (amino acids 5-29); red box represents DNA-binding domain (amino acids 95-289) and blue box represents the tetramerization motif (amino acids 319-358) (**B**) Spectrum of gene mutations and karyotype in 111 B-ALL patients who underwent NGS-based mutation profiling; the cases are segregated by *TP53* mutation status. The left column lists the tested genes, karyotype and Philadelphia chromosome (Ph) status; karyotype category was assessed by conventional cytogenetic studies and the status of Philadelphia chromosome was assessed by FISH and/or reverse-transcriptase polymerase chain reaction; the color legend is indicated in the panel below.

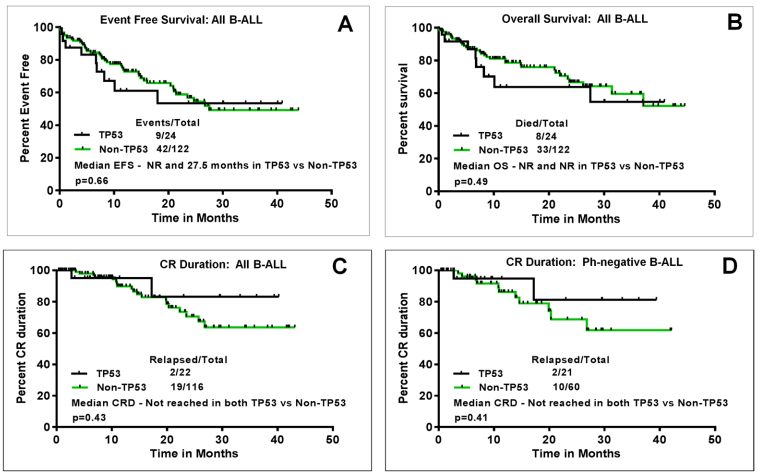

Figure 2.

Survival outcome of all B-ALL and Ph-negative B-ALL patients with and without *TP53* mutations after treatment with HCVD-based regimens (A) Median event-free survival (EFS) in *TP53* mutated and *TP53*-wild type B-ALL patients was “not reached” and 27.5 months respectively (p=0.66) (**B**) Median overall survival (OS) in both *TP53* mutated and *TP53*-wild type B-ALL patients was “not reached” (p=0.49) (**C**)**) (C)** Median complete remission (CR) duration in *TP53* mutated and *TP53*-wild type B-ALL patients was “not reached” in both (p=0.43) **(D)** Median CR duration in *TP53* mutated and *TP53*-wild type Ph-negative B-ALL patients was “not reached” in both (p=0.41).

Table 1

Summary of patient characteristics according to TP53 mutation status in patients with ALL treated with HCVAD-based regimens

	TP53 mutated (n=25)	*TP53* wild-type (n=139)	p-value
Parameter	**n (%)/ median (range)**		
Age (years)	64 (24-81)	47 (18-81)	0.007
Gender (Male/Female)	17/8	80/59	0.38
Hemoglobin (g/dL)	9.1 (5.3-11.7)	10 (7-16)	0.12
WBC (10^3/μL)	2.0 (0.6 - 75)	5.0 (0.0 - 232)	0.009
Platelet (10^3/μL)	22 (10 - 88)	40 (1 - 400)	0.02
Peripheral blasts (%)	8 (0 - 82)	22 (0 - 95)	0.2
BM Blasts (%)	72 (28 - 94)	82 (1 - 99)	0.11
Immunophenotype			
B-cell	24 (96%)	122 (88%)	0.31
T-cell	1 (4%)	17 (12%)	
Karyotype[*] n (%)			
Philadelphia chromosome[#]	1 (4)	58 (42)	0.0002
Low Hypodiploidy	11 (44)	1 (1)	0.0001
Diploid	5 (20)	40 (29)	0.5
High Hyperdiploidy	2 (8)	3 (2)	0.17
Tetraploidy	0	1 (1)	-
Complex	2 (8)	6 (4)	0.4
Others	2 (8)	23 (17)	0.4
Stem cell transplantation	2 (7)	21 (15)	0.53

[#]Detected by FISH and/or reverse-transcriptase polymerase chain reaction

[*]Karyotype was available for 23 patients in *TP53* mutated group and 132 patients in *TP53* wild-type group

Table 2

Treatment details for patients with B-ALL who were treated with frontline hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) or hyper-CVD (hyper-fractionated cyclophosphamide, vincristine and dexamethasone)-based regimens

	***TP53* mutated B-ALL n=24 (%)**	***TP53* wild-type B-ALL =122 (%)**
HCVAD + Monoclonal antibody	8 (33)	38 (31)
HCVAD + ofatumumab	7	29
HCVAD + rituximab	1	9
HCVD + Monoclonal antibody	12 (50)	16 (13)
HCVD + ofatumumab	1	0
HCVD + rituximab	0	1
HCVD + inotuzumab	2	4
HCVD + inotuzumab + rituximab	9	11
HCVAD R + TKI	1 (4)	58 (47)
HCVAD-R+ imatinib	0	3
HCVAD -R+ dasatinib	0	29
HCVAD-R+ ponatinib	1	26
Other regimen without monoclonal antibody	3 (13)	10 (9)
HCVAD	2	9
HCVD	1	1

Abbreviations: HCVAD, Hyper fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; HCVD, Hyper fractionated cyclophosphamide, vincristine and dexamethasone R, rituximab

Table 3

Summary of treatment response and outcomes in patients with B-ALL treated with frontline hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) or hyper-CVD (hyper-fractionated cyclophosphamide, vincristine and dexamethasone)-based regimens

	***TP53* mutated n=24**	***TP53* wild-type n=122**	**p-value**
CR (%)	20 (83)	111 (91)	0.25
MRD negativity at CR (%)	67	59	0.48
EFS overall			
Median (months)	NR	27.5	0.66
3-year (%)	53	50	
EFS Ph-negative ALL			
Median (months)	NR	27.5	0.68
3-year (%)	50	48	
OS overall			
Median (months)	NR	NR	0.49
3-year (%)	55	59	
OS Ph-negative ALL			
Median (months)	NR	31.4	0.60
3-year (%)	51	43	

Abbreviations: CR, complete remission; MRD, minimal residual disease; EFS, event-free survival; ALL, acute lymphoblastic leukemia; Ph, Philadelphia-chromosome; OS, overall survival