TPS6589 **Poster Session**

Anti-tumor activity of CoREST inhibitor, JBI-802 (dual epigenetic modifier of LSD1/HDAC6): An opportunity to treat essential thrombocythemia and MPN/MDS patients with thrombocytosis in ongoing phase 1/2 clinical trial.

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Background: Lysine specific demethylase 1 (LSD1) and histone deacetylase 6 (HDAC6) are epigenetic proteins associated with several diseases, including cancer. JBI-802 is a highly potent CoREST inhibitor with LSD1/HDAC6 selective dual inhibition that shows superior anti-tumor activity in several pre-clinical models with significant modulation of PD biomarkers that include CD11b, CD86 and acetylated alpha-tubulin. JBI-802 in first-in-human phase I clinical trial (NCT05268666) demonstrated a dose-proportional increase in exposure across cohorts and its correlation with on-target effects in therapy resistant advanced lung cancers patients. 2/2 immunotherapy resistant NSCLC patients displayed improvement in tumor-related symptoms with confirmed partial response (PR) in one NSCLC patient at 10 mg dose. Overall, JBI-802 was well tolerated and showed remarkable safety profile without affecting hemoglobin, with grade 3/4 thrombocytopenia as the only adverse event observed in 38% of patients at the higher dose. Dose-dependent decrease in platelets as a part of MOA of LSD1 and HDAC6 inhibition demonstrated that JBI-802 is pharmacologically active and provided an opportunity to treat patients with hematological malignancies like essential thrombocythemia (ET) and other myelodysplastic/myeloproliferative neoplasms (MDS/MPN) characterized by thrombocytosis. **Methods:** The ongoing phase 1/2 clinical trial will assess the safety and preliminary efficacy of orally administered JBI-802 in ET and MDS/MPN patients with thrombocytosis (ACTRN12624000478516) in a standard 3+3 design in 30 patients in two phases. Part 1: Dose Escalation Phase - Primary objective is to determine the recommended phase 2 dose (RP2D) of JBI-802 and safety in subjects with ET and MDS/MPN neoplasms with thrombocytosis, with dose-limiting toxicity as the primary endpoint during the monitoring period. Secondary objective is to evaluate the overall safety and tolerability, and to determine the preliminary antitumor activity along with characterization of pharmacokinetic (PK) profile of JBI-802 and its metabolites as well as clinical and hematologic responses. Part 2: Dose Expansion Phase – The objective is to obtain preliminary evidence of efficacy as defined by MDS/MPN IWG response criteria, which includes platelet count reduction, and response assessments of spleen size and volume, evaluation of hematology parameters and bone marrow aspiration/biopsy, and to further evaluate the overall safety and tolerability of JBI-802, along with characterization of PK and PD profile and changes in mutant allele frequencies. Study results will provide insights into the clinical potential of JBI-802 in treating ET and MDS/MPN patients relapsed and/or refractory to standard of care therapies. Clinical trial information: ACTRN12624000478516. Research Sponsor: None.