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IMPACT OF MULTI-HIT VS SINGLE-HIT *TP53* MUTATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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INTRODUCTION

- Presence of *TP53* mutations is a marker of poor prognosis in CLL and a predictor of chemorefractory disease
- Heterogeneity of specific sites of *TP53* mutations and impact of multi-hit *TP53* versus single-hit *TP53* status on outcomes are understudied

AIM

- To compare outcomes between multi-hit versus single-hit *TP53* mutation status in CLL patients
- To describe mutation profiles of specific sites of *TP53* mutations seen in clinical practice

METHOD

- Patients with CLL and *TP53* mutation(s) detected by Sanger sequencing between June 2014 and April 2021 at Mayo Clinic were identified
- Demographics, clinical characteristics, pathologic findings, treatment, and follow-up data were abstracted from the Mayo Clinic CLL database and additional chart review
- Multi-hit *TP53* status defined as presence of multiple *TP53* mutations or presence of both *TP53* mutation(s) and del17p.
- EFS and OS calculated from start of first treatment after *TP53* sequencing
- Discrete variables were compared using Chi-square or Fisher's exact tests
- Continuous variables were compared using Kruskal-Wallis test

RESULTS

Table 1: Baseline Characteristics

	Diagnosis	Time of TP53 Testing by Treatment Status	
	All Patients (n=145)	Untreated (n=63)	Treated (n=82)
	Number (%) or Median [range]	Number (%) or Median [range]	Number (%) or Median [range]
Age	59 [36-92]	70 [44-92]	67 [45-83]
Male sex	102 (70)	43 (68)	59 (72)
Rai stage			
0	56 (41)	19 (31)	9 (14)
I-II	62 (45)	28 (46)	20 (31)
III-IV	20 (15)	14 (23)	35 (55)
Missing	7	2	18
CLL-IPI risk			
Low (0-1)	3 (3)	2 (3)	0 (0)
Intermediate (2-3)	6 (6)	2 (3)	4 (6)
High (4-6)	33 (31)	14 (24)	10 (15)
Very High (7-10)	66 (61)	40 (69)	53 (79)
Missing	37	5	15
B2M > 3.5 mg/L	31 (33)	30 (58)	31 (69)
Missing	51	11	37
IGHV unmutated	94 (77)	40 (69)	58 (84)
Missing	23	5	13
CLL FISH results			
Del(17p)	29 (38)	32 (54)	40 (52)
Del (11q)	6 (8)	6 (10)	4 (5)
Trisomy 12	5 (7)	2 (3)	1 (1)
None detected	13 (17)	6 (10)	9 (12)
Del(13q)	22 (29)	12 (20)	20 (26)
Other (del14)	2 (3)	1 (2)	3 (4)
Missing	68	4	5
Cytogenetic abnormalities ≥ 3	8/13 (62)	8/17 (47)	24/35 (69)
Treatment Prior to TP53 Testing			
CIT only		NA	38 (46)
BTKi +/- CIT		NA	41 (50)
BTKi + BCL2i +/- CIT		NA	3 (4)

Figure 1: *TP53* Mutation Profile Map

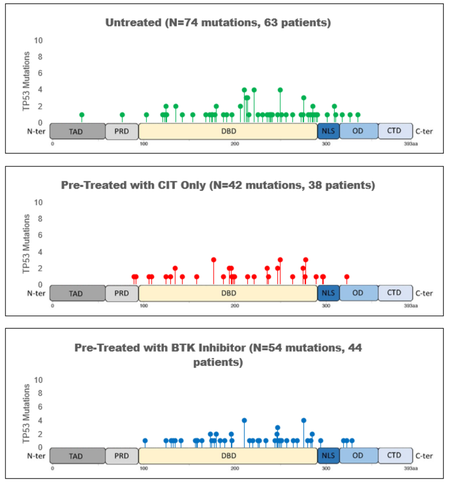
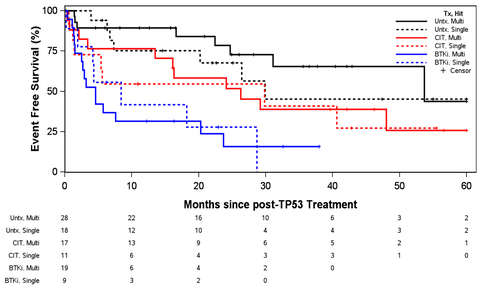
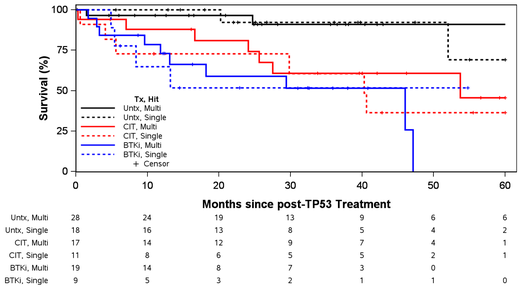


Figure 2: EFS by Treatment Status and *TP53* Mutation Status



Untx, Multi	28	22	16	10	6	3	2
Untx, Single	18	12	10	4	4	3	2
CIT, Multi	17	13	9	6	5	2	1
CIT, Single	11	6	4	3	3	1	0
BTKi, Multi	19	6	4	2	0		
BTKi, Single	9	3	2	0			

Figure 3: OS by Treatment Status and *TP53* Mutation Status



Untx, Multi	28	24	19	13	9	6	6
Untx, Single	18	16	13	8	5	4	2
CIT, Multi	17	14	12	9	7	4	1
CIT, Single	11	8	6	5	5	2	1
BTKi, Multi	19	14	8	7	3	0	
BTKi, Single	9	5	3	2	1	1	0

CONCLUSIONS

- Treatment outcomes did not differ significantly between patients with multi-hit vs single-hit *TP53* alterations, regardless of prior treatment exposure
- Specific sites of *TP53* mutations in our single-center cohort were heterogeneous without clear differences enriched by prior treatment exposure
- Future studies are needed to understand the clinical impact of specific *TP53* mutations

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