A Phase 1/2 Dose Escalation Study of the BCL-2 Inhibitor ZN-d5 and the WEE1 Inhibitor Azenosertib (ZN-c3) in Patients (Pts) With Acute Myeloid Leukemia (AML)

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BACKGROUND

• B-cell lymphoma 2 (BCL-2) is an anti-apoptotic protein and pathway inhibition combined with chemotherapy and/or targeted therapeutics has led to significant clinical benefit in pts with AML.1
• Disruption of cell cycle regulation may complement BCL-2 inhibition as many malignant cells are dependent on proteins that regulate cell cycle progression.2
• The cell cycle checkpoint protein, WEE1, is highly expressed in genomically unstable malignancies and inhibition of WEE1 induces tumor cell apoptosis.3,4
• It has been previously reported that the combination of ZN-d5 (an oral, selective BCL-2 inhibitor) and azenosertib (an oral, highly potent WEE1 inhibitor) synergistically enhance killing of AML cells both in vitro and in vivo, as well as in TP53-mutated models.5
• Based on this strong pre-clinical rationale, a Phase 1/2 study was designed to evaluate the novel combination of ZN-d5 and azenosertib in pts with relapsed/refractory (R/R) AML.

METHODS

Azenosertib (ZN-c3): A Novel, Selective, and Orally Bioavailable WEE1 Inhibitor

• WEE1 is a protein kinase that inhibits the activity of both CDK1 and CDK2 kinases and is involved in the regulation of G1/S, G2/M, and M phase cell cycle checkpoints.7 (Figure 1A)
  – WEE1 plays an important role during normal cell cycle progression but also in response to DNA damage and interacts with DNA damage response pathways.3
  – WEE1 inhibition causes cancer cells to proceed into mitosis without being able to repair damaged DNA, resulting in premature mitotic entry and apoptosis.5 (Figure 1B)
• WEE1 inhibition also increases replication stress by inducing aberrant firing of replication origins and depletion of nucleotide pools.6 (Figure 1B)

ZN-d5: A Potent BCL-2 Inhibitor Designed With Improved Selectivity for BCL-2

• The intrinsic apoptotic pathway is controlled by the BCL-2 protein family on the mitochondrial outer membrane.2,3
• BCL-2 inhibitors may restore the normal apoptosis process, making it an important target for cancer treatments (Figure 2)
• BH3 mimetics bind to BCL-2 proteins and displace pro-apoptotic factors to trigger apoptosis
• ZN-d5 is highly selective for BCL-2 over BCL-xL, resulting in reduced platelet toxicity in vitro

Mechanism of Action of BCL-2 Inhibitors

Study Design

• This phase 1/2 open-label study (ZN-d5-004C, NCT05682170) is determining the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetics (PK), and clinical activity of ZN-d5 + azenosertib in pts with AML (Figure 3)
• The phase 1 dose-escalation stage is based on a Bayesian Optimal Interval design
• Phase 2 is an open-label expansion to be conducted if supported by safety and efficacy data from the dose-escalation stage
• Prior to initiating dose-escalation for the ZN-d5 + azenosertib combination, an azenosertib monotherapy cohort is being enrolled, as it has not been previously administered to pts with hematologic malignancies.

Figure 3: ZN-d5-004C – Inhibition of BCL-2 and WEE1 in R/R AML: A Phase 1/2 Dose Escalation Study of the BCL-2 Inhibitor ZN-d5 and the WEE1 Inhibitor Azenosertib (ZN-c3) in Subjects with Relapsed or Refractory Acute Myeloid Leukemia

Study Endpoints

• Primary
  – Assess the safety and tolerability of ZN-d5 and azenosertib in combination and azenosertib monotherapy
  – Determine the MTD and RP2D for ZN-d5 and azenosertib in combination

• Secondary
  – Assess the activity of ZN-d5 and azenosertib in combination and azenosertib monotherapy
  – Characterize the PK of ZN-d5 and azenosertib in combination and the PK of azenosertib when administered as a monotherapy
  – Rate of and duration of remission (i.e., CR or PR)
  – Other relevant clinical endpoints

Patient Population

Key Inclusion Criteria

• Adults ≥ 18 years of age
• Histologically or cytologically confirmed AML, as defined by World Health Organization (WHO) 2016 revised criteria, including secondary and therapy-related AML
• Subjects must be relapsed or refractory to ≥3 prior lines of therapy which may include venetoclax-based regimens, induction chemotherapy, stem cell transplant, or salvage therapy
• Adequate organ function:
  – ALT and AST ≤3 × ULN (≤5 × ULN if leukemic disease in the liver)
  – Alkaline phosphatase ≤5 × ULN
  – Total bilirubin ≤1.5 × ULN (≤3 × ULN if Gilbert syndrome or if leukemia in the liver)
• WBC ≤20,000 mm−3 (30,000 mm−3 allowed if neutropenic
  – Platelet count ≥75,000 mm−3
• ECOG Performance Status 0-2
• Adequate renal function:
  – Creatinine clearance ≥60 ml/min
• Adequate bone marrow reserve:
  – ≥30% bone marrow blast in ≥1 marrow aspirate
• Adequate platelet reserve:
  – ≥100,000 mm−3 (≥75,000 mm−3 if neutropenia)
• Adequate lung function:
  – FEV1 ≥60% predicted
• Adequate cardiac function:
  – Left ventricular ejection fraction (LVEF) ≥50%

Key Exclusion Criteria

• Prior treatment with BCL-2 or WEE1 inhibitors
• Prior exposure to any investigational agent that interacts with the PK of ZN-d5 and/or azenosertib
• Significant co-morbidity
• Significant laboratory abnormality at baseline
• Presence of any active or serious infection
• Known or suspected human immunodeficiency virus (HIV) infection
• Active neoplastic disease (other than AML and/or chronic myeloid leukemia, CML)
• Significant abnormal laboratory test
• Significant cardiovascular disease

Study Sites

• This study is open and enrolling at 7 sites in the United States (Figure 4)

Figure 4: Currently Enrolling Study Site

REFERENCES

8. Mayo Clinic – Lankenau Cancer Center, Philadelphia, PA; 9Cancer Center - Froedtert Hospital, Milwaukee, WI; 10University of California, San Francisco, CA; 11MD Anderson Cancer Center, Houston, TX; 12University of Texas MD Anderson Cancer Center, Houston, TX