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A Phase I first-in-human, dose-escalation and expansion study to evaluate the safety and tolerability of NUC-3373 in patients with locally advanced, unresectable or metastatic solid malignancies

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Background

- Fluoropyrimidines remain a cornerstone of cancer treatment (e.g., 5-FU, capecitabine, FUDR)
- 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)[1]
  - The generation of toxic metabolites (FBAL) associated with hand-foot syndrome[2]
  - Key cancer resistance mechanisms:
    - Cellular uptake dependent upon nucleoside transporters[3]
    - Complex enzymatic activation to yield active anti-cancer metabolite FUDR-MP[3]
    - Thymidine phosphorylase (TP), commonly overexpressed in tumours[3] or introduced by mycoplasma infection[4], breaks down 5-FU
  - Short plasma half-life of 8-14 minutes
  - Prolonged administration times (>46 hours)
  - Off-target toxicity
- Effective new agents and combinations are required

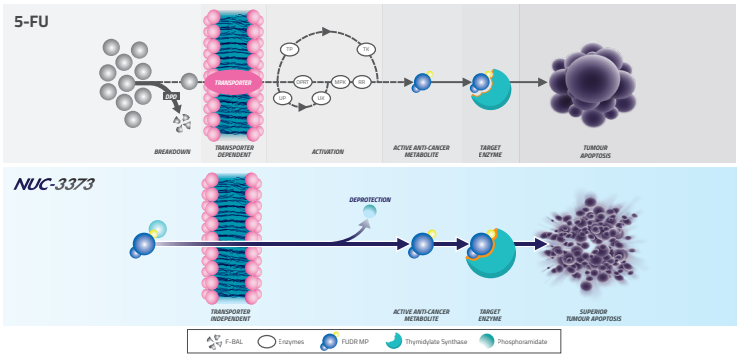
ProTides: NucleoTide Analogs

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

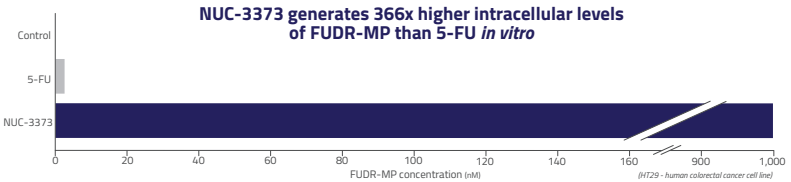
NUC-3373: A ProTide Transformation of 5-FU

- Designed to overcome the key 5-FU cancer resistance mechanisms[5,6]
  - Protected from breakdown by DPD or TP
  - Cellular uptake independent of nucleoside transporters
  - FUDR-MP generation independent of intracellular enzymatic activation
- Up to 330x greater cytotoxicity than 5-FU *in vitro*
- Significantly greater anti-cancer activity *in vivo* compared to 5-FU
- Favourable toxicology profile

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



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



Pharmacokinetics / Pharmacodynamics

- Linear and reproducible PK profile
- Intracellular FUDR-MP detectable at 5 minutes post-infusion with a $t_{1/2}$ of 14.9 ± 1.44 hours
- Intracellular FUDR-MP still present at 48 hours

	NUC-3373	5-FU
Plasma half-life	9.7 hours	8 -14 minutes
FUDR-MP (in PBMCs)	Detected (dose proportional)	Undetected[7]
Thymidylate Synthase inhibition	Strong	Weak
Intracellular levels of dTMP	Depleted	No change
Toxic metabolites (dhFU, FBAL)	Levels not clinically significant	High levels

Patient Case Studies

Colorectal Cancer

70 years, male
6 previous lines of therapy

1) 5-FU based chemoradiotherapy
2) FOLFIRI: for metastatic disease
3) CAPOX: relapsed within 2 months
4) FOLFIRI: relapsed within 8 months
5) LONSURF: relapsed within 3 months
6) Irinotecan: treatment for 1 month

NUC-3373: **Stable Disease**
Last cycle: **C10, D1**
PFS: **9 months**

Cholangiocarcinoma

60 years, female
1 previous line of therapy

1) Cisplatin + gemcitabine: relapsed within 6 months

NUC-3373: **Stable Disease**
Last cycle: **C12, D1**
PFS: **11 months**

Basal Cell Carcinoma

55 years, male
2 previous lines of therapy

1) Vismodegib: treatment for 11 months (best response PR)
2) Paclitaxel + carboplatin: treatment for 3 months (best response PR)

NUC-3373: **Stable Disease**
Last cycle: **C10, D1**
PFS: **10 months**

Study Design

Primary Objectives

- RP2D for NUC-3373 administered:
  - Weekly on days 1, 8, 15 and 22 of a 28-day cycle
  - Fortnightly on days 1 and 15 of a 28-day cycle

Secondary Objectives

- Safety and tolerability
- BOR, ORR, DoR, DCR, PFS
- PK and PD

Dose Administered

Patients received NUC-3373 at the following doses:

- **Part 1:** 125 mg/m² to 1500 mg/m² in the weekly schedule
- **Part 2:** 1500 mg/m² to 1875 mg/m² in the fortnightly schedule
- Dose escalation ongoing

Patient Characteristics

Characteristics	n
Patients (enrolled to date)	36
Median age (range)	60 (21-78)
Median prior chemo regimens (range)	3 (1-6)
ECOG PS 0 / 1 / 2	19 / 17 / 0

Primary Cancer Site	n
Colorectal	18
Pancreas (3); oesophagus (3); cervix (2)	8
Other (1): stomach; osteosarcoma; mesothelioma; cholangiocarcinoma; appendix; spindle cell sarcoma; rhabdomyosarcoma; lung; basal cell; alveolar	10

Safety

- NUC-3373 is well-tolerated
- Multiple cycles administered (median 2; range 0.25 -11.75)
- No hand-foot syndrome has been observed
- No Grade 4 AEs

Treatment Related AEs	n
Grade 3	5
Transaminitis	3
Fatigue	1
Shingles	1

Conclusion

- NUC-3373 overcomes the key cancer resistance mechanisms associated with 5-FU and capecitabine
- NUC-3373 generates high intracellular concentrations of FUDR-MP
- To date, 36 patients have been enrolled: Part I n=29; Part II n=7
- Weekly and fortnightly dosing regimens have been well-tolerated
- No unexpected AEs
- Encouraging early signs of activity have been observed
- Dose-escalation is ongoing to establish RP2D
- NuTide:302 will determine the RP2D of NUC-3373 in combination with agents commonly used in colorectal cancer
- NUC-3373 has the potential to offer a more effective and safer treatment option than 5-FU or capecitabine

Data current as of 25 Sept 2018. Data cleaning ongoing.

1. Diasio RB & Harris BE. *Clin Pharmacokinet* 1999; 16:215–237. 2. Miura K *et al. Cancers* 2010; 2:1717–1730. 3. Longley DB *et al. Nat Rev Cancer* 2003; 3:330–338. 4. Huang S *et al. World J Gastroenterol* 2001, 7: 266–269. 5. McGuigan C *et al. J Med Chem* 2011; 27:7247–7258. 6. Vande Voorde J *et al. Biochem Pharmacol* 2011; 82:441–452. 7. Derissen E *et al. Br J Pharmacol* 2016; 81:949–957.

FUDR-MP: *fluorodeoxyuridine-monophosphate* FBAL: *α-fluoro-β-alanine* dhFU: *dihydrofluorouracil*