#3081

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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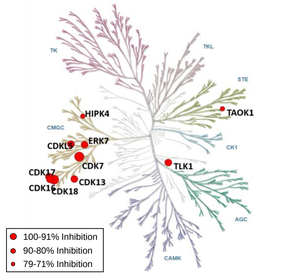
Background

SY-5609 is a highly selective and potent oral CDK7 inhibitor

- SY-5609 is an oral, non-covalent, highly selective and potent inhibitor of CDK7
- Under normal conditions, CDK7 controls two key biological processes that are frequently aberrant in cancer biology: transcription and cell cycle control

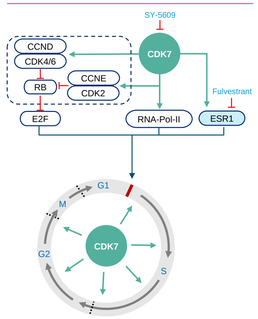
- 0.07 nM potency for CDK7
- 12,000- to 40,000-fold selective for CDK7 over CDK2, CDK9 and CDK12
- Only 4 of 485 kinases inhibited at ≥ 90% with 1uM SY-5609



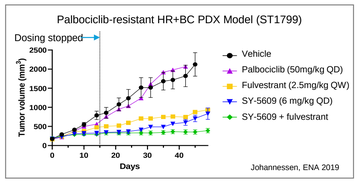
Johannessen, ENA 2019, abstract C091

Mechanistic rationale and pre-clinical data supports the use of SY-5609 in HR+/HER2- breast cancer

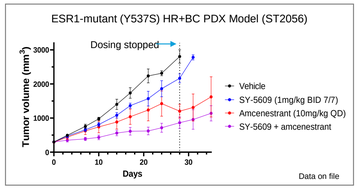
Aberrant hormonal signaling and cell cycle are vulnerabilities that can be targeted by CDK7 inhibition



SY-5609 potentiates estrogen receptor degrader activity in HR+ breast patient derived xenograft models



Johannessen, ENA 2019



Data on file

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 (Sharma et al, ESMO 2021)
- Evaluation of the SY-5609 plus fulvestrant combination began with an SY-5609 dose level and schedule that had cleared the single agent DLT evaluation period

Key Eligibility

- Post-menopausal women with HR+, HER2- breast cancer
- Failure of prior treatment with CDK4/6i + hormonal therapy
- No limits on prior lines of therapy

Key Endpoints

- Incidence of AEs and changes in laboratory values, ECGs, and vital signs

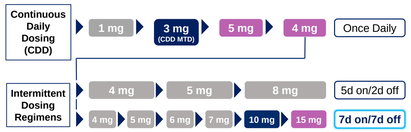
Assessments

- Safety and tolerability, including cycle 1 Dose Limiting Toxicities (DLTs) were evaluated.
- Tumor responses were assessed per RECIST v1.1

Results

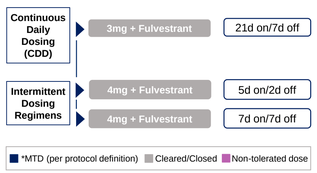
Study Summary: SY-5609 single agent (SA) safety informed dose and schedule of fulvestrant combination cohorts

Single-Agent Dose Escalation



- Single agent dose escalation
  - Ph 1 study enrolled select solid tumors
  - Dose and schedule exploration, including daily, 5d on/2d off, and 7d on/7d off schedules.
  - 7d on/7d off schedule allowed escalation to the maximum tolerated dose* (MTD) level of 10mg (n=3). 15mg was non-tolerated single agent dose using 7d on/7d off schedule.

Breast Cancer Combination with Fulvestrant



- After clearing SA cohorts on a variety of schedules, cohorts of SY-5609 in combination with fulvestrant were opened on the following schedules:
  - 21d on/7d off
  - 5d on/2d off
  - 7d on/7d off
- SY-5609 administered in combination with standard dose fulvestrant

■ *MTD (per protocol definition) ■ Cleared/Closed ■ Non-tolerated dose

Demographic and Baseline Disease Characteristics of Safety Population (N= 14)	
Median age – years (range)	63 (46-83)
Female, n (%)	14 (100)
Sites of metastatic disease, n (%)	
Liver	11 (78.6)
Bone	11 (78.6)
Lymph nodes	7 (50.0)
Lung	5 (35.7)
Other	5 (35.7)
Median no. prior therapeutic *regimens*, n (range)	6 (3-12)
≥ 5 prior regimens, n (%)	11 (78.6)
Prior Fulvestrant therapy, n (%)	12 (85.7)
Median no. prior hormonal agents, n (range) (other than fulvestrant)	2 (1-3)
Median no. non-hormonal agents, n (range)	5 (3-11)

Patients had advanced, heavily pre-treated disease with poor-risk features
Note: All enrolled patients received prior CDK4/6 per eligibility criteria

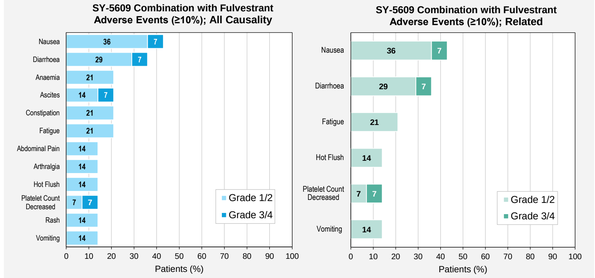
Source: 03Apr2023 Data snapshot

Patient Disposition Safety Population (N=14)	
Duration of Treatment: Median # days (range)	49 (2-336)
Patient Withdrawn from Treatment, n (%)	14 (100.0)
Disease Progression per RECIST v1.1	8 (57.1)
Symptomatic Disease Progression	3 (21.4)
Adverse Event	2 (14.3)
Withdrew Consent	1 (7.1)

Source: 03Apr2023 Data snapshot

Results

Safety Summary



SY-5609 combination with Fulvestrant Safety Population, N = 14
Only maximum toxicity grade was considered per MedDRA preferred term per patient

Source: 03Apr2023 Data snapshot

- 1 DLT reported in SY-5609 4mg 5d on/2d off + fulvestrant dose cohort: Grade 3 thrombocytopenia
- Majority of AEs were low grade and consistent with SY-5609 or fulvestrant
- No new safety signals were seen for the SY-5609+fulvestrant combination

Disease control rate (DCR) was 42%, including Stable Disease with target lesion shrinkage

SY-5609 Dose & Schedule + Fulvestrant	Response Evaluable[a] (N=12)	Best Overall Response	
		SD[b]	PD[b]
3mg 21d on/7d off	7	2	5
4mg 7d on/7d off	1	0	1
4mg 5d on/2d off	4	3	1

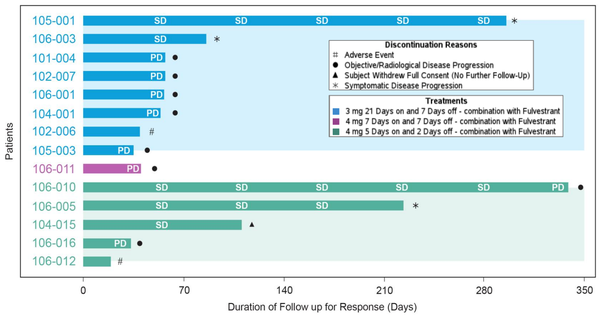
- 5 out of 12 response-evaluable patients achieved SD
  - 3 out of 5 patients with SD had target lesion regression

a) Response evaluable: all patients with at least one post baseline RECIST evaluation, or symptomatic disease progression

b) Abbreviations: SD: stable disease; PD: progressive disease

Source: 03Apr2023 Data snapshot

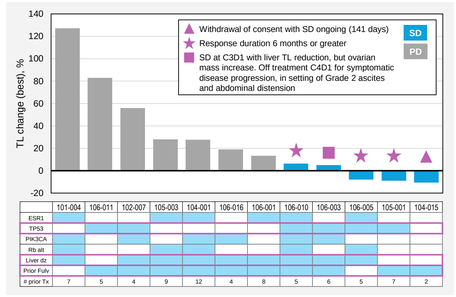
Durable disease control was observed in 25% (3/12) of response-evaluable patients, including 2 patients with SD and target lesion regressions



- Three patients (25%) remained on treatment with SD for greater than 6 months
  - 2/3 patients with SD had target lesion reductions
- Median duration of treatment: 49 days
- Duration of Follow-up for Response (months):
  - Mean: 3.79
  - Median: 1.87
  - Min-Max: 1.1-11.1

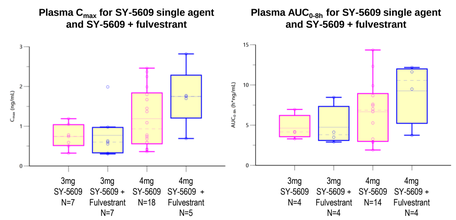
Results

Stable disease, including target lesion regression, observed in difficult-to-treat patients unlikely to respond to SOC



- Durable disease control observed in patients with *TP53* mutations, prior fulvestrant and/or liver disease
- No clear correlation of disease control with *ESR1*, *PIK3CA*, or RB pathway alteration.

Day 1 SY-5609 C_{max} and $AUC_{(0-8)}$ in combination with fulvestrant are comparable to single agent SY-5609 exposures



SY-5609 + fulvestrant show exposure range comparable to **SY-5609 Single Agent**

Solid horizontal line – mean
Dashed horizontal line – median
Lower end of box – lower 25th percentile
Upper end of box – upper 75th percentile
Lower whisker – lower 2.5th percentile
Upper whisker – upper 97.5th percentile

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.
- The mechanistic rationale for CDK7 inhibition in HR+, HER2- BC and the tolerability and encouraging early activity in this heavily pretreated population support future investigation of the combination with SY-5609 at higher doses in HR+, HER2- BC on a 7d on/7d off schedule.

Acknowledgements and Contact Information

We would like to acknowledge all the SY-5609-101 study centers and all the patients and their caregivers for their participation.

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