ISRCTN12606219 https://doi.org/10.1186/ISRCTN12606219

# A trial of radiotherapy for people receiving atezolizumab for cancer of the urinary system

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| **Submission date**<br>10/06/2021 | **Recruitment status**<br>No longer recruiting | [X] Prospectively registered<br>[ ] Protocol<br>[ ] Statistical analysis plan<br>[ ] Results<br>[ ] Individual participant data<br>[ ] Record updated in last year |
| **Registration date**<br>10/06/2021 | **Overall study status**<br>Ongoing | |
| **Last Edited**<br>06/03/2024 | **Condition category**<br>Cancer | |

**Plain English summary of protocol**

Background and study aims

RE-ARM is a clinical trial for people who are already receiving treatment with either a drug called atezolizumab or a similar drug called avelumab for bladder or urinary system cancer (urothelial cancer) which has spread to other parts of their body (metastasised). RE-ARM investigates whether giving additional radiotherapy alongside atezolizumab can improve how well it works. Atezolizumab is an immunotherapy drug which enhances the body's natural immune response against cancer. It normally starts working after the first few weeks of treatment, but it can start working later on (late response), even if at the start there was no clear effect.

Radiotherapy can also improve the body's cancer immune response. Previous studies suggest radiotherapy can be given safely in combination with immunotherapy and it may make it more likely to work. The RE-ARM study will assess whether giving people a short course of radiotherapy while they're taking atezolizumab will increase the number who then have a late response.

Who can participate?

People receiving atezolizumab or avelumab for metastatic urothelial cancer

What does the study involve?

102 participants will be enrolled and assigned to one of two groups at random. Half (51) will take atezolizumab on its own. The other half will take atezolizumab alongside a short course of radiotherapy targeted at one site of their cancer. Participants in both groups will continue to receive atezolizumab every three weeks until it is no longer helping to keep their cancer under control.

Participants will have check-ups every three weeks to check and treat any symptoms they may be having and scans every 9-12 weeks to check whether their cancer is responding to treatment. This schedule is based on the standard treatment and monitoring schedule used for atezolizumab. After people stop their atezolizumab treatment patients will continue to be followed up every 3 months.

What are the possible benefits and risks of participating?

There is no guarantee that participants will benefit directly from taking part in RE-ARM. Participants may have side effects from the study treatment and participants will be informed of

the potential for side effects caused by atezolizumab and radiotherapy via their doctor and the patient information sheet. The information we get from this study may help in treating people with metastatic urothelial cancer in the future

Where is the study run from?
The Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?
January 2021 to December 2025

Who is funding the study?
1. Cancer Research UK
2. Roche (Switzerland)

Who is the main contact?
Hannah Gribble, REARM-icrctsu@icr.ac.uk

### Study website
https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/our-research/clinical-trials/re-arm

## Contact information

### Type(s)
Scientific

### Contact name
Ms Hannah Gribble

### Contact details
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## Additional identifiers

### EudraCT/CTIS number
2020-004893-23

### IRAS number
280335

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
CPMS 48346, IRAS 280335

# Study information

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

### Acronym
RE-ARM

### Study objectives
Current study hypothesis as of 31/07/2023:
The addition of palliative radiotherapy to atezolizumab will improve cancer response for people who have been receiving atezolizumab or maintenance avelumab for metastatic urothelial carcinoma without previous response.

Previous study hypothesis:
The addition of palliative radiotherapy to atezolizumab will improve cancer response for people who have been receiving atezolizumab for metastatic urothelial carcinoma without previous response.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 09/03/2021, London - Surrey Borders REC (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH, UK; +44 (0)207 104 8120; surreyborders.rec@hra.nhs.uk), ref: 21/LO/0150

### Study design
Interventional randomized controlled trial

### Primary study design
Interventional

### Secondary study design
Randomised controlled trial

### Study setting(s)
Hospital

### Study type(s)
Treatment

### Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

## Health condition(s) or problem(s) studied
Urothelial cancer

## Interventions
Current interventions as of 31/07/2023:
DESIGN
RE-ARM is a phase II trial that will take place at several NHS hospitals around the country. It will recruit 102 participants from approximately 20 participating sites within the UK. The RE-ARM trial is for people with advanced urothelial cancer who are having atezolizumab or maintenance avelumab as part of their routine treatment, but have not had a response after the first 9 weeks of treatment. Patients who are able to continue to receive atezolizumab will be invited to join the trial by their doctor at the hospital where they are receiving treatment.

RANDOMISATION
Participants will have assessments within 28 days prior to entering the trial to check it is a suitable option for them.
Those assessments include:
1. Physical examination
2. Medical history
3. Full blood count, urea and electrolytes, amylase and liver function assessment
4. Thyroid function assessment
5. Blood tests for HIV, hepatitis B and hepatitis C
6. Assessment of symptoms and current medication
7. CT chest abdomen pelvis

Those who agree to join the trial will be allocated to one of two treatment groups:
1. Atezolizumab treatment on its own
2. Atezolizumab and having radiotherapy as well.

People who take part will be allocated to these groups at random by the central coordinating centre. This is to help make sure that any differences we see between treatment response in each group is due to the treatment they have received.
Participants will have a series of study visits, the timing of the visits and assessments to be performed are described below.

TREATMENT AND ASSESSMENT SCHEDULE:

Group 1 - Atezolizumab only
Participants will receive atezolizumab every 3 weeks for a maximum of two years or until it is no longer suitable for the participant to continue receiving atezolizumab.

Group 2 - Atezolizumab plus radiotherapy
Participants allocated to also receive radiotherapy will follow the same schedule as group 1 but will also receive radiotherapy during their first 3 weeks of atezolizumab treatment within RE-ARM. The radiotherapy treatment will be given over five visits during one week.

The assessment schedule will be the same for both group 1 and 2 and has been designed to mirror the standard assessment schedule for those being treated with atezolizumab as standard of care outside the trial setting as far as possible.

Assessments during atezolizumab treatment:
The following assessments should be conducted before each three-weekly cycle (within 72 hrs

prior to day 1):
• Physical examination
• Full blood count, urea and electrolytes, amylase, liver function assessment
• Thyroid function (every 6 weeks)
• Assessment of symptoms and current medication
• A CT scan of their chest, abdomen and pelvis (Every 9 weeks within the first year of treatment, then every 12 weeks within the second year of treatment. If the participants cancer has worsened a scan will be performed six weeks later, then twelve week later, before reverting back to the original schedule).

Assessments after atezolizumab treatment:
There will be no trial specific assessments after treatment is completed, however symptoms and side effects will continue to be monitored for 90 days after treatment completion and three monthly updates on health status will be collected from participating sites until trial closure /participants' death.
If participants agree to participate in the quality of life or sample sub-studies, assessments will take place at the following time points:

Quality of life:
Participants will complete a questionnaire called EORTC QLQ-C30 at screening, week 9, 6 and 12 months.

Sample collection sub-study:
Blood samples for research will be collected at screening, during radiotherapy for those in group 2, week 3, week 9 and if the participant's cancer becomes worse.

Previous interventions:
DESIGN
RE-ARM is a phase II trial that will take place at several NHS hospitals around the country. It will recruit 102 participants from approximately 20 participating sites within the UK. The RE-ARM trial is for people with advanced urothelial cancer who are having atezolizumab as part of their routine treatment, but have not had a response after the first 9 weeks of treatment. Patients who are able to continue to receive atezolizumab will be invited to join the trial by their doctor at the hospital where they are receiving treatment.

RANDOMISATION
Participants will have assessments within 28 days prior to entering the trial to check it is a suitable option for them.
Those assessments include:
• Physical examination
• Medical history
• Full blood count, urea and electrolytes, amylase and liver function assessment
• Thyroid function assessment
• Blood tests for HIV, hepatitis B and hepatitis C
• Assessment of symptoms and current medication
• CT chest abdomen pelvis

Those who agree to join the trial will be allocated to one of two treatment groups:
1. Continuing atezolizumab treatment on its own
2. Continuing atezolizumab and having radiotherapy as well.

People who take part will be allocated to these groups at random by the central coordinating centre. This is to help make sure that any differences we see between treatment response in each group is due to the treatment they have received.

Participants will have a series of study visits, the timing of the visits and assessments to be performed are described below.

TREATMENT AND ASSESSMENT SCHEDULE:
Group 1 - Atezolizumab only
Participants will receive atezolizumab every 3 weeks for a maximum of two years or until it is no longer suitable for the participant to continue receiving atezolizumab.
Group 2 - Atezolizumab plus radiotherapy
Participants allocated to also receive radiotherapy will follow the same schedule as group 1 but will also receive radiotherapy during their first 3 weeks of atezolizumab treatment within RE-ARM. The radiotherapy treatment will be given over five visits during one week.

The assessment schedule will be the same for both group 1 and 2 and has been designed to mirror the standard assessment schedule for those being treated with atezolizumab as standard of care outside the trial setting as far as possible.

Assessments during atezolizumab treatment:
The following assessments should be conducted before each three-weekly cycle (within 72 hrs prior to day 1):
• Physical examination
• Full blood count, urea and electrolytes, amylase, liver function assessment
• Thyroid function (every 6 weeks)
• Assessment of symptoms and current medication
• A CT scan of their chest, abdomen and pelvis (Every 9 weeks within the first year of treatment, then every 12 weeks within the second year of treatment. If the participants cancer has worsened a scan will be performed six weeks later, then twelve week later, before reverting back to the original schedule).

Assessments after atezolizumab treatment:
There will be no trial specific assessments after treatment is completed, however symptoms and side effects will continue to be monitored for 90 days after treatment completion and three monthly updates on health status will be collected from participating sites until trial closure /participants' death.
If participants agree to participate in the quality of life or sample sub-studies, assessments will take place at the following time points:
Quality of life:
Participants will complete a questionnaire called EORTC QLQ-C30 at screening, week 9, 6 and 12 months.
Sample collection sub-study:
Blood samples for research will be collected at screening, during radiotherapy for those in group 2, week 6, week 9 and if the participant's cancer becomes worse.

## Intervention Type
Drug

## Phase
Phase II

### Drug/device/biological/vaccine name(s)
Atezolizumab

### Primary outcome measure
Objective response rate according to RECIST v1.1 at 9 weeks after the start of study

### Secondary outcome measures
1. Objective response rate according to iRECIST at nine weeks after the start of study
2. Clinical benefit according to RECIST v1.1 at nine weeks after the start of study
3. Best response according to RECIST v1.1 at six months after the start of study
4. Duration of response measured using patient records at the end of the study
5. Time to progression measured using patient records at the end of the study
6. Progression free survival measured using patient records at the end of the study
7. Overall survival measured using patient records at the end of the study
8. Treatment related toxicity (CTCAE v5) at the end of the study
9. Patient reported quality of life (EORTC QLQ-C30 & EQ-5D-5L) up to 12 months

### Overall study start date
01/01/2021

### Completion date
31/12/2025

## Eligibility

### Key inclusion criteria
Current inclusion criteria as of 31/07/2023:
1. Histologically confirmed metastatic urothelial carcinoma not amenable to curative treatment with surgery or radiotherapy. Mixed histology is permitted if predominantly TCC
2. Patients experiencing progressive disease (according to local investigator assessment) during up to six months of treatment with either open-label atezolizumab* (first, second or third line¥) or maintenance avelumab (following platinum-based chemotherapy); or patients with an overall best response of stable disease after a minimum of 3 cycles and a maximum of six months of open label atezolizumab
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/avelumab or during atezolizumab or avelumab treatment
6. Satisfactory haematological and biochemical profile (Hb >90 g/L, Plt>100 x 109/L, WBC > 3.0 x 109/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

Previous 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
4. At least one additional RECIST v1.1 measurable lesion distant to planned site for 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

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
Planned Sample Size: 102; UK Sample Size: 102

## Key exclusion criteria
Current exclusion criteria as of 31/07/2023:
1. Any contraindication to atezolizumab treatment in the local investigator’s opinion (e.g. toxicity [see Section 9.2.8], rapidly progressive disease requiring alternative treatment such as chemotherapy)
2. Greater than 8 weeks since the last dose of atezolizumab or maintenance avelumab
3. Over 6 months’ treatment with atezolizumab or maintenance avelumab prior to randomisation
4. Planned or anticipated clinical need for palliative radiotherapy within 9 weeks following trial entry
5. Received any anti-PD1/PD-L1 or anti-CTLA-4 therapy prior to commencement of atezolizumab or maintenance avelumab
6. Received atezolizumab in combination with chemotherapy
7. Immunosuppressive treatment (apart from corticosteroids at a dose equivalent of prednisolone ≤10 mg daily) within 2 weeks prior to randomisation.
8. Contraindication to radiotherapy (e.g. radiation sensitivity syndrome)
9. 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
10. History of pneumonitis

11. Presence of known active brain metastases (brain metastases which have received treatment and are controlled do not preclude randomisation)
12. 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
13. Pregnant or lactating women
14. Administration of a live, attenuated vaccine within 28 days prior to study entry
15. Anticipated life expectancy <10 weeks

Previous exclusion criteria:
1. Any contraindication to continued atezolizumab treatment in the local investigator's opinion (e.g. toxicity, rapidly progressive disease requiring alternative treatment such as chemotherapy)
2. Received anti-PD1/PD-L1, anti-CTLA-4 therapy prior to commencement of atezolizumab
3. Received atezolizumab in combination with chemotherapy
4. Immunosuppressive treatment (apart from corticosteroids at a dose equivalent of prednisolone <=10mg daily) within 2 weeks prior to study entry
5. Contraindication to radiotherapy (e.g. radiation sensitivity syndrome)
6. Autoimmune disease requiring active immunotherapy treatment or with life-threatening complications. Patients with vitiligo, controlled psoriasis, autoimmune thyroid disease, and type 1 diabetes will be eligible.
7. History of pneumonitis
8. Presence of known active brain metastases (brain metastases which have received treatment and are controlled do not preclude trial entry)
9. 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
10. Pregnant or lactating women
11. Administration of a live, attenuated vaccine within 28 days prior to study entry
12. Anticipated life expectancy <10 weeks

### Date of first enrolment
19/07/2021

### Date of final enrolment
06/03/2024

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre
**Royal Marsden Hospital**
Downs Road
Sutton
United Kingdom
SM2 5PT

**Study participating centre**
**The Royal Marsden Hospital (london)**
Fulham Road
London
United Kingdom
SW3 6JJ

**Study participating centre**
**Charing Cross Hospital**
Fulham Palace Road
London
United Kingdom
W6 8RF

**Study participating centre**
**Southampton General Hospital**
Tremona Road
Southampton
United Kingdom
SO16 6YD

**Study participating centre**
**Royal Free Hospital**
Pond Street
London
United Kingdom
NW3 2QG

**Study participating centre**
**University College London Hospital**
250 Euston Road
London
United Kingdom
NW1 2PG

**Study participating centre**
**The James Cook University Hospital**
Marton Road
Middlesbrough

United Kingdom
TS4 3BW

**Study participating centre**
**Clatterbridge Cancer Centre**
Clatterbridge Hospital
Clatterbridge Road
Wirral
United Kingdom
CH63 4JY

**Study participating centre**
**Royal Devon and Exeter Hospital**
Barrack Road
Exeter
United Kingdom
EX2 5DW

**Study participating centre**
**Leicester General Hospital**
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

**Study participating centre**
**Belfast City Hospital**
51 Lisburn Rd
Belfast
United Kingdom
BT9 7AB

**Study participating centre**
**St Bartholomew's Hospital**
West Smithfield
London
United Kingdom
EC1A 7BE

### Study participating centre
**University Hospitals Coventry & Warwickshire**
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

### Study participating centre
**The Christie Clinic**
550 Wilmslow Road
Manchester
United Kingdom
M20 4BX

## Sponsor information

### Organisation
Institute of Cancer Research

### Sponsor details
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### Sponsor type
Research organisation

### Website
http://www.icr.ac.uk/

### ROR
https://ror.org/043jzw605

## Funder(s)

### Funder type
Charity

### Funder Name

Cancer Research UK

**Alternative Name(s)**
CR_UK, Cancer Research UK - London, CRUK

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
Other non-profit organizations

**Location**
United Kingdom

**Funder Name**
F. Hoffmann-La Roche

**Alternative Name(s)**
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
For-profit companies (industry)

**Location**
Switzerland

# Results and Publications

**Publication and dissemination plan**
The RE-ARM results will be presented at relevant international conferences and published in a peer reviewed journal when available. A lay summary will also be prepared to accompany the peer-reviewed publication.

**Intention to publish date**
01/12/2026

**Individual participant data (IPD) sharing plan**
The datasets generated during and/or analysed during the current study are/will be available upon request from rearm-icrctsu@icr.ac.uk.

**IPD sharing plan summary**
Available on request

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |