



Cyclacel's CYC065 and Venetoclax Demonstrate Therapeutic Potential and Anticancer Activity in Acute Myeloid and Chronic Lymphocytic Leukemias

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CYC065-venetoclax combination was well tolerated in AML and CLL dose escalation studies

BERKELEY HEIGHTS, N.J., Dec. 09, 2019 (GLOBE NEWSWIRE) -- Cyclacel Pharmaceuticals, Inc. (NASDAQ: CYCC, NASDAQ: CYCCP) ("Cyclacel" or the "Company"), a biopharmaceutical company developing innovative medicines based on cancer biology, today announced study design and preliminary data from two of the Company's Phase 1 studies evaluating a combination of CYC065, a CDK2/9 inhibitor, with venetoclax, a BCL2 inhibitor, to treat patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) and chronic lymphocytic leukemia (CLL) respectively. The data were presented on Saturday December 7, 2019 at poster presentations during the 61st American Society of Hematology Annual Meeting and Exposition in Orlando, Florida.

"We are excited to report initial data from our ongoing clinical evaluation of the combination regimen of CYC065 and venetoclax in patients with advanced leukemias," said Spiro Rombotis, President and Chief Executive Officer of Cyclacel. "The rationale behind these two dose escalation studies is to investigate a 'dual hit' strategy of simultaneously suppressing MCL1 and BCL2 proteins. Suppression of these 'pro-survival' proteins is thought to enable apoptosis in cancer cells that have become resistant to previous treatment. Preliminary evidence suggests that the combination is active and well tolerated. Our clinical program seeks to translate preclinical evidence of synergy with the combination to benefit patients with relapsed or refractory diseases."

The CYC065-venetoclax combination was well tolerated and no dose-limiting toxicities have been reported. No tumor lysis syndrome was observed. Three of nine patients with R/R AML/MDS enrolled in CYC065-03 at doses from 64 to 150mg/m² achieved decreases in leukemia blast cells in their peripheral blood as reported by investigators. The first two R/R CLL patients enrolled in CYC065-02 both failed ibrutinib and one also failed CAR-T cell treatment. Both patients achieved shrinkage of enlarged lymph nodes by CT scan on the combination of venetoclax and CYC065 dosed once every two weeks at 64mg/m². The patient who failed CAR-T cell therapy was MRD negative on the combination.

CYC065 dosed once every three weeks has demonstrated durable suppression of MCL1 in part 1 of a Phase 1 study in a majority of solid tumor patients treated at the recommended Phase 2 dose (RP2D). In the ongoing part 2 of the same study CYC065 is dosed four times every three weeks. One patient with MCL1 amplified endometrial cancer has achieved a radiographically confirmed partial response (PR) and a patient with cyclin E amplified ovarian cancer has achieved shrinkage of target tumor lesions of 20% after treatment with CYC065 as a single agent.

The combination of CYC065 and venetoclax has demonstrated preclinical synergy in both AML and CLL (including 17p deleted) models. In AML/MDS upregulation of MCL1 is associated with resistance to chemotherapy and/or venetoclax. In CLL upregulation of MCL1 is thought to be an escape mechanism for venetoclax treated cells.

Phase 1 CYC065-02 Study Details ([NCT03739554](#))

This ongoing clinical study is investigating a combination of CYC065 with venetoclax in patients with relapsed/refractory CLL. CYC065 is being administered intravenously via four-hour infusion on days 1 and 15 in combination with daily oral venetoclax. Initial dose escalation is 33% and 25% upon occurrence of the first dose limiting toxicity (DLT). The primary objective is determination of RP2D defined as the highest dose level at which less than one-third of at least six patients experience a DLT during the first treatment cycle. Treatment will continue until progression of disease, unacceptable toxicity or changes in patient condition that renders patients ineligible for further treatment. Laboratory tests and CT scans will be performed regularly to assess response according to standard criteria.

Phase 1 CYC065-03 Study Details ([NCT04017546](#))

This ongoing clinical study is investigating a combination of CYC065 with venetoclax in patients with relapsed/refractory AML or MDS. CYC065 is being administered intravenously via four-hour infusion on days 1 and 15 in combination with daily venetoclax on days 1 to 15. Initial dose escalation is 33% and 25% upon occurrence of the first dose limiting toxicity (DLT). The primary objective is determination of RP2D defined as the highest dose level at which less than one-third of at least six patients

experience a DLT during the first treatment cycle. Treatment will continue until progression of disease, unacceptable toxicity or changes in patient condition that renders patients ineligible for further treatment. Laboratory tests and bone marrow aspirate/biopsy will be performed to assess response according to standard criteria.

Cyclacel's Presentations Details at ASH 2019

Title: A Phase I Study Combining CDK2/9 Inhibitor CYC065 with Venetoclax, a BCL2 Inhibitor, to Treat Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

Session Name: 642. CLL: Therapy, excluding Transplantation: Poster I

Publication Number: 1761

Title: Combining CDK2/9 Inhibitor CYC065 with Venetoclax, a BCL2 Inhibitor, to Treat Patients with Relapsed or Refractory AML or MDS

Session Name: 616. Acute Myeloid Leukemia: Novel Therapy, excluding Transplantation: Poster I

Publication Number: 1379

Title: An Oral Combination Study of Novel Nucleoside Analogue Sapacitabine and BCL2 Inhibitor Venetoclax to Treat Patients with Relapsed or Refractory AML or MDS

Session Name: Acute Myeloid Leukemia: Novel Therapy, excluding Transplantation: Poster III

Publication Number: 3926

About CYC065

Cyclin dependent kinases (CDKs) are critical for cell cycle regulation and transcriptional elongation. Dysregulated CDKs have been linked to the cancer hallmarks of uncontrolled proliferation and increased survival. CYC065 is a potent, orally- and intravenously-available inhibitor of CDK2 and CDK9. CDK9 regulates transcription of genes through phosphorylation of RNA polymerase II (RNAP II) C-terminal domain (CTD). Through inhibition of CDK9, CYC065 suppresses CDK9-dependent gene expression and reduces the level of MCL1, a key anti-apoptotic protein.

CYC065 is in an ongoing Phase 1, first-in-human study in patients with advanced solid tumors. In this study, target engagement and durable suppression of the MCL1 biomarker were observed after a single dose of CYC065. Tumor shrinkage and stable disease were observed in five patients with MCL1-, MYC- or cyclin E-amplified advanced cancers treated at the recommended phase 2 dose. In part 2 of the study evaluating a more intensive dosing regimen, a confirmed partial response has been observed in a heavily pretreated patient with MCL1-amplified endometrial cancer. An oral formulation is being evaluated in part 3 of the study. CYC065 is also being evaluated in Phase 1 studies in combination with venetoclax in relapsed or refractory CLL and in relapsed or refractory AML or MDS. Preclinical data suggest that CYC065 may benefit patients with adult and pediatric hematological malignancies such as CLL, AML, ALL, B-cell lymphomas, multiple myeloma and certain cyclin E-addicted or MYC-amplified solid tumors, including HER2+ breast cancer, uterine serous carcinoma and neuroblastoma.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel Pharmaceuticals is a clinical-stage biopharmaceutical company developing innovative cancer medicines based on cell cycle, transcriptional regulation and DNA damage response biology. The transcriptional regulation program is evaluating CYC065 as a single agent in solid tumors and in combination with venetoclax in patients with relapsed or refractory CLL and AML/MDS. The DNA damage response program is evaluating an oral combination regimen of sapacitabine and venetoclax in patients with relapsed or refractory AML/MDS. An IST is evaluating an oral combination regimen of sapacitabine and olaparib in patients with BRCA mutant breast cancer. The anti-mitotic program is evaluating CYC140, a PLK1 inhibitor, in AML/MDS patients. Cyclacel's strategy is to build a diversified biopharmaceutical business focused in hematology and oncology based on a pipeline of novel drug candidates. For additional information, please visit www.cyclacel.com.

Forward-looking Statements

This news release contains certain forward-looking statements that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, the efficacy, safety and intended utilization of Cyclacel's product candidates, the conduct and results of future clinical trials, plans regarding regulatory filings, future research and clinical trials and plans regarding partnering activities. Factors that may cause actual results to differ materially include the risk that product candidates that appeared promising in early research and clinical trials do not demonstrate safety and/or efficacy in larger-scale or later clinical trials, trials may have difficulty enrolling, Cyclacel may not obtain approval to market its product candidates, the risks associated with reliance on outside financing to meet capital requirements, and the risks associated with reliance on collaborative partners for further clinical trials, development and commercialization of product candidates. You are urged to consider statements that include the words "may," "will," "would," "could," "should," "believes," "estimates," "projects," "potential," "expects," "plans," "anticipates," "intends," "continues," "forecast," "designed," "goal," or the negative of those words or other comparable words to be uncertain and forward-looking. For a further list and description of the risks and uncertainties the

Company faces, please refer to our most recent Annual Report on Form 10-K and other periodic and other filings we file with the Securities and Exchange Commission and are available at www.sec.gov. Such forward-looking statements are current only as of the date they are made, and we assume no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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