

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.

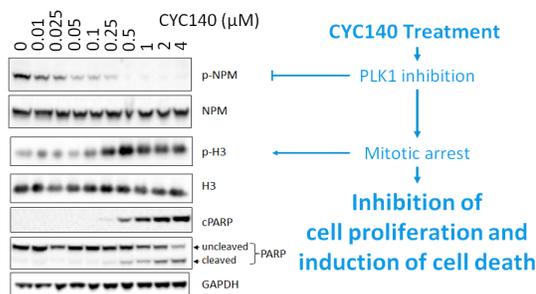


Figure 1: CYC140 in KYSE-410 esophageal cell line

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 $\geq 80\%$ at 5 μM . Unlike current inhibitors it is more PLK-centric and 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 of CYC140 include high potency, improved kinase selectivity for PLK1 and administration by both the intravenous and oral route. As PLK1 is essential for dividing cells, the shorter half-life of CYC140 enables optimal administration in patients 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). Recent data with a peer compound suggest that PLK1 inhibition may be effective in KRAS-mutated metastatic colorectal cancer.⁸
- AML, PLK1 inhibitors increased clinical response rate in combination with LDAC⁹ and demonstrated synergy with FLT3 inhibitor in AML cell models.¹⁰
- MYC overexpressing tumors, including AML. Reduction of MYC and/or MCL1 levels by PLK1 inhibitors may add synergy to BCL2 inhibition by agents such as venetoclax.¹¹

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 AML xenograft models.
- Esophageal cancer (OEC) cell lines are sensitive to CYC140 short-pulse dosing. In an OEC xenograft model potent, dose-dependent anti-tumor activity was observed using oral schedules.
- Other cancers in which PLK1 is overexpressed include breast, colon, head and neck, melanoma, NHL, NSCLC, ovarian, pancreatic, prostate, thyroid and pediatric cancers such as rhabdomyosarcoma.¹²

Combinations with EGFR inhibitors and anti-PD1/PDL1 immune therapies may also hold promise.^{13,14}

Hematological malignancies

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.¹⁵ CYC140 produced tumor free cures in a leukemia xenograft model after once per day oral dosing.⁷

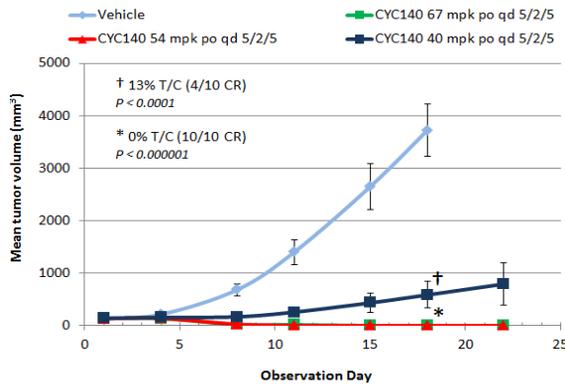


Figure 2: HL60 promyelocytic leukemia xenograft

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^{16,17,18}
- 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

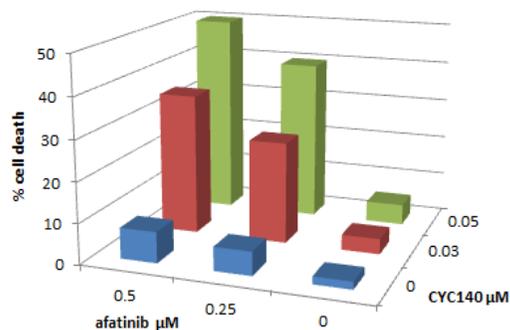


Figure 3: CYC140-afatinib synergy (KYSE-270 esophageal cells)

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.¹⁹ In OEC cell lines CYC140 is synergistic in combination with EGFR or PI3K pathway inhibitors.²⁰

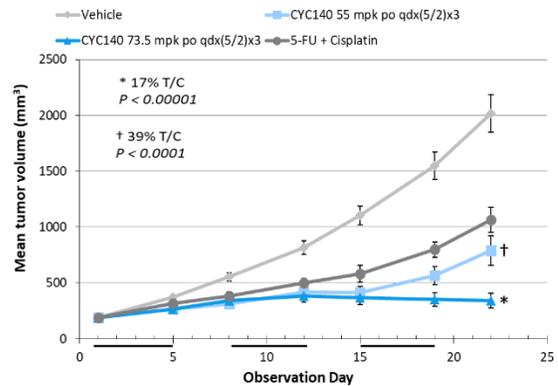


Figure 4: OE19 esophageal adenocarcinoma xenograft

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. Further studies are being planned.

Endnotes:

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

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