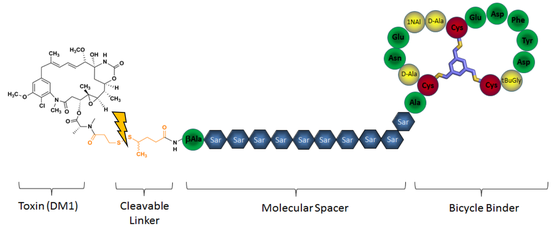
Pharmacokinetic (PK) assessment of BT1718: A phase 1/2a study of BT1718, a first in class bicycle toxin conjugate (BTC), in patients with advanced solid tumours

Abstract 5764

Natalie Cook[1], Udai Banerji[2], T.R. Jeffrey Evans[3], Andrea Biondo[2], Theodora Germetaki[1], Manreet Randhawa[3], Lisa Godfrey[4], Sawretse Leslie[4], Phillip Jeffrey[5], Mike Rigby[5], Gavin Bennett[5], Stephen Blakemore[5], Maria Koehler[6], Andrew Niewiarowski[4], Marc Pittman[4], Stefan N. Symeonides[4,7]

INTRODUCTION

BT1718 is a novel first in class bicyclic targeting peptide that selectively binds MT1-MMP (MMP-14) and is linked to the maytansinoid tubulin inhibitor DM1 by a cleavable disulfide linker. Bicycle Toxin Conjugates have a low molecular weight compared to other conjugated toxin approaches, enabling rapid tumour penetration and a short systemic half-life (<1h). These properties limit the body's exposure to payload to minimize damage to normal tissue.



The target MT1-MMP is a surface metalloproteinase involved in tissue remodelling through proteolysis of extracellular matrix components:

- Highly expressed in tumours with unmet medical need, such as triple negative breast cancer (TNBC) and non small cell lung cancer (NSCLC)
- Strong link with cell invasion and metastasis
- High tumour MT1-MMP expression correlates with poor outcomes in multiple tumour types
- High adjacent stromal expression and low expression in adult normal tissue

BT1718 has shown potent anti-tumour preclinical activity, causing complete regressions in CDX and PDX models at 3–10 mg/kg (human equivalent doses of 9–30 mg/m^2).

STUDY DESIGN

Open label, first in human phase I/IIa study of once-weekly (QW) and twice-weekly (BIW) dosing schedules in patients with advanced solid tumours. 4-week cycle: 1 hour intravenous (IV) infusions for 3 weeks, followed by a 1 week break. Trial objectives:

Objectives	
Primary	• Propose recommended Phase II dose (RP2D) by establishing the maximum tolerated dose (MTD) and maximum administered dose (MAD) of one or both dosing schedules (Phase I) • Safety and tolerability profile of BT1718 (Phase I/IIa)
Secondary	• Investigate pharmacokinetics (PK) of BT1718 in humans (Phase I) • Assess preliminary signals of BT1718 efficacy, in MT1-MMP-expressing tumours (Phase IIa)
Tertiary	• Explore potential predictive and pharmacodynamic biomarkers, including DM1 tumour levels

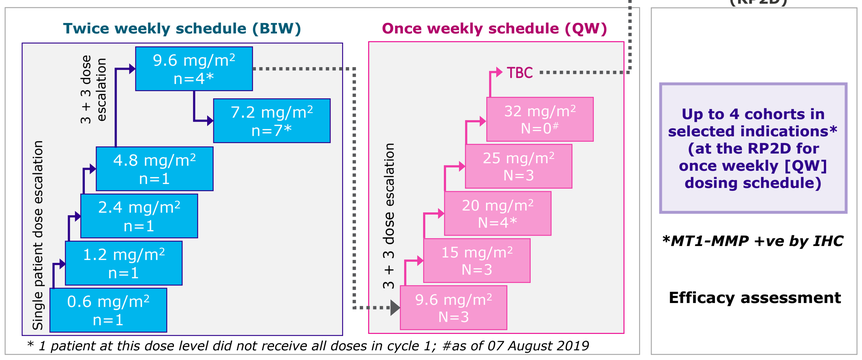
STUDY STATUS: Patient characteristics *(as of 07 August 2019)*

Characteristics	BIW Patients	QW Patients
No. of patients	15	13
Male/Female	8/7	6/7
Median age (range)	56 (27 – 72)	59 (22 – 77)

Tumour type	BIW	QW
• Gastrointestinal (lower)	1	0
• Gastrointestinal (upper)	3	0
• Genitourinary	2	1
• Gynecological	4	3
• Head & neck	0	2
• Sarcoma	3	3
• Skin	1	1
• Thoracic	1	3

STUDY STATUS: Dose Escalation

Dose Escalation Scheme *including dose levels and patient numbers*



** 1 patient at this dose level did not receive all doses in cycle 1; #as of 07 August 2019*

RESULTS: Safety and Efficacy *(as of 07 August 2019)*

Summary

- Two DLTs were reported at 9.6 mg/m^2 BIW: increased GGT (grade 4) and fatigue (grade 3), both of which resolved following cessation or interruption of treatment with BT1718.
- The most common related adverse event class reported to date has been grade 1-3 gastrointestinal disorders (18/28 patients), including nausea, diarrhoea and vomiting.
- Grade 1-2 related peripheral neuropathy occurred more commonly with increasing dose.
- With once weekly dosing, BT1718 appears tolerable at dose levels tested, with manageable toxicity.
- No objective responses (RECIST 1.1) observed to date in this unselected population. 13/24* patients had stable disease at the 8 week timepoint; one patient had ~14% reduction in target lesions at end of cycle 6, with ~45% decrease in one lesion. Mean number of cycles received was 3 months (n=28).

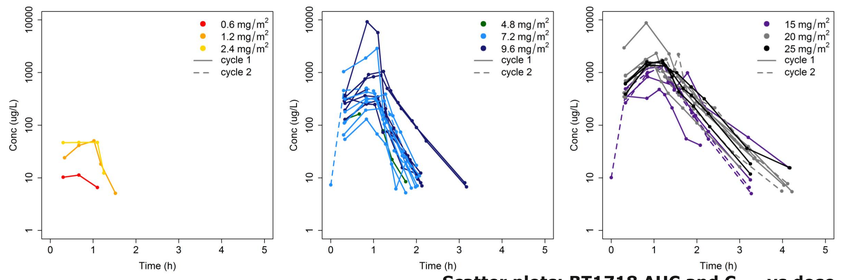
** includes those patients who had scan at week 8 or showed disease progression before week 8 scan*

Summary of adverse events: table shows drug-related events reported by ≥15% patients

SYSTEM ORGAN CLASS	Preferred term	Number of patients, n=28 (frequency)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anaemia	7 (25.0%)
GASTROINTESTINAL DISORDERS	Diarrhoea	10 (35.7%)
	Nausea	12 (42.9%)
	Vomiting	9 (32.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	9 (32.1%)
INVESTIGATIONS	Alanine aminotransferase increased	9 (32.1%)
	Aspartate aminotransferase increased	9 (32.1%)
	Blood alkaline phosphatase increased	5 (17.9%)
	Gamma-glutamyltransferase increased	5 (17.9%)
METABOLISM AND NUTRITION DISORDERS	Decreased appetite	9 (32.1%)
NERVOUS SYSTEM DISORDERS	Lethargy	6 (21.4%)
	Neuropathy peripheral	9 (32.1%)

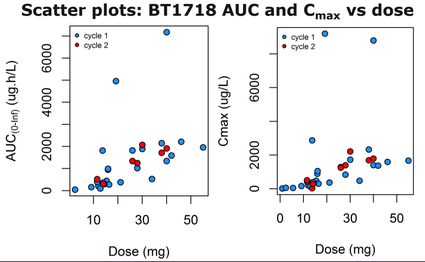
RESULTS: Pharmacokinetics

Spaghetti plots: BT1718 plasma concentration vs time after first doses in cycles 1 & 2



- BT1718 AUC was approximately dose proportional over the range 0.6 – 25 mg/m^2 and cycle 2 values were consistent with cycle 1.
- Mean (±SD) plasma clearance (CLp) was 33.6 (±24.5) L/h, with mean (±SD) volume of distribution (Vss) of 12.5 (±7.3) L, resulting in a terminal half-life ($t_{1/2}$) of 0.2 to 0.5 h.
- Analysis of 3 patient tumour samples indicated delivery of DM1 to tumour in 2 patients consistent with preclinical models.

Scatter plots: BT1718 AUC and C_{max} vs dose



CONCLUSIONS / SUMMARY

- AUC of BT1718 (following a 1h IV infusion) increases with dose, and is consistent between Cycles 1 and 2. Preliminary analysis of total DM1 levels in tumour indicates localisation of DM1 at tumour; further plasma and tumour DM1 analysis is ongoing to assess extent of DM1 retention in tumour.
- RP2D for twice weekly dosing determined as 7.2 mg/m^2. A greater total BT1718 dose per cycle was achieved using once weekly dosing (dose escalation ongoing at 32 mg/m^2); therefore, RP2D used in the expansion phase will be for once weekly schedule only.
- Although no RECIST objective responses were seen in an unselected population, an encouraging number of patients had stable disease and there has been evidence of tumour shrinkage. Once weekly RP2D will be assessed for efficacy in patients selected for tumoural MT1-MMP expression.

AUTHOR AFFILIATIONS / ACKNOWLEDGEMENTS

[1]University of Manchester & Christie NHS Foundation Trust, Manchester, UK; [2]Institute of Cancer Research & Royal Marsden NHS Foundation Trust, Sutton, UK; [3]University of Glasgow & Beatson West of Scotland Cancer Centre, Glasgow, UK; [4]Cancer Research UK Centre for Drug Development, London, UK; [5]Bicycle Therapeutics, Cambridge, UK; [6]Formerly at Bicycle Therapeutics; currently Repare Therapeutics; [7]University of Edinburgh, Edinburgh UK. Corresponding author: Stefan.Symeonides@ed.ac.uk

The authors do not have any conflict of interest to declare. The study is sponsored by Cancer Research UK.

York Bioanalytical Solutions Limited determined BT1718 concentrations in plasma; Physiomics plc conducted data analysis.

Thank you to all the patients who have kindly participated in this trial.