ATTAIN: Phase 3 Study of Etirinotecan Pegol (EP) versus Treatment of Physician’s Choice (TPC) in Patients With Metastatic Breast Cancer and Brain Metastases (BCBM)

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BACKGROUND
- Breast cancer brain metastases (BCBM) remain a challenging consequence of advanced breast cancer (ABC).
- It is estimated that the prevalence of brain metastases in unselected patients with metastatic breast cancer is as high as 30%.
- Treatment options for patients with brain metastases following prior 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.
- The blood-brain barrier prevents many chemotherapeutic agents used to control systemic disease from reaching effective concentrations in brain metastases.
- Currently no cytotoxic or molecularly targeted agent is approved for the treatment or prevention of breast cancer brain metastases.

ETIRINOTECAN PEGOL (EP)
- EP is a long-acting topoisomerase-1 inhibitor engineered to produce sustained exposure to irinotecan and its active metabolite SN38.
- In a mouse xenograft model of BCBM, EP exhibited preferential accumulation in brain tumors (100x higher compared to conventional irinotecan) and median survival of 74 days, with 50% of animals surviving to the end of the 91-day study.
- EP also avoids P-glycoprotein and BCRP/ABC2-mediated efflux, which could provide an added benefit for retention of SN38 in brain lesions.

ATTAIN STUDY

STUDY OBJECTIVES

PRIMARY OBJECTIVE
- Compare overall survival in patients with BCBM treated with EP vs TPC

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

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

DESIGN
- In ATTAIN (Figure 3), ~350 patients will be randomly assigned in a 1:1 ratio to receive either:
  - Single-agent etirinotecan pegol 145 mg/m² q21d as a 90-minute intravenous (IV) infusion on Day 1 of each treatment cycle until confirmed disease progression per RECIST version 1.1, intolerable toxicity, patient withdrawal of consent, or physician decision
  - Treatment of physicians’ choice (tellurium, irinotecan, docetaxel, or nab-paclitaxel) will be administered per standard of care until confirmed disease progression per RECIST version 1.1, intolerable toxicity, patient withdrawal of consent, or physician decision

STATISTICAL PLAN AND METHODS
- 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

ELIGIBILITY

KEY INCLUSION CRITERIA
- Metastatic locally confirmed carcinoma of the breast and a history of brain metastases that have not progressed since the scan following definitive local therapy
- Have undergone definitive local therapy of brain metastases (whole brain radiation; stereotactic radiation and/or surgical resection)
- Received prior anthracycline (unless contraindicated), a taxane, and capecitabine
- TNBC: received one prior cytotoxic regimen for ABC; all others, 2 prior cytotoxic regimens for ABC; HER2+: ABC must have received prior HER2-targeted therapy; HR+: ABC must have received hormonal 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 to be eligible for this 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 meningial carcinomatosis
- Chronic or acute GI disorders resulting in diarrhea of any severity 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, HIV, cirrhosis
- Requiring oxygen for >7 or more days in the 28 days prior to randomization; significant cardio-vascular impairment

ASSESSMENTS AND FOLLOW-UP
- Tumor imaging (including head imaging) will be performed at baseline, every 8 weeks for the first 24 weeks, and every 12 weeks thereafter until progressive disease (PD)
- Response will be based on RECIST v1.1 and RANO-BM specifications, as appropriate
- All patients will complete the EORTC QLQ-C30, version 3.0 with the BN-20 subscale, the EQ-5D-5L, and the BPI on Day 1 prior to infusion for each cycle and at the End of Treatment visit
- 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

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
- The primary analysis will be a two-sided log-rank test stratified by geographic region, ECOG, and tumor receptor status
- One interim analysis will be conducted when 50% of the 260 events have occurred (ie, 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

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