CYC140

Autumn 2018

Clinical stage differentiated PLK1 inhibitor for solid tumors and leukemias

A Targeted Cell Cycle Inhibitor

CYC140* is a novel, small molecule, selective, ATP-competitive, PLK1 inhibitor. It is highly differentiated from other PLK1 inhibitors, demonstrating potent and selective target inhibition, impressive efficacy and cures in human tumor xenografts at non-toxic doses. The pharmaceutical properties of CYC140 are improved over clinical stage PLK inhibitors some of which failed to meet the safety/tolerability/efficacy expectations in patients. Cyclacel's translational biology program supports the development of CYC140 in acute leukemias and solid tumors, including esophageal cancer. Following IND-enabling studies, a first-in-human (FIH) trial will be initiated in Q4 2018.

PLK1: Key Mitotic Regulator and Oncogene

Polo-like kinase 1 (PLK1) was first discovered in fruit flies in 1988.[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, preferential inhibition of PLK1 has been an important consideration to control cancer cell proliferation.

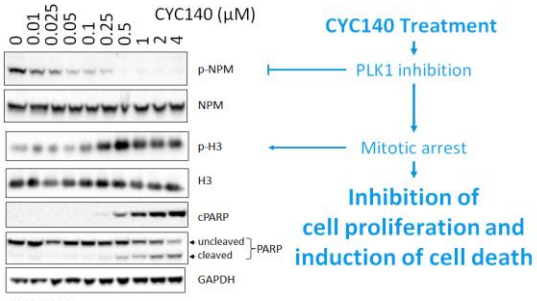

Figure 1: CYC140 in KYSE-410 esophageal cell line

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, paclitaxel, metformin and gemcitabine.[6] Thus, PLK1 inhibitor combinations may increase or restore tumor sensitivity to currently available agents.

CYC140 characteristics

Using a *de novo* ligand design approach, Cyclacel optimized a pharmacological scaffold and generated CYC140 against PLK1 with improved drug-like properties.[7] CYC140 is a very selective PLK1 inhibitor inhibiting only 9 out of 352 kinases by ≥50% at 5 μM. It has low nanomolar potency against PLK1 (IC_{50} ~3nM). PLKs -2 and -3 are 50-fold and >100-fold less sensitive to CYC140, than PLK1 respectively.

	PLK1	PLK2	PLK3
CYC140 IC_{50} (nM)	2.95	149	393
Ratio vs. PLK1	1	51	133

Data revealed that CYC140 has modest solubility at physiological pH and possesses a short residence time in the body. This may facilitate pulse administration in patients potentially minimizing effects on non-malignant hematopoietic cells and may improve therapeutic window.

Competitive positioning

CYC140 was optimized for solubility, cellular activity and pharmacokinetic profiles in comparison with benchmark PLK inhibitors volasertib (BI6727) and BI2536. Competitive advantages include high potency and kinase selectivity for PLK1 over PLK2, -3 and -4 and other kinases; intravenous and oral dosing.

Target Indications

CYC140 target indications under consideration are:

- Hematological malignancies and solid tumors with high proliferation rate;
- Myc overexpressing tumors, including AML. PLK1 inhibitor reduction of Myc and/or Mcl-1 levels may result in synergy with Bcl-2 inhibitors, i.e. venetoclax;
- PLK1 over-expressing tumors where levels of PLK1 correlate with patient prognosis (e.g. esophageal, gastric, NSCLC, ovarian and squamous cell carcinoma).

PLK1 Inhibition Therapeutic Rationale

Current evidence supports that PLK1 plays an active role in carcinogenic transformation.[2] Preclinical and translational investigation revealed that -

- Amongst hematological malignancies, various AML and ALL cell lines were highly sensitive to CYC140 treatment with appropriate target engagement. Additionally, complete response was observed in an AML xenograft model.
- Multiple esophageal cancer (OEC) cell lines were shown to be sensitive to short-pulse dosing of CYC140. Potent dose-dependent anti-tumor activity was also observed in a xenograft model using an oral daily schedule.

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.

Hematological malignancies

A high unmet medical need exists for AML 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 clinically viable target and has been implicated in AML. It is overexpressed in AML cell lines and a large percentage of samples from patients. PLK1 inhibition or knockdown preferentially blocks proliferation of leukemic rather than normal cells.[9] CYC140 produced tumor free cures in a leukemia xenograft model after once per day oral dosing.[7]

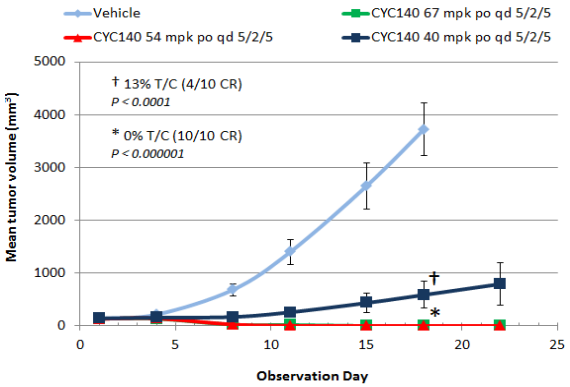

Figure 2: HL60 promyelocytic leukemia xenograft

Esophageal Cancer

OEC is an aggressive tumor with limited treatment options. New approaches focus on patient subsets with identifiable molecular defects. Based on encouraging preclinical data Cyclacel is exploring evaluation of CYC140 in advanced esophageal cancer.

- Approximately 79% of OEC overexpress PLK1
- Cell line data suggest combination opportunities with other targeted agents (i.e. afatinib pan-HER inhibitor)
- Prolonged stable disease was observed in Phase 1 with GSK PLK compound GSK461364

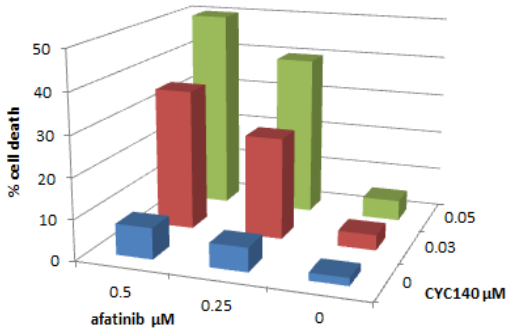

Figure 3: CYC140-afatinib synergy (KYSE-270 esophageal cells)

Targeted strategies for OEC in clinical development mainly involve RTK inhibitors in the FGFR pathway (EGFR, ErbB2, ErbB3, Met and FGFR2) upregulated singly in 51% and severally in 21% of OEC adenocarcinomas. In EOC cell lines CYC140 is synergistic in combination with EGFR or PI3K pathway inhibitors.[8]

A small subset expresses HER2 and for such patients palliative treatment may be offered, including trastuzumab added to cisplatin/fluoropyrimidine combination. Ramucirumab, anti-VEGF2R antibody, has been approved in combination with paclitaxel in select patients. High mutation burden in esophageal cancer may be relevant for immune checkpoint treatments (e.g. PD1/PDL-1 antibodies in selected patients).

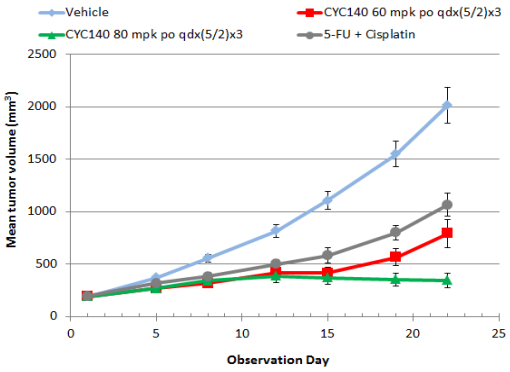

Figure 4: OE19 xenograft

Development Status

CYC140 has completed IND development. MD Anderson Cancer Center (MDACC) investigators will conduct the first-in-human Phase 1 study for CYC140 (activated after IRB clearance) as part of an alliance agreement with Cyclacel. The study will evaluate dose limiting toxicity, maximum tolerated dose and establish the recommended Phase 2 dose of CYC140 in patients with relapsed or AML, ALL, CLL, CML, or MDS. It will also assess the pharmacokinetic and pharmacodynamic profile of CYC140.

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. *Moureau, S. et al. AACR 2017 Abs 4178*
9. *Renner et al. Blood. 2009 114:659*

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