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NuTide:302 - A Phase Ib study of the ProTide NUC-3373 in combination with standard therapies in advanced colorectal cancer

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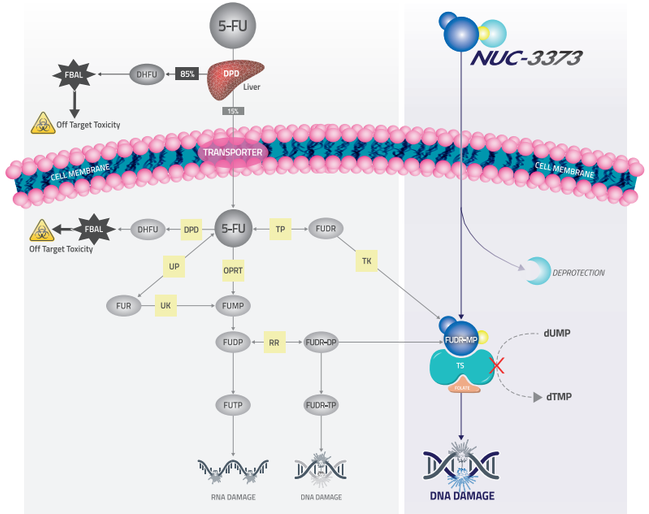
Background

- 5-fluorouracil (5-FU) is a key anti-cancer agent used across a broad range of tumors
- Fluorodeoxyuridine-monophosphate (FUDR-MP or FdUMP), the active anti-cancer metabolite of 5-FU, causes cell death via inhibition of thymidylate synthase (TS)[1]
  - Prevents the conversion of dUMP to dTMP
- Limitations of 5-FU include
  - Short plasma half-life (8-14 minutes)[2] necessitating prolonged administration (>46 hours)
  - Over 85% broken down by DPD[3]
  - Production of catabolites such as FBAL (implicated in hand-foot syndrome)
  - Decreased uptake via membrane transporters
  - Complex enzymatic activation; including thymidine phosphorylase (TP) and thymidine kinase (TK) conferring resistance

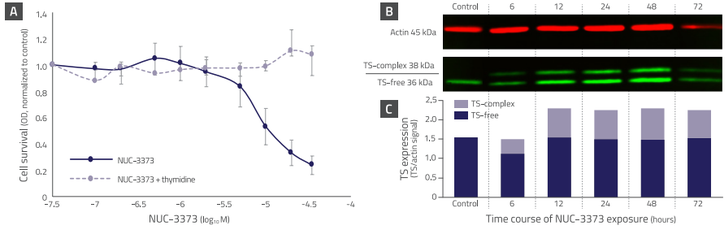
NUC-3373 bypasses the key cancer resistance pathways associated with 5-FU



NUC-3373: A targeted inhibitor of TS

- ProTide transformation of FUDR-MP, the active anti-cancer metabolite of 5-FU
- Designed to overcome the key 5-FU resistance mechanisms[4,5]
  - Protected from breakdown by DPD
  - Cellular uptake independent of membrane transporters
  - FUDR-MP generation independent of intracellular enzymatic activation
- NUC-3373 generates significantly higher levels of FUDR-MP compared to 5-FU[6]
- Currently being investigated in clinical studies
  - NuTide:301 - Phase Ib dose-finding study in solid tumors
  - NuTide:302 - Phase Ib combination study in colorectal cancer (CRC)

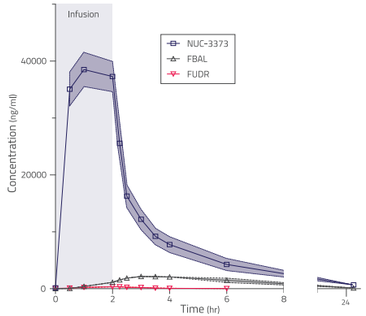
NUC-3373 targets the *de novo* pathway of dTMP synthesis in CRC cells



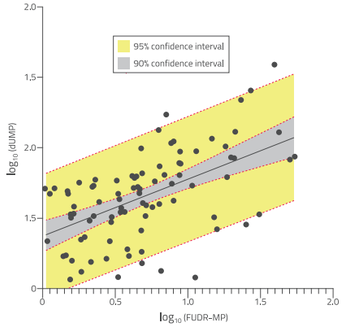
A: *The effect of 10 µg/mL thymidine supplementation in HCT116 cells exposed to NUC-3373.* **B:** *Western blot of TS-ternary complex and TS-free protein expression following exposure to 10 µM NUC-3373.* **C:** *Quantified TS-ternary complex and TS-free protein expression.*

- Exogenous thymidine rescues cells from NUC-3373-induced death, confirming that dTMP is essential for cell survival
- NUC-3373 forms TS-ternary complexes that were detected for at least 72 hours

PK profile and positive correlation between FUDR-MP and dUMP in clinical study NuTide:302 (n=20)



Plasma NUC-3373, FUDR and FBAL over time (95% CI).



Positive linear relationship between intracellular FUDR-MP and dUMP

	NUC-3373	FUDR	FBAL
C_{max} (µg/mL)	43.2	0.4	2.4
$AUC_{(0-t)}$ (µg.h/mL)	165.9	1.0	25.4
$T_{1/2}$ (h)	5.7	1.2	5.1

1500mg/m² over 2 hours; mean values reported

- Elimination half-life ($t_{1/2}\beta$) was 5.7 hours (range 3.9 - 10.8 hours; estimated over 3-24 hours)
- Low inter-patient variability for all parameters (co-efficient of variation 22-51%)
- Volume of distribution was high indicating extensive tissue absorption (171.6 L)
- Plasma FBAL low and not clinically significant
  - No hand-foot syndrome observed

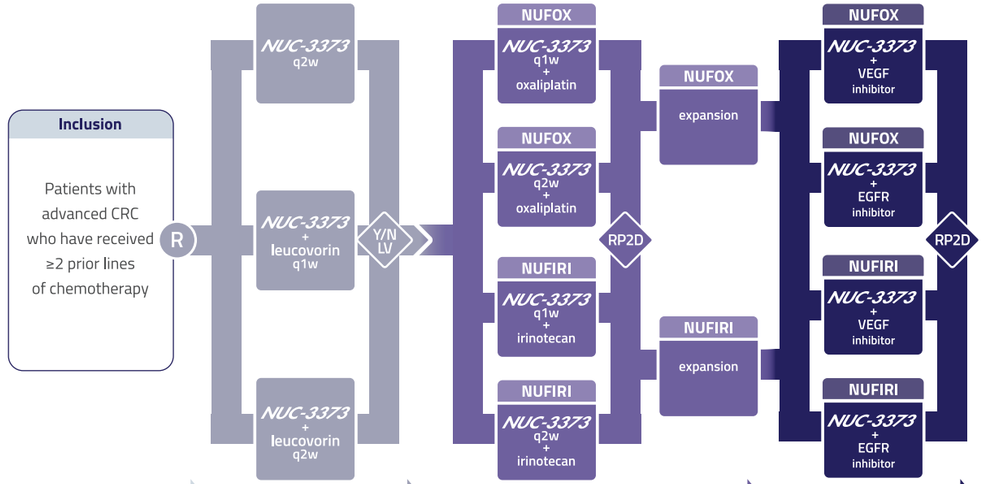
NuTide:302 (Phase 1b combination study)

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



q1w: Weekly administration
q2w: Alternate week administration

Study treatments

- Combination agents will be administered as per standard of care
- Patients will continue to receive NUC-3373 and combination agent(s) until progressive disease or unmanageable toxicity

Recruitment ongoing

- 4 US sites
- 2 UK sites

Summary

- NUC-3373 is specifically designed to overcome the key cancer resistance mechanisms associated with 5-FU
- NUC-3373 is targeted inhibitor of TS activity
- 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 demonstrates a favorable PK profile to date
- NUC-3373 has the potential to offer enhanced efficacy, an improved safety profile and a more convenient dosing regimen compared to 5-FU

REFERENCES: 1. Longley DB. *et al, Nat Rev Cancer* 2003; 3:330-338 2. Heggie GD. *et al, Cancer Research* 1987; 47:2203-2206 3. Diasio RB & Harris BE., *Clin Pharmacokinet* 1989; 16:215-237 4. McGuigan C. *et al, J Med Chem* 2011; 27;12:47-72 5. Vande Voorde J. *et al, Biochem Pharmacol* 2011; 82:44-452 6. Ghazaly E. *et al Ann Oncol* 2017; 25;Suppl_5:128

ABBREVIATIONS: 5-FU: 5-fluorouracil FUDR-MP/FdUMP: fluorodeoxyuridine monophosphate TS: thymidylate synthase dUMP: deoxyuridine monophosphate dTMP: deoxythymidine monophosphate DPD: dihydropyrimidine dehydrogenase FBAL: α-fluoro-β-alanine TP: thymidine phosphorylase TK: thymidine kinase CRC: colorectal cancer PK: pharmacokinetics GLP: good lab practice C_{max}: Maximum concentration AUC: area under the curve $T_{1/2}$: Half-life FUDR: fluorodeoxyuridine RP2D: recommended phase 2 dose LV: leucovorin PD: pharmacodynamics q1w: weekly administration q2w: alternate week administration

Data current as of 7 Oct 2019.