S165 A PHASE 1, DOSE ESCALATION TRIAL WITH NOVEL ORAL IRAK4 INHIBITOR CA-4948 IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA OR MYELODYSPLASTIC SYNDROME – INTERIM REPORT

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Background:
Interleukin-1 receptor-associated kinase 4 (IRAK4) plays a critical role in toll-like receptor (TLR) or interleukin-1 receptor (IL-1R) signaling pathway activation. This results in stimulation of NFκB, triggering inflammatory responses, oncogenesis and survival mechanisms of malignant cells. Genetic mutations of myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) include SF3B1 and U2AF1 affecting spliceosomes in 50% of cases that lead to expression of a longer, highly active isoform of IRAK4 (IRAK4-L) [1,2]. CA-4948 is a novel oral inhibitor of IRAK4 and FLT3 signaling.

Aims:
Assessment of safety, tolerability and recommended phase 2 dose (RP2D).

Methods:
This is an ongoing, phase 1 dose escalation trial (NCT 042787688). In a 3+3 design, enrolling adult patients with relapsed or refractory high-risk MDS or AML, CA-4948 is orally administered at dose level (DL) cohorts of 200, 300, 400, and 500 mg bid given continuously in 28-day cycles until limiting toxicity or disease progression. Primary objective: Safety and RP2D . Secondary: Early efficacy (ORR; evaluable: patients with baseline- and at least 1 follow-up malignancy assessments); pharmacokinetics (PK). Exploratory: Pharmacodynamic (PD) mechanism-of action (MoA) related biomarkers.

Results:
As of February 8, 2021, 15 patients (10 males, 5 females; median age 72, range: 32-84) have been enrolled with higher risk MDS by IPSS-R (N=8), and 7 with AML. Median number of prior therapies was 2 (range 1- 4). Most patients were transfusion dependent at baseline. Three dose levels of 200, 300, and 400 mg bid have been completed for DLT evaluation; DL 4 at 500 mg bid is open for enrollment. Treatment duration ranged from <1 to 7 months with enrollment ongoing.

Safety:

Treatment was generally safe and tolerable. No DLT was reported at the first 3 dose levels incl. 400 mg bid. One treatment-related dose reduction (Grade 3 dizziness) resulted in no toxicity-related discontinuation.

Pharmacokinetics/Pharmacodynamics:

Drug is rapidly absorbed with a half-life of 6 hours supporting bid dosing. Exposure increased dose proportionally. No major accumulation and no CYP450 inhibition or induction were observed. Pharmacodynamic results are pending, results will be included in presentation.

Efficacy:

Bone marrow blast reductions were observed at all tested dose levels in 8 of 9 (89%) evaluable patients with elevated blast counts at baseline. Responses included 1 CR with full hematologic recovery, 1 CRi with negative minimal residual disease, and 2 bone marrow CRs. Three patients had a spliceosome mutation, and all 3 patients achieved a marrow CR or better. Patients with objective responses also saw signs of hematologic recovery.

Conclusion:

CA-4948 monotherapy is so far well tolerated and with signs of clinical activity in this group of patients with advanced disease. Three of 3 patients with spliceosome mutations achieved a marrow CR or better. The study continues to define RP2D and to obtain definitive PK and PD profile.

References:

1) Smith MA. et al., 2019 Nat Cell Biol. 21(5): 640–650

2) Choudhary G et al., 2019. Blood 134 (Suppl 1): 4224

Keyword(s): Alternate splicing, AML, Inhibitor, MDS