ISRCTN Document Cover Page

ISRCTN Number	ISRCTN11160449
EudraCT Number	2016-004633-24
Sponsor Protocol Number	CRUKD/17/009
Official Trial Title	A Cancer Research UK Phase I/IIa clinical trial of BT1718 (a Bicycle drug conjugate) given intravenously in patients with advanced solid tumours.
Date of Cover Page Finalisation for Upload	09 October 2024
Document Included	Redacted Protocol (Version 10.0, dated 14 October 2022)

Protocol v10.0 (14 October 2022) has been selected by the Sponsor (Cancer Research UK) as the most appropriate protocol to be made available publicly, as this is the version that was most recently approved and used on the CRUKD/17/009 trial.

CANCER RESEARCH UK

Centre for Drug Development

A CANCER RESEARCH UK PHASE I/IIA TRIAL OF BT1718 (A BICYCLE DRUG CONJUGATE) GIVEN INTRAVENOUSLY IN PATIENTS WITH ADVANCED SOLID TUMOURS

Sponsor protocol number: CRUKD/17/009

EudraCT number: 2016-004633-24

Chief Investigator: Prof Udai Banerji

[redacted]

Sponsor: Cancer Research UK
Centre for Drug Development

[redacted]

PARTICIPATING INVESTIGATORS AND CENTRES:

Details of Principal Investigators and Investigational Sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File.

VERSION HISTORY:

Version No.	Date of issue	Reason for update
1.0	11 Oct 2017	Initial version submitted for Regulatory and Ethics approval
2.0	07 Dec 2017	Addition of sun exposure precaution prior to treatment and one week after treatment and advice where appropriate for male patients on the possibility of conservation of sperm prior to treatment (made at the request of the MHRA prior to approval)
3.0	10 May 2018	Change to the trial design to bring forward the once weekly dose escalation schedule (Phase I, Stage 2). Change to the starting dose definition and dose increments for the once weekly dose escalation schedule (Phase I, Stage 2). Change to the recruitment target for the dose escalation phase (Phase I, Stage 1 and 2). Pharmacokinetic blood [redacted] samples to be potentially collected in the expansion phase (Phase IIa, Parts A and B). [redacted] Addition of solution stability data and compatibility of infusion sets at 26 hours to allow reconstituted BT1718 drug product to be added to 5% dextrose bags and stored for up to 20 hours at 2 – 8 °C and then administered within 6 hours at room temperature. [redacted] [redacted] Other minor non-substantial changes and corrections.
4.0	11Jun2019	[redacted] [redacted] [redacted] Other minor non-substantial changes

5.0	07-Oct-2019	Change to the Phase IIa, expansion phase trial design to include the following cohorts: squamous non-small cell lung cancer (NSCLC) cohort, basket cohort, and additional expansion cohort(s) which may include squamous oesophageal cancers. Phase IIa, Part A (twice weekly schedule) will no longer be explored in this trial. Phase IIa expansion cohorts C & D are no longer applicable. The recruitment target for <u>each</u> expansion phase cohort will be approximately 16 evaluable patients. [redacted] Update to secondary objectives and endpoints: o To clarify that PK behaviour will be explored in both the dose escalation and expansion phase. Update to inclusion criterion 5: o Bilirubin parameter updated to include: *NB: >1.5 ULN, acceptable if <u>conjugated</u> bilirubin is ≤ 1.5x ULN* o Inclusion of gamma-glutamyl transferase (GGT) parameter Update to exclusion criterion 1 to clarify that patients on life-long hormone suppression therapy are not excluded. [redacted] Other minor non-substantial changes, including a change to the sponsor address.
6.0	28-Sep-2020	Update to inclusion criterion 11: Patients with significant cardiovascular disease are excluded as defined by: *a. Congestive heart failure requiring therapy (NYHA III or IV – Appendix 3) or known LVEF <40% (moderate to severe)* *b. History of unstable angina pectoris or myocardial infarction up to six months prior to trial entry, or of current poorly controlled angina (symptoms weekly or more)* *c. Presence of symptomatic or severe valvular heart disease (severe by local echographic criteria or AHA/ACC Stage C or D – Appendix 4)*

		d. History of a clinically significant cardiac arrhythmia up to six months prior to trial entry (asymptomatic atrial fibrillation or asymptomatic first-degree heart block are permitted) Inclusion of Appendix 4 - AHA/ACC Guideline. [redacted] Update to radiological assessment timeframe to end of every two cycles (Day 15 – Day 28). Update to clinical assessment timeframe to Day 15 – Day 28 of every two cycles. Update to PK sampling timepoints. PK samples will now be collected in Cycle 1 and across additional cycles (e.g. Cycle 2, Cycle 4, Cycle 6). Other administrative/minor non-substantial changes.
7.0	12-May-2021	Minor update to section 5.3.1 to specify that dose decision meetings may also be arranged during the expansion phase in response to emerging tolerability data. Minor update to section 5.4.4 to specify that dose reductions below the recommended phase 2 dose (RP2D) may be made for patients in the expansion cohorts based on ongoing tolerability monitoring and safety reporting. Minor update to section 5.7 to specify that vaccinations (including COVID-19 vaccines) are permitted for patients on this trial.
8.0	11-Nov-2021	[redacted] Update to specify that patients will also be replaced if MT1-MMP testing identifies that their baseline tumour sample had a low MT1-MMP H-score. Based on clinical experience to date, guidance has been updated to specify that patients should receive primary prophylaxis with anti-emetics prior to their first infusion of BT1718 and in the days following the infusion as clinically indicated. [redacted]

		[redacted] [redacted] Other administrative/minor non-substantial changes.
9.0	20-Jun-2022	Inclusion criterion number 5; removal of gamma-glutamyl transferase (GGT) parameter. Inclusion criterion number 2; clarification that one measurable lesion according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 that has objective progression on or after BT1718 therapy is not required to be measurable via radiological assessment. [redacted] Update to patient evaluability criteria to state: all patients who meet the eligibility criteria and receive ≥66% of the planned dose exposure of BT1718 within Cycle 1 and 2, or at least one full cycle, and have a baseline assessment of disease and at least one repeat assessment will be evaluable for response. Update to clarify that complete response (CR) and partial response (PR) need to be confirmed by a subsequent radiological assessment at least four weeks after initial radiological assessment. Update to clarify that clinical disease assessments must be repeated between Day 15 – Day 28 of every two cycles until disease progression or for up two years, or if clinical concern or suspicion of disease progression. The timing of baseline clinical assessment was also clarified. Update to definition of when recruitment may cease. Minor clarifications to help distinguish between dose escalation and dose expansion phases. Minor administrative changes.
10.0	14-Oct-2022	The end of trial has been amended including additional wording which aims to clarify how long survival follow-up should continue for the last patient before end of trial can be declared. Minor administrative change.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	[redacted]	[redacted]
	ADC	Antibody Drug Conjugates
	AE	adverse event
	AHA/ACC	American Heart Association/American College of Cardiology
	ALP	alkaline phosphatase
	ALT	alanine aminotransferase
	ALK	Anaplastic lymphoma Kinase
	ANC	absolute neutrophil count
	AST	aspartate aminotransferase
	AUC	area under the curve
B	BDC	Bicycle Drug Conjugate
	BP	blood pressure
	BSA	body surface area
C	CDD	Centre for Drug Development
	CI	Chief Investigator
	[redacted]	[redacted]
	CLT	total body clearance
	C_{max}	maximum observed plasma concentration
	CNS	central nervous system
	CR	complete response
	CRA	Clinical Research Associate
	CRUK	Cancer Research UK
	CSM	Clinical Study Manager
	CT	computerised tomography
	CTCAE	Common Terminology Criteria for Adverse Events
D	Day	calendar day
	DLT	dose limiting toxicity
	DM1	cytotoxic agent (N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine)
E	ECG	electrocardiogram
	eCRF	electronic case report form
	EDC	electronic data capture
	[redacted]	[redacted]
	EORTC	European Organisation for Research and Treatment of Cancer
F	FDG	Fluorodeoxyglucose
	[redacted]	[redacted]
	FIH	First in human
G	GCP	Good Clinical Practice
	GGT	gamma glutamyl-transferase
	GFR	glomerular filtration rate
	GI	Gastrointestinal
	GIST	Gastrointestinal stromal tumour
	GLP	Good Laboratory Practice
	GMP	Good Manufacturing Practice
H	h	hour
	Hb	haemoglobin
	HCG	human chorionic gonadotropin
	HED	human equivalent dose
	HER2	human epidermal receptor 2
	HIV	human immunodeficiency virus
	HNSTD	highest non-severely toxic dose

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	HRA	Health Research Authority
I	IB	Investigators Brochure
	ICD	Informed consent document
	ICH GCP	International Conference on Harmonisation of Good Clinical Practice
	[redacted]	[redacted]
	IMP	investigational medicinal product
	ITF	Investigator Trial File
L	LC/MSMC	Liquid chromatography-mass spectrometry mass spectrometry
M	MAD	maximum administered dose
	MT1-MMP	membrane type I matrix metalloproteinase
	min	minute(s)
	MHRA	Medicines and Healthcare products Regulatory Agency
	MRI	magnetic resonance imaging
	MTD	maximum tolerated dose
N	NCI	National Cancer Institute
	NSCLC	Non Small Cell Lung Cancer
	NYHA	New York Heart Association
O	ORR	objective response rate
	OS	overall survival
P	PD	progressive disease
	PD-1	programmed cell death protein 1
	PDX	patient-derived xenograft
	PET	positron emission tomography
	PI	Principal Investigator
	PFS	progression free survival
	PK	pharmacokinetic
	PR	partial response
R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours
	RP2D	recommended Phase II dose
S	SAE	serious adverse event
	SDV	source data verification
	SOC	standard of care
	SOP	standard operating procedure
	SUSAR	suspected unexpected serious adverse (drug) reaction
T	$T_{1/2}$	half-life
	T-DM1	ado-trastuzumab emtansine
	TEAE	treatment-emergent adverse events
	TK	Toxicokinetics
	TMA	Tumour microarray
	TNBC	Triple Negative Breast Cancer
U	UK	United Kingdom
	ULN	upper limit of normal
	USM	urgent safety measure
V	Vd_{SS}	steady state volume of distribution
	VHD	Valvular heart disease
W	WFI	water for injection
	WBC	white blood cell
	WHO	World Health Organisation

PROTOCOL SIGNATURES

Sponsor Signature:

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of UK law and the trial protocol. The Sponsor agrees to conduct the trial according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Signed by the Director of the Sponsor's Centre for Drug Development at Cancer Research UK:

Name: _____

Signature: _____

Date: _____

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2).

3 WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[4], the guidelines of Good Clinical Practice (GCP)[5], the Declaration of Helsinki[6], the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Name of site: _____

Signature: _____

Date: _____

4 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

5 ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2).

6 WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

1 PROTOCOL SYNOPSIS

Full title: A Cancer Research UK Phase I/IIa clinical trial of BT1718 (a Bicycle drug conjugate) given intravenously in patients with advanced solid tumours.

Short title: A Phase I/IIa trial of BT1718 in patients with advanced solid tumours.

Clinical trial primary objectives and endpoints:

Primary objectives	Endpoints
Dose escalation phase To propose a recommended Phase II dose (RP2D) for evaluation by establishing the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), of BT1718 given in patients with advanced solid tumours, at one or more dosing schedules.	Determine a dose at which no more than one out of six patients at the same dose level experiences a probable or highly probable BT1718-related dose limiting toxicity (DLT).
Dose escalation & expansion phase To assess the safety and toxicity profile of BT1718 in patients with advanced solid tumours.	Determine the frequency and causality of each Adverse Event (AE) to BT1718 and grade severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.02. The causality of all AEs will be assessed by the Investigator.

Full details of secondary and tertiary objectives can be found in Section 3.1.

Study Design: This is a multi-centre, first in human (FIH), Phase I/IIa, open label, dose escalation trial with an expansion phase, in patients with advanced solid tumours.

Study treatment:

This clinical trial will consist of two phases, Phase I and Phase IIa:

Phase I, dose escalation phase:

Phase I will consist of Stage 1 and Stage 2. Stage 2 may commence before Stage 1 is completed.

- **Stage 1** - BT1718 will be administered intravenously **twice weekly** for three out of four weeks until the recommended Phase II dose (RP2D) and/or MTD is established. Each cycle of treatment will consist of 28 days. BT1718 will be administered on Days 1, 4, 8, 11, 15 and 18. The starting dose will be 0.6 mg/m^2.
- **Stage 2** - BT1718 will be administered intravenously **once weekly** for three out of four weeks until the RP2D and/or MTD is established. Each cycle of treatment will consist of 28 days. BT1718 will be administered on Days 1, 8 and 15. The starting dose of the once weekly regime will be up to 100% of the overall weekly dose from the last completed cohort deemed safe from the twice weekly schedule (Phase I, Stage 1).

Phase I of the trial has completed.

Phase IIa, expansion phase:

Phase IIa will consist of two or more expansion cohorts:

- **Squamous Non-Small Cell Lung Cancer (NSCLC) cohort -** BT1718 will be administered intravenously at the **once weekly** RP2D established in Phase I Stage 2, in approximately 16 evaluable patients with squamous NSCLC (see section 5.4.4 for further details on RP2D dose adjustments).
- **Basket cohort** - BT1718 will be administered intravenously at the **once weekly** RP2D established in Phase I Stage 2, in approximately 16 evaluable patients with advanced solid tumours (excluding patients eligible for one of the other currently recruiting expansion cohorts). See section 5.4.4 for further details on RP2D dose adjustments.

- **Additional expansion cohort(s)** - an additional expansion cohort of approximately 16 evaluable patients with squamous oesophageal cancer may be opened after review of data obtained from the squamous NSCLC and basket expansion cohorts by the Joint Development Committee comprising of team members from the Sponsor, Bicycle Therapeutics Ltd and the Chief Investigator (CI). Other tumour types with a high incidence of MT1-MMP expression may be considered in future expansion cohort(s) and a substantial amendment will be submitted to the MHRA, REC and HRA for approval to define these populations.

Patient Population: In Phase I, the dose escalation phase, it is expected that between 50 and 60 patients with advanced solid tumours will be required, the final number will be dependent on the number of dose levels explored. In the Phase IIa, expansions at the optimal dose/schedule(s), patients will be enrolled with tumour types known to commonly overexpress MT1-MMP and where MT1-MMP overexpression is confirmed during retrospective and prospective selection. It is expected that up to an additional 70 patients will be required to complete this phase.

2 INTRODUCTION

2.1 Background

The membrane type I matrix metalloproteinase (MT1-MMP) protein is a member of the matrix metalloproteinase (MMP) family which are involved in tissue remodelling, mediated through proteolysis of collagen and other extracellular matrix components [1]. Overexpression of MT1-MMP in many solid tumours (including the surrounding stroma), is linked to cell invasion and migration [2]. This in turn is associated with poor prognosis and shorter survival in NSCLC [3, 4], breast cancer [5, 6] and other solid malignancies [7, 8 , 9].

Matrix metalloproteinase inhibitors have been investigated but failed for various reasons such as poor pharmacology, metabolic stability, sub-optimal bioavailability and/or DLTs [10]. Using an alternative approach, BT1718 has been developed to take advantage of the overexpression of MT1-MMP, not to inhibit its activity, but as a cell surface target to selectively bind and facilitate delivery of the cytotoxic DM1 payload to the tumour.

For this study, the target population will be adult patients with advanced solid tumour malignancies refractory to all appropriate standard of care (SOC) treatment options. With the potential for benefit not exclusively restricted to a definitive subset of tumour types, or a definitive MT1-MMP expression level, dose escalation is planned to be open to patients of all solid tumour types. However, in the Phase IIa expansions at the optimal dose/schedule(s), a clinical signal will be explored in an enriched population with tumour types known to commonly over-express MT1-MMP and where MT1-MMP over-expression is confirmed during prospective selection at enrolment. These tumour types were previously proposed to include tumours such as NSCLC, TNBC and sarcomas. Emerging tissue microarray data has now led to the selection of squamous NSCLC and squamous oesophageal amongst the tumour types with the highest expression.

2.1.1 Non-Small Cell Lung Cancer

Lung cancer is the second most common cancer in the United Kingdom (UK) and United States of America (USA) and the most common cause of cancer death in both countries. Outcomes are poor with just 10% having a 5-year survival. Non-Small Cell Lung Cancer (NSCLC) represents 87% of all lung cancer in the UK and comprises of adenocarcinomas, squamous cell carcinomas, large cell carcinomas as well as other, rarer, subtypes. Squamous lung cancer represents 25-30% of all lung cancers. Only a small proportion of patients have early disease amenable to curative surgery and while more may be suitable for radical (chemo) radiotherapy, cure rates are low [11].

With advanced or relapsed disease, treatment is palliative and prognosis poor. A minority (<10%) of patients have tumours that can respond to mutation-directed treatments with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) inhibitors. Chemotherapy has been the mainstay of therapy for most patients, now joined by immunotherapy [12-14]. For patients who are suitable for first line platinum doublet chemotherapy, median overall survival (OS) was still just 11 months [15, 16], although this has improved recently with the move to first-line immunotherapy or immunotherapy combinations. Second-line chemotherapy, such as docetaxel, had modest activity for those fit enough to receive it, with an objective response rate (ORR) of 8 to 12% (docetaxel, pemetrexed) [17-21]. Antibodies targeting the programmed cell death protein 1 (PD-1) checkpoint blockade replaced chemotherapy in the second-line, with an ORR of around 20% (nivolumab, pembrolizumab, atezolizumab) for second-line treatment and at least 30% where there is programmed death – ligand 1 (PD-L1) selection [17-19, 21] and have since moved first-line, either as monotherapy in selected patients, or in combination with chemotherapy. There is no SOC beyond these agents.

In this context, a promising new agent for NSCLC might therefore be expected to demonstrate an ORR greater than the 10% seen with previous second-line chemotherapy comparators, aiming for 30% in a selected population. Membrane type I matrix metalloproteinase is highly expressed in NSCLC, and particularly in squamous NSCLC, and BT1718 has shown excellent activity in multiple in vivo NSCLC models.

2.1.2 Squamous Oesophageal

Oesophageal cancer is the 14th most common cancer in the UK but is the 7th most common cause of cancer death (4th in males) as most cases are diagnosed at a late stage and cure rates are low (12-15%). Squamous cell carcinoma of the oesophagus accounts for about 30% of cases. It generally

affects the upper or middle oesophagus and, like squamous cell carcinoma of the head and neck, is linked with smoking, alcohol and other carcinogens via oral exposure. Human papilloma virus may also be implicated but less so than in head and neck cancers. Only around 20% of patients have disease amenable to potentially curative surgery but cure rates are low despite improvements in preoperative chemo(radio)therapy. Squamous cell oesophageal carcinoma may also be amenable to radical (chemo)radiotherapy, with outcomes for chemoradiotherapy similar to surgery and cure rates similarly low [22, 23].

With advanced or relapsed disease, treatment is palliative and prognosis poor. Around 30% of patients receive radiotherapy for local symptom control but the mainstay of treatment to improve survival is chemotherapy. For patients who are suitable for first line combination chemotherapy (usually including a fluoropyrimidine and a platinum), median overall survival (OS) is less than 12 months and fewer patients get to second or third line therapy where a taxane or irinotecan may be used and standard of care varies. Unlike adenocarcinoma of the oesophagus, targeted agents had not made an impact on squamous cell carcinoma of the oesophagus until the recent role for immunotherapy. The KEYNOTE-180 [24] and KEYNOTE-181 [25] trials have shown activity (ORR of around 20% versus <10% for second-line chemotherapy) and now survival benefit (10 months versus 7 months) for patients with PD-L1-positive squamous cell carcinoma of the oesophagus. This led to the July 2019 FDA approval of pembrolizumab for the second-line treatment of PD-L1-positive squamous cell carcinoma of the oesophagus [26].

In this context, a promising new agent for squamous cell carcinoma of the oesophagus might therefore be expected to demonstrate an ORR greater than the <10% seen with second-line chemotherapy comparators, aiming for 30% in a selected population. MT1-MMP is highly expressed in squamous cell carcinoma of the oesophagus.

2.2 Investigational medicinal product

BT1718 is a potent, highly selective Bicycle Drug Conjugate (BDC) developed by Bicycle Therapeutics Ltd, consisting of a novel bicyclic peptide (Bicycle), which binds selectively to membrane type 1-matrix metalloproteinase (MT1-MMP), which is connected through a molecular spacer and a cleavable disulfide linker to the potent cytotoxic tubulin inhibitor, DM1. Upon binding to tumour cells expressing MT1-MMP, the DM1 payload is activated by release from the conjugate where it can disrupt microtubule dynamics resulting in tumour cell death.

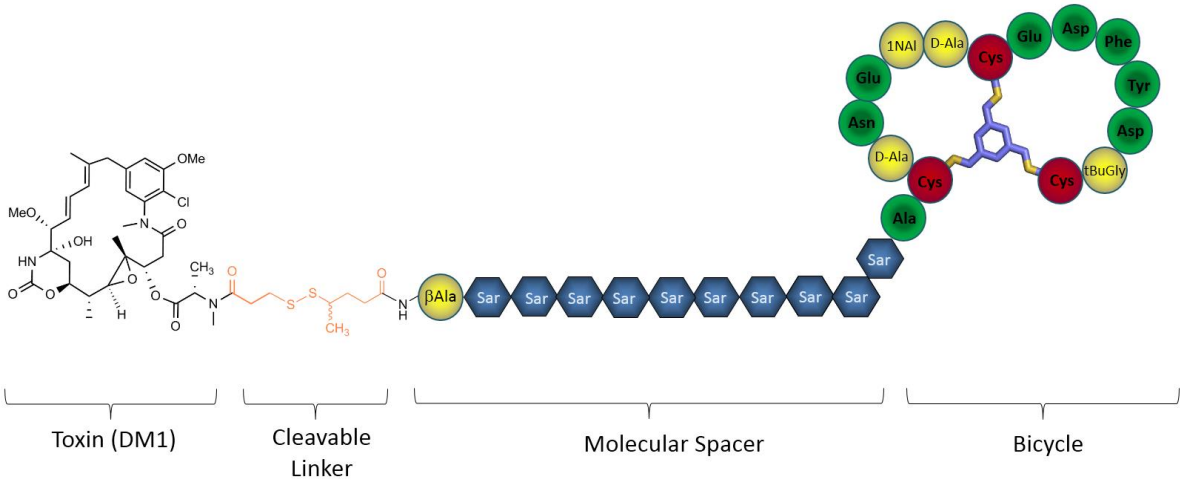
For additional information concerning BT1718, refer to the Investigator's Brochure (IB).

2.2.1 Structure of BT1718

BT1718 (see **Figure 1**) is designed by Bicycle Therapeutics Ltd comprising of the following components linked together in a single molecule:

1. A bicycle peptide, the "Bicycle Binder" cyclised with the chemical scaffold (1,3,5 Tris-Cysteinyl-Methylbenzene, TMB),
2. A molecular spacer (a sarcosine decamer with a beta-alanine N-terminus),
3. A cleavable linker (mono-hindered disulfide) and,
4. A maytansinoid tubulin inhibitor, DM1 (N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine).

Figure 1 Structure of BT1718



2.2.2 Mechanism of action of BT1718

BT1718 is a potent, highly selective BDC developed by Bicycle Therapeutics Ltd using their novel platform technology of constrained bicyclic peptide binders, from herein referred to as Bicycles. The BDCs, have a low molecular weight (3.5 kDA) in comparison to other conjugated toxin approaches, which enables rapid penetration of tumour tissue. Minimal systemic toxicity is expected due to its short half-life and excretion via the kidneys, potentially sparing gastrointestinal (GI) and hepatic toxicity, a frequent on target toxicity seen with small molecule cytotoxics and ADCs. BT1718 specifically binds to cell-surface MT1-MMP overexpressed on tumour cells, which facilitates delivery of its cytotoxic payload, DM1, to the tumour. Once released by tumour-localised cleavage of the linker, active unconjugated DM1 is then able to block normal microtubule function during cell division, ultimately leading to apoptosis, cell death and reduction of tumour size.

2.3 Safety considerations for the proposed trial

2.3.1 Non-clinical pharmacology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3.3 Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3.4 Summary of the non-clinical data

[redacted]

2.3.5 Justification of Starting dose

[redacted]

Therefore, the proposed starting dose for the FIH Phase I trial is 0.6 mg/m^2 twice weekly.

2.4 Clinical experience (Phase I trial (s)/other compounds in the same class)

No previous clinical studies have been conducted with BT1718. However, maytansine, parent analogue of, DM1 has been evaluated in clinical trials, DM1 has also been evaluated clinically as a component of ADCs, exemplified by T -DM1 which has been licensed by Roche Holding AG under the trade name Kadcyla®.

Maytansine (parent analogue of DM1)

Patients have been treated with maytansine on several different schedules, and the toxicities observed closely paralleled those reported in animal studies, including gastrointestinal toxicity (including nausea, vomiting, diarrhoea), alopecia, myelosuppression, elevated liver enzymes, superficial phlebitis and peripheral neurotoxicity. These effects were dose related and reversible. Doses and schedules evaluated included; treatment at 0.01 to 0.9 mg/m^2 for 3 days, repeated every 2 to 3 weeks. On this schedule, superficial phlebitis was observed at 0.15 mg/m^2, which was mitigated by diluting the drug and slowing the infusion rate. Gastrointestinal toxicity and elevated liver enzymes were observed at and above doses of 0.4 mg/m^2 and 0.6 mg/m^2 respectively and myelosuppression was evident at all doses. The safe dose on this schedule was deemed to be 0.5 mg/m^2, 3-fold higher than the dog HNSTD [38]. In another study, 0.015 to 0.9 mg/m^2 was administered on Day 1, 3 and 5 every 4 weeks [39]. Minimal toxicity was seen at doses of 0.45 mg/m^2 (total 1.35 mg/m^2) and lower. Toxicities were more severe and consistent at doses of 0.6 mg/m^2 and above [39]. A RP2D of 0.75 mg/m^2 was determined as the RP2D in solid tumours with thrombocytopenia, neurotoxicity and possible cardiac toxicity seen above this dose [39]. Weekly IV bolus or 24 hour infusions of DM1 escalating from 0.4 to 1.6 mg/m^2, saw 22% of patients receiving 1.1 mg/m^2 or above experiencing dose-limiting gastrointestinal toxicity. Neurologic toxicity was seen at a cumulative dose of 6 mg/m^2 (≥1.1 mg/m2/week) with haematological toxicity seen at nearly all doses [40]. A study evaluating a single infusion every 3 weeks reported a MTD of 2 mg/m^2, with the DLT being gastrointestinal toxicity being dose-limiting [41], the observed toxicity, along with limited signs of anti-tumour efficacy were sufficient to stop the clinical development of maytansine. In comparison, HNSTD in monkeys for maytansine was 0.5 mg/m^2 (5 doses) [42] and the HNSTD in monkeys for BT1718 was 18 mg/m^2 (equivalent 3.6 mg/m^2 DM1) twice weekly. In rats the lethal dose to 10% (LD10) following a single dose was 2.5 mg/m^2 [43], whereas the tolerated dose in rats was 6 mg/m^2 (1.2 mg/m2 DM1) administered twice weekly over four weeks. More recently the targeted delivery of maytansine, as part of trastuzumab emtansine, has demonstrated a greater clinical utility [44].

Antibody Drug Conjugates

Many ADCs are currently in clinical development, with most incorporating the auristatin (MMAE/MMMAF) or maytansinoid (DM1/DM4) tubulin inhibitor payloads, similar to the cytotoxic DM1 payload in BT1718 [45]. Common AEs reported from clinical trials with ADCs utilising DM1 are listed in Table 3. While these ADCs target a diverse array of different cancer targets, generally similar clinical and preclinical toxicity profiles have been observed. Common clinically observed AEs are anaemia, neutropenia, thrombocytopenia, elevations in liver enzymes, nausea and fatigue, with a subset of patients experiencing peripheral neuropathy irrespective of the antibody target. While BT1718 shared some of these toxicological findings in preclinical studies, a notable lack of liver and GI toxicity suggests that its differentiated distribution profile may avoid some of the toxicities observed with the ADCs. Taken together, the toxicity findings from clinical trials with these ADCs may provide some guidance regarding the AEs expected clinically for BT1718.

At the start of the clinical trial, the information referenced from the Investigator Brochure (IB) was current. Updates to the IB will not be reflected in this section so please refer to the most current version of the IB for up to date information.

Table 3 Summary of adverse events experienced with conjugated DM1

ADC	Target	Linker	Adverse events and clinical findings
T-DM1 (Kadcyla)	Anti-HER2	SMCC (Non-cleavable)	In the most recent trial, GATSBY, in HER2 positive gastric cancer [46, 47] the most common AEs were fatigue (33%), anaemia (21-33%), neutropenia (10%), thrombocytopenia (26%), GI AEs (25%, made up of constipation, vomiting, diarrhoea, nausea, abdominal pain), transaminitis (16%), peripheral neuropathy (10%) and rash (6%). All these AEs were also experienced in breast cancer trials [48].
IMGN529	anti-CD37	SMCC (Non-cleavable)	In the Phase I trial in relapsed or refractory B-Cell Non-Hodgkin Lymphoma (NHL), early onset Grade 3-4 neutropenia attributed to cytokine release was reported at 30 mg/m^2 (0.8 mg/kg). Prophylactic administration of steroids allowed further escalations with the treatment-emergent adverse events (TEAEs in >20% of the 31 patients)) being neutropenia (30%), fever (27%), asthenia (20%) and fatigue (20%) [49]. IMGN529 is currently recruiting a Phase II study in combination with ritixumab (NCT02564744).
AMG595	anti-EGFRvIII	Non-cleavable	Phase I in recurrent glioblastoma multiforme and/or anaplastic astrocytomas (NCT01475006). Like T-DM1, dose limiting toxicity was thrombocytopenia and has currently been dosed up to 111 mg/m^2 (3 mg/kg) [50] with full safety data not yet published.
Lorvotuzumab mertansine (IMGN901)	anti-CD56	SPP (cleavable)	A series of Phase I trials have been conducted with different schedules in solid malignancies; DLTs included fatigue, neuropathy, headache or meningitis-like symptoms, chest pain, dyspnea, and myalgias. Recommended Phase 2 dose (RP2D) was 60 mg/m^2 (3 consecutive days every 3 weeks). Overall, TEAEs were experienced by 96.9 % of all patients, the majority of which were Grade 1 or 2. The most commonly reported Grade 3 or 4 TEAEs were hyponatremia and dyspnea (each 8.2 %)[34]. Lorvotuzumab mertansine is currently being studied, using a dosing schedule of Day 1 and Day 8 every 21 days, in Phase II trials for haematological malignancies (NCT02420873) and in younger patients with Wilms tumour, rhabdomyosarcoma, neuroblastoma, pleuropulmonary blastoma, malignant peripheral nerve sheath tumour, or synovial sarcoma (NCT02452554).
Cantuzumab mertansine	Anti-CanAg	SPP (cleavable)	Three Phase I trials were conducted in solid tumours; one dosing every 3 weeks, another dosing weekly and a third dosing three-times per week in a 3 out of 4 weeks schedule. When administered once every 3 weeks, AEs included acute, transient and reversible elevations of hepatic transaminases, as well as nausea, vomiting, fatigue, and diarrhoea [32], The RP2D from this trial was 235 mg/m^2 every 3 weeks (~3.9 mg/m^2 DM1). Weekly administration had a MTD of 115 mg/m^2/week (~1.9 mg/m^2/week DM1) with DLTs identified as acute, transient elevation of hepatic transaminases and reversible fatigue [51], In a third Phase I trial, the ADC was administered IV three-times a week [33]. The MTD was 45 mg/m^2 (~0.75 mg/m^2 DM1), and the DLT was Grade 3 transaminitis. Hepatic, haematological, and neurosensory effects also occurred, but were rarely severe,
MLN2704	Anti-PSMA	SPP (cleavable)	In the initial Phase I trial evaluating 3 repeat doses at 4 week intervals the MTD was not determined. MLN2704 was given up to 343 mg/m^2/week per dose (ca. 5.7 mg/m^2 DM1). Drug–related Grade 3 toxicities occurred in three (13%) of 23 patients, including uncomplicated febrile neutropenia (the only DLT) in one patient, reversible elevations in hepatic transaminases, leukopenia, and lymphopenia. The most frequent Grade 1 or 2 toxicities included fatigue, nausea, and diarrhoea. Neuropathy occurred in eight (35%) of 23 patients, including five of six patients treated at 343 mg/m^2 [52]. In an additional Phase I trial, which explored multiple schedules, neurotoxicity was dose-limiting, with 44 of 62 patients exhibiting peripheral neuropathy, including 6 having Grade 3/4 neuropathy [53]. Other common toxicities included nausea (61%), fatigue (60%), anorexia (39%), and diarrhoea (39%). Overall, 15 patients (38%) discontinued treatment secondary to an adverse event.

ADC	Target	Linker	Adverse events and clinical findings
PEN - 221 (peptide drug conjugate) MW 1786	SSTR2	(cleavable)	A first in human Phase I/IIa trial of PEN-221, somatostatin analogue -DM1 conjugate, in patients with advanced neuroendocrine tumours or small cell lung cancer (NCT02936323). In the Phase I part of the trial, PEN-221 was given every 3 weeks at escalating doses ranging from 1 – 25 mg and was well tolerated with no DLTs in the first six cohorts (1 -18 mg; 20 patients). In Cohort 7 (25 mg), two out of three patients had DLTs that rapidly and fully resolved: Grade 3 ALT/AST rise (2 patients), of whom one had concurrent Grade 3 total bilirubin rise and Grade 3 mucositis. The most frequent (≥20% patients) PEN-221 related AEs were fatigue (43%), nausea (43%), diarrhoea (39%), vomiting, (26%), abdominal pain (22%), and decreased appetite (22%). The MTD was established at 18 mg (~9.5 mg/m^2 assumed to be ~3.9 mg/m^2 DM1 on the basis of 1:1 peptide:toxin ratio in 70 Kg patient) every 3 weeks and this dose schedule is being evaluated in the Phase IIa expansion cohorts [54].

2.4.1 Expected safety profile for BT1718

Haematopoietic changes

[redacted]
Haematological toxicity such as neutropenia, lymphopenia, erythropenia and thrombocytosis are not uncommon in agents that affect the cell cycle and these changes are clinically manageable. [redacted] BT1718 is likely to produce haematological changes in patients and as such, standard haematological evaluations will be undertaken as part of the clinical programme.

Renal and bladder changes

BT1718 and its possible peptidyl metabolites, are expected to be cleared through the kidney and bladder. [redacted] Standard blood (serum urea, creatinine) and urine tests (urinalysis for protein and blood) will be undertaken as part of the clinical programme. Further investigations would be initiated as clinically indicated.

Hepatic changes

[redacted] Hepatotoxicity has been a common finding for the predominantly hepatic-cleared maytansine and antibody-maytansinoid conjugates, but may be minimal for BT1718 [redacted] However, as a precaution standard liver function tests will be performed as part of the clinical programme. Further investigations or imaging would be initiated as clinically indicated.

Neuronal changes

Peripheral neuropathy is a common side effect of microtubule inhibitors [31] and has been a noted AE experienced with antibody-DM1 conjugates. [redacted]. Patients will be evaluated at study visits for any AEs relating to the nervous system. Symptom-directed clinical examination and further investigations or imaging would be initiated as clinically indicated. Further investigations or imaging would be initiated as clinically indicated

Skin

[redacted] Patients will be evaluated at study visits for any AEs related to the skin. In addition, DM1 and other chemotherapeutics can cause extravasation and/or are vesicants, irritants, inflammitants or exfoliants[7] [55, 56] and as a precaution BT1718 will be treated as a vesicant. Patients will be evaluated during treatment and at each study visit for evidence of extravasation. Standard local policies for management of vesicant extravasation will be followed, typically starting with stopping the infusion, aspirating if possible, topical hydrocortisone and ongoing review. The role of specific treatment such as heat or cold packs, dimethyl sulfoxide (DMSO) or hyaluronidase is unknown.

Gastrointestinal changes

[redacted]

[7] http://www.beatson.scot.nhs.uk/content/mediaassets/doc/Extravasation%20guidance.pdf

[redacted]

Gastrointestinal toxicity is therefore considered unlikely below the MTD in humans. Patients will be evaluated at study visits for any AEs relating to the GI tract (see pancreatic acinar section below). Further investigations or imaging may be initiated if clinically indicated.

Reproductive organ changes

Changes in the reproductive system are a common side effect of agents that affect the cell cycle. [redacted]

Reproductive changes may be a possible side effect of administration of BT1718. Patients will be advised of the potential impact of BT1718 on fertility and patients will be required to comply with the standard clinical trial contraceptive practices. The Phase I trial will be in refractory/relapsed patients whose prognosis and fertility are likely to be very limited, therefore in this context it is deemed an acceptable risk. Where appropriate for male patients who may be in a position to consider having or extending a family, the possibility of conservation of sperm should be discussed. Patients wishing to do so should also have a discussion of the implications of their own prognosis and of the possible effects of previous therapy on the production, function and genetic health of sperm.

Adrenal changes

[redacted] Administration of BT1718 could lead to changes in adrenal gland function including the zona glomerulosa (aldosterone secretion). As such, BP and standard clinical chemistry parameters will be evaluated as part of the clinical programme. Persistent unexplained hypo-/hyper-tension or altered potassium levels would be investigated further with serum renin:aldosterone, cortisol or ACTH assays as appropriate, and treatment such as fluids and steroid replacement, or conversely anti-hypertensives, initiated as clinically indicated.

Salivary gland changes

Dry mouth and associated toxicity are a common side effect with chemotherapy [37], with these symptoms tending to resolve within 3 to 4 weeks off treatment. [redacted]

Patients will be evaluated at study visits for any AEs, including dry mouth. Symptom-directed clinical examination/and or further investigations will be conducted as clinically indicated.

Pancreatic acinar changes

[redacted] Toxicity might be expected to manifest as impaired exocrine function of the pancreas. Patients will be evaluated at study visits for any AEs relating to the GI tract (see also gastrointestinal section above). Bloating, steatorrhoea and/or diarrhoea may be investigated further with faecal elastase evaluation and treatment such as CREON initiated as clinically indicated.

2.5 Rationale for the proposed trial

By targeting MT1-MMP expressing tumour cells, BT1718 is expected to induce selective tumour cell death. This would be expected to translate into objective radiological responses with an acceptable therapeutic window, and ultimately to improve PFS and OS for patients with MT1-MMP expressing tumours. Preclinical data has demonstrated activity in relevant models and toxicology has indicated monitorable and reversible toxicities, expected to be manageable in the clinic.

BT1718 has low molecular weight (3.5 kDA) in comparison to other conjugated toxin approaches, which enables rapid penetration of tumour tissue. In addition, preclinical PK and toxicokinetics estimates a 15 to 30 minute half-life, which is in contra-distinction to ADCs and suggests a more rapid on-off profile.

Hypothesised advantages over ADCs therefore include reduced systemic exposure of normal tissues to circulating BT1718, the ability to manage toxicity during recovery periods, as well as the improved tumour penetrance. Other potential advantages include a fixed peptide:conjugate ratio of 1:1 (c.f. ADCs where variable conjugation results in mixed populations) and with more scalable manufacturing as a small molecule (c.f. biologics such as ADCs).

Overexpression of MT1-MMP has been reported in NSCLC [3, 4], breast cancer [5, 6, 57] and other solid tumours [7, 8 , 9]. Work is ongoing in identifying those tumour types with the highest incidence of MT1-MMP overexpression. [redacted] Since the majority of cancers may express some MT1-MMP, and the relationship between efficacy and MT1-MMP expression is not fully delineated the dose escalation phase of the trial will not restrict recruitment based on levels of MT1-MMP expression, and will be open to patients of all solid malignancy types. In the Phase IIa, expansion phase at the optimal dose/schedule(s), patients will be enrolled with tumour types anticipated to commonly overexpress MT1-MMP and where raised high MT1-MMP overexpression is confirmed during prospective screening selection at enrolment. This confirmation of expression will test the hypothesis that MT1-MMP overexpression is expected to translate to favourable clinical outcomes for patients treated with BT1718. The tumour types currently proposed for the Phase IIa are squamous NSCLC, squamous oesophageal cancer and a basket cohort. Other tumour types with a high incidence of MT1-MMP expression may be considered in future expansions cohort(s) and would be specified in a future substantial amendment submitted to MHRA, REC and HRA for approval.

The route of administration will be intravenous as with most peptide-based molecules, as oral dosing would result in degradation. [redacted] Initially, twice weekly dosing will be evaluated [redacted] During the escalation phase, a once weekly regimen will also be explored, which is expected to be more convenient for patients [redacted]. The starting dose will be 0.6 mg/m^2 twice weekly, [redacted]

3 TRIAL DESIGN

3.1 Clinical trial objectives and endpoints

3.1.1 Primary objectives and endpoints

Primary objectives	Endpoints
Dose Escalation phase To propose a recommended Phase II dose (RP2D) for evaluation by establishing the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), of BT1718 given in patients with advanced solid tumours, at one or more dosing schedules.	Determine a dose at which no more than one out of six patients at the same dose level experiences a probable or highly probable BT1718-related DLT.
Dose escalation and expansion phase To assess the safety and toxicity profile of BT1718 in patients with advanced solid tumours.	Determine the frequency and causality of each AE to BT1718 and grade severity according to NCI CTCAE Version 4.02. The causality of all AEs will be assessed by the Investigator.

3.1.2 Secondary objectives and endpoints

Secondary objectives	Endpoints
Dose escalation phase and expansion phase To investigate the pharmacokinetic (PK) behaviour of BT1718 in human	Measurement of C_{max}, AUC, terminal elimination half-life ($t_{½}$), and other PK parameters of BT1718 in plasma, both as an intact and cleaved molecule.
Dose escalation and expansion phase To assess preliminary signals of BT1718 efficacy in dose escalation and in relevant tumour types with high expression of membrane type 1 matrix metalloproteinase (MT1-MMP) in the expansion phase	Assess anti-tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. Estimate progression-free survival, progression-free survival rate at six months, and OS (where available). Estimate duration of response.

3.1.3 Tertiary objectives and endpoints

Tertiary objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

3.2 Design of the clinical trial

This is a multi-centre, FIH, Phase I/IIa, open label dose escalation trial with an expansion phase, in patients with advanced solid tumours.

This clinical trial will consist of two phases, Phase I and Phase IIa (**Figure 3**).

Phase I, dose escalation phase:

Phase I will consist of Stage 1 and Stage 2. Stage 2 may commence before Stage 1 is completed:

- **Stage 1** - BT1718 will be administered intravenously **twice weekly** for three out of four weeks until the RP2D and/or MTD is established.

  Stage 1 will start with single patient cohorts and dose increases will initially be up to a maximum of 100%, driven by reported safety and any available PK data until such time that a Grade 2 or greater AE considered to be at least probably related to BT1718 is observed or until the dose exceeds 6 mg/m^2 twice weekly (i.e. 12 mg/m^2 over the week). Subsequent cohorts will revert to a standard 3+3 format with dose escalation steps up to 100% driven by reported safety and available PK data.

- **Stage 2 -** BT1718 will be administered intravenously **once weekly** for three out of four weeks until the RP2D and/or MTD is established.

  Stage 2 will open at a dose where there is expectation of potential biological activity based on available toxicity, PK and/or PD data from Stage 1. This stage will follow a 3+3 dose escalation design and will include a minimum of three evaluable patients at each dose level. Dose increases will be up to 100%, driven by reported safety and available PK data.

Phase I of the trial has completed.

Phase IIa, expansion phase

Phase IIa will consist of two or more expansion cohorts to include tumour types known to commonly over-express MT1-MMP and where MT1-MMP overexpression is confirmed during retrospective or prospective selection.

- **Squamous NSCLC cohort**- BT1718 will be administered intravenously at the **once weekly** RP2D established in Phase I, Stage 2 and will include approximately 16 patients, with MT1-MMP positive squamous NSCLC (see section 5.4.4 for further details on RP2D dose adjustments) . It is expected that a minimum of eight patients will have pre and post treatment biopsies (see section 7.1.3 and 7.2.2 for further details).
- **Basket cohort**- BT1718 will be administered intravenously at the **once weekly** RP2D established in Phase I, Stage 2 in approximately 16 patients with advanced solid tumours (excluding patients eligible for one of the other recruiting expansion cohorts). See section 5.4.4 for further details on RP2D dose adjustments It is expected that all patients (except patients with a very high MT1-MMP H-score if agreed with the Sponsor and PI) will have pre and post treatment biopsies (see sections 7.1.3 and 7.2.2 for further details). The squamous NSCLC and basket cohorts will run in parallel.
- **Additional expansion cohort(s)**– an additional expansion cohort of approximately 16 evaluable patients with squamous oesophageal cancer may be opened after review of data obtained from the squamous NSCLC and basket expansion cohorts by the Joint Development

Committee comprising of team members from the Sponsor, Bicycle Therapeutics Ltd and Chief Investigator (CI). It is expected that a minimum of eight patients will have pre and post treatment biopsies (see section 7.1.3 and 7.2.2 for further details). Other tumour types with a high incidence of MT1-MMP expression may be considered in future expansion cohort(s) and would be specified in a future amendment.

In Phase I, Stages 1 and 2, it is expected between 50 to 60 patients with advanced solid tumours, whose tumours have progressed through any suitable standard therapies, will be entered into this study. The final number of patients will depend on the number of dose escalations required to identify the MTD and/or RP2D, at one or more dosing schedules. In Phase IIa it is expected that up to an additional 70 patients will be evaluated.

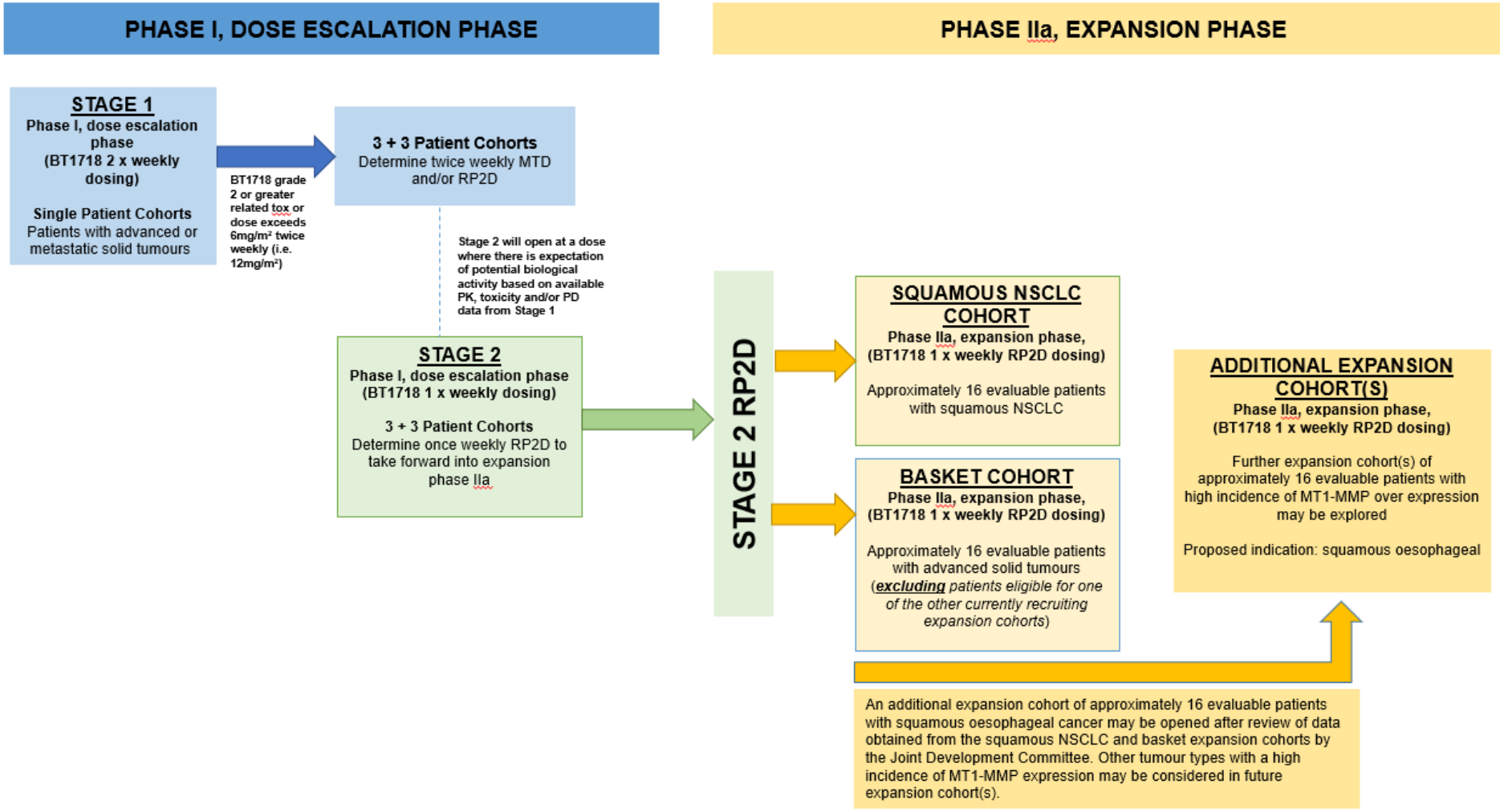
In Phase I, Stage 1, BT1718 will be administered intravenously **twice weekly** for three out of four weeks (dosing on Days 1, 4, 8, 11, 15 and 18). The starting dose will be 0.6 mg/m^2 and each cycle will last 28 days. Patients may continue treatment until disease progression (depending on the availability of BT1718).

In Phase I, Stage 2, BT1718 will be administered intravenously **once weekly** for three out of four weeks (dosing on Days 1, 8 and 15). The starting dose of the once weekly regime will be up to 100% of the overall weekly dose from the last completed cohort deemed safe from the twice weekly schedule (Phase I, Stage 1). Patients may continue treatment until disease progression (depending on the availability of BT1718).

Alternative dosing schedules may be considered by the Sponsor based on emerging data during the study, for example if the toxicology profile is benign with the twice weekly dosing regimen, continuous twice weekly dosing may be evaluated. Emerging data obtained during Phase I will be used in the decision to proceed with the Phase IIa stages. In addition, depending on the patient populations selected, an increased dosing frequency may also be considered. If any changes are made to the dosing schedule a substantial amendment will be submitted to the MHRA, REC and HRA for approval.

Phase I of the trial has completed.

Figure 3 Study design schema



3.3 Definition of dose limiting toxicity

Some of the DLT and MTD definitions are derived from the NCI CTCAE Version 4.02. Please note that not all of the events described as DLTs are fully supported by NCI CTCAE but are formed by amalgams of different events in order to assist with assessments of AEs.

A DLT is defined as a probably or highly probably **drug-related AE occurring during Cycle 1 (i.e. the first 28 days)** which fulfils one or more of the following criteria, despite appropriate supportive clinical management (however, all clinically significant toxicities will be considered in dose review decisions and the determination of the Phase II dose):

- Neutropenia Grade 4 (absolute neutrophil count [ANC] < 0.5 x 10^9/L) for ≥ seven days *see note;
- Febrile neutropenia with Grade 3 or 4 neutropenia ANC <1.0 x 10^9/L and a single temperature of ≥ 38.3°C or a sustained temperature ≥38 °C for more than one hour);
- Clinically significant infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L);
- Thrombocytopenia Grade 4:
    a) for ≥ five days *see note, or
    b) associated with active bleeding, or
    c) requiring platelet transfusion.
- Grade 3 or 4 toxicity to organs other than the bone marrow, EXCLUDING:
    - Grade 3 nausea;
    - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics; or
    - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals.
    - Transient, asymptomatic Grade 3 biochemical abnormalities if agreed by the Sponsor and the Study Team, including the Chief Investigator (CI).
- Fatal event;
- Any other related toxicity which leads to discontinuation of treatment in Cycle 1, or to a delay in dosing of >7 days (excluding where the delay is >7 days due to scheduling rather than a clinical decision);
- Any other related toxicity that is greater than at baseline and is judged to be a DLT by the Sponsor, including the CI and Principal Investigators (PIs).

***Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 7 (neutropenia) and Day 5 (thrombocytopenia) after the onset of the event to determine if a DLT has occurred. The investigator must continue to monitor the patient closely until resolution to Grade 3 or less**.

Dose limiting toxicities defined above will be considered for the purpose of dose escalation decisions; however, should cumulative toxicity become apparent this will also be taken into consideration when determining either the next dose level, the RP2D or the dose and schedule for the expansion phase.

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, the Sponsor must be informed immediately as this may affect dose escalation decisions.

3.4 Definition of maximum tolerated dose

If one instance of DLT as defined in (Section 3.3) is observed in a cohort of three patients, up to a total of six patients will be treated at that dose level. If one out of six patients experiences a DLT, dose escalation will continue. If two or more out of up to six patients experience a DLT, dose escalation will

stop and this dose will be defined as non-tolerated. A maximum of six evaluable patients will be treated at a dose below the non-tolerated level, to define the MTD.

The MAD will be defined as the highest dose received. This will usually represent the non-tolerated dose above the MTD, but may instead represent a maximum administrable dose if the feasible volume of infusion limits dose before toxicity does.

The RP2D for the expansion phases for both once weekly and twice weekly dosing will be determined following discussion of all clinically relevant toxicity, efficacy data, and PK results data by the CI, PIs and the Sponsor's Medical Advisor. All significant toxicities will be considered in the determination of the RP2D, including all available data from all cycles and cohorts of treatment.

3.5 Patient evaluability

3.5.1 Response

All patients who meet the eligibility criteria and receive at least one full cycle of IMP or ≥66% of the planned dose exposure of BT1718 within Cycle 1 and 2, and have a baseline assessment of disease and at least one repeat disease assessment will be evaluable for response.

In the expansion cohorts, baseline MT1-MMP H-score must also meet the positivity criteria for the patient to be evaluable.

Repeat assessments after at least four weeks are required in order for a patient to be confirmed as having a complete or partial response (CR or PR). To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of BT1718 is given.

3.5.2 Safety

All patients who meet the eligibility criteria and receive at least one administration of BT1718 will be evaluable for safety.

3.5.3 Dose Escalation

In the Phase I, Stage I, single patient dose escalation phase of this study, each patient must have received all of their planned doses of BT1718 during the first cycle (28 day DLT period) to make a decision to escalate to the next single patient cohort. If a patient does not receive all their planned doses of BT1718 during that cycle for reasons other than toxicity, a further evaluable patient may need to be recruited before a decision can be made.

Once the dose escalation cohorts are expanded following a 3+3 design, patients must have received ≥75% of their planned dose exposure of BT1718 during the first cycle (28 day DLT period) in order to dose escalate. If any patients in the three to six patient cohorts receive <75% of their planned doses during the first cycle (28 day DLT period) for reasons other than BT1718 related toxicity, further evaluable patients may need to be recruited before a decision can be made (see section 5.6.1).

Phase I of the trial has completed.

4 PATIENT SELECTION

4.1 Eligibility criteria

The patient must fulfil the eligibility criteria listed below:

4.1.1 Inclusion criteria

1. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up
2. **Phase I, dose escalation phase (Stages 1 and 2)**:
   - Histologically or cytologically proven advanced solid tumour, refractory to conventional treatment, or for which no conventional therapy is considered appropriate by the Investigator or is declined by the patient.

   Phase IIa, expansion phase:
   - Histologically or cytologically proven advanced solid tumour of particular interest based on pre-clinical and clinical data, refractory to conventional treatment, or for which no conventional therapy is considered appropriate by the Investigator or is declined by the patient. Phase IIa expansion cohorts will be:
     a. Squamous NSCLC cohort – retrospective MT1-MMP testing.
     b. Basket cohort (advanced solid tumours, excluding patients eligible for one of the other recruiting expansion cohorts) - high MT1-MMP expression by IHC assay using archival tumour sample (mandatory fresh tumour samples for those patients without available archival tumour samples or additional analysis is deemed necessary). Retrospective testing may be permitted for tumour types estimated to have high MT1-MMP positivity rates as per the Laboratory manual.
     c. Additional expansion cohort(s) of squamous oesophageal cancer if confirmed as recruiting by the Sponsor (see Section 3.2).
   - At least one measurable lesion according to RECIST Version 1.1, that has had objective progression on or after the last therapy
   - [redacted]
   - [redacted]
   - [redacted]
3. Life expectancy of at least 12 weeks
4. World Health Organisation (WHO) performance status of 0 - 1 (Appendix 1)
5. Haematological and biochemical indices within the ranges shown below. These measurements should be performed to confirm the patient's eligibility.

Laboratory Test	Value required
Haemoglobin (Hb)	≥90.0 g/L, or ≥100.0 g/L if transfusion within last four weeks
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelet count	≥100 x 10^9/L
Bilirubin	≤1.5 x upper limit of normal (ULN) *NB: >1.5 x ULN, acceptable if conjugated bilirubin is ≤1.5 x ULN*

Alanine amino-transferase (ALT), aspartate amino-transferase (AST) and alkaline phosphatase (ALP)	≤2.5 x ULN (or ≤5 x ULN if has liver metastases)
Renal function Either: Serum creatinine	 ≤1.5 x ULN
Or: Calculated creatinine clearance (using the Wright or Cockcroft & Gault [C&G] formula)	GFR ≥50 mL/min (uncorrected value)
Or: Isotope clearance measurement *	GFR ≥50 mL/min (corrected value)

* Isotope clearance result to be used to confirm eligibility if calculated C&G/Wright method results in a glomerular filtration rate (GFR) of =50 mL/min.

6. 16 years or over at the time consent is given
7. Consent to access and analyse any available archival tissue.

4.1.2 Exclusion criteria

1. Radiotherapy (except for palliative reasons), systemic anti-cancer therapy (with the exception of life-long hormone suppression such as LHRH agents in prostate cancer) or investigational medicinal products during the previous four weeks (six weeks for nitrosoureas, mitomycin-C) before treatment (or first dose of an immunotherapy during the previous 12 weeks).
2. Prior bone marrow transplant, myeloablative conditioning, or extensive radiotherapy to greater than 25% of bone marrow, within previous eight weeks of first BT1718 dose.
3. Ongoing toxic manifestations of previous treatments greater than NCI CTCAE Grade 1. Exceptions to this are alopecia, amenorrhea/oligospermia and any other ongoing toxic manifestation which in the opinion of the Investigator and the Medical Advisor should not exclude the patient.
4. Any central nervous system (CNS) metastases (unless had local therapy and are asymptomatic and radiologically-stable off steroids for the last four weeks).
5. Current or prior malignancy which could affect compliance with the protocol or interpretation of results. Patients with curatively-treated non-melanoma skin cancer, non-muscle-invasive bladder cancer, or carcinomas-in-situ are generally eligible.
6. Female patients who are able to become pregnant (or are already pregnant or lactating). However, those patients who have a negative serum or urine pregnancy test before enrolment and agree to use two forms of contraception (one effective form plus a barrier method) [oral, injected or implanted hormonal contraception and condom; intra-uterine device and condom; diaphragm with spermicidal gel and condom] or agree to sexual abstinence[8], effective from the first administration of BT1718, throughout the trial and for six months afterwards are considered eligible
7. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using a barrier method of contraception [condom plus spermicide] or to sexual abstinence[9] effective from the first administration of BT1718, throughout the trial and for six months

[8] Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

[9]Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

afterwards. Men with partners of child-bearing potential must also be willing to ensure that their partner uses an effective method of contraception for the same duration for example, hormonal contraception, intrauterine device, diaphragm with spermicidal gel or sexual abstinence). Men with pregnant or lactating partners must be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure of the foetus or neonate.

8. Surgery from which the patient has not yet recovered.

9. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.

10. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

11. Patients with significant cardiovascular disease are excluded as defined by:
    a. Current congestive heart failure requiring therapy (NYHA III or IV – Appendix 3) or known LVEF <40% (moderate to severe)
    b. History of unstable angina pectoris or myocardial infarction up to six months prior to trial entry, or of current poorly controlled angina (symptoms weekly or more)
    c. Presence of symptomatic or severe valvular heart disease (severe by local echographic criteria or AHA/ACC Stage C or D – Appendix 4)
    d. History of a clinically significant cardiac arrhythmia up to six months prior to trial entry (asymptomatic atrial fibrillation or asymptomatic first-degree heart block are permitted)

12. Previous known allergy to one of the constituents or excipients of BT1718.

13. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase I/IIa study of BT1718. Participation in an observational trial or interventional clinical trial which does not involve administration of an IMP and which would not place an unacceptable burden on the patient in the opinion of the Investigator and Medical Advisor would be acceptable.

14. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

4.2 Patient enrolment

Before enrolling the patient in the trial, the Investigator or designated representative should determine the eligibility of the patient during the trial screening period.

Eligible patients must be enrolled in the electronic data capture (EDC) system by site staff and then registered at the Centre for Drug Development (CDD) before they start treatment with BT1718. Eligible patients will be allocated a study number by the EDC system during the enrolment process. The CDD will send confirmation of the patient registration including the assigned dose level to the Investigator following enrolment of the patient. Study treatment may only be administered after confirmation has been received.

5 TREATMENT

5.1 Selection of the Phase I starting dose and schedule

[redacted]

Therefore, the proposed starting dose for the FIH Phase I trial is 0.6 mg/m^2 twice weekly.

5.2 Dosing schedule/treatment schedule

5.2.1 Phase I, dose escalation phase, Stage 1, dosing schedule/treatment schedule

BT1718 will be administered intravenously twice weekly for three out of four weeks (dosing on Days 1, 4, 8, 11, 15 and 18 +/- 1 day). Each cycle of treatment will consist of 28 days, and patients may continue until disease progression, depending on the availability of BT1718 (see Section 5.6). The starting dose will be 0.6 mg/m^2.

Phase I of the trial has completed.

5.2.2 Phase I, dose escalation phase, Stage 2, dosing schedule/treatment schedule

In addition to evaluating a twice weekly dosing schedule in Stage 1 above, a once weekly dosing schedule will also be evaluated in Stage 2. Stage 2 will open at a dose where there is expectation of potential biological activity based on available PK, toxicity and/or PD data from Stage 1.

BT1718 will be administered intravenously once weekly for three out of four weeks (dosing on Days 1, 8 and 15 +/- 1 day). Each cycle of treatment will consist of 28 days and patients may continue until disease progression, depending on the availability of BT1718. The starting dose of the once weekly regime will be up to 100% of the overall weekly dose from the last completed cohort deemed safe from the twice weekly schedule (Phase I, Stage 1). Stage 2 will include a minimum of three evaluable patients following a 3+3 design.

Alternative dosing schedules may be considered by the Sponsor based on emerging data during the study, for example if the toxicology profile is benign with the twice weekly dosing regimen, continuous bi-weekly dosing maybe evaluated. Emerging data obtained during Phase I may be used in the decision to proceed with the Phase IIa stages. In addition, depending on the patient populations selected, an increased dosing frequency may also be considered. If any changes are made to the dosing schedule a substantial amendment will be submitted to the MHRA, REC and HRA for approval.

Phase I of the trial has completed.

5.2.3 Phase IIa, expansion phase

BT1718 will be administered intravenously at the once weekly RP2D as defined by Phase I, Stage 2; refer to Section 5.2.2.

Please refer to section 3.2 for further details on the expansion cohorts.

5.3 Dose Escalation communication plan

5.3.1 Organisation and preparation for dose decision meetings

Dose decision meetings will be organised by the Sponsor for review of patient data after each patient in the single patient dose escalation cohorts has completed Cycle 1 (28 day DLT observation period). When cohorts are expanded to 3+3, dose decision meetings will be organised by the Sponsor for review of patient data once each cohort is complete.

Dose decision meetings may also be arranged during the expansion phase in response to emerging tolerability data, including a formal assessment after the first six patients.

Required attendees / functional groups are as defined in the Sponsor's SOP.

Prior to the dose decision meeting, the Sponsor will distribute the agenda and all necessary data to the meeting attendees, specifying which patients and data will form part of the review. The essential data to be reviewed to make decisions concerning changes in dose will be defined in the monitoring guidelines for the study. These will consist primarily of clinical data listings from Data Management, safety data listings from Pharmacovigilance and any available PK and [redacted] data from the analysing laboratory(ies).

5.3.2 Areas to be discussed at dose review meetings

Areas which should be discussed at the dose review meeting include but are not limited to:

- Outline any relevant criteria specified by the protocol relating to changes in dose levels to the attendees e.g. study dose escalation scheme, DLT criteria, criteria for expansion of cohorts etc. Patients treated since the last dose review meeting including BT1718 related AEs noted and duration of treatment.
- Assessment and agreement on any DLTs that may have occurred and resulting actions.
- Relevant PK [redacted] data available since the last dose decision meeting.
- Any additional relevant information relating to AEs or patient safety which may have arisen following distribution of listings for the meeting and will therefore not be documented in the listings.
- Any possible concern after the review of cumulative data e.g. toxicities.
- Assessment and agreement on the appropriate next dose level or other action such as dose expansion, dose reduction or halt to recruitment.

5.3.3 Follow-up of dose decision meetings

Following the meeting the Sponsor will prepare and disseminate minutes documenting what data was reviewed for which patients and with the outcome stated. DLTs and serious adverse events (SAEs) discussed (as defined in the protocol) will be documented fully in the minutes and listed by patient. If changes to these emerge as part of the review and discussion the minutes will reflect these and any actions to be taken as a result. Dose review meeting minutes will be distributed by the Sponsor to the CI, all study PIs and any other relevant site staff.

If due to exceptional circumstances, the CI is not able to attend the dose review meeting, the meeting minutes will be sent to the CI by email who will respond to confirm agreement as soon as possible with the dose decision prior to the recruitment of the next patient to the relevant cohort.

The outcome of the dose review will also be approved by the Sponsor's Head of Medical Sciences ahead of recruitment of the next patient to the relevant cohort. Patients can only be registered and treated on the study following email confirmation from the Sponsor to the site of the agreed dose level for the specific patient.

5.3.4 Dissemination of Safety data between dose decision meetings

Safety information relating to SAEs and DLTs will be collected and provided to the MHRA and REC as outlined in Section 9. Where the Sponsor becomes aware of significant relevant safety information (such as a DLT) during treatment of patients on the study, this will be communicated to all PIs and relevant site staff by email as soon as is reasonably possible. Updates regarding the DLT assessment and actions to be taken will also be provided by email where needed with follow-up phone-calls where required.

Phase I of the trial has completed.

5.4 Dose escalation scheme

5.4.1 Phase I, dose escalation phase, Stage 1 - (twice weekly dosing)

In Phase I, dose escalation phase, Stage 1, dose increases will initially be up to a maximum of 100% in the single patient cohorts, driven by reported safety data and any available PK data, until the first CTCAE Grade 2 toxicity considered by investigators to be at least probably related to BT1718 is observed, or until the dose exceeds 6 mg/m^2 twice weekly (i.e. 12mg/m^2 over the week). Subsequent cohorts will revert to a standard 3+3 format with dose escalation steps up to 100% driven by reported safety and available PK data. If a single DLT is seen among the initial three patients, the cohort will be expanded up to a total of six evaluable patients. The dose will be considered tolerable if less than two out of six evaluable patients experience a DLT.

In the single patient cohorts, the next patient can receive their first dose of BT1718 once the preceding patient has completed their DLT period (the first 28 days) and the Sponsor and study team has deemed it safe to proceed to the next cohort. In the 3+3 patient cohorts the first patient will be observed for toxicity for 7 days from Day 1 before subsequent patients receive their first dose of BT1718. Please refer to Section 5.3 for details of the process for dose escalation review and dissemination of information.

Patients who receive less than 75% of their planned doses during the first cycle (28 days DLT period) for reasons other than toxicity will not be evaluable for assessment of DLT for dose review decisions and may be replaced in the cohort. Reported safety information for these patients may however be considered to guide the percentage change in dose levels. In order to make the decision to escalate the BT1718 dose, the required number of evaluable patients must have completed one cycle (approximately 28 days).

Phase I of the trial has completed.

5.4.2 Phase I, dose escalation phase, Stage 2 - (once weekly dosing)

In Phase I, dose escalation phase (Stage 2) dose increases may be up to 100% of the previous dose level, and will be driven by reported safety and available PK data. If a single DLT is seen among the initial three patients, the cohort will be expanded up to a total of six evaluable patients. The dose will be considered tolerable if less than two out of six evaluable patients experience a DLT.

In the 3+3 patient cohorts the first patient will be observed for toxicity for 7 days from Day 1 before subsequent patients receive their first dose of BT1718. Please refer to Section 5.3 for details of the process for dose escalation review and dissemination of information.

Patients who receive less than 75% of their planned doses during the first cycle (28 days DLT period) for reasons other than toxicity will not be evaluable for assessment of DLT for dose review decisions and may be replaced in the cohort. Reported safety information for these patients may however be considered to guide the percentage change in dose levels. In order to make the decision to escalate the BT1718 dose, the required number of evaluable patients must have completed one cycle (approximately 28 days).

Phase I of the trial has completed.

5.4.3 Intra-patients dose escalations

No intra-patient dose escalation will be allowed.

5.4.4 Expansion of dose levels

If one instance of DLT as defined in Section 3.3 is observed in a cohort of three patients, up to six patients will be treated at that dose level. If one out of six patients experiences a DLT, dose escalation will continue. If two or more out of up to six patients experience a DLT, dose escalation will stop and this dose will be defined as non-tolerated. A maximum of six evaluable patients will be treated at a dose below the non-tolerated level to define the MTD.

The MAD will be defined as the highest dose received. This will usually represent the non-tolerated dose above the MTD, but may instead represent a maximum administrable dose if the feasible volume of infusion limits the dose before toxicity does.

If a new type of DLT or high number of DLTs/adverse events occur during the expansion phase at the RP2D, dosage reductions for patients in the expansion cohorts may be made based on ongoing tolerability monitoring and safety reporting. This will be continually monitored but also formally assessed after the first six patients have received two cycles of treatment. If a dose below the RP2D is being used and a patient is shown to tolerate that dose, their ongoing doses may be titrated up to (but not exceed) the RP2D.

Phase I of the trial has completed.

5.5 Dose modifications

5.5.1 Dose delays and reductions

Patients who experience a DLT (defined in Cycle 1 only) that resolves to Grade ≤1 or recovers to baseline within 15 days of the start of the DLT may recommence treatment, with the agreement of the PI, Sponsor and patient. The dose should be reduced to a lower dose level. If the AE has not resolved to Grade ≤1 or recovered to baseline within 15 days, the patient will be taken off-study. If the patient experiences a DLT at this reduced dose, either the same or different toxicity, there will be no further dose reductions and the patient will be withdrawn from the study.

Haematological toxicities

- Patients who experience a ≥Grade 3 haematological toxicity will have the subsequent doses omitted during that cycle until the toxicity resolves to <Grade 3. On resolution to <Grade 3, treatment can recommence at the same dose level during that cycle.
- If a clinically significant Grade 2 toxicity related to BT1718 (probably or highly probably) is still present when a patient is due to start the next cycle, that cycle should be delayed up to 14 days until the toxicity resolves to ≤Grade 1.
- The first time a dose is omitted or delayed, it may be given at the same dose the next time. However, if there is a subsequent need to omit or delay again, the dose should be reduced to a lower dose level (unless, in exceptional circumstances, the PI, Sponsor and patient agree that further dose omissions/delays are appropriate and provide effective control of toxicity).
- If toxicity remains clinically significant and does not recover to <Grade 2 within 15 days, the patient will be taken off-study.
- **Only one dose reduction will be allowed per patient unless, in exceptional circumstances, the PI, Sponsor and patient agree that further treatment is appropriate and that a dose reduction is expected to provide effective control of toxicity.**

Non-haematological toxicities:

Grade 2

- Patients who experience a clinically significant Grade 2 non-haematological toxicity related to BT1718 (probably or highly probably), that does not respond (<7 days) to supportive clinical management, will omit subsequent doses during that cycle until the toxicity resolves to ≤Grade 1 or baseline.
- If a clinically significant Grade 2 BT1718-related toxicity is still present when a patient is due to start the next cycle, that cycle should be delayed up to 14 days until the toxicity resolves to ≤Grade 1 or baseline.
- The first time a dose is omitted or delayed, it may be given at the same dose when recommencing. However, if there is a subsequent need to omit or delay again, the dose should be reduced to a lower dose level (unless, in exceptional circumstance, the PI, Sponsor and patient agree that further dose omissions/delays are appropriate and provide effective control of toxicity).
- If toxicity remains clinically significant and does not recover to ≤Grade 1 or baseline within 15 days, the patient will be taken off-study.

- **Only one dose reduction will be allowed per patient, unless, in exceptional circumstances, the PI, Sponsor and patient agree that further treatment is appropriate and that a dose reduction is expected to provide effective control of toxicity.**

Grade 3

- Patients who experience a Grade 3 non-haematological toxicity that does not rapidly respond (<3 days) to supportive clinical management, will omit subsequent doses during that cycle until the toxicity resolves to ≤Grade 1 or baseline (or non clinically significant Grade 2).
- If clinically significant ≥Grade 2 BT1718-related toxicity is still present when a patient is due to start the next cycle, that cycle should be delayed up to 14 days until the toxicity resolves to ≤Grade 1 or baseline.
- When patients recommence treatment after a Grade 3 non-haematological toxicity, the dose should be reduced to a lower dose level. If toxicity does not recover to ≤Grade 1 or baseline within 15 days, the patient will be taken off-study.
- **Only one dose reduction will be allowed per patient, unless, in exceptional circumstances, the PI, Sponsor and patient agree that further treatment is appropriate and that a dose reduction is expected to provide effective control of toxicity.**

Grade 4

- Patients who experience a Grade 4 non-haematological toxicity, or liver enzyme changes consistent with Hy's Law (bilirubin >2x ULN and ALT/AST >3x ULN, with no explanation other than drug), will cease further treatment and be taken off-study once accuracy of testing is confirmed.

5.6 Duration of treatment

Treatment should continue unless (a) the patient asks to be withdrawn, (b) there is evidence of disease progression, (c) the patient is experiencing unacceptable toxicity or (d) the Investigator feels the patient should be withdrawn for any other reason. Other reasons are listed in Section 11.

If the Sponsor and CI agree that a patient is benefiting from treatment with BT1718 (i.e. has stable or responding disease as measured by RECIST V1.1) and is not experiencing any clinically significant Grade 2 or greater BT1718-related AEs, the patient may continue with treatment until disease progression (depending on the availability of BT1718), after which the patient will be withdrawn from the trial. Follow up information should be collected as described in the protocol (see Section 7.4).

The Sponsor will review a full toxicity and efficacy profile including radiological data to confirm the reported objective response for that patient when considering whether the patient should continue to receive treatment. If the Sponsor decides not to allow the patient to continue treatment based on the information provided or on other information received, or for any other reason, then the Sponsor's decision is final.

5.6.1 Replacement of patients

5.6.1.1 Phase I, dose escalation phase (Stage 1 and Stage 2)

Patients will be replaced by another patient treated at the same dose level during the dose escalation phase if they receive less than 75% of planned dose exposure of BT1718 during the first cycle (28 day DLT period) for reasons other than BT1718-related (probably or highly probably) toxicity. For single-patient cohorts, patients may be replaced if they do not receive all their planned doses.

Phase I of the trial has completed.

5.6.1.2 Phase II, expansion phase

Patients will be replaced in the expansion cohorts if they receive less than one full cycle and less than 66% of the planned dose exposure of BT1718 within Cycle 1 and 2 for reasons other than drug-related (probably or highly probably) toxicity. Patients will also be replaced if retrospective MT1-MMP testing identifies that their baseline tumour sample had a low MTI-MMP H-score.

Replacement of patients will be confirmed by the Sponsor. There may be circumstances based on the emerging data from the trial or BT1718 availability that result in a patient not being replaced. This will be documented by the Sponsor.

5.7 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. This includes symptomatic clinical management of BT1718 related or unrelated AEs. Vaccinations, including COVID-19 vaccines are permitted. Some vaccinations may be subject to specific Sponsor risk assessment. Details (including name and start and stop dates of the concomitant medication given) must be recorded in the patient's medical records and details entered into the electronic case report form (eCRF).

Palliative radiotherapy may be given concomitantly for the control of bone pain or other symptoms. These irradiated lesions will not be evaluable for response.

The patient must not receive other anti-cancer therapy or investigational drugs while on the trial.

As in Section 5.5 above, dosing with BT1718 may also be delayed up to 15 days if required to manage toxicity, without a patient needing to be withdrawn from study.

5.8 Sun exposure precautions

[redacted] As such, although DM-1 containing drugs have not shown evidence of phototoxicity in patients, it must be considered a possibility and precautions around UV exposure are required whilst on treatment and for one week afterwards. Patients should avoid excessive sun exposure and when outdoors during the daytime, patients should wear protective clothing, including a hat and sunglasses where appropriate, and apply broad spectrum sunscreen with a high sun protection factor (SPF30 or above) to any potentially exposed skin. Sun beds are not to be used.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of BT1718

A complete certificate of analysis and a Qualified Person certification will be provided with each batch of the investigational medicinal product (IMP) BT1718.

For information on BT1718 and re-ordering of supplies, contact the Sponsor's Clinical Research Associate (CRA)/ Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies.

BT1718 will be supplied by:

[redacted]

The Manufacturing Organisation (Cancer Research UK Formulation Unit) must provide confirmation of the shipment to the CSM/CRA on despatch of the IMP.

The primary and secondary packaging for BT1718 will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP).

Prior to despatch of BT1718 to the clinical trial site a label detailing the investigator name and site name and site address will be added by the Manufacturer's Authorisations for IMPs licensed manufacturing in accordance with GMP to the secondary packaging (box).

An example of the approved label(s) can be found in the TMF and site Pharmacy File.

6.2 Pharmaceutical data

6.2.1 Formulation of BT1718

[redacted]

6.2.2 Storage conditions

All supplies must be stored in a secure, limited access storage area in the hospital pharmacy. BT1718 must be stored in its original packaging at -20°C ± 5ºC, protected from light.

6.2.3 Method of preparation of the IMP

Good aseptic practice must be employed when preparing solutions of BT1718 for infusion.

[redacted]

Please refer to the IMP Handling Guidelines located in the Pharmacy File for additional guidance.

Each vial of BT1718 is for single use only. Any unused contents and/or vials dispensed for patient use must be destroyed as per local policies and accounted for as described in Section 6.3.

6.2.4 Stability and labelling of the diluted BT1718

The prepared solution for infusion may be stored at 2-8°C for 20 hours, followed by 4 hours at room temperature (21°C ± 4°C) before administration. Infusion must be completed within 2 hours of administration beginning. From a microbiological point of view administration should take place as soon as possible after preparation of the diluted drug.

Labelling requirements for the reconstituted BT1718 can be found in the Pharmacy File.

Labelling requirements for the reconstituted/diluted BT1718 must include the following information:

Name of IMP; Batch Number; dose; total volume to be infused; date/time infusion prepared; expiry time/date; name of patient (and any other local requirements e.g. Pharmacy batch number).

6.2.5 BT1718 administration

Before administration, the exact dosage must always be double-checked by a second suitably qualified person. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

6.2.5.1 Monitoring during infusion

Vital signs (temperature, pulse rate, BP) should be monitored before and after the infusion and should be repeated if any concerns during treatment or observation. Patients with diabetes mellitus should have a glucose finger-prick test before and after each BT1718 infusion for at least the first two cycles and thereafter if clinically indicated.

Given the clinical experience to date, patients should receive primary prophylaxis with anti-emetics prior to their first infusion of BT1718 and in the days following the infusion as clinically indicated. Should a patient exhibit any adverse effects to BT1718, then alternative or additional medication may be administered as secondary prophylaxis for subsequent infusions. Should emerging safety data suggest that a change in primary prophylactic medication is necessary, the Sponsor will ensure this requirement is communicated to each investigator.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte-colony stimulating factor (GCSF) should not be used a primary or secondary prophylaxis during the study, nor solely to accelerate marrow recovery to increase dose density. However, the therapeutic use of GM-CSF or GCSF is permitted if there is an acute clinical requirement for bone marrow support (e.g. therapeutically in the case of febrile neutropenia). If at all possible, its use should be avoided within the patient's first cycle of BT1718 as establishing the duration of any leukopenia, neutropenia, erythropenia or thrombocytopenia forms part of the DLT assessment, however the patient's safety and wellbeing remain the primary concern in clinical decisions about bone marrow support.

6.2.6 Vein extravasation/accidental spillages

DM1 and other chemotherapeutics can cause extravasation and/or are vesicants, irritants, inflammitants or exfoliants[10] [55, 56] and as a precaution BT1718 will be treated as a vesicant. Careful attention should be paid to cannula siting, patency and any indication of extravasation during or after infusion. Standard local policies for management of vesicant extravasation should be followed, typically starting with stopping the infusion, aspirating if possible, topical hydrocortisone and ongoing review. The role of specific treatment such as heat or cold packs, DMSO or hyaluronidase is unknown. Gloves and a disposable apron should be worn at all times during preparation, checking, administration, disposable or management of spillage of BT1718.

6.3 BT1718 accountability

Accurate records of all BT1718 shipments, vials received, dispensed, destroyed and all BT1718 returns must be maintained. This inventory record must be available for inspection at any time by CRAs or

[10] http://www.beatson.scot.nhs.uk/content/mediaassets/doc/Extravasation%20guidance.pdf

CSMs. BT1718 supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator undertakes not to destroy any unused BT1718 unless authorised to do so by the Sponsor. Any unused vials must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form as well as on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of vials of BT1718 shipped to the centre, the number used and the number destroyed or returned. The pharmacy will be expected to give an account of any discrepancy.

7 INVESTIGATIONS SCHEDULE

In cases where a patient has investigations at a different hospital, e.g. weekly blood samples, scans and other investigations as appropriate, then it is the Investigator's responsibility to ensure he/she receives and reviews the reported results. These results must be available for source data verification (SDV). Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used. For scan results, the original images and reports must be available for comparison to any scan performed at the investigator site and be in a format that is suitable for comparison. For all other investigations, apart from the results, any supporting data must be made available for SDV or source data review.

The Investigator or delegate must inform the Sponsor of any changes to the laboratory normal ranges or to any laboratory accreditation and provide any new documentation.

7.1 Pre treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records.

Please also refer to the tabulated Schedule of Assessments in Section 7.5.

7.1.1 Obtaining written informed consent

Written informed consent must be obtained from the patient before any protocol-specific procedures are carried out.

Consent for analysis of initial archived or fresh screening tumour sample for MT1-MMP must be obtained prior to analysis of the sample for the trial and should be obtained pre screening (pre screening consent) or at the time of full trial consent (main consent form).

The patient must be given adequate time to think about their commitment to the study. If more than 28 days has passed since informed consent was obtained before the start of BT1718 dosing then the Investigator should consider whether repeat consent should be obtained from a patient. Should a newer approved version of the informed consent document (ICD) be available, then re-consent must be obtained before any protocol specific investigations are performed.

Only the PI and those Sub-Investigator(s) with delegated responsibility by the PI, and who have signed the Delegation Log, are permitted to obtain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The patient should sign and date the consent form in the presence of the Investigator, followed by the Investigator signature. The date of the signatures of both the patient and the PI/Sub-Investigator obtaining informed consent should be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of their disease and BT1718 and must also ensure that the patient is aware of the following points:

- That BT1718 is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge;
- The known toxicity of BT1718 and the possibility of experiencing side-effects;
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception (refer to Section 9.7);
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled;
- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the ICD must be given to the patient to keep and the original ICD must be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original document will be filed in the medical records and a copy kept in the ITF).

7.1.2 Pre screening (Phase IIa, expansion phase only) – Basket cohort only

Patients in Phase IIa, expansion phase (basket cohort only) should give separate written consent before sending archival tissue, or before obtaining and sending a fresh screening tumour biopsy sample, for MT1-MMP IHC profiling. Retrospective testing may be permitted for tumour types demonstrated to have high MT1-MMP positivity rates in the basket cohort as per the Laboratory manual.

The following should be performed/obtained within **six months before** the patient receives the first dose:

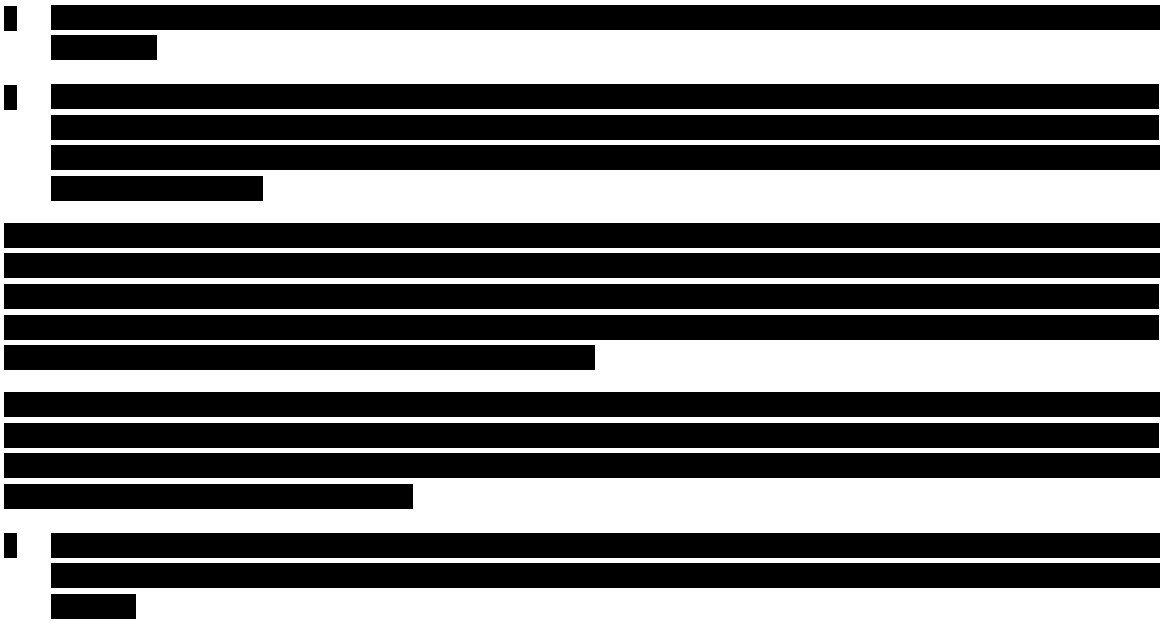
- **Archival sample retrieval**- retrieval of archival tumour sample for MT1-MMP IHC profiling;
- **Fresh tumour biopsy sample**- if archival tumour sample is not available or additional analysis is deemed necessary, obtain a fresh tumour biopsy sample for MT1-MMP IHC profiling.

For those patients where an archival tumour biopsy sample is not available or MT1-MMP IHC profiling or additional analysis is deemed necessary, a fresh screening tumour biopsy will be required to determine eligibility. The fresh screening tumour biopsy sample must be performed/obtained no more than **eight weeks** before the patient is expected to be enrolled.

7.1.3 Evaluations within 28 days prior to first administration of BT1718 (Day -28 to Pre dose on Cycle 1 Day 1)

The following must be performed/obtained **within 28 days before** the patient receives their first dose of BT1718. Existing results such as radiological measurements may be used even where these investigations were performed prior to the patient's provision of information consent for the study if they were performed within the required time window.

- Demographic details;
- Medical history including diagnosis (histological or cytological), prior treatment, concomitant conditions/diseases, baseline signs and symptoms and concomitant treatment);
- Radiological disease assessments: radiological measurements (computerised tomography [CT] or magnetic resonance imaging [MRI] scan of the chest, abdomen, pelvis and any other relevant sites) – must be performed **within four weeks** before the patient receives the first dose of BT1718 and reported to RECIST Version 1.1.
- Retrieval of archival tumour sample for retrospective assessment of MT1-MMP expression by IHC, as well as other molecular pathology techniques in the **dose escalation phase** and **expansion phase** (tumour indications with a high MT1-MMP positivity rate such as squamous NSCLC, as per the Laboratory manual);



Note that all AEs, including SAEs, must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (see Section 9 for further details).

7.1.4 Evaluations within 8 days of study inclusion (i.e. registration)

The following must be performed **within 8 days before** study inclusion:

- Complete physical examination;
- Height, weight, BSA, WHO performance status, temperature, pulse rate and BP (BP to be taken seated or lying after 5 minutes rest);
- Clinical disease assessments (if applicable): This must be within one week before the patient received the first dose of BT1718;
- 12 lead ECG;
- Female patients able to have children must have a negative result on a human chorionic gonadotropin (HCG) pregnancy test (serum or urine test is acceptable) prior to first BT1718 administration and 30 days after final administration only (*Note more frequent testing is unlikely to be appropriate unless specific concern, given patients' advanced disease, their limited prognosis, the unlikeliness of pregnancy, and sensitives around reminders of how cancer has impacted on their future/fertility/family-life*);
- Laboratory tests (blood/urine samples):
  - Haematology – Hb, WBC with two-point differential count (neutrophils, lymphocytes) and platelets;
  - Biochemistry – sodium, potassium, adjusted calcium, magnesium, phosphate, urea, creatinine, albumin, bilirubin, ALP, ALT and/or AST, GGT, fasting glucose;
  - Urinalysis – including pH, glucose, protein and blood;
  - Renal function – serum creatinine, calculated creatinine clearance (Wright or Cockroft & Gault) or Isotope clearance measurement (GFR scan). Isotope clearance result to be used if calculated C&G/Wright method results in a GFR=50 mL/min;
  - Coagulation tests – including INR/PT and APTT. Should be repeated before any biopsy procedure;

[redacted]

- Enrol the patient on the study once confirmed as eligible (see Section 4.2 Patient enrolment);

[redacted]

7.2 Evaluations during the trial

7.2.1 Day 1 of each cycle

The following must be performed on **Day 1** of each cycle **before** BT1718 administration:

- Weight and BSA: must be repeated on Day 1 of each cycle to calculate the dose required for BT1718 administration. The dose of BT1718 will only need to be recalculated should there be a 10% or greater change in weight since baseline, since last weight adjustment or where doses are reduced because of toxicity;
- 12 lead ECG: should be performed **before** BT1718 administration**, and within 1 ½ hours (+15 mins) after** BT1718 administration during Cycle 1 Day 1. On Cycle 2 Day 1 an ECG should be performed either **before or within 1 ½ hours (+15 mins) after** BT1718 administration. From Cycle 2 onwards ECGs should be repeated **before or within 1 ½ hours (+15 mins) after** BT1718 administration on Day 1 every two cycles (e.g. Cycle 4 Day 1, Cycle 6 Day 1);
- Haematology: detailed in Section 7.1.4;

- Biochemistry: detailed in Section 7.1.4. A fasting glucose result is not required except for baseline, so there is no need for the patient to fast before attending the hospital;
- Urinalysis: detailed in Section 7.1.4. This assessment should be repeated on **Day 22 (+/- 1 day)** of Cycle 1 only (i.e. when no BT1718 administration takes place);

[redacted]

[redacted]

[redacted]

7.2.2 Prior to each planned BT1718 administration

- Symptom-directed physical examination: if clinically indicated, a symptom-directed physical examination is to be performed **before** BT1718 administration;
- WHO performance status;
- Vital signs: Temperature, pulse rate and BP (BP to be taken seated or lying after 5 minutes rest) performed before BT1718 administration and **1 hour (+/- 15 mins)** post infusion. Should also be done during infusion if clinically indicated. These assessments should be repeated on **Day 22 (+/- 1 day)** of Cycle 1 only (i.e. when no BT1718 administration takes place);
- Patients with diabetes mellitus should have a glucose finger-prick test (non-fasting) **within 1 hour before and 1 hour (+ 15 mins) after** each BT1718 infusion for at least the **first two cycles** and thereafter if clinically indicated;
- Adverse events and concomitant medications: At each visit, before each BT1718 administration, an assessment of any AE experienced since the previous visit must be made by the Investigator, Research Nurse or suitably qualified member of the Investigator's team. The start and stop dates of the AE together with the relationship of the event to the BT1718 administration must be recorded in the medical records. All AEs must be graded according to NCI CTCAE Version 4.02 (See Section 9 for further details regarding AE reporting requirements). Any concomitant treatment must be recorded in the medical records;
- Laboratory tests:

  Haematology and biochemistry:

  - Haematology: detailed in Section 7.1.4 and
  - Core biochemistry: sodium, potassium, urea, creatinine, albumin, bilirubin, ALP, GGT, ALT and/or AST.

  Phase I, dose escalation phase, Stage 1

  During **Cycle 1** laboratory tests (as defined above) must be performed and checked prior to BT1718 administration on Days 1, 4, 8, 11, 15 and 18. Additional laboratory tests must also be performed on **Day 22** (i.e. when no BT1718 administration takes place). Laboratory tests may be performed up to **24 hours** prior BT1718 administration but results must be available and reviewed by the Investigator before BT1718 is given.

  During **Cycle 2 onwards** laboratory tests must be performed and checked prior to BT1718 administration on Days 1, 8 and 15 and thereafter if clinically indicated. After six cycles, the frequency of haematology and biochemistry assessments may decrease at the discretion of the PI and Sponsor but, at a minimum, must be performed on Day 1 of each cycle. Laboratory tests may be performed up to **24 hours** prior BT1718 administration but results must be available and reviewed by the Investigator before BT1718 is given.

  Phase I, dose escalation phase, Stage 2, and Phase IIa, expansion phase

  Laboratory tests must be performed and checked prior to BT1718 administration on Days 1, 8 and 15. Additional laboratory tests must also be performed on **Day 22** (i.e. when no BT1718

administration takes place). Laboratory tests may be performed up to **24 hours** prior BT1718 administration but results must be available and reviewed by the Investigator before BT1718 is given.

After six cycles, the frequency of haematology and biochemistry assessments may decrease at the discretion of the PI and Sponsor but, at a minimum, must be performed on Day 1 of each cycle. Laboratory tests may be performed up to **24 hours** prior BT1718 administration but results must be available and reviewed by the Investigator before BT1718 is given.

- Radiological disease assessment: This must be repeated **Day 15 – Day 28 of every two cycles**. Assessments may continue until disease progression or for up two years and can be performed more frequently than every two cycles, if clinical concern or suspicion of disease progression. Any CR or PR need to be confirmed by a subsequent assessment at least four weeks later. Radiological measurements (CT or MRI scan of the chest, abdomen, pelvis and any other relevant sites) –reported to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1.
- Clinical disease assessment (if applicable)**:** This must be repeated between **Day 15 – Day 28 of every two cycles.** Assessments may continue until disease progression or for up two years and can be performed more frequently than every two cycles, if clinical concern or suspicion of disease progression.

Other assessments during BT1718 treatment:

[redacted]

7.3 Evaluations at Off-study visit

Off study is defined as the date the decision is taken to withdraw the patient from the trial. Evaluations at the 'off-study' visit must be performed 28 days (+/- 7 days) after the last dose of BT1718. The following investigations should be performed wherever possible:

- Symptom-directed physical examination: if clinically indicated;
- WHO performance status, temperature, pulse rate and BP (BP to be taken seated or lying after 5 minutes rest);
- Haematology tests: detailed in Section 7.1.4;

- Biochemistry tests: detailed in Section 7.1.4; A fasting glucose result is not required, there is no need for the patient to fast before attending the hospital;
- Urinalysis: detailed in Section 7.1.4;
- Female patients able to have children must have a negative result on a HCG pregnancy test (serum or urine test is acceptable);
- 12 lead ECG;
- [redacted]
- Radiological assessment of tumour disease, unless the patient has been shown to have PD on a previous study scan or an assessment has been performed within the previous 28 days. Any CR or PR needs to be confirmed by a subsequent assessment at least four weeks later;
- Clinical assessment of disease if applicable;
- Assessment of AEs (also see Section 7.4);
- Review of concomitant medications and
- [redacted]

7.4 Follow-up

7.4.1 Safety follow-up

For eligible patients, SAE and AE collection and monitoring will continue until 28 days after the last administration of BT1718 or until the patient starts another anti-cancer therapy (see Section 9.3, Safety Reporting). Any drug-related AEs still ongoing after this period will be followed up monthly until resolution to baseline or stabilisation, unless the patient starts another anti-cancer treatment.

Should an Investigator become aware of any BT1718-related AEs or SAEs after this period, these must also be reported to the Sponsor within the expedited timelines in Section 9.4.

7.4.2 Efficacy and survival follow-up

Following pre screening informed consent, all patients should be followed up for survival until the end of the trial, where feasible, whether they subsequently start on trial treatment or not (Section 12). For those no longer on treatment, no further trial visits are required but the site trial team should check the status of the patient at least three monthly (through NHS/HSC electronic data records or by phone calls only if appropriate) until the patient starts another systemic anti-cancer therapy or when PD occurs (if not already occurred) and if the patient remains alive. End of trial may only be declared when all patients have either withdrawn from the trial, died, or completed a minimum of 12 months survival follow-up since their first administration of BT1718.

If the patient is lost to follow-up or has not progressed or died at the time of the final database lock for the Clinical Study Report (CSR), then the information will be censored as not known to have progressed/died at that time.

7.5 Schedule of events

7.5.1 Phase I, stage 1

Observation/ Investigation	**Pre screening (Expansion Phase only)**	**Pre treatment evaluations (screening period)**		**Cycle 1**							**Cycle 2 onwards**	**Off study**	**Follow-up**	**Survival Follow-up**
	6 months to Day-7	Within 28 days (Day -28 to Pre dose Day 1)	Within 8 days before study inclusion	Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Days 1, 4, 8, 11, 15 and 18	Off study: (28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Written informed consent	X	X												
Archival or fresh tumour biopsy for MT1-MMP ICH profiling (a)	X													
Demographics		X												
Medical history		X												
Adverse event evaluation		From date of informed consent		Continually review								X	Until resolution (m)	
Concomitant treatments		From date of informed consent		Continually review								X		
Radiological disease assessment		X		At the end of every two cycles (p) (q)								X (l)		
Clinical disease assessment (if applicable)			X	At the end of every two cycles (q)								X		
Pregnancy test (b)			X									X		

Observation/ Investigation	**Pre screening (Expansion Phase only)**	**Pre treatment evaluations (screening period)**		**Cycle 1**							**Cycle 2 onwards**	**Off study**	**Follow-up**	**Survival Follow-up**
	6 months to Day-7	Within 28 days (Day -28 to Pre dose Day 1)	Within 8 days before study inclusion	Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Days 1, 4, 8, 11, 15 and 18	Off study: (28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Physical examination (c)			X	Symptom-directed, repeat as clinically indicated								Symptom-directed (if clinically indicated)		
Height			X											
Weight (d)			X	X							X (Day 1 only)			
Body surface area (BSA)			X	X							X (Day 1 only)			
Bloods for haematology and biochemistry (e) (f)			X	X	X	X	X	X	X	X	X (Day 1, 8 and 15 only)	X		
Coagulation tests (g)			X											
Renal function			X											
Urinalysis			X	X						X	X (Day 1 only)	X		
Glucose finger-prick test before and after BT1718 administration (diabetic patients only) (h)				X	X	X	X	X	X		X			
Electrocardiogram (ECG) (i)			X	X							X (Day 1 only)	X		
BT1718 administration (+/- 1 day)				X	X	X	X	X	X		X			

Observation/ Investigation	**Pre screening (Expansion Phase only)**	**Pre treatment evaluations (screening period)**		**Cycle 1**							**Cycle 2 onwards**	**Off study**	**Follow-up**	**Survival Follow-up**
	6 months to Day-7	Within 28 days (Day -28 to Pre dose Day 1)	Within 8 days before study inclusion	Day 1	Day 4	Day 8	Day 11	Day 15	Day 18	Day 22	Days 1, 4, 8, 11, 15 and 18	Off study: (28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Temperature, blood pressure (seated or lying after 5mins rest) and pulse (r)			X	X	X	X	X	X	X	X	X	X		
WHO performance status			X	X	X	X	X	X	X	X	X	X		
[redacted]														
[redacted]														
Blood for PK (k)				*Refer to Lab manual for exact timings*										
[redacted]														
[redacted]														
[redacted]														
Follow-up contact for survival/ progression (n)														X

(a) Archival sample if available in Phase I, the dose escalation phase (retrospective MT1-MMP status). Tumour sample, whether archival or fresh, is **mandatory** in Phase IIa, the expansion phase to confirm patient eligibility. Archival tumour biopsy sample can be obtained within six months prior to the first dose. Fresh screening tumour biopsy must be performed/obtained within eight weeks prior to first dose.

(b) **Pregnancy test**: For female patients of child bearing potential.

(c) Complete **physical examination** to be performed Pre treatment then all subsequent examinations can be symptom-directed and only performed as clinically indicated

(d) Screening **weight** can be used to calculate BSA for Cycle 1.

(e) **Clinical laboratory assessments** should be performed within the previous seven days of Cycle 1 Day 1 and prior to each planned BT1718 administration on Days 1, 4, 8, 11, 15, 18 and 22 of Cycle 1. From Cycle 2 onwards, laboratory assessments must be performed and checked prior to BT1718 administration on Days 1, 8 and 15 and thereafter if clinically indicated. After six cycles, the frequency of haematology and biochemistry assessments may decrease at the discretion of the PI and Sponsor but, at a minimum, must be performed on Day 1 of each cycle. Laboratory tests may be performed up to 24 hours prior to BT1718 administration but results must be available and reviewed by the Investigator before BT1718 is given. On Day 1 of each cycle a full biochemistry assessment should be performed and on subsequent dosing days core biochemistry assessment should be performed.

(f) In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 7 (neutropenia) and Day 5 (thrombocytopenia) after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.

(g) To be repeated before biopsy procedure if done.

(h) To be done Cycle 1 and 2, within 1 hour **before** and 1 hour (+15 mins) **after** BT1718 administration, then clinically indicated thereafter.

(i) ECGs should be performed **before** BT1718 administration, and within **1 ½ hours (+15mins) after** BT1718 administration during Cycle 1 Day 1. On Cycle 2 Day 1 an ECG should be performed **before <u>or</u> within 1 ½ hours (+15 mins) after** BT1718 administration. From Cycle 2 onwards ECGs should be repeated on Day 1 every two cycles.

[redacted]

(k) **Pharmacokinetic (PK)** [redacted] **sample collection** - refer to the Laboratory Manual for specific timings.

(l) Unless performed within previous 28 days or PD seen on previous study scan.

(m) Monthly **follow-up** required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present at off-study visit. Monthly follow-up to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment.

(n) All patients should be followed up for first progression and for survival until the end of trial. For those no longer on treatment, the site trial team should check the status of the patient at least three monthly (through NHS/HSC electronic data records or by phone calls only if appropriate) to determine when PD occurs (if not already occurred) and if the patient remains alive.

[redacted]

(p) The timing of CT/MRI schedule may change in the expansion phase (Phase IIa) depending on tumour type. Any CR or PR needs to be confirmed by a subsequent assessment at least four weeks later.

(q) Assessments may continue until disease progression or for up two years and can be performed more frequently than every two cycles, if clinical concern or suspicion of disease progression.

(r) Temperature, blood pressure (seated or lying after 5mins rest) and pulse should be performed before and then repeated 1 hr (+/- 15 mins) after BT1718 administration.

NB: Phase I, Stage 1 is complete.

7.5.2 Phase I, stage 2 and Phase IIa, (once weekly dosing)

Observation/ Investigation	**Pre screening**	**Pre treatment evaluations (screening period)**		**Cycle 1**				**Cycle 2 onwards**	**Off study**	**Follow-up**	**Survival Follow-up**
	6 months to Day-7 **(Expansion phase only)**	Within 28 days (Day -28 to Pre dose Day 1)	Within 8 days before study inclusion	Day 1	Day 8	Day 15	Day 22	Days 1, 8 and 15	Off study: (28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Written informed consent	X	X									
Archival or fresh tumour biopsy for MT1-MMP IHC profiling (a)	X										
Demographics		X									
Medical history		X									
Adverse event evaluation		From date of informed consent		Continually review					X	Until resolution (m)	
Concomitant treatments		From date of informed consent		Continually review					X		
Radiological disease assessment		X		Day 15 – Day 28 of every two cycles (p) (q)					X (l)		
Clinical disease assessment (if applicable)			X	Day 15 – Day 28 of every two cycles (q)					X		
Pregnancy test (b)			X						X		
Physical examination (c)			X	Symptom-directed, repeat as clinically indicated					Symptom-directed (if clinically indicated)		
Height			X								
Weight (d)			X	X				X (Day 1 only)			
Body surface area (BSA)			X	X				X (Day 1 only)			

Observation/ Investigation	**Pre screening**	**Pre treatment evaluations (screening period)**		**Cycle 1**				**Cycle 2 onwards**	**Off study**	**Follow-up**	**Survival Follow-up**
	6 months to Day-7 **(Expansion phase only)**	Within 28 days (Day -28 to Pre dose Day 1)	Within 8 days before study inclusion	Day 1	Day 8	Day 15	Day 22	Days 1, 8 and 15	Off study: (28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
Bloods for haematology and biochemistry (e) (f)			X	X	X	X	X	X	X		
Coagulation tests (g)			X								
Renal function			X								
Urinalysis			X	X			X	X (Day 1 only)	X		
[redacted]			[redacted]	[redacted]				[redacted]	[redacted]		
Glucose finger-prick test before and after BT1718 administration (diabetic patients only) (h)				X	X	X		X			
Electrocardiogram (ECG) (i)			X	X				X (Day 1 only)	X		
BT1718 administration (+/- 1 day)				X	X	X		X			
Temperature, blood pressure (seated or lying after 5 mins rest) and pulse (r)			X	X	X	X	X	X	X		
WHO performance status			X	X	X	X	X	X	X		
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]		[redacted]			

Observation/ Investigation	**Pre screening**	**Pre treatment evaluations (screening period)**		**Cycle 1**				**Cycle 2 onwards**	**Off study**	**Follow-up**	**Survival Follow-up**
	6 months to Day-7 **(Expansion phase only)**	Within 28 days (Day -28 to Pre dose Day 1)	Within 8 days before study inclusion	Day 1	Day 8	Day 15	Day 22	Days 1, 8 and 15	Off study: (28 ±7 days after last dose of IMP)	At least monthly	Until end of trial
[redacted]											
[redacted]											
Blood for PK (k)				*Refer to Lab manual for exact timings*							
[redacted]											
[redacted]											
[redacted]											
Follow-up contact for survival/ progression (n)											X (n)

(a) Archival sample if available in Phase I, the dose escalation phase (retrospective MT1-MMP status). Tumour sample, whether archival or fresh, **mandatory** in Phase IIa, the expansion phase to confirm patient eligibility (retrospective testing for tumour types estimated to have high MT1-MMP positivity rates, as per the Laboratory manual). Archival tumour biopsy sample can be obtained within **six months** prior to the first dose. Fresh screening tumour biopsy/standard of care biopsy must be performed/obtained within **eight weeks** prior to first dose.

(b) **Pregnancy test**: For female patients of child-bearing potential.

(c) Complete **physical examination** to be performed Pre treatment then all subsequent examinations can be symptom-directed and only performed as clinically indicated

(d) Screening **weight** can be used to calculate BSA for Cycle 1.

(e) **Clinical laboratory assessments** should be performed within the previous seven days of Cycle 1 Day 1 and prior to each planned BT1718 administration on Days 1, 8 and 15 (and Day 22 in Cycle 1 only). After six cycles, the frequency of haematology and biochemistry assessments may decrease at the discretion of the PI and Sponsor but, at a minimum, must be performed on Day 1 of each cycle. Laboratory tests may be performed up to 24 hours prior to BT1718 administration but results must be available and reviewed by the Investigator before BT1718 is given. On Day 1 of each cycle a full biochemistry assessment should be performed and on subsequent dosing days core biochemistry assessment should be performed.

(f) In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 7 (neutropenia) and Day 5 (thrombocytopenia) after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.

(g) To be repeated before biopsy procedure if done.

(h) To be done Cycle 1 and 2, within 1 hour **before** and 1 hour (+15 mins) **after** BT1718 administration then clinically indicated thereafter.

(i) ECGs should be performed **before** BT1718 administration, and within **1 ½ hours (+15mins) after** BT1718 administration during Cycle 1 Day 1. On Cycle 2 Day 1 an ECG should be performed **before or within 1 ½ hours (+15 mins) after** BT1718 administration. From Cycle 2 onwards ECGs should be repeated on Day 1 every two cycles.

[redacted]

(k) **Pharmacokinetic (PK)** [redacted] **sample collection** - refer to the Laboratory Manual for specific timings. [redacted]

(l) Unless performed within previous 28 days or PD seen on previous study scan.

(m) Monthly **follow-up** required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present at off-study visit. Monthly follow-up to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment.

(n) All patients should be followed up for first progression and for survival until the end of trial (including patients who do not enter the main trial). For those no longer on treatment, the site trial team should check the status of the patient at least three monthly (through NHS/HSC electronic data records or by phone calls only if appropriate) to determine when PD occurs (if not already occurred) and if the patient remains alive. End of trial may only be declared when all patients have either withdrawn from the trial, died, or completed a minimum of 12 months survival follow-up since their first administration of BT1718.

[redacted]

(p) The timing of CT/MRI schedule may change in the expansion phase (Phase IIa) depending on tumour type. Any CR or PR needs to be confirmed by a subsequent assessment at least four weeks later.

(q) Assessments may continue until disease progression or for up two years and can be performed more frequently than every two cycles, if clinical concern or suspicion of disease progression.

(r) Temperature, blood pressure (seated or lying after 5mins rest) and pulse should be performed before and then repeated 1 hr (+/- 15 mins) after BT1718 administration.

[redacted]

8 PHARMACOKINETIC [redacted] ASSESSMENTS

8.1 Summary of PK [redacted] assessments

Please refer to the BT1718 Laboratory Manual for instructions of collection, handling and storage.

Sample collection schemes or imaging time points may be reconsidered during the study upon collection of further PK [redacted] data generated from the trial.

Table 5: Summary of PK [redacted] assessments

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Time points and approximate volume (once weekly)	Time points and approximate volume (twice weekly)
SECONDARY ENDPOINTS						
Pharmacokinetics of BT1718	LC/MSMS	To determine the PK profile of BT1718.	Blood (plasma)	Phase I, dose escalation phase (Stage 1 and 2) and in Phase IIa, expansion phase	Up to 24 timepoints for each patient across Cycle 1 and additional cycles (e.g. Cycle 2, 4, 6). Refer to Laboratory Manual for further details. Approximately 96 mL.	
TERTIARY ENDPOINTS						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[redacted].

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Time points and approximate volume (once weekly)	Time points and approximate volume (twice weekly)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Biomarker	Technology	Purpose of assay/Rationale	Type of sample	Patient group	Time points and approximate volume (once weekly)	Time points and approximate volume (twice weekly)
[redacted]					[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

8.2 Secondary assessments

8.2.1 BT1718 Pharmacokinetics (plasma)

Intact BT1718 and total DM1 (DM1 in BT1718, any peptidyl-DM1 metabolites of BT1718, and other DM1-containing mixed disulfides and free DM1) will be measured in plasma according to agreed standard operating procedures (SOPs) and validated methods, in Phase I, dose escalation phase (Stage 1 and 2) and in Phase IIa, expansion phase, dependent on emerging data.

Samples of blood will be collected from patients in Cycle 1 and across additional cycles (e.g. Cycle 2, Cycle 4 and Cycle 6). Pharmacokinetics will be assessed across the different cycles and the total will not exceed 24 samples. The approximate total volume of blood withdrawn from each patient will be 96 mL.

NB: PK assays and samples may be added or removed depending on emerging PK/clinical/pre clinical data from this and other trials, however the total blood volume will not exceed maximum volume specified above.

Please refer to the Study Laboratory Manual for handling, sample times, sample volume per time point, storage and shipment of samples.

8.3 Tertiary/research assessments

[redacted]

[redacted]

[redacted]

9 ASSESSMENT OF SAFETY

9.1 Investigator Responsibilities

The investigator is responsible for monitoring the safety of patients who have enrolled in the trial and for accurately documenting and reporting information as described in the following sections.

9.1.1 Medical Cover

The CI/PI is also responsible for ensuring patients have access to 24 hour advice and/or care. Patients will be provided with the necessary contact numbers for both normal working and out of hours care. A copy of the protocol must be made available out of hours to ward staff and clinicians on call so that the appropriate advice may be given to the patient, the patient's relative or other care giver (for example GP). The CI/PI must ensure that should the on call clinician or ward staff require more advice than is in this protocol, that they have access to the Investigator or delegated members of the Investigator's team who can answer any questions.

9.2 Adverse event definitions

9.2.1 Adverse event

An AE is any untoward, undesired or unplanned medical occurrence in a patient administered an investigational medicinal product (IMP), a comparator product or an approved drug.

An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

9.2.2 Serious adverse events

A serious adverse event is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening*;
- requires in-patient hospitalisation *or* prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – e.g. hospital admissions planned prior to the patient entering the trial; overnight stays for planned procedures such a blood transfusions (Section 9.4.1));
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event.**

* A life-threatening event is defined as an event when the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient

**A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events

For fatal SAEs, wherever possible report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term. When available the autopsy report will be provided to the Sponsor.

Any dose DLT must be reported to the Sponsor's CSM and CRA within 24 hours of site staff becoming aware of the DLT. The Sponsor's Pharmacovigilance Department must be copied into any initial or follow up email notification.

Other reportable events that must be treated as SAEs are listed below.

- Overdose with or without an AE.
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

Events of pregnancy must be reported and treated in the same way as SAEs:

Pregnancy. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the Pharmacovigilance Department on a pregnancy report form in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.

If during the course of the study, other medically important events are identified and there is a requirement to report specific events outside of the standard criteria, this will be communicated to site and the protocol will be updated to reflect this.

9.2.3 Suspected, unexpected, serious adverse reactions

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed by the sponsor for seriousness, causality and expectedness. The Pharmacovigilance Department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant REC(s) within the timelines specified in legislation (SI 2004/1031 as amended).

9.2.4 Determining adverse event causality

The relationship of an AE to the BT1718 is determined as follows.

Highly probable

- Starts within a time related to the IMP administration and
- No obvious alternative medical explanation.

Probable

- Starts within a time related to the IMP administration and
- Cannot be reasonably explained by known characteristics of the patient's clinical state.

Possible

- Starts within a time related to the IMP administration and
- A causal relationship between the IMP and the AE is at least a reasonable possibility.

Unlikely

- The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.

Not related

- The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of

significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken in to account when assessing the causality of an AE:

- Previous experience with the IMP and whether the AE is known to have occurred with the IMP.
- Alternative explanations for the AE such as concomitant medications, concurrent illness, nonmedicinal therapies, diagnostic tests, procedures or other confounding effects.
- Timing of the events between administration of the IMP and the AE.
- IMP blood levels and evidence, if any, of overdose.
- De-challenge, that is, if the IMP was discontinued or the dosage reduced, what happened to the adverse reaction?
- Re-challenge, that is, what happened if the IMP was restarted after the AE had resolved?
- Assessing the causality of an AE should be based on the information that is available at the time of reporting.

9.2.5 Expectedness

Assessment of expectedness for BT1718 will be made by the Pharmacovigilance Department against the current version of the IB.

9.3 Collection of safety information

9.3.1 Pre screening failures (Phase IIa only)

Following pre screening informed consent, any SAEs that are considered by the Investigator to be related to the pre screening biopsy must be reported to the Sponsor's Pharmacovigilance Department.

9.3.2 Screening failures

For patients who fail screening, SAEs must be reported to the Sponsor's Pharmacovigilance Department, from the date of main consent until the date the patient has been confirmed as ineligible.

9.3.3 Eligible patients

For eligible patients, SAE and AE collection and monitoring will commence at the time the patient provides written consent to participate in the trial and will continue until 28 days after the last administration of BT1718 or until the patient starts another anti-cancer therapy.

Should an Investigator become aware of any drug-related SAEs after this 28 day period, these must also be reported to the Sponsor within the expedited timelines in Section 9.4.

9.3.4 Follow-up of AEs and SAEs

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy (as per the Follow-up Section 7.4).

The Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department within 24 hours of first becoming aware of the follow up information. For fatal or life-threatening cases, follow-up information must be sought and reported to the Pharmacovigilance Department as soon as becoming aware.

9.3.5 Other safety information of interest

We will also collect information on the following situations, whether they are associated with an AE or not:

- Abuse or misuse

Any occurrences of these should be reported in the same manner as SAEs (Section 9.4).

9.4 Reporting of SAEs to the Sponsor's Pharmacovigilance Department

All SAEs, regardless of causality, must be reported to the Pharmacovigilance Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be e-mailed to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

[redacted]

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.02 must be used to grade the severity of each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Pharmacovigilance Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the form when sending the SAE report form to the Pharmacovigilance Department.

Should the Investigator become aware of any drug-related SAEs after the patient goes "off-study", these must also be reported to the Pharmacovigilance Department within the specified timelines specified above

9.4.1 Events exempt from being reported as SAEs to the Pharmacovigilance Department

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the eCRF.

Elective admissions – Elective admissions to hospital for procedures which were planned prior to entering the trial are not SAEs. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE.

Death due to disease progression- Cases of death due to disease progression do not require SAE reporting, unless considered related to the IMP.

9.5 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the paper SAE report form (which is used by the Pharmacovigilance Department only) and the data entered into the eCRF are consistent. The Sponsor's Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

9.6 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The MHRA and the REC must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- [redacted]
- [redacted]

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the REC within three days of USM initiation.

9.7 Pregnancy

Female patients who become pregnant from the time of giving written informed consent to the Off Study visit must be withdrawn from study treatment immediately.

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient (and parent / legal guardian, if appropriate) the potential dangers of becoming pregnant and also providing each patient (and parent / legal guardian, if appropriate) with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- Oral, injected or implanted hormonal contraceptives and condom (Contraceptives should be used for four weeks before the patient joins the study)
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.

Contraceptives should be effective before the patient is enrolled on the trial, throughout the trial and for six months after completing the trial.

Alternatively the patient may agree to sexual abstinence, effective from the first administration of BT1718, throughout the trial and for *six* months afterwards. Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

It should be explained to male patients (and parent / legal guardian, if appropriate) that if his partner is pregnant or breast-feeding when he enters the study, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to BT1718.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six of last IMP administration must be reported to the Pharmacovigilance department within 24 hours of the site staff becoming aware of it using a Pregnancy Report Form (provided in the ITF). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. In addition, the Investigator must be made aware of the need to obtain contact details for the patient's or patient's partner's General Practitioner. The Pharmacovigilance Department will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Report Form.

The Investigator should document within the patient notes the patient confirming consent for the sponsor to collect pregnancy follow up information. In case the partner of a patient becomes pregnant, a consent form should be provided to the patient's partner in order to obtain consent for collecting privacy data in accordance with the data protection act.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with BT1718 and occurring up to six months after the last BT1718 administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until 12 months after birth, if the patient or patient's partner has consented to this.

10 ASSESSMENT OF EFFICACY

10.1 Measurement of disease

Disease must be measured according to the RECIST V1.1 given in Appendix 2.

10.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before a patient receives their first dose of BT1718. The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments must be performed within four weeks (28 days) before starting treatment with BT1718. The interval between the last anti-cancer therapy and these measurements must be at least four weeks. All clinical measurements to assess response must be performed within **one** week before the first dose of BT1718.

Complete responses (CR) and partial responses (PR) need to be confirmed by a subsequent assessment at least four weeks later. Stable disease criteria must be met at least once and at least six weeks after the initial dose of BT1718 is given to be defined as SD. There is no requirement for repeat assessments to be performed in order for the patient to be assigned a status of SD.

Copies of the scans must be available for external independent review if requested by the Sponsor.

10.2.1 Baseline evaluations

These must include radiological measurements of lesions in the chest, abdomen, and pelvis by CT scan or MRI scan and/or other radiological measurements as clinically indicated or clinical measurements as appropriate e.g. assessment of palpable lesions or measurement of tumour markers. Tumour marker data (if applicable) can add useful data in the clinical interpretation of radiological assessment, but does not have the validation of RECIST radiological assessment and will be treated as exploratory to support the interpretation of individual cases. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses (See Appendix 2 Section 1.2.1 of RECIST 1.1 criteria).

10.2.2 Evaluations during and at 'off-study'

Tumour assessments must be repeated Day 15 – Day 28 of every two cycles or more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients who are removed from the trial for reasons other than PD must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST 1.1 criteria.

10.3 Tumour response

All patients who meet the eligibility criteria and receive ≥ 66% of the planned dose exposure of BT1718 within Cycle 1 and 2, or at least one full cycle and have a baseline assessment of disease and at least one repeat disease assessment will be evaluable for response. Patients who develop clear evidence of PD without a formal disease assessment will be considered non-responders. Confirmatory repeat assessments are required at least four weeks after an initial indication of CR or PR, in order for the

patient to be assigned a status of confirmed CR or PR. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of BT1718 is given.

Should rapid tumour progression occur before the completion of four weeks the patient will be classified as having early progression.

Tumour response should be classified as “not evaluable”, only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by the Sponsor may undertake an independent review of the Investigator’s assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the study. Any independent reviewer’s assessment will also be documented in the final CSR along with the assessment made by the Investigator. The eCRF will reflect the Investigator’s opinion.

10.3.1 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF.

10.3.2 Other definitions of outcome

Toxic death: Any death to which drug toxicity is thought to have a major contribution.

Early death: Death during the first 28 days of treatment.

11 PATIENT WITHDRAWAL BEFORE COMPLETION OF TREATMENT SCHEDULE

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until 28 ± 7 days after last BT1718 administration). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'off-study' assessments should be performed ideally before any subsequent therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who are removed from the trial due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from the trial.

- Adverse Event (AE)/SAE;
- Withdrawal of consent;
- Serious deviation from the trial protocol (including persistent patient attendance failure and persistent non-compliance);
- Sponsor's decision to terminate the trial;
- Withdrawal by the Investigator for clinical reasons not related to BT1718;
- Evidence of disease progression;
- Pregnancy (for female patients during the study)

12 DEFINING THE END OF TRIAL

The 'end of trial' is defined as the date when the last patient has completed the 'off-study' visit or the final follow-up (whichever is the latter). The 'off-study' visit is scheduled to take place 28 +/-7 days after the last dose of BT1718 administration. End of trial may only be declared when all patients have either withdrawn from the trial, died, or completed a minimum of 12 months survival follow-up since their first administration of BT1718.

IMP will be available for two years from the latest date that any remaining patients started treatment. After this, any remaining patients will come off-study and the trial will end as above.

The end of trial cannot be declared while any patient is still having study visits or while study data are still being collected, e.g. progression-free or OS data.

If an arrangement becomes possible where patients can continue on prolonged or extended use of IMP, beyond the end of trial, that arrangement will be distinct from the trial and will not prevent the end of trial being declared.

It is the responsibility of the CDD to inform the MHRA and the REC within 90 days of the 'end of the trial' that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

Recruitment will cease when:

- The drug is considered too toxic to continue treatment before the required number of patients have been recruited.
- The stated number of patients to be recruited has been reached.
- The stated objectives of the trial are achieved.
- The stated objectives of the trial are likely to be met but the trial is stopped due to lack of efficacy (the trial will be closed to recruitment on the date of this decision).

Regardless of the reason for termination, all data available for patients at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, the Sponsor and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The final analysis will be conducted after one of the following conditions is met:

- The trial is terminated early
- The end of trial as defined in Section 12 has been reached.

13.1 Sample size

Phase I, dose escalation phase

The number of patients required for the phase I will depend on the number of dose levels required to be explored to determine the MTD. It is anticipated that approximately 50 to 60 patients will be entered between Stages 1 and 2, the final number will depend on the number of dose escalations required and the number of evaluable patients.

Phase I of the trial has completed.

Phase IIa, expansion phase

Squamous NSCLC cohort – approximately 16 evaluable patients with squamous NSCLC will be recruited in this cohort to further characterise the tolerability of the RP2D in this population and an early exploration of clinical and biological activity.

Basket cohort – approximately 16 evaluable patients with advanced solid tumours will be recruited in this cohort to further characterise the tolerability of the RP2D in this population and an early exploration of clinical and biological activity.

Squamous oesophageal cancer cohort – following review of data obtained from the squamous NSCLC and basket expansion cohorts by the Joint Development Committee a as described in Section 3.2, approximately 16 evaluable patients with squamous oesophageal cancer may be recruited in this cohort to further characterise the tolerability of the RP2D in this population and an early exploration of clinical and biological activity. Other tumour types with a high incidence of MT1-MMP expression may be considered in future expansion cohort(s) and would be specified in a future amendment.

To assess clinical activity, objective response rate will be considered in terms of the confidence in excluding activity at a desired response rate (e.g. >30-40%) and for exceeding an undesirable response rate (e.g. <10-20%), reflecting an A'Hern single-stage clinical trial model for binomial distributions, with the Sargent three-outcome approach describing intermediate results. In a 16 patient cohort, less than 3 responses would exclude a response rate of 30% with 80% power, while 3 or more responses would indicate a response rate of 10% or greater with a significance level of 0.2. Similarly, less than 5 responses would exclude a response rate of 40% with 80% power, while 5 or more responses would indicate a response rate of 20% or greater with a significance level of 0.2. Hence 16 patients is a reasonable cohort size to permit some comparison of observed response rates against such benchmarks.

Activity within the squamous NSCLC and/or basket cohorts will be considered in the decision to begin enrolment in the squamous oesophageal cancer cohort

13.2 Presentation of data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

13.3 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using NCI CTCAE Version 4.02.

Adverse events will be reported for each dose level and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and unrelated events.

13.4 Pharmacokinetics

The plasma concentration/time data will be analysed using non-compartmental methods. The PK parameters to be determined for intact BT1718 include C_{max}, [redacted], AUC, $t_{1/2}$, [redacted]. The PK parameters to be determined for total DM1 include C_{max}, [redacted], AUC and $t_{1/2}$.

[redacted]

13.5 Pharmacodynamics

[redacted]

13.6 Anti-tumour activity

Documenting anti-tumour activity is a secondary objective of this trial. Patients must receive ≥66% of the planned dose exposure of BT1718 within Cycle 1 and 2, or at least one full cycle and have a baseline assessment of disease and at least one repeat assessment to be evaluable for response. Patients in the expansion phase must meet the MT1-MMP positivity rate to be evaluable for this objective. Objective responses, the best tumour response achieved by each patient while on trial and the time to progression will be presented in the data listings by cohort.

The response rate (proportion of evaluable patients with objective response) will be reported by cohort. Progression free survival will be calculated from trial entry until the time of documented disease progression or death (whichever occurs first). Patients who are alive and progression free or lost to follow up at the time of analysis will be censored at the time the patient was last known to be alive and progression free. Overall survival will be calculated from trial entry until the time of death from any cause. Patients who are alive or lost to follow up at the time of analysis will be censored at the time the patient was last known to be alive. Duration of response will be measured from the date of the first scan where response was seen until date of first RECIST V1.1 progression or death. Median PFS, OS and duration of response will be presented. The PFS and OS rate at 6 months will also be presented. 95% confidence intervals will be reported.

14 ADMINISTRATION

This trial is conducted under a clinical trial authorisation and approval from the MHRA and the relevant REC(s) will be obtained before the start of this trial. This trial is sponsored and monitored by the Cancer Research UK, CDD. Applicable regulatory requirements are described in this section.

14.1 Protocol deviations and amendments

The protocol should be adhered to throughout the conduct of the study, if a situation arises where the conduct of the study may not be in line with the protocol, then site should contact the CDD to discuss this.

Amendments to the protocol may only be made by the Sponsor. A protocol amendment may be subject to review by the assigned Ethics Committee, HRA and the MHRA. Written documentation of the Ethics Committee and HRA (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

14.2 Serious breach of GCP

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

In order that the Sponsor can fulfil their obligations in terms of reporting serious breaches of GCP to the MHRA within seven calendar days of identification, site staff must inform the Sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the Sponsor.

14.3 Completion of the electronic case report form (eCRF)

Electronic CRFs approved by the Sponsor will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Delegation Log provided by the Sponsor and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised users will be included on a user list in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of BT1718 used in this trial. The data must be collected and processed with adequate precautions to ensure patient confidentiality and compliance with applicable data privacy protection according to the applicable regulations. The data collected will comply with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

Data will be entered directly into eCRF by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the trial all eCRFs are retained and archived by the Sponsor and a PDF copy provided to the Investigator who is responsible for archiving at site.

14.4 Trial performance, monitoring, auditing and inspection

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. The sponsor must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the Sponsor's CRA will be responsible for monitoring data quality in accordance with their SOPs. A strategic monitoring approach, including targeted source data verification, will be implemented where appropriate.

Before the study start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check pharmacokinetic and pharmacodynamic samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

At the end of the trial all unused BT1718 supplied must be destroyed at site (only once authorised to do so by the CRA or CSM).

It is the responsibility of the Sponsor to notify the REC of the 'end of the trial'. (See definition in Section 12).

During the course of the trial, the Quality Assurance Department of the CDD, or external auditors contracted by the CDD, may conduct an on-site audit visit (ICH Topic E6 (R1) Guideline for Good Clinical Practice Sections 1.6).

Principal Investigators conducting this trial will accept the potential for inspection by the MHRA.

14.5 Source document verification

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore, it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor appointed to audit the trial, NHS Trust staff and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

14.6 Clinical study report

At appropriate intervals, interim data listings will be prepared to give the Investigator the possibility to review the data and check the completeness of information collected. All clinical data will be presented at the end of the trial on final data listings. The sponsor will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the trial. Summary results of the trial will be provided by the Sponsor to the MHRA and to the REC.

14.7 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The

Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), E6 (R2) including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and SAE report forms, shall show whether the Investigator has complied with the principles and guidelines of GCP.

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by the sponsor. Records must not be destroyed without prior written approval from the Sponsor.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

14.8 Ethical considerations

Before starting the trial, the protocol and ICD must go through the CDDs external review process, and be approved by the Protocol and Safety Review Board and receive the favourable opinion of the assigned REC.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and Chief/Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

14.9 Indemnity

This trial is sponsored by Cancer Research UK (CRUK) and therefore injury to a patient caused by the compounds under trial will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

14.10 Publication policy and press releases

Results of this trial must be submitted for publication. The sponsor must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to the sponsor at least 28 days in advance of being submitted for publication to allow time for the sponsor to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to the sponsor at least 14 days in advance of being released.

Authors must acknowledge that the trial was sponsored by and performed with the support of the sponsor. The CI should be the principal author and any Investigator recruiting ≥ 10% of patients should be listed as an author - with position prioritised in order of numbers of patients recruited.

The contribution of the sponsor should be recognised by at least one member of staff being included as an author on the publication.

15 REFERENCES

1. Pahwa, S., M.J. Stawikowski, and G.B. Fields, *Monitoring and Inhibiting MT1-MMP during Cancer Initiation and Progression.* Cancers (Basel), 2014. **6**(1): p. 416-35.
2. Kessenbrock, K., V. Plaks, and Z. Werb, *Matrix Metalloproteinases: Regulators of the Tumor Microenvironment.* Cell, 2010. **141**(1): p. 52-67.
3. Wang, Y.Z., et al., *MMP-14 overexpression correlates with poor prognosis in non-small cell lung cancer.* Tumour Biol, 2014. **35**(10): p. 9815-21.
4. Zhou, H., et al., *Significance of semaphorin-3A and MMP-14 protein expression in non-small cell lung cancer.* Oncology Letters, 2014. **7**(5): p. 1395-1400.
5. Laudanski, P., et al., *Increased serum level of membrane type 1-matrix metalloproteinase (MT1-MMP/MMP-14) in patients with breast cancer.* Folia Histochem Cytobiol, 2010. **48**(1): p. 101-3.
6. Têtu, B., et al., *The influence of MMP-14, TIMP-2 and MMP-2 expression on breast cancer prognosis.* Breast Cancer Research, 2006. **8**(3): p. R28-R28.
7. Akanuma, N., et al., *MicroRNA-133a regulates the mRNAs of two invadopodia-related proteins, FSCN1 and MMP14, in esophageal cancer.* Br J Cancer, 2014. **110**(1): p. 189-198.
8. Peng, C.W., et al., *Combined features based on MT1-MMP expression, CD11b + immunocytes density and LNR predict clinical outcomes of gastric cancer.* J Transl Med, 2013. **11**: p. 153.
9. Landolt, L., et al., *Clear Cell Renal Cell Carcinoma is linked to Epithelial-to-Mesenchymal Transition and to Fibrosis.* Physiol Rep, 2017. **5**(11).
10. Vandenbroucke, R.E. and C. Libert, *Is there new hope for therapeutic matrix metalloproteinase inhibition?* Nat Rev Drug Discov, 2014. **13**(12): p. 904-927.
11. CRUK. *http://www.cancerresearchuk.org/about-cancer/type/lung-cancer/about/types-of-lung-cancer*. 2014.
12. Reck, M., et al., *Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2016. **375**(19): p. 1823-1833.
13. Gandhi, L., et al., *Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2018. **378**(22): p. 2078-2092.
14. Paz-Ares, L., et al., *Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2018. **379**(21): p. 2040-2051.
15. Scagliotti, G.V., et al., *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol, 2008. **26**(21): p. 3543-51.
16. Schiller, J.H., et al., *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.* N Engl J Med, 2002. **346**(2): p. 92-8.
17. Borghaei, H., et al., *Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(17): p. 1627-39.
18. Brahmer, J., et al., *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(2): p. 123-35.
19. Fehrenbacher, L., et al., *Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial.* Lancet, 2016. **387**(10030): p. 1837-46.
20. Hanna, N., et al., *Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.* J Clin Oncol, 2004. **22**(9): p. 1589-97.

21. Herbst, R.S., et al., *Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.* Lancet, 2016. **387**(10027): p. 1540-50.
22. CRUK, *https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer*. 2016.
23. Lordick, F., et al., *Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol, 2016. **27**(suppl 5): p. v50-v57.
24. KEYNOTE-180, *https://clinicaltrials.gov/ct2/show/results/NCT02559687*.
25. KEYNOTE-181, *https://clinicaltrials.gov/ct2/show/NCT02564263*.
26. FDA, *https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-esophageal-squamous-cell-cancer*. 2019.
27. Poon, K.A., et al., *Preclinical safety profile of trastuzumab emtansine (T-DM1): mechanism of action of its cytotoxic component retained with improved tolerability.* Toxicol Appl Pharmacol, 2013. **273**(2): p. 298-313.
28. FDA, *CENTER FOR DRUG EVALUATION AND RESEARCH, Application No. 25427Orig1s000 Pharmacology review Non-clinical pharmacology and toxicology studies to support Kadcyla (adotrastuzumab emtansine) BLA 125427 for the treatment of patients with HER2-positive, metastatic breast cancer*, J.K. Leighton, Editor. 2013.
29. Shen, B.Q., et al., *Non-Clinical Disposition and Metabolism of DM1, a Component of Trastuzumab Emtansine (T-DM1), in Sprague Dawley Rats.* Drug Metab Lett, 2015. **9**(2): p. 119-31.
30. Seely, J.C. and K.S. Frazier, *Regulatory Forum Opinion Piece*: Dispelling Confusing Pathology Terminology: Recognition and Interpretation of Selected Rodent Renal Tubule Lesions.* Toxicol Pathol, 2015. **43**(4): p. 457-63.
31. Grisold, W., G. Cavaletti, and A.J. Windebank, *Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention.* Neuro Oncol, 2012. **14 Suppl 4**: p. iv45-54.
32. Tolcher, A.W., et al., *Cantuzumab mertansine, a maytansinoid immunoconjugate directed to the CanAg antigen: a phase I, pharmacokinetic, and biologic correlative study.* J Clin Oncol, 2003. **21**(2): p. 211-22.
33. Rodon, J., et al., *Cantuzumab mertansine in a three-times a week schedule: a phase I and pharmacokinetic study.* Cancer Chemother Pharmacol, 2008. **62**(5): p. 911-9.
34. Shah, M.H., et al., *Phase I study of IMGN901, a CD56-targeting antibody-drug conjugate, in patients with CD56-positive solid tumors.* Investigational New Drugs, 2016. **34**: p. 290-299.
35. EMA/749228, *Assessment report: Kadcyla International non-proprietary name: Trastuzumab emtansine, Procedure No. EMEA/H/C/002389/0000. European Medicine Agency. EMA/749228/2013 Committee for Medicinal Products for Human Use (CHMP)*. 2013.
36. Sibaud, V., et al., *[Pigmentary disorders induced by anticancer agents. part I: chemotherapy].* Ann Dermatol Venereol, 2013. **140**(3): p. 183-96.
37. CRUK. *http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/cancer-drugs/side-effects/your-mouth-and-cancer-drugs*. 2013.
38. Cabanillas, F., et al., *Phase I study of maytansine using a 3-day schedule.* Cancer Treat Rep, 1978. **62**(3): p. 425-8.
39. Eagan, R.T., et al., *Early clinical study of an intermittent schedule for maytansine (NSC-153858): brief communication.* J Natl Cancer Inst, 1978. **60**(1): p. 93-6.
40. Chahinian, A.P., et al., *Phase I study of weekly maytansine given by iv bolus or 24-hour infusion.* Cancer Treat Rep, 1979. **63**(11-12): p. 1953-60.
41. Chabner, B.A., et al., *Initial clinical trials of maytansine, an antitumor plant alkaloid.* Cancer Treat Rep, 1978. **62**(3): p. 429-33.

42. Thake, D.C., et al., *Toxicity of Maytansine (NSC 153858) in Dogs and Monkeys.* PB - U.S. National Technical Information Service, 1975. **Feb 1975, 244628**.

43. Mugera, G.M. and J.M. Ward, *Acute toxicity of maytansine in F344 rats.* Cancer Treat Rep, 1977. **61**(7): p. 1333-8.

44. Krop, I.E., et al., *Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial.* Lancet Oncol, 2014. **15**(7): p. 689-99.

45. Jackson, D. and D. Stover, *Using the Lessons Learned From the Clinic to Improve the Preclinical Development of Antibody Drug Conjugates.* Pharmaceutical Research, 2015. **32**(11): p. 3458-3469.

46. Shah, M.A., *Update on Metastatic Gastric and Esophageal Cancers.* Journal of Clinical Oncology, 2015. **33**(16): p. 1760-1769.

47. Kang, Y.K., et al., *A randomized, open-label, multicenter, adaptive phase 2/3 study of trastuzumab emtansine (T-DM1) versus a taxane (TAX) in patients (pts) with previously treated HER2-positive locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (LA/MGC/GEJC).* in *2016 Gastrointestinal Cancers Symposium*. 2016, J Clin Oncol. p. suppl 4S; abstr 5.

48. Diamantis, N. and U. Banerji, *Antibody-drug conjugates—an emerging class of cancer treatment.* British Journal of Cancer, 2016. **114**: p. 362–367.

49. Stathis, A., et al., *A Phase I Study of IMGN529, an Antibody-Drug Conjugate (ADC) Targeting CD37, in Adult Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma (NHL).* Blood, 2014. **124**(21): p. 1760-1760.

50. Wang, J., W.C. Shen, and J.L. Zaro, *Antibody-Drug Conjugates: The 21st Century Magic Bullets for Cancer.* 2015: Springer International Publishing.

51. Helft, P.R., et al., *A Phase I Study of Cantuzumab Mertansine Administered as a Single Intravenous Infusion Once Weekly in Patients with Advanced Solid Tumors.* Clinical Cancer Research, 2004. **10**(13): p. 4363-4368.

52. Galsky, M.D., et al., *Phase I trial of the prostate-specific membrane antigen-directed immunoconjugate MLN2704 in patients with progressive metastatic castration-resistant prostate cancer.* J Clin Oncol, 2008. **26**(13): p. 2147-54.

53. Milowsky, M.I., et al., *Phase 1/2 multiple ascending dose trial of the prostate-specific membrane antigen-targeted antibody drug conjugate MLN2704 in metastatic castration-resistant prostate cancer.* Urol Oncol, 2016. **34**(12): p. 530 e15-530 e21.

54. Johnson, M.L., et al., *First in human phase 1/2a study of PEN-221 somatostatin analog (SSA)-DM1 conjugate for patients (PTS) with advanced neuroendocrine tumor (NET) or small cell lung cancer (SCLC): Phase 1 results.* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 4097-4097.

55. Kreidieh, F.Y., H.A. Moukadem, and N.S. El Saghir, *Overview, prevention and management of chemotherapy extravasation.* World Journal of Clinical Oncology, 2016. **7**(1): p. 87-97.

56. Carpenito-Moyet, L.J., *Nursing Care Plans and Documentation: Nursing Diagnoses and Colloborative Problems*. 2005: Lippincott Williams & Wilkins.

57. Li, Y., et al., *The overexpression membrane type 1 matrix metalloproteinase is associated with the progression and prognosis in breast cancer.* American Journal of Translational Research, 2015. **7**(1): p. 120-127.

16 APPENDICES

16.1 APPENDIX 1: WHO PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

16.2 APPENDIX 2: ASSESSMENT OF DISEASE RESPONSE

Assessment of disease response in this study should be performed according to the RECIST criteria specified below.

New response evaluation criteria in solid tumours (RECIST criteria): Revised RECIST guideline (version 1.1)

E.A. Eisenhauer *et al*. (2009) *European Journal of Cancer* **45:** 228-247

Note that this is an abridged version of the RECIST criteria. Please refer to the above article for detailed appendices and if in doubt.

1. Measurability of tumour at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in the publication from Eisenhauer et al.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy:

The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers:

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.

Cytology, histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1).

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts *et al*. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. An example in **Figure 3** of the publication by Eisenhauer et al.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non- pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'.

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment:

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease.

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease.

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-positron emission tomography (PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. Should a response not be documented until after the end of therapy in this trial, post treatment assessments may be considered in the determination of best overall response as long as no alternative anti-cancer therapy has been given. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1. Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response in this trial is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and confirmed after 4 weeks, and PD on last assessment has a best overall response of confirmed PR). All CRs or PRs must be confirmed after at least 4 weeks, until which time they are "unconfirmed" CRs or PRs. The date of PR or CR is then the initial date when response was first noted, rather than the date of the confirmatory scan. When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable. A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Table 1 – Time point response: patients with target (+/–non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD(a) NE
Not all evaluated	No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

(a) 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required

Overall response	Overall response	BEST overall response
First time point	Subsequent time point(s)	
CR	CR	CR
CR	PR	SD, PD or PR(a)
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
(a) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 to 3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

16.3 APPENDIX 3: NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I – patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II – patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III – patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV – patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

16.4 APPENDIX 4: AMERICAN HEART ASSOCIATION/ AMERICAN COLLEGE OF CARDIOLOGY (AHA/ACC) GUIDELINE

Stages of Progression of Valvular Heart Disease

STAGE	DEFINITION	DESCRIPTION
A	**At risk**	Patients with high factors for development of VHD
B	**Progressive**	Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C	**Asymptomatic severe**	Asymptomatic patients who have the criteria for severe VHD:
		C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated
		C2: Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle
D	**Symptomatic severe**	Patients who have developed symptoms as a result of VHD