Phase 2 study of NUC-3373, leucovorin, irinotecan (NUFIRI) + bevacizumab vs FOLFIRI + bevacizumab for the second-line treatment of patients with advanced/metastatic colorectal cancer (NuTide:323)

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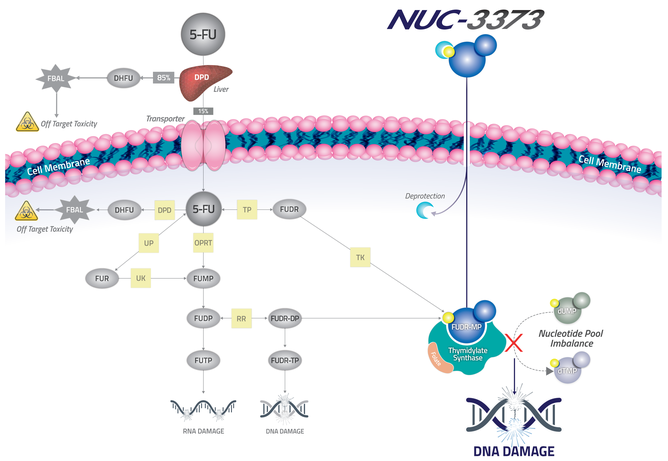
BACKGROUND

- CRC 3rd most common cancer[1]
- Global incidence 1.9 million and deaths 935,000 annually[1]
- Limited treatment options for 2nd line CRC
  - mPFS ~ 5-7 months[2]
  - mOS ~ 11-15 months[2]
- 5-FU remains the cornerstone of treatment for CRC, despite several limitations
  - Rapidly degraded by DPD[3]
    - Short plasma half-life (8-14 mins)[4] requires long infusions (46-hour)
    - Generation of FBAL (associated with hand-foot syndrome)
  - Generation of FUTP (associated with diarrhea, mucositis, myelosuppression)
  - Cell entry requires nucleobase transporters
  - Complex enzymatic activation

NUC-3373 overcomes key limitations associated with 5-FU



NUC-3373: A targeted inhibitor of TS

- Phosphoramidate transformation of FUDR[5,6]
  - Resistant to breakdown by DPD
  - Enters cells independently of nucleobase transporters
  - Directly delivers FUDR-MP intracellularly
  - Low levels of toxic metabolites (FBAL, FUTP)
- Generates high intracellular levels of active anti-cancer metabolite FUDR-MP[7]
  - Causes an imbalance in the nucleotide pool leading to DNA damage and cell death[7]
  - Induces ER stress and DAMPs release leading to immunogenic cell death[8,9]
- Long plasma half-life allows for short infusion duration

Prior Studies

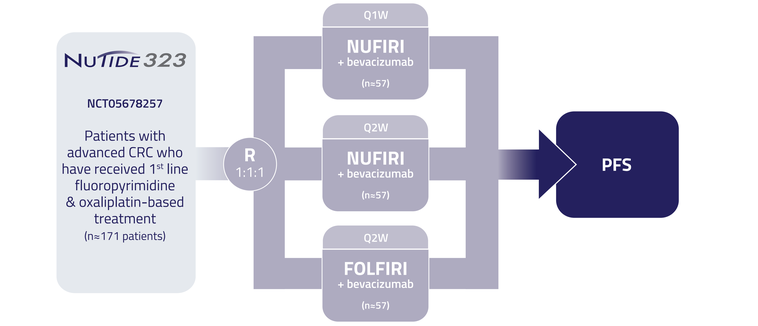
NuTide 301 - NUC-3373 monotherapy[10]

- Phase 1 first-in-human, dose escalation study in previously treated patients with advanced solid tumors
  - NUC-3373 MTD established (2500 mg/m²)
  - Well-tolerated and encouraging signs of anti-tumor activity

NuTide 302 - NUC-3373 in combination[11]

- Phase 1b/2 dose escalation study designed to investigate NUC-3373 combinations (NUFIRI±bev; NUFOX±bev) in previously treated patients with CRC
  - MTDs established
    - NUFIRI-bev: 1500 mg/m² NUC-3373 + 400 mg/m² LV + 180 mg/m² irinotecan + 5 mg/kg bevacizumab
    - NUFOX-bev: 1875 mg/m² NUC-3373 + 400 mg/m² LV + 85 mg/m² oxaliplatin + 5 mg/kg bevacizumab
  - NUC-3373 combinations have favorable safety profiles
- NUFIRI-bev & NUFOX-bev have demonstrated prolonged disease control and signs of anti-tumor activity

NuTide:323 Study Design



Q1W NUFIRI-bev: 1,500 mg/m² NUC-3373 (Q1W) + 400 mg/m² LV (Q1W) +180 mg/m² irinotecan (Q2W) + 5 mg/kg bevacizumab (Q2W)
Q2W NUFIRI-bev: 1,500 mg/m² NUC-3373 (Q2W) + 400 mg/m² LV (Q2W) +180 mg/m² irinotecan (Q2W) + 5 mg/kg bevacizumab (Q2W)
Q2W FOLFIRI-bev: 400 mg/m² bolus 5-FU followed by 2,400 mg/m² continuous IV 5-FU (Q2W) + 400 mg/m² LV (Q2W) + 180 mg/m² irinotecan (Q2W) + 5 mg/kg bevacizumab (Q2W)
NUC-3373 is given as a 2 hour IV infusion

Objectives

Primary

- Compare PFS of NUFIRI-bev (two dosing schedules) to FOLFIRI-bev
- Determine optimal NUFIRI-bev dosing schedule

Secondary

- Compare tumor response, duration of response, and survival of NUFIRI-bev to FOLFIRI-bev
- Assess safety and tolerability of NUFIRI-bev compared to FOLFIRI-bev

Stratification factors

- RAS status (KRAS mt vs NRAS mt vs wt)
- Prior bevacizumab treatment (Yes vs No)
- Duration of prior line of therapy (≤6 months vs >6 months)

Patient Population

Key Inclusion Criteria

- Age ≥ 18 years; life expectancy ≥12 weeks; ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)
- Known RAS and BRAF status
- Must have received ≥2 months of 1st line FOLFOX/CAPOX or have relapsed ≤ 6 months of completing FOLFOX/CAPOX adjuvant therapy
- Known UGT1A1 status or consent to testing

Key Exclusion Criteria

- Prior irinotecan therapy
- Mutant $BRAF^{V600E}$
- MSI high or dMMR
- Hypersensitivity/current contraindications to 5-FU, FUDR, or capecitabine
- Symptomatic CNS or leptomeningeal metastases

Primary endpoint

- PFS

Secondary endpoints

- ORR
- DoR
- DCR
- Maximum % change in tumor size
- OS
- Safety
- PK

Statistical considerations

- 171 patients randomized on 1:1:1 basis (57 patients per arm)
- Final analysis planned after 139 PFS events

Preliminary Safety

TEAEs (≥10% of safety population) after the first 40 patients enrolled (aggregated data)

Preferred term	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	TOTAL (%)
Nausea	13	15	0	28
Diarrhea	13	10	3	26
Asthenia	13	3	5	21
Decreased appetite	8	10	0	18
Vomiting	5	13	0	18
Alopecia	10	0	0	10

- No Grade 4 or 5 TEAEs
- 4 patients experienced treatment related SAEs
  - G2 infusion related reaction
  - G3 diarrhea
  - G3 extravasation
  - G3 pulmonary embolism & G3 general physical health deterioration

Data cleaning ongoing: data cut-off date 12 September 2023

Participating Countries

France, Germany, Italy, Spain, United Kingdom, USA

STUDY SUMMARY

- Phase 2 study across 61 sites in 6 countries
- No new safety signals identified in first 40 patients
- NUFIRI-bev has the potential to become a new standard of care for 2nd line CRC patients

Further study information: **NuTide323@nucana.com**

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ABBREVIATIONS: 5-FU: 5-fluorouracil AE: adverse event Bev: bevacizumab BRAF: v-raf murine sarcoma viral oncogene homolog B1 CAPOX: capecitabine + oxaliplatin CNS: central nervous system CRC: colorectal cancer DAMP: damage-associated molecular pattern DCR: disease control rate DHFU: dihydrofluorouracil dMMR: deficient mismatch repair DNA: deoxyribonucleic acid DoR: duration of response DPD: dihydropyrimidine dehydrogenase dUMP: deoxyuridine monophosphate dTMP: deoxythymidine monophosphate ECOG PS: Eastern Cooperative Oncology Group performance score ER: endoplasmic reticulum FBAL: alpha-fluoro-beta-alanine FOLFIRI: 5-FU + LV + irinotecan FOLFOX: 5-FU + LV + oxaliplatin 5'-UDP: fluorouridine diphosphate FUDR: fluorodeoxyuridine FUDR-DP: fluorodeoxyuridine diphosphate FUDR-MP: fluorodeoxyuridine monophosphate FUDR-TP: fluorodeoxyuridine triphosphate FUTP: fluorouracil triphosphate IV: intravenous KRAS: Kirsten rat sarcoma virus LV: leucovorin MSI: microsatellite instability MTD: maximum tolerated dose NRAS: neuroblastoma ras viral oncogene homolog NUFIRI: NUC-3373 + LV + irinotecan NUFOX: NUC-3373 + LV + oxaliplatin ORR: overall response rate OS: overall survival OPRT: orotate phosphoribosyl transferase PFS: progression free survival PK: pharmacokinetics Q1W: once weekly Q2W: once every 2 weeks RAS: rat sarcoma virus RECIST: response evaluation criteria in solid tumors RR: ribonucleotide reductase SAE: serious adverse event TK: thymidine kinase TP: thymidine phosphorylase TEAE: treatment emergent adverse event TRAE: treatment related adverse event TS: thymidylate synthase UK: uridine kinase UGT1A1: UDP glucuronosyltransferase family 1 member A1 UP: uridine phosphorylase