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NuTide:302 - A Phase Ib study to assess the safety, pharmacokinetics and clinical activity of the ProTide NUC-3373 when combined with standard agents used in colorectal cancer

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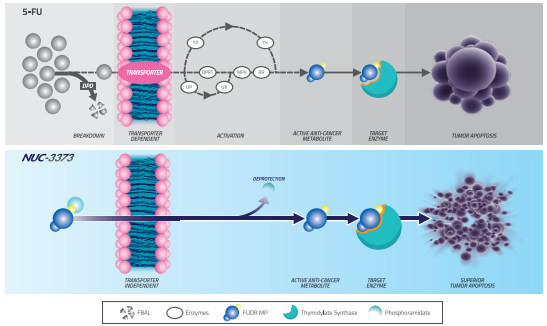
Background

- Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women[1] and has a 5-year survival rate of 10% for patients with metastatic disease
- 5-fluorouracil (5-FU) remains standard of care for patients with CRC, as monotherapy or in combination with other agents
- Fluorodeoxyuridine-monophosphate (FUDR-MP), the anti-cancer metabolite of 5-FU, causes cell death by:
  - Inhibiting thymidylate synthase (TS)
  - Reducing the pool of deoxythymidine monophosphate (dTMP)
- Poor response to 5-FU is a consequence of:
  - Over 85% of 5-FU broken down by dihydropyrimidine dehydrogenase (DPD)[2]
  - Limited dosing due to side effects caused by the accumulation of toxic metabolites[3]
  - Key cancer resistance mechanisms:
    - Cellular uptake dependent on nucleoside transporters[4]
    - Complex enzymatic activation to yield active anti-cancer metabolite FUDR-MP[4]
    - High tumor (or mycoplasma infection-induced) expression of thymidine phosphorylase (TP) which breaks down 5-FU[5]
- Short plasma half-life (8-14 minutes) results in prolonged administration times (>46 hours)
- Effective new agents and combinations are required

NUC-3373 bypasses the key cancer resistance pathways of 5-FU



NUC-3373

A ProTide Transformation of 5-FU

- Designed to overcome the key 5-FU resistance mechanisms[6,7]
  - Protected from breakdown by DPD or TP
  - Cellular uptake independent of nucleoside transporters
  - FUDR-MP generation independent of intracellular enzymatic activation
- 366x greater cytotoxicity than 5-FU *in vitro*
- Significantly greater anti-cancer activity *in vivo* compared to 5-FU
- Favorable toxicology profile compared to 5-FU

NuTide:301 - NUC-3373 first-in-human study in advanced solid tumors

- Study ongoing, interim data presented ESMO 2018 (n=36)[8]
- 14 primary cancer types: 50% CRC
- NUC-3373 well-tolerated, multiple cycles administered (median to; range 0.25 - 11.75)
- Maximum tolerated dose has not been reached
- Grade 3 treatment-related AEs: transaminitis (3), fatigue (1), shingles (1)
- No Grade 4 AEs

NUC-3373 has an advantageous pharmacokinetic profile compared to 5-FU

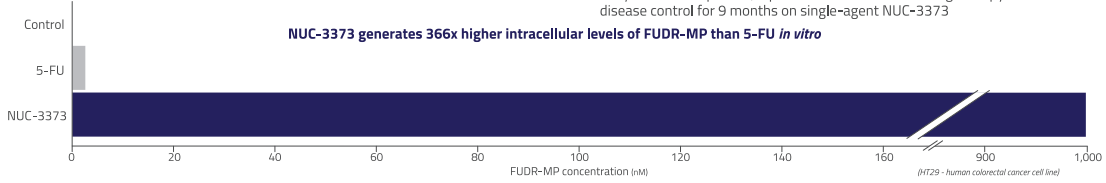
- Linear and reproducible PK profile
- Intracellular FUDR-MP detectable at 5 minutes post-infusion with a $t_{1/2}$ of 14.91 hours (±1.44)
- Intracellular FUDR-MP still present at 48 hours

NUC-3373 PK profile comparison with 5-FU in NuTide:301 study

	NUC-3373	5-FU
Plasma half-life	9.7 hours	8-14 minutes
FUDR-MP (in PBMCs)	Detected (dose proportional)	Undetected[9]
TS inhibition	Strong	Weak
Intracellular levels of dTMP	Depleted	No change
Toxic metabolites (dhFU, FBAL)	Levels not clinically significant	High levels

- Encouraging signs of clinical activity observed
  - 70-year-old CRC patient, 5 prior lines of 5-FU-containing therapy: disease control for 9 months on single-agent NUC-3373

NUC-3373 generates 366x higher intracellular levels of FUDR-MP than 5-FU *in vitro*



NuTide:302 study design

Primary objective

- RP2D for NUC-3373 in combination with agents commonly used in the treatment of CRC

Secondary objectives

- Safety and tolerability
- Pharmacokinetics (PK)
- Anti-tumor activity (per RECIST 1.1)
- Effect of leucovorin (LV) on NUC-3373 PK and PD

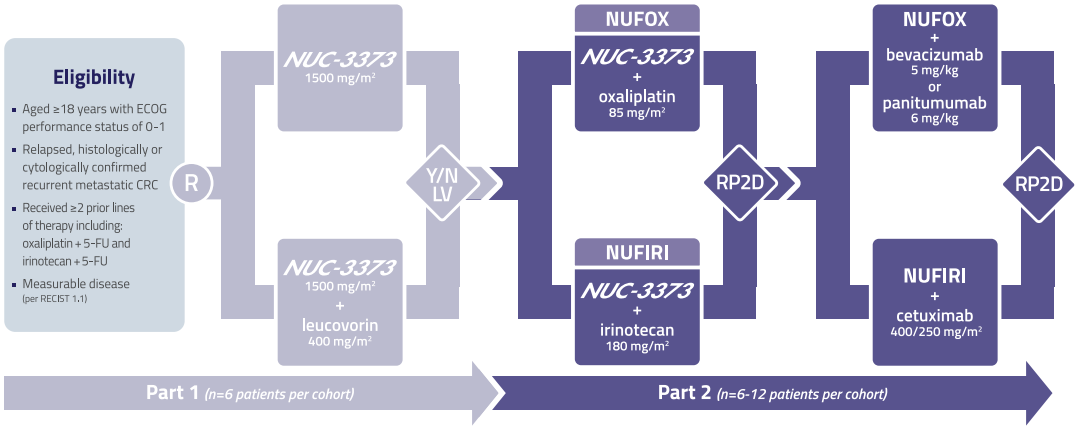
Exploratory objectives

- Markers of resistance to 5-FU
- Relationships between PK, PD and clinical activity

Translational Research

- Exploration of the basis for response or resistance to treatment
- Genomic, transcriptomic, and proteomic analyses
- PK and PD analyses

NuTide:302
Two-part study of NUC-3373 in patients with recurrent metastatic CRC



Study Treatments

- Treatment cycles are 28 days in duration with treatment every two weeks (q2w)
- Patients will continue to receive NUC-3373 and combination agent(s) until progressive disease or unmanageable toxicity
- NUC-3373 dose escalations established from the ongoing NuTide:301 study

Recruitment status at 1st January 2019

- **Part 1** 8 patients recruited to date in US and Europe
- **Part 2** study planned in US and Europe

Summary

- NUC-3373 is specifically designed to overcome the key cancer resistance mechanisms associated with 5-FU
- NuTide:302 study will determine the optimal dose of NUC-3373 in combination with agents commonly used in the treatment of patients with CRC
- NUC-3373 has the potential to offer enhanced efficacy, a favorable safety profile and a more convenient dosing regimen compared to 5-FU

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