Next Generation Capecitabine (NGC-Cap) in Phase 1b Trial Significantly Increases 5-FU Exposure While Improving Safety Profile Compared to Capecitabine

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David Young[1], Sian Bigora[1], Mary Nyberg[1], Kayla Parks[1], Amit Mahipal[2], Patrick Boland[3], Eric J. Feldman[4], Howard Hochster[3]. [1]Processa Pharmaceuticals, Hanover, Maryland; [2]UH Cleveland Medical Center, Cleveland, Ohio; [3]Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey; [4] Montefiore Medical Center, Bronx, New York.

Abstract

Background: Capecitabine (Cape) at the recommended dose of 1,000 – 1,250 mg/m² BID has been shown to frequently cause clinically meaningful side effects such as myelosuppression and hand-foot syndrome (HFS), both of which may require dose modification, interruption, or discontinuation. HFS is caused by 5-FU catabolites while myelosuppression is caused by 5-FU anabolites. NGC-Cap combines ethynyl-uracil (PCS6422), an irreversible inhibitor of the DPD catabolism enzyme, and Cape.

Methods: The Phase 1b trial is a 3+3 design with ascending Cape doses from 75 mg QD to 300 mg BID. Cape is given 7 days on/7 days off every 14 days with a single dose of PCS6422 given 16-24 hours before the start of every cycle. The 5-FU AUC(0-9 hrs), Cmax, and T1/2 were calculated on Day 1 of Cape when DPD inhibition is at its maximum. New cohorts are opened following a review of the safety data by a cohort review committee after the second cycle. Blood samples are obtained for PK analysis of PCS6422, Cape, and Cape metabolites. All patients have cancer refractory or intolerant to existing available therapies. Radiological tumor response evaluation (RECIST 1.1) is performed every 8 weeks.

Results: 18 patients were enrolled in the first 4 dose levels of Cape in NGC-Cap. The 5-FU AUC (geometric mean, CV%) for the 150 and 225 mg BID NGC-Cap cohorts were 3,802 (23%) and 6,311 (37%) ng-hr/ml, respectively. These AUCs were approximately 5-10 times the AUC(0-inf) of 698 (33%) previously reported for a larger dose of approximately 2,250 mg of monotherapy Cape (Mono-Cape) (Reigner 1998). Similarly, the 5-FU Cmax (geometric mean, CV%) for these 2 cohorts were greater at 694 (22%) and 1,056 (28%) ng/ml than the Cmax of Mono-Cape at 310 (50%). The 5-FU T1/2 (arithmetic mean, CV%) of 3.54 (18%) and 5.72 (51%) hrs for these two NGC-Cap cohorts were also much longer than the 0.84 (25%) hrs for Mono-Cape. Although 150 and 225 mg BID NGC-Cap cohorts produced greater Cmax and AUC levels than Mono-Cape, the side effect profile from anabolites for the 150 mg cohort was better than Mono-Cape while the profile for the 225 mg cohort was similar to Mono-Cape. The extremely low FBAL catabolite formation and exposure (AUC of < 250 vs 31,400 for Mono-Cape) across all NGC-Cap doses also resulted in only 1 patient having Grade 1 HFS.

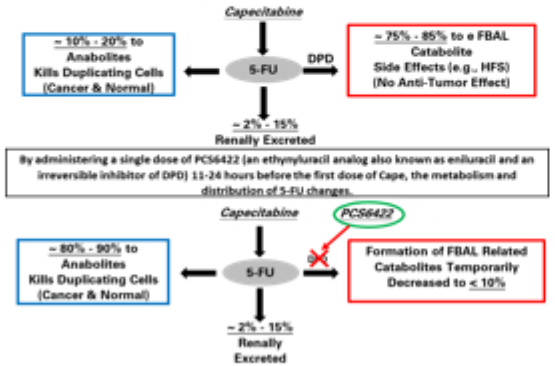
Conclusion: The trial has revealed some of the potential benefits of NGC-Cap.

1. NGC-Cap can provide a greater 5-FU exposure based on AUC and Cmax with a better or similar side effect profile.
2. Side effects from the 5-FU catabolites are minimal and less severe for NGC-Cap.
3. Side effects from 5-FU anabolites are dependent on 5-FU exposure with less exposure leading to fewer side effects that may also be less severe.
4. NGC-Cap is to be further evaluated in a Phase 2 trial with the expectation that NGC-Cap will provide a better efficacy and safety profile than Cape.

Introduction

Capecitabine (Cape) is an oral pro-drug of 5-FU. The prescribing label for Cape recommends doses of 1,000 and 1,250 mg/m² BID in 14/7 cycles (14-days on & 7-days off) for breast and colorectal cancer, respectively. These dosage regimens have been shown to frequently cause side effects such as myelosuppression and hand-foot syndrome (HFS) which often require dose modifications. HFS is caused by the 5-FU catabolite, FBAL, formed when 5-FU is metabolized by the dihydropyrimidine dehydrogenase enzyme (DPD).

Introduction (continued)



Methods and Materials

- The study is a 3+3 dose escalation trial in advanced, relapsed or refractory gastrointestinal tract cancer patients.
- The objective is to determine the recommended dosage range (RDR), including the recommended Phase 2 dose(s) (RP2D) and maximum tolerated dose (MTD).
- A single dose of PCS6422 is given 16-24 hrs before the start of every Cape dosing cycle of 7 days on/7 days off (defined in Study as Days 2-8 on and Days 9-15 off).
- Safety and efficacy was monitored on an ongoing basis.
- Blood samples were obtained for PK analysis (AUC, T1/2, Cmax) of Cape and its metabolites (eg, 5-FU and FBAL) on Day 2 and 8 (first day and last day of Cape).
- The efficacy data collection is ongoing and is not presented in this poster.

Results and Discussion

Patient Enrollment: A total of 18 patients were enrolled in Cohort 1 (70 mg qd of Cape) through Cohort 4 (225 mg BID of Cape) (Table 1).

Table 1. Brief Description of Cohorts and Patient Enrollment

Cohort	PCS6422 Regimen (1 +14)	Capecitabine Regimen (7+7)	Status Enrollment Completed
1	40 mg on Day 1 of each cycle	75 mg QD Day 2-8	1 Pts enrolled, 1 Pt RECIST Evaluated[AA]
2A+2D	40 mg on Day 1 of each cycle	75 mg BID Day 2-8	6 Pts enrolled, 5 Pts RECIST Evaluated[AA]
3	40 mg on Day 1 of each cycle	150 mg BID Day 2-8	4 Pts enrolled, 3 Pts RECIST Evaluated[AA]
4	40 mg on Day 1 of each cycle	225 mg BID Day 2-8	7 Pts enrolled, 3 Pts RECIST Evaluated[AA]
5	40 mg on Day 1 of each cycle	300 mg BID Day 2-8	Not To Be Enrolled**

[AA] Patients are included in "Pt RECIST Evaluated" when at least 1 RECIST evaluation occurred during NGC-Cap treatment
** Safety Cohort Committee decided dosing in Cohort 5 would likely not be safe given safety profile of Cohort 4

Results and Discussion (continued)

- 5-FU AUC, Cmax and T1/2 on Day 2 for all cohorts were much greater than the AUC (> 5x), Cmax (> 1.5x) and T1/2 (> 4x) reported in literature and label (Reigner 1998, Xeloda Label 2022) even though the Cape doses in NGC-Cap are < 10% of the typical labelled dose of Cape (Table 2).
- Day 2 NGC-Cap FBAL Cmax, AUC were less than reported for monotherapy Cape.
- 5-FU and FBAL PK parameters changed between Day 2 and Day 8.
- De novo formation of DPD must be occurring between Day 2 and Day 8.
- Since FBAL/5-FU AUC ratio was < 25 on Day 8 compared to monotherapy Cape's previously reported ratio > 40, DPD levels had not returned to baseline on Day 8.

Table 2. 5-FU and FBAL AUC and T1/2 after NGC-Cap Dose on Day 2 and Day 8 for each Cohort and Historical Report after Monotherapy Cape

Study Day	Parameter	Statistic	Cohort 1* 70 mg QD (n=1)	Cohort 2A&2D[A] 75 mg BID (n=6)	Cohort 3* 150 mg BID (n=4)	Cohort 4[C] 225 mg BID (n=7)	PK parameters Normalized to 1,250 mg/m² BID of Monotherapy Cape (Reigner 1998)
2	5-FU AUC[0-∞] (ng/mL*h)	Mean±SD (CV%)	ND	3468.7±1305.4[F] (37.7)	4551±1221 (26.8)	6889±2851[H] (41.4)	698 [33]
2	5-FU $t_{1/2}$ (h)	Mean±SD (CV%)	3.641	3.63±0.44 (12.1)	3.54±0.62 (17.5)	4.45±2.29[F] (51.5)	0.84 [25]
2	FBAL AUC[0-∞] (ng/mL*h)	Mean±SD (CV%)	ND	109.7 ±65.0[AA] (62)	248.7±303.7[AA] (42)	265.7±273.8[AA] (103)	31400 [30]
2	FBAL $t_{1/2}$ (h)	Mean±SD (CV%)	ND	ND	ND	ND	2.55 [19]
8	5-FU AUC[0-τ] (ng/mL*h)	Mean±SD (CV%)	ND	380.5±40.3[F] (21.3)	388.3±249.3 (132.4)	387.0±95.2[F] (50.5)	698 [33]
8	5-FU $t_{1/2}$ (h)	Mean±SD (CV%)	ND	0.6±0.2[F] (28.8)	0.90±0.24[F] (26.8)	1.08±0.76 (70.5)	0.84 [25]
8	FBAL AUC[0-τ] (ng/mL*h)	Mean±SD (CV%)	ND	2030±1403.0[F] (69.1)	2540±885.4[F] (34.9)	3857±734.2[F] (18.5)	31400 [30]
8	FBAL $t_{1/2}$ (h)	Mean±SD (CV%)	2.449	3.82±2.39 (62.3)	2.95±0.62[F] (20.9)	4.96±1.02[F] (20.6)	2.55 [19]

[A] Cohort 1: PCS6422 (0 mg Day 1; Capecitabine 75 mg QD Day 2-8); [B] Cohort 2A and 2D: PCS6422 (0 mg Day 1; Capecitabine 75 mg BID Day 2-8); [C] Cohort 3: PCS6422 40 mg Day 1; Capecitabine 150 mg BID Day 2-8); [D] Cohort 4: PCS6422 (0 mg Day 1; Capecitabine 225 mg BID Day 2-8); [E] 5-FU on Day 8 should be equal to approximately AUC/4 at 25% CV%; properties are linear and the same across days; [F] Only determinable in 3 of 6 patients; [G] Only determinable in 2 of 7 patients; [H] Only determinable in 5 of 7 patients; [I] Only determinable in 3 of 6 patients; [J] Only determinable in 2 of 6 patients; [K] Only determinable in 4 of 7 patients; [L] AUC[0-∞] because AUC/4 could not be determined since $t_{1/2}$ was Not Determined (ND); ND - Not determinable

Safety Evaluation: The incidence of Treatment Emergent Adverse Events (TEAE), Treatment Emergent Serious Adverse Events (TESAE), and Treatment Related Adverse Events (TRAE) are presented in Table 3. The adverse events associated with NGC-Cap were mainly related to the anabolites of 5-FU (e.g., myelosuppression, GI) and not the catabolites of 5-FU (e.g., HFS, cardiotoxicity).

Table 3: Summary of TEAEs and TRAEs by Cohort (Cut-off date 18 Jan 2024)

	Cohort 1 (N=1)	Cohort 2A+2D (N=6)	Cohort 3 (N=4)	Cohort 4 (N=7)	Xeloda Label
Number of Patients with TEAEs [n (%)]	1 (100)	6 (100)	4 (100)	7 (100)	
Number of TEAEs	14	47	48	43	
Number of Patients with Grade 3-5 TEAEs [n (%)]	0	2 (33.3)	1 (25.0)	5 (71.4)	
Number of Grade 3-5 TEAEs	0	4	8	11	
Number of Patients with TESAEs [n (%)]	0	1 (16.7)	1 (25.0)	3 (42.9)**	
Number of Patients with DLTs [n (%)]	0	0	0	0	
Number of Deaths [n (%)]	0	0	0	1 (14.3)	
TRAEs Related to PCS6422					
All TRAEs n (%) E	0 (0.00) 0	3 (50.0) 9	3 (75.0) 18	5 (71.4) 13	
Grade 3-5 TRAEs n (%) E	0 (0.00) 0	0 (0.0) 0	1 (25.0) 2	3 (42.9) 6	
TRAEs Related to Capecitabine					
All TRAEs n (%) E	1 (100) 9	3 (50.0) 6	3 (75.0) 16	6 (85.7) 22	(~80)
Grade 3-5 TRAEs n (%) E	0 (0.00) 0	0 (0.0) 0	1 (25.0) 1	4 (57.1) 7	(~20)

Results and Discussion (continued)

Catabolite and Anabolite Safety Analysis: The incidence of the catabolite related AEs (e.g., HFS) is much less in this Phase 1b study compared to what is reported in the Xeloda label while the anabolite incidence appears to be greater for NGC-Cap (Table 4).

Table 4: Incidence of Side Effects Associated with 5-FU Catabolites or 5-FU Anabolites (Cut-off 18 Jan 2024)

	Cohorts 1-4 (N=18)	Grade 1-2	Grade 3+
Number of Patients with Catabolite Related AEs as n (%)	2 (11.1%)	2 (11.1%)	0.00%
Xeloda Label 2022 - % of Patients with Catabolite Related AEs	60%	43%	17%
Number of Patients with Anabolite Related AEs as n (%)	12 (66.7%)	8 (44.5%)	4 (22.2 %)
Xeloda Label 2022 - % of Patients with Anabolite Related AEs (e.g. Neutropenia)	18%	10%	8%

Dose Modifications Because of TEAEs and TRAEs: Modifications to the dosage regimens occurred given the seriousness of the AEs. AEs resulting in modifications included AEs such as neutropenia, platelet count decrease, peripheral sensory neuropathy, urinary tract infection, pneumonitis (fatal), and ascites. The modifications included dose reductions, dose interruptions, and dose discontinuations.

Table 5: Number of Patients Requiring Dose Modifications Because of TEAEs and TRAEs

	Cohort 1 (N=1)	Cohort 2A+2D (N=6)	Cohort 3 (N=4)	Cohort 4 (N=7)
Dose Reduction Pts Due to AEs n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
Dose Interruption Pts Due to AEs n (%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	3 (42.9%)
Dose Discontinuation Pts Due to AEs n (%)	0 (0.0%)	1 (16.7%)	0 (00.0%)	3 (42.9%)
Total Pts Modified Dosage Regimen Due to AEs n (%)	0 (0.0%)	1 (16.7%)	2 (50.0%)	5 (71.4%)

MTD and RDR: Dose modifications were much greater for Cohort 4 than Cohort 1, 2, or 3. Given the severity of the AEs and the number of AEs requiring dose modifications, the Cohort Safety Review Committee unanimously determined that the dose could not be escalated to Cohort 5. The MTD was defined as 225 mg BID and the RDR to be evaluated in the Phase 2 trial will be 150 to 225 mg BID.

Conclusions

- **NGC-Cap at 150 & 225 mg BID of Cape provides much greater 5-FU exposure and much lower FBAL exposure for the first few days of Cape treatment than monotherapy Cape even though the monotherapy Cape dose is > 9-10x the Cape dose in NGC-Cap.**
- **DPD de novo formation begins within 48-72 hours after PCS6422 dosing based on the increase in FBAL plasma concentration over time.**
- **The incidence of all TRAEs for 150 mg BID and 225 mg BID were similar to Cape monotherapy as reported in the Xeloda label while the incidence of Grade 3-5 TRAEs were similar for Cohort 3 and greater for Cohort 4 (Table 3).**
- **Although efficacy has not been reported in this poster presentation, the possibility of having an improved efficacy profile is likely given the much greater 5-FU exposure and potential increase in the distribution of 5-FU to cancer cells.**

Contact

Dr. David Young, PharmD., Ph.D.
President, R&D
Processa Pharmaceuticals, Inc.
[redacted]
443.974.3333
www.processapharma.com

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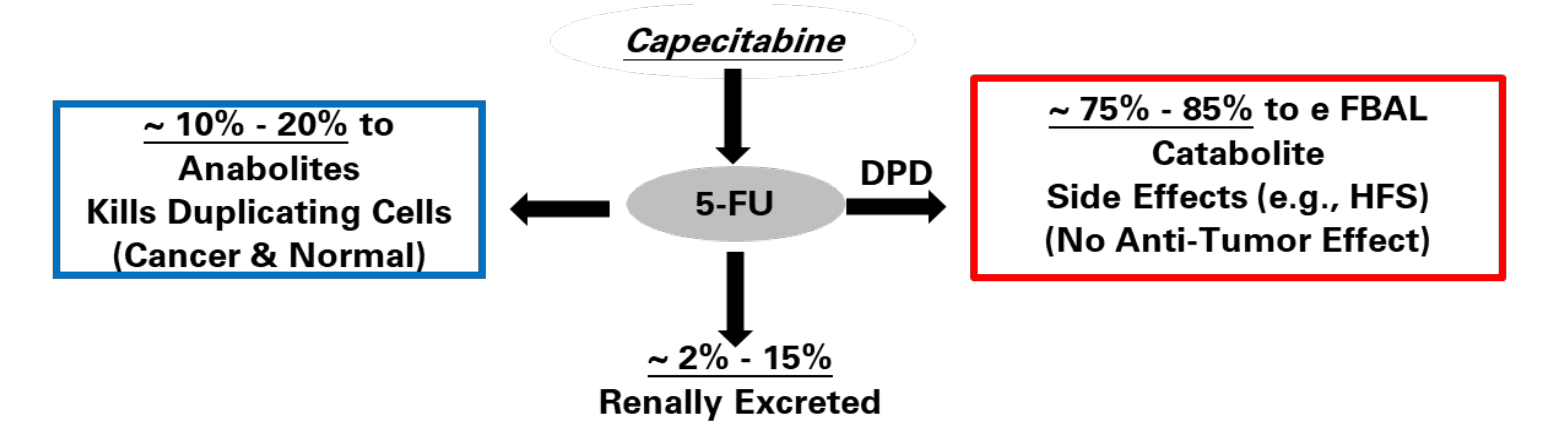
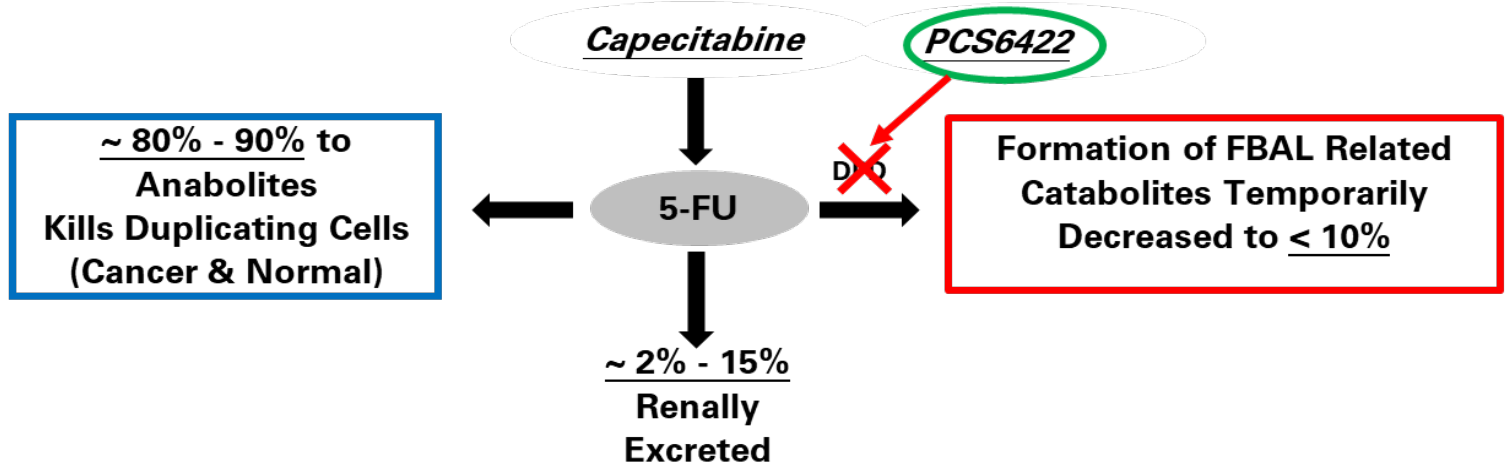


By administering a single dose of PCS6422 (an ethynyluracil analog also known as eniluracil and an irreversible inhibitor of DPD) 11-24 hours before the first dose of Cape, the metabolism and distribution of 5-FU changes.



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2A+2D	40 mg on Day 1 of each cycle	75 mg BID Day 2-8	6 Pts enrolled, 5 Pts RECIST Evaluated^^
3	40 mg on Day 1 of each cycle	150 mg BID Day 2-8	4 Pts enrolled, 3 Pts RECIST Evaluated^^
4	40 mg on Day 1 of each cycle	225 mg BID Day 2-8	7 Pts enrolled, 3 Pts RECIST Evaluated^^
5	40 mg on Day 1 of each cycle	300 mg BID Day 2-8	Not To Be Enrolled**

^^ Patients are included in "Pt RECIST Evaluated" when at least 1 RECIST evaluation occurred during NGC-Cap treatment

** Safety Cohort Committee decided dosing in Cohort 5 would likely not be safe given safety profile of Cohort 4

Results and Discussion (continued)

- 5-FU AUC, Cmax and T1/2 on Day 2 for all cohorts were much greater than the AUC (> 5x), Cmax (> 1.5x) and T1/2 (> 4x) reported in literature and label (Reigner 1998, Xeloda Label 2022) even though the Cape doses in NGC-Cap are < 10% of the typical labelled dose of Cape (Table 2).
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- Since FBAL/5-FU AUC ratio was < 25 on Day 8 compared to monotherapy Cape's previously reported ratio > 40, DPD levels had not returned to baseline on Day 8.

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2	5-FU AUC(0-τ) (ng/mL*h)	Mean±SD (CV%)	ND	3466.7±1305.4[i] (37.7)	4551±1221 (26.8)	6889±2851[h] (41.4)	698 (33)
2	5-FU $t_{½}$ (h)	Mean±SD (CV%)	3.641	3.60±0.44 (12.1)	3.54±0.62 (17.5)	4.45±2.29[h] (51.5)	0.84 (25)
2	FBAL AUC_{0-9} (ng/mL*h)	Mean±SD (CV%)	ND	109.7 ±45.6[i,m] (42)	248.7±103.7[m] (42)	265.7±273.8[m] (103)	31400 (30)
2	FBAL $t_{½}$ (h)	Mean±SD (CV%)	ND	ND	ND	ND	2.55 (19)
8	5-FU AUC(0-τ)[e] (ng/mL*h)	Mean±SD (CV%)	ND	189.5±40.3[j] (21.3)	188.3±249.3[f] (132.4)	187.0±95.2[h] (50.9)	698 (33)
8	5-FU $t_{½}$ (h)	Mean±SD (CV%)	ND	0.6±0.2[j] (28.8)	0.90±0.24[f] (26.8)	1.08±0.76 (70.5)	0.84 (25)
8	FBAL AUC(0-τ)[e] (ng/mL*h)	Mean±SD (CV%)	ND	2030±1403.0[i] (69.1)	2540±885.4[f] (34.9)	3857±714.2[k] (18.5)	31400 (30)
8	FBAL $t_{½}$ (h)	Mean±SD (CV%)	2.449	3.82±2.38[j] (62.3)	2.95±0.62[f] (20.9)	4.96±1.02[k] (20.6)	2.55 (19)

[A] Cohort 1: PCS6422 40 mg Day 1; Capecitabine 75 mg QD Day 2-8; [b]Cohort 2A and 2D: PCS6422 40 mg Day 1; Capecitabine 75 mg BID Day 2-8; [c]Cohort 3: PCS6422 40 mg Day 1; Capecitabine 150 mg BID Day 2-8; [d]Cohort 4: PCS6422 40 mg Day 1; Capecitabine 225 mg BID Day 2-8; [e] AUC(0-τ) on Day 8 should be equal to approximately AUC∞ at Day 2 if PK; properties are linear and the same across days; [f] Only determinable in 3 of 4 patients; [g] Only determinable 2 of 7 patients; [h] Only determinable in 5 of 7 patients; [i] Only determinable in 3 of 6 patients; [j] Only determinable 2 of 6 patients; [k] Only determinable in 6 of 7 patients; [m] AUC(0-9) because AUC∞ could not be determined since $t_{½}$ was Not Determined (ND); ND - Not determinable

Safety Evaluation: The incidence of Treatment Emergent Adverse Events (TEAE), Treatment Emergent Serious Adverse Events (TESAE), and Treatment Related Adverse Events (TRAE) are presented in Table 3. The adverse events associated with NGC-Cap were mainly related to the anabolites of 5-FU (e.g., myelosuppression, GI) and not the catabolites of 5-FU (e.g., HFS, cardiotoxicity).

Table 3: Summary of TEAEs and TRAEs by Cohort (Cut-off date 18 Jan 2024)

	Cohort 1 (N=1)	Cohort 2A+2D (N=6)	Cohort 3 (N=4)	Cohort 4 (N=7)	Xeloda Label
Number of Patients with TEAEs [n (%]	1 (100)	6 (100)	4 (100)	7 (100)	
Number of TEAEs	14	47	48	43	
Number of Patients with Grade 3-5 TEAEs [n (%]	0	2 (33.3)	1 (25.0)	5 (71.4)	
Number of Grade 3-5 TEAEs	0	4	8	11	
Number of Patients with TESAEs [n (%]	0	1 (16.7)	1 (25.0)	3 (42.9)**	
Number of Patients with DLTs [n (%]	0	0	0	0	
Number of Deaths [n (%]	0	0	0	1 (14.3)	
TRAEs Related to PCS6422					
All TRAEs n (%) E	0 (0.00) 0	3 (50.0) 9	3 (75.0) 18	5 (71.4) 13	
Grade 3-5 TRAEs n (%) E	0 (0.00) 0	0 (0.0) 0	1 (25.0) 2	3 (42.9) 6	
TRAEs Related to Capecitabine					
All TRAEs n (%) E	1 (100) 9	3 (50.0) 6	3 (75.0) 19	6 (85.7) 22	(~80)
Grade 3-5 TRAEs n (%) E	0 (0.00) 0	0 (0.0) 0	1 (25.0) 1	4 (57.1) 7	(~20)

Results and Discussion (continued)

Catabolite and Anabolite Safety Analysis: The incidence of the catabolite related AEs (e.g., HFS) is much less in this Phase 1b study compared to what is reported in the Xeloda label while the anabolite incidence appears to be greater for NGC-Cap (Table 4).

Table 4: Incidence of Side Effects Associated with 5-FU Catabolites or 5-FU Anabolites (Cut-off 18 Jan 2024)

	Cohorts 1-4 (N=18)	Grade 1-2	Grade 3+
Number of Patients with Catabolite Related AEs as n (%)	2 (11.1%)	2 (11.1%)	0.00%
Xeloda Label 2022 - % of Patients with Catabolite Related AEs	60%	43%	17%
Number of Patients with Anabolite Related AEs as n (%)	12 (66.7%)	8 (44.5%)	4 (22.2 %)
Xeloda Label 2022 - % of Patients with Anabolite Related AEs (e.g. Neutropenia)	13%	10%	3%

Dose Modifications Because of TEAEs and TRAEs: Modifications to the dosage regimens occurred given the seriousness of the AEs. AEs resulting in modifications included AEs such as neutropenia, platelet count decrease, peripheral sensory neuropathy, urinary tract infection, pneumonitis (fatal), and ascites. The modifications included dose reductions, dose interruptions, and dose discontinuations.

Table 5: Number of Patients Requiring Dose Modifications Because of TEAEs and TRAEs

	Cohort 1 (N=1)	Cohort 2A+2D (N=6)	Cohort 3 (N=4)	Cohort 4 (N-7)
Dose Reduction Pts Due to AEs n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
Dose Interruption Pts Due to AEs n (%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	3 (42.9%)
Dose Discontinuation Pts Due to AEs n (%)	0 (0.0%)	1 (16.7%)	0 (00.0%)	3 (42.9%)
Total Pts Modified Dosage Regimen Due to AEs n (%)	0 (0.0%)	1 (16.7%)	2 (50.0%)	5 (71.4%)

MTD and RDR: Dose modifications were much greater for Cohort 4 than Cohort 1, 2, or 3. Given the severity of the AEs and the number of AEs requiring dose modifications, the Cohort Safety Review Committee unanimously determined that the dose could not be escalated to Cohort 5. The MTD was defined as 225 mg BID and the RDR to be evaluated in the Phase 2 trial will be 150 to 225 mg BID.

Conclusions

- **NGC-Cap at 150 & 225 mg BID of Cape provides much greater 5-FU exposure and much lower FBAL exposure for the first few days of Cape treatment than monotherapy Cape even though the monotherapy Cape dose is > 9-10x the Cape dose in NGC-Cap.**
- **DPD de novo formation begins within 48-72 hours after PCS6422 dosing based on the increase in FBAL plasma concentration over time.**
- **The incidence of all TRAEs for 150 mg BID and 225 mg BID were similar to Cape monotherapy as reported in the Xeloda label while the incidence of Grade 3-5 TRAEs were similar for Cohort 3 and greater for Cohort 4 (Table 3).**
- **Although efficacy has not been reported in this poster presentation, the possibility of having an improved efficacy profile is likely given the much greater 5-FU exposure and potential increase in the distribution of 5-FU to cancer cells.**