A Phase I first-in-human, dose-escalation and expansion study to evaluate the safety and tolerability of NUC-3373 in patients with locally advanced, unresectable or metastatic solid malignancies

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Background

- Fluoropyrimidines remain a cornerstone of cancer treatment (e.g., 5-FU, capecitabine, FUDR)
- FUDR-MP, the anti-cancer metabolite of 5-FU, causes cell death by:
  - Inhibiting thymidylate synthase (TS)
  - Reducing the pool of deoxythymidine monophosphate (dTMP)
- Poor response to 5-FU is a consequence of:
  - Over 85% of 5-FU broken down by dihydropyrimidine dehydrogenase (DPD)
  - The generation of toxic metabolites (FBAL) associated with hand-foot syndrome
- Key cancer resistance mechanisms:
  - Cellular uptake dependent upon nucleoside transporters
  - Complex enzymatic activation to yield active anti-cancer metabolite FUDR-MP
  - Thymidine phosphorylase (TP), commonly overexpressed in tumours or introduced by mycoplasma infection, breaks down 5-FU
  - Short plasma half-life of 8-14 minutes
  - Prolonged administration times (>46 hours)
- Favourable toxicology profile
- Significantly greater anti-cancer activity
- FUDR-MP generation independent of intracellular enzymatic activation
- Cellular uptake independent of nucleoside transporters
- Broad clinical utility
- Transformative phosphoramidate chemistry

NUC-3373: A ProTide Transformation of 5-FU

- Designed to overcome the key 5-FU cancer resistance mechanisms
  - Protected from breakdown by DPD or TP
  - FUDR-MP generation independent of intracellular enzymatic activation
  - Up to 330x greater cytotoxicity than 5-FU in vitro
  - Significantly greater anti-cancer activity in vivo compared to 5-FU
  - Favourable toxicology profile

Pharmacokinetics / Pharmacodynamics

- Linear and reproducible PK profile
- Intra- and inter-rater FUDR-MP detectable at 5 minutes post-infusion with a T1/2 of 14.9 ± 1.44 hours
- Intra- and inter-rater FUDR-MP still present at 48 hours

ProTides: NucleoTide Analogs

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

Study Design

- RP2D for NUC-3373 administered
- Fortnightly on days 1 and 15 of a 28-day cycle

Characteristics

- n
- Patient age (years): 36
- Median age (range): 60 (17-89)
- Median prior chemotherapeutic regimen: 8
- ECOG PS: 1/17/0

Primary Objectives

- Safety and tolerability
- BOR, ORR, DoR, DCR, PFS
- PK and PD

Secondary Objectives

- Safety
- BOR, ORR, DoR, DCR, PFS
- PK and PD

Dose Administered

- Patients received NUC-3373 at the following doses:
  - Part 1: 125 mg/m² to 1500 mg/m² in the weekly schedule
  - Part 2: 1500 mg/m² to 1875 mg/m² in the fortnightly schedule
- Dose escalation ongoing

Dose escalation:

- NUC-3373 is well-tolerated
- Multiple cycles administered (median 2; range 0.25 - 11.75)
- No hand-foot syndrome has been observed
- No Grade 4 AEs

Safety

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- Multiple cycles administered (median 2; range 0.25 - 11.75)
- No hand-foot syndrome has been observed
- No Grade 4 AEs

Treatment Related AEs

- Grade 3
- Transaminitis
- Grade 4
- Fatigue
- Sickness

Patient Case Studies

- Colorectal Cancer
  - 70 years, male
  - 6 previous lines of therapy
- Cholangiocarcinoma
  - 60 years, female
  - 1 previous line of therapy
- Basal Cell Carcinoma
  - 55 years, male
  - 2 previous lines of therapy

Conclusion

- NUC-3373 bypasses the key cancer resistance pathways of 5-FU and capecitabine
- NUC-3373 generates 366x higher intracellular levels of FUDR-MP than 5-FU in vitro
- To date, 36 patients have been enrolled: Part I n=29; Part II n=7
- NUC-3373 overcomes the key cancer resistance mechanisms associated with 5-FU and capecitabine
- NUC-3373 is well-tolerated
- Multiple cycles administered (median 2; range 0.25 - 11.75)
- No unexpected AEs
- Encouraging early signs of activity have been observed
- Dose-escalation is ongoing to establish RP2D
- NUC-3373:302 will determine the RP2D of NUC-3373 in combination with agents commonly used in colorectal cancer
- NUC-3373 has the potential to offer a more effective and safer treatment option than 5-FU or capecitabine