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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Preliminary Results from a Phase 1b/2 Open-Label, Multicenter, Dose Optimization Clinical Study of the Safety, Tolerability, and Pharmacokinetic (PK) and Pharmacodynamic (PD) Profiles of Cfi-400945 As a Single Agent or in Combination with Azacitidine in Patients (Pts) with Acute Myeloid Leukemia, Myelodysplastic Syndrome or Chronic Myelomonocytic Leukemia (TWT-202)

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Background: CFI-400945 is a potent, selective, orally administered, first-in-class inhibitor of the serine/threonine kinase Polo-like kinase 4 (PLK4), a unique Polo-like kinase family member, that is a conserved upstream regulator of centriole duplication. Dysregulation of PLK4 expression causes loss of centrosome numeral integrity, promotes genomic instability and also potentially enables cancer cells to tolerate genomic instability (Mason et al, Cancer Cell 2014). Its inhibition likely causes mitotic catastrophe. An investigator-initiated study (IIS) demonstrated clinical activity in relapsed/refractory AML with adverse cytogenetics. Dose limiting toxicity was colitis, sepsis and the RP2D 96 mg, three CR's (9 evaluable pts) across 2 dose levels were observed [Data on File, Murphy et al]. We report updated data on a company sponsored study (TWT-202; NCT04730258).
Study Design and Methods: TWT-202 is a study of CFI-400945 with 3+3 design in escalation and Simon 2 stage in expansion. For Part 1 (CFI-400945), pts with relapsed and/or refractory AML, MDS, or CMML after >1 prior therapy will be included. Pts with MDS or CMML must have progressed or no response after 4 cycles of hypomethylating agents. For Part 2, (CFI-400945 with azacitidine), pts should have relapsed and/or refractory AML, untreated MDS or CMML. Untreated pts ineligible for intensive therapy may be included. The maximum tolerated dose (MTD) is defined as the dose where dose-limiting toxicities (DLTs) are <1 out of 6 at or below the maximally administered dose. Pharmacokinetics (PK) and pharmacodynamic (PD) markers will be assessed.
Results: At 2May2023 cut, 26 pts were enrolled into Part 1. Eighteen (69%) pts had AML, 4 (15%) MDS, 4 (15%) CMML. The median number of prior therapies was 3 (range 1-8), 7 (27%) pts had received a previous stem cell transplant. Twenty (77%) were male, the median age 68 years (range 22, 85). Approximately 80% pts with AML were adverse risk by ELN 2022 criteria. Six pts with AML had TP53 mutations. At 21 days on/7 days off schedule, 5 pts received 32mg, 4 pts 48mg, 3 pts 64mg, 5 pts 80mg, 9 pts 96mg daily. The 28 days on/0 days off schedule was introduced at 96mg, 3 pts enrolled, with 0 DLTs to date. There was 1 DLT at 96mg on the 21/7 schedule (fungemia, gastroparesis, septic shock, enteritis). There have been 23 (89%) SAEs with the following occurring in >3 pts (febrile neutropenia (13 pts), sepsis (5 pts), diarrhea (4 pts), pneumonia (4 pts)). Common treatment emergent adverse events (TEAE) in > 5 pts, all grades, all doses; febrile neutropenia-15 pts (58%), nausea-11 pts (42%), diarrhea, vomiting-both 10pts (39%), hypokalemia- 9 pts (35%), dsypnea, hypophosphatemia-8pts each (31%), anemia-7pts (27%), and abdominal pain, fatigue, hypomagnesemia, pneumonia -6 pts each (23%). 31 % (33 events, 8 pts) ≥grade 3 TEAE's were considered related to CFI-400945 . Three pts (50%) with AML (all with prior venetoclax based therapies) at the 96mg dose level (21/7) from 6 evaluable achieved a response after 1 cycle. One pt (85M) with ELN2022 adverse genetics:

complex karyotype, TP53 mutation, achieved CRi, and remains in remission after 3 cycles. One pt (70M) with AML (ELN2022 adverse genetics, complex cytogenetics, TP53 mutation), 2 prior regimens, achieved an MLFS and is pending count recovery. Third pt (51M) had AML normal cytogenetics, ELN 2022 adverse genetics (RUNX1, IDH2, SRSF2), and had relapsed/refractory disease after 5 regimens. The pt achieved an MLFS, however medical complications not related to study drug resulted in dose reduction, therapy hold and subsequent relapse. Pharmacokinetic (PK) evaluations indicated mean terminal-life ranged from 7 - 12 hours. Low accumulation was observed after 21d (AR <2-fold). Exposure in this study is overlapped with that observed in the IIS (Data on File, Murphy et al) study. PD studies evaluating the effect of CFI-400945 on markers of mitosis, ploidy and centriole function are ongoing.

Conclusion: CFI-400945 has been generally well tolerated in this difficult to treat patient population, including patients whose disease progressed on or following venetoclax based therapies. Three of 6 evaluable patients with AML achieved a response (MLFS=2, CRi=1) at the 96mg dose. PK characteristics support daily dosing of CFI-400945 and PD studies are ongoing. Dose expansions are planned and a combination with azacitidine will open shortly.

Murphy et al, Data on File, PMCC
Mason et al Cancer Cell 26, 163-176

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