NuTide:302 A Phase Ib study of NUC-3373 in combination with standard therapies in advanced/metastatic colorectal cancer

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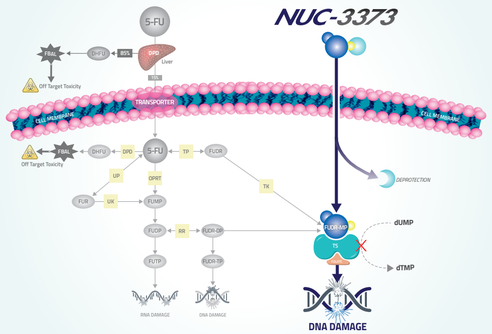
BACKGROUND

- CRC 3rd most common cancer ▪ Incidence: 1.8 million ▪ 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 (associated with hand-foot syndrome)
  - Cell entry requires nucleoside transporters
  - Complex enzymatic activation

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



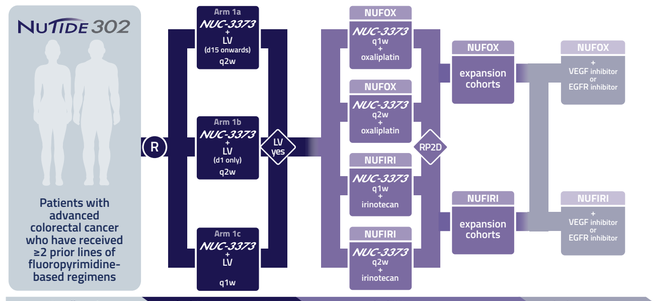
NUC-3373: A targeted inhibitor of TS

- 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
  - Does not require TK or TP for activation
  - Low levels of toxic metabolites (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:
  - RP2D established (2,500 mg/m²)
  - Well-tolerated and encouraging signs of activity

NuTide:302 Study



Primary endpoint:
- RP2D

Secondary endpoints:
- Safety ▪ Anti-tumor activity ▪ PK

RESULTS (Part 1 interim)

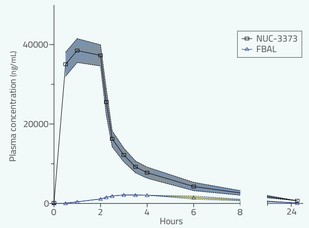
- 37 patients (Arm 1a=10; Arm1b=11; Arm 1c (1500)=11; Arm 1c (2500)=5)
- Median age: 58 years (range 33-75)
- Median prior lines of therapy: 4 (range 2-13)

NUC-3373 has a favorable safety profile

Category	NUC-3373 (n=37)		5-FU IV[10] (n=143)		5-FU Bolus[11] (n=593)		Capecitabine[11] (n=596)	
	All Grades (%)	G3 or G4 (%)	All Grades (%)	G3 or G4 (%)	All Grades (%)	G3 or G4 (%)	All Grades (%)	G3 or G4 (%)
Diarrhea	**30**	**0**	**45**	**6**	**61**	**12**	**55**	**15**
Nausea	46	3	55	4	51	4	43	4
Vomiting	38	0	32	3	30	5	27	5
Mucositis/Stomatitis	**8**	**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/lethargy	54	3	NR	NR	46	4	42	4
Anemia	24	5	91	2	79	2	80	3
Neutropenia	**0**	**0**	**48**	**13**	**46**	**21**	**13**	**3**
Elevated bilirubin	5	5	36	11	17	6	48	23
	Heavily pre-treated patients (median 4 prior lines) 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	

- NUC-3373 is well-tolerated at 1500 mg/m² and 2500 mg/m²
- 1 patient had 1 Grade 4 treatment-related AE (elevated bilirubin)
- 10 patients had Grade 3 treatment-related AEs (2 x elevated ALT, 1 elevated AST, 1 elevated alkaline phosphate, 1 elevated bilirubin, 1 anemia, 1 hyponatremia, 1 fever, 1 nausea, 1 fatigue)
- FUTP, the primary cause of 5-FU toxicity and a dose-limiting factor,[12] has not been detected in PBMCs from NUC-3373 treated patients (assay limit of detection: 0.001 pmol per 10^6 cells)
- FUTP detected in PBMCs from patients treated with 5-FU[13] (1.0-3.0 pmol per 10^6 cells) and capecitabine[13] (0.086 pmol per 10^6 cells)

NUC-3373 has a favorable PK profile, is efficiently converted in FUDR-MP and generates high intracellular levels

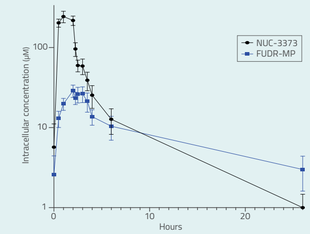


NUC-3373 plasma

- Long plasma half-life compared to 5-FU:
  - NUC-3373: 6-14 hours*
  - 5-FU: 8-14 minutes
- Large volume of distribution compared to 5-FU indicating extensive tissue absorption (190 L vs 17 L[14])
- Generates low plasma concentrations of FBAL
- Dose proportional increase in NUC-3373 C_{max} and AUC

(Mean; 95% CI) (n=17, 1500 mg/m²)

*NuTide:301 & NuTide:302; with ≥24 hour sampling

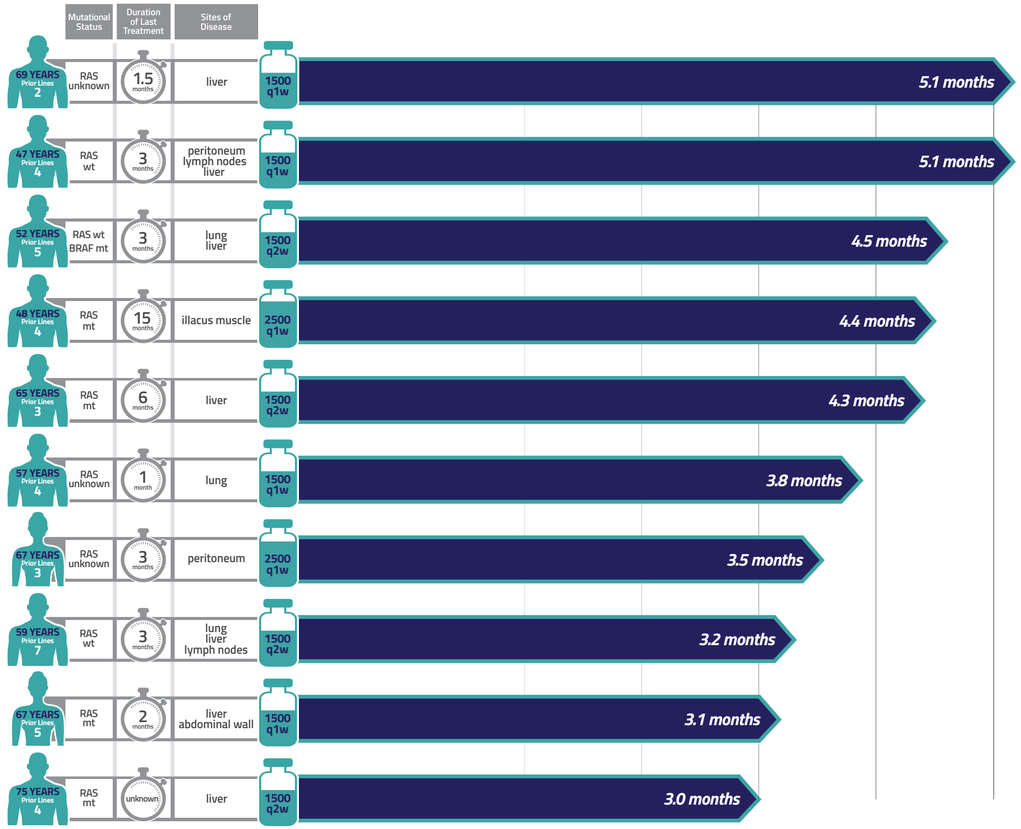


NUC-3373 intracellular metabolite (FUDR-MP)

- High intracellular levels of FUDR-MP compared to 5-FU (31 µM vs 0.1 µM[15])
- Long intracellular half-life of FUDR-MP (12-20 hours)
- Direct correlation between plasma NUC-3373 AUC and intracellular (PBMC) FUDR-MP AUC
- Intracellular FUDR-MP levels increase dose proportionally

(Mean; 95% CI) (n=17, 1500 mg/m²)

PATIENT CASE STUDIES



- Encouraging signals of efficacy in heavily pre-treated patients that had progressed on prior fluoropyrimidines
- Five patients experienced tumor shrinkage, including:
  - **40% reduction Partial Response*** (CAPOX: 3 months. FOLFIRI: 3 months. Lonsurf: 3 months. **NUC-3373:** PR -40%; 3.5 months)
  - **28% reduction in a fluoropyrimidine refractory patient** (CAPOX: PD +35% in 2 months. FOLFIRI: PD in 1.5 months. **NUC-3373:** SD -28%; 5.1 months)
- DCR of 62% (SD lasting ≥8 weeks) in the efficacy evaluable population (26 patients with post-baseline tumor assessments)

*confirmatory scan not performed (as per protocol)

CONCLUSION

- NUC-3373 is a targeted inhibitor of TS designed to overcome the key cancer resistance mechanisms associated with 5-FU
- NUC-3373 has favorable safety profile with no FBAL (hand-foot syndrome) or FUTP (GI or hematologic toxicity) associated Grade 3 or 4 AEs
- NUC-3373 has an attractive PK profile: long plasma half-life and high intracellular levels of FUDR-MP (active metabolite) compared to 5-FU
- Encouraging efficacy signals observed in heavily pre-treated CRC patients with NUC-3373 (including one patient with a PR)
- NUC-3373 has the potential to offer enhanced efficacy, an improved safety profile and a more convenient dosing regimen compared to 5-FU
- NUC-3373 is currently being investigated in combination with LV, oxaliplatin or irinotecan in Part 2 of NuTide:302
- A registrational study of NUC-3373 in 2L CRC patients (NuTide:323) is planned

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ABBREVIATIONS: 5-FU: 5-fluorouracil ALP: alkaline phosphatase ALT: alanine aminotransferase AE: adverse event AUC: area under the curve BRAF: B-Raf/v-Raf murine sarcoma viral oncogene homolog B CAPOX: capecitabine/oxaliplatin C_{max}: maximum concentration CRC: colorectal cancer CV: coefficient of variation DAMPs: damage-associated molecular patterns DHFU: 5,6-dihydro-5-fluorouracil DPD: dihydropyrimidine dehydrogenase dTMP: deoxythymidine monophosphate dUMP: deoxyuridine monophosphate 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: mean tolerated dose NUFIRI: NUC-3373 / LV / irinotecan NUFOX: NUC-3373 / LV / oxaliplatin OPRT: orotate phosphoribosyl transferase q1w: weekly dosing q2w: alternate weekly dosing RAS: rat sarcoma gene RP2D: recommended phase 2 dose RR: ribonucleotide reductase TK: thymidine kinase TP: thymidine phosphorylase TS: thymidylate synthase UK: uridine kinase UP: uridine phosphorylase VEGF: vascular endothelial growth factor

Data cleaning ongoing, data cut off 26 November 2020