A first-in-human study of NUC-7738, a 3′-dA phosphoramidate, in patients with advanced solid tumors or lymphoma (NuTide:701)

Abstract Number: TPS3147
Registry Number: NCT03829254
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Background

- Nucleoside analogs form backbone therapy for solid and hematological malignancies
- 3′-deoxyadenosine (3′-dA; cordycepin): adenosine derivative first isolated from *Cordyceps sinensis*
- Adenosine required for many molecular processes, including DNA and RNA synthesis
- 3′-deoxyadenosine triphosphate (3′-dATP), the anti-cancer metabolite of 3′dA, causes cell death by incorporation into RNA and DNA
- 3′-dA not successful in clinical studies to date due to cancer resistance mechanisms, including:
  - Rapid enzymatic degradation by adenosine deaminase (ADA)
  - Cellular uptake dependent on nucleoside transporters (hENT1)
  - Conversion to the active metabolite (3′-dATP) dependent on rate limiting phosphorylation by adenosine kinase (AK)
- Resistance to chemotherapy associated with poor survival prognosis
- Effective new agents are required

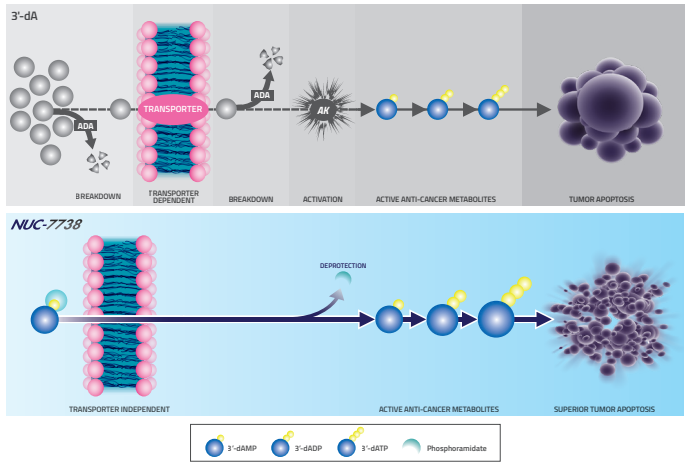
ProTides: NucleoTide Analogs

- A new class of anti-cancer agents
- Transformative phosphoramidate chemistry
- Increase intracellular levels of anti-cancer metabolites
- Broad clinical utility

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

- ProTide transformation of 3′-dA
- Overcomes key 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

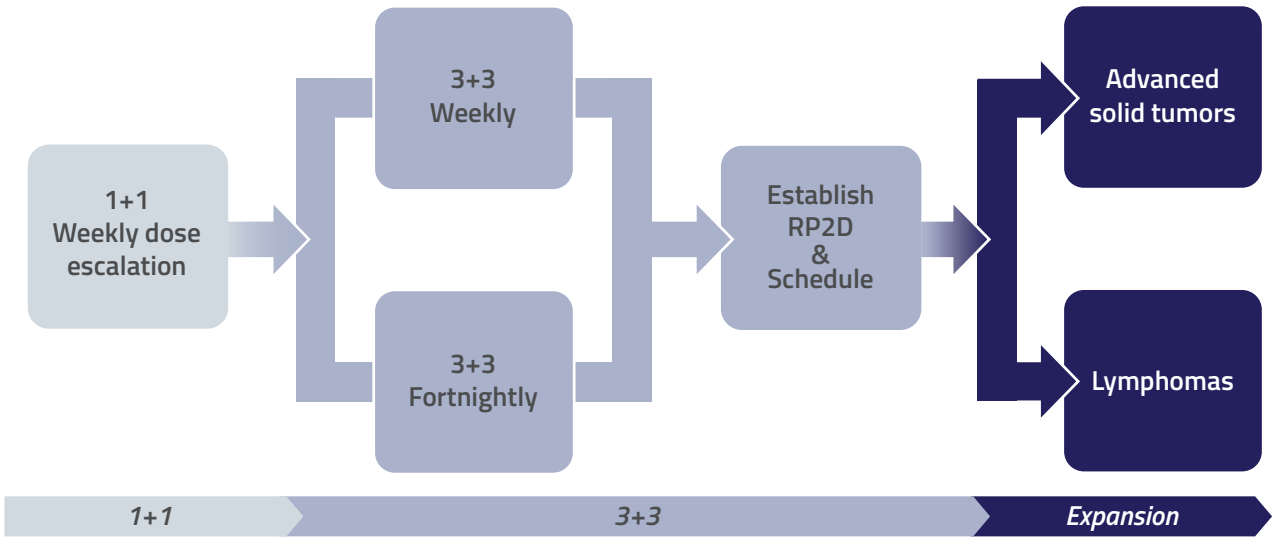
NUC-7738 overcomes the key cancer resistance mechanisms of 3′dA



NUC-7738 Maintains Cytotoxicity Under Cancer Resistance Conditions

- NUC-7738 up to 185-times greater anti-cancer activity than 3′-dA across a range of human cancer cell lines
- NUC-7738 generated up to 19-times higher levels of the active anti-cancer metabolite, 3′-dATP, than 3′-dA in human cancer cell lines
- Unlike 3′-dA, NUC-7738 cytotoxicity was not affected by the key cancer resistance conditions

NuTide:701 Study Design



First-in-human Phase I study of NUC-7738

PART 1
Patients with advanced solid tumors
not amenable to standard chemotherapy

TREATMENT
14-day cycles
NUC-7738 starting dose: 14 mg/m²
Dose-escalation in weekly (Days 1 & 8)
and fortnightly (Day 1) schedules

RP2D & Schedule

PART 2
Patients with advanced solid tumors
or lymphoma

TREATMENT
14-day cycles
Expansion at the RP2D &
schedule determined by Part 1

PRIMARY OBJECTIVES	SECONDARY OBJECTIVES	EXPLORATORY OBJECTIVES
▪ Safety & tolerability ▪ Recommended Phase II dose	▪ Pharmacokinetics ▪ Anti-cancer activity (BOR, ORR, DoR, DCR, DoSD & PFS)	▪ Biomarker evaluation ▪ Pharmacodynamics

STUDY OPEN TO RECRUITMENT

Summary

- NUC-7738 designed to overcome the key cancer resistance mechanisms associated with 3′-dA
- NuTide:701 study will determine the RP2D and schedule of NUC-7738 in patients with advanced solid tumors or lymphoma

BOR: Best overall response DCR: Disease control rate DoR: Duration of response DoSD: Duration of stable disease PFS: Progression-free survival