

CYC065

WINTER 2019-20 Transcriptional Regulation CDK2/9 Inhibitor Program

CYC065¹ is a highly-selective, orally- and intravenously-available, 2nd generation inhibitor of cyclin dependent kinases (CDK) 2 and 9. Translational biology supports development as a stratified medicine for cancers dependent on MCL1, CDK2/cyclin E and MYC for proliferation, survival and resistance to treatment. Preclinical data suggest that CYC065 may benefit patients with adult and pediatric hematological malignancies such as AML, ALL, B-cell lymphomas, CLL, multiple myeloma and, certain cyclin E-addicted and MYC-amplified tumors, such as HER2+ breast cancer, uterine serous carcinoma and neuroblastoma. In a Phase 1 study durable target engagement and suppression of the MCL1 biomarker were observed after a single dose of CYC065. In a more frequent dosing schedule partial response has been achieved in a patient with MCL1 amplified endometrial cancer and stable disease with 29% shrinkage in a patient with cyclin E amplified ovarian cancer.

Mechanism of Action

CDK enzymes act as cell cycle regulators and play pivotal roles in regulation of transcription, DNA repair and metastatic spread. Dysregulated CDKs targeted by CYC065 can drive particular cancer subtypes:

- CDK2 is a driver of cell cycle transition and when dysregulated enabler of G1 checkpoint bypass;
- CDK9 is an effector of dysregulated transcription of certain genes (incl. cyclins, MCL1, MYC) through phosphorylation of RNA polymerase II.

Overexpression of MCL1 has been shown to aid in evasion of chemotherapy and/or targeted agents in cancer cells, including inhibitors of other members of the anti-apoptotic BCL2 family, such as venetoclax (ABT-199, Venclexta®, AbbVie). CYC065 suppresses MCL1 expression via inhibition of CDK9.

CYC065 clinical trials in progress

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| • Dose escalation study, part 1; i.v.; in solid tumors (Completed) | Ph1 |
| • Dose escalation study, part 2, i.v., frequent dosing; in solid tumors | Ph1 |
| • Dose escalation study, part 3; oral; in solid tumors | Ph1 |
| • In combination with venetoclax in R/R CLL | Ph1 |
| • In combination with venetoclax in R/R AML/MDS | Ph1 |

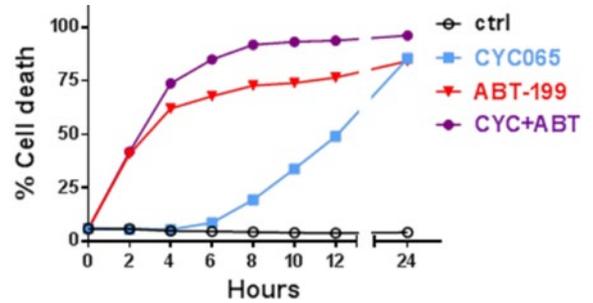


Figure 1: Synergistic cell killing activity of CYC065 and ABT-199 (venetoclax) in primary CLL model²

There is a clear biological rationale for a combination approach to simultaneously suppress BCL2 and MCL1. Preclinical data in CLL models, including 17p deleted models, support this premise showing prolonged downregulation of MCL1 and potent apoptosis induction.²

Competitive Positioning

Based on preclinical and early clinical data CYC065 offers an improved therapeutic window and lower myelosuppressive potential than pan-CDK inhibitors.

Three recently approved CDK4/6 inhibitors have validated the class and cell cycle inhibition strategies. Palbociclib (Ibrance®, Pfizer), constitutes an important therapeutic advance, causing prolonged cell cycle arrest and senescence in combination with endocrine therapy (ET) in ER+/HER2- breast cancer. Recent data confirmed cyclin E as a marker of resistance in these patients and CDK2 as the key kinase responsible for escape.³ Addition of CYC065 to this regimen may enhance durability of palbociclib + ET treatment outcome in these patients. In contrast to CDK2/9 inhibition by CYC065, CDK4/6 inhibition has not been shown to modulate MCL1.

CDK9 inhibition induces apoptotic tumor cell death through transcriptional downregulation of cancer cell survival pathway proteins, including MCL1. CDK2 inhibition enhances cell cycle arrest and may overcome cyclin E dependent resistance to CDK4/6 inhibitors.⁴

MCL1 dependent cancers

MCL1 is overexpressed in many cancers. Knockdown of MCL1 leads to cancer cell death and resensitization to drug treatment.⁵ CLL and AML cell survival depends on the expression of anti-apoptotic proteins, including MCL1, BCL2 and others.

Targeting MCL1 and/or BCL2 releases pro-death signals and commits leukemia cells to apoptosis. MCL1 expression can modulate resistance to BCL2 and is known to be upregulated in lymph node CLL cells, possibly leading to resistance to venetoclax.

Durable MCL1 suppression was shown in the majority of

patients treated at RP2D. Stable disease was observed in 6 patients with MCL1 overexpression, or cyclin E or MYC amplification. The best response was prolonged stable disease for about one year.

Rapid and complete cell death was induced in CLL and multiple myeloma cell lines after short exposure to CYC065 in the presence of stromal cells which confer protection from standard treatments.^{6,7} Consistent with the pro-apoptotic mechanism of CYC065, MCL1 down-regulation was observed. CYC065 synergizes with venetoclax in preclinical models at clinically achievable concentrations, supporting clinical investigation of combination regimens of CYC065 and venetoclax.^{8,9,10}

Drug resistance in AML has been attributed among others to high levels of MCL1. AML cell lines are highly sensitive to CYC065¹⁰. CYC065 has single agent activity in AML xenografts and the potential to be combined with approved AML therapies. In leukemia cells harboring the rearranged Mixed Lineage Leukemia gene (MLLr), CYC065 reduced both MCL1 expression and CDK9 dependent transcription of MLL-regulated leukemogenic genes.¹¹

MYC-addicted cancers

MYC proto-oncogenes encode MYC family proteins which are overexpressed in over 50% of human cancers often via gene amplification. MYC proteins are transcriptional regulators which promote cancer cell growth and survival by increasing the expression of target genes involved in cell metabolism and growth. MYCN gene amplification is found in 45% of high-risk neuroblastomas (NB), a childhood cancer with <10% long term survival. CDK9 mediates transcriptional regulation of MYCN.

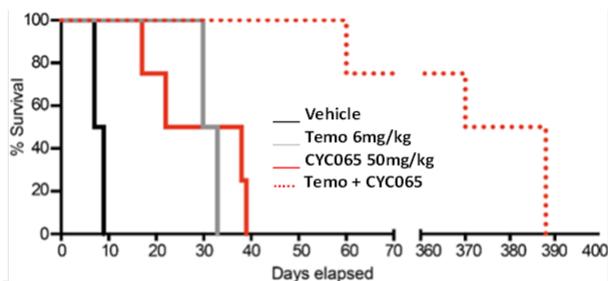


Figure 2: CYC065 prolongs survival in Th-MYCN neuroblastoma model

NB cell lines with MYCN amplification are highly sensitive to CYC065. CYC065 transcriptionally downregulates MYCN expression causing tumor regression in an aggressive genetic model of MYCN driven cancer and prolongs survival in MYCN-addicted NB xenografts.¹² CYC065 has been shown to reduce MYC expression in NB, B-cell lymphoma and triple negative breast cancer.⁸

Selected Clinical Studies

CYC065-01 Part 1: In 26 patients with solid tumors, recommended phase 2 dose (RP2D) has been established at 192 mg/m² as a 4-hour infusion once every 3 weeks.

CYC065-01 Part 2: Part 2 of the study is enrolling patients with advanced solid tumors evaluating an intermittent dosing schedule of 1-hour infusion at days 1, 2, 8, 9 in a 3-week cycle. PR has been achieved in a patient with MCL1 amplified endometrial cancer and stable disease with 29% shrinkage in a patient with cyclin E amplified ovarian cancer.

CYC065-01 Part 3: Part 3 is enrolling patients receiving an oral formulation of CYC065 to assess safety, PK/PD and bioavailability. All 065-01 studies are being conducted at Dana Farber Cancer Institute.

CYC065-02 in R/R CLL: A Phase 1 study is enrolling R/R CLL patients to investigate clinical benefit of i.v. CYC065 and venetoclax combination at MD Anderson and other sites.

CYC065-03 in R/R AML/MDS: A Phase 1 study is enrolling R/R AML/MDS patients to investigate clinical benefit of i.v. CYC065 and venetoclax combination at MD Anderson.

Endnotes:

1. An experimental drug under clinical investigation. Not approved for human use.
2. Rong, et al, AACR 2017 Abs 5095
3. Turner, et al, 2019 JCO 37:1169-1178
4. Caldon, et al, Mol. Cancer Ther. 2012, 11:1488
5. Quinn et al 2011 Expert Opin. Investig. Drugs 20:1397
6. Chen, et al, AACR 2010 Abs 4431
7. Pozzi, et al, 2010 ASH Ann Meet Abs 2999
8. MacKay, et al, AACR-NCI-EORTC 2015 Abs 182
9. Frame et al AACR 2016 Abs 1309
10. Zheleva, et al, SOHO 2015 Abs 213
11. Chen et al, AACR 2018 Abs 3905/5
12. Poon E et al Childhood Cancer Meeting 2016, September 5 – 7th, London, UK, Abs. 1-19

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