**Summer 2020 Transcriptional Regulation CDK2/9 Inhibitor Program**

Fadraciclib (a.k.a. CYC065) 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 fadraciclib 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 fadraciclib. 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 fadraciclib 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). Fadraciclib suppresses MCL1 expression via inhibition of CDK9.

---

**Fadraciclib clinical trials in progress**

- 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

---

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 fadraciclib 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 fadraciclib to this regimen may enhance durability of palbociclib + ET treatment outcome in these patients. In contrast to CDK2/9 inhibition by fadraciclib, 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.

**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...
Fadraciclib has single agent activity in AML to high levels of MCL1. AML cell lines are highly sensitive to transcriptional regulation of MYCN. In 45% of high-risk neuroblastomas (NB), a childhood metabolism and growth. MYCN gene amplification is found by increasing the expression of target genes involved in cell regulators which promote cancer cell growth and survival are overexpressed in over 50% of human cancers often via MYC proto-oncogenes encode MYC family proteins which MYC-addicted cancers MYCN expression causing tumor regression in an aggressive genetic model of MYCN driven cancer and prolongs survival in MYCN-addicted NB xenografts. Fadraciclib has been shown to reduce MYC expression in NB, B-cell lymphoma and triple negative breast cancer.

Drug resistance in AML has been attributed among others to high levels of MCL1. AML cell lines are highly sensitive to fadraciclib. Fadraciclib 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), fadraciclib reduced both MCL1 expression and CDK9 dependent transcription of MLL-regulated leukemogenic genes.

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.

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

Fadraciclib was developed in collaboration with ICR, London.

Contact Information
Cyclacel Pharmaceuticals, Inc. www.cyclacel.com
200 Connell Drive #1500 info@cyclacel.com
Berkeley Heights, NJ 07922 1 James Lindsay Place
200 Connell Drive #1500 Dundee DD1 5JJ, UK
+1 (908) 517-7330 +44 (1382) 206 062

© Copyright 2020 Cyclacel Pharmaceuticals, Inc. All Rights Reserved. The Cyclacel logo and Cyclacel® are Cyclacel Pharmaceuticals, Inc. trademarks.

This document contains forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995 about financial results and estimates, business strategy, clinical trial plans and research and development programs of Cyclacel Pharmaceuticals, Inc. By their nature, forward-looking statements and forecasts involve risks and uncertainties because they relate to events and depend on circumstances that will occur in the future. A number of factors could cause actual results and developments to differ materially and are discussed under “Risk Factors” in our quarterly and annual reports filed with the SEC. The information in this presentation is current as of this date. Cyclacel does not take any responsibility to update such information.

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

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

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 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. Durable 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 fadraciclib 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. fadraciclib 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. fadraciclib and venetoclax combination at MD Anderson.