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A trial of hormone therapy and abemaciclib for early breast cancer

Submission date 31/01/2022	**Recruitment status** Recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 28/03/2022	**Overall study status** Ongoing	
Last Edited 08/07/2024	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-hormone-therapy-and-abemaciclib-for-early-breast-cancer-poetic-a

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

Contact information

Type(s)
Scientific

Contact name
Dr Stephen Johnston

ORCID ID
http://orcid.org/0000-0002-9072-2749

Contact details
Royal Marsden NHS Foundation Trust
Fulham Road London
London
United Kingdom
SW3 6JJ
+44 (0)208 7224349
poetic-a-icrctsu@icr.ac.uk

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271343

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NCT04584853

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CRCTSU/2019/10068, IRAS 271343, CPMS 44805

Study information

Scientific Title
POETIC-A: Pre-Operative Endocrine Therapy for Individualised Care with Abemaciclib

Acronym
POETIC-A

Study objectives
To determine the benefit of adding abemaciclib to standard adjuvant endocrine therapy (ET) in a sub-population of ER+/HER2- breast cancer who exhibit early evidence suggestive of sub-optimal endocrine responsiveness and high risk of disease relapse.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 14/04/2020, London - Chelsea Research Ethics Committee (Skipton House, 80 London Road, London, SE1 6LH, United Kingdom; +44 (0)207 104 8029; chelsea.rec@hra.nhs.uk), ref: 20/LO/0196

Study design
Phase III multi-centre 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 contact details to request a participant information sheet

Health condition(s) or problem(s) studied

Operable invasive breast cancer which is ER positive and HER2 negative, with high (20%) 5-year risk of relapse with endocrine therapy (ET) alone in postmenopausal women

Interventions

Current interventions as of 12/01/2024:
The trial has two parts:
1. A registration part
In this part patients receive aromatase inhibitor treatment (either 2.5 mg letrozole daily or 1 mg anastrozole daily) for at least 10 days immediately prior to surgery if they fit the eligibility criteria of the trial.

2. A randomised intervention part:
In this part patients who are eligible by virtue of a centrally assessed high Ki67 at surgery (Ki67S) will be asked to consent to the randomised part of the study where they will be allocated in a 1:1 ratio. Treatment allocation is by computer-generated random permuted blocks, stratified by age, use of chemotherapy, and time on pre-surgical AI.

They will be randomised to receive either:
1. Endocrine therapy alone for 5 years, or
2. Endocrine therapy for 5 years + abemaciclib for 2 years

In both groups, endocrine therapy will be prescribed as per standard of care for an expected duration of at least 5 years or until evidence of disease recurrence or other discontinuation criteria are met. The choice of endocrine therapy is as per clinician's decision and may include non-steroidal AI (letrozole or anastrozole), steroidal AI (exemestane) or tamoxifen.

Abemaciclib will be administered at a dose of 150 mg twice daily for 2 years and it is provided as 50 mg tablets. It should be taken with a glass of water, with at least 6 hours separating doses. All patients on both arms of the trial will be followed up to 5 years after Week 1 Day 1.

Previous interventions:
The trial has two parts:
1. A registration part
In this part patients receive aromatase inhibitor treatment (either 2.5 mg letrozole daily or 1 mg anastrozole daily) for at least 10 days immediately prior to surgery if they fit the eligibility criteria of the trial.

2. A randomised intervention part:
In this part patients who are eligible by virtue of a centrally assessed high Ki67 at surgery (Ki67S) will be asked to consent to the randomised part of the study where they will be allocated in a 1:1 ratio. Treatment allocation is by computer-generated random permuted blocks, stratified by age, use of chemotherapy, time on pre-surgical AI and the Aromatase Inhibitor Resistant-CDK4/6 Inhibitor Sensitive (AIR-CIS) signature.

They will be randomised to receive either:
1. Endocrine therapy alone for 5 years, or
2. Endocrine therapy for 5 years + abemaciclib for 2 years

In both groups, endocrine therapy will be prescribed as per standard of care for an expected duration of at least 5 years or until evidence of disease recurrence or other discontinuation criteria are met. The choice of endocrine therapy is as per clinician's decision and may include non-steroidal AI (letrozole or anastrozole), steroidal AI (exemestane) or tamoxifen.

Abemaciclib will be administered at a dose of 150 mg twice daily for 2 years and it is provided as 50 mg tablets. It should be taken with a glass of water, with at least 6 hours separating doses. All patients on both arms of the trial will be followed up to 5 years post-randomisation.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Abemaciclib

Primary outcome measure
Time to tumour (local or distant disease) recurrence, defined as the time from randomisation to local, regional or distant tumour recurrence or death from breast cancer without prior notification of relapse. Second primary cancers and inter-current deaths will be treated as censoring events. Ongoing follow up through routine data sources via electronic data linkage (from the patients' national medical records) annually until the end of the study.

Secondary outcome measures
Current secondary outcome measures as of 12/01/2024:
1. Relapse-free survival, defined as the time from randomisation to local, regional or distant tumour recurrence or death from any cause
2. Time to distant recurrence, defined as the time from randomisation to distant tumour recurrence. Second primary cancers and inter-current deaths will be treated as censoring events
3. Breast cancer-specific survival, defined as time from randomisation to death from breast cancer (with or without prior notification of relapse). Inter-current deaths will be treated as censoring events
4. Overall survival, defined as the time from randomisation to death from any cause
5. Quality of life: patient-reported quality of life measured using validated questionnaires which will be defined before the commencement of the relevant sub-study
6. Grade 3/4 adverse events, serious adverse events (SAEs) and hospitalisations assessed by Common Terminology Criteria for Adverse Events, version 5 (CTCAE v5)
7. Treatment-related deaths, defined as death occurring at any time point after randomisation and assessed to be possibly, probably or definitely related to the intervention

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Previous secondary outcome measures as of 19/12/2022 to 12/01/2024:
Ongoing follow-up through routine data sources via electronic data linkage (from the patients' national medical records) annually until the end of the study:
1. Relapse-free survival, defined as the time from randomisation to local, regional or distant tumour recurrence or death from any cause
2. Time to distant recurrence, defined as the time from randomisation to distant tumour recurrence. Second primary cancers and inter-current deaths will be treated as censoring events

3. Breast cancer-specific survival, defined as time from randomisation to death from breast cancer (with or without prior notification of relapse). Inter-current deaths will be treated as censoring events
4. Overall survival, defined as the time from randomisation to death from any cause
5. Quality of life: patient-reported quality of life measured using validated questionnaires which will be defined before the commencement of the relevant sub-study
6. Grade 3/4 adverse events, serious adverse events (SAEs) and hospitalisations assessed by Common Terminology Criteria for Adverse Events, version 5 (CTCAE v5)
7. Treatment-related deaths, defined as death occurring at any time point after randomisation and assessed to be possibly, probably or definitely related to the intervention

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Previous secondary outcome measures:
Ongoing follow up through routine data sources via electronic data linkage (from the patients' national medical records) annually until the end of the study:
1. Relapse-free survival, defined as the time from randomisation to local, regional or distant tumour recurrence or death from any cause
2. Time to distant recurrence, defined as the time from randomisation to distant tumour recurrence. Second primary cancers and inter-current deaths will be treated as censoring events
3. Breast cancer-specific survival, defined as time from randomisation to death from breast cancer (with or without prior notification of relapse). Inter-current deaths will be treated as censoring events
4. Overall survival, defined as the time from randomisation to death from any cause
5. Quality of life: patient-reported quality of life measured using validated questionnaires which will be defined before the commencement of the relevant sub-study
6. Grade 3/4 adverse events, serious adverse events (SAEs) and hospitalisations assessed by Common Terminology Criteria for Adverse Events, version 5 (CTCAE v5)
7. Treatment-related deaths: patient-reported quality of life will be measured using validated questionnaires which will be defined before the commencement of the relevant sub-study

Overall study start date
06/12/2018

Completion date
31/03/2032

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/01/2024:
Registration:
1. Women determined to be postmenopausal according to established local criteria
2. Diagnosed with operable invasive breast cancer with a clinical/radiological tumour size ≥1.0 cm.
3. Grade 2 or 3 tumours.
4. Preoperative full assessment completed (including bilateral breast examination and imaging with mammogram +/- ultrasound/MRI as performed locally)
5. Tumour ER-positive. ER positivity is defined as ≥1% cells staining positive (or equivalent Allred Score of ER ≥3 out of 8)
6. Tumour HER2 negative or HER2 status unknown. HER2 negativity will be defined as per the

2018 American Society of Clinical Oncology and the College of American Pathologists (ASCO /CAP) updated guidelines. Patients whose HER2 status is pending/unknown at the time of registration will be allowed to register for the trial. However, please note that only patients who are confirmed to be HER2 negative will be eligible to join the randomised part.
7. Received or planned to receive 10 days to 6 months of anastrozole or letrozole prior to surgery
8. Written informed consent to enter the registration part of the trial and to the donation of tissue
9. The patient has given written informed consent prior to any study-specific procedures and is willing and able to make herself available for the duration of the study and amenable and able to follow study schedule during treatment and follow-up and for the use of routinely collected electronic health and related records

Randomisation:
1. Patient previously consented and registered for screening component of POETIC-A
2. Tumour HER2 negative. HER2 negativity will be defined as per the 2018 ASCO/CAP updated guidelines
3. Centrally confirmed Ki67 ≥8% following pre-surgical AI
4. Patient is expected by the time of treatment initiation to have undergone definitive surgery for the primary breast tumour with clear radial margins as judged by the multidisciplinary team, and will have completed any adjuvant chemotherapy or radiotherapy (if prescribed)
5. Surgical staging of the axilla must have been undertaken by sentinel node biopsy, axillary sampling or dissection
6. The patient is randomised in time for treatment to start no later than 3 months after completion of non-endocrine therapy (defined as the final fraction of radiotherapy, Day 1 of the final cycle of chemotherapy or the date of the final surgical procedure)
7. The patient is able to swallow oral medications (excluding transient side effects from adjuvant non-endocrine treatment, if randomised before the end of this treatment)
8. The patient intends to take adjuvant endocrine therapy for at least 5 years
9. The patient has given written informed consent prior to any study-specific procedures (for the randomised intervention part), is willing to donate tissue from diagnostic biopsy, and is willing and able to make herself available for the duration of the study and to follow the study schedule during treatment and follow-up and for the use of routinely collected electronic health and related records

Week 1 Day 1:
1. Patient must have undergone definitive surgery for the primary breast tumour with clear radial margins as judged by the multidisciplinary team.
2. Adjuvant chemotherapy, if prescribed, must have been completed prior to Week 1 Day 1, and patients must have recovered (Common Terminology Criteria for Adverse Events, version 5 [CTCAE v5] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to Week 1 Day 1. A washout period of a minimum of 28 days from day 1 of the last cycle of treatment is required.
3. Adjuvant radiotherapy, if prescribed, must have been completed prior to Week 1 Day 1, and patients must have recovered (Grade ≤1) from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and Week 1 Day 1.
4. Week 1 Day 1 is scheduled to take place no later than three months after completion of non-endocrine therapy (defined as the final fraction of radiotherapy, Day 1 of the final cycle of chemotherapy or the date of the final surgical procedure, whichever is latest).
5. The patient is able to swallow oral medications.
6. The patient has adequate organ function for all of the following criteria defined as:
6.1. ANC ≥1.5 × 10(9)/l

6.2. Platelets ≥100 × 10(9)/l
6.3. Haemoglobin ≥8 g/dl
6.4. Total bilirubin ≤1.5 × upper limit of normal (ULN). Patients with Gilbert's syndrome with total bilirubin ≤2.0 x ULN and direct bilirubin within normal limits are permitted
6.5. ALT and AST ≤3 × ULN

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Previous inclusion criteria as of 19/12/2022 to 12/01/2024:
Registration:
1. Women determined to be postmenopausal according to established local criteria
2. Diagnosed with operable invasive breast cancer with a clinical/radiological tumour size ≥1.5 cm. Patients who enter the trial after surgery can do so based on a locally measured Ki67 of ≥8% at surgery (following ≥10 days of pre-surgical AI therapy). They will still be eligible for registration even if their tumour at baseline was <1.5cm, assuming they meet all other eligibility criteria.
3. Preoperative full assessment completed (including bilateral breast examination and imaging with mammogram +/- ultrasound/MRI as performed locally)
4. Tumour ER-positive. ER positivity is defined as ≥1% cells staining positive (or equivalent Allred Score of ER ≥3 out of 8)
5. Tumour HER2 negative or HER2 status unknown. HER2 negativity will be defined as per the 2018 American Society of Clinical Oncology and the College of American Pathologists (ASCO /CAP) updated guidelines. Patients whose HER2 status is pending/unknown at the time of registration will be allowed to register for the trial. However, please note that only patients who are confirmed to be HER2 negative will be eligible to join the randomised part.
6. Received or planned to receive 10 days to 6 months of anastrozole or letrozole prior to surgery7. Written informed consent to enter the registration part of the trial and to the donation of tissue
8. The patient has given written informed consent prior to any study-specific procedures and is willing and able to make herself available for the duration of the study and amenable and able to follow study schedule during treatment and follow-up and for the use of routinely collected electronic health and related records

Randomisation:
1. Patient previously consented and registered for screening component of POETIC-A
2. Tumour HER2 negative. HER2 negativity will be defined as per the 2018 ASCO/CAP updated guidelines
3. Centrally confirmed Ki67 ≥8% following pre-surgical AI
4. Aromatase Inhibitor Resistant-CDK4/6 Inhibitor Sensitive (AIR-CIS) signature analysis has been performed by the central laboratory and available result confirmed by ICR-CTSU
5. Patient must have undergone definitive surgery for the primary breast tumour with clear radial margins as judged by the multidisciplinary team
6. Surgical staging of the axilla must have been undertaken by sentinel node biopsy, axillary sampling or dissection
7. Adjuvant chemotherapy, if prescribed, must have been completed prior to randomisation and patients must have recovered (Common Terminology Criteria for Adverse Events, version 5 [CTCAE v5] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomisation. A washout period of a minimum of 28 days from day 1 of the last cycle of treatment is required.
8. Adjuvant radiotherapy, if prescribed, must have been completed prior to randomisation, and patients must have recovered (Grade ≤1) from the acute effects of radiotherapy. A washout period of at least 14 days is required between the end of radiotherapy and randomisation.

9. The patient should be randomised no later than 3 months after completion of non-endocrine therapy (defined as the final fraction of radiotherapy, Day 1 of the final cycle of chemotherapy or the date of the final surgical procedure)
10. The patient is able to swallow oral medications
11. The patient has adequate organ function for all of the following criteria defined as:
11.1. ANC ≥1.5 × 10(9)/l
11.2. Platelets ≥100 × 10(9)/l
11.3. Haemoglobin ≥8 g/dl
11.4. Total bilirubin ≤1.5 × upper limit of normal (ULN) patients with Gilbert's syndrome with total bilirubin ≤2.0 x ULN and direct bilirubin within normal limits are permitted
11.5. ALT and AST ≤3 × ULN
12. The patient intends to take adjuvant endocrine therapy for at least 5 years
13. The patient has given written informed consent prior to any study-specific procedures (for the randomised intervention part), willing to donate tissue from diagnostic biopsy, and is willing and able to make herself available for the duration of the study and to follow the study schedule during treatment and follow-up and for the use of routinely collected electronic health and related records

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Previous inclusion criteria:
Registration:
1. Postmenopausal women defined at diagnosis as:
1.1. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient; OR
1.2. Documented bilateral oophorectomy
2. Diagnosed operable invasive breast cancer with a clinical/radiological tumour size ≥1.5 cm
3. Tumour ER-positive. ER positivity is defined as ≥1% cells staining positive (or equivalent Allred Score of ER ≥3 out of 8)
4. Tumour HER2 negative or HER2 status unknown. HER2 negativity will be defined as per the 2018 American Society of Clinical Oncology and the College of American Pathologists (ASCO /CAP) updated guidelines. Patients whose HER2 status is pending/unknown at the time of registration will be allowed to register for the trial. However, please note that only patients who are confirmed to be HER2 negative will be eligible to join the randomised part.
5. Received or planned to receive 10 days to 6 months of anastrozole or letrozole prior to surgery
6. No evidence of metastatic spread by standard assessment according to local guidelines
7. Written informed consent to enter the registration part of the trial and to the donation of tissue
8. No medical condition or other factor likely to preclude entry to randomised part of the study if eligible e.g. patient would not be suitable to receive abemaciclib due to concomitant medications or medical history.
9. The patient has given written informed consent prior to any study-specific procedures and is willing and able to make herself available for the duration of the study and amenable and able to follow study schedule during treatment and follow-up and for the use of routinely collected electronic health and related records.
10. Patients who enter the trial after surgery can do so based on a locally measured Ki67 of ≥8%

at surgery (following ≥10 days of pre-surgical AI therapy). They will still be eligible for registration even if their tumour at baseline was <1.5cm, assuming they meet all other eligibility criteria.

Randomisation:
1. Patient previously consented and registered for screening component of POETIC-A
2. Tumour HER2 negative. HER2 negativity will be defined as per the 2018 ASCO/CAP updated guidelines
3. Centrally confirmed Ki67 ≥8% following pre-surgical AI
4. Aromatase Inhibitor Resistant-CDK4/6 Inhibitor Sensitive (AIR-CIS) signature analysis has been performed by the central laboratory and available result confirmed by ICR-CTSU
5. Patient must have undergone definitive surgery for the primary breast tumour with clear radial margins as judged by the multidisciplinary team
6. Surgical staging of the axilla must have been undertaken by sentinel node biopsy, axillary sampling or dissection
7. Adjuvant chemotherapy, if prescribed, must have been completed prior to randomisation and patients must have recovered (Common Terminology Criteria for Adverse Events, version 5 [CTCAE v5] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomisation. A washout period of a minimum of 28 days from day 1 of the last cycle of treatment is required.
8. Adjuvant radiotherapy, if prescribed, must have been completed prior to randomisation, and patients must have recovered (Grade ≤1) from the acute effects of radiotherapy. A washout period of at least 14 days is required between the end of radiotherapy and randomisation.
9. The patient should be randomised no later than 3 months after completion of non-endocrine therapy (defined as the final fraction of radiotherapy, Day 1 of the final cycle of chemotherapy or the date of the final surgical procedure)
10. The patient is able to swallow oral medications
11. The patient has adequate organ function for all of the following criteria defined as:
11.1. ANC* ≥1.5 × 10e9/l
11.2. Platelets ≥100 × 10e9/l
11.3. Haemoglobin ≥8 g/dl
11.4. Total bilirubin ≤1.5 × upper limit of normal (ULN) patients with Gilbert's syndrome with total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted
11.5. ALT and AST ≤3 × ULN
12. The patient intends to take adjuvant endocrine therapy for at least 5 years
13. The patient has given written informed consent prior to any study-specific procedures (for the randomised intervention part), willing to donate tissue from diagnostic biopsy, and is willing and able to make herself available for the duration of the study and to follow the study schedule during treatment and follow-up and for the use of routinely collected electronic health and related records.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex

Female

Target number of participants
8,000 patients registered and screened, 2,032 patients randomised

Key exclusion criteria
Current exclusion criteria as of 12/01/2024:
Registration:
1. Men and pre-/peri-menopausal women
2. Intended or actual use of HRT or any other oestrogen-containing medication (including vaginal oestrogens) within 4 weeks prior to planned surgery (date when surgical tissue sample being taken). Note: patients with a Mirena coil in situ at the time of registration are not excluded.
3. Patients who commenced pre-surgical AI therapy >6 months prior to surgery
4. Prior endocrine therapy for breast cancer or breast cancer prevention
5. Prior neoadjuvant chemotherapy for breast cancer
6. Evidence of metastatic disease
7. Locally advanced breast cancer not amenable to surgery
8. Bilateral invasive breast cancer (excluding contralateral ductal or lobular carcinoma in situ [DCIS/LCIS])
9. Multiple unilateral tumours with different ER and/or HER2 status. Synchronous DCIS/LCIS, as well as multifocal disease with homogenous ER/HER2 status, is allowed if at least one lesion is at least 1.0 cm; the largest lesion should be used for sample collection and CRF completion. If ER /HER2 status of smaller foci is unknown at time of registration, patients can be registered; however, note that congruity of receptor status will need to be confirmed by the time of randomisation (unless smaller foci are <10mm and receptor status is unknown).
10. Previous invasive breast cancer except for ipsilateral DCIS/LCIS treated >5 years previously by locoregional therapy alone or contralateral DCIS/LCIS treated by locoregional therapy at any time
11. Any invasive malignancy diagnosed within the previous 5 years (other than non-melanoma skin cancer or cervical carcinoma in situ)
12. Any other medical condition likely to exclude the patient from subsequent randomisation part (see Randomisation)

Randomisation:
1. Patient has received prior CDK4/6 inhibitor therapy
2. Patient is planned to receive adjuvant abemaciclib as standard of care.
3. Any patient with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded. Note: patients with a history of venous catheter occlusion by thrombus that did NOT surround the catheter, and the lumen could be made patent by appropriate measures (for example, saline or thrombolytic agent), are not excluded
4. The patient has a serious/or uncontrolled pre-existing medical condition(s) that, in the judgment of the investigator, is likely to preclude study treatment (such as severe renal impairment, [for example, estimated creatinine clearance <30 ml/min], interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or pre-existing Crohn’s disease or ulcerative colitis or a pre-existing chronic condition resulting in baseline Grade 2 diarrhoea)
5. The patient has a personal history of any of the following conditions: syncope of cardiovascular aetiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Note: patients with controlled atrial fibrillation diagnosed more than 30 days prior to randomisation are not excluded

6. The patient has received an experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer, prior to randomisation, or is currently enrolled in any other type of medical research (for example: medical device) judged by the Chief Investigator not to be scientifically or medically compatible with this study
7. The patient has any known active systemic bacterial infections (that would be expected to require IV antibiotics at the time of initiating study treatment), systemic fungal infection or detectable viral infection (such as known HIV positivity or with known active hepatitis B or C, e.g. hepatitis B surface antigen-positive), which would be expected to preclude study treatment. Screening is not required for enrolment.
8. Evidence of metastatic disease or local recurrence
9. Multiple unilateral tumours with different ER and/or HER2 status (DCIS/LCIS are permitted, and confirmation of congruent ER/HER2 status is not necessary for lesions less than 10 mm)

Week 1 Day 1:
1. Patient has received any CDK4/6 inhibitor therapy since randomisation.
2. Any newly occurring or diagnosed VTE since randomisation (for example, DVT of the leg or arm and/or PE). Note: patients with a history of venous catheter occlusion by thrombus that did NOT surround the catheter, and the lumen could be made patent by appropriate measures (for example, saline or thrombolytic agent), are not excluded.
3. Any newly occurring or diagnosed medical conditions since randomisation that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, [for example, estimated creatinine clearance <30 mL/min], interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy, major surgical resection involving the stomach or small bowel, or condition resulting in baseline Grade 2 diarrhoea).
4. Any newly occurring or diagnosed cardiovascular conditions since randomisation such as: syncope of cardiovascular aetiology, ventricular arrhythmia of pathological origin (including, but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.
5. Major surgery within 14 days prior to Week 1 Day 1.
6. The patient has received an experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer, prior to Week 1 Day 1, or is currently enrolled in any other type of medical research (for example: medical device) judged by the Chief Investigator not to be scientifically or medically compatible with this study.
7. Any active systemic bacterial infections (requiring IV antibiotics at time of Week 1 Day 1), systemic fungal infection or detectable viral infection (such as known HIV positivity or active hepatitis B or C, e.g. hepatitis B surface antigen positive). Screening is not required for initiation of treatment.
8. Evidence of metastatic disease or local recurrence

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Previous exclusion criteria as of 19/12/2022 to 12/01/2024:
Registration:
1. Men and pre-/peri-menopausal women
2. Grade 1 tumours. For patients who enter the trial after surgery - patients with a grade 1 tumour at diagnosis will still be eligible for registration if they have Ki67 ≥8% at surgery (following ≥10 days of pre-surgical AI therapy), as measured at the local site, and meet all other eligibility criteria
3. Intended or actual use of HRT or any other oestrogen-containing medication (including vaginal oestrogens) within 4 weeks prior to planned surgery (date when surgical tissue sample being taken). Note: patients with a Mirena coil in situ at the time of registration are not excluded.
4. Patients who commenced pre-surgical AI therapy >6 months prior to surgery
5. Prior endocrine therapy for breast cancer or breast cancer prevention

6. Prior neoadjuvant chemotherapy for breast cancer
7. Evidence of metastatic disease
8. Locally advanced breast cancer not amenable to surgery
9. Bilateral invasive breast cancer (excluding contralateral ductal or lobular carcinoma in situ [DCIS/LCIS])
10. Multiple unilateral tumours with different ER and/or HER2 status. Synchronous DCIS/LCIS, as well as multifocal disease with homogenous ER/HER2 status, is allowed if at least one lesion is at least 1.5 cm; the largest lesion should be used for sample collection and CRF completion. If ER /HER2 status of smaller foci is unknown at time of registration, patients can be registered; however, note that congruity of receptor status will need to be confirmed by the time of randomisation.
11. Previous invasive breast cancer except for ipsilateral DCIS/LCIS treated >5 years previously by locoregional therapy alone or contralateral DCIS/LCIS treated by locoregional therapy at any time
12. Any invasive malignancy diagnosed within the previous 5 years (other than non-melanoma skin cancer or cervical carcinoma in situ)
13. Any other medical condition likely to exclude the patient from subsequent randomisation part (see Randomisation)

Randomisation:
1. Patient has received prior CDK4/6 inhibitor therapy
2. Any patient with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded. Note: patients with a history of venous catheter occlusion by thrombus that did NOT surround the catheter, and the lumen could be made patent by appropriate measures (for example, saline or thrombolytic agent), are not excluded
3. The patient has a serious/or uncontrolled pre-existing medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, [for example, estimated creatinine clearance <30 ml/min], interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or pre-existing Crohn’s disease or ulcerative colitis or a pre-existing chronic condition resulting in baseline Grade 2 diarrhoea)
4. The patient has a personal history of any of the following conditions: syncope of cardiovascular aetiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Note: patients with controlled atrial fibrillation diagnosed more than 30 days prior to randomisation are not excluded
5. The patient has had major surgery within 14 days prior to randomisation
6. The patient has received an experimental treatment in a clinical trial within the last 30 days or 5 half-lives, whichever is longer, prior to randomisation, or is currently enrolled in any other type of medical research (for example: medical device) judged by the Chief Investigator not to be scientifically or medically compatible with this study
7. The patient has active systemic bacterial infections (requiring IV antibiotics at the time of initiating study treatment), systemic fungal infection or detectable viral infection (such as known HIV positivity or with known active hepatitis B or C (e.g. hepatitis B surface antigen-positive). Screening is not required for enrolment.
8. Evidence of metastatic disease
9. Multiple unilateral tumours with different ER and/or HER2 status (DCIS/LCIS are permitted, and confirmation of congruent ER/HER2 status is not necessary for lesions less than 10 mm)

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Previous exclusion criteria:
Registration:
1. Men and pre-/peri-menopausal women
2. Grade 1 tumours*
3. Intended or actual use of HRT or any other oestrogen-containing medication (including vaginal oestrogens) within 4 weeks prior to planned surgery (date when surgical tissue sample being taken). Note: patients with a Mirena coil in situ at the time of registration are not excluded.
4. Patients who commenced pre-surgical AI therapy >6 months prior to surgery
5. Prior endocrine therapy for breast cancer or breast cancer prevention
6. Prior neoadjuvant chemotherapy for breast cancer
7. Evidence of metastatic disease
8. Locally advanced breast cancer not amenable to surgery
9. Bilateral invasive breast cancer (excluding contralateral ductal carcinoma in situ [DCIS])
10. Multiple unilateral tumours with different ER/PgR/HER2 status, grade or type (e.g. ductal vs lobular) i.e. anything that suggests two or more different cancers. Multifocal disease with homogenous ER/PgR/HER2 status, grade and type is allowed if at least one lesion is at least 1.5 cm; the largest lesion should be used for sample collection and CRF completion
11. Previous invasive breast cancer except for ipsilateral DCIS/lobular carcinoma in situ (LCIS) treated >5 years previously by locoregional therapy alone or contralateral DCIS/LCIS treated by locoregional therapy at any time
12. Any invasive malignancy diagnosed within the previous 5 years (other than non-melanoma skin cancer or cervical carcinoma in situ)
13. Any other medical condition likely to exclude the patient from subsequent randomisation part (see Randomisation)
*For patients who enter the trial after surgery - patients with a grade 1 tumour will still be eligible for registration if they have Ki67 ≥8% at surgery (following ≥10 days of pre-surgical AI therapy), as measured at the local site, and meet all other eligibility criteria

Randomisation:
1. Patient has received prior CDK4/6 inhibitor therapy
2. Any patient with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded. Note: patients with a history of venous catheter occlusion by thrombus that did NOT surround the catheter, and the lumen could be made patent by appropriate measures (for example, saline or thrombolytic agent), are not excluded
3. The patient has a serious/or uncontrolled pre-existing medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (such as severe renal impairment, [for example, estimated creatinine clearance <30 ml/min], interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or pre-existing Crohn's disease or ulcerative colitis or a pre-existing chronic condition resulting in baseline Grade 2 diarrhoea)
4. The patient has a personal history of any of the following conditions: syncope of cardiovascular aetiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Note: patients with controlled atrial fibrillation diagnosed more than 30 days prior to randomisation are not excluded
5. The patient has active systemic bacterial infections (requiring IV antibiotics at the time of initiating study treatment), systemic fungal infection or detectable viral infection (such as known HIV positivity or with known active hepatitis B or C (e.g. hepatitis B surface antigen-positive). Screening is not required for enrolment
6. Evidence of metastatic disease

Date of first enrolment

23/12/2020

Date of final enrolment
30/09/2026

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Royal Marsden Hospital
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Queen Elizabeth Hospital
Queen Elizabeth Hospital
King’s Lynn
United Kingdom
PE30 4ET

Study participating centre
Great Western Hospital
Marlborough Road
Swindon
United Kingdom
SN3 6BB

Study participating centre
Royal Marsden Hospital
Downs Road
Sutton

United Kingdom
SM2 5NG

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Royal Albert Edward Infirmary
Wigan Lane,
Wigan
United Kingdom
WN1 2NN

Study participating centre
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Poole General Hospital
Longfleet Road
Poole
United Kingdom
BH15 2JB

Study participating centre

University College Hospital (London)
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Royal Berkshire Hospital
London Road
Reading
United Kingdom
RG1 5AN

Study participating centre
Harrogate District Hospital
Lancaster Park Road
Harrogate
United Kingdom
HG2 7SX

Study participating centre
Royal Sussex County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

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

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

Study participating centre
East Surrey Hospital
Canada Avenue
Redhill
United Kingdom
RH1 5RH

Study participating centre
Ysbyty Gwynedd
Penrhosgarnedd
Bangor
United Kingdom
LL57 2PW

Study participating centre
Dumfries and Galloway Royal Infirmary
Garroch Cargenbridge
Dumfries
United Kingdom
DG2 8RX

Study participating centre
Glan Clwyd Hospital
Sarn Lane
Rhyl
United Kingdom
LL18 5UJ

Study participating centre
Ninewells Hospital
Dundee
Dundee
United Kingdom
DD1 9SY

Study participating centre
Blackpool Victoria Hospital
Whinney Heys Road
Blackpool

United Kingdom
FY3 8NR

Study participating centre
Royal Shrewsbury Hospital
Mytton Oak Road
Shrewsbury
United Kingdom
SY3 8XQ

Study participating centre
Kingston Hospital
Galsworthy Road
Kingston upon Thames
United Kingdom
KT2 7QB

Study participating centre
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

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

Study participating centre
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre

Royal Cornwall Hospitals NHS Trust
Royal Cornwall Hospital
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Mid Yorkshire Hospitals NHS Trust
Pinderfields Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

Study participating centre
Burnley General Hospital
Casterton Avenue
Burnley
United Kingdom
BB10 2PQ

Study participating centre
Royal Blackburn Hospital
Haslingden Road
Blackburn
United Kingdom
BB2 3HH

Study participating centre
Ipswich Hospital
Heath Road
Ipswich
United Kingdom
IP4 5PD

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
Lothian

United Kingdom
EH4 2XU

Study participating centre
St John's Hospital
Howden W Road
Howden
Livingston
United Kingdom
EH54 6PP

Study participating centre
Royal Surrey County Hospital Guildford
Egerton Road
Guildford
United Kingdom
GU2 7XX

Study participating centre
Milton Keynes University Hospital NHS Foundation Trust
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

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

Study participating centre
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

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

Study participating centre
Forth Valley Royal Hospital
Stirling Road
Larbert
United Kingdom
FK5 4WR

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

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
United Kingdom
M8 5RB

Study participating centre

University Hospitals of North Tees and Hartlepool
Hardwick Road
Stockton-on-Tees
United Kingdom
TS19 8PE

Study participating centre
Barnet Hospital
Wellhouse Lane
Barnet
United Kingdom
EN5 3DJ

Study participating centre
Chase Farm Hospital
127 the Ridgeway
Enfield
United Kingdom
EN2 8JL

Study participating centre
Warwick Hospital
Lakin Road
Warwick
United Kingdom
CV34 5BW

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
Llandough Hospital
Penlan Road
Llandough
Penarth
United Kingdom
CF64 2XX

Study participating centre
St George's University Hospitals
Blackshaw Road, Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Calderdale Royal Hospital
Huddersfield Road
Halifax
United Kingdom
HX3 0PW

Study participating centre
Huddersfield Royal Infirmary
Acre Street
Huddersfield
United Kingdom
HD3 3EA

Study participating centre
Lincoln County Hospital
Greetwell Road
Lincoln
United Kingdom
LN2 5QY

Study participating centre
Pilgrim Hospital
Sibsey Road

Boston
United Kingdom
PE21 9QS

Study participating centre
University Hospitals of Morecambe Bay NHS Foundation Trust
Ashton Road
Lancaster
United Kingdom
LA1 4RP

Study participating centre
Borders General Hospital
Huntlyburn Terrace
Melrose
United Kingdom
TD6 9BS

Study participating centre
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
Wansbeck General Hospital
Woodhorn Lane
Ashington
United Kingdom
NE63 9JJ

Study participating centre
Kettering General Hospital
Rothwell Road
Kettering
United Kingdom
NN16 8UZ

Study participating centre
Musgrove Park Hospital (taunton)
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
Worcestershire Acute Hospitals NHS Trust
Worcestershire Royal Hospital
Charles Hastings Way
Worcester
United Kingdom
WR5 1DD

Study participating centre
George Eliot Hospital
Lewes House
College Street
Nuneaton
United Kingdom
CV10 7DJ

Study participating centre
Maidstone and Tunbridge Wells NHS Trust
The Maidstone Hospital
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Sponsor information

Organisation
Institute of Cancer Research

Sponsor details
Institute of Cancer Research
Cotswold Road
Sutton
England

United Kingdom
SM2 5NG
+44 (0)207 153 5360
RDCCR@rmh.nhs.uk

Sponsor type
University/education

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

ROR
https://ror.org/043jzw605

Funder(s)

Funder type
Industry

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
Eli Lilly and Company

Alternative Name(s)
Lilly, Eli Lilly & Company, Eli Lilly & Co., Eli Lilly And Co

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Results will be presented at international conferences and made available through peer-reviewed publications. Written results written in lay terms will be provided to the clinicians responsible for the care of trial participants at that time. Clinical teams will be asked to use professional judgement to decide when and how to convey results to individual participants and /or next of kin.

Intention to publish date
31/03/2033

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be available on request from the POETIC-A trial team via poetic-a-icrctsu@icr.ac.uk via completion of a data access request form after such time that the primary analysis publication and any other key analyses have been completed. Optional advanced consent/authorisation for the possible future sharing of information collected about patients will be obtained at study entry.

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