A Randomised phase II trial of Enhancement of efficacy of Atezolizumab by Radiotherapy in Metastatic urothelial carcinoma

PROTOCOL

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Sponsor:	The Institute of Cancer Research
Funder:	Roche
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

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The RE-ARM trial has been endorsed by Cancer Research UK's Clinical Research Committee (CRC) and is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

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ICR-CTSU (a UKCRC registered and NCRI cancer clinical trials unit) is responsible for the central coordination of the trial on behalf of the sponsor.

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Sample collection

The Targeted Therapy Group (Principal Investigator Prof Timothy Illidge) at the University of Manchester is responsible for receiving tissue samples collected within RE-ARM.

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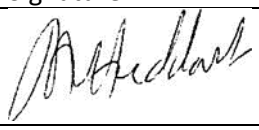
The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, key ICR-CTSU staff and a lay representative. Principal Investigators and key study personnel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

Protocol Authorised by:

Name & Role	Signature	Date
Professor Robert Huddart (Chief Investigator)		31/05/2022

This protocol describes the RE-ARM 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.

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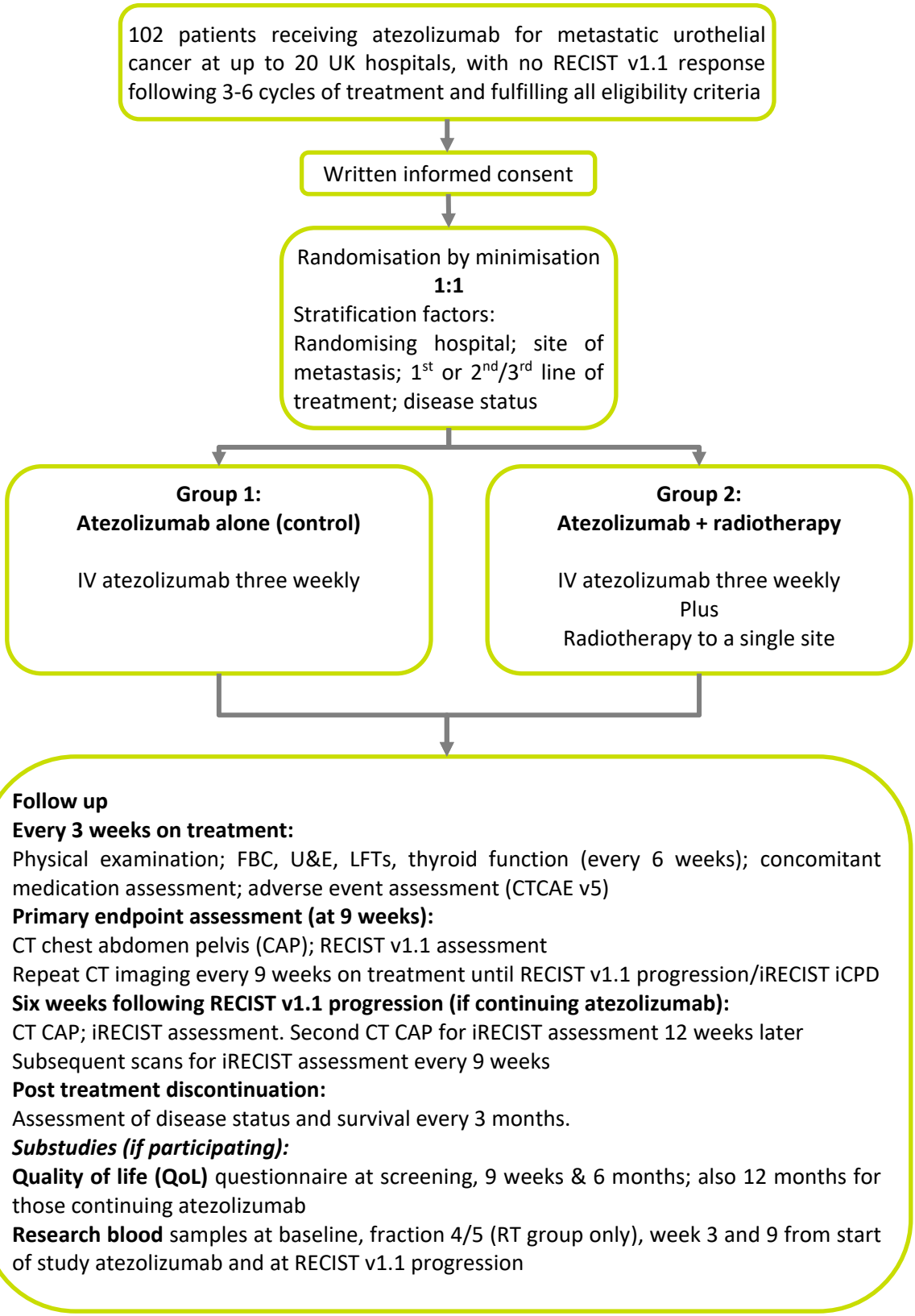
RE-ARM TRIAL SUMMARY

PROTOCOL TITLE	**RE-ARM:** A Randomised phase II trial of Enhancement of efficacy of Atezolizumab by Radiotherapy in Metastatic urothelial carcinoma
TARGET DISEASE	Metastatic urothelial cancer
STUDY OBJECTIVES	**Primary objective:** To assess whether radiotherapy to the primary site or a metastatic lesion can improve response to atezolizumab. **Secondary objectives:** To determine toxicity, response according to iRECIST, clinical benefit (PR, CR and SD at 9 weeks), time to progression, progression free survival, overall survival and patient reported quality of life. Exploratory objectives: To correlate changes in biomarkers with toxicity, response to treatment and survival.
STUDY DESIGN	Randomised controlled open label phase II trial with a group-sequential design.
TRIAL POPULATION	Patients receiving atezolizumab for metastatic transitional cell carcinoma of the urothelial tract.
RECRUITMENT TARGET	102 patients.
TREATMENT REGIMEN	Atezolizumab +/- radiotherapy to the primary site or a metastatic lesion. All participants will receive intravenous atezolizumab 1200mg three weekly until loss of clinical benefit or unmanageable toxicity up to a maximum of 2 years' treatment. Radiotherapy (if allocated), 20Gy in 5 fractions. The first dose should be delivered during the first cycle of on study atezolizumab, starting on day 1 cycle 1 if possible. Target volume will be the investigator defined gross tumour volume (GTV) plus 0.5 cm. CTV plus 0.5 – 1.0 cm will be the planning target volume (PTV).
PRIMARY ENDPOINT	Response at 9 weeks (RECIST v1.1)
SECONDARY ENDPOINTS	Response according to iRECIST; clinical benefit at 9 weeks; best response up to 6 months; duration of response; time to progression; progression free survival; overall survival; treatment related toxicity; patient reported quality of life.
EXPLORATORY ENDPOINTS	Molecular and pathological changes in response to atezolizumab +/- radiotherapy
FOLLOW UP	Participants will have CT chest, abdomen and pelvis imaging every 9 weeks in the first year and every 12 weeks in the second, or until RECIST v1.1 progression/iRECIST iCPD and treatment discontinuation. Following discontinuation of atezolizumab participants will be assessed for disease status and survival every 3 months.

TRIAL SCHEMA



Primary endpoint: Response at 9 weeks (RECIST v1.1)

Secondary endpoints: Response according to iRECIST; clinical benefit; best response; duration of response; time to progression; progression free survival; overall survival; treatment related toxicity; patient reported QoL.

1. INTRODUCTION

1.1. Background

Bladder cancer is the 10th most common cancer in the UK, with around 10,000 new diagnoses per year. Between 17% and 20% of bladder cancer patients have metastases at first diagnosis. This group has a one year survival of 33%(1).

Atezolizumab is a checkpoint inhibitor which targets the PD-L1 protein on cancer cells. PD-L1 signals to the PD-1 protein on immune cells, causing them to identify cancer as normal cells. Atezolizumab is designed to block those signals and expose the cancer cells to the immune system.

Atezolizumab is one of few treatment options available for patients with metastatic urothelial carcinoma(2, 3) and has been demonstrated within the IMvigor210 phase II study to induce durable responses in 15%-20% of patients(4, 5). This is consistent with data from the preceding atezolizumab phase I/II trial(6) and data on other PD1/PD-L1 inhibitors(7). Whilst the rate of response observed in IMvigor210 was higher in patients whose tumours had high PD-L1 expression (27%; 95% CI: 19-37), responses were also seen in PD-L1 negative patients, with an overall response of 15% (11-20) in patients receiving treatment following progression on platinum based chemotherapy(5). A subsequent phase III trial, IMvigor211, which compared atezolizumab to second line chemotherapy brought equivocal results. The trial had a hierarchical design testing first outcome in patients positive for the PDL1 biomarker (PDL1 2/3+ patients). As there was no significant difference in this population (atezolizumab median 11·1 months [95% CI 8·6-15·5; n=116] vs chemotherapy 10·6 months [8·4-12·2; n=118) stratified hazard ratio [HR] 0·87, 95% CI 0·63-1·21; p=0·41)(8) further formal statistical analysis was precluded. In the subsequent exploratory analysis all patient intention-to-treat analysis, atezolizumab showed superior survival with 12 month survival of 39% after atezolizumab versus 32% after chemotherapy (Stratified HR 0·85, 95% CI 0·73–0·99). This result mirrored the results seen with the PD1 inhibitor, pembrolizumab, that demonstrated a significant survival advantage versus second line chemotherapy in an unstratified population (median survival 10.3 months (95% confidence interval [CI], 8.0 to 11.8) versus 7.4 months (95% CI, 6.1 to 8.3 (hazard ratio for death, 0.73; 95% CI, 0.59 to 0.91; P = 0.002).

Subsequently, activity has been shown in a parallel cohort of cisplatin-ineligible patients treated with first line atezolizumab within IMvigor210. 119 patients received one or more doses of atezolizumab. An objective response rate for atezolizumab of 23% (95% CI 16 to 31), was achieved with 19 of 27 responses ongoing at a median of 18 months follow up. Median overall survival was 15·9 months (10·4 to not estimable)(4). Comparable results have been seen for similar agents(9). More recently the early results of the IMvigor130 study showed that a combination of atezoluzimab and gemcitabine plus cisplatin or carboplatin improved progression free survival by a median of two months compared to chemotherapy alone(10).

As the result of these data atezolizumab, pembrolizumab and nivolumab have been licensed by the EMA for the treatment of urothelial cancer after chemotherapy and atezolizumab and pembrolizumab have been licensed for first line treatment of cisplatin-ineligible patients. Based on emerging confidential data from phase 3 trials, the license in first line setting was restricted to patients who are PDL1 positive in July 2018.

Under the IMvigor210 protocol, patients with initial radiological progression who met pre-specified criteria could continue treatment, if felt clinically appropriate by their treating clinician. 121 of 310 patients in a group pre-treated with platinum continued treatment under these circumstances. A proportion of these (17%) went on to have a clinical response despite initial progression and others developed disease stability(5).

1.2. Abscopal response

PD-L1 positivity is a dynamic process and radiotherapy may lead to upregulation of PD-L1 expression in tumours(11). Radiotherapy can also augment both the innate and adaptive immune response to tumours(12) and lead to release of immunogenic tumour-related antigens. Though the immune response to radiotherapy alone may be weak, it can be enhanced by the combined use of immunomodulatory drugs and in this context radiotherapy can act as an in situ vaccine(13). Generation of an anti-tumour T cell response is important for a lasting clinical response to immunotherapy. Emerging pre-clinical and clinical studies indicate that radiotherapy in combination with immunotherapy leads to both the diversification and intensification of T-

cell receptor clones in the blood(14-18). This can lead to an abscopal response i.e. tumour shrinkage at a distance from the radiotherapy field.

In vivo studies indicate that anti-CTLA4 immunotherapy and radiotherapy can successfully induce both direct and abscopal responses in murine models of breast and colorectal cancer(19). In this context, repeated moderate size fractions of radiotherapy (5x6Gy or 3x8Gy), rather than single ablative doses (1x20Gy) were better at stimulating an abscopal response(20). At a mechanistic level, repeated moderate size fractions of radiotherapy optimally stimulate the cGAS/STING/type 1 interferon pathway whereas larger fractions trigger the DNA exonuclease Trex1 thus attenuating STING pathway activation(19). In mouse models of renal cancer and melanoma, the combination of stereotactic radiotherapy (SABR) plus PD-1 blockade induced more complete regression of the irradiated primary tumour (synergistic effect), compared to SABR alone or SABR plus control antibody(21). The combination of SABR plus PD-1 blockade therapy resulted in a 66% reduction in size of non-irradiated tumours outside the SABR radiation field.

1.3. Radiotherapy fractionation and immune response

As described above, optimal radiotherapy fractionation schedules in combination with immune checkpoint blockade has been explored extensively in pre-clinical models. In this context, moderate sized fractionation (5x6Gy or 3x8Gy) appears to optimally stimulate a type 1 interferon response in mice, which then drives a downstream abscopal response(20). The total dose of radiotherapy is also important as demonstrated by the fact that 3x8Gy gave significantly better responses than a single 8Gy fraction(19). Optimisation of dose fractionation has not been carried out in a human context, although the 3x8Gy schedule has been investigated in combination with immune checkpoint blockade in both metastatic non-small cell lung cancer(17) and metastatic urothelial carcinoma(22). The non-randomised nature of both of these studies means it is impossible to ascertain whether an abscopal effect is occurring or whether clinical responses are entirely due to immunotherapy alone. However, the rates of disease control are encouraging and support further translation of rational schedules, based on pre-clinical data, into clinical trials.

1.4. Known risks and benefits of immunotherapy in combination with radiotherapy

In a human context, a number of case reports in a range of cancers, particularly in melanoma and non-small cell lung cancer, describe remarkable systemic responses to radiotherapy when given during immune modulatory treatment(23-28). The combination of anti PD1-based immunotherapy and palliative hypofractionated radiotherapy appears to be well tolerated by patients(29). In a recent meta-analysis of 16 studies which included 451 patients with metastatic melanoma treated with radiotherapy and the CTLA-4 inhibitor, ipilimumab, an abscopal effect was reported in 26.5% patients (median effect across 8 studies that quantified the abscopal response rate) and median overall survival was 19 months(30). In a non-randomised study of 39 heavily pre-treated patients with metastatic non-small cell lung cancer receiving radiotherapy and ipilimumab, a radiological response rate of 33% was seen in evaluable patients. Adverse events were typical of ipilimumab and were not increased with the addition of radiotherapy.

In metastatic urothelial carcinoma, a phase I study assessed 3 x 8Gy administered either just before the first cycle of pembrolizumab or just before the third cycle(22). This study showed acceptable toxicity profiles with no dose limiting toxicities and only one grade three treatment-related adverse event. In addition, in this small study, encouraging clinical responses were seen in the cohort receiving radiation just before the third cycle of pembrolizumab. The PLUMMB study investigated 36Gy/6 fractions administered to the whole bladder in combination with pembrolizumab. Significant toxicity occurred with this dose fractionation with three out of five patients experiencing grade 3 bladder toxicity and a further patient experiencing grade 3 bowel toxicity(31). As a consequence, the trial design has been amended with a reduction in total radiotherapy dose to 30Gy/5 fractions. Collectively, these studies indicate that radiation administered in combination with immune checkpoint blockade is worthy of further study in bladder cancer. However, careful choice of radiotherapy fractionation schedules is necessary to achieve induction of type 1 interferon yet avoid dose-limiting toxicity, particularly in the pelvis.

1.5. Study rationale

RE-ARM will explore whether the additional late responses as observed in IMvigor210 could be enhanced with radiotherapy in patients receiving atezolizumab for the treatment of metastatic urothelial carcinoma.

PD1/PD-L1 treatment has proven benefit for a subset of patients with metastatic urothelial carcinoma. As the study tests a drug-radiation combination therapy, a randomised design was selected to enable quantification of the impact of radiotherapy on response, given that a late response is observed in a subset of patients receiving atezolizumab in the absence of additional intervention. As tumour shrinkage is hypothesised (the abscopal effect), response was deemed a preferable primary endpoint over progression-free survival. If this study demonstrates that radiotherapy treatment increases atypical responses in patients on PD-L1 therapy with minimal impact on toxicity, this could substantially expand the number of patients who benefit from immunotherapy treatment. The trial has a two stage design to allow early termination if sufficient activity is not observed in the experimental group.

Translational work within the study may offer insights to the dynamic process of PD-L1 expression and immune activation that may have implications for tumours that are currently unresponsive to immune therapy across cancer types.

2. TRIAL OBJECTIVES

2.1. Primary objective

The primary objective is to assess whether radiotherapy enhances response to atezolizumab (RECIST v1.1).

2.2. Secondary objectives

Secondary objectives are to assess treatment related toxicity, response according to iRECIST, clinical benefit, progression-free survival, overall survival and patient reported quality of life.

2.3. Exploratory objectives

To correlate changes in biomarkers with toxicity, response to treatment and survival

3. TRIAL DESIGN

RE-ARM is a multi-centre randomised controlled phase II trial of atezolizumab with or without radiotherapy in metastatic urothelial carcinoma. It has a group-sequential design incorporating a formal stopping rule for lack of efficacy.

4. STUDY ENDPOINTS

4.1. Primary endpoint

Objective response (CR [complete response] + PR [partial response] according to RECIST v1.1) at 9 weeks after start of study treatment.

4.2. Secondary endpoints

- Response according to iRECIST
- Clinical benefit at 9 weeks after starting study treatment (CR/PR/SD according to RECIST v1.1)
- Best response up to 6 months according to RECIST v1.1 and iRECIST
- Duration of response
- Time to progression
- Progression free survival
- Overall survival
- Treatment related toxicity
- Patient reported quality of life, assessed using the EORTC QLQ-C30 (32) & EQ-5D-5L (33)

4.3. Exploratory endpoints

Molecular and pathological changes in response to atezolizumab +/- radiotherapy.

5. PATIENT SELECTION & ELIGIBILITY

5.1. Number of participants

Planned recruitment is 102 participants, 51 in each randomised group.

5.2. Source of participants

Participants will be recruited from approximately 20 participating sites in the UK. Potential participants will be identified in oncology clinics.

ICR-CTSU encourages investigators to consider equality, diversity and inclusion when recruiting participants into its trials.

Eligibility criteria are listed below – if there are any queries regarding a potential participant's eligibility for RE-ARM please contact the RE-ARM trial manager (REARM-icrctsu@icr.ac.uk).

5.3. Inclusion criteria

1. Histologically confirmed metastatic urothelial carcinoma not amenable to curative treatment with surgery or radiotherapy. Mixed histology is permitted if predominantly TCC.
2. Received a minimum of 3 cycles and maximum of 6 cycles of open label atezolizumab treatment* (either first, second or third line¥) with an overall best response of stable disease according to local investigator assessment.
3. At least one extra-cranial metastatic site suitable for radiotherapy (see section 9.1).
4. At least one RECIST v1.1 measurable lesion distant to the planned site of radiotherapy.
5. No radiotherapy within four weeks prior to starting pre-study atezolizumab or during atezolizumab treatment.
6. Satisfactory haematological and biochemical profile (Hb >90 g/L, Plt>100 x 10^9/L, WBC > 3.0 x 10^9/L, creatinine < 1.5 ULN, AST or ALT <3X ULN, bilirubin <1.5x ULN).
7. ECOG PS 0-1.
8. Age ≥18 years.
9. Written informed consent.

* In accordance with therapeutic indications as stated in the current summary of product characteristics.

¥ Neoadjuvant treatment received more than a year prior to trial entry will not be considered a line of treatment.

5.4. Exclusion criteria

1. Any contraindication to continued atezolizumab treatment in the local investigator's opinion (e.g. toxicity (see section 9.6), rapidly progressive disease requiring alternative treatment such as chemotherapy).
2. Planned or anticipated clinical need for palliative radiotherapy within nine weeks following trial entry.
3. Received anti-PD1/PD-L1, anti-CTLA-4 therapy prior to commencement of atezolizumab.
4. Received atezolizumab in combination with chemotherapy.
5. Immunosuppressive treatment (apart from corticosteroids at a dose equivalent of prednisolone ≤10mg daily) within 2 weeks prior to randomisation.
6. Contraindication to radiotherapy (e.g. radiation sensitivity syndrome).
7. Autoimmune disease requiring active immunotherapy treatment or with life threatening complications. Patients with vitiligo, controlled psoriasis, autoimmune thyroid disease, type 1 diabetes will be eligible.
8. History of pneumonitis.
9. Presence of known active brain metastases (brain metastases which have received treatment and are controlled do not preclude randomisation).
10. Active HIV, hepatitis B or hepatitis C infection – patients with asymptomatic or controlled disease may join the trial following review and approval by the Chief Investigator. Participants with these conditions, either active or previous, are not eligible to provide samples for the translational substudy.

11. Pregnant or lactating women.
12. Administration of a live, attenuated vaccine within 28 days prior to study entry.
13. Anticipated life expectancy <10 weeks.

5.5. Lifestyle guidelines

Female participants must be surgically sterile or be post-menopausal, or must agree to use effective contraception during the period of therapy and for five months after the last dose of study treatment.

Male participants must be surgically sterile or must agree to use effective contraception if their partner is of child bearing age during the period of therapy and for five months after the last dose of study treatment.

Effective contraception is defined as double barrier contraception (e.g. condom plus spermicide in combination with a diaphragm, cervical cap or intrauterine device).

6. SCREENING

6.1. Screening log

All participating sites will be required to keep a log of all patients with metastatic urothelial carcinoma receiving atezolizumab who are potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Date PIS given (if applicable)
- Trial ID (if applicable)

This information will be used by the TMG to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU.

6.2. Procedure for obtaining informed consent

The Principal Investigator (or designated individual) must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with participation. Patients who are receiving atezolizumab from hospital stock for metastatic urothelial carcinoma should be made aware of the trial. Once a patient is deemed potentially eligible for the trial, they should be given the current ethics approved RE-ARM 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.

No protocol required assessments should be conducted until the RE-ARM 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.

Patients who consent to RE-ARM will be asked to consent to donate archival tissue and blood samples for translational studies. Patients should be made aware that participation in the sample collection sub-study is entirely voluntary.

Patients who consent to RE-ARM will be asked to consent to regular completion of the EORTC QLQ-C30 and EQ-5D-5L questionnaires. Patients should be made aware that participation in the quality of life sub-study is entirely voluntary.

Confirmation of the patient's eligibility, 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 investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

6.3. Participation in other clinical trials

Participation in previous clinical trials does not preclude entry into RE-ARM.

RE-ARM patients will not be permitted to participate in any other trials of investigational medicinal products whilst they are being treated within RE-ARM.

Participation in other research studies will be considered on a case by case basis by the TMG.

7. RANDOMISATION

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

Patients should be randomised by emailing the ICR-CTSU randomisation service on:

randomisation-icrctsu@icr.ac.uk

and requesting a call back.
The randomisation email account is monitored 09.00-17.00 (UK time) Monday to Friday.

Randomisation should take place within two weeks prior to the planned start date of study atezolizumab. An eligibility and randomisation checklist must be completed prior to randomisation.

The following information will be required at randomisation:

- Name of hospital, consultant and person calling to randomise patient
- Confirmation that patient has given written informed consent for trial and for any sub-studies;
- 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
- Planned site of radiotherapy
- Line of treatment (first or second/third)
- Confirmation of whether the patient has metastasis to the liver and/or bone (yes/no)
- Disease status (progressive disease/stable disease)
- Date of last atezolizumab administration
- Planned start date of study atezolizumab (gaps between hospital stock and study drug should be minimised, with study drug planned to commence within 5 weeks from date of last hospital stock atezolizumab dose)
- Anticipated start date of radiotherapy (if allocated)

The caller will be given the patient's unique randomisation number (Trial ID) and treatment allocation.

ICR-CTSU will send written confirmation to the data management contact and pharmacist at the recruiting site to confirm a patient's entry into the trial.

8. TRIAL ASSESSMENTS

8.1. Screening assessments

The following assessments should be conducted within 28 days prior to randomisation unless otherwise indicated:

- Physical examination
- Medical history
- ECOG performance status assessment
- Full blood count, urea and electrolytes, amylase and liver function assessment
- Thyroid function assessment
- Serology (HIV, hepatitis B, hepatitis C) (within 12 months prior to randomisation)
- Concomitant medication assessment
- Adverse event assessment (CTCAE v5)
- CT chest abdomen pelvis (CAP) and RECIST v1.1 assessment*
- QoL sub-study questionnaire (if participating): EORTC QLQ-C30 and EQ-5D-5L

*The planned site of radiotherapy should not be used for RECIST v1.1 assessment (as either a target or non-target lesion), but measurement of this lesion should be recorded on the dedicated eCRF.

8.2. Baseline blood samples

If the participant is taking part in the translational substudy, the following samples should be obtained after randomisation and prior to commencement of trial treatment:

- EDTA 10ml x 3, Tempus 3ml and Streck 10ml

8.3. On-treatment assessments

Patients will receive study atezolizumab 1200mg IV three weekly until loss of clinical benefit or unmanageable toxicity. If allocated, radiotherapy should start on the same day as the first cycle of study atezolizumab if possible. For further details see section 9 – Trial Treatment.

The following assessments should be conducted before each three-weekly cycle of atezolizumab (within 72 hrs prior to day 1):

- Physical examination as clinically indicated
- Full blood count, urea and electrolytes, amylase, liver function assessment
- Concomitant medication assessment
- Adverse event assessment (CTCAE v5)

Every six weeks:

- Thyroid function (every 6 weeks) - *results do not need to be available on day 1*

Translational sub-study sample schedule (if participating):

- RT patients only at fraction 4 or 5 - EDTA 10ml x 3 and Tempus 3ml
- Week 3 from start of study atezolizumab - EDTA 10ml x 3 and Tempus 3ml
- Week 9 from start of study atezolizumab (primary endpoint) - EDTA 10ml x 3, Tempus 3ml and Streck 10ml

Quality of life sub-study questionnaire schedule - EORTC QLQ-C30 and EQ-5D-5L (if participating):

- Week 9
- Six months
- Any participants still receiving atezolizumab at 12 months

8.4. Primary endpoint assessment (9 weeks after start of study atezolizumab):

In addition to the above assessments:

- CT chest abdomen pelvis (CAP)
- RECIST v1.1 assessment

Primary endpoint assessment should be conducted nine weeks after the start of study treatment, irrespective of any treatment gaps that may have occurred.

Subsequent CT CAP assessments should be conducted every 9 weeks in the first year, then every 12 weeks in the second year until treatment discontinuation. RECIST v1.1 assessments should be conducted on each scan until RECIST v1.1 progression. CT CAP can be conducted according to local practice in line with RECIST imaging recommendations (34). This consists of, as a minimum, use of contiguous slices, with a slice thickness of ≤5mm and IV contrast (unless contraindicated). RECIST assessments should be conducted in accordance with the details in Appendices A1. RECIST and A2. iRECIST.

The planned site of radiotherapy, as specified at randomisation, should not be used for RECIST v1.1 assessment, irrespective of whether or not the participant was allocated to receive radiotherapy. However, please record the measurement for this lesion on the dedicated eCRF.

If atezolizumab is being withheld, CT CAP should still take place at the expected time-points unless the patient has permanently discontinued treatment.

8.5. Treating beyond progression

At the discretion of the treating clinician atezolizumab may be continued past RECIST v1.1 progression until loss of clinical benefit. Patients with rapidly progressive or symptomatic disease with an alternate treatment option should be advised to discontinue trial treatment and have standard of care treatment. See Appendix A4 for guidance on continuing/discontinuing trial treatment and scan assessments required.

8.6. Procedure at RECIST v1.1. progression for patients continuing treatment

Participants who continue treatment post RECIST v1.1 progression should continue to be followed up according to the schedule above, with CT scans scheduled as described below (also see Appendix A4).

- A CT CAP for the purposes of iRECIST assessment should be conducted 6 weeks following confirmation of progressive disease according to RECIST v1.1.
- Should the patient continue on treatment following their first iRECIST assessment, subsequent CT CAP should be conducted for further iRECIST assessment at the following intervals:
    - 12 weeks after first iRECIST assessment
    - Every 9 weeks thereafter in the first year post start of study treatment, then every 12 weeks in the second year
- Translational sub-study samples (if participating): EDTA 10ml x 3, Tempus 3ml and Streck 10ml should be taken at RECIST v1.1 progression. If progression occurs at the primary endpoint bloods only need to be taken once.

8.7. Procedure at RECIST v1.1. progression for patients discontinuing treatment

- Physical examination
- Full blood count, urea and electrolytes, amylase, liver function assessment
- Translational sub-study samples (if participating): EDTA 10ml x 3, Tempus 3ml and Streck 10ml should be taken at progression. If progression occurs at the primary endpoint bloods only need to be taken once.

8.8. Discontinuation from treatment and post-treatment follow up*

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
- Loss of clinical benefit
- Unmanageable toxicity
- Pregnancy

Participants who discontinue treatment should continue to have scans at protocol determined intervals until RECIST v1.1. progression or commencement of further systemic treatment. Participants should be followed up:

- For disease status and survival every three months up to two years after study entry and every six months thereafter.
- Patients should be monitored for immune related toxicity for 90 days post treatment completion or until initiation of further systemic treatment, if sooner.

*Patients with confirmed iRECIST progression (iCPD) would be expected to discontinue study atezolizumab. If it is considered in the patient's best interest to continue treatment this should be discussed with the RE-ARM Chief Investigator (via REARM-icrctsu@icr.ac.uk) and, once agreed, the patient should continue to be followed up as per iUPD until treatment discontinuation (see Appendix A4).

8.9. Discontinuation from follow-up

If a patient withdraws from further follow-up the change of participation status form should be submitted to ICR-CTSU . Sites should report whether the patient simply no longer wishes to attend trial follow up visits or any other aspect of the trial (eg substudies), or whether the patient has withdrawn consent for any further information to be sent to the ICR-CTSU.

8.10. Schedule of assessments

Time point *(all cycle numbers relate to on-trial atezolizumab)* Activity	Screening[1]	Cycle 1	Cycle 2	Cycle 3	Week 9 **(Primary endpoint)**	Cycle 4	Cycle 5 - 34	RECIST v1.1 progression	Continuation of treatment post RECIST v1.1 progression (to cycle 34)	Discontinuation of treatment
Written informed consent	X									
Confirmation of eligibility	X									
Medical history	X									
Assessment of ECOG PS	X									
Serology (HIV, hepatitis B, hepatitis C) (within 12 months prior to randomisation)	X									
Clinical assessment - physical exam[2]	X	X	X	X		X	X	X	X	
FBC, U&E, amylase, LFTs[2,3]	X	X	X	X		X	X	X	X	
Thyroid function tests[2]	X	X		X			X[5]		X[5]	
Concomitant medication assessment[2]	X	X	X	X		X	X		X	
Adverse event assessment (CTCAE v5)[2]	X	X	X	X		X	X		X	X[8]
CT chest, abdomen, pelvis assessed with RECIST v1.1[4]	X				X		X[6]			
CT chest, abdomen, pelvis assessed with iRECIST[4]									X[7]	
RT to single metastasis (if allocated)		X								
Intravenous atezolizumab (day 1)		X	X	X		X	X		X	
Stop atezolizumab										X
Disease status and survival										X[9]

Footnotes

1. Within 28 days before randomisation unless otherwise stated.
2. Assessments should be conducted within 72 hours prior to day one of each three-weekly cycle. Following screening, physical examinations should be conducted as clinically indicated.
3. To include Hb, Plt, WBC, creatinine, sodium, potassium, ALP, AST or ALT, bilirubin and amylase as a minimum.

4. CT CAP with RECIST v1.1 or iRECIST assessment as appropriate should be conducted at the expected time point irrespective of any delays to atezolizumab administration. The planned site of radiotherapy should not be used for RECIST v1.1 or iRECIST assessment (as either a target or non-target lesion), but measurement of this lesion should be recorded on the dedicated eCRF where required.
5. Thyroid function assessments should be conducted every 6 weeks.
6. CT CAP with RECIST v1.1 assessment should be conducted every 9 weeks within the first year, every 12 weeks within the second year for those patients continuing treatment. See appendix A4.
7. Upon RECIST v1.1 assessment of PD, for patients continuing treatment, CT CAP should be conducted with iRECIST assessment 6 weeks later, then 12 weeks later for those patients without iCPD and continuing treatment. Following this CT CAP with iRECIST assessment should continue every 9 weeks within the first year of study treatment and every 12 weeks within the second year until iCPD or discontinuation of treatment. See appendix A4.
8. Assessment of immune related toxicities up to 90 days post treatment completion (prior to initiation of any further treatment).
9. Disease status and survival should be assessed every 3 months post atezolizumab discontinuation up to two years after the start of study treatment, then every 6 months thereafter

8.10.1. Sub-study schedule of assessments

Time point *(all week/month numbers relate to the start of on-trial atezolizumab)* / Activity	Screening	Baseline – post randomisation	Fraction 4 or 5 of RT (RT group only)	Week 3	Week 9 **(Primary endpoint)**	RECIST v1.1 progression	6 months	12 months
Translational sub-study sample acquisition schedule								
Blood: EDTA 10ml x 3, Tempus 3ml		X	X	X	X	X[1]		
Blood: Streck 10ml		X			X	X[1]		
Access to FFPE blocks from diagnostic procedures[4]	X							
Quality of Life (QoL) sub-study schedule								
EORTC QLQ-C30 and EQ-5D-5L	X[2]				X		X	X[3]

Footnotes

1. Blood samples to be taken at RECIST v1.1 progression (if this did not occur at 9 weeks).
2. Within 28 days before randomisation.
3. QoL to be assessed at 6 months for all sub-study patients and 12 months for all sub-study patients who are still being treated with atezolizumab.
4. FFPE tumour tissue samples will be requested retrospectively and should not be sent without the prior notice of ICR- CTSU.

9. TRIAL TREATMENT

All participants will receive atezolizumab, the investigational medicinal product within RE-ARM. Participants in the atezolizumab plus radiotherapy group will also receive radiotherapy to the primary site or a metastatic lesion.

9.1. Radiotherapy

Patients randomised to radiotherapy will receive radiotherapy to the primary site or a pre-specified metastatic lesion. The planned site of radiotherapy must be specified at trial entry (prior to randomisation) and this lesion must not be used for RECIST assessment, whether or not the patient is allocated to receive radiotherapy. Radiotherapy treatment guidelines are provided below. Any queries regarding radiotherapy requirements should be directed to the RE-ARM trial manager.

9.1.1. Radiotherapy target selection

It is recommended that the lesion selected to receive radiotherapy:

- Should be a lesion that is progressing, if applicable
- May be RECIST v1.1 measurable or non-measurable e.g. bone or bladder
- Should be 1.5cm to 10cm in diameter. If not available a larger lesion can be selected and partially treated
- Should not have been previously irradiated

9.1.2. Radiotherapy treatment timelines

Radiotherapy should preferably be started on the first day of the first cycle of on study atezolizumab but, if this is not feasible, should be started as soon as possible after the first on study atezolizumab dose and completed before the second on study cycle commences.

The RE-ARM trial manager should be contacted for advice if problems are anticipated achieving the radiotherapy treatment timelines provided at randomisation for any participant.

9.1.3. Radiotherapy treatment technique

The radiotherapy dose will be 20Gy in 5 fractions to be delivered over 1 week.

Treatment can start on any day of the week.

The treatment technique will be as per normal clinical practice with the aim of delivering treatment with minimal toxicity. Conformal or IMRT/VMAT delivery will be preferred but less complex fields will be accepted e.g. single fields to spinal vertebrae.

9.1.4. Target volume definition

The Clinical Target Volume (CTV) will be the investigator defined gross tumour volume (GTV) plus 0.5 cm. An additional 0.5 - 1.0cm margin will be added to the CTV to form the planning target volume (PTV). The PTV should have a minimum diameter of 3.5 cm and not exceed a maximum diameter of 12 cm. The treated target site may be RECIST measurable or non-measurable.

Ideally, the whole lesion will be irradiated however partial irradiation is permitted in order not to exceed the maximum allowable PTV.

9.1.5. Dose volume constraints

The dose to the measured lesion(s) used for RECIST assessment should be <4Gy (20% of target dose). The maximum and median dose to the measured lesion will be recorded (if within 10cm of the irradiated lesion or within the encompass of one or more beams). Any lesion which receives 4Gy or more should not be used for RECIST reporting.

9.1.6. Organs at risk

Dose constraints for organs at risk should be in accordance with local policy.

9.1.7. Radiotherapy treatment scheduling and gaps

A gap of up to 3 days is acceptable in the event of machine service or breakdown. If the treatment machine is unavailable for more than 3 days, please contact the RE-ARM trial manager.

9.1.8. Palliative radiotherapy

Participants in both groups are permitted to received palliative radiotherapy following trial entry if clinically indicated. This should be reported on the appropriate CRF.

9.2. Atezolizumab

9.2.1. IMP dose and schedule

Atezolizumab should be started within 2 weeks following randomisation. Sites must use the RE-ARM allocated atezolizumab stock provided.

Atezolizumab is administered intravenously over 30 to 60 minutes at a dose of 1200mg on a 21 day cycle, until loss of clinical benefit or unmanageable toxicity. The infusion is not intended to be administered via push or bolus.

9.2.2. IMP prescription and dispensing

Atezolizumab should be prescribed by the Principal Investigator or delegated clinician using the specific RE-ARM prescription and dispensed by the hospital pharmacy using RE-ARM allocated atezolizumab stock.

Atezolizumab should be prepared by a healthcare professional in accordance with the pharmacy guidance notes. Preparation should be:

- Performed under aseptic conditions by trained personnel in accordance with good practice rules, especially with respect to the aseptic preparation of parenteral products.
- Prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- Followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of aseptic conditions.

Do not shake. Twenty mL of atezolizumab concentrate should be withdrawn from the vial and diluted into a polyvinal chloride (PVC), polyolefin (PO), polyethylene (PE) or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL. The bag should be gently inverted to mix the solution in order to avoid foaming. Chemical and physical in-use stability has been demonstrated for up to 24 hours at ≤ 30 °C and for up to 30 days at 2 °C to 8 °C from the time of preparation. For microbiological control purposes it is recommended that the prepared infusion should be administered immediately or no longer than 24 hours after preparation at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.

9.2.3. Patient cards

Small wallet sized cards can be produced by ICR-CTSU on request by the participating site. Each card will state:

- The name of the participating site
- That the patient is participating in the RE-ARM trial

- That the patient is taking atezolizumab
- An emergency contact number for the participating site

9.2.4. Duration of atezolizumab treatment

Participants will receive treatment until loss of clinical benefit or unmanageable toxicity up to a maximum of two years after starting RE-ARM allocated atezolizumab.

9.2.5. Supportive care

Supportive care should be given in accordance with the current summary of product characteristics and local policy.

9.2.6. Concomitant therapy

All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the study drugs may be given at the discretion of the investigator. All concomitant medications must be recorded in the patient's notes, as well as the appropriate pages of the CRF.

Systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab. Atezolizumab dosing should be delayed until complete withdrawal of immunosuppressants and reduction of corticosteroids to ≤ 10 mg prednisolone or equivalent per day.

9.2.7. Non-permissible medications/therapies

No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

Use of concomitant cytotoxic chemotherapy is not permitted during study treatment.

Use of live-attenuated vaccines is not permitted during study treatment (use of inactivated vaccines for prophylaxis is permitted).

9.2.8. Dose modifications – atezolizumab

Atezolizumab dose reductions are not recommended. Recommended treatment modifications in the case of adverse reactions are detailed below.

Immune related adverse reaction	**Severity (NCICTCAE v5)**	**Treatment modification**
Pneumonitis	Grade 1	Consider treatment delay, monitor every 2-3 days
	Grade 2	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day
	Grade 3 or 4	Permanently discontinue atezolizumab
Hepatitis	Grade 2:	Withhold atezolizumab

Immune related adverse reaction	Severity (NCICTCAE v5)	Treatment modification
	(ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN)	Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Permanently discontinue atezolizumab Consider hepatology referral
Colitis	Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic colitis	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Consider gastroenterology referral
	Grade 4 diarrhoea or colitis (life threatening; urgent intervention indicated)	Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold atezolizumab **Hypothyroidism***:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing **Hyperthyroidism:** Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving Consider endocrinology referral
Adrenal insufficiency	Symptomatic	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy Consider endocrinology referral

Immune related adverse reaction	Severity (NCICTCAE v5)	Treatment modification
Hypophysitis	Grade 2 or 3	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy Consider endocrinology referral
	Grade 4	Permanently discontinue atezolizumab
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Premedication with antipyretic and antihistamines may be considered. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue atezolizumab
Rash	Grade 3	Withhold atezolizumab Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day
	Grade 4	Permanently discontinue atezolizumab
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All grades	Permanently discontinue atezolizumab
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold atezolizumab Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day

Immune related adverse reaction	Severity (NCICTCAE v5)	Treatment modification
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab
Myocarditis	Grade 2	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per cay
	Grade 3 and 4	Permanently discontinue atezolizumab
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue atezolizumab
Myositis	Grade 2 or 3	Withhold atezolizumab
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue atezolizumab
Other immune-related adverse reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day.
	Grade 4 or recurrent Grade 3	Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)

9.2.9. Missed doses

If a planned dose of atezolizumab is missed it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration should be adjusted to maintain a 3-week interval between doses. If a patient does not receive atezolizumab for more than 12 weeks trial treatment should be discontinued.

9.2.10. Overdoses

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

9.2.11. Discontinuation and subsequent therapy

Atezolizumab should be discontinued if patients are no longer deriving clinical benefit or in the case of severe toxicity (see section 9.6). Further treatment will be at the local clinician's discretion.

9.2.12. Supply and distribution

Atezolizumab is manufactured and provided free of charge by Roche to participating sites for use following participants' randomisation.

Roche are responsible for distribution of atezolizumab to participating sites, as detailed in the pharmacy guidance notes.

No drug will be distributed to participating centres unless ICR-CTSU is satisfied that the required approvals and agreements and initiation procedures are complete.

9.2.13. Formulation, packaging, storage conditions and labelling

Atezolizumab is provided as a concentrate for solution for infusion. Each 20 mL vial of concentrate contains 1,200 mg atezolizumab. Vials should be stored in a refrigerator (2 °C – 8 °C) and should not be frozen. Vials should be stored in the outer carton in order to protect from light.

The participating site is responsible for segregating atezolizumab supplied by Roche from other hospital stock in a dedicated area stating that the stock is for RE-ARM study. At the time of dispensing it is the responsibility of the site to comply with Annex 13 labelling requirements for the final IV infusion prior to administration.

9.2.14. Pharmacy responsibilities and drug accountability

After randomisation participants should receive RE-ARM allocated atezolizumab stock. The study drug must not be used for treatment of patients who are not randomised RE-ARM participants.

Records must be kept of all deliveries, dispensing and destruction in accordance with the RE-ARM Pharmacy Guidance Notes. These records may be requested by ICR-CTSU during the trial to monitor supply and usage of stock. Account must be given of any discrepancies and certificates of delivery and return must be signed.

10. RADIOTHERAPY QUALITY ASSURANCE (QA)

No trial specific radiotherapy quality assurance process is required. All participating sites will be asked to confirm prior to activation that they have received a recent independent dosimetry audit.

11. PHARMACOVIGILANCE

11.1. Definitions

11.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant administered an investigational medicinal product; the event does not necessarily have a causal relationship with the treatment or usage.

11.1.2. Special situations

The following special situations should be reported in accordance with section 11.3 even in the absence of an AE:

- Data related to on-study atezolizumab usage during pregnancy or breastfeeding (see section 11.8), data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

Accidental overdose and medication error, are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of the drug. In some situations, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria then they should be reported as SAEs in accordance with section 11.3.

11.1.3. Product complaints

A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial. Product complaints related to the study drug should be reported in accordance with section 11.3.

11.1.4. Adverse Events of Special Interest (AESIs)

AEs experienced by any patient receiving study atezolizumab which meet any of the criteria listed below are considered AESIs, and should be reported to the ICR-CTSU within the same timeframe as SAEs, as detailed in Section 11.3:

- Autoimmune haemolytic anaemia
- Cytokine-release syndrome
- Grade ≥2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
- Hypersensitivity
- Immune-related adrenal insufficiency
- Immune-related colitis
- Immune-related diabetes mellitus
- Immune-related Guillan-Barré syndrome
- Immune-related hepatitis including AST or ALT >10 x ULN
- Immune-related hyperthyroidism
- Immune-related hypophysitis
- Immune-related meningoencephalitis
- Immune-related Myasthenic Syndrome / Myasthenia Gravis
- Immune-related myocarditis
- Immune-related myositis
- Immune-related nephritis
- Immune-related ocular inflammatory toxicity
- Immune-related pancreatitis
- Immune-related pneumonitis
- Immune-related severe cutaneous reaction
- Immune-related vasculitis
- Influenza-like illness

- Infusion-related reactions
- Rhabdomyolysis
- Systemic immune activation
- Systemic inflammatory response syndrome
- Systemic lupus erythematosus

If any AESI also meets the definition of an SAE, an SAE report should be completed and submitted together with the AESI form.

11.1.5. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that occurs after the commencement of study treatment and within 90 days following the last administration 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

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant 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.

11.1.6. Serious Adverse Reaction (SAR)

A serious adverse reaction is an SAE that is suspected as having a causal relationship to the investigational medicinal product, 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).

11.1.7. 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 medication). 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 medication). 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.

11.1.8. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the safety information provided in the applicable Summary of Product Characteristics (SmPC), and is assessed as unexpected by the Chief Investigator.

11.2. Reporting adverse events to ICR-CTSU

Any toxicity, sign or symptom that occurs after commencement of study treatment and within 30 days of the last administration of study treatment, which is not unequivocally due to progression of disease, should be considered an AE. Out of range laboratory values should only be reported as AEs if they are clinically relevant (i.e. indicative of a clinical sign or symptom). The sign/symptom should be reported as the AE and the associated laboratory value provided as additional information where relevant.

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

The severity of AEs should be graded according to CTCAE v5. 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.

11.3. Reporting SAEs, AESIs, special situations and product complaints to ICR-CTSU

Any SAE, AESI, occurring after the commencement of study treatment and up to 90 days following the last dose of study drug must be reported. Special situation or product complaints should be reported when the investigator becomes aware of the incident.

Any SAEs that occur more than 90 days after the last dose of study drug that, in the opinion of the Principal Investigator, are related to the study drug should be reported to ICR-CTSU if the Principal Investigator becomes aware of them.

All SAEs, AESIs, special situations or product complaints should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the relevant RE-ARM SAE/AESI/other incident form (as applicable).

SAE reports should be sent to:

The ICR-CTSU safety desk

sae-icr@icr.ac.uk

copying **REARM-icrctsu@icr.ac.uk**

For the attention of the RE-ARM Trial team

As much information as possible, including the Principal Investigator's assessment of causality for SAE reports, 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. All reported SAEs will be forwarded to Roche by ICR-CTSU.

All reported AESIs, special situations and product complaints should be sent to REARM-icrctsu@icr.ac.uk and will be forwarded to Roche following receipt at ICR-CTSU.

11.4. Review of serious adverse events

The Chief Investigator (or designated representative) will assess all reported SAEs 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 drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see 11.5).

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.

11.5. Expected Radiotherapy Adverse Events

The following adverse event will be classed as expected within the RE-ARM trial if they are assessed as being related to radiotherapy: fatigue; nausea/vomiting; diarrhoea; skin irritation/reaction; skin atrophy; mucositis; gastritis; colitis; shortness of breath; dysurea frequency.

The above listed events should be reported within the trial CRF database and under the reporting timeframes given for SAEs above if it meets the relevant reporting criteria.

11.6. Expedited reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the main REC, Roche and all other interested parties within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the main REC, Roche within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, main REC and Roche as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

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

11.7. 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.

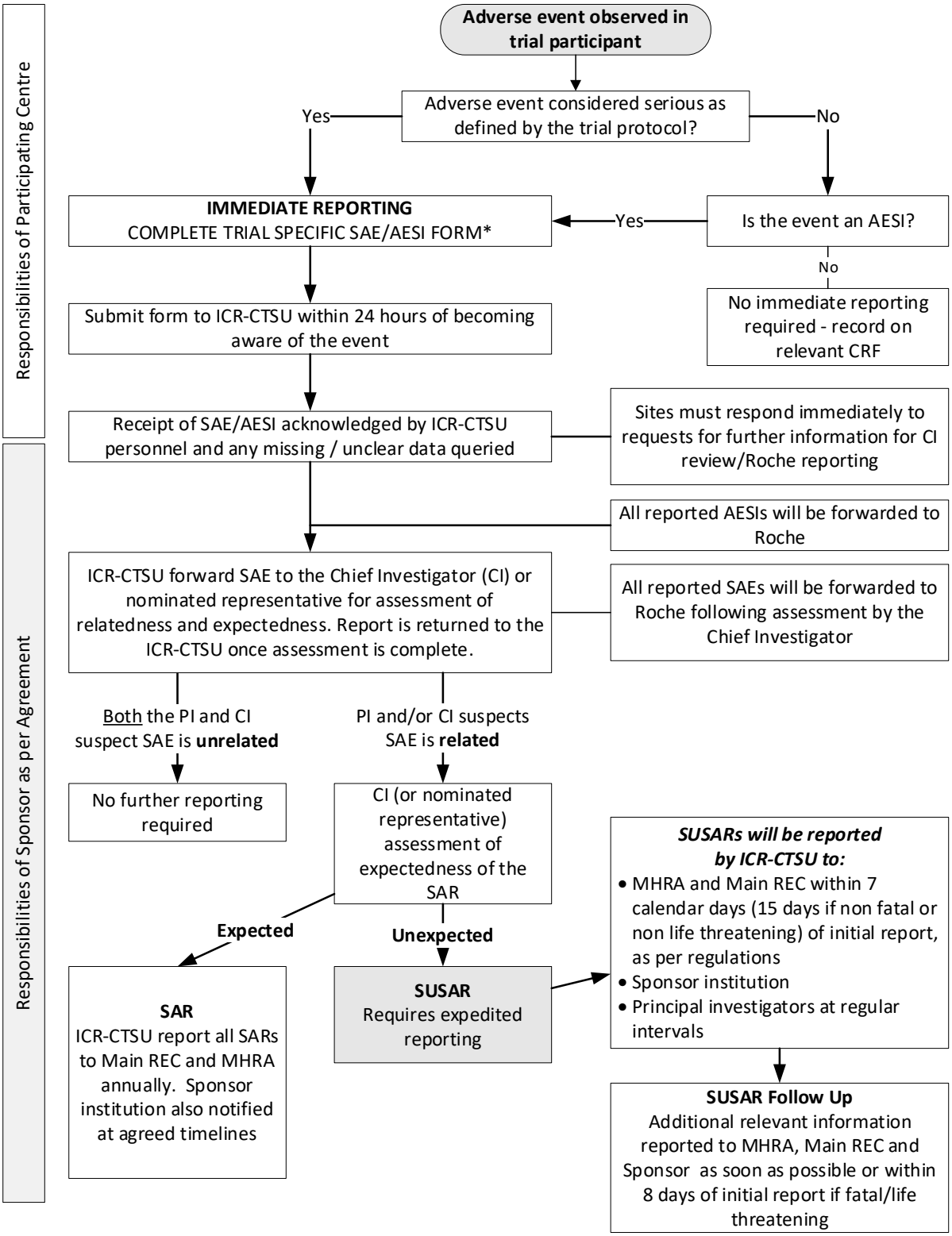
11.8. Annual reporting of serious adverse reactions

An annual report will be provided to the MHRA and the main REC by ICR-CTSU at the end of each reporting year.

11.9. Reporting pregnancies

Pregnancy is considered a special situation for the purposes of RE-ARM and should be reported in accordance with the above SAE reporting timelines. If any trial participant or a trial participants' partner becomes pregnant while receiving study drug or up to five months after receiving study drug, 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 AE reporting, and action following report



All SAEs should be followed up until resolution.
*If any AESI also meets the definition of an SAE, an SAE report should be completed and submitted together with the AESI form

12. STATISTICAL CONSIDERATIONS

12.1. Statistical design and sample size justification

The trial design is an adaptive 2-arm randomised group-sequential design with a formal interim assessment to stop recruitment early if the number of responses in the experimental arm is not higher than in the control arm.

In the IMvigor210 study a response rate of 17% was reported in patients who initially progressed. To detect an absolute increase of at least 15% in response rate at 9 weeks for the experimental arm compared with the control arm (assuming 15% response in control, 1:1 randomisation) with 80% power using a 1-sided z-test with 0.2 significance level requires 92 evaluable patients. An interim analysis will take place when 23 patients per arm have completed the 9 week primary endpoint response assessment with a formal stopping rule that the trial will close to recruitment if the z-test statistic is not higher than the futility boundary of 0 (i.e. if there are not more responses in experimental arm versus control). The futility boundary for the final analysis is 0.68.

Allowing for a 10% non-evaluable rate at 9 weeks gives a planned overall sample size of 102 patients. The non-evaluable rate will be monitored during the trial; any major departures requiring adjustment to the overall sample size required to recruit 92 evaluable participants will be discussed with the independent oversight committees.

The required sample size calculations were performed using the group sequential testing option in nQuery + nTerim v4.0 and in-house written R-codes. The bespoke R-codes were required in order to amend the futility boundaries so that the boundary at the interim analysis is 0 (i.e. requiring at least 1 more response in the experimental arm versus control).

12.2. Treatment allocation

All trial participants will receive atezolizumab.

Participants will be randomised between continuing atezolizumab only and continuing atezolizumab with a course of radiotherapy on a 1:1 basis.

Treatment allocation is by minimisation with a random element; balancing factors will be randomising centre, line of treatment (first v 2nd/3rd), metastasis of liver and/or bone (yes/no) and disease status (stable vs progressive disease).

12.3. Endpoint definitions

12.3.1. Primary endpoint

Objective response (CR [complete response] + PR [partial response] according to RECIST v1.1) at 9 weeks after start of study treatment.

12.3.2. Secondary endpoints

- Objective response according to iRECIST (iCR + iPR)
- Clinical benefit at 9 weeks according to RECIST v1.1 (CR, PR, SD)
- Best response up to 6 months, defined as specified in A1.10
- Duration of response, defined as time from objective response until recurrence or progressive disease (PD)
- Time to progression, defined as time from randomisation until confirmation of progression
- Progression free survival, defined as time from randomisation until progression or death from any cause
- Overall survival, defined as time from randomisation until death from any cause
- Treatment related toxicity (CTCAE v5)

- Patient reported quality of life (assessed using the EORTC QLQ-C30 and EQ-5D-5L questionnaires) at 9 weeks and 6 months for all patients participating in the QoL substudy. In addition any QoL sub-study patients still being treated with atezolizumab at 12 months should be asked to complete the EORTC QLQ-C30 and EQ-5D-5L at this timepoint. The primary outcome measure will be overall quality of life, measured by the EORTC QLC-C30 qlobal health/QoL subscale score.

12.3.3. Exploratory endpoint

Molecular and pathological changes in response to atezolizumab +/- radiotherapy

12.4. Statistical analysis plan

Primary endpoint

Objective response rate (CR [complete response] + PR [partial response]) at 9 weeks after start of study treatment will be compared between the two trial arms using a chi-squared test or Fisher's exact test, as appropriate, and an estimate of the difference in proportions of responders calculated with a 95% confidence interval.

Blinded central review of objective responses will be conducted retrospectively.

A supplementary analysis will consider objective response rate at 9 weeks as above, but incorporating the (planned) radiotherapy site within the RECIST v1.1 assessment (where it met the criteria for a RECIST v1.1 target lesion) to assess the impact of excluding this lesion in the principal analysis.

Secondary endpoints

Objective response rate according to iRECIST and clinical benefit according to RECIST v1.1 will be compared between trial arms as per the primary endpoint. Best response will be tabulated according to trial arm.

Duration of response, time to progression, progression free survival and overall survival will be presented according to trial arm using Kaplan-Meier survival plots and analysed using log-rank tests and Cox proportional hazards models. Rates of progression free and overall survival will be estimated at 12 and 24 months.

Treatment-related toxicity will be presented according to grade and trial arm.

Quality of life data will be analysed using standard algorithms to derive scores and handle missing data according to the questionnaire's scoring manual. The primary outcome measure for patient reported quality of life will be overall quality of life measured by the EORTC QLQ-C30 global health/quality of life subscale score, which will be treated as a continuous variable. Subscale scores will be compared between treatment groups at individual time points, as well as the change from baseline to Week 9 and 6 months, using ANCOVA adjusting for baseline scores. Additional analyses of EORTC QLQ-C30 subscales will dichotomise change in subscale scores from baseline to each follow-up timepoint according to whether or not patients have experienced a deterioration of >10 points, and compared between groups using chi-squared tests or Fisher's exact test, as appropriate. Analyses to account for the longitudinal nature of the data (generalised estimating equations) may also be used. Secondary QoL outcomes of interest include the EORTC QLQ-C30 subcales for physical functioning, role functioning and fatigue, individual domains and utility scores from the EQ-5D-5L.

QoL sub-study patients who are still being treated with atezolizumab at 12 months will be asked to complete the questionnaire at this timepoint. QoL data for this subset of patients will be compared with their baseline QoL data taking into account relevant covariates including other treatments taken, to explore the impact of long term use of atezolizumab on QoL.

Exploratory analyses will be conducted to investigate whether response varies according to site of target lesion. Details will be specified in the Statistical Analysis Plan.

Analyses of efficacy outcomes will be by intention-to-treat; safety analyses will be in the per protocol population.

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

12.5. Interim analyses and stopping rules

Recruitment will be closely monitored by the Trial Management Group (TMG) with escalation to the independent Trial Steering Committee should it fall below 50% of target after 12 months recruitment (or later). An Independent Data Monitoring Committee (IDMC) will review the accumulating toxicity data approximately 6 months after the first patient is recruited and at least annually in confidence.

Formal interim analysis will be performed when 23 patients per arm have completed the 9 week primary endpoint response assessment in accordance with the group sequential design described in section 12.1. Unless the IDMC advise otherwise, recruitment will continue whilst the interim analysis is carried out, as it is likely that the number of additional patients recruited before the results are known will be small (expected recruited rate is 5 patients per month).

13. TRIAL MANAGEMENT

13.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up 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. 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.

13.2. Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and 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 sponsor. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

13.3. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be set up to 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 TMG and approved by the TSC.

The IDMC will meet in confidence at regular intervals, and at least annually. They will review the results of each formal interim analysis. 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 the MHRA.

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.

14. RESEARCH GOVERNANCE

14.1. Sponsor responsibilities

The sponsor of RE-ARM is the Institute of Cancer Research (ICR).

14.2. Participating site responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the sponsor and the individual site.

14.3. Roche responsibilities

Roche is responsible on behalf of the sponsor for the manufacture, packing, labelling and distributing of study drug to site in accordance with Good Manufacturing Practice and all applicable local legislation. Responsibilities are defined in an agreement between Roche and the sponsor. Should the agreement be terminated early and local investigators consider that continued treatment is in the patient's best interest the local investigator should submit an unsolicited request to Roche. Roche will review each request in good faith and will make decisions on each request on a case by case basis.

15. TRIAL ADMINISTRATION & LOGISTICS

15.1. Site activation

Before recruitment can commence at a site, the site agreement must have been signed by all required signatories, the required trial documentation (as specified by ICR-CTSU) must be in place and a site initiation must have taken place. Site initiation may be by video/teleconference or by on site visit if requested by the Principal Investigator or if deemed appropriate by ICR-CTSU. ICR-CTSU will provide the final confirmation that recruitment can commence at a site.

15.2. Data acquisition

Electronic Case Report Forms (eCRF) 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.

The clinical data should be reported on the RE-ARM eCRFs to the ICR-CTSU in a timely manner. Specific guidance on how data will be collected will be detailed in trial guidance notes. On receipt at ICR-CTSU, eCRFs will be recorded as received and any missing data will be reported to the originating site.

15.3. 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.

15.4. 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.

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.

If circumstances require, remote monitoring may be carried out in lieu of a site visit.

15.5. Completion of the study and definition of study end date

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

15.6. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

16. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

16.1. Trial approvals

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

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, regulatory approval from the MHRA and HRA approval. Before recruiting patients, the Principal Investigator at each site is responsible for gaining the required local approvals.

16.2. 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 The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the Research Governance Framework for Health and Social Care and the principles of GCP.

16.3. Informed consent

Patients should be asked to sign the current ethics approved RE-ARM 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 inspection. The current ethics approved RE-ARM 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.

16.4. 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 NHS 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 and the regulatory authorities 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.

16.5. Data protection

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

16.6. Insurance and liability

Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements.

17. FINANCIAL MATTERS

This trial is investigator designed and led, has been endorsed by the Clinical Research Committee of Cancer Research UK, and 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 sponsor has received an Investigator Initiated Research grant (IIR) from Roche for the conduct of this trial.

18. 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. Authorship of all publications will usually be in accordance with ICMJE guidance. All publications associated with the trial should be published open access.

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

19. ASSOCIATED STUDIES

19.1. Translational study

All patients who consent to the trial who fulfil sample collection eligibility criteria will be asked to consent to donate blood samples over a number of time-points during participation. Blood collection tubes will be provided to sites and shipped to the receiving lab using pre-paid packaging.

Consent will also be sought for access to routinely collected diagnostic formalin fixed paraffin embedded tissue blocks.

Further details are provided in Appendix A3.

19.2. Quality of Life Study

All trial participants will be asked to consent to completion of the EORTC QLQ-C30 and EQ-5D-5L questionnaires over a number of time-points during participation in the trial.

Quality of Life (QoL) will be a secondary endpoint in the main trial and will be analysed as described in the statistical analysis plan. Further details are provided in Appendix A5.

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21. APPENDICES

A1. RECIST

Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 criteria should be used for the assessment of treatment outcomes. A summary is given below but investigators should always refer to the published guidelines. Note that the planned site of radiotherapy, as specified at randomisation, should not be used for RECIST v1.1 assessment, irrespective of whether or not the participant was allocated to receive radiotherapy.

A1.1 Evaluation of measurable and non-measurable lesions

- Measurable disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology / histology.
- Measurable lesions – lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm by chest X-ray, or ≥ 10 mm by CT/MRI scan or clinical exam.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Malignant lymph nodes must be ≥15 mm in the short axis when assessed by CT scan to be considered measurable.
- Non-measurable lesions – all other lesions, including small lesions and malignant lymph nodes (longest diameter <10 mm, or pathological lymph nodes with ≥10 to <15 mm short axis) i.e., leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, blastic bone lesions and also abdominal masses that are not confirmed and followed by imaging techniques.
- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- The utilisation of endoscopy and laparoscopy for objective tumour evaluation is not advised. The utilisation of such techniques should be restricted to confirming complete pathological response when biopsies are obtained.

A1.2 Baseline documentation of target and non-target lesions

- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.
- A sum of the longest diameters (LD) for all target lesions will be calculated and reported as the baseline sum of LD. The baseline sum LD will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

A1.3 Response criteria

A1.3.1 Documentation of new lesions

- The presence of a new lesion should be unequivocal: i.e. Not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).
- A lesion identified at a follow-up visit in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

A1.3.2 Lesions that become 'too small to measure'

- If lesions or lymph nodes recorded as target lesions at baseline become too faint on CT scan to assign an exact measure, a default value of 5mm should be assigned. This default value is derived from the 5mm CT slice thickness
- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm.

A1.4 Evaluation of target lesions

Response criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions (lymph nodes must be <10mm short axis)
Partial Response (PR)	At least 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started and at least 5mm absolute increase in this sum or the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

A1.5 Evaluation of non-target lesions

Response criteria	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete response / Stable disease (SD)	Persistence of one or more non-target lesions
Progressive disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions *

* To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. Although a clear progression of a non-target lesion is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or Chief Investigator).

A1.6 Evaluation of overall response

The table below provides a summary of the overall response calculation at each time point.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
CR	Not-evaluated*	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

A1.7 Confirmation of disease progression

For equivocal findings of progression (e.g. Very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

A1.8 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

A1.9 Duration of stable disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

A1.10 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until disease progression. The patient's best overall response assignment will depend on the findings of both target and non-target disease and the appearance of new lesions.

Best overall response is defined as the best response across all time points. For example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR.

A1.11 Central review

Blinded central review of objective responses will be conducted in order to protect against any reporting bias.

A2. iRECIST

A2.1 Definitions

- Evaluable for adverse events.

  All patients will be evaluable for adverse event evaluation from the time of their first treatment.

- Evaluable for response.

  All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

See appendix A4 for criteria for continuing treatment past RECIST 1.1 disease progression.

A2.2 iRECIST response assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

A2.3 Confirming progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). The first confirmatory scan should be performed 6 weeks after iUPD (at least 4 weeks, but no longer than 8 weeks after iUPD).

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

A2.4 New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

A2.4.1 Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)

iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: opreviously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or osize or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	Non-iUPD/PD	Non-iUPD/PD
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** In any lesion category. *** Previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

A2.4.2 iRECIST best overall response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD
Table assumes a randomised study where confirmation of CR or PR is not required. NE = not evaluable that cycle. Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.					

A2.5 Response and stable disease duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

A2.6 Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely

disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

A2.6.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

A2.6.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

A2.6.3 CT, MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

A2.6.4 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

A2.6.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

A2.6.6 Tumour markers

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

A2.6.7 Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease

A3. Translational research studies

A3.1 Introduction

The immunological changes occurring during abscopal responses are not well understood, particularly in a human context. A recent report of a clinical trial of anti-CTLA4 plus radiotherapy has identified that the distinct expansion and contraction of tumour-specific T cell receptor (TCR) clones is associated with a response to immunotherapy/radiotherapy combination treatment.(17) This study also reported that radiotherapy can trigger transcriptional upregulation of neo-antigens that were previously expressed at only very low levels – this work established a new mechanism by which radiotherapy can be immunogenic. In addition, upregulation of type 1 interferon during radiotherapy was associated with a significantly higher chance of a tumour response in the above clinical trial, which provides human qualification of the mechanistic insights from murine models discussed in the introduction to this protocol. These exciting findings need to be investigated in other tumour types, and across a range of immunotherapy and radiotherapy schedules, to establish if such biological changes are central to the generation of abscopal responses.

The translational sub-study of RE-ARM aims to characterise the genomic and immune landscape (and how the immune response to the tumour develops over time), by analysis of pre-trial diagnostic tumour tissue, and blood samples collected before, during and after atezolizumab +/- radiotherapy treatment. The depth and range of analysis is guided by the practicalities of sample collection, and will depend on the amount and quality of tissue available after processing (eg RNA/DNA extracted from tissue), for individual patients. We will particularly focus immunologically on i) analysis of peripheral blood mononuclear cells (PMBC), ii)changes in plasma cytokines, iii) T cell receptor sequencing (TCRseq) in pre-treatment tumour and blood over time and iv) RNA/DNA sequencing. This will characterise blood PBMC composition, circulating cytokine levels and the TCR repertoire, and how these parameters change during treatment with atezolizumab and radiotherapy. This could enable longitudinal monitoring of tumour-specific immune changes without the need for repeat tumour biopsies.

RE-ARM participants will be asked to provide prospective consent for access to routinely collected tumour tissue in formalin fixed paraffin blocks. Participants will also be asked to donate blood samples. Analyses of these samples are likely to be hypothesis generating and will serve to refine translational questions to be addressed in larger downstream immuno-radiation oncology studies as well as offer insights to the dynamic process of immune activation that may have implications for tumours that are currently unresponsive to immune therapy across cancer types.

Consenting to provide these samples is optional and patients will be asked to provide written informed consent at the time of trial entry. Participants who do not consent to provide samples will still be able to join the RE-ARM trial.

A3.2 Sample collection eligibility

RE-ARM participants with an active or past history of HIV or hepatitis are ineligible to provide samples for this study. Samples should not be taken from patients with either suspected or confirmed COVID-19. See the RE-ARM trial guidance notes for further details.

A3.3 Blood sample collection

RE-ARM participants will be asked to provide three 10ml whole blood EDTA samples and one 3ml whole blood Tempus sample. These samples should be collected at baseline (after randomisation prior to the start of study treatment), at fraction 4 or 5 (for RT pts only), week 3 and week 9 from the start of study atezolizumab and at RECIST v1.1 progression (where RECIST v1.1 progression takes place after week 9 only).

RE-ARM participants will also be asked to provide one 10ml whole blood Streck sample at baseline, week 9 and RECIST v1.1 progression (where RECIST v1.1 progression takes place after week 9 only).

Blood samples should be taken at the same time as routine blood tests where possible to minimise inconvenience to participants.

A3.3.1 Blood sample shipping and storage

Participating centres will be provided with EDTA, Tempus and Streck tubes and shipping materials. No processing is required on site. Blood samples will be sent to the University of Manchester. Details of blood sample collection and shipment requirements are provided in the RE-ARM trial guidance notes.

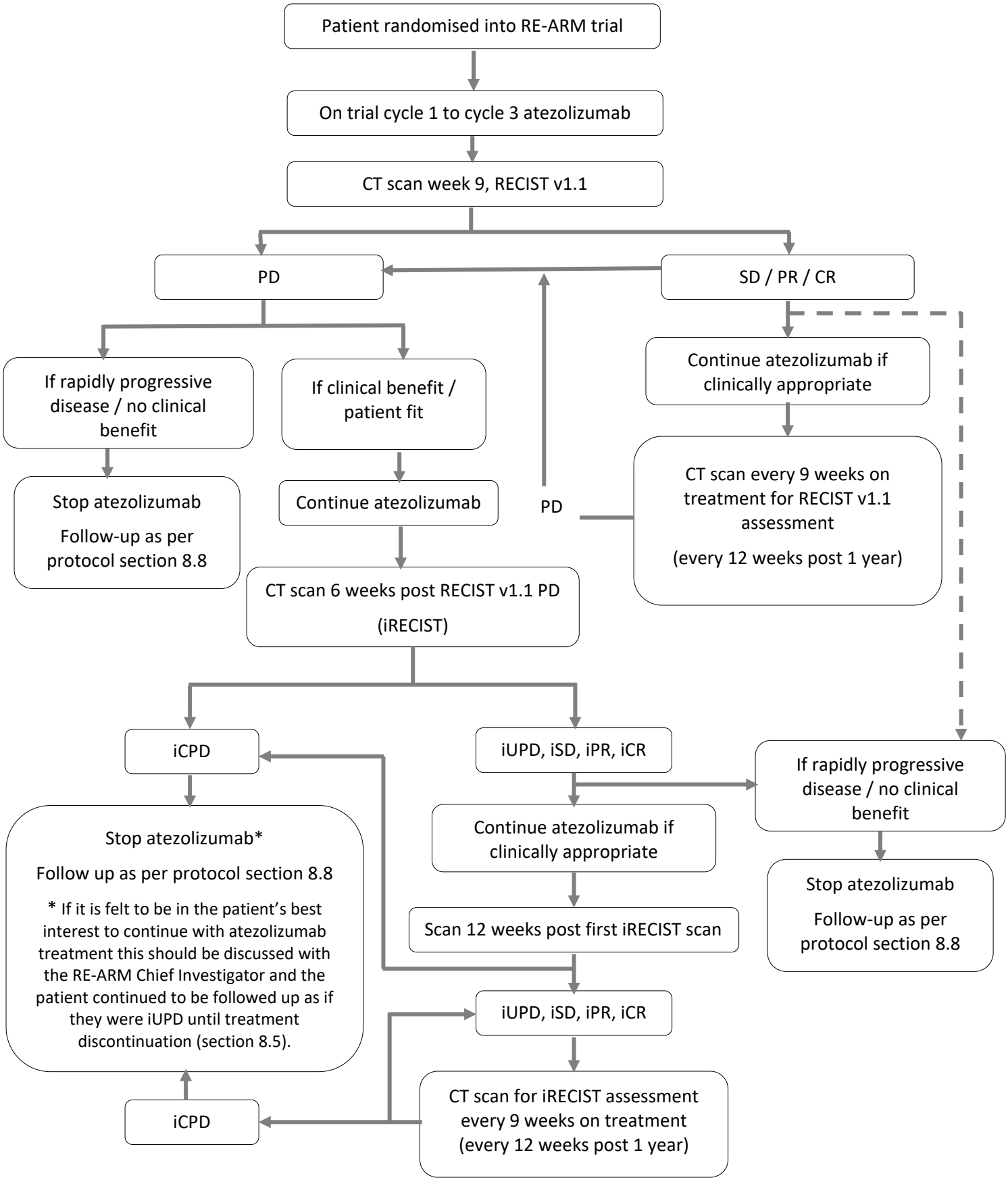
A3.4 RE-ARM FFPE tissue collection

Patients at centres participating in RE-ARM will be asked to provide consent for access to routinely collected tumour tissue from diagnostic procedures in formalin fixed paraffin blocks. FFPE tumour tissue samples will be requested retrospectively and should not be sent without the prior notice of ICR- CTSU. FFPE tumour tissue will be sent to and stored at the University of Manchester before being transferred to The Institute of Cancer Research.

A3.5 Tissue custodianship and access arrangements

As Sponsor, The Institute of Cancer Research, on behalf of the RE-ARM Trial Management Group, is the custodian of the biological samples collected within RE-ARM. Trial biospecimens will be registered on the appropriate national databases.

A4. Treatment and scan assessment algorithm



A5. Quality of Life study

A5.1 Background

The impact on quality of life (QoL) of a radiotherapy-immunotherapy drug combination for patients with metastatic urothelial carcinoma has not been widely assessed; RE-ARM presents the opportunity to investigate this. Since there is currently no validated metastatic bladder(35) or immunotherapy quality of life measurement tool available, the EORTC QLQ-C30 (32), which is widely used in other immunotherapy trials (including IMvigor130, Checkmate-275(36) and KEYNOTE-045(37)), has been selected to assess participants' general QoL in the RE-ARM trial. Participants will also be asked to complete the EQ-5D-5L (33), a short instrument which provides a generic measure of health status.

A5.2 Hypothesis

- Adding radiotherapy to atezolizumab will not have a detrimental impact on a patient's QoL.

Patients treated with a combination of radiotherapy and atezolizumab will not have a worse overall QoL subscale score (change from baseline to 9 weeks/6 months) compared to patients treated with atezolizumab alone.

All hypothesis testing will be considered exploratory as the trial is not powered to test QoL endpoints

A5.3 Quality of life measures

Patients will complete the EORTC QLQ-C30 and EQ-5D-5L questionnaires, which are standardised and validated instruments that provide a simple descriptive profile of health status. The EORTC QLQ-C30 comprises a global health status/QoL subscale, five functional subscales and nine symptom subscales/items, and an overall summary score can be derived. The EQ-5D-5L measures five dimensions of health and self-rated health status.

A5.4 Study design

Patients are eligible for the QoL sub-study if they fulfil the RE-ARM eligibility criteria. Participants will be asked in the patient information sheet to consent to regular completion of the EORTC QLQ-C30 and EQ-5D-5L questionnaires. Patients who decline to take part in the RE-ARM QoL study will remain eligible for the main trial. QoL is a secondary endpoint in the main trial.

A5.5 Timing of data collection

Participants will be asked to complete the questionnaire after informed consent is obtained during their clinic visit at the following time points: i) screening, before treatment allocation is known, ii) 9 weeks (cycle 4), iii) 6 months , and iv) 12 months for patients still being treated with atezolizumab.

A5.6 Compliance

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

A5.7 Statistical considerations

Standard algorithms will be used to derive scores and handle missing data according to the questionnaire's scoring manual. Specifically, if at least half of the items from the scale have been answered, we will assume the missing items have values equal to the average of those items which are present for that respondent. The primary outcome measure will be overall quality of life, measured by the EORTC QLC-C30 qlobal health/QoL subscale score. Secondary QoL outcomes of interest include the EORTC QLQ-C30 subcales for physical functioning, role functioning and fatigue, individual domains and utility scores from the EQ-5D-5L. Subscale scores will be compared between treatment groups at individual time points, as well as the change from baseline to Week 9 and 6 months adjusting for baseline scores. Additional analyses of EORTC QLQ-C30 subscales will dichotomise change in subscale scores from baseline to each follow-up timepoint according to whether or not patients have experienced a deterioration of >10 points. Analyses to account for the

longitudinal nature of the data (generalised estimating equations) may be used. At 12 months any patients who are continuing treatment with atezolizumab will be asked to complete the questionnaire. 12-month data will be compared with baseline data (taking into account relevant covariates including other treatments) to explore the impact of long term use of atezolizumab on QoL. To make some adjustment for multiple testing a significance level of 1% will be used for comparisons of quality of life endpoints. An analysis plan will be developed in consultation with the TMG.

A6. ECOG performance status

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

A7. GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under Curve
CAP	Chest Abdomen Pelvis
CI	Chief Investigator
CIS	Carcinoma In Situ
CR	Complete Response
CRF	Case Report Form
CRN	Clinical Research Network
CT	Computed Tomographic
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DCF	Data Capture Form
DFS	Disease Free Survival
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
FBC	Full Blood Count
FFPE	Formalin-Fixed Paraffin-Embedded
G-CSF	Growth Colony-Stimulating Factors
GFR	Glomerular Filtration Rate
GTV	Gross Tumour Volume
Hb	Haemoglobin
HR	Hazard Ratio
HRA	Health Research Authority
IB	Investigator's Brochure
ICR	The Institute Of Cancer Research
ICR-CTSU	The Institute of Cancer Research Clinical Trials and Statistics Unit
IDMC	Independent Data Monitoring Committee
LFT	Liver Function Test
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
PD	Progressive Disease
PI	Principal Investigator
PIS	Patient Information Sheet
Plt	Platelets
PR	Partial Response
PTV	Planning Target Volume
Qol	Quality of Life
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

SD	Stable Disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Transitional Cell Carcinoma
TMG	Trial Management Group
TSC	Trial Steering Committee
U+E	Urea & Electrolytes
ULN	Upper Limit of Normal
VMAT	Volumetric Modulated Arc Therapy
WBC	White Blood Cell
WHO	World Health Organisation