A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined with Standard Adjuvant Endocrine Therapy versus Standard Adjuvant Endocrine Therapy Alone in Patients with High-Risk, Node-Positive, Early -Stage, Hormone Receptor-Positive, Human Epidermal Receptor 2-Negative, Breast Cancer

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This study has been transitioned to CTIS with ID 2023-509671-17-00 check the CTIS register for the current data. The primary objective is To evaluate the efficacy, in terms of invasive disease-free survival (IDFS), as defined by the STEEP System,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON56125

Source
ToetsingOnline

Brief title
monarchE: I3Y-MC-JPCF

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, HR+/HER2- breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Breast cancer, CDK4/6 inhibition, High-level Ki67 expression, HR+ / HER2-

Outcome measures

Primary outcome

Primary endpoints:

IDFS, as defined by the STEEP System (Hudis et al. 2007) (Section 10.3.1.1 of

the clinical protocol) - cohort 1 only

Secondary outcome

Overall efficacy for patients with Ki67 index >=20% (for patients in cohort 1

and cohort 2 as determined by central lab) is determined by IFDS, as defined by

the STEEP system.

Efficacy of abemaciclib plus adjuvant endocrine therapy versus adjuvant

endocrine therapy alone is measured by DRFS and OS.

Safety endpoints will include but are not limited to the following:

- TEAEs, SAEs, and hospitalizations

- Clinical laboratory tests, vital signs, and physical examinations

The relationship between abemaciclib, exposure and clinical (efficacy and safety) outcomes will be evaluated via steady-state trough abemaciclib concentration (Cmin,ss), hazard ratio for IDFS, DRFS, OS, other efficacy and safety endpoints.

Study description

Background summary

Breast cancer is the most frequent cancer among women and is a major cause of cancer-related deaths worldwide. It is estimated that more than 1.67 million new cases of breast cancer occurred worldwide in women in 2012. The hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2) breast cancer subtype is the most prevalent of breast cancer subtypes and accounts for approximately 70% of all breast cancers.

Approximately 90% of patients with breast cancer are diagnosed at an early stage of their disease. These patients are treated with curative intent and as such are candidates for local treatments including surgery followed very often by radiotherapy depending on the surgical approach and regional disease extension. After surgery, the indication of adjuvant systemic therapy is based on estimated individual risk of disease relapse and predicted sensitivity to available systemic therapies (that is, estrogen receptor [ER]/progesterone receptor and HER2 status). Most validated clinical and pathological features that may indicate a higher risk of distant disease relapse and therefore the need for adjuvant treatment include large primary tumor size, involvement and degree of involvement of axillary lymph nodes, and high histologic grade.

With current standard of care adjuvant therapy, approximately 30% of women with HR+ breast cancer initially diagnosed with early stage disease experience distant relapse with metastases. Consequently, there is a critical need for more optimal adjuvant therapy in patients with early HR+ breast cancer who have a high likelihood of distant recurrence.

Ki67 antigen is encoded by the MKI67 gene and is a nuclear protein expressed in all phases of the cell cycle other than the G0 phase and has been reported as an independent prognostic factor in early breast cancer. In HR+ breast cancer, patients with high levels of Ki67 have been shown to have higher disease recurrence rates while receiving adjuvant endocrine therapy following surgery. High-level Ki67 expression (that is, >=20%) by immunohistochemistry (IHC) performed centrally is believed to be a valid factor for high-risk patient

selection in Study MonarchE.

Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6, respectively). CDK4 and CDK6 promote cell growth by facilitating the progression of cells from the G1 to the S-phase of the mammalian cell cycle. Abemaciclib inhibits CDK4/CDK6-dependent phosphorylation of Rb, which subsequently blocks proliferation by inhibiting the progression of these cells from the G1 phase into the S and G2/M phases of the cell cycle.

In early neoadjuvant breast cancer setting, the ongoing neoMONARCH Phase 2 open-label, randomized study (JPBY, neoMONARCH) showed an acceptable safety profile for abemaciclib (a dose twice daily) as monotherapy and in combination with anastrozole, with reduction of breast cancer tumor cell proliferation marker (Ki67 index) to a significantly greater extent than anastrozole alone.

MonarchE study aims to evaluate abemaciclib in combination with standard adjuvant endocrine therapy, in patients with node-positive, early stage, HR+, HER2-, invasive breast cancer at high risk of recurrence as determined by clinical and pathological features. Historical data estimate the 5-year disease-free survival rate for the MonarchE-defined population between 80% and 85%. Therefore, at least 15% of the patient population intended to be enrolled into MonarchE study fail to be cured by the current standard of care adjuvant therapy. Optimizing standard adjuvant therapy by adding novel targeted therapies is warranted for patients with early breast cancer and at high risk of disease recurrence.

Study objective

This study has been transitioned to CTIS with ID 2023-509671-17-00 check the CTIS register for the current data.

The primary objective is To evaluate the efficacy, in terms of invasive disease-free survival (IDFS), as defined by the STEEP System, for patients with HR+, HER2- early stage breast cancer for a dose of abemaciclib twice daily plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone

The secondary objectives are:

-To evaluate the efficacy, in terms of IDFS, for patients with HR+, HER2- early stage breast cancer with Ki67 index >=20% by central lab

- To evaluate the efficacy of abemaciclib plus adjuvant endocrine therapy versus adjuvant endocrine therapy alone in terms of DRFS and OS

- To assess the safety profile of abemaciclib plus adjuvant endocrine therapy compared to adjuvant endocrine therapy alone

- To evaluate the relationship between abemaciclib, exposure and clinical (efficacy and safety) outcomes

- To evaluate abemaciclib plus adjuvant endocrine therapy, versus adjuvant endocrine therapy alone, in terms of general oncology and breast cancer selfreported health-related quality of life (FACT-B 37-item questionnaire), endocrine therapy-specific symptoms (the FACT-ES 19-item subscale and 2 FACIT-sourced items of cognitive symptoms and 3 FACIT-sourced items for bladder symptoms), and fatigue experienced during abemaciclib and/or endocrine therapy (the FACIT-F 13-item subscale).

- To evaluate health status to inform decision modeling for health economic evaluation using the EQ-5D-5L.

The exploratory objective is
- to assess the relationship between biomarkers and clinical outcome.
- to compare the prognostic significance (in terms of IDFS) of Ki-67 in pre- versus post-neoadjuvant therapy samples as assessed by central laboratory

Study design

MonarchE is a multicenter, randomized, open-label, Phase 3 study of standard adjuvant endocrine therapy of physician*s choice with or without abemaciclib in patients with high-risk, node-positive, early stage, HR+, HER2- breast cancer, who completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy).

Patients in both treatment arms will receive standard adjuvant endocrine therapy of physician*s choice (such as tamoxifen or an aromatase inhibitor, with or without ovarian function suppression per standard practice). Patients in both arms may have up to 12 weeks of
endocrine therapy following their last non-endocrine therapy (surgery, chemotherapy, or radiotherapy) prior to randomization, and the same or another endocrine therapy will be continued during the course of the study until meeting discontinuation criteria (Section 8). Adjuvant treatment with fulvestrant is not allowed at any time during the study. Patients must be randomized within 16 months of definitive breast surgery for the current malignancy. Patients randomized to the experimental arm will receive a dose of abemaciclib orally twice daily for up to 2 years or until discontinuation criteria are met, whichever occurs first. Endocrine therapy will be taken as prescribed during the on-study treatment period (Years 1 and 2). In Year 3 and beyond, standard adjuvant endocrine therapy will continue to complete at least 5 years per investigator*s discretion as part of standard of care.

Intervention

Patients will be randomized to one of the following treatment arms:

- Arm A - Abemaciclib plus standard adjuvant endocrine therapy
- Arm B - Standard adjuvant endocrine therapy alone

MonarchE protocol defines study treatment as abemaciclib and /or endocrine therapy during the first 2 years of the on-study treatment period.

Treatment with abemaciclib will be given for up to 2 years or until discontinuation criteria are met. In both arms, treatment with endocrine therapy given until discontinuation criteria are met. In Year 3 and beyond, continue standard adjuvant endocrine therapy to complete at least 5 years, if this is medically appropriate.

Study burden and risks

The study drug is accompanied by certain risks. Very Common Side Effects (>=10% of patients) related to the use of abemaciclib given alone were:

• Loose stools (diarrhea, 90.2%).
• Lack of energy (fatigue, 65.2%).
• Feeling sick to the stomach with a sense of wanting to throw up (nausea, 64.4%).
• Low appetite (decreased appetite, 45.5%).
• Decreased number of white blood cells count in the blood; this may make infections more likely to occur (neutropenia, 37.1%; leukopenia, 17.4%).
• Being sick to the stomach (vomiting, 34.8%).
• Low red blood cell count in the blood that may make you feel more tired (anemia, 25.0%).
• Decreased number of platelets in the blood; this may cause bruising, difficulty with clotting of blood, or bleeding easily (thrombocytopenia, 20.5%).
• Dry mouth (13.6%).
• Inflammation or ulcers inside the mouth (stomatitis, 13.6%).
• Taste changes or bad taste in the mouth (dysgeusia, 12.1%).
• Hair loss (alopecia, 12.1%).

The study procedures, including blood draws, also have certain risks. The study drug, the study procedures and the combination may also have other, unknown risks. Please refer to the subject information sheet and the Investigator's Brochure for a detailed description of the risks, including additional risks that exist when abemaciclib is given in combination with endocrine therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Female (regardless of menopausal status) or male >=18 years of age (or of an acceptable age according to local regulations, whichever is older).
2. The patient has confirmed HR+, HER2-negative (HER2-), early stage resected invasive breast cancer without evidence of distant metastases. For local HR+/HER2-confirmation considerations, please refer to section 6.1(2) of the Clinical Protocol.
Patients with bilateral breast cancer (diagnosis of invasive tumors in both breasts simultaneously or within 6 months of each other) can be eligible if all lesions tested on both sides are HR+/HER2- and adequate surgery has been performed in both breasts (see inclusion criterion [3]). The Lilly Clinical Research Physician and Clinical Research Scientist (CRP/CRS) must be consulted for all cases of bilateral breast cancer.

3. The patient must have undergone definitive surgery of the primary breast tumor(s). For details around surgery, please see protocol page 29/30.
4. The patient must have tumor tissue from breast (preferred) or lymph node for exploratory biomarker analysis available prior to randomization.
5. Patients must be node positive (microscopic and macroscopic tumor involvement are allowed; ipsilateral internal mammary and supraclavicular lymph nodes are allowed, but will not count toward the number of positive lymph nodes) and fulfill one of the following criteria:
A. pathological tumor involvement in >=4 ipsilateral axillary lymph nodes.
OR
B. Pathological tumor involvement in 1 to 3 ipsilateral axillary lymph node(s) (for patients who received neoadjuvant therapy also cytological tumor involvement at time of initial diagnosis is allowed) and meet at least 1 of the following criteria:
1. Grade 3 as defined by a combined score of at least 8 points per the modified Bloom-Richardson grading system (Elston and Ellis 1991), also known as the Nottingham scale, or equivalent following discussion with the Lilly CRP/CRS
- pathological primary invasive tumor size >=5 cm (for patients who received neoadjuvant therapy primary tumor size >=5 cm on breast imaging is allowed). Note: if tumor size is needed to meet eligibility criteria, patients with multifocal/multicentric tumors may be eligible based on the addition of diameters of the individual lesions following discussion with the Lilly CRP/CRS.
- Ki-67 index of >=20% (for Cohort 2) on untreated breast tissue as determined by the investigational assay (described in Section 3.2.1) at the Study JPCF central laboratory. See Section 9.8.1 for Ki-67 sample requirements.
6. The patient must be randomized within 16 months from the time of definitive breast cancer surgery.
7. If the patient is currently receiving or initiating standard adjuvant endocrine therapy at time of study entry, she/he may receive up to 12 weeks of endocrine therapy until randomization following the last non-endocrine therapy (surgery, chemotherapy, or radiation), whichever is last.
Use of GNRH analogues for ovarian suppression is not considered endocrine therapy for the purposes of this criterion. Note: Adjuvant treatment with fulvestrant is not allowed.
8. Patients who received or will be receiving adjuvant chemotherapy must have completed adjuvant chemotherapy prior to randomization and patients must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade <=1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomization. Patients who are not candidates for adjuvant chemotherapy or decline chemotherapy are permitted. Patients may also have received neoadjuvant chemotherapy. A washout period of at least 21 days is required between last adjuvant chemotherapy dose and randomization (provided the patient did not receive radiotherapy).
9. Patients who received or will be receiving adjuvant radiotherapy must have completed radiotherapy prior to randomization, 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 randomization.

10. The patient has recovered from surgical side effects following definitive breast surgery based on investigator discretion (for example, adequate wound healing complications or seroma complications).
11. Text was omitted with protocol(a); see Criterion [1]]
12. Women of reproductive potential must have a negative blood pregnancy test at baseline (within 14 days prior to randomization) and agree to use highly effective contraceptive methods to prevent pregnancy during the study and for 12 weeks following the last dose of study treatment. Males must agree to use an acceptable method of birth control and to not donate sperm during the study and for at least 12 weeks following the last dose of study treatment. Refer to Appendix 4 of the clinical protocol for definitions of highly effective methods of contraception.
13. The patient has a performance status <=1 on the Eastern Cooperative Oncology Group Scale
14. The patient has adequate organ function for all of the following criteria, as defined in section 6.1(14) of the Clinical Protocol. Please refer to the revisions in the Protocol section.
15. The patient is able to swallow oral medications.
16. The patient has given written informed consent prior to any study-specific procedures and is willing and able to make herself/himself available for the duration of the study and amenable and able to follow study schedule during treatment and follow-up.

Exclusion criteria

17. The patient has metastatic disease (including contralateral axillary lymph nodes) or lymph node-negative breast cancer. Patients with inflammatory breast cancer are excluded. Inflammatory carcinoma should not apply to a patient with neglected locally advanced breast cancer presenting late in the course of their disease (American Joint Committee on Cancer [AJCC] staging system for breast cancer 8th edition, Hortobagyi et al. 2017). The investigator should consult with the Lilly CRP/CRS regarding eligibility of patients with neglected inflammatoid disease.
18. Patients with a history of previous breast cancer are excluded, with the exception of ipsilateral DCIS treated by locoregional therapy alone >=5 years ago. Patients with a history of contralateral DCIS treated by local regional therapy at any time may be eligible. Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix), unless in complete remission with no therapy for a minimum of 5 years from the date of randomization are excluded. For patients with a history of other non-breast cancers within 5 years from the date of randomization and considered of very low risk of recurrence per investigator*s judgment (for example, papillary thyroid cancer treated with surgery), eligibility is to be discussed with the Lilly CRP/CRS.
19. Females who are pregnant or lactating.

20. The patient has previously received treatment with any CDK4 and CDK6 inhibitor.
21. The patient is receiving concurrent exogenous reproductive hormone therapy (for example, birth control pills or hormone replacement therapy, or megestrol acetate). Appropriate washout period between last dose of exogenous hormone therapy and randomization is up to the investigator*s medical judgment (for example, applying 5 times the half-life elimination rule). Note: topical vaginal estrogen therapy is permitted if all other non-hormonal options are exhausted.
22. The patient has previously received endocrine therapy for breast cancer prevention (tamoxifen or raloxifene or aromatase inhibitors).
23. The patient has serious preexisting 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 dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn*s disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhea).
24. The patient has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible. Any patient with a history of VTE (for example, DVT of the leg or arm and/or PE) will be excluded.
25. The patient has active systemic infections (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, or detectable viral infection requiring systemic therapy) or viral load (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrollment.
26. The patient has had major surgery within 14 days prior to randomization.
27. 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 randomization, or is currently enrolled in any other type of medical research (for example: medical device) judged by the sponsor not to be scientifically or medically compatible with this study. Co-enrollment to other studies may be allowed following consultation with the Lilly CRP/CRS.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-12-2017
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	abemaciclib
Generic name:	abemaciclib

Ethics review

Approved WMO Date:	14-06-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-08-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-10-2017
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-08-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
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Approved WMO Date:	24-04-2021
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Approved WMO Date:	04-06-2021
Application type:	Amendment
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Approved WMO Date:	27-05-2022
Application type:	Amendment
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Approved WMO Date:	06-03-2023
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Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509671-17-00
EudraCT	EUCTR2016-004362-26-NL
ClinicalTrials.gov	NCT03155997
CCMO	NL61631.028.17

Study results

Results posted:	16-04-2021

Actual enrolment: 19

First publication
25-09-2020