First In Human Phase I study of NUC-3373, a nucleotide analogue designed to overcome fluoropyrimidine drug resistance mechanisms

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BACKGROUND

NUC-3373: Designed to overcome S-PU resistance mechanisms

A pyrimidine Nucleoside Analogue

A prodrug of 5-Fluouracil (5-FU): active metabolite of 5-FU

S-PU resistance mechanisms:

- Thymidylate Kinase (TK)
  - Required for S-PUR to 5-FU-MP
- Thymidylate Phosphorylase
  - Degradates 5% of S-PUR
- High levels associated with poor survival in colorectal cancer
- 5-FU: Required for S-PUR cellular uptake

MODE OF ACTION / METABOLISM

NUC-3373 is a potent anti-cancer agent

NUC-3373 shows up to 310x greater activity than 5-FU across a broad range of S-PUR sensitive and resistant cancer cell lines.

NUC-3373 is resistant to PDP degradation

- In the absence of PDP inhibitor (gimeracil), NUC-3373 levels remain unchanged while S-FU levels are significantly decreased (90%) (Fig. 2)

NUC-3373 demonstrates a favorable toxicity profile

- In formal toxicology studies NUC-3373 is significantly better tolerated than 5-FU
- The main toxicity associated with 5-FU after a single dose is not observed with NUC-3373.
- NUC-3373 is rapidly distributed into tissues following oral or intravenous administration.
- Phase I AUC values show low correlation of NUC-3373 dose and PDMP (‘mitotane’; NUC-3373 ratio of 0.10 and 0.03, respectively).

RESULTS

NUC-3373 overcomes all the main cancer resistance mechanisms

- Thymidylate Kinase (TK)
  - NUC-3373 inhibited activity in TK-deficient cancer cells
- Thymidylate Phosphorylase (TP)
  - NUC-3373 is resistant to TP degradation

NUC-3373 achieves high intracellular levels of active agent PDMP

- PDMP levels generated by NUC-3373 remain high in all key cancer resistance cells (overexpression of TK, SFU, TP, NPT, CM1)

NUC-3373 demonstrates superior inhibition of tumour growth in vivo

- NUC-3373 inhibited significantly greater reduction in tumour weight and volume than 5-FU in human xenograft breast and ovarian xenografts.
- NUC-3373 significantly extended tumour volumes doubling time compared to control (Fig. 5).

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