A novel nucleotide analogue that overcomes the key cancer resistance mechanisms associated with poor survival

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Acelarin: A novel nucleotide analogue that overcomes the key cancer resistance mechanisms associated with poor survival

**BACKGROUND**
- A novel generation of chemo-therapeutically active nucleoside analogues
- Innovative phosphoramide chemistry
- Designed to overcome key cancer resistance mechanisms
- Broad clinical utility to benefit the majority of cancer patients
- Superior efficacy and safety profile

**METHODS**

**ProTides**
- Overcomes key resistance mechanisms associated with gemcitabine
- Activator is independent of deoxycytidine kinase (dCK)
- Cellular uptake is independent of nucleoside transporters (hENT1)
- DNA replication inhibitors blocked after hENT1 inhibition using dipyridamole

**Formal Toxicology Study**
- Dose escalation study to determine the RP2D, safety, PK
- Stability Study
- Cytidine deaminase assay
- UV spectrum recorded from the reaction mixture

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**Cytotoxic Activity Studies**
- Using multi-cell cancer lines, including gemcitabine resistant PANC-1 cells
- Utilising inhibitors 2T2D and NBTI to mimic cancer resistance lines
- Formal Toxicology Study
- Dose escalation study to determine the RP2D, safety, PK and antitumour activity of Acelarin
- Patients with advanced, rapidly progressing solid tumours

**Phase I Study (ProGen1)**
- Phase I study to determine the RP2D, safety, PK and antitumour activity of Acelarin
- Patients with advanced, rapidly progressing solid tumours

**Acelarin Achieves High Intracellular Active Moiety Levels**
- Gemcitabine is converted to its active triphosphate form in the presence of dCK inhibition (using 100µM deoxycytidine as a substrate competitor)
- Acelarin achieves 13x higher intracellular dFdCTP levels than gemcitabine in pancreatic cancer cells
- Acelarin is being developed for patients with pancreatic, biliary, ovarian and NSCLC cancers

**Acelarin is Better Tolerated Than Gemcitabine**
- Acelarin’s MTD is a higher than gemcitabine in toxicology studies with Beagle dogs

**Acelarin is Achieving High Disease Control Across a Variety of Solid Tumors**
- A novel nucleotide analogue that overcomes the key cancer resistance mechanisms associated with poor survival
- A novel generation of chemo-therapeutically active nucleoside analogues
- Innovative phosphoramide chemistry
- Designed to overcome key cancer resistance mechanisms
- Broad clinical utility to benefit the majority of cancer patients
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**RESULTS**

**Acelarin Cytotoxicity**
- Acelarin achieves significant gain in tumour volume in xenografts of MiaPaCa-2 human pancreatic cancer cells
- Acelarin is more cytotoxic in RT112 resistant and resistant pancreatic cell lines

**Acelarin Overcomes Cancer Resistance**
- Cellular activation is independent of dCK
- Acelarin more cytotoxic than gemcitabine in RT112 bladder cancer cells and retains activity despite dCK inhibition (using deoxycytidine as a substrate competitor)

**Acelarin Achieves High Intracellular Active Moiety Levels**
- Gemcitabine is converted to its active triphosphate form (dFdCTP) after phosphorylation by dCK
- Inhibition of dCK by 2T2D reduces gemcitabine conversion to its active triphosphate form
- Acelarin is independent of dCK and produces high levels of dFdCTP in the presence of dCK inhibitors

**Acelarin’s Superior Inhibition of Tumour Growth**
- Acelarin achieves significantly greater reduction in tumour volume than gemcitabine in xenografts of MiaPaCa-2 human pancreatic cancer cells
- Acelarin is more cytotoxic than gemcitabine in RT112 resistant and resistant pancreatic cell lines

**Acelarin is Better Tolerated Than Gemcitabine**
- Acelarin’s MTD is a higher than gemcitabine in toxicology studies with Beagle dogs

**Acelarin’s Clinical Pharmacokinetics**
- A novel nucleotide analogue that overcomes the key cancer resistance mechanisms associated with poor survival
- A novel generation of chemo-therapeutically active nucleoside analogues
- Innovative phosphoramide chemistry
- Designed to overcome key cancer resistance mechanisms
- Broad clinical utility to benefit the majority of cancer patients
- Superior efficacy and safety profile

**Acelarin achieves 13x higher intracellular dFdCTP levels than gemcitabine in patients**

**CONCLUSION**
- A novel nucleotide analogue that overcomes the key cancer resistance mechanisms associated with poor survival
- A novel generation of chemo-therapeutically active nucleoside analogues
- Innovative phosphoramide chemistry
- Designed to overcome key cancer resistance mechanisms
- Broad clinical utility to benefit the majority of cancer patients
- Superior efficacy and safety profile

**Acelarin is achieving high disease control across a variety of solid tumors**

**Acelarin is being developed for patients with pancreatic, biliary, ovarian and NSCLC cancers**

**Ongoing: 42 patients recruited to date**

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