ACELARATE – A Phase III, open label, multicentre randomised clinical study comparing Acelarin (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

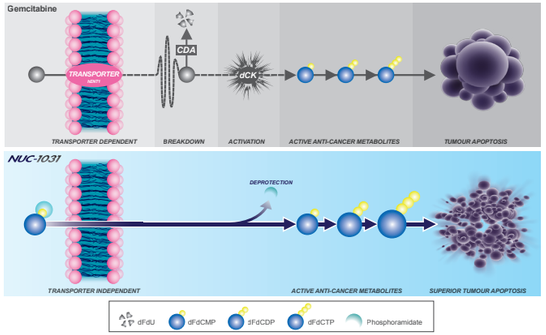
ProTides: NucleoTide Analogues

- 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
- 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
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 and 2
- Unsuitable for combination chemotherapy
- 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 who have relapsed following previously resected pancreatic cancer are eligible
- Patients randomised 1:1 to either NUC-1031 (825 mg/m^2) or gemcitabine (1000 mg/m^2) on days 1, 8 & 15

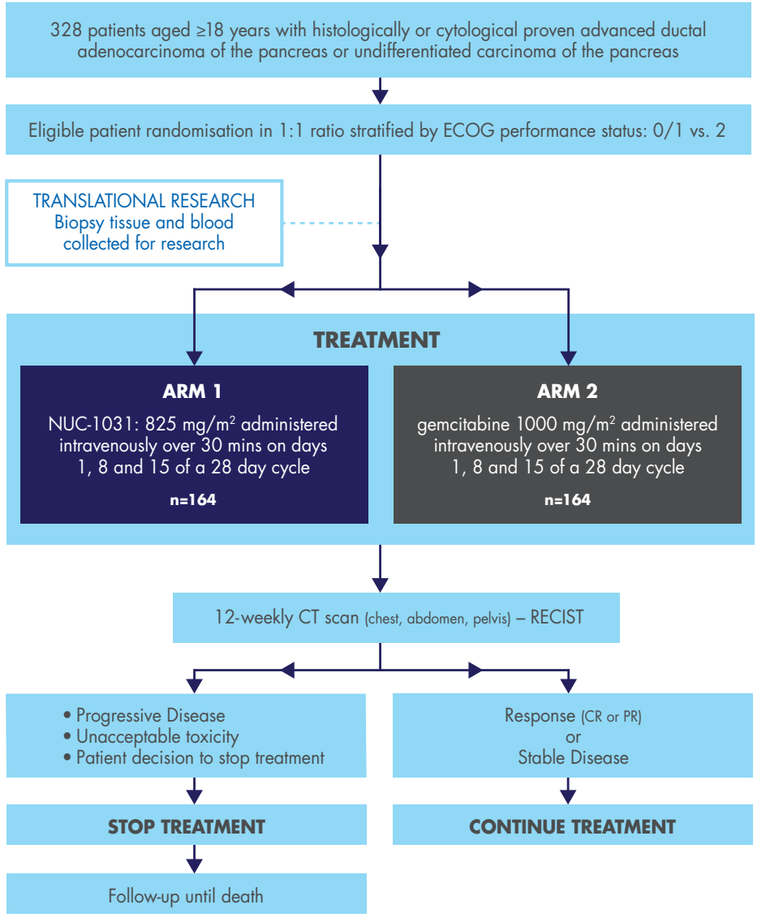
Objectives

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)



Statistical Considerations

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

Treatment Arms

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

Patients to be treated until disease progression in both arms

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 – JANUARY 2018

- Over 100 patients treated to date
- 30 sites recruiting in the UK
- Additional European sites to open in 2018

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

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; 27:513-542 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