LETTER TO THE EDITOR

Genomic landscape of patients in a phase II study of zanubrutinib in ibrutinib- and/or acalabrutinib-intolerant patients with B-cell malignancies

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Patient demographics and baseline information.

Characteristics	Cohort 1 (Intolerant to ibrutinib) (n=56)	Cohort 2 (Intolerant to ibrutinib and/or acalabrutinib) (n=15)	Total (N=71)
Indication, n (%)			
CLL	37 (66.1)	9 (60.0)	46 (64.8)
WM	9 (16.1)	2 (13.3)	11 (15.5)
SLL	6 (10.7)	2 (13.3)	8 (11.3)
MCL	2 (3.6)	1 (6.7)	3 (10.3)
MZL	2 (3.6)	1 (6.7)	3 (4.2)
Age, median (range), year	71 (49-91)	73 (51-87)	71 (49-91)
Male, n (%)	30 (53.6)	9 (60.0)	39 (54.9)
ECOG PS 0, n (%)	33 (58.9)	8 (53.3)	41 (57.7)
No. of prior therapy regimens, median (range)	1 (1-12)	2 (1-6)	1.0 (1-12)
Prior BTKi, n (%)	56 (100)	15 (100)	71 (100)
Ibrutinib monotherapy	48 (85.7)[b]	7 (46.7)[a]	54 (76.1)
Ibrutinib combination therapy	9 (16.1)[b]	0	9 (12.7)
Acalabrutinib monotherapy	0	8 (53.3)	7 (9.9)
Time on prior BTKi[c], median (range), months	10.61 (1.1-73.7)	3.33 (0.5-26.9)	NA
Zanubrutinib exposure, median (range), months	17.0 (0.6-28.5)	14.5 (0.5-19.6)	17.0 (0.5-28.5)
Follow-up, median (range), months	21.2 (1.0-31.7)	10.4 (1.1-20.9)	19.4 (1.0-31.7)

[a] Seven patients in cohort 2 had both prior ibrutinib and acalabrutinib therapies. [b] One patient received ibrutinib combination therapy followed by ibrutinib monotherapy. [c] Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2. Data cutoff: 6 June 2022.

BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NA, not applicable; PD, progressive disease; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Figure S1. Somatic mutation spectra throughout the whole protein sequences of the four most frequently mutated genes. Lollipop plots depicting common mutations in *TP53* (A), *ATM* (B), *SF3B1* (C), *NOTCH1* (D), and *CHK2* (E). Protein domains and mutation type are color-coded and described in figure legends. Del, deletion; Ins, insertion.

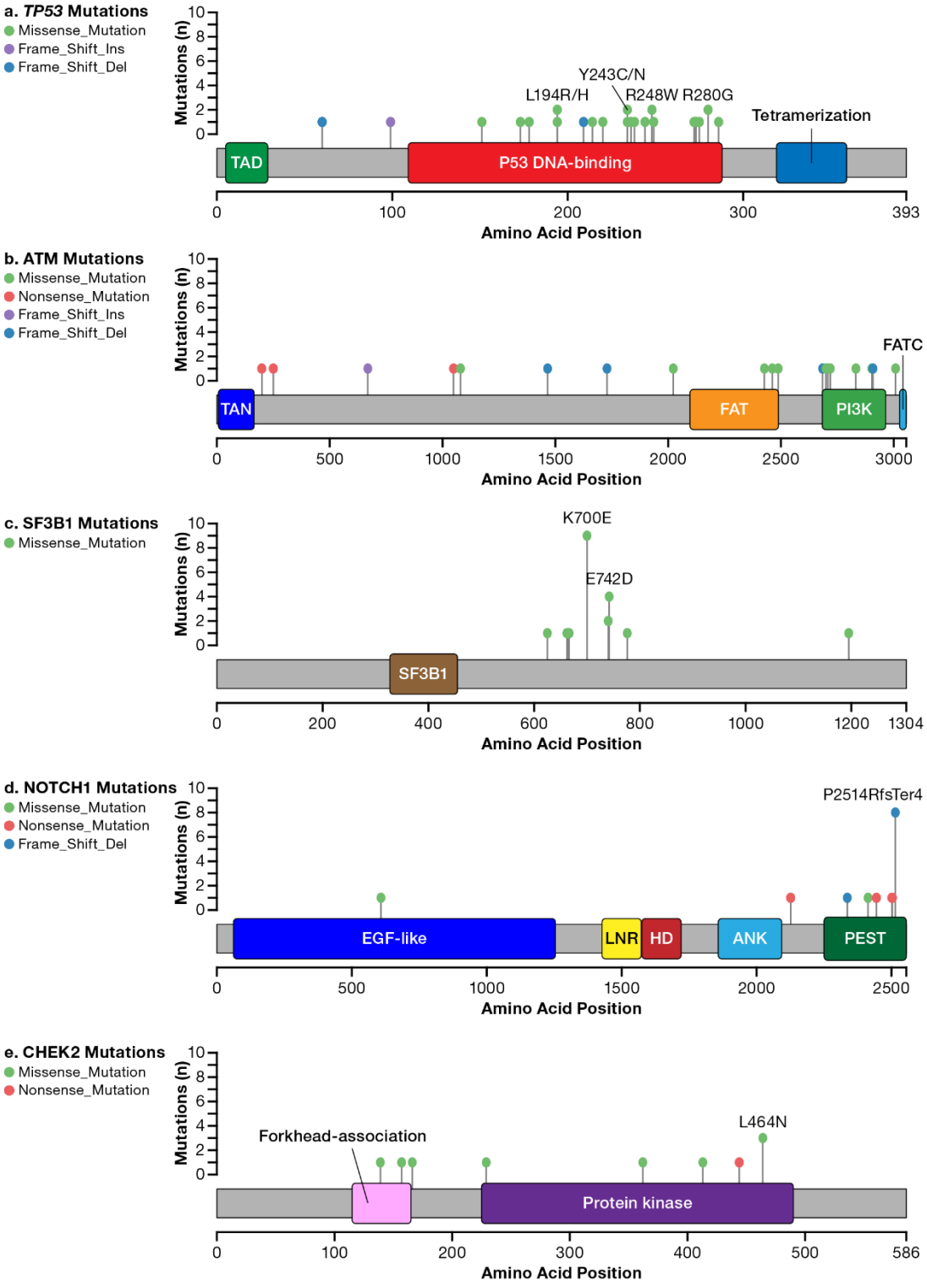

Table S2. Patients with progressive disease who did not have mutations in *BTK* or *PLCG2* had mutations in other known BTK inhibitor resistance genes at baseline.

Patient	Indication	Baseline gene mutations associated with progressive disease
4	CLL	*ATM*, *FBXW7*
5	MCL	*CCND1-IGH* fusion
6	CLL	*MCL1*, *TP53*
7	CLL	*TP53*, *SF3B1*, *FBXW7*
8	CLL	*TP53*, *NOTCH1*, *BRAF*, *SF3B1*, *MAPK14*

BTK, Bruton tyrosine kinase gene; CLL, chronic lymphocytic leukemia, MCL, mantle cell lymphoma; *PLCG2*, *phospholipase C gamma 2* gene.