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(Treatments to shrink tumors before surgery, radiation or other forms of nondrug therapy) to use the investigational drug (Darovasertib) in patients with a type of cancer in the middle of the eye wall.

Submission date	Recruitment status	[ ] Prospectively registered
22/09/2023	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
02/04/2024	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
10/04/2024	Eye Diseases	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Patients with large, localized uveal melanomas (cancer in the middle of the eyewall) currently are treated with either removal of the eyeball (enucleation) or radiation directed at the tumor to kill or shrink it. In uveal melanoma, targeted radiation therapy (brachytherapy) is commonly used, where small radioactive beads are targeted to the eye for a few days using a plaque implant. Enucleation and radiation therapy often result in loss of useful vision. New treatments are needed to help reduce the frequency and severity of this vision loss. IDE196 (also known as darovasertib) has been shown to shrink uveal melanoma tumors in clinical trial patients who have cancer only in the eye and/or cancer that has spread outside the eye (metastatic cancer). For patients with cancer in the eye, IDE196 treatment improved the visual symptoms associated with melanoma. Based on clinical trial results, it is thought that treatment with IDE196 may help to avoid the need to remove the eye and/or decrease the amount of radiation given during brachytherapy. Hence, the eye may be preserved and/or useful vision improved. Reducing the amount of local therapy given directly to the tumor may also improve any potential symptoms, side effects, and treatment complications of current therapies.

Who can participate?

Adult patients aged over 18 years old with localized uveal melanoma

What does the study involve?

This clinical trial will test the effect of IDE196 treatment before (as neoadjuvant therapy) and after (as adjuvant therapy) the planned enucleation or radiation therapy. The adjuvant therapy with IDE196 may serve to kill any tumor that might be left after the previous treatment.

What are the possible benefits and risks of participating?
Previous studies of IDE196 showed that a dose of 300 mg taken twice daily had a tolerable and safe profile for uveal melanoma patients.

Blood Sampling: Blood draws may cause fainting, pain and/or bruising. Rarely, there may be a small blood clot or infection where the needle punctures the skin. Blood will be taken at various times during the study and the amount of blood collected each time is different, ranging from 27 – 83 mL (2 – 6 tablespoons) per visit. For participants in the extended PK sampling, the amount of blood taken at these visits will be up to 12 ml (less than 1 Tablespoon) total. The blood pressure cuff may also cause discomfort or bruising of the upper arm.
Surgery or Radiation Treatment: IDE196 will be interrupted before any surgery or radiation therapy and restarted after initial healing from the surgery or radiation. It is unknown if treatment with IDE196 could contribute to any complications resulting from the surgery or radiation. Study staff will provide a hospital-specific full list of risks associated with the surgery or radiation treatment.
Tumor Imaging (CT or MRI Scans): The patient should inform the physician or technologist if they are pregnant, or suspect to be, as this exam may cause harm to unborn babies. There will be no pregnant participants enrolled.
The patient will receive MRI scans in this study. Some people may have anxiety and claustrophobia (fear of being in small places) associated while inside the MRI machine. An injection of a solution may be given to obtain better pictures of the inside of your body. The injection may make you sick to your stomach, pass out, or have pain, warmth, swelling, bruising, a small blood clot or infection at the injection site.
Biopsy: With a biopsy, tissue may be removed by using a fine needle (also called a fine needle aspirate biopsy) or removed from the eye or body by other means. The patient will have their tumor tissue biopsied during their primary local therapy, and an optional tumor biopsy if cancer grows. The study doctor will inform the patient in detail about the risks associated with the biopsy procedure. In general, having a biopsy can cause pain, swelling, bleeding and/or infection at the site where the biopsy needle is inserted through the skin. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.
Electrocardiograms (ECGs): The sticky pads used for the test may cause skin irritation. When taking off the sticky pads the patient may experience discomfort like removing a plaster.
Eye Exams: The patient might experience side effects from the procedures used to prepare the eye for the exams, like from the use of the anesthetic or dilating drops. These side effects may include eye pain, bloodshot eyes, irregularity or swelling of tissues inside or around your eyeball, or visual disturbances. After the exams, the patient will have an increased sensitivity to light and should wear sunglasses and exercise caution when driving.
Contraception and Pregnancy: Women who are pregnant or breastfeeding cannot take part in this trial. The patient must confirm, to the best of your knowledge, that they are not pregnant now, and that they do not intend to become pregnant during the trial.

Managing Risks and Side Effects
Low Blood Pressure: Low blood pressure symptoms have typically occurred within 1 to 4 hours after the first or second dose of IDE196 and went away quickly with intravenous (IV) fluids, or an interruption or lowering of the study medication dose. They will be asked to remain in the clinic for 2 hours after their first dose of study medication in both Part 1 and Part 2 of the study. They should not drive or operate heavy machinery while taking the study medication until they know how the treatment is affecting them. The study team will watch the patient carefully and train them on how to manage this possible side effect.
Nausea, Vomiting or Diarrhea: Eat smaller more frequent meals (including before taking the study drug) with significant fat and protein content to reduce nausea/vomiting. In addition, it is recommended to drink 2 glasses of water together with meals and before each study treatment

dose.
Skin Issues: IDE196 may cause the patient to develop skin rashes, acne-like rashes, and dry and /or itching skin. They should avoid direct exposure to the sun by wearing clothing, shoes and hats that fully cover the skin. In addition, recommendations to limit rash risk include minimizing washing with hot water and avoidance of both skin irritants and moisturizers that contain alcohol.
Interaction of IDE196 and Other Medications: If the patient decides to take part in this study, they may be asked to stop taking some medications that they are currently using for the entire study. If they stop their regular medication, their health might get worse. The patient should ask the study doctor about what medications they cannot take in order to be able to participate in this study.

Where is the study run from?
University College London Hospitals (UK)

When is the study starting and how long is it expected to run for?
September 2023 to March 2029

Who is funding the study?
IDEAYA Biosciences (USA)

Who is the main contact?
Dr Heather Shaw

Contact information

Type(s)
Public, Scientific, Principal investigator

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ClinicalTrials.gov (NCT)
NCT05907954

Clinical Trials Information System (CTIS)
2023-506683-14

Integrated Research Application System (IRAS)
1008546

Protocol serial number
IDE196-009

Study information

Scientific Title
(Neo)adjuvant IDE196 (darovasertib) in patients with localised ocular melanoma

Study objectives
To evaluate the tolerability and safety of IDE196 given in the neoadjuvant and adjuvant setting and to evaluate the clinical utility of response to IDE196 in primary uveal melanomas.

The secondary objectives were to evaluate the antitumor activity of IDE196 as neoadjuvant therapy, assessment of visual acuity loss, to evaluate the rate of local disease recurrence, and to evaluate the rate distant recurrence.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/12/2023, North East- York Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048143; york.rec@hra.nhs.uk), ref: 23/NE/0190

Primary study design
Interventional

Study design
Interventional study

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Large, localized uveal melanomas in patients

Interventions
The schedule of events is pharmacokinetic & pharmacodynamic assessments, tumour tissue samples, efficacy assessments and safety assessments.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
darovasertib [IDE-196] , IDE196 [IDE196]

Primary outcome(s)
1. The incidence of adverse events (AEs) leading to dose interruption, modification, and discontinuation during neoadjuvant or adjuvant therapy
2. The incidence of Grade 3 or 4 AEs and clinically significant laboratory abnormalities during neoadjuvant or adjuvant therapy
3. Cohort 1 – number of patients converted from requiring enucleation to radiation (e.g., plaque brachytherapy
4. Cohort 2 – comparison in radiation to the fovea as modeled before and after IDE196 neoadjuvant therapy

The intermediate endpoint to be assessed at the time of primary local therapy is the change in modeled radiation dose at the fovea as assessed before and after neoadjuvant IDE196 treatment. Radiation will be modeled by central dosimetry, including quantification through dose area/volume histogram analysis.

Key secondary outcome(s)
1. Bidirectional measurements which determine the T-stage (T-category) and include the apical thickness and largest basal diameter
2. Loss ≥15 letters by Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score, 1 year after completion of primary local therapy
3. Patients will undergo standard ophthalmology follow-up to assess for local disease progression or recurrence
4. Patient will undergo risk-based surveillance for distant RFS per assessment by standard of care imaging per baseline prognostic risk assessment as determined by T-stage/category, genetic evaluation, and/or gene expression profiling

Quantification and assessment of canonical uveal melanoma mutations in cfDNA pre- and postneoadjuvant treatment, as well as during adjuvant therapy and throughout recurrence follow-up. Requires initial sequencing evaluation of GNAQ/11

Completion date
31/03/2029

Eligibility

Key inclusion criteria
Patients must meet all of the following inclusion criteria:
1. Must be at least 18 years of age.
2. Is able to provide written, informed consent before initiation of any study-related procedures, and is able, in the opinion of the Investigator, to comply with all the requirements of the study.
3. Has an initial primary diagnosis of localized uveal melanoma (no evidence of distal and/or extraocular disease) as clinically determined by the treating Investigator, with a plan to undergo either enucleation or plaque brachytherapy. [Note: Patients with local relapse after prior primary therapies are excluded]

Cohort 1:
3.1. Clinically diagnosed uveal (not iris) melanoma in which enucleation is recommended and meets the following criteria:
3.1.1. Up to 22 mm in largest basal diameter (LBD)
3.1.2. Up to 15 mm in thickness

3.2. NOTE: cancer cannot have attributes that necessitate enucleation regardless of response to therapy (e.g., extraocular disease, hemorrhage, blind painful eye, evidence of optic nerve invasion, etc.)

Cohort 2:
3.3. Clinically diagnosed uveal (not iris) melanoma in which plaque brachytherapy is recommended, meets the following criteria, and places the patient at significant risk of loss of useful vision in the affected eye:
3.3.1. At least 6 mm in LBD
3.3.2. At least 3 mm in thickness
3.3.3. NOTE: sub-foveal or >180-degree optic nerve-involved tumors are excluded

4. Able to safely swallow orally administered medication.
5. If prognostication and mutational status have not been evaluated as the standard of care, the participant must be willing to provide a buccal swab plus a fine needle aspirate (FNA) or enucleation biopsy either prior to neoadjuvant treatment or at the time of primary local therapy (plaque placement or enucleation). The patient must be able to hold medications (aspirin, anticoagulation) per standard pre-operative protocols.
6. Has Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (Appendix 4, [Section 14.4]) (Karnofsky ≥70%).
7. Lacks evidence of progressive secondary underlying ocular disease in either eye that will confound longitudinal visual acuity assessments (e.g., macular degeneration, diabetic retinopathy, neovascular glaucoma, etc).
8. Has adequate organ function:
8.1. Absolute neutrophil count ≥1500/mm3 without the use of hematopoietic growth factors
8.2. Platelet count ≥100,000/mm3 (must be at least 2 weeks post-platelet transfusion and not receiving platelet-stimulating agents)
8.3. Hemoglobin ≥9.0 g/dL (must be at least 2 weeks post-red blood cell transfusion and not receiving erythropoietic-stimulating agents)
8.4. Total bilirubin ≤1.5 x the upper limit of normal (ULN). For patients with documented Gilbert's disease, total bilirubin ≤3.0 mg/dL is allowed
8.5. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN
8.6. Serum albumin ≥3.0 g/dL
8.7. Creatinine Clearance ≥60 mL/min/1.73 m2 by Cockroft-Gault equation (Appendix 1, [Section 14.1]) or serum creatinine ≤1.5 x ULN
8.8. Prothrombin time/International Normalized Ratio (INR) or partial thromboplastin time test results at screening ≤1.5 x ULN (this applies only to patients who do not receive therapeutic anticoagulation)
9. Female patients of childbearing potential must be non-pregnant, nonlactating, and have a negative serum human chorionic gonadotropin pregnancy test result within 28 days prior to the first IDE196 administration.
9.1. Females of childbearing potential who are sexually active with a nonsterilized male partner agree to use effective methods of contraception from screening (see Appendix 5 [Section 14.4]), throughout the study period and agree to continue using such precautions for 30 days after the final dose of IDE196
9.2. Non-sterilized males who are sexually active with a female of childbearing potential must agree to use effective methods of contraception from Day 1 throughout the study period and for 90 days after the final dose of IDE196

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Sex
All

Key exclusion criteria
The presence of any of the following would exclude a patient from being eligible for the study:
1. Has received previous treatment with a protein kinase C (PKC) inhibitor.
2. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to the study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type.
3. Has uncontrolled human immunodeficiency virus (HIV).
4. Has active infection requiring therapy, positive tests for Hepatitis B surface antigen (HBsAg) with detected Hepatitis B virus (HBV) DNA or positive Hepatitis C antibody with detected Hepatitis C virus (HCV) ribonucleic acid (RNA).
5. Has a malabsorption disorder that would interfere with the absorption of IDE196.
6. Requires any medication that cannot be discontinued prior to study entry and that is considered to be any of the following:
6.1. Known to be strong inducers or inhibitors of cytochrome P450 (CYP)3A4/5
6.2. Known to be substrates of CYP3A4/5 with a narrow therapeutic index
6.3. Known to be sensitive substrates to p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter 3 (OAT3), multidrug and toxin extrusion (MATE)-1 and MATE-2K
6.4. Drugs with a known and possible risk of QT prolongation, except for the specific use of oral granisetron, ondansetron or dolansetron for the management of nausea and vomiting (note: intravenous formulations are prohibited)
7. Women of childbearing potential planning to become pregnant during the study.
8. Has impaired cardiac function or clinically significant cardiac diseases, including any of the following:
8.1. History or presence of ventricular tachyarrhythmia
8.2. Presence of unstable atrial fibrillation (ventricular response >100 beats per minute); patients with stable atrial fibrillation are eligible, provided they do not meet any of the other cardiac exclusion criteria
8.3. Unstable angina or acute myocardial infarction ≤6 months prior to starting IDE196 treatment
8.4. Other clinically significant heart disease (e.g., symptomatic congestive heart failure; uncontrolled arrhythmia or history of labile hypertension or poor compliance with an antihypertensive regimen)
8.5. Corrected QT interval using Fridericia's formula (QTcF) >480 msec on baseline electrocardiogram (ECG) (mean of baseline values). If electrolytes are abnormal, they may be corrected and baseline electrocardiograms (ECGs) should be repeated (Appendix 2, [Section 14.2])
9. Has any other condition that may increase the risk associated with study participation or may

interfere with the interpretation of study results and, in the opinion of the Investigator, would make the patient inappropriate for entry into the study.
No waivers of inclusion or exclusion criteria will be granted by the Investigator for any patient enrolled on the study.

Date of first enrolment
14/08/2023

Date of final enrolment
18/12/2024

Locations

Countries of recruitment
United Kingdom

Australia

Canada

France

Germany

Italy

Netherlands

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
UBC Late Stage (UK)

Funder(s)

Funder type
Industry

Funder Name
IDEAYA Biosciences

Results and Publications

Individual participant data (IPD) sharing plan
When data becomes available and validated, we will share information at conferences (for example: abstracts, posters, and oral presentations), and submit it to journals (for example: manuscripts). In addition, the final study report/data will be published on clinicaltrials.gov

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