NUC-3373 in combination with irinotecan (NUFIRI) or oxaliplatin (NUFOX) & bevacizumab for second-line treatment of patients with advanced colorectal cancer (NuTide:302)

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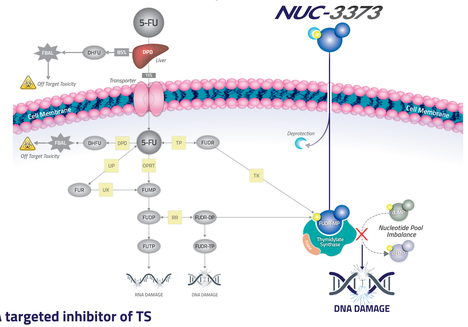
BACKGROUND

- CRC 3rd most common cancer[1] ▪ Global incidence 1.9 million and deaths 935,000 annually[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] 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

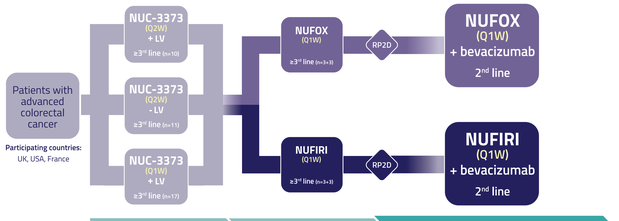
NUC-3373 overcomes key limitations associated with 5-FU



NUC-3373: A targeted inhibitor of TS

- Phosphoramidate transformation of FUDR[4,5.]
  - 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[6]
  - Causes an imbalance in the nucleotide pool leading to DNA damage and cell death[6]
  - Induces ER stress and DAMPs release leading to immunogenic cell death[7,8]
- Long plasma half-life allows for short infusion duration

NuTide:302 Study - Phase 1b/2



NUFOX-bev = 1,875 mg/m² NUC-3373 (Q1W), 400 mg/m² LV (Q1W), 85 mg/m² oxaliplatin (Q2W) and 5 mg/kg bevacizumab (Q2W)

NUFIRI-bev = 1,500 mg/m² NUC-3373 (Q1W), 400 mg/m² LV (Q1W), 180 mg/m² irinotecan (Q2W) and 5 mg/kg bevacizumab (Q2W)

Objectives: Anti-cancer activity, safety, PK of NUC-3373 in combination with oxaliplatin and bevacizumab or irinotecan and bevacizumab

NUFOX-bev

Patients with mCRC who had received 1 prior fluoropyrimidine and irinotecan-containing therapy

Baseline Characteristics (n=6)

Age, years	median (range)	64 (37-72)
Sex	male	3 (50%)
	female	3 (50%)
ECOG PS	0	0
	1	6 (100%)
Metastatic sites	≤3	1 (17%)
	≥4	5 (83%)
Liver metastases	Y	3 (50%)
	N	3 (50%)
BRAF status	wt	5 (83%)
	mt	0
	unknown	1 (17%)
RAS status	wt	3 (50%)
	mt	3 (50%)
Prior Bev	Y	0
	N	6 (100%)
Adjuvant CT	Y	5 (83%)
	N	1 (17%)

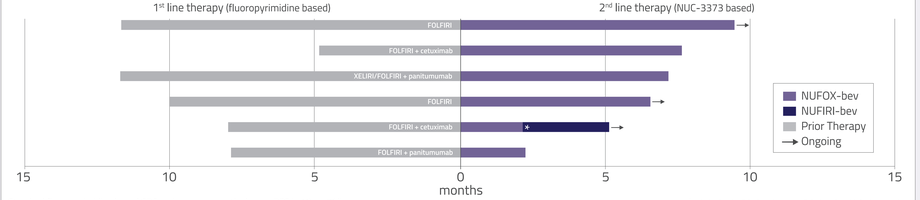
Treatment Related AEs (n=6)

	All Grades	Grade 3
Nausea	6 (100%)	1 (17%)
Diarrhea	5 (83%)	0
Fatigue	3 (50%)	0
Flushing	3 (50%)	0
Vomiting	3 (50%)	1 (17%)
Headache	3 (50%)	0
Abdominal pain	2 (33%)	0
Constipation	2 (33%)	0
Decreased appetite	2 (33%)	0
Dizziness	2 (33%)	0
Anemia	1 (17%)	0
Dysgeusia	1 (17%)	0
Platelet count decreased	1 (17%)	0

All Grade TRAEs with an incidence of ≥10% in combined NUFIRI/NUFOX population. NUC-3373 ± combinations related AEs

- No Grade 4 or 5 TRAEs
- 2 pts experienced Grade 3 TRAEs; nausea & vomiting (1), hypokalemia (1)
- No discontinuations due to AEs
- NUFOX-bev well-tolerated

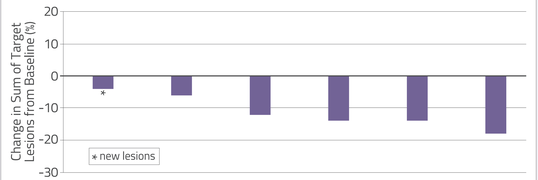
Progression Free Survival



Standard fluoropyrimidine based CRC regimens ~5 months longer PFS in 1st vs 2nd line

*switched to NUFIRI-bev due to oxaliplatin-related infusion reaction

Best % Change in Tumor Burden



CONCLUSION

- NUC-3373 can be combined with agents commonly used in CRC at their standard doses
- Favorable safety profiles for NUFIRI-bev & NUFOX-bev
- Prolonged disease control and signs of anti-tumor activity
  - Several patients achieved similar or greater PFS in 2nd line NUC-3373 based therapy vs 1st line fluoropyrimidine based therapy
- More convenient dosing schedule compared to 5-FU (2-2.5h vs 46h)
- Randomized Phase 2 study currently investigating safety and efficacy of NUFIRI-bev vs FOLFIRI-bev in 2nd line patients with CRC (NuTide:323, NCT05678257)

NUFIRI-bev

Patients with mCRC who had received 1 prior fluoropyrimidine and oxaliplatin-containing therapy

Baseline Characteristics (n=8)

Age, years	median (range)	56 (40-81)
Sex	male	6 (75%)
	female	2 (25%)
ECOG PS	0	5 (63%)
	1	3 (38%)
Metastatic sites	≤3	1 (13%)
	≥4	7 (88%)
Liver metastases	Y	4 (50%)
	N	4 (50%)
BRAF status	wt	6 (75%)
	mt	1 (13%)*
	unknown	1 (13%)
RAS status	wt	4 (50%)
	mt	4 (50%)
Prior Bev	Y	1 (13%)
	N	7 (88%)
Adjuvant CT	Y	1 (13%)
	N	7 (88%)

*3rd line patient

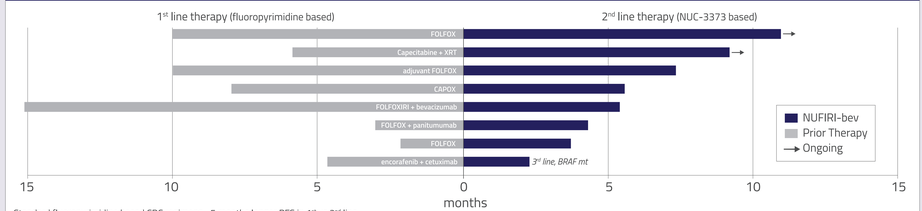
Treatment Related AEs (n=8)

	All Grades	Grade 3
ALT increased	5 (63%)	2 (25%)
AST increased	5 (63%)	0
Diarrhea	5 (63%)	0
Nausea	4 (50%)	0
Anemia	3 (38%)	0
Fatigue	2 (25%)	0
Flushing	2 (25%)	0
Vomiting	2 (25%)	0
Abdominal pain	1 (13%)	0
Constipation	1 (13%)	0
Decreased appetite	1 (13%)	0
Dysgeusia	1 (13%)	0
Platelet count decreased	1 (13%)	0

All Grade TRAEs with an incidence of ≥10% in combined NUFIRI/NUFOX population. NUC-3373 ± combinations related AEs

- No Grade 4 or 5 TRAEs
- 2 pts experienced Grade 3 TRAEs; ALT increased & pancreatitis (1), ALT increased (1)
- No discontinuations due to AEs
- NUFIRI-bev well-tolerated

Progression Free Survival



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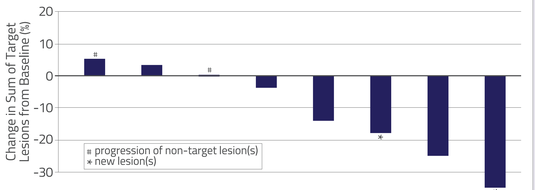
Best % Change in Tumor Burden



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ABBREVIATIONS: 5-FU: 5-fluorouracil AE: adverse event ALT: alanine aminotransferase Bev: bevacizumab BRAF: v-raf murine sarcoma viral oncogene homolog B1 CAPOX: capecitabine + oxaliplatin CT: chemotherapy CRC: colorectal cancer DAMP: damage-associated molecular pattern DHFU: dihydrofluorouracil DNA: deoxyribonucleic acid 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 FUDP: fluorouridine diphosphate FUDR: fluorodeoxyuridine FUDR-DP: fluorodeoxyuridine diphosphate FUDR-MP: fluorodeoxyuridine monophosphate FUDR-TP: fluorodeoxyuridine triphosphate FUTP: fluorouracil triphosphate LV: leucovorin mCRC: metastatic colorectal cancer mt: mutant NUFIRI: NUC-3373 + LV + irinotecan NUFOX: NUC-3373 + LV + oxaliplatin OPRT: orotate phosphoribosyl transferase PFS: progression free survival PK: pharmacokinetics Q1W: once weekly Q2W: once every 2 weeks RP2D: recommended phase 2 dose RR: ribonucleotide reductase TK: thymidine kinase TP: thymidine phosphorylase TRAE: treatment related adverse event TS: thymidylate synthase UK: uridine kinase UP: uridine phosphorylase wt: wild type XELIRI: irinotecan and capecitabine XRT: radiotherapy

Data cleaning ongoing; data cut-off date 22 August 2023