**WINTER 2019-20 Transcriptional Regulation CDK2/9 Inhibitor Program**

CYC065\(^1\) 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**

- Dose escalation study, part 1; i.v.; in solid tumors \((\text{Completed})\) 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

**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 CYC065 8. CYC065 has single agent activity in AML with <10% long term survival. CDK9 mediates transcriptional regulation of MYCN.

MYCN-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.

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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.

Endnotes:

2. Rong, et al, AACR 2017 Abs 5095
11. Chen et al, AACR 2018 Abs 3905/5

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