[177Lu]Lu-NeoB in Combination With Ribociclib and Fulvestrant in Participants With ER+, HER2- and GRPR+ Advanced Breast Cancer

Last Update: Apr 18, 2025
A Phase Ib Dose Finding Study Assessing Safety and Activity of [177Lu]Lu-NeoB in Combination With Ribociclib and Fulvestrant in Participants With Estrogen Receptor Positive, Human Epidermal Growth Factor Receptor-2 Negative and Gastrin Releasing Peptide Receptor Positive Advanced Breast Cancer Experiencing Early Relapse From (Neo)Adjuvant Endocrine Therapy or Who Have Progressed on Endocrine Therapy in Combination With a CDK4/6 Inhibitor for Advanced Disease
ClinicalTrials.gov Identifier:
NCT05870579
Novartis Reference Number:CAAA603B12101
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All compounds are either investigational or being studied for (a) new use(s). Efficacy and safety have not been established. There is no guarantee that they will become commercially available for the use(s) under investigation.

Study Description

The purpose of this trial is to estimate the recommended dose (RD) of \[177Lu\]Lu-NeoB in combination with ribociclib and fulvestrant in participants with estrogen receptor (ER) positive (ER+), human epidermal growth factor receptor-2 (HER2) negative (HER2-) and gastrin releasing peptide receptor (GRPR) positive (GRPR+) advanced breast cancer experiencing early relapse from (neo)adjuvant endocrine therapy or who have progressed on endocrine therapy in combination with a CDK4/6 inhibitor for advanced disease. The study comprises of a dose escalation part and, a concurrent backfill part.

1. The dose escalation part will estimate the RD of \[177Lu\]Lu-NeoB in combination with ribociclib and fulvestrant; four provisional dose levels are planned to be tested: 100 millicurie (mCi) (initial dose), 150mCi, 200 mCi and 250mCi in cohorts of 3 to 6 participants. After inclusion of each cohort of 3 to 6 participants, the incidence rate of DLTs will be compared to the pre-defined toxicity rate boundaries to decide whether the next cohort will receive a lower, higher or same dose or whether the trial will be terminated.
2. The backfill part will allow enrollment to a previously cleared dose level (during escalation part) in order to obtain additional safety, tolerability as well as preliminary efficacy data. During the backfill part, the cumulative incidence rate of DLTs will also be compared to the pre-defined toxicity rate boundaries to determine if escalation should be restarted from a lower dose level.
3. The recommended dose (RD) will be determined considering all available data from the escalation and backfill part.

During screening, study participants will receive the investigational imaging agent \[68Ga\]Ga-NeoB. An additional administration of the \[68Ga\]Ga-NeoB will be performed potentially at Cycle 2 Day 15, and within 4-8 weeks from the last administration of \[177Lu\]Lu-NeoB for a positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI). Study treatment will include \[177Lu\]Lu-NeoB

on day 1 of each 28-day cycle (+ =\< 3 days) for 6 cycles, ribociclib (once daily; days 1 to 21 in a 28-day cycle) and fulvestrant (C1D1, C1D15, C2D1 and every 28 days thereafter) until disease progression. Pre- and perimenopausal women and men will additionally receive goserelin on day 1 of every cycle.

During the treatment period participants will be required to attend a site visit approximately every 28 days, on the first day of each cycle (as well as on C1D2, C1D3, C1D8, C1D15, C2D15, C3D3 and C5D3), to undergo study treatment administration, dosimetry and safety assessments. Tumor assessments are performed every 8 weeks until month 18, every 12 weeks until month 36 and as clinically indicated thereafter, until disease progression. After study treatment discontinuation, participants will be followed up for safety for 8 weeks after their last study treatment administration. Beyond the initial 8 weeks of safety follow-up, all participants will be followed up every 12 weeks until month 36 and every 24 weeks thereafter until month 60 for a total of 5 years from the participant's enrollment in the study, or until death, lost to follow-up, or withdrawal of consent (WoC), whichever occurs first.

The end of study is defined as the date of the last visit, scheduled procedure or follow up (or date of death, WoC or lost to follow up, whichever occurs first) of the last participant in the study globally, or at 5 years from the date of the last participant enrolled, whichever occurs earlier.

Condition
Breast Cancer
Phase
Phase1
Overall Status
Recruiting
Number of Participants
48
Start Date
Nov 13, 2023
Completion Date
Jan 26, 2032
Gender
All
Age(s)
18 Years - 100 Years (Adult, Older Adult)

Interventions

Drug

Fulvestrant

500 mg at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and every 28 days thereafter
Other

Goserelin

For pre/peri-menopausal women and men only.
Drug

Ribociclib

600 mg once daily (OD) days 1 to 21 every 28 days
Drug

[177Lu]Lu-NeoB

Study participants will receive \[177Lu\]Lu-NeoB once every cycle
Drug

[68Ga]Ga-NeoB

\[68Ga\]Ga-NeoB serves as a radioactive imaging compound to be used for PET imaging for localization of GRPR positive lesions, at screening, potentially at Cycle 2 Day 15 visit, and between 4 and 8 weeks after the last administered dose of \[177Lu\]Lu-NeoB. \[68Ga\]Ga-NeoB will be administered as a single intravenous (i.v.) dose.

Eligibility Criteria

Key Inclusion criteria:

* Adult female or male \>= 18 years of age at the time of informed consent
* Histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive with ER \>10% (regardless of progesterone receptor (PgR) expression) breast cancer by local laboratory testing (based on the most recently analyzed tissue sample)
* HER2 negative breast cancer defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (e.g. fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), or silver in situ hybridization (SISH)) test is required by local laboratory testing (based on the most recently analyzed tissue sample)
* Participant has advanced (loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or radiotherapy) or metastatic) breast cancer

Participants may be:

1. relapsed with documented evidence of relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy (+/- CDK4/6 inhibitor) with no treatment for advanced disease OR
2. relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (except fulvestrant) (+/- CDK4/6 inhibitor) for advanced disease OR
3. advanced breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (except fulvestrant) (+/- CDK4/6 inhibitor) Note: Participant who relapsed with documented evidence of relapse on/or within 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for advanced disease will NOT be included in the study. At least one target lesion (i.e., a measurable lesion as per RECIST 1.1) in the baseline stand-alone CT or MRI, showing \[68Ga\]Ga-NeoB uptake on PET/CT or PET/MRI scoring 2 or higher, based on the Visual Scoring Scale.

* Adequate bone marrow and organ function as defined by the laboratory values.
* Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed locally:
* QT interval corrected by Fridericia's formula (QTcF) interval at screening \< 450 msec
* Mean resting heart rate 50-90 bpm (determined from the ECG)

* Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Key Exclusion criteria:

* More than one line of prior treatment in the advanced/metastatic setting. Participant shouldn't have received prior fulvestrant treatment.
* Documented evidence of prior ribociclib dose reduction due to safety reasons either in adjuvant setting or for advanced disease.
* Relapse or disease progression within 6 months of receiving a CDK4/6 inhibitor therapy either in adjuvant setting or for advanced disease. Symptomatic visceral disease or any disease burden that makes the participant ineligible for ribociclib plus endocrine treatment per the Investigator's best judgment.
* Presence of central nervous system (CNS) involvement unless meeting BOTH of the following criteria: 1) At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment. 2) Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
* Currently receiving warfarin or other Coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin, or fondaparinux is allowed.
* Diagnosis of inflammatory breast cancer at screening
* Child Pugh score B or C
* History or current diagnosis of impaired cardiac function, clinically significant cardiac disease or ECG abnormalities indicating significant risk of safety for participants.
* Known or expected hypersensitivity to any of the study drugs or any of their excipients.
* Prior administration of a radiopharmaceutical unless 10 or more half-lives have elapsed before injection of \[68Ga\]Ga-NeoB or \[177Lu\]Lu-NeoB
* Participant has received extended-field RT=\< 4 weeks or limited field RT=\< 2 weeks prior to start of treatment and has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia or other toxicities not considered a safety risk for the participant at Investigator's discretion) and/or prior external beam radiation therapy (EBRT) to more than 25% of the bone marrow.
* Participant is currently receiving or has received systemic corticosteroids =\< 2 weeks prior to starting study treatment, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
* Participant has a history of or ongoing acute pancreatitis within 1 year of screening.
* Participant is currently receiving any of the following substances and cannot be discontinued 7 days prior to starting study treatment:
* Concomitant medications, herbal supplements, and/or fruits (e.g., grapefruit, pummelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of cytochrome P450 (CYP) 3A4
* Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
* Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes (TdP) that cannot be discontinued or replaced by safe alternative medication (e.g., within 5 half-lives or 7 days prior to starting study treatment)
* Participant is currently receiving NEP inhibitors (e.g.Entresto®, racecadotril) and images for dosimetry assessments cannot be acquired for this participant.

Other protocol-defined inclusion/exclusion criteria may apply.

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