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

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BACKGROUND

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

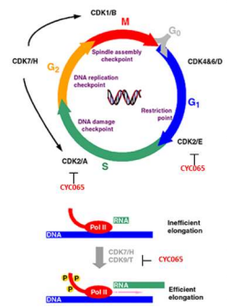
The primary abnormality in CLL is a defect in apoptosis (Kitada S *et al*., Blood, 1998)

- 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 S *et al*., Blood, 2016)

Pharmacological suppression of MCL1 alone or in combination with venetoclax may improve the outcome of this disease

CYC065 – A NOVEL CDK2/9 INHIBITOR



CYC065 is a potent inhibitor of CDK2 and CDK9

- *In vitro* kinase potency (IC_{50}) :

  CDK2 = 5 nM

  CDK9 = 26 nM

- Cellular activity: Av. IC_{50} = 0.35 µM

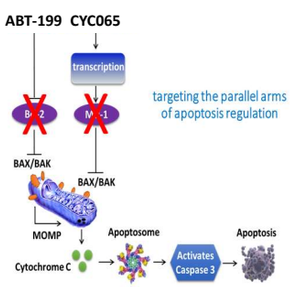
CDK9 regulates gene transcription through phosphorylation of RNA Pol II

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

CDK2 inhibition increases MCL1 protein degradation

Currently in phase 1 studies in solid tumors, CLL, AML and MDS

CYC065 AND VENETOCLAX COMBINATION IN CLL



targeting the parallel arms of apoptosis regulation

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

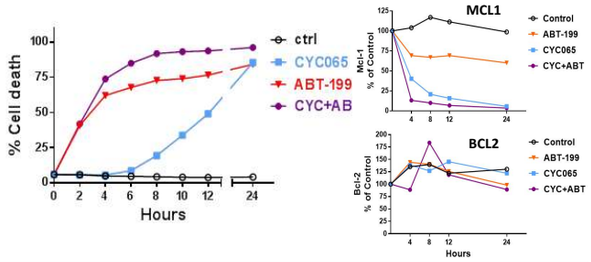
Venetoclax approved for treatment of CLL:

- ORR: 71-79%; CR: ~20% (R/R CLL with 17p del) (Roberts *et al.*, CCR 2016)

Tumor microenvironment ↑ MCL1 diminishing venetoclax effect (Smith *et al.*, Blood 2007; Oppermann *et al.*, Blood 2016)

↓MCL1 overcomes venetoclax resistance in stimulated CLL (Smith *et al.*, Blood 2007)

CYC065 DECREASES MCL1 AND INCREASES EFFICACY OF VENETOCLAX AGAINST PRIMARY CLL

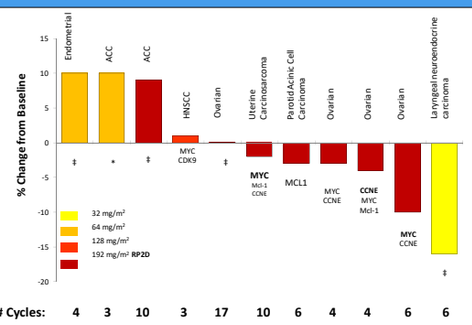


CYC065 IN SOLID TUMOR PATIENTS

CYC065-01: Single agent, First-in-Human

- Part 1 (i.v. BSA based) completed; RP2D is 192 mg/m^2 by 4–hour infusion once every 3 weeks
  - CYC065 exposure increases with dose; half-life 1.6 to 3.9 hours
  - 11/13 dosed at RP2D had durable suppression of MCL1
  - 5/13 had SD with measurable target lesion shrinkage including 3 SDs lasting 6 and 10 cycles
- Part 2 (i.v. flat dose) ongoing at 213 mg by 1 hour infusion on Day 1, 2, 8 and 9 every 3 weeks
  - 1 PR 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

CYC065-01 (PART 1): CLINICAL RESPONSE



# Cycles:	4	3	10	3	17	10	6	4	4	6	6

‡ no information. * complex deletions/gains. High copy gains shown in bold. Do KT et al., AACR 2018 Abs CT037.

CYC065-VENETOCLAX COMBINATION (CYC065-02): OBJECTIVES

Primary

- Determine maximum tolerated dose (MTD) of CYC065 administered in combination with venetoclax

Secondary

- Evaluate pharmacokinetics
- Assess pharmacodynamic markers (RNA Pol II CTD P-Ser2 and MCL1 levels in PBMCs)
- Document preliminary evidence of antitumor activity

ELIGIBILITY CRITERIA

Key Inclusion Criteria:

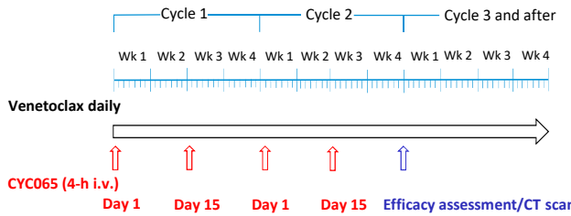
- CLL relapsed or refractory to standard treatment(s) including those with Richter transformation
- On stable dose of venetoclax for at least one week after completing ramp-up phase
- Hemoglobin ≥ 8.0 mg/dL, absolute neutrophil count (ANC) ≥ 750/µL, platelets ≥ 50,000 µL
- Total bilirubin ≤ 1.5 x ULN, ALT ≤ 1.5 x ULN
- Creatinine ≤ 1.5 x ULN or creatinine clearance > 60 mL/minute (Cockcroft formula)

DOSE LIMITING TOXICITY DEFINITION

- Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
- Other Grade 3/4 non-hematological toxicity with exception of alopecia
- Grade 4 anemia
- Neutropenic fever or Grade 4 neutropenia lasting longer than 7 days
- Grade 3 thrombocytopenia associated with bleeding or Grade 4 thrombocytopenia
- Treatment delay > 2 weeks due to adverse events that are definitely, probably or possibly related to CYC065

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

TREATMENT SCHEMA



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

Starting dose: 64 mg/m^2

33% dose escalation until 1/3 experiences DLT

25% dose escalation after first DLT

At least 6 patients will be treated at RP2D

ENROLLMENT

3 sites open

Two patients dosed at 64 mg/m^2

- Both had prior treatment with BTK inhibitor
- One patient also had anti-CD20 antibodies, CAR T cell therapy
- Best responses are 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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