CYC140

Summer 2019

Clinical stage, differentiated PLK1 inhibitor for solid tumors and leukemias

A Targeted Cell Cycle Inhibitor

CYC140* is a novel, small molecule, ATP-competitive, selective, PLK1 inhibitor, which has demonstrated potent and selective target inhibition, and impressive efficacy and cures in human tumor xenografts at non-toxic doses. CYC140's improved pharmaceutical properties (over previous clinical PLK1 inhibitors) are being studied in a translational biology program in acute leukemias and solid tumors. A first-in-human (FiH) Phase 1 trial is enrolling patients.

PLK1: Key Mitotic Regulator and Oncogene

Polo-like kinases (PLKs) were first discovered in fruit flies by Prof. D. Glover, Cyclacel's former Chief Scientist.[1] PLK1 is a serine/threonine kinase with a central role in cell division, or mitosis, and is an important regulator of the DNA damage checkpoint.[2] Knock out of PLK1 leads to embryonic lethality in mice.[3]

When overexpressed, the PLK1 oncogene causes cellular transformation, overrides the DNA damage checkpoint, contributes to checkpoint adaptation, supports invasion through the extracellular matrix and paves the way for aneuploidy. It is frequently overexpressed in cancer tissues, where its level of expression correlates with aggressiveness which has prognostic implications for outcomes.

PLK1 expression is low or absent in non-cancerous proliferating tissues. Because of its extensive involvement in tumorigenesis, inhibition of PLK1 has been an important consideration to control cancer cell proliferation.

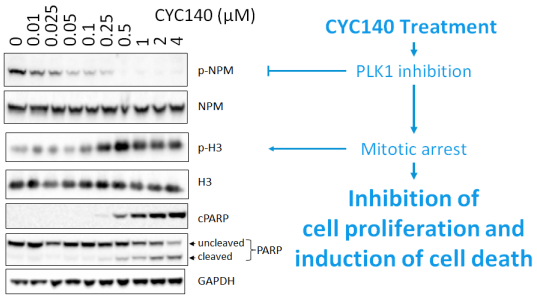

Figure 1: CYC140 in KYSE-410 esophageal cell line

Both small molecule inhibitors and antisense/siRNA against PLK1 have been shown to block tumor cell proliferation through prolonged mitotic arrest that induces cell death in cancer cells.[4,5] In addition, PLK1 is involved in conferring resistance to cancer cells against several chemotherapy drugs, including doxorubicin, gemcitabine, metformin and paclitaxel.[6] PLK1 inhibitor combinations may therefore increase or restore tumor sensitivity to available treatments.

CYC140 characteristics

Using a *de novo* ligand design approach, Cyclacel optimized a pharmacological scaffold to generate CYC140.[7] CYC140 is a selective PLK1 inhibitor inhibiting 3 out of 352 kinases by ≥80% at 5 μM. It has low nanomolar potency against PLK1 and over 50- and 100-fold greater potency than PLK2 and PLK3 respectively.

	PLK1	PLK2	PLK3
CYC140 IC_{50} (nM)	3	149	393
Ratio vs. PLK1	1	51	133

Competitive positioning

CYC140 was optimized for solubility, cellular activity and pharmacokinetic profile in comparison with benchmark PLK inhibitors volasertib (BI6727) and BI2536. Competitive advantages include high potency, improved kinase selectivity for PLK1 vs. other PLKs and other kinases, shorter half-life, and administration by both the intravenous and oral route. As PLK1 is essential for dividing cells, comparatively short half-life is important to facilitate pulse dosing in patients and control the duration of PLK1 inhibition, potentially minimizing effects on non-malignant hematopoietic cells and improving therapeutic window.

Target Indications

Indications under consideration are:

- Hematological malignancies and solid tumors with high proliferation rate;
- PLK1 over-expressing tumors with levels correlating with patient prognosis (e.g. esophageal, gastric, NSCLC, ovarian and squamous cell carcinoma);
- AML, PLK1 inhibitors increased clinical response rate in combination with LDAC[8] and demonstrated synergy with FLT3 inhibitor in AML cell models.[9]
- MYC overexpressing tumors, including AML. PLK1 inhibitor reduction of MYC and/or MCL1 levels may result in synergy with BCL2 inhibitors, i.e. venetoclax.[10]

PLK1 Inhibition Therapeutic Rationale

PLK1 plays an active role in carcinogenic transformation.[2] Preclinical and translational studies have demonstrated that:

- AML and ALL cell lines are highly sensitive to CYC140 treatment, showing appropriate target engagement. Cures were observed in an AML xenograft model.
- Esophageal cancer (OEC) cell lines are sensitive to CYC140 short-pulse dosing. Potent, dose-dependent anti-tumor activity was observed in an OEC xenograft model using oral schedules.

Other cancers in which PLK1 is overexpressed and correlates with poor prognosis include breast, colon, head and neck, melanoma, NHL, NSCLC, ovarian, pancreatic, prostate and thyroid. Combinations with EGFR inhibitors and anti-PD1/PDL1 immune therapies hold promise.[11,12]

Hematological malignancies

A high unmet medical need exists for AML patients unfit for chemotherapy and high risk MDS patients. First line therapy benefits less than 50% of patients, often with short durability and modest effects on survival. Novel modalities are therefore urgently needed.

PLK1 is a promising therapeutic target in AML. It is overexpressed in cell lines and a large percentage of samples from patients. PLK1 inhibition or knockdown preferentially blocks proliferation of leukemic rather than normal cells.[13] CYC140 produced tumor free cures in a leukemia xenograft model after once per day oral dosing.[7]

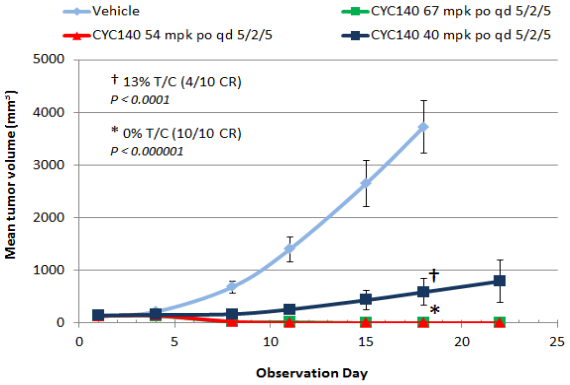

Figure 2: HL60 promyelocytic leukemia xenograft

Esophageal Cancer

OEC is an aggressive tumor with limited treatment options. New approaches are studying patient subsets with identifiable molecular defects.

- 70-97% of OEC overexpress PLK1[14,15,16]
- Cell line data suggest combination opportunities with other targeted agents including EGFR inhibitors
- Prolonged stable disease in OEC was observed in Phase 1 with PLK inhibitor GSK461364

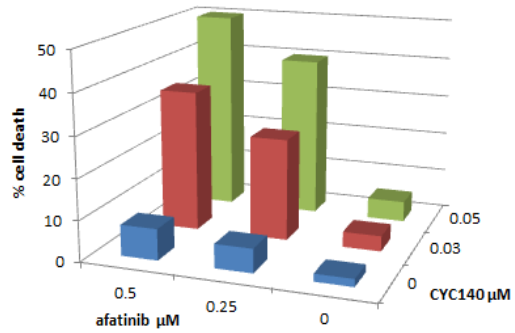

Figure 3: CYC140-afatinib synergy (KYSE-270 esophageal cells)

Targeted strategies for OEC in clinical development may involve RTK inhibitors in the FGFR pathway (EGFR, ErbB2, ErbB3, Met and FGFR2). 51% of esophageal adenocarcinomas overexpress at least one of these targets, and 21% overexpress two or more.[17] In OEC cell lines CYC140 is synergistic in combination with EGFR or PI3K pathway inhibitors.[18]

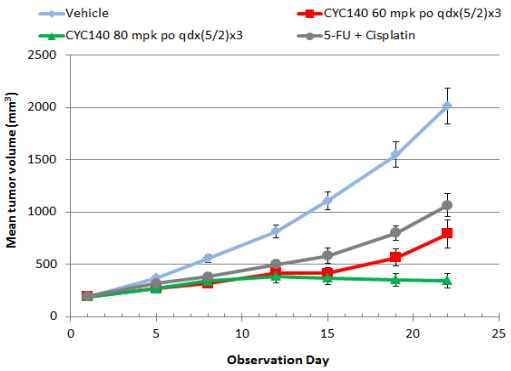

Figure 4: OE19 esophageal adenocarcinoma xenograft

Development Status

CYC140 is being evaluated in a Phase 1, first-in-human study at the MD Anderson Cancer Center. Investigators are evaluating dose limiting toxicity, maximum tolerated dose, establishing recommended Phase 2 dose, and assessing pharmacokinetic and pharmacodynamic profile in patients with advanced leukemias or MDS.

Endnotes:

* *CYC140 is an experimental drug under clinical investigation and it is not approved for human use.*

1. *Sunkel CE, Glover DM. J Cell Sci 1988. 89:25–38.*
2. *Cholewa et al. Cancer Res 2013. 73:6848-55.*
3. *Lu L-Y et al. Mol Cell Bio 2008. 28:6870-6876.*
4. *Spankuch et al. Oncogene 2007. 26:5793.*
5. *Liu et al. Mol Cell Biol. 2006. 26:2093.*
6. *Gutteridge et al. Mol Cancer Ther. 2016. 15:1427-35.*
7. *Hollick et al. AACR 2010 Abs 4435.*
8. *Dohner, H. et al. Blood 2014. 124:1426-1433.*
9. *Kosco K et al. AACR 2018 Abs 7602.*
10. *Xiao D et al. Mol. Cell 2016. 64: 493-506.*
11. *Wang Y et al. Oncotarget 2016. 7:47998-48010.*
12. *Li M et al. J Onc 2018. 2018:1-13.*
13. *Renner et al. Blood. 2009. 114:659.*
14. *Feng YB et al. Int J Cancer 2009. 124:578-88.*
15. *Tokumitsu Y et al. Int J Oncol 1999. 15:687-692.*
16. *Zhao C et al. J Cancer Res Clin Oncol 2010. 136:9-16.*
17. *Patterson AL et al. J Pathol. 2013. 230:118-28.*
18. *Moureau, S. et al. AACR 2017 Abs 4178.*

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