

Clonal shifts of TP53 mutations in patients treated with BTK and BCL2 inhibitors: analysis of accompanying genomic changes

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OBJECTIVES

- We aimed to investigate mechanisms underlying pronounced clonal shifts of TP53-mutated clones during treatment with BTK (BTKi) or BCL2 inhibitors (BCL2i).
 - We focused on accompanying genomic changes that may drive or counteract TP53 clonal dynamics.

CONCLUSIONS

- Clonal shifts of TP53 mutations under BTKi/BCL2i are rare, even in heavily pretreated patients.
- In contrast to CIT, a significant reduction of TP53-mutant population can occur under targeted therapy but is typically associated with expansion of aggressive, genomically altered subclones.
- In cases of TP53-mutant clonal expansion or competition, complex karyotypes involving del(17p13) and/or resistance mutations in BTK or BCL2 frequently emerge.
- Single-cell analysis confirmed that targeted therapies exert strong selective pressure, promoting convergent evolution of resistance-associated variations independently across multiple clones.

ACKNOWLEDGMENTS

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DISCLOSURES

No disclosures

INTRODUCTION

- The clonal expansion of TP53-deficient clones is frequently observed in patients receiving chemoimmunotherapy (CIT), while the diminishing of the TP53-deficient cell population is extremely rare in the CIT context.
- TP53 aberrations confer less selective advantage under drugs inhibiting BcR signaling or BCL2.
- Clonal shifts involving TP53 mutations have been occasionally observed upon inhibitor treatment, but the extent to which additional genomic alterations contribute to such shifts, and which genomic lesions might outcompete TP53-dysfunctional clones, is not yet fully understood.

METHODS

- Single-centre patients with CLL treated with targeted agents were repeatedly tested for presence of TP53 mutations
- NGS on purified B-cells with a limit of detection of 0.3% variant allele frequency (VAF) was used.
- Serial samples from selected cases with marked TP53 clonal shifts underwent genomic profiling using:
 - NGS panel LYNX [1] covering 72 lymphoma-associated genes and genome-wide chromosomal aberrations
 - and/or whole-exome sequencing combined with genomic arrays.
- Single-cell DNA sequencing (Tapestri CLL panel) was carried out in one representative case.

RESULTS

- We searched for marked TP53-mut clonal shifts in a cohort of 171 patients with CLL treated with BCLi or BTKi.
 - Most patients were CIT-pretreated (96%; range 1-10 prior lines, median 2).
 - TP53 mutations were detected in 108 patients (63%).
- Three main patterns of TP53-mut clonal evolution were identified in 18 patients (Table 1, Figures 1, 2):
 - Diminishing: TP53-mutated population diminished from a baseline VAF>5%
 - Increase: VAF difference between timepoints >20%
 - Exchange: replacement of the dominating TP53-mut clone by another TP53 mutation
- Identified genomic changes involved mainly resistance-associated mutations (BTK/BCL2 genes) and/or complex genomic changes (Table 1, Figure 2).
- Single-cell DNA sequencing of case 1225 from group 3 revealed convergent emergence of four independent BTK-mutated clones arising within distinct TP53-mutated subclones, along with ongoing clonal evolution involving SPEN and NOTCH1 (Figure 3).

REFERENCES

1. Navrkalova V, et al. J Mol Diagn. 2021 Aug;23(8):959-974.

Table 1. Characteristics of patients with TP53 clonal shifts

| Pattern of TP53 clonal evolution | Patient no. | IGHV | Inhibitor type | Months on treatment | Reason for treatment stop | Number of non-targeted therapy lines prior inhibitor therapy | Event accompanying TP53 clonal shift | Status 17p |
|----------------------------------|-------------|------|----------------|---------------------|---------------------------|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------|
| Diminishing | 5 | U | Ibr | 48 | progression | 8 | BTK: c.1442G>C p.C481S 12.5%; GA not analyzed | deletion diminishing |
| | 842 | U | Ven | 34 | progression | 5 | BCL2: c.309C>A p.Asp103Glu 35.2%; BCL2: c.307G>T p.Asp103Tyr 0.4% | deletion diminishing |
| | 1502 | M | Ibr | 51 | adverse events | 0 | unknown | negative stable |
| | 2457 | U | Ven | 16 | progression | 2 | high CK involving chr 2, 8 and 9 CDKN2A/B biallelic loss | negative stable |
| Increase | 319 | U | Ibr | 5 | progression | 0 | not analyzed | deletion diminishing cLCH increasing |
| | 338 | U | Ibr | 47 | progression | 4 | BTK: c.1442G>C p.Cys481Ser 71% | deletion emergence |
| | 2524 | U | Ibr | 27 | progression | 1 | not analyzed | deletion increasing |
| | 392 | U | Ven | 21 | progression | 1 | chromothripsis chr1 | negative stable |
| | 1228 | U | Ibr | 17 | progression | 1 | not analyzed | deletion increasing |
| | 1692 | U | Aca, Ibr | 48 | progression | 2 | not analyzed | cLCH |
| | 1726 | U | Ven | 6 | progression | 3 | not analyzed | deletion increasing |
| | 462 | U | Ibr | 53 | progression | 3 | high CK involving chr 3, 6, 8 and 17 | deletion emergence |
| Exchange | 165 | U | Ven | 62 | progression | 1 | BCL2: c.338C>G p.Ala113Gly 6.3%; BCL2: c.319_330dup p.Arg107_Arg110dup 3%; BCL2: c.467T>A p.Val156Asp 1% | negative stable |
| | 248 | U | Ven | 22 | progression | 10 | not analyzed | deletion persistent |
| | 1003 | U | Ven | 31 | progression | 4 | unknown | negative stable |
| | 1392 | U | Ibr | 10 | progression | 3 | high CK involving chr 1, 6, 8, 9, 11, 13, 17 and 21 | deletion emergence |
| | 1311 | U | Ibr | 24 | progression | 3 | not analyzed | deletion persistent |
| | 1225 | U | Ibr | 46 | progression | 3 | BTK: c.1442_1443delinsCT p.Cys481Ser 70%; BTK: c.1442G>C p.Cys481Ser 3 clones: 15%, 10%, 5% | deletion increasing |

U – unmutated IGHV, M – mutated IGHV, Ibr – ibrutinib, Ven – venetoclax, GA – genomic aberrations, CK – complex karyotype

Figure 2. Clonal evolution of TP53 mutations and chromosomal aberrations

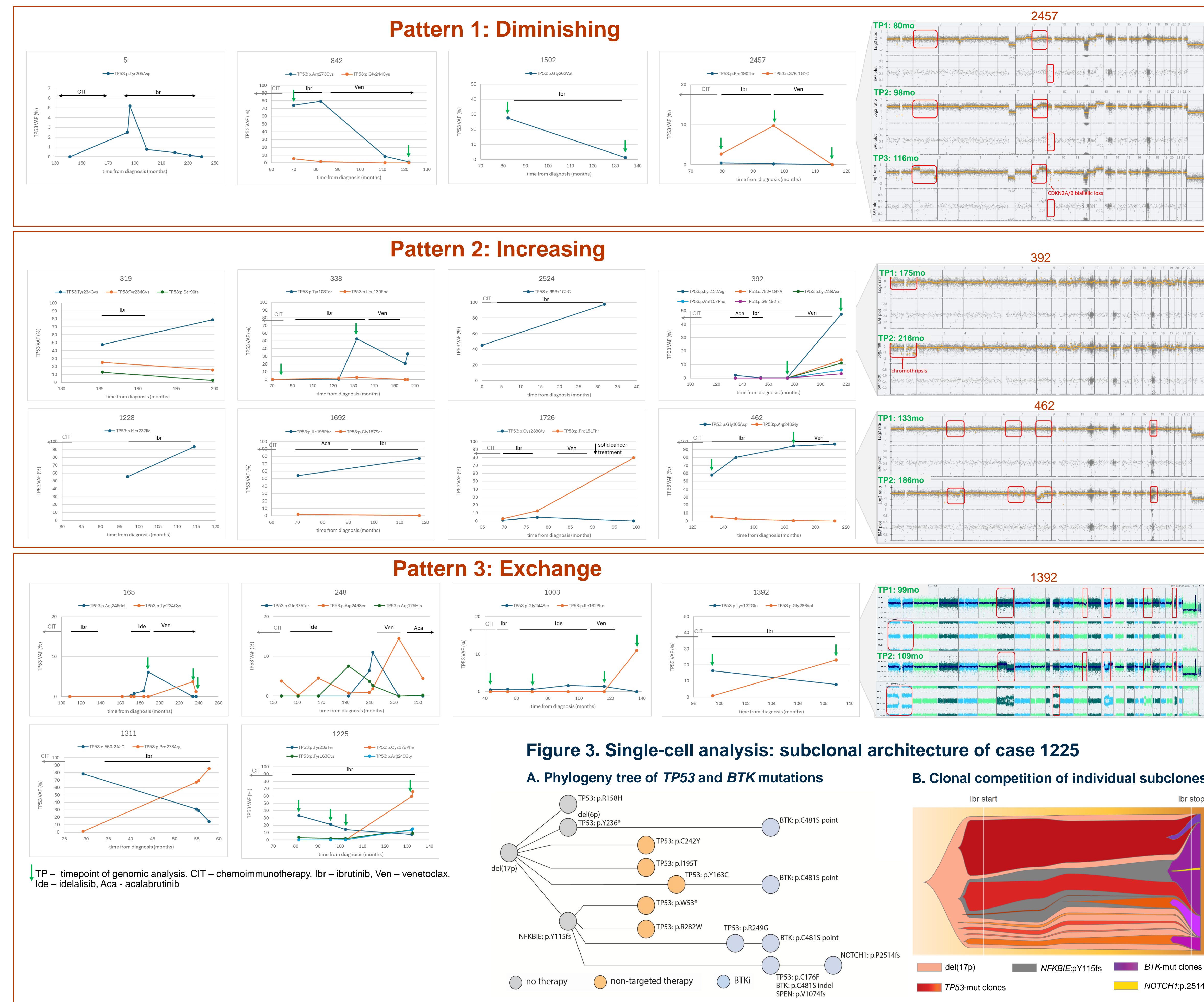


Figure 1. Treatment and sampling history of patients with TP53 clonal shifts

