FADRACICLIB

Winter 2021 Transcriptional Regulation CDK2/9 Inhibitor Program

Fadraciclib (a.k.a. CYC065)[1,2] 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 inhibits CDK9 and suppresses MCL1.

Fadraciclib clinical trials

Dose escalation, part 1 and part 2 i.v.; in solid tumors	**Ph1**
Dose escalation study, part 3, oral, in solid tumors	**Ph1**
In combination with venetoclax in R/R CLL; i.v.	**Ph1**
In combination with venetoclax in R/R AML/MDS	**Ph1**
Single agent studies in solid tumors and heme malig. (in planning)	**Ph1b/2**

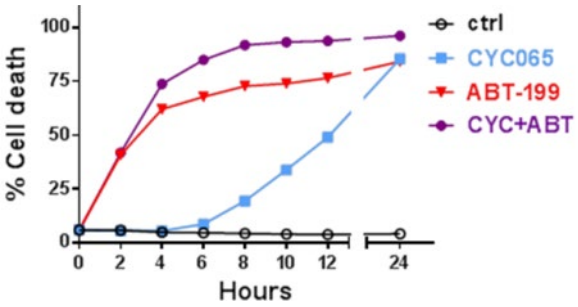

Figure 1: Synergistic cell killing activity of fadraciclib and ABT-199 (venetoclax) in primary CLL model[3]

There is a clear biological rationale for concurrently suppressing BCL2 and MCL1. Preclinical data in CLL models, including 17p deleted models, showed prolonged downregulation of MCL1 and potent apoptosis induction.[3]

Competitive Positioning

Preclinical and early clinical data on fadraciclib offer an improved therapeutic window and lower myelosuppressive potential than pan-CDK inhibitors.

Three approved CDK4/6 inhibitors have validated the class and cell cycle inhibition strategies. Palbociclib (Ibrance®, Pfizer) improved survival outcome in ER+/HER2- breast cancer patients. However, recent data suggest that cyclin E emerges as a marker of resistance in these patients and CDK2 as the key kinase responsible for escape.[4] Considering the mechanism of action of fadraciclib it is expected that addition of fadraciclib to this regimen may enhance durability of palbociclib + ET treatment outcome in these patients.

CDK9 inhibition induces apoptotic tumor cell death through downregulation of survival proteins, including MCL1. CDK2 inhibition enhances cell cycle arrest and therefore may overcome cyclin E dependent resistance to CDK4/6 inhibitors.[5] The oral formulation of fadraciclib with both CDK2/9 inhibition is leading the way in this class of compounds.

MCL1 dependent cancers

MCL1 is overexpressed in many cancers. Knockdown of MCL1 resulted in cancer cell death and resensitization to drug treatment.[6] 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 recommended phase 2 dose (RP2D) in Phase 1 study. Stable disease was observed in 6 patients with MCL1 overexpression, or cyclin E or MYC amplification.

Rapid and complete cell death was observed in CLL and multiple myeloma cell lines after short exposure to fadraciclib in the presence of stromal cells which confer protection from standard treatments.[7,8] Consistent with the pro-apoptotic mechanism of fadraciclib, MCL1 down-regulation was observed. Fadraciclib synergizes with venetoclax in preclinical models supporting clinical investigation of fadraciclib + venetoclax combination.[9,10,11]

Drug resistance in AML has been attributed among others to high levels of MCL1. AML cell lines are highly sensitive to fadraciclib[11]. 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.[12]

MYC-addicted cancers

MYC family of proteins are overexpressed in >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.

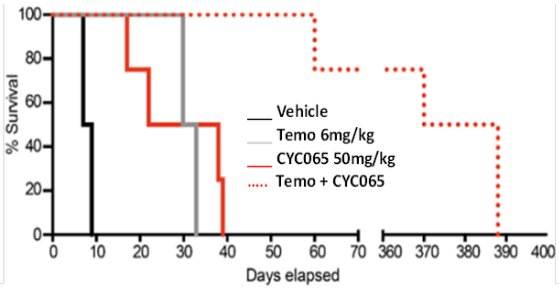

Figure 2: CYC065 prolongs survival in Th-MYCN neuroblastoma model

NB cell lines with MYCN amplification are highly sensitive to 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.[13] Fadraciclib has been shown to reduce MYC expression in NB, B-cell lymphoma and triple negative breast cancer.[9]

Selected Clinical Studies

CYC065-01 Part 1: The RP2D has been established in patients with solid tumors at 192 mg/m^2 as a 4-hour infusion once every 3 weeks.

CYC065-01 Part 2 evaluated intermittent dosing schedule of 1-hour infusion on days 1, 2, 8, 9 in a 3-week cycle in patients with advanced solid tumors. Durable PR with 96% reduction in tumor volume has been achieved in an endometrial cancer patient (MCL1 amplified) and stable disease with 29% shrinkage in an ovarian cancer patient (cyclin E amplified).

CYC065-01 Part 3 is investigating an oral formulation of fadraciclib at identical schedule as of Part 2 to assess safety, PK/PD and bioavailability. Preliminary data presented at the EORTC-NCI-AACR (ENA) triple meeting in October 2020 showed nearly overlapping PK profile of oral and i.v. dosing at equivalent doses.[14]

CYC065-02 in R/R CLL: A Phase 1 study is enrolling R/R CLL patients in i.v. fadraciclib and venetoclax combination.

CYC065-03 in R/R AML/MDS: A Phase 1 study is enrolling R/R AML/MDS patients in i.v. fadraciclib and venetoclax combination.

Further studies with oral fadraciclib are being planned in solid tumors, lymphomas and leukemias.

Endnotes:

1. *An experimental drug under clinical investigation. Not approved for human use.*
2. *Frame S et al, 2020 PLOS One*
3. *Rong, et al, 2017 AACR Abs 5095*
4. *Turner, et al, 2019 JCO 37:1169-1178*
5. *Caldon, et al, 2012 Mol. Cancer Ther, 11:1488*
6. *Quinn et al 2011 Expert Opin. Investig. Drugs 20:1397*
7. *Chen, et al, 2010 AACR 2010 Abs 4431*
8. *Pozzi, et al, 2010 ASH Ann Meet Abs 2999*
9. *MacKay, et al, 2015 EORTC-NCI-AACR Abs 182*
10. *Frame et al, 2016 AACR _Abs 1309*
11. *Zheleva, et al, 2015 SOHO Abs 213*
12. *Chen et al, 2018 AACR Abs 3905/5*
13. *Poon E et al, Childhood Cancer Meeting 2016, September 5 – 7th, London, UK, Abs. 1-19*
14. *Do KT et al, ENA Oral Presentation; October 2020*

Fadraciclib was developed in collaboration with ICR, London.

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