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 women[1]
- Patients with platinum-resistant ovarian cancer have limited treatment options

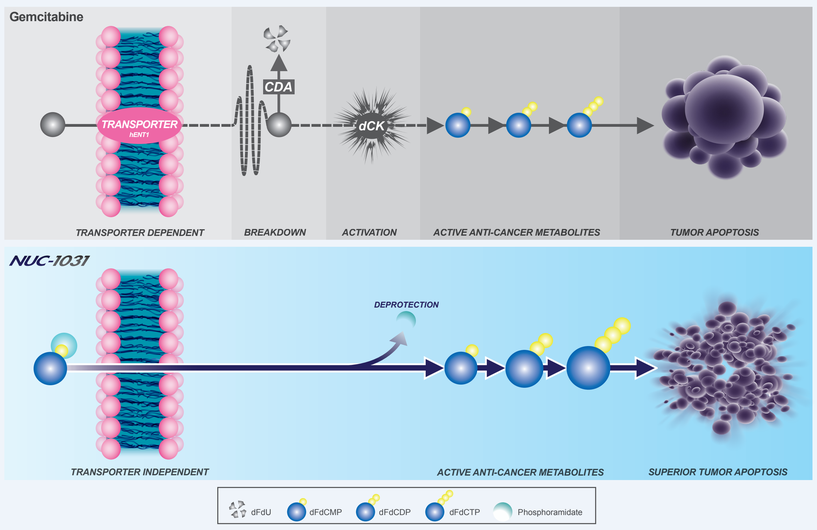
ProTides: NucleoTide Analogs

- 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 mechanisms[2,3]
  - 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 overcomes the key cancer resistance mechanisms of gemcitabine



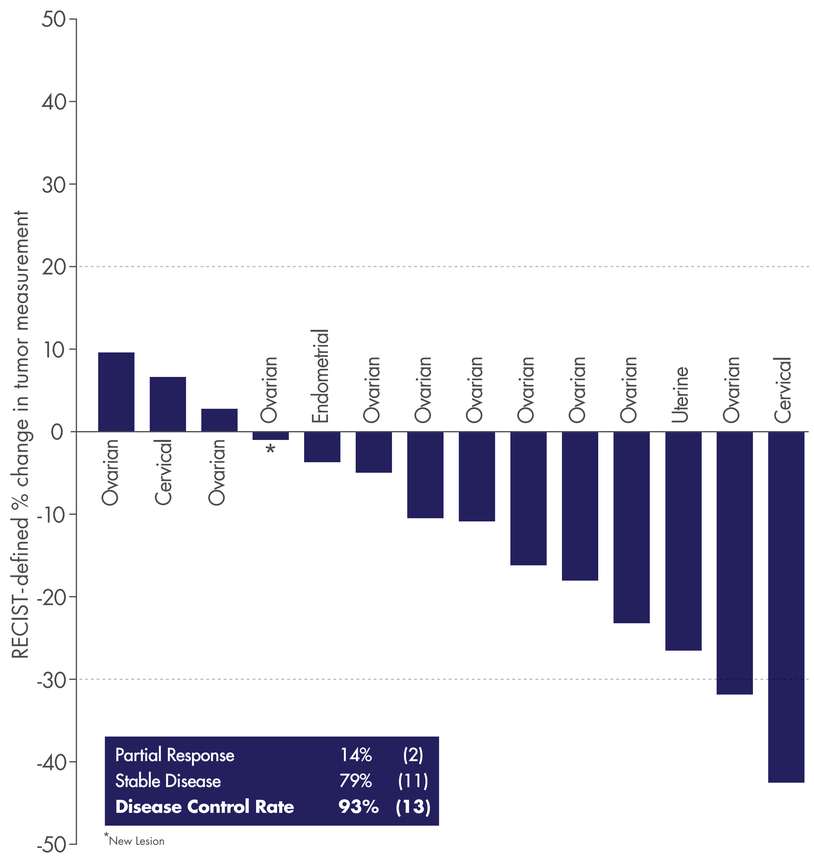
- NUC-1031 generated 217- times higher intracellular concentrations of active anti-cancer metabolite, dFdCTP than gemcitabine

PRO-001 Study

Efficacy in Gynecological Cancer Patient Subset[3]

- 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

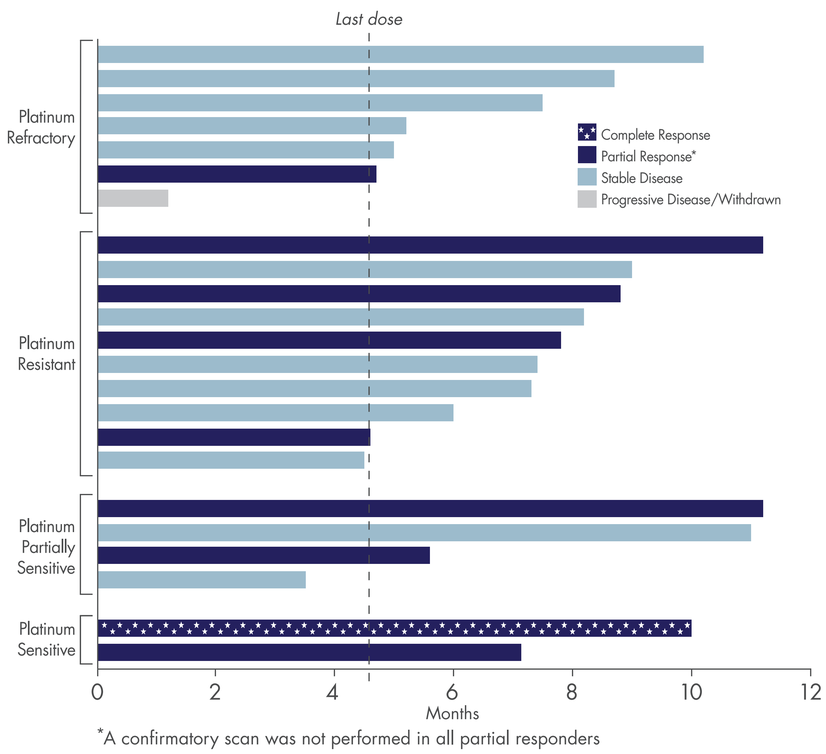


PRO-002 Study

Efficacy with NUC-1031 + Carboplatin Combination[4,5]

- 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-002: Progression-Free Survival by platinum status



*A confirmatory scan was not performed in all partial responders

PRO-105 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 (GCIG criteria including CA125)
- Overall Survival
- Safety
  - Assess NUC-1031 administered over multiple cycles
  - Explore relationships between NUC-1031 PK/PD and clinical activity

Exploratory

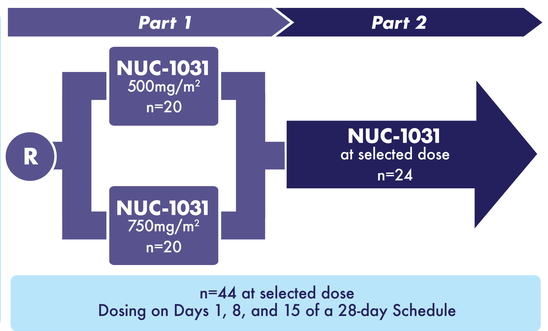
- Genomic, transcriptomic and proteomic biomarkers
- Quality of Life (FOSI-18 & EQ-5D-5L)

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



Patients stratified for BRCA mutation status and number of prior chemotherapy lines

- Patients are 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

1. Siegel R *et al, CA Cancer J Clin* 2014; 64: 9–29 2. Slusarczyk *et al, J Med Chem* 2014; 27:513-542 3. Blagden *et al, J Clin Oncol* 2015;33; Suppl abstr 2514
4. Blagden *et al, J Clin Oncol* 2016;34; Suppl abstr 5565 5. Blagden *et al, Ann Oncol* 2017; 28; Suppl abstr 5; 968P