Full title:

A Phase I Trial of the Hypoxia Modifier Atovaquone in Combination with Radical Concurrent Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer

Short title:

Atovaquone with Radical ChemorADIotherapy in locally Advanced NSCLC

Statistical Analysis Plan

Version V1.0 – 17Jun2021

Based on Protocol version V2.0 – 23Mar2020

Trial registration: 2019-002097-30

Role	Name	Title
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CONTENTS

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the **Cancer Research UK -funded multicentre single-arm trial of the hypoxia modifier atovaquone in combination with radical concurrent chemoradiotherapy in locally advanced non-small cell lung cancer (ARCADIAN).** The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Key personnel

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1.2 Changes from previous version of SAP

The following table is a summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_17Jun2021	CQ	V2.0 – 23Mar2020	Not applicable as this is the 1st issue

2. BACKGROUND AND OBJECTIVES

2.1 Background and rationale

The following table summarises the study protocol.

Full Title of study:	A Phase I Trial of the Hypoxia Modifier Atovaquone in Combination with Radical Concurrent Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer	
Short Title:	Atovaquone with Radical ChemorADIotherapy in locally Advanced NSCLC	
Trial Acronym:	ARCADIAN	
Clinical Phase:	Phase I	
Study Design:	Single arm, open-label trial utilising Time To Event Continual Reassessment Method (TiTE-CRM)	
Objectives and endpoints	The primary objective is to determine the maximum tolerated dose (MTD), and therefore recommended phase II dose (RPTD), of atovaquone when combined with radical concurrent chemoradiotherapy. The full list of study objectives and endpoints is in Section 2.2.	
Planned enrolment:	20 evaluable participants	
Target Population:	Patients with locally advanced Non-Small Cell Lung Cancer planned to be treated with concurrent chemoradiotherapy	
Investigational Medicinal Products	**Name of drug**	**Formulation, dose, route of administration**
	Atovaquone	Suspension, oral, twice daily, dose to be allocated per TiTE-CRM: 450 mg, 600 mg, 675 mg or 750 mg (all doses PO BD)
	Cisplatin	80 mg/m^2 IV on days 1 & 22
	Vinorelbine	15 mg/m^2 IV on days 1, 8, 22 & 29
Other interventions:	Thoracic radiotherapy: 66 Gy in 33 fractions, once daily, 5 days a week (Monday-Friday)	
Study duration:	31 months (start of recruitment to close out)	
Treatment Duration	Up to 9.5 weeks of atovaquone treatment, with concurrent chemoradiotherapy for 6.5 of these weeks	
Follow-up duration	Six months (26-28 weeks) post completion of chemoradiotherapy	
End of study	Last Patient Last Visit	

2.2 Objectives

The table below shows the full list of trial objectives and corresponding outcome measures. Objectives in grey will be not analysed by trial statisticians within CSM so are not covered by this SAP.

Primary Objective	**Endpoints/ Outcome measures**	**Time point(s) of evaluation of this end point**	**Analysis population**
To determine the maximum tolerated dose (MTD), and therefore recommended phase II dose (RPTD), of atovaquone when combined with radical concurrent chemoradiotherapy in patients with non-small cell lung cancer (NSCLC)	The dose of atovaquone associated with no more than 48% dose limiting toxicity (DLT) rate (target toxicity level)	From week -2/-3 until three months post-completion of CRT	All patients who have received at least one dose of atovaquone
Secondary Objectives			
To assess the safety and toxicity profile of atovaquone in combination with radical	Adverse events graded per Common Terminology Criteria for Adverse Events	From screening/baseline until six months post completion of CRT	All patients who have received at least one dose of atovaquone

concurrent chemotherapy for NSCLC	(CTCAE) v4.03		
To confirm feasibility of measuring hypoxia metagene signature using 3'RNA-Seq in diagnostic NSCLC samples	Hypoxia metagene signature from diagnostic tissue using 3'RNA-Seq	At baseline	
To assess pre-treatment agreement of: 1. FMISO PET-CT with plasma miR-210 level 2. FMISO PET-CT with tumour hypoxia gene expression	▪ Tumour hypoxic volume determined by FMISO PET-CT ▪ Plasma miR-210 level ▪ Hypoxia metagene signature from diagnostic tissue using 3'RNA-Seq	Week -2/-3 (prior to atovaquone treatment)	1. All patients with outcome measures from both the baseline FMISO PET-CT scan and the baseline blood sample
To assess agreement in changes in FMISO PET-CT and plasma miR-210 level following two weeks (+/- 7 days) of atovaquone	▪ Tumour hypoxic volume determined by FMISO PET-CT ▪ Plasma miR-210 level	▪ Week -2/-3 (prior to atovaquone treatment) ▪ Following two weeks (+/- 7 days) of atovaquone treatment	All patients with outcome measures from FMISO PET-CT scans and blood samples taken at both time points
To assess the tumour response rate at three months following treatment	Response to treatment assessed per Response Evaluation Criteria in Solid Tumours (RECIST) V1.1	Three months post completion of CRT	All patients who commence chemoradiotherapy treatment within the study
Exploratory Objectives			
To assess the relationship between: 1. plasma atovaquone levels and hypoxia response as measured by FMISO PET-CT 2. plasma atovaquone levels and plasma miR-210 level	▪ Plasma atovaquone concentration ▪ Tumour hypoxic volume determined by FMISO PET-CT ▪ Plasma miR-210 level	▪ Week -2/-3 (prior to atovaquone treatment) ▪ Following two weeks (+/- 7 days) of atovaquone treatment	All patients with an outcome measure from the PK assessment and outcome measures from: 1. blood samples taken at both time points 2. FMISO PET-CT scans taken at both time points

3. STUDY METHODS

3.1 Trial Design/framework

Arcadian is a single arm, open-label phase I dose escalation trial using the Time-To-Event Continual Reassessment Method (TiTE-CRM) i.e. a model-based approach to determine the maximum tolerated dose (MTD) of atovaquone in combination with concurrent CRT in patients with NSCLC.

Patients will receive an oral suspension of atovaquone twice daily. The four atovaquone dose levels to be assessed in the TiTE-CRM is as follows:

Dose level	
1	450 mg
2	600 mg
3	675 mg
4	750 mg

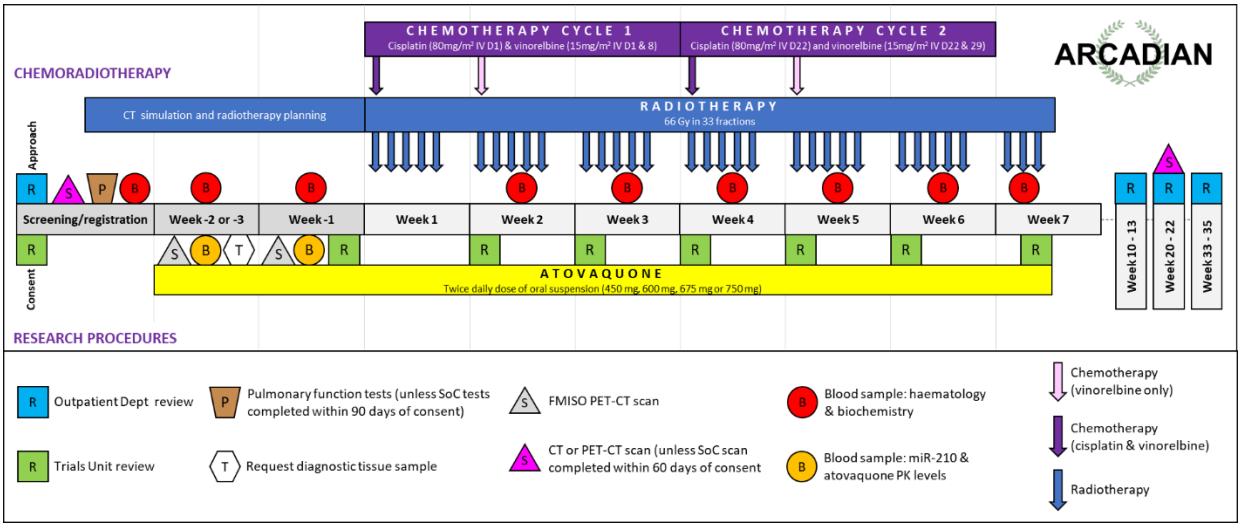
Patients will receive atovaquone alone for 1 to 3 weeks during a run-in period followed by 6.5 weeks of concurrent chemoradiotherapy (CRT). The 6.5 weeks of CRT consists of two cycles: Cisplatin (80 mg/m^2 IV)

on days 1 & 22, Vinorelbine (15 mg/m^2 IV) on days 1, 8, 22 & 29 and thoracic radiotherapy: 66 Gy in 33 fractions, once daily, 5 days a week (Monday-Friday). Therefore, the total treatment duration is expected to be up to 9.5 weeks.

Patients will have follow-up visits at approximately 1, 3 and 6 months after completion of CRT.

The TiTE-CRM will take into account toxicity from the start of the atovaquone run-in period to 12 weeks (84 days) after completion of CRT, so the end of the toxicity assessment period will be approximately the time of the 3 months post-CRT visit.

The figure below shows the study schema



3.2 Randomisation and Blinding

This study is not randomised.

3.3 Sample Size

The sample size will be 20 evaluable patients. Evaluable patients are patients enrolled in the study who received at least one dose of atovaquone.

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

The TMG will meet following each interim analysis, and as necessary, to review toxicity data and decide on dose escalation.
The first two participants recruited will receive the lowest dose of atovaquone (Dose 1: 450 mg BD).
Subsequent eligible patients will be continuously recruited but no dose escalation will be considered until we have at least 12 weeks of safety data for one or both of the first two participants (or at least one participant on dose 1 if the first 2 are not evaluable).
There will be an interim analysis each time a new patient is enrolled. At each interim analysis, the TiTE-CRM model will use all currently available data to recommend the dose to assign the new patient. This analysis will follow the methods for the primary analysis described in Section 6.2. All dose recommendations made by the model will be reviewed by the TMG. The TMG will either approve the dose allocation recommendation or select a lower dose on the basis of clinical review of the data.

In order to escalate to a higher dose of atovaquone, there must be at least one patient on the previous highest dose who fulfils the following criteria:

- Completed ≥1 full cycle of CRT (i.e. at least three weeks of RT)
- Received ≥50% the specified dose of cisplatin
- Taken ≥75% their allocated dose of atovaquone
- Not experienced a DLT

The template for the first TMG dose decision report is given in Appendix 2. Changes may be made to this template as the trial progresses but note that the original template will not be updated as it refers only to the first dose decision meeting.

The TMG will include the Chief Investigator, Co-Investigators, Clinical Trial Manager, Trial Statistician and others as required. TMG membership and decision-making procedures will be documented in the TMG charter.

There is no independent Data and Safety Monitoring Committee (DSMC) for this trial. The Safety Review Committee (SRC) will be convened, as required, to review DLTs and dose escalation decisions made by the TMG. In the event of the TMG being unable to conclude on a dose recommendation, the SRC will meet to decide. The SRC will consist of:

1. Trial Statistician
2. OCTO trial management representative
3. Either:
    a. One Medical Oncologist and one Clinical Oncologist or
    b. Two Clinical Oncologists

Additionally, since the window to observe toxicities is long, the TMG may opt to pause recruitment whilst on-trial patients complete their treatment. The trial will stop for safety (i.e. before reaching the maximum number of patients specified by the sample size) if there is sufficient evidence to suggest that the lowest dose is too toxic. More specifically, we will consider dose level 1 (450mg) to be too toxic if, given all the available data, there is more than 70% probability that the DLT rate is greater than the target toxicity level of 48%.

The SRC Charter document for this trial will define the exact membership and who should be present for decisions to be made. Further internal or external experts may be consulted by the SRC, as necessary. Any PI can request an ad hoc SRC meeting at any time in order to facilitate the immediate communication of any emerging safety issues during the course of the trial.

The Independent Radiotherapy and Imaging Oversight Committee (RIOC) will act as the Trial Steering Committee (TSC). The role of RIOC is to provide oversight for the trial on behalf of the Sponsor and Funders. RIOC will provide overall supervision of the safe and effective conduct of the trial, as further defined in the RIOC charter. At least annually, RIOC will review trial progress against agreed milestones, adherence to protocol, and patient safety, and consider new information. RIOC has the authority to recommend study closure where appropriate. Membership of RIOC includes PPI representation.

3.5 Timing of Final Analysis

Final analysis will take place after all enrolled patients have either completed their six-month follow up visit or have withdrawn from the study.

3.6 Blinded analysis

This is not a blinded trial.

3.7 Statistical Analysis Outline

Section 18 (Statistical Analysis Plan) of the protocol includes the following:

All patients enrolled in the study and who received at least one dose of atovaquone will be accounted for and included in the analyses. The number of patients who were not evaluable, who died or withdrew before treatment began will be recorded. The distribution of follow-up time will be described, and the number of patients lost to follow-up will be given.
The analysis will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, study drug accountability and other data that impact on the general conduct of the study.
Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or do not complete the required safety observations will be described and evaluated separately. Treatment-related toxicity will be tabulated by type and grade of toxicity. All patients will be evaluable for toxicity from time of the first treatment. Adverse events will be summarised by the number of patients experiencing each type of event. The grades and causality will be reported.

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

There will be no statistical significance level defined for Arcadian as it is a dose-finding trial and dose recommendations will be based on the posterior probabilities calculated by the dose-toxicity model using all available data at each time.

4.2 Definition of Analysis Populations

The analysis population for the primary and secondary safety analysis is all patients who have received at least one dose of atovaquone. See Section 2.2 for the definitions of the analysis populations for the other endpoints.

Sensitivity analysis for the primary endpoint will be carried out including only patients who have received >75% of the full prescribed dose of atovaquone up to time of assessment. Patients who have had a DLT will be included irrespective of amount of atovaquone received.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including numbers of participants assigned to a schedule, receiving intended treatment, completing the study protocol, and analysed for the primary outcome will be provided following CONSORT. Protocol violations/deviations and information relating to the screening data including the number of ineligible patients entering the study, together with reasons will be reported. Information on number of participants screened, found to be ineligible (with reasons where available), refused to participate (with reasons where available) will also be included.

A CONSORT diagram will be prepared, an example CONSORT diagram is given in Appendix 3

5.2 Withdrawal from treatment and/or follow-up

Withdrawals/loss to follow-up together with reasons will be reported by atovaquone dose schedule. Also see Appendix 3.

5.3 Baseline Comparability

Baseline characteristics, including important demographic and clinical variables will be reported for all evaluable patients.

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented.

5.4 Unblinding

This trial is not blinded.

5.5 Description of Compliance with Intervention

A summary of the total amount of atovaquone received and the total amount of CRT received will be presented by assigned atovaquone dose schedule. Further detail related to compliance to atovaquone and each CRT component will be presented descriptively in tables and graphs. Any withdrawals from treatment or consent will be presented. See tables and graphs in Appendix 3.

5.6 Reliability

Safety and treatment compliance data will be regularly checked and cleaned, this may involve checking that data is complete e.g. not missing CTCAE grade and consistent across CRFs.

Variables derived from raw data using a computer program may be checked by hand for 5% of patients randomly sampled.

6. ANALYSIS

6.1 Outcome Definitions

Primary outcome

To determine the maximum tolerated dose (MTD), and therefore recommended phase II dose (RPTD), of atovaquone when combined with radical concurrent chemoradiotherapy

The outcome is the occurrence (yes/no) of a DLT within the DLT assessment period. For patients without a DLT, time observed within the DLT assessment period will also be taken into account in the analysis. The total i.e. maximum duration of the DLT assessment period for each patient is the length of the atovaquone run-in period (1-3 weeks) which will be pre-specified before the patient starts treatment, plus the length of CRT treatment (6.5 weeks= 45 days) plus follow-up duration (12 weeks = 84 days). At final analysis, patients without a DLT will have completed the DLT period unless they withdrew early. The MTD will be the dose level with posterior mean DLT rate closest to the target toxicity level of 48% when the dose-toxicity model is updated for the final analysis.

For the definition of a DLT, see Appendix 4.

Secondary outcomes

To assess the safety and toxicity profile of atovaquone in combination with radical concurrent chemotherapy

Adverse events from the first dose of atovaquone to six months post completion of CRT will be presented (see Appendix 3).

To confirm feasibility of measuring hypoxia metagene signature using 3'RNA-Seq in diagnostic NSCLC samples

To assess agreement of FMISO PET-CT with plasma miR-210 level and tumour hypoxia gene expression pre-treatment with atovaquone

Hypoxia assessed using the baseline FMISO PET-CT scan will be measured using tumour to blood ratio (TBRvolume) (ml).

Plasma miR-210 level will be derived from the baseline blood sample.

Baseline is at week -2/-3 prior to receiving the first dose of atovaquone.

To assess agreement in changes in FMISO PET-CT and plasma miR-210 level following two weeks (+/- 7 days) of atovaquone

Change in FMISO PET-CT will be the % change between TBRvolume (ml) derived from the baseline and pre-CRT scans.

Change in plasma miR-210 level will be the % change between miR-210 level derived from the baseline and pre-CRT blood samples.

Baseline is at week -2/-3 prior to receiving the first dose of atovaquone and pre-CRT is at week -1 (two weeks (+/- 7 days) after starting atovaquone and prior to receiving any CRT.

To assess the tumour response rate at three months following treatment

Tumour response will be measured according to the RECIST V1.1 criteria, this endpoint will be the response taken at the assessment three months after the completion of CRT (at 13-15 weeks post-CRT).

Response will be classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or "not evaluable" (NE), as measured from their baseline scan to three months post-CRT scan. See Appendix 2 of the protocol for response category criteria.

The protocol states 'To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements must be confirmed by two observations at least 4 weeks apart.' The Chief investigator has confirmed that it was never the intention for patients to receive a second scan to confirm CR/PR status, furthermore it is not standard of care and it is not included in the MPE dose assessment or IRAS application, so it cannot be done with our current ethics so the disease response will only be taken at the three months post CRT visit. There is currently no plan to update the protocol to amend this minor error.

To be assigned a status of stable disease (SD), tumour measurements must have met the SD criteria at least once, a minimum of six weeks after study treatment is started.

Should rapid tumour progression occur before the completion of treatment, the patient will be classified as having early progression (EP).

Tumour response should be classified as "not evaluable" (NE), only when it is not possible to classify it under another response category (e.g., when baseline and/or follow-up assessment is not performed or not performed appropriately).

Exploratory outcomes

To assess the relationship between plasma atovaquone levels and hypoxia response as measured by FMISO PET-CT and plasma miR-210 level

Plasma atovaquone levels (µM) will be derived from the pre-CRT blood samples.

Hypoxia response will be measured using TBRvolume (ml) derived from the baseline and pre-CRT FMISO PET-CT scans.

Plasma miR-210 level will be derived from the baseline and pre-CRT blood samples.

6.2 Analysis Methods

Primary analysis

To determine the maximum tolerated dose (MTD), and therefore recommended phase II dose (RPTD), of atovaquone when combined with radical concurrent chemoradiotherapy

All trial patients who received at least one dose of atovaquone will be included in the primary analysis. The same analysis is used during dose escalation as for the final analysis.

The analysis will follow the TiTE-CRM. A two-parameter logistic model will be used to model the relationship between dose and toxicity i.e. the dose toxicity curve (DTC). Dose recommendations following the first two evaluable patients will be made using all current toxicity data as follows:

- Data for patients who have completed the DLT assessment period or experienced a DLT will contribute full information to this model.
- Data for patients who have not completed the DLT assessment period will contribute partial information to the model, weighted proportionally to the observed portion of their time window, and treating them as not experiencing a dose limiting toxicity. The weight function is defined in the equation below as w_j.

There are 4 atovaquone doses which are coded x = 1:4. Assuming dose 1 is the reference dose, d^*, we have treated J patients with dose x_j, $j = 1, \dots J$, then we model the probability of a DLT occurring using the weighted likelihood given by

$$L(\theta) = \prod_{j=1}^{J} \left[\theta_{x_j} * w_j\right]^{y_j} \left[(1 - \theta_{x_j}) * w_j\right]^{1-y_j}$$

where

$$y_j = \begin{cases} 1 \; if \; dlt \; occured \\ 0 \; if \; no \; DLT \end{cases}$$

$g\left(\theta_{x_j}\right) = logit\left(\theta_{x_j}\right) = \log(\alpha) + \beta \log\left(\frac{x_j}{d^*}\right)$ this is the unweighted two-parameter logistic model

$$w_j = \begin{cases} 1 \; if \; y_j = 1 \\ \min\left(1, \frac{u_j}{T_j}\right) \; if \; y_j = 0 \end{cases}$$

u_j = time patient j has been followed for and T_j = total DLT window for patient j = pre-specified run-in time + 45 days + 84 days (note: as patients are followed up in the trial beyond the DLT observation period, u_j can exceed T_j in which case the weight for patient j in the model will still be 1).

Further detail on the chosen prior distributions for the parameters and simulation results is described in Appendix 1.

See Neuenschwander, Branson and Gsponer (2008) and Cheung YK and Chappell R (2000) for descriptions of the model

Dose-escalation rules

At each analysis the dose recommended by the toxicity model will be the dose with posterior mean DLT rate closest to the target toxicity level of 48%, subject to no dose skipping. However in order to escalate to the next dose, there must also be at least one patient on the previous highest dose fulfilling the following criteria:

- Completed ≥1 full cycle of CRT (i.e. at least three weeks of RT)
- Received ≥50% the specified dose of cisplatin
- Taken ≥75% their allocated dose of atovaquone
- Not experienced a DLT

There is no restriction on dose de-escalation.

Early stopping

At each analysis, the TMG will be recommended to stop the trial early for safety if there is greater than 70% probability that the DLT rate at the lowest dose (dose 1) exceeds the target toxicity level of 48% i.e. if P(risk of DLT>0.48|dose = 1, current data) > 0.7, which would suggest the lowest dose is too toxic.

Definition of MTD

The MTD will be the final recommended dose after the trial has completed recruitment and all participants had completed the DLT window (or had a DLT/withdrawn) using all data accumulated in the trial. The MTD will constitute the RPTD.

If the trial stops early for toxicity, the MTD will be assumed to be lower than dose 1 and the RPTD will not be established.

Secondary and tertiary analyses

There will be no formal analysis of the secondary or tertiary objectives. See template in Appendix 3 for tables and figures that will be presented.

6.3 Missing Data

Primary outcome

The trials team will be informed within 24 hrs if a DLT has been identified. Furthermore a dedicated CRF has been designed which captures only the data required for dose-escalation decisions including key treatment compliance data.

Secondary and tertiary outcomes

Every effort will be made for complete collection and recording of data. Any missing scans or missing blood sample collection will be presented with reasons for missingness. The number of available outcome measures for each secondary and tertiary endpoint i.e. TBRvolume values from the FMISO PET-CT scan, miR-210/PK atovaquone values from blood samples and the number of patients with treatment response from the 3 months post-CRT CT/PET-CT scan will be presented.

No data imputation is planned.

6.4 Sensitivity Analysis

Sensitivity analysis on the primary outcome will be carried out:

- On the sensitivity population defined in Section 4.2 at each interim analysis and for the final analysis

- On the primary analysis population but with a toxic scenario, i.e. assuming patients that currently have insufficient follow-up have a DLT, at each interim analysis

The model and analysis method remain the same as described for the primary analysis.

6.5 Pre-specified Subgroup Analysis

No subgroup analyses are planned.

6.6 Supplementary/ Additional Analyses and Outcomes

There are no supplementary or additional analyses planned.

6.7 Harms

This analysis will be based on the primary analysis population and will be presented as given in Appendix 3.

6.8 Health Economics and Cost Effectiveness (where applicable)

There is no health economics and cost effectiveness analysis.

6.9 Meta-analyses (if applicable)

No meta-analysis is planned

7. VALIDATION OF THE PRIMARY ANALYSIS

Before the trial starts, code for generating dose decisions will be validated by creating a large dataset, and comparing results from analysis using standard logistic regression with the trial code. Although results will not be identical due to the differences between frequentist and Bayesian analyses, with fairly vague priors and a large dataset parameter estimates should be similar. Validation will be stored in the statistical eTMF.

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS or R. The relevant package and version number will be recorded in the Statistical report.

Analysis for dose allocation decisions (i.e. TMG reports) and the primary analysis will be carried out using R and OpenBugs, the version number will be recorded in each TMG report. For these analyses, the R package checkpoint() will be used to install R packages as they were on a given date e.g. 13th January 2020 for future reproducibility.

9. REFERENCES

Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics. 2000 Dec;56(4):1177-82

Neuenschwander, Branson and Gsponer (2008). Critical aspects of the Bayesian approach to phase I cancer trials. Stats in Med, 27:2420-2439

10. GLOSSARY OF ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CRT	Chemoradiotherapy
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
RIOC	Radiotherapy and Imaging Oversight Committee
RPTD	Recommended Phase II Dose
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
TiTE-CRM	Time-To-Event Continual Reassessment Method
TMG	Trial Management Group
TSC	Trial Steering Committee

11. APPENDIX 1 (SEPARATE DOCUMENT)

12. APPENDIX 2 (SEPARATE DOCUMENT)

13. APPENDIX 3 (SEPARATE DOCUMENT)

14. APPENDIX 4

Definition of a Dose Limiting Toxicity

DLTs are defined as any of the following occurring between the start of trial treatment until three months post CRT, and assessed by the Principal Investigator as possibly, probably or definitely related to atovaquone and/or to chemoradiotherapy. If an event is believed to be possibly, probably or definitely related to treatment with Durvalumab rather than trial IMPs, it may be reported as an SAE rather than a DLT. DLTs must be reported **within 24 hours** of the site becoming aware.

DLTs will be defined as per NCI CTCAE v4.03 and include:

- Grade ≥4 absolute neutrophil count (ANC) (<0.5 x 10^9/L) for >7 days
- Grade ≥3 febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) lasting >3 days
- Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L)
- Grade ≥3 thrombocytopenia (platelets <25 x 10^9/L)
- Clinically significant bleeding attributed to grade 3 thrombocytopenia or requiring platelet transfusion
- Grade ≥3 oesophagitis
- Grade ≥3 pneumonitis onset within 3 months of starting radiotherapy
- Grade ≥3 nausea or vomiting not controlled by optimal outpatient anti-emetic treatment for ≥5 days
- Grade ≥3 diarrhoea despite optimal outpatient anti-diarrhoeal medication use

- Any toxicity causing a delay of radiotherapy completion by greater than one week
- An elevation of ALT or AST >5 x ULN lasting 8 days or more
- A concurrent elevation of ALT or AST (>3 × ULN) and total bilirubin (>2 × ULN) in whom there is no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation
- Other grade ≥3 effects thought to be clinically significant and directly related to the combination of atovaquone with chemoradiotherapy