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

Gautam Borthakur[1], Tapan M. Kadia[1], Hind Al Azzawi[1], Daniella Zheleva[2], David Blake[2], Judy Chiao[2]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX and [2]Cyclacel Ltd, Dundee, Scotland, UK

BACKGROUND

AML and MDS occur primarily in older patients

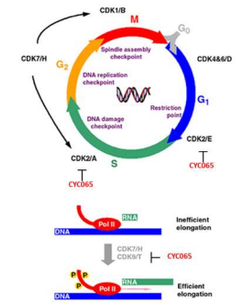
- No effective therapies for persistent or progressive disease after standard chemotherapy and hypomethylating agents (HMA)

Dysregulated apoptosis plays a central role in disease progression and drug resistance

- Anti-apoptotic proteins are upregulated in advanced MDS
- MCL1, key anti-apoptotic protein in BCL2 family, is essential for development and sustained growth in AML (Glaser SP *et al.*, Genes and Development, 2012)
- Upregulation of MCL1 is associated with resistance to chemotherapy and venetoclax (Pan R *et al.*, Blood, 2015; Li X *et al.*, Oncotargets and Therapy, 2019)

Pharmacological suppression of MCL1 alone or combination with venetoclax and chemotherapy may improve outcomes

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

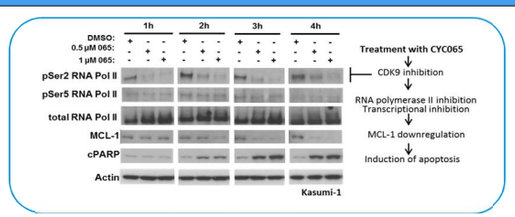
CDK9 regulates gene transcription through phosphorylation of RNA Pol II

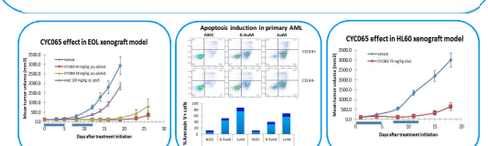
- CDK9 inhibition blocks new mRNA transcription leading to loss of MCL1 anti-apoptotic protein

CDK2 inhibition increases MCL1 protein degradation

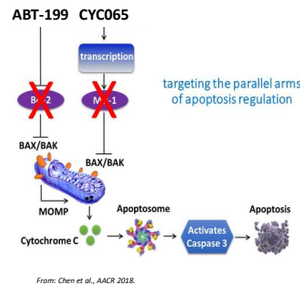
Currently in phase 1 studies in solid tumors, CLL, AML and MDS

CYC065 DEMONSTRATED POTENT ANTI-TUMOR EFFECT IN AML MODELS





CYC065 AND VENETOCLAX COMBINATION IN AML



From: Chen et al., AACR 2018.

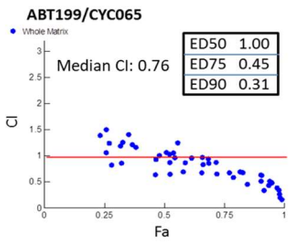
Venetoclax (ABT-199) has modest single agent activity in AML

- MCL1 dependence correlates with resistance to venetoclax (Konopleva M *et al.*, Cancer Discovery, 2016)

Preclinical study demonstrated synergy of CYC065 and venetoclax

- Suppression of both BCL2 and MCL1 likely more beneficial than individual inhibition (MacKay C *et al.*, AACR-NCI-EORTC 2015 Abs B182)

CYC065 AND VENETOCLAX COMBINATION SYNERGISTIC IN AML



Combination Index (CI) values: <1 indicates synergy; <0.3 strong synergy (Chou & Talalay, Cancer Res. 2010)

Preclinical Example:
(Saladino C *et al.*, AACR 2015, Abs 1650)

THP-1 cells treated with 7 x 7 concentration matrix for 72 h

Top concentration:

- CYC065 0.8 µM (1:1.2 dilution)
- ABT-199 0.5 µM (1:2 dilution)

Cell viability by Alamar Blue assay

CYC065 and ABT-199 were synergistic in all leukemia cell lines tested – AML (THP-1 & HEL) and ALL (Jurkat & SEM)

Similar results using 6 h concomitant pulse treatment

Please visit Abstract 3938 (Chantkran W et al.) for further studies on CYC065 and venetoclax combination in AML models

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

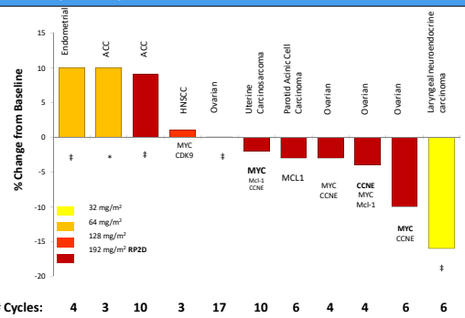
- CYC065 exposure increases with dose; half-life 1.6 to 3.9 hours
- 11/13 dosed at RP2D had durable suppression of MCL1
- 5/13 had SD with measurable target lesion shrinkage including 3 SDs lasting 6 and 10 cycles

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



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

CYC065-VENETOCLAX COMBINATION (CYC065-03): OBJECTIVES

Primary

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

Secondary

- Evaluate pharmacokinetics of CYC065 and venetoclax
- Assess pharmacodynamic markers (RNA Pol II CTD P-Ser2 and MCL1 levels in PBMCs)
- Document evidence of antitumor activity

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:

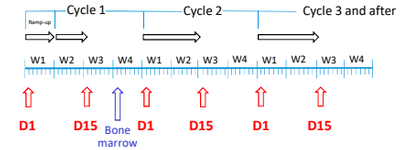
- APL or extramedullary myeloid tumor without bone marrow involvement

DOSE LIMITING TOXICITY DEFINITION

- Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
- Other Grade 3/4 non-hematological toxicity with the exception of alopecia
- Pancytopenia with a hypocellular bone marrow (≤ 5% cellularity) and no evidence of leukemia, lasting longer than 42 days

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

DOSING SCHEDULE AND ESCALATION



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 (recommended phase 2 dose) RP2D

ENROLLMENT

Dose Level (mg/m^2)	AML Type	Prior Therapies	Cycles Received
64 (n=2)	Pre by MDS	Azacitidine	2
	Pre by MDS	Azacitidine, decitabine, venetoclax, gemtuzumab ozogamicin, glasdegib, low dose ara-C	2 (>50% ↓ peripheral blasts)
85 (n=3)	Pre by MDS	Fludarabine/ara-C/venetoclax , azacitidine, decitabine/venetoclax	2
	Pre by MDS	Decitabine/gemtuzumab ozogamicin/venetoclax	1
	De novo	Fludarabine/ara-C/idarubicin, 1st transplant, 2nd transplant, azacitidine/venetoclax, fludarabine/ara-C	1 (>50% ↓ peripheral blasts)
113 (n=2)	De novo	Ara-C/idarubicin, clofarabine/cladribine, 1st transplant, decitabine/venetoclax, 2nd transplant, azacitidine/venetoclax	1
	De novo	FLAG-IDAC, 1st transplant, azacitidine, decitabine, 2nd transplant, azacitidine/venetoclax, MCL1 inhibitor	2 (ongoing) (30% ↓ peripheral blasts)
150 (n=2)	De novo	Ara-C/idarubicin, Allo BMT, decitabine/venetoclax, azacitidine/venetoclax	1 (ongoing)
	De novo	AraC/idarubicin/nivolumab, 1st transplant, decitabine/venetoclax, 2nd transplant, quizartinib/venetoclax, cladribine/low dose ara-C/giltertinib, fludarabine/ ara-C, AMG-427	1 (ongoing)

FUTURE DIRECTIONS

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

Exploratory study of biomarkers that may predict response

Abstract #1379, Annual Meeting of the American Society of Hematology, December 7-10, 2019, Orlando, Florida. Poster contains interim data (unaudited) of ongoing study as of November 2019. Supported by Cyclacel Ltd, Dundee, Scotland, UK. Conflict of interest disclosure: [3] Cyclacel employees.