Uptake is independent of nucleoside transporters.

Resistant to deaminase-mediated breakdown.

Release the activated monophosphate agent within the cell.

ProTides gemcitabine releasing the toxic metabolite (dFdU).

BACKGROUND

3. Nucleoside Transporter: Gemcitabine

High Expression of intracellular CDA

TOXIC: Phase I first-in-human study of the novel nucleotide analogue ProTide technology NUC-1031
dFdC triphosphate
dFdC diphosphate
dFdC monophosphate
dFdU (toxic metabolite)

Patients aged >18 years with relapsed/refractory advanced solid tumours refractory to standard treatment.

Schedule B: NUC-1031 administered on days 1, 5, 8, 12, 15, 19 of a 4 weekly cycle for up to 6 cycles.

Schedule A: NUC-1031 administered on days 1, 8, 15 of a 4 weekly cycle for up to 6 cycles.

Methods

o Preliminary antitumour activity

Secondary

o Pharmacokinetic profile

o Evaluate safety profile

Objectives

Patients Characteristics

Two DLTs were observed: Grade 3 injection site pain (1000mg/m² Schedule A) and Grade 5 pulmonary embolus (55%) and elevated liver function tests (64%).

The most frequently recorded Grade 1 and 2 AEs were taste disturbance/dysgeusia (64%), anorexia (64%), constipation (33%), and elevated liver function tests (64%).

No AEs were unexpected.

Very few AEs were definitely or probably related to NUC-1031.

261 AEs reported, of which 13 were classed as SAEs. Events of Grade 3 and above are reported in Table 2.

Table 1. Patients Characteristics & Status

<table>
<thead>
<tr>
<th>CANCER INDICATION</th>
<th>DEMOGRAPHICS</th>
<th>NUMBER ENROLLED</th>
<th>CURRENT STATUS</th>
<th>PERCENTAGE/ COUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>Male 72 Female 375</td>
<td>DLT (discontinued)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>43 (55%)</td>
<td>STABLE DISEASE (ongoing)</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>2</td>
<td>67 (86%)</td>
<td>ONGOING</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. SAEs of any causality observed in patients (n=11)

<table>
<thead>
<tr>
<th>SCHEDULE A</th>
<th>SCHEDULE B</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>750mg/m² (n=11)</td>
<td>1000mg/m² (n=1)</td>
<td>375mg/m² (n=5)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>G3</td>
<td>G3</td>
<td>G3</td>
</tr>
<tr>
<td>G3</td>
<td>G5</td>
<td>G4</td>
</tr>
<tr>
<td>G3</td>
<td>G3</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>G3</td>
<td>G3</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>G3</td>
<td>G3</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>G3</td>
<td>G3</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>G3</td>
<td>G3</td>
<td>2 (18%)</td>
</tr>
</tbody>
</table>

**Background:**

ProTides

- Novel generation of anticancer agents (nucleotide analogues)
- Innovative phosphoramidate technology combined with existing nucleoside analogues.
- Designed to overcome key cancer resistance mechanisms.
- Intended to benefit the majority of cancer patients.
- Improved efficacy and safety profile.

**NUC-1031**

- Overcomes the 3 key cellular resistance mechanisms associated with gemcitabine treatment:
  1. Enzymatic loss of expression of intracellular kinases
  2. Deaminase: High Expression of intracellular deaminases
- Strong antiproliferative activity in vitro and in vivo.

**Study Design**

**Objectives**

- Primary
  - Decrease in tumour size measured by RECIST
- Secondary
  - Pharmacokinetic profile
  - Preliminary antitumour activity

**Methods**

- Sequential dose-escalating cohorts (2+3 design), with NUC-1031 administered as a 5-10 minute IV bolus injection.
- Schedule A: NUC-1031 administered on days 1, 8, 15 of a 4 week cycle for up to 6 cycles.
- Schedule B: NUC-1031 administered on days 1, 5, 8, 12, 15, 19 of a 4 week cycle for up to 6 cycles.
- Patient Population:
  - Patients aged ≥18 years with relapsed/refractory solid tumours refractory to standard treatment.

**Results**

**Patients Characteristics**

- 11 patients enrolled to date with study recruitment ongoing.
- 7 females, 4 males.
- Mean age 61 years.
- Average number of previous chemotherapy regimens 2.1

**Pharmacokinetics**

- NUC-1031 is detected in plasma up to 24 hours EOI.
- 1% of NUC-1031 is converted to gemcitabine (dFdC).
- Plasma Cmax of the toxic deaminated gemcitabine analogue (dFdU) is significantly lower (10x lower) than reported for gemcitabine. This confirms that NUC-1031 is resistant to deaminase in patients.

**Patient Safety**

- 29 AEs reported, of which 13 were classified as SAEs. Events of Grade 3 and above are reported in Table 2.
- Very few AEs were definitely or probably related to NUC-1031.
- No AEs were unexpected.
- Very few AEs were definitely or probably related to NUC-1031.
- The most frequently recorded Grade 1 and 2 AEs were taste disturbance/dysgeusia (64%), anorexia (64%), constipation (33%) and elevated liver function tests (64%).
- Two DLTs were observed: Grade 3 injection site pain (1000mg/m² Schedule A) and Grade 5 pulmonary embolus (55%) and elevated liver function tests (64%).
- No AEs were unexpected.
- Very few AEs were definitely or probably related to NUC-1031.

**Conclusions**

- Encouraging clinical activity of NUC-1031 monotherapy from preliminary data in patients with solid malignancies.
- PK results show very high intracellular levels of gemcitabine triphosphate with low accumulation of dFdU in study participants.
- Biomarkers will be evaluated in the upcoming expansion cohort.
- NUC-1031 overcomes all 3 key resistance mechanisms associated with gemcitabine.