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

PRETAXID: Nucleotide Analog
- Designed to overcome key cancer resistance mechanisms
- Transformative phosphoramide chemistry
- Increased intracellular levels of active anticancer metabolite, dATCP
- Broad clinical utility

NUC-1031: The First Anti-Cancer Pretaxid
- NUC-1031 is a first-in-class nucleotide analog
- A Proline transformation of genetaxid
- Overcomes the key genetaxid resistance mechanisms
- Cellular uptake independent of nucleoside transporters (hENTs)
- Activation independent of deoxyribonucleosides (dXN)
- Protected from breakdown by cytidine deaminase (CDM)
- Greater efficacy
- Reduction in toxic metabolites

NUC-1031 bypasses the key cancer resistance pathways to gemcitabine

STUDY DESIGN

Objectives
- Determine recommended Phase II dose (RP2D) of NUC-1031 + carboplatin combination
- Secondary Objectives
- 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 (0.6, 1.2, 2.5, 5.0 mg/kg) administered on days 1 & 8 + carboplatin (50 mg/m²) on day 1

Patient Population
- Adult females with epithelial cancer of the ovary, fallopian tube or primary peritoneum
- At least 26 months from completion of platinum-containing regimen

RESULTS

Patient Characteristics
- 25 patients (mean age 64 years)
- 3 prior chemotherapy regimens (small range 2-5)
- 10 patients received prior carboplatin + gemcitabine
- ECOG status: 9 positive, 4 negative, 12 unknown
- 25% patients received endocrine therapy (1/2) (6)

Pharmacokinetics
- Intracellular Anti-Cancer Nucleotide dATCP
- Combination with carboplatin rapidly generated very high intracellular dATCP levels (Cmax = 13.3 ± 12.3 ng/mL, C trough = 0.7 ± 1.7 ng/mL
- High dATCP levels maintained for 24 hours

Safety Profile
- NUC-1031 + carboplatin well-tolerated
- No unexpected AEs reported
- 6 dosing toxicities (35%) in 4 patients
- 2 Grade 4 thrombocytopenia (10% of NUC-1031 415 mg/m² + carboplatin AUC2)
- 3 Grade 3 fatigue (NUC-1031 415 mg/m² + carboplatin AUC2)
- 1 Grade 4 neutropenia (NUC-1031 700 mg/m² + carboplatin AUC2)
- No thrombocytopaenia in the platinum partial responders or sensitive patients (n=7)

Most Common (>10%) Patients: Grade 3/4 AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NUC-1031 415 mg/m²</th>
<th>Carboplatin AUC2</th>
<th>Total (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>42% (9)</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3% (1)</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>23%</td>
<td>19%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>17% (3)</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>13%</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

CONCLUSION

- NUC-1031 + carboplatin is an effective combination
  - ORR 19%
  - SD 57%
  - CRR 6%
- Response is well tolerated
- dATCP, myelosuppression and fatigue
- No unexpected AEs
- NUC-1031 is stable in plasma and rapidly generated high intracellular levels of active anticancer metabolite, dATCP, that was maintained for 24 hours
- PFS was 5.0 months (90% CI: 1.4 - 11.0) for NUC-1031 on days 1 & 8 + AUCs carboplatin 1 day 1, q2d
- NUC-1031 can be combined with carboplatin at an AUCs of 45, online generation
- NUC-1031 can be used in Phase II study (PROC-105) for patients with platinum resistant ovarian cancer
- Phase II study planned for combination of NUC-1031 + carboplatin for patients with platinum sensitive ovarian cancer