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 (Looyer, 2005).
- Recent preclinical studies support the hypothesis how these processes could be effectively controlled by inhibiting the expression of transcriptional factors through inhibition of CDK7, and have identified SY1365 as a potentially important new therapeutic target in solid tumors and hematologic malignancies.

SY-1365

- SY1365 is a first-in-class selective and potent covalent CDK7 inhibitor.
- CDK7 inhibition with SY1365 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 (Krawiszewski 2014, Christensen 2014, Wang 2015, Chopra 2014).
- Preclinical studies in solid tumor and hematologic malignancies show treatment with SY1365 leads to antitumor activity, showing a synergistic effect in vivo and complete regression in vivo xenograft models.

SY1365 Profile

- Short PK half-life (3-4 hours) with sustained PD effect (90-hour half-life).
- Highly selective: does not significantly bind to CDK9 or cell cycle CDKs.

Mechanism of Action

SY1365 inhibits tumor growth in TNBC in vivo model

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 chemotherapy
- TNBC: must have received prior platinum based chemotherapy
- Ovarian Cancer (high-grade serous type): must have received prior platinum doublet chemotherapy
- Prior exposure to cell cycle CDK inhibitors such as CDK4 and CDK6
- Patients with advanced solid tumors. The primary objectives are to assess the safety and tolerability of SY-1365 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 any tumors of histology to evaluate PK 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 in PBMCs & tumor tissue (PD)
- 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 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

- Chemotherapy or limited field radiation within 2 weeks, wide field radiation within 4 weeks, or irinotecan or mitomycin C within 6 weeks prior to entering the study.
- Receiving 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-authorized antitumor 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 CDK9 and CDK7 inhibitors alvocidib (Flavopiridol), dinaciclib, and seliciclib. Exception: previous exposure to cell cycle CDK inhibitors such as CDK4 and CDK9 (eg, palbociclib) is allowed.