Phase 1b/2 open label, multi-arm, parallel cohort dose finding and expansion study of NUC-3373 in combination with pembrolizumab in patients with advanced solid tumors or docetaxel in patients with lung cancer (NuTide:303)

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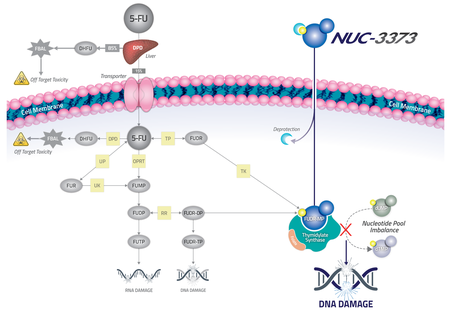
BACKGROUND

- 5-FU forms the backbone treatment for numerous solid tumors, despite several limitations
  - Rapidly degraded by DPD[1]
    - Short plasma half-life (8-14 mins)[2] requires long infusions (46 hours)
    - Generation of FBAL (associated with hand-foot syndrome)
  - Generation of FUTP (associated with diarrhea, mucositis, myelosuppression)
  - Cell entry requires nucleobase transporters
  - Complex enzymatic activation

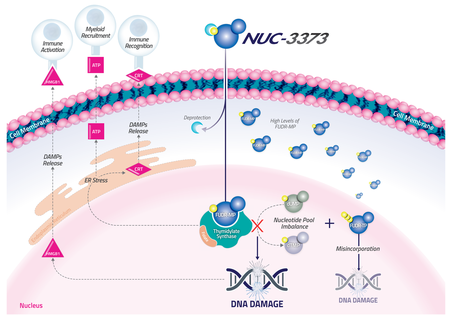
NUC-3373: A targeted TS inhibitor

Overcomes key limitations associated with 5-FU



- Phosphoramidate transformation of FUDR[3,4]
  - 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[5]

Promotes anti-cancer immune environment



- Induces ER stress via accumulation of TS ternary complexes[6]
- Causes release of DAMPs[7]
- Activates the innate immune system (NK cell response)[8]
- Enhances immunogenic cell death in combination with anti-PD-1[9]

NuTide:303 Study

NuTide 303 MODULE 1 — NUC-3373 in combination with pembrolizumab for the treatment of patients with advanced solid tumors

Rationale

- Immune checkpoint inhibitors (ICIs) exert anti-cancer effects by modulating interactions between tumor and immune cells
- Although ICIs have altered the treatment landscape for numerous cancers, many patients do not respond, or develop resistance
- Novel treatment combinations are required to potentiate the activity of ICIs
- NUC-3373 induces DAMPs leading to immunogenic cell death[10]
- NUC-3373 promotes an anti-cancer immune environment and is an attractive combination partner for ICIs

Patients with advanced solid tumors → NUC-3373 + pembrolizumab → Expansion cohorts

Enrollment → Phase 1b → Phase 2

Starting doses: 1875 mg/m² NUC-3373 & 400 mg/m² LV on days 1, 8 & 15, + 200 mg pembrolizumab on day 1 of a 21-day cycle

Objectives

- Determine safety & tolerability
- Evaluate anti-tumor activity

Key Inclusion Criteria

- Confirmed diagnosis of a solid tumor, with evidence of locally advanced/unresectable or metastatic disease, for which pembrolizumab treatment would be appropriate
- Must have progressed on ≤2 prior lines of therapy for advanced/metastatic disease

Key Exclusion Criteria

- Any prior toxicity attributed to checkpoint inhibitors that resulted in discontinuation of therapy
- Patients who have received >2 prior lines of therapy or who have received >1 prior line of an immunotherapy-containing regimen for advanced/metastatic disease
- History of hypersensitivity or current contra-indications to 5-FU, FUDR, capecitabine, pembrolizumab (or components)

Primary endpoints

- Safety & tolerability (Phase 1b)
- ORR (Phase 2)

Secondary endpoints

- Safety (Phase 2)
- ORR (Phase 1b only)
- Maximum % change from baseline in tumor size
- DCR
- PFS
- DoR
- OS
- DoSD

Current study status

- 3 patients dosed

Safety data (first cohort)

- No DLTs
- No Grade 3 or 4 treatment related AEs
- 2 pts experienced Grade 1 NUC-3373 related AEs: diarrhea & vomiting (1); flushing & nausea (1)
- 1 pt experienced a Grade 1 pembro related SAE: dizziness

NuTide 303 MODULE 2 — NUC-3373 in combination with docetaxel for the treatment of patients with NSCLC or pleural mesothelioma

Rationale

- Pemetrexed, a folate anti-metabolite that inhibits TS, is indicated for non-squamous NSCLC and pleural mesothelioma
- 5-FU (TS inhibitor) has limited clinical utility in lung cancer
  - High tumor expression of DPD correlated with low overall survival[11, 12]
- NUC-3373 may be a promising treatment option in lung cancer
  - Potent inhibitor of TS in both squamous and non-squamous NSCLC cells[13]
  - Resistant to breakdown by DPD

Patients with advanced NSCLC or mesothelioma → NUC-3373 + docetaxel → Expansion cohorts

Enrollment → Phase 1b → Phase 2

Starting doses: 750 mg/m² NUC-3373 & 400 mg/m² LV on days 1 & 22, + 55 mg/m² docetaxel on day 8 of a 28-day cycle

Objectives

- Determine safety & tolerability
- Evaluate anti-tumor activity

Key Inclusion Criteria

- Confirmed diagnosis of NSCLC (any histology) or pleural mesothelioma (any histology) with evidence of locally advanced/unresectable or metastatic disease
- Must have progressed on, or were unable to tolerate, 1 or 2 prior lines of cytotoxic chemotherapy-containing standard of care regimens for advanced/metastatic disease

Key Exclusion Criteria

- History of hypersensitivity or current contra-indications to 5-FU, FUDR, capecitabine
- Prior history of hypersensitivity or current contra-indication to docetaxel, polysorbate 80, ethanol (anhydrous) or citric acid
- Patients who have received prior treatment with docetaxel for advanced/metastatic disease

Primary endpoints

- MTD, Safety (Phase 1b)
- ORR (Phase 2)

Secondary endpoints

- Maximum % change from baseline in tumor size
- ORR (Phase 1b only)
- DCR
- PFS
- DoR
- OS
- DoSD

Current study status

- 3 patients dosed

Safety data (first cohort)

- No DLTs
- No Grade 4 TRAEs
- 1 pt experienced Grade 3 TRAEs: diarrhea & vomiting
- 1 pt experienced Grade 2 TRAEs: appetite decreased, dysgeusia, fatigue, nausea & constipation
- 2 pts experienced Grade 1 TRAEs: mucositis & rhinorrhea (1); diarrhea & pyrexia (1)

STUDY SUMMARY

- NUC-3373 combinations well-tolerated in first dosing cohorts
- Recruitment ongoing

Further study information: **NuTide303@nucana.com**

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ABBREVIATIONS: 5-FU: 5-fluorouracil ATP: adenosine triphosphate CRT: calreticulin CRC: colorectal cancer DAMP: damage-associated molecular pattern DNA: deoxyribonucleic acid dUMP: deoxyuridine monophosphate dTMP: deoxyuridine triphosphate DHFU: dihydrofluorouracil DPD: dihydropyrimidine dehydrogenase DCR: disease control rate DLT: dose-limiting toxicity DoR: duration of response DoSD: duration of stable disease ER: endoplasmic reticulum FBAL: alpha-fluoro-beta-alanine FUDR- Fluorodeoxyuridine FUDR-DP: fluorodeoxyuridine diphosphate FUDR-MP: fluorodeoxyuridine monophosphate FUDR-TP: fluorodeoxyuridine triphosphate FUTP: fluorouracil triphosphate FUR: fluorouridine FUDP: fluorouridine diphosphate HMGB1: high mobility group box protein 1 ICI: immune checkpoint inhibitor ICD: immunogenic cell death LV: leucovorin MTD: maximum tolerated dose NK: natural killer NSCLC: non-small cell lung cancer OPRT: orotate phosphoribosyl transferase ORR: overall response rate OS: overall survival PD-1: programmed cell death protein 1 PFS: progression free survival RR: ribonucleotide reductase SAE: serious adverse event TK: thymidine kinase TP: thymidine phosphorylase TS: thymidylate synthase TRAE: treatment related adverse event UK: uridine kinase UP: uridine phosphorylase

Data cleaning ongoing: data cut-off date 18 September 2023