neoMONARCH: A Phase 2 Neoadjuvant Trial Comparing the Biological Effects of 2 Weeks of Abemaciclib (LY2835219) in Combination with Anastrozole to those of Abemaciclib Monotherapy and Anastrozole Monotherapy and Evaluating the Clinical Activity and Safety of a Subsequent 14 Weeks of Therapy with Abemaciclib in Combination with Anastrozole in Postmenopausal Women with Hormone Receptor Positive, HER2 Negative Breast Cancer

Published: 19-08-2015
Last updated: 20-04-2024

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

Summary

ID

NL-OMON43863

Source
ToetsingOnline

Brief title
NeoMONARCH

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
HER2 negative breastcancer, HR+

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Abemaciclib, Anastrozole, Breast Cancer

Outcome measures

Primary outcome

The primary objective of Study I3Y-MC-JPBY (JPBY) is to compare the biological

activity of

abemaciclib in combination with anastrozole, abemaciclib monotherapy, and

anastrozole monotherapy by

assessing the percentage change from the baseline value in Ki67 expression

after 2 weeks of therapy.

Efficacy:

* percent change in Ki67 expression from baseline to the core biopsy 2 weeks

after the start of treatment

* pCR defined as absence of invasive cancer in the breast and sampled regional lymph nodes

* clinical response of the breast tumor to therapy as assessed by caliper measurement

* radiologic response of the breast tumor as assessed by radiologic or ultrasound assessment

Safety:

* adverse events

Health Outcomes:

* EORTC QLQ-C30

Pharmacokinetics:

* PK of abemaciclib and its metabolites and anastrozole

Pharmacodynamics:

* Ki67

Biomarkers:

* Whole blood, plasma, and tissue samples will be tested for biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcomes.

Secondary outcome

The secondary objectives of the study are to evaluate after 14 additional weeks of neoadjuvant therapy:

-pathologic complete response defined as absence of invasive cancer in the breast and

sampled regional lymph nodes

-clinical objective response (Response Evaluation Criteria in Solid Tumors

[RECIST]

criteria 1.1)

-radiologic response (RECIST criteria 1.1)

-safety and tolerability

-symptom burden via the European Organization for Research and Treatment of

Cancer

Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30) instrument

-pharmacokinetics of abemaciclib and anastrozole.

Exploratory Objectives

-to assess the association between biomarkers and biological, pathological, and

clinical

outcome(s)

-to evaluate the relationship between abemaciclib exposure and response

variables, such

as Ki67, change in tumor size, and clinical response

Study description

Background summary

Abemaciclib (LY2835219) is a potent oral small-molecule dual inhibitor of cyclin-dependent
kinases 4 and 6 (CDK 4 and 6) that has demonstrated evidence of clinical activity as

monotherapy in an expansion cohort of women with metastatic breast cancer (mBC) evaluated in Study I3Y-MC-JPBA. This cohort included 47 patients with a median of 7 prior systemic regimens. Among the 36 patients with hormone receptor positive (HR+) mBC, the median progression-free survival (PFS) was 8.8 months, and there were 12 confirmed partial responses (PR) for an objective response rate of 33.3%. These clinical results support further investigation of abemaciclib as a monotherapy in patients with HR+ mBC. Another small molecule CDK 4 and 6 inhibitor, palbociclib, has been evaluated in combination with letrozole in a randomized Phase 2 study (Finn et al. 2015). The efficacy and safety of the combination regimen was compared to that of letrozole monotherapy in 165 patients with HR+, human epidermal growth factor 2 negative (HER2-) advanced breast cancer. The combination of palbociclib and letrozole conferred a superior PFS (median of 20.2 months versus 10.2 months, hazard ratio = 0.488 p=0.0004), and enhanced the clinical benefit rate (81% versus 58%) and response rate (43% versus 33%) relative to that achieved by letrozole alone. These Phase 1 and 2 data have supported the initiation of Phase 3 studies evaluating endocrine therapies in combination with either abemaciclib or palbociclib for the treatment of patients with advanced HR+ mBC.

Study I3Y-MC-JPBY is a multicenter, open-label, randomized Phase 2 study comparing the biological effects of a 2-week course of abemaciclib in combination with anastrozole to those of abemaciclib monotherapy and anastrozole monotherapy for women with early-stage HR+, HER2- breast cancer. Following the randomized portion of the study, all patients will receive anastrozole and abemaciclib combination therapy for 14 weeks in order to maximize the likelihood of benefit. Clinical and pathologic response and the safety profile will be assessed following a total of 16 weeks of therapy.

Study objective

The primary objective of Study I3Y-MC-JPBY (JPBY) is to compare the biological

activity of
abemaciclib in combination with anastrozole, abemaciclib monotherapy, and anastrozole monotherapy by
assessing the percentage change from the baseline value in Ki67 expression after 2 weeks of therapy.

Study design

Study JPBY is a multicenter, open-label, randomized Phase 2 trial comparing the biological effects
of abemaciclib in combination with anastrozole to those of abemaciclib monotherapy and anastrozole
monotherapy. Participants in this study will initially be randomized to receive 2 weeks of treatment with either
abemaciclib in combination with anastrozole, abemaciclib monotherapy, or anastrozole monotherapy.
Randomization will be stratified by progesterone receptor (PgR) status and tumor size). Following the 2 weeks of
initial therapy, all patients will receive abemaciclib in combination with anastrozole for 14 weeks.

Intervention

Test Product, Dosage, and Mode of Administration: Abemaciclib will be supplied as capsules administered
orally, 150 mg every 12 hours
Reference Therapy, Dose, and Mode of Administration: Anastrozole will be supplied as tablets administered
orally, 1 mg daily
Planned Duration of Treatment: 4 months
Follow-up (postdiscontinuation): 30 days

Study burden and risks

There are several risks involved with the study drug. The most common side effects(greater than or equal to 10% of patients) associated with abemacliclib are:
• loose stools (64.2%)
• feeling sick to the stomach (44.3%)
• lack of energy (39.8%)
• low levels of the white blood cells that fight bacterial infection (27.0%)
• being sick to the stomach (24.1%)
• low levels of the blood cells responsible for clotting (21.3%)
• low levels of all white blood cells, which could increase the risk of infection (21.0%)
• low red blood cell count (17.6%)

• low appetite (17.6%)
• increase of a substance in the blood that may indicate reduced kidney function (14.5%)

To reduce the incidence and severity of diarrhea prophylactic anti-diarrheal medication will be administered.

Anastrozole and loperamide can also cause side effects, as well as the study procedures, although some of the study procedures would also take place as part ot standard care.
The drugs and the study procedures and the combinations thereof, may also lead to other, unknown risks.
The risks are desribed in the subject information sheet and informed consent form.

To maximize the likelihood of benefit for patients participating in the study, all patients will receive the combination of abemaciclib and anastrozole for a further 14 weeks following the initial 2 weeks of randomized therapy.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:
[1] are female and >=18 years of age
[2] have postmenopausal status, defined as meeting one of the following conditions:
* prior bilateral oophorectomy
* age >=60 years
* age <60 years and amenorrheic (non-treatment-induced amenorrhea secondary to tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range.
[3] histologically or cytologically proven adenocarcinoma of the breast
[4] Clinical Stage I breast tumor >=1 cm in diameter, Stage II, or Stage IIIA or IIIB breast cancer (according to the AJCC Staging Manual, 7th Edition [Edge et al. 2010]). Multifocal disease is allowed if confined to 1 breast, and if each tumor is HR+, HER2- and at least 1 tumor is >=1 cm.
[5] at least 1 measureable lesion according to RECIST criteria by physical examination or imaging tests
[6] breast cancer that is HR+, HER2-
* to fulfill the requirement for HR+ disease, a breast cancer must express, by immunohistochemistry (IHC), at least 1 of the hormone receptors (estrogen receptor [ER], progesterone receptor [PgR] as defined in the relevant American Society of Clinical Oncology [ASCO]/College of American Pathologists [CAP] Guidelines [Hammond et al. 2010])
* to fulfill the requirement of HER2- disease, a breast cancer must not demonstrate, at initial diagnosis or upon subsequent biopsy, overexpression of HER2 by either IHC or in-situ hybridization (ISH), as defined in the relevant ASCO/CAP guidelines (Wolff et al. 2013)
[7] neoadjuvant endocrine monotherapy is deemed to be a suitable therapy
[8] primary breast cancer that is suitable for baseline core biopsy (provision of baseline core biopsy specimen is mandatory)
[9] Eastern Cooperative Oncology Group (ECOG) performance status score <=1
[10] patient is willing to comply with treatment, tissue acquisition, and follow-up
[11] patient is able to swallow capsules and tablets
[12] have adequate organ function, including
* hematologic: absolute neutrophil count (ANC) >=1.5 x 109/L, platelets >100 x 109/L, and hemoglobin >=8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the

discretion of the investigator. However, initial study drug treatment must not begin earlier than the day of the erythrocyte transfusion.
* hepatic: bilirubin <=1.5 times the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=3.0 times ULN. Subjects with Gilbert*s syndrome, confirmed by genotyping or Invader UGTIA1 molecular assay prior to study entry must have total bilirubin <3.0 times ULN.
* renal: serum creatinine <=1.5 times ULN
[13] have given written informed consent prior to any study-specific procedures

Exclusion criteria

[14] are currently enrolled in a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drugs used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
[15] bilateral invasive breast cancer
[16] metastatic breast cancer (local spread to axillary or internal mammary lymph nodes is permitted)
[17] inflammatory breast cancer, defined as the presence of erythema or induration involving one third or more of the breast
[18] concurrent therapy with any other non-protocol anti-cancer therapy
[19] history of any other malignancy within the past 5 years, with the exception of non-melanoma skin cancer or carcinoma-in-situ of the cervix
[20] prior systemic therapy or radiotherapy for invasive or non-invasive breast cancer in the same breast as currently being treated
[21] prior radiotherapy to the ipsilateral chest wall for any malignancy
[22] prior anti-estrogen therapy with raloxifene, tamoxifen, aromatase inhibitor, or other selective estrogen receptor modulator (SERM), either for osteoporosis or prevention of breast cancer. Prior hormone-replacement therapy is permitted.
[23] concurrent treatment with postmenopausal hormone replacement therapy. Prior treatment must be stopped for at least 28 days prior to first baseline biopsy.
[24] have received treatment with a drug that has not received regulatory approval for any indication within 14 days of randomization for a nonmyelosuppressive or 21 days of randomization for a myelosuppressive agent
[25] have had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound and site(s)
[26] have received recent (within 28 days prior to randomization) yellow fever vaccination
[27] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn*s disease or ulcerative colitis)
[28] have personal history within the last 12 months of any of the following

conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
[29] have received an autologous or allogeneic stem-cell transplant
[30] have active bacterial or fungal infection or detectable viral infection (for example, human immunodeficiency virus [HIV] or viral hepatitis). Screening is not required for enrollment.
[31] male subjects
[32] known hypersensitivity to loperamide hydrochloride or to any of the excipients

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abemaciclib
Generic name:	Abemaciclib
Product type:	Medicine
Brand name:	anastrozole
Generic name:	anastrozole

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Loperamide
Generic name:	Loperamide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-08-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-09-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-04-2016
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-02-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2017
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
EudraCT	EUCTR2014-005486-75-NL
ClinicalTrials.gov	NCT02441946
CCMO	NL54222.028.15

Study results

Results posted: 13-09-2019

First publication

05-10-2018