Tolerability and Preliminary Clinical Activity of SY-5609, a Highly Potent and Selective Oral CDK7 Inhibitor, in Patients with Advanced Solid Tumors

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Mini oral session – Developmental therapeutics

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Study Design and Methods

- SY-5609 is an oral, non-covalent, highly selective and potent inhibitor of CDK7
- CDK7 controls two key processes that, when deregulated, are important in cancer biology: transcription and cell cycle control
- SY-5609 proof of mechanism shown by *POLR2A* PD changes was previously demonstrated in solid tumor patients *(Papadopoulos, ENA 2020, Abstract #180)*

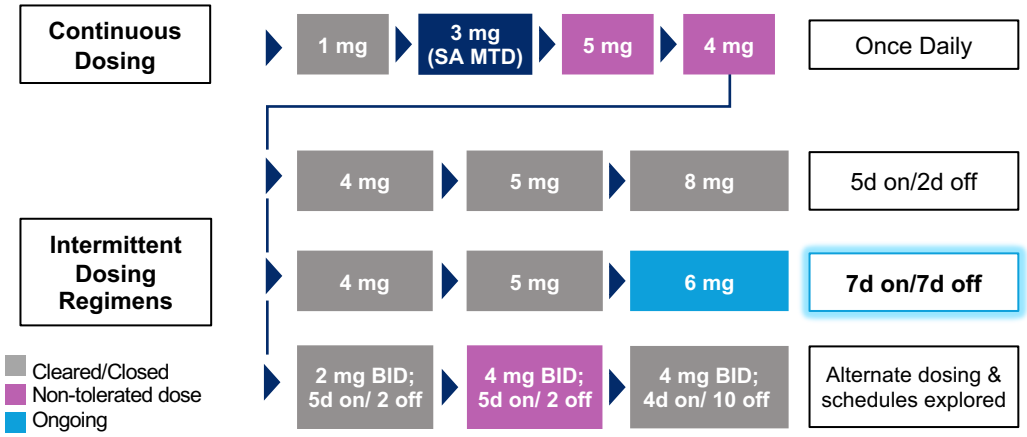
Methods

- Phase 1, FIH study
- Standard 3+3 dose escalation with select extension cohorts
- Enrolled advanced refractory breast, colorectal, lung, ovarian or pancreatic cancer *and* any histology with documented RB molecular alterations

Objectives

- Safety, tolerability, and MTD of SY-5609
- Safety and tolerability of SY-5609 + fulvestrant in breast cancer
- Preliminary antitumor activity
- PK and exploratory PD studies

SY-5609-101 Single-Agent Dose Escalation Schema



SY-5609 in combination with fulvestrant was evaluated in breast cancer at 3mg and 4mg at intermittent schedules. Further enrollment in this cohort has been stopped to prioritize efforts in the other dose escalation cohorts

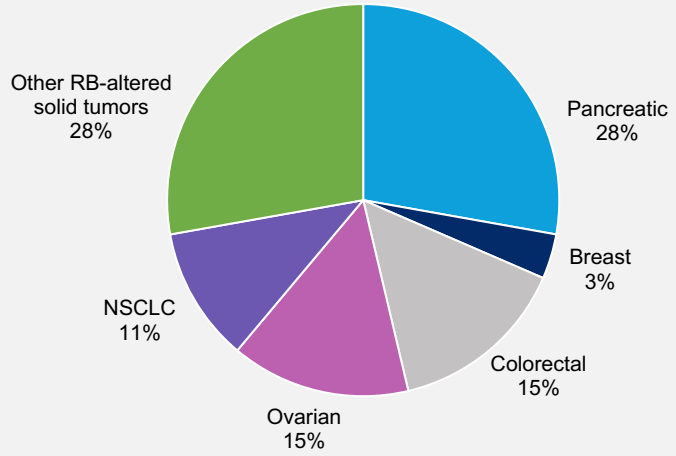
Intermittent schedules have allowed dose escalation beyond continuous dosing MTD (3 mg/day)

Currently enrolling in 6 mg/d cohort on 7d on/7d off schedule

Baseline Characteristics and Patient Disposition

Baseline Characteristics		
	SY-5609 Single-Agent N = 54	**SY-5609 + fulvestrant N = 14**
Median Age, years (range)	65.5 (44-81)	63 (46-83)
Gender, n (%) Female	34 (63)	14 (100)
Median # prior therapies (range)	4 (1-8)	4.5 (1-12)
≥ 5 Prior therapies, n (%)	22 (41)	7 (50)

Tumor Types (%) – Single-Agent Cohorts (N = 54)



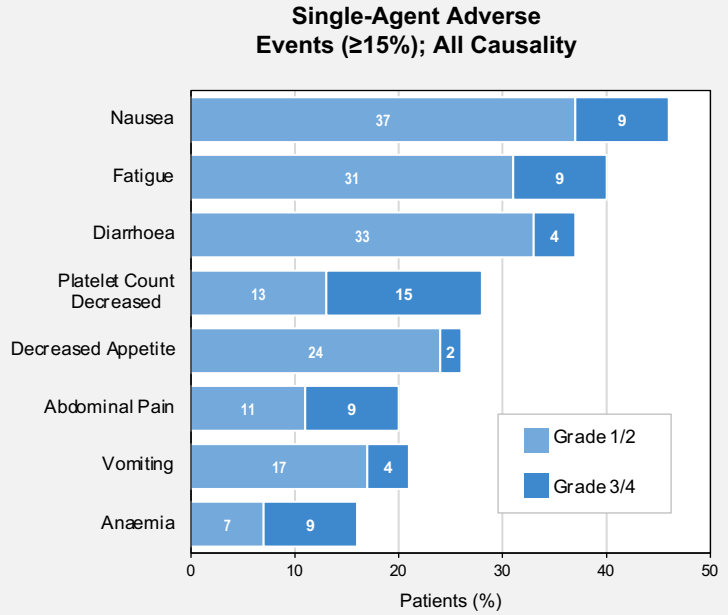
Patient Disposition		
	SY-5609 Single-Agent N = 54	**SY-5609 + fulvestrant N = 14**
Duration of Treatment: Median days (range)	50.5 (7-344)	49 (19-273)
Patients continuing to dose	8 (14.8)	4 (28.6)
Patients withdrawn from treatment	46 (85.2)	10 (71.4)
Disease Progression (per RECIST)	31 (57.4)	7 (50.0)
Symptomatic Disease Progression	7 (13.0)	2 (14.3)
Adverse Event	4 (7.4)	1 (7.1)
Withdrew Consent/ Investigator Decision/ Other	4 (7.4)	0

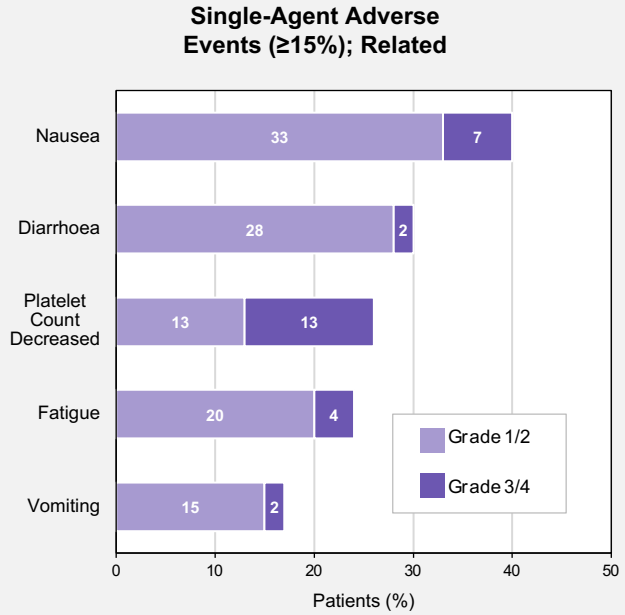
Data cut date – 06Jul2021

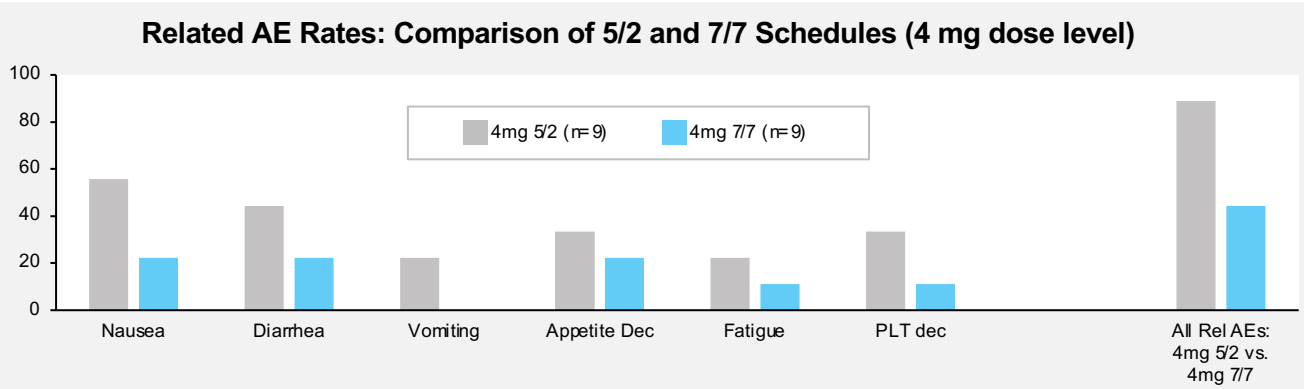
SY-5609 Single-Agent Safety Profile is Manageable, and Tolerability is Improved with Intermittent Dosing Regimens

- Majority of AEs were low-grade and reversible
- Most frequent TEAEs: GI, fatigue, thrombocytopenia, anemia
- Rates of related AEs were lowest with 7/7 schedule
- DLTs observed across cohorts were:
  - Thrombocytopenia (3), nausea (2), colitis (2), abdominal pain (1), fatigue (1), mucositis (1) & hypotension (1)
- Safety profile was similar for SY-5609 + fulvestrant combination cohort

7d on/7d off intermittent dosing schedule best enhanced tolerability







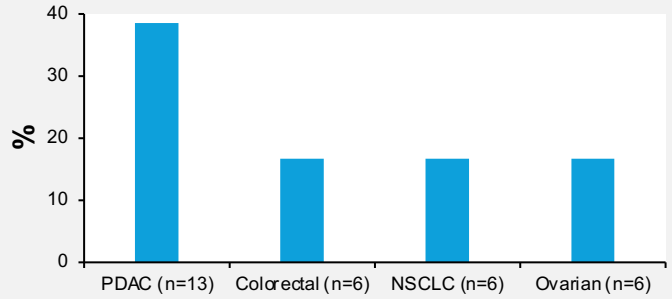
Single-Agent Safety Population, N = 54, Data cut date – 06Jul2021

Single-Agent Clinical Activity Demonstrated in Multiple Tumor Types; Notable Activity in PDAC

Single-Agent Clinical Activity: Overall Summary

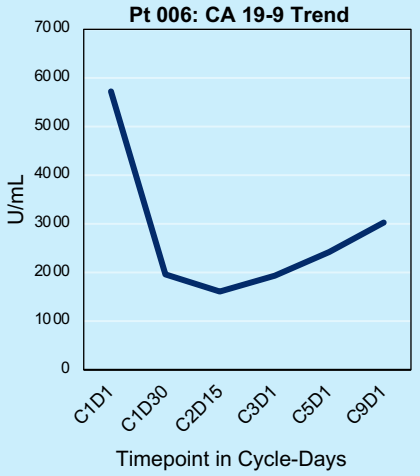
- SD was best response in 13/45 (28.9%) patients
  - SD with tumor regression: 6/13 patients (-9.1% to -20%)
  - SD achieved in daily and intermittent dose cohorts with doses as low as 3 mg/d, including a 25% SD rate in 7d on/7d off cohorts
- Tumor marker decreases: 1 ovarian cancer pt with GCIG response (84% CA-125 decrease) and associated 18% target lesion regression; 3 PDAC pts with decreases in CA 19-9
- *POLR2A* PD changes sustained for at least 3 days post drug cessation and target PD levels are achieved at steady state at doses ≥3 mg

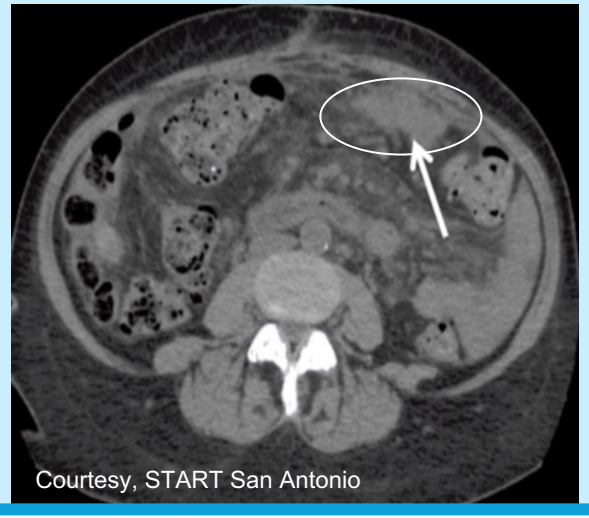
DCR* for Disease Cohorts with > 5 pts

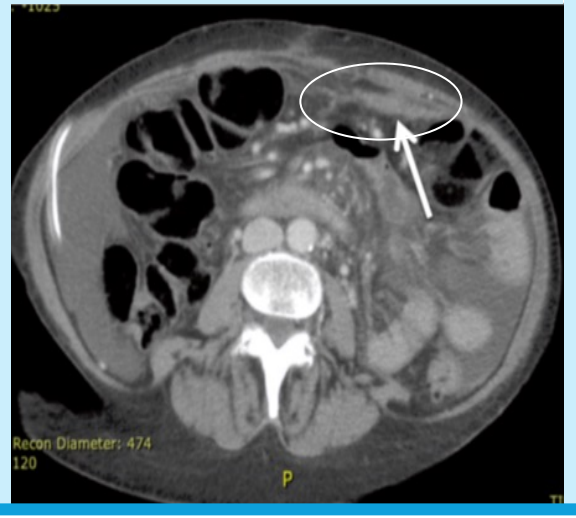


*Disease Control Rate (DCR) = SD + PR + CR

Pt 006: PDAC - Durable SD (10 cycles; 7+ mos on 3 mg 7/7); 20% decrease in T1, 72% CA 19-9 decrease; 3 prior regimens (FOLFIRINOX x 3.5 mos, Xeloda x 1.5 mos, Gem/nabPac x 10 mos)







Clinical Activity in PDAC (n = 13)

- Median # prior therapies = 4 (range, 2-7)
- PDAC DCR = 38.5% (5/13 pts had SD)
  - All SD pts received prior Gem/nabPac *and* FU-based therapy (FOLFIRINOX/ OFF/FOLFOX)
  - 1 pt with durable SD (see left panel)
  - 4 pts with SD on treatment for 69-74 days
- CA 19-9 decrease in 3 of 4 pts with serial levels (32%, 44%, 72% max decrease)

Conclusions

- The safety profile for SY-5609 is predictable, and AEs are generally low-grade and manageable; most common AEs were fatigue, GI symptoms, thrombocytopenia and anemia.
- The 7d on/7d off regimen successfully enhanced tolerability, allowing escalation to levels beyond the continuous dosing MTD (3 mg/day), with ongoing dosing at 6 mg/day in 7d on/7d off regimen.
- Encouraging single-agent clinical activity was seen in refractory, heavily pretreated solid tumors, at doses that are well tolerated, and at which target PD has been demonstrated.
- The 7d on/7d off regimen is supported by pre-clinical data* and clinical *POLR2A* PD data, evidence of clinical anti-tumor activity on the 7d on/7d off regimen, and a safety profile and dosing interval that is compatible with multiple therapeutic combination partners.
- Encouraging single-agent clinical activity in PDAC, including disease control rate more than double of that observed for other tumor types, and pre-clinical data demonstrating synergy with gemcitabine* support evaluation of SY-5609 in combination with standard chemotherapy in pancreatic cancer in an expansion portion of the ongoing Phase 1 study.

*See ESMO 2021 posters #2862/14P, #2352/13P

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