ProGem1: Phase I first-in-human study of the novel nucleotide analogue NUC-1031 in adult patients with advanced solid tumours

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BACKGROUND

ProTides
- Next generation of anticancer agents (nucleotide analogues).
- Innovative phosphoramidate technology combined with existing nucleoside analogues.
- Designed to overcome key cancer resistance mechanisms.
- Intended to benefit the majority of cancer patients.
- Improved efficacy and safety profile.

NUC-1031
- Overcomes the 3 key cellular resistance mechanisms associated with gemcitabine treatment:
  1. Kinase: Low expression of intracellular kinases
  2. Deaminase: High Expression of intracellular deaminases
  3. Nucleoside Transporter: Low Expression of cell surface transporters.
- Strong antiproliferative activity *in vitro* and *in vivo*.

Mode of Action / Metabolism

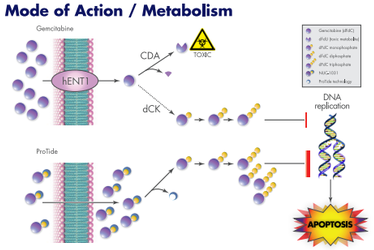

Figure 1. NUC-1031 overcomes the key resistance mechanisms associated with gemcitabine

Gemcitabine
- Deoxycytidine kinase essential for the rate limiting phosphorylation step that activates the agent.
- Cytidine deaminase degrades and inactivates gemcitabine releasing the toxic metabolite (dFdU).
- Nucleoside transporter hENT1 required for cellular uptake through the plasma membrane.

ProTides
- Release the activated monophosphate agent within the cell.
- Resistant to deaminase-mediated breakdown.
- Uptake is independent of nucleoside transporters.
- Administered at 4x gemcitabine MTD, with significantly less dFdU, in toxicology studies.

STUDY DESIGN

Objectives
- Primary
  - o Determine RP2D
  - o Evaluate safety profile
- Secondary
  - o Pharmacokinetic profile
  - o Preliminary antitumour activity

Methods
- Sequential dose-escalating cohorts (3+3 design), with NUC-1031 administered as a 5-10 minute IV bolus injection.
- Schedule A: NUC-1031 administered on days 1, 8, 15 of a 4 weekly cycle for up to 6 cycles.
- Schedule B: NUC-1031 administered on days 1, 5, 8, 12, 15, 19 of a 4 weekly cycle for up to 6 cycles.

Patient Population
- Patients aged >18 years with relapsed/refractory advanced solid tumours refractory to standard treatment.

RESULTS

Patients Characteristics
- 11 patients enrolled to date with study recruitment ongoing
- 7 females, 4 males
- Mean age 61 years
- Average number of previous chemotherapy regimens 2.1

Table 1. Patients Characteristics & Status

CANCER INDICATION	DEMOGRAPHICS			NUMBER OF COMPLETED CYCLES						CURRENT STATUS (and best RECIST)
	Previous Chemotherapy Courses	Age	Initial Dose Level (mg/m²)	1	2	3	4	5	6	
Schedule A										
Pancreatic	1	62	500							PROGRESSIVE DISEASE
Pancreatic	2	66	500							PROGRESSIVE DISEASE
Breast	2 (+3 hormonal)	67	500							STABLE DISEASE (ongoing)
Ovarian	3	58	500							STABLE DISEASE (ongoing)
Endometrial	2	60	750							STABLE DISEASE (ongoing)
Colorectal (caecum)	4	71	1000							DLT (discontinued)
Schedule B										
Cholangiocarcinoma	2	43	375							STABLE DISEASE (ongoing)
Colorectal (sigmoid)	3	73	375							STABLE DISEASE (ongoing)
Unknown primary	1	37	375							STABLE DISEASE (ongoing)
Pancreatic	1	72	375							DLT (discontinued)
Endometrial	2	67	375							ONGOING

Patient Safety
- 261 AEs reported, of which 13 were classed as SAEs. Events of Grade 3 and above are reported in Table 2.
- Very few AEs were definitely or probably related to NUC-1031.
- No AEs were unexpected.
- The most frequently recorded Grade 1 and 2 AEs were taste disturbance/dysgeusia (64%), anorexia (64%), constipation (55%) and elevated liver function tests (64%).
- Two DLTs were observed: Grade 3 injection site pain (1000mg/m² Schedule A) and Grade 5 pulmonary embolus (375mg/m² Schedule B).

Table 2. SAEs of any causality observed in patients (n=11)

ADVERSE EVENT		SCHEDULE A				SCHEDULE B		TOTAL (%)
		500mg/m² (n=4)		750mg/m² (n=11)	1000mg/m² (n=1)	375mg/m² (n=5)		
		G3	G4	G3	G3	G3	G5	
Gastrointestinal	Abdominal pain	2						2 (18%)
Respiratory	Lung infection		1			2		3 (27%)
	Dyspnoea		1					1 (9%)
	Pleural effusion					1		1 (9%)
Procedural	Injection site pain				1			1 (9%)
Vascular	Deep vein thrombosis					1		1 (9%)
	Pulmonary embolus	1					1	2 (18%)
	Hypotension				1			1 (9%)
Investigations	Elevated liver enzymes	1				2		3 (27%)
	Neutropaenia			1	1	1		3 (27%)
	Lymphopaenia					2		2 (18%)
	Thrombocytopaenia	1				1		2 (18%)
Musculoskeletal	Musculoskeletal pain					2		2 (18%)
Lymphatic System	Lower limb oedema					1		1 (9%)
General	Fatigue				1			1 (9%)
	Pyrexia				1	3		4 (36%)

Pharmacokinetics
- NUC-1031 is detected in plasma up to 24 hours EOI.
- <1% of NUC-1031 is converted in plasma to gemcitabine (dFdC).
- Plasma Cmax of the toxic deaminated gemcitabine analyte (dFdU) is significantly lower (10x lower) than reported for gemcitabine. This confirms that NUC-1031 is resistant to deamination in plasma.

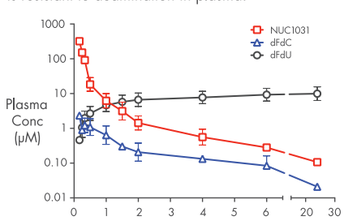

Figure 2. Mean plasma concentrations (±SD) of NUC-1031, gemcitabine (dFdC) and deaminated gemcitabine (dFdU) on Day 1 for all 11 study participants following one 5-10 min IV infusion of NUC-1031 (concentrations normalised to 500mg/m² dose).

- Intracellular gemcitabine triphosphate (dFdCTP), the active moiety, is detected up to 24 hours EOI.
- Cmax reached at 20-30 minutes EOI.
- Long half life (t½ = 9 hours).
- Reproducible between Day 1 and Day 15.

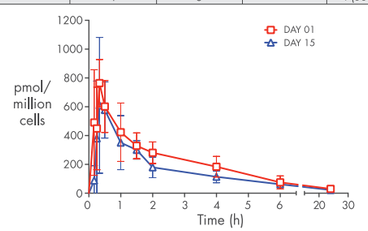

Figure 3. Mean intracellular concentrations (±SD) of gemcitabine triphosphate (dFdCTP) on Day 1 after receiving 10 minute IV infusion of NUC-1031 (concentrations normalised to 500mg/m² dose).

- NUC-1031 achieves **33x** higher intracellular gemcitabine triphosphate (dFdCTP) levels than gemcitabine (published studies).

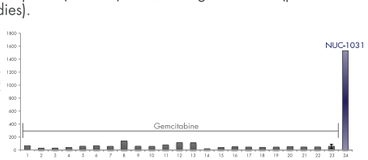

Figure 4. Comparison of intracellular dFdCTP levels between gemcitabine (taken from published studies) and NUC-1031. NUC-1031 generates 33x higher concentration than gemcitabine.

- NUC-1031 is excreted in urine mainly as dFdU (5-57% of the dose excreted in the first 24 hours EOI). Only 0.1-0.5% of NUC-1031 excreted in urine as dFdC and 1-4% as the parent compound.

Case Report
Patient 004 is a 67 year old woman diagnosed with Grade 2 invasive ductal carcinoma of the breast (ER +ve, HER2 –ve) in 2002. She underwent surgery and then received adjuvant epirubicin + docetaxel, radiotherapy and maintenance hormone therapy with tamoxifen then anastrozole until 2010. In 2010, she developed metastatic disease and was initially treated with fulvestrant but switched to capecitabine on disease progression in 2012. Her metastatic disease progressed further after 4 months of capecitabine and she was started on a Phase I trial of a PI3K inhibitor. This was discontinued after 2 cycles due to progression of her visceral disease. She started NUC-1031 in December 2012 and has recently completed 6 cycles of study treatment (NUC-1031) to RECIST Stable Disease. She has requested compassionate continuation of NUC-1031.

Clinical Activity
- The study is currently ongoing and has recruited 11 patients to date.
- 6 have ongoing RECIST Stable Disease.
- 2 have Progressive Disease.
- 2 have discontinued following DLTs (Table 2).

CONCLUSIONS
- Encouraging clinical activity of NUC-1031 monotherapy from preliminary data in patients with solid malignancies.
- PK results show very high intracellular levels of gemcitabine triphosphate with low accumulation of dFdU in study participants.
- Biomarkers will be evaluated in the upcoming expansion cohort.
- NUC-1031 overcomes all 3 key resistance mechanisms associated with gemcitabine.

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