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POSTER ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Clonal Hematopoiesis-Related Mutations Are Associated with Favorable Clinical Benefit Following Luspatercept Treatment in Patients with Lower-Risk Myelodysplastic Syndromes: A Subgroup Analysis from the Phase 3 COMMANDS Trial

Maroof Hasan[1], *Sadanand Vodala*[1], *Sheida Hayati*[2], *Guillermo Garcia-Manero, MD*[3], *Anita K. Gandhi, PhD*[4], *Rajasekhar N.V.S. Suragani, PhD*[1]

[1] Hematology, Translational Medicine and Disease Team, Bristol Myers Squibb, Summit, NJ
[2] Informatics and Predictive Sciences, Bristol Myers Squibb, Princeton, NJ
[3] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[4] Translational Development and Diagnostics, Bristol Myers Squibb, Summit, NJ

Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is a common age-related condition arising from somatic mutations in hematopoietic stem cells that leads to mutant cell clonal progeny in the blood (variant allele frequency [VAF] > 2%) and is found in 10%-30% of people > 70 years of age. CHIP-related mutations (eg, DNA methyltransferase 3 alpha [*DNMT3A*], tet methylcytosine dioxygenase 2 [*TET2*], ASXL transcriptional regulator 1 [*ASXL1*], splicing factor 3b subunit 1 [*SF3B1*]) are associated with increased inflammation and elevated risk of developing hematologic malignancies, including myelodysplastic syndromes (MDS)/acute myeloid leukemia, and are an independent risk factor for cardiovascular complications. Recently, patients with MDS were reported to have high rates of cardiovascular co-morbidities including elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of cardiovascular and all-cause mortality. Currently, no treatments targeting CHIP mutations or associated complications are available. Luspatercept is currently approved for anemia in adult patients with lower-risk MDS (LR-MDS) with ring sideroblasts who require red blood cell (RBC) transfusions (≥ 2 RBC units/8 weeks) after erythropoiesis-stimulating agent (ESA) treatment failure. Recently, the phase 3 COMMANDS trial (NCT03682536) reported superiority of luspatercept over ESAs in reducing transfusion burden in ESA-naive patients with LR-MDS.
Aims: We investigated the association between the most frequent CHIP-related mutations (*DNMT3A*, *TET2*, *ASXL1*, *SF3B1*) and clinical outcomes in patients treated with luspatercept from the COMMANDS trial.
Methods: Genomic DNA was isolated from bone marrow (BM) mononuclear cells, and 36 myeloid-specific somatic gene mutations were identified by targeted next-generation sequencing (400X; sensitivity 3%; Munich Leukemia Laboratory information system) at baseline. Hematologic parameters (eg, hemoglobin [Hb], complete blood counts), transcriptome data (bulk BM RNA sequencing [RNA-Seq] data) and cytokines/chemokines (peripheral blood) were assessed at baseline and week 24.
Results: Overall, 145 patients in the luspatercept arm of the COMMANDS trial were included in the current analyses, of whom 85% (123/145) (Figure 1A) had the most frequent CHIP-related mutations (eg, *DNMT3A*, *TET2*, *ASXL1*, and *SF3B1*) with a VAF of 3%-50%. Modest positive correlations were observed between *DNMT3A*, *TET2* and *SF3B1* baseline VAF and monocyte percentage ($P = 0.024$, $P = 0.015$, and $P = 0.005$, respectively). Baseline Hb levels were lower in patients with frequent CHIP-related mutations than in those with less frequent/other somatic mutations. Luspatercept treatment significantly reduced anemia from baseline in patients with CHIP-related mutations (primary endpoint response 62%; n/N = 76/123). Concomitant with the Hb increase ($\Delta = +1.0$ mg/dL; $P < 0.001$), we observed improvements in other cell counts, including white blood cell counts ($\Delta = +0.7 \times 10^9$ cells/L; $P = 0.01$). In addition, luspatercept treatment in patients with CHIP-related mutations was associated with downregulation of inflammatory gene signatures (Figure 1B) and proinflammatory cytokines/chemokines, including hepcidin ($\Delta = -43.9$ ng/mL; $P < 0.001$). Furthermore, we observed upregulation of an anti-inflammatory regulator (growth/differentiation factor 15) following treatment. Most importantly, significant downregulation of NT-proBNP levels ($\Delta = -330$ pg/mL; $P < 0.05$) was observed in patients with LR-MDS who received luspatercept.
Conclusions: This retrospective subgroup analysis of patients in the COMMANDS trial with the most frequent CHIP-related mutations (*DNMT3A*, *TET2*, *ASXL1* and *SF3B1*) demonstrated novel effects of luspatercept in clonal hematopoiesis-related consequences including improvements in anemia, cytopenias, and reduced inflammation. Most importantly, NT-proBNP and elevated hepcidin levels were significantly downregulated in responders following luspatercept treatment. These results war-

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rant evaluation of luspatercept in patients with high-risk CHIP mutations including clonal cytopenia of undetermined significance and patients with anemia of inflammation.

Disclosures Hasan: *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Vodala:** *Bristol Myers Squibb:* Current Employment; *Mabgenex:* Membership on an entity's Board of Directors or advisory committees. **Hayati:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Garcia-Manero:** *Bristol Myers Squibb:* Other: Medical writing support, Research Funding; *Genentech:* Research Funding; *AbbVie:* Research Funding. **Gandhi:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Suragani:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.

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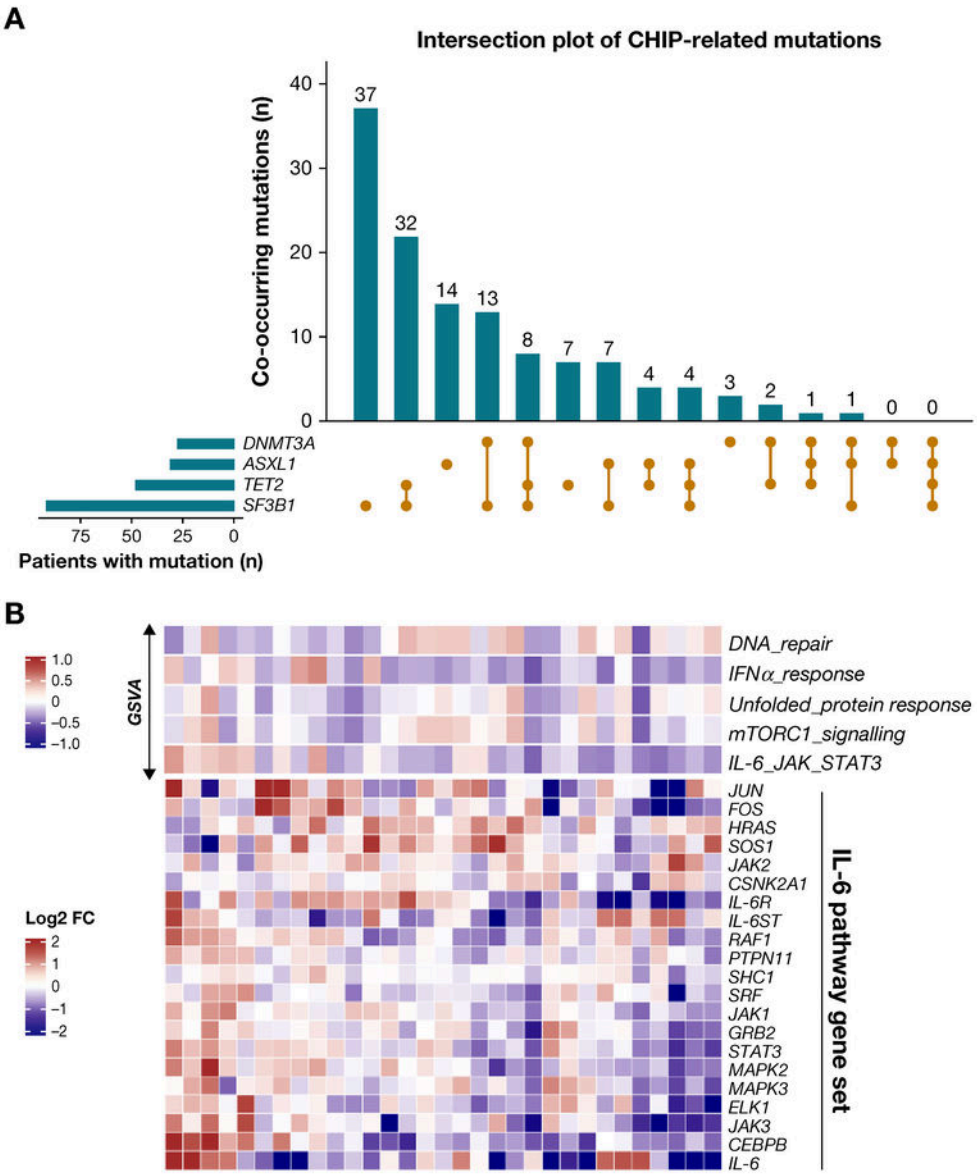
Figure 1. Prevalence of the most frequent CHIP-related mutations (*DNMT3A*, *TET2*, *ASXL1*, and *SF3B1*) in the COMMANDS trial



Upper heatmap shows the post-treatment GSVA score for 31 patients with CHIP-related gene mutations with paired pre- and post-treatment RNA-Seq data; lower heatmap shows fold-change from baseline in the IL-6 pathway gene set. Red indicates upregulation and blue indicates downregulation.

ASXL1, ASXL transcriptional regulator 1; CEBPB, CCAAT enhancer binding protein beta; CHIP, clonal hematopoiesis of indeterminate potential; CSNK2A1, casein kinase 2 alpha 1; DNMT3A, DNA methyltransferase 3 alpha; ELK1, ETS like-1 protein; FC, fold change; GRB, growth factor receptor bound protein; GSVA, gene set variation analysis; HRAS, Harvey rat sarcoma virus oncogene; IFNα, interferon; IL, interleukin; JAK, janus kinase; MAPK2, mitogen activated protein kinase 2; MAPK3, mitogen activated protein kinase 3; mTORC1, mammalian target of rapamycin complex 1; PTPN11, protein tyrosine-protein phosphatase non-receptor type 11; SF3B1, splicing factor 3b subunit 1; SOS1, son of sevenless homolog 1; SRF, serum response factor; STAT, signal transducer and activator of transcription; TET2, tet methylcytosine dioxygenase 2.

Figure 1

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