Phase 1 Results of CYT-0851, a Monocarboxylate Transporter (MCT) Inhibitor, in Combination with Capecitabine or Gemcitabine in Advanced Solid Tumors

Abstract # 3099

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Background and Rationale

Monocarboxylate transporters (MCTs) are plasma membrane proteins that bi-directionally transport monocarboxylates (e.g. lactate, pyruvate, and ketones) and are upregulated in cancers where they correlate with poor prognosis **(Fig 1).** Metabolic reprogramming is a hallmark of cancer and is characterized by increased dependence on lactate-producing glycolysis. CYT-0851 inhibits MCT function in glycolytic cancer cells leading to an accumulation of intracellular lactate that impairs glycolysis and inhibits tumor cell growth**.**

CYT-0851 directly binds to MCT1 with a K_D of 89 nM and potently inhibits its transport function. It also inhibits MCT4 function at higher, but physiological relevant, concentrations in vitro. In a synthetic lethality CRISPR screen, the *TYMS* gene (thymidylate synthetase, a target of 5-fluorouracil [5-FU]), was identified as one of the top hits (**Fig 2**). The combination of 5-FU with CYT-0851 synergistically inhibited cancer cell growth in a subset of cell lines. Similarly, CYT-0851 and gemcitabine treatment resulted in combinatorial cell growth inhibition in cell line models.

In a phase 1 monotherapy study (ASCO 2022), responses were observed in solid tumors and NHL. The MTD of CYT-0851 was 600 mg QD, with dose-limiting starvation ketoacidosis, and the recommended phase 2 dose was 400 mg QD.

This is the first report of preliminary results of an ongoing phase 1 dose escalation study of the combination of CYT-0851 and capecitabine, and CYT-0851 and gemcitabine, with a data cut-off of May 1, 2023.*

Figure 1: MCTs are Membrane Transporters Fundamental to Cancer Survival

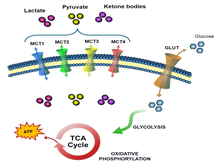
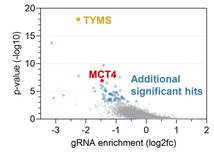


Figure 2: Additional synthetic lethal hits generated from pancreatic cancer cell line CYT-0851 sensitivity CRISPR screen



Study Objectives

Primary	To determine the recommended Phase 2 dose (RP2D) and maximum-tolerated dose (MTD) of CYT-0851 in combination with capecitabine and gemcitabine in solid tumors
Secondary	To evaluate the safety and tolerability
	To determine the pharmacokinetic parameters and optimal dosing regimen for each combination
	To characterize the preliminary anti-tumor activity for each combination

Methods – Study Design

Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria	
• ECOG 0-1 • Measurable disease by disease-specific criteria • Advanced solid tumors • Breast, HNSCC, ovarian, soft-tissue sarcoma, and pancreatic cancer	**CYT-0851/Capecitabine** • Absolute neutrophil count < 1.0 x 10^9/L • Platelets < 75 x 10^9/L • Hemoglobin < 9.0 g/dL • Creatinine Clearance < 50 mL/min (cape) • AST/ALT > 2.0 x ULN	**CYT-0851/Gemcitabine** • Absolute neutrophil count < 1.5 x x 10^9/L • Platelets < 100 x 10^9/L • Hemoglobin < 9.0 g/dL • Creatinine Clearance < 40 mL/min • AST/ALT > 2.0 x ULN

Phase 1 Combination Study Design

	CYT-0851/Capecitabine	CYT-0851/Gemcitabine
Cycle Duration	21 Days	28 Days
CYT-0851	100 mg – 400 mg PO QD	100 mg – 400 mg PO QD
Chemotherapy	1000 mg/m^2 PO BID on D 1-14	1000 mg/m^2 IV D 1, 8 and 15

Dose-escalation proceeded 3+3 design; Starting Dose = 100 mg QD with cape or gem
Up to 9 patients are allowed to be backfilled into the highest cleared dose level

Treatment was administered until disease progression, unacceptable toxicity, or withdrawal

Response assessments every 2 cycles (6 weeks – cape or 8 weeks – gem) by RECIST v1.1

Results

Demographics and Disposition

- Enrollment in combination cohorts started on January 4, 2022 and is ongoing at 16 US sites
- As of a data cutoff of May 1, 2023, 35 patients have been enrolled in Ph1 combination cohorts, 22 in combination with capecitabine and 13 in combination with gemcitabine

Table 1: Demographics and Characteristics

Characteristics	851/Cape Total (n=22) n (%)	851/Gem Total (n=13) n (%)
Female	19 (86.4)	10 (76.9)
Male	3 (13.6)	3 (23.1)
Median age (range)	66 (51-78)	65 (25-78)
ECOG Performance Status		
0	10 (45.5)	3 (23.1)
1	12 (54.5)	9 (69.2)
Prior Lines of Therapy		
Median (range)	5 (1-14)	3 (1-9)
1	1 (4.5)	2 (15.4)
2	1 (4.5)	3 (23.1)
≥ 3	19 (86.4)	8 (61.5)
Tumor Type		
Pancreatic	9 (40.9)	4 (30.8)
Ovarian	12 (54.5)	1 (7.7)
Head and Neck	0	1 (7.7)
Sarcoma	0	7 (53.8)

Figure 3: Patient Enrollment and Disposition

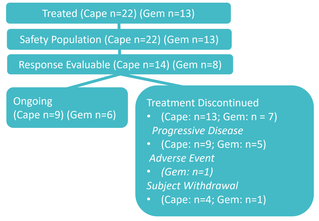


Table 2: Enrollment by CYT-0851 Dose Level

	CYT-0851 Dose Level									
	CYT-0851/Capecitabine Cohorts					CYT-0851/Gemcitabine Cohorts				
	100 mg QD	200 mg QD	300 mg QD	400 mg QD	Total	100 mg QD	200 mg QD	300 mg QD	400 mg QD	Total
N	3	4	3	12	22	6	4	3	0	13

Dose-Escalation and Determination of MTD

- Capecitabine: 0 pts experienced a DLT at any dose level and 3 patients had TRAEs requiring dose modification
- Gemcitabine: Post-amendment where DLT redefined, 1 pt experienced a DLT at 300 mg CYT-0851 and 8 patients had TRAEs requiring dose modification

Table 3: Capecitabine/Gemcitabine DLTs and TRAEs Requiring CYT-0851 Dose Modification

Dose Level	N Cape/Gem	n with DLTs Cape/Gem	TRAE requiring modification Cape/Gem	Description of Adverse Event
100 mg QD	3/6	0/0	0/2	Gem: neutrophil count decreased, thrombocytopenia
200 mg QD	4/4	0/0	1/4	Cape: mucosal inflammation Gem: neutropenia, neutrophil count decreased, anaemia, fatigue, vomiting
300 mg QD	3/3	0/1	1/2	Cape: anaemia Gem: neutropenia, decreased appetite; 1 pt with DLT of hyperglycaemia and starvation ketoacidosis resolved and has not recurred upon retreatment at a reduced dose
400 mg QD	12/ -	0/-	1/-	Cape: fatigue

Safety

- All TRAEs- Cape: 45.5% of pts reported any grade events and 9.1% have reported Gr3/4 across all cohorts; Gem: 69.2% of pts reported any grade events and 46.2% have reported Gr3/4 across all cohorts
- Most common TRAEs- Cape: fatigue (27.3%), decreased appetite (13.6%), nausea (13.6); Gem: fatigue (38.5%), anemia (23.1%), neutropenia (23.1%)
- No treatment-related deaths have been reported

Figure 4: Treatment-Emergent Adverse Events occurring in ≥ 10 % of Patients by Relatedness

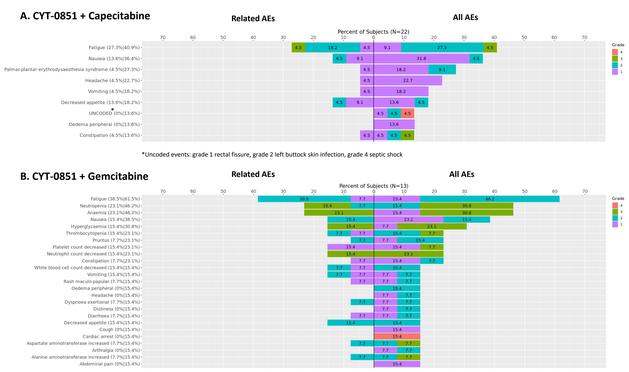


Table 4: Safety Overview by Combination Cohort and Dose Level

	Capecitabine Cohorts					Gemcitabine Cohorts			
	100 mg QD (n=3)	200 mg QD (n=4)	300 mg QD (n=3)	400 mg QD (n=12)	Total (n=22)	100 mg QD (n=6)	200 mg QD (n=4)	300 mg QD (n=3)	Total (n=13)
Subjects With at Least One Related TEAE	2	2	1	5	10	3	4	2	9
Subjects With at Least One Related Grade>=3 TEAE	0	1	1	0	2	1	3	2	6
Subjects With at Least One Related Serious TEAE	0	0	1	0	1	0	0	2	2
Subjects With at Least One Related TEAE Leading to Drug Withdrawal	0	0	0	0	0	0	0	0	0
Subjects With at Least One Related TEAE Leading to Drug Interruption	0	1	1	0	2	2	2	2	6
Subjects With at Least One Related TEAE Leading to Dose Reduction	0	0	0	1	1	1	2	0	3
Subjects With at Least One DLT	0	0	0	0	0	0	0	1	1

Pharmacokinetic Analysis

- Exposure of CYT-0851 in combination with capecitabine or gemcitabine exhibits dose proportional behavior and was similar between combination therapy and monotherapy
- Mean steady-state trough levels achieved for CYT-0851 in combination therapy exceed levels where preclinical studies demonstrated activity

Figure 5: CYT-0851 Pharmacokinetic Profiles Across Combination Dose Levels

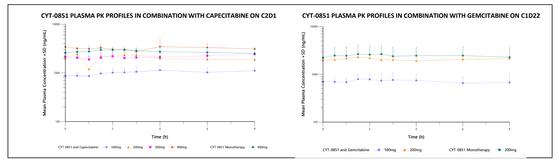


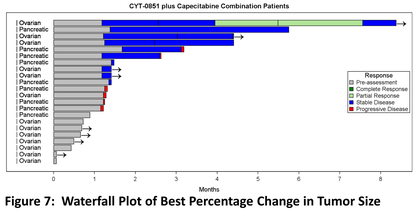
Table 5: Summary of CYT-0851 Pharmacokinetic Parameters Across Combination Dose Levels

CYT-0851 Human Pharmacokinetics Summary						
Pharmacokinetic Parameter	CYT-0851 Dose					
	CYT-0851/Capecitabine				CYT-0851 /Gemcitabine	
	100 mg QD (n=3)	200 mg QD (n=2)	300 mg QD (n=2)	400 mg QD (n=2)	100 mg QD (n=3)	200 mg QD (n=3)
T_{max} (h)[a]	3 (1.5, 4)	2.25 (1.5, 3)	5.5 (3, 8)	2.75 (1.5, 4)	3 (1.5, 4)	1.5 (1, 8)
C_{max} (ng/mL)[b]	1240 ± 207	2540 ± 757	2530 ± 113	4000 ± 566	812 ± 263	1970 ± 1730
AUC_{0-t} (ng.h/mL)[b]	7410 ± 1920	13600 ± 7060	17300 ± 1120	25600 ± 4220	5470 ± 1910	13000 ± 13400

[a]: median (min, max) [b]: geometric mean ± standard deviation (SD)

Clinical Activity in Solid Tumors with CYT-0851/Capecitabine

Figure 6: Swimmer's Plot of Duration of Treatment and Response



- 14 pts response evaluable with RECIST measurements available
- 1 confirmed PR in a pt with ovarian cancer with treatment ongoing in cycle 12 at 300 mg
- 9 pts had SD
- The overall disease control rate was 71.4%

Figure 7: Waterfall Plot of Best Percentage Change in Tumor Size

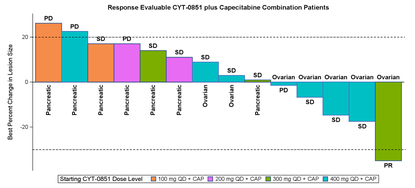
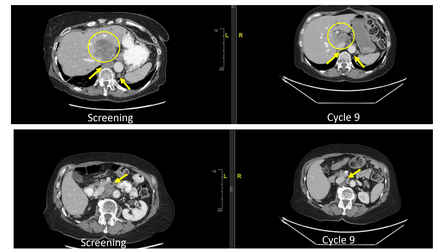


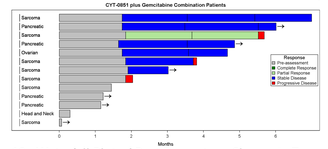
Fig 8: PR in Ovarian Cancer with CYT-0851 (300 mg) + Capecitabine



Pt 184: 67-year-old female with high grade serous ovarian cancer previously treated with 11 lines of therapy, including carboplatin, paclitaxel, gemcitabine, bevacizumab, topotecan, Doxil, pembrolizumab, cyclophosphamide. Her most recent two therapies were nab-paclitaxel/bev and pemetrexed with best response of PD. She was treated with CYT-0851 starting at 300 mg QD and experienced a PR after 7 cycles, confirmed at 9 cycles, shown here (study day 167), with – 35% reduction in the sum of target lesion longest diameters. She continues on treatment at Cycle 12.

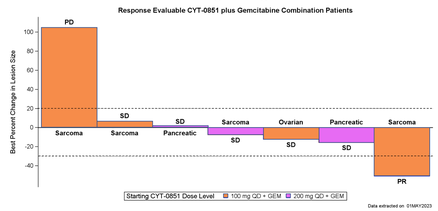
Clinical Activity in Solid Tumors with CYT-0851/Gemcitabine

Figure 9: Swimmer's Plot of Duration of Treatment and Response



- 8 pts with solid tumors were response evaluable
- 1 confirmed PR in a patient with soft tissue sarcoma at month 2
- 6 pts with SD
- Disease control rate 87.5%

Figure 10: Waterfall Plot of Best Percentage Change in Tumor Size



Conclusions

- Exposure of CYT-0851 in combination with capecitabine or gemcitabine exhibits dose proportional behavior and was similar between combination therapy and monotherapy
- 400 mg CYT-0851 was selected as the RP2D in combination with capecitabine as no DLTs were observed at any dose and the MTD was not identified
- Dose escalation of CYT-0851 + gemcitabine has cleared the 200mg level and is ongoing
- Both combinations have demonstrated an acceptable safety and tolerability profile without any unanticipated toxicities at clinically active doses
- Encouraging antitumor activity has been observed with a confirmed PR in heavily pretreated patients with both combination regimens
- In the CYT-0851/cape combination, encouraging preliminary activity was observed in the seven evaluable ovarian cancer patients, with one confirmed PR and five SDs. The 400 mg cohort is being expanded with additional patients with ovarian cancer

Acknowledgments

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