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ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Bomedemstat (IMG-7289), an LSD1 Inhibitor, Manages the Signs and Symptoms of Essential Thrombocythemia (ET) While Reducing the Burden of Cells Homozygous for Driver Mutations

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The ultimate goal in the treatment of ET is to eliminate mutant cells with the capacity to both proliferate and self-renew. Lysine-specific demethylase-1, LSD1, is an enzyme critical for regulating the proliferation of hematopoietic stem cells and the maturation of progenitors (Sprussel *et al.* 2012). Bomedemstat is an orally active LSD1 inhibitor that reduces platelets, inflammatory cytokines, and the mutant cell burden in mouse models of myeloproliferative neoplasms (Jutzi *et. al.*, 2019). All current treatments - hydroxyurea, interferon, or anagrelide - have their limitations and do not substantially affect the natural history of ET.

IMG-7289-CTP-201 was a global, open-label, Phase 2b study of bomedemstat (IMG-7289, MK-3543) taken once daily for 24+ weeks in patients with ET resistant to or intolerant of at least one standard treatment (NCT04254978). The primary endpoint was reduction of platelets to <400 x 10^9/L in the absence of new thromboembolic events. Exploratory endpoints included changes in frequencies of mutant alleles (VAF) assessed by deep sequencing (median exonic depth =1784 reads) of 261 genes of germline and somatic DNA. Homozygosity of mutant alleles was imputed when VAF >50% and/or loss-of-heterozygosity (LOH) was evident based on the difference between the minor allele frequency of flanking single nucleotide polymorphisms ("MAF method") in germline *versus* granulocyteDNA. Single cell genotypes (scDNA) (Tapestri ®) were de-

termined in stem/progenitor (CD34+) and monocytes (CD14+) cells in patients with LOH (using the MAF method) showing a decrease in LOH in whom follow-up samples were available.

For patients treated ≥24 wks, 95% (61/64) had reduced platelet counts to ≤400 x 10^9/L without new thromboembolic events, in a median time of 10 wks. In the first 48 weeks, four patients experienced a thromboembolic event (*per* PI) (1 PE, 2 TIAs, and 1 transient global amnesia). Of the 14/73 (19%) patients with Day 1 WBC count >10 x 10^9/L, 100% treated for ≥24 wks had reduced the WBC count to ≤10 x 10^9/L; mean Hb remained stable. In patients with baseline MPN-SAF TSS >20 (28/73), at Wk 24, 78% (18/23) experienced an improvement with 52% (12/23) improving ≥10 points. The median baseline score for worst fatigue was 4.0 (N=73); by Wk 24, the score had improved to 3.0 (N=62).

Among all patients (N=73), the most common AEs regardless of causality were dysgeusia (55%), constipation (38%), thrombocytopenia (34%), and arthralgia (27%). Twenty-four patients reported serious AEs (SAE), with related events (*per* PI) in 4 patients. Twenty-one patients discontinued treatment, 11 due to AEs (3 for dysgeusia), 7 subject's decisions, 1 PI decision, 1 disease progression, and 1 unrelated death due to aspiration pneumonia. There have been no safety signals or deaths related to drug in patients treated for up to 979 days. At Wk 24, 86% patients remained on study and 75% at Wk 48.

At ˜Wk 24, 39 of 46 (85%) of evaluable patients had a decrease in driver VAF (Fig. 1). The greatest changes in VAF occurred in patients with cells homozygous for a driver mutation (Fig. 1). Nine of ten patients with homozygous driver clones had follow-up data: by bulk sequencing of germline+granulocyte DNA, 7 showed a reduction in the proportion of homozygous cells. In all cases tested, scDNA of CD14+ (monocytes) and CD34+ (stem/progenitor) cells were qualitatively similar to results obtained with bulk granulocyte sequencing (Fig.2). By bulk sequencing, the proportion of homozygous cells dropped by a mean of 66% (-4% to -100% (-100% = homozygosity not detectable)). Decreases in LOH by bulk and sc sequencing during treatment with bomedemstat were identified in patients with homozygosity at *JAK2, CALR*, and *MPL*.

This study demonstrates that treatment with bomedemstat results in a consistent hematologic response in the majority of patients with ET. Further, deep bulk sequencing of germline+granulocyte DNA reveals LOH (*i.e.*, homozygosity) events with high accuracy that enables determination of the distribution of homozygote, heterozygote and wild-type genotypes. Furthermore, this study shows that sequencing germline+granulocyte DNA provides a reliable qualitative view of the impact of treatment on the genotypic distribution among CD34+ cells as revealed by scDNA genotyping. Finally, bomedemstat showed activity reducing stem/progenitor cells homozygous for mutations in *JAK2, CALR*, and *MPL*.

Disclosures Goethert: *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Consultancy; *GlaxoSmithKline:* Consultancy; *Proteros Biostructures:* Honoraria; *zr pharma&:* Honoraria; *BMS:* Consultancy, Honoraria, Other: travel expenses; *Incyte:* Consultancy, Honoraria, Other: travel expenses; *Ariad:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Other: travel expenses; *AOP Pharma:* Consultancy, Honoraria, Other: travel expenses; *Abbvie:* Consultancy; *CTI BioPharma:* Consultancy. **Gill:** *Novartis:* Consultancy, Other: Conference Support, Research Funding; *GSK:* Consultancy; *BMS:* Consultancy; *Pfizer:* Consultancy, Other: Conference support; *PharmaEssentia:* Consultancy, Other: Conference Support, Research Funding; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Palandri:** *Novartis, BMS, Celgene, GSK, Amgen, AbbVie, Karyopharm, AOP, Sierra Oncology, Janssen:* Consultancy, Honoraria. **Ross:** *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *Keros:* Consultancy; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Menarini:* Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Honoraria, Research Funding. **Cochrane:** *Janssen-Cilag:* Speakers Bureau; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *Beigene:* Research Funding. **Larsen:** *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Halpern:** *Abbie, Notable Labs, Agios:* Consultancy; *Imago Bioscience, Bayer, Gilead, Jazz, Incyte, Karyopharm Therapeutics, Disc Medicine:* Research Funding. **Shortt:** *Novartis:* Consultancy, Speakers Bureau; *Mundipharma:* Consultancy, Speakers Bureau; *Astellas:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding; *Otsuka:* Consultancy; *Pfizer:* Consultancy; *Amgen:* Research Funding; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Rossetti:** *CTI BioPharma Corp:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Medical Writing, Speakers Bureau; *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Integra Connect:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Medical Writing, Speakers Bureau; *Leukemia and Lymphoma Society:* Membership on an entity's Board of Directors or advisory committees; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *MPN Support Group:* Speakers Bureau. **Liang:** *Janssen:* Other: travel and accommodation; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Marchetti:** *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Wilson:** *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Innes:** *Imago Biosciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Hanna:** *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Stevenson:** *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding. **Vannucchi:** *GSK:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AbbVie:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Incyte:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *AOP:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Blueprint:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Membership on an entity's Board of Directors or advisory

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Figure 1

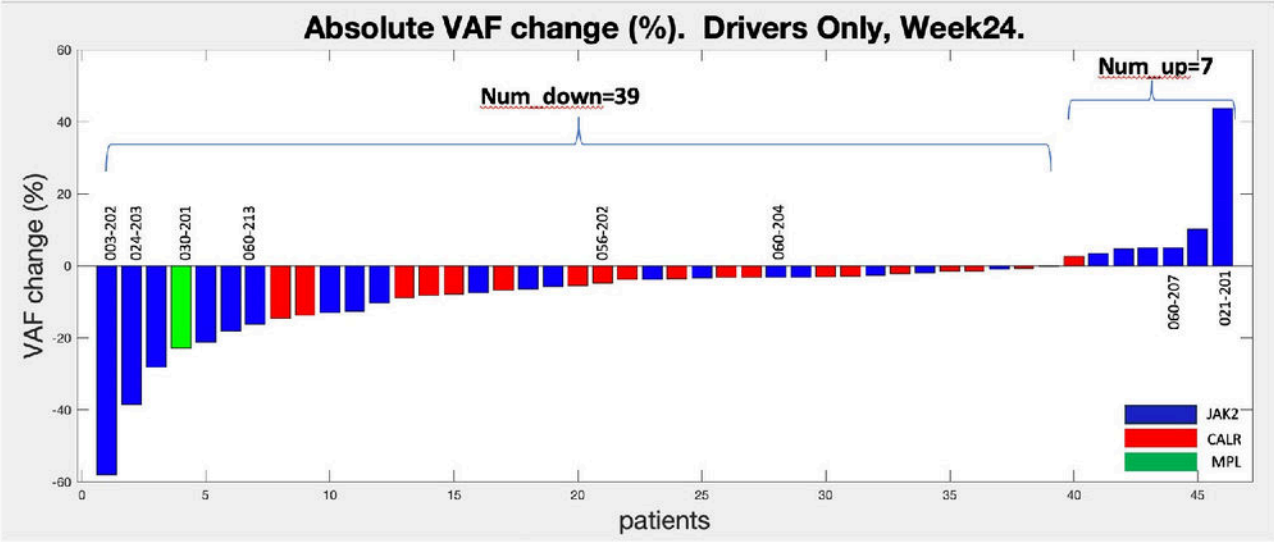

Figure 2

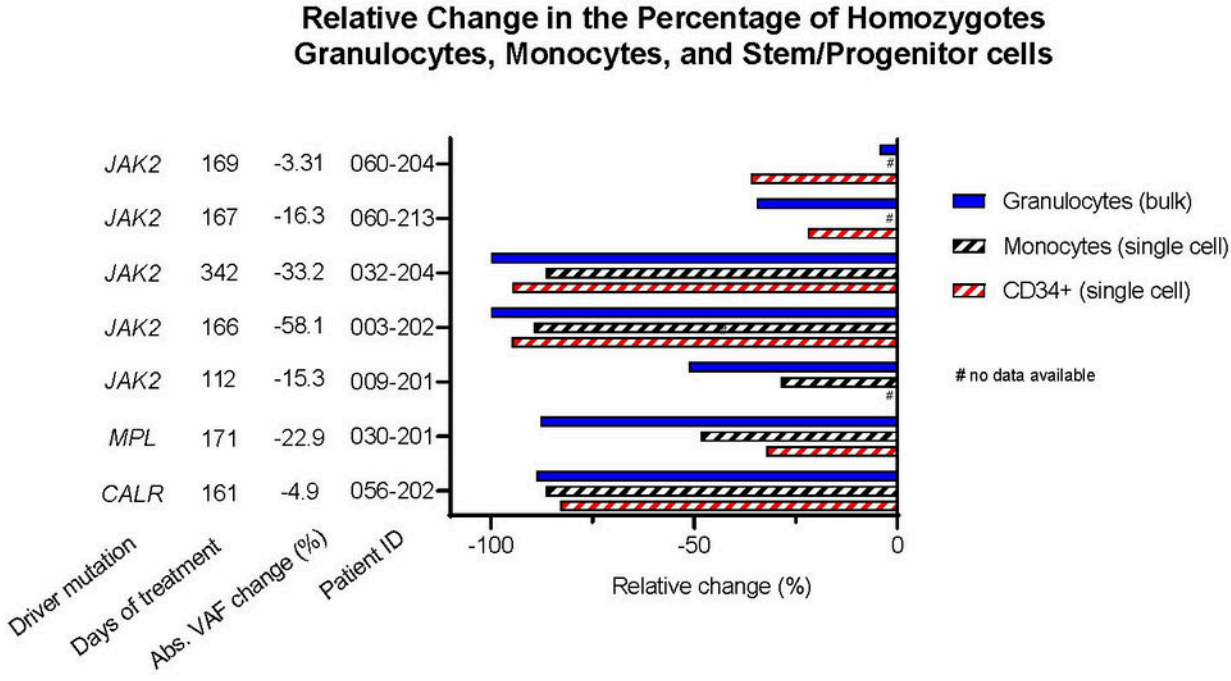

Figure 1

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