Interim pharmacokinetic and pharmacodynamic data from the first-in-human study of NUC-3373, a pyrimidine nucleotide analogue, in patients with advanced solid tumours


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**BACKGROUND**

Key cancer resistance mechanisms linked to reduced efficacy, poor prognosis and differential toxicity with S-1 FUUR (5FU regimen)

Poor PK properties of S-FU often necessitate prolonged administration times (e.g. 48 hours)

Fluoropyrimidine antagonism of FUUDR is the main anticancer metabolite of S-FU, which binds to and inhibits thymidylate synthase (TS), leading to cell cycle death

**S-FU Resistance Mechanisms**

**Susceptibility to breakdown**

- Over 85% of S-FU is broken down by dihydrofolate reductase (DHFR).
- Thymidylate (TMZ), possibly overproduced in tumours or introduced by malarial infection, also breaks down S-FU.

**Metabolic degeneration results in generation of toxic metabolites, such as dihydrofolate (DHF) and dihydrofolic acid (FAD)**

**Requirement of activation**

- S-FU is a prodrug that requires complex inhibitory enzymatic activation to generate FUUDR.
- Inhibitory enzymatic activation is linked to poor prognosis.

**Resistance by transport**

- Low expression of the nucleoside transporter NET1 is associated with S-FU resistance.

**NUC-3373 and S-FU mechanism of action**

**NUC-3373**

A pyrimidine nucleotide analogue designed to overcome key cancer resistance mechanisms associated with S-FU.

- A phosphonamide of FUUDR.
- Inhibits TS with an IC50 higher in cellular levels of FUUDR than S-FU in vitro.
- Up to 330x significantly greater cytotoxicity in vitro than S-FU.
- Significantly greater anti-cancer activity in vivo compared to S-FU.
- Not degraded by DHFR, unlike S-FU.
- Favoured toxicity profile compared to S-FU.

**RESULTS**

Plasma NUC-3373 and Intracellular FUDR-MP pharmacokinetics

- NUC-3373 administered as a short IV infusion on days 1, 8, 15 and 22 of a 28-day cycle in the ongoing NCT0430180 study.
- The first 6 patient cohorts received NUC-3373 at 125 mg/m2, 250 mg/m2, 500 mg/m2 and 750 mg/m2.
- Plasma and intracellular metabolites measured by LC/MS/MS, western blots of extracted proteins, PAGE.
- Intracellular NUC-3373 was detectable in 5 minutes post-injection with an IC50 of 1.6 x 10^-4 M and cell kill present at 64 hours.
- Intracellular NUC-3373 and AUC were linearly correlated to DMP in the 500 mg/m2 cohort 6.3 µM predicted DMP of 33.9 µM/10^9 cells and intracellular NUC-3373 was detectable in 64 hours.

**CONCLUSION**

- NUC-3373 is a novel pyrimidine nucleotide analogue that overcomes the key cancer resistance mechanisms associated with S-FU, and other acetoin analogues, and it is more efficacious.
- NUC-3373 generates very high intracellular concentrations of the active antineoplastic metabolite, FUUDR-MP
- TS is efficiently inhibited and repressed into TS, depleting the pool of DMP within 24 hours.
- Lack of toxic metabolic generation, suggestion of an improved tolerability profile compared to S-FU.
- NUC-3373 is resistant to S-1 FUUR-mediated cytotoxicity.
- NUC-3373 has an advantageous PK/PD profile compared to S-FU, which may allow for a more convenient dosing regimen, favourable toxicity profile and enhanced efficacy.
- Dose escalation is ongoing to establish the PK/PD profile.