ATTAIN Phase 3 Study of Etilinotecan Pegol versus Treatment of Physician’s Choice in Patients With Metastatic Breast Cancer Who Have Stable Brain Metastases Previously Treated With an Anthracycline, a Taxane, and Capecitabine

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Background

- Treatment of patients with breast cancer brain metastases (BCBM) remains a challenging consequence of advanced breast cancer (ABC)
- The incidence of brain metastases in unselected patients with metastatic breast cancer is estimated to be as high as 30%
- Treatment options following local surgery and/or radiotherapy remain limited
- There is no standard treatment that has been shown to benefit patients with previously treated central nervous system (CNS) metastases
- Small prospective trials with systemic therapy have shown only modest response rates and short duration of palliative benefit
- Currently no cytotoxic or molecularly targeted agent is approved for the treatment or prevention of BCBM

BEACON Phase 3 Trial

- The randomized Phase 3 BEACON trial compared etilinotecan pegol (EP) 145 mg/m² every 3 weeks to treatment of physician’s choice (TPC; eribulin, vinorelbine, gemcitabine, nab-paclitaxel, paclitaxel, ixabepilone, or docetaxel) with an anthracycline, a taxane, and capecitabine
- Grade 3 adverse events (48% vs 63% with TPC, unadjusted P=0.0001)
- EP prolonged median overall survival (OS) by 2.1 months (12.4 vs 10.3 months; HR=0.87, P=0.08)
- Quality of life was improved with EP compared to TPC
- Although OS did not reach statistical significance, there was a clinically meaningful improvement in OS in a predefined subgroup of patients with BCBM

ATTAIN Study

Study Objectives

PRIMARY OBJECTIVE

- Compare overall survival (OS) in patients with BCBM treated with EP vs TPC

SECONDARY OBJECTIVES

- Compare objective response rates (ORR) (RECIST v1.1) for peripheral lesions; RANO-BM13 for CNS lesions by central imaging
- Compare progression-free survival (PFS) (RECIST, RANO-BM, and overall)
- Compare clinical benefit rate (CBR)
- Compare duration of response
- Compare health-related quality of life (HRQoL), including neurological function via BN-20 subscale
- Evaluate the safety and tolerability profile of EP
- Evaluate pharmacokinetics, pharmacoeconomics, UGT1A1, and ESMO Magnitude of Clinical Benefit Scale

EXPLORATORY OBJECTIVE

- Identify biomarkers that correlate with response, PFS, and OS

Eligibility

Key Inclusion Criteria

- Histologically-confirmed carcinoma of the breast and a history of brain metastases that are non-progressing
- Have undergone definitive local therapy of brain metastases (whole brain radiation; stereotactic radiation and/or surgical resection; combination therapy (whole-brain radiation with or without stereotactic radiation or surgery)) must be completed at least 14 days prior to randomization; single modality therapy must be completed at least 7 days prior to randomization
- Received prior anthracycline (unless contraindicated), a taxane, and capecitabine
- Prior systemic treatment:
  - TNBC: one prior cytotoxic regimen for ABC
  - HER2+: two prior cytotoxic regimens for ABC; must have received prior HER2-targeted therapy
  - HR+: two prior cytotoxic regimens for ABC; must have received hormone therapy
- ECOG PS 0 or 1
- Adequate organ and marrow function

Key Exclusion Criteria

- Last dose of anticancer therapy within 14 days of randomization (HER2-targeted therapy must be discontinued for the duration of the trial)
- Prior treatment for cancer with a camptothecin-derived agent
- Brain metastases amenable to local therapy but without completion of such therapy
- Disease consistent with leptomeningeal disease or meningeval carcinomatosis
- Chronic or acute Gl disorders resulting in diarrhea of any grade
- Receiving enzyme-inducing anti-epileptic drugs within 14 days of randomization
- High-dose chemotherapy followed by stem cell transplantation (autologous or allogeneic)
- Receiving pharmacology therapy for Hepatitis B or C, tuberculosis, or HIV, cirrhosis
- Requiring oxygen for 7 or more days in the 28 days prior to randomization; significant cardiovascular impairment

Assessments and Follow-up

Clinical

- Tumor imaging (including brain imaging) will be performed at baseline, every 8 weeks for the first 24 weeks, and every 12 weeks thereafter until PD
- Response will be based on RECIST v1.1 and RANO-BM specifications, as appropriate
- Follow-up for survival information may be conducted via phone, clinic visit, or patient chart review approximately every 12 weeks following the End of Treatment visit
- Follow-up contacts will continue until death, withdrawal from the study by patient, patient is lost to follow-up, or study termination

Quality of Life

- All patients will complete the EORTC QLQ-C30, version 3.0 with the BN-20 subscale, the EQ-SD-SLTM, and the BFI on Day 1 prior to inference for each cycle and at the End of Treatment visit

Biomarkers, Pharmacokinetics, and Pharmacogenetics

- PK sampling will be performed in a subset of patients
- UGT1A1 testing will occur in patients randomized to EP
- Plasma cfDNA will be assessed at baseline and serially on-study for potential predictive markers of efficacy
- BFI, Brief Fatigue Inventory; BN-20, brain neoplasms 20-questions; cfDNA, circulating cell-free tumor DNA; EORTC QLQ-C30, European Organisation for Treatment of Cancer Quality of Life Core 30; EQ-SD-SLTM, EuroQol 5D; PD, progressive disease; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases

Statistical Design – Promising Zone Adaptive Design

- Goal: Identify predictive factors for OS and PFS
- 191 OS events
- 147 pts enrolled
- BFI on Day 1 prior to inference for each cycle and at the End of Treatment visit
- OS interim analysis: 147 pts enrolled
- OS events re-estimation: Events re-estimation based on conditional power
- Chi-squared test for OS

Status

- Enrollment is open in 3 Regions, 9 Countries
- For participating trial sites please visit https://clinicaltrials.gov, and search NCT02915744

References


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