A Phase II open-label study of NUC-1031 in patients with platinum-resistant ovarian cancer (PRO-105)

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Background
- Ovarian cancer is the most common cause of gynecological cancer death and the fifth leading cause of death from cancer in women¹.
- Patients with platinum-resistant ovarian cancer have limited treatment options.

ProTides: NucleoTide Analogs
- A new class of anti-cancer agents.
- Transformative phosphoramidate chemistry.
- Designed to overcome key cancer resistance mechanisms.
- Increased intracellular levels of active anti-cancer metabolites.
- Broad clinical utility.

NUC-1031: The First Anti-Cancer ProTide
- A ProTide transformation of gemcitabine.
- Overcomes key resistance mechanisms²,³
  - 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 generated 217-times higher intracellular concentrations of active anti-cancer metabolite, dFdCTP than gemcitabine.

PRO-001 Study

Efficacy in Gynecological Cancer Patient Subset³
- Highly active as a single agent in relapsed/refractory gynecological cancers (median prior chemotherapy regimens 3.5).
- 18 patients treated with NUC-1031; 14 patients response evaluable (received ≥2 cycles and CT scan).
  - 93% Disease Control Rate (DCR) in evaluable patients.
  - 2 Partial Responses (PR) and 11 Stable Diseases (SD).
- Well tolerated. Best overall response in PRO-001 gynecological cancer subset.

PRO-002 Study

Efficacy with NUC-1031 + Carboplatin Combination⁴,⁵
- Highly active as a combination therapy with carboplatin in both platinum-resistant and platinum-sensitive patients (median prior chemotherapy regimens 3).
- 25 patients treated with NUC-1031 + carboplatin; 23 patients response evaluable.
  - 96% DCR in evaluable patients.
  - 1 Complete Response (CR), 8 PRs*, 13 SDs.
- Well tolerated.
- Levels of active anti-cancer metabolite, dFdCTP, are further increased when NUC-1031 is combined with carboplatin.

PRO-005 Study Design

Primary objectives
- Objective Response Rate at selected dose (500mg/m² or 750mg/m²).

Secondary objectives
- Change from baseline in tumor size.
- Duration of Overall Response.
- Progression-Free Survival.
- Time to Disease Progression.
- Disease Control Rate.
- Best Overall Response (GOG criteria including CA125).
- Overall Survival.
- Safety.
  - Assess NUC-1031 administered over multiple cycles.
  - Explore relationships between NUC-1031 PK/PD and clinical activity.

Exploratory
- Genomic, transcriptomic and proteomic biomarkers.
- Quality of Life (FOSI-18 & EQ-5D-5L).

Patient Population
- Platinum-resistant epithelial cancer of the ovary, fallopian tube or primary peritoneum.
- ≥3 prior lines of chemotherapy.
- Aged ≥18 years.
- ECOG performance status of 0 or 1.
- Measurable disease, as defined by RECIST.

PRO-105 Study Schema

Patients with platinum-resistant epithelial cancer of the ovary, fallopian tube or primary peritoneum who have received ≥3 lines of chemotherapy.

Patient stratified for BRCA mutation status and number of prior chemotherapy lines.

Patients randomized to NUC-1031 at 500mg/m² or 750mg/m² on days 1, 8 and 15 of a 28-day cycle (Part 1).

- Stratified for:
  - BRCA 1/2 mutation status.
  - 3 or >3 prior chemotherapy lines.

- One dose level will be selected for further evaluation in Part 2 based on safety, PK, dosing intensity and clinical activity.

- Enrollment will continue in Part 2 until 44 response evaluable patients are recruited at the selected dose.

Recruitment Status
- 35 patients have been randomized into Part 1.
- 15 US and 8 UK sites are currently recruiting.

Summary
- NUC-1031 previously shown to be highly active and well tolerated in patients with advanced gynecological cancer (PRO-001 / PRO-002 studies).
- PRO-105 will determine the optimal dose of NUC-1031 for treatment of patients with platinum-resistant ovarian cancer who have received ≥3 prior lines of chemotherapy.

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