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ACELARATE – A randomised Phase III, open label, clinical study comparing NUC-1031 with gemcitabine in patients with metastatic pancreatic carcinoma

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Background

- Pancreatic ductal adenocarcinoma (PDAC) predicted to be second-leading cause of cancer-related death by 2030[1]
- Gemcitabine remains standard of care for patients with metastatic PDAC not suitable for combination therapy, but less than 10% of patients respond[2]
- Resistance to chemotherapy reduces patient survival
- Effective new agents and combinations are required

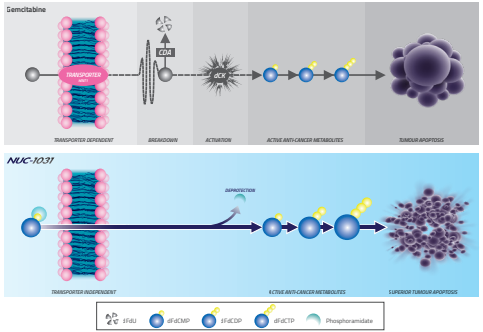
ProTides: NucleoTide Analogs

- 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
- Broad clinical utility

NUC-1031: The First Anti-Cancer ProTide

- NUC-1031 (Acelarin) is a first-in-class nucleotide analogue
- A ProTide transformation of gemcitabine
- Overcomes key gemcitabine resistance mechanisms[3,4]
  - 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 bypasses the key cancer resistance pathways of gemcitabine



PRO-001: First-in-Human Study

- Highly active as a single agent in relapsed/refractory cancers[5]
  - 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 elevated transaminases
- Generated considerably higher intracellular levels of the active anti-cancer metabolite, difluorodeoxycytidine triphosphate (dFdCTP), compared with gemcitabine on an equimolar basis[4]
  - 217× greater C_{max}
  - 139× greater AUC

Study Design

Patient Population

- Aged ≥18 years
- Patients who have relapsed following previously resected pancreatic cancer are eligible
- Unsuitable for combination chemotherapy
- ECOG performance status of 0, 1 and 2
- Histologically or cytologically proven PDAC or undifferentiated carcinoma of the pancreas
- Metastatic disease precluding curative surgical resection or definitive locally directed therapies such as chemo-radiation
- Patients randomised 1:1 to either NUC-1031 (825 mg/m²) or gemcitabine (1000 mg/m²) on days 1, 8 & 15

Objectives

Primary

- Overall Survival (OS)

Secondary

- Progression Free Survival
- Response Rate and DCR
- Quality of Life (EORTIC QLQ-C30 and EORTIC 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

TRANSLATIONAL RESEARCH
Biopsy tissue and blood collected for research

TREATMENT

ARM 1
NUC-1031: 825 mg/m² administered intravenously over 30 mins on days 1, 8 and 15 of a 28-day cycle
n=164

ARM 2
gemcitabine 1000 mg/m² administered intravenously over 30 mins on days 1, 8 and 15 of a 28-day cycle
n=164

12-weekly CT scan – RECIST

Response (CR or PR) or Stable Disease → **CONTINUE TREATMENT**

Progressive Disease
Unacceptable toxicity
Patient decision → **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[6]
- Single analysis for futility to be performed when 50% of the events (i.e., 132 deaths) have been observed

Treatment Arms

Arm	Treatment	Dose	Route	Cycle	Treatment Days
Arm 1	NUC-1031	825 mg/m²	IV	28 days	Days 1, 8 and 15
Arm 2	gemcitabine	1000 mg/m²	IV	28 days	Days 1, 8 and 15

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

Data current as of 1 Sept 2018. Data cleaning ongoing.

1. Rahib et al. Cancer Res 2014; 74:2913-2921 2. Conroy et al, NEJM 2011; 364:1817-1825 3. Slusarczyk et al. J Med Chem 2014; 57:1531-1542 4. Blagden et al. Cancer Res 2016; 76: Suppl abstr CT028 5. Blagden et al. J Clin Oncol 2015; 33: Suppl abstr 2514 6. Philip et al. Clin Cancer Res 2014; 20:4176-4185