NUC-3373, a targeted inhibitor of thymidylate synthase, in patients with advanced colorectal cancer

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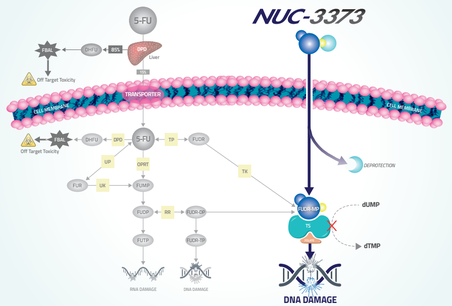
BACKGROUND

- 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



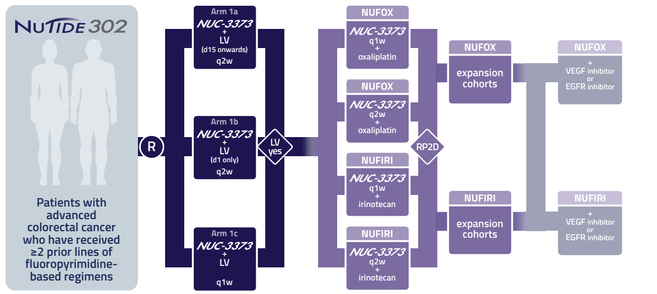
NUC-3373: A targeted inhibitor of TS

- 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 (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



Primary endpoint:
- RP2D

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

- Heavily pre-treated patient population: 4 prior lines of therapy (range: 2-13)
- Hard to treat patients with limited options

RESULTS (Part 1)

Patient characteristics (n=38)

Male, n (%)	21 (55)
Female, n (%)	17 (45)
ECOG (0/1)	19/19
Age, years, median (range)	58 (33-75)
Prior lines of therapy, median (range)	4 (2-13)
No of metastatic sites, median (range)	2 (1-6)
Liver involvement, n (%)	28 (74)
Prior chemotherapy	
5-FU, n (%)	38 (100)
Oxaliplatin, n (%)	38 (100)
Irinotecan, n (%)	38 (100)
Prior anti-angiogenic, n (%)	22 (58)
Prior EGFR inhibitor, n (%)	19 (50)

NUC-3373 has a favorable safety profile

	Possibly / probably-related to NUC-3373	
Preferred Term	All grades n (%)	Grade 3-4 n (%)
Nausea	16 (42)	2 (5)
Fatigue	13 (34)	1 (3)
Vomiting	13 (34)	0
Diarrhea	12 (32)	0
Infusion-related reaction	6 (16)	0
Feeling hot	5 (13)	0
Flushing	5 (13)	0
Anemia	3 (8)	1 (3)
Bilirubin increased	3 (8)	2 (5)
ALT increased	3 (8)	2 (5)
Abdominal pain	2 (5)	0
Decreased appetite	2 (5)	0
Pyrexia	2 (5)	1 (3)
Tachycardia	2 (5)	0
Rash	2 (5)	0
ALP increased	2 (5)	2 (5)
Hyponatremia	1 (3)	1 (3)
AST increased	1 (3)	1 (3)

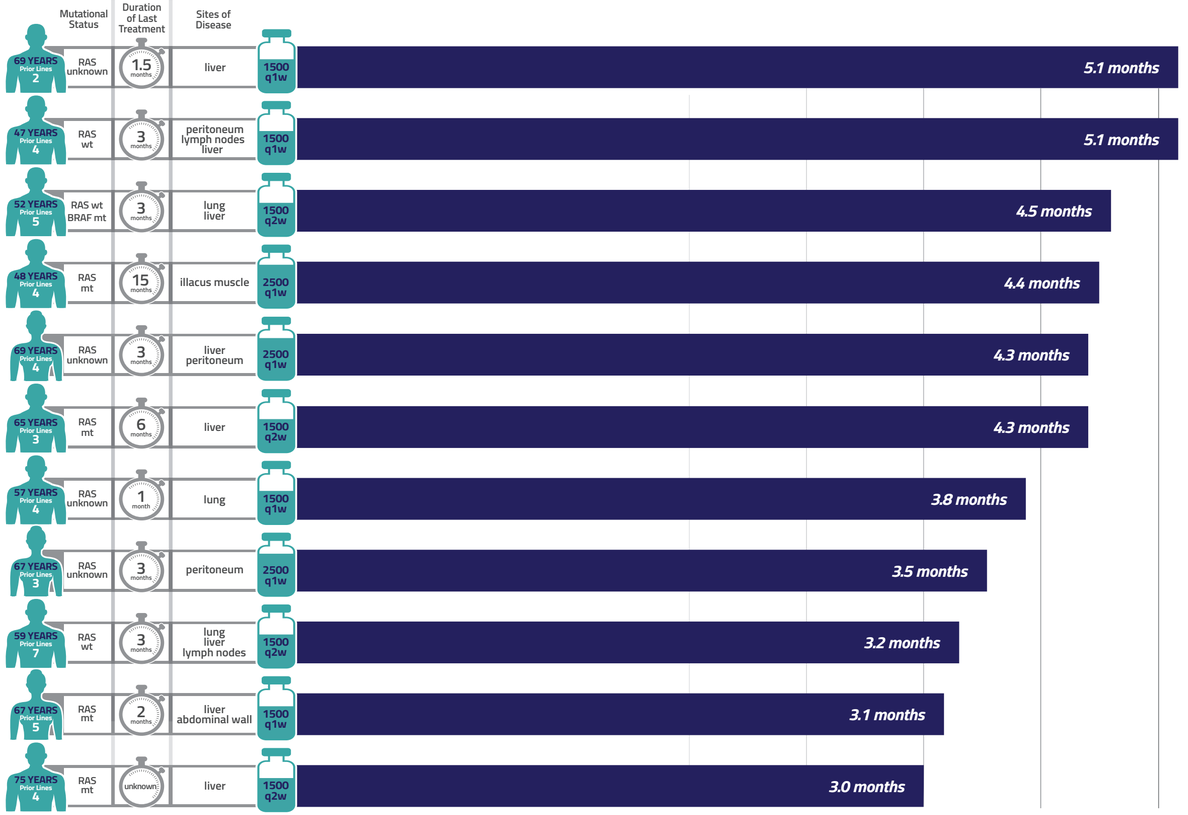
NUC-3373 related AE events occurring in ≥5% patients or grade 3-4 in any patient

- 7 patients experienced G3 events related to NUC-3373 and 1 patient experienced G4 event (bilirubin increased) related to NUC-3373

Encouraging safety profile in heavily pre-treated population (median 4 prior lines)

- A lower incidence of NUC-3373 related G3 and G4 events have been reported with the overall AE profile comparable to previously reported placebo arms in late line CRC studies[10, 11]
- 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)
- FBAL levels were low and clinically insignificant with no hand-foot syndrome

PATIENT CASE STUDIES



- Encouraging signs of anti-tumor activity with reductions in overall tumor burden in 3 patients
  - **40% reduction in target lesion** (adj. CAPOX: 3 months. FOLFIRI: 3 months. Lonsurf: 3 months. NUC-3373: -40%; 3.5 months)
  - **28% reduction in fluoropyrimidine refractory patient** (CAPOX: PD +35% in 2 months. FOLFIRI: PD in 1.5 months. NUC-3373: -28%; 5.1 months)
  - **15% reduction in heavily pretreated patient with BRAF mutation** (5 prior lines)
- DCR of 62% (SD lasting >8 weeks) in efficacy evaluable population (26 patients with post-baseline tumor assessments)

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
- 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 and either 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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Data cleaning ongoing, data cut off 01 March 2021

ABBREVIATIONS: 5-FU: 5-fluorouracil AE: adverse event ALT: alanine aminotransferase ALP: alkaline phosphatase AUC: area under the curve AST: aspartate aminotransferase 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 DCR: disease control rate DHFU: 5,6-dihydro-5-fluorouracil 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 PR: partial response PD: progressive disease RAS: rat sarcoma gene 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