

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

<b>Submission date</b> 11/03/2015	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 16/03/2015	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 02/12/2022	<b>Condition category</b> Cancer	<input type="checkbox"/> 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?

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## Contact information

### Type(s)

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**Additional identifiers****Protocol serial number**

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

### **Study type(s)**

Treatment

### **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(s)**

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.

### **Key secondary outcome(s)**

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

### **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 not 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

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

18 years

### **Sex**

All

### **Total final enrolment**

**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

**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)**

NBCFaustralia, NBCF

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Trusts, charities, foundations (both public and private)

**Location**

Australia

## Results and Publications

**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?
<a href="#">Results article</a>	results	01/03/2019	05/06/2020	Yes	No