A Phase Ib study of NUC-1031 and carboplatin combination for patients with recurrent ovarian cancer

Sarah Blagden[1,2], Ajithkumar Sukumaran[2], Chathunissa Gnanaranjan[3], Victoria Woodcock[1], Magdalena Slusarczyk[4], Michaela Serpi[4], David Harrison[5], Mark Middleton[1], Hani Gabra[2], Essam Ghazaly[3]

1) Early Phase Trials Unit, Department of Oncology, University of Oxford, UK 2) Department of Oncology, Hammersmith Hospital, Imperial College, London, UK 3) Centre for Haemato-Oncology, Barts Cancer Institute, London, UK
4) School of Pharmacy and Pharmaceutical Sciences, Cardiff University, UK 5) School of Medicine, University of St Andrews, UK

BACKGROUND

- Resistance to chemotherapy reduces patient survival
- Limited effective treatment for recurrent ovarian cancer
- Requirement for new agents and combinations

ProTides: NucleoTide Analogues

- Overcome cancer drug resistance
- New class of anti-cancer agents
- Innovative phosphoramidate chemistry
- Broad clinical utility

NUC-1031: The First Anti-Cancer ProTide

- A ProTide transformation of gemcitabine
- Overcomes all the known gemcitabine resistance mechanisms:
  - Cellular uptake independent of nucleoside transporters (hENT1)
  - Activation independent of deoxycytidine kinase (dCK)
  - Protected from inactivation by cytidine deaminase (CDA)
    - Greater stability
    - Reduction in potentially toxic metabolites

NUC-1031: First-in-Human Study

- Strong efficacy signal[1] including patients with ovarian cancer[2]
  - 90% Disease Control Rate (PR 1; SD 8; n=10)
  - Progression Free Survival 8.3 months
- Well tolerated
  - No unexpected Adverse Events (AEs)
  - Manageable myelosuppression & reversible transaminase elevation
- Generates high intracellular levels of the active anti-cancer metabolite, dFdCTP
  - 27x greater AUC of dFdCTP than gemcitabine
    (AUC$_{0\text{-}24h}$: 4.4 nmol/10^6 cells.hr vs. 0.16 nmol/10^6 cells.hr)

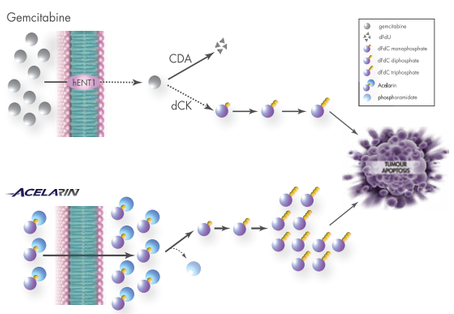


Figure 1. NUC-1031 bypasses all the known cancer resistance pathways to gemcitabine

STUDY DESIGN

Objectives

- Primary
  - Determine recommended Phase II dose (RP2D) of NUC-1031 and carboplatin combination
- Secondary
  - Evaluate safety profile and tolerability
  - Evaluate Objective Response Rate
  - Evaluate Disease Control Rate
  - Evaluate Progression Free Survival
  - Evaluate Pharmacokinetics Profile

Methods

- Sequential dose-escalating cohorts (3 + 3 design), with NUC-1031 administered on days 1 & 8 with carboplatin on day 1, q3-weekly for 6 cycles

Patient Population

- Patients aged ≥18 years with epithelial cancer of the ovary, fallopian tube or primary peritoneum
- Relapsed having previously received platinum-containing chemotherapy regimen

RESULTS

Patient Characteristics

- 22 patients
- Median age 65 years (range 37-77)
- Median 3 prior chemotherapy regimens (range 2-6)
- 17 patients platinum resistant including 7 refractory; 4 partially platinum sensitive; 1 platinum sensitive
- 16 patients had high grade serous carcinomas
- 20/22 patients evaluable for efficacy (received ≥2 cycles + CT scan)

Pharmacokinetics

Plasma

NUC-1031 PK profile remains consistent when administered in combination with carboplatin or as a single agent
(combination vs. single agent; all values normalised to 500 mg/m^2 dose)

- AUC$_{0\text{-}24h}$: 144.7 µM.hr vs. 137.6 µM.hr
- $T_{1/2}$: 4.6 hours vs. 4.8 hours
- Cl: 3.4 L vs. 3.5 L
- V_d: 0.049 L/Kg vs. 0.043 L/Kg

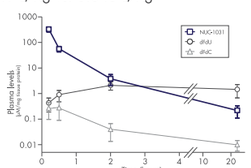


Figure 2. Plasma levels of NUC-1031, dFdC and dFdU over time. Doses normalised to 500 mg/m^2

Intracellular dFdCTP

Levels of active metabolite, dFdCTP, are further increased when NUC-1031 is combined with carboplatin

- 97% increase in dFdCTP AUC$_{0\text{-}24h}$
  (208.7 µM/mgTP.hour normalised to 500 mg/m^2 dose)
- 40% increase in dFdCTP C_{max}
  (14.9 µM/mgTP normalised to 500 mg/m^2 dose)

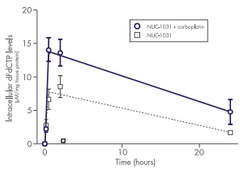


Figure 3. Intracellular dFdCTP levels achieved by NUC-1031 + carboplatin compared to single agent NUC-1031. Doses normalised to 500 mg/m^2

Safety Profile

- NUC-1031 + carboplatin well tolerated
  - No unexpected adverse events reported
- 5 Dose Limiting Toxicities (DLTs) in 4 patients
  - 2 thrombocytopaenia Grade 4
    (NUC-1031 625 mg/m^2 and 750 mg/m^2 + carboplatin AUC4)
  - 2 fatigue Grade 3 (NUC-1031 625 mg/m^2 + carboplatin AUC4)
  - 1 neutropaenia Grade 4 (NUC-1031 750 mg/m^2 + carboplatin AUC4)
- 9 Serious Adverse Events reported in 7 patients: fatigue, thrombocytopaenia (3), infection, vomiting, hyponatraemia, urinary tract infection, respiratory tract infection and dyspnoea
- No DLTs in NUC-1031 500 mg/m^2 + carboplatin AUC5 cohort

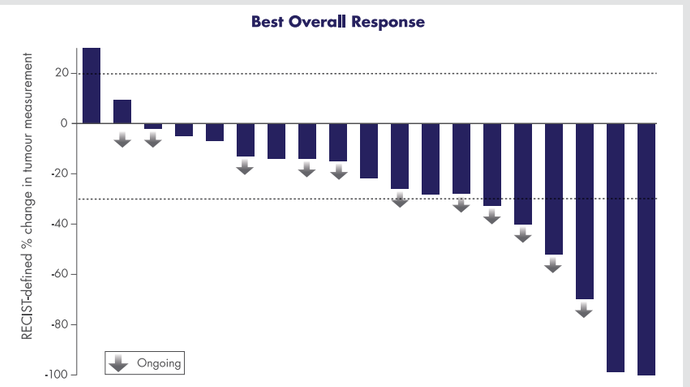
AEs Grade 3 or 4*

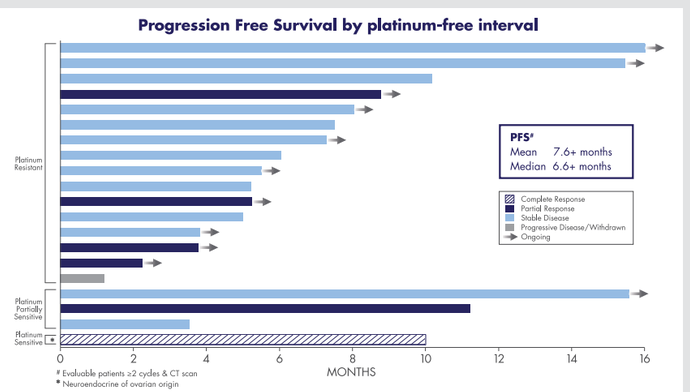
Dose (NUC-1031 + carboplatin)	500mg/m^2 + AUC5	625mg/m^2 + AUC4	750mg/m^2 + AUC4	750mg/m^2 + AUC5
Patient Numbers	**9**	**6**	**6**	**1**
Neutropaenia	3	3	4	1
Leucopaenia	1	1	4	1
Lymphopaenia			3	
Thrombocytopaenia	3	2	2	
Anaemia	1	1	1	
Fatigue		3	2	

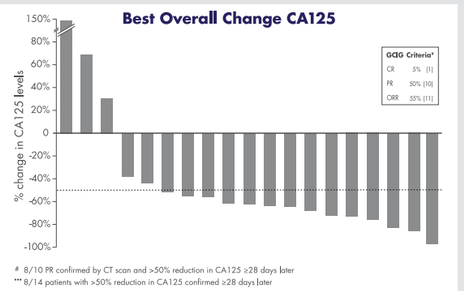
* Occurring in ≥10% patients and considered definitely, probably or possibly related to treatment

Efficacy

- Strong efficacy signal for NUC-1031 + carboplatin
  - 95% DCR in RECIST evaluable patients
  - PFS 6.6 months durable & ongoing
  - 74% of patients achieved >50% reduction in CA125***







8/10 PR confirmed by CT scan and >50% reduction in CA125 ≥28 days later
** 8/14 patients with >50% reduction in CA125 confirmed ≥28 days later

Disease Control Rate RECIST#

	All Patients (n=22)		Evaluable Patients* (n=20)	
	n	%	n	%
Complete Response§	1	5	1	5
Partial Response§	5	23	5	25
Objective Response Rate	6	**28**	6	**30**
Stable Disease	13	59	13	65
Disease Control Rate	19	**86**	19	**95**

Disease Control Rate = CR + PR + SD
* Evaluable patients ≥2 Cycles of NUC-1031 + CT scan
§ 3/5 PR confirmed by CT scan ≥28 days later; CR unconfirmed

CONCLUSIONS

NUC-1031 + carboplatin combination

- Regimen is efficacious
  - ORR: 30%
  - DCR: 95%
  - PFS: 6.6 months durable & ongoing
- Regimen is well tolerated
  - DLTs: myelosuppression & fatigue (transient)
  - No unexpected AEs
- PK data suggest positive interaction between agents
  - High intracellular levels of the active metabolite dFdCTP
- RP2D: NUC-1031 500 mg/m^2 + carboplatin AUC5
- Future studies in platinum sensitive ovarian cancer planned

(1) Blagden et al., 2015a ASCO Poster (2) Blagden et al., 2015b ASCO Poster

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