COMPLETE

# NUTIDE:302 - PART 1

COLORECTAL CANCER - PHASE 1b STUDY

## Designed to assess the safety of NUC-3373 in combination with leucovorin

**Key Eligibility Criteria**

- Patients with colorectal cancer who had exhausted all other therapeutic options
- Received ≥2 prior lines of fluoropyrimidine-based regimens

→ **NUC-3373** Q2W ± LV

→ **NUC-3373** Q2W ± LV

→ **NUC-3373** Q1W ± LV

**Objectives**
- Establish NUC-3373 safety in combination with leucovorin

**Key endpoints**
- Safety & tolerability
- Anti-tumor activity
- PK

**Patient population**
- Heavily pre-treated (≥3rd line), with ≥2 prior lines of fluoropyrimidines

| Number of patients | Age (median) | Prior chemotherapy regimens (median) |
|---|---|---|
| 38 | 58 (range 33-75) | 4 (range 2-13) |

| | | |
|---|---|---|
| Sex | Male<br>Female | 21 (55%)<br>17 (45%) |
| ECOG PS | 0<br>1 | 19 (50%)<br>19 (50%) |
| Metastatic sites, n | 1-3<br>≥4 | 19 (50%)<br>19 (50%) |
| Prior anti-VEGF inhibitor | Yes<br>No | 22(58%)<br>16 (42%) |
| Prior anti-EGFR inhibitor | Yes<br>No | 19 (50%)<br>19 (50%) |

Berlin *et al* (2021) Ann Oncol; 32: Suppl 5 Abstract ID 745P (ESMO September 2021). Data cut-off: April 15, 2021

## Favorable safety profile compared to 5-FU

- NUC-3373 was well tolerated in patients who had exhausted all other therapeutic options
  - Low rates of Grade 3 or 4 toxicities, particularly those associated with FUTP and FBAL (i.e. neutropenia, diarrhea, mucositis/stomatitis and hand-foot syndrome)

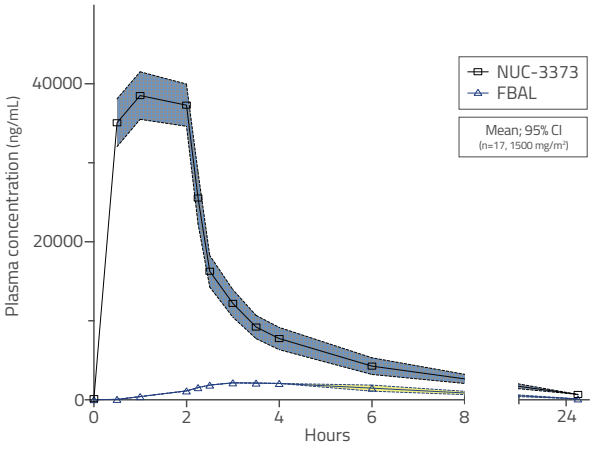
| | 5th line treatment (median) | | 1st line treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| | NUC-3373 (n=38)[1] | | 5-FU Bolus (n=219)[2] | | 5-FU CIV (n=143)[2] | | Capecitabine (n=596)[3] | |
| | All Grades, n(%) | G3 or G4, n(%) | All Grades, n(%) | G3 or G4, n(%) | All Grades, n(%) | G3 or G4, n(%) | All Grades, n(%) | G3 or G4, n(%) |
| **Neutropenia** | **0** | **0** | **99** | **67** | **48** | **13** | **13** | **3** |
| Anemia | 18 | 5 | 99 | 6 | 91 | 2 | 80 | 3 |
| **Diarrhea** | **32** | **0** | **70** | **13** | **45** | **6** | **55** | **15** |
| Nausea | 45 | 5 | 68 | 8 | 55 | 4 | 43 | 4 |
| Vomiting | 42 | 0 | 46 | 4 | 32 | 3 | 27 | 5 |
| **Mucositis/stomatitis** | **11** | **0** | **76** | **17** | **29** | **3** | **25** | **3** |
| **Hand-foot syndrome** | **0** | **0** | NR | NR | **13** | **1** | **54** | **17** |
| Dermatitis | 11 | 0 | 30 | 1 | 20 | 0 | 27 | 1 |
| Fatigue/asthenia | 47 | 5 | 65 | 12 | 48 | 4 | 42 | 4 |
| Elevated bilirubin | 11 | 5 | 92 | 8 | 36 | 11 | 48 | 23 |

NUC-3373 treatment emergent adverse events, selected relevant to comparator data. NR: not reported. CIV: Continuous Intravenous Infusion
1. Berlin *et al* (2021) Ann Oncol; 32: Suppl 5 Abstract ID 745P (ESMO September 2021). Data cut-off: April 15, 2021 2. Camptosar Label 3. XELODA label

## Improved pharmacokinetic profile compared to 5-FU

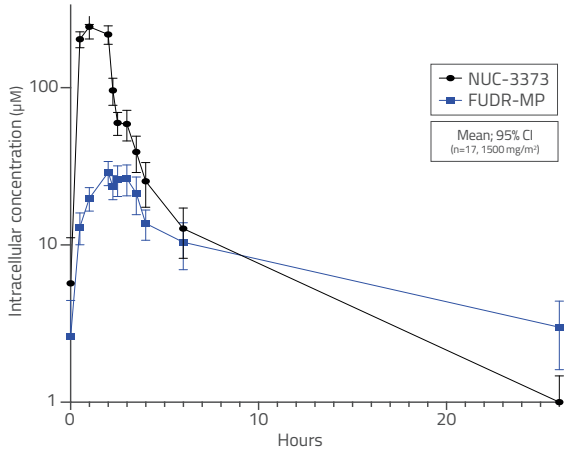
### Plasma

- Long half-life compared to 5-FU (6-14 hrs vs 8-14 mins)
- Large volume of distribution indicating extensive tissue absorption compared to 5-FU (190 L vs 17 L)




### Intracellular

- High levels of FUDR-MP compared to 5-FU (31 µM vs 0.1 µM)
- Long half-life of FUDR-MP (12-20 hrs)




## Favorable metabolite profile compared to 5-FU or capecitabine

| | NUC-3373 | 5-FU | Capecitabine |
|---|---|---|---|
| Intracellular FUDR-MP (pmol/$10^6$ cells) | 11.7[1] | 0.04[2] | <LLOQ[2] |
| Intracellular FUTP (pmol/$10^6$ cells) | <0.001[1*] | 1-3[3] | 0.086[3] |
| Plasma FBAL (AUC) (µg.h/mL per month) | 51[1] | N/A | 958[4] |

- No FUTP (the 5-FU and capecitabine metabolite that has been implicated in toxicities including neutropenia, mucositis and diarrhea) has been detected in patients treated with NUC-3373
- Low levels of FBAL (the 5-FU and capecitabine metabolite implicated in hand-foot syndrome, cardiotoxicity and neurotoxicity) have been observed in patients treated with NUC-3373

1. NuCana data on file; 2. Derissen et al (2015) J Pharm Biomed; 110; 3. Derissen *et al* (2016) Br J Clin Pharmacol; 81(5) 4. Gieschke *et al* (2003) Br J Clin Pharmacol; 55(3)
*Below the level of detection; N/A- data not available to our knowledge

## Encouraging signs of efficacy in patients who had exhausted all other treatment options

**67 YRS** Colorectal Cancer

Prior lines of therapy
1. CAPOX (adjuvant): for **3 months** relapsed 9 months post-adjuvant therapy
2. FOLFIRI: progressed within **3 months**
3. Lonsurf: progressed within **3 months**

**NUC-3373** 2500 mg/m² Q1W
**Partial response 3.5 months**
**40% reduction in target lesion**

**69 YRS** Colorectal Cancer

Prior lines of therapy
1. CAPOX: progressed within **2 months** tumor **increase of 35%**
2. FOLFIRI: progressed within **1.5 months**

**NUC-3373** 1500 mg/m² Q1W
**Stable disease 5.1 months***
**28% reduction in tumor volume**

**52 YRS** Colorectal Cancer

Prior lines of therapy
1. FOLFOX (adjuvant): for **4 months** relapsed 4 months post-adjuvant therapy
2. FOLFIRI: progressed within **6 months**
3. Irinotecan + panitumumab: progressed within **6 months**
4. Irinotecan + panitumumab + telaglenastat: progressed within **6 months**
5. Nivolumab + enadenotucirev: progressed within **3 months**

**NUC-3373** 1500 mg/m² Q2W
**Stable disease 4.5 months**
**15% reduction in tumor volume**

*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

Graham *et al* (2020) Ann Oncol 31: Suppl 4 Abstract ID :464P (ESMO September 2020). Data cut-off: August 14, 2020 Coveler *et al* (2021) J Clin Oncol 39: Suppl 3 Abstract ID: 93 (ASCO GI January 2021). Data cut-off: November 26, 2020

## Key takeaways

**NUC-3373 has shown encouraging signs of anti-tumor activity in a heavily pre-treated patient population**

**NUC-3373 has a favorable safety profile**

**NUC-3373 has a long plasma half-life & generates high intracellular levels of active anti-cancer metabolite**