

Fall 2017

**Clinical stage CDK2/9 inhibitor with development potential in Mcl-1, MYC and CDK2/cyclin E dependent cancers**

CYC065<sup>1</sup> is a highly-selective, orally- and intravenously-available, 2nd generation inhibitor of cyclin dependent kinases (CDK) 2 and 9. It causes apoptotic death of cancer cells at sub-micromolar concentrations. Translational biology supports the development of CYC065 as a stratified medicine for cancers dependent on Mcl-1, MYC and CDK2/cyclin E for proliferation, survival and resistance to chemotherapy. Nonclinical studies show that CYC065 may benefit patients with adult and pediatric hematological malignancies, including chronic lymphocytic, acute myeloid and acute lymphocytic leukemias, B-cell lymphomas and multiple myelomas. In preclinical models CYC065 induced regression or tumor growth inhibition in HER2-positive breast cancer addicted to cyclin E that is resistant to trastuzumab, in Cyclin E amplified uterine serous carcinoma and reduced tumor burden and prolonged survival in NMYC-amplified neuroblastoma models.

**Mechanism of Action**

CDKs are an enzyme family discovered as cell cycle regulators, but now understood to include pivotal functions in the regulation of transcription, DNA repair and metastatic spread. The precise selectivity of an individual CDK inhibitor molecule for certain preferred CDK/cyclin partner protein complexes is key to targeting particular tumor types and avoiding undesirable side effects through non-specific antiproliferative activity. When dysregulated CDKs can be drivers of particular cancer sub-sets. CYC065 targets:

- CDK2, which drives cell cycle transition and when dysregulated enables G1 checkpoint bypass;
- CDK9, which is an effector of dysregulated transcription of certain genes (incl. cyclins, Mcl-1, MYC) through phosphorylation of RNA polymerase II;
- CDK2 and CDK9 are targets for the inhibition of DNA damage repair pathways.

CYC065 is mechanistically similar to Cyclacel’s first generation CDK inhibitor, seliciclib, 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.

**In vitro potency and selectivity of CYC065**

CDK	2	5	9	3	7	4	1
CYC065 IC <sub>50</sub> (nM)	5	21	26	29	193	232	578
Ratio to CDK2		4	5	6	39	46	116

**Competitive Positioning**

A selective CDK2/9 inhibitor, CYC065 offers an improved therapeutic window and lower myelosuppressive potential than pan-CDK inhibitors that also target CDK1 which is cytotoxic for all proliferating cells whether malignant or not. CDK1 inhibition also counteracts the degradation of Mcl-1, protecting cancer cells from anticancer agent activity.

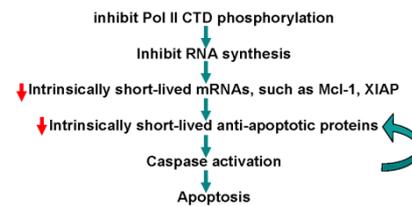
Approved and clinical stage CDK4/6 inhibitors e.g. palbociclib, provide an important therapeutic advance, causing

prolonged cell cycle arrest and senescence in certain solid tumors in combination with endocrine therapy. In contrast CDK9 inhibition induces apoptotic tumor cell death through transcriptional downregulation of cancer cell survival pathways. CDK2 inhibition can enhance cell cycle arrest, and may overcome CDK2/cyclin E dependent resistance to CDK4/6 inhibitors.<sup>2</sup>

**Mcl-1 dependent cancers**

The Myeloid cell leukemia sequence-1 (Mcl-1) is a key regulatory (anti-apoptotic) protein in a major cell death pathway. Mcl-1 is overexpressed in many cancer types as a survival and drug resistance mechanism and multiple studies show that knockdown of Mcl-1 leads to cancer cell death and re-sensitization to drug treatment.<sup>3</sup> CYC065 targets Mcl-1 expression via inhibition of CDK9.

**Mechanism of action of Cdk9 inhibitors in CLL**



**Chronic lymphocytic leukemia (CLL)** is characterized as being dependent on the expression of anti-apoptotic proteins for survival including Mcl-1 and a related protein Bcl-2. In this context, targeting Mcl-1 or Bcl-1 releases pro-death signals to commit CLL cells to apoptosis. Venetoclax (Venclexta®, AbbVie) inhibits Bcl-2 and was recently approved to treat CLL with 17p deletion after at least one prior therapy; the pan-CDK inhibitors flavopiridol and dinaciclib have shown efficacy in CLL clinical trials, providing clinical proof-of-concept for the targeting of anti-apoptotic pathways in leukemias. Mcl-1 expression can modulate resistance to Bcl-2 inhibition and is known to be upregulated in lymph node CLL cells, possibly leading to resistance to venetoclax.

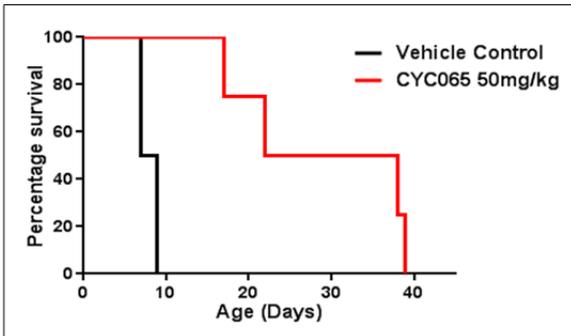
Rapid and complete cell death was induced in CLL and multiple myeloma (MM) cell lines after short exposure to CYC065 in the presence of stromal cells which confer protection from standard chemotherapies.<sup>4,5</sup> Mcl-1 down-regulation was observed, consistent with the pro-apoptotic mechanism of CYC065. CYC065 synergises with venetoclax in preclinical models<sup>6,7</sup> supporting the clinical exploration of CYC065 in CLL in combination with venetoclax.

Drug resistance in **acute myeloid leukemia (AML)** has been attributed to high levels of Mcl-1. AML cell lines are highly sensitive to CYC065<sup>8</sup>, 5 to 8 hours treatment is sufficient to achieve induction of cell death. CYC065 has single agent efficacy in AML xenografts and the potential to be combined with approved AML chemotherapies. In leukemia cells harbouring the rearranged Mixed Lineage Leukemia gene (MLLr) cells reduced both Mcl-1 expression and CDK9 dependent transcription of MLL-regulated leukemogenic genes.<sup>8</sup>

**MYC-addicted cancers**

The 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. Amplification of the MYCN gene is found in 45% of high-risk neuroblastoma, a childhood cancer with <10% long term survival. CDK9 is involved in the transcriptional regulation of MYCN.

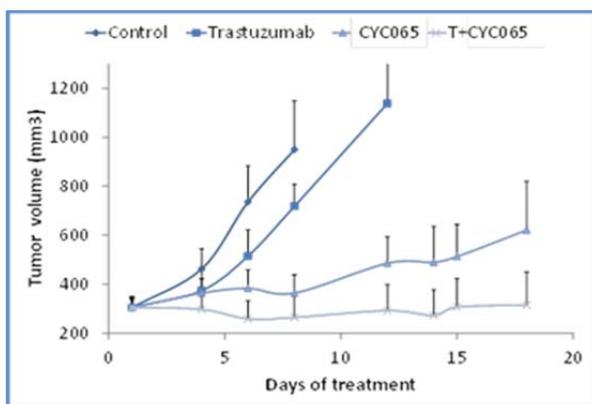


**CYC065 prolongs survival in Th-MYCN model of neuroblastoma**

Neuroblastoma cell lines with MYCN amplification are highly sensitive to CYC065 cytotoxicity, CYC065 transcriptionally downregulates MYCN expression in MYCN neuroblastoma, causes tumor regression in an aggressive genetic model of MYCN driven cancer and prolongs survival in MYCN-addicted neuroblastoma xenografts.<sup>9</sup> CYC065 may have therapeutic potential in neuroblastoma with amplification of the MYCN oncogene and in other cancers where MYC overexpression is implicated in tumorigenesis or drug-resistance, where CYC065 has been shown to reduce MYC expression, e.g. B-cell lymphoma, triple negative breast cancer.<sup>6</sup>

#### Reversal of CDK2/cyclin E mediated drug resistance

Preclinical and clinical evidence shows that CDK2/cyclin E activation or cyclin E (CCNE) overexpression is a mechanism of resistance to trastuzumab resistance in metastatic breast cancer, drug resistance in triple negative breast cancers, breast cancer aromatase inhibitor (AI) therapy including AI plus CDK4/6 inhibitor combination therapy, and chemotherapy resistance in high grade serous ovarian cancers. CYC065 resensitized trastuzumab-resistant breast cancer to apoptotic cell killing, was effective against uterine serous carcinomas (USC) with amplified/overexpressed cyclin E and synergistic with PIK3CA inhibition *in vivo*, together a new therapeutic option in USC.<sup>10,11,12</sup>



**CYC065 in trastuzumab resistant HER2+ve BC**

#### DNA damage response impaired tumors

Cancer susceptibility is increased in the presence of germline mutations in genes encoding DDR proteins, e.g. homologous recombination (HR) repair genes BRCA1 and BRCA2. Cancers with defective DDR signaling have background DNA damage levels that increase susceptibility to drugs causing further DNA

damage or inhibiting DDR. An ongoing combination trial of seliciclib, Cyclacel's 1<sup>st</sup> generation CDK2/9 inhibitor with sapacitabine, Cyclacel's oral nucleoside analogue which causes DNA damage repaired by the HR pathway has shown clinical benefit.<sup>13</sup> CYC065 decreases the expression of repair genes BRCA1 and BRCA2 and synergises with sapacitabine in cell line studies.<sup>5</sup>

#### Development Status

The CYC065 recommended Phase 2 dose (RP2D) has been determined in advanced cancers.<sup>14</sup> Seven dose cohorts were studied, from 8 to 288 mg/m<sup>2</sup>/day as a 4-hour infusion once every 3 weeks. At the RP2D of dose level 6 reduction of the Mcl-1 biomarker was observed in 7 of 9 evaluable patients for at least 24 hours following the dose of CYC065. Dose limiting toxicity at dose level 7 was reversible neutropenia, febrile neutropenia and diarrhea. PK parameters demonstrated dose proportional increases in CYC065 exposure. Anticancer activity was reported by the investigators in patients with Mcl-1 (ovarian cancer: reduction of CA-125 tumor marker levels), MYC (larynx: radiographic tumor shrinkage) and Mcl-1/cyclin E (ovarian: radiographic tumor shrinkage) amplified tumors.

Part 2 of the study will evaluate a schedule of CYC065 given on 2 days/week for 2 weeks of a three week cycle and aims to enrich for patients with cyclin E amplified tumors, including subsets of high grade serous ovarian and uterine cancers. Cyclacel also plans to start a Phase 1/2 study testing CYC065 in combination with venetoclax, a Bcl-2 inhibitor approved for chronic lymphocytic leukemia, where we believe Mcl-1 suppression will be beneficial.

#### Endnotes:

1. An experimental drug under clinical investigation. Not approved for human use.
2. Caldon, et al, *Mol. Cancer Ther.* 2012, 11:1488
3. Quinn et al 2011 *Expert Opin. Investig. Drugs* 20:1397
4. Chen, et al, *AACR 2010 Abs* 4431
5. Pozzi, et al, 2010 *ASH Ann Meet Abs* 2999
6. MacKay, et al, *AACR-NCI-EORTC 2015 Abs* 182
7. Frame et al, *AACR 2016 Abs* 1309
8. Zheleva, et al, *SOHO 2015 Abs* 213
9. Poon E et al *Childhood Cancer Meeting 2016, September 5 – 7th, London, UK, Abs.* 1-19
10. Scaltriti, et al, 2011 *PNAS* 108:3761
11. Cocco, et al, 2016 *BJC* 115:303-311
12. Akli, et al, 2011 *Cancer Res* 71:3377
13. Tolaney et al *J Clin Oncol* 34, 2016 (suppl; abstr 2503)
14. Cyclacel press release 7 August 2017

Cyclacel discovered CYC065 and other novel CDK inhibitors in a medicinal chemistry collaboration with the Cancer Research UK Centre for Cancer Therapeutics at The Institute of Cancer Research (ICR), London, UK.

#### Contact Information

Cyclacel Pharmaceuticals, Inc.  
(NASDAQ: CYCC; NASDAQ: CYCCP)  
200 Connell Drive #1500  
Berkeley Heights, NJ 07922  
+1 (908) 517-7330

[www.cyclacel.com](http://www.cyclacel.com)  
[info@cyclacel.com](mailto:info@cyclacel.com)  
1 James Lindsay Place  
Dundee DD1 5JJ, UK  
+44 (1382) 206 062

© Copyright 2017 Cyclacel Pharmaceuticals, Inc. All Rights Reserved. The Cyclacel logo and Cyclacel® are trademarks of Cyclacel Pharmaceuticals, Inc.

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.