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Statistical Analysis Plan

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A phase I study to assess the safety and tolerability of pembrolizumab in combination with fixed rate gemcitabine chemotherapy in patients with leiomyosarcoma and undifferentiated pleomorphic sarcoma (GEMMK Study)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ABPI	Association of the British Pharmaceutical Industry
ADC	apparent diffusion coefficient
AE	adverse event
alk phos/ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
ATM	Ataxia telangectasia mutated
ATR	Ataxia telangectasia and Rad3-related
AUC	area under the curve
BP	blood pressure
C_{max}	maximum observed plasma concentration
CPT	Cell Preparation Tube
CR	complete response
CRF	case report form
CR-UK	Cancer Research UK
CT	computed tomography
CTA	clinical trial authorisation
Day	calendar day
DDR	DNA damage response
DLT	dose limiting toxicity
DMR	Dose modification ratio
DNA-PK	DNA-dependent protein kinase
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetra-acetic acid
ELISA	Enzyme-linked immunosorbent assay
FDR	Fixed Dose Rate
GGT	Gamma-glutamyl transpeptidase
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice

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Abbreviation or special term	Explanation
g/dL	gram(s) per decilitre
GFR	Glomerular Filtration Rate
GI_{50}	Concentration for half-maximal growth inhibition
GMP	Good Manufacturing Practice
GSK3b	Glycogen synthase kinase 3 beta
Gy	Gray
Hb	Haemoglobin
HNSTD	Highest non-severely toxic dose
IC_{50}	Half maximal inhibitory concentration
ICMJE	International Committee of Medical Journal Editors
IHC	Immunohistochemistry
IMP	investigational medicinal product
INR	International normalised ratio
IR	Ionising radiation
ITF	Investigator Trial File
ITT	Intention to Treat
L/h	litres per hour
LDH	Lactate Dehydrogenase
LENT-SOMA	Late Effects of Normal Tissue - Subjective, Objective, Management, Analytical
LVEF	left ventricular ejection fraction
MTD	Maximum tolerated dose
mg	Milligram
mg/m^2	milligram per square metre
MHRA	Medicines and Healthcare products Regulations Agency
mmHg	Millimetres of mercury
MRI	magnetic resonance imaging
NTD	non-tolerated dose
PBMC	Peripheral blood mononuclear cells
PDc	pharmacodynamics
PD	progressive disease
P-gp	P-glycoprotein
PET	positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic

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Abbreviation or special term	Explanation
PR	partial response
PT	Prothrombin time
QC	quality control
QP	Qualified Person
QTc	Corrected Q-T interval
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RPA	Replication protein A
SAE	serious adverse event
SD	stable disease
SDV	source data verification
SJS	Stevens Johnson syndrome
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SRC	safety review committee
STD_{10}	Severely toxic dose for 10% of animals
STS	Soft Tissue Sarcomas
SUSAR	suspected unexpected serious adverse (drug) reaction
$T_{1/2}$	terminal elimination half-life
TEN	toxic epidermal necrolysis
TSC	Trial Steering Committee
T_{max}	time to reach C_{max}
TGI	Tumour growth inhibition
ULN	upper limit of normal
UPS	Undifferentiated pleomorphic sarcoma
USM	urgent safety measure
WBC	white blood cell
WHO	World Health Organisation

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AMENDMENT HISTORY

Date	Brief description of change
11.4.18	First draft

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1. Study Details

1.1. Study objectives

Objectives of Primary Endpoint

- To evaluate the safety and tolerability of a fixed dose rate of gemcitabine when administered in combination with pembrolizumab.

Objectives of Secondary Endpoint

- To establish the appropriate dose of gemcitabine for use in combination with pembrolizumab the expansion cohort.
- To obtain evidence of the anti-tumour activity of gemcitabine in combination with pembrolizumab in patients with advanced leiomyosarcoma and undifferentiated pleomorphic sarcoma, according to RECIST.

Objectives of Exploratory Endpoint

- To explore the relationship between PD-L1 tumour expression and immune response
- To complement other work aimed at generating a sarcoma "immunoscore" created from Immunophenotyping samples from the Royal Marsden Sarcoma Unit tissue bank correlated with progression-free and overall survival
- To explore other predictive biomarkers of immune response to PD-L1 inhibition in leiomyosarcoma and undifferentiated pleomorphic sarcoma.

1.2. Study design

This is a two part, phase I, single centre dose escalation and dose expansion study to establish the safety, tolerability and pharmacokinetics of pembrolizumab in combination with different dose levels of fixed dose rate gemcitabine in patients with newly diagnosed metastatic or inoperable leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS), for whom gemcitabine monotherapy is deemed appropriate, or in patients with previously treated leiomyosarcoma and undifferentiated pleomorphic sarcoma, not including gemcitabine, with disease progression documented in the 12 weeks prior to enrolment.

There will be a maximum of 18 patients in the dose-escalation cohort (part A) and the starting dose will be a fixed dose rate (FDR) gemcitabine of 800 mg/m^2 on day 1 and 8 of 21 days cycles in combination of 200 mg of pembrolizumab given as an infusion on day 1 every 3 weeks. There will be a minimum of three and a maximum of six evaluable patients entered per dose cohort and each patient will continue to receive treatment cycles of gemcitabine in combination with pembrolizumab for as long as he/she is, in the opinion of the investigator, deriving clinical benefit and continues to meet re-treatment criteria. Treatment will continue until disease progression or is stopped because of toxicity. There will be an option to continue pembrolizumab alone in patients with SD or response who stop

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gemcitabine for toxicity before completing 6 cycles of combination therapy. During the dose-escalation phase, safety, tolerability, biological and clinical activity will be assessed and the maximum tolerated dose (MTD) will be established.
The MTD cohort (part B) will then be expanded to a total of 12 patients in order to further evaluate the safety and tolerability of that dose as well as to preliminarily assess response to therapy.
A mandatory tumour biopsy will be collected prior to the start of treatment for pre-treatment testing for PD-L1 expression, Immunophenotyping and extent and localization of tumour infiltrating lymphocytes and following 3 cycles of therapy for analysis of potential markers of tumour response on post-treatment tissue. Additional mandatory bloods will be collected for analysis of potential circulating immune markers. Patient genetic material will also be collected for analysis of potential markers of tumour response and future pharmacogenetic analyses. Provision of genetic material is not mandatory for participation in the main study.

After 3 patients have completed one cycle of treatment (21 days), data will be reviewed by Safety Review Committee (SRC) before proceeding to recruit more patients. The SRC will advise on the need for further monitoring by TMG.

1.3. Number of subjects

There will be a maximum of 18 patients in part A. The trial will continue to recruit a further 12 patients in part B at the MTD determined in part A. We expect to recruit all patients in part A (3+3 design) within the first 12 months of the study recruitment period. Since the part B (expansion phase) will be descriptive 12 patients will be sufficient as it is expected to recruit a further 12 patients in the last 12 months of the study recruitment period.

2. Analysis Sets

2.1. Definition of analysis sets

Intention to Treat (ITT) population: All patients consented and registered into the study and have had treatment.

The SRC and end of study analysis will include the ITT population unless stated otherwise.

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2.2. Violations and deviations

All patients who have been consented and registered into the trial that meet the inclusion/exclusion criteria as defined in the protocol will be included in the analysis. Any protocol violations and deviations will be stated in the analysis

3. Primary and Secondary Endpoints

Primary Endpoint

To establish the maximum tolerated dose (MTD) of pembrolizumab that can be safely combined with Gemcitabine in the absence of dose limiting toxicities (DLTs)

Secondary Endpoints

To make a preliminary evaluation of response by using RECIST v1.1 to document best response rate, best reduction in tumour size and progression free survival, assessed 9 weeks after start of therapy

Exploratory Endpoints

Immunophenotyping of pre- and post-treatment (9 weeks) biopsies (FFPE samples, density and phenotype of tumour infiltrating lymphocytes; CD3+, CD8+, CD45, FoxP3 and PD1)

4. Analysis Methods

4.1. General principles

Qualitative data will be summarised by number of observations and percentages. Quantitative data will be summarised by means, standard deviations and minimum and maximum value. Where appropriate, results will be presented with 95% CIs.

4.2. Analysis methods

Primary Endpoint

Toxicities will be tabulated as frequencies and proportions. All AEs and SAEs reported in the trial will be listed within a table.

Secondary Endpoints

All patients in part A and part B will be included in the secondary endpoint analysis regardless of which dose level they are treated.

Overall best response rate will be presented as a proportion of patients with a response of CR or PR at 9 weeks of starting treatment according to the RECIST criteria. This will be presented with the appropriate 95% CI.

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Best reduction in tumour size will be presented as waterfall plots.

Progression free survival will be calculated using Kaplan Meier methods. This will be defined from starting treatment to date of progression or death where any progression free surviving patients will be censored at last follow up. The median and 9 week PFS will be presented with the 95% CI.

Other secondary endpoints data will be reported descriptively by listing for all the recruited patients.

Exploratory Endpoints

All patients in part A and part B will be included in the secondary endpoint analysis.

Immunophenotype of pre and post treatment (9 weeks), location of tumour infiltrating lymphocytes and response stratification according to tumour PD-L1 expression will be presented as descriptive statistics where any qualitative data will be presented as frequencies, proportions and 95% CIs and any quantitative data will be presented with mean, SD, median, IQR and ranges.

To identify predictive biomarkers of immune response to PD-L1, univariate binary logistic regression analyses will be conducted. Any biomarkers with a p value<0.1 will be entered into a forward stepwise multivariate model with known prognostic factors.

5. Changes of Analysis from Protocol

N/A

6. Timing of Statistical Analysis

The formal statistical analysis will be at the end of trial. However, a report with study data listing will be presented to the SRC for safety review at pre-specified time points.

7. References

None

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8. Data checking plan

Once all data has been entered into the database, the study data needs to be checked for accuracy against the CRFs.

All primary endpoint data will be checked for 100% accuracy.

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Peer Reviewer

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Study Statistician

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Chief Investigator

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Date