ELSEVIER

Blood 142 (2023) 4552–4553

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

The *SF3B1* K666 Hotspot Mutation Confers Unfavourable Disease Risk across Major Myeloid Neoplasm Subgroups

Jennifer O Sullivan[1,2], *Amy Wood*[3], *Sean Wen, BSc, MSc, PhD*[4], *Angela Hamblin, MD PhD*[5], *Sonia Fox, BSc*[6], *Christina Yap, PhD*[7], *Mary Frances McMullin, MDFRCPath,FRCP*[8], *Nicholas C. P. Cross, PhD*[9], *Claire N Harrison*[10], *Adam J Mead, MRCP, FRCPath, PhD*[11]

[1] Dept of Haematology, Guys and St Thomas' NHS Foundation Trust, London, United Kingdom
[2] Medical Research Council (MRC) Weatherall Institute of Molecular Medicine (WIMM) and NIHR Biomedical Research Centre, University of Oxford, Oxford, United Kingdom
[3] Weatherall Institute of Molecular Medicine, Oxford, United Kingdom
[4] Haematopoietic Stem Cell Biology Laboratory, Medical Research Council Molecular Haematology Unit, Medical Research Council Weatherall Institute of Molecular Medicine, University of Oxford, Cambridge, United Kingdom
[5] Cancer and Haematology Centre, The Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
[6] Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Science, Birmingham, GBR
[7] The Institute of Cancer Research, ICR's Clinical Trials and Statistics Unit, Sutton, GBR
[8] Haematology, Belfast City Hospital, Queen's University Belfast, Belfast, United Kingdom
[9] University of Southampton, Salisbury, GBR
[10] Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom
[11] Medical Research Council (MRC) Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, National Institute for Health Research Biomedical Research Centre, University of Oxford, Oxford, United Kingdom

SF3B1 is the most prevalent splicing factor mutated in myeloid neoplasms, detected in 20-30% of patients with myelodysplasia (MDS) and associated with a milder disease phenotype. *SF3B1* mutations are typically single nucleotide variations occurring in hotspots in the HEAT domain. Disease-specific *SF3B1* hotspot predilection is observed; for example, K700E is most common in MDS and R625 in uveal melanoma. The K666 hotspot has been associated with increased risk of MDS disease progression to acute myeloid leukemia (AML). However, the prognostic impact across all myeloid neoplasms inclusive of myeloproliferative neoplasms (MPN) and MDS/MPN overlap syndromes has not been established.

Mutation information was collated from available datasets inclusive of unpublished clinical trial cohorts across patients with myeloid neoplasms (MDS, MPN, MDS/MPN, AML) and patients with solid malignancies and clonal hematopoiesis (CH). *SF3B1* hotspot mutations were correlated with additional somatic mutations, disease type and other clinical parameters. Overall, 11,744 patients with myeloid neoplasms; MDS (n=4275), AML (n=3526), MDS/MPN (n=192), MPN (n=3751) and 24,146 patients with solid malignancies and CH were included in this analysis. *SF3B1* mutations were present in 11.1% of patients; 21.3% MDS, 4.1% AML, 51% MDS/MPN and 3.7% MPN. In MDS, *SF3B1* mutations were predominantly present in low risk MDS (23.8%) as compared with 4.1% in intermediate to high risk MDS. This contrasts with MPN where *SF3B1* mutations were present at a higher frequency in more advanced MPN (5.5% in treatment-resistant ET, 8.8% in all MF cases and further augmented at 14% in JAK inhibitor resistant high-risk thrombocytopenic MF) as compared with earlier phase MPN (2.1% and 1.3% in ET and PV respectively). In MPN *SF3B1*-mutant cases, JAK-STAT signaling driver mutation frequency and distribution were in line with published data; 65.6% *JAK2*V617F-mutated, 18.8% *CALR*-mutated, 8.5% *MPL*-mutated and 7% triple negative.

As previously described, *SF3B1* K700E hotspot mutations were most prevalent (frequency 49.1%), followed by K666, H622 and R625 hotspot mutations at 20.6%, 7.6% and 6.1% respectively. K700E was enriched as expected in MDS cohorts and K666 hotspot mutations were enriched in AML (42%). Although less common in MDS (11.6 - 17.8%), the frequency of K666 mutation correlated with higher IPSS-M risk category in MDS (p=0.001; chi-squared test). In contrast to MDS, *SF3B1* K666 was the dominant hotspot in MPN ranging 46-70% in frequency across subtypes from earlier to more advanced MPN such as MF (Fig 1A).

SF3B1 K700E mutations were more often co-mutated with epigenetic mutations such as in *DNMT3A*, *TET2*, *EZH2* and *KMT2C* genes (Fig 1B) whereas *SF3B1* K666 mutations were significantly co-mutated with NPM1 and FLT3 in AML cases (odds ratio,

OR, 25.6 and 4.2 respectively, p-value <0.0001) and *JAK2*V617F in MPN cases (OR 3.2, p<0.0001). *SF3B1* K666 mutations also showed a trend towards significant co-occurrence with adverse prognostic mutations in AML; *PHF6*, *PTPN11* and *RUNX1*. No differences were observed for *SF3B1* hotspots for *CALR* or *MPL*-mutated MPN but numbers were too few to draw conclusions. In patients with *SF3B1* mutations, 58% were male and K666 hotspot was more frequent in males (21% as compared with 11% in females, p<0.001, chi-squared test). There were no hotspot differences observed in age, ethnicity, bloods counts or karyotype where data was available for this analysis. In CH, *SF3B1* mutations were detected in 0.5% with K700E (34.2%) and K666 (26.7%) frequencies equivalent (p=0.24).

In summary, this large multi-cohort myeloid neoplasm analysis reveals myeloid disease-specific *SF3B1* hotspot propensity. The K666 hotspot was frequent in MPN, particularly in persons with advanced disease where *SF3B1* mutations are more prevalent than earlier phase MPN. We conclude that different *SF3B1* hotspots are associated with distinct clinical phenotypes and in chronic myeloid malignancies; K666 *SF3B1* mutation is associated with adverse clinical course. Additional studies to elucidate the distinct biological effects of different *SF3B1* mutations are warranted.

Disclosures O Sullivan: *Novartis:* Honoraria; *Morphosys:* Honoraria. **Wen:** *AstraZeneca:* Current Employment. **McMullin:** *Novartis:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AOP:* Speakers Bureau; *Incyte:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *CTI:* Membership on an entity's Board of Directors or advisory committees; *Sierra oncology:* Membership on an entity's Board of Directors or advisory committees; *GSK:* Membership on an entity's Board of Directors or advisory committees. **Harrison:** *GSK:* Honoraria, Speakers Bureau; *CTI:* Honoraria, Speakers Bureau; *Morphosys:* Honoraria, Speakers Bureau; *AOP:* Honoraria, Speakers Bureau; *Novartis:* Honoraria, Research Funding, Speakers Bureau; *BMS:* Honoraria, Speakers Bureau; *Galecto:* Honoraria, Speakers Bureau; *Abbvie:* Honoraria, Speakers Bureau. **Mead:** *Roche:* Research Funding; *Pfizer:* Consultancy, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Alethiomics Ltd:* Consultancy, Current equity holder in private company, Other: Cofounder & equity holder, Research Funding; *Gilead:* Consultancy, Speakers Bureau; *Relay Therapeutics:* Consultancy, Speakers Bureau; *GSK:* Consultancy, Speakers Bureau; *Incyte:* Consultancy, Speakers Bureau; *University of Oxford:* Patents & Royalties: 2203947.3 ; *CTI:* Consultancy, Speakers Bureau; *Sierra Oncology:* Consultancy, Speakers Bureau; *Karyopharm:* Consultancy, Speakers Bureau; *Galecto:* Consultancy, Research Funding, Speakers Bureau; *Sensyn:* Consultancy, Speakers Bureau; *Celgene/BMS:* Consultancy, Research Funding, Speakers Bureau; *AbbVie:* Consultancy, Other: investigator for AbbVie sponsored trials, Speakers Bureau.

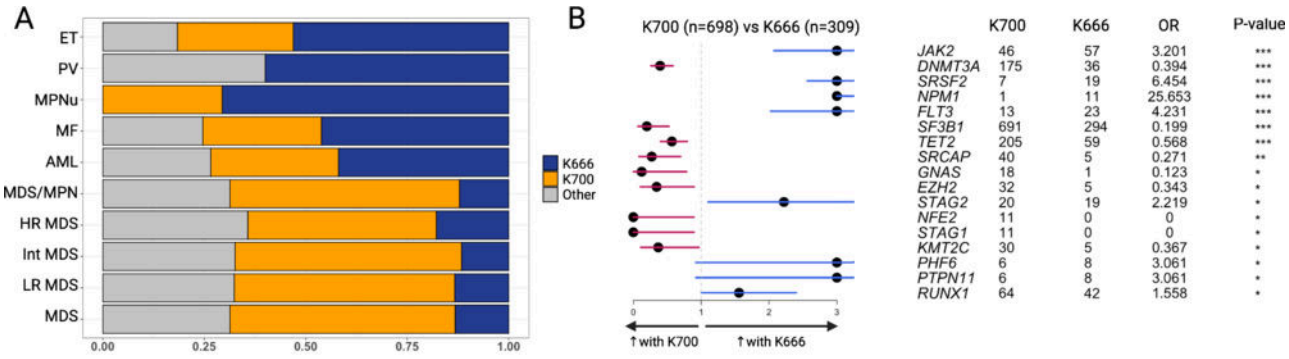

Figure 1. (A) Barplot showing hotspot distribution across myeloid neoplasms. **(B)** Forest plot illustrating results of logistic regression analyses of additional somatic mutations enriched either in patients with *SF3B1* K700 or K666 mutations. OR=odds ratio where 1= no effect. P-value: ***<0.001, **<0.01, *<0.05.

Figure 1

https://doi.org/10.1182/blood-2023-185043