NuTide:302 Pharmacokinetic analysis of NUC-3373 with and without leucovorin in patients with previously treated metastatic colorectal cancer

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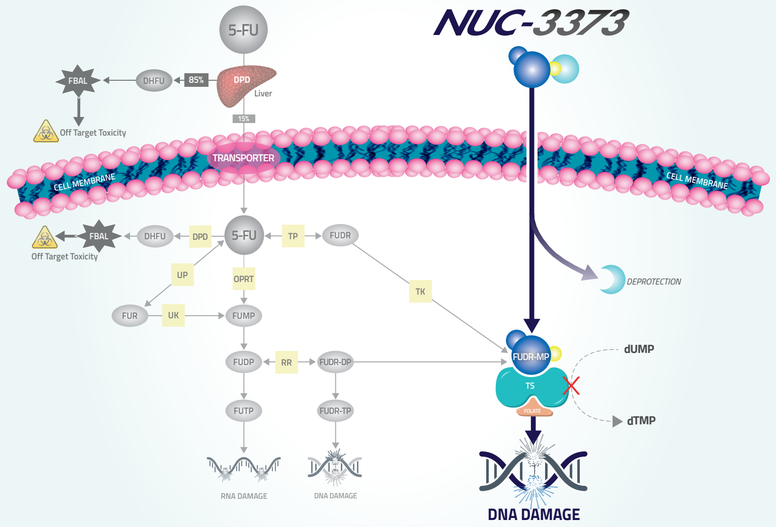
BACKGROUND

- CRC is the third most commonly diagnosed cancer, with a global incidence of 1.8 million cases and 880,000 deaths in 2018[1]
- 5-FU remains the cornerstone of treatment for patients with CRC, however it has 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; including TP-TK pathway

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



NUC-3373: A targeted inhibitor of TS

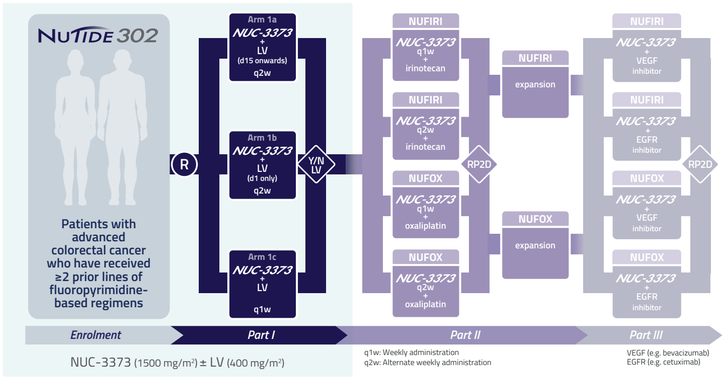
- ProTide transformation of FUDR-MP[4,5], the active anti-cancer metabolite of 5-FU, that is:
  - Resistant to breakdown by DPD
  - Able to enter cells independently of nucleoside transporters
  - Does not require TK or TP for activation
- Generates high levels of FUDR-MP[6], which binds to TS:
  - Causing an imbalance in the nucleotide pool (dUMP: dTMP) leading to DNA damage and cell death
  - Induces ER stress and DAMP release[7-9]

NuTide:301 study (NUC-3373 monotherapy)

- Phase I first-in-human, dose-escalation study in patients with advanced solid tumours:
  - Dose-escalation ongoing (current dose 3,250 mg/m^2)
  - Encouraging early signs of activity reported
  - Well-tolerated (MTD not yet reached)

METHODS

NuTide:302 Study Design



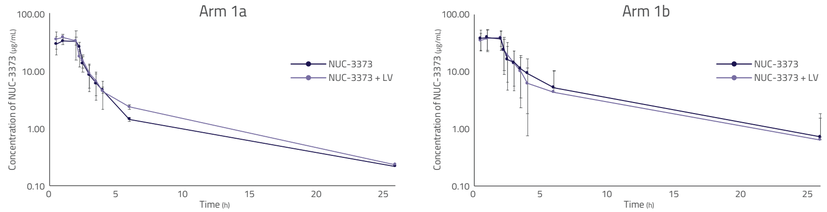
Primary endpoint:
- RP2D

Secondary endpoints:
- Safety and tolerability
- Anti-tumour activity
- PK

RESULTS (Part 1 interim)

- 32 patients; age 33-75 years (median: 58)
- Heavily pre-treated with a median of 4.5 prior lines of therapy (range 2-11)

NUC-3373's favourable PK parameters unchanged by LV



Parameter	NUC-3373 Mean (%CV)	NUC-3373 + LV Mean (%CV)
C_{max} (µg/ml)	39.6 (37)	42.1 (32)
AUC (0-t)(µg-h/ml)	135.0 (77)	149.0 (68)
Elimination half-life (hours)	5.0 (26)	5.1 (25)
Volume of distribution (L)	193.0 (41)	174.0 (45)
Clearance (L/hour)	30.9 (49)	27.0 (49)

PK matched profiles from q2w dosed patients (Arms 1a & 1b, n=16)

NUC-3373 has a favourable safety profile that is not affected by LV

- 1 patient had a Grade 4 treatment related AE (bilirubin elevation)
- 3 patients had Grade 3 treatment related AEs - all, except fatigue, were confounded by disease-related low grade events at baseline (1 hyponatremia; 1 fatigue; 1 nausea, 1 fever, 1 elevated ALT, 1 elevated ALP)
- No patients experienced hand-foot syndrome, cardiotoxicity or neurotoxicity

PATIENT CASE STUDIES

Metastatic Colorectal Cancer

Encouraging tumour shrinkage and stable disease observed in heavily pre-treated patients (≥ 2 prior lines of therapy) refractory to or relapsed on prior fluoropyrimidines

RAS unknown
2 PRIOR LINES
CAPOX progressed within 2 months tumour increase of 35%
FOLFIRI progressed within 1.5 months
Target Lesions: 2 (both liver)
STUDY TREATMENT
NUC-3373 (1500 mg/m² q1w; Arm 1c)
28% reduction in target lesions
Stable Disease: 5 Months*
*patient missed 6 consecutive doses due to COVID-19 and progressed, but continued on study for a total of 8 months due to clinical benefit
69 years, Male

BRAF D594G mutant (RAS wildtype)
5 PRIOR LINES
FOLFOX (adjuvant) for 4 months, Relapsed 4 months post-adjuvant therapy
FOLFIRI progressed within 6 months
Irinotecan + panitumumab progressed within 6 months
Irinotecan + panitumumab + telaglenastat progressed within 6 months
Nivolumab + enadenotucirev (oncolytic virus) progressed within 3 months
Target Lesions: 3 (2 lung;1 liver)
STUDY TREATMENT
NUC-3373 (1500 mg/m² q2w; Arm 1b)
15% reduction in target lesions
Stable Disease: 5 Months
52 years, Male

RAS unknown
4 PRIOR LINES
CAPOX (neoadjuvant/adjuvant) for 6 months, Relapsed 2 months post-adjuvant therapy
FOLFIRI progressed within 3 months
Lonsurf progressed within 2 months
RXC004 (Wnt inhibitor) progressed within 1 month
Target Lesions: 3 (all lung)
STUDY TREATMENT
NUC-3373 (1500 mg/m² q1w; Arm 1c)
Stable Disease: 4 Months
57 years, Male

RAS mutant
3 PRIOR LINES
CAPOX (adjuvant) for 6 months, Relapsed 4 years post-adjuvant therapy
FOLFIRI progressed within 6 months
FOLFOX progressed within 6 months
Target Lesions: 2 (both liver)
STUDY TREATMENT
NUC-3373 (1500 mg/m² q2w; Arm 1b)
Stable Disease: 4 Months
65 years, Male

RAS wildtype
5 PRIOR LINES
Capecitabine/CAPOX (adjuvant) for 7 months, Relapsed 6 years post-adjuvant therapy
FOLFIRI + bevacizumab for 3 months, Treatment holiday for 6 months
FOLFIRI + bevacizumab progressed after 5 months
Panitumumab progressed within 2 months
Irinotecan + panitumumab + telaglenastat progressed within 3 months
Target Lesions: 4 (2 lung; 1 liver; 1 lymph node)
STUDY TREATMENT
NUC-3373 (1500 mg/m² q2w; Arm 1b)
Stable Disease: 3 Months
59 years, Male

RAS mutant
5 PRIOR LINES
FOLFOX (adjuvant) for 5 months, Relapsed 2 years post-adjuvant therapy
FOLFIRI for 5 months
Irinotecan + Lonsurf + bevacizumab for 33 months
CAPOX progressed within 1 month
Regorafenib progressed within 2 months
Target Lesions: 2 (1 liver; 1 abdomen)
STUDY TREATMENT
NUC-3373 (1500 mg/m² q1w; Arm 1c)
Stable Disease: 3 Months
67 years, Female

CONCLUSION

- NUC-3373 is a targeted inhibitor of TS designed to overcome key cancer resistance mechanisms associated with 5-FU
- NUC-3373's favourable PK and tolerability profile unchanged by LV
- Encouraging efficacy signals observed in heavily pre-treated CRC patients with NUC-3373 ± LV
- 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 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 events 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 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 14 August 2020.