First in human Phase I/II study of NUC-1031 in patients with advanced gynaecological cancers

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BACKGROUND

- Resistance to chemotherapy limits patient survival
- Limited treatment options for relapsed gynecological cancers

ProTides: NucleoTide Analogues

- A new class of anti-cancer agents
- Innovative phosphoramidate technology
- Overcome key cancer resistance pathways

NUC-1031: The First Anti-Cancer ProTide

- Overcomes all the key cancer resistance mechanisms associated with gemcitabine:
  - Cellular uptake independent of nucleoside transporters (hENT1)
  - Activation independent of deoxycytidine kinase (dCK)
  - Protected from cytidine deaminase inactivation (CDA)
    - Greater stability
    - Reduction in potentially toxic metabolite (dFdU)

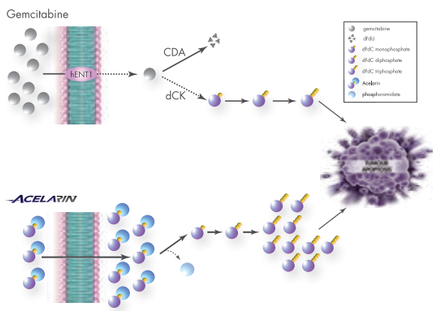


Figure 1. NUC-1031 bypasses all the key gemcitabine resistance pathways

STUDY DESIGN

Objectives

- Primary
  - Determine recommended Phase II dose
  - Assess safety profile
- Secondary
  - Define PK and PD profiles
  - Evaluate anti-tumour activity

Methods

- Sequential dose-escalating cohorts (3 + 3 design), with NUC-1031 administered as a short IV bolus injection
- Schedule A: NUC-1031 administered on days 1, 8, 15 of a 4 week cycle (n=17)
- Schedule B: NUC-1031 administered on days 1, 5, 8, 12, 15, 19 of a 4 week cycle (n=1)

Patient Population

- Patients aged ≥18 years with advanced, solid tumours relapsed/refractory to all standard treatments

RESULTS

Patient Characteristics

- Total of 18 patients with gynaecological cancers:
  - 12 Ovary (10 high grade serous (HGS) cancers)
  - 3 Endometrial
  - 2 Cervical
  - 1 Fallopian tube
- 14/18 patients received at least 2 cycles of NUC-1031
- Mean age 59 years (range 42-78)
- Average 3.5 prior chemotherapy regimens
- Total of 18 patients with gynaecological cancers:
  - All 10 HGS patients were platinum resistant
  - Average platinum resistant interval 3.7 months (range 0.3-6.9)

Pharmacokinetics

Plasma

- NUC-1031 plasma half life is more favourable than gemcitabine (8.3 hours versus 1.5 hours respectively)

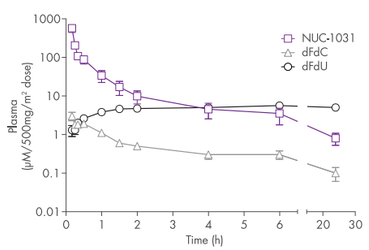


Figure 2. Plasma concentrations of NUC-1031, dFdC and dFdU

Intracellular dFdCTP

- C_{max} reached at 30 minutes after end of injection
- Long half life: 12.2 hours
- At 24 hours NUC-1031 achieves levels of dFdCTP higher than reported for gemcitabine at its C_{max} at 2 hours

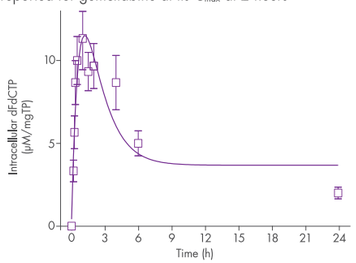
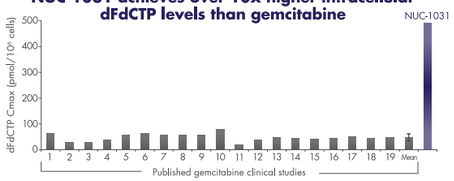


Figure 3. Intracellular concentrations of dFdCTP achieved by NUC-1031

NUC-1031 achieves over 10x higher intracellular dFdCTP levels than gemcitabine



Patient Safety

- No unexpected Adverse Events (AEs)
- Most common AEs* Grade 1 or 2 were: fatigue; transaminitis; nausea; anemia; thrombocytopaenia

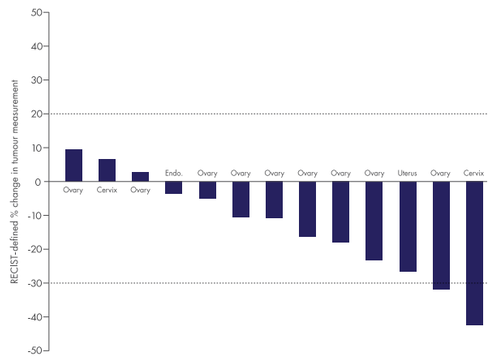
AEs Grade 3 or 4 occurring in ≥ 5% patients*

Schedule	A						B
Dose (mg/m²)	675 mg/m²	725 mg/m²	750 mg/m²	825 mg/m²	900 mg/m²	1000 mg/m²	375 mg/m²
Patient numbers	1	2	2	2	5	2	1
Blood and Lymphatic System Disorders							
Neutropaenia		1	1		1	2	1
Leucopaenia		1				1	1
Thrombocytopaenia				1		1	
General Disorders and Administration Site Conditions							
Fatigue	1			1	2		
Hepatobiliary Disorders							
Increased ALT		1				1	

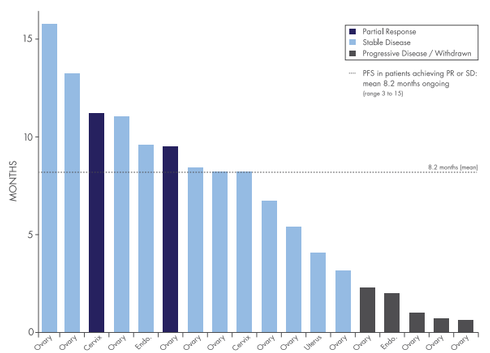
*Considered definitely, probably or possibly related to NUC-1031

Efficacy

Best Overall Response



Progression Free Survival



Disease Control Rate RECIST*

	All Patients (n=18)		Evaluable Patients (n=14)+	
	n	%	n	%
Partial Response	2	11	2	14
Stable Disease	11	61	11	79
Disease Control	13	**72**	13	**93**

*Disease Control = PR + SD

+Evaluable patients ≥ 2 Cycles of NUC-1031

Patient Case Studies

Cervix
51 years, poorly differentiated squamous cell cervical cancer
Cisplatin then radiotherapy: relapsed within 6 months
Carboplatin + paclitaxel + cediranib: relapsed within 4 months
NUC-1031: Partial Response (43% reduction in tumour volume)
PFS = 11 months.

Ovary
58 years, bilateral serous ovarian cancer
Carboplatin + paclitaxel: relapsed within 8 months
Caelyx + VEGFR-2: relapsed within 9 months
Paclitaxel: disease progression
NUC-1031: Stable Disease (11% reduction in tumour volume)
PFS = 15 months.

Fallopian Tube
61 years, with endometrioid adenocarcinoma of Fallopian tube
Carboplatin + paclitaxel: relapsed 32 months later
Carboplatin + paclitaxel + cediranib: relapsed within 4 months
Paclitaxel: relapsed within 7 months
Carboplatin + paclitaxel + AKT inhibitor: progressive disease
NUC-1031: Partial Response (32% reduction in tumour volume)
CA125 reduced by 91% (372 to 35)
PFS = 9 months.

CONCLUSIONS

- Impressive disease control rate in refractory gynaecological cancers
- Durable PFS of 8.2 months (ongoing)
- Well tolerated with no unexpected AEs
- Generates high intracellular levels of the active agent dFdCTP
- Overcomes key cancer resistance pathways
- Ongoing Phase I/II study in combination with carboplatin
- Phase III global studies planned in ovarian cancer

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