CYC140

Fall 2017

Clinic ready differentiated PLK1 inhibitor for esophageal cancer and acute leukaemias

A Targeted Cell Cycle Inhibitor

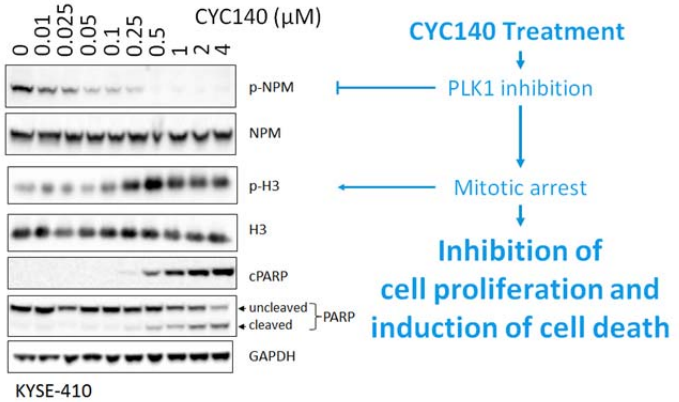
CYC140* is a novel, small molecule, selective PLK1 ATP site inhibitor. CYC140 is highly differentiated from other PLK1 inhibitors, demonstrating potent and selective target inhibition, impressive efficacy and cures in human tumor xenografts at non-toxic doses. The pharmaceutical properties of CYC140 are improved over clinical stage PLK inhibitors. CYC140 has completed IND-enabling studies and is the subject of a translational biology program focussed on esophageal cancer and acute leukaemias.

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] The cell cycle is comprised of a series of events culminating in cell growth and division. Cell cycle checkpoint control detects and repairs flaws in DNA that could lead to cancer cell proliferation. PLK1 plays a key role in regulation of mitotic entry, spindle formation, mitotic exit and cytokinesis.

Plk1 is frequently overexpressed in cancer tissues, where its level of expression correlates with aggressiveness and has prognostic value for predicting outcomes. In contrast, PLK1 expression is low or absent in non-cancer proliferating tissues. Cultured cells can be transformed by Plk1 overexpression and these cells can induce tumors in nude mice.[3] PLK1 is an oncogene and when overexpressed it causes cellular transformation, overrides the DNA damage checkpoint, contributes to checkpoint adaptation, supports invasion through extracellular matrix and paves the way for aneuploidy.

CYC140 mechanism of action (KYSE-410 esophageal cell line)



PLK1 Inhibition - Therapeutic Rationale

Current evidence supports the notion that oncogene dependence on PLK1 is not a late occurrence in carcinogenesis and it is likely that PLK1 plays an active role in carcinogenic transformation.[2] Preclinical evidence suggests that PLK1 expression may be necessary for cancer cell survival and PLK1 is overexpressed in a variety of cancers, including melanoma, breast, ovarian, thyroid, colon, prostate, pancreatic, head and neck, non–small cell lung cancer, and non-Hodgkin lymphomas.

Cancer cell proliferation is blocked *in vitro* and *in vivo* by small-molecule PLK1 inhibitors and PLK1 antisense/siRNA and PLK1 inhibition causes mitotic arrest and subsequent induction of apoptosis in cancer cells.[4,5] PLK1 is involved in the mechanisms of resistance to several chemotherapy drugs, including doxorubicin, paclitaxel, metformin, and gemcitabine.[6] Thus, in combination PLK1 inhibitors may increase or restore tumor sensitivity to currently used agents.

CYC140 characteristics

Using *de novo* ligand design approach, Cyclacel generated a pyrimidodiazepinone scaffold from which several lead compounds and subsequently the clinical candidate CYC140 were selected following optimization for drug-like properties.[7] CYC140 is a very selective PLK1 inhibitor inhibiting only 9 out of a panel of 352 kinases by 50% or more at 5 µM. CYC140 is a potent PLK1 inhibitor (IC50 ~3nM) and is >50 fold more potent against PLK1 than PLK2, and >100 fold less potent against other PLKs and non PLK kinases.

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

In malignant esophageal cancer cells, CYC140 causes an increase in the proportion of cells in mitosis and a G2 cell cycle arrest, which leads to prolonged cell growth arrest and death. In non-malignant esophageal cells, the arrest is transient and the cells recover.

Competitive positioning

CYC140 was optimized for solubility, cellular activity and pharmacokinetic profiles in comparison with benchmark PLK1 inhibitors volasertib and BI2536. Competitive advantages include high potency and kinase selectivity for PLK1 over PLK2, PLK3 and PLK4 and over other kinases; pharmaceutical properties allowing both intravenous and oral dosing; and PK properties allowing short pulse intermittent dosing regimens.

The predicted short drug elimination half-life of CYC140 and lower cellular retention should allow use of a pulse dosing regimen in order to minimize effects on non-malignant hematopoietic cells, thus improving the therapeutic window compared with benchmark clinical PLK inhibitors.

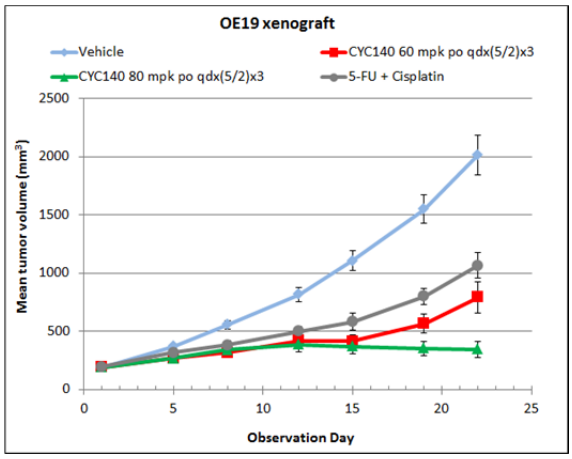
Target Indications

Target indications of PLK1 inhibitors are tumors with PLK1 over-expression in which levels correlate with patient prognosis (e.g. esophageal, NSCLC, ovarian, squamous cell carcinoma, gastric carcinoma).

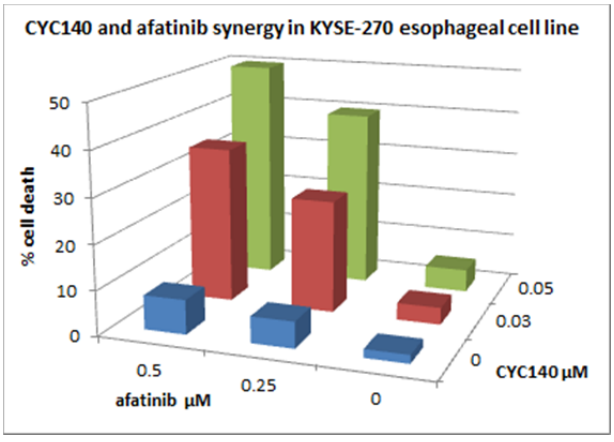
Esophageal Cancer

Currently, our preferred solid tumor indication is advanced esophageal cancer (OEC).

A key role of PLK1 in esophageal tumorigenesis has been proposed, as about 79% of OEC over-express PLK1. Interestingly, prolonged stable disease in 4 of 6 enrolled esophageal cancer patients were reported in the Phase 1 study of PLK1 inhibitor GSK461364. Our mechanistic studies show that OEC cell lines are highly sensitive to short pulse dosing of CYC140. CYC140 demonstrated potent, dose dependent anti-tumor efficacy at well tolerated doses in preclinical xenograft models of esophageal cancer.[8] CYC140 has good oral and intravenous bioavailability and will be developed as an intravenous drug for OEC patients, due to their difficulty with swallowing.



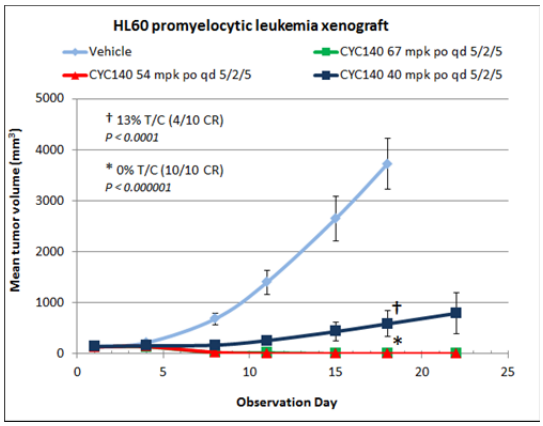
OEC is an aggressive tumor and the 7th highest cause of cancer death with a rapidly rising incidence (particularly in EU and US males, although likely to qualify for orphan status based on current thresholds). Etiology has been linked with nitrosamine exposure, tobacco and alcohol use. In the UK, 1 year survival is 30% and 5 year survival is <10%. Mostly diagnosed at inoperable metastatic stage, response rates are less than 20%. Treatments are limited and new approaches focus on patient subsets with identifiable molecular defects. A small subset of OEC expresses Her2 and such patients can be treated with palliative chemotherapy including trastuzumab added to a cisplatin/fluoropyrimidine combination.



Targeted strategies for OEC in clinical development mainly involve the use of RTK inhibitors in the FGFR pathway (EGFR, ErbB2, ErbB3, Met and FGFR2) which are upregulated singly in 51% and severally in 21% of OEC adenocarcinomas. In EOC cell lines CYC140 is synergistic in combination with EGFR or PI3 kinase pathway inhibitors.[8]

Hematological malignancies

It has been shown that Plk1 is overexpressed in AML cell lines and in a large percentage of samples from patients, and that its 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]



Development Status

CYC140 has completed IND-enabling studies and is being prepared for first-in-human (FIH) directed development.

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. *Smith et al. Biochem. Biophys. Res. Commun. 1997. 234:397*
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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