UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K
CURRENT REPORT

PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): April 11, 2024

Commission file number 001-39531

PROCESSA PHARMACEUTICALS, INC.

(Exact name of Registrant as Specified in its Charter)

Delaware	**45-1539785**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification Number)**

7380 Coca Cola Drive, Suite 106, Hanover, Maryland 21076
(Address of Principal Executive Offices, Including Zip Code)

(443) 776-3133
(Registrant's Telephone Number, Including Area Code)

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common stock: Par value $.0001	PCSA	Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation Disclosure.

David Young, President, R&D for Processa Pharmaceuticals, Inc. ("***Processa***") presented two abstracts at the AACR Annual Meeting 2024 including new data on the NGC Cap Phase 1b trial.

The NGC-Cap preliminary data was included in the abstract and additional data was presented in the full poster. The poster presented has subsequently been modified from the version previously presented.

The amended full posters have been made available in the "Publications" section on Processa's website, located at https://www.processapharmaceuticals.com and are available as Exhibit 99.1 and 99.2 attached hereto.

Processa undertakes no duty or obligation to publicly update or revise the information contained in this report, although it may do so from time to time through the filing of other reports or documents with the Securities Exchange Commission, through press releases, or through other public disclosure, including in the "Investors" section of Processa's website. Processa routinely uses its website as a means of disclosing material non-public information and for complying with its disclosure obligations under Regulation FD.

The information in this Item 7.01 and Exhibits 99.1 and 99.2 attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 9.01. Financial Statements and Exhibits.

Exhibit No.	Exhibit Description
99.1	Next generation capecitabine (NGC-Cap) in Phase 1b trail significantly increases 5-FU exposure while improving safety profile compared to capecitabine, April 8, 2024.
99.2	Application of Phase 1 and pre-clinical data to assist in determining the optimal dosage regimen for cancer drugs using the principals of Project Optimus, April 9, 2024.
104	Cover Page Interactive Data File (formatted as Inline XBRL)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, hereunto duly authorized, on April 11, 2024.

PROCESSA PHARMACEUTICALS, INC.
Registrant

By: */s/ George Ng*
George Ng
Chief Executive Officer

Processa Pharmaceuticals

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

CT103

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 ethynyluracil (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.

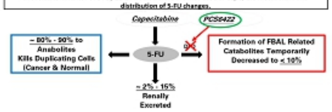
1. NGC-Cap can provide a greater 5-FU exposure based on AUC and Cmax with a better or similar side effect profile.
2. Side effects from the 5-FU catabolites are minimal and less severe for NGC-Cap.
3. Side effects from 5-FU anabolites are dependent on 5-FU exposure with less exposure leading to fewer 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)

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.



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 Pt enrolled, 1 Pt RECIST Evaluated^^
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 "Pts 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 75 mg QD (n=1)	Cohort 2A&2D 75 mg BID (n=6)	Cohort 3 150 mg BID (n=4)	Cohort 4 225 mg BID (n=7)	PK parameters Normalized to 1,250 mg/m² BID of Monotherapy Cape (Reigner 1998)
2	5-FU AUC(0-t) (ng/mL*h)	Mean±SD (CV%)	ND	3466.7±1305.4 (37.7)	4551±1221 (26.8)	6889±2851 (41.4)	698 (33)
2	5-FU t½ (h)	Mean±SD (CV%)	3.641	3.60±0.44 (12.1)	3.54±0.62 (17.5)	4.45±2.29 (51.5)	0.84 (25)
2	FBAL AUC0-t (ng/mL*h)	Mean±SD (CV%)	ND	109.7±45.6 (42)	248.7±103.7 (42)	265.7±273.8 (103)	31400 (30)
2	FBAL t½ (h)	Mean±SD (CV%)	ND	ND	ND	ND	2.55 (19)
8	5-FU AUC(0-t) (ng/mL*h)	Mean±SD (CV%)	ND	189.5±40.3 (21.3)	188.3±249.3 (132.4)	187.0±95.2 (50.9)	698 (33)
8	5-FU t½ (h)	Mean±SD (CV%)	ND	0.6±0.2 (28.8)	0.90±0.24 (26.8)	1.08±0.76 (70.5)	0.84 (25)
8	FBAL AUC(0-t) (ng/mL*h)	Mean±SD (CV%)	ND	2030±1403.0 (69.1)	2540±885.4 (34.9)	3857±714.2 (18.5)	31400 (30)
8	FBAL t½ (h)	Mean±SD (CV%)	2.449	3.82±2.38 (62.3)	2.98±0.62 (20.8)	4.96±1.02 (20.6)	2.55 (19)

* Cohort 1: PCS6422 40 mg Day 1; Capecitabine 75 mg QD Day 2-8; Cohort 2A and 2D: PCS6422 40 mg Day 1; Capecitabine 75 mg BID Day 2-8; Cohort 3: PCS6422 40 mg Day 1; Capecitabine 150 mg BID Day 2-8; Cohort 4: PCS6422 40 mg Day 1; Capecitabine 225 mg BID Day 2-8; AUC(0-t) on Day 8 should be equal to approximately AUC∞ at Day 2 if PK properties are linear and the same across days; Only determinable in 3 of 4 patients; Only determinable 2 of 7 patients; Only determinable in 5 of 7 patients; Only determinable in 3 of 6 patients; Only determinable 2 of 6 patients; Only determinable in 6 of 7 patients; AUC(0-9) because AUC∞ could not be determined since t½ 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.**

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Processa Pharmaceuticals

Application of Phase 1 and Pre-clinical Data to Assist in Determining the Optimal Dosing Regimen (ODR) for Cancer Drugs Using the Principles of Project Optimus

LB278

David Young, Sian Bigora, Peter Franks, Mary Nyberg, Yvonne Madden. Processa Pharmaceuticals, Hanover, Maryland

Abstract

Background: In 2022 and 2023 FDA introduced the Project Optimus initiative and the Draft Guidance "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases." The FDA's desire is to move away from the maximum tolerated dose (MTD) approach in the development of all oncology drugs and to determine and justify the ODR, requiring one to evaluate the exposure-response relationship for both the safety and efficacy of oncology drugs. This approach has made the oncology drug developer re-examine their previous beliefs and reconsider the design of the clinical and pre-clinical studies. Processa has begun to implement the ODR evaluation in Phase 1 and pre-clinical studies and will be providing examples as well as how the findings may potentially affect the design of Phase 2/3 trials.

Methods/Results: For Next Generation Irinotecan (NGC-Iri), the toxicity and tumor growth inhibition after NGC-Iri administration (as well as tissue distribution of NGC-Iri) were compared to irinotecan in xenograft transplanted mice. Tumor growth inhibition remained constant at 100% for an NGC-Iri dose at the MTD and at 50% of the MTD. However, tumor growth inhibition after irinotecan administration decreased from 100% at the MTD to approximately 64% at 50% of the MTD. The differences seen in the tumor inhibition when NGC-Iri and irinotecan were administered illustrate that the exposure-efficacy profile of NGC-Iri follows a different pattern than the exposure-safety profile and is different from the irinotecan exposure-efficacy profile even though the active molecule is the same. The dose of NGC-Iri can be decreased to improve safety while not significantly sacrificing efficacy, different than what was seen with irinotecan. In a second example, we are evaluating the PK-safety relationship of a different Next Generation drug in our ongoing Phase 1 trial. We have recently found that the exposure-safety relationship is different for our NGC drug than for the approved drug with the same cancer-killing metabolite(s). Based on the difference in exposure-response in the Phase 1 study, we are designing the Phase 2 trial to determine the potential ODR.

Conclusion: Both preclinical and Phase 1 oncology trials can be designed to better understand the exposure-response relationships for safety and efficacy which will then help the drug developer in designing the Phase 2 and 3 trials for eventual FDA approval of the ODR.

Introduction to Project Optimus

- Historically, selection of the dosage regimen for oncology drugs was based on the maximum tolerated dose (MTD) safety-efficacy.
  - Safety & efficacy were assumed to be linked (i.e., increase toxicity increases cancer killing effect).
  - The Recommended Phase 2 Dose (RP2D) advancing to Phase 2 and 3 was typically the MTD.
  - Dose ranging efficacy/safety studies were not required for oncology drugs as required for other drugs.
- In 2021 FDA introduced Project Optimus which led to FDA's optimal dosing regimen (ODR) Draft Guidance "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases" (Draft ODR Guidance) requiring:
  - Evaluation of the possible dose/exposure – response relationship for both safety and efficacy and
  - Clinical evidence and justification for a Recommended Dose Range (RDR) of at least 2-3 doses to be evaluated in Phase 2 as well as the ODR to use for Phase 3 and approval.
- FDA has noted that by NOT identifying the ODR, a poorly characterized dose and schedule may lead to:
  - Selection of a dosage regimen in Phase 3 that provides more toxicity without additional efficacy and/or
  - Toxicities requiring dose reductions, treatment interruptions, and/or treatment discontinuation.
- Project Optimus states that all cancer drugs may not follow the same dose/exposure – safety or efficacy pattern (Figure 1A versus Figure 1B) making the burden to define the relationship the sponsors responsibility.

Figure 1A. Assumed in the MTD Design: Dose-Response for Efficacy Parallels Toxicity

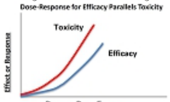
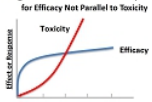


Figure 1B. Possible that Dose-Response for Efficacy Not Parallel to Toxicity



Project Optimus Starts with Preclinical Studies

- Preclinical pre-IND enabling studies in oncology typically include:
  - In vitro and in vivo pharmacology studies to assess tumor response,
  - Toxicology studies to define the no-observed-adverse-effect level (NOAEL) and the MTD, and
  - ADME (absorption, distribution, metabolism, excretion) and pharmacokinetic (PK) studies.
- Some limits of these studies when defining the dose/exposure – response (safety or efficacy) relationships are that the response is often evaluated at few doses and the doses chosen are typically closer to the MTD and not lower doses.
- Pre-clinical dose/exposure – response curves for safety and efficacy may provide insight into the clinical dose/exposure – response curves.

- Next Generation Irinotecan (NGC-Iri) is a pro-drug of SN-38 (the active metabolite of irinotecan). A molecular nano-motor (MNM) which interacts with tumor cell membranes preferentially over normal cells is linked to SN-38 allowing more of the SN-38 to enter the tumor core and less into other tissues compared to irinotecan.

Figure 2. Tissue distribution Differences of SN-38 after NGC-Iri (Tumor/Muscle Ratio = 200) vs Irinotecan (Tumor/Muscle Ratio = 15)

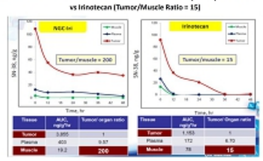
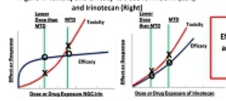


Table 1: Tumor Growth Inhibition for NGC-Iri and Irinotecan at Different

Dose	NGC-Iri	Irinotecan
MTD	100%	85%
½ MTD	100%	64%
¼ MTD	100%	53%

NGI-Iri Efficacy Maintained at Doses with Less Toxicity (e.g., 25% x MTD) while Irinotecan Efficacy Decreases

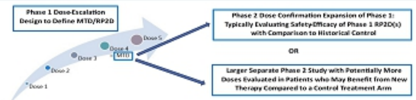
Figure 4. Toxicity and Efficacy vs Dose for NGC-Iri (Left) and Irinotecan (Right)



Shapes of the Toxicity and Efficacy Dose-Response Curves are Different for NGC-Iri while the Shapes are Similar for Irinotecan

Phase 1 Design Considerations Given Project Optimus and the Determination of the ODR

- Previously, the objective of the First-in-human (FIH) oncology studies was to identify the MTD and RP2D (most often the MTD) in patients, either by conducting a:
  - Phase 1/2 study identifying the MTD during Phase 1 dose escalation in patients who have "no satisfactory alternative therapies", followed by expansion of selected Cohorts to further evaluate safety and efficacy or
  - Phase 1 study to identify the MTD in patients who have "no satisfactory alternative therapies", followed by a larger Phase 2 study in patients who "may have alternative treatments".


Phase 1 Dose-Escalation Design to Define MTD/RP2D
Dose 1
Dose 2
Dose 3
Dose 4
Dose 5
MTD
Phase 2 Dose Confirmation Expansion of Phase 1: Typically Evaluating Safety-Efficacy of Phase 1 RP2D(s) with Comparison to Historical Control
OR
Larger Separate Phase 2 Study with Potentially More Doses Evaluated in Patients who May Benefit from New Therapy Compared to a Control Treatment Arm

BASED ON PROJECT OPTIMUS INITIATIVE

- FIH Phase 1 should be modified to provide initial clinical information on both safety and efficacy from which at least 2-3 possible doses, including the MTD, can be selected as the Recommended Dose range (RDR) to run in a more comprehensive Phase 2 study to define the potential ODR.
- The 2 potential designs are 1) Phase 1/2 with dose confirmation expansion or 2) Phase 1 followed by separate Phase 2 study. Some considerations to consider when deciding on the design of the Phase 1 study are presented in Table 2.

Table 2: Some Considerations When Designing FIH Phase 1 to Determine the RDR for Phase 2 and 3

	Design Considerations
Patient Inclusion in Phase 1	Patients with no satisfactory alternative therapies
Cancer Type for Project Optimus Analysis	Phase 1 dose escalation may be mixture of cancers, but Phase 2 to define ODR needs to be more selective
Phase 1 Dose/Exposure - Response to Define RDR	Safety and efficacy to be evaluated (e.g., % of an AE by cohort, duration of clinical benefit by patient)
Number of Phase 1 Doses Selected for RDR	≥ 2, including the MTD
Arms to be Evaluated in Phase 2	Phase 1/2 cohort expansion ≥ 2 + historical control or Separate Phase 2 ≥ 2 + active or historical control

Processa Separated Phase 1 and 2 Studies Based on FDA's Following Recommendations

- Phase 2 & 3 should target a different cancer patient population than Phase 1 dose escalation.
- Dose/exposure-response analysis of Phase 1 to define the RDR for Phase 2.
- The RDR should include ≥ 2 regimens when conducting ODR Phase 2 evaluation.
- Phase 2 needs to include a randomized active control arm.

Conclusions

- **Preclinical dose/exposure – toxicity/efficacy studies can provide some guidance on the pattern of the dose/response relationships as illustrated with NGC-Iri.**
- **Phase 1 studies can provide data to begin developing dose/exposure-toxicity/efficacy relationships if designed appropriately.**
- **Even with the small number of patients in Phase 1, the PK, toxicity, and efficacy data provides guidance to select the RDR for a Phase 2 safety/efficacy evaluation and Project Optimus analysis.**
- **Sponsors must consider that a Phase 1 study followed by a Phase 2 safety/efficacy study may be the design of choice given the requirements of FDA and Project Optimus.**

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