• Breast cancer brain metastases (BCBM) remain a challenging consequence of advanced breast cancer (ABC). It is estimated that the prevalence of brain metastases in untreated patients with metastatic breast cancer is as high as 30%. Treatment options for patients with brain metastases following prior surgical therapy and/or radiotherapy remain limited.

• Currently no cytotoxic or molecularly targeted agent is approved for BCBM. In a mouse-xenograft model of BCBM, EP avoided P-glycoprotein and BCRP/ABCG2-mediated efflux, which could provide an added benefit for retention of 500 mg/m² in brain lesions.

• Clinical features of BCBM include young age, estrogen receptor-negative status, and high tumor grade.

• Current evidence suggests that EP is a next-generation long-acting topoiso-merase-1 inhibitor engineered to produce a next-generation structure-activity relationship. In a mouse-xenograft model of BCBM, EP avoided P-glycoprotein and BCRP/ABCG2-mediated efflux, which could provide an added benefit for retention of 500 mg/m² in brain lesions.

• In a milestone event, EP is the first and only G1 barrier P-glycoprotein/BCRP/ABCG2 inhibitor to demonstrate clinical activity in a randomized phase 3 trial in BCBM.

• The randomized Phase 3 BEACON trial compared etirinotecan pegol (EP) 145 mg/m² q21d for 3 weeks to treatment of physician’s choice (TPC) in one arm of a 2:1 ratio (246 patients per arm; 492 total). It is a global trial with a median follow-up of 36 months.

• EP has demonstrated statistically significant improvement in OS for a predefined subgroup of patients with a history of brain metastases at baseline (12.4 vs 10.3 months; HR 0.87, =0.08).

• The trial will be conducted in 17 countries in 3 regions: Europe (25%), Latin America (45%), and Asia (30%). The primary endpoint is OS, with secondary endpoints including PFS and OS for patients with brain metastases at baseline.

• EP is the first and only G1 barrier P-glycoprotein/BCRP/ABCG2 inhibitor for the treatment of patients with brain metastases following prior surgical therapy and/or radiotherapy.

ATTAIN Study

Study Objectives

• Primary Objective: OS in patients with BCBM treated with EP vs TPC

• Secondary Objectives:
  - PFS in patients with BCBM treated with EP vs TPC
  - Efficacy endpoints: confirmed objective response rate, confirmed complete response rate, duration of response, duration of stable disease, duration of progression-free survival (PFS, using 12 weeks as the cutoff point for disease progression), best overall response, and general health status (using the EuroQoL-5D and European Organization for Research and Treatment of Cancer Quality of Life Core 30 [EORTC QLQ-C30] questionnaire).

• Safety and tolerability endpoints: ototoxicity, neutropenia, skin toxicity, common adverse events, serious adverse events, and study withdrawals

Eligibility

• Key Inclusion Criteria:
  - Histologically confirmed adenocarcinoma of the breast and a history of brain metastases that are non-progressing
  - Have undergone definitive local therapy of brain metastases (whole brain radiation with or without stereotactic radiation or surgery) but without completion of such therapy
  - Prior treatment for cancer with a camptothecin-derived agent
  - Adequate organ and marrow function
  - Performance status of 0-1
  - Significantly measurable or non-measurable disease
  - Life expectancy of at least 12 weeks
  -愿意放弃生育

• Key Exclusion Criteria:
  - Receiving concomitant antiangiogenic therapy
  - Brain metastases that are non-progressing
  - Prior treatment for cancer with a camptothecin-derived agent
  - A significant cardiovascular impairment

Statistical Plan and Methods

• The trial is planned to enroll 260 patients, with a maximum of 50% missing data. The sample size is determined by the primary endpoint of OS for patients with brain metastases at baseline.

• PFS and OS data will be analyzed using the Kaplan-Meier method.

• The primary analysis will be performed on an intent-to-treat basis.

• The trial is designed to detect an improvement of survival from 6 to 9 months with a Hazard Ratio of 0.7 at an overall significance level of 0.05.

• The primary analysis will be a hazard-ratio log rank test stratified by geographic region, ECOG PS, and tumor receptor status.

• An interim analysis will be conducted when 50% of the 260 events have occurred. The purpose of the interim analysis is to determine whether early termination of the study due to overreaching efficiency, or due to futility can be supported.