A first-in-human study of NUC-7738, a ProTide transformation of 3′-deoxyadenosine, in patients with advanced solid tumors (NuTide:701)

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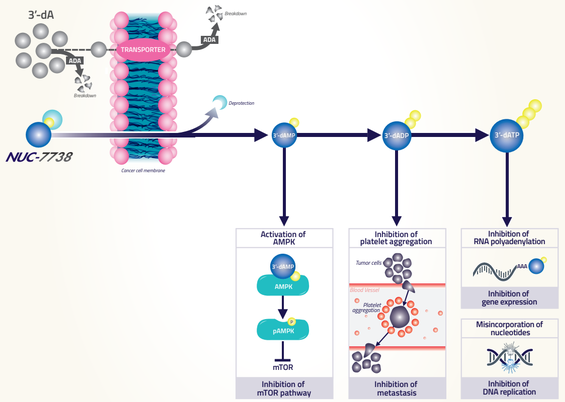
BACKGROUND

- Nucleoside analogs form the backbone therapy for solid and hematological malignancies
- 3′-deoxyadenosine (3′-dA; cordycepin) isolated from *Cordyceps sinensis*
- 3′-deoxyadenosine triphosphate (3′-dATP) believed to cause cell death by inhibiting DNA and RNA replication[1]
- 3′-dA not successful in clinical studies due to cancer resistance mechanisms, including
  - Rapid enzymatic breakdown by adenosine deaminase (ADA)
  - Cellular uptake dependent on nucleoside transporters (hENT1)
  - Reliance on adenosine kinase (AK) for activation

NUC-7738: Multiple potential anti-cancer modes of action



NUC-7738: A ProTide transformation of 3'-dA

- Overcomes 3′-dA resistance mechanisms
  - Protected from breakdown by ADA
  - Cellular uptake independent of nucleoside transporters (hENT1)
  - 3′-dATP generation independent of enzymatic activation by AK

STUDY DESIGN - NuTide:701

Primary objectives
- Safety
- RP2D

Secondary objectives
- PK
- Efficacy (BoR, ORR, DoR, PFS)

Patient population
- Aged ≥ 18 years, ECOG PS 0 or 1
- Advanced solid tumors not amenable to standard therapy

RESULTS (interim)

Patient Characteristics
- 29 patients treated; age 39-77 (median; 63)
- Median prior lines therapy; 2.5 (1-7)

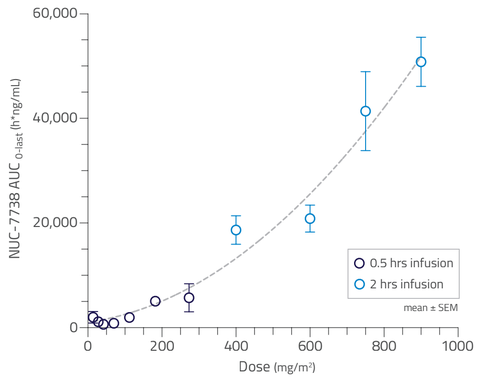
Primary tumor types
- Melanoma (5 cutaneous; 3 ocular)
- Colorectal (3), Cervical (2), Lung (2)
- Breast (2), Ovarian (2), Pancreatic (2)
- Gastric (2), Oesphageal (1), Biliary tract (1)
- Leiomyosaracoma (1), Mesothelioma (1)
- Jejunal (1), Endometrial (1)

NUC-7738 Dosing
- Completed dose 14-900 mg/m² Q1W (IV infusion 30-120 mins)
- Current dose 1350 mg/m² Q1W
- Dose escalation ongoing

Safety profile
- NUC-7738 is well tolerated
  - No Grade 3 or 4 treatment-related AEs
  - 9 patients experienced Grade 2 treatment-related AEs
  - No DLTs

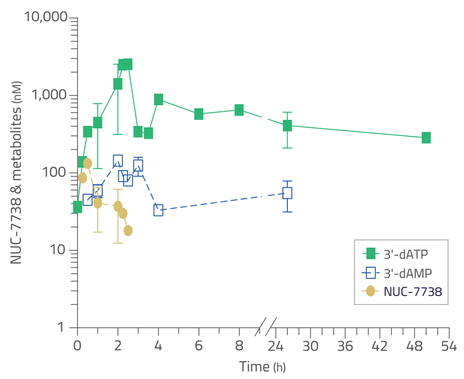
NUC-7738 is efficiently converted into 3′-dATP

Plasma Profile



Patients (n=27) dosed at 14-900 mg/m²

Intracellular Profile



Patients (n=3) dosed 900 mg/m²

- Dose proportional increase in C_{max} and AUC
- Prolonged half-life with 3′-dATP present (>50 hours)

Patient Details	Prior Lines	NUC-7738 (Starting Dose)	Treatment Duration & Information
Metastatic Melanoma (cutaneous)  **62 Years, Female** **1 Target Lesion:** pelvic side wall	**1) Nivolumab + ipilimumab** discontinued due to toxicity, 1 month **2) CK7 inhibitor** progressed within 1 month	**14 mg/m²** (8 dose escalations)	**18 months** (Stable Disease for 12 months)* **Target Lesion 1: 14% reduction** *Ongoing pleural effusion resolved: no further drainage required and lung function normalized*
Metastatic Melanoma (cutaneous)  **65 Years, Female** **1 Target Lesion:** lung	**1) Nivolumab + ipilimumab** discontinued due to toxicity, 1 month	**400 mg/m²** (1 dose escalation)	**11 months** (Stable Disease for 9 months)* **Target Lesion 1: 7% reduction** *NUC-7738 treatment enabled complete resection (R0)*
Metastatic Lung Adenocarcinoma  **65 Years, Male** **2 Target Lesions:** both lung	**1) Carboplatin + pemetrexed** progressed 6 months **2) Docetaxel** progressed 4 months	**42 mg/m²** (4 dose escalations)	**6 months** (Stable Disease for 2 months)* **Target Lesion 1: 46% reduction** **Target Lesion 2: Changed in character** *Small dense core surrounded by larger diffuse "ground-glass" periphery*

* Treatment beyond PD allowed per protocol for patients still receiving benefit

CONCLUSION

- NUC-7738 is a novel ProTide with multiple potential anti-cancer mechanisms of action
- NUC-7738 is designed to overcome key cancer resistance mechanisms of 3′-dA (cordycepin)
- NuTide:701 study will establish the RP2D of NUC-7738 in patients with solid tumors
- Interim data from NuTide:701 study demonstrate
  - Anti-cancer activity and prolonged disease control
  - Favorable tolerability profile
  - Efficient intracellular conversion to active metabolite, 3′-dATP
- NuTide:701 study recruitment ongoing

ABBREVIATIONS: 3′-dA: 3′-deoxyadenosine 3′-dATP: 3′-deoxyadenosine triphosphate ADA: adenosine deaminase AE: adverse event AK: adenosine kinase AMPK: 5′adenosine monophosphate-activated protein kinase AUC: area under the curve BoR: best overall response C_{max}: maximum concentration DLT: dose-limiting toxicity DNA: deoxyribonucleic acid DoR: duration of response hENT1: human equilibrative nucleoside transporter 1 IV: intravenous mTOR: mammalian target of rapamycin ORR: objective response rate pAMPK: phospho-AMPK PD: progressive disease PFS: progression free survival PBMC: peripheral blood mononuclear cell Q1W: weekly dosing RNA: ribonucleic acid RP2D: recommended phase 2 dose

REFERENCES: 1. Chen LS *et al*, 2008 *Br J Haematol*. 140: 682–691

The first author has no conflicts of interest to declare

Data cleaning ongoing; data cut off 20 July 2021