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An early phase study of ABT-199 in combination with tamoxifen in metastatic ER-positive breast cancer

Submission date
11/03/2015

Recruitment status
No longer recruiting

Registration date
16/03/2015

Overall study status
Completed

Last Edited
02/12/2022

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The purpose of this research is to determine if a combination of ABT-199 and tamoxifen is safe in patients with metastatic breast cancer. This research is also looking to establish how well this combination works and to determine the safest dose of the study drug in humans as a treatment for this type of breast cancer. There are two phases in this study. The first is a dose escalation phase where the maximum tolerated dose (MTD) of the new treatment is determined. The second phase is a dose expansion phase, where additional participants will be recruited into the study to further test the MTD.

Who can participate?
Adult women (aged over 18) with metastatic breast cancer that is oestrogen receptor positive.

What does the study involve?
Participants are recruited into either the dose escalation phase or dose expansion phase of the study depending upon when they decide to enrol. Before the study starts, they are asked to sign a consent form. Each participant then goes through a series of tests to see whether the study is suitable for them. These tests include reviewing the participants medical and medication history, a physical examination, an electrocardiogram (ECG), CT and bone scans (to locate and measure tumours), taking urine and blood samples for testing and asking about how able they are to do their usual daily activities. If a participants test results are satisfactory, they are enrolled into the study. They are asked to visit the study hospital once a week for the first 4 weeks, and then at least once a month after that. Both the study medications (ABT-199 and tamoxifen) are tablets to be taken once a day by mouth with breakfast and a glass of water. Participants are given their first dose of both study medications in the hospital clinic. Subsequently, both tablets are provided for the participants to take at home every day with clear instructions on how to take the tablets. During the visits to the hospital, each participant has blood tests, CT scans and bone scans (if applicable) to determine if they are responding to treatment and to ensure that they are not having major side-effects as a result of the treatment. They are also asked if they are happy to have tissue biopsies of their cancer about a month after treatment. This is optional but strongly encouraged as it provides valuable information about how the drug affects the cancer.

Each participant continues to take the study tablets as long as they are able to tolerate them, and if their cancer continues to respond. Each participant is monitored for side-effects after they have completed the study. Participants can, of course, choose to withdraw their participation from the study at any time.

What are the possible benefits and risks of participating?
It is possible that the study medications may slow cancer growth. However, this is not guaranteed and participants may not receive any direct benefit from this research. It is likely that information obtained from this research may help with treatment for future patients with cancer. Participants may suffer from mild, moderate or severe side effects caused by the treatment.

Where is the study run from?
The study is run from a number of hospitals in Melbourne, Australia. The lead site is the Royal Melbourne Hospital.

When is the study starting and how long is it expected to run for?
May 2014 to December 2023

Who is funding the study?
This research has been initiated at the Royal Melbourne Hospital by the study doctor, and is funded in joint by a grant from the Victoria Cancer Agency, the National Breast Cancer Foundation, and research support from the pharmaceutical company AbbVie.

Who is the main contact?
1. Professor Geoff Lindeman (scientific)
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Contact information

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
A Phase 1b Study of Bcl-2 inhibition with ABT-199 in combination with tamoxifen in metastatic ER-positive breast cancer

Acronym
m-BEP (Breast)

Study objectives
It is hypothesised that the combination treatment of ABT-199 and tamoxifen will be safe and will show a sufficient level of activity in patients with ER positive, Bcl-2 positive metastatic breast cancer to warrant further investigation in later phase trials.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Melbourne Health Human Research Ethics Committee (HREC), 16/12/2014, ref: 2014.226

Study design
This is an investigator led, open label, multi centre, interventional study.

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Metastatic breast cancer

Interventions
The study will be conducted in 2 consecutive stages:
1. Dose Escalation Stage with a total of 5 dose cohorts of the interventional drug. Subjects will be treated in a standard 3+3 dose escalation method with the aim of establishing the Maximum Tolerated Dose (MTD).
2. Dose Expansion Stage. Once the MTD is established in the Dose Escalation Stage, additional subjects will be enrolled in the second stage. These subjects will all receive the MTD with the aim of establishing the safety profile at the MTD and detecting efficacy signal of combination therapy with ABT-199 and tamoxifen.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ABT-199

Primary outcome measure
1. Maximum tolerated dose (MTD)
2. Dose-limiting toxicities (DLTs)
Both reported within the first 4 weeks of treatment with the combination of ABT-199 and tamoxifen. This will be measured by assessing side-effects experienced by subjects during the first 4 weeks of treatment.

Secondary outcome measures
1. Toxicities measured using CTCAE v4.0 - ongoing throughout study treatment
2. Response as defined by RECIST v1.1 within the first 24 weeks of treatment
3. Progression-free survival (PFS) measured from the date of commencement of treatment with the combination of ABT-199 and tamoxifen until disease progression or death prior to progression from any cause
4. Overall survival measured from the date of commencement of treatment with the combination of ABT-199 and tamoxifen until death from any cause.
5. Clinical benefit rate as defined by:
5.1. Achievement of a complete or partial response during the first 24 weeks of treatment with the combination of ABT-199 and tamoxifen; or
5.2. Maintenance of stable disease until 24 weeks after commencement of treatment according to RECIST v1.1 guidelines
6. Biological response assessed using:
6.1. Change in Ki67 expression assessed by immunohistochemistry after 4 weeks of treatment at the MTD . This will be assessed using the MIB-1 antibody, with the percentage of positively immunostained nuclei in relation to quiescent non-proliferating cells calculated (known as the Ki67 index)
6.2. Change in activated caspase-3 (or TUNEL) expression after 4 weeks of combination treatment with ABT-199 and tamoxifen at the MTD

Overall study start date
01/05/2014

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Subjects >18 years of age
2. Signed informed consent
3. Histological or cytological confirmation of metastatic carcinoma of the breast with the following tumour molecular characteristics:
3.1. ER positive (>1% positive stained carcinoma cells)
3.2. Bcl-2 positive (defined as >10% cells with at least moderate cytoplasmic staining; intensity 2-3 on 0-3 scale)
3.3. HER2 non-amplified
4. Subjects must nor have received tamoxifen within the last 3 months.
5. Subject must have evaluable or measurable disease (bone-only metastases are allowed).
6. Eastern Cooperative Oncology Group (ECOG) performance score of 1 or above.
7. Subjects of childbearing potential must have a negative serum pregnancy test.

8. Subject must have adequate organ and marrow function.
9. Life expectancy >6 months
10. Subjects must be suitable for oral drug administration.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
A total of 6-30 subjects will be recruited in the dose escalation stage, depending on the number of dose cohorts required to reach dose limiting toxicity. An additional 24 subjects will then be recruited in the dose expansion stage of the study. In total, between 30 to 54 subjects will be recruited to the study.

Total final enrolment
57

Key exclusion criteria
1. Subjects who have previously been exposed to ABT-199
2. Absolute contraindication to tamoxifen use
3. Subjects who are pregnant or lactating
4. Subjects with uncontrolled CNS metastases
5. Any anti-cancer therapy received within 21 days of study treatment including chemotherapy, radiotherapy or other investigational therapy
6. Subjects who are taking warfarin
7. Subjects who have had major surgery within 21 days of the first dose of study drug
8. Subject has received the following agents within 7 days prior to the first dose of study drug:
8.1. Steroid therapy for anti-neoplastic intent
8.2. CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin
8.3. Potent CYP3A inducers such as rifampicin, carbamazepine, phenytoin and St John's Wort
9. Subjects with active uncontrolled infection
10. Known history of HIV infection, Hepatitis B or C
11. History of other malignancies within the past 5 years except for treated BCC, SCC, malignant melanoma <1mm, localised thyroid cancer or cervical carcinoma in situ
12. Other history of medical or psychiatric condition that may interfere with the subject's participation in the study
13. Subjects with childbearing potential who refuse to use effective contraception during and for up to 30 days after study drug discontinuation
14. Subjects on contraception that is oestrogen or progestin based (Mirena accepted).
15. Subjects who are on hormone replacement therapy

Date of first enrolment
01/05/2015

Date of final enrolment
31/12/2018

Locations

Countries of recruitment
Australia

Study participating centre
Royal Melbourne Hospital
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Sponsor information

Organisation
Melbourne Health

Sponsor details
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/04z4kmw33

Funder(s)

Funder type
Industry

Funder Name

AbbVie

Alternative Name(s)
AbbVie Inc., AbbVie U.S., AbbVie US, Allergan

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Victorian Cancer Agency

Alternative Name(s)
Victorian Cancer Agency, Department of Health and Human Services, VCA

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Australia

Funder Name
National Breast Cancer Foundation

Alternative Name(s)
NBCF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Australia

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal
A primary manuscript has been published in 2019 - Lok et al Cancer Discovery
A second follow-up manuscript including extended follow-up data and exploratory endpoints will be published - anticipated December 2023

Intention to publish date

31/12/2023

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2019	05/06/2020	Yes	No