Final results from the first in human Phase I/II study of NUC-1031 in patients with solid tumours

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BACKGROUND

ProTides: NucleoTide Analogues

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

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)

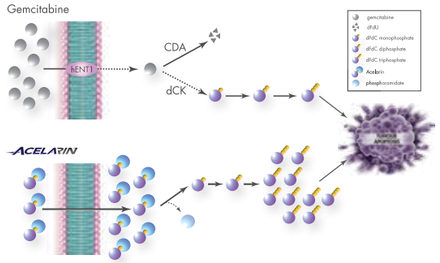


Figure 1. NUC-1031 bypasses all the key gemcitabine resistance pathways

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=62)
- Schedule B: NUC-1031 administered on days 1, 5, 8, 12, 15, 19 of a 4 week cycle (n=6)

Patient Population

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

RESULTS

Patient Characteristics

- 68 patients (46 female, 22 male)
- Mean age 56 years (range 20-83)
- Average 2.7 prior chemotherapy regimens
- 18 primary tumour sites: Ovary 12; Pancreas 9; Biliary 7; Lung 7; Colon 7; Breast 4; CUP 3; Endometrium 3; Mesothelioma 3; Oesophageal 3; Cervix 2; Fallopian tube 1; Trophoblast 1; Renal 1; Adrenal 1; Gastric 1; Anal 1; Thymus 1; Osteosarcoma 1

Pharmacokinetics

Plasma

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

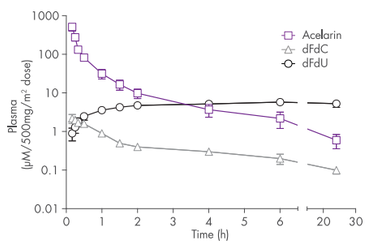


Figure 2. Plasma concentrations of NUC-1031, dFdC and dFdU

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
- High dFdCTP levels maintained after 19 cycles (no emergence of cancer resistance)

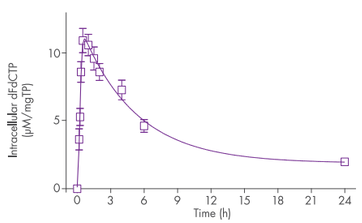
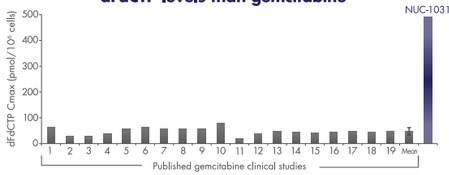


Figure 3. Intracellular concentrations of dFdCTP achieved by NUC-1031

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: transaminitis; fatigue; decreased WBC; thrombocytopaenia
- 26 Serious Adverse Events*
- 5 patients had Grade 4 AEs*: neutropaenia; thrombocytopaenia; sepsis; raised GGT; dyspnoea; posterior reversible encephalopathy syndrome (PRES); hypomagnesaemia
- 4 DLTs were observed:
  - Grade 3 elevated ALT (725 mg/m² & 1000 mg/m²)
  - Grade 4 thrombocytopaenia (750 mg/m² & 1000 mg/m²)

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

Schedule	A							B
Dose (mg/m²)	500 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	4	3	6	8	16	15	7	6
Blood and Lymphatic System Disorders								
Neutropaenia			1	3		5	2	1
Lymphopaenia			1			5		2
Thrombocytopaenia	1			2	2		1	1
Leucopaenia			1	1		1	1	1
General Disorders and Administration Site Conditions								
Fatigue		1			2	5	2	
Gastrointestinal Disorders								
Nausea				1			1	
Hepatobiliary Disorders								
Increased ALT			1				1	2
Increased AST								2
Hypoalbuminaenia				1		1		
Metabolism and Nutrition Disorders								
Hypomagnesaemia		1		1				
Hyponatraemia		1		1				
Anorexia				1			1	
Respiratory, Thoracic and Mediastinal Disorders								
Pulmonary Embolus	1					1		

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

Efficacy

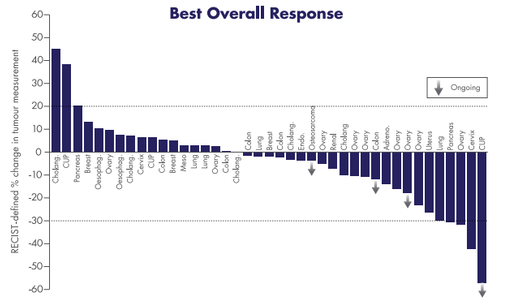
Disease Control Rate RECIST*

	All Patients (n=68)		Evaluable Patients (n=49)+	
	n	%	n	%
Partial Response	5	7	5	10
Stable Disease	33	49	33	67
Disease Control	38	**56**	38	**78**

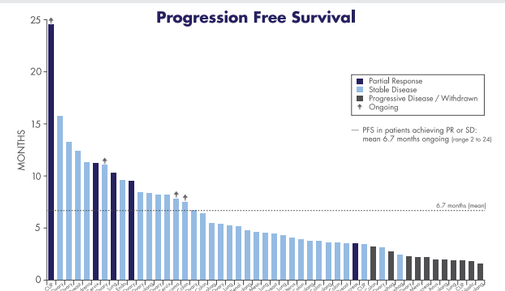
*Disease Control = PR + SD

+Evaluable patients ≥ 2 Cycles of NUC-1031

Best Overall Response



Progression Free Survival



Patient Case Studies

Pancreas
Female, 69 years, pancreatic cancer with liver metastases
Progressed on gemcitabine
Biomarkers: low hENT1; low dCK; high CDA
NUC-1031: Partial Response
92% reduction in CEA; 73% reduction in CA19.9
PFS = 4 months.

Ovary
Female, 61 years, ovarian adenocarcinoma with multi-site metastases
5 prior chemotherapy regimens (platinum refractory)
Biomarkers: low hENT1; low dCK; normal CDA
NUC-1031: Partial Response
91% reduction in CA125
PFS = 10 months.

Biliary
Female, 48 years, cholangiocarcinoma with liver, lung and peritoneal metastases
Refractory to gemcitabine + cisplatin
Biomarkers: no tissue available
NUC-1031: Stable Disease (10% reduction in tumour volume)
PFS = 8 months.

Lung
Female, 60 years, metastatic NSCL adenocarcinoma
3 prior chemotherapy regimens
Biomarkers: low hENT1; low dCK; high CDA
NUC-1031: Partial Response
PFS = 10 months.

CUP
Male, 54 years, unknown primary with lung and liver metastases
Progressed on epirubicin + cisplatin + capecitabine
Biomarkers: unknown hENT1; high dCK; high CDA
NUC-1031: Partial Response (58% reduction in tumour volume)
PFS = 24 months ongoing.

CONCLUSIONS

NUC-1031

- Impressive disease control in a high proportion of patients
- Durable PFS of 6.7 months (ongoing)
- Active in a broad range of cancers
- Disease control in patients refractory to/relapsed on prior chemotherapy, including gemcitabine
- Well tolerated with no unexpected AEs
- Generates high intracellular levels of the active agent dFdCTP
- Overcomes key cancer resistance pathways
- Molecular characterisation may aid future patient selection
- Phase III global studies planned in ovarian, biliary and pancreatic cancers

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