A Cancer Research UK phase I/IIa trial of BT1718 (a first in class Bicycle Toxin Conjugate) given intravenously in patients with advanced solid tumours.

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5Low expression in adult normal tissue
• High adjacent tumour stroma expression
• Expression correlated to poor outcomes
• Strong link with cell invasion, metastasis
• High expression in tumours with unmet medical need, including short systemic half-life, potentially reducing toxicity.

**Background - Target**

**MT1-MMP (MMP-14)** - surface metalloproteinase involved in tissue remodelling through proteolysis of extracellular matrix components
- Highly expressed in tumours with unmet medical need, including triple negative breast cancer (TNBC) and non small cell lung cancer (NSCLC)
- Strong link with cell invasion, metastasis
- Expression correlated to poor outcomes
- High adjacent tumour stroma expression
- Low expression in adult normal tissue

**Background - Drug**

**BT1718** - novel first in class bicyclic targeting peptide that binds MT1-MMP and is linked to the maytansinoid tubulin inhibitor DM1 by a cleavable disulfide linker.

Bicycle Toxin Conjugates have a low molecular weight in comparison to other conjugated toxin approaches, enabling rapid penetration and a short systemic half-life, potentially reducing toxicity.

**Background - Predictive Biomarker**

**Trial Design**

**Open label first in human phase I/IIa study** - primary objective to propose a recommended phase 2 dose (RP2D) and schedule of BT1718. Secondary objectives include pharmacokinetic (PK) parameters, and preliminary clinical responses in biomarker pre-defined cohorts of patients. Tertiary objectives include correlative blood and tissue biomarker studies.

- Accelerated dose escalation design with single patient cohorts until grade 2 drug related toxicity, then a 3+3 design to maximum tolerated dose and RP2D
- Starting with twice a week schedule IV; will also explore once a week schedule
- Parallel expansions in MT1-MMP +ve patients, exploring clinical & biological activity, to refine schedule, biomarkers & population for final efficacy expansions

**Current Status**

Cohorts 1, 2 & 3 have been completed without DLT and single patient escalation continues. Our thanks to all the patients that have kindly participated in the trial.