Trial Design of a First-in-Human Phase 1 Evaluation of SY-1365, a First-in-Class Selective CDK7 Inhibitor, with Initial Expansions in Ovarian and Breast Cancer

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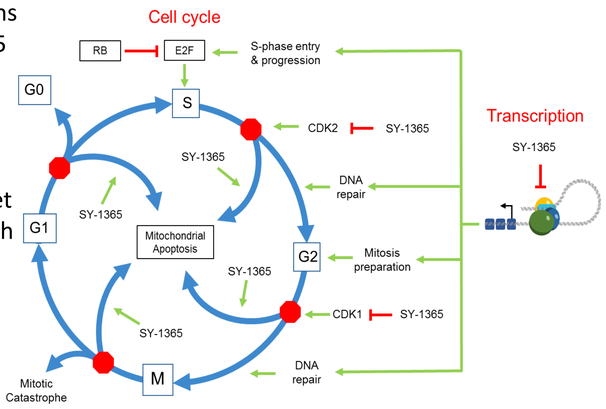
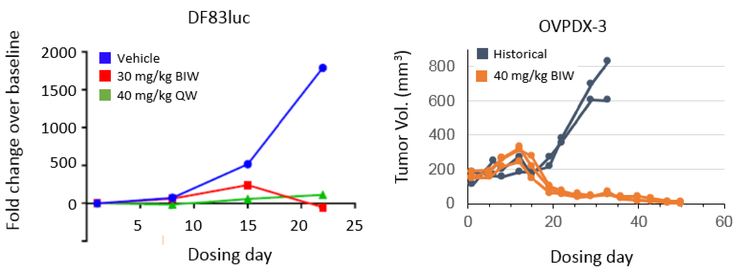
Summary

- SY-1365 is a first-in-class selective CDK7 inhibitor
- By inhibiting CDK7, SY-1365 is believed to preferentially induce apoptosis in cancer cells by lowering expression of key tumor-driving genes, transcription factors, and anti-apoptotic proteins
- Pre-clinical data supports the therapeutic potential of SY-1365 in a range of hematologic and solid tumors including ovarian and breast cancer
- Preclinical data in PDX models of heavily pretreated ovarian cancer demonstrate the potential for SY-1365 irrespective of BRCA status or PARP inhibitor sensitivity (Konstantinopoulos et al., AACR 2018); Preclinical data also support combination with carboplatin
- Preclinical models of SY-1365 demonstrate synergy with fulvestrant and the potential for SY-1365 in HR positive, HER2 negative metastatic breast cancer patients who progressed following CDK4/6 inhibitor plus AI treatment
- SY-1365 is currently in dose escalation in patients with advanced solid tumors, with expansion cohorts in ovarian and breast cancer as a single agent and in combination expected to open in mid-2018



SY-1365 Shows Activity in Ovarian Cancer Models

SY-1365 induces tumor growth inhibition, including complete regressions, in ovarian cancer PDX models



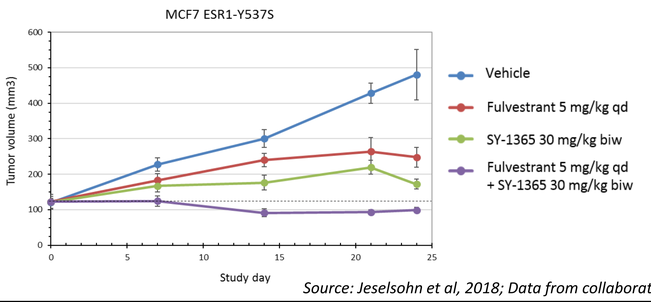
- Responses observed in 10/17 (59%) PDX models tested
- Responses observed in PDXs derived from heavily pre-treated patients
- Responses observed irrespective of BRCA status or olaparib sensitivity
- Responses associated with alterations in mitochondrial apoptosis and RB pathways

Source: Konstantinopoulos et al., AACR 2018

SY-1365 Shows Activity in HR+ Breast Cancer Models

- In breast cancer, SY-1365 induced cell death *in vitro* across sub-types and displayed synergy when combined with fulvestrant in HR+ models
- Recent data have shown that some patients eventually develop resistance to CDK4/6 inhibitors via various mechanisms including RB loss

SY-1365 Antitumor Activity in Combination with Fulvestrant in HR Positive Breast Cancer Xenografts



Growth of MCF7 tumor xenografts expressing ESR1-Y537S following treatment with SY-1365 and/or fulvestrant.
Error bars: standard error of the mean

Source: Jeselsohn et al, 2018; Data from collaboration with Dana-Farber Cancer Institute

Measuring SY-1365 Target Occupancy

- SY-1365 target engagement in PBMCs and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment
- CDK7 occupancy analyses over the dosing interval will guide dose and schedule optimization during dose escalation in patients based on pre-clinical PK/PD efficacy modeling

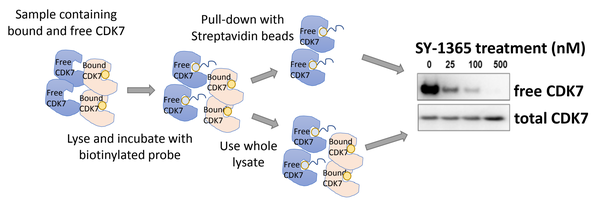


Fig A) Schematic for CDK7 occupancy assay determining target occupancy. For higher throughput, this method was adapted to a MSD plate-based method. The % occupancy is calculated as 100 x $CDK7_{bound}$ (B) / $CDK7_{total}$ (T).

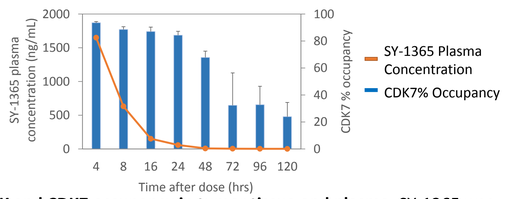


Fig B) SY-1365 PK and CDK7 occupancy in tumor tissue and plasma. SY-1365 was administered as a single iv dose (40 mg/kg) to HL-60 tumor-bearing mice. Plasma and tumor tissue were harvested from three mice per time point. SY-1365 plasma concentrations were determined using LC-MS/MS. CDK7 tumor occupancy was determined as described in Figure A.

Study Contact

For more information on the study, please contact Kristin Stephens at kstephens@syros.com

Trial Design

Part 1 Dose Escalation Phase	Part 2 Expansion Phase
Any advanced solid tumors	**Cohort 1**: Advanced Ovarian Cancer 3+ prior lines treatment Single Agent SY-1365 N=24
Bi-Weekly Dosing Schedule • Begin with "Accelerated escalation" schedule – single patient cohorts until DLT or ≥ Gr 2 related AE in cycle 1 • Then open standard 3+3 escalation cohorts	**Cohort 2**: Relapsed Ovarian Cancer Prior platinum, Still Sensitive SY-1365 + carboplatin N=24
Weekly Dosing Schedule • Standard 3+3 escalation	**Cohort 3**: Ovarian Cancer Primary Platinum Refractory Single Agent N=12
1. **Evaluate safety to define MTD for both dosing schedules** 2. **Analyze PK and CDK7 occupancy at all dose levels** 3. **Determine optimal dose and schedule to explore in Part 2 Expansion Cohorts**	**Cohort 4**: Advanced Solid Tumors (Any) Tumor biopsies (pre- and post-) Single Agent N=10
	Cohort 5: HR+ Metastatic Breast Cancer Post-CDK4/6 + AI treatment SY-1365 + fulvestrant N=12

- Multi-center, open-label Phase 1 trial expected to enroll approximately 117 patients in two parts
- Primary Objective is to assess the safety and tolerability of SY-1365 alone and in combination
- Both parts will analyze PK and PD (in blood and tumor tissue) and explore candidate biomarkers predictive of response to SY-1365

Part 1 – Single Agent Dose-Escalation

- SY-1365 is administered intravenously on two dosing schedules, weekly and twice-weekly for 3 weeks of each 4-week cycle
- Regimen optimization is based upon safety, PK, and PD (blood and tumor tissue) data prior to initiation of Part 2

Part 2 – Expansion Phase

- Preliminary anti-tumor activity and safety will be evaluated in approximately 82 patients across 5 cohorts
- SY-1365 is administered as a single agent, in
- combination with carboplatin, and in combination with fulvestrant
- PD endpoints will be evaluated in paired tumor biopsies from patients enrolled into Part 2, Cohort 4

Key Inclusion Criteria

Inclusion

- At least 1 measurable lesion by RECIST 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate hepatic, renal, and bone marrow function
- Tumor type, disease status, and prior treatment requirements as presented in study schema

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
- Part 2, Cohort 1-3: low grade ovarian cancer (eg. Low grade serous, mucinous carcinoma) are not eligible
- Part 2, Cohort 2: Prior adverse reaction to carboplatin (severe allergic reaction, progressive neuropathy, persistent cytopenias) that would preclude re-treatment with carboplatin. Platinum desensitization is allowed with Sponsor approval.
- Part 2, Cohort 5:
  - Prior treatment with chemotherapy in the advanced/metastatic setting or with fulvestrant
  - Advanced/metastatic disease that is symptomatic and/or with visceral spread

Key Study Endpoints

Primary:

Part 1: Dose limiting toxicities & treatment emergent adverse events

Part 2: Incidence of treatment-emergent AEs at the recommended dose and schedule for:

- Single-agent SY-1365
- SY-1365 combined with carboplatin
- SY-1365 combined with fulvestrant

Secondary:

Part 1 and Part 2

- PK measurements in plasma
- Percent occupancy of CDK7 by SY-1365 in PBMCs and tumor tissue
- Relationship between PK parameters and CDK7 occupancy

Part 2 only:

- Clinical activity measures by RECIST v 1.1, investigator-assessed
- Time to events: TTR, PFS, OS, and DoR

Exploratory

Part 1 and Part 2

- Modulation of downstream biological pathway impact of SY-1365 measured by quantifying changes in gene expression following SY-1365 transcriptional inhibition
- Exploration of candidate biomarkers and molecular characterization of tumor tissue and/or peripheral blood and correlation with clinical response or resistance to SY-1365
- **Part 1 only:** Preliminary assessment of clinical activity and time to event endpoints

Current Trial Status

- SY-1365-101 opened in May 2017 in the United States
- Dose escalation is ongoing
- Planned expansion cohorts are expected to open mid-year 2018