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

BACKGROUND
Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults.

The primary abnormality in CLL is a defect in apoptosis (Kitada S et al., Blood, 1998).

- CLL depends upon the overexpression of anti-apoptotic proteins (MCL1, BCL2) for survival.

Venetoclax (ABT-199), a BCL2 inhibitor, is one of the most active agents against CLL. However, upregulation of MCL1 is associated with resistance to venetoclax (Oppermann J et al., Blood 2016).

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**CYC065-01 (PART 1): CLINICAL RESPONSE**

- **Part 1**: Efficacy in solid tumors (single agent, first-in-human).

  - Part 1 (i.e. BSA based) completed; RP2D is 192 mg/m².

  - 5/13 had SD with measurable target lesion shrinkage including 3 SDs lasting 6 to 10 cycles.

  - 11/13 dosed at RP2D had durable suppression of MCL1.

  - 19% and 1 SD with 19% target lesion shrinkage.

  - Part 3 (oral flat dose) ongoing at 150 mg once daily on Day 1, 2, 8 and 9 every 3 weeks.

**CYC065 IN SOLID TUMOR PATIENTS**

- CYC065 is a potent inhibitor of CDK2 and CDK9.

- In vitro kinase potency (IC₅₀): CDK2 = 5 nM, CDK9 = 26 nM.

- Cellular activity: Av. IC₅₀ = 0.35 μM.

- CDK9 regulates gene transcription through phosphorylation of RNA Pol II.

- CDK9 inhibition blocks new mRNA transcription leading to the loss of MCL1, a key anti-apoptotic protein.

- CDK2 inhibition increases MCL1 protein degradation.

- CYC065 is currently in phase 1 studies in solid tumors, CLL, AML, and MDS.

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**CYC065 AND VENETOCLAX COMBINATION IN CLL**

- **ABT-199**

  - CYC065 inhibits CDK9-driven transcription - depletes the intrinsically short-lived anti-apoptotic protein MCL1 and induces apoptosis in CL cells regardless of prognostic factors and treatment history (Chen et al., AACR 2010 and 2018).


- Tumor microenvironment → MCL1 diminishing venetoclax effect (Smith et al., Blood 2007; Oppermann et al., Blood 2016). A-MCL1 overcomes venetoclax resistance in stimulated CLL (Smith et al., Blood 2007).

**TREATMENT SCHEMA**

- One to 6 patients will be entered at a given CYC065 dose level.

- Maximum Tolerated Dose (MTD) = RP2D: dose level at which less than one-third experiences DLT.

- 33% dose escalation until 1/3 experiences DLT.

- 25% dose escalation after first DLT.

- At least 6 patients will be treated at RP2D.

**ENROLLMENT**

- Two patients dosed at 64 mg/m².

- Both had prior treatment with BTK inhibitor.

- One patient also had anti-C20 antibodies, CAR T cell therapy.

- Best responses were SD with some shrinkage of lymphadenopathy.

- One patient had negative MRD in peripheral blood after 5 cycles.

**FUTURE DIRECTIONS**

- Plan to include patients who have positive MRD after a venetoclax-based regimen.

- Plan to open a second part using a more dose intense schedule.

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**REFERENCES**

- Smith et al., AACR 2018 Abs CT037.

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