HALT

Targeted therapy with or without dose intensified radiotherapy for oligo-progressive disease in oncogene-addicted lung tumours

PROTOCOL

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The HALT trial is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

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The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. A copy of the current membership of the TMG can be obtained from the HALT Trial Manager at ICR-CTSU.

Protocol Authorised by:

Name & Role	Signature	Date
Dr Fiona McDonald (Chief Investigator)		17/08/2022

This protocol describes the HALT trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of patients outside of this trial.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

HISTORY OF PROTOCOL AMENDMENTS

PROTOCOL VERSION AND DATE	SUMMARY OF CHANGES
Version 2.0, 3rd July 2017	**Clarification on patient participation in other Clinical Trials** • To be considered on a case by case basis by the Trial Management Group with due consideration given to the needs of the patient and impact on the conduct and outcome of both trials.
Version 3.0, 12th October 2017	**Administrative updates** • ISRCTN and ClinicalTrials.gov identifiers added. **Primary endpoint updated** • Progression defined as a ≥ 20% change from baseline in an individual lesion. **Radiotherapy Quality Assurance process updated** • To detail the process of the prospective individual review requirements prior to a patient commencing treatment. • Define the use of the EORTC QA platform. Additional minor clarifications throughout.
Version 4.0, 25th June 2018	**Blood sample updates** • Trial schema updated to provide clarification that there are 6 sampling time points only – at baseline, after the first SBRT fraction (treatment group only), 8 weeks, 5 months and 8 months post-randomisation and upon progression. • Clarification that blood samples are only to be collected from randomised patients. • Confirmation that only further ctDNA blood samples are to be collected upon disease progression. **Exclusion criteria updated** • To confirm that patients with either progressing or newly diagnosed brain metastases not amenable to radical surgery or SRS will be excluded. • Confirmation that treated brain metastases that have remained clinically and radiologically stable for ≥ 6 months are permissible. **Adverse Event reporting updated** • Reporting of radiotherapy grade ≥4 events clarified as being those occurring between 140 days and 1 year after randomisation. • Clarification of SAEs to be assessed by the Chief Investigator, including all SAEs reported as related to the study treatment, which for the purposes of this trial will be SBRT. • Pneumothorax included on expected SAEs related to fiducial marker insertion. • Inclusion of non-UK site safety reporting requirements. **Other updates** • PET-CT scans are permitted. • RECIST analysis not applicable in confirming disease progression • Guidance included that appointments for fiducial marker insertion should be booked in advance of randomisation to avoid delays in commencing SBRT treatment. • Confirm that the ICR Research PACS system is called XNAT. Additional minor clarifications throughout.
Version 5.0, 23rd November 2020	**Administrative updates** • Update to trial contacts, including: scientific coordination, statistician and trial manager. • Updated process for reporting SAEs to the ICR-CTSU, now by email only. **Exclusion criteria**

	• Further clarification around the exclusion criteria for brain metastases to indicate those identified at the time of trial entry, and to give examples of acceptable previous treatments (e.g. palliative radiotherapy or systemic therapy) for brain metastases that have remained stable for ≥ 6 months. **Virtual MDT process updated** • New radiology review process defined, whereby sites who have previously submitted ≥3 patients for vMDT review may have the option of a streamlined process without the need for a full vMDT review if considered appropriate. **Other updates** • Clarify requirements of CT-PET scans provided and expectation for baseline image modality to be used for subsequent follow-up imaging assessments. • Further defined baseline assessments, specifically around toxicity assessments required per treatment group. • Table and footnotes updated for the schedule of assessments to clarify the assessments required for each visit. Additional minor clarifications throughout.
Version 6.0, 11th February 2021	**Eligibility and SBRT suitability updated:** • To treat lesions up to 7cm in size (previously 5cm). • To treat up to and including 5 OPD lesions (previously ≤3) at any one point in time. **Pre-screening imaging timeframe** • Update to allow flexibility up to 1 month prior to registration, for scans conducted outside the trial to be used for trial eligibility assessments.

Version 7.0, 11th August 2021	• **Criteria defined to permit OPD diagnosis based on PET avidity**
	• **Toxicity assessments**
	  ○ Removal of RTOG and continuation of CTCAE only
	  ○ Addition of toxicity assessment 1 year following radiotherapy treatment to capture SAEs up to 1 year as previously described.
	• **Repeat SBRT**
	  ○ Flexibility added around the time interval required for repeat SBRT where considered clinically suitable by the vMDT.
	Additional minor clarifications throughout.

Version 7.1, 17th August 2022	• **Registration and randomisation process updated** • **Minor clarification to eligibility criteria around requirement for a radiologically confirmed response to TKI** • **Updated stratification upon randomisation based on mutation type to EGFR vs. other mutation.** • **Removal of dose tables already contained within the HALT radiotherapy and quality assurance guidelines.**

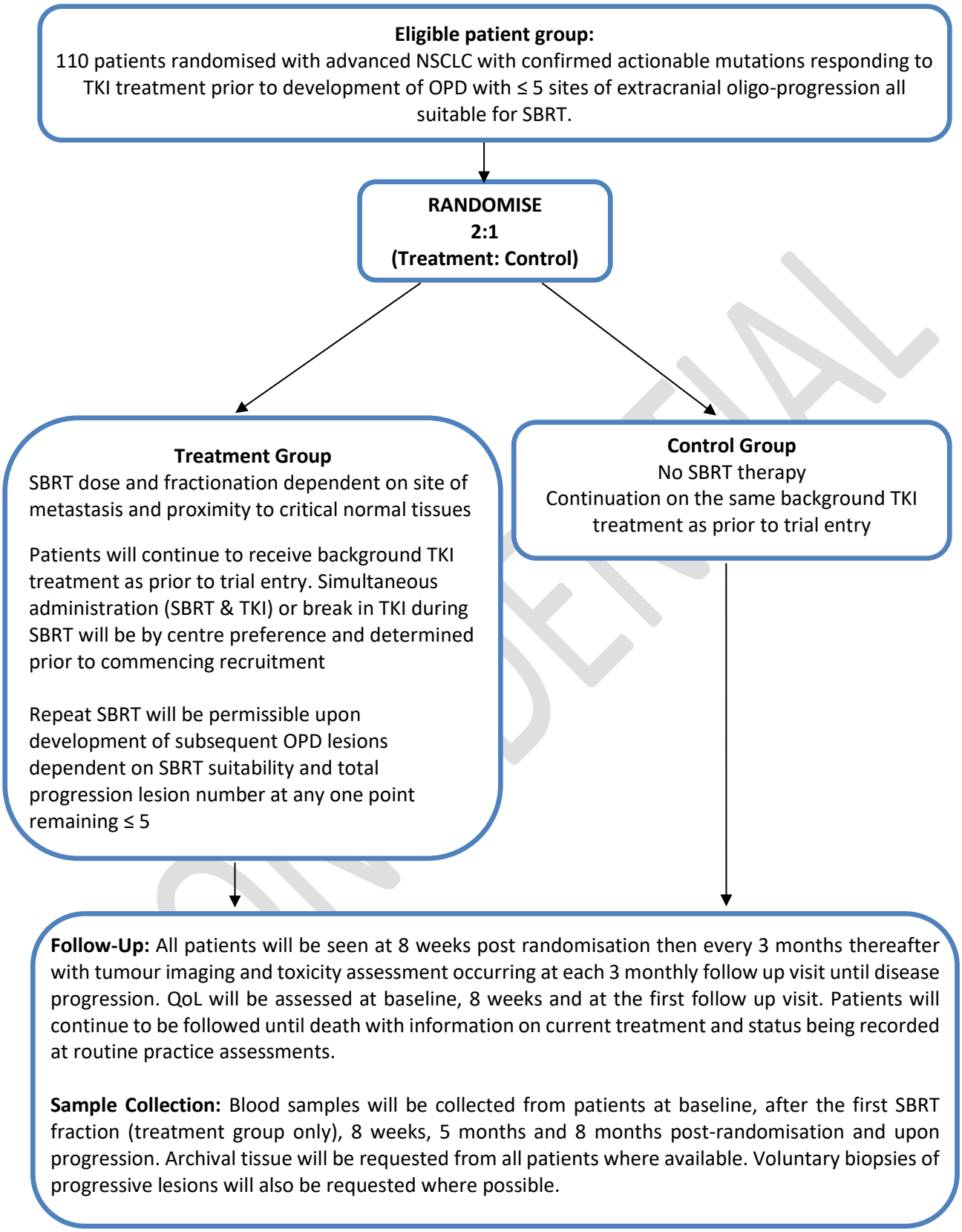
CONTENTS

HALT TRIAL SUMMARY

PROTOCOL TITLE	Targeted therapy with or without dose intensified radiotherapy for oligo-progressive disease (OPD) in oncogene-addicted lung tumours
TARGET DISEASE	Advanced mutation positive non-small cell lung cancer (NSCLC)
STUDY OBJECTIVES	To determine whether in patients with mutation positive advanced NSCLC the use of SBRT to ≤ 5 sites of OPD with continuation of TKI improves progression-free survival (PFS) compared with continuation of TKI alone
STUDY DESIGN	Randomised, multi-centre, phase II/III trial with integrated transition period to phase III trial
TRIAL POPULATION	Patients with advanced NSCLC with defined actionable mutation responding to targeted TKI therapy prior to development of confirmed OPD defined as ≤ 5 sites of extracranial oligoprogression
RECRUITMENT TARGET	110 patients randomised for phase II component
TRIAL TREATMENT	Patients will be randomised 2:1 to receive: • SBRT with continued background TKI • Continued background TKI alone Patients allocated to SBRT will receive a dose and fractionation schedule dependent on metastatic site and proximity to critical normal tissues. All patients will continue on background treatment with TKI until change in therapy is clinically indicated as per standard care
PRIMARY ENDPOINT	Progression free survival defined as the time from randomisation to the first of one of the following events or death from any cause: • Clinically symptomatic progression requiring palliative tumour-specific oncological intervention (e.g. change in systemic therapy or localised non-SBRT radiotherapy) as determined by the treating physician • New or existing intra-cranial lesions not amenable to radical surgery or SRS • Development of new extra-cranial lesions or progression of existing extra-cranial lesions not meeting the criteria for SBRT treatment (e.g. size > 7cm) • Development of >5 new or progressing extra-cranial lesions at any one point in time (i.e. widespread progression)
SECONDARY ENDPOINTS	• Time to change in systemic therapy or clinical decision that patient not suitable for further systemic therapy • Overall survival • Patterns of disease progression • Radiotherapy toxicities (acute and late) using CTCAE • Quality of Life • Time to failure of next line of systemic therapy • Measurement of resistant sub-clones in ctDNA
EXPLORATORY ENDPOINTS	• Deep sequencing analysis will be used to model tumour evolution, neo-antigen burden and genomic instability in paired tumour tissue at OPD baseline and at the time of

	further progression (where available) in addition to ctDNA samples. • Where PET imaging has been undertaken (as per standard site practice), assessment of PET findings in relation to clinical outcome.
FOLLOW UP	All patients will be assessed 8 weeks post randomisation. Subsequent follow-up visits will be aligned with routine care and will occur at 3 monthly intervals from the end of treatment assessment visit.

HALT TRIAL SCHEMA



1 INTRODUCTION

1.1 Background

Lung cancer is the leading cause of cancer death in Europe with approximately 449,000 new cases diagnosed and approximately 388,000 deaths attributed to the disease in 2012, equating to over 1000 deaths per day[1]. The majority of patients (87%) present with non-small cell lung cancer (NSCLC) and 36% of those have advanced metastatic disease. Across the spectrum of lung cancer the 5 year survival rate has changed little over the last 60 years (from 3% to 8%), with progress in improving outcomes continuing to lag significantly behind other common cancers.

1.2 Molecular heterogeneity of NSCLC and first-line targeted treatment options

Our understanding of the biology and molecular mechanisms driving the development of lung cancer has advanced significantly over recent decades and it is becoming apparent that significant heterogeneity exists within this disease at the molecular level. Genomic profiling has allowed the classification of molecular subtypes based on the identification of distinct driver oncogenes and within the histologically defined subtypes of NSCLC, known oncogenic driver mutations have been identified in up to 60% of lung adenocarcinomas and 50-80% of squamous cell carcinomas, including the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS-1 [2,3]. With the development of novel targeted therapies and chemotherapeutic strategies the systemic management of subpopulations of patients with mutation positive advanced NSCLC has been transformed.

Approximately 5-20% of Caucasian patients with NSCLC have an activating EGFR mutation with a further 4-7% of patients displaying rearrangements in the ALK protein, with less frequent mutations including MET, BRAF, PIK3CA, HER2 mutations and ROS1 rearrangements [4]. In the molecularly defined EGFR mutation and ALK rearrangement populations targeted therapy using tyrosine kinase inhibitors (TKIs) has produced higher response rates, extended progression free survival (PFS) and reduced side effects compared with standard comparator chemotherapy [5-9]. However despite this initial activity acquired resistance eventually develops with median PFS of 8-10 months in patients with ALK rearrangements and 9-13 months in patients with EGFR mutations. Ultimately all such patients will develop progressive disease and novel strategies are needed to further improve progression-free and overall survival.

1.3 Acquired resistance to targeted therapies

The molecular mechanisms associated with the development of acquired resistance are varied. For patients with EGFR mutations, the most common is development of a secondary EGFR mutation such as the gatekeeper T790M point mutation in exon 20 of the EGFR gene [10]. Other resistance mechanisms identified to date involve bypass signalling pathways with amplification of molecules such as MET which can circumvent the effects of inhibition of EGFR on downstream signalling pathways [4]. Mutations in additional intracellular signalling molecules such as PIK3CA, HER2, BRAF and STAT3 have also been identified [4]. Additionally phenotype changes can occur, specific to small cell lung cancer or to NSCLC with evidence of epithelial to mesenchymal transformation [11]. Whilst

significant advances have been made in understanding the pathways leading to acquired resistance to EGFR targeted therapy the mechanisms involved in up to 30% of instances remain unknown [4]. Resistance to ALK targeted treatments also develop through a variety of mechanisms including ALK mutations and upregulation of EGFR/HER1, HER2 and HER3 as well as c-kit amplification [12].

1.4 Patterns of disease progression upon acquired resistance and subsequent treatment options

It is now recognised that differing patterns of disease progression are observed following initial response to TKI and subsequent development of acquired resistance. Some patients have rapid widespread progression where repeat biopsy is recommended in particular to assess for phenotype change, for example transformation to small cell cancer, to direct systemic chemotherapy according to the pathology report. Other patients have widespread gradual progression. For these patients third generation TKIs will increasingly become available to provide further systemic therapy options, for example Osimertinib for patients with T790M EGFR point mutation [13,14]. However, T790M mutations represent a minority of these patients and chemotherapy remains the standard of care for symptomatic T790M negative patients and other targetable resistance mechanisms with suboptimal clinical outcomes. However, for clinically stable patients with widespread gradual progression, continuation of TKI beyond RECIST progression criteria is also an option [15].

An important additional subset of patients demonstrates only limited sites of progression, known as oligo-progressive disease (OPD). Published data on the proportion of patients progressing with an oligo-progressive pattern of disease range from 15-47% [16-18]. Re-biopsy series of progressing lesions suggest development of TKI resistant sub-clones at these sites of progression that are selected in a Darwinian manner with the ability to contribute to systemic re-seeding of new sites of distant disease and subsequent widespread disease progression [19-21]. The other non-progressing sites of disease may not harbour such sub-clones with acquired resistance and potentially remain oncogene addicted and sensitive to initial TKI therapy. Optimal post-progression therapy should not be systematically always tailored according to RECIST progression criteria with delaying the switch for clinically stable patients being an option. Small cases series indicate potential benefit from adding local therapy to sites of OPD to extend the length of time patients derive clinical benefit from such targeted agents and international guidelines for consideration of adding in local therapy for patients with clinically stable OPD reflect this [15 16,18]. However randomised data are needed to assess the true clinical benefit of the addition of local therapy for this group of patients.

1.5 Stereotactic Body Radiotherapy

Advances in radiation delivery technology and image guidance have allowed the development of novel radiotherapy techniques including Stereotactic Body Radiotherapy (SBRT)[22]. Originally developed by physicians in Sweden as an alternative to surgical resection to treat brain metastases, SBRT is now being used to treat both primary and metastatic sites throughout the body, including intrathoracic, liver, adrenal and bony metastases.

SBRT involves the delivery of high dose radiation to small, well-defined tumour targets whilst limiting the dose received to surrounding normal tissue. By restricting the exposure of adjacent tissue and organs SBRT is able to deliver ablative doses to target lesions leading to increased local lesion control rates with acceptable levels of toxicity [23].

The additional benefit that may be gained by treating OPD sites with SBRT prior to any change in systemic treatment is an important consideration that needs assessment. It may be possible to eradicate TKI resistant sub-clones within oligo-progressive lesions using the focused radiation of SBRT. This may in turn change the natural history of disease progression by delaying widespread relapse, prolonging clinical benefit from TKI treatment and improving overall outcome.

1.6 Description of population

The patient population being assessed within the HALT trial will be those with advanced NSCLC and confirmed actionable mutations on a TKI as any line of systemic therapy for which initial response to TKI treatment is followed by development of OPD. In the first instance this will incorporate EGFR and ALK mutations however as and when additional actionable mutations enter routine practice patients with these mutations will also be eligible to enter the trial. TKI responders will be defined as those who demonstrate radiological response indicating continued TKI therapy as determined at the routine assessment following initiation of TKI treatment (usually two to three months after commencing TKI). In order to standardise the definition of radiological OPD suitable for SBRT and to confirm patient eligibility based on this definition a virtual MDT consisting of clinical members of the HALT trial team including a consultant radiologist will be established. Further details regarding the HALT virtual MDT are provided in Section 6.

1.7 Study rationale

The use of SBRT to treat local sites of disease both in the primary and metastatic setting is becoming more widespread; however there is limited data currently available to support the use of this technique in the treatment of OPD following the development of acquired resistance to TKIs in patients with advanced NSCLC. Single centre case series have been conducted in the U.S. which add support to the concept of local therapy for sites of OPD within this patient population however in the absence of a randomised comparator group the interpretation and clinical utility of the results is limited [16,18].

The additional benefit that may be gained by treating OPD sites with SBRT prior to any change in systemic treatment is an important consideration that needs assessment via a randomised clinical trial with an appropriate control group. It may be possible to eradicate TKI resistant subclones within oligoprogressive lesions using the focused radiation of SBRT which may in turn change the natural history of disease progression by delaying widespread relapse. This in turn could prolong the clinical benefit obtained by patients from TKI treatment and improve overall outcome.

1.8 Translational research

The use of repeat invasive tissue biopsies at multiple time points to continually assess the molecular profile of tumours in patients with mutation positive metastatic NSCLC is impractical. However, alternative non-invasive approaches may offer potential to monitor this. One such approach is to monitor circulating tumour DNA (ctDNA) in the blood. ctDNA is detected in cancer patients across a range of tumour types and is an attractive biomarker for lung cancer as it can provide non-invasive insight into the tumour genome [24,25]. ctDNA levels reflect response to treatment and disease progression as indicated in a limited case series showing the potential of using ctDNA to differentiate between residual tissue post radiation and relapse. ctDNA may provide an important insight into disease status of patients with OPD treated with ablative therapy. HALT provides a unique opportunity to evaluate OPD using ctDNA as a non-invasive method to track response to SBRT and identify further progression. The spatiotemporal relationship between genetic aberrations in progressive lesions and ctDNA genetic aberrations can also be explored. As proof of principle for the role of SBRT in OPD it is hypothesised that an emerging resistance mutation in ctDNA at the time of OPD would become undetectable following successful SBRT to the resistant disease sub-clone in the treated oligo-progressive lesions.

No biomarker currently exists to predict for clinical benefit from the addition of SBRT in OPD. In addition to the local effect of SBRT on TKI resistant sub-clones in oligo-progressive lesions, the potential 'abscopal' effect of high dose per fraction radiation on the patient's immune system is considered one of the mechanisms of potential clinical benefit. ctDNA circulating immune biomarkers and tumour tissue, where available, offer an opportunity to prospectively assess the role of the immune system in the response to SBRT. The focus of the translational research will be on identifying clinically translatable biomarkers to identify patients who are likely to benefit from SBRT versus patients where transition to the next line of systemic therapy would be appropriate.

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective of the trial is to determine whether in patients with mutation positive advanced NSCLC the use of SBRT to ≤ 5 sites of OPD with continuation of TKI improves PFS compared with continuation of TKI alone

2.2 Secondary Objectives

The secondary trial objectives are to assess:

- Time to change in systemic therapy
- Overall survival (planned phase III primary endpoint)
- Patterns of disease progression
- Clinician and patient reported acute and late toxicity (CTCAE v4.0)
- Quality of life
- Clearance of detectable resistant sub-clones measurable in ctDNA in SBRT arm
- Time to failure of next line treatment

2.3 Exploratory Objectives

- Comparison of archival tumour DNA with ctDNA to assess baseline OPD
- Analysis of circulating biomarkers to assess ctDNA kinetics and tumour evolution following SBRT.
- Identification of circulating immune biomarkers of response to SBRT.
- Analysis of paired pre and post treatment tissue biopsies (where available).
- Where PET imaging has been undertaken (as per standard site practice), assessment of trial outcomes.

3 TRIAL DESIGN

HALT is a randomised, multi-centre phase II/III trial designed to assess whether the use of SBRT to treat oligo-progressive disease can prolong the period of clinical benefit obtained from targeted therapy. Patients will be randomised to receive SBRT or no SBRT (2:1) with all patients continuing to receive background targeted therapy as per clinical guidelines. HALT incorporates an integrated phase II/III trial design with transition to full phase III dependent on feasibility data obtained during the phase II, more detail regarding transition and determining factors are detailed in Appendix A1.

A virtual MDT consisting of clinical members of the HALT trial team including a consultant radiologist will assess eligibility for trial entry based on the confirmation of OPD and suitability of all lesions to SBRT treatment. The HALT virtual MDT may also review progression events occurring in both control and treatment groups and possible progression within SBRT treated lesions if required by local teams. Further details of these assessments are provided in Section 6.

4 STUDY ENDPOINTS

4.1 Primary Endpoint

Progression free survival defined as the time from randomisation to the first of one of the following events or death from any cause:

- Clinically symptomatic progression requiring palliative tumour-specific oncological intervention (e.g. change in systemic therapy or localised non-SBRT radiotherapy) as determined by the treating physician.
- New or existing intra-cranial lesions not amenable to radical surgery or SRS.
- Development of new extra-cranial lesions or progression of existing extra-cranial lesions not meeting the criteria for SBRT treatment (e.g. size >7cm)
- Development of >5 new or progressing extra-cranial lesion at any one point in time (i.e. widespread progression)

Progression will be assessed radiologically at each clinic visit following randomisation or more frequently if clinically indicated. The scans at time of trial entry will be used as the baseline for assessment. Determining progression of new or existing extra-cranial OP lesions, as stated above, will

be by assessment of % change of individual lesions compared to the baseline scan, with progression defined as a ≥ 20% change from baseline in an individual lesion. In these instances, the criteria for determining progression meeting the primary endpoint definition will be based on an assessment of SBRT suitability as defined below. This method will be used to determine OPD in both the control and SBRT treatment groups to minimise bias in determining PFS events. The HALT virtual MDT should review progression events in both groups and research teams at participating centres will be required to upload the scans indicating further progressive disease for review.

Where local progression is suspected in SBRT-treated lesions, consideration should be given to performing independent imaging in the form of PET/CT and or MRI for diagnostic clarification as assessment of progression can be complicated by post treatment related changes around the tumour. In these instances images may be reviewed by the HALT virtual MDT including a consultant radiologist and, where inconclusive, a second CT, PET/CT or MRI with at least an 8 week time interval will be performed to confirm disease status. Research teams at participating centres will be required to upload the scan indicating progression in the SBRT treated lesion(s) and the repeat scan to assess disease status. At each extra-cranial scan the HALT PFS event criteria (Appendix 2) should be followed to determine PFS events.

Further details regarding the HALT virtual MDT can be found in Section 6 of this document.

Criteria for determining SBRT suitability

Progression of new or existing extra-cranial OP lesions in control and treatment groups will be assessed against the following SBRT suitability criteria:

- Size – To be considered suitable for SBRT, lesions must remain at or below 7cm. Parameters for the measurement of lesions will be in accordance with standard RECIST v1.1 procedures.
- Co-morbidities – conditions which would preclude the safe delivery of SBRT will be assessed. A non-exhaustive list will be detailed in the HALT RT planning and delivery guidelines and research teams at site should consult this when assessing patient suitability for SBRT in both the control and treatment groups.
- Structural pre-determinants – The HALT RT planning and delivery guidelines provide detailed information as to the structural pre-determinants that would preclude the safe delivery of SBRT. Patients in both the control and treatment groups should be assessed using these guidelines to confirm SBRT suitability.

4.2 Secondary Endpoints

- Time from randomisation to start of next line of systemic therapy or clinical decision that patient not suitable for further systemic therapy as determined by the treating physician, or death.
- Overall survival – time from randomisation until death from any cause

- Patterns of disease progression identified from CT scans / PET-CT scans taken at 3 monthly intervals to further document natural history of oncogene-addicted NSCLC
- Radiotherapy toxicities (acute and late) assessed using CTCAE v4.0 (clinician and patient versions where available). Acute events are defined as ≤ 90 days post SBRT start date (applicable for each subsequent course of SBRT where relevant) and late events are defined as > 90 days, both assessed using CTCAE v4.0.
- Quality of Life – assessed using EQ-5D-5L and the EORTC QLQ-C30
- Measurement of resistant sub-clones in ctDNA measured at baseline, post-randomisation and upon progression.
- Time to failure of next line treatment – time from randomisation to switch from next line of active systemic therapy.

4.3 Exploratory Endpoints

- Deep sequencing analysis will be used to model tumour evolution, neo-antigen burden and genomic instability in paired tumour tissue at OPD baseline and at the time of further progression (where available) in addition to ctDNA samples.
- Where PET imaging has been undertaken (as per standard site practice), assessment of PET findings in relation to clinical outcome.

5 PATIENT SELECTION & ELIGIBILITY

5.1 Number of Participants

The aim is to randomise 110 participants for the phase II component of the trial; anticipated to be 73 patients randomised to the treatment group (SBRT treatment), 37 randomised to the control group (no SBRT treatment). It is estimated that 138 patients will need to be registered in order for 110 patients to be randomised.

5.2 Source of Participants

Participants will be recruited from approximately 20 sites in the UK plus additional sites from participating countries within the EORTC network. Potential participants will be identified in oncology clinics and discussed at local Multi-Disciplinary Team (MDT) meetings.

5.3 Inclusion Criteria

1. Male or female, ≥ 16 years of age
2. Established histological diagnosis of advanced NSCLC, not suitable for radical treatment, with defined actionable mutation receiving targeted TKI therapy
3. Radiologically confirmed response to TKI therapy (assessed locally usually 2-3 months post commencing TKI)
4. Confirmed OPD defined as ≤ 5 extracranial sites of progressive disease. All sites must be visible, imaging defined targets and suitable for treatment with SBRT as determined by the virtual MDT and in accordance with the HALT Radiotherapy planning and delivery guidance document.

5. Adequate baseline organ function to allow SBRT to all relevant targets
6. Predicted life expectancy ≥ 6 months
7. Karnofsky Index ≥ 60% and ECOG 0-2
8. Provision of written informed consent

5.4 Exclusion Criteria

1. > 5 extracranial sites of progressive disease
2. Progressing or newly diagnosed brain metastases identified at the time of trial entry, not amenable to radical surgery or SRS. Previously treated brain metastases (i.e. palliative radiotherapy or systemic therapy) which have remained clinically and radiologically stable for ≥ 6 months are permissible.
3. Prior radiotherapy near the oligoprogressive lesion precluding ablative SBRT. Suitability of lesions for ablative SBRT as part of the trial defined in section 4.1 of this document and will be determined by the HALT virtual MDT
4. Co-morbidities considered clinically precluding the safe use of SBRT (as detailed in the HALT radiotherapy planning and delivery guidelines).
5. Any psychological, sociological or geographical issue potentially hampering compliance with the study
6. Pregnancy

5.5 Life Style Guidelines

Participants randomised to receive SBRT must be surgically sterile or if female be post-menopausal, or must agree to use effective contraception during the period of therapy. Patients in the control group should continue to follow local guidelines for TKI therapy. Effective contraception is defined as double barrier contraception (e.g. condom plus spermicide in combination with a diaphragm, cervical cap or intrauterine device).

6 VIRTUAL MDT

A virtual MDT will be established as part of the HALT trial to provide consistent interpretation and central confirmation of patient eligibility, and where necessary assessment of progression events meeting the primary endpoint in both the control and treatment groups and assessment of progression in lesions treated with SBRT. The HALT virtual MDT will consist of clinical members of the HALT trial team in addition to at least one independent radiologist. As a minimum, 2 clinicians and 1 radiologist will be required for individual scan assessment.

It is intended that the Research PACS (XNAT) software system, housed and maintained at the Institute of Cancer Research, will be used to manage the required image upload and review process. Named individuals at each participating centre will be provided with access details to allow upload of the relevant anonymised patient scans and reports where available onto a secure server.

Where considered appropriate by the vMDT, centres having previously submitted ≥3 patients for vMDT review where no issues in confirmation of oligoprogression or SBRT suitability have been identified, will be permitted to follow a streamlined radiology review. This would consist of full central

radiology review of the required patient scans, as with the usual virtual MDT process, with full review by the vMDT not considered necessary unless radiology identified specific issues for discussion. The decision to move to a streamlined review would be on a per centre basis following consensus approval by the vMDT.

6.1 Eligibility Assessment

Research teams at site will be required to upload imaging scans and reports relating to the following time points to enable assessment of eligibility:

- Scan informing decision to commence current line of TKI therapy
- Scan indicating best and/or initial response to current line of TKI therapy
- Scan prior to current OPD scan (if different from scan above)
- Scan identifying current oligoprogression

The virtual MDT will assess eligibility based on number of OPD sites and SBRT suitability of all OP lesions. An assessment of tumour burden will also be conducted for patients considered eligible. If patients have been previously treated for brain metastases, MRI and/or contrast CT brain scans may be requested to confirm stable disease ≥ 6 months.

Criteria for PET-avid OPD lesions

Progression of new or existing OPD lesions can be diagnosed based on FDG avidity on PET-CT when there is no change in size/morphology of the lesion confirmed by CT. All patients where OPD is diagnosed by PET-CT should be discussed at a HALT virtual MDT.

OPD diagnosed on PET is defined as:

a) A new lesion in which SUVmax is above background SUV when compared to the scan indicating best response to current line TKI. If no previous scan is available for comparison, further interval PET imaging should be considered or if the lesion is not easily visible on CT a diagnostic MRI should be considered to confirm OPD.

b) *OR* increase in SUV max of ≥ 30% and an absolute increase by 0.8 units compared to the nadir/previous scan as available.

Progression should continue to be assessed as described in section 4.1, defined as a ≥ 20% change from baseline in an individual lesion. However, subsequent follow-up PET-CT scans can be used to evaluate any new OPD lesions suitable for repeat SBRT for those randomised to SBRT treatment.

6.1.1 Tumour Burden

Tumour burden will be assessed using the following statement:

On the basis of initial metastatic disease pattern and if allocated to the SBRT group, would SBRT be performed on all known disease?

If YES – this would represent a low tumour burden
If NO – this would represent a high tumour burden

This information will be requested at randomisation to minimise any bias occurring due to imbalanced distribution of tumour burden between the two groups.

7 SCREENING

7.1 Screening Log

All participating sites will be required to keep a log of all participants with locally assessed radiologically defined oligoprogression upon TKI treatment potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Number of patients approached/accepting/declining participation/ineligible
- Screening outcome
- Trial ID (if applicable)
- Reasons for ineligibility / not approaching / declining as applicable (if available)

This information will be used to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU from the screening log.

7.2 Procedure for Obtaining Informed Consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. No protocol required assessments should be conducted until the appropriate consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the site investigator file (SIF), which must be available for verification by ICR-CTSU study staff at any time.

Participants should be given the current ethics approved HALT patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial, and the opportunity to ask any further questions.

As part of the HALT trial, all patients will be asked to consent to the mandatory provision of research blood samples. In addition patients may be asked to consent to participate in the HALT translation sub-study involving the use of archival tissue where available and the provision of fresh tissue biopsies upon progression, where appropriate. Patients will also be asked to consent to participate in the HALT Quality of Life sub-study. Patients should be made aware that participation in the HALT translational sub-study or the quality of life sub-study is entirely voluntary. Refusal to participate in either sub-study will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received. Further information regarding the HALT translational and quality of life sub-studies can be found in Section 19 of this document.

To facilitate linkage with routinely collected healthcare data patients will also be asked to consent to the collection of their full name, date of birth, hospital number, postcode and NHS number. Further details regarding the maintenance of confidentiality relating to the collection of these details can be found in Section 16.4 of this document.

7.3 Participation in other Clinical Trials

Patients who fulfil the HALT eligibility criteria will be given the opportunity to participate in the trial if they have participated in other clinical trials prior to recruitment. However, in instances where patients, having previously completed HALT participation by meeting the trial primary endpoint, go on to develop further oligoprogressive disease outside of the trial, these patients would not be considered eligible for re-entry into HALT. Participation in other clinical trials will be considered on a case by case basis by the Trial Management Group with due consideration given to the needs of the patient and impact on the conduct and outcome of both trials.

8 REGISTRATION

Once informed consent has been obtained, participants must be registered centrally with the trials unit (ICR-CTSU) before protocol required screening assessments commence.

Patients should be registered by emailing ICR-CTSU to request a call back on:
randomisation-icrctsu@icr.ac.uk09:00-17:00 (UK time) Monday to Friday

The following information will be required at registration:

- Name of hospital, consultant and person registering patient
- Confirmation that the patient has given written informed consent for trial participation and for any sub-studies and the date consent obtained
- Patient's initials, hospital number and date of birth

The caller will be given the patient's unique registration number (Registration ID). Assessments of eligibility to be performed are detailed in section 10.1. Please note that CT scans/MRI scans/PET-CT scans performed as part of standard clinical practice, prior to registration, can be used if conducted ideally within 14 days, but at least within 1 month prior to registration. The patient scans must be uploaded as soon as possible after registration for review by the virtual MDT.

9 RANDOMISATION

Patients must be randomised centrally by the trials unit (ICR-CTSU) before trial treatment can commence.

Patients should be randomised by emailing ICR-CTSU to request a call back on:
randomisation-icrctsu@icr.ac.uk 09:00-17:00 (UK time) Monday to Friday

Randomisation should take place as soon after the date of consent as possible, once all eligibility assessments have been conducted and patient eligibility confirmed. Patients randomised to receive

SBRT should commence treatment within 4 weeks of randomisation. An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, patient's named consultant, name of SBRT planning clinician (if different from named consultant) to deliver SBRT to specific metastatic site and person randomising the patient
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number (or equivalent for international participants)
- EGFR vs other mutation (e.g. ALK, ROS-1 and MET)
- Number and location of extra-cranial OPD lesion(s)
- Tumour burden, classified as either 'high' or 'low' as evaluated by the virtual MDT (further details provided in Section 6)

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation. Patients will be allocated to receive either SBRT and continuation of background TKI (SBRT treatment group) or continuation of background TKI alone (control group).

ICR-CTSU will email confirmation to the named contact(s) at the recruiting site to confirm a patients' entry into the trial.

Patients randomised to receive SBRT should commence treatment within 4 weeks of randomisation. Any delays encountered in commencing SBRT treatment should be notified to and discussed with the ICR-CTSU HALT trial team and the Chief Investigator

10 TRIAL ASSESSMENTS

All trial specific assessments must only be completed once the patient has provided informed consent for trial participation.

10.1 Screening Assessments

It is recommended that the following assessments are conducted within 30 days prior to randomisation unless otherwise indicated.

- CT scan/PET-CT scan confirming disease progression and current OPD (CT component of PET-CT should be of diagnostic quality). Baseline imaging modality should be used for subsequent follow-up imaging assessments. Scans conducted outside the trial can be used if performed ideally within 14 days, but at least within 1 month prior to registration; otherwise a repeat scan will be required to confirm eligibility. Central confirmation of OPD and suitability of all progressing lesions for SBRT will be performed by the HALT virtual MDT. Further details of this process can be found in Section 6.
- Complete medical history and physical examination
- Assessment of performance status (Karnofsky Index and ECOG)

- Local confirmation of diagnosis of advanced NSCLC with defined actionable mutation
- Evidence of confirmed radiological response to current TKI therapy (assessed locally usually within 2-3 months of commencing TKI therapy)
- Contrast enhanced CT or MRI brain scan to exclude new or progressing intracranial disease not suitable for surgery or SRS. If suitable scan was taken at the time of OPD confirmation a repeat scan is not necessary however this must be within 30 days prior to randomisation. Patients found to have new or progressing intracranial disease should be discussed at the local neuro-oncology MDT. If the intracranial disease is amenable to either surgery or SRS to the brain, the patient should have their intracranial disease treated accordingly and may enter the trial following this treatment provided they still meet the eligibility regarding their systemic disease. Having received treatment, patients may proceed to trial entry and commence trial treatment as indicated in the protocol (i.e. for patients randomised to the treatment group, SBRT should be delivered within 4 weeks of randomisation). Intracranial disease identified at trial entry not amenable to surgery or SRS is criteria for exclusion from the trial.
- Screening blood tests to assess suitability for SBRT depending on sites of OPD (please refer to HALT RT Planning and Delivery guidelines document for further details).
- Pregnancy test (if applicable)

The following assessments are required to confirm suitability for SBRT dependent on the location of OPD lesion(s) and confirm patient eligibility:

- Liver OPD lesions: INR and DMSA scan (or local equivalent for assessment of kidney function)
- Lung OPD lesions: Pulmonary function tests (FEV1, FVC and TLCO/KCO), baseline O_2 saturations, baseline, MRC dyspnoea score
- Adrenal OPD lesions: DMSA scan (or local equivalent for assessment of kidney function), baseline cortisol measurement

The following baseline assessments should be conducted once patient has been randomised:

- Baseline conditions
    - Patients randomised to both the control and treatment arms should have CTCAE assessments at baseline and at each subsequent follow up visit as indicated.
- Baseline quality of life questionnaire (completed prior to patient awareness of treatment allocation)
- Research blood sample collection
- Archival tumour block collection (if applicable)

10.2 Pre-SBRT Treatment Assessments

Consideration should be given as to whether repeat organ function tests (as performed at screening) are required (e.g. blood tests, pulmonary function tests) as per OPD site, prior to each course of SBRT (initial, subsequent SBRT upon further oligoprogression) as detailed in the HALT RT Planning and Delivery guidelines document. A physical exam, including Karnofsky index and ECOG performance

assessment may also be required prior to delivery of repeat SBRT. Assessments should be conducted within 7 days prior to commencing SBRT treatment.

10.3 Post-treatment Follow-up

All patients will be assessed 8 weeks post randomisation and then subsequently at 3 monthly intervals (from 8 week assessment date) in line with routine care until disease progression is confirmed. The following assessments will be performed at each visit:

- Karnofsky Index and ECOG performance status
- Toxicity assessment including MRC dyspnoea score
- Post treatment QoL questionnaire (at 8 weeks post randomisation and first subsequent follow-up visit).
- Full blood count, urea, electrolytes and liver function tests (first 3 month visit only, not required thereafter)
- Tumour imaging assessment (imaging requirements at follow up visits will be determined by lesion location as identified at trial entry. The same imaging modality used at baseline should be used for subsequent follow-up assessments. Consideration should be given for repeat CT contrast/MRI brain as required)
- Current medication / treatment

Research blood samples will be taken at 8 weeks, 5 months and 8 months post-randomisation and upon progression (for patients randomised to receive SBRT an additional sample will be taken after delivery of the first fraction of SBRT).

Repeat SBRT – Only those patients allocated SBRT treatment at randomisation should be offered repeat SBRT treatment upon development of new OPD lesions or progression of existing extracranial lesions not progressing at trial entry, where the total number of progressing lesions at any one point remains ≤ 5. Suitability of new OPD lesions for further SBRT will be based on the same criteria as at trial entry (visible, imaging defined targets suitable for SBRT, ≤7cm). Where multiple lesions are treated over the course of the trial, composite dose volume data must be assessed and all normal tissue dose constraints need to be met by the composite plan. Particular caution is required where isodose lines overlap serial organs. Any previous radiotherapy before trial entry should also be taken into account. 50% isodose lines for plans to individual lesions should not overlap. A maximum of 5 thoracic lesions, 3 abdominal and 3 pelvic lesions can be considered for SBRT with composite planning confirming all normal tissue dose constraints are met.
Central confirmation of suitability may be provided following review of tumour imaging and/or planning scans by the virtual MDT if requested by the local research team. A period >3 months since the last SBRT treatment is required before commencing repeat SBRT. However, repeat SBRT can be considered within a shorter time interval if an early interval scan has been requested by the vMDT, or where the total number of OPD lesions to be treated remain ≤5 and this has been agreed by the vMDT.

Re-irradiation – Further SBRT treatment of progressing OPD lesions previously treated with SBRT either as part of the trial or prior to trial entry is not permitted in the HALT trial. Assessment of progression in previously treated OPD lesions should be as defined in Section 4 Primary Endpoint.

Disease Progression **-** Upon confirmation of disease progression meeting the primary endpoint no further post-treatment follow up assessments are required. Patients should continue to attend routine clinic visits as per local practice and the procedure upon further disease progression detailed below should be followed.

If disease progression is suspected in the period between 3 monthly visits (>1 month prior to next scheduled visit) (i.e. development of clinical symptoms suggestive of disease progression) all post-treatment follow-up assessments as detailed above should be conducted. If progression is confirmed and no further SBRT is possible (control group/lesion not suitable to SBRT) patients should follow the procedure upon further disease progression (Section 10.4) from their next scheduled visit.

10.4 Procedure upon further Disease Progression

All patients will continue background TKI treatment until a change in systemic therapy is indicated. This will be according to local clinical assessment and as per standard of care. Information regarding the local criteria used to determine a change in systemic treatment will be requested with details being provided by sites using the appropriate HALT eCRF.

Patient status will be reviewed at routine clinical visits until death. The following information should be recorded on the appropriate eCRF at each scheduled visit.

- Patient status
- Current treatment
- Assessment of toxicities - required at first 3 month visit post disease progression and at 1 year after last dose of radiotherapy treatment (for SBRT arm only).

Upon confirmation of disease progression the following should be collected:

- Blood samples for ctDNA analysis

10.5 Discontinuation from Treatment

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression or recurrence
- Unacceptable toxicity
- Pregnancy

Participants who discontinue treatment should continue to be followed up as detailed above.

10.6 Discontinuation from Follow-up

If a patient withdraws from further follow-up the appropriate eCRF form should be submitted to ICR-CTSU stating whether the patient simply no longer wishes to attend trial follow up visits (but retains

consent for future data collection from medical records) or whether the patient has withdrawn consent for further information to be sent to the ICR-CTSU. In the very rare event that a patient requests no further follow-up data collection, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing.

10.7 Schedule of Assessments

Visit/Assessment	Pre-trial entry					3 monthly follow-up visits [e]					
	Pre-registration	Screening [a]	Baseline [b]	Post-fraction 1 of SBRT [c]	8 weeks follow-up [d]	5 month follow up (First 3 monthly follow-up)	8 month follow up (Second 3 monthly follow-up)	Further 3 monthly follow-ups	Pre-repeat SBRT [c]	Disease progression	Post-progression follow-ups
Informed Consent	X										
CT Chest / Abdomen / Pelvis or PET-CT confirming OPD [f]	X										
Contrast enhanced CT /MRI Brain		X									
Karnofsky index/ECOG PS		X	X [i]		X	X	X	X	X		
Medical History		X									
Physical examination (height, weight, blood pressure)		X	X [i]								
Full blood count, urea, electrolytes and Liver function tests		X	X [i]		X	X [n]					
Pregnancy test		X									
Liver OPD lesions only: INR and DMSA [g]		X	X [i]						X		
Lung OPD lesions only: Pulmonary function tests (FEV1, FVC and TLCO), baseline O_2 stats, baseline dyspnoea score		X	X [i]						X		
Adrenal OPD lesions only: DMSA [g], baseline cortisol		X	X [i]						X		
Baseline conditions			X								
Tumour imaging	X [h]				X [l]	X [l]	X [l]	X [l]			
Tumour assessment					X	X	X	X			
Toxicity assessment			X		X	X	X	X			X [o]
Quality of Life questionnaire			X [j]		X	X [n]					
Research blood samples			X	X	X [m]	X	X			X [m]	
Tissue samples			X [k]							X [k]	
Patient health status										X	X
Current treatment										X	X

Footnotes

[a] – All assessments to be conducted within 30 days prior to randomisation unless otherwise indicated
[b] – To be completed after eligibility has been confirmed
[c] – SBRT patients only
[d] – The first visit will occur 8 weeks (+/- 5 days) after date of randomisation
[e] – Subsequent visits will occur 3 monthly there after (+/- 5 days)
[f] – Imaging assessments should be conducted ideally within 14 days, but at least within 1 month prior to registration
[g] – A DMSA is recommended to assess differential kidney function where exposure of one of the kidneys to high doses is expected. Appropriate alternative methods of assessment are permitted according to local clinical guidelines. Only required at pre-randomisation timepoint
[h] – Additional imaging according to lesion location (e.g. MRI spine - optional) required if previous scan is > 1 month prior to registration
[i] – Tests are not mandated at this time point but consideration should be given as to their necessity prior to each course of SBRT treatment (initial, subsequent on further oligoprogression).
For further details please refer to the HALT RT Planning and Delivery guidelines. Any assessments should be conducted <7 days prior to treatment
[j] – The baseline quality of life questionnaire should be completed after randomisation, prior to patient awareness of treatment allocation
[k] – Archival block or biopsy samples to be collected if patient has consented to donate tissue samples
[l] – Anatomical sites imaged at point of enrolment should continue to be assessed at follow-up assessments (i.e. brain metastases)
[m] – Research blood samples will be collected from patients receiving SBRT after delivery of the first fraction. For all patients a sample should be collected upon progression
[n] – First 3 monthly visit only, not required thereafter
[o] – Toxicity assessment required at first visit post disease progression and at 1 year after last dose of radiotherapy treatment (for SBRT arm only)

11 TRIAL TREATMENT

Patients will be randomly allocated 2:1 to receive SBRT plus continuation of background TKI (SBRT treatment group) or continuation of background TKI alone (control group).

11.1 Continuation or interruption of background TKI during SBRT course

Current uncertainty exists regarding the safety of concomitant use of TKI during SBRT treatment. Whilst a break in background TKI therapy whilst receiving SBRT treatment is aimed at minimising the risk of radiation toxicity associated with simultaneous administration of SBRT and TKI, the risk of disease flare whilst off TKI is also a considerable concern. A survey of UK and European oncologists conducted as part of the development of HALT indicated no consensus of opinion as to the best approach. Centres participating in HALT will therefore be given the option to either continue background TKI treatment alongside SBRT or stop TKI treatment during SBRT (with a minimum break of one day before the first SBRT fraction and one day after delivery of the last fraction).

Prior to commencing recruitment for the trial all centres must indicate their chosen policy as to whether they opt for a break in TKI therapy for all patients randomised to receive SBRT or whether they opt to continue administration of TKI during SBRT for all patients randomised to receive SBRT. For centres opting to interrupt TKI therapy during SBRT treatment patients must stop TKI at least one day prior to the first dose of SBRT and re-commence no earlier than one day after the last dose of SBRT. For centres opting to continue TKI therapy during SBRT treatment no changes to dose or frequency of TKI therapy is required.

11.2 Treatment timelines

SBRT treatment should commence within 4 weeks post randomisation. Appointments for fiducial marker insertion should be booked in advance of randomisation to avoid delays in commencing SBRT treatment.

11.3 SBRT Planning

Radiotherapy planning should be carried out in accordance with the guidelines in the current version of the HALT Radiotherapy Planning and Delivery Guidelines document, available on request from ICR-CTSU (HALT-icrctsu@icr.ac.uk).

11.4 Treatment technique

Highly conformal treatment planning is a pre-requisite for SBRT. SBRT may be delivered using a specialist SBRT platform, such as CyberKnife or with a linear accelerator with SBRT capabilities. Any SBRT delivery platform is acceptable as long as the individual centre has demonstrated they are able to comply with the radiotherapy standards laid out in this protocol and the HALT Radiotherapy Planning and Delivery Guidelines document.

11.5 Dose prescription

The recommended dose and fractionation options that can be used are detailed within the current version of the HALT radiotherapy and quality assurance guidelines. Where a range of doses is provided it is advised that the maximum dose that can be achieved whilst meeting the OAR planning constraints is prescribed.

11.6 SBRT Scheduling

Initial SBRT treatment should commence within 4 weeks of randomisation, subsequent rounds of treatment (as necessary upon further progression not meeting the primary endpoint) should be scheduled as per local guidelines. SBRT can start on any day of the week and will be delivered as per the table above and detailed in the HALT Radiotherapy Planning and Delivery Guidelines document, where the maximum number of days treatment should be delivered being dependent on the dose fractionation schedule being used. If the maximum duration for the SBRT course is exceeded due to patient or radiotherapy service delivery factors please contact the HALT trial manager (halt-icrctsu@icr.ac.uk).

11.7 Radiotherapy Quality Assurance (QA)

The NCRI Radiotherapy Trials Quality Assurance (RTTQA) group, in collaboration with the EORTC for European sites, will oversee the quality assurance of the SBRT delivered within the trial to ensure the safety and consistency of radiotherapy delivery at participating sites. Prior to inclusion in the trial, individual centres will need to demonstrate they have robust procedures in place to ensure high quality RTTQA planning and delivery guidelines will be met. During recruitment and prior to any repeat SBRT treatment, prospective review will be performed for all patients. The review will assess the

outlining and planning protocol compliance and must be completed before the patient commences treatment. For further information please refer to the HALT Radiotherapy Planning and Delivery Guidelines document.

All data from both UK and European centres will be uploaded via the EORTC RTQA platform. Further information is provided in the HALT Radiotherapy Planning and Delivery Guidelines and in the HALT Trial Guidance Notes.

11.8 Supportive Care and Concomitant Therapies

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the treatment may be given at the discretion of the investigator. All concomitant medications (including start/stop dates, dose/frequency, route of administration and indication) must be recorded in the patient's notes, as well as on the appropriate eCRF.

12 Safety Reporting

12.1 Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient administered a study treatment; the event does not necessarily have a causal relationship with the treatment.

For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of the trial (i.e. randomisation) and during the follow-up period should be considered as an AE, in the opinion of the Chief Investigator.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after randomisation and within the following 140 days and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

For repeat SBRT treatment (where applicable) any untoward medical occurrence that occurs within 90 days of the last fraction of subsequent SBRT and fulfils one of the criteria above should be reported according to serious adverse event reporting timelines.

In addition, any radiotherapy grade ≥4 events occurring between 140 days and 1 year after randomisation or 90 days and 1 year after any repeat SBRT should be reported according to serious adverse event reporting timelines.

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)
A serious adverse reaction is an SAE that is suspected as having a causal relationship to the SBRT treatment, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial treatment
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Related **Unexpected Serious Adverse** Event
An adverse event that meets the definition of serious and is assessed by the CI or nominative representative as:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence (see Appendix 6)

12.2 Reporting Adverse Events to ICR-CTSU

For non-UK reporting requirements please see Appendix A7

Any toxicity, sign or symptom that occurs after randomisation which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant electronic CRF and submitted to ICR-CTSU.

- **Toxicity evaluation**

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4 scoring criteria will be used for all toxicity assessments for patients randomised to both the treatment (SBRT) and control groups.

The severity of AEs should be graded according to the appropriate CTCAE criteria. For each AE, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome, only the main disease/syndrome should be reported.

12.3 Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs following randomisation and up to 140 days post randomisation must be reported. All SAEs occurring up to 90 days post subsequent SBRT (treatment group only, where applicable) must be reported. As detailed above, radiotherapy related SAEs occurring > 140 days post randomisation (or > 90 days post subsequent SBRT) and at 1 year following last dose of radiotherapy treatment (for SBRT arm only) should also be reported.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the HALT SAE form and emailing to:

The ICR-CTSU safety desk
Email address: sae-icr@icr.ac.uk
For the attention of the HALT Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

All SAE forms must be completed signed and dated by the Principal Investigator or designated representative.

12.4 Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all SAEs reported as related to the study treatment, which for the purposes of this trial will be SBRT, for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.)

SAEs assessed as having a causal relationship to study treatment and as being unexpected will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 12.5). Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

12.5 Expedited Reporting of Related Unexpected SAEs

If an SAE is identified as being related and unexpected by the Chief Investigator it will be reported by ICR-CTSU to the main REC, the Sponsor and all other interested parties within 15 days of being notified of the event.

The Principal Investigators at all actively recruiting sites will be informed of any related unexpected SAEs occurring within the trial at appropriate intervals.

The collaborative group in each participating country will report related unexpected SAEs as per their local requirements to IECs and local investigators.

12.6 Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator or designee becomes aware of the outcome.

12.7 Annual Safety Reporting

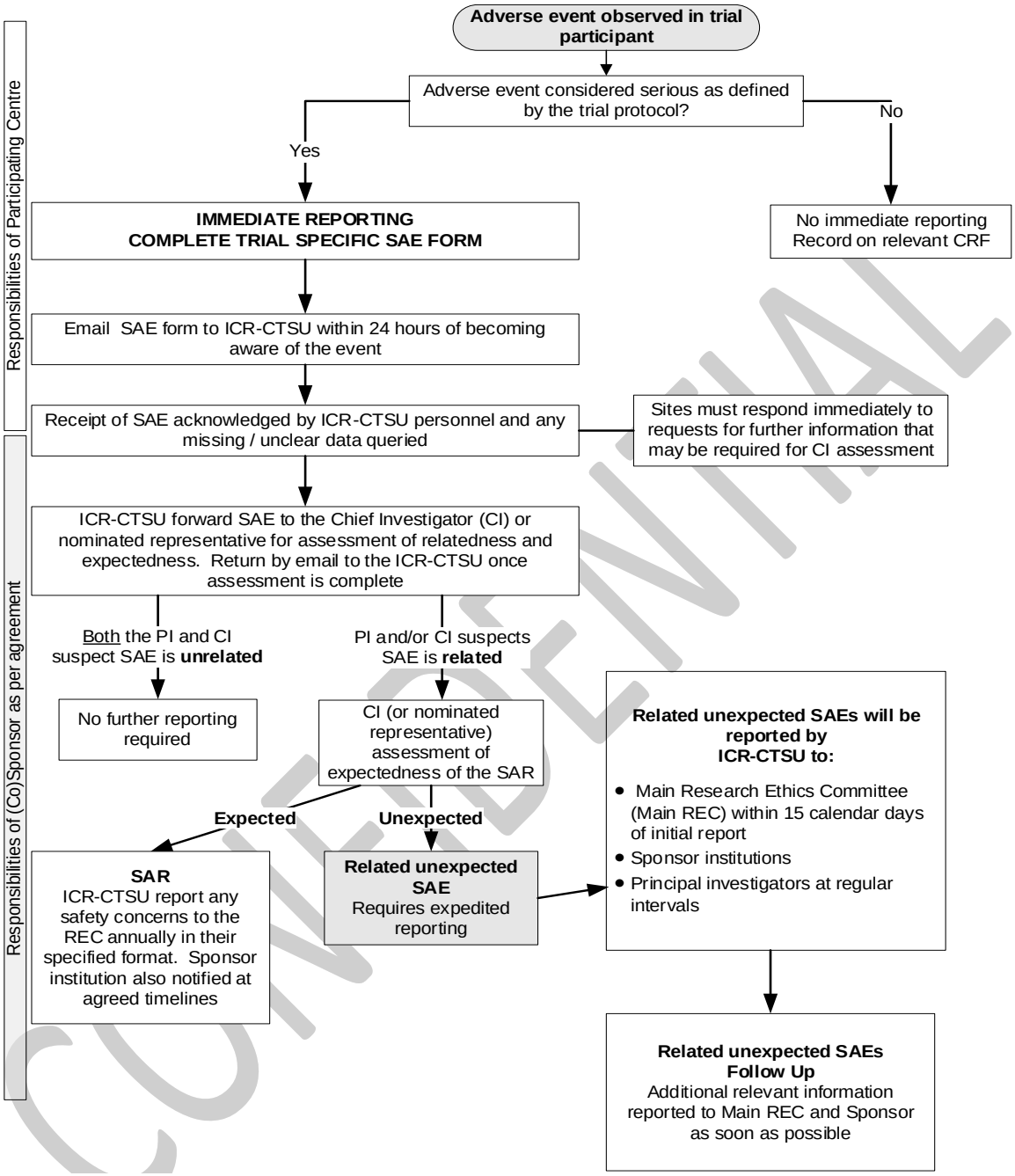
An annual progress report will be provided to the main REC by ICR-CTSU and copied to the Sponsor and the collaborative group in each participating country at the end of the reporting year. This will include data about related unexpected SAEs and whether any safety concerns have arisen during the reporting period.

12.8 Reporting Pregnancies

If any trial participant becomes pregnant while receiving trial treatment or up to 90 days after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU.

If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 3: Flow diagram for SAE reporting, and action following report



NB. All SAEs should continue to be followed up as specified above

13 STATISTICAL CONSIDERATIONS

13.1 Statistical Design and Sample Size Justification

HALT is a randomised, multi-centre, phase II/III study with planned international participation. The integrated phase II/III trial incorporates a transition to full phase III dependent on feasibility data obtained during the phase II trial. This design offers the most efficient use of time and resource compared to a standalone phase II trial followed by a separate phase III trial and allows maximum return of information in a relatively short timeframe. Progression to the phase III trial will be dependent on emerging feasibility data from the phase II trial including recruitment rates; safety and extent of opportunities for international participation (see section 11.5). With the development of novel actionable mutations and TKIs continuing to emerge both the phase II and III components of the study have proposed adaptive aspects to allow inclusion of additional patient groups with OPD on any other targeted treatments as they are introduced into routine practice.

Limited data is available on oligo-progression in patients with NSCLC, however a median time from radiological oligo-progression to widespread progression when continuing on a TKI alone (as per the control group) of approximately 3 months was estimated following a survey of U.K. oncologists and clinical members of the trial team. Furthermore, most oncologists surveyed considered 3 months to be a suitable level of additional benefit for the addition of SBRT (experimental treatment) to be considered a worthwhile intervention. Therefore median PFS for the SBRT group is assumed to be 6 months. Using these estimates together with a significance level of 5% (two-sided), 90% power, a 2:1 allocation ration (SBRT treatment:control), 110 randomised patients (anticipated 73:37) in total is required to obtain 97 PFS events. The sample size calculation uses the log rank test due to the possibility of non-proportional hazards.

The sample size calculation assumes a recruitment period of 36 months with a 6 monthly accrual percentage of total of 5%: 10%: 15%: 20%: 25%: 25% with a minimum of 6 months follow-up (total duration 42 months). It is assumed that the lost to follow up rate will be <1% due to the frequency of follow-ups in line with routine practice and the short expected median time to reaching the primary endpoint.

It is estimated that up to 20% of patients will be registered and found not to be eligible. In order for 110 patients to be randomised it is estimated that 138 patients will need to be registered. Data to base these estimates on is limited and therefore the Independent Data Monitoring Committee (IDMC) and Trial Management Group (TMG) will review the number of patients registered during the trial.

Phase III trial: an average median overall survival of 12 months (mutation types combined) in the control group is anticipated at this stage. The number of patients required for the phase III trial will be influenced considerably by the designated magnitude of minimum clinically important difference and this estimate will be refined after the phase II trial. Using the log rank method as above and assuming a 5-year recruitment period, a total of 272-875 patients (power 80%, alpha 5%) would be required to detect a 6 month or 3 month improvement in overall survival with SBRT (12 to 18 month and 12 to 15 month improvement respectively) and it is anticipated that the designated number of patients

required will lie within this range. It is envisaged that patients recruited to the phase II component will also contribute to the phase III endpoint given the rare population and the integrated design. Assumptions made about the phase III trial design and sample size will be re-assessed for relevance and suitability during the transition phase (Appendix 1). Should the target sample size for phase III be at the lower end of the range recruitment is likely to be completed more quickly.

13.2 Treatment Allocation

Treatment allocation is by minimisation with a random element; balancing factors will be mutation type (e.g. EGFR or other actionable mutation), tumour burden (high vs. low) and treating centre. The virtual MDT will access the scan first used to diagnose metastatic disease and the diagnostic CT scan in order to determine if the patient was allocated to the SBRT arm, would SBRT be performed on *all* known disease. If yes this would indicate low tumour burden, if no high tumour burden. The virtual MDT will inform sites whether the patient has high or low tumour burden.

13.3 Statistical Analysis Plan

Analyses of efficacy will be according to the intention to treat principle. Time to event endpoints will be presented using Kaplan Meier survival plots and compared between treatment groups using the log-rank test. Hazard ratios will be derived from Cox proportional hazards models or methods such as restricted mean survival should the assumption of proportionality not be met. A planned subgroup analysis will explore treatment effect by mutation status (e.g. EGFR+ vs. other mutation), however it is recognised there is limited power to estimate these subgroup effects and thus analyses will be interpreted with the appropriate caution.

Patterns of further disease progression will be summarised by treatment group to document the natural history of oncogene-addicted lung disease.

Acute and late toxicity related to SBRT treatment, both physician and patient reported, will be analysed separately and summarised as frequencies and percentages at each time point with adjustment made for multiple testing. The proportion experiencing toxicity of any grade and grade ≥3 will be presented and any comparisons made between randomised treatment groups using Fisher's exact tests. All safety analyses will use a safety population which will be pre-defined in the Statistical Analysis Plan.

Quality of life (QoL) data will be analysed using standard algorithms to derive scores and handle missing data according to the chosen questionnaire's scoring manual. Descriptive statistics (median, IQR, range) will be presented by treatment group at each timepoint. Analyses to account for the longitudinal nature of the data may also be used.

The integral translational work will include assessment of ctDNA clearance as a binary outcome with comparison between randomised treatment groups made using Fisher's exact tests. Logistic regression models will be used to adjust for any relevant baseline characteristics. Exploratory analyses

will look at the genetic relationship between baseline circulating biomarkers and archival tumour samples.

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

13.4 Interim Analyses and Stopping Rules

The TSC will monitor recruitment rate and may recommend trial closure if it is significantly lower than expected and continuation of the trial is deemed futile.

A futility analysis will be conducted after 50% of the PFS events have been recorded (49 PFS events, ~70 patients recruited). If the HR >1.0 then treatment with SBRT will be deemed futile. This analysis will contribute to the decision for continuation to phase III.

The IDMC will review emerging safety data. This will include a formal safety review after 10 patients recruited to SBRT given concurrently with background TKI have completed the 3 month follow-up visit to assess the impact of concurrent background TKI on radiotherapy toxicity and after 10 patients recruited to SBRT given sequentially with the background TKI have completed the 3 month follow-up visit to assess disease flare (defined as disease progression occurring between stopping background TKI and restarting background TKI following completion of (initial) SBRT treatment).

In all patients randomised to SBRT, consideration will be given to stopping the trial should the rate of grade 4/5 acute radiotherapy-related toxicity (defined as within 90 days of last treatment administration, including repeat SBRT treatment as applicable) be unacceptable (to be agreed by the TMG and IDMC a priori).

14 TRIAL MANAGEMENT

14.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

14.2 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will comprise an independent Chairman and at least two further independent members with clinical or statistical expertise (at least one member must be a statistician). The TSC will meet at regular intervals, and at least annually. The TSC will provide expert independent oversight of the trial on behalf of the Sponsor and funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

14.3 Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) will monitor the progress of the trial and will comprise a Chairman and at least two further members with clinical or statistical expertise (at least one member must be a statistician). Membership of the IDMC will be proposed by the CI, ICR-CTSU or wider TMG and endorsed by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC and CRUK.

The IDMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

15 RESEARCH GOVERNANCE

15.1 Sponsor Responsibilities

The Sponsor of this clinical trial is the Institute of Cancer Research (ICR). The Sponsor is responsible for securing the arrangements to initiate, manage and finance the trial.

A coordinating group in each participating (non-UK) country will be delegated responsibility for trial initiation and conduct in that country on behalf of the Sponsor, as defined in an agreement between the Sponsor and the coordinating group.

15.2 Participating Site Responsibilities

Responsibilities of participating sites are defined in an agreement between the individual participating site and the Sponsor (UK) or the coordinating group delegated that responsibility by the Sponsor (non-UK).

16 TRIAL ADMINISTRATION & LOGISTICS

16.1 Site activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Sites will be notified via email when all requirements have been met and recruitment can commence. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

16.2 Investigator training

Each centre will be required to have completed the comprehensive pre-trial section of the quality assurance programme prior to commencing recruitment as detailed in the Radiotherapy Planning and Delivery Guidelines. To avoid duplication, every effort will be made to align quality assurance programmes with those of previous RTTQA approved trials (e.g. CORE) to minimise additional QA requirements. The radiotherapy QA programme will continue throughout the trial, with investigator training as required.

16.3 Data Acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

Data will be collected remotely from sites using the MACRO® database system and stored on ICR secure servers. Anonymised patient scans will be uploaded remotely onto the Institute's Research PACS (XNAT) system and stored on ICR secure servers.

16.4 Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

16.5 On-Site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring along with access to eCRF data.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

16.6 Completion of the Study and Definition of Study End Date

The study end date is deemed to be the date of last data capture.

16.7 Archiving

Essential trial documents should be retained according to local policy. Documents should be securely stored and access restricted to authorised personnel.

17 PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

17.1 Trial Approvals

This trial has been formally assessed for risk by ICR-CTSU.

In the UK, ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee for multi-centre trials and the Health Research Authority (HRA). Before entering patients, the Principal Investigator at each site is responsible for obtaining local R&D confirmation of site capacity and capability to conduct the trial.

The coordinating group in each country, on behalf of the Sponsor, will ensure that the trial has received all relevant ethical, regulatory and institutional approval prior to the recruitment of any patients.

17.2 Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Sponsor and in accordance with relevant national guidelines.

17.3 Informed Consent

Patients should be asked to sign the current ethics approved HALT consent form at trial entry after receiving both verbal and written information about the trial, having been given sufficient time to

consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for monitoring and audit. The current ethics approved HALT patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

17.4 Patient Confidentiality

Patients will be asked to consent to their full name being collected at trial entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected healthcare data and ensure accuracy in handling biological samples.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

17.5 Data Protection

ICR-CTSU will comply with all applicable data protection laws.

17.6 Liability

The coordinating group in each country will ensure that appropriate indemnity arrangements are place to meet the potential legal liabilities of investigators conducting the trial.

18 FINANCIAL MATTERS

This trial is investigator designed and led and has been approved by the Clinical Research Committee of Cancer Research UK.

ICR has received funding from Cancer Research UK for the central coordination of the trial. In the UK, the trial meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England. The trial is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio. NCRN resources should therefore be made available for the trial to cover UK specific research costs.

The coordinating group in each country will ensure that sufficient funding is available for the coordination and conduct of the trial.

19 PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies.

No investigator may present or attempt to publish data relating to the HALT trial without prior permission from the TMG.

20 ASSOCIATED STUDIES

20.1 Translational study

20.1.1 Comparison of archival tumour DNA with ctDNA to assess baseline OPD

Collection and next generation sequencing of archival tumour DNA and ctDNA at baseline to assess the mutational heterogeneity of oligoprogressive NSCLC will be performed. We hypothesize that the different possible mechanisms of resistance to EGFR/ALK TKI may affect sensitivity to SBRT.

20.1.2 Analysis of circulating biomarkers to assess ctDNA kinetics and tumour evolution following SBRT.

The half life of ctDNA is 0.5-2 hours. We intend to assess the release of ctDNA following the first and last fraction of SBRT to quantify the magnitude of diversity of cfDNA as a marker of response to SBRT. We hypothesis that those patients with the highest fold change in ctDNA from peak level to nadir at first follow-up will have prolonged benefit from SBRT. We will monitor ctDNA levels during follow-up and at subsequent progression. We hypothesize that ctDNA will be useful to detect early relapse in the setting of SBRT.

20.1.3 Identification of circulating immune biomarkers of response to SBRT.

Abscopal responses, regression of lesions distant from the irradiated site, have been documented in patients treated with external beam radiotherapy. Immune responses as a result of antigen release or immunogenic cell death in the context of ionising radiation are thought to be responsible for this. We hypothesize that clinically translatable biomarkers of the immune response, detectable in the peripheral blood, will predict patient likely to have durable clinical benefit (disease control > 6 months) following SBRT.

The above translation studies will be supported by the analysis of paired pre and post treatment tissue biopsies (where available).

20.2 Quality of Life study

Quality of Life (QoL) will be a secondary endpoint in the main trial and will be analysed as described in detail in the statistical analysis plan.

20.2.1 Quality of life measures

Patient reported outcomes will be measured using the EORTC QLQ C30 and the EQ-5D-5L. Patients will complete the EORTC QLQ C30 general cancer questionnaire and the EQ-5D-5L questionnaire, which is a brief standardised instrument that provides a simple descriptive profile of their health status.

20.2.2 Study design

Patients are eligible for the QoL/PRO study if they fulfil the HALT eligibility criteria. Participants will be asked in the patient information sheet to consent to regular completion of QoL/PRO questionnaires. Patients who decline to take part in the HALT QoL study will remain eligible for the main trial. QoL/PRO is a secondary endpoint in the main trial and the primary time point of interest is 8 weeks after randomisation for both groups of patients.

20.2.3 Timing of data collection

Participants will be asked to complete the questionnaires after informed consent is obtained during their clinic visit at the following time points; 1) before treatment allocation is known to the patient (treatment vs control group)), 2) 8 weeks post randomisation and 3) during the first 3 monthly follow-up visit.

20.2.4 Compliance

Missing data may hamper interpretation of PRO. Missing data may arise because participants do not complete the questionnaires at the appropriate time (unit non-response), or because patients may miss questions within the questionnaires (item non-response). During the study, compliance with PRO questionnaire completion will be monitored by the trial oversight committees.

20.2.5 Statistical considerations

Patient reported outcome analyses will be used to supplement results of clinician assessed treatment toxicity; therefore a formal sample size calculation has not been performed. An analysis plan will be developed in consultation with the TMG with key endpoints identified from each questionnaire. Standard algorithms will be used to derive scores and handle missing data in quality of life questionnaires. Quality of life data will be presented at individual time-points and analyses to account for the longitudinal nature of the data may be used.

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A1. Phase II to III transition - Rationale and Considerations

Design and Rationale

HALT has been designed as a randomised, multi-centre, phase II/III study with planned international participation. The study incorporates a seamless transition from phase II to III providing a more efficient use of time and resources whilst minimising the total number of patients required; patients recruited to the phase II will contribute to the primary endpoint of overall survival in the phase III trial. The transition to the phase III trial will be dependent on feasibility data obtained during the phase II study and securing of appropriate funding for the phase III trial.

The current protocol supports the phase II trial and transition period with a subsequent funding application required to support the phase III trial.

Assessment of phase III feasibility

It is anticipated that the criteria for determining advancement from the phase II trial to the phase III will occur at approximately halfway through the trial (estimated 50% PFS, approximately 70 patients recruited), a pragmatic timepoint chosen to maximise the information gained about recruitment, compliance and safety while allowing sufficient data to be collected to allow a formal futility analysis to be conducted. The following criteria will be assessed at this timepoint:

Recruitment	Phase II recruitment rates will be assessed to determine whether this is on target (subsequent to incremental setup phase). The predicted impact of international participation will also be considered. The likelihood of delivering the required phase III sample size will be evaluated following updated projected numbers informed by the first half of the phase II trial and evidence from contemporary literature.
Futility analysis	The futility of the SBRT strategy as defined in HALT will be assessed after approximately 50% of events (~70 patients recruited) have occurred.
Compliance	Compliance rates will be reviewed as a measure of trial feasibility. If a procedure/process can be identified to be a significant cause of non-compliance, the trial can be adapted to increase compliance rates
Safety	Grade 4/5 acute SBRT-related toxicity incidence and acceptability as determined by the IDMC Acceptable patient toxicity levels at centres where SBRT given concurrently with background TKI, as assessed by the IDMC Acceptable disease flare cases at centres treating patients sequentially with SBRT followed by background TKI as assessed by the IDMC

The independent HALT Trial Steering Committee will use the information obtained by the feasibility assessment including any advice and recommendations from the IDMC to guide its decision as to whether progression to a phase III trial should proceed.

If the HALT TSC determine the criteria have not be reached to a sufficient degree and advise against proceeding to a phase III the phase II trial will proceed to its conclusion as detailed in this protocol. Proposed actions for of transition to phase III.

If the decision to proceed to the phase III is made, additional funding will be required to support the development and conduct of the trial. The interim analysis planned during the phase II is intended to occur at a timepoint that allows a sufficient period of time to apply and obtain funding whilst allowing

recruitment to continue ahead of the phase III trial. A period of 12 months from interim analysis to funding confirmation is anticipated to allow sufficient time to apply and obtain funding. Recruitment will continue to the phase II trial during this period and it is possible that accrual will continue past the phase II required sample size depending on the rate of recruitment and timeframe for funding confirmation (given the constraints of funding application deadlines).

i) *Funding is confirmed for the phase III trial* - Following confirmation of funding a 6 month period is anticipated to allow for the appropriate approvals and documentation to be put in place prior to commencing the phase III trial. The seamless transition from phase II to phase III will allow recruitment to continue during this period with patients contributing to the phase III trial.

ii) *Funding is not confirmed for the phase III trial* - If funding approval is not received, recruitment will cease as quickly as possible once the phase II sample size has been reached to limit any over-recruitment. All patients randomised will contribute to the phase II primary endpoint of progression free survival.

Sample Size and statistical design of the phase III trial

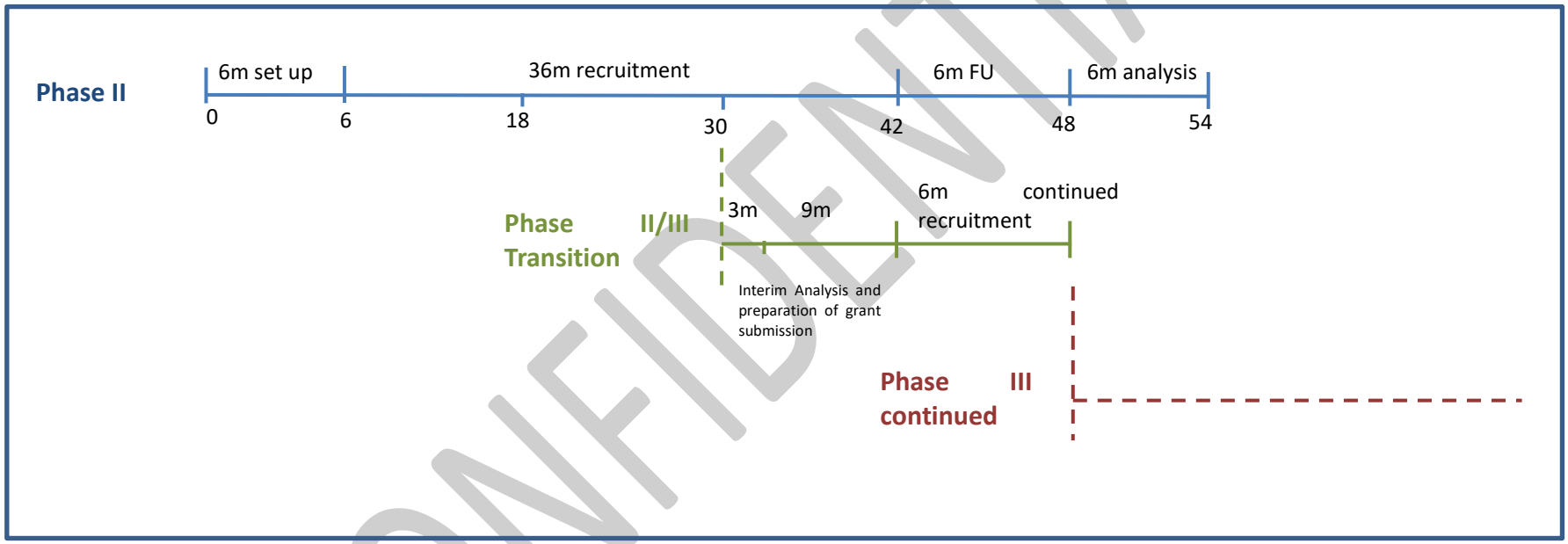
The primary endpoint of the phase III trial is expected to be overall survival. At this stage an average median survival of 12 months is anticipated in the control group. The number of patients required for the phase III will be influenced considerably by the designated magnitude of minimum clinically important difference and the estimate below will be refined following the phase II trial:

Assuming a 5 year recruitment period, a total of 272-875 patients (power 80%, alpha 5%) would be required to detect a 6 month or 3 month improvement in overall survival with SBRT (12 to 18 month and 12 to 15 month improvement respectively). It is anticipated that the designated number of patients required will lie within this range. Given the rare population and the integrated design of the trial it is envisaged that patients recruited to the phase II component will also contribute to the phase III endpoint.

Patients recruited to phase II will contribute to the primary endpoint of overall survival in the phase III trial. It is anticipated that the method proposed by Jenkins M et al. [26] will be used to avoid bias given patients recruited to phase II will also be used to determine PFS (a criterion for moving to a phase III trial). Briefly, overall survival will be calculated separately for patients recruited to the phase II part and those additional patients recruited subsequent to the phase II. Overall survival comparisons are not performed until the end of the phase III trial. P-values for overall survival in each set of patients at this point will be combined [27].

Assumptions made about the phase III trial design and sample size will be re-assessed for relevance and suitability during the transition phase.

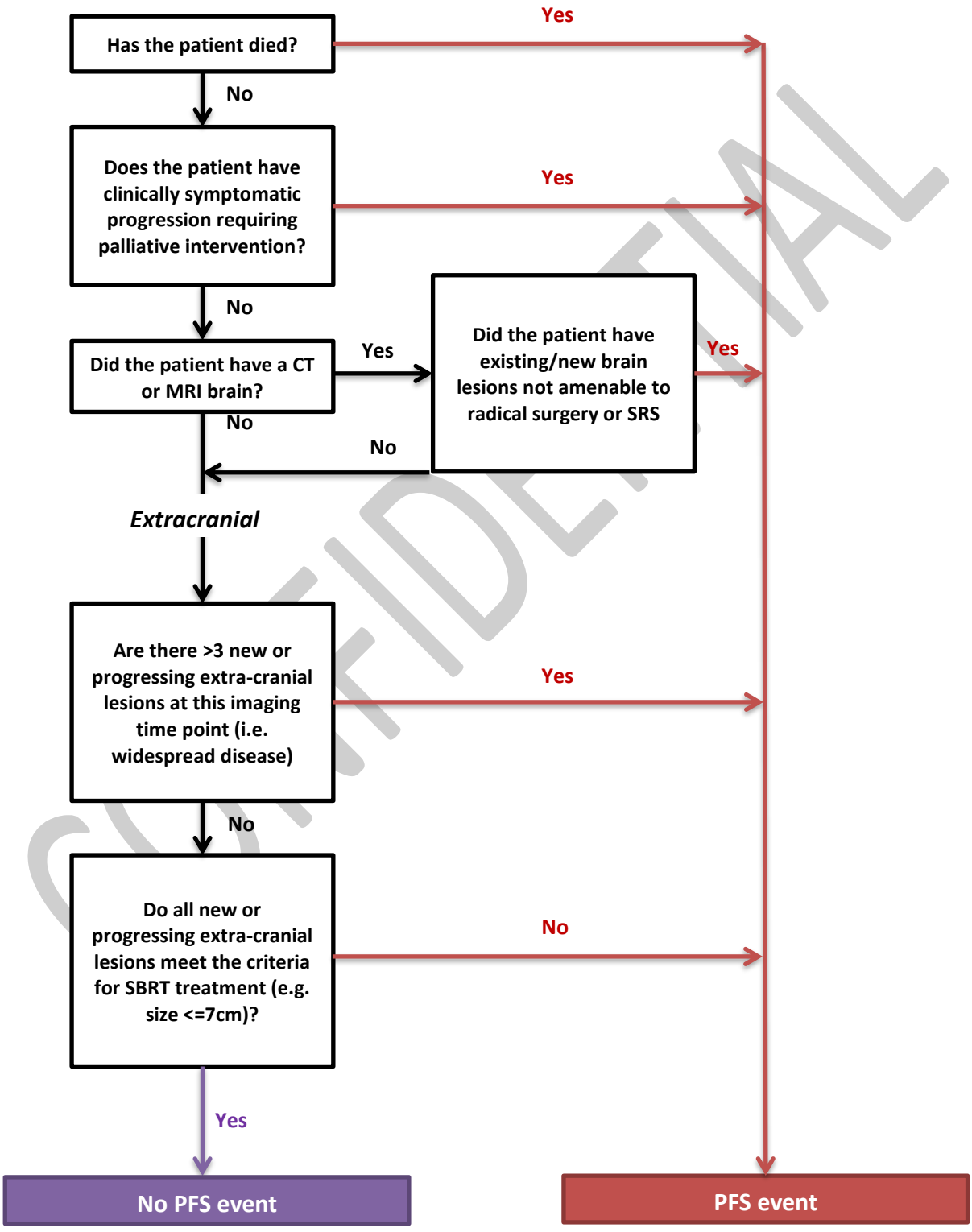
HALT Phase II/III Transition Timelines



A2. Progression Free Survival (PFS) Classification Flow Chart

This flow chart should be used at each extracranial scan following trial entry. The flowchart addresses the **intention** of treating with SBRT so allows for assessment in the control group as well as the SBRT (treatment) group

HALT PFS event criteria



A3. MRC Dyspnoea Scale

MRC Dyspnoea Scale	
Grade	**Degree of breathlessness related to activity**
1	Not troubled by breathless except on strenuous exercise
2	Short of breath when hurrying on a level or when walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking 100 yards, or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing/undressing

A4. WHO performance status

Grade	*Performance Status*
0	*Able to carry out all normal activity without restriction.*
1	*Restricted in physically strenuous activity but ambulatory and able to carry out light work.*
2	*Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.*
3	*Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.*
4	*Completely disabled; cannot carry on any self-care; totally confined to bed or chair.*

A5. Karnofsky Score

Score	*Status*
100	*Normal; no complaints; no evidence of disease.*
90	*Able to carry on normal activity; minor signs or symptoms of disease.*
80	*Normal activity with effort; some signs or symptoms of disease.*
70	*Cares for self; unable to carry on normal activity or to do active work.*
60	*Requires occasional assistance, but is able to care for most of their personal needs.*
50	*Requires considerable assistance and frequent medical care.*
40	*Disabled; requires special care and assistance.*
30	*Severely disabled; hospital admission is indicated although death not imminent.*
20	*Very sick; hospital admission necessary; active supportive treatment necessary.*
10	*Moribund; fatal processes progressing rapidly.*
0	*Dead*

A6. Expected serious adverse events

The following adverse events are considered expected if grade ≤2 and are exempt from SAE reporting procedures detailed in the protocol. Events should however still be reported to ICR-CTSU using the appropriate CRF.

SBRT group

Thoracic and mediastinum

- Pericarditis
- Dysphagia
- GI haemorrhage
- Gastritis
- Cough
- Pneumonitis
- Dyspnoea

L1-3, Liver, Adrenal, Kidney, Para-aortic

- Nausea
- Vomiting
- Spinal fracture
- Upper GI ulcer
- Duodenal/Gastric ulcer
- Upper GI bleeding
- Liver enzymes: ALT
- Bilirubin

L4-5, Sacrum, pelvic bones, pelvic nodes/side wall

- Diarrhoea
- Proctitis
- Lower GI ulcer
- Lower GI bleeding
- Rectal Haemorrhage
- Haematuria
- Urinary frequency
- Urinary incontinence
- Urinary retention
- Urinary urgency

General

- Fever
- Fatigue
- Myelitis

Dermatology/Skin

- Dermatitis
- Hair loss (to treatment area)

Related to fiducial marker insertion

- Bleeding
- Sepsis (urinary and systemic)
- Pneumothorax

A7. Non-UK safety reporting requirements

The site Principal Investigator or designee is responsible for reporting SAEs to the ICR-CTSU as per the protocol.

The EORTC will report related unexpected SAEs as per national requirements to IECs and local investigators.

Further Sponsor safety reporting notification requirements will be agreed in the international site agreements.

A8. Translational study collection (6 sampling points per patient)

	Baseline	Post fraction 1 of SBRT ~0.5-1 hour post treatment	First follow-up visit (8 weeks post randomisation)	Follow-up Month 5 & 8	Progression
TISSUE	**FFPE Research Block**				**FFPE Research Block**
BLOOD	**GL DNA**: 10ml (EDTA) **cfDNA**: 2 x 10ml (Streck tube) **RNA**: 1 x Tempus™ tube	**cfDNA**: 2 x 10ml (Streck tube)	**cfDNA**: 2 x10ml (Streck tube) **RNA**: 1 x Tempus™ tube	**cfDNA**: 2 x 10ml (Streck tube)	**cfDNA**: 2 x 10ml (Streck tube)

GL DNA = Germ Line DNA (collected in EDTA tube)

cfDNA = circulating free tumour DNA (Streck tube)

RNA = RNA for analysis of T cell Repertoire from peripheral blood (1 x Tempus™ blood RNA tube – 3ml blood draw)

FFPE Research Block: When available additional cores from biopsy of oligoprogressive lesions should be placed in a separate pot for fixation in FFPE at baseline and at the time of progression if biopsy was clinically indicated. Clinical diagnostic requirements take precedence.

A9. GLOSSARY

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CI	Chief Investigator
CIS	Carcinoma In Situ
CRF	Case Report Form
DCF	Data Capture Form
DFS	Disease Free Survival
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FBC	Full Blood Count
G-CSF	Growth Colony-Stimulating Factors
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
IB	Investigator's Brochure
ICR	The Institute Of Cancer Research
IDMC	Independent Data Monitoring Committee
LFT	Liver Function Test
MDT	Multi-disciplinary team
MRC	Medical Research Council
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OAR	Organs At Risk
PI	Principal Investigator
PIS	Patient Information Sheet
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised controlled trial
RTTQA	NCRI Radiotherapy Trials Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT	Stereotactic Body Radiotherapy
SMPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TMG	Trial Management Group
TSC	Trial Steering Committee
U+E	Urea & Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organisation