COOPERATIVE EFFECTS OF *U2AF1*-S34 AND *BCOR* MUTATIONS IN MYELOID NEOPLASMS

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INTRODUCTION

- *U2AF1* mutations occur in approximately 7-11% of myeloid neoplasms and cluster at two zinc-finger hotspots, S34 and Q157.[1]
- Both hotspot mutations have been associated with different co-mutations and clinical characteristics.[1]
- In myelodysplastic syndromes (MDS), S34 mutations are predominant and are associated with worse overall survival and higher rates of leukemic transformation.[1,2]
- Distinct hematopoietic phenotypes have been described in *U2AF1* mutant mice.[3] However, hotspot-level clinical data across real-world patients with myeloid neoplasms remain incompletely defined.

AIMS

- The primary objective of this study is to investigate the clinical association and characteristics of *U2AF1*-S34 and Q157 mutations across myeloid neoplasms.
- The secondary objective is to define the prognostic impact of cooperating mutations.

METHOD

Study Cohort

- We analyzed 1,829 patients with myeloid neoplasms (CMML n=318, MDS n=1,186, MDS/MPN n=150, MPN n=27, AML n=148).

Mutation classification

- *U2AF1* mutations were classified as S34 or Q157.

Data analysis

- Co-mutation frequencies were compared using Fisher's exact test.
- Multivariable Cox proportional hazards regression was adjusted for age, *ASXL1*, *TP53*, *TET2*, HMA therapy, and CPSS-Mol risk score for the CMML cohort.

CONCLUSIONS

- In this large cohort of myeloid neoplasms, S34 and Q157 exhibited markedly distinct co-mutation patterns: S34 with *BCOR*, Q157 with *ASXL1*.
- Patients with S34/*BCOR* co-mutation represent a previously uncharacterized adverse-risk group in myeloid neoplasms (median OS 10.1 months).

RESULTS

- In total, 196 patients (10.7%) carried *U2AF1* variants: S34 in 98 (50%) and Q157 in 98 (50%).
- Compared to wild type, *U2AF1*-mutated patients had significantly lower OS (**Figure 1A**).
- Within the *U2AF1*-mutated cohort, both S34 and Q157 were independently associated with inferior OS (**Figure 1A**).
- *BCOR* mutations were significantly more common in S34 mutants, whereas *ASXL1* mutations were more common in Q157 mutants (**Figure 1B**).
- Co-occurring *U2AF1* S34 and *BCOR* mutations identified a high-risk subset (n = 31) with a median OS of 10.1 months, compared with 13.5 months for S34 alone, 35.8 months for *BCOR* alone, and 51.5 months for WT/WT (**Figure 1C**).

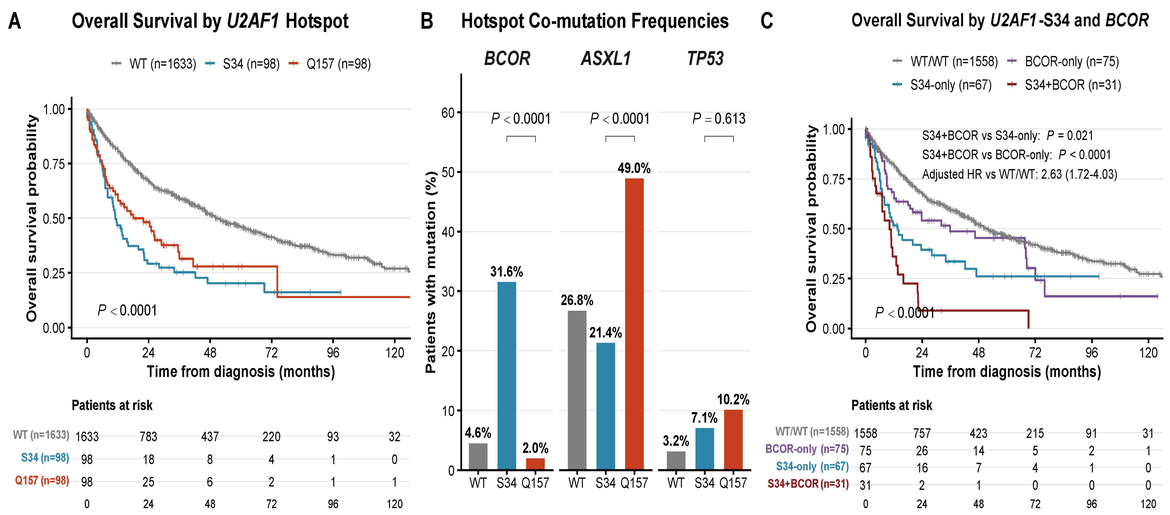

Figure 1. Hotspot-specific co-mutation patterns and overall survival in *U2AF1*-mutant myeloid neoplasms.
(A) Frequency of *BCOR, ASXL1* and *TP53* co-mutation by *U2AF1* hotspot.
(B) Overall survival by *U2AF1* hotspot.
(C) Overall survival by *U2AF1*-S34 and *BCOR* co-mutation.

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