#3080

Phase 1/1b Study of SY-5609, a Selective and Potent CDK7 Inhibitor, in Advanced Solid Tumors and in 2L/3L Pancreatic Ductal Adenocarcinoma (PDAC) in Combination with Gemcitabine +/- nab-paclitaxel

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Background

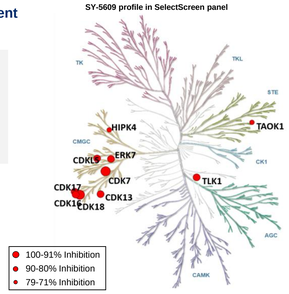
SY-5609 is a highly selective and potent oral CDK7 inhibitor

- SY-5609 potency and selectivity:
  - 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

CDK7 controls two key biological processes that are frequently aberrant in cancer biology: transcription and cell cycle control

Johannessen, ENA 2019, abstract C091

SY-5609 profile in SelectScreen panel



SY-5609 single agent (SA) dose/schedule exploration led to selection of 7d on/7d off (7/7) schedule for further escalation and combination approaches

- In SA escalation portion of study, 7/7 schedule optimized tolerability beyond maximum tolerated dose (MTD) of continuous daily dosing (CDD) and enabled further single agent (SA) escalation and combination approaches[1]
  - Activity noted in multiple tumor types across a range of doses and schedules

SA clinical activity in patients (pts) with PDAC, preclinical data and mechanistic rationale support exploration of the combination of SY-5609 with chemotherapy in PDAC

- SA activity in PDAC included durable stable disease (SD), target lesion reductions, and decreases in CA 19-9
- SY-5609 inhibits growth and synergizes with gemcitabine in pre-clinical studies in PANC-1 cells *in vitro* and in PDAC xenografts *in vivo*[2]
- Cell cycle and Rb checkpoint vulnerabilities in PDAC support a mechanistic rationale for CDK7 inhibition in PDAC

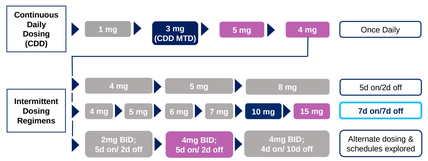
[1]Sharma M., et al. ESMO 2021; [2]Henry S., et al ESMO 2021

Study Design

	SY-5609 Single Agent (SA)	PDAC Safety Lead-Ins (SLI)
Study Design	• 3+3 SA dose escalation with select extension cohorts	• 3+3 escalation • Escalated SY-5609 dose using 7/7 schedule in combination with standard doses of gemcitabine (gem) +/- nab-paclitaxel (nab-pac) administered intravenously on a biweekly schedule
Key Eligibility Criteria	• Advanced refractory breast, colorectal, lung, ovarian, pancreatic cancer *or* any histology with documented RB molecular alterations	• Histologically confirmed metastatic PDAC • **SY-5609/Gem dose:** 2L/3L refractory to FOLFIRINOX or modified FOLFIRINOX • **SY-5609/Gem/nab-pac dosage**: 2L refractory to FOLFIRINOX or modified FOLFIRINOX
Key Objectives	**Primary:** Safety, tolerability, and MTD of SY-5609 **Secondary:** PK **Exploratory:** Preliminary antitumor activity and exploratory PD studies	**Primary:** Safety, tolerability, and MTD of SY-5609 in combination with gem +/- nab-pac **Secondary:** PFS, ORR, DCR, TTR, and DOR **Exploratory:** PK, PD, CA 19-9 trends

Results: SY-5609 Single Agent

Single-agent dose escalation: Study summary



Study progress

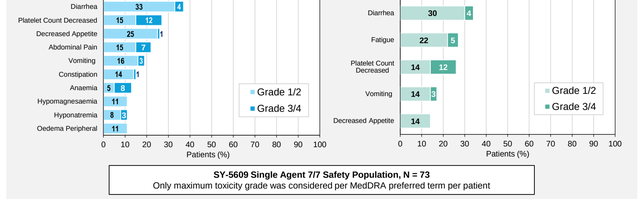
73 pts enrolled across all SA cohorts

- 33 patients enrolled in 7/7 cohorts
- 15mg identified as non-tolerated dose using 7/7 schedule
- MTD* level was 10mg (n=3) using 7/7 schedule
- Data snapshot: 03 April 2023

Single Agent: Demographic and Baseline Disease Characteristics of Safety Population (N = 73)	
Median age – years (range)	65 (44-81)
Male – n (%)	28 (38.4)
Female – n (%)	45 (61.6)
Tumor type – n (%)	
PDAC	24 (32.9)
Colorectal	12 (16.4)
Lung	8 (11.0)
Breast	5 (6.9)
Ovarian	19 (12.3)
Rb-altered cohort	15 (20.6)
Previous lines of therapy – median (range)	4 (1-8)

Single Agent Patient Disposition (Safety population; N =73)	
Duration of Treatment: Median days (range)	49 (4-287)
Continuing to dose, n (%)	0
Withdrawn from treatment – n (%)	73 (100.0)
Progression by RECIST v1.1	47 (64.4)
Symptomatic Progression	13 (17.8)
Withdrew Consent	5 (6.8)
Death	0
Adverse Event	8 (10.9)

SY-5609 single agent safety summary: Majority of AEs are low grade and reversible



SY-5609 Single Agent 7/7 Safety Population, N = 73
Only maximum toxicity grade was considered per MedDRA preferred term per patient

SY-5609 single agent safety summary: 7d on/7d off schedule improves tolerability and maximizes ability to escalate SY-5609

- No new emerging safety trends at higher doses
  - Most frequent TEAEs: GI-related, fatigue and decreased platelet counts
- Tolerability of 7d on/7d off dosing schedule has allowed escalation to an MTD of 10mg, which is > 3x the continuous daily dosing MTD (3mg)
- Dose limiting toxicity (DLT) summary of 7/7 schedule cohorts (4-7mg, 10 & 15 mg dose levels; n=33):
  - One pt with DLT at 4 mg dose level (G4 thrombocytopenia, G3 mucositis, G3 hypotension)
  - Two pts with DLTs at 15mg dose level (G4 thrombocytopenia)
  - Single-agent 15mg dose level established as a non-tolerated dose

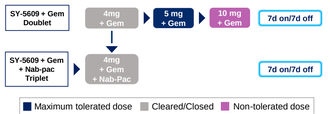
BOR Summary for Response Evaluable[a] Patients by Cohort

Best Overall Response (BOR)	Single Agent Regimens other than 7/7 (CDD, 5d on/2d off, 4d on/10d off) (N=37)	Single agent 7/7					
		Dose Level (No. of response evaluable[b] patients)					
		4mg (N=9)	5mg (N=6)	6mg (N=5)	7mg (N=6)	10mg (N=3)	Total (N=29)
Complete Response	0	0	0	0	0	0	0
Partial Response (PR), n (%)	0	0	0	0	0	0	0
Stable Disease (SD), n (%)	11 (29.7)	3 (33.3)	1 (16.7)	0	1 (16.7)	3 (100.0)	8 (27.6)
Progressive Disease (PD), n (%)	26 (70.3)	6 (66.7)	5 (83.3)	5 (100.0)	5 (83.3)	0	21 (72.4)
DCR (%)	29.7	33.3	16.7	0	16.7	100	27.6

(a) Response evaluable population was defined as all patients who had at least one post baseline RECIST re-staging evaluation, or symptomatic disease progression as end of treatment reason.
(b) Patients in 15 mg 7d on/7d off cohort (n=3) were not response-evaluable

Results: SY-5609 + Gem +/- Nab-Pac

PDAC safety lead-in: Study summary



Study progress

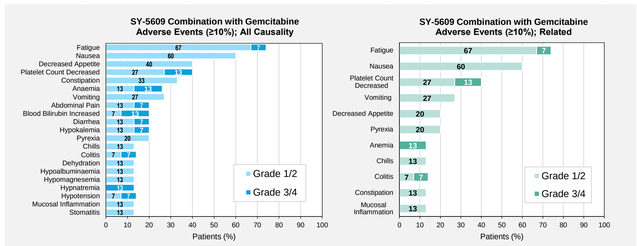
- 4mg doublet was tolerated and doublet was escalated to 5mg, then 10mg
- Once the 4mg doublet cohort cleared the DLT period, a 4mg triplet cohort was opened
- 18 pts enrolled in doublet and triplet safety lead-in cohorts
  - 15 pts enrolled in doublet cohorts
  - 3 pts enrolled in triplet cohort
- MTD for doublet was 5mg SY-5609 + gem 1000 mg
  - 10mg SY-5609 + gem 1000mg was NTD
- MTD and NTD not formally established for triplet; 4mg SY-5609 triplet cohort cleared DLT period
- Data snapshot: 03 April 2023

PDAC SLI: Demographic and Baseline Disease Characteristics of Safety Population (N=18)	SY-5609 + Gem (N = 15)	SY-5609 + Gem + nab-pac (N = 3)
Median age – years (range)	68 (53–88)	67 (66–72)
Male, n (%); Female, n (%)	10 (66.7); 5 (33.3)	3 (100.0); 0 (-)
Sites of metastatic disease – n (%)		
Liver	13 (86.7)	2 (66.7)
Lung	6 (40.0)	2 (66.7)
Peritoneum	5 (33.3)	1 (33.3)
Lymph nodes	3 (20.0)	1 (33.3)
Other	3 (20.0)	2 (66.6)
Previous lines of therapy – n (%)		
1	6 (40.0)	3 (100.0)
2	9 (60.0)	0
BOR to most recent prior therapy		
Partial Response	1 (6.7)	1 (33.3)
Stable Disease	2 (13.3)	1 (33.3)
Progressive Disease	4 (26.7)	0
Unknown	8 (57.1)	1 (33.3)

PDAC SLI Patient Disposition (Safety population; N = 18)	SY-5609 + Gem (N = 15)	SY-5609 + Gem + nab-pac (N = 3)
Duration of SY-5609 Treatment: Median days (range)	49 (7-161)	28 (21-190)
Withdrawn from treatment, n (%)	15 (100.0)	3 (100.0)
Progression by RECIST	10 (66.7)	1 (33.3)
Symptomatic Progression	0	1 (33.3)
Withdrew Consent / PI Decision	2 (13.3)	1 (33.3)
Death	1 (6.7)	0
Adverse Event	2 (13.3)	0

Low rate of discontinuations due to AEs
Most patients withdrew from treatment due to progressive disease

AE summary for SY-5609 + gem doublet: AEs are primarily low grade and reversible (n=15)



SY-5609 combination with Gemcitabine Safety Population, N = 15
Only maximum toxicity grade was considered per MedDRA preferred term per patient

PDAC SLI Safety summary: SY-5609 doublet and triplet

- Majority of AEs are low grade and reversible
- Observed AEs are consistent with SY-5609 or gem +/- nab-pac
- No new safety signals emerged with combination
- DLT summary
  - SY-5609 + gem doublet (n=15)
    - 1 patient experienced a DLT (G3 diarrhea) in 5mg + gem dose cohort
    - 2 patients experienced grade 4 thrombocytopenia DLT in 10mg + gem dose cohort
  - SY-5609 + gem/nab-pac triplet (n=3)
    - No DLTs reported

Best Overall Response in Response-Evaluable population (n=14)	SY-5609 + Gem			SY-5609 + Gem + nab-Pac	Total (N=14)
	4mg SY-5609 (Resp-evaluable, n= 4)	5mg SY-5609 (Resp-evaluable, n= 5)	10mg SY-5609 (Resp-evaluable, n= 3)	4mg SY-5609 (Resp-evaluable, n= 2)	
Complete Response	0	0	0	0	0
Partial Response, n (%)	1 (25.0)	0	0	0	1 (7.1)
Stable Disease, n (%)	0	3 (60.0)	0	1 (50.0)	4 (28.6)
Progressive Disease, n (%)	3 (75.0)	2 (40.0)	3 (100.0)	1 (50.0)	9 (64.3)
ORR, n (%)	25	0	0	0	1 (7.1)
DCR, (%)	25	60	0	50	35.7

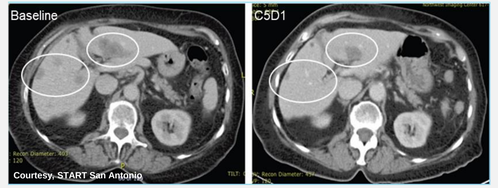
A 33% DCR, including a PR, was observed in 4/12 response-evaluable patients on the SY-5609 gemcitabine doublet at doses of 4, 5, 10mg SY-5609

SY-5609 + gem + nab-pac
- Response-evaluable population, n=2
- Median duration of treatment: 28 days

SY-5609 + gem
- Response-evaluable population, n=12
- Median duration of treatment: 49 days

Confirmed PR and ≥ 90% tumor marker reduction with SY-5609 + gem

Patient with PDAC in 2nd line enrolled in SY-5609 4mg + gem doublet cohort



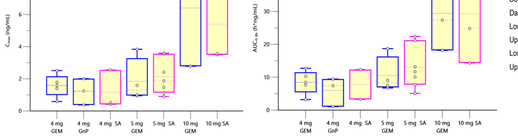
CT scans show 32% decrease in Target Lesions (TL)

	%Δ TL	CA 19-9	CEA
Baseline	n/a	60,357 U/mL	200 ng/mL
C3D1	-16.2%	13,094 U/mL	84.5 ng/mL
C5D1	-32%	1,407 U/mL	19.2 ng/mL
C7D1	-32%	968 U/mL	5.3 ng/mL
Total %Δ	-32%	-98%	-90%

- 75 y/o in 2L with m*KRAS12V* and m*SMAD4*; s/p 1L FOLFIRINOX, PD after 1st cycle
- Multiple liver target and non-target lesions
- Received SY-5609 (4mg) + gem; only low-grade events reported
- Off study on C7D1 while still in PR due to non-disease related medical issues

Pharmacokinetics and Pharmacodynamics

Day 4 SY-5609 C_{max} and $AUC_{(0-8)}$ in combination with gem and gem/nab-pac are comparable to single agent SY-5609 exposures



- **SY-5609 PK updates for single agent, doublet, and triplet**
  - Single agent: There is dose proportionality up to 10mg dose level. Exposure increases from 10 to 15 mg QD, with analysis limited due to small sample size with inter-patient variability at 15mg dose level.
  - Doublet and triplet: PK exposures of SY-5906 (C_{max} and AUC_{0-8h}) are similar when SY-5609 is administered alone or in combination with gem, or gem + nab-pac.
- **As exposures increase, target lesions more likely to remain stable or decrease in size, supporting an exposure-activity relationship**
- ***POLR2A* fold change max increases with dose escalation, suggesting dose-dependent target engagement**
  - POLR2A-fold change PD_{max} continues to be dose-proportional at 10mg (highest dose evaluated)

Conclusions

- SY-5609 SA dose escalation is complete, following extensive exploration of dose and schedule. The 7/7 schedule has been selected for further development.
- SY-5609 has an acceptable safety profile, with primarily low grade AEs, and no new safety signals emerging at higher SA doses tested alone or in combination with gem +/- nab-pac using a 7/7 SY-5609 dosing schedule.
- Encouraging clinical activity observed in patients with advanced, heavily pre-treated cancers treated with SA SY-5609, and in patients with 2L/3L metastatic PDAC treated with SY-5609 and gem +/- nab-pac.
  - Single agent activity on 7/7 schedule is comparable to other schedules explored, including more dose-intense regimens.
- SY-5609 exposures in combination with chemotherapy are comparable to exposures achieved with single agent SY-5609.
- POLR2A fold PD changes remain dose proportional up to 10mg (highest dose tested).

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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