NUC-3373, a ProTide transformation of 5-FU, in combination with oxaliplatin (NUFOX) or irinotecan (NUFIRI) in patients with advanced colorectal cancer (NuTide:302)

Andrew L Coveler[1], Aglaia Skolariki[2], Kristen K Ciombor[3], Hélène Marijon[4], Janet S Graham[5], Mary Linton Peters[6], Stacey A Cohen[1], Niharika B Mettu[7], Michelle Myers[8], Elisabeth Oelmann[8], Jeffrey D Bloss[8], Sarah P Blagden[2], Aimery de Gramont[4], Jordan Berlin[3], and TR Jeffry Evans[5]

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

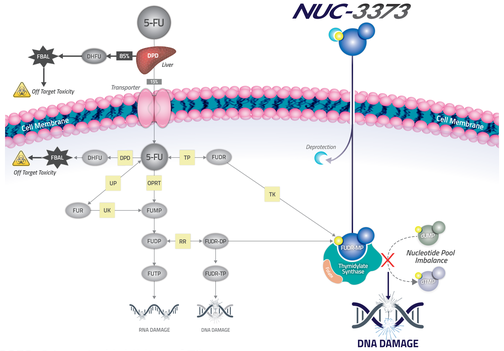
FPN Number: **354P**

Email: **acoveler@uw.edu**

Background

- CRC 3rd most common cancer ▪ Incidence: 1.9 million[1] ▪ Annual deaths: 935,000[1]
- 5-FU remains the cornerstone of treatment for CRC, despite several limitations
  - Rapidly degraded by DPD[2]
    - Short plasma half-life (8-14 mins)[3] necessitates prolonged (46-hour) infusions
    - Generation of FBAL (associated with hand-foot syndrome)
  - Generation of FUTP (associated with dose-limiting RNA toxicities; diarrhea, mucositis, myelosuppression)
  - Cell entry requires nucleoside transporters
  - Complex enzymatic activation

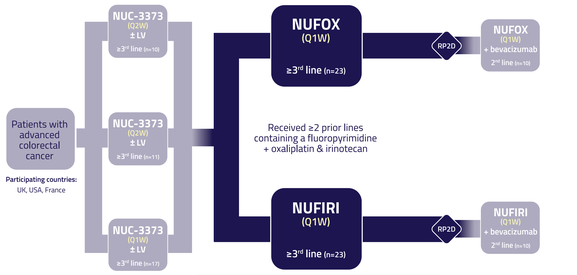
NUC-3373 overcomes key limitations associated with 5-FU



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[7]
  - Induces ER stress and DAMP release leading to immunogenic cell death[8,9]

NuTide:302 Study - Phase 1b/2



NUC-3373 minimum infusion durations;
1500 mg/m² -120 mins
1875 mg/m² -150 mins
2250 mg/m² -180 mins

Objectives:
NUC-3373 + LV RP2D in combination with oxaliplatin (NUFOX) or irinotecan (NUFIRI), safety, PK, anti-tumor activity

NUFOX NUFOX NUFOX NUFOX **NUFOX** NUFOX NUFOX NUFOX NUFOX

Baseline Characteristics (n=23)

Age, years	Median (range)	61 (40-75)
Gender	Male Female	11 (48%) 12 (52%)
ECOG PS	0 1	12 (52%) 11 (48%)
Metastatic Sites, n	1-3 ≥4	14 (61%) 9 (39%)
RECIST Target Lesions	Liver Lung Abdomen Lymph nodes Other	13 (57%) 13 (57%) 7 (30%) 5 (22%) 7 (30%)
KRAS Mutated*	Yes No	16 (70%) 6 (26%)
Prior Lines	Median (range)	3 (2-8)
Prior Lines, n	2 3 4 5+	7 (30%) 8 (35%) 3 (13%) 5 (22%)
Prior Bev Exposure	Yes No	11 (48%) 12 (52%)

*1 pt KRAS status unknown
All patients had received prior 5-FU, oxaliplatin & irinotecan

Safety Profile

NUC-3373 / oxaliplatin Dose (mg/m²)	1500 / 85 n=4		1875 / 85 n=10 MTD		2250 / 85 n=9		Total n=23	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Nausea	3 (75%)	0	5 (50%)	1 (10%)	5 (56%)	1 (11%)	13 (57%)	2 (9%)
Diarrhea	2 (50%)	0	4 (40%)	0	4 (44%)	0	10 (43%)	0
Vomiting	2 (50%)	0	4 (40%)	1 (10%)	4 (44%)	0	10 (43%)	1 (4%)
Stomatitis	0	0	1 (10%)	0	2 (22%)	0	3 (13%)	0
ALT increased	2 (50%)	2 (50%)	1 (10%)	0	2 (22%)	1 (11%)	5 (22%)	3 (13%)
AST increased	1 (25%)	0	2 (20%)	0	2 (22%)	0	5 (22%)	0
Appetite decreased	1 (25%)	0	3 (30%)	0	3 (33%)	0	7 (30%)	0
Hypokalemia	0	0	1 (10%)	1 (10%)	1 (11%)	0	2 (9%)	1 (4%)
Hyperuricemia	0	0	0	0	1 (11%)	1 (11%)	1 (4%)	1 (4%)
Anemia	0	0	1 (10%)	0	5 (56%)	0	6 (26%)	0
Thrombocytopenia	0	0	1 (10%)	1 (10%)	1 (11%)	0	2 (9%)	1 (4%)
Fatigue	3 (75%)	0	5 (50%)	0	5 (56%)	2 (22%)	13 (57%)	2 (9%)
Infusion-related reaction	1 (25%)	0	2 (20%)	0	1 (11%)	0	4 (17%)	0
Headache	1 (25%)	0	0	0	2 (22%)	0	3 (13%)	0
Feeling hot	2 (50%)	0	0	0	1 (11%)	0	3 (13%)	0
Chills	0	0	0	0	3 (33%)	1 (11%)	3 (13%)	1 (4%)
Pyrexia	0	0	0	0	1 (11%)	1 (11%)	1 (4%)	1 (4%)
Infection	0	0	0	0	1 (11%)	1 (11%)	1 (4%)	1 (4%)

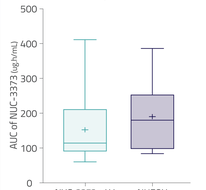
21 out of 23 patients experienced a TRAE

TRAEs reported are related to NUC-3373 or NUC-3373 & oxaliplatin; All grade TRAEs with incidence of ≥10% in any dose cohort; All grade 3 TRAEs reported

- No Grade 4 or 5 TRAEs
- Discontinuation rate due to adverse events was low (13%)
- MTD: NUC-3373 1875 mg/m² + LV 400 mg/m² + oxaliplatin 85 mg/m²
- DLTs in 3 patients
  - Grade 3 fatigue (2 pts at NUC-3373 2250 mg/m²) + oxaliplatin 85 mg/m²)
  - Grade 3 ALT increased / Grade 2 bilirubin increased (1 pt at NUC-3373 2250 mg/m² + oxaliplatin 85 mg/m²)

Pharmacokinetics

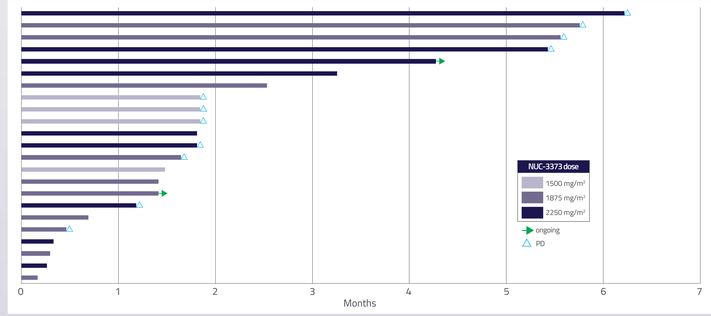
- Preliminary data indicate that oxaliplatin had no impact on NUC-3373 exposure



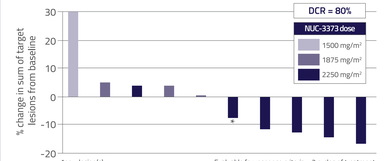
	NUC-3373 + LV n=17	NUFOX n=8
C_{max} (µg/mL)	39	38

NUC-3373 dose at 1500 mg/m², Data presented as min, max & median (25th-75th percentile), + =mean

Time on Treatment



Best Overall Response in Evaluable Patients



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Baseline Characteristics (n=23)

Age, years	Median (range)	56 (36-74)
Gender	Male Female	8 (35%) 15 (65%)
ECOG PS	0 1	12 (52%) 11 (48%)
Metastatic Sites, n	1-3 ≥4	12 (52%) 11 (48%)
RECIST Target Lesions	Liver Lung Abdomen Lymph nodes Other	17 (74%) 14 (61%) 5 (22%) 8 (35%) 9 (39%)
KRAS Mutated*	Yes No	17 (74%) 5 (22%)
Prior Lines	Median (range)	4 (2-10)
Prior Lines, n	2 3 4 5+	5 (22%) 3 (13%) 6 (26%) 9 (39%)
Prior Bev Exposure	Yes No	14 (61%) 9 (39%)

*1 pt KRAS status unknown
All patients had received prior 5-FU, oxaliplatin & irinotecan

Safety Profile

NUC-3373 / irinotecan Dose (mg/m²)	1500 / 120 n=4		1500 / 150 n=4		1500 / 180 n=9 MTD		1875 / 180 n=6		Total n=23	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Nausea	2 (50%)	0	2 (50%)	1 (25%)	4 (44%)	0	2 (33%)	0	10 (43%)	1 (4%)
Diarrhea	3 (75%)	0	1 (25%)	0	1 (11%)	0	2 (33%)	1 (17%)	7 (30%)	2 (9%)
Vomiting	2 (50%)	0	0	0	2 (22%)	0	2 (33%)	0	6 (26%)	0
Colitis	0	0	1 (25%)	0	0	0	1 (17%)	1 (17%)	2 (9%)	1 (4%)
ALT increased	2 (50%)	0	1 (25%)	0	2 (22%)	2 (22%)	0	0	5 (22%)	2 (9%)
AST increased	2 (50%)	0	0	0	1 (11%)	0	0	0	3 (13%)	0
ALP increased	0	0	0	0	1 (11%)	1 (11%)	0	0	1 (4%)	1 (4%)
Appetite decreased	1 (25%)	0	0	0	2 (22%)	0	2 (33%)	0	5 (22%)	0
Hypomagnesemia	0	0	1 (25%)	0	2 (22%)	0	0	0	3 (13%)	0
Anemia	0	0	2 (50%)	0	2 (22%)	0	1 (17%)	0	5 (22%)	0
Fatigue	1 (25%)	0	1 (25%)	0	3 (33%)	1 (11%)	2 (33%)	1 (17%)	7 (30%)	2 (9%)
Proteinuria	0	0	1 (25%)	1 (25%)	0	0	0	0	1 (4%)	1 (4%)

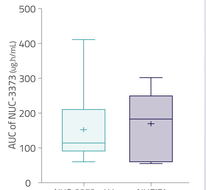
18 out of 23 patients experienced a TRAE

TRAEs reported are related to NUC-3373 or NUC-3373 & irinotecan; All grade TRAEs with incidence of ≥10% in any dose cohort; All grade 3 TRAEs reported

- No Grade 4 or 5 TRAEs
- Discontinuation rate due to adverse events was low (9%)
- MTD: NUC-3373 1500 mg/m² + LV 400 mg/m² + irinotecan 180 mg/m²
- DLTs in 3 patients
  - Grade 3 ALT/ALP increased (1 pt at NUC-3373 1500 mg/m² + irinotecan 180 mg/m²)
  - Grade 3 colitis (1 pt at NUC-3373 1875 mg/m² + irinotecan 180 mg/m²)
  - Grade 3 fatigue (1 pt at NUC-3373 1875 mg/m² + irinotecan 180 mg/m²)

Pharmacokinetics

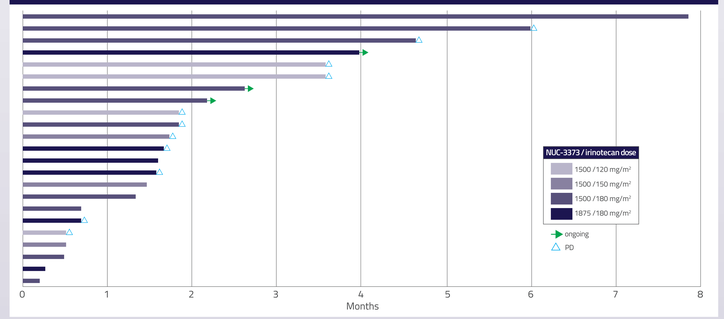
- Preliminary data indicate that irinotecan had no impact on NUC-3373 exposure



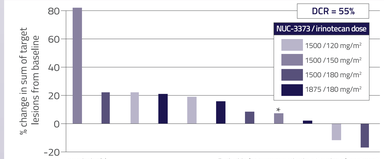
	NUC-3373 + LV n=17	NUFIRI n=11
C_{max} (µg/mL)	39	32

NUC-3373 dose at 1500 mg/m², Data presented as min, max & median (25th-75th percentile), + =mean

Time on Treatment



Best Overall Response in Evaluable Patients



Conclusions & Future Plans

- NUFOX & NUFIRI have favorable safety profiles compared to FOLFOX[10] & FOLFIRI[11] historical data
- RP2D for NUC-3373
  - NUFOX: NUC-3373 1875 mg/m² + LV 400 mg/m² + oxaliplatin 85 mg/m²
  - NUFIRI: NUC-3373 1500 mg/m² + LV 400 mg/m² + irinotecan 180 mg/m²
- NUC-3373 PK profile unchanged by oxaliplatin or irinotecan
- NUC-3373 has a convenient dosing schedule
- Encouraging signs of anti-tumor activity in heavily pretreated patients who have received prior 5-FU, oxaliplatin and irinotecan
  - Prolonged SD: NUFOX - 6 patients >3 months; NUFIRI - 6 patients >3 months
- **Future Plans**
  - Randomized Phase 2 Study (NuTide:323) NUFIRI-bev vs FOLFIRI-bev in second-line CRC initiated

REFERENCES: 1. World Health Organization International Agency for Research on Cancer (IARC). GLOBOCAN 2020. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf 2. Diasio RB & Harris BE 1999 *Clin Pharmacokinet.* 16:215–237 3. Heggie GD *et al.*, 1987 *Cancer Research;* 47:2203–2206 4. McGuigan C *et al.*, 2011 *Med Chem;* 27:7247–7258 5. Vande Voorde J *et al.*, 2011 *Biochem Pharmacol;* 82:441–452 6. Ghazaly E *et al.*, 2017 *Ann Oncol.* Suppl_5:218 7. Bre J *et al.*, 2022 *Cancer Res;* 82: Suppl_12:1835 8. McKissock FG *et al.*, 2020 *Cancer Res;* 80: Suppl_16:1848 9. Read OJ *et al.*, 2022 *Cancer Res;* 82: Suppl_12:1113 10. Eloxatin prescribing information 11. Camptosar prescribing information

ABBREVIATIONS: 5-FU: 5-fluorouracil ALP: alkaline phosphatase ALT: alanine aminotransferase AST: aspartate aminotransferase AUC: area under the curve C_{max}: maximal concentration CRC: colorectal cancer DAMP: damage-associated molecular pattern DCR: disease control rate DHFU: dihydrofluorouracil DLT: dose-limiting toxicity DNA: deoxyribonucleic acid DPD: dihydropyrimidine dehydrogenase ECOG PS: Eastern Cooperative Oncology Group performance score ER: endoplasmic reticulum FBAL: alpha-fluoro-beta-alanine FOLFIRI: 5-FU + leucovorin + irinotecan FOLFOX: 5-FU + leucovorin + oxaliplatin FUDP: fluorouridine diphosphate FUDR: fluorodeoxyuridine FUDR-DP: fluorodeoxyuridine diphosphate FUDR-MP: fluorodeoxyuridine monophosphate FUDR-TP: fluorodeoxyuridine triphosphate FUTP: fluorouracil triphosphate KRAS: Kirsten rat sarcoma virus LV: leucovorin MTD: maximum tolerated dose NUFIRI: NUC-3373 + leucovorin + irinotecan NUFOX: NUC-3373 + leucovorin + oxaliplatin OPRT: orotate phosphoribosyl transferase PD: progressive disease RECIST: response evaluation in solid tumors RP2D: recommended phase 2 dose RR: ribonucleotide reductase SD: stable disease TK: thymidine kinase TP: thymidine phosphorylase TRAE: treatment-related adverse event TS: thymidylate synthase UK: uridine kinase UP: uridine phosphorylase