NUC-7738, a novel ProTide transformation of 3′-deoxyadenosine, in patients with advanced solid tumors

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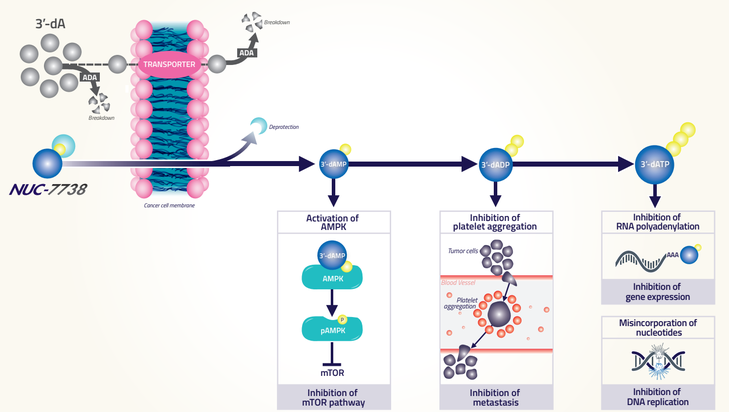
BACKGROUND

- 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) causes 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

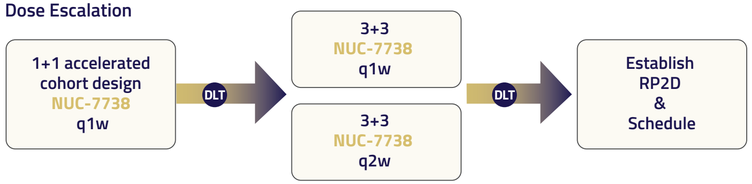


NUC-7738: A ProTide transformation of 3′-dA

- 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

NUTIDE:701 STUDY DESIGN

Dose Escalation



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 (n=21)

Male , n (%)	9
Female, n (%)	12
Median age, years (range)	63 (46-76)
Prior lines of therapy, median (range)	3 (1-5)
ECOG PS status (0/1)	9/12

Primary Tumor Types

Melanoma	6*
Cervical	2
Lung	2
Colorectal	2
Breast	2
Other	1#

*Melanoma subtypes: 3 cutaneous; 3 ocular
#Ovarian; biliary tract; leiomyosarcoma; mesothelioma; jejunal; endometrial; gastric

Study Status

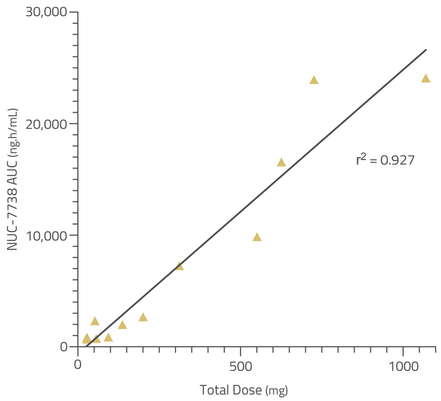
- 21 patients treated
- Dose range 14 - 900 mg/m^2 (IV infusion from 30-120 mins) q1w
- Dose escalation continuing

Safety Profile

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

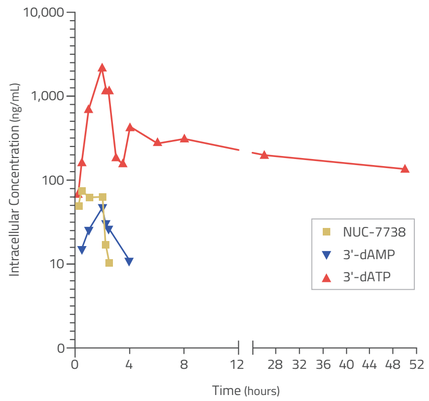
NUC-7738 is efficiently converted into 3′-dATP with a long intracellular half-life

Plasma Profile



Patients (n=11) dosed between 14 - 600 mg/m^2

Intracellular Profile



Patients (n=7) dosed between 400 - 900 mg/m^2

- Dose proportional increase in C_{max} and AUC
- Efficient conversion of NUC-7738 to 3′-dATP
- High levels of active metabolite, 3′-dATP in PBMCs
- Prolonged half-life with 3′-dATP present (> 50 hours)

PATIENT CASE STUDIES

Metastatic Melanoma (cutaneous)

62 Years, Female
2 prior lines

Prior Lines	Target Lesions	Study Treatment	Treatment Duration
1) Nivolumab + ipilimumab: discontinued within **1 month** 2) CK7 inhibitor: progressed within **1 month**	**1** (pelvic side wall)	**NUC-7738** Starting dose 14 mg/m^2 q1w (8 dose escalations)	**18 months** (Stable disease for 12 months*) Target Lesion 1: **14% reduction**

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

Metastatic Melanoma (cutaneous)

65 Years, Female
1 prior line

Prior Lines	Target Lesions	Study Treatment	Treatment Duration
1) Nivolumab + ipilimumab: discontinued within **1 month**	**1** (lung)	**NUC-7738** Starting dose 400 mg/m^2 q1w (1 dose escalation)	**9 months** (ongoing) (Stable disease for 8 months*) Target Lesion 1: **7% reduction**

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

Metastatic Lung Adenocarcinoma

65 Years, Male
2 prior lines

Prior Lines	Target Lesions	Study Treatment	Treatment Duration
1) Carboplatin + pemetrexed: progressed at **6 months** 2) Docetaxel: progressed at **4 months**	**2** (both lung)	**NUC-7738** Starting dose 42 mg/m^2 q1w (4 dose escalations)	**6 months** Target Lesion 1: **46% reduction** Target Lesion 2: **Lesion changed in character** (smaller dense core; larger diffuse 'ground-glass' periphery)

- Clinical efficacy observed in patients who have exhausted all other therapeutic options

CONCLUSION

- NUC-7738 is a novel nucleotide analog with multiple potential anti-cancer mechanisms of action
- NUC-7738 is designed to overcome key cancer resistance mechanisms of 3′-dA (cordycepin)
- NuTide:701 will establish the RP2D of NUC-7738 in patients with solid tumors
- Interim data from NuTide:701 demonstrate:
  - Anti-cancer activity and prolonged stable disease
  - Favorable tolerability profile
  - Efficient conversion to active metabolite, 3′-dATP
- NuTide:701 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 ECOG PS: eastern cooperative oncology group performance status 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 q2w: alternative week dosing RNA: ribonucleic acid RP2D: recommended phase 2 dose

Data cleaning ongoing; data cut of 1 March 2021