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

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BACKGROUND
AML and MDS occur primarily in older patients.
• No effective therapies for persistent or progressive disease after standard chemotherapy and hypomethylating agents (HMA).
• Disruptive mutations in MCL1, a key anti-apoptotic protein in BCL2 family, is essential for development and sustained growth in AML (Gislon SP et al, Genes and Development, 2012)
• Suppression of both BCL2 and MCL1 likely more beneficial than individual inhibition (Macay C et al, AACR-NCI-EORTC 2015 Abs R182)

VENETOCLAX COMBINATION IN AML

DOSING SCHEDULE AND ESCALATION

VENTOCXAN COMBINATION (CYC065-03): OBJECTIVES

ELIGIBILITY CRITERIA

Key Inclusion Criteria:
• Relapsed or refractory AML and MDS with ≥10% blasts in bone marrow or peripheral blood
• Total bilirubin ≤ 1.5 x ULN, ALT ≤ 2.5 x ULN
• Creatinine ≤ 1.5 x ULN or creatinine clearance > 60 mL/minute (Cockcroft formula)
• At least 2 weeks from prior chemotherapy, radiation therapy, major surgery, or other investigational anticancer therapy

Key Exclusion Criteria:
• AML or extramedullary myeloid tumor without bone marrow involvement

DOSE LIMITING TOXICITY DEFINITION

Maximum Tolerated Dose (MTD) = RP2D: Dose level at which less than one-third of at least 6 pts experienced a DLT during first treatment cycle

FUTURE DIRECTIONS

Plan to open a second part using a more dose-intense schedule
Exploratory study of biomarkers that may predict response

ENROLLMENT
At least 6 patients will be treated at (recommended phase 2 dose) RP2D

64 (n=2)
• AML: Assistincte, decitabine, venetoclax, gemcitabine, carmustine, cladribine, low dose ara-C
• Pre by MDS: Assistincte, decitabine, venetoclax, gemcitabine, carmustine, cladribine, low dose ara-C
• Pre by MDS: Fludarabine/gemcitabine, ansamitocin, decitabine, venetoclax, fludarabine
• Pre by MDS: Decitabine/gemcitabine, ansamitocin/venetoclax

85 (n=3)
• De novo: Fludarabine/gemcitabine, ansamitocin, decitabine, venetoclax, fludarabine
• De novo: Ans/C/daunorubicin, cladribine, decitabine, 1st transplant, decitabine/venetoclax, 2nd transplant, decitabine/venetoclax
• De novo: Ans/C/daunorubicin, cladribine, decitabine, 1st transplant, decitabine/venetoclax, fludarabine
• De novo: Ans/C/daunorubicin, cladribine, decitabine, 2nd transplant, venetoclax, fludarabine

113 (n=2)
• De novo: Ans/C/daunorubicin, cladribine, decitabine, 1st transplant, decitabine/venetoclax, 2nd transplant, decitabine/venetoclax
• De novo: Decitabine/gemcitabine, ansamitocin/
venetoclax, fludarabine
• De novo: Decitabine/gemcitabine, ansamitocin/venetoclax

150 (n=2)
• De novo: Ans/C/daunorubicin, cladribine, 1st transplant, decitabine/venetoclax, 2nd transplant, decitabine/venetoclax, venetoclax 40 mg/m2/day for 3 days/week
• De novo: Ans/C/daunorubicin, cladribine, decitabine/venetoclax, ansamitocin/venetoclax
• De novo: Ans/C/daunorubicin, cladribine, decitabine/venetoclax

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