**ATTAIN Study**

**Study Objectives**

**PRIMARY OBJECTIVE**

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

**SECONDARY OBJECTIVES**

- Compare objective response rate (ORR) (RECIST v1.1 for peripheral lesions; RANO-BM 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, pharmacodynamics, 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 study)
- 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 meningi carcinomatosis
- Chronic or acute GI 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 RECISTv1.1 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-5L, and the BFI on Day 1 prior to infusion for each cycle and at the End of Treatment visit

**Biomarkers, Pharmacokinetics, and Pharmacogenetics**

- PK sampling will be performed in a subset of patients
- Response will be evaluated on RECISTv1.1 and RANO-BM specifications, as appropriate
- Plasma cfDNA will be assessed at baseline and serially on-study for potential predictive markers of efficacy

**Statistical Plan and Methods**

- The study is powered for detecting superiority of EP versus TPC in OS. A total of 350 patients will be enrolled to observe at least 260 required deaths to test the primary hypothesis of superiority; this provides 90% power to detect an improvement of survival from 6 to 9 months with a Hazard Ratio of 0.67 at an overall significance level of 0.05
- The primary analysis will be a two-sided log-rank test stratified by geographic region, ECOG PS, and tumor receptor status
- One interim analysis will be conducted when 50% of the 260 events have occurred (i.e., 130 deaths). The purpose of the interim analysis is to determine whether early termination of the study due to overwhelming efficacy, or due to futility can be supported

**References**