The ROYAL MARSDEN NHS Foundation Trust

Protocol Title and CCR number: <E.g. xxxxxx (CCRXXXX)>	Targeted Radiotherapy in Androgen-suppressed Prostate cancer patients - TRAP (CCR4781)
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Sponsor:	The Royal Marsden NHS Foundation Trust
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Contents

List of Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
CCR	Joint RM / ICR Committee for Clinical Research
CI	Confidence Interval
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
ctDNA	Circulating Tumour DNA
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DWI	Diffusion-weighted Imaging
ECOG	Eastern Cooperative Oncology Group
IDMC	Independent Data Monitoring Committee
IQR	Interquartile range
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PFS	Progression Free Survival
PSA	Prostate Specific Antigen
QA	Quality Assurance
RM-CTU	Royal Marsden Clinical Trials Unit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBRT	Stereotactic Body Radiotherapy
SD	Standard deviation
SOP	Standard Operating Procedure
UK	United Kingdom
WBDWMRI	Whole Body Diffusion Weighted MRI

Amendment history

Date	Version	Timing in relation to analysis	Brief description of change	Justification for change
06.10.2023	1.0	Final analysis	N/A	N/A

1. Trial Summary

Polyclonal seeding from metastases is thought to result in polymetastatic disease. Stereotactic body radiotherapy (SBRT) to a metastasis could prevent the development of further metastases and may reverse resistance to Abiraterone/Enzalutamide which usually necessitates that patient start chemotherapy, reducing quality of life. As metastatic disease is genetically heterogeneous, often most of the metastases are controlled by Abiraterone/Enzalutamide, but one or two lesions may become resistant and start to grow. If these could be ablated with SBRT it may be possible to prolong the response time to Abiraterone/Enzalutamide and postpone chemotherapy.

Circulating tumour DNA (ctDNA) has been shown to track emerging dominant metastatic clones in circulation. If ablation of these with radiotherapy causes disappearance of this clone, then for the first time, this trial, will establish the pivotal link between current management of patients (PSA and imaging) and ctDNA as a marker of disease.

The TRAP trial will recruit 84 men with castration-resistant prostate cancer (CRPC) who have responded to Abiraterone/Enzalutamide but now have one or two progressing/new lesions on imaging. These lesions will receive 30 Gray in 5 fractions (or 36 Gray in 6 fractions weekly) with SBRT and remain on Abiraterone/Enzalutamide. Patients will have whole body diffusion-weighted MRI (WBDWMRI) at baseline and 6 months post radiotherapy. Plasma for ctDNA will be taken at baseline and at four time points after radiotherapy.

The MRI and ctDNA results will be used to create a biomarker panel which predicts a PFS of >6months. The primary end point is progression-free survival, with secondary endpoints of acute and late toxicity, quality of life and PSA control. SBRT in this setting has the potential to create new pathways of care whilst developing the optimum use of existing treatments to benefit men across the UK. This strategy will also repurpose an existing drug and maximise benefit from Abiraterone/Enzalutamide.

2. Trial objectives

2.1 Primary Objective

- To determine the median progression-free survival following SBRT to oligoprogressing sites.

2.2 Secondary Objectives

- To establish the local control rate after SBRT for oligoprogression.
- To determine whether circulating tumour (ctDNA) fraction decreases after SBRT to sites of oligoprogression, and whether the kinetics of ctDNA are predictive.
- To establish if Whole Body Diffusion Weighted MRI (WBDWMRI) and / or ctDNA and / or patient or tumour demographics at baseline can predict those patients most likely to benefit from SBRT (i.e. predict those who will have progression-free survival for 6 months or more, in comparison to the biomarker negative cohort who are expected to have a progression-free survival of 4 months).
- To record PSA response and overall survival after SBRT.
- To monitor acute and late toxicity from SBRT in a metastatic cohort.

- Capture of EQ-5D Health Questionnaire responses.

2.3 Exploratory Objectives

• To establish if it possible to define a biomarker panel which is present in at least 40% of oligoprogressing patients and which predicts for progression free survival (median PFS) of more than 6 months.
• To ascertain time-to-delay of next line of treatment in the biomarker positive versus the negative groups
• To conduct a sub-group analysis of median PFS of local prostate oligoprogression versus metastatic oligoprogression.
• To explore whether the kinetics of ctDNA predict time to progression or precede clinical or radiological progression.

3. Trial Methods

3.1 Trial design

A multi-centre phase II trial in patients with oligoprogression treated with Stereotactic Body RadioTherapy (SBRT).

3.2 Randomisation

Not applicable.

3.3 Sample Size

Assuming median progression-free survival of the existing (i.e., null median PFS) and the novel treatments (i.e., alternative median PFS) are 4 and 6 months, respectively, with 24 months accrual time, 30 months maximum follow up time and 2-sided type 1 error of 5%, a sample size of 84 provides 96% power for one-sample Log-Rank test. Note: the power calculated using an in-house R script. The R script output is identical to the output of one arm survival analysis – CRAB: Cancer Research and Biostatistics – https://stattools.crab.org/Calculators/oneArmSurvivalColored.html. The study has been overpowered to improve the chance of biomarker exploration (exploratory outcome) which is likely to affect the survival. Progression-free survival is defined as the time between the final day of SBRT and the first confirmed progression (as defined in Section 6.1) or start of next line of therapy or date at which the clinician decides to stop Abiraterone/Enzalutamide, whichever occurs sooner.

3.4 Framework

Non randomised, prospective cohort study.

3.5 Statistical Interim Analysis and stopping guidance

There is no formal interim analysis planned.

Stopping a trial early

There are no formal statistical stopping rules or guidelines.

3.6 Timing of Final Analysis

The Primary endpoints data analysis will be conducted after all patients have been recruited according to estimated sample size and the last patient recruited has had their 6 months follow-up post-SBRT.

The final analysis for the other secondary endpoints will be conducted after the last recruited patient had 24 months follow-up assessment post-SBRT.

3.7 Timing of outcome assessment

Primary outcome analysis will be done once all patients recruited have completed their 6 months follow up post-SBRT.

Secondary outcome analysis will be done as follows:

- Once all patients have received SBRT, ctDNA will be analysed.
- Overall local control will be analysed 6 months post SBRT *
- Acute toxicity will be assessed at the end of radiotherapy fraction 5/6 (+/- 3 days), at week 4 (+/- 5 days) and at week 12 from the end or radiotherapy). Acute toxicity will be presented as maximal grade of CTCAE toxicity at each time point and cumulative acute toxicity up to and including week 12 from final fraction of radiotherapy. Late toxicities at 6, 12, 18 and 24 months from the start of radiotherapy and will be presented as maximal CTCAE grade at each time point and cumulative incidence of worst toxicity between 6 and 24 months. Data received outside of the protocol defined windows will be attributed to the closest protocol timepoint. *
- QOL will be analysed once patients have completed 6 months follow-up *. Subsequent QOL analysis will be done at 24 months
- Time to next therapy will be measured from end of SBRT to start of new therapy *
- Baseline WBDWMRI will be assessed once patients have had their baseline and 6-month scans and have completed 6 months of post-SBRT follow up
- Overall survival will be assessed after patients have finished their SBRT until 24 months follow-up *
- PSA absolute level and kinetics will be assessed at 3,6, 12 and 24 months after patients have completed their SBRT *

* denotes endpoints to be reported in initial primary endpoint publication

Exploratory endpoint analysis:

- Further publications focussing on imaging review (including diffusion characteristics of treated vs untreated lesions, ability of imaging to predict for early progression, long term control of irradiated metastases) will be presented in due course. Imaging parameters will be correlated with 6 month progression-free survival and local control.
- ctDNA analysis will focus on characterising mutations seen in circulating tumour DNA and correlating quantity and genotype with clinical outcomes. Kinetics of ctDNA after SBRT will be examined.

4. Statistical Principles

4.1 Confidence Intervals and P values

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided.

4.2 Adherence and protocol deviations

Any deviations from the radiotherapy protocol need to be notified to the Chief investigator in writing/email. If radiotherapy does not commence within 56 days of consent, this constitutes a protocol deviation and should be reported as such. Radiotherapy in this setting is not known to be time-critical, so protocol deviations unlikely to impact progression-free survival assessment. Treatment should aim to be completed in 10 days, with the exception of weekly prostate radiotherapy which may be up to 6 weeks. Apart from this, treatment courses which occur over more than 19 days should be reported as a protocol deviation. All eligible patient data will be used and reported regardless of protocol deviations.

Violations and deviations will be summarised using descriptive statistics. It will be in a table format to report the categories in frequencies and percentages

4.3 Analysis populations

The analysis population for the primary and secondary endpoints will consist of all eligible patients who have received at least one fraction of SBRT treatment.

5. Trial Population

5.1 Screening Data

Patient recruitment was based on inclusion/exclusion criteria therefore it will be assessed to confirm only eligible patients were recruited on the study.

5.2 Eligibility

All eligible and treated patients will be included in the final analysis and any non-eligible patients identified will be reported with the reasons of ineligibility. The numbers will be reported as part of baseline characteristics.

5.3 Recruitment

Please see protocol for details of recruitment procedures.

5.4 Withdrawal/ Follow up – level of withdrawal

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial. However, if the Investigator removes a patient from the trial or if the patient declines further participation, a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised and reported descriptively.

5.5 Baseline patient characteristics

Patients will be described with respect to: age, centre, PSA value at diagnosis (ug/l), Gleason sum score at diagnosis, ECOG Performance Status, No. oligo-progressing lesions, disease burden (site, number) of treated sites, disease burden sites for all other lesions that occurred previously and treatment history including % of patients who have received prior chemotherapy.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD and range if data are normal and median, IQR and range if data are skewed. Minimum and maximum values will also be presented for continuous data.

6. Analysis

6.1 Outcome definitions

Primary outcome

Time to Progression or Death from date of final SBRT fraction to event. Disease progression is defined if at least one of the following points are met

- **PSA progression**: PSA must rise by at least 25% over post-SBRT baseline (set at 4 weeks), confirmed by a second reading at least 4 weeks later.

- **Radiological progression:** Defined as at least 2 new lesions on bone scan or unequivocal RECIST progression of soft tissue on CT, or evidence on other local imaging of disease progression (e.g. PET or MRI progression).
- **Symptomatic progression:** new or progressing symptoms at the site of a metastasis.
- **Date at which the clinician decides to stop Abiraterone/Enzalutamide or starts new line of therapy**, whichever occurs sooner.

Secondary outcomes

- Overall local control (defined as stable disease or partial response of irradiated metastases 6 months post SBRT) on CT, Bone scan, PET (if done) and WBDWMRI. Patients will be separately recorded as local control yes/ no on conventional imaging (CT, Bone scan and/or PET) and local control yes/no on WBDWMRI. This analysis will be done directly from imaging data so not captured on the database and will be reported in the subsequent imaging paper.
- Proportion of patients with oligoprogression who have detectable circulating tumour DNA at baseline
- ctDNA response to SBRT defined as proportion of patients who convert from detectable at baseline to undetectable circulating tumour DNA at any timepoint up to 6 months after SBRT.
- PSA kinetics at 3, 6, 9 and 12 months after SBRT, including percentage of patients with a PSA below 75%, 50% and 25% of pre-SBRT baseline.
- Acute toxicities (at the end of radiotherapy fraction 5/6 (+/- 3 days), at week 4 (+/- 5 days) and at week 12 from the end of radiotherapy) and late toxicities (at 6, 12, 18 and 24 months from the start of radiotherapy) as per CTCAE v4.0. Prevalence of maximal grade toxicity at each timepoint will be recorded and cumulative incidence of each grade of toxicity over the acute toxicity period will be presented. Toxicities occurring in >5% patients will be listed individually.
- QoL assessed using the EQ 5D Questionnaire at end of SBRT, 4 weeks post SBRT, 3 months and 6 months post SBRT and then at 3-monthly intervals until disease progression.
- Time to next therapy (months) defined as time from end of SBRT to start of new systemic therapy or death. Name of next therapy will be reported.
- Proportion of patients where WBDWMRI detects further metastases at baseline compared to CT and bone scan/PET at same timepoint. This endpoint will be assessed directly from imaging data, rather than on the database.
- Association between WBDWMRI at baseline (number of metastases, DWI characteristics) and prognosis after SBRT (defined as progression at 6 months post-treatment)
- Overall survival at 12 & 24 months after the end of SBRT until the date of death from any cause. Patients who remain alive at the time of the analysis will be censored at the date of last follow up

Exploratory outcome

- Establish a biomarker panel which is present in at least 40% of oligoprogressing patients and which predicts for progression-free survival (median PFS) of more than 6 months. If the median PFS is longer than 9 months then we will explore a baseline biomarker panel which predicts for a PFS of >12 months.

- Time-to-delay of next line of treatment in the biomarker positive versus the negative groups
- Sub-group analysis of median PFS of local prostate oligoprogression versus metastatic oligoprogression.
- Explore whether the kinetics of ctDNA after SBRT predict time to progression or precede clinical or radiological progression.

6.2 Analysis Methods

Primary Endpoint analysis

Calculate time from end of SBRT to Progression or Death from any cause (Progression Free Survival – PFS) using Kaplan Meier method. Patients who remain alive with no progression recorded at the time of the analysis will be censored at the date of last follow up. A one-sample Log-Rank test will be used to compare the observed PFS of the patients (alternative PFS) with their expected (null) PFS (based on 4 months median PFS using the existing treatment) with 2-sided type I error of 5%. Kaplan–Meier estimator of survival function, and median survival with 95% Confidence interval will also be reported.

Secondary endpoint analysis

- Proportion of patients who achieved overall local control (PR+SD) at 6 months after SBRT (+/- 2 months) will be calculated with 95% CI. Descriptive statistics (frequencies and percentages) will be reported for each level of response .
- Number and proportion of patients with oligoprogression who have detectable circulating tumour DNA at baseline will be reported with 95% CI.
- Number and proportion of patients with ctDNA change (from detectable to undetectable up to 6 months post-SBRT) will be reported with 95% CI.
- Descriptively summarise and report the PSA kinetics at 3, 6, 9 and 12 months after SBRT using mean/median and SD or IQR as appropriate in the groups of patients with and without progression at 6 months. Similarly, report in the groups the number and percentage of patients in the categories of baseline (pre-SBRT) PSA below 75%, 50% and 25%.
- Summarise the CTCAE grades for acute(up to 30 days post-SBRT) and late(from 31 days post-SBRT) toxicities at each visit and report numbers and percentages of patients in each CTCAE grade, plus cumulative toxicity at each grade during the acute and late periods separately.
- Describe the individual items of EQ-5D quality of life at each visit using frequencies and percentages. Overall questionnaire scores at each visit will be summarised using median and interquartile range. Also, display the change from the baseline to each time-point graphically.
- OS will be analysed similarly to primary endpoint PFS. Survival function and median survival time with 95% confidence intervals will be estimated using Kaplan Meier curve. Cox proportional hazard regression models will be used to adjust for prognosis factors(age, months since starting Abiraterone/Enzalutamide, performance status) where appropriate.
- Time to next therapy(months) will be estimated using survival function and median survival with 95% confidence using Kapla Meire curve.
- Association between WBDWMRI at baseline (number of metastases, DWI characteristics) and prognosis after SBRT will be assessed using Correlation, and/or regression and/or survival (for prognosis) models whenever appropriate.

- Proportion of patients where WBDWMRI detects further metastases at baseline will be calculated with 95% CI. Descriptive statistics (frequencies and percentages) will be reported.

6.3 Missing data

During the trial, monitors appointed by the RM QA Manager, will be responsible for monitoring data quality in accordance with relevant standard operating procedures (SOPs). Incoming data will be monitored for protocol compliance and if any inconsistent or missing data is identified queries will be discussed with the site for resolution. Any systematic inconsistencies may trigger an on-site monitoring visit.

Prior to any analysis offline data completeness checks will be done by Trial Manager/delegate and trial statistician and any queries will be raised with trial team. Missing data will be reported as part of the data description in a form of number of subjects missing data items. Formal methods such as multiple imputation will not be used.

Number at risk will be reported graphically for the oncological endpoints above including PFS, local control and OS. For toxicity data, numbers of patients returning data at each point will be reported.

6.4. Exploratory/ additional analyses

6.4.1. Exploratory analyses

Exploratory endpoints Analysis – Not covered by this SAP. To be analysed separately by the clinical team(Imaging team led by Dr Nina Tunariu (RMH) and Genomics team led by Professor Gert Attard (UCL))

Imaging:
Descriptive analysis of the size, location and imaging characteristics of metastases will be analysed, both at baseline and during the study
Metrics of disease response including CT, bone scan, PET and WBDWMRI will analysed on the 3 month and.6 month scans.

ctDNA:
If a significant proportion of patients have detectable ctDNA at baseline, then we will characterise kinetics of ctDNA over time, and perform detailed analysis of mutational patterns, where possible.

Biomarker development:
As per secondary endpoints below, we will use the above data to develop and refine a patient phenotype which predicts for longer PFS, using baseline clinical, ctDNA and/or imaging data.

6.4.2. Subgroup analysis

A planned subgroup analysis of the median PFS in patients with local prostate oligoprogression versus metastatic oligoprogression. Methods employed will include Kaplan-Meier analysis or the Cox-Proportional Hazard Regression model or other appropriate survival model to estimate the hazard ratio.

6.5. Safety

In the TRAP trial, SAEs will be collected from the start date of the patient's radiotherapy (or the date of insertion of fiducials, where used) until 30 days from the end of radiotherapy treatment. All events will be recorded in the medical notes and the appropriate section of the CRF and/or AE log. Sites will be expected to complete a study specific SAE Reporting Form and must send to RM-CTU/the Chief Investigator within 24 hours/next working day since being notified of the event. The number (and percentage) of occurrences of each AE/SAE will also be presented. No formal statistical testing will be undertaken.

7. Statistical Packages

The analysis will be carried out using Stata 17.0 or subsequent versions.

8. Data Management & Central Statistical Monitoring Plan

The SAP have been drafted and will be executed in line with Central Statistical Monitoring and Data management plan.

9. Independent Data Monitoring Committee (IDMC)

An IDMC has been set up with membership and remit as defined in an IDMC Charter. The purpose of the Committee is to ensure the ongoing safety of trial participants through regular scrutiny of trial safety related data. The IDMC membership includes the trial statistician who periodically examine data for anomalies and outliers, such as too few or too many events.

10. Changes from protocol

Overall survival will, in addition to 12 and 24 months, be reported at 6 months.

11. Roles and Responsibility – non-signatory names and contribution

	SAP contributor 1
Name	Sabine Dreibe
Affiliation	Royal Marsden NHS Foundation Trust
Role	Statistician

	SAP contributor 2
Name	Kabir Mohammed
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	SAP contributor 3
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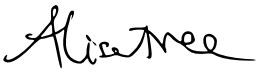
	SAP contributor 4
Name	Dr Alison Tree
Affiliation	Royal Marsden NHS Foundation Trust
Role	Chief Investigator

12. Roles and Responsibility – signatures

Trial Statistician	 Digitally signed by Sabine Dreibe Date: 2023.10.06 16:15:45 +01'00'	06/10/2023	
	Sabine Dreibe	Date	
Peer Reviewer	Amina Tran Digitally signed by Amina Tran Date: 2023.10.06 17:16:35 +01'00'	06.10.2023	
	Amina Tran	Date	
Chief Investigator		**6.10.2023**	
	Dr Alison Tree	Date	