Clinical CDK2/9 inhibitor with development potential in MCL1, MYC and cyclin E dependent cancers

CYC065\textsuperscript{1} is a highly-selective, orally- and intravenously-available, 2nd generation inhibitor of cyclin dependent kinases (CDK) 2 and 9. Preclinical data suggest that CYC065 may benefit patients with adult and pediatric hematological malignancies such as CLL, AML, ALL, B-cell lymphomas, multiple myeloma and certain cyclin E-addicted and MYC-amplified solid tumors, such as HER2+ breast cancer, uterine serous carcinoma and neuroblastoma. Translational biology supports development of CYC065 as a stratified medicine for cancers dependent on MCL1, MYC and CDK2/cyclin E for proliferation, survival and resistance to treatment. In a Phase 1 clinical study durable target engagement and durable suppression of the MCL1 biomarker were observed after a single dose of CYC065.

**Mechanism of Action**

The CDK enzyme family act as cell cycle regulators and play pivotal roles in regulation of transcription, DNA repair and metastatic spread. The precise selectivity of individual CDK inhibitors for certain preferred CDK/cyclin protein complexes is key to targeting particular tumor types and avoiding undesirable side effects through non-specific antiproliferative activity. Dysregulated CDKs targeted by CYC065 can drive particular cancer subtypes:

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

CYC065 is mechanistically similar to seliciclib, Cyclacel’s first generation CDK inhibitor, but with significantly improved metabolic stability, efficacy and potency in vitro and in vivo. CYC065 causes proportionally greater CDK9 inhibition leading to improved efficacy in hematological malignancies.

**Competitive Positioning**

As a selective CDK2/9 inhibitor, CYC065 offers an improved therapeutic window and lower myelosuppressive potential than pan-CDK inhibitors based on preclinical and early clinical data. For example CDK1 inhibition counters degradation of MCL1 protecting cancer cells from anticancer agent activity. Three recently approved CDK4/6 inhibitors have validated the class and cell cycle inhibition strategies. Palbociclib (Ibrance\textsuperscript{®}, 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 this.\textsuperscript{2} Addition of CYC065 to this regimen may enhance durability of palbociclib + ET treatment outcome in these patients.

Ribociclib (Kisqali\textsuperscript{®}, Novartis) and abemaciclib (Verzenio\textsuperscript{®}, Lilly) offer broadly similar benefit to palbociclib in patients with breast cancer in combination with aromatase inhibitors (AI). 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 CDK2/cyclin E dependent resistance to CDK4/6 inhibitors.\textsuperscript{3}

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\textsuperscript{®}, AbbVie). CYC065 suppresses MCL1 expression via inhibition of CDK9. 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 (Figure 1), showing prolonged downregulation of MCL1 and potent apoptosis induction.\textsuperscript{4}

**MCL1 dependent cancers**

MCL1 is overexpressed in many types of cancer. Multiple studies show that knockdown of MCL1 leads to cancer cell death and resensitization to drug treatment.\textsuperscript{5,6}

**Chronic lymphocytic leukemia (CLL)** cell survival depends on the expression of anti-apoptotic proteins, including MCL1 and BCL2. In this context, targeting MCL1 or BCL2 releases pro-death signals and commits CLL cells to apoptosis. Venetoclax, a BCL2 inhibitor, has been approved as a 1\textsuperscript{st} and 2\textsuperscript{nd} line CLL treatment. The pan-CDK inhibitors flavopiridol and dinaciclib have shown efficacy in CLL clinical trials, providing clinical proof-of-concept for targeting anti-apoptotic pathways. MCL1 expression can modulate resistance to BCL2 inhibition and is known to be upregulated in lymph node CLL cells, possibly leading to resistance to venetoclax.

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.\textsuperscript{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.\textsuperscript{8,9}
In acute myeloid leukemia (AML), drug resistance has been attributed among others to high levels of MCL1. AML cell lines are highly sensitive to CYC065. 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.

Reversal of CDK2/cyclin E mediated drug resistance
Preclinical and clinical evidence shows that CDK2/cyclin E activation or cyclin E overexpression is a mechanism of drug resistance in metastatic breast cancer. This has been shown for HER2+, triple negative and ER+ breast and high grade serous ovarian cancers, as resistance to trastuzumab, AI, AI plus CDK4/6 combinations, and chemotherapy respectively. CYC065 resensitized trastuzumab-resistant cells to apoptotic cell killing, was effective against uterine serous carcinomas (USC) with amplified/overexpressed cyclin E and was synergistic with PIK3CA inhibition in vivo.12

Development Status

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. 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.

CYC065-01 Part 2: Part 2 of the study is enrolling patients with advanced solid tumors, in particular those with amplification of MCL1, MYC or cyclin E. Effectiveness of intermittent dosing of CYC065 with 1-hour infusion at days 1, 2, 8, 9 in a 3-wk cycle is being investigated at the Dana-Farber Cancer Institute.

CYC065-01 Part 3: Part 3 will evaluate safety, PK/PD and activity of an oral formulation of CYC065. The study has been submitted to IRB at Dana-Farber Cancer Institute.

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

CYC065-03 in R/R AML/MDS: This Phase 1 study is about to open at MD Anderson to evaluate CYC065 and venetoclax combination in R/R AML/MDS patients.

Studies in other mechanistically relevant hematological malignancies and solid cancers are being planned.

Endnotes:
4. Rong, et al, AACR 2017 Abs 5095
11. Chen et al, AACR 2018 Abs 3905/5

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