NuTide:701 A first-in-human study of NUC-7738, a 3'-dA phosphoramidate, in patients with advanced solid tumours

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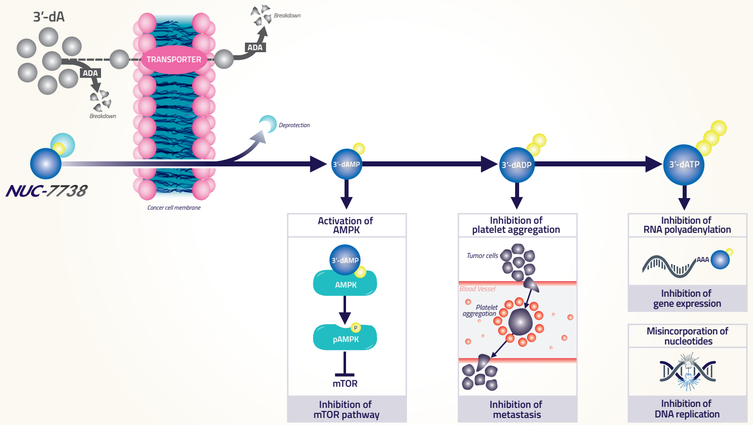
BACKGROUND

- Nucleoside analogs form the backbone therapy for solid and haematological 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

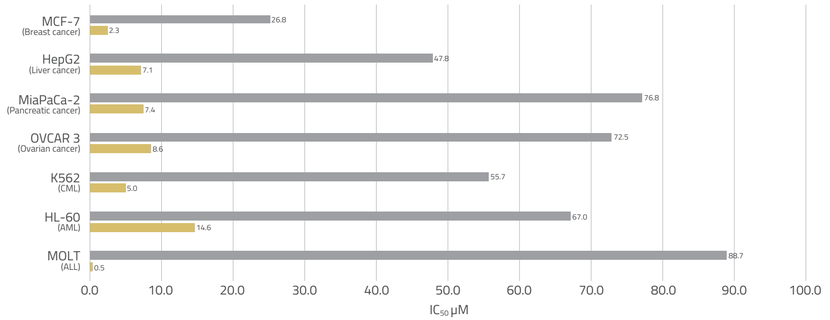
NUC-7738: Multiple potential anti-cancer modes of action



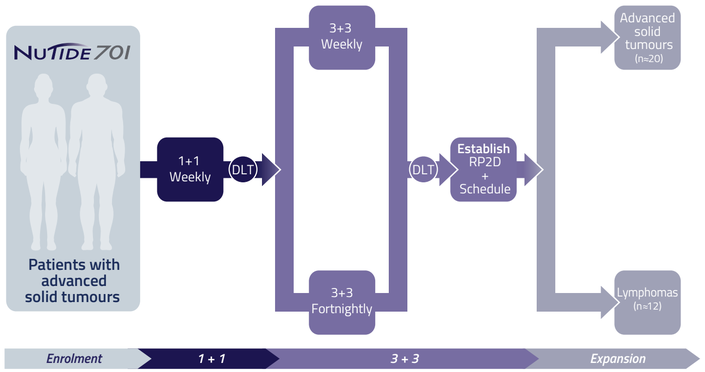
NUC-7738: A ProTide transformation of 3'-dA

- 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

NUC-7738 has potent anti-cancer activity across a broad range of malignant cell lines (up to 185-times greater than 3'-dA)



NUTIDE:701 STUDY DESIGN



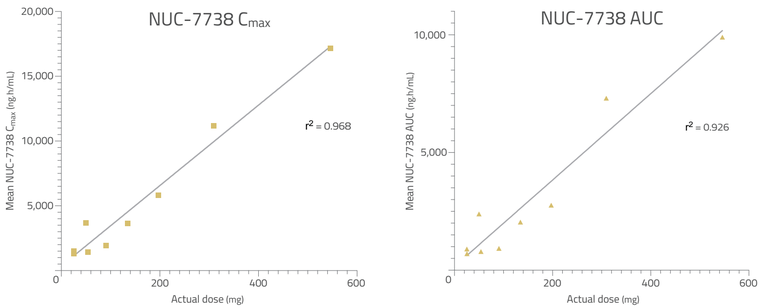
Study status

- 14 patients treated
- Dose range 14 - 400 mg/m^2 (IV infusion from 30-120 mins) q1w
- Intrapatient dose escalation continuing

Safety profile

- NUC-7738 is well tolerated:
  - No Grade 3 or 4 treatment-related AEs
  - No discontinuations due to AEs
  - No DLTs

Pharmacokinetic profile



Patients (n=9) dosed between 14 - 400 mg/m^2

- NUC-7738 has a predictable PK profile:
  - Dose proportional increase in C_{max} and AUC
- Preliminary intracellular (PBMCs) data indicate:
  - Efficient conversion of NUC-7738 to 3'-dATP
  - Persistence of 3'-dATP post-infusion

PATIENT CASE STUDIES

Metastatic Melanoma - 2 Prior Lines

HISTORY

Original lesion identified T2b N(unknown) M0 melanoma

Stage III Received lymphadenectomy and routine therapy

Stage IV metastatic disease Lung metastases

PRIOR TREATMENT

Primary resection Right leg, cutaneous melanoma

Radiation therapy Right groin

Nivolumab & ipilumumab (Oct-Nov 2018) Discontinued due to toxicity

Investigational CK7 inhibitor (Mar-Apr 2019) Discontinued due to progression

Target Lesion: 1 (pelvic side wall)

STUDY TREATMENT

NUC-7738
Starting Dose: 14 mg/m^2
Highest Dose Received: 400 mg/m^2
Number of Dose Escalations: 7

SAFETY

Treatment-related AEs: Dysgeusia (G2, successfully treated with artificial saliva spray); Nausea (G2, resolved); Fatigue (G1, resolved); Muscular pain (G1, resolved); Hypoglycemia (G1, resolved)

TREATMENT DURATION

15 Months (ongoing)

Clinical Benefit

Tumour volume
- Reduction in of 14% following 8 weeks of treatment
- Stable Disease maintained for 12 months
- Treatment continued beyond progression due to ongoing clinical benefit (see below)
- Disease control re-established from month 12 to 15 (ongoing)

Pleural effusion resolved
- Patient had ongoing pleural effusion at the time of study entry which required regular drainage
- Following initiation of NUC-7738, pleural effusion resolved: no drainage required and lung function normalised

62 Years, Female

Metastatic Lung Adenocarcinoma - 2 Prior Lines

HISTORY

Original lesion identified (2015)
Diagnosed as T4 N0 M0 lung adenocarcinoma at thoracoscopy and wedge biopsy (2015)

PRIOR TREATMENT

Radical radiotherapy (2016) 55Gy in 20 fractions

CT relapse with multiple lung metastases (2017) Disease now T$_4$ N0 M1

Carboplatin & pemetrexed (Apr-Oct 2018) Partial response
25% dose reduction: neutropaenia

Docetaxel (Apr-Jul 2019) Progressive disease (low volume)
Cycle 2 dose reduction: diarrhoea and fatigue

No immunotherapy offered due to pulmonary fibrosis and PD-L1 0%

Target Lesions: 2 (both lung)

STUDY TREATMENT

NUC-7738
Starting Dose: 42 mg/m^2
Highest Dose Received: 273 mg/m^2
Number of Dose Escalations: 4

SAFETY

Treatment-related AEs:
No AEs observed
One Grade 3 pneumonia not related to NUC-7738 resulted in a dose omission

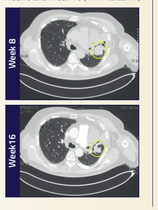
TREATMENT DURATION

6 Months

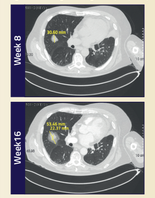
Clinical Benefit

Tumour volume
- Increased between Week 1 and Week 8, but patient remained on treatment due to ongoing clinical benefit (asymptomatic of disease)
- Reduced between Week 8 and Week 16 in one lesion and changes in character observed in the other (see below)

Target Lesion 1: Encouraging signs of anti-tumour activity with a **46% reduction** in lesion between Week 8 and Week 16 (41mm to 22mm)



Target Lesion 2: Lesion changed in character, with a smaller dense core surrounded by a larger diffuse "ground-glass" periphery



65 Years, Male

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 tumours
- Interim data from NuTide:701 demonstrate:
  - Signals of anti-cancer activity at low doses
  - Favourable tolerability profile
  - Generation of intracellular 3'-dATP
- NuTide:701 recruitment ongoing

REFERENCES: Chen LS *et al* 2008. *Br J Haematol* 140:682-691

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 C_{max}: maximum concentration DLT: dose-limiting toxicity DNA: deoxyribonucleic acid hENT1: human equilibrative nucleoside transporter 1 IV: intravenous mTOR: mammalian target of rapamycin pAMPK: phospho-AMPK PBMC: peripheral blood mononuclear cell q1w: weekly dosing RNA: ribonucleic acid RP2D: recommended phase 2 dose

Data cleaning ongoing, data current as of 14 August 2020.