The ROYAL MARSDEN

Statistical Analysis Plan

CCR #:	4640
Version Number:	2.0
Date (dd/mmm/yy):	19/08/2022
Study protocol Version:	V3.0
EUDRAC #:	2017-001316-11
Clinicaltrials.gov ID:	NCT03602833

A**velumab and hy**P**ofractionated** P**a**L**liative radiotherapy in metastatic soft-tissu**E **sarcoma (APPLE Study)**

The ROYAL MARSDEN

TABLE OF CONTENTS **PAGE**

The ROYAL MARSDEN

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADL	Activities of daily living
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Chief Investigator
CL	Clearance
Cmax	Maximum Plasma Concentration
Cmin	Minimum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computerized Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
CTIMP	Clinical Trial of Investigational Medicinal Product
CTLA-4	Cytotoxic T-lymphocyte-associated protein *4*
CTV	Clinical Target Volume
DAI	Dosage and Administration Instructions
DC	Dendritic Cells
DILI	Drug induced liver injury
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee

The ROYAL MARSDEN

DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
DW-MRI	Diffusion weighted magnetic resonance imaging
EC	Ethics Committee
ECG	Electrocardiogram
ECI	Evidence of Clinical Interest
ECOG	Easter Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EMEA	European Medicines Agency
EOT	End of Treatment
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FDA	Food and Drug Administration
FFPE	Formalin Fixed, Paraffin Embedded
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
GTV	Gross Target Volume
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMGB1	High-mobility group box 1
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICR	Institute of Cancer Research
ICRU	International Commission on Radiation Units and Measurements
IEC	Independent Ethics Committee
IFN	Interferon
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product

The ROYAL MARSDEN

IMPD	Investigational Medicinal Product Dossier
INR	International Normalized Ratio
irAE	Immune-related AE
IRB	Institutional Review Board
irECI	Immune-related Events of Clinical interest
irRC	Immune-related response criteria
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to treat
IV	Intravenous
LC	Local Control
LFT	Liver Function Test
LLN	Lower limit normal
MA	Marketing Authorisation
mAb	Monoclonal Antibody
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MS	Member State
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
NK	Natural Killer
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OAR	Organs at risk
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PI	Principal Investigator

The ROYAL MARSDEN

PIC	Participant Identification Centre
PIS	Participant Information Sheet
PK	Pharmacokinetics
PP	Per protocol
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTV	Planning Target Volume
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RM	G-SOPs
RNA	Ribonucleic Acid
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAR	Serious Adverse Reaction
SD	Stable Disease
SDV	Source Data Verification
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPC	Summary of Product characteristics
SRC	Safety Review Committee
SSI	Site Specific Information
StD	Standard Deviation
STS	Soft tissue sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
T4	free thyroxine

The ROYAL MARSDEN

TEAE	Treatment Emergent Adverse Event
TIL	Tumour Infiltrating Lymphocytes
TMF	Trial Master File
TMG	Trial Management Group
TO	Target occupancy
Treg	Regulatory T cells
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USM	Urgent safety measures
WBC	White Blood Cell

The ROYAL MARSDEN

AMENDMENT HISTORY

Date	Brief description of change
06.03.19	First draft
03.08.22	• Clarify timing of analyses • Clarify who will be analysing the exploratory endpoints • Update acute and late toxicity populations • Data checking will be conducted by a CSM • Change of study statistician

The ROYAL MARSDEN

1. Study Details

1.1. Study objectives

Primary Objective

Objective: To assess the safety and tolerability of combining hypofractionated radiotherapy (36 Gy in 12 fractions delivered daily over 2.5 weeks), with avelumab, an anti-PD-L1 antibody, treating advanced STS.

Secondary Objectives

Objective 1: To evaluate local control rates at 3 months achieved by combining avelumab with hypofractionated radiotherapy (based on CT/diffusion-weighted MRI).

Objective 2: To evaluate progression free (PFS) and overall survival (OS).

Objective 3: To evaluate acute toxicity, defined as toxicity occurring up to 11 weeks following initiation of combined radiotherapy and avelumab.

Objective 4: To evaluate late toxicity, defined as toxicity occurring during the period commencing 11 weeks and one day after the initiation of radiotherapy and avelumab until confirmed disease progression or initiation of new anti-cancer treatment therapy.

Objective 5: To assess the frequency of PD-1/PD-L1 expression in advanced STS and evaluate PFS against PD-L1 expression.

Exploratory Objectives

Objective 1: To determine individual tumour response rate in non-irradiated STS metastases measured by RECIST 1.1 and irRC at 3 months and 6 months after treatment with avelumab and radiotherapy. This will be used to determine local control and assess abscopal effect.

The ROYAL MARSDEN

Objective 2: To evaluate whether hypofractionated radiotherapy combined with avelumab treating advanced STS results in a measurable change in anti-tumour immunity.

Objective 3: Identification of tissue and serum biomarkers that correlate with immunological response to therapy.

1.2. Study design

This is a single centre open label, non-randomized, non-placebo phase 1 clinical trial to establish the safety and tolerability of avelumab in combination with radiotherapy in patients with advanced soft tissue sarcomas (STS). Metastatic STS patients receiving radiotherapy to a tumour deposit above the diaphragm in the thorax, trunk or extremity, will receive hypofractionated radiotherapy (36 Gy in 12 fractions, delivered daily). This study will recruit 12 patients and run as a fixed dose study with starting dose of 10mg/kg. Patients will continue on the treatment regimen unless they progress, suffer unacceptable toxicities, or withdraw from the trial. Recruitment is estimated to take 12 months and it is anticipated that a median 12 cycles of avelumab will be delivered over an elapsed time of 6 months. The maximum survival follow-up is estimated to be 24 months. Therefore the end of the study (i.e. follow-up completed in last patient recruited) is anticipated to be no more than 3 years and 6 months from the administration of the first dose of avelumab to the first patient.

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

Following entering the first 3 patients, recruitment will be deferred until they have been assessed for acute toxicity (i.e. 11 weeks from the initiation of combined radiotherapy and avelumab) by the SRC before recruitment of patients 4 to 6 can proceed. The SRC will review toxicity following recruitment of patient 6. If the incidence of DLT occurs it is within acceptable limits as deemed by the SRC and in

the absence of grade 3/4 toxicity (RTOG ACUTE radiation Morbidity). The cohort will be expanded up to 12 patients after reviewed from the SRC committee.

2. Analysis Sets

2.1. Definition of analysis sets

- The intention-to-treat (ITT) population

The ITT population will consist of all patients who receive 1 dose of avelumab and 1 fraction of radiotherapy.

- Acute toxicity population

The acute toxicity population will consist of all patients who received at least 1 dose of avelumab and at least 1 fraction of radiotherapy with at least one toxicity assessment (may be assessed upto 11 weeks from start of radiotherapy and avelumab treatment).

- Late toxicity/efficacy population

The late toxicity population will include all patients who received at least one dose of avelumab and at least one fraction of radiotherapy and have at least one toxicity assessment from 11 weeks and 1 day from the start of radiotherapy and avelumab treatment until confirmed disease progression or initiation of new anti-cancer treatment therapy.

- Other secondary and exploratory objectives/endpoints population

This population will include all patients who received at least one dose of avelumab and at least one fraction of radiotherapy.

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

The ROYAL MARSDEN

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 assess whether Avelumab at a fixed dose of 10mg/kg can be safely combined with hypofractionated radiotherapy to the thorax, trunk or limb will be in absence of dose limiting toxicity (DLT).

Secondary Endpoints

1. To assess the proportion of patients treated with a combination of avelumab and radiotherapy with local control of soft-tissue sarcoma at 3 months.
2. To assess the PFS and OS achieved with a combination of avelumab and radiotherapy followed by maintenance avelumab in patients with metastatic soft-tissue sarcoma at 6 months and 1 year. PFS will be defined from start of avelumab to date of progression or death. Any progression free and alive patients will be censored at last followup. OS will be defined from date of start of avelumab to date of death or censored at last followup.
3. To measure the rate of acute ≥ grade 2 toxicity for 11 weeks following initiation of radiotherapy and avelumab.
4. To assess the rate of late ≥ grade 2 toxicity assessed from 11 weeks and one day following the initiation of avelumab and radiotherapy until confirmed disease progression or initiation of new anti-cancer treatment therapy.
5. To measure PFS and OS in PD-L1 positive population at 6 months and 1 year.

Exploratory Endpoints

1. To assess the RECIST and irRC criteria response rates to treatment in (non-irradiated) soft-tissue sarcoma metastases at 3 and 6 months.
2. Analysis of research blood samples for ctDNA.
3. Characterisation of Tumour infiltrating lymphocytes (TILs) and tumour antigens in serum and tissue samples (as outlined in the immunotherapy trial manual).

The ROYAL MARSDEN

4. Analysis of expression of immune-related gene panel by tumour and infiltrating immune cells, in pre- and post-radiotherapy tumour samples using Nanostring technology.

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 or median and IQR/range. Where appropriate, results will be presented with two sided binomial 95% CIs unless otherwise stated.

4.2. Analysis methods

Primary & Secondary Endpoint

This study will recruit patients (radiation tumour target volume above diaphragm). Acute toxicity will be reported by week using CTCAEv4 grades, using the acute toxicity population. Worst grade will be reported as counts and percentages, by type of toxicity and over all types. Numbers of patients with missing and non-missing toxicity assessments will be reported for each week. Worst grades by type of toxicity and overall types will also be reported at all time points up to and including week 11 from the start of radiotherapy. The number and reasons for withdrawal before treatment completion will be stated. Acute toxicity will be reported for all patients grouped together regardless of dose level or disease stage.

Late toxicity will be reported by time point. The number and percentage of worst grade at that time point by type of toxicity, and overall types will be reported. Number of patients with missing and non-missing toxicity assessment will also be reported for each week. The late toxicity endpoint of the study will be reported as the number and percentage of patients experiencing any ≥ grade 2 and ≥ grade 3 late toxicity from week 11 and 1 day from the start of radiotherapy treatment. This will be reported at month 6 and month 12 from completion of radiotherapy. The late toxicity population will be used for all endpoints. An additional time to event analysis will be performed using Kaplan-Meier methods to show time to any ≥ grade 3toxicity from 11 weeks and 1 day from the start of radiotherapy and avelumab treatment. Late toxicity will be reported for all patients grouped together regardless of dose level or disease stage.

The ROYAL MARSDEN

Duration of local control will be measured from end of radiotherapy to date of first recorded local progression, using Kaplan-Meier methods. Patients without local progression will be censored at date of last follow-up or death from any cause. The percentage and 95% confidence intervals for rate of local control at 3 months after end of radiotherapy will be given. The late toxicity population will be used for this endpoint. Local control will be reported for all patients comprising the cohort.

Progression free survival and overall survival will be reported using Kaplan Meier methods, and will be measured from the start of avelumab treatment in the acute toxicity population. Survival rates and 95% confidence intervals will be given at 1 and 2 years.

Exploratory Endpoints

RECIST response rates to treatment in (non-irradiated) soft-tissue sarcoma metastases at 3 and 6 months will be calculated as frequencies and percentages in the ITT population will be stated together with reasons for early withdrawal. The rest of the endpoints will be analysed by the clinical team.

5. Changes of Analysis from Protocol

N/A

6. Timing of Statistical Analysis

First analysis

This will include:

- Baseline characteristics
- Treatment details
- Primary endpoint
- Local control rate at 3 months
- Acute toxicities
- Late Toxicities
- RECIST response rates at 3 and 6 months

The ROYAL MARSDEN

Follow-up analysis

This will be analysed at least 1 year from last patient registration and will include:

- OS
- PFS
- OS/PFS in the PD-L1 positive population (this may be a case review if numbers are less than 10)

Study data listings have been presented to the SRC for safety review after 3 patients have completed one cycle of treatment (21 days) before proceeding to recruit more patients.

7. Missing data

No imputations will be calculated.

8. Data checking plan

A CSM will be conducted prior to all analyses in line with the CSM plan.

9. Statistical Package(s)

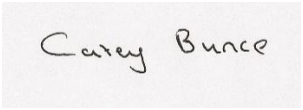
All analyses will be conducted using STATA 17.0

10. References

None

The ROYAL MARSDEN

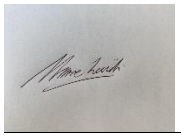
Avelumab and hyPofractionated PaLliative radiotherapy in metastatic soft-tissuE sarcoma (APPLE Study)

		20/8/2022
Peer Reviewer		
	Catey Bunce	Date
Study Statistician		19/08/2022
		
	Komel Khabra	Date

The ROYAL MARSDEN

A**velumab and hy**P**ofractionated** P**a**L**liative radiotherapy in metastatic soft-tissu**E **sarcoma (APPLE Study)**

Chief Investigator



30.8.22

Dr Shane Zaidi

Date