ISRCTN67463316 https://doi.org/10.1186/ISRCTN67463316

Is datopotamab deruxtecan plus durvalumab more effective than datopotamab deruxtecan alone at treating patients with metastatic breast cancer?

Submission date
07/05/2025

Recruitment status
Recruiting

Registration date
30/06/2025

Overall study status
Ongoing

Last Edited
30/06/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
This study is being carried out to see if datopotamab deruxtecan in combination with durvalumab is effective than datopotamab deruxtecan alone in treating PDL1-negative advanced or metastatic triple-negative breast cancer (TNBC). Breast cancer is the most common malignancy in women and the second most common cancer overall. The term TNBC is used to define tumours that do not express oestrogen receptors, progesterone receptors and HER2 receptors. TNBC comprises 10 -15% of all breast cancers. It remains the subtype with the poorest outcome and there is a significant need to develop new therapies for this group of patients, especially. Moreover, the PDL1-negative tumour has demonstrated no benefit from standard first-line treatment of chemotherapy plus immune checkpoint inhibitors. Datopotamab deruxtecan is an antibody drug conjugate (ADC) that targets tumour-associated calcium signal transducer 2, TROP2, a transmembrane protein that is highly expressed in various epithelial tumors, including breast cancer. Durvalumab is an immune checkpoint inhibitor and is expected to stimulate the patient's antitumour immune response by binding to PD-L1 and shifting the balance toward an antitumour response. The preclinical and clinical evidence have suggested synergistic activity between antibody drug conjugate and immune checkpoint inhibitor.

Who can participate?
Patients aged 18 years and over with PDL1-negative advanced or metastatic TNBC

What does the study involve?
Patients will be randomly placed into one of two treatment groups. One group will receive datopotamab deruxtecan in combination with durvalumab and the other group will receive datopotamab deruxtecan alone. Treatment will continue unless there is evidence of unacceptable toxicity, disease progression, or if the patient requests to stop the treatment or dies. Safety and tolerability as well as progression-free survival, overall survival, clinical benefit rate, duration of response and duration of clinical benefit and quality of life will be assessed.

What are the possible benefits and risks of participating?
This trial aims to find out information that may help people with advanced or metastatic triple-negative breast cancer. It is thought that this new drug treatment may be effective against this cancer type, and it must be compared with the current standard of care. We cannot guarantee that there will be a benefit to you during your treatment, as this is unknown at this stage.
The study medication may cause side effects. Participants will be asked by the study doctor or nurse about any problems they have at each visit. They can also telephone between visits if they are concerned. Possible side effects of study medications are listed in the PIS. All study drugs are administered directly into a vein through a cannula. Patients may experience pain, redness, swelling or itching at the administration site. Risks associated with drawing blood from the arm include pain, bruising, light-headedness and rarely infection. Patients will undergo CT scans of the chest/abdomen/pelvis with contrast material, or, if contrast is not suitable, they may have CT scans of the chest without contrast plus MRI scans of the abdomen/pelvis. Patients may also receive a CT head scan with contrast in cases where CNS metastases are clinically suspected, as per clinical practice. If a CT head scan with contrast is not suitable, they may have a CT head scan without contrast material plus an MRI head scan. CT scans use ionising radiation to form images. Ionising radiation can cause cell damage, which may, after many years or decades, turn cancerous, but the chance of this happening is extremely small. MRI scans are painless and safe and don’t expose the body to ionising radiation. Contrast material may need to be taken by mouth and/or injected into a vein. Oral contrast may cause side effects such as nausea, constipation, diarrhoea, and abdominal bloating. Pain, bruising, redness, swelling, and/or infection may occur at the administration site. An allergic reaction to the contrast material is possible. Clinical staff will treat any side effects as required.

It is not known what effects the study medication has on an unborn child. It is important that adequate contraception is used from signing the informed consent form and continue to use it throughout the total duration of the drug treatment and the drug washout period (at least 7 months after the last dose of Dato-DXd or if Dato-DXd has been discontinued more than 7 months previously and durvalumab was still ongoing, 90 days after the last dose of durvalumab).

Where is the study run from?
Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
May 2025 to January 2030

Who is funding the study?
AstraZeneca UK

Who is the main contact?
bci-diamond@qmul.ac.uk

Plain English summary under review with external organisation

Contact information

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Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2024-519913-76-00

Integrated Research Application System (IRAS)
1011098

ClinicalTrials.gov (NCT)
NCT06954480

Protocol serial number
1011098

Study information

Scientific Title
An open-label randomised, Phase II trial of datopotamab deruxtecan plus durvalumab versus datopotamab deruxtecan in patients with PDL1-negative metastatic triple-negative breast cancer

Acronym
DIAMOND

Study objectives
Primary objective:
To demonstrate the superiority of Dato-DXd plus durvalumab relative to Dato-DXd alone in patients with PD-L1-negative tumours as measured by progression-free survival (PFS).

Secondary objectives:
1. To compare Dato-DXd plus durvalumab relative to Dato-DXd alone in patients with PD-L1-negative tumours as measured by overall survival (OS), response rates (ORR), clinical benefit rate (CBR), duration of response (DoR) and duration of clinical benefit (DoCB).
2. To assess changes in quality of life (QoL) as assessed by patient-reported outcomes (PROs) in patients treated with Dato-DXd plus durvalumab versus Dato-DXd.
3. To evaluate the safety and tolerability of Dato-DXd plus durvalumab versus Dato-DXd.

Ethics approval required
Ethics approval required

Ethics approval(s)
submitted 07/05/2025, South Central - Berkshire B Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)2071048029, +44 (0)207 104 8276, +44 (0) 207 104 8256; berkshireb.rec@hra.nhs.uk), ref: 25/SC/0166

Study design
Open-label randomized international multi-centre trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Locally advanced or metastatic PD-L1 negative, triple-negative breast cancer

Interventions
Arm A: Datopotamab deruxtecan 6 mg/kg plus durvalumab 1120 mg on day 1 Q3W, both administered via IV
Arm B: Datopotamab deruxtecan only 6 mg/kg on day 1 Q3W, administered via IV

Patients will be randomised in a 1:1 manner to receive one of the two above treatment arms via randomisation on the Interactive Response Technology (IRT) system. Once the screening data has been entered on the eCRF and checked by the sponsor, authorisation will be given to the site staff to randomise the patient.

Treatment for both arms will continue unless there is evidence of unacceptable toxicity, disease progression, voluntary patient withdrawal or death. Upon completion of the study treatment, patients will enter a follow-up period during which data on cancer therapy, disease status and survival status will be collected. All patients will be followed up for survival every 6 months for a period of 2 years post the last patient treatment discontinuation.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Datopotamab deruxtecan, durvalumab

Primary outcome(s)
Superiority of Dato-DXd plus durvalumab relative to Dato-DXd alone in patients with PD-L1-negative tumours as measured by progression-free survival (PFS). PFS is defined as the time from the date of randomisation to the date of first documented confirmed tumour progression (using RECIST 1.1) or death from any cause, whichever occurs first in all patients.

Key secondary outcome(s))
1. Compare Dato-DXd plus durvalumab relative to Dato-DXd alone in patients with PD-L1-negative tumours as measured by overall survival (OS). OS is defined as the time from randomisation to death from any cause in all patients, assessed on average up to 12 months.
2. Compare Dato-DXd plus durvalumab relative to Dato-DXd alone in patients with PD-L1-negative tumours as measured by objective response rates (ORR), clinical benefit rate (CBR), duration of response (DoR) and duration of clinical benefit (DoCB). DoR is defined as the time from first documentation of CR or PR to confirmed disease progression using RECIST 1.1, or death on study from any cause, whichever occurs first, in patients with objective response assessed on average up to 12 months. 2. DoCB is calculated as time (in months) from randomisation to progression or death from any cause in patients with a clinical benefit assessed on average up to 12 months.
3. Assess changes in quality of life (QoL) as assessed by patient-reported outcomes (PROs) in patients treated with Dato-DXd plus durvalumab versus Dato-DXd. Changes in quality of life measured by the time to deterioration (TTD) from the time of enrolment to the safety visit (90 days +/- 7 days after the last dose). Assessed up to at least 122 PFS events have occurred.
4. Safety and tolerability of Dato-DXd plus durvalumab versus Dato-DXd. Incidence, nature and severity of adverse events with severity determined according to CTCAE v5.0. This will be measured from the time of enrolment to the safety visit (90 days +/- 7 days after the last dose). Assessed up to at least 122 PFS events have occurred.

Completion date
31/01/2030

Eligibility

Key inclusion criteria
1. Willing and able to provide written informed consent
2. Ability to comply with the protocol
3. Female and male ≥18 years of age
4. Triple-negative disease, defined as tumour cells being:
4.1. Negative for ER with <10% of tumour cells positive for ER on IHC or IHC score (Allred) of ≤3
4.2. Negative for PR with <10% of tumour cells positive for PR on IHC or IHC score (Allred) of ≤3 or PR unknown, and
4.3. Negative for HER2 with 0, 1+ or 2+ intensity on IHC and no evidence of amplification on ISH
5. PDL1 negative, defined as 22C3 CPS<10
6. Patients must have:
6.1. At least one lesion, not previously irradiated, that can be measured accurately at baseline as

≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computed tomography (CT) or magnetic resonance imaging (MRI) performed within 28 days prior to randomisation which is suitable for accurate repeated measurements, or
6.2. Lytic or mixed (lytic + sclerotic) bone lesions in the absence of measurable disease as defined above; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible
Patients who cannot be assessed by the CT or MRI should be excluded from the study.
7. Representative formalin-fixed paraffin-embedded (FFPE) breast tumour samples with an associated pathology report from the primary or recurrent cancer that are determined to be available and sufficient for central testing OR tumour accessible for biopsy.
8. ECOG performance status 0-1
9. Adequate haematologic and end-organ function within 28 days prior to the first study treatment defined by the following:
9.1. ANC ≥1500 cells/µL (1.5 x 10e9/L) (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
9.2. WBC >2500/µL (2.5 x 10e9/L)
9.3. Platelet count ≥100,000/µL (100 x 10e9/L) (transfusion not permitted within 28 days of study medication)
9.4. Haemoglobin ≥9.0 g/dL (90 g/L) with no blood transfusions (packed red blood cells)
9.5. Serum albumin ≥3 g/dL
9.6. AST (SGOT) or ALT (SGPT) and ALP ≤2.5 times the institutional upper limit of normal (ULN), bilirubin ≤1.5 x ULN (patients with liver metastases who have AST or ALT ≤5 x the institutional ULN may be enrolled)
9.7. aPTT ≤1.5 × the institutional ULN, INR <1.5 and absence of evidence of impaired hepatic synthesis function. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
9.8. Serum Creatinine ≤1.5 x ULN
9.9. Glomerular filtration rate ≥ 40 mL/min as assessed by standard methodology at the investigating center (i.e., Cockcroft-Gault, MDRD or CKD-EPI formulae, EDTA clearance or 24 h urine collection)
9.10. No evidence of haematuria: +++ on microscopy or dipstick
10. Patients of childbearing potential are eligible provided they have a negative serum or urine pregnancy test on Cycle 1, Day 1 (within 72 hours) of study treatment, preferably as close to the first dose as possible. Patients must agree to use adequate contraception, defined as those methods with a failure rate of < 1 % per year beginning 14 days before the first dose of study drug and for 7 months after the last dose of study drug. Also, participants must not donate, or retrieve for their own use, ova at any time during this study and for at least 7 months after the last dose of treatment. Preservation of ova should be considered prior to randomisation or the first dose of the study intervention.
11. Body Weight > 30 kg

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 years

Sex
All

Key exclusion criteria
1. Prior chemotherapy, immunotherapy (including durvalumab) or treatment with PARP inhibitors for advanced or metastatic breast cancer
2. Prior treatment with immune checkpoint inhibitors (eg atezolizumab, pembrolizumab) or DNA topoisomerase I or TROP2- or HER2-targeting ADCs and TROP2 targeted therapy in the (neo) adjuvant setting within 6 months from the end of treatment and randomisation into this study
3. Patients with prior allogeneic stem cell or solid organ transplantation.
4. Patients must not have a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent), or had oral or IV steroids for 14 days prior to the first dose of study drug
5. Administration of a live vaccine within 30 days prior to the first dose of study drug.
6. Active or prior documented autoimmune or inflammatory disorders
7. History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, radiation pneumonitis, organizing pneumonia requiring steroids, or evidence of active pneumonitis on screening chest CT scan.
8. Active infection requiring systemic therapy.
9. History of HIV infection
10. Known active hepatitis infection or hepatitis C.
11. Known history of active tuberculosis
12. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.
13. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the study protocol.
14. Concurrent treatment with other experimental drugs or participation in another clinical trial with therapeutic intent within 28 days prior to randomisation.
15. Pregnant and lactating female patients.
16. Major surgical procedure within 4 weeks prior to randomisation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis.
17. Malignancies other than breast cancer within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)
18. Severe infections within 28 days prior to randomisation in the study, including but not limited to hospitalization for complications of infection, bacteraemia, or severe pneumonia.
19. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy
20. Uncontrolled intercurrent illness
21. History of leptomeningeal carcinomatosis
22. Has clinically significant corneal disease
23. Has a history of severe hypersensitivity reactions to other monoclonal antibodies
24. History of active primary immunodeficiency
25. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
26. Brain metastases or neoplastic spinal cord compression. Patients whose brain metastases

have been treated may participate provided they show radiographic stability (defined as two brain images, both of which are obtained after treatment of the brain metastases). These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression. In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤10 mg/day of prednisone or its equivalent and anticonvulsants for at least 14 days prior to the start of treatment.
27. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from three ECGs (within 15 minutes at 5 minutes apart).
28. Patients who have received prior anti–PD-1, anti PD-L1 or anti CTLA-4

Date of first enrolment
31/07/2025

Date of final enrolment
31/07/2027

Locations

Countries of recruitment
United Kingdom

England

Germany

Korea, South

Spain

Study participating centre
St Bartholomews Hospital
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Study participating centre
Velindre Cancer Centre
Velindre Road
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Study participating centre

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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca UK

Alternative Name(s)
AstraZeneca UK Limited, AZ

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication