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POSTER ABSTRACTS

624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Preliminary Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of KT-333, a Targeted Protein Degrader of STAT3, in Patients with Relapsed or Refractory Lymphomas, Large Granular Lymphocytic Leukemia, and Solid Tumors

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Background: KT-333is a first-in-class, potent, highly selective, heterobifunctional small molecule degrader of the signal transducer and activator of transcription 3 (STAT3) protein. Aberrant activation of STAT3 resulting from activating mutations or deregulated cytokine signaling underlies various malignancies including peripheral T-cell lymphomas (PTCL), cutaneous T-cell lymphoma (CTCL), and large granular lymphocytic leukemia (LGL-L). Approximately 70% of human cancers including hematological malignancies and solid tumors exhibit increased levels of phosphorylated STAT3 (pSTAT3), a biomarker of pathway activation. In non-clinical studies, treatment with KT-333 resulted in durable tumor regressions with weekly (QW) or once every two weeks IV administration in STAT3-dependent T cell lymphomas. STAT3 degradation also sensitized immunocompetent mouse models of solid and liquid cancers to anti-PD1(ASH 2021, SITC 2021).
Methods: The ongoing open-label, Phase 1a/1b study is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary clinical activity of KT-333 administered as a QW IV infusion on Day 1, 8, 15 and 22 (28-day cycle) in patients (pts) with B- and T-cell lymphomas, Hodgkin's lymphoma and advanced solid tumors (ST) relapsed/refractory (R/R) to at least two prior systemic therapies and LGL-L and T-cell prolymphocytic leukemia R/R to at least one prior therapy. Cycle 1 and 2 blood samples are collected for KT-333 plasma concentrations and to measure changes in STAT3 protein expression in peripheral blood mononuclear cells (PBMCs) using targeted mass spectrometry. Whole blood RNA sequencing measures mRNA levels of STAT3 regulated targets. Plasma levels of inflammatory biomarkers are measured with Luminex. STAT3 degradation and other related biomarker changes in tumor are assessed in patients with accessible tumors. (NCT05225584).
Results: As of July 10, 2023, 21 pts were treated at five dose levels (DL) in Phase 1a with a mean number of 5.8 doses. Pts included B-cell non-Hodgkin's lymphoma (n=1: DL5), Hodgkin's lymphoma (HL) (n=1: DL4), CTCL (n=3: DL1, 2 and 4), PTCL (n=1: DL2), LGL-L (n=2: DL5) and ST (n=13: DL1-4) with median age of 61 years (range 30,77) and ECOG performance status of

0 (n=7) or 1 (n=14). No DLTs and no KT-333 related serious adverse events (SAE) were reported. The most common AEs were Grade 1 and 2 and included constipation, fatigue, nausea and anemia. Best response among pts evaluable for response at data cut-off (not including CTCL or HL pts at DL4 or any DL5 pts) included one partial response after two cycles in a CTCL pt at DL2 and SD after two cycles in three ST pts treated at DL3 and DL4. PD data in blood available for DL1-4 demonstrated robust, dose-dependent, and sustained STAT3 degradation in PBMC. The mean maximum degradation of STAT3 by targeted mass spectrometry over the first two weeks in Cycle 1 by DL was (% (range; n)): DL1: 69.9% (52.6% to 84.1%; n=4), DL2: 73.5% (65.5% to 80.7%; n=3), DL3: 79.9% (72.3% to 90.4 %; n=3) and DL4: 86.6% (78.9% to 95.9 %; n=4) with absolute quantification of STAT3 peptides falling below lower limit of quantification of the assay for one pt in DL3 and two in DL4. STAT3 pathway inhibition in blood was demonstrated via transcriptional downregulation of a canonical JAK/STAT3 target, *SOCS3*, which correlated with changes in STAT3 protein levels. KT-333 also resulted in dose-dependent downregulation of STAT3-regulated inflammatory biomarkers C-reactive protein and serum amyloid A protein in plasma. KT-333 demonstrated linear PK with plasma exposure increasing with dose and reaching levels close to those predicted to be efficacious.

Conclusion: The emerging clinical data demonstrate that KT-333 is a potent degrader of STAT3 as demonstrated in PBMCs at doses that are well tolerated. These data provide the first evidence of STAT3 targeted protein degradation in humans with associated STAT3 pathway inhibition, along with potential early signs of antitumor activity, highlighting the potential of heterobifunctional degraders for targeting previously undruggable transcription factors implicated in diseases. Based on non-clinical data and PK/PD modeling, the high levels of degradation achieved so far are expected to be clinically efficacious in STAT3-dependent malignancies. Accrual is ongoing, and analyses from additional patients will be presented at the meeting.

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