# PRO-002: A Phase Ib dose-escalation study of NUC-1031 with carboplatin for recurrent ovarian cancer

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## BACKGROUND

- Resistance to chemotherapy reduces patient survival
- Limited effective treatments for recurrent ovarian cancer
- Effective new agents and combinations required

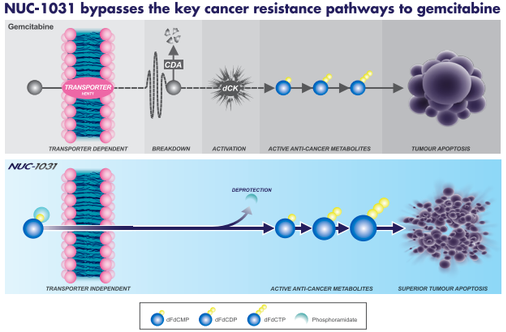
### ProTides: NucleoTide Analogues

- Designed to overcome key cancer resistance mechanisms
- Transformative phosphoramidate chemistry
- Increased intracellular levels of active anti-cancer metabolite, dFdCTP
- Broad clinical utility

### NUC-1031: The First Anti-Cancer ProTide

- NUC-1031 is a first-in-class nucleotide analogue
- A ProTide transformation of gemcitabine
- Overcomes the key gemcitabine resistance mechanisms[1,2]
  - Cellular uptake independent of nucleoside transporters (hENT1)
  - Activation independent of deoxycytidine kinase (dCK)
  - Protected from breakdown by cytidine deaminase (CDA)
    - Greater stability
    - Reduction in toxic metabolites

### NUC-1031 bypasses the key cancer resistance pathways to gemcitabine




### PRO-001: First-in-Human Study

- Highly active as a single-agent in relapsed/refractory cancers[3]
  - 78% disease control rate (DCR) in advanced solid tumours
  - 93% DCR in patients with gynaecological cancers
- Well-tolerated
  - No unexpected adverse events (AEs)
  - Manageable myelosuppression and reversible transaminase elevation
- Generated considerably higher intracellular levels dFdCTP compared with gemcitabine on an equimolar basis[2]
  - 217× greater $C_{max}$
  - 139× greater AUC

## STUDY DESIGN

### Objectives

Primary
- Determine recommended Phase II dose (RP2D) of NUC-1031 + carboplatin combination

Secondary
- Evaluate safety profile and tolerability
- Objective Response Rate (ORR)
- Clinical Benefit Rate (CBR)
- Progression Free Survival (PFS)
- Pharmacokinetics (PK)

### Methods

- 4 dose cohorts with NUC-1031 (500, 625 & 750 mg/m²) administered on days 1 & 8 + carboplatin (AUC 4 or 5) on day 1, q3-weekly for ≤6 cycles

### Patient Population

- Aged ≥18 years with epithelial cancer of the ovary, fallopian tube or primary peritoneum
- Relapsed ≤24 months from completion of platinum-containing regimen

## RESULTS

### Patient Characteristics

- 25 patients (median age 64 years)
- 3 prior chemotherapy regimens (median; range 2-6)
- 10 patients received prior carboplatin + gemcitabine
- BRCA status: 9 positive; 4 negative; 12 unknown
- 23 patients response evaluable (received ≥1 cycle)
- Status from last platinum-containing regimen:
  - 10 platinum resistant
  - 7 platinum refractory
  - 4 partially platinum sensitive
  - 2 platinum sensitive

### Pharmacokinetics

Intracellular Active Anti-Cancer Metabolite: dFdCTP

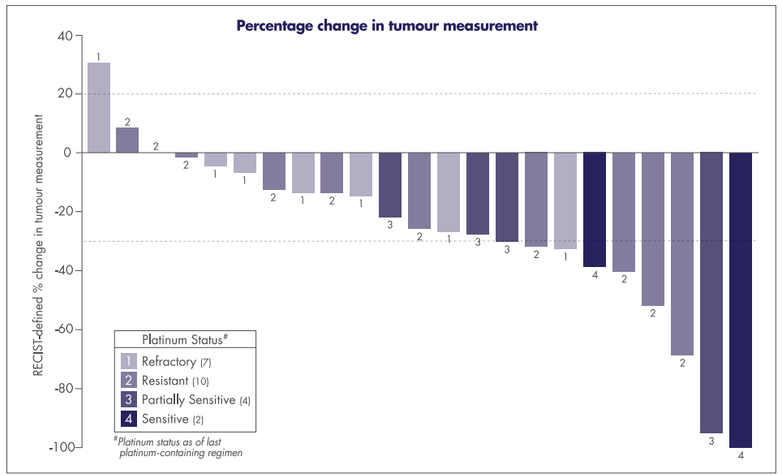
- Combination with carboplatin rapidly generated very high intracellular dFdCTP levels ($C_{max}$=14.0 µM/mg, Tissue Protein/500 mg/m² and $T_{max}$=30 min)
- High dFdCTP levels maintained for 24 hours

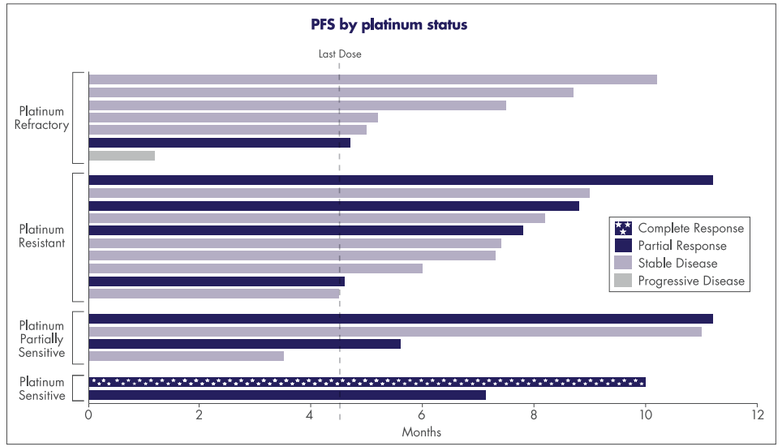
### Safety Profile

- NUC-1031 + carboplatin well tolerated
  - No unexpected AEs reported
- 6 dose-limiting toxicities (DLTs) in 4 patients:
  - 2 Grade 4 thrombocytopaenia (NUC-1031 625 mg/m² & 750 mg/m² + carboplatin AUC4)
  - 3 Grade 3 fatigue (NUC-1031 625 mg/m² + carboplatin AUC4)
  - 1 Grade 4 neutropaenia (NUC-1031 750 mg/m² + carboplatin AUC4)
- No thrombocytopaenia in the platinum partially sensitive or sensitive patients (n=7)

### Most Common (≥10% patients) Grade 3/4 TEAEs

| NUC-1031 + carboplatin | 500 mg/m² + AUC5 (n=12) | 625 mg/m² + AUC4 (n=6) | 750 mg/m² + AUC4 (n=6) | 750 mg/m² + AUC5 (n=1) | Total (n=25) |
|---|---|---|---|---|---|
| Neutropaenia | 42% (5) | 50% (3) | 67% (4) | 100% (1) | 52% (13) |
| Leukopaenia | 8% (1) | 17% (1) | 67% (4) | 100% (1) | 28% (7) |
| Thrombocytopaenia | 33% (4) | 33% (2) | 33% (2) | 0 | 32% (8) |
| Fatigue | 0 | 50% (3) | 17% (1) | 0 | 16% (4) |
| Anaemia | 17% (2) | 17% (1) | 0 | 0 | 12% (3) |
| Lymphopaenia | 0 | 0 | 50% (3) | 0 | 12% (3) |




### Efficacy

- Overall Response Rate*: 39% (n=9)
  - Complete Response: 4% (n=1)
  - Partial Response: 35% (n=8)
- Stable Disease: 57% (n=13). Duration 7.4 months (range 3.5-11.0 months)
- Clinical Benefit Rate (RECIST Best Response CR, PR, SD ≥12 weeks): 96% (n=22)
- PFS: 7.4 months (range 1-11 months)
- 3/6 patients resistant to their first platinum-containing regimen (carboplatin + taxol) achieved a PR
- 17 platinum refractory/resistant patients achieved an ORR of 29%
- 6 platinum partially sensitive/sensitive patients achieved an ORR of 67%
- 1 patient had previously progressed on olaparib and achieved a PR (39% tumour volume reduction, PFS 7.2 months)

### Best Overall Response

| | All Patients (n=25) | | Evaluable Patients (n=23) | |
|---|---|---|---|---|
| | n | % | n | % |
| Complete Response | 1 | 4 | 1 | 4 |
| Partial Response | 8 | 32 | 8 | 35 |
| **Objective Response Rate** | 9 | **36** | 9 | **39** |
| Stable Disease | 13 | 52 | 13 | 57 |
| **Clinical Benefit Rate** | 22 | **89** | 22 | **96** |

*A confirmatory scan was not performed in all responders

## CONCLUSION

- NUC-1031 + carboplatin is an effective combination:
  - ORR 39%
  - SD 57%
  - CBR 96%
- Regimen is well-tolerated
  - DLTs: myelosuppression and fatigue
  - No unexpected AEs
- NUC-1031 is stable in plasma and rapidly generated high intracellular levels of active anti-cancer metabolite, dFdCTP, that were maintained for 24 hours
- RP2D was 500 mg/m² NUC-1031 on days 1 & 8 + AUC5 carboplatin day 1, q21d
  - NUC-1031 can be combined with carboplatin at an AUC5, unlike gemcitabine
- NUC-1031 currently in Phase II study (PRO-105) for patients with platinum resistant ovarian cancer
- Phase III study planned for combination of NUC-1031 + carboplatin for patients with platinum sensitive ovarian cancer

1. Slusarczyk *et al. J Med Chem* 2014; 27:513-542. 2. Blagden *et al.* AACR poster 2016. 3. Blagden *et al.* ASCO poster 2015.

Data current as of 1 Sept 2017. Data cleaning ongoing.