A Phase Ib open label study to assess the safety and pharmacokinetics of NUC-3373, a nucleotide analog, given in combination with standard agents used in colorectal cancer treatment (NuTide:302)

Abstract Nº: TPS3617
Registry Nº: NCT03428958
Email: sarah.blagden@oncology.ox.ac.uk

SP Blagden[1], TRJ Evans[2], E Ghazaly[3], C Gnanaranjan[3], A De Gramont[4], J Tabernero[5], JD Berlin[6]

1) Early Phase Clinical Trials Unit, Churchill Hospital, University of Oxford NHS Trust, Oxford, UK. 2) University of Glasgow, Beatson Institute for Cancer Research, Glasgow, UK.
3) Centre for Haemato-Oncology, Barts Cancer Institute, London, UK. 4) Department of Medical Oncology, Institut Hospitalier Franco-Britannique, Levallois-Perret, France.
5) Early Drug Development Unit, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, CIBERONC, Universitat Autonoma de Barcelona, Barcelona, Spain.
6) Henry-Joyce Cancer Clinic, The Vanderbilt Clinic, Nashville, TN, USA.

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, either as monotherapy or in combination with other chemotherapies
- Fluorodeoxyuridine-monophosphate (FUDR-MP) is the main anti-cancer metabolite of 5-FU, which binds to and inhibits thymidylate synthase (TS), reducing the pool of deoxythymidine monophosphate (dTMP), leading to cancer cell death
- Key cancer resistance mechanisms are linked to reduced efficacy, poor prognosis and off-target toxicity with a 5-FU regimen[2]
- Poor PK properties of 5-FU, including a plasma half-life of 8-14 minutes, necessitate prolonged administration times, often over 46 hours
- Effective new agents and combinations are required

5-FU Resistance Mechanisms

Susceptibility to breakdown

- Over 85% of 5-FU is broken down by dihydropyrimidine dehydrogenase (DPD)[3]
- Thymidine phosphorylase (TP), commonly overexpressed in tumors[2] or introduced by mycoplasma infection[4], also breaks down 5-FU
- Metabolic degradation results in generation of toxic metabolites such as dihydrofluorouracil (dhFU), which is associated with hand-foot syndrome

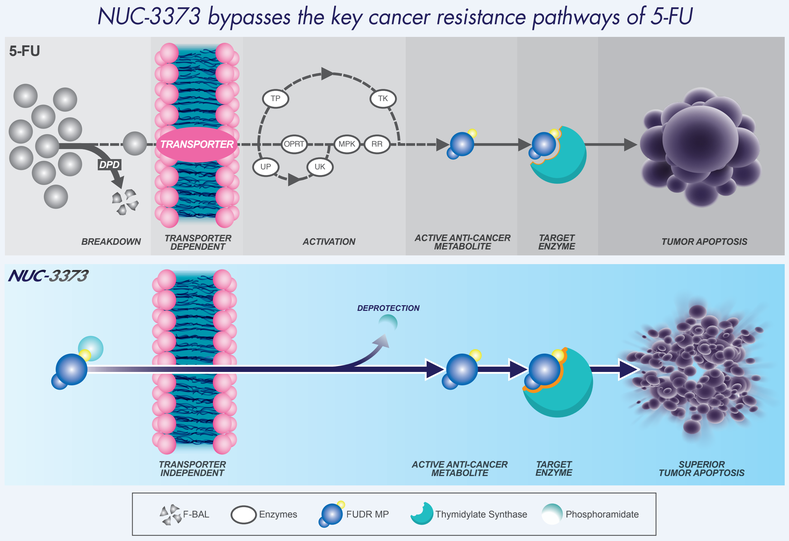
Requirement of activation

- 5-FU is a pro-drug that requires complex intracellular enzymatic activation to generate FUDR-MP[2]
- Deficient enzymatic activation is linked to poor prognosis

Reliance on active transport

- Low expression of the nucleoside transporter hENT1 is associated with 5-FU resistance[5]

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



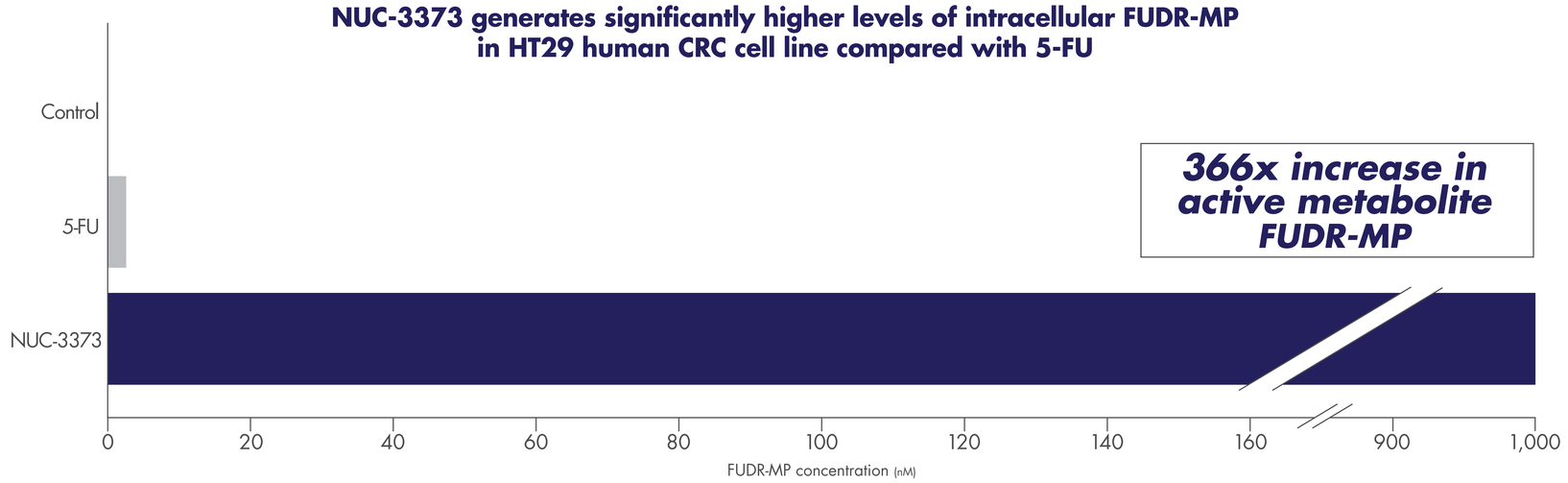
ProTides: NucleoTide Analogs

- A new class of anti-cancer agents
- Transformative phosphoramidate chemistry
- Increase intracellular levels of active anti-cancer metabolites
- Broad clinical utility

NUC-3373: A ProTide Transformation of 5-FU

- Designed to overcome key 5-FU resistance mechanisms[6,7]
- Generates 366× higher intracellular levels of FUDR-MP than 5-FU in human CRC cells *in vitro*
- Up to 330× significantly greater cytotoxicity than 5-FU *in vitro*
- Significantly greater anti-cancer activity *in vivo* compared to 5-FU
- Not degraded by DPD or TP
- Favorable toxicology profile

NUC-3373 generates significantly higher levels of intracellular FUDR-MP in HT29 human CRC cell line compared with 5-FU



NuTide:301 Study

NUC-3373 first-in-human study in advanced solid tumors

- This study is ongoing and the results are based on interim data (n=21)[8]
- Patients had 10 primary cancer types, with the majority (57%) being CRC
- NUC-3373 showed an advantageous pharmacokinetic (PK) /pharmacodynamic (PD) profile compared to 5-FU, which may allow for a more convenient dosing regimen, favorable safety profile and enhanced efficacy
  - o Intracellular FUDR-MP detectable at 5 minutes post-infusion with $t_{1/2}$ of 14.9±1.4 hours and still present at 48 hours
  - o TS was efficiently inhibited and sequestered into ternary complexes, depleting the pool of dTMP within 2-4 hours
  - o The toxic metabolite dhFU was undetectable, suggestive of an improved tolerability profile compared to 5-FU
- Based on these data, the NuTide:302 study was initiated to investigate NUC-3373 in combination with other anti-cancer agents in patients with recurrent CRC

NUC-3373 PK profile comparison with 5-FU

	NUC-3373	5-FU
Plasma $t_{1/2}$	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 metabolite (dhFU)	Undetected	High levels

NuTide:302 Study Design

Primary objective

- Determine a recommended dose of NUC-3373 in combination with agents commonly used in the treatment of CRC

Secondary objectives

- Safety and tolerability in each combination
- Effects of each combination agent on PK of NUC-3373
- Anti-tumor activity of each combination
- Effect of leucovorin (LV) when added to NUC-3373 on PK and PD parameters (Part 1)

Exploratory objectives

- Assess markers of resistance to 5-FU in blood and pre-treatment tumor samples
- Relationships between NUC-3373 PK, PD and clinical activity

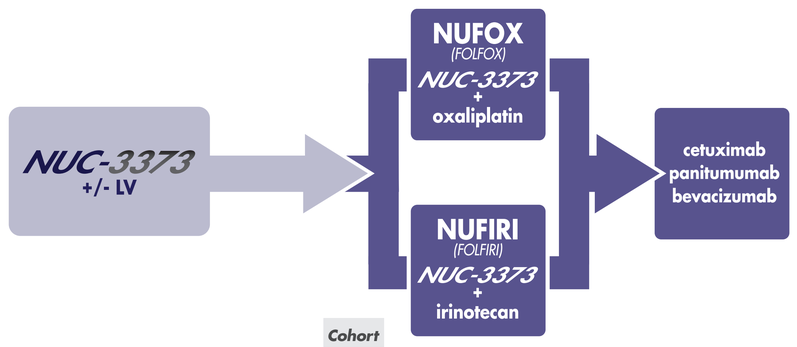
Patient Population

- Aged ≥18 years with an ECOG performance status of 0-1
- Locally advanced/unresectable or metastatic CRC
- Relapse after ≥2 prior lines of therapy; one must be an oxaliplatin + 5-FU containing regimen and one must be an irinotecan + 5-FU containing regimen
- Measurable disease as defined by RECIST

Methods

- Patients treated every 2 weeks until disease progression

NuTide:302: Patients with recurrent metastatic CRC



Cohort	Part 1 (Randomized, n=6 patients per arm)	Part 2 (+/- LV) Assignment to Cohorts at investigator discretion (n=6-12 patients per Cohort)
1a	NUC-3373 → 2wk w/o → NUC-3373+LV	
1b	NUC-3373+LV → 2wk w/o → NUC-3373	
2a		NUC-3373 + oxaliplatin
3a		NUC-3373 + irinotecan
2b		NUC-3373 + oxaliplatin + bevacizumab
2c		NUC-3373 + oxaliplatin + panitumumab
3b		NUC-3373 + irinotecan + cetuximab

STUDY STATUS

- Study open with sites in the US, UK, Spain and France

SUMMARY

- NUC-3373 is specifically designed to overcome the key cancer cell resistance mechanisms associated with 5-FU
- The 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 a more effective and safer treatment option than 5-FU

1. GLOBOCAN, 2012 2. Longley DB *et al. Nat Rev Cancer* 2003, 3: 330–338. 3. Diasio RB & Harris BE. *Clin Pharmacokinet* 1999, 16: 215–237.
4. Huang S *et al. World J Gastroenterol* 2001, 7: 266–269. 5. Tsujie M *et al. Anticancer Res* 2007;27:2241–2249.
6. McGuigan C *et al. J Med Chem* 2011, 27:7247–7258. 7. Vande Voorde J *et al. Biochem Pharmacol* 2011, 82:441–452.
8. Ghazaly E *et al. ESMO* 2017, Poster 385-P (Abstract 3432). 9. Derissen E *et al. Br J Pharmacol* 2016, 81:949-957.