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:

ARCADIAN: Atovaquone with Radical ChemorADIotherapy in locally Advanced NSCLC

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Medical Monitor
During office hours: Clinical Queries should be directed to the ARCADIAN Trial Office (details as above) for action.

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Patient Registration: To register a patient on the trial please email the completed and scanned registration form to the ARCADIAN Trial Office: octo-ARCADIAN@oncology.ox.ac.uk.

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PROTOCOL SYNOPSIS

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	**Endpoints**
Primary Endpoint:	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)
Secondary Endpoints:	To assess the safety and toxicity profile of atovaquone in combination with radical concurrent chemotherapy for NSCLC	Adverse events graded per Common Terminology Criteria for Adverse Events (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
	To assess agreement of FMISO PET-CT with plasma miR-210 level and tumour hypoxia gene expression pre-treatment with atovaquone	• Tumour hypoxic volume determined by FMISO PET-CT • Plasma miR-210 level • Hypoxia metagene signature from diagnostic tissue using 3'RNA-Seq
	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
	To assess the tumour response rate at three months (13-15 weeks) following treatment	Response to treatment assessed per Response Evaluation Criteria in Solid Tumours (RECIST) V1.1
Exploratory Endpoint:	To assess the relationship between plasma atovaquone levels and hypoxia response as measured by FMISO PET-CT and plasma miR-210 level	• Plasma atovaquone concentration • Tumour hypoxic volume determined by FMISO PET-CT • Plasma miR-210 level
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	

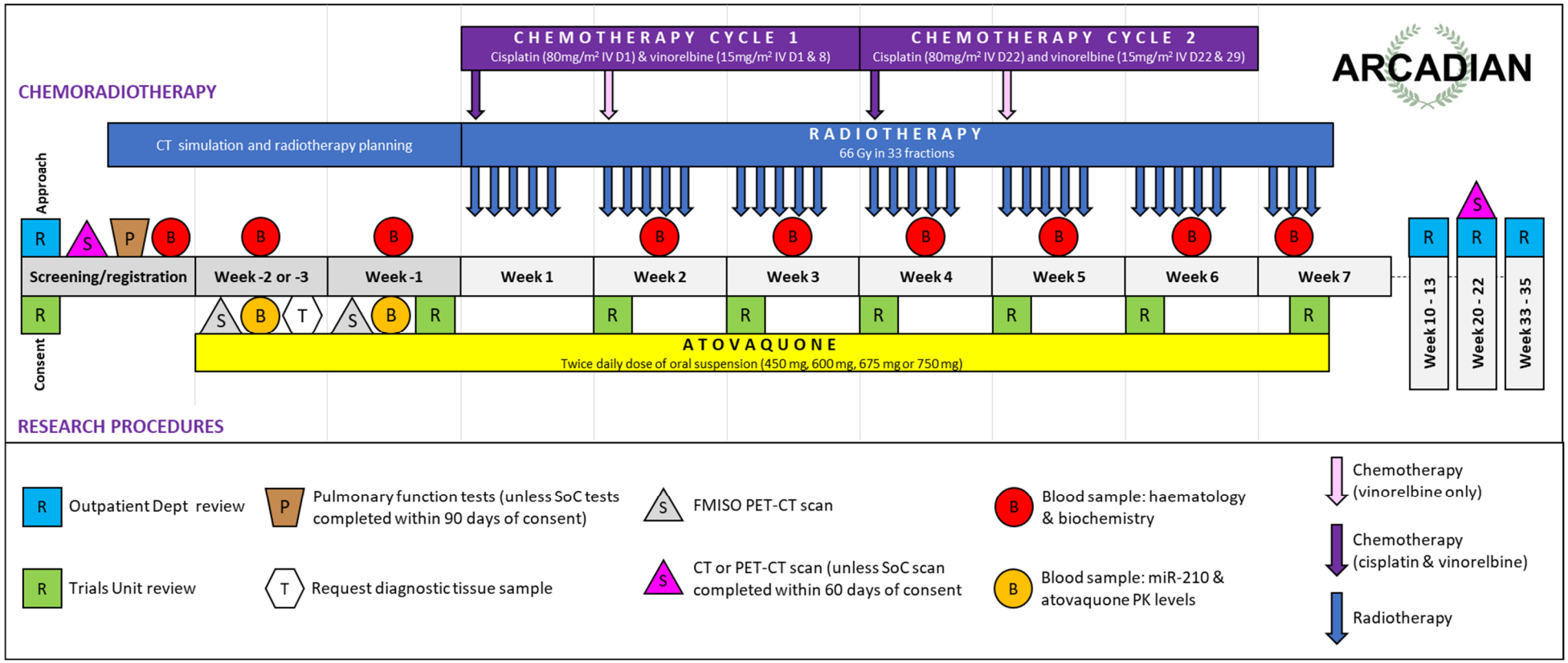
SUMMARY SCHEDULE OF EVENTS

		ATOVAQUONE RUN IN		CHEMORADIOTHERAPY							FOLLOW UP		
Procedure \ **Timing**	**Screening**[a]	**Week -2/-3**	**Week -1**[b]	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**[c]	**Week 10-13** 1 month (3-6 wks) post-CRT	**Week 20-22** 3 months (13-15 wks) post-CRT	**Week 33-35** 6 months (26-28 wks) post-CRT
		Day -21 to -8	Day -7 to -1	Day 1 to 7	Day 8 to 14	Day 15 to 21	Day 22 to 28	Day 29 to 35	Day 36 to 42	Day 43 to 49	Day 64 to 91	Day 134-154	Day 231-245
Informed consent	X												
Vital signs	X	X[d]	X		X	X	X	X	X	X			
Height	X												
Weight	X		X		X	X	X	X	X	X			
Physical exam	X	X[d]	X		X	X	X	X	X	X	X	X	
ECOG performance status	X	X[d]	X		X	X	X	X	X	X	X	X	
Haematology & biochemistry[e]	X	X[d]	X		X	X	X	X	X	X			
Pregnancy test (WOCBP only)	X				X				X		X		
Medical history	X												
Pulmonary function tests (FEV1 and TLCO)	X[f]												
CT or PET-CT scan[g]	X[h]											X[i]	
Atovaquone dispensing		X		New bottle to be dispensed as required, each contains up to 21 days treatment									
Atovaquone treatment completion[j]		XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXXXXXX XXXXXXX	XXX XXX			
Radiotherapy	CT simulation and RT planning			XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXX			
Cisplatin[k]				X			X						
Vinorelbine[l]				X	X		X	X					
Request diagnostic tissue for hypoxia metagene		X											
PK blood sample		X	X										
Research blood sample for hypoxia biomarkers[m]		X	X										
FMISO PET-CT		X	X										
Atovaquone dosing compliance review			X	X	X	X	X	X	X	X			
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT assessment		X[n]	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Commencement of other cancer therapies[0]											X		

[a] Eligibility tests and patient registration should be completed within two weeks of receiving a screening number (see section 4.5)
[b] The end of atovaquone run in appointment (including FMISO PET-CT scan) should be carried out as close to day 1 of CRT as possible (ideally Friday of week -1 with CRT commencing Monday of week 1, but within a maximum of one week prior to commencing CRT)
[c] The week 7 visit should ideally be held on the last day of RT
[d] Week -2/-3 assessments need not be repeated if screening tests have been carried out within 2 weeks of atovaquone dispensing visit
[e] Haematology & biochemistry (Haematology - haemoglobin, white blood cells with differential neutrophils and lymphocyte count and platelets; Biochemistry - sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase and/or alanine aminotransferase and lactate dehydrogenase; International Normalised Ratio). Tests will be carried out locally in site labs

[f] Previously completed standard of care FEV1 & TLCO need not be repeated, provided this is within 90 days of informed consent date
[g] CT or PET-CT of brain/chest/abdomen or chest/abdomen/pelvis, as per local standard of care
[h] Previously completed standard of care PET-CT or CT scans need not be repeated provided this is within 60 days of informed consent date
[i] Patients prescribed Durvalumab may have their follow-up CT scan up to 17 weeks post-CRT (i.e. up to week 24)
[j] Atovaquone taken orally, twice daily, at dose selected per process defined in section 17.3
[k] Cisplatin (80 mg/m^2 IV) administered on D1 & 22
[l] Vinorelbine (15 mg/m^2 IV) administered on D1, 8, 22 & 29
[m] miR-210
[n] This visit falls within the DLT reporting period. However, DLTs will be retrospectively reported from the week -1 visit
[o] E.g. Durvalumab, if clinically indicated

STUDY SCHEMA



ABBREVIATIONS

FMISO	^{18}F-fluoromisonidazole
3'RNA-seq	3' RNA-sequencing
ADR	Adverse drug reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP/PA	Anterior posterior/posterior anterior
AST	Aspartate aminotransferase
ATOM	Atovaquone as Tumour HypOxia Modifier
BD	Twice daily
BP	Blood pressure
BSA	Body surface area
C	Celsius
CAIX	Carbonic Anhydrase IX (9)
CBCT	Cone Beam Computed Tomography
cm	Centimetre
CR	Complete response
CRF	Case Report Form
CRT	Chemoradiotherapy
CT	Computed Tomography
CTA	Clinical Trials Authorisation
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DAHANCA	Danish Head and Neck Cancer Group
DLT	Dose limiting toxicity
D_{max}	Maximum dose
DRR	Digitally reconstructed radiograph
EBUS	Endobronchial ultrasound
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FEV1	Forced expiration volume
FFPE	Formalin-fixed paraffin-embedded
g	Gramme
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General practitioner
GSK	GlaxoSmithKline
GTV	Gross tumour volume
Gy	Gray (radiation dose unit)
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HRA	Health Research Authority
HTA	Human Tissue Act
HV	Hypoxic volume
IB	Investigator brochure
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image-guided radiation therapy
IMP	Investigational Medicinal Product
IMRT	Intensity modulated radiotherapy
INR	International normalised ratio (blood clotting test)

ISF	Investigator site file
ITV	Internal target volume
IUD	Intrauterine device
IV	Intravenous
kV-CBCT	Kilo-voltage cone beam computed tomography
L	Litre
LDH	Lactate dehydrogenase
LPLV	Last visit of the last patient undergoing the trial
m	Metre
MBq	Megabecquerel (unit of radioactivity)
mg	Milligrammes
MHRA	Medicines and Healthcare Products Regulatory Authority
miR-210	A MicroRNA with altered expression in tumour tissue
mL	Millilitre
MLC	Multileaf collimator
mm	Millimetre
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MV	Megavoltage
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluated
NHS	National Health Service
NIHR	National Institute of Health Research
nIMP	Non-Investigational Medicinal Product
NSCLC	Non-small cell lung cancer
OAR	Organs at risk
OCR	Oxygen consumption rate
OCTO	Oncology Clinical Trials Office
OCTRU	Oxford Clinical Trials Research Unit
OPD	Outpatient Department
PCP	Pneumocystis pneumonia
PD	Pharmacodynamics
PD	Progressive disease
PDPP	Protocol decision point plan
PET	Positron Emission Tomography
pg	Picogrammes
PI	Principal Investigator
PK	Pharmacokinetics
PO	Administered orally
PPI	Proton pump inhibitor
PR	Partial response
PRV	Positioning reference volume
PTV	Planning target volume
QA	Quality assurance
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
R&D	Research and development
RA	RapidArc
REC	Research Ethics Committee
RECIST	Response evaluation criteria in solid tumours
RIOC	Radiotherapy & Imaging Oversight Committee
RPTD	Recommended Phase Two Dose
RSI	Reference Safety Information
RT	Radiotherapy
RT/LT	Right/left
RTOG	Radiation Therapy Oncology Group
RTP	Radiation treatment planning
RTTQA	Radiotherapy trials quality assurance

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable disease
SDV	Source data verification
SmPC	Summary of Product Characteristics
SOC	Standard of care
SOP	Standard operating procedure
SUP/INF	Superior/inferior
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised uptake value
TBR	Tumour to blood ratio
TD5/5	Tolerance dose yielding 5% risk of a particular outcome at 5 years
TDS	Three times daily
TiTE-CRM	Time To Event Continual Reassessment Method
TLCO	Transfer factor of the lung for carbon monoxide
TMG	Trial Management Group
µmol	Micromoles
V*x*	Lung volume receiving ≥*X* Gy of radiation
VEGF	Vascular Endothelial Growth Factor
VMAT	Volumetric modulated arc therapy
WBC	White blood cell(s)
WOCBP	Women of child bearing potential

1 INTRODUCTION

1.1 Background

Patient population

Lung cancer is the leading cause of cancer death in the UK with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases [1]. A third of patients with NSCLC present with locally advanced (stage III) non-metastatic disease and treatment with concurrent chemoradiotherapy has become the standard of care for patients with good performance status. However, despite significant improvements in technical radiotherapy delivery, clinical outcomes for patients treated with 'curative intent' remain extremely poor with survival rates at five years largely unchanged at only 15% [2]. Suboptimal locoregional control contributes to these poor outcomes and therefore developing novel radiosensitisers for this purpose represents a significant unmet clinical need for this patient population.

Tumour hypoxia and radiotherapy

Many solid tumours, including NSCLC, are typically dependent upon an abnormal, poorly functioning vasculature for oxygen delivery [3]. Coupled with the high metabolic requirements of many tumours, this leads to an imbalance in oxygen supply and demand. The resulting hypoxic microenvironment is recognised as promoting an aggressive phenotype, including resistance to drug treatment, and increased metastatic potential [4]. Although tumour hypoxia is associated with adverse patient outcomes regardless of which treatment modality is used, the profound radiation resistance caused by tumour hypoxia leads to particularly poor outcomes for patients treated with radiotherapy or CRT [5]. There is therefore significant interest in developing effective hypoxia modifying therapies which can be safely combined with radiotherapy.

Previous hypoxia modifying strategies aimed at overcoming hypoxia-induced radioresistance have primarily focused on improving the oxygen supply to tumours. These have unfortunately yielded only limited success and none are currently in widespread routine clinical use. The reasons for this are multifactorial and include poor trial design, absence of predictive therapeutic biomarkers and the use of sub-optimal hypoxia modifying agents [6]. In particular, the importance of appropriately selecting patients who will benefit from hypoxia targeted therapy has become well-recognised. For example, it has been demonstrated retrospectively that the addition of nimorazole, an oxygen mimetic, to radiotherapy treatment in patients with head and neck cancer (DAHANCA 5) would have resulted in significantly greater clinical benefits (locoregional control and disease specific survival) if a hypoxia gene expression classifier had been used to select patients with hypoxic tumours [7]. In a separate study in this tumour site, patients with tumours classified as hypoxic using ^{18}F-fluoromisonidazole (FMISO) PET-CT imaging had greater benefit from the addition of the hypoxia-activated cytotoxic agent tirapazamine when combined with chemoradiotherapy [8].

Therefore, a paradigm shift in the approach to addressing tumour hypoxia in clinical studies is required to prevent further futile trials in this field, with the focus not only on developing deliverable and more efficacious agents, but also on using hypoxia biomarkers to enable appropriate patient selection for treatment.

This study will be the first trial to combine atovaquone, a promising novel hypoxia modifier with radiation and aims to assess safety whilst developing candidate hypoxia biomarkers to further confirm efficacy and guide future hypoxia trial design.

1.2 Investigational Medicinal Products used in the study

Atovaquone

Atovaquone has EU marketing authorisation and is indicated for acute treatment of mild to moderate Pneumocystis pneumonia (PCP). It is also used in combination with proguanil for malaria prophylaxis. The recommended oral (PO) dose for PCP is 750 mg (5 mL) twice a day (BD) for 21 days.

In vitro studies have demonstrated that atovaquone at clinically relevant concentrations significantly reduces oxygen consumption in a number of tumour cell lines [9]. Subcutaneous murine tumour models have been used to confirm that oral atovaquone causes a significant reduction in tumour hypoxia. Our data suggests that atovaquone causes these effects by reducing oxidative phosphorylation in mitochondria.

750 mg BD oral atovaquone has also been demonstrated to reduce tumour hypoxia in patients with NSCLC in the ATOM (Atovaquone as Tumour HypOxia Modifier) window-of-opportunity study (unpublished data). ATOM participants received 7-17 days treatment with atovaquone, shorter than the treatment duration for PCP, but sufficient for blood atovaquone levels to reach steady state.

Atovaquone was exceptionally well tolerated by ATOM participants with very few side effects reported. The ATOM trial protocol included an option to escalate atovaquone dose to 1000 mg BD if no effect on tumour hypoxia was seen at 750 mg BD, however efficacy was seen at 750 mg and therefore the higher dose was not investigated. Higher dosing regimens [750 mg three times daily (n=8) and 1500 mg twice daily (n=8)] have been given safely in HIV infected volunteers [10].

Participants in the ATOM trial were awaiting surgery for NSCLC and received no concurrent chemotherapy or radiotherapy. In recognition that ARCADIAN will combine atovaquone with concurrent chemoradiotherapy (CRT), the first participants will receive a lower dose of atovaquone (450 mg BD). Pre-clinical data gives no indication that atovaquone will exacerbate the side effects of CRT, but such an effect cannot be conclusively ruled out. Escalation to doses of atovaquone up to and including 750 mg BD, if appropriate, will be guided by the Time-to-Event Continual Reassessment Method (TiTE-CRM) statistical model.

ARCADIAN participants will receive two weeks (+/- 7 days) of treatment with atovaquone prior to commencing CRT. As demonstrated in the ATOM trial, seven days of treatment is sufficient to achieve a reduction in tumour hypoxia. Patients will not have their CRT delayed due to enrolment on the trial, as atovaquone run in will occur while patients are waiting for their standard of care CRT to begin. Atovaquone treatment will then continue concurrently with CRT, for a total duration of 59 days (+/- 7 days).

Cisplatin and vinorelbine
Concurrent CRT is the standard of care for patients with locally advanced NSCLC and good performance status. The CRT regime used is variable across the UK with variation in the type of chemotherapy (e.g. cisplatin and etoposide vs. cisplatin and vinorelbine) and the number of cycles of chemotherapy (two or four). Participants in the ARCADIAN trial will receive two cycles of cisplatin and vinorelbine. This has been selected due to being a widely accepted regimen in the UK, and one that is deliverable at the intended research sites. Vinorelbine has also been chosen in preference to etoposide as atovaquone has been found to increase plasma levels of etoposide and its metabolite when given for PCP prophylaxis to children undergoing treatment for acute lymphoblastic leukaemia.

1.3 Other research interventions

Radiotherapy
Concurrent CRT is the standard of care for patients with locally advanced NSCLC and good performance status. There is variation in the radiotherapy regime used across the UK, with schedules delivered as standard of care including 55 Gy in 2.75 Gy fractions, 60 Gy in 2 Gy fractions and 66 Gy in 2 Gy fractions. Participants in the ARCADIAN trial will receive 66 Gy in 33 fractions of 2 Gy. This is an established treatment regimen in the UK and deliverable at the intended research sites.

FMISO PET-CT
The most widely used method for measuring tumour hypoxia in the clinical setting is PET imaging with radiotracers which accumulate in hypoxic tissues, such as ^{18}F-misonidazole (FMISO). This particular method has been shown to be more effective at detecting reoxygenation states than alternative techniques [11]. The imaging and reconstruction protocols on the scanners at Oxford and Edinburgh will be set up by the collaborating physicist to ensure high quality and comparable FMISO PET-CT data from both sites is obtained. Scan analysis will be conducted by a PET-CT consultant radiologist and physicist in Oxford with extensive experience in FMISO PET-CT using well-recognised tumour-to-blood parameters. In the event that FMISO is unavailable (e.g. due to failure in the manufacturing process), trial participants will continue in the study, but will not be required to undergo tumour hypoxia imaging.

FMISO PET-CT technique:
An activity of 370 MBq (+/- 10%) of FMISO will be injected and a 10-minute acquisition image obtained four hours post-injection. CT will be performed for localisation and PET attenuation correction (a 4DCT technique will be used where possible). Tumour outlining will be performed by an experienced PET-CT radiologist and any metastases (nodal or extranodal) identified within the PET field of view also outlined and included in the analysis. A background mean standardised uptake value (SUV_{mean}) should be obtained by outlining blood in the descending aorta. To determine the tumour hypoxic volume (HV), voxel-by-voxel SUVs will be divided by the background SUV_{mean} to provide tumour-to-blood ratio (TBR) values for each tumour voxel. Voxels with TBR ≥ 1.4 will be classified as hypoxic, consistent with previously published data [12]. Volumes of hypoxic voxels before and after atovaquone treatment will be compared and a ≥10% reduction in hypoxic volume (HV) will be defined as a response.

HV measurements will also be compared to plasma hypoxia marker data and hypoxia metagene signature data. Additional information can be found in the separate imaging guidelines document.

1.4 Rationale for the study

Non-clinical

Mathematical modelling studies have suggested that reducing the oxygen demand of tumours is likely to be a more effective way of reducing tumour hypoxia than increasing oxygen delivery [13]. The novel concept of reprogramming tumour cell metabolism by reducing oxidative phosphorylation to decrease the oxygen consumption rate (OCR) has therefore developed rapidly [14]. Recently, the commonly prescribed antimalarial drug atovaquone was demonstrated to cause a rapid reduction in OCR in multiple different tumour cell lines by reducing oxidative phosphorylation through inhibition of complex III of the electron transport chain [9]. Treatment with atovaquone led to the eradication of tumour hypoxia in 3D-spheroid and subcutaneous xenograft models, and caused a marked increase in tumour radiosensitivity in tumour regrowth delay models. The tumour radiosensitising effects of atovaquone appear to be entirely mediated through effects on hypoxia (a tumour-specific phenomenon) as it does not alter intrinsic cell radiosensitivity. Of note, atovaquone is also significantly more effective than the oxygen mimetic, nimorazole [9]. Collectively these data strongly support the hypothesis that adding atovaquone to chemoradiotherapy will improve outcomes without increasing normal tissue toxicity. Furthermore, as atovaquone is well-tolerated and inexpensive we feel it represents an ideal candidate to take forward into clinical testing as a novel radiosensitiser.

Clinical

Atovaquone as a hypoxia modifier clinical proof-of-concept: the ATOM trial

To initiate clinical studies investigating whether atovaquone holds significant promise as a hypoxia modifying and thus radiosensitising drug, a window-of-opportunity clinical trial in patients with operable NSCLC – the 'Atovaquone as Tumour HypOxia Modifier' (ATOM) trial was completed in late 2018. The primary endpoint of this study utilised tumour hypoxia imaging to assess the effect of atovaquone treatment at the top licenced dose of 750 mg BD on tumour hypoxia. FMISO PET-CT scans were arranged at baseline and repeated following approximately 14 days of atovaquone treatment and the tumour HV compared. Tumour regions with a tumour-to-blood FMISO uptake ratio (TBR) ≥1.4 at four hours post-injection were defined as being hypoxic [12]. Of the 15 patients who received atovaquone treatment 11 patients (73%) were classed as responders (defined as ≥10% reduction in HV) with a median reduction in HV of 28% in these patients. Importantly, as expected from decades of clinical experience using atovaquone, we have observed no toxicity associated with atovaquone use during the ATOM study.

Other compounds such as metformin have also previously been shown to reduce OCR and decrease hypoxia in pre-clinical models [15]. However, to the best of our knowledge there is currently no clinical trial data confirming these effects. A recent study combining metformin with radical chemoradiotherapy in locally-advanced NSCLC did not show improvement in clinical outcomes [16]. Moreover, our pre-clinical data suggests that atovaquone causes a much greater reduction in tumour hypoxia than metformin does at clinically achievable concentrations [9]. Therefore, atovaquone is currently the best available compound to decrease tumour hypoxia by reducing OCR and this trial is well supported by both pre-clinical and now emerging clinical data.

Combining atovaquone with chemoradiotherapy in NSCLC

Patients will receive two weeks (+/- 7 days) of atovaquone to ensure stable plasma concentrations (achieved after seven days) and then continue treatment throughout CRT. Atovaquone dose will be assigned as per a TiTE-CRM statistical model. The first trial participants will receive 450 mg BD. In the absence of unacceptable toxicity, subsequent patients will be assigned doses up to and including 750 mg BD.

If this study demonstrates that combining atovaquone with radical CRT for NSCLC is well tolerated and the recommended phase II dose (RPTD) is established, we plan to conduct further trials to investigate its effect on radiotherapy outcomes in this patient population. However, prior to embarking on large efficacy studies, it is important to establish a clear strategy for selection of patients with hypoxic tumours, and therefore patients who are likely to benefit from hypoxia modification with atovaquone by further developing candidate hypoxia biomarkers. It is well-recognised that a lack of hypoxia-dependant patient selection in clinical studies has been responsible for numerous promising hypoxia modifying agents showing only modest clinical benefit and is one of the main reasons why currently no hypoxia treatments are in widespread clinical use. The need for the development and utilisation of hypoxia biomarkers for this purpose is now well-accepted in this field and is one of the important aims of this trial. In addition, such biomarkers would further evaluate hypoxia response to atovaquone, as well as other novel hypoxia modifiers, in future clinical studies.

ARCADIAN hypoxia biomarker strategy

Currently, hypoxia PET-CT imaging with tracers such as FMISO are the most accepted and widely used technique in hypoxia clinical research. However, performing these scans in large studies is prohibitively expensive and associated with significant logistical challenges including limited availability of FMISO and significant impact on radiology department resources. Utilising FMISO PET-CT in large clinical trials, or subsequently integrating this imaging modality into clinical practice to guide clinical decision making, is therefore unlikely to be feasible. As a result, there is a clear need to establish alternative and clinically deliverable biomarkers. In this study we aim to utilise a previously described hypoxia biomarker, microRNA 210 (miR-210), and tumour tissue hypoxia metagene expression analysis, and assess their performance to detect hypoxia by comparing to FMISO PET-CT.

More specifically, under hypoxic conditions miR-210 becomes highly upregulated in response to hypoxia-inducing factors [17]. It has been demonstrated that elevated serum levels of miR-210, as measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR), are indicative of poor clinical outcomes in NSCLC [18]. Additionally, a previously validated hypoxia gene expression signature has been shown to be a prognostic biomarker in different tumour types [19]. In the ARCADIAN trial both these biomarkers will be investigated.

Summary of ARCADIAN hypoxia biomarker aims:

- To confirm the feasibility of measuring the hypoxia metagene signature using RNA sequencing (3'RNA-seq) on diagnostic tissue in patients with NSCLC.

- To assess the agreement of plasma miR-210 levels and tumour hypoxia metagene with FMISO PET-CT to further support their use as measures of hypoxia in NSCLC and to develop a clear strategy for hypoxia-dependant selection of patients for future large efficacy studies.

- To assess agreement in the observed changes in plasma miR-210 levels and FMISO PET-CT following atovaquone treatment. This information will be crucial to not only further establish atovaquone as a hypoxia modifier, but provide important information to guide future trial design, in particular with regards to determining sample size.

2 TRIAL DESIGN

This is a phase I, single arm, open-label trial that will utilise a TiTE-CRM to determine the maximum tolerated dose (MTD) of atovaquone in combination with concurrent CRT in NSCLC. Twenty evaluable participants will be recruited at two centres.

Twice daily oral atovaquone will be added to standard concurrent CRT: 66 Gy in 33 fractions, once daily, 5 days a week (Monday-Friday), with cisplatin (80 mg/m^2 IV on days 1 and 22 of CRT) and vinorelbine (15 mg/m^2 IV on days 1, 8, 22 and 29 of CRT). Whilst awaiting CRT to start, patients will receive two weeks (+/- 7 days) of oral atovaquone to ensure steady state is reached (after seven days). Wherever possible, two weeks of atovaquone treatment should be administered prior to CRT, but in appreciation of the difficulty often experienced in radiotherapy scheduling and planning as well as treatment targets, a +/- 7 days window is permitted. In addition, hypoxia biomarker data will be collected at baseline (start of atovaquone run-in) and following two weeks (+/- 7 days) of atovaquone. Atovaquone will then be continued without break for the duration of CRT with the CRT schedule remaining constant for all patients at both centres. Assessment for DLTs will be from the first scheduled dose of atovaquone until three months after completion of CRT. CT scans performed at the three-month follow up visit will be reviewed to collect tumour response data.

The trial will start at the lowest dose of atovaquone (450 mg BD). Two participants will receive this dose and escalation will only be considered when we have 12 weeks of safety data (a high-risk period of developing dose-limiting toxicity, DLT) for at least one participant at this dose level, thus preventing inappropriate early dose escalation. Following this initial safety run in, eligible patients will be continuously recruited and the TiTE-CRM will be used to recommend the dose of atovaquone for each patient, as detailed in section 17.3.

Refer to the schedule of events and flow chart for details of the study visits and procedures.

2.1 Duration of patient participation

Participants will be in the study for up to 38 weeks. This is composed of up to three weeks of treatment prior to initiation of CRT, 6.5 weeks of CRT and follow-up for six months (26-28 weeks) post CRT (see summary schedule of events).

2.2 Post-trial care and follow-up

Following the last study visit, patients will receive standard care.

3 OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoints/ Outcome measures	Time point(s) of evaluation of this end point
• 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
Secondary Objectives		
• To assess the safety and toxicity profile of atovaquone in combination with radical concurrent chemotherapy for NSCLC	• Adverse events graded per Common Terminology Criteria for Adverse Events (CTCAE) v4.03	• From screening/baseline until six months post completion of CRT
• 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 agreement of FMISO PET-CT with plasma miR-210 level and tumour hypoxia gene expression pre-treatment with atovaquone	• 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)
• 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
• 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
Exploratory Objectives		
To assess the relationship between plasma atovaquone levels and hypoxia response as measured by FMISO PET-CT 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

4 PATIENT SELECTION

Patients will be identified in thoracic oncology clinics in Edinburgh and Oxford Cancer Centres (and referring clinics) and once the decision has been made to proceed with radical concurrent CRT, the trial will be discussed with patients and the patient information sheet provided. Patients will be given at least 24 hours to decide whether to participate and if interested, a consent and screening visit will be arranged.

Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria.

4.1 Eligibility criteria for entry into the study

Inclusion criteria:

A patient will be eligible for inclusion in this study if all of the following criteria apply:

1. Histologically or cytologically confirmed diagnosis of locally advanced NSCLC and selected for treatment with full dose radical concurrent CRT
2. At least one measurable lesion greater than 2 cm maximal length in any direction on routine imaging (CT or PET-CT scan performed in the 60 days prior to consent)
3. Male or female, age $\geq$ 18 years
4. ECOG performance status 0 or 1
5. Adequate pulmonary function tests for thoracic radiotherapy (FEV1 and TLCO, >40% predicted)
6. Haematological and biochemical indices within the ranges shown below:

Lab Test	Value required
Bilirubin	≤1.5 x upper limit of normal (ULN)
ALT and/or AST	≤2.5 x ULN
Creatinine clearance	Calculated creatinine clearance (using Cockcroft-Gault or Wright formula) or measured* creatinine clearance ≥60 mL/min
Absolute neutrophil count	≥1.5x10^9/L
Platelets	≥100x10^9/L
Haemoglobin	≥90 g/L
INR	≤1.5

* The radioisotope method of assessing glomerular filtration rate may be utilised if clinically indicated

7. The patient is willing and able to comply with the protocol scheduled follow-up visits and examinations for the duration of the study
8. Written (signed and dated) informed consent and be capable of co-operating with protocol

4.2 Exclusion criteria:

A patient will not be eligible for the trial if any of the following apply:

1. Pregnant or breast-feeding women, or women of childbearing potential unless effective methods of contraception are used
2. Previous systemic chemotherapy or biological therapy within 21 days of commencing atovaquone treatment
3. Treatment with any other investigational agent as part of a clinical trial within 28 days of study enrolment
4. Previous thoracic radiotherapy
5. Known previous adverse reaction to atovaquone or its excipients
6. Active hepatitis, gallbladder disease or pancreatitis
7. Impaired gastrointestinal function that may significantly alter absorption of atovaquone
8. Concurrent administration of warfarin in the 14 days prior to starting atovaquone
9. Concurrent administration of known electron transport chain inhibitors (e.g. metformin). A wash-out period prior to administration of atovaquone is required (e.g. 4 days for metformin). Refer to section 10.3 for further details.
10. An additional cancer diagnosis that the treating clinician feels may significantly impact planned CRT treatment tolerability or treatment outcome
11. Established diagnosis of pulmonary fibrosis
12. Established diagnosis of connective tissue disorder (e.g. scleroderma or systemic lupus erythematosus)
13. Cardiac morbidity such as angina, myocardial infarction in the previous six months, unstable angina or uncontrolled hypertension, left ventricular failure or severe valvular disease

14. Other serious illness or medical conditions (such as major surgery in the four weeks prior to study entry or uncontrolled infection)
15. Other psychological, social or medical condition, physical examination finding or a laboratory abnormality that the Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results
16. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV (testing is not required as part of trial screening)

4.3 Protocol deviations and waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a clinical study. Changes to the approved protocol need prior approval unless for urgent safety reasons.

Investigators must contact OCTO to obtain guidance and/or clarification as necessary if unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion. OCTO will contact the Chief Investigator or clinical coordinators as necessary. Investigators should not request a protocol waiver to enter a patient who does not satisfy the selection criteria.

The Investigator must document and explain any deviations from the approved protocol. The Investigator should promptly report any important deviations that might impact patient safety, data integrity or be a possible serious breach (see 23.6 below) to the Trial Office. Deviations will be monitored, followed up and any corrective actions put into place as part of central monitoring activities (see the separate Central Monitoring Plan for details).

4.4 Re-screening if patient does not meet inclusion/exclusion criteria first time round

Patients failing the screening process are ineligible for the trial. Patients will not be rescreened unless imaging or lung function tests are not within the required timeframe. In these cases, imaging can be repeated and the patient reconsidered for the trial.

4.5 Patient registration procedure

Trial sites must contact OCTO to check the availability of a screening slot before giving out a patient information sheet. If a slot is available, OCTO will issue a screening number and the patient may then be approached to consider participation. The site should register the participant within two weeks of receiving the screening number or confirm that the patient has declined to participate/failed screening assessments. If more than two weeks are needed to complete registration the Trial Office should be contacted to agree an extension.

Before entering a patient onto the trial, the Principal Investigator or designee will confirm eligibility. If in any doubt the Chief Investigator and Trial Office must be consulted before entering the patient. **Protocol waivers should not be requested to enter patients who are not eligible.**

A Screening Log must be kept of all patients considered for the trial, including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the Screening Log must be sent to the Trial Office on request, but **without patient identifiers**. The original log must be retained on site in the investigator site file (ISF).

To register a patient:

After checking patient eligibility, site staff will complete the trial Registration Form. Scan the Registration Form and email to: octo-ARCADIAN@oncology.ox.ac.uk.

The Trial Office will check the submitted form and register the patient on the trial. Confirmation of the patient's trial number will be emailed to the PI & other relevant site contacts. Where possible the assigned dose of atovaquone will be communicated at the same time as trial number, or where further time is needed to complete dose assignment (as per process detailed in section 17.3 and the separate Protocol Decision Point Plan), dose will be confirmed by the Trial Office as soon as possible after registration.

5 TRIAL ASSESSMENTS AND PROCEDURES

Please refer to the Schedule of Events given at the front of this protocol. Details of all protocol evaluations and investigations must be recorded in the patient's medical record for extraction onto the case report form (CRF), with the exception of central laboratory assay results and analysis of research imaging.

5.1 Detailed guidance for trial assessments and procedures

5.1.1 Informed consent

Potential participants will be given a current, approved version of the patient information sheet and consent form. They will also receive clear verbal information about the study detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have at least 24 hours to consider the information provided and the opportunity to question the Investigator, their GP or other independent parties before deciding whether to participate.

The Investigator who obtains consent must be suitably qualified and experienced. All delegates must be authorised by the Principal Investigator to obtain consent. The Investigator is responsible for ensuring that the trial consent procedures comply with current applicable GCP regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be satisfied that the patient has made an informed decision before taking consent. The patient and the Investigator must personally sign and date the current approved version of the informed consent form in each other's presence. A copy of the information and signed consent form will be given to the participant. The original signed form will be retained in the Investigator Site File, whilst a copy is to be filed in the medical record. If the Trust has a different policy to these terms and conditions, sites should discuss this at the stage of site activation before the trial is opened at the site.

Patients will also be asked to consent to collect names and NHS numbers to allow flagging with NHS Digital (and Scottish equivalent) so that long term outcome data can be collected in future ethically-approved trials. This will be an optional question on the standard informed consent form.

5.1.2 Contraceptive/pregnancy counselling

All participants must be advised on the need to use reliable methods of contraception during the study. The advice should include:

- The acceptable methods, including: male or female sterilisation, implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), and abstinence. N.B. abstinence is only acceptable if refraining from heterosexual intercourse during the entire period of risk associated with the study drugs (periodic abstinence is unacceptable). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
- The recommendation that a barrier method should be used in addition to another form of contraception.
- Both males and females should continue to take these precautions for a minimum six months after the last dose of the study drugs.
- That any pregnancy (also applies to female partners of male trial subjects) occurring within six months of the last administration of study drug should be notified by the trial participant to the study team. The pregnancy will be followed up and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be reported, even if the participant is discontinued from the study.

5.1.3 Medical history and concomitant medications

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g. prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within four weeks prior to the first day of atovaquone run-in.

5.1.4 Physical examination

A complete physical examination should be carried out at screening. This should include an evaluation of the head, and the cardiovascular, dermatological, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic case report form (eCRF). Height and weight should be measured and recorded in the eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed if clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

5.2 Pre-dosing evaluations (screening and baseline)

Screening/baseline evaluations are to be conducted within two weeks prior to start of protocol therapy (except CT or PET-CT scanning, which must be within 60 days of informed consent and pulmonary function tests, which must be within 90 days of informed consent). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of trial therapy.

- Written informed consent
- Demographic details: age, sex, and self-reported race/ethnicity
- Medical History (as detailed in 5.1.3)
- Concomitant medications (as detailed in 5.1.3)
- Complete physical examination (as detailed in 5.1.4)
- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, respiratory rate, oxygen saturation and temperature
- Pulmonary function tests for thoracic radiotherapy: FEV1 and TLCO (if standard of care tests have not been done in the 90 days prior to consent)
- Height, weight and body surface area (BSA)
- ECOG performance status
- Blood tests:
    - Haematology - Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and lactate dehydrogenase (LDH)
    - International Normalised Ratio (INR)
- Adverse event assessment (SAEs will be collected from the time a patient consents)
- Pregnancy test (females of childbearing potential only) - serum or urine Human Chorionic Gonadotropin (HCG) test to rule out pregnancy at study entry; results must be obtained and reviewed before the first dose of atovaquone is administered or any ionising imaging is performed.
- CT or PET-CT scan of brain/chest/abdomen or chest/abdomen/pelvis (if standard of care scan has not been done in the 60 days prior to consent)
- Radiotherapy planning (refer to detailed guidance in section 12)

Results of standard of care tests or examinations performed before obtaining informed consent and before the start of trial treatment may be used; such tests do not need to be repeated for screening provided that they have been completed within the specified time window.

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria. The patient should then be registered on the trial (as detailed in section 4.5) before the first dose of trial treatment.

5.3 Evaluations during the study

5.3.1 Evaluations during week -2 or -3 (day 1 of atovaquone treatment)

On the day the first dose of atovaquone is taken:

- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, respiratory rate and temperature*
- Symptom-directed physical examination, if clinically indicated (as detailed in 5.1)*
- ECOG performance status*
- Blood tests:
    - Haematology (as per screening bloods detailed in 5.2)*
    - Biochemistry (as per screening bloods detailed in 5.2)*
    - Atovaquone pharmacokinetics (PK)
    - Plasma marker of hypoxia (miR-210)
- Adverse event assessment (SAEs will be collected from the time a patient consents)
- New or changes to existing medications
- FMISO PET-CT scan (as per detailed guidance provided in trial imaging manual)
- Request retrieval of archival diagnostic tumour sample for research purposes
- Dispense atovaquone and advise patient on dietary requirements

* Week -2/-3 assessments need not be repeated if screening tests have been carried out within 2 weeks of atovaquone dispensing visit.

5.3.2 Evaluations during week -1 (following two weeks (+/- 7 days) of atovaquone treatment)

- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, respiratory rate and temperature
- Weight
- Symptom-directed physical examination, if clinically indicated (as detailed in 5.1)
- ECOG performance status
- blood tests:
    - Haematology (as per screening bloods detailed in 5.2)
    - Biochemistry (as per screening bloods detailed in 5.2)
    - Atovaquone pharmacokinetics (PK)
    - Plasma marker of hypoxia (miR-210)
- Adverse events and DLTs since the previous assessment - clinician to identify clearly in medical notes any AE that is a DLT according to criteria for this protocol
- New or changes to existing medications
- FMISO PET-CT scan (as per detailed guidance provided in trial imaging manual)
- Review patient compliance with atovaquone dosing
- Dispense additional supply of atovaquone if this will be needed prior to next review (opened bottles may be used for up to 21 days)

The week -1 visit (including FMISO PET-CT scan) should be carried out as close to day 1 of CRT as possible. Ideally on Friday of week -1 with CRT commencing Monday of week 1, but within a maximum of one week prior to commencing CRT. Following completion of the week -1 visit and atovaquone run-in patients will commence standard of care chemoradiotherapy in week 1. During chemoradiotherapy the following evaluations are required:

5.3.3 Evaluations during week 1

- Adverse events and DLTs since the previous assessment
- New or changes to existing medications
- Review patient compliance with atovaquone dosing
- Dispense additional supply of atovaquone if this will be needed prior to next review (opened bottles may be used for up to 21 days)

5.3.4 Evaluations during weeks 2, 3, 4, 5, 6 and 7:

Once per week complete the following assessments:

- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, respiratory rate and temperature
- Weight
- Symptom-directed physical examination, if clinically indicated (as detailed in 5.1)
- ECOG performance status

- Blood tests:
    - Haematology (as per screening bloods detailed in 5.2)
    - Biochemistry (as per screening bloods detailed in 5.2)
- Pregnancy test (weeks 2 and 6 only)
- Adverse events and DLTs since the previous assessment
- New or changes to existing medications
- Review patient compliance with atovaquone dosing
- Dispense additional supply of atovaquone if this will be needed prior to next review (opened bottles may be used for up to 21 days)

5.4 End of study evaluations following completion of chemoradiotherapy treatment

5.4.1 Evaluations during 1-month (week 10-13) follow up

- Symptom-directed physical examination, if clinically indicated (as detailed in 5.1)
- ECOG performance status
- Pregnancy test
- Adverse events and DLTs since the previous assessment
- New or changes to existing medications

5.4.2 Evaluations during 3-month (week 20-22) follow up

- Symptom-directed physical examination, if clinically indicated (as detailed in 5.1)
- ECOG performance status
- Adverse events and DLTs since the previous assessment
- New or changes to existing medications
- CT scan

5.4.3 Evaluations during 6-month (week 33-35) follow up

- Adverse events since the previous assessment

Follow-up evaluations

Following end of study evaluations patients will return to follow-up as per standard of care in the NHS.

Patients may commence Durvalumab treatment after CRT is completed, even if they are still within the trial follow up window. Treatment with Durvalumab should be documented on the patient's eCRF. Response rates and number of patients who have been prescribed Durvalumab will be reported in the final analysis.

6 EARLY PATIENT WITHDRAWAL

Treatment Withdrawal

During the course of the trial, a patient may withdraw early from treatment. This may happen for a number of reasons, including:

- Unacceptable toxicity
- AE/SAEs requiring discontinuation
- Loss to follow-up
- Significant protocol deviation or inability to comply with trial procedures
- Clinical decision
- Patient decision

When the patient stops treatment, the 'End of Treatment' Form needs to be completed, and any other relevant CRFs (example SAE Form) and the Trial Office notified within 24 hours. The reason for withdrawing from treatment early, should be clearly documented in the medical records.

Patients who have stopped treatment early should continue to be invited to all follow-up visits and assessments, unless patient consent for follow-up is withdrawn.

Participants have the option to consent to NHS Digital follow-up. This will entail completion of a separate tracing sheet which will contain the participant's name and NHS number, and will therefore be kept securely by the Trial Office. This will enable future ethically-approved trials to trace participants' outcome data for long term follow up.

Consent Withdrawal
Consent withdrawal means that a patient has expressed a wish to withdraw from the study altogether. Under these circumstances, the site needs to document all relevant discussions in the patient notes and notify the Trial Office, which will allow the office to mark all future CRFs as not applicable.

Data and samples collected prior to participant consent withdrawal will be used for trial analysis. Participants who initially consented to be registered with NHS Digital or equivalent will remain on the system so that important long term follow up data can be requested from NHS Digital, unless the patient specifically requests that permission is withdrawn to do so.

Under these conditions, Investigators are still responsible for following up any SAEs until resolution.

6.1 Patient evaluability and replacement

Patients will not be replaced since the TiTE-CRM uses all accumulated data. However, the TMG may decide to recruit an additional patient if drop-out occurs early in the treatment schedule for reasons other than a DLT. The dose allocated to the additional patient may not necessarily be the same, as this will be determined by the TiTE-CRM model, taking into account accumulated toxicity data at that time point. In the specific situation where one of the first two patients needs to be replaced, the dose allocated to the additional patient will be 450 mg bd, to ensure this dose level is evaluated before escalating to higher doses as per detailed process in section 17.3.

All patients who receive at least one dose of atovaquone will be evaluable for the safety analysis. All patients who commence chemoradiotherapy treatment within the study will be evaluable for response.

7 SAMPLES FOR LABORATORY ANALYSIS

7.1 Samples to be analysed in local Trust's laboratories

Diagnostic Laboratories
Samples for haematology and biochemistry analysis will be labelled with standard patient identifiers and sent to the local hospital diagnostic laboratory. Results will be processed in the standard way and entered into the routine hospital reporting system. Samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice.

Pathology
The routine diagnostic pathology samples and additional research samples taken at diagnosis will also be labelled, processed and reported according to local hospital protocols. Where sufficient diagnostic material is available, tissue should also be submitted for central laboratory analysis, as detailed in the following sections and separate Sample Handling Manual.

7.2 Samples to be sent to and analysed in a Central Laboratory

During weeks -2/-3 and week -1, additional blood samples of approximately 25 mL will be taken in order to evaluate plasma atovaquone concentration and hypoxia biomarker levels.

7.2.1 Pharmacokinetic assays

For atovaquone PK studies, plasma will be retained and dispatched to a central laboratory for HPLC plasma atovaquone concentration measurement (refer to Sample Handling Manual for specific details).

7.2.2 Plasma hypoxia marker (miR-210)

For plasma hypoxia biomarker analysis, plasma will be retained and dispatched to a central laboratory for qRT-PCR measurement of miR-210 (refer to Sample Handling Manual for specific details).

7.2.3 Hypoxia metagene expression

In cases with sufficient diagnostic tissue, a section of formalin-fixed paraffin-embedded (FFPE) tissue will be obtained and sent to a central laboratory for tumour tissue extraction and hypoxia metagene analysis using the 3'RNA-seq method. This is the optimal technique available to obtain such data from limited and low quality FFPE tissue samples, as is often the case in NSCLC.

More specifically, a previously validated hypoxia gene expression signature will be measured using diagnostic biopsy FFPE samples. We will utilise 3'RNA-seq as it has clear advantages over alternative and now more dated sequencing and array techniques. 3'RNA-seq can accurately estimate gene expression even if applied to low quality or degraded samples and it requires only 100 pg total RNA input. This is an important consideration in our patient population, as diagnostic tissue can often be very scarce. Importantly, modern RNA-seq techniques are relatively inexpensive and when performed on already obtained diagnostic tissue can be easily incorporated into larger clinical studies, or potentially routine diagnostic work-up thereafter.

We will not require patients to undergo additional tissue sampling in appreciation of the difficulty and often repeated attempts required to obtain sufficient diagnostic tissue in this patient population. Also, given the short time window to get patients on treatment and to start CRT, mandating additional tissue may result in a delay in treatment that we feel would be unacceptable.

7.2.4 Summary of samples/assays to be taken during the study

The full list of samples required for central laboratory analysis is as follows:

Time Point	Week -2 or -3	Week -1
Blood sample for PK analysis	X	X
Blood sample for plasma biomarker (miR210)	X	X
Request diagnostic tissue sample for hypoxia metagene	X	

Trial sites will be provided with a separate Sample Handling Manual with detailed arrangements for sample collection, immediate processing, labelling and shipment. Whenever possible, all blood samples will be taken at the same time as blood samples are taken prior to chemotherapy, therefore minimising discomfort and inconvenience to the patient.

7.3 Labelling and confidentiality of samples sent

All samples sent to central analytical laboratories will be labelled with the trial code, trial patient number, and date taken. Should a laboratory receive any samples carrying unique patient identifiers the recipient must immediately obliterate this information and re-label.

7.4 Clinical reporting of exploratory research assay results

The results of central laboratory research assays are exploratory and are not intended to influence the individual patient's medical care. Findings will not be reported routinely to the responsible clinician except in the unlikely event that the result might be beneficial to the patient's clinical management.

7.5 Trial sample retention at end of study

The Chief Investigator has overall responsibility for custodianship of the trial samples. Laboratories are instructed to retain any surplus samples pending instruction from the Chief Investigator on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research study, any surplus samples may be retained for use in other projects that have received ethical approval. Hence, any surplus study samples and study information may be transferred to a licensed tissue bank where they will be stored for use in any future ethically approved medical research. Patients are required to authorise these procedures by signing the consent form. This will identify them by name and/or patient study number, and will be sent to the tissue bank along with their samples. Patients can withdraw permission to use their samples in these ways at any time, without affecting their participation in the study. Banked samples will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

7.6 Withdrawal of consent for sample collection and/or retention

A patient may withdraw consent to provide samples for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in the medical record and will inform the Trial Office accordingly. The Investigator should discuss with patients the valuable use of samples that have already been provided and under circumstances where these samples have already been processed, it would not be possible to destroy such samples.

7.7 Correlative hypoxia biomarker studies

Where possible, data from imaging and plasma hypoxia markers from the ARCADIAN trial will be combined with such data obtained from the ATOM trial to increase the patient sample size.

8 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

The trial is investigating the use of atovaquone suspension in combination with chemoradiotherapy. Atovaquone, cisplatin and vinorelbine are all considered Investigational Medicinal Products (IMPs) in this trial due to the investigation of these drugs being used in a novel combination.

8.1 Treatment dose

Atovaquone

Atovaquone doses to be tested are listed in the table below. The dose received by each participant will be decided per the process detailed in section 17.3. All doses are given orally (PO) and twice daily (BD).

Atovaquone dose level	Atovaquone dose
Level 1 (starting)	450 mg PO BD
Level 2	600 mg PO BD
Level 3	675 mg PO BD
Level 4	750 mg PO BD

Cisplatin and vinorelbine

Two 21-day cycles of cisplatin and vinorelbine chemotherapy will be given concurrently during radiotherapy treatment, as follows:

Chemotherapy agent	Chemotherapy dose	Timing of dose
Cisplatin	80 mg/m^2	Days 1 & 22
Vinorelbine	15 mg/m^2	Days 1, 8, 22 & 29

It is acceptable for chemotherapy to commence up to two days after radiotherapy is started. Any delays to chemotherapy treatment during cycle one should result in a corresponding delay to cycle two (see section 8.3.2).

8.2 Duration of treatment

Atovaquone

Patients will receive two weeks (+/- 7 days) of atovaquone prior to starting CRT, treatment will then continue concurrently with CRT. The last dose of atovaquone will be on the morning of the last fraction of radiotherapy. Total duration of atovaquone treatment will be 59 days (+/- 7 days), unless stopped earlier for toxicity or any other reason.

Cisplatin and vinorelbine

Patients will receive two 21-day cycles of cisplatin/vinorelbine as part of their CRT treatment. Chemotherapy will commence (along with RT) on day 1 in week 1, with the last dose of vinorelbine administered on day 29 (week 5). This will follow two weeks (+/- 7 days) of atovaquone treatment, which will be continued throughout CRT. Altogether, patients will receive chemotherapy on 4 days during the trial (unless omitting doses is clinically indicated). Details of chemotherapy treatment received will be recorded in the eCRF.

8.3 Management of drug administration

Atovaquone

Patients will be instructed to take atovaquone oral suspension twice daily with each dose self-administered using a provided syringe, preferably in the morning and evening, and at approximately the same time each day. The bioavailability of atovaquone is increased up to three-fold when administered with fat containing food. Patients will therefore be asked to take atovaquone with a meal, if possible one containing a high fat content (e.g. butter, whole milk, cheese, ice cream, eggs, etc.).

If a patient misses a dose, the dose should be taken later, provided the patient remembers within four hours. If the patient does not remember within four hours, the missed dose should be omitted. Doses should not be doubled to make up for missed doses. If a patient vomits after taking the suspension, the dose should not be replaced.

Cisplatin and vinorelbine

Cisplatin and vinorelbine chemotherapy should be administered concurrently with radiotherapy, as detailed in section 8.1.2. Cisplatin and vinorelbine will be supplied from hospital stock and administered according to local practice and SmPC guidelines. Dispensing labels must be completed for all patients, but trial-specific labelling of these chemotherapy drugs is not required. On days where chemotherapy is delayed for administrative reasons (for example, holidays or weather), this will not be considered a protocol deviation, provided the full planned dose of radiotherapy is administered. Omissions of cisplatin should be resumed as soon as possible. Single-day vinorelbine omissions due to holidays or weather, or for other clinically indicated reasons do not need to be reinstated.

Days 1 & 22
Pre-chemotherapy hydration • 1 L 0.9% sodium chloride infusion over 2 hours
Pre-chemotherapy medications • Dexamethasone • Mannitol (if urine output <100 mL/hr) • A 5-HT3 antagonist and NK1 antagonist may be given
Chemotherapy • Cisplatin – 80 mg/m^2 infusion in 500 mL of 0.9% sodium chloride over 1 hour • Vinorelbine – 15 mg/m^2 supervised infusion in 50 mL of 0.9% sodium chloride over 5 minutes
Post-chemotherapy hydration • Cisplatin – 1 L 0.9% sodium chloride / 10 mmol magnesium sulphate / 20 mmol potassium chloride infusion over 2 hours • Vinorelbine – 100 mL 0.9% sodium chloride infusion (first 3 minutes supervised at 600 mL/hr, then 1000 mL/hr to finish)
Take home drugs • Dexamethasone • Ciprofloxacin • Movicol sachet • Cyclizine*

Days 8 & 29
Chemotherapy • Vinorelbine – 15 mg/m^2 supervised infusion in 50 mL of 0.9% sodium chloride over 5 minutes
Take home drugs • Ciprofloxacin

See section 10 for details of supportive medications.

* Note that **metaclopramide must NOT be given** as an antiemetic, as it may alter plasma levels of atovaquone (see section 10 for further details).

Patient monitoring and management of hypersensitivity and extravasation will be as per local hospital policy.

8.4 Special precautions

Atovaquone

Unopened bottles of atovaquone have a shelf life of 12 months when stored at room temperature (not exceeding 25°C). If room temperature is expected to exceed this, bottles should be kept in a cool, dark location. Bottles may be refrigerated if necessary, but should never be placed in the freezer. Opened bottles of atovaquone suspension can be stored for up to 21 days at room temperature, but must be kept away from extremes of heat or moisture (so should not be kept, for example, in a bathroom).

Cisplatin and vinorelbine

Refer to cisplatin and vinorelbine SmPCs for special warnings and precautions for use.

8.5 Actual versus ideal body weight

Atovaquone

Not applicable - atovaquone dose will not be adjusted for body weight.

Cisplatin and vinorelbine

Doses of cisplatin and vinorelbine will be calculated for each patient based on actual weight. The patient's weight should be recorded prior to every chemoradiotherapy cycle to determine dose of chemotherapy. See section 8.7 for BSA calculation.

8.6 Dose modification

Atovaquone

If chemotherapy is reduced or stopped, atovaquone should be continued.

If RT is suspended for less than seven consecutive days for reasons other than toxicity, atovaquone treatment can also be suspended (at the clinician's discretion), but restarted with RT.

If RT is interrupted for less than seven days due to toxicity, atovaquone should be stopped when RT is discontinued and not restarted.

Interruptions of RT of greater than seven days for toxicity reasons (related to IMPs, CRT or the combination thereof) are defined as DLTs, in which case atovaquone should be permanently discontinued.

If a patient experiences toxicity that is thought to be directly related to atovaquone treatment and not controlled by supportive medication, then atovaquone should be discontinued, rather than the dose reduced, and it should not be restarted. Investigators are encouraged to discuss such decisions to discontinue atovaquone with the CI. See section 9 for effects defined as dose limiting toxicities and reporting procedure.

Single agent atovaquone treatment is not usually associated with significant side effects and as this drug has been prescribed for many years it has a well-established toxicity profile. It is not expected that addition of atovaquone to CRT will increase side effects, however this may occur and will be reported as part of the safety and DLT assessment, if applicable.

Cisplatin and vinorelbine

The following dose modification schedule is recommended for haematological and biochemical abnormalities on chemotherapy. As each patient's clinical circumstances are unique, these are intended as a guide only.

Haematology for cisplatin:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Chemotherapy dose
≥1.5	And	≥100	100%
<1.5	Or	<100	Delay one week and reassess
<1.0	–	–	Delay one week, give additional 5 days antibiotics and reassess

Haematology for vinorelbine:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Chemotherapy dose
≥1.5	And	≥100	100%
<1.5	And	<100	Omit
Febrile neutropenia	Or	Grade ≥4 haematological toxicity	75%

Renal dysfunction for cisplatin:

Creatinine clearance (mL/min)	Chemotherapy dose
>60	100%
40-60	62.5%
<40	Discontinue

Oto- and neurotoxicity for cisplatin:

Ototoxicity or neurotoxicity	Chemotherapy dose
< Grade 3	100%
≥ Grade 3	Discontinue

Hepatic dysfunction for vinorelbine:

ALT		Total bilirubin	Chemotherapy dose
<5 x ULN	And	<2 x ULN	100%
>5 x ULN	And/or	>2 x ULN	70%

If urea is more than 7.0 mmol/L or creatine clearance drops by 20%, discuss with Principal Investigator. Precede day 8 & 29 vinorelbine with 500 mL 0.9% sodium chloride infusion.

Add daily GCSF if patient has had:

- Previous chemotherapy
- Previous pneumonectomy
- Febrile neutropenia during previous chemotherapy cycle
- Chemotherapy delay of >7 days due to neutropenia
- Grade 4 neutropenia

8.7 Calculating and recalculating BSA/doses

Atovaquone

Not applicable – atovaquone dose is not calculated according to body surface area (BSA).

Cisplatin and vinorelbine

BSA is calculated according to the DuBois and DuBois formula. If a patient's weight changes by ≥ 10% from baseline (see section 8.5), then drug doses should be recalculated. If a patient's weight changes by <10% the dose may be adjusted according to local policy/clinician's discretion, but is not an absolute requirement.

8.8 Dose capping and dose banding

Atovaquone

Not applicable – no doses are to be capped/banded.

Cisplatin and vinorelbine

No doses are to be capped.

Dose banding can be applied according to local policy. The Trials Office will request each site to state up front whether or not dose banding will be used.

8.9 Compliance

Atovaquone

Patients will be asked to report if they have any missed doses of atovaquone during their weekly clinic visits. Data should be recorded in the clinical record and entered into an eCRF in order to monitor compliance for dose decisions.

Patients should be asked to bring any unused/remaining trial medicines (empty, open or unopened) with them to each clinic visit. At each visit, the patient's supply of atovaquone should be checked and an additional bottle dispensed if needed prior to the next visit (after first opening, the suspension may only be stored for up to 21 days). The trial visits at which resupply is required will vary between participants, dependent on the duration of atovaquone treatment received prior to starting CRT.

Accountability logs are required for atovaquone. Site staff will collect and measure patient returns which must be recorded on the drug accountability log. Accountability Logs should be returned to the Trial Office as requested.

Cisplatin and vinorelbine
Cisplatin and vinorelbine compliance will be monitored via the clinical record.

8.10 Management of overdose

Atovaquone
There is no specific antidote for atovaquone, however several cases of overdose have been published – none of which resulted in life-threatening or fatal side effects [20]. Patients experiencing toxicities upon mis-dosing or over-dosing will be treated at the discretion of the Investigator with adequate supportive care and followed until full recovery.

Cisplatin and vinorelbine
Refer to guidance provided in the SmPC documents for cisplatin and vinorelbine regarding recommendations following overdose.

Administration of a dose of trial drug exceeding that permitted by the trial protocol should be notified to the Trial Office. Any toxicity resulting from administration of an overdose of trial drug should also be reported as an adverse event/serious adverse event (as appropriate) as per reporting processes detailed in section 14.

9 DOSE LIMITING TOXICITY

9.1 Definition of a Dose Limiting Toxicity

All patients who have received at least one dose of atovaquone will be evaluable for DLTs.

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 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

Dose limiting toxicities must be reported **within 24 hours** of the site becoming aware using the SAE form (even if the event does not meet the definition of an SAE). Scan the form and email as an attachment to octo-safety@oncology.ox.ac.uk.

See section 14 for safety reporting procedures.

DLTs will be processed to support dose decisions according to procedures detailed in Section 17 and the separate Protocol Decision Point Plan.

10 OTHER TREATMENTS (NON-IMPS)

10.1 Support medication

Patients will be given the following medication as part of their CRT treatment:

Days 1 & 22 (cisplatin & vinorelbine)
Pre-chemotherapy medications • Dexamethasone - 12 mg IV • Mannitol (if urine output <100 mL/hr) - 10%, 500 mL IV over 30 minutes post-chemo A 5-HT3 antagonist and aprepitant may be given, according to local policy (e.g. Akynzeo®)
Take home drugs • Dexamethasone - 4 mg BD for 3 days following cisplatin treatment • Ciprofloxacin - 250 mg BD for 14 days following vinorelbine treatment • Movicol sachet - 1-2 daily, 14 days following cisplatin treatment, then as needed • Cyclizine* - 50 mg TDS for up to 5 days following cisplatin treatment, then as needed

Days 8 & 29 (vinorelbine only)
Take home drugs • Ciprofloxacin - 250 mg BD for 14 days following vinorelbine treatment

* It is important that nausea should be managed with antiemetic therapy **other than metoclopramide,** which may alter plasma levels of atovaquone.

10.2 Concomitant medication and non-drug therapies

Concomitant medication to treat diarrhoea such as loperamide given at a standard dose should be considered for grade 1-2 diarrhoea along with oral hydration and dietetic measures. More severe diarrhoea should be treated appropriately at the Investigator's discretion and may include IV fluid administration. Skin rash will be managed at the Investigator's discretion and may include the use of anti-histamines and corticosteroids.

Corticosteroids may be given to patients who have been prescribed Durvalumab to manage the side effects of immune-mediated reactions.

Other concomitant medication may be given as medically indicated. All patients will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous four weeks prior to the first treatment visit. They must also inform the Investigator about any new medication started while in the trial. Details (including indication, doses, frequency and start/stop dates) of concomitant medication taken during the trial until the completion of the off-study visit must be recorded in the medical record and the appropriate CRF.

10.3 Prohibited therapies and (potential) drug interactions

Patients should not be prescribed other anti-cancer or investigational therapies while participating in this study (with the exception of Durvalumab, see Section 5.4). However, if there is evidence of disease progression on completion of CRT and there is clinical need to commence anti-cancer therapy, this should not be withheld and the CI should be informed.

Concurrent administration of warfarin within the 14 days prior to starting atovaquone is prohibited.

Concurrent administration of known electron transport chain inhibitors is prohibited (due to possible alteration of hypoxia interpretation). Commonly used electron transport chain inhibitors include:

- Metformin
- Phenformin
- α-Tocopheryl succinate
- Arsenic trioxide

Metformin must not be administered within four days before starting atovaquone. For other electron transport chain inhibitors, the length of wash-out period will be discussed and agreed by the trial team with reference to the available drug reference data.
Concomitant administration with the following drugs is prohibited because they are known to reduce plasma concentrations of atovaquone:

- Rifampicin or rifabutin
- Metoclopramide (give an alternative antiemetic if required)
- Tetracycline
- Efavirenz or boosted protease-inhibitors

Atovaquone can increase the levels of etoposide and its metabolite. Atovaquone has high plasma protein binding and should therefore be used in caution with other drugs with high protein binding and narrow therapeutic windows.

Please refer to the Summary of Product Characteristics (SmPC) for atovaquone for further details.

Drug	**Details**	**Timescale (if applicable)**
Warfarin	Atovaquone may increase plasma levels of warfarin	Prohibited during trial and within 14 days prior to starting atovaquone
Metformin	Electron transport inhibitors, possible alteration of hypoxia interpretation	Prohibited during trial and within 4 days prior to starting atovaquone
Phenformin		Contact trial team
α-Tocopheryl succinate		Contact trial team
Arsenic trioxide		Contact trial team
Rifampicin or rifabutin	Reduce plasma concentration of atovaquone	Prohibited
Metoclopramide		
Tetracycline		
Efavirenz		
Other boosted protease-inhibitors		
Etoposide	Atovaquone can increase plasma levels of etoposide and its metabolite	Prohibited

Refer to the SmPCs for cisplatin and vinorelbine for details of drug interactions.

11 DRUG MANAGEMENT

11.1 Drug supplies

Atovaquone (IMP) will be purchased by the site pharmacy as commercial stock. Any brand of 750 mg/5 mL oral suspension atovaquone may be procured, according to local policy. The arrangements for funding atovaquone will be detailed in the trial site agreement.

Cisplatin and vinorelbine should be supplied from trial site's own stock and funded locally.

All supportive medication is to be sourced and funded locally.

11.2 Drug ordering and receipt

The local Investigator and Pharmacy are responsible for liaising to ensure that commercial supplies of atovaquone, cisplatin and vinorelbine are held in stock as necessary to supply the recruited patients.

11.3 Handling and storage

Unopened bottles of atovaquone may be stored at controlled room temperature up to 25^{o}C. Unopened containers have a shelf life of 12 months. After first opening, the suspension may be stored for up to 21 days. Patients who are continuing treatment with atovaquone must therefore be resupplied with a new bottle of atovaquone at intervals of 21 days or less.

11.4 Labelling

The responsible Pharmacy will ensure that IMP supplies dispensed for trial use are appropriately labelled in accordance with all applicable regulatory requirements.

- Atovaquone – bottles that are given to patients should also be labelled with full information regarding the trial. These labels are included in the Pharmacy File provided by OCTO upon site activation.
- Cisplatin & vinorelbine – chemotherapy drugs administered as standard of care will be labelled as per local practice and are not required to have trial specific labels.

Emergency contact details will be supplied to the participant on the trial label.

Local labels can be used as long as they contain exactly the same information as in the labels provided, and must be approved by OCTO prior to use.

11.5 Dosing dispensing

Atovaquone
Atovaquone will be dispensed in a high-density polyethylene bottle with child resistant polypropylene closure, containing atovaquone suspension. A measuring syringe will be included. One bottle contains sufficient drug for up to 21 days treatment for one patient at 750 mg per dose. Therefore, participants taking lower doses of atovaquone will have excess medication left after 21 days which must be returned to the clinical trial pharmacy for compliance monitoring and disposal.

Cisplatin and vinorelbine
Refer to the SmPCs for full prescribing information and details of drug reconstitution, administration and stability.

11.6 Drug accountability

Drug accountability records must be maintained for atovaquone. Drug Accountability Logs are provided. Hospitals may amend the Drug Accountability Logs provided or use their own documentation if they capture all the information requested on the Drug Accountability Logs, but must be approved by OCTO prior to use.

For cisplatin and vinorelbine, pharmacy records must detail; patient's name/identifier, date and dose dispensed and batch number of drug. It is expected that pharmacy aseptic unit worksheets will be sufficient.

11.7 Drug returns from patients

Patient returns of atovaquone should be returned to the clinical trial pharmacy. End of treatment returns should be made on or following the last day of radiotherapy. Pharmacy staff will collect and measure patient returns using the weight of the returned bottle (minus bottle standard weight), converted to fluid in mL. Returns must be recorded in the patient's Accountability Log and a scanned copy sent to the Trial Office as requested.

11.8 Drug destruction

Any patient returns of atovaquone should be disposed of at site according to local hospital policy, after first weighing returned bottles to document the volume of solution returned. A record of destruction should be kept as per local policy.

Destruction of unused/expired cisplatin and vinorelbine is also per local hospital policy.

11.9 Occupational safety

Atovaquone is not expected to pose an occupational safety risk to site staff under normal conditions of use and administration.

Cisplatin and vinorelbine are cytotoxic and appropriate precautions should be taken during handling, as per local hospital policy.

12 RADIOTHERAPY

Patients registered for the trial will receive concurrent thoracic radiation therapy consisting of 66 Gy in 33 fractions, once daily, 5 days a week (Monday-Friday), prescribed according to the International Commission on Radiation Units and Measurements (ICRU) 83. Radiation treatment should ideally commence on a Monday, but delays of up to two days are acceptable. Prior to inclusion of any patient on this study, the radiation oncologist will evaluate the thoracic CT scan in order to ensure that the treatment volumes are unlikely to significantly exceed the specified normal tissue constraints.

12.1 Simulation

Patients should be positioned on a flat CT couch using appropriate immobilisation device (e.g. vac-bag, wingboard), preferably in the supine position with arms supported above their head. Simulation will consist of a free-breathing helical CT image for target and organs at risk (OAR) delineation and dosimetry planning, followed by a free-breathing 4D-CT. The extent of the helical planning CT scan must be sufficient to include all potential organs at risk. As a guide, contiguous axial slices will be obtained from the upper cervical spine to the lower edge of the liver, taking care to include all lung parenchyma on the planning scan. Axial slices of 2.5 mm should be utilised, but up to 3 mm is permitted. The extent of the 4D-CT should be equivalent to the helical planning CT scan. In the absence of 4D-CT, fluoroscopy may be used to assess tumour motion. Intravenous contrast should be used for central tumours to differentiate disease from blood vessels or atelectasis. This will be specifically requested on the planning request form and given at the time of the planning scan.

Please refer to the separate radiotherapy guidance document for details on volumes, margins, organ at risk constraints, plan optimisation and quality assurance to ensure that standard of care is consistent across sites.

12.2 Planning

6-10 MV photons will be used for planning using a forward-planned intensity modulated radiotherapy (IMRT) treatment plan. Where possible, this should utilise volumetric modulated arc therapy (VMAT), but static field is permissible.

12.3 Treatment delivery

Treatment requires a linac with CBCT capabilities for IMRT/VMAT delivery. Weekly clinical assessments are required during CRT.

As a minimum, daily online CBCT should be performed for the first three days of treatment, and then at least weekly thereafter. Local procedure should be followed regarding set up queries.

Additional imaging (at the treatment unit or in pre-treatment) can be used if there is any uncertainty regarding patient positioning.

On days when both chemotherapy and radiation are administered, it is recommended that radiation should follow within 30 to 60 minutes of the completion of chemotherapy or post-cisplatin hydration. When this is not feasible for logistical reasons, radiotherapy may be delivered out with this window and may be prior to the administration of chemotherapy or post-cisplatin hydration. On days where chemotherapy is delayed for administrative reasons (for example, holidays or weather), this will not be considered a protocol deviation, provided the full planned dose of radiotherapy is administered.

12.4 Management of unscheduled gaps

ARCADIAN patients will be treated as RCR category 1 patients. Unscheduled gaps in radiotherapy should be limited to no more than 2 consecutive planned fractions, where possible.

Where delivery of radiotherapy is interrupted for reasons other than toxicity, RCR guidance on managing unscheduled interruptions should be followed:

- Where possible, patients should be transferred to a matched linear accelerator on the day of interruption

Where this is not possible, clinicians should consider the following:

- Treating patients at weekends and on public holidays
- Treating patients twice daily, with a minimum of 6 hrs between therapies
- Using Biologically Equivalent Dose (BED) calculations to derive an alternative treatment schedule with an alternative number of fractions to complete the course in the planned time, but perhaps accepting a higher BED in normal tissues
- Treating patients with extra fractions where compensation cannot be achieved within the original planned time

Any toxicity resulting in delay in radiotherapy for greater than one week is considered a DLT (see section 9).

12.5 Chemoradiotherapy toxicity

The acute adverse events expected for chemoradiotherapy are summarised in the following table. This data is derived from the combined cohorts of the IDEAL-CRT trial [21]. This nonrandomised phase 1/2 trial enrolled stage II and III NSCLC patients, who received RT doses between 63 Gy and 73 Gy in 30 once-daily fractions over 40 days, concurrent with 2 cycles of cisplatin and vinorelbine.

Toxicity*	**Rate (%)**
Oesophagitis (Grade <3)	94
Oesophagitis (Grade ≥3)	6
RT pneumonitis (Grade <3)	97
RT pneumonitis (Grade ≥3)	4
White blood cell decreased	13
Lymphocyte decreased	11
Neutrophil decreased	15
Lung infection	22
FEV decreased	15
Dyspnoea	9
Co-diffusing capacity decreased	7
Fatigue	7
Pulmonary embolism	7
Late radiation fibrosis	6
Nausea	6
Anorexia	5
Chest pain	5
Hearing impairment/reduction/loss	5
Vomiting	5
Febrile neutropenia	4
Diarrhoea	2

*Data from IDEAL-CRT [21].

Radiation toxicity will be graded as per NCI CTCAE v4.03. The management of radiation side effects should be as per local protocol. The Investigators are advised to suspend the use of chemotherapy given with radiation if they believe that continuing chemotherapy administration will compromise delivery of full-dose radiation in an uninterrupted manner.

12.6 Radiotherapy quality assurance

The QA programme for the study will be co-ordinated by the National Radiotherapy Trials QA (RTTQA) Group. The details of the programme can be found on the RTTQA website, www.rttrialsqa.org.uk. In the first instance, any queries regarding radiotherapy quality assurance for ARCADIAN should be addressed to the national Radiotherapy Trials QA group (RTTQA) contact (rttrialsqa.enh-tr@nhs.net).

Pre-Trial QA Programme
All Pre-Trial QA is completed prior to centre activation for the trial and consists of:

- Facility Questionnaire (FQ): General and trial specific questions on equipment, software, techniques and procedures to be used for the trial.
- Dosimetry Audit: Centres must have successfully completed the IMRT credentialing programme through the RTTQA group.

On-trial QA Programme
Real time review of all patients will be required for the first patient treated in each site and there will be timely retrospective review of radiotherapy for the rest of the patients. All images, outlines, plan and dose data (DICOM) should be submitted to the RTTQA contact who will co-ordinate review of the data to check protocol compliance as each patient is recruited.

13 EVALUATION OF RESPONSE

13.1 Measurement of disease for solid tumour

For the secondary endpoint of tumour response rate, disease must be measured according to the RECIST V1.1 criteria, where applicable, given in Appendix 2.

13.2 Tumour assessment

A clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the study treatment. The same methods that detect lesions at baseline will be used to follow these lesions throughout the study. 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.

Baseline evaluations
These will include radiological measurements of the extent of disease by CT or PET-CT scan of brain/chest/abdomen or chest/abdomen/pelvis, with or without contrast as requested by the treating clinician. All areas of disease present must be mentioned (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded 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 recommended to aid external independent review of responses (see separate Central Monitoring Plan for details).

Evaluation after end of treatment
Tumour assessment will be repeated three months after completion of CRT. All lesions measured at baseline must be measured at the subsequent disease assessment, and recorded on the scan report. All non-measurable lesions noted at baseline must be reported as present or absent.

Investigators must ensure that their 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 criteria.

13.3 Tumour response

All patients will have their response classified as complete response (CR), partial response (PR), early progression (EP) or “not evaluable” (NE), as measured from their baseline scan to their follow up scan at the end of treatment. See Appendix 2 for response category criteria.

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.

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).

The applicable overall response category for each visit that includes disease assessment must be recorded in the medical record for inclusion in the appropriate CRF in OpenClinica.

13.4 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 three weeks of treatment that is not a toxic death.

14 SAFETY REPORTING

The Investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study.

Adverse event monitoring starts from the time the patient consents to the study until the patient's last study visit (at 6 months post-CRT). During this timeframe, all AEs which are serious must be reported to OCTO, as detailed in Section 14.6. This includes SAEs occurring before patients are registered. Should an Investigator become aware of any study drug-related SAEs following this period, these must also be reported as stated below.

All reportable AEs will be followed to a satisfactory conclusion. Any reportable drug-related AEs that are unresolved at the end of treatment visit are to be followed up by the Investigator until resolution or stabilisation.

All AEs reported to the Trial Office will be processed according to internal SOPs. The Trial Office may request additional information for any AE as judged necessary.

14.1 Adverse Event Definitions

An Adverse Event or experience (AE) is any untoward medical occurrence in a study subject temporally associated with the administration of an investigational medicinal product (IMP) or a comparator product, whether or not considered related to the IMP or a comparator product. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and/or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

A Serious Adverse Event (SAE) is any AE, regardless of dose, causality or expectedness, that:

Results in death	
Is life-threatening	This refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalisation or prolongs existing inpatient hospitalisation	In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
Results in persistent or significant incapacity or disability	This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which do not constitute a substantial disruption.

Is a congenital anomaly or birth defect	
Is any other medically important event	Defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any new primary cancer must be reported as an SAE. Pregnancies occurring within six months of the end of CRT must also be reviewed as to whether they meet SAE criteria (see section 15). **Any event meets the definition of a DLT should be reported as an SAE (even if it doesn't meet the definition of an SAE).**

All dose-limiting toxicities should be notified to the Trial Office via the SAE expedited reporting system, even where the event does not meet the definition of an SAE as defined above (see section 14.6 for procedure).

An Adverse Drug Reaction (ADR) is an AE which is considered to be causally related to any dose of the IMP. This means that a causal relationship between the IMP and the AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An Unexpected Drug Reaction is an adverse drug reaction, the nature or severity of which, is not consistent with applicable product information (referring to information in SmPC or Investigator's Brochure, IB).

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unapproved investigational product or SmPC for an approved product).

14.2 Clinical laboratory abnormalities and other abnormal assessments as AEs and SAEs

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. electrocardiograms, X-rays and scans) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above. **By definition, all CTCAE Grade 3 or 4 laboratory abnormalities should usually be reported as SAEs.** However, if a lab result is categorised as Grade 3 or 4 but did not fulfil the safety reporting criteria for an SAE (asymptomatic, not life threatening, no intervention), it is the clinician's decision whether to report the event. If the event is not reported the reason why should be documented in the patient notes.

If a laboratory abnormality is part of a diagnosis, the diagnosis should be reported as an AE/SAE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g. record thrombocytopenia rather than decreased platelets). Discuss with clinician regarding significance.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

14.3 Determining adverse event causality

A Serious Adverse Reaction (SAR) is a SAE that may be related to any IMP either on its own or in combination with RT. The assessment of "relatedness" must be determined by a medically qualified individual and is primarily the responsibility of the PI at site or agreed designee. AEs that will be considered related will include any AE that is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using the following:

Classification	Relationship	Definition
Drug-related	Definitely related	• Starts within a time related to the study drug administration *and* • No obvious alternative medical explanation
	Probably related	• Starts within a time related to the study drug administration *and* • Cannot be reasonably explained by known characteristics of the patient's clinical state
	Possibly related	• Starts within a time related to the study drug administration *and* • A causal relationship between the study drug and the adverse event is at least a reasonable possibility
Not drug related	Probably not related	• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.
	Definitely not related	• The AE is definitely not associated with the study drug administered

The Investigator must endeavour to obtain sufficient information to confirm the causality of the adverse event (i.e. relation to surgery, study drug, background treatment, other illness, progressive malignancy etc.) and give their opinion of the causal relationship between each AE and study drug. 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 specialist opinion.

14.4 Reference safety information (RSI) for assessment of expectedness

The reference safety information (RSI) for the trial which lists all the expected side effects associated with trial treatment is:

- **For atovaquone:** section 4.8 of the SmPC for atovaquone.
- **For cisplatin:** section 4.8 of the SmPC for cisplatin.
- **For vinorelbine:** section 4.8 of the SmPC for vinorelbine.

Please note that the list of expected side effects in the atovaquone SmPC are those listed for treatment of mild to moderate Pneumocystis pneumonia and in patients who are intolerant of co-trimoxazole therapy. It is therefore possible that in this study population other side effects may occur, or the patient might suffer a more severe reaction.

Equally, the list of expected side effects in the SmPCs for cisplatin and vinorelbine are those listed for patients receiving standard chemoradiotherapy or chemotherapy alone. It is therefore possible that in this study population, where combination of atovaquone is used with standard chemoradiotherapy, other side effects may occur, or the patient might suffer a more severe reaction.

A copy of the current approved version of the RSI documents must be held in the Investigator Site File for reference. The SmPCs used as RSI are the versions provided by OCTO (approved for use in this trial by the MHRA). It is not specified that any particular brand of cisplatin or vinorelbine must be prescribed, however irrespective of the brand prescribed, the RSI to be referenced is provided by OCTO. N.B. this may not be the latest SmPC version available online. Any change or update to the RSI during the trial will be made via a substantial amendment.

Expected AEs due to chemoradiotherapy are listed in section 12.5.

14.5 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

All SUSARS will be reported to the Responsible Authority and main REC by the Trial Office within the required timelines:

- Fatal or life threatening SUSARs will be reported within seven days of the Trial Office receiving the initial report. Any additional significant information will be reported within eight days of sending the first report.
- All other SUSARs will be reported within 15 days of the Trial Office receiving the initial report. Any additional, significant information must be reported within a further 15 days.

In addition, other safety issues qualify for expedited reporting where they might materially alter the current risk assessment of an IMP or be sufficient to change IMP administration or the overall conduct of the trial.

14.6 Expedited reporting of SAEs

The following SAE reporting requirements apply regardless of the Investigator's assessment of the causality or expectedness of the SAE. All SAEs should be notified to the Trial Manager by phone or email and reported on the trial SAE report form (see SAE report form and completion guidelines). This should be completed, scanned and emailed within **24 hours** of becoming aware of the event to:

Pharmacovigilance Office, OCTO
Email: octo-safety@oncology.ox.ac.uk
Tel no: 01865 617082

If the SAE has not been reported within the specified timeframe, a reason for lateness must be provided when sending the SAE Report Form.

Investigators should also adhere to their local Trust/Board policy for incident and SAE reporting in research.

14.7 Follow-up of Serious Adverse Events

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE is a suspected SUSAR, then follow up information must be provided as requested by the Trial Office.

If new or amended information on a reported SAE becomes available, the Investigator should report this on a new SAE form using the completion guidelines.

SAEs that are considered to be probably or definitely unrelated to any trial intervention will not be followed up and monitored.

14.8 Reporting Adverse Events on the CRF

All AEs, including Serious AEs must be recorded on the eCRF for registered patients, unless otherwise specified in section 14.9. The information provided will include date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome and relationship of the AE to study drug. Any concomitant medications or any other therapy used to treat the event must be listed. The Investigator will provide an "other" cause for serious AEs considered to be unrelated to the study drug. Sites should ensure data entered into the eCRF is consistent with the SAE report information where applicable.

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

Terms and Grading of Events

All adverse events and toxicities must be graded according to the NCI Common Terminology Criteria for adverse events (NCI CTCAE) Version 4.0 (currently up to Version 4.03). Toxicity grades should be recorded on the eCRF. These will be coded by OCTO to the MedDRA version current on the date of MHRA approval of the trial.

14.9 Events exempt from being reported as AE/ SAEs

Progression of underlying disease

Disease progression and resultant death will be captured on the CRF. Adverse events including hospitalisation that are clearly consistent with disease progression will not be reported as individual AE/SAEs. Clinical symptoms of progression will only be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms, but is not supported by tumour measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments.

Death on study

Death due to disease under study is to be recorded on the Death CRF form, providing the death is not unexpected or if a causal relationship suspected. The Investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to the study IMP or other protocol treatment intervention is suspected.

Elective admissions and supportive care

Elective admissions to hospital for patient convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting. Hospital admission for the following supportive care procedures are considered standard for this patient group and should not be reported as SAEs:

- Non-emergency admission for feeding tube placement
- A visit to accident and emergency or other hospital department for less than 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anti-cancer therapy in the absence of any other SAEs

14.10 Informing Investigators of new safety information

Regular dose decision meetings will be held during which new safety information will be disseminated and discussed. Principal Investigators should attend such meetings, or send an appropriate representative.
Principal Investigators are responsible for briefing their study team and onward transmission to their R&D office as appropriate. The Trial Office or the Chief Investigator will ensure that all Investigators are kept informed in a timely manner, as new safety profile information becomes available.

14.11 Summary of trial safety reporting requirements

Event	DLT	SAE	AE/SAE	
AE/SAE defined as Dose limiting toxicity (DLT) Defined as per NCI CTCAE v4.03	**Email SAE reporting form within 24 hours**		**Report in AE CRF**	**Non-reportable**
Grade ≥4 absolute neutrophil count (ANC) (<0.5 x 10^9/L) for >7 days	**X**		**X**	
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	**X**		**X**	
Infection (documented clinically or microbiologically) with grade 3 or 4	**X**		**X**	

neutropenia (ANC <1.0 x 10^9/L)				
Grade ≥3 thrombocytopenia (platelets <25 x 10^9/L)	**X**		**X**	
Clinically significant bleeding attributed to grade 3 thrombocytopenia or requiring platelet transfusion	**X**		**X**	
Grade ≥3 oesophagitis	**X**		**X**	
Grade ≥3 pneumonitis onset within 3 months of starting radiotherapy	**X**		**X**	
Grade ≥3 nausea or vomiting not controlled by optimal outpatient anti-emetic treatment for ≥5 days	**X**		**X**	
Grade ≥3 diarrhoea despite optimal outpatient anti-diarrhoeal medication use	**X**		**X**	
Any toxicity causing a delay of radiotherapy completion by greater than one week	**X**		**X**	
An elevation of ALT or AST >5 x ULN lasting 8 days or more	**X**		**X**	
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	**X**		**X**	
Other grade ≥3 effects thought to be clinically significant and directly related to the combination of atovaquone with chemoradiotherapy	**X**		**X**	
Medically important events in the context of this trial	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non-reportable**
Events believed to be possibly, probably or definitely related to treatment with Durvalumab rather than trial IMPs		**X**	**X**	
AE/SAEs, abnormal assessments and laboratory results	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non-reportable**
AE is life-threatening		**X**	**X**	
AE requires in-patient hospitalisation or prolongs existing inpatient hospitalisation		**X**	**X**	
AE results in persistent or significant incapacity or disability		**X**	**X**	
AE is a congenital anomaly or birth defect		**X**	**X**	
AE is any other medically important event		**X**	**X**	
All other grade ≥3 AEs, assessments, abnormal laboratory results, if clinically significant		**X**	**X**	
All other grade ≤2 AEs, assessments, abnormal laboratory results, if clinically significant			**X**	
Grade ≥3 laboratory results not fulfilling safety reporting criteria		**X[1]**	**X[1]**	
Disease progression and death	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non-reportable**
Clinical symptoms, assessments or laboratory results associated with disease progression				**X**
Hospitalisation for disease progression				**X**
Non-emergency admission for feeding tube placement				**X**
A visit to accident and emergency or other hospital department for less than 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)				**X**
Admissions as per protocol for a planned medical/surgical procedure				**X**
Routine health assessment requiring admission for baseline/trending of health status				**X**
Medical/surgical admission other than to remedy ill health and planned prior to entry into the study				**X**
Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention				**X**
Admission for administration of anti-cancer therapy in the absence of any other SAEs				**X**
Death		**X[2]**	**X[3]**	

[1] If a lab result is categorised as Grade 3 or 4 but did not fulfil the safety reporting criteria for an SAE (asymptomatic, not life threatening, no intervention), it is the clinician's decision whether to report the event. If the event is not reported the reason why should be documented in the patient notes.

[2] If death is possibly related directly to atovaquone or the combination of atovaquone + radiotherapy +/- chemotherapy.

[3] Providing the death is not unexpected or if a causal relationship is not suspected. The investigator must clearly state whether a causal relationship to atovaquone + radiotherapy +/- chemotherapy is suspected, and if so, whether the death was expected or unexpected.

15 PREGNANCY

Pregnancies (in a participant or partner) occurring while participating in this trial require expedited reporting. A pregnancy form should be completed, scanned and emailed to the Trial Office within the same timelines as an SAE. All reported pregnancies should be followed and the outcome reported using the same form. If the outcome of the pregnancy meets any of the criteria for seriousness, it must also be reported as an SAE. Examples of pregnancy outcomes that are SAEs include reports of:

- Congenital anomalies or developmental delay, in the foetus or the child
- Foetal death and spontaneous abortion
- Suspected adverse reactions in the neonate that are classified as serious

Women who become pregnant should be withdrawn from trial treatment immediately. Any pregnancy occurring up to the patient's last study visit (i.e. in the six months following CRT) should be reported by the participant to the Trial Office.

16 DEFINING THE END OF TRIAL

For this study the end of the trial is defined as: "The last visit of the last patient undergoing the trial (LPLV)".
The study will be stopped when:

- The stated number of patients to be recruited is reached.
- The stated objectives of the study are achieved.

The Sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

17 STATISTICAL CONSIDERATIONS

17.1 Study design

This is a phase I, single arm, open label, two-centre study. The primary objective is to identify the MTD, and thus RPTD, of atovaquone when combined with concurrent CRT in NSCLC using a Bayesian TiTE-CRM design.

The CRM is a model-based method for finding the maximum tolerated dose (MTD) under the defining monotonicity assumption which posits that toxicity increases monotonically with increasing dose, and that efficacy also increases with increasing dose. The objective is to find the dose with a probability of experiencing a Dose Limiting Toxicity (DLT) close to a pre-specified target toxicity level. The TiTE-CRM is a modified version of the CRM that allows late-onset toxicities to be accounted for without fully observing a patient before recruiting the next and is therefore particularly advantageous for radiotherapy trials where toxicities are often observed later than in studies using systemic therapy alone. A major advantage of the TiTE-CRM is the fact that it uses all current accumulated information to decide which dose to assign the next patient. A further advantage of this design is that it will be able to include partial information on patients who could not be formally evaluated for DLTs due to withdrawal, treatment discontinuation or death, that is unrelated to treatment within the DLT assessment period (from week-2/-3 to three months post-CRT). In addition, the method results in shorter study duration as it is not necessary for a patient to be observed for the full observation period before recruiting the next patient, and also more patients are treated close to the MTD.

Toxicity will be scored according to NCI CTCAE v4.03 with DLT definition as stated in Section 9. The trial aims to identify the MTD which is the dose associated with no more than 48% DLT rate (target toxicity level). This is based on the fact that standard concurrent CRT for NSCLC is often associated with a significant Grade $\geq$3 toxicity rate. Average rates of Grade $\geq$3 oesophagitis are in the region of 25%, although reported rates are variable and can be as high as 48%.
In addition, rates of Grade $\geq$3 pneumonitis as high as 32% have been reported and haematological toxicity when using platinum-doublet chemotherapy can also be significant in this patient population [22]. The atovaquone treatment schedule lasts for up to 9.5 weeks, with patients followed up at the end of the DLT assessment period (at three months post-CRT). An additional follow-up occurs a further three months later (at six months post-CRT), to provide a total trial observation window of up to 38 weeks.

17.2 The TiTE-CRM model

A two-parameter Bayesian logistic model with weak priors will be used. The priors are calibrated to ensure the model provides sensible recommendations early in the trial. With this model we can obtain a distribution for the probability of DLT rate given a specific dose d based on all available data. This is a posterior probability distribution for dose d. We write P(T>0.48|Data, dose = d) to mean the posterior probability that the DLT rate is greater than 48% on dose d, given the data observed so far.

At each dose decision (to assign a dose to the next patient), data for patients who have completed the DLT assessment period or experienced a DLT will contribute full information to this model. Only partial information is known for patients who are currently on trial, within the DLT assessment period, or have stopped treatment in the DLT assessment period for reasons other than a DLT. This partial information contributes to the model, weighted proportionally to the observed portion of their toxicity time window and treating them as not experiencing a DLT.

17.3 Dose selection during the trial

The trial will start at the lowest dose of atovaquone (Dose 1: 450 mg BD). Two participants will receive this dose and escalation will only be considered when we have at least 12 weeks of safety data (high risk period of developing DLT) for at least one participant at this dose level, thus preventing inappropriate early dose escalation. Following this initial safety run in, all eligible patients will be continuously recruited. The TiTE-CRM model will be fitted every time a new patient is registered to recommend the dose of atovaquone from the possible doses: 450 mg, 600 mg, 675 mg or 750 mg. The dose recommended will be the dose with posterior mean DLT rate closest to the target toxicity level, subject to no dose skipping.

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 data provided to the model is binary (1 or 0 for experiencing a dose limiting toxicity or not) and thus information about severity of toxicities is not used. Whilst the model is carefully designed to make sensible decisions based on what the TMG would do in a certain situation, ultimately, the model and decision rules act as a guide. All dose recommendations made by the model will be reviewed by the TMG. The TMG will meet in person, teleconference, or via correspondence, and either approve the dose allocation recommendation or select a different dose on the basis of clinical review of the data. 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 if there is sufficient evidence to suggest that the lowest dose is too toxic. More specifically, we will consider dose level 1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 48%.

We considered a number of scenarios to ensure that the trial design was appropriate. For each scenario, 1000 simulations were performed to assess and improve the model-based trial design. Full details of the simulated performance of the design under these scenarios are available in the Statistical Analysis Plan.

Further detail of the dose selection process will be defined in a separate Protocol Decision Point Plan (PDPP). Data used to inform dose selection will include all relevant data points as defined in the PDPP entered on the trial database prior to performing a data extract for the purpose of running the TiTE-CRM model. The trial management team will work with trial sites to ensure data contained in the database is as complete and accurate as possible prior to each dose selection decision. However, due to the need to make timely decisions, data extracts may have missing data or include data that has not been fully cleaned. Source Data Verification (SDV) of data against the patient notes will only be completed where this is indicated by the trial risk assessment.

17.4 Sample size

The sample size will be 20 evaluable patients.

The estimated accrual for this study is one patient per month and therefore the maximum patient accrual is expected to be completed within 20 months. Additional time is required to allow safety data collection to be collected to ensure all patients complete the DLT assessment window.

17.5 MTD and RPTD definition

The MTD will be the final recommended dose after the trial has completed recruitment using all data accumulated in the trial. The MTD will constitute the recommended phase II dose (RPTD).

17.6 Stopping the trial

The trial will stop for safety if there is sufficient evidence that the lowest dose is too toxic (if $P(T>0.48|\text{dose} = 1, \text{current data}) > 0.7$).

18 STATISTICAL ANALYSIS PLAN

All patients who receive at least one dose of atovaquone, regardless of how much treatment received and follow-up completed, will contribute to analysis. It is therefore important that every effort is made to encourage patients, including those patients who do not receive/complete their allocated treatment, to attend for follow-up clinic visits to avoid bias in the analysis of the results.

A detailed Statistical Analysis Plan will be available from the time the first patient is recruited and will be finalised before any analysis is undertaken. The analysis plan will be written in accordance with the current OCTRU standard operating procedures and will be finalised and agreed by the trial statistician and the CI. Sites must report any unintended deviations to OCTO according to the procedure outlined in site training.

18.1 Inclusion in analysis

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 the time of their first treatment. Adverse events will be summarised by the number of patients experiencing each type of event. The grades and causality will be reported.

18.2 Subgroup analysis

No subgroup analysis is planned.

18.3 Interim Analyses

For each patient recruited after the initial two patients, the TiTE-CRM model will use all current available data to recommend the dose to assign the patient.

18.4 Procedures for reporting any deviation(s) from the original statistical plan

Any deviations from the original statistical plan will be described and justified in the final report.

18.5 Final analysis

Based upon projected accrual rates, this trial is expected to complete recruitment within 20 months of opening to recruitment. Final analysis will be after all patients have either completed their six-month follow up visit, have experienced a DLT, or have withdrawn from the study.

19 TRIAL COMMITTEES

19.1 Trial Management Group (TMG)

The Chief Investigator will chair a TMG responsible for overseeing the successful conduct and publication of the trial.

The TMG will include Chief Investigator, Co-Investigators, Clinical Trial Manager, Trial Statistician and others as required. The TMG will meet as necessary to discuss toxicity data and to decide on dose escalation. TMG membership and decision-making procedures will be documented in the TMG charter.

19.2 Data and Safety Monitoring

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 main outcomes will be analysed as stated in the analysis plan and will not be analysed as an interim analysis. 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

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.

19.3 Trial Steering Committee

The Independent Radiotherapy and Imaging Oversight Committee (RIOC) will act as the 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.

20 DATA MANAGEMENT

20.1 Database considerations

Data management will be performed via a web-based, bespoke trial database (OpenClinica). OpenClinica is a dedicated and validated clinical trials database designed for electronic data capture. See: http://www.openclinica.org. The Trial Office will provide sites with instructions and a video link for training purposes.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file, except where patients have consented to NHS Digital flagging. In this case, patients will have their name and NHS number stored in a secure section of a digital database (RRAMP) for secure transfer to NHS Digital.

20.2 Case report forms (CRFs)

The Investigator and study site staff will ensure that data collected on each subject is recorded in the CRF as accurately and completely as possible. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s). CRF entries will not contain any source data (unless otherwise specified in the completion instructions provided by the Trial Office). It is important to ensure that:

1. The relevant CRFs are completed.
2. All CRF data are verifiable in the source documentation or the discrepancies must be explained.
3. CRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible.
4. Data queries are resolved and documented by authorised study staff in a timely fashion. The reason for the change or correction should be given where appropriate.
5. As much data as possible is entered and cleaned in preparation for each study database lock point.

Note: 'in a timely fashion' means within no more than five working days of the initial event and within 14 days of receipt of a data query, unless otherwise specified.

The above considerations also apply to patients who are withdrawn early. If a patient withdraws from the study, the reason must be noted on the appropriate form and the patient must be followed-up as per protocol.

20.3 Importance of rapid data return

Data analysis will be performed in real-time based on all relevant available data to best inform the atovaquone dose to allocate to the next patient. It will also provide safety monitoring. For these reasons, it is important that data is collected and made available on OpenClinica swiftly, no more than five working days of the initial event and within 14 days of receipt of a data query unless otherwise specified.

In the event of data which is critical to a dose decision, the Trial Office may request that sites provide data in less than 5 working days.

20.4 Accounting for missing, unused, or spurious data.

The statistical analysis plan describes the procedure for accounting for missing, unused or spurious data.

21 CLINICAL STUDY REPORT

All clinical data will be presented at the end of the study as data listings. These will be checked to confirm the lists accurately represents the data collected during the course of the study. The trial data will then be locked and a final data listing produced. The clinical study report will be based on the final data listings. The locked trial data may then be used for analysis and publication.

22 STUDY SITE MANAGEMENT

22.1 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete the delegation log provided prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

22.2 Study site set up and activation

The Principal Investigator leading the investigational study site is responsible for providing all required core documentation. Mandatory Site Training organised by the Trial Office must be completed before the site can be activated. The Trial Office will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the trial database and able to enter patients.

22.3 Study documentation

The Trial Office will provide an Investigator File, Pharmacy File and Radiology File to each investigational site containing the documents needed to initiate and conduct the study. The Trial Office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications, must be retained in the site files as necessary to reconstruct the conduct of the trial.

23 REGULATORY AND ETHICAL CONSIDERATIONS

The Sponsor and Investigators will ensure that this protocol will be conducted in compliance with the UK Clinical Trials Regulations [23], and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

23.1 Ethics, HRA and regulatory approvals

The protocol, patient information sheet, consent form and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC). HRA approval will also be obtained prior to initiating the study.

This study will be conducted under a UK Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Authorisation (CTA). Approval to conduct the study will be obtained from the Responsible Authority prior to initiating the study.

23.2 NHS Research Governance

Investigators are responsible for ensuring they obtain local Trust management agreement to conduct the trial in accordance with local arrangements and policies.

23.3 Protocol amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the Responsible Authority application (if applicable), the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product(s) used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study.

All amendments will be generated and managed according to the Trial Office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC, HRA, regulatory and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients (see below).

It is the 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 Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

23.4 Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the Trial Office IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the Trial Office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The Trial Office will follow written procedures to implement the changes accordingly.

23.5 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined a formal decision to:

1. Interrupt the treatment of subjects already in the trial for safety reasons;
2. Stop recruitment on safety grounds; or
3. Stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The Trial Office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

23.6 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

1. The safety or physical or mental integrity of the subjects of the trial; or
2. The scientific value of the trial”

In the event that a serious breach is suspected, the Trials Office must be contacted within one working day. In collaboration with the CI, the serious breach will be reviewed by the Trials Office and, if appropriate, the Trials Office will report it to the REC committee, Regulatory Authority and the relevant NHS host organisation within seven calendar days.

23.7 Trial Reports

This protocol will comply with all current applicable Regulatory Authority, Research Ethics Committee and Sponsor reporting requirements.

The Trial Office will determine which reports need to be circulated to Principal Investigators and other interested parties. Study sites are responsible for forwarding trial reports they receive to their local Trust as required.

23.8 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

24 EXPENSES AND BENEFITS

The Trial Office is unable to provide reimbursement for patients’ travel expenses incurred by participating in this trial. Sites should, where possible, use local funding arrangements to reimburse patients reasonable travel expenses for visits additional to normal care. Sites should provide clear information to patients on the funding available and any requirements (e.g. production of receipts).

25 QUALITY ASSURANCE

25.1 Risk assessment

A risk assessment and a monitoring plan will be prepared before the study opens and will be reviewed throughout the study if necessary in the light of significant changes while the study is ongoing, or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

25.2 Monitoring

Regular monitoring will be performed according to the monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The Investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report data will be validated using appropriate set criteria, range and verification

checks. The study site must resolve all data queries in a timely manner. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution. For other non-critical data items, OCTO staff may resolve data queries centrally, providing the correct answer is clear. Such changes will be clearly identified in the CRF and the study site informed.

Study sites will also be monitored remotely and/or by site visit as necessary to ensure their proper conduct of the trial. OCTO staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Monitoring reports will be sent to the site in a timely fashion. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance.

Sites will provide copies of the following participant information to the Trial Office on request for remote monitoring purposes. All patient personal identifiers must be obliterated from the information except where explicit consent for release of personal information has been obtained from the patient:

- Participant screening log

25.3 Audit and Regulatory Inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the Trial Office without delay.

26 RECORDS RETENTION & ARCHIVING

During the clinical trial and after trial closure, the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects must be retained in accordance with applicable national legislation and the host institution policy.

Retention and storage of laboratory records and imaging data must also follow these guidelines.

Retention and storage of central laboratory records supporting pharmacokinetic (PK) endpoints and the disposition of samples donated via the trial must also comply with applicable legislation and Sponsor requirements.

It is the University of Oxford's policy to store data for a minimum of five years. Investigators may not archive or destroy study essential documents or samples without written instruction from the Trial Office.

27 PATIENT CONFIDENTIALITY

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of:

- The CRF, where participant initials and year of birth may be added
- The NHS Digital tracing form (if patients have consented to long term follow up) – where participant name and NHS number will be required

All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

The Investigator site must maintain the patient's anonymity in all other communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

28 STUDY FUNDING

The ARCADIAN trial is funded by the Clinical Research Committee (Clinical Trial Awards) on behalf of Cancer Research UK (C34326/A27515). This trial is further supported via the University of Oxford Department of Oncology core clinical and research infrastructure underpinned by strategic research programme grant funds. As a Cancer Research UK funded trial, ARCADIAN is eligible for inclusion on the NIHR portfolio; local research network support should be available at each site taking part to support entry of participants into this trial (via the NIHR in England and in Scotland via NHS Research Scotland).

29 SPONSORSHIP AND INDEMNITY

29.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship and authorise the trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator and Sponsor will be put in place between the parties.

29.2 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

29.3 Contracts/Agreements

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate. A Clinical Trial Agreement (CTA) will be placed between the Sponsor and participating organisations prior to site activation.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

Ownership of intellectual property (IP) generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

30 PUBLICATION POLICY

The sponsor will retain ownership of all data arising from the trial. The intention is to publish this research in a specialist peer-reviewed scientific journal on completion of the trial. The results may also be presented at scientific meetings and/or used for a thesis.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. Authors will acknowledge that the trial was Sponsored by and performed with the support of the Sponsor and other funding bodies as appropriate.

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APPENDIX 1: ECOG PERFORMANCE SCALE

Activity Performance Description	Score

Fully active, able to carry out all on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. 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

APPENDIX 2: MEASUREMENT OF DISEASE - RECIST CRITERIA

RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS

Objective tumour response and time of progression will be measured according to the RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document:

Eisenhauer, EA, Therasse, P, Bogaerts, J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

And also available at: http://www.eortc.be/RECIST

B.1 Measurability of tumour lesions at baseline

B.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumour lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using callipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres) by use of a ruler or callipers. 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.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- **Target Lesions.** When more than one measurable tumour lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. 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*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.
- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

B.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). 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. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm 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 recommended. If feasible, imaging is preferred.
- **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 ≥ 20 mm 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 5 mm 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). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization 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 normalize 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 when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

B.2 Tumour response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. Refer to the table B1and table B2 below.

- Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumour markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.
- Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

- Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment, for example where the tumour burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table B1: Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Patients with Target lesions ± non-target lesions				
CR	CR	No	CR	Normalization of tumour markers All tumour nodes < 10 mm Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with non-target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers All tumour nodes < 10 mm Documented at least once ≥ 4 weeks from baseline
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least four weeks later. The best overall response can be interpreted from Table B2.

Table B2: Response assessment after subsequent scan

Response: First time point	Subsequent time point	BEST overall response	Also requires
CR	CR	CR	Normalization of tumour markers All tumour nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
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	
* May consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.			

B.2.1 Frequency of tumour re-evaluation

Response will only be evaluated at one timepoint.

B.2.2 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met.

B.3 Reporting of tumour response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring before the first per protocol time point of tumour re-evaluation. The responsible Investigator will decide if the cause of death is malignant disease, toxicity or other cause.
Patients for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

APPENDIX 3: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Details of Changes made
N/A	V1.0	30Jan2020	N/A - first version
N/A – amended prior to approval.	V2.0	23Mar2020	On request of MHRA during approval process: - Reduction of dose limiting toxicity rate (target toxicity level) from 50% to 48%. - Amendment of SAE reporting period to reflect AE reporting period (from consent to 6 months post-CRT).