SY-5609, a Potent and Selective CDK7 Inhibitor, Potentiates BTK Inhibitor Activity in Mantle Cell Lymphoma Preclinical Models
Liv Johannesssen1, Priyanka Sawant2, Anthony D'Ippolito2, Nan Ke2, Ariel Lefkowitz2, Matthew Eaton2, Wojciech Dworakowski2, Maria Rosario, Susan Henry2, Graeme Hodgson2
Syros Pharmaceuticals, Inc., Cambridge, MA; 1Stockholder or 2employee and stockholder of Syros Pharmaceuticals, Inc.; contact: shenry@syros.com

Background and rationale

SY-5609 potentially inhibits proliferation of MCL cell lines in vitro

- SY-5609 is a key regulator of transcription and cell cycle progression and has been implicated in multiple tumor types driven by aberrant transcriptional (MYC, ESR1) and/or aberrant cell cycle control (loss of RB pathway checkpoint function) mechanisms.
- SY-5609 is a potent, selective, and oral CDK7 inhibitor in development in patients with advanced solid tumors, including patients with RB pathway alterations (NCT04247126).
- Mantle cell lymphoma (MCL) is an aggressive B cell lymphoma characterized by aberrant transcriptional (MYC, ESR1) signaling through Bruton's Tyrosine Kinase (BTK), a strong activator of downstream transcriptional programs that drive cell proliferation and survival (e.g. NF-KB).

Here we report on the activity of SY-5609 in models of MCL, providing rationale for the evaluation of SY-5609, including in combination with BTK inhibitors, in patients with MCL.

SY-5609 inhibits Mino cell proliferation at concentrations that also induce POLR2A to levels observed in SY-5609-treated patient PBMCs

- SY-5609 shows synergistic antiproliferative activity with the BTK inhibitor acalabrutinib in Mino cells, and potentiates antitumor activity of acalabrutinib in Mino xenografts.

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Combination of SY-5609 and acalabrutinib leads to increase in proportion of Mino cells with sub-G1 DNA content, a marker of cell death

SY-5609 potently inhibits proliferation of MCL cell lines in vitro

- SY-5609 is a potent and selective CDK7 inhibitor, potentiates BTK inhibitor activity in Mantle Cell Lymphoma Preclinical Models.

Conclusions

- SY-5609 potently inhibits proliferation of MCL cell lines in vitro.
- SY-5609 antiproliferative activity in MCL cell line Mino is associated with POLR2A PD changes comparable to those observed in PBMCs from patients with advanced solid tumors treated with SY-5609 at a tolerable dose and regimen.
- SY-5609 shows synergistic antiproliferative activity with the BTK inhibitor acalabrutinib in Mino cells in vitro, and potentiates acalabrutinib antitumor activity in Mino xenografts in vivo.
- The combination of SY-5609 and acalabrutinib in Mino cells in vitro, at subtherapeutic concentrations of either single agent, is associated with:
  - Decreased expression of CCND1, CCNE1, and E2F2 proteins, key regulators of RB checkpoint function and cell cycle progression
  - Increased proportion of cells with sub-G1 DNA content, a marker of cell death.
- A Phase 1b safety and preliminary efficacy study of SY-5609, including in combination with a BTK inhibitor, is planned for patients with relapsed/refractory MCL.

1. GR50: concentration of SY-5609 that inhibits growth rate by 50% (GR = 0.5).
2. GRmax: minimum GR value.
3. GEC50: concentration at point midway between top and bottom asymptote of fitted curve.
4. All treatments to be compared with vehicle.
5. All regimens well-tolerated: no body weight loss observed at end of treatment (day 25).

Results shown are representative of 3 independent experiments.

Combination of SY-5609 and acalabrutinib decreases expression of key regulators of RB checkpoint function and cell cycle progression in Mino cells

- SY-5609 (10nM) induces G1 arrest.
- Acalabrutinib (20nM) does not induce cell cycle changes by 72 hours.
- Combination induces an increase of cells with sub-G1 DNA content (a marker of dead or dying cells).

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Conclusions

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- A Phase 1b safety and preliminary efficacy study of SY-5609, including in combination with a BTK inhibitor, is planned for patients with relapsed/refractory MCL.