Supplementary Table S1: Patients characteristics

Patient characteristics	**FILO-NGS (n=336)**
Median age (year), [min; max]	70 [23; 98]
Cytogenetics, n (%)	
Trisomy 12	16/129 (14%)
Del(17p)	108/207 (52%)
Del(11q)	19/148 (13%)
Complex karyotype	56/134 (42%)
IGHV status, n(%)	
Mutated	63/236 (27%)
Unmutated	172/236 (73%)
Treatment, n(%)	
Untreated	81/222 (37%)
Treated	141/222 (63%)

Supplementary Table S2: *TP53* mutation spectrum in the FILO cohort

	Number of variants (%)
Missense	429 (75)
Nonsense	34 (5.9)
Synonymous	0 (0)
Splice site[1]	39 (6.8)
Intronic	0 (0)
Frameshift	53 (9.3)
Inframe	13 (2.3)
Total	568 (100)
Variants per patient	
1 variant	222(66)
2 variants	57 (17)
3 variants	33 (10)
4 and + variants	24 (7)
Total	336 (100)

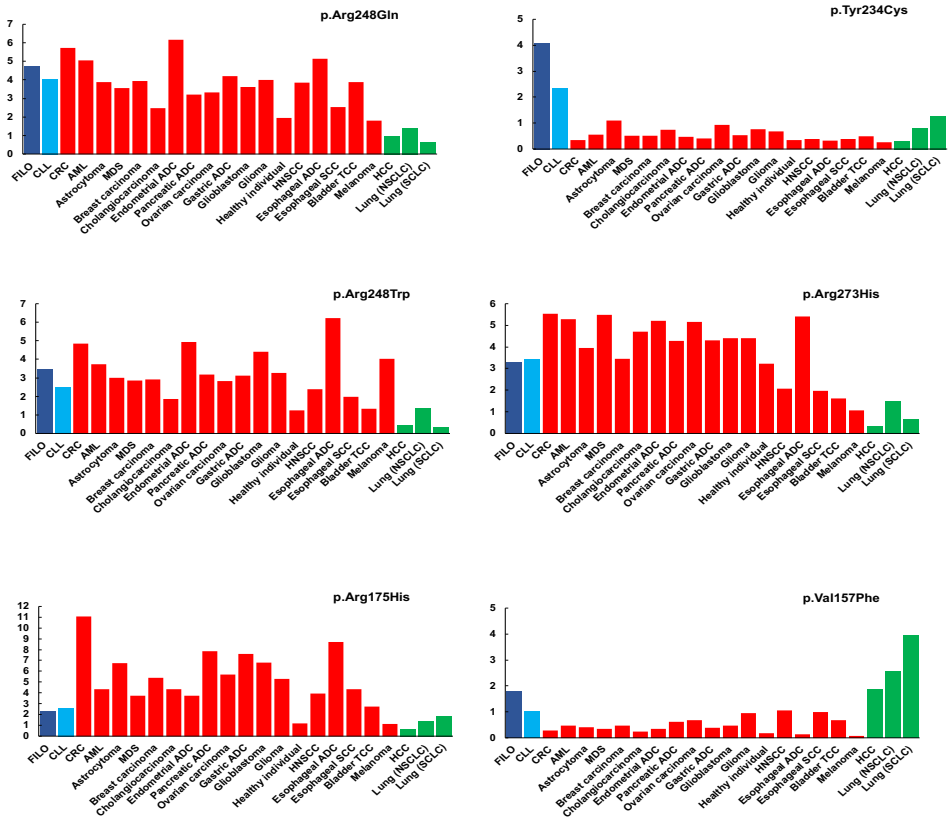
[1] Invariant positions +1. +2, -1 or -2 of donor and acceptor splice.

Supplementary Figure S1. TP53 variant p.Tyr234Cys is more frequent in CLL than in any other cancer.

A

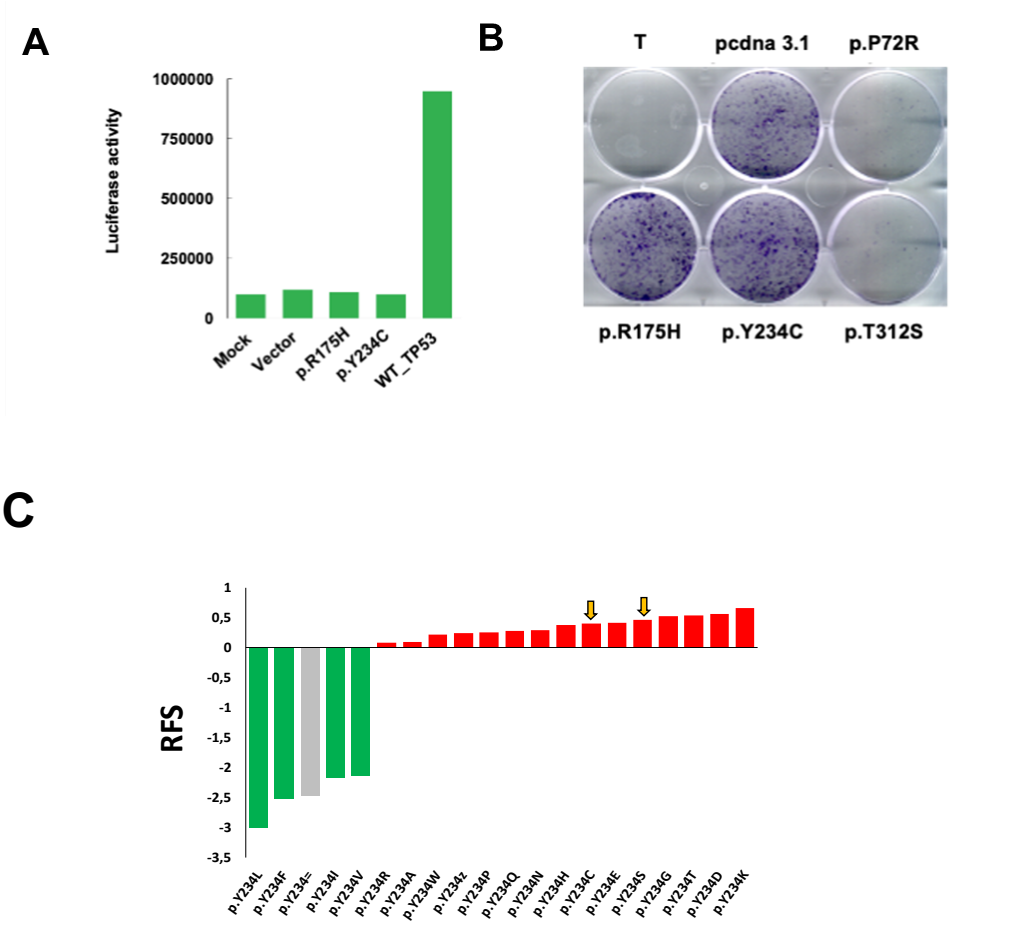
	FILO	CLL	CRC	AML	Astrocytoma	Breast
p.Arg248Gln	1 (4.73%)	1 (4.04%)	2 (5.71%)	2 (5.05%)	4 (3.88%)	2 (3.93%)
p.Tyr234Cys	2 (4.07%)	5 (2.32%)	32 (0.35%)	31 (0.54%)	10 (1.09%)	27 (0.51%)
p.Arg248Trp	3 (3.42%)	4 (2.51%)	6 (4.83%)	5 (3.73%)	5 (2.99%)	4 (2.91%)
p.Arg273His	4 (3.26%)	2 (3.44%)	3 (5.52%)	1 (5.28%)	3 (3.95%)	3 (3.46%)
p.Arg175His	5 (2.28%)	3 (2.64%)	1 (11.0%)	3 (4.35%)	2 (6.74%)	1 (5.37%)
p.Val157Phe	6 (1.79%)	13 (1.02%)	40 (0.29%)	35 (0.46%)	27 (0.40%)	31 (0.46%)
p.Tyr163Cys	7 (1.79%)	12 (1.02%)	21 (0.41%)	20 (0.77%)	17 (0.81%)	10 (1.27%)
p.Gly245Ser	8 (1.79%)	10 (1.30%)	7 (3.96%)	17 (1.01%)	8 (1.70%)	12 (1.15%)
p.His179Arg	9 (1.63%)	8 (1.34%)	23 (0.41%)	13 (1.16%)	13 (1.02%)	14 (1.03%)
p.His179Arg	10 (1.63%)	9 (1.34%)	24 (0.41%)	14 (1.16%)	14 (1.02%)	15 (1.03%)
p.Arg273Cys	11 (1.46%)	7 (1.72%)	5 (5.19%)	6 (2.64%)	1 (19.5%)	7 (2.18%)
p.Arg249Ser	12 (1.30%)	23 (0.69%)	60 (0.20%)	85 (0.15%)	82 (0.13%)	36 (0.42%)
p.His214Arg	13 (1.30%)	22 (0.69%)	56 (0.22%)	58 (0.31%)	32 (0.40%)	88 (0.15%)
p.Ile195Thr	14 (1.30%)	16 (0.92%)	25 (0.41%)	15 (1.08%)	16 (0.88%)	17 (0.95%)
p.Tyr220Cys	15 (1.14%)	6 (2.32%)	12 (0.87%)	4 (4.04%)	7 (1.97%)	6 (2.20%)

B



A: Rank and frequency of missense TP53 variants in the FILO cohort (FILO) or in the UMD_TP53 database. **CLL:** TP53 variants from CLL patients included in UMD_TP53 excluding FILO data; **CRC:** colorectal carcinoma; **AML:** acute myeloid leukemia. **B**: Frequency of p.Tyr234Cys is compared to 5 classical TP53 hot spots of mutation. Dark blue: CLL from the FILO cohort; light blue: data from CLL included in UMD; green: cancers known to be strongly associated with carcinogen exposure. Variants.p.Val157Phe associated with either aflatoxin B1 or benzo[a]pyrene is found predominantly in liver and lung cancer.

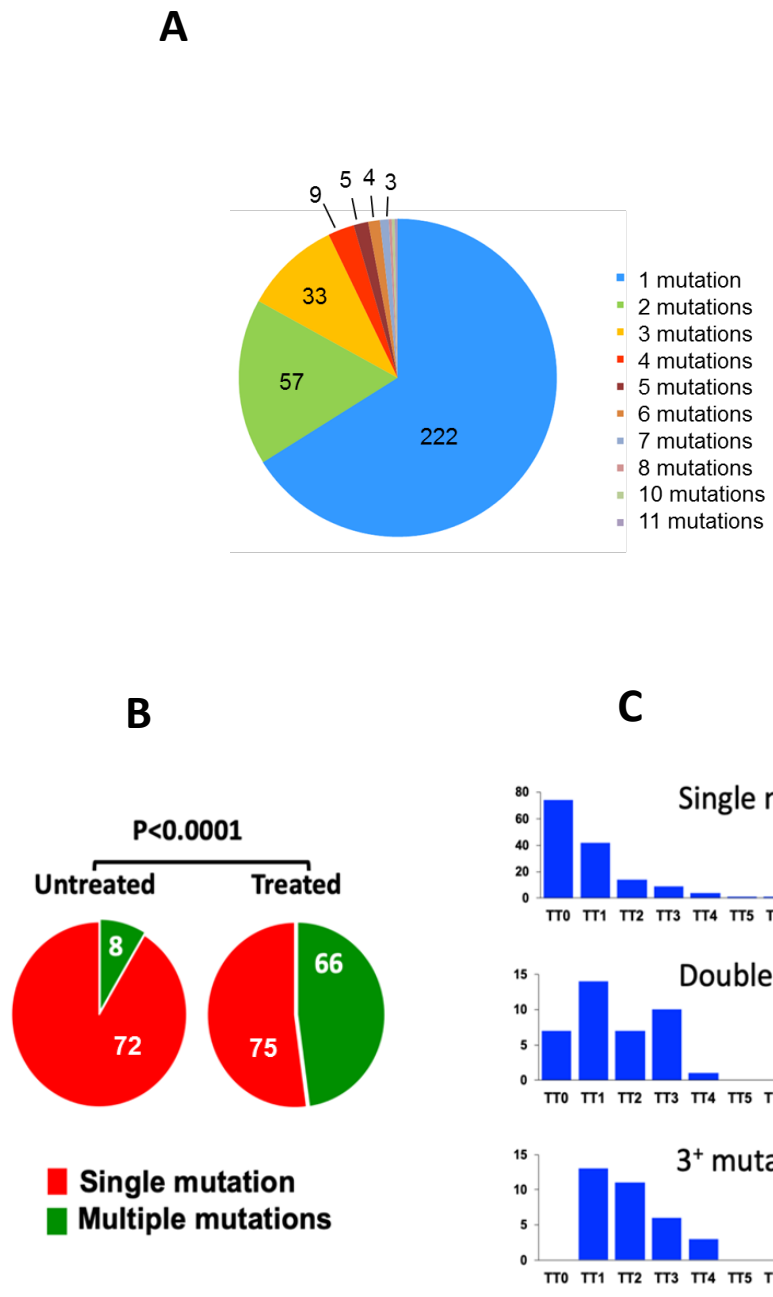
Supplementary Figure S2. TP53 variant p.Tyr234Cys is defective.



A: Overexpression of TP53 in the p53 null H1299 cell line was performed to check the antiproliferative activity of the various variants. Although, wt TP53 or p.Thr312Ser (a variant that does not display any loss of activity) leads to a profound reduction of colony number, p.Tyr234Cys and the hot spot variant p.Arg175His are unable to induce growth arrest. T: untransfected cells. H1299 cells were plated into 6-well plates and transfected on the following day with Lipofectamine 2000 (Life Science). Twenty-four hours after transfection, cells were dissociated and plated at a density of 5,103 cells per well in 6-well plates in selective media with G418 at a concentration of 1 mg /ml. Cells were then stained after 14 to 16 days with crystal violet. **B:** p.Tyr234Cys is unable to transactivate a reporter gene with the WAF1 response element. Luciferase assay was performed in H1299 cells plated in 96-well plates (2,000 cells per well). After 48 hours, cells were transfected using Lipofectamine 2000. Seventy-five nanograms of reporter gene and 5 ng of p. 53 plasmid were used for each well. The luciferase activity was tested 24 hours after transfection. Each assay was performed in triplicate and TP53 variants were tested at least 4 times in

separate experiments. **C**: The majority of TP53 variants at position 234 are dysfunctional. Data from the large scale analysis performed by Kotler et al. were extracted and included in UMD_TP53. The relative fitness score (RFS) for each TP53 variant defined its capacity to induce growth arrest in H1299 cells. Any variant with a RFS value higher than -0.5 (in red) are defined as non-functional. Wild type TP53 is shown in grey. Variant p.Tyr234Cys and p.Tyr234Ser identified in the FILO cohort are indicated with an arrow (1).

Supplementary Figure S3 : TP53 mutated patients frequently multiple clones



A: Distribution of the number of mutations in tumors from the NGS subset of the FILO cohort. **B**: Number of treated or untreated patients among those expressing one or multiple *TP53* variants. **C**: Number of patients expressing one, two or more than two (3+) *TP53* variants according to the number of lines of traitement. TT0 to TT11: number of successive treatments received by the patients.