ENCODE IDEAS

FINANCIAL SUMMARY TABLE

Symbol	PCSA
Exchange	NASDAQ
Current Price	$10.89
52 week High	$12.75
52 week Low	$3.40
O/S	~15.5mm*
Market Cap est	~$168mm*
Average Volume (3M)	~50.1k
Cash	~$25mm*
Debt	$0mm*

*pro forma estitmate; inclusive of recent raise of $10.2mm, prior raise of $19.2mm and 1/11/21 corporate presetntaion

KEY CATALYST DATES

2Q 2021	PCS6422 Ph1b First Patient In
2Q 2021	PCS499 Ph2b First Patient In
3Q 2021	PCS6422 Ph1b Interim Data Release
4Q 2021	PCS499 Ph2b Interim Data Release

KEY DISCLOSURES

Encode Ideas, L.P. owns stock in the covered company. Encode Ideas, L.P. has been engaged by Processa to provide research coverage and awareness. Encode Ideas, L.P. intends to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter.

Processa Pharmaceuticals, Inc. (PCSA)
INITIATION REPORT

February 22, 2021

HIGH CONVICTION INVESTMENT IDEA

We believe through clinical success with their lead assets, PCS6422 and PCS499, Processa can achieve a market cap of >500mm by 2023, reflecting a nearly 3x multiple from its recent share price of $10.89 (2/19/21).

Encode Ideas L.P. is initiating coverage on Processa Pharmaceuticals as a high conviction idea. Processa's pipeline is constructed of development-stage assets that have substantial legacy human data, where the company believes a new approach (dosing, indication, trial design, etc.) can unlock latent value. Processa's management (David Young, Questcor) and board (Khalid Islam, Gentium, and Fennec) have a history of successful drug reclamation projects. The company's lead asset, eniluracil or PCS6422, was a GSK drug that has been studied in over 1,500 cancer patients, where Processa believes slight changes to the dosing regimen and study design can address previous shortcomings. The other pipeline product of note, PCS499, comes from Concert Pharmaceuticals, where it was studied in Ph2 for diabetic nephropathy, but Processa believes it is better suited for a rare dermatology indication, Necrobiosis Lipoidica (NL). We are enthusiastic about both assets, in particular PCS6422, and feel if there is latent value in either or both, this is the team that can unearth it.

PCS6422 is a potent and irreversible inhibitor of DPD, an enzyme responsible for the rapid metabolization and degradation of one of the most commonly used chemotherapies, 5-FU. 5-FU, and its oral prodrug form, capecitabine (Xeloda®, Roche), are mainstay therapies for the management of colorectal and breast cancer, but their bioavailability and tolerability are negatively impacted by the presence of DPD. Knocking down DPD, by dosing PCS6422 with capecitabine, should dramatically dramatically reduce the efficacious dose of capecitabine while improving tolerability, and potentially efficacy. We believe Processa poured over the legacy data and regulatory interactions and concluded that a different dosing regimen and pivotal study design, can unlock the significant latent value of PCS6422. Their clinical path starts with a Ph1b study, with PCS6422 in combination with capecitabine in patients with advanced GI cancers, scheduled to start imminently. We will be watching for positive signs from this study throughout 2H21, validating Processa's PCS6422/capecitabine dosing strategy, and early signs of improved safety. We believe the Ph1b study is a major de-risking event for Processa, paving a path to a late-stage, potentially pivotal study, in early-23. Processa is initially focused on colorectal cancer, but with capecitabine widely used in other cancers, most notably breast, the addressable market potential for PCS6422 could be much larger.

PCS499, an oral small molecule, is a deuterated analog of one of the major metabolites of FDA-approved pentoxifylline (PTX or Trental®, Sanofi). Approved for intermittent claudication, there are anecdotal reports of high-dose PTX working for NL, a rare skin disorder with no FDA-approved products. Processa has secured orphan drug designation for PCS499 in NL, cleared an IND, and generated a small, albeit encouraging, amount of data in a Ph2a study in patients with severe, ulcerative NL (uNL). Processa will be initiating a placebo-controlled Ph2b study 1H21 in uNL patients and has guided interim data could be available as soon as 4Q21. Success in the upcoming Ph2b study should allow Processa to move into a single pivotal Ph3 study by 1H23.

Later this year, investors should get their first look at whether PCS6422 and PCS499 are performing as expected. More conclusive data will then be available throughout 2022, determining whether either, or both, assets has a viable path to Ph3. We believe both assets have a good chance of success in their upcoming studies, with more conviction weighted towards PCS6422, given the bounty of legacy data. In our opinion, Processa, with two clinical assets for unaddressed markets, and several data catalysts in 2H21 and into 2022, is very affordable at its current ~$170mm market cap. We believe by 2023, Processa could have one, or more, programs in Ph3, warranting a substantial bump in valuation, which we estimate to be >$500mm.

5-FU - The History

Fluorouracil (5-FU) is a fluoropyrimidine chemotherapeutic agent used in the treatment of a wide variety of malignancies. 5-FU is a cornerstone treatment for many different types of cancers, most notably, colorectal and breast, either as monotherapy or in combination with other chemotherapy agents (estimated two million patients annually). Originally 5-FU was developed and administered as an IV bolus however, in the U.S., preferences for 5-FU administration gradually shifted from IV bolus injection to infusion via a pump. Since 5-FU exhibits poor absorption in the gastrointestinal (GI) tract when administered orally, prodrugs such as capecitabine have been developed to provide a more convenient alternative to IV 5-FU administration. The various modes of administration are all efficacious, but have different tolerability profiles;

- Bolus 5-FU: prone to hematological side effects, inconvenient
- IV Infusion 5-FU: improved hematological profile vs bolus, but higher incidence of GI issues and HFS, inconvenient
- Oral 5-FU: improved hematological profile vs bolus, but higher incidence of GI issues and HFS, very poor bioavailability, convenient
- Capecitabine: improved hematological profile vs bolus, improved GI issues vs oral, higher incidence of HFS vs bolus, infusion and oral, convenient

PCS6422 - The Need

Processa is developing PCS6422, a DPD inhibitor, in combination with FDA-approved capecitabine, for the treatment of metastatic colorectal cancer (mCRC). DPD is responsible for the rapid metabolization and degradation of 5-FU leading to poor bioavailability. DPD's metabolism of 5-FU also produces the metabolite F-BAL, which is implicated in a painful side effect, hand-foot syndrome (HFS), in >50% of capecitabine treated patients. HFS can range from mild to moderate (grade 1 & 2), with symptoms including redness, swelling, and burning, to severe (grade >2), with symptoms escalating to include blistering, ulceration, and difficulty using extremities. HFS is a leading cause of dose reduction, treatment interruption, and treatment discontinuation with capecitabine. There is strong mechanistic rationale, and supporting clinical data, that DPD inhibition can reduce the incidence and

severity of HFS in patients taking capecitabine.

The interpersonal variability of endogenous DPD levels can lead to life-threatening toxicities from 5-FU treatment. For most patients, high 5-FU doses (capecitabine is dosed up to 4,000 mg/day), are needed to overcome degradation by DPD and ensure sufficient drug is on-board to exert its anti-tumor effect. However, for the 3-7% of the population that are DPD deficient, producing little to no enzyme, standard 5-FU doses can be lethal. In fact, in 2015, FDA approved Vistogard for the emergency treatment of 5-FU overdoses, to address DPD deficiency. On the other end of the DPD spectrum, there are data suggesting patients that overexpress DPD are likely to be refractory to all forms of 5-FU treatment. So whether it's HFS caused by DPD's production of F-BAL, the risk of life-threatening toxicities due to DPD deficiency, or the overexpression of DPD preventing 5-FU from working, it is apparent there is a medical need to appropriately manage DPD levels when using 5-FU.

PCS6422 is a potent and irreversible inhibitor of DPD, that can virtually eliminate DPD production for up to 2 weeks with one dose. The proposed benefits of combining a DPD inhibitor with 5-FU treatment include; (1) predictable 5-FU dosing by eliminating interpersonal variability of endogenous DPD (2) significantly lower doses of 5-FU required due to improved bioavailability (3) improved tolerability, notably lower incidence of HFS and potentially other side effects (4) improved patient outcomes - tumor response and survival. Processa have reviewed the substantial legacy data on PCS6422, including two Ph3 mCRC studies (GSK) and a large Ph2 metastatic breast cancer (MBC) study (Adherex/Fennec), and believe they know where these companies erred in their development, and what needs to be done to revitalize the asset.

PCS6422 - The History

GSK completed two Ph3 studies in mCRC with PCS6422 dosed concurrently with oral 5-FU (not the prodrug), and took an New Drug Application (NDA) to FDA's doorsteps before opting not to file. Their large >900 patient U.S. study showed that oral PCS6422/5-FU vs I.V. 5-FU/Lv (leucovorin, commonly dosed with 5-FU) did not meet the protocol-specified definition of equivalence on overall survival (OS). Although the study did not achieve its primary endpoint of statistical equivalence on OS, it did show PCS6422 dosed concurrently with 5-FU was not statistically inferior and generally better tolerated than the I.V. control arm (see table below). GSK, encouraged by these findings, held a pre-NDA meeting with FDA, but based on the Agency's feedback, opted not to develop PCS6422 further.

Results of the North American Pivotal Phase III Trial Colorectal Cancer

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD n (%)	Median PFS Days
EU/5-FU/Lv	74	1 (1)	18 (24)	38 (51)	57 (77)	125
Xeloda	61	0 (0)	18 (30)	27 (44)	45 (74)	126

*Although considerably less toxic, oral EU/5-FU produced less antitumor activity tham iv 5-FU/leucovorin

Adherex Technologies (renamed Fennec Pharmaceuticals in 2014) acquired PCS6422 in 2004. Adherex believed, based on new preclinical findings, that dosing PCS6422 simultaneously with 5-FU, as GSK had done in their large Ph3 colorectal cancer studies, could be attenuating the anti-tumor effects of 5-FU. The company adopted a dosing schedule to minimize the ratio of PCS6422 to 5-FU by giving PCS6422 12-18hrs before the first dose of 5-FU. This new dosing regimen was put to the test in a Ph2 MBC study powered to show the superiority of PCS6422/5-FU/Lv (dosing PCS6422 the day prior to oral 5-FU) vs monotherapy capecitabine on progression-free survival (PFS). The study was stopped early, based on the assumption that it would not reach the statistical threshold for superiority, although the interim data (see table below) clearly demonstrated the two arms had similar efficacy. Adherex, by this time known as Fennec, divested PCS6422 to Elion Oncology in 2016.

Arm 1: EU/5-FU/Lv vs Arm 2: Xeloda

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD n (%)	Median PFS Days
EU/5-FU/Lv	74	1 (1)	18 (24)	38 (51)	57 (77)	125
Xeloda	61	0 (0)	18 (30)	27 (44)	45 (74)	126

*Adherex Technologies 2013 Corporate Presentation

Although the ownership of PCS6422 has changed hands several times, the rationale for its development has not - knocking down DPD should improve the bioavailability, tolerability, and potentially efficacy of 5-FU. We need to look no further than the existence of Vistogard as evidence of the important role, and risk, DPD plays when using 5-FU. In Europe and Japan, a fixed-dose combination that includes an oral 5-FU prodrug and a DPD inhibitor has been approved for years. Developed by Otsuka Pharmaceuticals, and known as Teysuno, S-1, or TS-1, it includes the reversible DPD inhibitor, gimeracil. As a reversible DPD inhibitor, gimeracil must be dosed concurrently with 5-FU. To the best of our knowledge, the development of Teysuno/S-1/TS-1 in the United States is not being actively pursued.

PCS6422 - The Path Forward

As described above, the medical need for DPD inhibition while using 5-FU is clear, the path to approval less so. In early 2020 Elion met with FDA and subsequently filed a new IND for PCS6422 in combination with capecitabine for the treatment of mCRC. Processa acquired PCS6422 in October 2020, so they were clearly comfortable with the FDA meeting minutes from Elion and believe there is an efficient clinical and regulatory path forward. Our assumption is that a potential pivotal study design was discussed with FDA that likely included a primary safety endpoint of HFS and either a co-primary or secondary efficacy endpoint (likely objective response rate or PFS) powered for non-inferiority. This study design would have the highest probability of success, and arguably lowest regulatory hurdle. We would also highlight that Teysuno was approved by the European Medicines Agency

(EMA) based on a non-inferiority endpoint vs 5-FU.

The study design and path to approval for PCS6422 outlined above is our base case, but in our opinion there is also a best case scenario possible, whereby PCS6422/capecitabine demonstrates superior efficacy vs. monotherapy capecitabine. Both GSK and Adherex were developing PCS6422 with oral 5-FU, which is known to have poor GI tolerability (predominantly diarrhea) as a common dose-limiting toxicity (DLT). Adherex used a daily dose of 30mg/m2 of oral 5-FU in their Ph2b MBC study. However, Grem at al, has published data showing that drug exposure (area under the curve) of ~30mg/m² oral 5-FU dosed after PCS6422 was only 60% of a standard I.V. 5-FU dose. These data would imply that historical studies have used suboptimal oral 5-FU doses when in combination with PCS6422. Even with suboptimal dosing, Adherex was able to show that PCS6422 when dosed with 30mg/m² oral 5-FU had similar efficacy to monotherapy capecitabine. Processa has wisely abandoned oral 5-FU in their development plans, focusing instead on combining PCS6422 with capecitabine. By using capecitabine instead of oral 5-FU, the GI related DLTs that limited dose for Adherex and GSK, shouldn't be as prevalent, allowing Processa to push capecitabine dosing to optimal levels. This would lead us to the conclusion that if PCS6422 combined with suboptimally dosed oral 5-FU demonstrated equivalence to capecitabine, there is a distinct possibility that PCS6422 combined with an optimized dose of capecitabine, could show superior efficacy.

There is also a growing amount of clinical data correlating DPD levels and clinical response, whereby low-DPD levels are predictive of favorable outcomes and high-DPD levels poorer outcomes. Adherex's Ph2b MBC study provides some relevant clinical insight to arguably support this DPD thesis. In that study 10 patients on the capecitabine monotherapy arm who rapidly progressed (tumor progression at their first scan - approx 45-days) crossed over to the PCS6422 arm. Of this group of crossover patients, 9 experienced disease control (3 complete responders, 6 stable disease) on the PCS6422/5-FU/Lv regimen. This is quite a remarkable finding, given the active chemotherapy, 5-FU, remains basically the same between the two arms. DPD overexpression is the likely explanation for this finding, whereby patients with high intra-tumoral DPD levels are resistant to capecitabine due to poor 5-FU bioavailability, but once crossed over, DPD levels are dramatically reduced with PCS6422, improving the bioavailability of 5-FU, allowing it to exert its antitumor benefit.

We think PCS6422/capecitabine could show superior efficacy to capecitabine monotherapy in a pivotal study. If this were the case, the peak sales potential for PCS6422 would be materially higher than under a scenario where HFS and non-inferiority were the Ph3 outcome. Superiority versus capecitabine would compel PCS6422's use and allow for premium pricing, potentially seeing PCS6422 achieve peak sales close to that of capecitabine, which flirted with $2b.

Processa will be initiating a Ph1b study with PCS6422 in combination with capecitabine imminently. The company hasn't disclosed details of the study yet, but we can infer a few details from their corporate presentation

and regulatory filings. The Ph1b will dose escalate capecitabine, starting at very low doses, after pre-dosing with PCS6422 a day earlier. Based on published preclinical data, and comments in their SEC filings, where Processa references up to 14-days of DPD inhibition with one dose of PCS6422, it seems apparent that PCS6422 will be dosed bi-weekly, while capecitabine will be dosed 7-days on, 7-days off. Processa believes the Ph1b study should validate that pre-treatment with PCS6422 leads to; (1) substantially lower maximum tolerated dose (MTD) compared to standard capecitabine dosing (2) improved PK, notably improved 5-FU exposure and reduction in F-BAL (3) improved capecitabine tolerance, most notably lower incidence of HFS (4) tumor response data in-line, or better, than historical capecitabine efficacy in the GI cancer setting.

We expect the first look at the Ph1b data will be 4Q21 once MTD of capecitabine has been determined. In addition to MTD, important PK data should be available in the 2H21, including PK levels of 5-FU and its metabolites. If at MTD, Processa sees levels of 5-FU and its desirable metabolites, that are reflective of an efficacious dose, while also seeing lower levels of undesirable metabolites, most notably F-BAL, that are reflective of better tolerability, then investors can likely infer that PCS6422 is working as expected. We anticipate safety and efficacy data in 1H22, from a larger cohort of patients enrolled at MTD.

PCS499

Processa is developing PCS499, a deuterated (hydrogen atoms are substituted by deuterium atoms) analog of one of the major metabolites of FDA-approved pentoxifylline (PTX), for the treatment of Necrobiosis Lipoidica (NL). NL is a chronic skin disorder caused by collagen degeneration that is characterized by asymptomatic yellowish-brown plaques on the skin, often on the lower extremities (shins). In more severe cases, ulceration can occur, often due to minor contact trauma. Processa estimates there are upwards of 50,000 NL patients in the U.S. with ulcers (uNL). There are currently no FDA-approved treatments for NL. Processa has received orphan drug designation for PCS499 for the treatment of NL.

There are anecdotal reports of high-dose PTX (1.2g/day) being effective for the treatment of NL. As a deuterated analog of PTX, Processa believes PCS499 could be safely given at even higher doses, up to 1.8g/day. The company recently completed an open-label Ph2a study with PCS499 in 12 NL patients. Although the final study data haven't been published or reported yet, Processa has disclosed that PCS499 was well tolerated at 1.8g/day, characterizing all side effects as mild. Of the 12 patients treated, 2 patients with uNL experienced complete closure of their wounds while on PCS499. The remaining 10 patients, with less severe NL and no ulceration, experienced limited improvement with PCS499 treatment.

After meeting with FDA in 2020, Processa is planning on initiating a randomized placebo-controlled Ph2b study with PCS499 in patients with uNL in 1H21. We don't have any additional information on the study design at this

time, but assume it will follow a similar dosing regimen as the earlier Ph2a, with a 6-month treatment period (PCS499 1.8g/day or placebo), followed by an open-label extension period. The primary endpoint will almost certainly be the percentage of patients with complete wound closure, PCS499 vs placebo. Processa has suggested that an interim data look could occur by 4Q21. If Processa generates positive data with PCS499 in uNL, we believe FDA should be amenable to an efficient single Ph3 registrational study path. Although uNL is a niche indication, the broader wound healing market is enormous, and success in uNL with PCS499, could open up the possibility of Processa pursuing larger wound indications in the future.

Deeper Pipeline

Processa in-licensed an 5-HT4 agonist from Yuhan Corporation last year. Now known as PCS12852, Processa believes this asset has potential for the treatment of GI motility disorders. Initial human data generated by Yuhan, demonstrated the safety of PCS12852 and some early signs of efficacy with improved gastric emptying rate. Processa plans to meet with FDA shortly to discuss Ph2 plans for PCS12852. We would expect clearance of an IND for PCS12852 and initiation of a Ph2 study, likely in gastroparesis, by mid-21.

Leadership

David Young, PhD, PharmD, CEO of Processa, was a board member (2006-2009) and Chief Scientific Officer (2009-2014) of Questcor Pharmaceuticals, where he played an integral role in modernizing the Acthar Gel label and obtaining FDA approval for infantile spasms. In 2014 Questcor was acquired by Mallinckrodt for $5.8b. Over his career he has been a key team member on more than 30 NDA/supplemental NDA approvals. We believe Dr. Young's extensive experience interacting with FDA on pivotal study designs and challenging approvals / label expansions will be a valuable attribute as Processa advances its pipeline, in particular, PCS6422 into Ph3.

We would also highlight Khalid Islam, PhD, who joined the board shortly after the 2020 Nasdaq uplist. Dr. Islam is an advisor to the venture group Kurma Biofund (Paris). He is currently the Chairman of the board at Fennec Pharmaceuticals Inc. (Nasdaq: FENC), Gain Therapeutics Inc., Minoryx Therapeutics SL and Immunomedics Inc. (Nasdaq: IMMU), which was recently acquired for $21b by Gilead Sciences (Nasdaq: GILD). Dr. Islam was the chairman and CEO of Gentium S.p.A. (Nasdaq: GENT; 2009-2014) where he led its transition to a profitable company that subsequently sold to Jazz Pharmaceuticals (Nasdaq: JAZZ) for $1b. We believe Dr. Islam's experience shepherding Gentium's lead asset, defibrotide, through EMA approval, after an earlier regulatory rebuff, could be valuable to Processa in its future regulatory interactions.

Financial Considerations

Processa listed on Nasdaq in October 2020, after completing a $19.2mm financing at $4.00. They recently raised an additional $10.2mm at $7.75. We estimate the company has pro-forma cash of ~$25mm. They have guided that their current treasury will see them into 2023. After their recent raise, Processa has approximately 15.5mm shares outstanding. Insider ownership is ~25%, and Manchester Management (and its partners), a fund we know well, own ~10%. We suspect once the company starts delivering data from their studies with PCS6422 and/or PCS499, that deeper science funds will begin to participate.

Notable Risks

Notable risks to our investment thesis include; (1) clinical setbacks in either or both of Processa's clinical programs (PCS6422 and PCS499) (2) COVID-19 related risks, most notably study delays, and risk to data integrity (3) regulatory issues, whereby FDA requires additional studies beyond the efficient clinical path(s) we have elucidated above (4) competitive risk, more relevant for PCS6422, where new technologies could erode the 5-FU/capecitabine market (5) capital market issues, whereby capital becomes challenging and/or excessively expensive to access.

Executive Summary

Processa Pharmaceuticals is a clinical stage biopharmaceutical company focused on the development of drug products that are intended to provide treatment for and improve the survival and/or quality of life of patients who have unmet medical needs or conditions and for whom there are no alternative treatments.

Processa's pipeline includes three potential drug candidates:

- PCS6422 - for metastatic colorectal cancer and breast cancer,
- PCS499 - for ulcerative necrobiosis lipoidica, and
- PCS12852 - for gastrointestinal motility/gastroparesis.
-

The potential market for each of these products is estimated to be in excess of $1 billion.

PCS6422

Fluorouracil (5-FU) is a fluoropyrimidine chemotherapeutic agent used in the treatment of a wide variety of malignancies including gastric, pancreatic, breast, and colorectal cancer. In the body 5-FU is converted to three main active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP). For 5-FU to exert its effect it enters cells via a facilitated transport mechanism and is converted to FdUMP. FdUMP complexes with the enzyme thymidylate synthase, inhibiting the production of the compound deoxythymidine monophosphate (dTMP). dTMP is essential for DNA replication and repair, and depletion of this compound results in an imbalance of intracellular nucleotides leading to double-stranded breaks in DNA by the enzyme endonuclease. In addition, 5-FU also serves as a pyrimidine analog by mis-incorporating into RNA and DNA in place of uracil or thymine. The overwhelming damage of DNA repair machinery caused by these mechanisms ultimately results in cell death of rapidly proliferating cells.

Originally 5-FU was developed and administered as an IV bolus however, preferences for 5-FU administration gradually shifted to intravenous infusion. Orally administered 5-FU exhibits poor absorption in the gastrointestinal tract therefore, prodrugs such as Capecitabine have been developed to provide an alternative to intravenous 5-FU administration.

More than 80% of intravenously administered 5-FU is metabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) and is converted to dihydrofluorouracil (DHFU). DHFU is then converted into the soluble molecule 5-fluoro-βalanine and is eliminated in the urine. DPD activity is not constant in individuals and is thus one of the factors responsible for the inter- and intra-patient variability seen in the pharmacokinetic and pharmacodynamic outcomes of patients treated with 5-FU.

The use of 5-FU carries the risk of severe adverse events in up to 30% of patients. One such adverse event is Hand-Foot Syndrome (HFS). HFS is a cutaneous adverse event that although not life threatening, can severely disrupt the daily lives of patients. In addition, HFS is a leading cause of treatment interruption, dosage reduction, or therapy discontinuation for patients on a Capecitabine regimen.

PCS6422 also known as Eniluracil, is an uracil analogue, which irreversibly inhibits DPD within one hour of administration. In the presence of PCS6422, bioavailability of 5-FU increases to approximately 100%, the half-life is prolonged to 4 to 6 hours, and systemic clearance is reduced > 20-fold to values comparable to the glomerular filtration rate. Renal excretion instead of DPD-related catabolism becomes the principal route of elimination of oral 5-FU given with PCS6422. PCS6422 is neither toxic nor active as a single agent in animals, however, it potentially improves the antitumour efficacy and therapeutic index of 5-FU.

PCS6422 has been extensively studied. Early clinical trials suggested that the combination of 5-FU/PCS6422 was effective in treating several types of solid tumors with decreased toxicity including reductions in the occurrence and severity of HFS. However, despite promising Phase II data PCS6422 was abandoned after two large Phase III trials failed to demonstrate the equivalence of 5-FU/PCS6422 with 5-FU and Leucovorin.

The two multicenter Phase III studies were conducted in patients with colorectal cancer and PCS6422 was administered in 10-fold excess to 5-FU. It is believed that the dose of PCS6422 used during these trials was not optimal, and that PCS6422 was not administered early enough to irreversibly affect the DPD enzyme. As a result The PCS6422 regimen tended to produce less antitumor benefit than the control arm utilizing the standard regimen of 5-FU and Leucovorin. Subsequent preclinical work suggested that when excess PCS6422 is present at the same time as 5-FU, it diminished the antitumor activity of 5-FU. Processa believes these data support further

exploring the dosing of PCS6422 several hours before 5-FU to allow its clearance before the administration of 5-FU.

Processa has completed pharmacology, toxicology and manufacturing work on PCS6422 and are proposing to initiate a Phase 1b study to confirm the safety and PK of a fixed dose of PCS6422 with increasing doses of Capecitabine in patients with advanced gastrointestinal solid tumors. The study is expected to begin dosing patients in the first half of 2021 with the final report expected in the second half of 2022. Subsequently. Processa plans to initiate a Phase 2/3 study in the first half of 2023.

PCS499

PCS499 is an oral tablet that is a deuterated analog of one of the major metabolites of Pentoxifylline. Pentoxifylline is a methylxanthine derivative with potent hemorheological properties. It is used to improve blood flow in patients with circulation problems to reduce aching, cramping, and tiredness in the hands and feet. It works by decreasing the thickness (viscosity) of blood. This allows blood to flow more easily, especially in the small blood vessels of the hands and feet. In the U.S. Pentoxifylline is marketed for the treatment of intermittent claudication but is also used to treat leg ulcers, strokes, high-altitude sickness, eye and ear disorders, and sickle cell disease and to treat pain from diabetic neuropathy.

PCS499 metabolizes qualitatively to the same active moieties as Pentoxifylline but quantitatively has different amounts of these metabolites. An issue with Pentoxifylline is that it has dose limiting side effects which can limit its use. However, preclinical and clinical evidence indicate that PCS499 may have less side effects compared to Pentoxifylline which may allow for higher doses to be administered.

Necrobiosis lipoidica is a chronic, disfiguring condition affecting the skin and tissue under the skin typically on the lower extremities. Necrobiosis lipoidica presents more commonly in women than in men and occurs more often in people with diabetes. Ulceration occurs in approximately 30% of necrobiosis lipoidica patients, which can lead to more severe complications, such as deep tissue infections and osteonecrosis. Currently there are no approved treatments for necrobiosis lipoidica in the United States.

Processa has chosen ulcerative necrobiosis lipoidica as PCS499's first indication and has obtained orphan designation. In a small study, necrobiosis lipoidica patients tolerated PCS499 well and at greater doses than Pentoxifylline. In addition, two patients with necrobiosis lipoidica ulcers had complete closing of all their original wounds.

Processa is currently planning a Phase 2B study of PCS499 which is scheduled to start dosing necrobiosis lipoidica patients during the first half of 2021, with an interim analysis in the fourth quarter of 2021, and the final report for this trial is expected in the second half of 2022.

PCS12852

PCS12852 is a novel, potent and highly selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist. Other 5-HT receptor agonists with less 5-HT4 selectivity have been shown to successfully treat gastrointestinal motility disorders such as chronic constipation, constipation-predominant irritable bowel syndrome, functional dyspepsia and gastroparesis. Less selective 5-HT4 agonists have been either removed from the market or not approved because of the cardiovascular side effects associated with the drugs binding to other 5-HT receptors.

Two clinical studies have been previously conducted by Yuhan with PCS12852. In the first trial, the safety and tolerability of PCS12852 was evaluated after single and multiple oral doses in healthy subjects. PCS12852 increased stool frequency with faster onset when compared to Prucalopride, an FDA approved drug for the treatment of chronic idiopathic constipation. Compared to the Prucalopride group, the PCS12852 dose groups showed higher stool frequency for 24 hours following single dosing and had faster onset of spontaneous bowel movements (SBMs) with comparable or relatively higher Bristol Stool Form Scale score (lower stool consistency) for 24 hours following first dosing. All doses of PCS12852 were safe and well tolerated and no serious adverse events occurred during the study. The most frequently reported adverse events were headache, nausea and diarrhea which were temporal, manageable, and reversible within 24 hours. There were no clinically significant changes in platelet aggregation or electrocardiogram parameters including no sign of QTc prolongation in the study.

The second study conducted was a trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PCS12852 immediate release formulation and delayed release formulation after multiple oral doses. PCS12852 was safe and well tolerated after single and multiple administrations. The most

frequent adverse events for both the immediate and delayed release formulations were headache, nausea, and diarrhea, but the incidences of these adverse events were comparable with those of the Prucalopride group. Both formulations of PCS12852 showed pharmacologic activity as assessed using various pharmacodynamic parameters for stool assessment.

Processa is currently planning a Phase 2A study of PCS12852 which is scheduled to start dosing patients during the second half of 2021. The final report for this trial is expected in 2023.

Conclusion

In conclusion, Processa is developing three potential assets with indications that have a market size estimated to be in excess of $1 billion each. Clinical trials involving each asset are expected to begin in either the first half (PCS6422 and PCS499) or second half of 2021 (PCS12852).

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1 Introduction

1.1 Processa Pharmaceuticals

Processa Pharmaceuticals (Processa) is a clinical stage biopharmaceutical company focused on the development of drug products that are intended to provide treatment for and improve the survival and/or quality of life of patients who have unmet medical needs or conditions or for whom there are no alternative treatments available.

Processa's developmental approach involves:

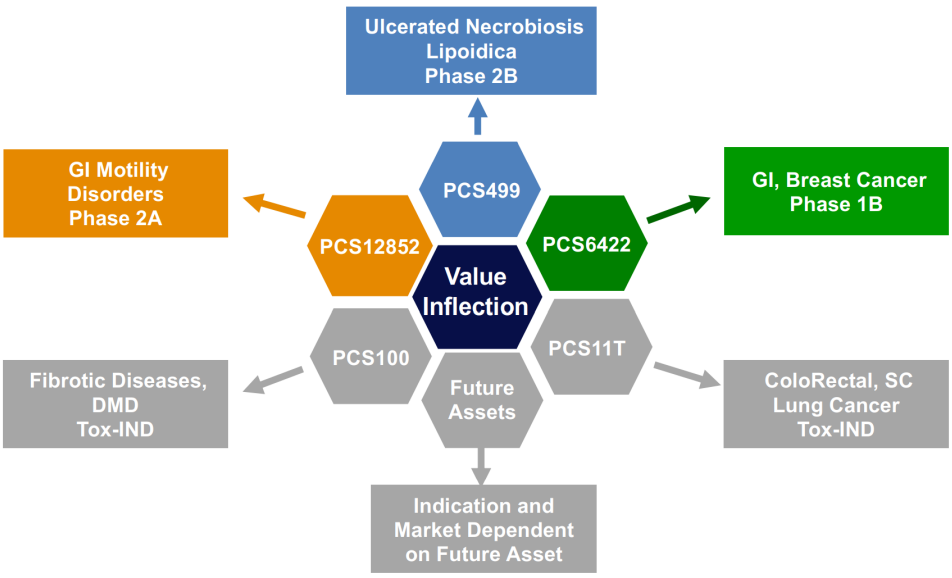
- Identifying drugs that have potential efficacy in patients with an unmet medical need, as demonstrated by some clinical evidence that the targeted pharmacology of the drug provides clinical efficacy in the targeted patient population;
- Identifying drug products that have been developed or approved for other indications but can be repurposed to treat those patients who have an unmet medical need; and
- Identifying drugs that can be quickly developed such that within 2-4 years, critical value-added clinical milestones can be achieved while advancing the drug closer to commercialization.

Processa's active pipeline currently includes three main assets:

- PCS6422 - which was in-licensed from Elion Oncology, Inc. for metastatic colorectal cancer and breast cancer,
- PCS499 - which was in-licensed from CoNCERT Pharmaceuticals, Inc. for ulcerative necrobiosis lipoidica, and
- PCS12852 - which was in-licensed from Yuhan Corporation for gastrointestinal (GI) motility/gastroparesis.

The potential market for each of these assets is estimated to be in excess of $1 billion (Figure 1).

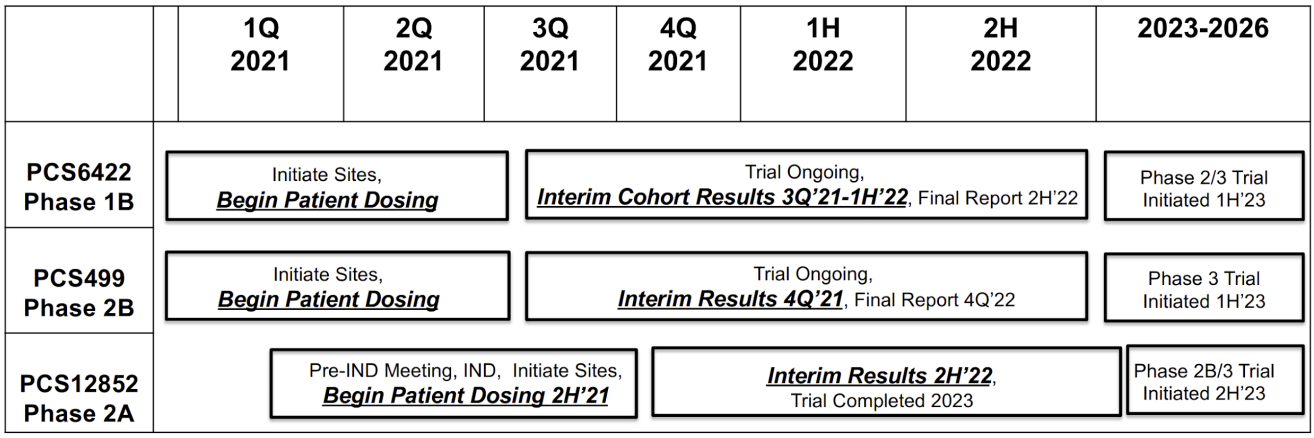
Figure 1 Processa Assets and Indications



(Processa Corporate Presentation January 2021)

Processa has provided guidance on the timelines for the development of each of their drug candidates. The timelines have been summarized in Figure 2 below. It is anticipated that during the first half of 2021 patient dosing of PCS6422 in a Phase 1B trial will be initiated. Likewise patient dosing of PCS499 in a Phase 2B study will also be started in the first half of 2021. The final reports for both trials are expected in the second half of 2022. Patient dosing for a Phase 2A study of PCS12852 will be initiated in the second half of 2021, with the trial expected to be completed in 2023.

Figure 2 Processa Program Timelines



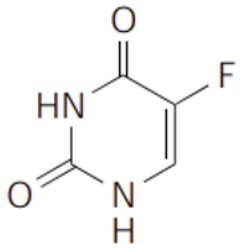
(Processa Corporate Presentation January 2021)

2 Discussion

2.1 PCS6422

Fluoropyrimidines are the cornerstone of treatment for many different types of cancers, either as monotherapy or in combination with other chemotherapy agents (estimated two million patients annually). Fluorouracil (5-FU) is a fluoropyrimidine chemotherapeutic agent used in the treatment of a wide variety of malignancies. 5-FU is an analogue of uracil with a fluorine atom replacing the hydrogen atom at the C-5 position (Figure 3). Systemic use of 5-FU is United States (U.S.) Food and Drug Administration (FDA) approved for the treatment of gastric adenocarcinoma, pancreatic adenocarcinoma, breast carcinoma, and colorectal adenocarcinoma (Fluorouracil Injection, Prescribing Information).

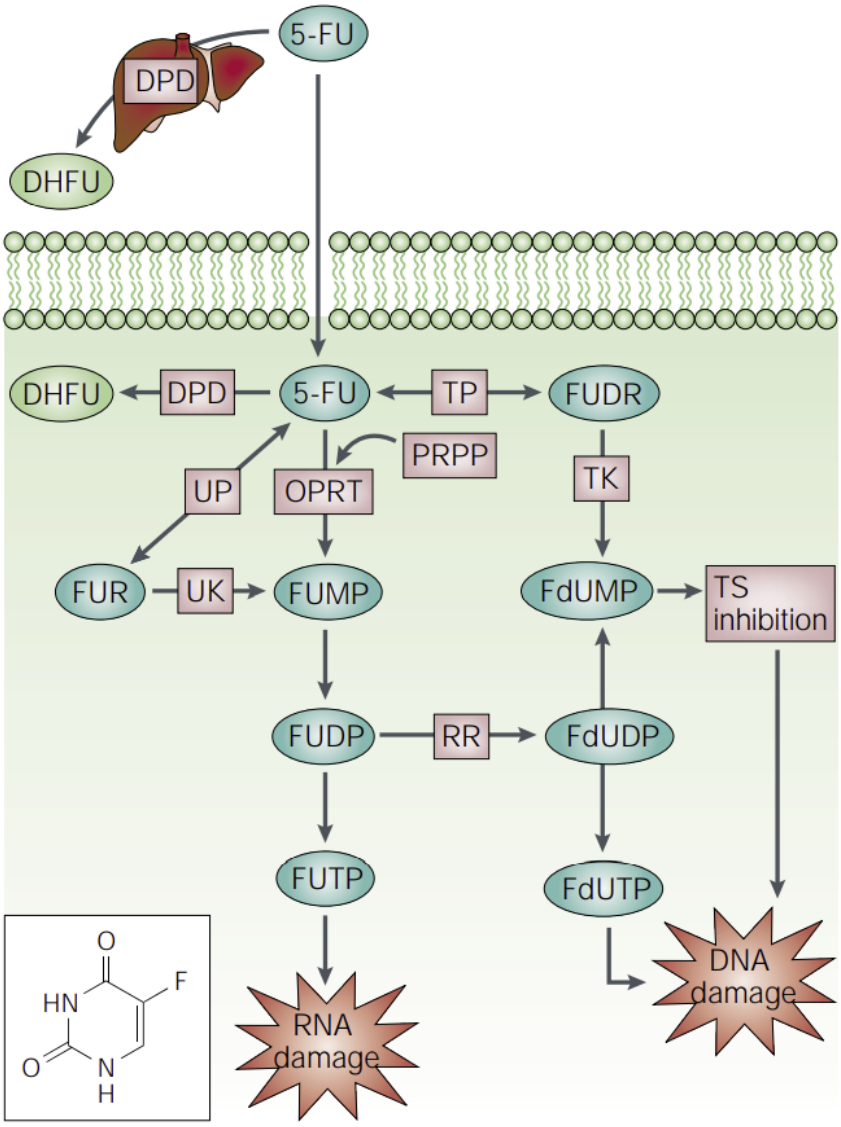
Figure 3 Chemical Structure of 5-FU



Although 5-FU in combination with other chemotherapeutic agents improves response rates and survival in breast, as well as head and neck cancers, it is in colorectal cancer (CRC) that 5-FU has had the greatest impact. 5-FU-based chemotherapy improves overall and disease-free survival of patients with resected stage III CRC (IMPACT, 1995). Nonetheless, response rates for 5-FU-based chemotherapy as a first-line treatment for advanced CRC are only 10–15% (Johnston and Kaye, 2001). The combination of 5-FU with other chemotherapies such as IRINOTECAN (Irinotecan Injection, Prescribing Information) and OXALIPLATIN (Oxaliplatin Injection, Prescribing Information) has improved the response rates for advanced CRC to 40–50% (Giacchetti et al., 2000; Douillard et al., 2000).

In the body 5-FU is converted to three main active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP) (Figure 4). The main mechanism of 5-FU activation is conversion to fluorouridine monophosphate (FUMP), either directly by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate (PRPP) as the cofactor, or indirectly via fluorouridine (FUR) through the sequential action of uridine phosphorylase (UP) and uridine kinase (UK). FUMP is then phosphorylated to fluorouridine diphosphate (FUDP), which can be either further phosphorylated to the active metabolite fluorouridine triphosphate (FUTP) or converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR). In turn, FdUDP can either be phosphorylated or dephosphorylated to generate the active metabolites FdUTP and FdUMP, respectively. An alternative activation pathway involves the thymidine phosphorylase (TP) catalysed conversion of 5-FU to fluorodeoxyuridine (FUDR), which is then phosphorylated by thymidine kinase (TK) to FdUMP (reviewed by Longley et al., 2003).

Figure 4 Metabolism of 5-FU

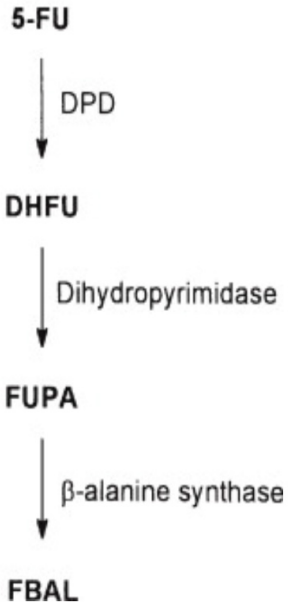


(Longley et al., 2003)

For 5-FU to exert its mechanism of action it first enters cells via a facilitated transport mechanism and is converted to FdUMP (see above). FdUMP complexes with the enzyme thymidylate synthase, inhibiting the production of the compound deoxythymidine monophosphate (dTMP). dTMP is essential for deoxyribonucleic acid (DNA) replication and repair, and depletion of this compound results in an imbalance of intracellular nucleotides leading to double-stranded breaks in DNA by the enzyme endonuclease. In addition to inhibition of thymidylate synthase, 5-FU also serves as a pyrimidine analog by mis-incorporating into ribonucleic acid (RNA) and DNA in place of uracil or thymine. The overwhelming damage of DNA repair machinery caused by these mechanisms ultimately results in cell death of rapidly proliferating cells (reviewed by Casale and Crane, 2020).

The rate-limiting enzyme in 5-FU catabolism is dihydropyrimidine dehydrogenase (DPD), which converts 5-FU to dihydrofluorouracil (DHFU) (Diasio and Harris, 1989). DHFU is then converted into the soluble molecule 5-fluoro-βalanine (F-BAL) and is eliminated in the urine (Figure 5). More than 80% of an intravenously (IV) administered dose of 5-FU is metabolized by DPD (Diasio and Harris, 1989; Peters et al., 1993). DPD activity is not constant in individuals and is thus a factor responsible for the inter- and intra-patient variability in the pharmacokinetic (PK) and pharmacodynamic (PD) outcomes of 5-FU treatment.

Figure 5 Catabolism of 5-FU

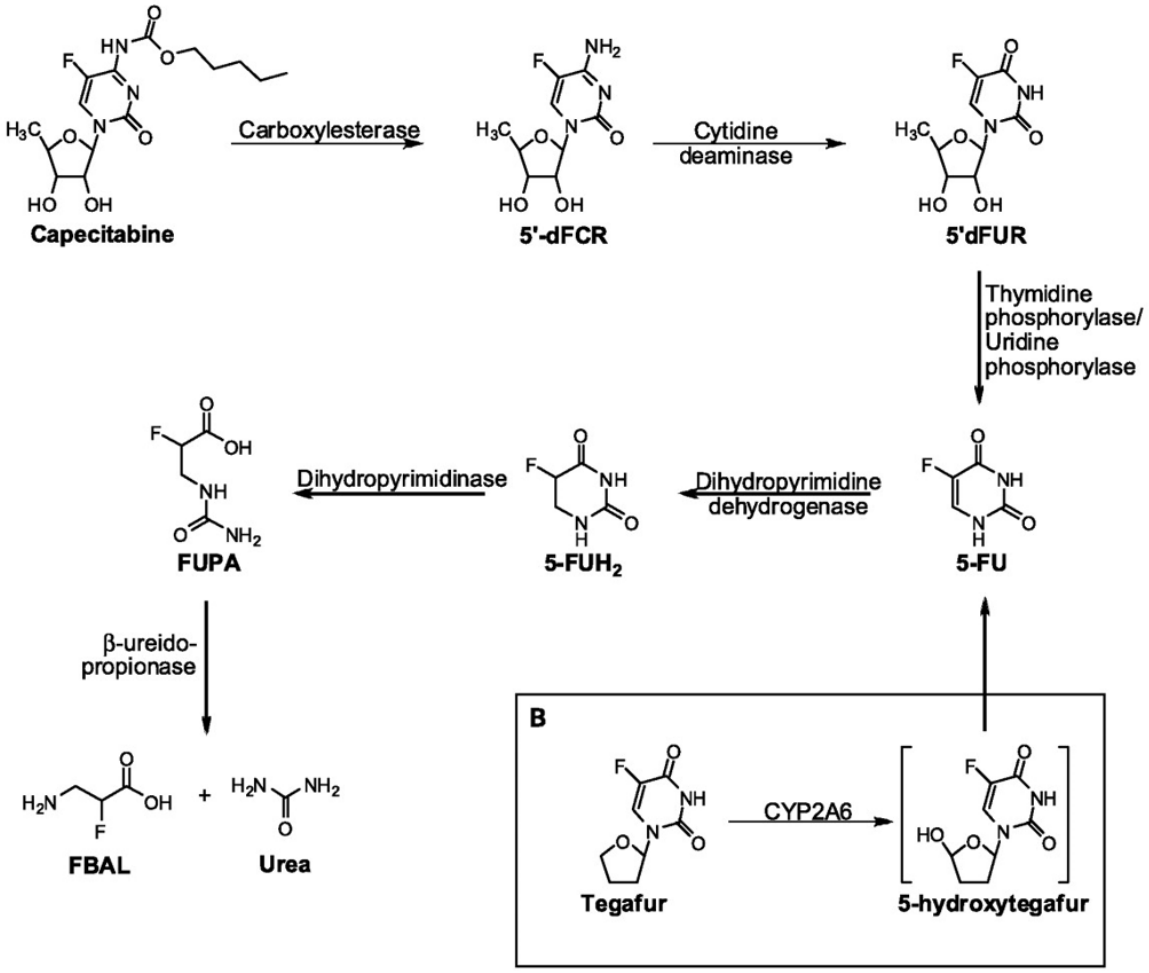


Intrinsic overexpression of DPD by malignant cells has been shown in vitro to extend resistance to 5-FU (Longley and Johnston, 2005). High levels of DPD messenger ribonucleic acid (mRNA) expression in CRC cells have also been associated with 5-FU resistance (Salonga et al., 2000). This has been demonstrated as an intrinsic mechanism of resistance, but available data is not yet conclusive on DPD as a means of acquired resistance. In addition, DPYD gene expression has been investigated as a biomarker of treatment resistance, but this has also not been shown to be clinically relevant (Yanagisawa et al., 2007; Vallbohmer et al., 2006).

Originally 5-FU was developed and administered as an IV bolus however, in the U.S., preferences for 5-FU administration have gradually shifted from IV bolus injection to infusion via a pump. Since 5-FU exhibits poor absorption in the gastrointestinal (GI) tract when administered orally, prodrugs such as Capecitabine have been developed to provide an alternative to IV 5-FU administration.

Capecitabine is authorised for the treatment of patients with localised colon cancer, advanced CRC, abdominal cancer, and breast cancer. It is also standard treatment for patients with localised rectal cancer in combination with radiotherapy, patients who fail to achieve pathological complete remission following neoadjuvant chemotherapy for triple-negative breast cancer, and for other 5-FU-sensitive cancers (Capecitabine, Prescribing Information). Capecitabine is converted to 5-FU via a three-step enzymatic process, the final step of which is mediated by thymidine phosphorylase (Figure 6). Given this enzyme is overexpressed in tumor compared with normal tissue, Capecitabine derived 5-FU is preferentially generated within the tumor tissue, conferring relatively selective cytotoxicity to the tumor (Wan et al., 2006; Ciccolini et al., 2004; Miwa et al., 1998).

Figure 6 Metabolic Pathways of Capecitabine and Tegafur



(Yen-Revollo et al., 2008)

The use of 5-FU carries the risk of severe adverse events (SAEs) in up to 30% of patients (Mikhail et al., 2010; Meta-Analysis Group in Cancer et al., 1998). The oral pill (Capecitabine) has certain side effects that are different from the 5-FU IV administered version. Kadoyama et al. (2012) reviewed the safety profiles of IV 5-FU (Table 1) compared with oral Capecitabine (Table 2) using adverse event reports (AERs) submitted to the FDA's Adverse Event Reporting System (AERS).

Table 1 Adverse Events Most Frequently Associated with the Use of 5-FU

Adverse Event	Number
Diarrhea	1076
Vomiting	774
Nausea	715
Dehydration	708
Neutropenia	658
Pyrexia	631
Febrile neutropenia	494
Abdominal pain	415
Pulmonary embolism	345
Mucosal inflammation	344
Asthenia	342

Thrombocytopenia	328
Anemia	316
Hemoglobin decreased	312
Hypotension	306
Leukopenia	277
Sepsis	277
Decreased appetite	256
Pneumonia	252
White blood cell count decreased	251
N is the number of co-occurrences. Official Preferred Terms (PT) terms of MedDRA version 13.0 are listed. The total number of co-occurrences with 5-FU was 40,284, and 864 AEs were extracted as 5-FU-associated AEs with 23,690 co-occurrences in total. The AEs were extracted when at least 1 of 4 indices met the criteria: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), the information component (IC), and the empirical Bayes geometric mean (EBGM).	

(Kadoyama et al., 2012)

Table 2 Adverse Events Most Frequently Associated with the Use of Capecitabine

Adverse Event	Number
Diarrhea	1790
Vomiting	843
Nausea	842
Dehydration	694
Death	626
Disease progression	500
Pyrexia	490
Palmar-plantar erythrodysaesthesia syndrome	456
Fatigue	386
Asthenia	385
Mucosal inflammation	325
Abdominal pain	305
Osteonecrosis	288
Decreased appetite	284
Neutropenia	276
Sepsis	244
Malignant neoplasm progression	242
General physical health deterioration	219
Pulmonary embolism	198
Hemoglobin decreased	191
N is the number of co-occurrences. Official PT terms of MedDRA ver. 13.0 are listed. The total number of co-occurrences with capecitabine was 34,928, and 802 adverse events were extracted as capecitabine-associated adverse events with 20,290 co-occurrences in total. The adverse events were extracted when at least 1 of 4 indices met the criteria: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), the information component (IC), and the empirical Bayes geometric mean (EBGM).	

(Kadoyama et al., 2012)

The AEs commonly found between the two treatments included neutropenia, diarrhea, nausea, vomiting, pyrexia, pulmonary embolism, mucosal inflammation, asthenia, a decrease of hemoglobin level, and sepsis. More concerning side effects that require monitoring in patients receiving systemic 5-FU chemotherapy included neutropenia, pyrexia, pulmonary embolism, thrombocytopenia, and leukopenia (Kadoyama et al., 2012). Further the data from Kadoyama et al. (2012) also suggests that myelosuppression was more frequently accompanied by the use of 5-FU than Capecitabine (Table 3), whereas GI toxicity (Table 4) were more frequently associated with Capecitabine.

Table 3 Signal Detection for 5-FU- and Capecitabine-associated Myelosuppression

Adverse Event	Treatment	N	PRR (χ2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Leukopenia	5-FU	277	5.282* (952.334)	5.323* (4.727,5.191)	2.368* (2.197, 2.540)	5.224* (4.720)
	Capecitabine	115	2.520* (103.730)	2.526* (2.103, 2.949)	1.306* (1.041, 1.570)	2.432* (2.081)
Neutropenia	5-FU	658	6.912* (3272.836)	6.986* (6.465, 7.507)	2.755* (2.643, 2.867)	6.808* (6.382)
	Capecitabine	276	3.315* (441.127)	3.327* (2.955, 3.700)	1.707* (1.535, 1.878)	3.241* (2.931)
Thrombocytopenia	5-FU	328	2.749* (360.868)	2.759* (2.473, 3.042)	1.442* (1.284, 1.599)	2.699* (2.463)
	Capecitabine	180	1.735 (55.060)	1.737* (1.500, 1.974)	0.782* (0.570, 0.993)	1.708 (1.509)

N = Number of Co-occurrences; PRR = Proportional Reporting Ratio; ROR = Reporting Odds Ratio; IC = Information Component; EBGM = Empirical Bayes Geometric Mean; CI = Confidence Interval

(Kadoyama et al., 2012)

Table 4 Signal Detection for 5-FU- and Capecitabine-associated Gastrointestinal Toxicity

Adverse Event	Treatment	N	PRR (χ2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
Diarrhea	5-FU	1076	3.246* (1625.228)	3.256* (3.064, 3.448)	1.667* (1.579, 1.754)	3.169* (3.013)
	Capecitabine	1790	6.383* (7716.174)	6.435* (6.135, 6.736)	2.606* (2.537, 2.675)	6.104* (5.870)
Nausea	5-FU	715	1.364 (68.113)	1.365* (1.268, 1.463)	0.440* (0.333, 0.547)	1.355 (1.274)
	Capecitabine	842	1.865 (329.449)	1.868* (1.744, 7.991)	0.881* (0.782, 0.980)	1.839 (1.737)
Vomiting	5-FU	774	2.174* (481.110)	2.179* (2.029, 2.329)	1.120* (1.000, 1.250)	2.143* (2.019)
	Capecitabine	848	2.745* (912.239)	2.752* (2.570, 2.935)	1.431* (1.332, 1.530)	2.689* (2.540)

N = Number of Co-occurrences; PRR = Proportional Reporting Ratio; ROR = Reporting Odds Ratio; IC = Information Component; EBGM = Empirical Bayes Geometric Mean; CI = Confidence Interval

(Kadoyama et al., 2012)

Hand-foot syndrome (HFS) is a cutaneous AE that occurs in some patients treated with fluoropyrimidines. Although it is not life threatening, HFS can severely disrupt the daily lives of patients. HFS is a leading cause of patient treatment interruption, dosage reduction, or therapy discontinuation. The safety analysis by Kadoyama et al. (2012) suggests that HFS was more frequently associated with Capecitabine than 5-FU treatment (Table 5).

Table 5 Signal Detection for 5-FU- and Capecitabine-associated Hand-foot Syndrome

Treatment	N	PRR (χ2)	ROR (95% two-sided CI)	IC (95% two-sided CI)	EBGM (95% one-sided CI)
5-FU	64	6.059* (265.364)	6.116* (4.779, 7.452)	2.478* (2.124, 2.832)	5.952* (4.774)
Capecitabine	456	50.368* (21762.799)	54.596* (49.588, 59.604)	5.488* (5.350, 5.626)	49.485* (45.787)
N = Number of Co-occurrences; PRR = Proportional Reporting Ratio; ROR = Reporting Odds Ratio; IC = Information Component; EBGM = Empirical Bayes Geometric Mean; CI = Confidence Interval					

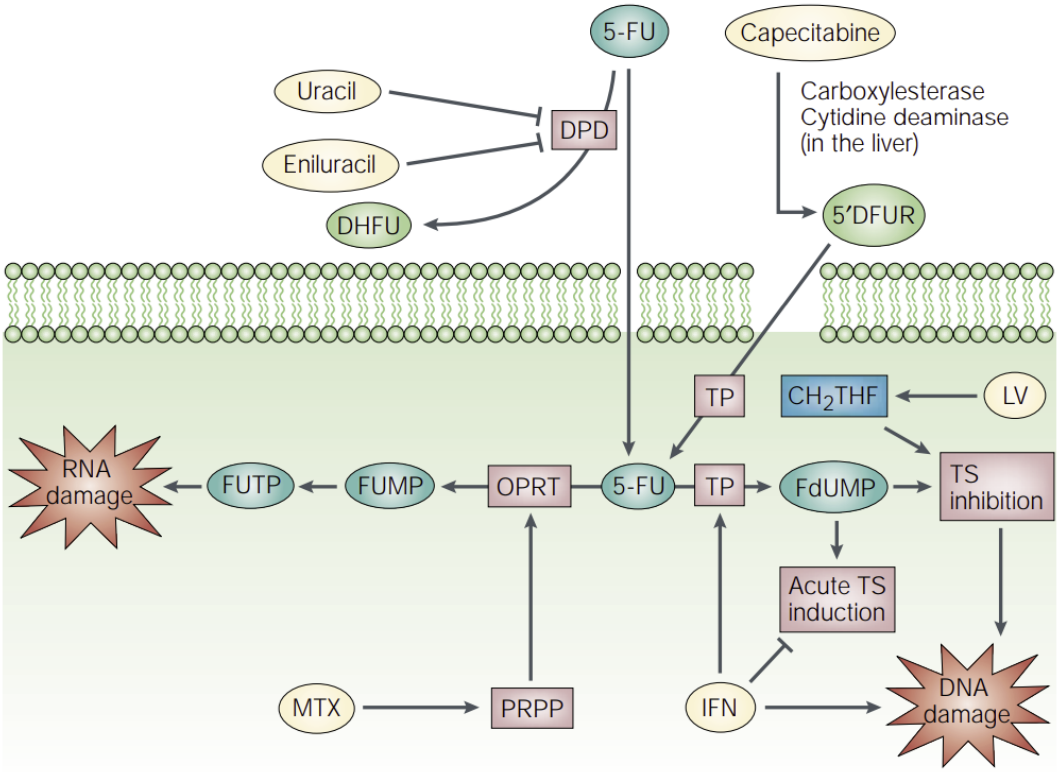
(Kadoyama et al., 2012)

Several strategies that have been explored to modulate the anticancer activity of 5-FU (Figure 7). These strategies include the addition of:

- Leucovorin
- Methotrexate
- Interferons and
- Eniluracil or Uracil

Leucovorin (LV) increases the intracellular pool of 5,10-methylene tetrahydrofolate, thereby enhancing thymidylate synthase inhibition by FdUMP. Methotrexate (MTX) is thought to increase 5-FU activation by increasing phosphoribosyl pyrophosphate levels. Interferons (IFNs) have been reported to enhance thymidine phosphorylase activity, abrogate acute TS induction caused by 5-FU treatment and enhance 5-FU-mediated DNA damage. Eniluracil and uracil inhibit DPD-mediated degradation of 5-FU. (Longley et al., 2003).

Figure 7 Modulation of the Anticancer Activity of 5-FU



(Longley et al., 2003)

In August of 2020, Processa entered into a License Agreement with Elion Oncology, Inc. to acquire an exclusive contingent license to globally develop, manufacture and commercialize Eniluracil which is also known as PCS6422, 776C85, and 5-ethynyluracil.

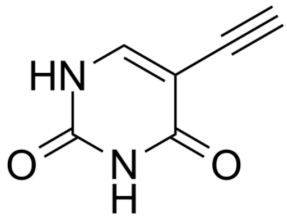
2.1.1 PCS6422/Eniluracil

2.1.1.1 PCS6422 Mechanism of Action

PCS6422 is an uracil analogue, which irreversibly inhibits DPD within one hour of administration (Figure 8).

PCS6422 inactivates DPD by initially forming a reversible complex with a Ki of 1.6 +/- 0.2 μM. This initial complex yields inactivated enzyme with a rate constant of 20 +/- 2 min^{-1} (kinact). Thymine competitively decreases the apparent rate constant for inactivation of DPD by PCS6422. The absorbance spectrum of PCS6422-inactivated DPD is different from that of reduced enzyme. These optical changes are correlated with the loss of enzymatic activity. PCS6422 inactivates DPD with a stoichiometry of 0.9 mol of inactivator per mol of active site (Porter et al., 1992).

Figure 8 Chemical Structure of PCS6422



In the presence of PCS6422, bioavailability of 5-FU increases to approximately 100%, the half-life is prolonged to 4 to 6 hours, and systemic clearance is reduced > 20-fold to values comparable the glomerular filtration rate (46 to 58 mL/min/m^2). Renal excretion (approximately 45% to 75%), instead of DPD-related catabolism, is the principal route of elimination of oral 5-FU given with PCS6422. Chronic daily administration of oral 5-FU 1.0 mg/m^2 twice daily with PCS6422 20 mg twice daily produces 5-FU steady-state concentrations (8-38 ng/mL) similar to those achieved with protracted IV administration on clinically relevant dose-schedules.

The PK behavior of oral PCS6422 is similar to that for oral 5-FU. Administration of PCS6422 10 to 20 mg twice daily completely inactivates DPD activity both in peripheral blood mononuclear (PBM) cells and in colorectal tumor tissue, with prolonged inhibition of DPD after discontinuation of PCS6422 treatment has been noted. In the presence of PCS6422, oral administration of 5-FU is feasible and variation in 5-FU exposure is reduced (Baker et al., 2000).

2.1.1.2 Preclinical Data

PCS6422 is neither toxic nor active as a single agent in animals, however, it improves the antitumour efficacy and therapeutic index of 5-FU. Schilsky and Kindler, (2000) found that the cytotoxicity of 5-FU was enhanced one- to five-fold in cell lines treated with PCS6422 plus 5-FU compared with 5-FU alone. In rats with advanced CRC, PCS6422 increased the therapeutic index of 5-FU six-fold compared with a two-fold increase with leucovorin (LV) and N-(phosphonacetyl)-L-aspartate (PALA) (Table 6) and cures were only achieved with the PCS6422/5-FU combination (Cao et al., 1994).

Table 6 Efficacy and Therapeutic Index of 5-FU with Modulators

Treatment	Schedule	MTD	MED	Maximum CR	Therapeutic Index
		mg/kg/day	mg/kg/day	%	MTD/MED
5-FU Alone	4-day Infusion	35	35	14	1.0
	Daily x 4	35	>35	0	<1
	Weekly x 3	100	100	12	1.0
5-FU + LV	Daily x 4	25	>25	0	<1
	Weekly x 3	75	50	63	1.5
5-FU + PALA	Daily x 4	25	25	13	1.0
	Weekly x 3	75	50	75	1.5

5-FU + EU	Daily x 4	10	1.75	100	6.0
	Weekly x 3	15	2.5	100	6.0
CR = Complete Response; EU = Eniluracil, PCS6422; LV = Leucovorin; MED = Dose where 10 to 25% of Rats Bearing Colon Carcinoma Had Sustained Complete Response on Day 90 Post-treatment; MTD = Maximum Dose Not Causing Drug-related Lethality in Tumor-bearing Rats; PALA = N-(phosphonacetyl)-L-aspartate.					

(Cao et al., 1994)

In dogs, dose-limiting neurotoxicity of 5-FU at high doses was abolished with the coadministration of PCS6422. This observation has been explained by the prevention of formation of the potentially neurotoxic metabolite F-BAL, after the inhibition of DPD.

Elion/Processa evaluated the potential for the combination of PCS6422 with Capecitabine as a treatment of advanced GI tumors. Nonclinical efficacy data indicated that in CRC models, pre-treatment with PCS6422 enhanced the antitumor activity of Capecitabine. PCS6422 increased the antitumor potency of Capecitabine while not increasing the toxicity. The antitumor efficacy of the combination of PCS6422 and Capecitabine was tested in several xenograft animal models with human breast, pancreatic and CRC cells. These preclinical xenograft models demonstrated that PCS6422 potentiated the antitumor activity of Capecitabine and significantly reduced the dose of Capecitabine required to be efficacious (Processa Pharmaceuticals Website).

2.1.1.3 Clinical Safety Data

PCS6422 was studied in the late 1990s and early 2000s as a DPD inhibitor (Ahmed et al., 1999). The results of these studies suggested PCS6422 produced antitumor efficacy with a low incidence of severe toxicities.

In 1998, Hohneker conducted a safety analysis of a chronic 28-day dosing regimen of PCS6422/5-FU that involved data from 108 patients treated in three different studies.

- FUMA1003 - a phase I dose-escalation trial for the 28-day dose regimen,
- FUMA2003 - a phase II breast cancer trial reported by Rivera et al., 1998, and
- FUMA2006 - a phase II colorectal cancer trial reported by Mani et al., 1998.

The most frequently occurring nonhematologic toxicities for the 28-day PCS6422/5-FU regimen were GI in nature. Severe (grade 3 and 4) diarrhea occurred in fewer than 10% of patients and were found to completely resolve with treatment discontinuation. Severe nausea and vomiting occurred in 5% and 2% of patients, respectively.

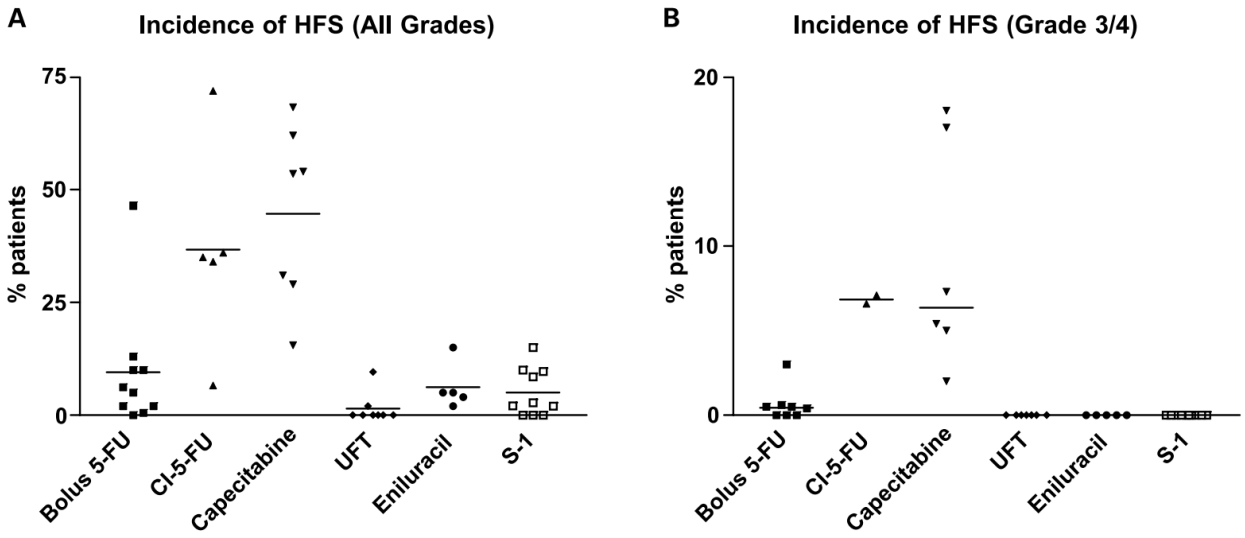
The hematologic toxicity of the PCS6422/5-FU combination has been summarized below. Grade 4 granulocytopenia occurred in 1% of patients. Severe thrombocytopenia requiring platelet transfusion was rare. The incidence of marked myelosuppression with the chronic 28-day regimen was low, pointing to the observation that diarrhea usually occurred in the absence of marked myelosuppression (Hohneker, 1998). The relative lack of concomitant diarrhea and granulocytopenia may lower the risk of sepsis or morbidity that would require hospitalization, as occurs in some patients treated with IV regimens of 5-FU/LV.

The toxicity profile for PCS6422/5-FU was similar for patients with different types of cancer. However, breast cancer patients appeared to have a higher incidence of granulocytopenia than CRC patients. Granulocytopenia grade 2 occurred in 14% of patients with breast cancer and 5.5% of patients with CRC. This difference was believed to be related more to the effects of previous chemotherapy than to the tumor type itself, since all breast cancer patients had previously received anthracyclines and taxanes, whereas the CRC patients had not received any previous chemotherapy for metastatic disease. Interestingly, the incidence of diarrhea grade 2 was higher in the CRC population than in the breast cancer population (25% vs 14%); this difference may be related to previous surgical procedures, but a disease effect could be ruled out (Hohneker, 1998).

The causative mechanism for HFS toxicity is unknown, however, it usually resolves with discontinuation of treatment. Fewer than 5% of patients experienced this adverse reaction when treated with the chronic 28-day dosing schedule of PCS6422/5-FU (Hohneker, 1998). Patients treated with continuous infusion 5-FU or Capecitabine are consistently reported to have greater risk of developing HFS of all grades (6.6-71.9%, median 35.5%) than patients on a DPD inhibitor (0-15%, median 2%) (Llovet et al., 2001; Douillard et al., 2002; Carmichael et al., 2002; Adimi et al., 2002; Bajetta et al., 2007; Lin et al., 2006; Petrioli et al., 2004; Smith et al., 2000; Mani et al., 2000; Skovsgaard et al., 2001; Rivera et al., 2002; Ajani et al., 2006; Goto et al., 2006; Lenz et al., 2007; Ichinose et al., 2004; Hirata et al., 1999; Ohtsu et al., 2000; van den Brande et al., 2003; Peters et al., 2003; Chollet et al., 2003; Sakata et al., 1998; Borner et al., 2002). Furthermore, HFS induced by continuous infusion 5-FU or

Capecitabine is more often of grade 3 or grade 4 (2-18%, median 7.1%) (Cassidy et al., 2003; Scheithauer et al., 2003; Schmoll et al., 2007; Lin et al., 2006; Abushullaih et al., 2002) compared to bolus 5-FU (0.4-3%, median 0.5%) (Chau et al., 2005; Smith et al., 2004, Cassidy et al., 2002; Scheithauer et al., 2003; Schmoll et al., 2007). Whereas HFS is occasionally caused by 5-FU/PCS6422, it is nearly always grade 1 or grade 2. These patients very rarely develop severe HFS when on a 5-FU/PCS6422 regimen.

Figure 9. Incidence of HFS in Patients on Fluoropyrimidine Treatments



(Yen-Revollo et al., 2008)

In conclusion, there is accumulating evidence from clinical trials that show the benefits of DPD inhibition on decreasing the risk of HFS. This reduction in the occurrence and severity of HFS is a potential advantage for treatment with the PCS6422 in combination with 5-FU.

2.1.1.4 Clinical Efficacy Data

Early clinical trials suggested that the combination of 5-FU/PCS6422 was effective in treating several types of solid tumors with decreased toxicity. The clinical trials examining the effects of 5-FU and PCS6422 in cancer patients have been summarized in Table 7 below. Additional information on each individual trial can be provided upon request.

Despite promising Phase II data with an improved safety profile, further research of PCS6422 was abandoned after two large Phase III trials suggested 5-FU/PCS6422 had inferior efficacy compared with 5-FU and Leucovorin (Van Cutsem et al., 2001; Schilsky et al., 2002). The two multicenter Phase III studies were conducted in patients with CRC with PCS6422 administered in 10-fold excess to 5-FU. It is believed that the dose of PCS6422 used during these trials was not optimal, and that PCS6422 was not administered early enough to irreversibly affect the DPD enzyme, thus the regimen tended to produce less antitumor benefit than the control arm with the standard regimen of 5-FU/LV without PCS6422. Later preclinical work suggested that when PCS6422 was present at the same time as and in excess to 5-FU, it diminished the antitumor activity of 5-FU, which the Processa Team believe supports the proposal of exploring clinically dosing PCS6422 several hours before 5-FU to allow its clearance before the administration of 5-FU (Processa Pharmaceuticals Website).

Processa is proposing to initiate a Phase 1b study to confirm the safety and PK of a fixed dose of PCS6422 with increasing doses of Capecitabine in patients with advanced GI solid tumors. The objectives of the study are to:

- To evaluate the safety and dose-limiting toxicities (DLTs), and to identify the maximum tolerated dose (MTD) and the recommended phase 2/3 dose (RP23D) of Capecitabine when administered ~20 hours after a single, fixed, oral dose of PCS6422 40 mg and dosed for 7 days in patients with advanced, refractory GI tract tumors.
- To characterize the PK profile of Capecitabine, 5-FU, and the main metabolites F-BAL, DFCR, and DFUR in blood and of F-BAL in the urine.
- To characterize the PK profile of PCS6422 when administered in combination with Capecitabine.
- To evaluate the tolerability and safety of eniluracil with Capecitabine therapy at the RP23D.
- To gain preliminary evidence of the antitumor activity of PCS6422 with Capecitabine in advanced GI tumors.

The study is expected to begin dosing in the first half of 2021 with the final report expected in the second half of 2022. Subsequently. Processa plans to initiate a Phase 2/3 study in the first half of 2023.

2.2 PCS499

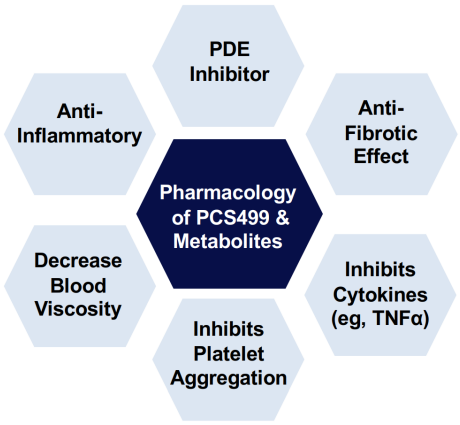
PCS499 is an oral tablet that is a deuterated analog of one of the major metabolites of Pentoxifylline (PTX or Trental®). Pentoxifylline is a methylxanthine derivative with potent hemorheological properties. It is used to improve blood flow in patients with circulation problems to reduce aching, cramping, and tiredness in the hands and feet. It works by decreasing the thickness (viscosity) of blood. This change allows blood to flow more easily, especially in the small blood vessels of the hands and feet. In the U.S. it is marketed for the treatment of intermittent claudication but is also used to treat leg ulcers, strokes, high-altitude sickness, eye and ear disorders, and sickle cell disease and to treat pain from diabetic neuropathy (Pentoxifylline Prescribing Information).

PCS499 metabolizes qualitatively to the same active moieties as Pentoxifylline but quantitatively has different amounts of these metabolites. An issue with Pentoxifylline is that it has dose limiting side effects which can hamper its use. However, preclinical and clinical evidence indicate that PCS499 may have less side effects compared to Pentoxifylline which may allow for higher doses to be administered (Processa Pharmaceuticals Website).

Processa has identified necrobiosis lipoidica (NL) as their lead indication for PCS499. NL is a chronic, disfiguring condition affecting the skin and the tissue under the skin typically on the lower extremities with no currently approved FDA treatments. NL presents more commonly in women than in men and occurs more often in people with diabetes. Ulceration occurs in approximately 30% of NL patients, which can lead to more severe complications, such as deep tissue infections and osteonecrosis threatening the life of the limb. Approximately 22,000 - 55,000 people in the U.S. and more than 120,000 people outside the U.S. are affected with ulcerated NL.

The degeneration of tissue occurring at the NL lesion site may be caused by a number of pathophysiological changes, which has made it extremely difficult to develop effective treatments for this condition. PCS499 and its metabolites affect a number of biological pathways which could contribute to the pathophysiology associated with NL (Figure 10). Therefore, PCS499 may provide a novel treatment solution for NL.

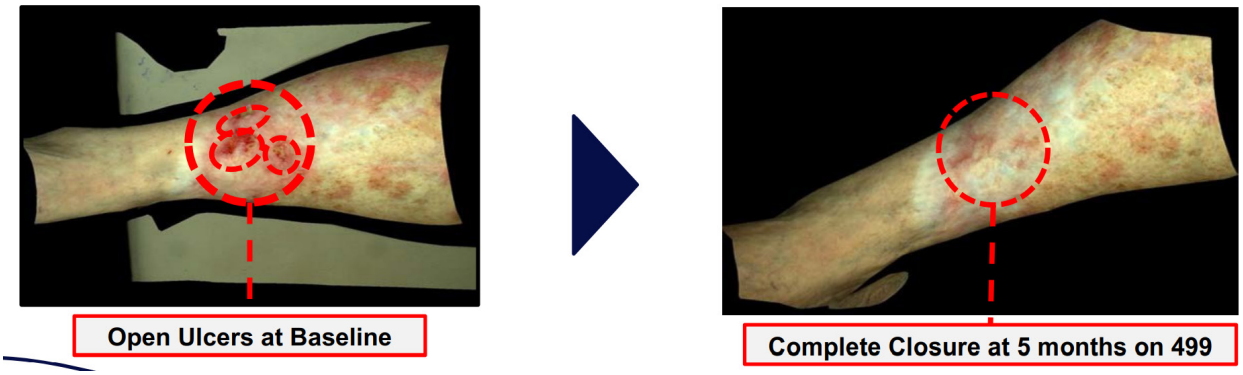
Figure 10 Diverse Pharmacological Properties of PCS499



(Processa Corporate Presentation January 2021)

In a small Phase 2A study, NL patients tolerated PCS499 well and at greater doses than Pentoxifylline. In addition, two patients with NL ulcers showed complete closing of all their original wounds (Figure 11) (Processa Corporate Presentation January 2021).

Figure 11 Changes in NL Ulcers after Treatment with PCS499



(Processa Corporate Presentation January 2021)

Processa is currently planning a Phase 2B study of PCS499 in NL patients. The trial is scheduled to start during the first half of 2021 with the final report expected in the second half of 2022.

2.3 PCS12862

PCS12852 is a novel, potent and highly selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist. Other 5-HT receptor agonists with less 5-HT4 selectivity have been used to successfully treat GI motility disorders such as chronic constipation, constipation-predominant irritable bowel syndrome, functional dyspepsia and gastroparesis. Less selective 5-HT4 agonists, such as Cisapride, have been either removed from the market or not approved because of the cardiovascular side effects associated with the drugs binding to other receptors.

Studies of PCS12862 have shown that it is more potent (Table 7) and selective for 5-HT4 compared to other 5-HT4 drugs and has a wider safety margin against the negative cardiovascular side effects (Processa Corporate Presentation January 2021).

Table 7 Comparative Potency of 5-HT4 Receptor Agonist PCS12852 to Other 5-HT4 Drugs

Compound	Binding Affinity (IC_{50} nM)	Agonistic Activity (EC_{50} nM)
PCS12862	0.05	0.0048
Prucalopride	4.2	0.016
Tegasetrag	15.4	0.25
Velusetrag	20	5
TAK-954	0.4	0.5
EC_{50} = Effective Concentration 50%; IC_{50} = Inhibitory Concentration 50%		

(Processa Corporate Presentation January 2021)

Two clinical studies have been previously conducted by Yuhan with PCS12852. In the first-in-human clinical trial, the initial safety and tolerability of PCS12852 were evaluated after single and multiple oral doses in healthy subjects. PCS12852 increased stool frequency with faster onset when compared to Prucalopride, an FDA approved drug for the treatment of chronic idiopathic constipation (Prucalopride Prescribing Information). Compared to the group receiving Prucalopride, the PCS12852 dose groups showed higher stool frequency for 24 hours following single dosing and had faster onset of spontaneous bowel movements (SBMs) with comparable or relatively higher Bristol Stool Form Scale score (lower stool consistency) for 24 hours following first dosing. In addition, based on an increase of ≥ 1 SBM/week from baseline during 7-day multiple dosing, the PCS12852 dose group had a higher percent of patients with an increase than the prucalopride group. All doses of PCS12852 were safe and well tolerated and no serious adverse events occurred during the study. The most frequently reported AEs were headache, nausea and diarrhea which were temporal, manageable, and reversible within 24 hours. There were no clinically significant changes in platelet aggregation or electrocardiogram (ECG) parameters including no sign of QTc prolongation in the study (Processa Pharmaceuticals Website).

The second study conducted was a Phase 1/2A clinical trial to evaluate the safety, tolerability, PK and PD of PCS12852 immediate release (IR) formulation and delayed release (DR) formulation after multiple oral dosing.

PCS12852 was safe and well tolerated after single and multiple administrations. The most frequent AEs for both the IR and DR formulations of PCS12852 were headache, nausea and diarrhea, but the incidences of these AEs were comparable with those of the prucalopride 2 mg group. These AEs, which were transient and mostly mild in severity, are also commonly observed with other 5-HT4 agonists. Both formulations of PCS12852 also showed pharmacologic activity as assessed using various PD parameters for stool assessment (Processa Pharmaceuticals Website).

Processa is currently planning a Phase 2A study of PCS12852 which is scheduled to start dosing patients during the second half of 2021. The final report for this trial is expect in 2023.

3 Conclusions

Processa is a clinical stage biopharmaceutical company focused on the development of drug products that are intended to provide treatment for and improve the survival and/or quality of life of patients who have unmet medical needs or conditions for whom there are no alternative treatments.

Processa's pipeline includes three main potential drug candidates:

- PCS6422
- PCS499
- PCS12852

PCS6422 is an uracil analogue, which irreversibly inhibits DPD. It is currently being developed for coadministration with Capecitabine for treatment of metastatic colorectal and breast cancer. Processa has completed pharmacology, toxicology and manufacturing work on PCS6422 and are in the process of initiating a Phase 1b study to confirm the safety and PK of a fixed dose of PCS6422 with increasing doses of Capecitabine in patients with advanced gastrointestinal solid tumors. The study is expected to begin dosing patients in the first half of 2021, with an interim analysis in the third quarter of 2021, and the final report expected in the second half of 2022. Subsequently, Processa plans to initiate a Phase 2/3 study in the first half of 2023.

PCS499 is a deuterated analog of one of the major metabolites of Pentoxifylline. It is currently being developed as a treatment for ulcerative necrobiosis lipoidica. A Phase 2B study of PCS499 in necrobiosis lipoidica patients is being planned and the trial is scheduled to start during the first half of 2021 with the final report for the study is expected in the second half of 2022.

PCS12852 is a novel, potent and highly selective 5-hydroxytryptamine 4 receptor agonist. It is currently being developed as a treatment for gastrointestinal motility dysfunction disorder. A Phase 2A study of PCS12852 is being planned and the trial is scheduled to start dosing patients during the second half of 2021. The final report for the study is expected sometime in 2023.

Processa's stated developmental approach involves:

- Identifying drugs that have potential efficacy in patients with an unmet medical need;
- Identifying drug products that have been developed or approved for other indications but can be repurposed to treat those patients who have an unmet medical need; and
- Identifying drugs that can be quickly developed such that within 2-4 years, critical value-added clinical milestones can be achieved while advancing the drug closer to commercialization.

All three assets appear to fall within Processa's development framework, and each is believed to have a billion dollar market potential.

4 References

Abushullaih S, Saad ED, Munsell M, Hoff P. Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. Cancer Invest. 2002;20:3-10.

Adimi P, Hansen F, Kjaer M, Aabo K, Keldsen N, Pfeiffer P, Sandberg E, Jakobsen A. Oral fluoropyrimidines in the treatment of advanced colorectal cancer: results of two consecutive phase II trials. Acta Oncol. 2002;41:202-203.

Adjei AA, Reid JM, Diasio RB, Sloan JA, Smith DA, Rubin J, Pitot HC, Alberts SR, Goldberg RM, Hanson LJ, Atherton P, Ames MM, Erlichman C. Comparative pharmacokinetic study of continuous venous infusion fluorouracil and oral fluorouracil with eniluracil in patients with advanced solid tumors. J Clin Oncol. 2002;20(6):1683-91.

Ahmed FY, Johnston SJ, Cassidy J, O'Kelly T, Binnie N, Murray GI, van Gennip AH, Abeling NG, Knight S, McLeod HL. Eniluracil treatment completely inactivates dihydropyrimidine dehydrogenase in colorectal tumors. J Clin Oncol 1999;17:2439.

Ajani JA, Lee FC, Singh DA, Haller DG, Lenz HJ, Benson AB 3rd, Yanagihara R, Phan AT, Yao JC, Strumberg D. Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol. 2006;24:663-637.

Bajetta E, Di Bartolomeo M, Buzzoni R, Mariani L, Zilembo N, Ferrario E, Lo Vullo S, Aitini E, Isa L, Barone C, Jacobelli S, Recaldin E, Pinotti G, Iop A. Uracil/ftorafur/leucovorin combined with irinotecan (TEGAFIRI) oroxaliplatin (TEGAFOX) as first-line treatment for metastatic colorectal cancer patients: results of randomised phase II study. Br J Cancer. 2007;96:439-444. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360030/pdf/6603493a.pdf

Baker SD, Diasio RB, O'Reilly S, Lucas VS, Khor SP, Sartorius SE, Donehower RC, Grochow LB, Spector T, Hohneker JA, Rowinsky EK. Phase I and pharmacologic study of oral fluorouracil on a chronic daily schedule in combination with the dihydropyrimidine dehydrogenase inactivator eniluracil. J Clin Oncol. 2000;18(4):915-926.

Baker SD, Khor SP, Adjei AA, Doucette M, Spector T, Donehower RC, Grochow LB, Sartorius SE, Noe DA, Hohneker JA, Rowinsky EK. Pharmacokinetic, oral bioavailability, and safety study of fluorouracil in patients treated with 776C85, an inactivator of dihydropyrimidine dehydrogenase. J Clin Oncol. 1996;14(12):3085-3096.

Baker SD. Pharmacology of fluorinated pyrimidines: eniluracil. Invest New Drugs. 2000;18(4):373-381.

Benson AB, Mitchell E, Abramson N, Klencke B, Ritch P, Burnhan JP, McGuirt C, Bonny T, Levin J, Hohneker J. Oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. Ann Oncol. 2002;13(4):576-581. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2961875-2

Borner MM, Schoffski P, de Wit R, Caponigro F, Comella G, Sulkes A, Greim G, Peters GJ, van der Born K, Wanders J, de Boer RF, Martin C, Fumoleau P. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. Eur J Cancer. 2002;38:348-358.

Cao S, Rustum YM, Spector T. 5-ethynyluracil (776C85): Modulation of 5-fluorouracil efficacy and therapeutic index in rats bearing advanced colorectal carcinoma. Cancer Res. 1994;54:1507–1510. https://cancerres.aacrjournals.org/content/54/6/1507.full-text.pdf

Capecitabine, Prescribing Information. Medline Plus. https://medlineplus.gov/druginfo/meds/a699003.html
Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oza A, Skovsgaard T, Munier S, Martin C. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2002;20:3617-3627.

Casale J, Crane JS. Fluorouracil. [Updated 2020 Mar 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549808/

Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger U, Garin A, Graeven U, McKendric J, Maroun J, Marshall J, Osterwalder B, Pérez-Manga G, Rosso R, Rougier P, Schilsky RL; Capecitabine Colorectal Cancer Study Group. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol. 2002;13: 566-575. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2961878-8

Chau I, Norman AR, Cunningham D, Tait D, Ross PJ, Iveson T, Hill M, Hickish T, Lofts F, Jodrell D, Webb A, Oates JR. A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Ann Oncol 2005;16:549–557. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2947738-7

Chollet P, Schöffski P, Weigang-Köhler K, Schellens JH, Cure H, Pavlidis N, Grünwald V, De Boer R, Wanders J, Fumoleau P; EORTC Early Clinical Studies Group. Phase II trial with S-1in chemotherapy-naive patients with gastric cancer. A trial performed by the EORTC Early Clinical Studies Group (ECSG). Eur J Cancer. 2003;39:1264-1270.

Ciccolini J, Evrard A, Cuq P. Thymidine phosphrylase and fluoropyrimidines efficacy: a Jekyll and Hyde story. Curr Med Chem Anti-Canc Agents 2004;4:71–81.

Czito BG, Hong TJ, Cohen DP, Petros WP, Tyler DS, Pappas TN, Yu D, Lee CG, Lockhart AC, Morse MA, Fernando N, Hurwitz HI. A phase I study of eniluracil/5-FU in combination with radiation therapy for potentially resectable and/or unresectable cancer of the pancreas and distal biliary tract. Cancer Invest. 2006;24(1):9-17.

Czito BG, Hong TJ, Cohen DP, Tyler DS, Lee CG, Anscher MS, Ludwig KA, Seigler HF, Mantyh C, Morse MA, Lockhart AC, Petros WP, Honeycutt W, Spector NL, Ertel PJ, Mangum SG, Hurwitz HI. A Phase I trial of preoperative eniluracil plus 5-fluorouracil and radiation for locally advanced or unresectable adenocarcinoma of the rectum and colon. Int J Radiat Oncol Biol Phys. 2004;58(3):779-785.

de Bono JS, Twelves CJ. The oral fluorinated pyrimidines. Invest New Drugs 2001;19:41–59.

de Lima Lopes G Jr, Dicksey JS, Peters WP, Palalay M, Chang AY. Final results of a prematurely discontinued Phase 1/2 study of eniluracil with escalating doses of 5-fluorouracil administered orally in patients with advanced hepatocellular carcinoma. Cancer Chemother Pharmacol. 2011;68(4):1067-1073.

Diasio R B, Harris BE. Clinical pharmacology of 5-fluorouracil. Clin. Pharmacokinet. 1989;16:215–237.

Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000;355(9209):1041-1047.
Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2002;20:3605-3616.

Fluorouracil Injection, Prescribing Information. Medline Plus. https://medlineplus.gov/druginfo/meds/a682708.html

Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Lévi F. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2000 Jan;18(1):136-47.

Goto A, Yamada Y, Yasui H, Kato K, Hamaguchi T, Muro K, Shimada Y, Shirao K. Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer. Ann Oncol 2006;17:968-973. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2943577-1

Grem JL, Harold N, Shapiro J, Bi DQ, Quinn MG, Zentko S, Keith B, Hamilton JM, Monahan BP, Donavan S, Grollman F, Morrison G, Takimoto CH. Phase I and pharmacokinetic trial of weekly oral fluorouracil given with eniluracil and low-dose leucovorin to patients with solid tumors. J Clin Oncol. 2000;18(23):3952-3963.

Guo XD, Harold N, Saif MW, Schuler B, Szabo E, Hamilton JM, Monahan BP, Quinn MG, Cliatt J, Nguyen D, Grollman F, Thomas RR, McQuigan EA, Wilson R, Takimoto CH, Grem JL. Pharmacokinetic and pharmacodynamic effects of oral eniluracil, fluorouracil and leucovorin given on a weekly schedule. Cancer Chemother Pharmacol. 2003;52(1):79-85.

Heslin MJ, Yan J, Weiss H, Shao L, Owens J, Lucas VS, Diasio RB. Dihydropyrimidine dehydrogenase (DPD) rapidly regenerates after inactivation by eniluracil (GW776C85) in primary and metastatic colorectal cancer. Cancer Chemother Pharmacol. 2003;52(5):399-404.

Hirata K, Horikoshi N, Aiba K, Okazaki M, Denno R, Sasaki K, Nakano Y, Ishizuka H, Yamada Y, Uno S, Taguchi T, Shirasaka T. Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. Clin Cancer Res. 1999;5:2000-2005. https://clincancerres.aacrjournals.org/content/5/8/2000.full-text.pdf

Hohneker JA. Clinical development of eniluracil: current status. Oncology (Williston Park). 1998;12(10 Suppl 7):52-56. https://www.cancernetwork.com/view/clinical-development-eniluracil-current-status

Humerickhouse RA, Dolan ME, Haraf DJ, Brockstein B, Stenson K, Kies M, Sulzen L, Ratain MJ, Vokes EE. Phase I study of eniluracil, a dihydropyrimidine dehydrogenase inactivator, and oral 5-fluorouracil with radiation therapy in patients with recurrent or advanced head and neck cancer. Clin Cancer Res. 1999;5(2):291-298. https://clincancerres.aacrjournals.org/content/5/2/291.full-text.pdf

Ichinose Y, Yoshimori K, Sakai H, Nakai Y, Sugiura T, Kawahara M, Niitani H. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. Clin Cancer Res. 2004; 10:7860-7864. https://clincancerres.aacrjournals.org/content/10/23/7860.full-text.pdf

IMPACT. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet. 1995;345:939–944.

Irinotecan Injection, Prescribing Information. Medline Plus. https://medlineplus.gov/druginfo/meds/a608043.html

Johnston PG, Kaye S. Capecitabine: a novel agent for the treatment of solid tumors. Anticancer Drugs. 2001;12:639–646.

Jones SF, Greco FA, Hainsworth JD, Patton JW, Barton JH, Willcutt NT, Baker MN, McGuirt PV, Levin J, Burris HA 3rd. A phase I trial of weekly paclitaxel plus prolonged oral eniluracil/5-fluorouracil in patients with refractory malignancies. Oncologist. 2002;7(5):444-450. https://theoncologist.onlinelibrary.wiley.com/doi/epdf/10.1634/theoncologist.7-5-444

Kadoyama K, Miki I, Tamura T, Brown JB, Sakaeda T, Okuno Y. Adverse event profiles of 5-fluorouracil and capecitabine: data mining of the public version of the FDA Adverse Event Reporting System, AERS, and reproducibility of clinical observations. Int J Med Sci. 2012;9(1):33-39. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222088/pdf/ijmsv09p0033.pdf

Keith B, Guo XD, Zentko S, Harold N, Schuler B, Quinn M, Shapiro J, Grem JL. Impact of two weekly schedules of oral eniluracil given with fluorouracil and leucovorin on the duration of dihydropyrimidine dehydrogenase inhibition. Clin Cancer Res. 2002;8(5):1045-1050. https://clincancerres.aacrjournals.org/content/8/5/1045.full-text.pdf

Knowling M, Browman G, Siu L, Khoo K, Cooke A, Tannock I, Klaassen D, Cripps C, Goss G, Matthews S, Clarke R, Seymour L. A National Cancer Institute of Canada clinical trials group phase II study of eniluracil (776C85) and oral 5-fluorouracil in patients with advanced squamous cell head and neck cancer. Ann Oncol. 2001;12(7):919-922. https://www.annalsofoncology.org/article/S0923-7534(19)54174-6/pdf

Leichman CG, Chansky K, Macdonald JS, Doukas MA, Budd GT, Giguere JK, Abbruzzese JL; Southwest Oncology Group. Biochemical modulation of 5-fluorouacil through dihydropyrimidine dehydrogenase inhibition: a Southwest Oncology Group phase II trial of eniluracil and 5-fluorouracil in advanced resistant colorectal cancer. Invest New Drugs. 2002;20(4):419-424.

Lenz HJ, Lee FC, Haller DG, Singh D, Benson AB 3rd, Strumberg D, Yanagihara R, Yao JC, Phan AT, Ajani JA. Extended safety and efficacy data on S-1plus cisplatin in patients with untreated, advanced gastric carcinoma in a multicenter phase II study. Cancer. 2007;109:33-40. https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.22329

Lin EH, Curley SA, Crane CC, Feig B, Skibber J, Delcos M, Vadhan SR, Morris J, Ayers GD, Ross A, Brown T, Rodriguez-Bigas MA, Janjan N. Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? Am J Clin Oncol. 2006;29:232-239.

Lin PC, Chen WS, Chao TC, Yang SH, Tiu CM, Liu JH. Biweekly oxaliplatin plus 1-day infusional fluorouracil/leucovorin followed by metronomic chemotherapy with tegafur/uracil in pretreated metastatic colorectal cancer. Cancer Chemother Pharmacol. 2006;60:351-360.

Llovet JM, Ruff P, Tassopoulos N, Castells L, Bruix J, El-Hariry I, Peachey M. A phase II trial of oral eniluracil/5-fluorouracil in patients with inoperable hepatocellular carcinoma. Eur J Cancer. 2001;37:1352-1358.

Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330-338. http://fulltext.calis.edu.cn/nature/nrc/3/5/nrc1074.pdf

Mani S, Beck T, Chevlen E, et al: A phase II open-label study to evaluate a 28-day regimen of oral 5-fluorouracil (5-FU) plus 776C85 for the treatment of patients with previously untreated metastatic colorectal cancer (CRC). Proc Am Soc Clin Oncol. 1998;17:281a.

Mani S, Hochster H, Beck T, Chevlen EM, O'Rourke MA, Weaver CH, Bell WN, White R, McGuirt C, Levin J, Hohneker J, Schilsky RL, Lokich J. Multicenter phase II study to evaluate a 28-day regimen of oral fluorouracil plus eniluracil in the treatment of patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2000;18(15):2894-901.

Marsh JC, Catalano P, Huang J, Graham DL, Cornfeld MJ, O'Dwyer PJ, Benson AB 3rd. Eastern Cooperative Oncology Group phase II trial (E4296) of oral 5-fluorouracil and eniluracil as a 28-day regimen in metastatic colorectal cancer. Clin Colorectal Cancer. 2002;2(1):43-50.

Meropol NJ, Niedzwiecki D, Hollis D, Schilsky RL, Mayer RJ; Cancer and Leukemia Group B. Phase II study of oral eniluracil, 5-fluorouracil, and leucovorin in patients with advanced colorectal carcinoma. Cancer. 2001;91(7):1256-1263.

Meta-Analysis Group In Cancer, Lévy E, Piedbois P, Buyse M, Pignon JP, Rougier P, Ryan L, Hansen R, Zee B, Weinerman B, Pater J, Leichman C, Macdonald J, Benedetti J, Lokich J, Fryer J, Brufman G, Isacson R, Laplanche A, Quinaux E, Thirion P. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. J Clin Oncol. 1998;16(11):3537-3541.

Mikhail SE, Sun JF, Marshall JL. Safety of capecitabine: a review. Expert Opin Drug Saf. 2010;9(5):831-841.
Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer. 1998;34(8):1274–1281.

Morgan-Meadows S, Thomas JP, Mulkerin D, Berlin JD, Bailey H, Binger K, Volkman J, Alberti D, Feierabend C, Marrocha R, Arzoomanian RZ, Wilding G. Phase I study of eniluracil, oral 5-fluororacil and gemcitabine in patients with advanced malignancy. Invest New Drugs. 2002;20(4):377-382.

Ochoa L, Hurwitz HI, Wilding G, Cohen D, Thomas JP, Schwartz G, Monroe P, Petros WP, Ertel VP, Hsieh A, Hoffman C, Drengler R, Magnum S, Rowinsky EK. Pharmacokinetics and bioequivalence of a combined oral formulation of eniluracil, an inactivator of dihydropyrimidine dehydrogenase, and 5-fluorouracil in patients with advanced solid malignancies. Ann Oncol. 2000;11(10):1313-1322. https://www.annalsofoncology.org/article/S0923-7534(19)55668-X/pdf

Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K, Taguchi T. Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. Br J Cancer. 2000;83:141-145. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2363492/pdf/83-6691236a.pdf

Oxaliplatin Injection, Prescribing Information. Medline Plus. https://medlineplus.gov/druginfo/meds/a607035.html
Pentoxifylline, Prescribing Information. Medline Plus. https://medlineplus.gov/druginfo/meds/a685027.html

Peters GJ, Noordhuis P, Van Kuilenburg AB, Schornagel JH, Gall H, Turner SL, Swart MS, Voorn D, Van Gennip AH, Wanders J, Holwerda U, Smid K, Giaccone G, Fumoleau P, Van Groeningen CJ. Pharmacokinetics of S-1, an oral formulation of ftorafur, oxonic acid and 5-chloro-2,4-dihydroxypyridine (molar ratio 1:0.4:1) in patients with solid tumors. Cancer Chemother Pharmacol. 2003;52:1-12.

Petrioli R, Sabatino M, Fiaschi AI, Marsili S, Pozzessere D, Messinese S, Correale P, Civitelli S, Tanzini G, Tani F, De Martino A, Marzocca G, Lorenzi M, Giorgi G, Francini G. UFT/leucovorin and oxaliplatin alternated with UFT/leucovorin and irinotecan in metastatic colorectal cancer. Br J Cancer. 2004;90:306-309. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2409570/pdf/90-6601521a.pdf

Porter DJ, Chestnut WG, Merrill BM, Spector T. Mechanism-based inactivation of dihydropyrimidine dehydrogenase by 5-ethynyluracil. J Biol Chem. 1992;267:5236–5242.

Processa Corporate Presentation January 2020. https://processapharmaceuticals.com/ppt/Processa-Corporate-Deck-Jan-6-2021.pdf

Prucalopride Prescribing Information, Medline Plus.

Rivera E, Chang JC, Semiglazov V, Burdava O, Kirby MG, Spector T. Eniluracil plus 5-fluorouracil and leucovorin: treatment for metastatic breast cancer patients in whom capecitabine treatment rapidly failed. Clin Breast Cancer. 2014;14(1):26-30.

Rivera E, Chevlen E, Eckardt J et al: A phase II open-label study to evaluate a 28-day oral regimen of 5-fluorouracil (5-FU) plus 776C85 for the treatment of patients with taxane and anthracycline resistant advanced breast cancer: Preliminary results. Proc Am Soc Clin Oncol. 1998;17:113a.

Rivera E, Sutton L, Colwell B, Graham M, Frye D, Somerville M, Conklin HS, McGuirt C, Levin J, Hortobagyi GN. Multicenter phase II study of a 28-day regimen of orally administered eniluracil and fluorouracil in the treatment of patients with anthracycline- and taxane-resistant advanced breast cancer. J Clin Oncol. 2002;20(4):987-993.

Rivera E, Valero V, Cristofanilli M, Frye DK, Booser DJ, Rosales MM, Hortobagyi GN. Phase I study of eniluracil and oral 5-fluorouracil in combination with docetaxel in the treatment of patients with metastatic breast carcinoma.

Cancer. 2002;94(9):2321-2326. https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.10488

Rothenberg ML, Benedetti JK, Macdonald JS, Seay TE, Neubauer MA, George CS, Tanaka MS Jr, Giguere JK, Pruitt BT, Abbruzzese JL. Phase II trial of 5-fluorouracil plus eniluracil in patients with advanced pancreatic cancer: a Southwest Oncology Group study. Ann Oncol. 2002;13(10):1576-1582. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2963768-3

Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1M tegafur-0.4 M gimestat-1M otastat potassium) in advanced gastric cancer patients. Eur J Cancer. 1998;34:1715-1720.

Salonga D, Danenberg KD, Johnson M, Metzger R, Groshen S, Tsao-Wei DD, Lenz HJ, Leichman CG, Leichman L, Diasio RB, Danenberg PV. Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. Clin Cancer Res. 2000;6(4):1322-7132. https://clincancerres.aacrjournals.org/content/clincanres/6/4/1322.full.pdf

Scheithauer W, McKendrick J, Begbie S, Borner M, Burns WI, Burris HA, Cassidy J, Jodrell D, Koralewski P, Levine EL, Marschner N, Maroun J, Garcia-Alfonso P, Tujakowski J, Van Hazel G, Wong A, Zaluski J, Twelves C; X-ACT Study Group. Oral capecitabine as an alternative to I.V. 5-fluorouracilbased adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. Ann Oncol. 2003;14:1735-1743. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2964254-7

Schilsky RL, Bukowski R, Burris H 3rd, Hochster H, O'Rourke M, Wall JG, Mani S, Bonny T, Levin J, Hohneker J. A multicenter phase II study of a five-day regimen of oral 5-fluorouracil plus eniluracil with or without leucovorin in patients with metastatic colorectal cancer. Ann Oncol. 2000;11(4):415-420. https://www.annalsofoncology.org/article/S0923-7534(19)55016-5/pdf

Schilsky RL, Hohneker J, Ratain MJ, Janisch L, Smetzer L, Lucas VS, Khor SP, Diasio R, Von Hoff DD, Burris HA 3rd. Phase I clinical and pharmacologic study of eniluracil plus fluorouracil in patients with advanced cancer. J Clin Oncol. 1998;16(4):1450-1457.

Schilsky RL, Kindler HL. Eniluracil: an irreversible inhibitor of dihydropyrimidine dehydrogenase. Expert Opin Investig Drugs. 2000;9(7):1635-49.

Schilsky RL, Levin J, West WH, Wong A, Colwell B, Thirlwell MP, Ansari RH, Bell WN, White RL, Yates BB, McGuirt PV, Pazdur R. Randomized, open-label, phase III study of a 28-day oral regimen of eniluracil plus fluorouracil versus intravenous fluorouracil plus leucovorin as first-line therapy in patients with metastatic/advanced colorectal cancer. J Clin Oncol 2002;20:1519–1526.

Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, Price T, Lim R, Van Cutsem E, Park YS, McKendrick J, Topham C, Soler-Gonzalez G, de Braud F, Hill M, Sirzén F, Haller DG. Phase III trial of capecitabine

plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol. 2007;25:102-109.

Shepard DR, Mani S, Kastrissios H, Learned-Coughlin S, Smith D, Ertel P, Magnum S, Janisch L, Fleming GF, Schilsky RL, Ratain MJ. Estimation of the effect of food on the disposition of oral 5-fluorouracil in combination with eniluracil. Cancer Chemother Pharmacol. 2002;49(5):398-402.

Skovsgaard T, Davidson NG, Piccart MJ, Richel DJ, Bonneterre J, Cirkel DT, Barton CM; Eniluracil/Fluorouracil Breast Cancer Study Group. A phase II study of oral eniluracil/fluorouracil in patients with anthracycline-refractory or anthracycline- and taxane-refractory advanced breast cancer. Ann Oncol 2001;12:1255–1257. https://www.annalsofoncology.org/article/S0923-7534(19)54293-4/pdf

Smith IE, A'Hern RP, Coombes GA, Howell A, Ebbs SR, Hickish TF, O'Brien ME, Mansi JL, Wilson CB, Robinson AC, Murray PA, Price CG, Perren TJ, Laing RW, Bliss JM; TOPIC Trial Group. A novel continuous infusional 5-fluorouracil-based chemotherapy regimen compared with conventional chemotherapy in the neo-adjuvant treatment of early breast cancer: 5 year results of the TOPIC trial. Ann Oncol. 2004;15:751-758. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2955774-X

Smith IE, Johnston SR, O'Brien ME, Hickish TF, de Boer RH, Norton A, Cirkel DT, Barton CM. Low-dose oral fluorouracil with eniluracil as first-line chemotherapy against advanced breast cancer: a phase II study. J Clin Oncol. 2000;18(12):2378-2384.

Vallböhmer D, Kuramochi H, Shimizu D, Danenberg KD, Lindebjerg J, Nielsen JN, Jakobsen A, Danenberg PV. Molecular factors of 5-fluorouracil metabolism in colorectal cancer: analysis of primary tumor and lymph node metastasis. Int J Oncol. 2006;28(2):527-533. https://www.spandidos-publications.com/ijo/28/2/527

Van Cutsem E, Sorensen J, Cassidy J, et al. International phase III study of oral eniluracil (EU) plus 5-fluorouracil (5-FU) versus intravenous (IV) 5-FU Plus leucovorin in the treatment of advanced colorectal cancer (ACC) [abstract 522]. Proc Am Soc Clin Oncol 2001;20.

Van den Brande J, Schöffski P, Schellens JH, Roth AD, Duffaud F, Weigang-Köhler K, Reinke F, Wanders J, de Boer RF, Vermorken JB, Fumoleau P. EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. Br J Cancer. 2003;88:648-653. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376342/pdf/88-6600781a.pdf

Wan L, Cao D, Zeng J, Yan R, Pizzorno G. Modulation of uridine phosphorylase gene expression by tumor necrosis factor-α enhances the antiproliferative activity of the capecitabine intermediate 5′-deoxy-5-fluorouridine in breast cancer cells. Mol Pharmacol 2006;69:1389–1395. https://molpharm.aspetjournals.org/content/molpharm/69/4/1389.full.pdf

Yanagisawa Y, Maruta F, Iinuma N, Ishizone S, Koide N, Nakayama J, Miyagawa S. Modified Irinotecan/5FU/Leucovorin therapy in advanced colorectal cancer and predicting therapeutic efficacy by expression of tumor-related enzymes. Scand J Gastroenterol. 2007;42(4):477-4784.

Yen JL, McLeod HL. Should DPD analysis be required prior to prescribing fluoropyrimidines? Eur J Cancer 2007;43:1011–1016.

Yen-Revollo JL, Goldberg RM, McLeod HL. Can inhibiting dihydropyrimidine dehydrogenase limit hand-foot syndrome caused by fluoropyrimidines? Clin Cancer Res. 2008 Jan 1;14(1):8-13. https://clincancerres.aacrjournals.org/content/clincanres/14/1/8.full.pdf

Yip D, Karapetis C, Strickland AH, Steer C, Holford C, Knight S, Harper P. A dose-escalating study of oral eniluracil/5-fluorouracil plus oxaliplatin in patients with advanced gastrointestinal malignancies. Ann Oncol. 2003;14(6):864-866. https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2963555-6

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