Background

Pancreatic ductal adenocarcinoma (PDAC) predicted to be second-leading cause of cancer-related death by 2030

Gemcitabine remains standard of care for patients with metastatic PDAC not suitable for combination therapy, but less than 10% of patients respond

Resistance to chemotherapy reduces patient survival

Effective new agents and combinations are required

ProTides: NucleoTide Analog

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

NUC-1031: The First Anti-Cancer ProTide

• NUC-1031 (Avilane) is a first-in-class nucleotide analogue
• A ProTide transformation of gemcitabine
• Overcomes key gemcitabine resistance mechanisms
  • Cellular uptake independent of nucleoside transporters (hENT1)
  • Actuation independent of deoxycytidine kinases (dCK)
  • Protected from breakdown by cytidine deaminase (CDA)
    • Greater stability
    • Reduction in toxic metabolites

NUC-1031 bypasses the key cancer pathway resistances of gemcitabine

PRO-001: First-in-Human Study

• Highly active as a single agent in relapsed/refractory cancers
  • 79% 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 elevated transaminases

• Generated considerably higher intracellular levels of the active anti-cancer metabolite, difluorodeoxycytidine triphosphate (dFTdP), compared with gemcitabine on an equimolar basis
  • 217× greater Cmax
  • 139× greater AUC

Study Design

Patient Population

• Aged ≥18 years
• Patients who have relapsed following previously resected pancreatic cancer are eligible
• Unfit for combination chemotherapy
• ECOG performance status of 0, 1 and 2

Objectives

Primary
• Overall Survival (OS)

Secondary
• Progression Free Survival
• Response Rate and DCR
• Quality of Life (EORTC QLQ-C30 and EORTC QLQ-PAN26)
• Safety (SAE or Grade 3 toxicity)

328 patients aged ≥18 years with histologically or cytologically proven advanced ductal adenocarcinoma of the pancreas or undifferentiated carcinoma of the pancreas

Eligible patient randomisation in 1:1 ratio stratified by ECOG performance status: 0/1 vs. 2

TREATMENT

Arm 1
• NUC-1031 825 mg/m2 administered intravenously over 30 mins on days 1, 8 and 15
• 28-day cycle

Arm 2
• Gemcitabine 1000 mg/m2 administered intravenously over 30 mins on days 1, 8 and 15
• 28-day cycle

12-weekly CT scan – RECIST

Response (CR or PR) or Stable Disease

Progressive Disease Unacceptable toxicity Patient decision

CONTINUE TREATMENT

STOP TREATMENT

Follow-up until death

Statistical Considerations

• 328 patients
• 264 events to detect an HR of 0.705 for OS, equating to an increase in median OS of approximately 2 months or a 13% improvement in 1 year OS
• Median OS of 6 months anticipated for the control arm
• Single analysis for futility to be performed when 50% of the events (i.e., 132 deaths) have been observed

Treatment Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
<th>Dose</th>
<th>Route</th>
<th>Cycle</th>
<th>Treatment Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>NUC-1031</td>
<td>825 mg/m2</td>
<td>IV</td>
<td>28 days</td>
<td>Days 1, 8 and 15</td>
</tr>
<tr>
<td>Arm 2</td>
<td>Gemcitabine</td>
<td>1000 mg/m2</td>
<td>IV</td>
<td>28 days</td>
<td>Days 1, 8 and 15</td>
</tr>
</tbody>
</table>

Translational Research

Translational research will explore the predictive benefit of NUC-1031 over gemcitabine

• Genomic/proteomic sampling
• Pharmacokinetic sampling
• Additional core tissue samples

Recruitment Status – September 2018

• 152 patients randomised to date
• 33 sites recruiting in the UK
• Additional international sites to open

Summary

• NUC-1031 rationally designed to overcome all key cancer cell resistance mechanisms associated with gemcitabine
• The ACELARATE study is comparing the efficacy and safety of NUC-1031 to gemcitabine in patients with metastatic PDAC