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Accelerating the development and implementation of DNA damage inhibitor and radiotherapy treatment (with or without immunotherapy) in head and neck squamous cell carcinoma

Submission date 02/02/2021	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 02/02/2021	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 16/04/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-radiotherapy-and-targeted-treatment-for-head-and-neck-cancer-adept-ddr

Current plain English summary as of 29/10/2021:
Background and study aims
Head and neck squamous cell carcinoma (HNSCC) is a disease in which cancer cells arise in the mouth (oral cavity), the middle part of the throat (oropharynx), the lower part of the throat (hypopharynx) or the voice box (larynx) or other parts of the head and neck area. There are around 12,000 cases of HNSCC in the UK per year. Radiotherapy is currently the standard treatment offered. The aim of this study is to investigate the safety and effects of the 'study drug', an anti-cancer drug, called AZD6738 (ceralasertib) when given in combination with radiotherapy treatment. It is thought that combining AZD6738 (ceralasertib) with radiotherapy may enhance clinical outcomes for patients, and this study is conducted to ensure that the combination treatment is not causing a substantial increase in toxicity (the side effects seen in the body) by selecting optimum doses of AZD6738 (ceralasertib). The trial will take place at several hospitals across the UK.

Who can participate?
Patients aged 18 years and over with HNSCC

What does the study involve?
Up to 60 patients will be recruited to receive the study drug. The aim is to find the maximum dose of AZD6738 (ceralasertib) that is safe to give patients when combined with radiotherapy (also called the maximum tolerated dose). The starting dose for the trial was determined by looking at data from a similar study which used this drug. The maximum tolerated dose will be achieved by gradually increasing the dose that is given in each group of patients entering

Treatment Arm 1. The doses range from 20 mg to be taken twice a day for 5 days, up to 80 mg taken twice a day for 20 days. Once the maximum dose has been reached, the dose will not be increased any further.
The researchers will also recruit up to 20 patients as a control group. Control group patients will not receive the study drug but it is important for the researchers to collect information on patients who are receiving radiotherapy alone for comparison. The study also has additional parts:
Quality of life questionnaires: This will help the researchers to find out about how the treatment might affect quality of life and well-being. They think it is very important to find out how patients taking part in the ADePT-DDR trial feel, both emotionally and physically, and to study any side effects in some detail.
Pharmacokinetic testing - optional: The researchers will collect blood samples for pharmacokinetic testing to see how the drug is absorbed into the body. This part of the study is optional.
ADePT-DDR Collect - optional: The researchers will collect blood samples and use tissue samples which have already been taken in order to perform research into how different treatments affect the body. This part of the study is optional.

What are the potential benefits and risks of taking part?
There is evidence that in general patients who participate in studies have better outcomes than those who do not. However, the researchers cannot predict whether patients will benefit directly from taking part in this trial. It may be that the treatment they obtain increases the chance of cure. However, the researchers cannot guarantee the trial will help patients, but the information they get from this trial will help the future treatment of patients with HNSCC. There are possible side effects associated with the treatment delivery and tests. These are explained in the Patient Information Sheet.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run from?
June 2019 to May 2028

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
Miss Jasmin Cheang, j.cheang@bham.ac.uk

Previous plain English summary:
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The researchers will also recruit up to 20 patients as a control group. Control group patients will not receive the study drug but it is important for the researchers to collect information on patients who are receiving radiotherapy alone for comparison. The study also has additional parts:
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Contact information

Type(s)

Scientific

Contact name
Miss Jasmin Cheang

Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
2020-001034-35

Integrated Research Application System (IRAS)
277083

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RG_19-138, CPMS 46666, IRAS 277083

Study information

Scientific Title
Accelerating the Development and implementation of Personalised Treatments of DNA Damage Response agents and radiotherapy +/- immunotherapy for head and neck squamous cell cancer (ADePT DDR)

Acronym
ADePT-DDR

Study objectives
To evaluate the safety and efficacy of different DDR agents, or different immunotherapy agents and/or DDR and immunotherapy combinations, together with radiotherapy in patients with head and neck squamous cell carcinoma being treated curatively.

This open-label, multi-centre, platform trial will evaluate the safety and efficacy of different DNA Damage Repair (DDR) agents, or different immunotherapy agents and/or DDR and immunotherapy combinations, together with radiotherapy in patients with head and neck

squamous cell carcinoma (HNSCC) being treated curatively. The trial protocol will allow for the evaluation of new DDR agents for roll-on to a randomised Phase II/III trial. The initial component of this trial protocol will open with a single-arm dose-finding phase Ib/IIa trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/10/2020 South Central-Berkshire B Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 0207 1048310; berkshireb.rec@hra.nhs.uk), REC ref: 20/SC/0319

Study design
Open-label multi-centre platform trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Primary head and neck squamous cell carcinoma (HNSCC): laryngeal, hypopharyngeal, oropharyngeal cancer

Interventions
Treatment Arm 1 patients will receive radiotherapy treatment (70 Gy) in 35 fractions across 7 weeks. They will also receive AZD6738 tablets for between 5 and 20 days. The dose given will depend on the dose level allocated to each patient. 20 control patients will also be recruited. The control patients will receive radiotherapy only.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
AZD6738 (ceralasertib)

Primary outcome(s)
Recommended dose and safety profile of AZD6738 in combination with radiotherapy as determined by dose-limiting toxicities evaluated by CTCAE v5.0. The recommended dose will be determined by collecting toxicity data, which will then be reviewed by a safety committee. The dose-limiting toxicity (DLT) period will be up to 12 months after the end of treatment. However, dose-escalation decisions can be made 8 weeks after the end of treatment of the third patient within each cohort.

Key secondary outcome(s))

Complete response rates of primary tumour and nodal metastasis on positron emission tomography- computed tomography (PET-CT)/CT scan or magnetic resonance imaging (MRI) performed 12-16 weeks after the end of radiotherapy

Completion date
01/05/2028

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 29/10/2021:
1. Provision of informed consent prior to any trial-specific procedures
2. Patients must be aged ≥18 years of age
3. Histological or cytological confirmation of head and neck squamous cell carcinoma
4. Patients must have an MDT recommendation for treatment with radical radiotherapy (and where patients would be eligible to receive 70 Gy in 35 F), and not had previous treatment for head and neck cancer
5. At least one measurable lesion that can be accurately assessed at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for repeated assessment as per RECIST 1.1.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 within 28 days prior to randomisation with no deterioration to >1 over the previous 2 weeks
7. Patients must have normal organ and bone marrow function measured within 14 days prior to registration as defined below:
7.1. Haemoglobin ≥10 g/dl (with no blood transfusion or erythropoietin use within past 28 days)
7.2. Absolute neutrophil count ≥ 1.5 x 10^9/l
7.3. Platelet count ≥100 x 10^9/l (with no platelet transfusions within last 28 days)
7.4. Total bilirubin ≤1.5 x upper limit of normal (ULN) unless the patient has documented Gilbert' s syndrome
7.5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 x ULN
7.6. Patients must have creatinine clearance (CrCl) of ≥51 ml/min estimated or measured using standard methodology at the investigating centre (i.e. Cockcroft-Gault, MDRD, CK-EPI, EDTA or 24 hr urine)
8. Females must not be breastfeeding.
Women of childbearing potential and their partners, who are heterosexually active, must agree to the use of two highly effective forms of contraception in combination (as described in section 5.1.1) from the signing of the informed consent, throughout the period of taking trial treatment and for at least 6 months after last dose of trial drug(s), or they must totally/truly abstain from any form of sexual intercourse.
Male patients who are sexually active must be willing to use barrier contraception for the duration of the trial and for 1 week after the last trial drug administration, with no childbearing women.
Male patients must use a condom during treatment and for 6 months after the last dose of trial drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing potential and must not donate sperm for 6 months after the last dose of trial drug.
Female partners of male patients should also use a highly effective form of contraception (see section 7.4.1 for acceptable methods) for 6 months after the last dose of trial drug(s) if they are of childbearing potential. True abstinence for either sex is an acceptable form of contraception and must be documented as such.
9. Postmenopausal or evidence of non-child-bearing status for women of childbearing potential;

negative urine or serum pregnancy test within 28 days of trial treatment and confirmed prior to treatment on Day 1. Postmenopausal is defined as:
9.1. Aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
9.2. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation, radiation-induced oophorectomy with last menses > 1 year ago
9.3. Amenorrhoeic for 12 months and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and plasma oestradiol levels in the postmenopausal range for the institution for women under 50
10. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations
11. For inclusion in the optional biomarker research, patients must fulfil the following criteria:
11.1. Provision of informed consent for biomarker research
If a patient declines to participate in the optional biomarker research, the patient can still participate in the trial.

Previous participant inclusion criteria:
For inclusion in the trial patients should fulfil the following criteria:
1. Provision of informed consent prior to any trial-specific procedures
2. Patients must be aged ≥18 years of age
3. Histological or cytological confirmation of head and neck squamous cell carcinoma
4. Patients must have an MDT recommendation for treatment with radical radiotherapy (and where patients would be eligible to receive 70 Gy in 35 F), and not had previous treatment for head and neck cancer
5. At least one measurable lesion that can be accurately assessed at baseline by computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for repeated assessment as per RECIST 1.1.
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 within 28 days prior to randomisation with no deterioration to >1 over the previous 2 weeks
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7.1. Haemoglobin ≥10 g/dl (with no blood transfusion or erythropoietin use within past 28 days)
7.2. Absolute neutrophil count ≥ 1.5 x 10^9/l
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8. Females must not be breastfeeding.
Women of childbearing potential and their partners, who are heterosexually active, must agree to the use of two highly effective forms of contraception in combination (as described in section 5.1.1) from the signing of the informed consent, throughout the period of taking trial treatment and for at least 1 month after last dose of trial drug(s), or they must totally/truly abstain from any form of sexual intercourse.
Male patients who are sexually active must be willing to use barrier contraception for the duration of the trial and for 1 week after the last trial drug administration, with no childbearing women.
Male patients must use a condom during treatment and for 6 months after the last dose of trial drug(s) when having sexual intercourse with a pregnant woman or with a woman of childbearing

potential and must not donate sperm for 6 months after the last dose of trial drug.
Female partners of male patients should also use a highly effective form of contraception (see section 7.4.1 for acceptable methods) for 6 months after the last dose of trial drug(s) if they are of childbearing potential. True abstinence for either sex is an acceptable form of contraception and must be documented as such.
9. Postmenopausal or evidence of non-child-bearing status for women of childbearing potential; negative urine or serum pregnancy test within 28 days of trial treatment and confirmed prior to treatment on Day 1. Postmenopausal is defined as:
9.1. Aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
9.2. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation, radiation-induced oophorectomy with last menses > 1 year ago
9.3. Amenorrhoeic for 12 months and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and plasma oestradiol levels in the postmenopausal range for the institution for women under 50
10. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations
11. For inclusion in the optional biomarker research, patients must fulfil the following criteria:
11.1. Provision of informed consent for biomarker research
If a patient declines to participate in the optional biomarker research, the patient can still participate in the trial.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria as of 29/10/2021:
1. Patients with T1-2 N0 disease
2. A diagnosis of ataxia telangiectasia or other radiosensitivity syndrome
3. Cytotoxic chemotherapy, hormonal or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted. A duration of 30 days or 5 half-lives (whichever is longer) is required for patients treated with non-cytotoxic drugs). The minimum washout period for immunotherapy is 42 days
4. With the exception of alopecia and Common Terminology Criteria for Adverse Events (CTCAE) grade 2 neuropathy, any unresolved toxicities from prior therapy ≥ CTCAE v5.0 grade 2
5. Any of the following cardiac diseases currently or within the last 6 months (by New York Heart Association (NYHA) ≥ Class 2 where applicable):
5.1. Unstable angina pectoris

5.2. Congestive heart failure or known reduced left ventricular ejection fraction (LVEF) < 55%
5.3. Acute myocardial infarction
5.4. Conduction abnormality not controlled with pacemaker or medication e.g. complete left bundle branch block, third degree heart block
5.5. Significant ventricular or supraventricular arrhythmias e.g. (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
5.6. Patients at risk of brain perfusion problems, e.g., medical history of carotid stenosis or pre-syncopal or syncopal episodes, history of transient ischaemic attacks (TIAs)
5.7. Uncontrolled hypertension (CTCAE v5.0, grade 2 or above) requiring clinical intervention
6. Mean resting corrected QT interval (QTc) >470 msec for females and >450 for men, obtained from 3 electrocardiograms (ECGs) 2-5 minutes apart using the Fredericia formula. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congestive heart failure, unstable angina pectoris, acute myocardial infarction, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age, conduction abnormality not controlled with pacemaker or medication
7. Patients with relative hypotension (<90/60 mm Hg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of > 20 mm Hg
8. Concomitant use of known potent cytochrome P (CYP) 3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir). The required washout period prior to starting trial treatment is 2 weeks. Moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) can be used with caution.
9. Concomitant use of known potent cytochrome P450 inducers (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort).
9.1. The required washout period prior to starting trial treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
9.2. Moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil) are allowed and can be used with caution.
9.3. Please note that patient prescription or non-prescription drugs or other products known to be CYP3A4 and/or CYP2B6 substrates or CYP3A4 and/or CYP2B6 substrates with a narrow therapeutic index are allowed but should be used with caution. Exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced and additional monitoring may be required. Strong inhibitors of CYP28 should be contraindicated.
10. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases that places the patient at unacceptable risk of toxicity or non-compliance. Examples include, but are not limited to, active bleeding diatheses, renal transplant, uncontrolled major seizure disorder, severe chronic obstructive pulmonary disease (COPD), superior vena cava syndrome, extensive bilateral lung disease on High-Resolution CT scan, severe Parkinson's disease, active inflammatory bowel disease, psychiatric condition, or active infection including any patient known to have hepatitis B, hepatitis C and human immunodeficiency virus (HIV) or requiring systemic antibiotics, antifungals or antiviral drugs. Screening for chronic conditions is not required.
11. A known hypersensitivity to AZD6738 or any excipient of the product or any contraindication to the drug under study as per local prescribing information.
12. Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

Previous participant exclusion criteria:
Patients should not enter the trial if any of the following exclusion criteria are fulfilled.
1. Patients with T1-2 N0 disease

2. A diagnosis of ataxia telangiectasia or other radiosensitivity syndrome
3. Cytotoxic chemotherapy, hormonal or non-hormonal targeted therapy within 21 days of Cycle 1 Day 1 is not permitted. A duration of 30 days or 5 half-lives (whichever is longer) is required for patients treated with non-cytotoxic drugs). The minimum washout period for immunotherapy is 42 days
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5.4. Conduction abnormality not controlled with pacemaker or medication e.g. complete left bundle branch block, third degree heart block
5.5. Significant ventricular or supraventricular arrhythmias e.g. (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
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12. Refractory nausea and vomiting, chronic gastrointestinal diseases or previous significant bowel resection, with clinically significant sequelae that would preclude adequate absorption of AZD6738.

Date of first enrolment
01/05/2021

Date of final enrolment
01/05/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TH

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes