A Phase Ib study of NUC-3373, a targeted inhibitor of thymidylate synthase, in combination with standard therapies in patients with advanced colorectal cancer (NuTide:302)

Jordan Berlin[1], Andrew L. Coveler[2], Kristen K Ciombor[1], Farasat Kazmi[3], Janet S Graham[4], Mary Linton Peters[5], Jeffrey W Clark[6], Michelle Myers[7], Aimery de Gramont[8], T.R. Jeffry Evans[4], Sarah P Blagden[3]

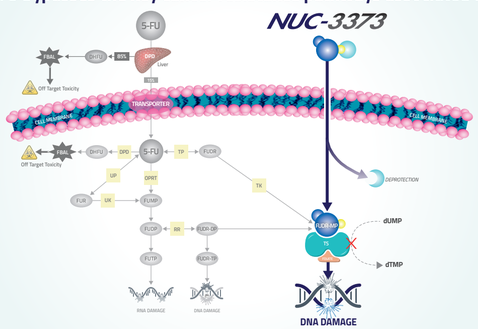
1) Vanderbilt University Medical Center, Nashville, TN, USA
2) Seattle Cancer Care Alliance/University of Washington, Seattle, WA, US
3) Early Phase Clinical Trials Unit, Churchill Hospital, University of Oxford, Oxford, UK
4) Beatson West of Scotland Cancer Centre/University of Glasgow, Glasgow, UK
5) Beth Israel Deaconess Medical Center, Boston, MA, US
6) Massachusetts General Hospital, Boston, MA, US
7) NuCana plc, Edinburgh, UK
8) Franco-British Institute, Levallois-Perret, France

No: 475P
NCT No: NCT03428958
EudraCT Number: 2017-002062-53
Email: michellemyers@nucana.com

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 (NUC-3373 monotherapy)

- Phase I first-in-human, dose-escalation study in patients with advanced solid tumors
  - MTD established (2,500 mg/m²)
  - Well-tolerated and encouraging signs of activity

NuTide:302 study

Originally designed to investigate NUC-3373 based combinations in heavily pre-treated CRC patients

Part I

Assessed NUC-3373 ± leucovorin (LV) Q1W & Q2W

NUC-3373 IV infusion: 1500 mg/m² given over 2 hours; 2500 mg/m² given over 4 hours

Part II

To investigate increasing doses of NUC-3373 + LV Q1W in combination with either oxaliplatin (NUFOX) or irinotecan (NUFIRI)

- Active and recruiting

Part III

Designed to establish optimal combinations of NUFOX/NUFIRI with VEGF and EGFR pathway inhibitors

RESULTS (Part I)

- 38 patients; age 33-75 (median; 58)
- Heavily pre-treated; median 4 prior lines (range 2-13)

Favorable safety profile in heavily pre-treated population

	NUC-3373 (n=38)*		5-FU IV (n=143)[10]		5-FU Bolus (n=593)[11]		Capecitabine (n=596)[11]	
Category	All Grades (%)	G3 or G4 (%)	All Grades (%)	G3 or G4 (%)	All Grades (%)	G3 or G4 (%)	All Grades (%)	G3 or G4 (%)
Neutropenia	**0**	**0**	48	13	46	21	13	3
Anemia	18	5	91	2	79	2	80	3
Diarrhea	**32**	**0**	45	6	61	12	55	15
Nausea	45	5	55	4	51	4	43	4
Vomiting	42	0	32	3	30	5	27	5
Mucositis/Stomatitis	**11**	**0**	29	3	62	15	25	3
Hand-foot syndrome	**0**	**0**	13	1	6	1	54	17
Dermatitis	11	0	20	0	26	1	27	1
Fatigue/asthenia	47	5	48	4	46	4	42	4
Elevated bilirubin	11	5	36	11	17	6	48	23
	Heavily pre-treated patients NUC-3373 ± LV Q1W or Q2W		First-line patients 5-FU/LV infusional days 1&2, Q2W		First-line patients 5-FU/LV bolus days 1-5, Q4W		First-line patients Capecitabine BID, 2wks on, 1wk off	

- Grade 4 treatment-related AE (1x elevated bilirubin)
- Grade 3 treatment-related AEs (2x elevated ALT, 2x elevated ALP, 2x nausea, 2x anemia, 1x elevated AST, 1x hyponatremia, 1x fever, 1x fatigue)
- No FBAL (hand-foot syndrome) or FUTP[12] (neutropenia or diarrhea) associated Grade 3 or 4 AEs
- LV did not affect the safety or PK profile of NUC-3373

* NUC-3373 All-cause adverse events, selected relevant to comparator data

Encouraging efficacy signals observed in heavily pre-treated CRC patients

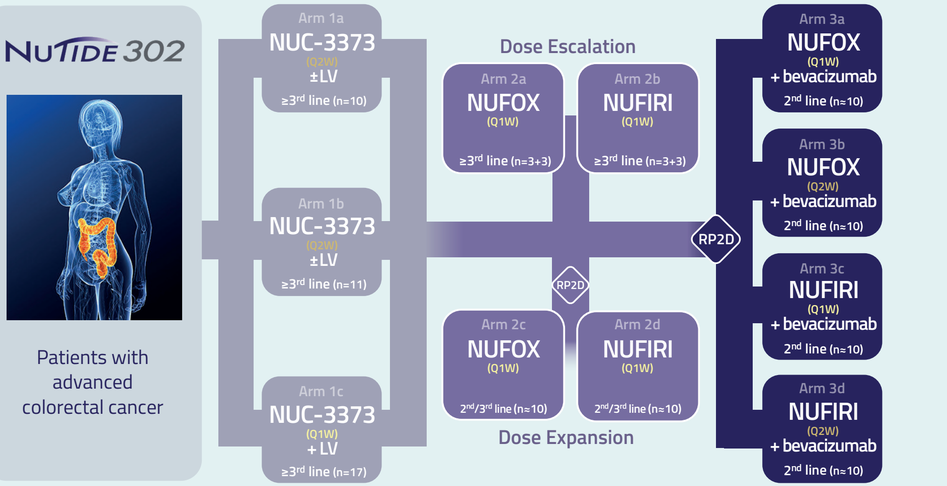
Selected case studies in patients who achieved ≥3 months on study

- 40% reduction in target lesion (adj. CAPOX 3 months; FOLFIRI 3 months; Lonsurf 3 months; NUC-3373 [-40%] 3.5 months)
- 28% reduction in overall tumor burden; fluoropyrimidine refractory patient (CAPOX [+35%] 2 months; FOLFIRI PD 1.5 months; NUC-3373 [-28%] 5.1 months)
- 15% reduction in overall tumor burden; heavily pretreated patient with BRAF mutation (5 prior lines)

NuTide:302 amendment

- Based on encouraging safety, PK and efficacy signals in heavily pre-treated patients (Part I), protocol was expanded
- Inclusion of less heavily pre-treated patient population
  - Second-line patients
- Updated from Phase Ib to Phase Ib/II
- Protocol amendment approved in USA, UK and France

Expanded Phase Ib/II study design



NUFOX (Q1W) = NUC-3373 + LV Q1W + oxaliplatin Q2W
NUFOX (Q2W) = NUC-3373 + LV Q2W + oxaliplatin Q2W
NUFIRI (Q1W) = NUC-3373 + LV Q1W + irinotecan Q2W
NUFIRI (Q2W) = NUC-3373 + LV Q2W + irinotecan Q2W

Additional cohorts may be opened.

Current study status

- Part I recruitment complete
- Part II (Arms 2a & 2b) ongoing

CONCLUSION

- NUC-3373 is a targeted TS inhibitor designed to overcome the key cancer resistance mechanisms associated with 5-FU
- NUC-3373 has the potential to offer enhanced efficacy, an improved safety profile and a more convenient dosing regimen compared to 5-FU
- NuTide:302 has been expanded to a Phase Ib/II study and allows enrollment of second-line CRC patients
- A registrational study of NUC-3373 for the second-line treatment of patients with CRC is planned (NuTide:323)

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ABBREVIATIONS: 5-FU: 5-fluorouracil AE: adverse event ALT: alanine aminotransferase ALP: alkaline phosphatase AST: aspartate aminotransferase BRAF: B-Raf v-Raf murine sarcoma viral oncogene homolog B CAPOX: capecitabine/oxaliplatin CRC: colorectal cancer DAMPs: damage-associated molecular patterns DHFU: 5,6-dihydro-5-fluorouracil DNA: deoxyribonucleic acid DPD: dihydropyrimidine dehydrogenase dTMP: deoxythymidine monophosphate dUMP: deoxyuridine monophosphate ECOG PS: eastern cooperative oncology group performance status EGFR: endothelial growth factor receptor ER: endoplasmic reticulum FBAL: α-fluoro-β-alanine FOLFIRI: 5-FU / LV / irinotecan FOLFOX: 5-FU / LV / oxaliplatin 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 LV: leucovorin MTD: maximum tolerated dose NUFIRI: NUC-3373 / LV / irinotecan NUFOX: NUC-3373 / LV / oxaliplatin OPRT: orotate phosphoribosyl transferase Q1W: weekly dosing Q2W: alternate weekly dosing Q4W: dosed every 4 weeks PD: progressive disease PK: pharmacokinetics RAS: rat sarcoma gene RNA: ribonucleic acid RP2D: recommended phase 2 dose RR: ribonucleotide reductase SD: stable disease TK: thymidine kinase TP: thymidine phosphorylase TS: thymidylate synthase UK: uridine kinase UP: uridine phosphorylase VEGF: vascular endothelial growth factor

The first author has no conflicts of interest to declare

Data cleaning ongoing, data cut off 15 Apr 2021