Final results of first-in-human study of the ProTide thymidylate synthase inhibitor **NUC-3373**, in patients with advanced solid tumours **(NuTide:301)**

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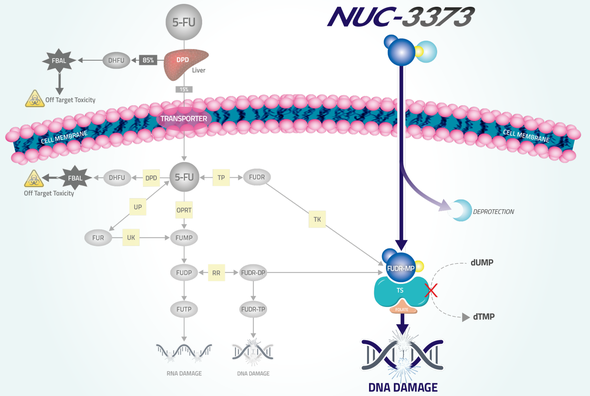
BACKGROUND

- CRC 3rd most common cancer • Incidence: 1.8 million • Annual deaths: 880,000[1]
- 5-FU remains the cornerstone of treatment for CRC, despite having several limitations
  - Rapidly degraded by DPD[2]
  - Short plasma half-life (8-14 mins)[3] necessitates prolonged (46 hour) infusions
  - Generation of toxic catabolites such as FBAL and FUTP
- Cell entry requires nucleoside transporters
- Complex enzymatic activation

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



NUC-3373: A targeted inhibitor of TS

- ProTide transformation of FUDR-MP[4,5], the active anti-cancer metabolite of 5-FU
  - Resistant to breakdown by DPD
  - Able to enter cells independently of nucleoside transporters
  - Low levels of toxic catabolites (FBAL, FUTP)
- Generates high levels of FUDR-MP[6], which binds to TS
  - Causes an imbalance in the nucleotide pool leading to DNA damage and cell death
  - Induces ER stress and DAMP release leading to immunogenic cell death[7-9]

NuTide:301

- Phase I, two part, dose-escalation study of NUC-3373 in patients with advanced solid tumours
- Study conducted at 3 UK centres between Jan 2016 and Feb 2021

Key eligibility criteria

- Patients aged ≥18 years with any solid tumour not amenable to standard therapy, refractory to standard therapy or for which no standard therapy exists
- ECOG PS 0-2
- Measurable or evaluable disease per RECIST 1.1
- Adequate bone marrow, hepatic and renal function LVEF ≥ 50%
- Negative pregnancy test for females of childbearing age
- No Intercurrent illness
- No residual toxicities >grade 1

PART I – NUC-3373
(125 mg/m² - 3250 mg/m²)
IV infusion on days 1, 8, 15 & 22 of a 28-day cycle (Q1W)

PART II – NUC-3373
(1500 mg/m² - 2500 mg/m²)
IV infusion on days 1 & 15 of a 28-day cycle (Q2W)

Primary Endpoints: Establish NUC-3373 RP2D & schedule

Secondary Endpoints: Safety & tolerability, Anti-tumour activity, PK, PD and others

- Computed Tomography (CT)-based tumour assessments were performed at screening and after every 2 cycles until progression
- NUC-3373 treatment continued until unacceptable toxicity or progressive disease

RESULTS

Primary reasons for discontinuation	Part I, n (%) (n=46)	Part II, n (%) (n=16)
Progressive disease (RECIST v1.1)	29 (63)	15 (94)
AEs	7 (15)	0
Investigator decision	3 (7)	0
Withdrawal of consent (patient choice)	2 (4)	0
Unacceptable toxicity	1 (2)	0
Other	4 (9)	1 (6)

ITT population

- 62 patients: Part I (n=46); Part II (n=16)

Safety evaluable population

- 59 patients were dosed with NUC-3373
  Part I (n=43)
  Part II (n=16)
- Median age 59 years (range 20-77)

Tumour types

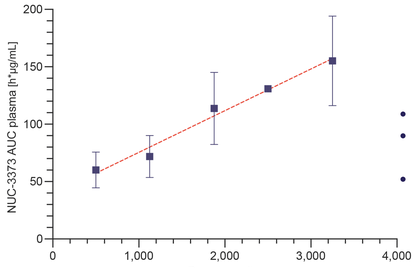
- CRC (28), Oesphago-gastric (6), Pancreatic (4), Cervical (2), Other (22)
- Median prior therapies 3 (range 0-11)

Safety

- NUC-3373 has an encouraging safety profile
- 10 patients experienced Grade 3 events related to NUC-3373 (Part I, n=8; Part II, n=2)
- No Grade 4 events were related to NUC-3373
- No NUC-3373 related deaths
- 4 Dose Limiting Toxicities (DLTs) in 4 patients
  - G3 transaminitis (n=2), 500 mg/m², 1875 mg/m²
  - G2 headache (n=1), 3250 mg/m²
  - G3 hypotension (n=1) 3250 mg/m²
- RP2D for NUC-3373 monotherapy was 2500 mg/m² given Q1W by ≤4 hour I.V. infusion

Safety event	Part I – Q1W, n (%) (n=43 patients)							RP2D		Part II – Q2W, n (%) (n=16 patients)		
	125 mg/m² (n=3)	250 mg/m² (n=6)	500 mg/m² (n=8)	750 mg/m² (n=4)	1125 mg/m² (n=3)	1500 mg/m² (n=3)	1875 mg/m² (n=6)	2500 mg/m² (n=6)	3250 mg/m² (n=4)	1500 mg/m² (n=4)	1875 mg/m² (n=6)	2500 mg/m² (n=6)
SAE	0	3	4	2	1	0	2	**1**	2	3	1	3
Any AE (inc. SAEs)	3	6	8	4	3	3	6	**6**	4	4	6	6
G3/4 AEs	0	3	2	2	3	0	3	**4**	2	3	1	4
Treatment Related AE (any grade)	3	5	7	4	3	3	6	**5**	4	4	5	4
Treatment Related AE (Grade ≥3)	0	0	1	0	2	0	2	**1**	2	1	1	0
AE/SAEs requiring treatment discontinuation	0	3	2	0	0	0	0	**0**	2	0	0	0
DLTs			1				1		2			

Pharmacokinetics



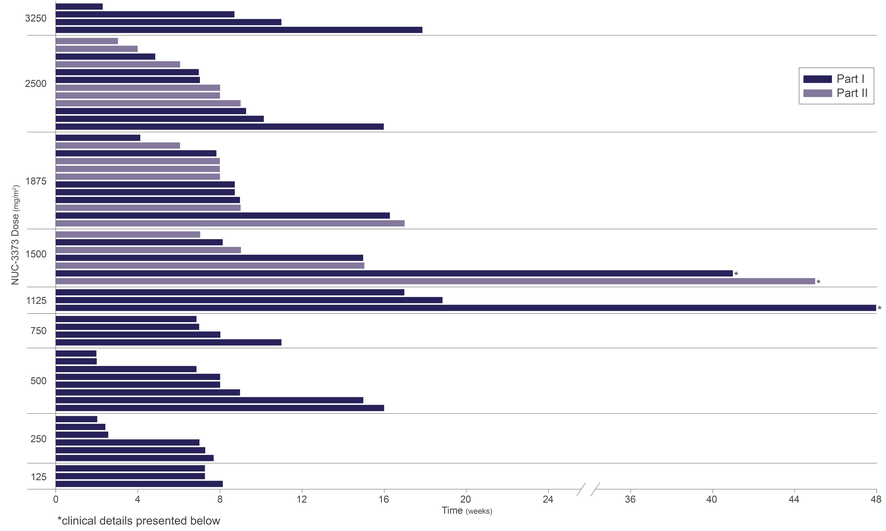
Patients (n=19) dosed at 500 - 3250mg/m²

Dose proportional increase of NUC-3373 AUC with dose

- Dose proportional increase in NUC-3373 C_{max} and AUC
- Long plasma half-life (6-14 hours)[10] compared to 5-FU (8-14 mins)
- Intracellular FUDR-MP levels increase in a dose proportional manner and are substantially higher (~300 times) compared to those reported for 5-FU[11]

Efficacy

- Clinical responses were observed with best response of durable stable disease (SD)
  - Part I: SD, n=12 (26%) • Part II: SD, n=3 (19%)
- 3 patients achieved prolonged SD (≥9 months)*



*clinical details presented below

Patient case studies

Colorectal Cancer

70 years, male
6 previous lines of therapy
1) 5-FU based chemoradiotherapy (adjuvant)
2) FOLFIRI: for metastatic disease
3) CAPOX: progressed within 2 months
4) FOLFIRI: progressed within 8 months
5) LONSURF: progressed within 3 months
6) Irinotecan: treatment for 1 month

NUC-3373: Stable Disease
PFS: 9 months
Dose: 1500 mg/m² Q1W

Basal Cell Carcinoma

55 years, male
2 previous lines of therapy
1) Vismodegib: treatment for 11 months
2) Paclitaxel + carboplatin: treatment for 3 months

NUC-3373: Stable Disease
PFS: 10 months
Dose: 1500 mg/m² Q2W

Cholangiocarcinoma

60 years, female
1 previous line of therapy
1) Cisplatin + gemcitabine: progressed within 6 months

NUC-3373: Stable Disease
PFS: 11 months
Dose: 1125 mg/m² Q1W

CONCLUSIONS

- **NUC-3373 is a TS inhibitor designed to overcome key cancer resistance mechanisms associated with 5-FU**
- **NUC-3373 is efficiently converted into active anti-cancer metabolite (FUDR-MP)**
- **NUC-3373 shows a favourable safety profile with encouraging signs of anti-cancer activity; including in 5-FU pre-treated patients**
- **Recommended Phase 2 Dose of NUC-3373 monotherapy is 2500mg/m² Q1W**
- **NUC-3373 is currently being investigated in combination with agents commonly used in CRC (NuTide:302 Phase Ib/II; NCT03428958)**

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ABBREVIATIONS: 5-FU: 5-fluorouracil. AE: adverse event. AUC: area under curve C_{max}: maximum concentration CRC: colorectal cancer. CT: computed tomography DAMPs: damage-associated molecular patterns DPFU: 5,6-dihydro-5-fluorouracil DLT: dose limiting toxicity DNA: deoxyribonucleic acid DPD: dihydropyrimidine dehydrogenase. dTMP: deoxythymidine monophosphate dUMP: deoxyuridine monophosphate ECOG PS: eastern cooperative oncology group performance status ER: endoplasmic reticulum FBAL: α-fluoro-β-alanine FUDP: fluorouridine diphosphate FUDR: fluorodeoxyuridine FUDR-DP: fluorodeoxyuridine diphosphate FUDR-MP: fluorodeoxyuridine monophosphate FUDR-TP: fluorodeoxyuridine triphosphate FUMP: fluorouridine monophosphate. FUR: fluorouridine. FUTP: fluorouridine triphosphate IV: intravenous infusion LVEF: left ventricular ejection fraction OPRT: orotate phosphoribosyl transferase Q1W: weekly dosing. Q2W: alternate weekly dosing. PD: progressive disease PFS: progression free survival PK: pharmacokinetics RNA: ribonucleic acid RP2D: recommended phase 2 dose RR: ribonucleotide reductase SAE: serious adverse event SD: stable disease. TK: thymidine kinase TP: thymidine phosphorylase. TS: thymidylate synthase UK: uridine kinase. UP: uridine phosphorylase

The first author has no conflicts of interest to declare

Data cleaning ongoing, data cut off 17 Aug 2021

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