ABC-08: A phase Ib, multi-centre, open-label study of a first-in-class nucleotide analogue NUC-1031 in combination with cisplatin in patients with locally advanced/metastatic biliary tract cancers

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BACKGROUND
- No agents ‘approved’ specifically for the treatment of advanced/metastatic biliary tract cancer
- Current standard of care remains gemcitabine + cisplatin (ABC-02)1
- No clinical studies since ABC-02 have reported an extension in overall survival
- Resistance to chemotherapy reduces patient survival
- Effective new agents and combinations are required

ProTides: Nucleotide Analogues
- A new class of anti-cancer agents
- Designed to overcome key cancer resistance mechanisms
- Transformative phosphoramidate chemistry
- Increase intracellular levels of active anti-cancer metabolites, difluorodeoxycytidine triphosphate (dFdCTP)
- Broad clinical utility

NUC-1031: The First Anti-Cancer ProTide
- NUC-1031 is a first-class nucleotide analogue
- A ProTide transformation of gemcitabine
- Overcomes key gemcitabine resistance mechanisms1,2
- Cellular uptake independent of nucleoside transporters (hENT1)
- Activation independent of deoxycytidine kinase (dCK)
- Overcomes key gemcitabine resistance mechanisms2,3
- Broad clinical utility

TRANSPORTER INDEPENDENT
- Protected from breakdown by cytidine deaminase (CDA)
- Activation independent of deoxycytidine kinase (dCK)
- Cellular uptake independent of nucleoside transporters (hENT1)
- Overcomes key gemcitabine resistance mechanisms2,3
- NUC-1031 is a first-in-class nucleotide analogue

PRO-001: First-in-Human Study
- Highly active as a single agent in relapsed/refractory cancers1,4
- 78% disease control rate (DCR) in advanced solid tumours
- 93% DCR in patients with advanced gynaecological cancers
- Well-tolerated
- No unexpected adverse events (AEs)
- Manageable myelosuppression and reversible transaminase elevation
- Generated considerably higher intracellular levels of dFdCTP compared with gemcitabine on an equimolar basis1
- 217x greater Cmax
- 19x greater AUC

TUMOUR APOPTOSIS
- Intracellular dFdCTP levels were durable (mean t1/2=22 hours)
- Cells derived from patient’s peripheral blood mononuclear cells
- Superior to published studies

STUDY DESIGN
Objectives
Primary
- Assess safety of NUC-1031 in combination with cisplatin
- Determine the recommended Phase II dose of NUC-1031 in combination with cisplatin

Secondary
- Efficacy
- Progression-free survival
- Response rate
- Overall survival

Methods
Starting dose of NUC-1031 in Cohort 1 was 625 mg/m2 administered IV on days 1 and 8 in combination with cisplatin (25 mg/m2) of a 21-day schedule (Cohort 1: results presented).
The Cohort 2 dose of NUC-1031 was 725 mg/m2.
Treatment to continue until intolerable toxicity or progressive disease

Patient Population
- Aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- Not previously treated/conn/metastatic histology/lymphoid confirmed cholangiocarcinoma, gallbladder or ampullary carcinoma
- No prior systemic therapy

Efficacy
- Strong efficacy signal for NUC-1031 (625 mg/m2) in combination with cisplatin (25 mg/m2)
  1) Complete Response (13%), 3 Partial Responses (38%), 1 Stable Disease (81%)
  Objective Response Rate = 50%
  Disease Control Rate = 63%
- Therapies with SD had sufficient tumour shrinkage to allow surgical resection

Objectives
- A Phase III study comparing NUC-1031 + cisplatin versus gemcitabine + cisplatin as first-line treatment of patients with advanced/metastatic biliary tract cancer
- A Phase III study comparing NUC-1031 + cisplatin versus cisplatin as frontline treatment of patients with advanced/metastatic biliary tract cancer is planned

Patient Characteristics
- 8 patients (2/3 levels)
- Median age 65 years (range 55-79)
- 6 patients received ≥1 cycle

TUMOUR APOPTOSIS
- Superior to published studies

ABC-08
- NUC-1031 + cisplatin
- gemcitabine + cisplatin

ABC-02
- NUC-1031 + cisplatin
- gemcitabine + cisplatin

ABC-08
- Objective Response Rate = 50%
- Disease Control Rate = 63%

ABC-02
- Objective Response Rate = 26.1%

Partial Response
- 38% (1/8)
- 25.5% (4/16)

Objective Response Rate
- 50% (4/8)
- 62.5% (2/8)

Methods
- Pharmacokinetics
  - PK analysis of first-in-human PRO-001 study

Cohort 1 Pharmacokinetic Parameters (n=4)
- NUC-1031 plasma (µg/mL)
- dFdCTP intracellular (µg/mL)

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<th>Time (h)</th>
<th>NUC-1031</th>
<th>dFdCTP</th>
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<td>12.41</td>
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<tr>
<td>2</td>
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CONCLUSIONS
- ABC-08 Cohort 1 data demonstrated strong efficacy signals
  - Objective Response Rate = 50%
  - Stable Disease = 50%
  - Disease Control Rate = 63%
- Regimen is well-tolerated
  - No unexpected AEs
  - No DIs
- NUC-1031 is stable in plasma and generates significant intracellular levels of the active anti-cancer metabolite, dFdCTP
- Trial Management Group review of Cohort 1 and 2 data established that the Cohort 1 dose was optimal
- NUC-1031 at 625 mg/m2 + cisplatin at 25 mg/m2 is an attractive and effective combination for treatment of patients with advanced/metastatic biliary tract cancer
- A Phase III study comparing NUC-1031 + cisplatin versus gemcitabine + cisplatin as frontline treatment of patients with advanced/metastatic biliary tract cancer is planned

ABC-08
- Objective Response Rate = 93%
- Disease Control Rate = 88%
- No grades 4 and 5 toxicity

Primary Toxicities
- No unexpected AEs
- Only 4 patients (50%) experienced grade 3 or 4 toxicity
- Aged ≥18 years with ECOG performance status of 0-1

Secondary Toxicities
- Less than 10% toxicity grade 3 or 4
- Only 4 patients (50%) experienced grade 3 or 4 toxicity
- Aged ≥18 years with ECOG performance status of 0-1

Disease Control Rate = 63%
- Disease Control Rate = 38%
- Disease Control Rate = 26.1%

ABC-02
- Objective Response Rate = 26.1%
- Disease Control Rate = 63%

ABC-08
- Objective Response Rate = 93%
- Disease Control Rate = 88%
- No grades 4 and 5 toxicity

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