Abstract
TPS3662

First-in-human Phase I Study of SY-5609, an Oral, Potent, and Selective Noncovalent CDK7 Inhibitor, in Adult Patients with Select Advanced Solid Tumors

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Background

- CDK7 is a key regulator of two biological processes that drive tumor development: transcription and cell cycle control
- SY-5609 is an oral, noncovalent, highly selective and potent inhibitor of CDK7
- Preclinically, SY-5609 induces apoptosis, preferentially targeting cancer cells over non-tumor cells, and demonstrates robust antitumor activity in a range of solid tumor PDX models
- In PDX models derived from multiple solid tumor indications, including HGSOC, SCLC, CRC*, and TNBC,SY-5609 demonstrates deep and sustained tumor regressions, including activity in models known to be resistant to standard of care therapies
- Enrichment for response was observed in HGSOC, SCLC, and TNBC PDX models with alterations in RB pathway genes
- A multi-center, open label Phase 1 study was initiated in patients with advanced solid tumors, including relapsed and/or refractory ovarian, breast, colorectal, or lung cancer, and those with any solid tumor histology with molecular evidence of deregulated RB cell cycle control

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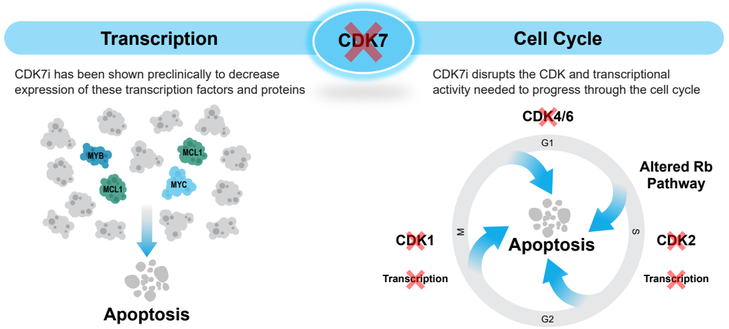
Effect of CDK7 Inhibition on Cancer Cells



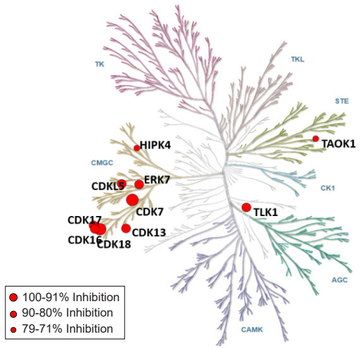
Methods

- This first in human, dose escalation study is designed to determine the safety and tolerability of SY-5609 and to evaluate the pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of SY-5609
- SY-5609 is administered orally once daily, for 28 days of each 4-week cycle
- An alternative dosing regimen may be evaluated if needed for patient safety or for a better understanding of the dose-toxicity or dose-exposure relationship of SY-5609
- Intra-patient dose escalation is permitted
- Dose-limiting toxicities and severity of adverse events will be graded using the National Cancer Institute Toxicity Criteria (NCI-CTCAE) v5.0
- Assessment of response and progression status will be evaluated every two cycles using the definitions from the RECIST v1.1
- Candidate biomarkers that may predict response to SY-5609 will be explored
  - Circulating tumor DNA (ctDNA) will be collected at two timepoints during the study
  - Optional fresh tumor biopsies will be collected for molecular analyses

SY-5609 Profile

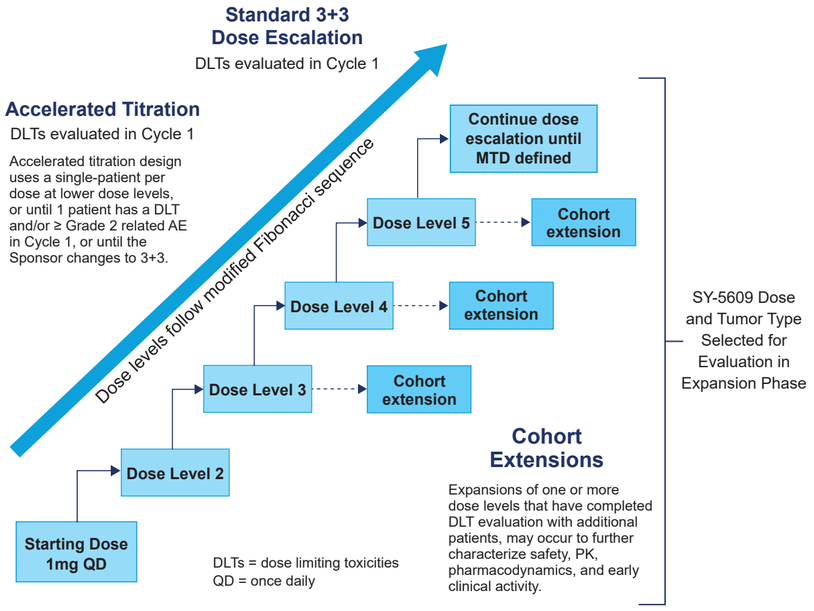
SY-5609 is a highly potent and selective CDK7 inhibitor

- 0.065 nM affinity for CDK7
- 13,000- to 49,000-fold more selective for CDK7 over CDK2, CDK9 and CDK12
- Only 4 of 485 kinases inhibited ≥ 90% at 1μM SY-5609



Hu S., et al., AACR 2019, Abstract 4421

Study Design



Key Eligibility

Key Inclusion

- At least 1 measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Diseases for which standard curative or palliative measures do not exist or are no longer effective, including:
  - Histologically confirmed metastatic or unresectable breast, ovarian, lung, or colorectal cancers, or
  - Any metastatic or unresectable solid tumor histology with evidence of deregulated RB cell cycle control (mutation or homozygous deletion of *RB1, CDKN1A,* or *CDKN2A*, or focal high-level amplification of *CCNE1, CCND1, CCND2, CDK4,* or *CDK6*) based on available molecular test results and after Sponsor review to confirm eligibility
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and life expectancy > 3 months
- All toxicities from prior cancer therapies must have resolved to ≤ Grade 1 before enrollment, except for acquired endocrine disorders post immunotherapy that have resolved to ≤ Grade 2 with appropriate hormone replacement therapy

Key Exclusion

- Chemotherapy or limited field radiotherapy within 2 weeks, wide field radiotherapy within 4 weeks, or nitrosoureas or mitomycin C within 6 weeks before entering the study
- Received any other investigational agents within 4 weeks before enrollment, or < 5 half-lives since completion of previous investigational therapy, whichever is shorter
- Received previous noncytotoxic, US Food and Drug Administration–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, dinaciclib, seliciclib, and SY-1365
  - *Exception:* Previous exposure to cell cycle CDK inhibitors such as inhibitors of CDK4 and CDK6 (ie, palbociclib) is allowed.
- Known brain metastases or carcinomatous meningitis
  - *Exception:* Previously treated brain metastatic disease that remains stable on magnetic resonance imaging ≥ 4 weeks before enrollment, without steroids or antiepileptic medications, is allowed.

Study Objectives

Primary Objectives

- To assess the safety and tolerability of orally administered SY-5609 by determining the maximum tolerated dose and dose-limiting toxicities associated with the study drug

Secondary Objectives

- Evaluate the pharmacokinetic effects of SY-5609

Exploratory Objectives

- Evaluate the pharmacodynamic effects of SY-5609*
- Evaluate the preliminary antitumor activity of SY-5609 in patients with select advanced solid tumor malignancies
- Identify candidate biomarkers predictive of response to SY-5609

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Key Endpoints

Primary Endpoints

- Dose limiting toxicities (Cycle 1), incidence of treatment emergent adverse events, and changes in clinical laboratory values, electrocardiograms (ECGs), and vital sign measurements

Secondary Endpoints

- PK parameters in plasma

Exploratory Endpoints

- Effect between SY-5609 dose and pharmacodynamic responses in cells and tissues
- Preliminary assessment of clinical activity
- Exploration of the relationship between clinical activity and molecular markers detected in tumor tissue and blood

Study Summary

- This is a multi-center, open-label Phase 1 study expected to enroll approximately 60 adult patients with ovarian, breast, colorectal, or lung cancer, and patients with any solid tumor histology with molecular evidence of deregulated RB cell cycle control, for which standard curative or palliative measures do not exist or are no longer effective
- Initial dose levels utilize an accelerated single-patient titration design. A traditional 3+3 design begins after either one patient has a DLT and/or Grade 2 related AE during Cycle 1, the accelerated dose levels clear, or the Sponsor decides to transition to a 3+3 design
- To further characterize safety, PK, PD and early clinical activity, any dose level that has cleared the DLT evaluation may be extended to enroll up to a total of 12 patients while dose escalation proceeds
- An amendment to characterize the safety of SY-5609 in combination with fulvestrant in HR+/HER2- mBC patients post-CDK4/6 inhibitors is planned. These patients will receive SY-5609 on a 21-day on/7-day off schedule
- Data from this trial will support dose selection for further evaluation of antitumor activity of SY-5609 as a single agent and in combination with other therapies
- Trial opened in Jan 2020
- ClinicalTrials.gov identifier: NCT04247126

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