Tolerability and Preliminary Activity of the Potent, Selective, Oral CDK7 Inhibitor SY-5609 in Combination with Fulvestrant in Patients with Advanced Hormone-Receptor-Positive (HR+), HER2- Breast Cancer (BC)

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Background
- SY-5609 is a highly selective and potent oral CDK7 inhibitor.
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- Under normal conditions, CDK7 controls two key biological processes that are frequently altered in cancer biology: transcription and cell cycle control.
- 0.07-0.08 potency for CDK7.
- 12,000- to 40,000-fold selectivity for CDK7 over CDK9 and CDK12.
- Only 4 of 485 kinases inhibited at ≥ 90%.

Methods
- Evaluation of the SY-5609 monotherapy in safety, pharmacology, and preliminary activity in an open-label dose-escalation study with 179 patients with advanced, refractory HR+ BC.
- SY-5609 was combined with fulvestrant in patients with advanced, refractory metastatic breast cancer.
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- Phase 1 single-agent dose escalation study enrolled select solid tumors (Devisse et al., 2021).

Results
- Study Summary: SY-5609 single agent (SA) safety informed dose and schedule of fulvestrant combination cohorts
  - Single-agent dose escalation: 1 mg/kg BID 7/7 on 4/21/2021.
  - Dose and schedule expansion including 5 mg/kg QD, 3 mg/kg BID, and 1 mg/kg QD.
  - 78% of 78 evaluable patients achieved overall response (OR; 95% CI 67-89).
  - ORR > 90% for SY-5609 single agent.

Mechanistic rationale and pre-clinical data supports the use of SY-5609 in HR+/HER2- breast cancer
- Aberrant hormonal signaling and cell cycle vulnerabilities that can be targeted by CDK7 inhibition.
- PIK3CA, ESR1, TP53, and RB pathway.

Study Design
- SY-5609 was combined with fulvestrant in patients with advanced, refractory metastatic breast cancer.
- Phase 1 single agent dose escalation study enrolled select solid tumors (Devisse et al., 2021).
- Evaluation of the SY-5609 plus fulvestrant combination began with an SA SY-5609 level and schedule that had cleared the single agent DLT evaluation period.

Key Eligibility
- Postmenopausal women with HR+, HER2- breast cancer.
- Failure of prior treatment with CDK4/6 + hormonal therapy.
- No limits on prior lines of therapy.

Assessments
- Adverse events and tolerability within cycle 1 Dose Limiting Toxicities (DLTs) were evaluated.
- Tumor responses were assessed per RECIST v1.1.

Key Endpoints
- Plasma exposure was measured using the non-compartmental approach, and compared to pharmacodynamic and safety endpoints.

Demographic and Baseline Disease Characteristics of Safety Population (N=14)
- Gender, n (%): 10 (71.4).
- Race: 11 (78.6).
- Median age: 61 (25-83).
- Sites of metastatic disease: bone (85.7), lung (78.6), liver (50.0), other (50.0).
- Median prior therapeutic regimen, n (range): 6 (2-12).
- Prior Fulvestrant therapy, n (%): 11 (78.6).
- Median prior hormonal agents, n (range) (other than fulvestrant): 2 (1-6).
- Median prior non-hormonal agents, n (range): 3 (1-6).

Patient Disposition Safety Population (N=14)
- Duration of Treatment: Median: 6.0 months (range: 0.5-30.6).
- Patient Withdrawn from Treatment, n (%): 5/14 (35.7).
- Symptomatic Disease Progression: 3/14 (21.4).
- Adverse Event: 2/14 (14.3).
- Withdrawal Consent: 1/14 (7.1).

Conclusions
- SY-5609 + fulvestrant has an acceptable safety profile on a variety of dosing schedules consistent with single-agent SY-5609 or fulvestrant, with no new safety signals emerging from the combination at evaluated doses and dosing schedules.
- Encouraging early activity, even at low doses and over a range of dosing schedules, with a 42% DCR and 3 patients on study ≤ 6 months in a cohort with advanced, heavily pre-treated disease. Opportunity may exist to improve upon this activity with an optimized dose and schedule.
- SY-5609 exposures in combination with fulvestrant are comparable to exposures achieved with SY-5609 monotherapy.

Acknowledgements and Contact Information
- We would like to acknowledge all the SY-5609-011 study partners and all the patients and their caregivers for their participation.
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Figures
- Day 1 SY-5609 Cmax and AUC0 inf in combination with fulvestrant are comparable to single agent SY-5609 exposures.
- SY-5609 + fulvestrant has an acceptable safety profile on a variety of dosing schedules consistent with single-agent SY-5609 or fulvestrant, with no new safety signals emerging from the combination at evaluated doses and dosing schedules.
- Durable disease control was observed in 25% (3/12) of response-evaluable patients, including 2 patients with SD and target lesion regressions.
- Stable disease, including target lesion regression, observed in difficult-to-treat patients unlikely to respond to SOC

Source: 03Apr2023 Data snapshot

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