Abstract 425TiP

A Phase 1 Study of SY-1365, a Selective CDK7 Inhibitor, in Adult Patients with Advanced Solid Tumors

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Background

Transcriptional Cyclin-dependent Kinases (CDKs)

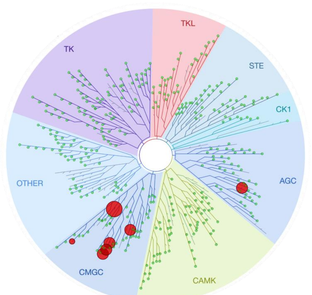
- Active transcription of genes defining the oncogenic state has been shown to be critical to tumor progression in a variety of cancers.
- Cyclin-dependent kinases (CDKs) represent a family of kinases which not only activate the different stages of cell cycle but also play a critical role in transcriptional regulation, participating in the initiation, elongation and processing of cellular transcripts (Loyer, 2005).
- Recent preclinical studies support the hypothesis that some cancers could be effectively controlled by inhibiting the expression of oncogenic transcription factors through inhibition of CDK7, and have identified CDK7 as a potentially important new therapeutic target in solid tumors and hematologic malignancies.

SY-1365

- SY-1365 is a first in class selective and potent covalent CDK7 inhibitor.
- CDK7 inhibition with SY-1365 induces apoptosis and preferentially kills cancer cells over non-cancerous cells.
- CDK7 activity has been implicated in malignancies with transcriptional dependencies such as SCLC, TNBC, ovarian cancer, MYCN-amplified neuroblastoma, and various hematologic malignancies including AML and T-ALL. (Kwiatowski 2014, Christensen 2014, Wang 2015, Chipmuro 2014)
- Preclinical studies in solid tumor and hematologic malignancies show treatment with SY-1365 leads to antitumor activity, showing apoptosis in vitro and complete regressions in *in vivo* xenograft models.
- A phase I study was initiated in patients with advanced solid tumors. The primary objectives are to assess the safety and tolerability of SY-1365 administered intravenously as a single agent, and to determine dose-limiting toxicities, maximum tolerated dose, and the recommended phase 2 dose. Secondary objectives include assessment of a PK/PD relationship, and preliminary antitumor activity.

SY-1365 Profile

DiscoveRx kinome scan at 1μM SY-1365

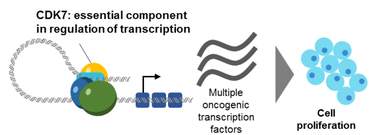


- Covalent
- Highly potent
  - Enzymatic IC_{50} = 22 nM
  - Cellular IC_{50} < 20 nM
- Short PK half-life(1-3 hours) with sustained PD effect (69-hour half-life)
- Highly selective; does not significantly bind to CDK9 or cell cycle CDKs

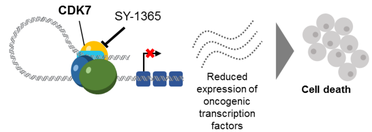
Mechanism of Action

CDK7 Inhibition targets transcriptionally driven cancers dependent on increased expression of disease driving transcription factors

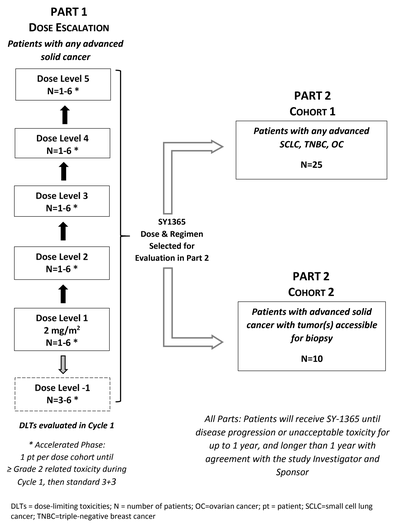
CDK7 is a key player in driving transcription



Inhibiting CDK7 decreases expression of oncogenic TFs

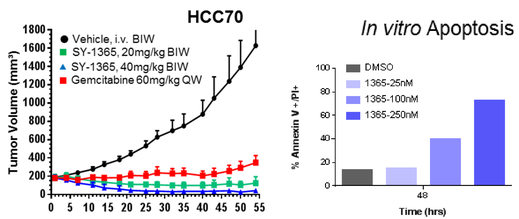


Study Design



DLTs = dose-limiting toxicities; N = number of patients; OC=ovarian cancer; pt = patient; SCLC=small cell lung cancer; TNBC=triple-negative breast cancer

SY-1365 Inhibits Tumor Growth in TNBC In vivo Model



SY-1365 shows tumor growth inhibition including regressions in TNBC xenograft models

Study Summary

- Multi-center, open-label Phase 1 trial expected to enroll approximately 70 patients with advanced solid tumors.
- Initially, SY-1365 will be administered intravenously twice weekly for 3 weeks of each 4-week cycle with regimen adjustment to weekly allowed.
- Regimen optimization will be based upon PK, PD, safety, and early activity data prior to an expansion phase to evaluate preliminary antitumor activity of SY-1365 in 25 patients with SCLC, TNBC or ovarian cancer.
- A second expansion cohort will enroll 10 patients with tumors of any histology to evaluate PD endpoints in paired tumor biopsies.
- SY-1365 target engagement in peripheral blood mononuclear cells and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment.
- Downstream biological pathway impact of SY-1365 will be measured by quantifying changes in gene expression as a result of transcriptional inhibition. Additional variables such as tumor cell proliferation, apoptosis and CDK7 expression will be investigated when tissue is available
- This trial opened in May 2017. ClinicalTrials.gov identifier: NCT03134638

Key Eligibility Criteria

Key Inclusion

- At least 1 measurable lesion by RECIST 1.1
- Prior treatment (Part 2, Cohort 1 only)
  - SCLC: must have received prior platinum doublet therapy
  - TNBC: must have received prior taxane therapy
  - Ovarian Cancer (high-grade serous type): must have received prior platinum doublet therapy, and in the opinion of the Investigator is unlikely to benefit from additional lines of platinum-based therapy
- All toxicities (except alopecia) from prior cancer treatments must have resolved to ≤ Grade 1 or returned to baseline levels prior to enrollment
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

Key Exclusion

- Chemotherapy or limited field radiotherapy within 2 weeks, wide field radiotherapy within 4 weeks, or nitrosoureas or mitomycin C within 6 weeks prior to entering the study
- Received any other investigational agents within 4 weeks prior to enrollment, or < 5 half-lives since completion of previous investigational therapy, whichever is shorter
- Received previous non-cytotoxic, FDA-approved anticancer agent within previous 2 weeks, or < 5 half-lives since completion of previous therapy, whichever is shorter
- Prior exposure to transcriptional kinase family CDK inhibitors, such as the CDK7 and CDK9 inhibitors alvocidib (Flavopiridol), dinaciclib, and seliciclib. Exception: previous exposure to cell cycle CDK inhibitors such as CDK4 and CDK6 (eg, palbociclib) is allowed

Key Endpoints

Primary:

- Dose limiting toxicities & treatment emergent adverse events

Exploratory:

- Modulation of downstream biological pathway effects and markers of CDK7 inhibition on gene transcription programs
- Molecular characterization of tumor tissue and correlation with clinical response or resistance to SY-1365

Secondary:

- PK measurements of SY-1365 in blood plasma following single and multiple doses.
- Modulation of CDK7 occupancy in PBMCs & tumor tissue (PD)
- Clinical activity of SY-1365 as measured by the Objective Response Rate (ORR), and rate of complete response (CR), partial response (PR), stable disease (SD), clinical benefit (CB), and time to response (TTR), duration of response (DoR), and progression-free survival (PFS)

References & Contacts

References:

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- Wang et al. CDK7-Dependent Transcriptional Addiction in Triple-Negative Breast Cancer. Cell. 2015
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