Patients with chronic lymphocytic leukemia (CLL) harboring del17p13 display poor survival because of advanced disease at diagnosis, short time to first treatment, and high risk of chemoresistance to alkylating agents and purine analogues (1–5). Because of these adverse features, patients harboring del17p13 currently represent a major challenge (6). Given the expanding options available for CLL treatment, early identification of del17p13 is of clinical relevance and has practical implications for therapeutic stratification of patients with CLL (7).

TP53 maps to 17p13.1 and is regarded as the candidate tumor suppressor gene hit by del17p13. Besides deletion, TP53 may be inactivated through somatic mutations. TP53 mutations occur in ~10% of CLLs at diagnosis, and have been described within unfavorable CLL subsets such as fludarabine-refractory CLL or CLL with prolymphocytic morphology (8–14). Whereas up to two-thirds of del17p13 CLL also harbor TP53 mutations, a fraction of CLL carry TP53 mutations without del17p13 (1, 4, 14). At present, it is unknown whether TP53 mutations in the absence of del17p13 confer the same biological profile, clinical features, and outcome displayed by
del17p13 CLL. Also, the independent prognostic relevance of TP53 mutations in relationship to del17p13 and other biological prognosticators remains undescribed to date.

Current diagnostic guidelines suggest to screen CLL patients for del17p13, but not for TP53 mutations (7). Therefore, patients with TP53 disruption due only to mutations are not recognized at diagnosis. We reasoned that detecting all TP53 genetic abnormalities at the time of diagnosis might be potentially useful for improving CLL clinical management. These considerations prompted us to assess whether TP53 mutations carry any prognostic value that is independent of del17p13. We show that TP53 mutations are an independent predictor of overall survival, treatment-free survival, and chemorefractoriness.

Materials and Methods

Patients. The study was based on a consecutive series of 308 patients with previously untreated CLL who presented for initial evaluation at the Division of Hematology of the Amedeo Avogadro University of Eastern Piedmont, Novara, Italy (n = 224) and at the Division of Hematology and Bone Marrow Transplantation of the University of Siena, Siena, Italy (n = 84) from January 1996 to June 2006. The database was updated for the analysis in November 2007. Median follow-up of patients that were alive was 54.3 months. No patient was lost at follow-up. All patients provided informed consent in accordance with local institutional review board requirements and Declaration of Helsinki guidelines. Diagnosis of CLL was based on National Cancer Institute Working Group criteria and confirmed by a flow cytometry score of >3 in all cases (15, 16).

The following clinical variables were recorded at presentation: (a) date of diagnosis, age, sex; (b) Binet stage, spleen size (centimeters below the left costal margin), number of nodal areas involved; (c) lymphocyte count, hemoglobin, platelet count, serum β2-microglobulin (reference range, 1.8-2.3 mg/dL), lactate dehydrogenase (LDH; reference range, 200-450 units/L).

The following biological variables were analyzed on fresh or cryopreserved peripheral blood mononuclear cells collected at CLL diagnosis: (a) mutations of TP53 exons 2 to 10; (b) IGHV gene usage and homology to germ line; (c) fluorescence in situ hybridization (FISH) karyotype for del13q14, +12, del17p13, and del11q22-q23; (d) CD38 and ZAP70 expression.

During follow-up, the following variables were recorded: (a) date of first-line treatment, (b) type and number of lines of treatment, (c) date of refractoriness to alkylating agents and date of refractoriness to fludarabine-based regimens, and (d) date of death.

Analysis of TP53 mutations. Mutation analysis of TP53 exons 2 to 10 was done by DNA direct sequencing on an ABI Prism 3100 automated DNA sequence analyzer (Applied Biosystems; refs. 8, 9). Mutations were confirmed on both strands on independent amplimers and validated by the IARC TP53 Mutation Database4 and the UMD TP53 Mutation Database5 (17, 18). The distribution of mutations on the TP53 molecule was assessed using the IARC TP53 Mutation Database (17, 19). The residual transactivation activity of TP53 alleles carrying missense mutations was estimated in silico according to the aforementioned databases (17, 18, 20).

Analysis of IGHV rearrangements. IGHV rearrangements were amplified from genomic DNA and directly sequenced (21). Sequences were aligned on ImMunoGeneTics directories, and considered mutated if homology to the corresponding germ line gene was <98%.

Flow cytometry. A FACScanilbur flow cytometer (Becton Dickinson) was used for flow cytometric analysis. Expression of CD38 and ZAP70 was analyzed as reported (22). Cutoff points of 30% and 20% were used to define positivity for CD38 and ZAP70, respectively.

Interphase FISH. Probes (Vysis) used for FISH analysis were LSI13 and LSI13S319 for detection of del13q14; CEP12 for detection of aneuplody of chromosome 12; LSIp53 for detection of del17p13; and LSIATM for detection of del11q22-q23. Nuclei were counterstained with 4',6-diamidino-2-phenylindole and antifade, and signals were visualized using an Olympus BX51 microscope (Olympus Italia). For each probe, at least 500 interphase cells with well-delineated fluorescent spots were examined.

Statistical analysis. Overall survival (OS) was measured from date of CLL diagnosis to date of last follow-up or death. Time to progression (TTP) was measured from date of CLL diagnosis to date of progressive and symptomatic disease according to National Cancer Institute Working Group guidelines, death, or last follow-up (15). Refractory disease was defined as treatment failure (stable disease or progressive disease during treatment) or disease progression within 6 months from antileukemic therapy (7). Time to chemorefractoriness was measured from date of first-line treatment until date of refractoriness to fludarabine-based regimens, date of alkylator refractoriness in patients who had never been exposed to fludarabine, death, or last follow-up. Time to fludarabine refractoriness was measured from date of first exposure to fludarabine-based regimens until date of refractoriness to fludarabine-based regimens, death, or last follow-up.

Categorical variables were compared by χ² test or exact tests when appropriate. Continuous variables were compared by Mann-Whitney test. Survival analysis was done by Kaplan-Meier method using log-rank statistics to test for significant associations (23). Multivariate analysis was done by Cox proportional hazard regression (24). A forward stepwise selection algorithm was used. A variable was entered into the model if the probability of its score statistic was ≤0.05. A variable was removed from the model if the probability of its removal statistic was ≥0.10.
Characterization of the CLL cohort. The study was based on a consecutive series of 308 (164 males and 144 females) previously untreated CLL. Biological and clinical characteristics at diagnosis are representative of the disease (Table S1). Median age was 67 years (25th-75th percentile, 59-73). According to the Binet staging system, 231 of 308 (75.0%) patients were in stage A, 40 of 308 (13.0%) patients were in stage B, and 37 of 308 (12.0%) patients were in stage C. Median hemoglobin level was 13.6 g/dL (25th-75th percentile, 12.6-14.8), median platelet count was 191 × 10^9/L (25th-75th percentile, 148-236), median serum LDH was 360 units/L (25th-75th percentile, 304-428), and median β2-microglobulin was 2.4 mg/L (25th-75th percentile, 1.8-3.4).

Considering biological prognosticators, IGHV homology ≥98% occurred in 115 of 303 (38.0%) patients, CD38 ≥30% in 92 of 301 (30.6%) patients, and ZAP70 ≥20% in 113 of 267 (42.3%) patients. Del13q14 was observed in 151 of 297 (50.8%) cases, normal FISH in 79 of 297 (26.6%) cases, +12 in 60 of 297 (20.2%) cases, del11q22-q23 in 24 of 297 (8.1%) cases, and del17p13 in 34 of 297 (11.4%) cases. CLL with del17p13 displayed a median of 62% (25th-75th percentile, 0.6-13.0%) interphase nuclei harboring del17p13.

Molecular and clinical characterization of CLL harboring TP53 mutations. At CLL diagnosis, TP53 mutations (n = 32) were documented in 31 of 308 (10.0%) patients (Table S2). One patient carried two mutations on independent alleles. All mutations were validated by the IARC TP53 Mutation Database and the UMD TP53 Mutation Database, and reflected the TP53 mutation profile reported in CLL (17, 18). All TP53 mutations predicted functional consequences. Among 26 missense mutations, the median residual transactivation activity compared with germ line TP53 was 8.9% (25th-75th percentile, 0.6-13.0%), and was ≤20% in 22 of 26 (84.6%) mutations (17, 18, 20). All microdeletions and microinsertions (4/32; 12.5%) led to frameshift mutations. One nonsense mutation introduced a stop codon at position 213, and one mutation affected the 3′ splicing site of exon 8. TP53 mutations affected exon 4 in 2 of 32 (6.2%) cases, exon 5 in 6 of 32 (18.7%) cases, exon 6 in 5 of 32 (15.6%) cases, exon 7 in 9 of 32 (28.1%) cases, and exon 8 in 10 of 32 (31.2%) cases. No mutations were found in exons 2, 3, 9, and 10.

Mutations affecting coding sequences were tested for distribution on TP53 functional domains (18, 19). Twenty-nine of 31 (93.5%) mutations targeted the TP53 DNA-binding domain, whereas two frameshift mutations affected the proline-rich motif outside the DNA-binding domain (18, 19). TP53
Fig. 1. Kaplan-Meier curves of OS according to TP53 mutations and del17p13. Univariate analysis identified TP53 mutations (A) and del17p13 (B) as risk factors of short OS.
the overlap between these two genetic lesions were targeted by mutations in 7 of 31 (22.5%) cases (19).

codons directly involved in DNA binding or zinc atom ligation were targeted by mutations in 7 of 31 (22.5%) cases (19).

The biological and clinical features of CLL harboring TP53 mutations are summarized in Table 1. At diagnosis, TP53 mutations associated with advanced Binet stage (P = 0.002), thrombocytopenia (P = 0.002), elevated β2-microglobulin (P = 0.046), higher number of FISH lesions (P < 0.001), and occurrence of del17p13 (P < 0.001). Despite the statistical association between TP53 mutations and del17p13 in the whole cohort, the overlap between these two genetic lesions was restricted to a fraction of patients. By combining the results of FISH and TP53 mutation analyses in cases for which both data were available (n = 297), 44 of 297 (14.8%) CLL carried TP53 inactivation through mutation and/or deletion. Of these, 18 of 44 (40.9%) cases showed TP53 mutation paired to del17p13, 10 of 44 (22.7%) cases showed TP53 mutations in the absence of del17p13, and 16 of 44 (36.3%) cases showed del17p13 in the absence of TP53 mutations.

TP53 mutations predict OS independent of del17p13. After a median follow-up of 54.3 months from diagnosis, 65 of 308 patients had died. Median OS of the whole series was 196.6 months for patients without del17p13, 10 of 44 (22.7%) cases showed TP53 mutations and del17p13 in the absence of del17p13, and 16 of 44 (36.3%) cases showed del17p13 in the absence of TP53 mutations.

Table 2. Multivariate analysis for OS, chemorefractoriness, and fludarabine refractoriness in CLL

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>OS*</td>
<td></td>
<td></td>
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<tr>
<td>Age &gt;65 y</td>
<td>4.98 (2.45-10.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Binet B-C</td>
<td>3.01 (1.67-5.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP53 mutations</td>
<td>3.20 (1.52-6.70)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to chemorefractoriness †</td>
<td>3.97 (2.09-7.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP53 mutations</td>
<td>2.55 (1.39-4.66)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>2.27 (1.28-3.85)</td>
<td>0.004</td>
</tr>
<tr>
<td>IGHV homology ≥98%</td>
<td>1.88 (1.02-3.44)</td>
<td>0.041</td>
</tr>
<tr>
<td>Time to fludarabine refractoriness †</td>
<td>6.72 (2.61-17.21)</td>
<td>&lt;0.001</td>
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</tbody>
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Abbreviations: 95% CI, 95% confidence interval; P, P value calculated by Cox analysis.
† Covariates at CLL diagnosis that entered the analysis were TP53 mutations, IGHV gene homology, del17p13, CD38 expression, age, Binet stage, and levels of LDH and β2-microglobulin.
‡ Covariates that entered the analysis were TP53 mutations, IGHV gene homology, del17p13, CD38 expression, age, number of lines of treatment, and fludarabine-based treatment.
§ Covariates that entered the analysis were TP53 mutations, IGHV gene homology, del17p13, CD38 expression, age, and number of lines of treatment.

The value of TP53 mutations in predicting chemorefractoriness was also assessed within the group of patients who had been exposed to fludarabine (n = 88). In this patient subgroup, multivariate analysis selected TP53 mutations as the sole independent predictor of short time to fludarabine refractoriness (HR, 6.72; P < 0.001; Table 2). Other covariates included in the multivariate analysis and not selected as predictors of short time to chemorefractoriness were del17p13 (P = 0.210), CD38 ≥30% (P = 0.645), and fludarabine-based treatment (P = 0.867).

The outcome were compared in CLL groups characterized by (a) TP53 mutations without del17p13 (n = 10), (b) del17p13 without TP53 mutations (n = 16), (c) concomitance of TP53 mutations and del17p13 (n = 18), and (d) absence of TP53 disruption, i.e., absence of both TP53 mutations and del17p13 (n = 253). CLL harboring any type of TP53 disruption were biologically and clinically similar. First, compared with CLL without TP53 disruption, cases harboring TP53 mutations only, del17p13 only, or both TP53 mutations and del17p13, uniformly displayed a higher prevalence of unfavorable biological and clinical features at diagnosis and display similar outcome.

Biological and clinical features at diagnosis as well as outcome were compared in CLL groups characterized by (a) TP53 mutations without del17p13 (n = 10), (b) del17p13 without TP53 mutations (n = 16), (c) concomitance of TP53 mutations and del17p13 (n = 18), and (d) absence of TP53 disruption, i.e., absence of both TP53 mutations and del17p13 (n = 253). CLL harboring any type of TP53 disruption were biologically and clinically similar. First, compared with CLL without TP53 disruption, cases harboring TP53 mutations only, del17p13 only, or both TP53 mutations and del17p13, uniformly displayed a higher prevalence of unfavorable biological and clinical features at diagnosis and display similar outcome.

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prognosticators, including IGHV homology of ≥98% (86/248, 34.7% versus 6/10, 60.0% versus 10/16, 62.5% versus 10/18, 55.6%, respectively; \( P = 0.021 \)), advanced Binet stage (49/253, 19.4% versus 5/10, 50.0% versus 10/16, 62.5% versus 8/18, 44.4%, respectively; \( P < 0.001 \)), and elevated \( \beta \)2-microglobulin (93/232, 40.1% versus 5/8, 62.5% versus 10/13, 76.9% versus 10/16, 62.5%, respectively; \( P = 0.013 \); Fig. 3). The overall distribution of unfavorable prognosticators did not differ among CLL harboring TP53 mutations only, del17p13 only, or both lesions (\( P = 0.131 \); Fig. 3). Second, compared with CLL without TP53 disruption, cases harboring TP53 mutations only, del17p13 only, or both lesions uniformly showed an increased risk of progression to symptomatic disease requiring treatment according to National Cancer Institute Working Fig. 2. Kaplan-Meier curves of time to chemorefractoriness according to TP53 mutations and del17p13. Univariate analysis identified TP53 mutations (A) and del17p13 (B) as risk factors of short time to chemorefractoriness.
group criteria \((P < 0.05\) for pairwise comparisons; Fig. 4A; ref. 15). Third, compared with CLL without \(TP53\) disruption, OS was uniformly poor in all CLL subgroups harboring any type of \(TP53\) disruption \((P < 0.05\) for pairwise comparisons; Fig. 4B).

With respect to chemorefractoriness, patients harboring \(TP53\) mutations only and patients harboring both \(TP53\) mutation and del17p13 were characterized by short time to chemorefractoriness compared with patients without any \(TP53\)

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**Fig. 3.** Overall distribution of unfavorable prognosticators among CLL harboring \(TP53\) mutations only, del17p13 only, or both lesions. Grids detail the distribution of 14 prognostic markers, i.e., CD38 expression \(>30\%\), ZAP70 expression \(>20\%\), IGHV homology \(<98\%\), presence of del(11q22-23), presence of +12, age \(>65\) years, Binet stage B-C, peripheral blood lymphocytes (PB Ly) \(<20 \times 10^9/L\), platelets (PLT) \((150 \times 10^9)L\), hemoglobin (Hb) \(<13 g/dL\), involvement of more than three nodal areas, presence of splenomegaly, LDH \(>1\) upper limit of normal (ULN), \(\beta_2\)-microglobulin (B2M) \(>2.5\) mg/L, in CLL harboring \(TP53\) mutations only \((n = 10; A)\), del17p13 only \((n = 16; B)\), or both \(TP53\) mutations and del17p13 \((n = 18; C)\). Black boxes, presence of the unfavorable prognostic marker; open boxes, absence of the unfavorable prognostic marker; gray boxes, missing data. \(\chi^2\) test compares the distribution of unfavorable prognostic markers among CLL harboring \(TP53\) mutations only, del17p13 only, or both lesions.
alteration or to patients harboring del17p13 only (P < 0.05 for pairwise comparisons; Fig. 4C). CLL that at diagnosis harbored del17p13 without TP53 mutations showed a significantly longer time to chemorefractoriness compared with CLL who at diagnosis carried both del17p13 and TP53 mutations (median, 55.2 versus 5.5 months, respectively; P = 0.003; Fig. 4C). Notably, at diagnosis, the percentage of deleted nuclei was significantly lower in CLL harboring del17p13 only (median, 45.0%; 25th-75th percentiles, 7.3-67.4%) compared with CLL with both del17p13 and TP53 mutations (median, 66.5%; 25th-75th percentiles, 52.1-77.9%, respectively; P = 0.020).

Acquisition of TP53 mutations is a mechanism of chemorefractoriness in CLL. Clonal evolution leading to acquisition of TP53 mutations or deletion may be a mechanism of chemorefractoriness in CLL otherwise devoid of TP53 abnormalities at diagnosis (6, 25, 26). Sequential samples were available for 14 CLL who had no TP53 abnormalities at diagnosis and who later developed chemorefractoriness. In these patients, samples obtained at the time of chemorefractoriness showed acquisition of TP53 abnormalities in 5 of 14 (35.7%) cases. Two patients acquired TP53 mutations (Arg273His and del13069-13071), two patients acquired del17p13, and one patient acquired both TP53 mutations (Arg213stop) and del17p13.

The acquisition of additional TP53 abnormalities at the time of chemorefractoriness was also documented in patients with...
CLL who at diagnosis harbored a single alteration affecting the TP53 locus. In fact, three of three patients with CLL who at diagnosis harbored del17p13 but no TP53 mutations acquired TP53 mutations (Pro177Ser, Met237Ile, His179Leu) at the time of chemorefractoriness.

**Discussion**

In this study, we document that (a) the association of TP53 mutations with short survival and chemorefractoriness is independent of del17p13 and other biological prognosticators; (b) CLL presenting with TP53 mutations in the absence of del17p13 fare as poorly as CLL carrying del17p13.

Del17p13 is a widely accepted marker of poor CLL outcome and chemoresistance (1–5). In contrast, the prognostic relevance of TP53 mutations in CLL is poorly characterized, and it is currently unknown whether TP53 mutations carry prognostic value that is independent of del17p13 (10, 11). Here, we extensively screened a large CLL cohort for both TP53 mutations and del17p13. The approach chosen for mutational analysis encompassed the whole TP53 mutational hotspot (exons 5-8) and extended to flanking both exon 5’ (exons 2-4) and exon 3’ (exons 9 and 10). Our results show that TP53 mutations at CLL diagnosis predict short survival and high risk of chemoresistance in a manner that is independent of del17p13 and of other potential confounding covariates, both biological and clinical.

At diagnosis, the distribution of TP53 mutations and del17p13 in individual patients overlaps only partially. Accordingly, a fraction of CLL with TP53 disruption present only with TP53 mutation in the absence of del17p13. These patients are not recognized by routine diagnostic approaches to CLL, which includes screening of del17p13 but not of TP53 mutations. At diagnosis, patients with TP53 mutations but no del17p13 represent 3.4% of all CLL. This frequency should not be disregarded because it accounts for 20% of CLL carrying TP53 disruption at diagnosis, and is superimposable to the frequency of CLL carrying del17p13 in the absence of TP53 mutations.

CLL harboring TP53 mutations without del17p13 share similar clinico-biological features and outcome with the more frequent subset of del17p13 CLL. First, CLL harboring TP53 mutations without del17p13 display a profile of unfavorable prognosticators similar to that of del17p13 CLL, and including IGHV homology of ≥98%, frequent presentation in advanced stage, and association with proliferation markers. Second, CLL harboring TP53 mutations without del17p13 as well as del17p13 CLL are characterized by a similar risk of progression to symptomatic disease requiring treatment. Third, both CLL harboring TP53 mutations without del17p13 and del17p13 CLL are characterized by similarly short OS.

The only other study that explored the prognostic relevance of TP53 mutations in relation to del17p13 failed to identify the negative effect on outcome of TP53 mutations in the absence of del17p13 (27). Grever et al. (27) identified 28 TP53 mutations among 228 symptomatic and previously untreated CLL entering the Intergroup Trial E2997. Of the 22 TP53 mutated patients who were also studied by FISH, 7 cases carried both TP53 mutations and del17p13, whereas the remaining 15 patients harbored TP53 mutations but not del17p13 (27). Several key features might explain the discrepancy between our study and the study by Grever et al. (27). In our cohort, all mutations (a) affected TP53 coding exons or splicing sites, (b) were confirmed by DNA direct sequencing, and (c) were validated by the IARC TP53 Mutation Database for CLL4 and the UMD TP53 Mutation Database5 (17, 18). In contrast, of the 28 TP53 sequence variations reported by Grever et al. (27), only 11 were TP53 mutations confirmed by DNA sequencing, whereas 11 variations were known polymorphisms. 2 were intronic changes, and 4 were detected by denaturing gradient gel electrophoresis but not confirmed by DNA sequencing. Both in CLL and in other types of cancers, the prognostic effect of TP53 sequence variations other than true mutations is doubtful (28–30). Differences in the choice of clinical endpoints may further explain the discrepancy between the two studies. In fact, our primary end point was OS, whereas the end point chosen by Grever et al. (27) was progression-free survival after first-line treatment with fludarabine or fludarabine plus cyclophosphamide.

In addition to survival, TP53 mutations seem to be a powerful predictor of chemorefractoriness. This association is not only documented by actuarial analysis of cases harboring TP53 mutations at CLL diagnosis, but is also reinforced by the finding that patients acquire TP53 alterations at the time of chemoresistance. In vitro models are in support of our clinical observation because TP53 mutant CLL are refractory in vitro to purine analogues and alkylators, and display a defect in activating proapoptotic responses after DNA damage (10, 31–33).

CLL that at diagnosis harbored del17p13 without TP53 mutations displayed a significantly longer time to chemoresistance than CLL with TP53 mutations already at diagnosis. Notably, CLL with del17p13 only showed a significantly lower percentage of deleted nuclei compared with CLL with both del17p13 and TP53 mutations. In addition, CLL with del17p13 only acquired TP53 mutations at chemoresistance. Based on these data, clonal evolution with the acquisition of a second TP53 event may be required for the development of a refractory phenotype.

Our results indicate that an IGHV homology of ≥98% is also an independent predictor of chemoresistance along with TP53 mutations. An IGHV homology of ≥98% identifies a subgroup of CLL at higher risk of clonal evolution, and therefore, is more prone to acquire genetic lesions that in turn may favor chemoresistance (26, 34). Indeed, in our study all eight cases that acquired TP53 mutations or deletion at the time of chemoresistance displayed IGHV homology of ≥98%.

Besides TP53 mutations and deletion, other mechanisms of TP53 dysfunction may be operative in CLL (28, 35–38). These mechanisms may involve the ATM and MDM2 genes that regulate TP53 function at the protein level. Notably, ATM mutations and MDM2 polymorphisms causing aberrant MDM2 expression have been shown to harbor prognostic relevance in CLL (35, 37, 38). Because TP53 mutations and deletion did not recapitulate all cases of chemoresistance in our study, an integrated evaluation of all mechanisms of TP53 dysfunction should be done in future studies.

These results may be relevant for the clinical management of CLL. Because current diagnostic practices screen only for TP53 genetic abnormalities that are detectable by FISH (7), patients presenting with TP53 mutations in the absence of del17p13 at...
mutation analysis of exons 5 to 8 may represent a practical strategy for detecting TP53 mutations, and should be considered for a comprehensive prognostic characterization of patients with CLL who are candidates for treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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The Prognostic Value of TP53 Mutations in Chronic Lymphocytic Leukemia Is Independent of Del17p13: Implications for Overall Survival and Chemorefractoriness

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