TRANSPORTER INDEPENDENT dFdCMP CONTINUE TREATMENT

- Protected from breakdown by cytidine deaminase (CDA)
- Resistance to chemotherapy reduces patient survival
- Gemcitabine remains standard of care for patients with metastatic

NUC-1031 (Acelarin) is a first-in-class nucleotide analogue

NUC-1031: The First Anti-Cancer ProTide

- Broad clinical utility
- Increase intracellular levels of active anti-cancer metabolites
- Designed to overcome key cancer resistance mechanisms
- A new class of anti-cancer agents

ProTides: Nucleotide Analogues

- Effective new agents and combinations are required

patients respond 2 PDAC not suitable for combination therapy but less than 10% of

Gemcitabine


BREAKDOWN CDA

Deamination

TRANSPORTER DEPENDENT ACTIVE ANTI-CANCER METABOLITES

TRANSPORTER INDEPENDENT ACTIVE ANTI-CANCER METABOLITES

Greater stability

ACELARATE – A Phase III, open label, multicentre randomised clinical study comparing Acelarin (NUC-1031) with gemcitabine in patients with metastatic pancreatic cancer

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BACKGROUND

- Pancreatic ductal adenocarcinoma (PDAC) predicted to be second leading cause of cancer-related death by 20301
- Gemcitabine remains standard of care for patients with metastatic PDAC, not suitable for combination therapy but less than 10% of patients respond2
- Resistance to chemotherapy reduces patient survival
- Effective new agents and combinations are required

Tumour ProTides: Nucleotide Analogues

- NUC-1031 is a first-in-class nucleotide analogue
- A ProTide transformation of gemcitabine
- Bypasses the rate-limiting step for effective drug delivery. NUC-1031 is a ProTide of gemcitabine that is resistant to breakdown by cytidine deaminase (CDA)

STUDY DESIGN

- Eligible patient randomisation in a 1:1 ratio stratified by ECOG performance status: 0/1 vs. 2
- Biopsy tissue and blood for genomic/proteomic sampling
- Translational research will explore the predictive benefit of NUC-1031 over gemcitabine

Patient Population

- Aged ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 and 2
- Unfit for combination chemotherapy
- Histologically or cytologically proven advanced ductal adenocarcinoma of the pancreas or undifferentiated carcinoma of the pancreas
- Metastatic disease precluding curative surgical resection or definitive local treatments
- Unsuitable for combination chemotherapy

Objectives

- Overall Survival (OS)
- Progression Free Survival
- Response Rate and DCR
- Quality of Life (EORTC QLQ-C30 and EORTC QLQ-PAN26)
- Safety (G0-G3 toxicity)

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

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

Arm 1 NUC-1031

Arm 2 gemcitabine

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

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 basis4
- 217x greater Cmax
- 139% greater AUC

Clinical Activity

- 93% DCR in patients with advanced gynaecological cancers
- 78% DCR in advanced solid tumours

Comparison with gemcitabine

- Anti-cancer metabolite, difluorodeoxycytidine triphosphate (dFdCTP), generated considerably higher intracellular levels of the active anti-cancer metabolite, difluorodeoxycytidine triphosphate (dFdCTP), compared with gemcitabine on an equimolar basis4
- 217 X greater Cmax
- 139% greater AUC

TUMOUR APOPTOSIS

- Superior tumour apoptosis

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

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

Arm 1 NUC-1031

Arm 2 gemcitabine

Follow-up until death

12-weekly CT scan (chest, abdomen, pelvis) – RECIST

TREATMENT

- Progressive Disease
- Unacceptable toxicity
- Patient decision to stop treatment
- Response (CR or PR) or Stable Disease

RESPONSE

- Overall Survival (OS)
- Progression Free Survival
- Median OS of 6 months anticipated for the control arm 6
- 30 sites recruiting in the UK
- Over 100 patients treated to date

Statistical Considerations

- 328 patients required
- 284 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 4 months anticipated for the control arm7
- Single analysis for futility to be performed when 50% of the events occur (n = 132 deaths) have been observed

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