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Darovasertib is being used in comparison to crizotinib versus investigators' choice of treatment for negative (no specific marker) in this rare type of eye cancer which has been spread to other parts of the body, beyond the eye.

Submission date
06/10/2023

Registration date
13/12/2023

Last Edited
09/01/2024

Recruitment status
Recruiting

Overall study status
Ongoing

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The experimental study medications used in this trial are IDE196 (darovasertib) together with crizotinib. IDE196 is an investigational (experimental) new medication which blocks a protein in your body called Protein Kinase C (PKC). Approximately 90% of patients with uveal melanoma have a genetic mutation in GNAQ/GNA11 which results in abnormal activity in PKC. The tumour may depend on the effects of PKC in order to survive and grow. By blocking PKC with IDE196, it is hoped that tumour growth and tumour size may be reduced. IDE196 has not been approved by the UK Medicines and Healthcare products Regulatory Agency or any other regulatory authorities in the world. IDE196 has been studied in two other clinical trials in Australia, Europe, and North America and has been shown to be tolerable. Crizotinib (also marketed as Xalkori) is an approved medication used to treat a certain kind of lung cancer but has not yet been approved to treat metastatic uveal melanoma. Although crizotinib has been approved for use in lung cancer by the MHRA and certain other health authorities, it has not been approved for use when combined with IDE196. Crizotinib blocks a protein called mesenchymal epithelial transition factor (MET). If MET is overactive, it can cause abnormal growth and survival of tumour cells. Most uveal melanomas have increased expression of MET which is thought to contribute to both the growth and spread of uveal melanomas.

Who can participate?
Patients aged 18 years old and over with uveal melanoma

What does the study involve?
Some participants who enroll in this study will be assigned to receive a standard-of-care treatment (the usual treatment given by your study doctor for metastatic uveal melanoma)

instead of the experimental treatment. They will either receive a medication called Pembrolizumab, or a medication called Dacarbazine or a combination of two medications called Ipilimumab plus Nivolumab.

What are the possible benefits and risks of participating?
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.
Tumour Imaging (CT or MRI Scans): The patient should inform the physician or technologist if you are pregnant, or suspect to be, as this exam may cause harm to unborn babies. There will be no pregnant participant 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 tumour tissue biopsied during their primary local therapy, and an optional tumour biopsy if the 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 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. The will be asked to remain in clinic for 2 hours after their first dose of study medication in both Part 1 and Part 2 of the study. The 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 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?
Mount Vernon Cancer Centre (UK)

When is the study starting and how long is it expected to run for?
September 2023 to December 2027

Who is funding the study?
IDEAYA Biosciences (USA)

Who is the main contact?
Dr Paul Nathan, p.nathan@nhs.net

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2023-506686-66

Integrated Research Application System (IRAS)
1008602

ClinicalTrials.gov (NCT)
NCT05987332

Protocol serial number
IDE196-002, CPMS 58015

Study information

Scientific Title
IDE196 (DAROVASERTIB) in combination with crizotinib versus investigator's choice of treatment as first-line therapy in HLA-A2 negative metastatic uveal melanoma

Acronym
IDE196-002 Study

Study objectives
To compare IDE196 + crizotinib to investigator's choice of treatment with respect to PFS per RECIST 1.1 as assessed by blinded independent central review (BICR)
To compare IDE196 + crizotinib to investigator's choice of treatment with respect to OS

To evaluate the safety and tolerability (the degree to which a patient can tolerate a side effect) of IDE196 in combination with crizotinib.
To assess the best dose of IDE196 plus crizotinib combination.
To compare IDE196 plus crizotinib to the investigator's choice of treatment with respect to living without the tumour advancing per RECIST 1.1 as assessed by the doctor.
To compare IDE196 and crizotinib to the physician's choice of treatment with respect to tumour changes and how long the benefit of treatment lasts per RECIST 1.1 as assessed by a blinded expert independent central review committee and physician assessment.
To compare how the patient feels before and after treatment, based on "Quality of Life" questionnaires. Quality of Life is a measurement of how people being treated generally feel and how well they can function in daily living. The patient being treated completes these questions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Pending approval; ref: 23/WA/0293

Study design
Randomized controlled open-label parallel-group study

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Metastatic uveal melanoma

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

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Darovasertib [darovasertib] , crizotinib [crizotinib]

Primary outcome(s)
1. PFS, defined as the time from randomization to the first documented date of disease progression or death due to any cause, whichever occurs first.
2. OS, defined as the time from randomization to date of death due to any cause

Key secondary outcome(s))
1. Treatment-emergent adverse events (TEAEs), laboratory test abnormalities, ECG and vital sign changes.
2. Study intervention discontinuation due to AEs
3. Dose-exposure-response (safety and efficacy) relationship
4. Plasma concentration profiles and pharmacokinetic (PK) parameters including but not limited to Cmax, Ctrough, Tmax, AUC0-t, T1/2, Racc
5. PFS, defined as the time from randomization to the first documented date of disease progression or death due to any cause, whichever occurs first
6. Objective response rate (ORR), defined as the proportion of participants with a complete response (CR) or a partial response (PR) as best response
7. Disease control rate (DCR) (defined as CR or PR, or stable disease [SD] ≥12 weeks)
8. Best objective response (BOR)
9. Duration of response (DOR), defined as the time from the first documented evidence of a CR or PR until disease progression or death due to any cause, whichever occurs first
10. Time to response
11. Change from baseline over time and between treatment arms in EORTC QLQ-C30 and EuroQoL (EQ)-5D-5L scores

Completion date
31/12/2027

Eligibility

Key inclusion criteria
Participants 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 histological or cytological confirmed UM with metastatic disease
4. HLA-A*02:01 negative
5. Must meet the following criteria related to prior treatment:

5.1. No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy
5.2. No prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization
5.3. Prior ablations or surgical resection of oligometastatic disease are allowed
5.4. Prior neoadjuvant or adjuvant therapy is allowed provided administered in the curative setting in participants with localized disease and a minimum of 4 weeks (28 days) has elapsed between the end of neoadjuvant/adjuvant treatment and the start of study treatment.
5.4.1. Participants who have received a combination of anti-PD(L)1 plus anti-CTLA-4 as prior neoadjuvant/adjuvant treatment should not receive ipilimumab + nivolumab as Investigator's Choice therapy
5.4.2. Participants who have received an anti-PD(L)1 agent as prior neoadjuvant/adjuvant treatment should not receive pembrolizumab as Investigator's Choice therapy
5.4.3. Participants who have received a dacarbazine-containing regimen as prior neoadjuvant /adjuvant treatment should not receive dacarbazine as Investigator's Choice therapy
6. Has a representative archival metastatic tumour specimen in paraffin blocks with an associated pathology report or a minimum of 16 formalin-fixed paraffin embedded (FFPE) slides is mandatory. If archival tissue block is exhausted or not available, then a tissue biopsy FFPE sample is required unless a biopsy is not medically feasible. Only tissue from a surgical resection or a core needle, punch, or excisional/incisional biopsy sample collection will be accepted. Fine needle aspiration (FNA) samples are not acceptable.
7. Has measurable disease per RECIST 1.1, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with computer tomography (CT) or magnetic resonance imaging (MRI) scan. An enlarged lymph node must be ≥15 mm in short axis to be a measurable lesion.
8. Able to be safely administered and absorb study therapy
9. Has ECOG performance status 0 or 1.
10. Has a life expectancy of ≥3 months.
11. Has adequate organ function (screening assessment must be obtained within 14 days of first dose of study treatment):
11.1. Absolute neutrophil count ≥1500/mm3 without the use of hematopoietic growth factors
11.2. Platelet count ≥100,000/mm3 (must be at least 2 weeks post-platelet transfusion and not receiving platelet-stimulating agents)
11.3. Hemoglobin ≥9.0 g/dL (must be at least 2 weeks post-red blood cell transfusion)
11.4. Total and direct bilirubin ≤1.5 x the upper limit of normal (ULN). For participants with documented Gilbert's disease, total bilirubin ≤3.0 mg/dL is allowed
11.5. Aspartate transferase (AST) and alanine transferase (ALT) ≤3 x ULN in the absence of documented liver metastases; ≤5 x ULN in the presence of liver metastases.
11.6. Serum albumin ≥3.0 g/dL.
11.7. Creatinine clearance ≥45 mL/min by Cockcroft-Gault equation (see Appendix 1, Section 14.1).
11.8. Prothrombin time/International Normalized Ratio (INR) or partial thromboplastin time test results at screening ≤1.5 x ULN (this applies only to participants who do not receive therapeutic anticoagulation; participants receiving therapeutic anticoagulation should be on a stable dose for at least 2 weeks prior to the first dose of study drug).
12. Women of childbearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during study treatment (see Appendix 5 Section 14.5), and must agree to continue using such precautions for 6 months after the final dose of study treatment; cessation of birth control after this point should be discussed with a responsible physician. Highly effective methods of contraception are described in Appendix 5 Section 14.5.
13. Male participants must be surgically sterile or must agree to use double barrier

contraception methods from enrollment through treatment and for 6 months following administration of the last dose of study treatment.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
The presence of any of the following would exclude a participant from being eligible for the study:
1. Has received previous treatment with a PKC inhibitor (including prior treatment with IDE196) or an inhibitor directly targeting MET, or an inhibitor directly targeting GNAQ/11.
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 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 AEs from prior anti-cancer therapy that have not resolved to Grade ≤1 except for alopecia or anemia.
3.1. Any ongoing diarrhea requires discussion with the Sponsor Medical Monitor
3.2. Endocrinopathies resulting from previous immunotherapy are considered part of medical history and not an AE.
3.3. Stable Grade 2 neuropathy is allowed
4. Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to study Day 1. Participants with brain metastases are eligible if lesions have been treated with localized therapy and there is no evidence of progression for at least 4 weeks by MRI prior to the first dose of study drug.
5. Known acquired immunodeficiency syndrome (AIDS)-related illness.
NOTE: human immunodeficiency virus (HIV) seropositive participants who are healthy and low risk for AIDS related outcomes could be considered eligible. Eligibility criteria for HIV positive participants should be evaluated and discussed with Sponsor Medical Monitor and will be based on current and past cluster of differentiation 4 (CD4) and T cell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment. Also, the potential for drug-drug interactions should be taken into consideration.
6. Active adrenal insufficiency (eg, not stable on replacement therapy), active colitis, or active inflammatory bowel disease.
7. History of interstitial lung disease, active pneumonitis, or history of pneumonitis from prior therapies requiring corticosteroid treatment. However, history of grade 1 only pneumonitis OR prior radiation pneumonitis can be discussed with the Medical Monitor for consideration of

inclusion.
8. History of syncope (except due to an acute medical condition [eg, hemorrhage] that is not likely to reoccur and with permission of the Sponsor Medical Monitor) within 6 months of the first dose of study treatment. Any history of potential syncope should be clarified and verified if possible. All participants with prior history of syncope should be discussed with the Sponsor Medical Monitor.
9. Active infection requiring systemic antibiotic therapy. Participants requiring systemic antibiotics for infection must have completed therapy at least 1 week prior to the first dose of study drug
10. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the participant has a history of HBV or HCV infection. NOTE: participants with suspected hepatitis or human immunodeficiency virus (HIV) should be discussed with the Sponsor Medical Monitor.
11. Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumour biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary)
12. Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumour mass
13. Use of hematopoietic colony-stimulating factors (CSF) (eg, granulocyte [G]-CSF, granulocyte-macrophage [GM]-CSF, macrophage [M]-CSF) within 2 weeks prior to start of study drug. An erythroid-stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the participant is not red blood cell transfusion dependent.
14. Receives treatment with medications that cannot be discontinued prior to study entry and that are considered to be any of the following (see Table 19):
14.1. Known risk for QT prolongation, except for the specific use of oral 5-HT3 Receptor Antagonists (eg. granisetron, ondansetron or dolansetron) for the management of nausea and vomiting (note: intravenous formulations are prohibited)
14.2. Known to be strong inducers or inhibitors of cytochrome P (CYP)3A4/5
14.3. Known to be substrates of CYP3A4/5 with a narrow therapeutic index
14.4. Known to be sensitive substrates to P-gp, BCRP, OAT3, MATE-1 and MATE-2K

Date of first enrolment
17/07/2023

Date of final enrolment
30/11/2025

Locations

Countries of recruitment
United Kingdom

Australia

Belgium

Canada

France

Germany

Israel

Italy

Netherlands

Poland

Spain

Switzerland

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
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes