Phase 1 Dose Expansion Results of CYT-0851, a Monocarboxylate Transporter (MCT) Inhibitor, in Combination with Capecitabine in Platinum-Resistant Ovarian Cancer

Poster LB_A13

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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 physiologically 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 growth in a subset of cancer cell lines **(Fig 3)**.

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. In the phase 1 dose escalation trial of CYT-0851 plus capecitabine, 400 mg QD was identified as the recommended phase 2 dose (ASCO 2023).

This is the preliminary report of an expansion cohort of 10 evaluable patients with platinum-resistant advanced ovarian cancer that were treated with CYT-0851, 400 mg QD in combination with capecitabine, 1000 mg/m^2 PO BID x 14 days every 21 days. One additional pt treated at the 300 mg dose level was evaluable and added to the analysis with a data cut-off of Sep 26, 2023.*

Figure 1: MCTs are Membrane Transporters Fundamental to Cancer Survival

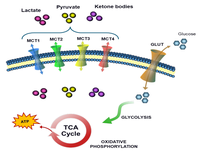


Figure 2: Additional synthetic lethal hits from CYT-0851 sensitivity CRISPR screen

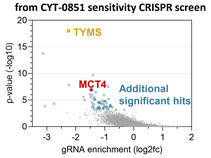
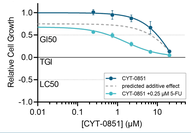


Figure 3: CYT-0851 synergizes with 5-FU in pancreatic cancer cell line



Study Objectives

Primary	To evaluate the safety and tolerability
Secondary	To determine the pharmacokinetic parameters and optimal dosing regimen for the combination
	To characterize the preliminary anti-tumor activity for the 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
  • Expansion: Platinum resistant ovarian cancer only
	CYT-0851/Capecitabine
	• Absolute neutrophil count < 1.0 × 10^9/L
	• Platelets < 75 × 10^9/L
	• Hemoglobin < 9.0 g/dL
	• Creatinine clearance < 50 mL/min (capecitabine)
	• AST/ALT > 2.0 x ULN

Phase 1 Combination Study Design

CYT-0851 + Capecitabine

Cycle Duration: 21 Days
CYT-0851: 100 mg – 400 mg PO QD
Capecitabine: 1000 mg/m^2 PO BID on D 1-14

Dose-escalation proceeded 3+3 design; Starting Dose = 100 mg QD with capecitabine
Expansion Up to 9 patients are allowed in the highest cleared dose level

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

Response assessments every 2 cycles (6 weeks) by RECIST v1.1

Results

Demographics and Disposition

- 14 Patients with ovarian cancer were enrolled in the CYT-0851 + capecitabine combination cohorts, 11 were evaluable for response, 3 (27%) remain on treatment

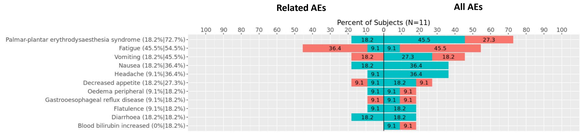
Table 1: Demographics and Patient Characteristics

Characteristics	N (%) Total (n=11)
Median age (range)	64 (52-76)
Race/Ethnicity	
White	9 (82%)
African American Black	1 (9%)
American Indian/Alaskan native	1 (9%)
Hispanic or Latino	3 (27%)
Not Hispanic or Latino	8 (73%)
Prior therapies	
Median (range)	6 (2-14)
2	1 (9%)
≥3	10 (91%)
Platinum resistant	7 (64%)
Platinum refractory	4 (36%)
Performance Status	
0	7 (64%)
1	4 (36%)

Safety

- All TEAEs- 91% of pts reported any grade events, and 73% reported a treatment related adverse event
- 18% Reported a grade 3/4 adverse event, and no patient reported any treatment related grade 3/4 adverse event
- There were no grade 5 adverse events
- There were no treatment related adverse events leading to CYT-0851 dose reduction or discontinuation
- Most common TRAEs- fatigue (46%), palmar-plantar erythrodysaesthesia syndrome (18%) , vomiting (18%), decreased appetite (18%), diarrhoea (18%), and nausea (18%), all grade 1 or 2

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



Treatment Compliance

- Median CYT-0851 dose compliance with continuous daily dosing was 99% (range 94– 100%).
- There were no treatment discontinuations or CYT-0851 dose reductions for treatment related adverse events.

Pharmacokinetic Analysis

- Exposure of CYT-0851 in combination with capecitabine 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

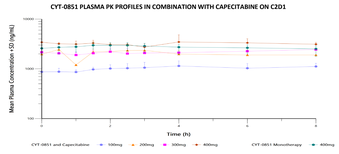


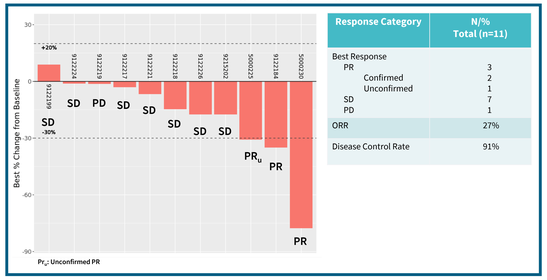
Table 2: Summary of CYT-0851 Pharmacokinetic Parameters Across Combination Dose Levels

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

*: median (min, max) b: geometric mean ± standard deviation

Clinical Activity in Ovarian Cancer with CYT-0851 + Capecitabine

Figure 6: Waterfall Plot of Best Percentage Change in Target Lesion Size



Response Category	N/% Total (n=11)
Best Response	
PR	3
Confirmed	2
Unconfirmed	1
SD	7
PD	1
ORR	27%
Disease Control Rate	91%

Figure 7: Sum of Target Lesion Sizes by RECIST

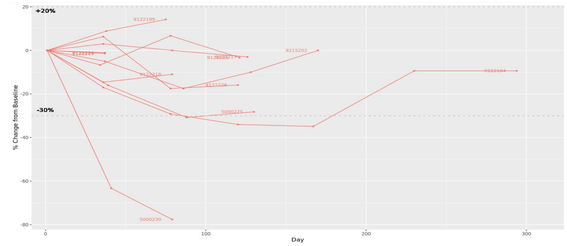


Figure 8: Kaplan-Meier Estimate of Progression-free Survival (days)

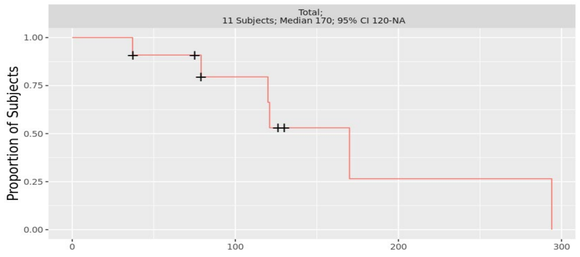


Figure 9: Swimmer's Plot of Duration of Treatment and Response

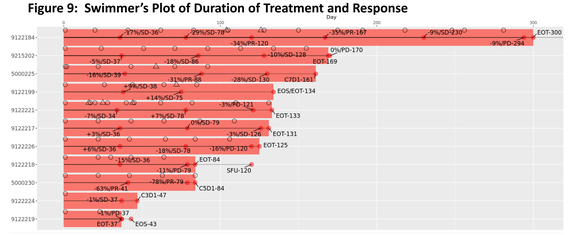
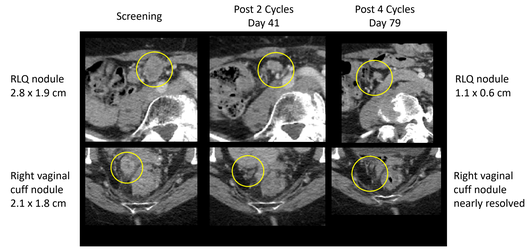
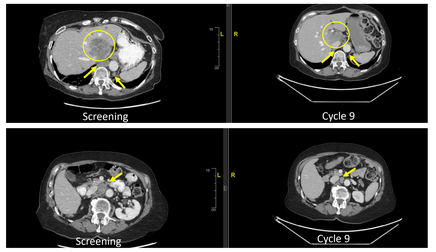


Figure 10: Confirmed PR in Ovarian Cancer with CYT-0851 (400 mg) + Capecitabine



Pt 230: 72-year-old platinum refractory female with high grade serous ovarian cancer previously treated with carboplatin/paclitaxel, niraparib, carboplatin/liposomal doxorubicin, gemcitabine, and experimental therapy. She was treated with CYT-0851, 400 mg QD + capecitabine and experienced a PR after 2 cycles, with 63% reduction in the sum of target lesion longest diameters, confirmed after 4 cycles, with 78% tumor reduction.
She continues treatment in Cycle 5.

Figure 11: Confirmed PR in Ovarian Cancer with CYT-0851 (300 mg) + Capecitabine



Pt 184: 67-year-old platinum refractory female with high grade serous ovarian cancer previously treated with 11 lines of therapy, including carboplatin, paclitaxel, gemcitabine, bevacizumab, topotecan, liposomal doxorubicin, pembrolizumab, and cyclophosphamide. Her most recent two therapies were nab-paclitaxel/bevacizumab and pemetrexed with best response of PD. She was treated with CYT-0851, 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 discontinued therapy on day 300 for PD.

Conclusions

- The combination of CYT-0851 and capecitabine has demonstrated an acceptable safety and tolerability profile without any unanticipated toxicities at clinically active doses
- The combination of CYT-0851 and capecitabine is an oral outpatient regimen that appears active in heavily pretreated platinum refractory and platinum resistant ovarian cancer
- The disease control rate of 91% and unconfirmed response rate of 27% in platinum refractory and platinum resistant ovarian cancer is promising and warrants further exploration
- Furthermore, this regimen should be evaluated in other tumor types commonly treated with 5-FU, including breast and colorectal cancer

Acknowledgments

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