Phase 1/2 Study of Onvansertib, a PLK1 Inhibitor, in Combination with Decitabine in Patients with Relapsed or Refractory Acute Myeloid Leukemia

A.M. Zeidan, MBBS, MHS, J.J. Lin, MD, M.S. Rocker MD, PHD, G.I. Schiller, MD, P.A. Patel, MD, A.J. Spira, PHD, MD, FACCP, M.J. Tsai, MD, E. Samuels, BS, L.L. Silverman, MD, PHD, M. Ridgler, MD, M. Erlander, PHD, F.E. Wang, MD, PhD1
1-Vanderbilt University, Nashville, TN; 2-Vanderbilt University Medical Center; 3-Yale School of Medicine; 4-University of Texas MD Anderson Cancer Center, Houston, TX; 5-Johns Hopkins Medicine, Baltimore, MD; 6-Virginia Commonwealth University, Richmond, VA; 7-Medstar Washington Hospital Center, Washington, DC; 8-University of Minnesota, Minneapolis, MN; 9-CancerCare Oncology Group, Scottsdale, AZ; 10-Data Safety Monitoring Board, Atlanta, GA

Background

New Treatment Options are Needed for Patients with Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML)

• R/R AML patients have limited therapeutic options, especially in the absence of tangible treatment options for patients with k-ras mutations
• Outcomes are dismal for R/R AML patients; median overall survival <6 months

Onvansertib, an Oral, and Highly Selective, Potent PLK1 Inhibitor (1, 2), represents a Promising New Targeted Therapy for R/R AML

• PLK1 is a serine/threonine kinase, a master regulator of mitosis and assembly in AML
• Onvansertib is a third-generation PLK1 inhibitor with a half-life of ~24 hours
• In AML preclinical models, onvansertib demonstrated potent anti-tumor activity as a single agent and in combinations, including venetoclax-resistant models

Phase 1/2 Trial Design and Objectives

Study Design

• Study population: R/R AML with up to 3 prior lines of therapy (phase 1b) and 1 line of prior therapy (phase 2) or treatment-naive relapse patients not eligible for salvage therapy
• Treatment-related AML or APL are excluded
• Dosing schedule: Onvansertib starting dose 12 mg/m2, days 1 through 5 = 1 dose-level (20 mg/m2), days 1 through 5 in a 28-day cycle
• Phase 1 dose escalation (3+3 design) to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RPO2D)
• 10% incremental dose increase in successive cohorts of 3 patients
• Dose limiting toxicities (DLTs) evaluated during the 1st cycle
• Phase 2 expansion of the RPO2D on onvansertib

Study Objectives

• Primary Objectives:
  - Phase 1b: Assess safety to identify DLTs and determine the MTD or RPO2D
  - Phase 2: Assess safety, tolerability and anti-leukemic activity of the RPO2D

• Secondary Objectives (Phase 1b/2):
  - Analyze pharmacodynamics
  - Evaluate predictive biomarkers associated with response to treatment
  - Assess target engagement in circulating leukemic cells

Patient Enrollment and Baseline Characteristics

Enrollment as of February 19, 2020

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<th>Dose Level</th>
<th>Eligible Patients</th>
<th>Dose Escalation</th>
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Clinical Course of Phase 1b/2 patients

| Phase 1b/2 patients | Clinical Response | CR/CRi | PR | MR | CR/CRi

| Phase 1b/2 patients | Phase 1b (n=23) | Phase 2 (n=13) | CR/CRi | PR | MR | CR/CRi

| Phase 1b/2 patients | Phase 1b (n=23) | Phase 2 (n=13) | CR/CRi | PR | MR | CR/CRi

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Safety

All-Causality-Treatment-Related Adverse Events Reported in ≥10% patients (n=10, patients)

| Grade 1 | Grade 2 | Grade 3 | Grade 4 | Toxicity

| Grade 1 | Grade 2 | Grade 3 | Grade 4 | Toxicity

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| Grade 1 | Grade 2 | Grade 3 | Grade 4 | Toxicity

Target Engagement in Circulating Blasts is Associated with Decrease in Bone Marrow Blasts

• Translational control tumor biomarkers (CTB) of the subfamily of PUS and phosphorylated TCF7 were identified as a specific marker for PLK1 activity in vivo in preclinical models
• pTC7/TCP7 was assessed by capillary Western blot in monoclonal cells isolated from blood samples collected on Day 1 before treatment and 3h post-dose in patients with circulating blasts

• Phase 1 identified correlations between target engagement and decreased bone marrow blasts
• Phase 2 confirmed correlations between target engagement and decreased bone marrow blasts

Biomarker Analyses

| Phase 1b/2 patients | Phase 1b (n=23) | Phase 2 (n=13) | CR/CRi | PR | MR | CR/CRi

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| Phase 1b/2 patients | Phase 1b (n=23) | Phase 2 (n=13) | CR/CRi | PR | MR | CR/CRi

Conclusions

• Onvansertib in combination with decitabine was well tolerated
• MTD was established at 60 mg/m2 with no DLT through this dose
• MTD-related toxicities were primarily hematological; skin toxicities were observed at higher onvansertib doses
• Anti-leukemic activity was observed
• A wide range of onvansertib doses (27 to 50 mg/m2)
• Phase 1b/2 CRi rate was 34% through all doses and 10% at the 4 higher dose levels (27 – 40 mg/m2)

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