Phase 3 Study of Etirinotecan 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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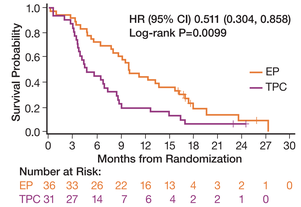
Background

- Breast cancer brain metastases (BCBM) remain a challenging consequence of advanced breast cancer (ABC)
- It is estimated that the incidence of brain metastases in unselected patients with metastatic breast cancer is as high as 30%[1]
- 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[2-6]
- 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[3,7]

Figure 1. Overall Survival for Patients With Stable, Treated Brain Metastases in the BEACON Phase 3 Trial

- 67 patients with a history of baseline brain metastases randomized
- Significant reduction in risk of death with EP relative to TPC
- EP: n=36, [events=31]; median OS (95% CI) 10.0 months (7.8, 15.7)
- TPC: n=31, [events=29]; median OS (95% CI) 4.8 months (3.7, 7.3)

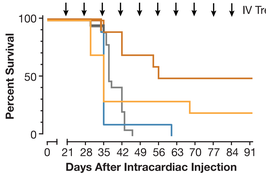
Based on these results, a Phase 3 trial (the ATTAIN Trial) was designed for this population of high unmet medical need



BEACON Phase 3 Trial

- The randomized Phase 3 BEACON trial compared etirinotecan pegol (EP) 145 mg/m^2 every 3 weeks to treatment of physician's choice (TPC; eribulin, vinorelbine, gemcitabine, *nab*-paclitaxel, paclitaxel, ixabepilone, or docetaxel) in women with ABC[8]
  - Grade 3 adverse events were significantly less common with EP (48% vs 63% with TPC, 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 with TPC
- Although OS did not reach statistical significance, there was a clinically meaningful and statistically significant improvement in OS for a predefined subgroup of patients with a history of brain metastases at baseline (**Figure 1**)

Figure 2. EP Prolongs Survival of Animals with Triple-Negative Breast Cancer Brain Metastases



	Median Survival (Days)
Vehicle (n=18)	37
EP (50 mg/kg IV) (n=10)	74
EP (10 mg/kg IV) (n=10)	35
Irinotecan (50 mg/kg IV) (n=10)	35

Intracardiac injection of MDA-MB-231BR cells in mice; treatment starts after brain metastases are established (21 days after tumor injection); IV dosing q7d for duration of study

Etirinotecan Pegol (EP)

- EP is a next-generation 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 (**Figures 2 and 3**)[9,10]
  - Concentrations clinically achievable at the recommended dose of EP in patients
- EP also avoids P-glycoprotein and BCRP/ABCG2-mediated efflux, which could provide an added benefit for retention of SN38 in brain lesions

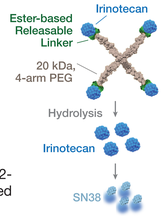
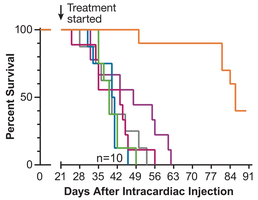


Figure 3. EP Prolongs Survival of Animals with Triple-Negative Breast Cancer Brain Metastases vs TPC



	Median Survival (Days)
Vehicle	38
EP (50 mg/kg)	86
Docetaxel	39
Vinorelbine	43
Eribulin	40
Gemcitabine	48

EP significantly different from TPC (P<0.05)

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-BM[11] for CNS lesions)
- 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 (see last column for more complete explanation of biomarkers planned)

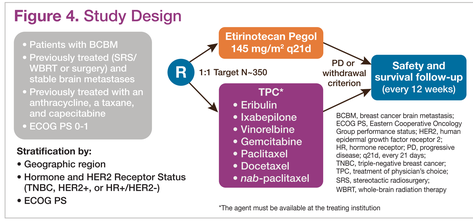
RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; ESMO, European Society for Medical Oncology

Design

In ATTAIN (Figure 4), ~350 patients will be randomly assigned in a 1:1 ratio to receive either:

- Single-agent etirinotecan pegol 145 mg/m^2 q21d as a 90-minute intravenous (IV) infusion on Day 1 of each treatment cycle
- Treatment of physicians' choice (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel) administered per standard of care
- Treatment until confirmed disease progression per RECIST version 1.1, intolerable toxicity, patient withdrawal of consent, or physician decision

Figure 4. Study Design



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
- 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 meningeal 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

Status

- The trial will be conducted in 20 countries in 3 regions
- Enrollment is open
- For participating trial sites please visit https://clinicaltrials.gov, and search NCT02915744

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-5D-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
- UGT1A1 testing will occur in patients randomized to EP
- Plasma cftDNA will be assessed at baseline and serially on-study for potential predictive markers of efficacy

BFI, Brief Fatigue Inventory; BN-20, brain neoplasms 20-question; cftDNA, circulating cell free tumor DNA; EORTC QLQ-C30, European Organisation for Treatment of Cancer Quality of Life Core 30; EQ-5D-5, EuroQoL 5D; PD, progressive disease; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases

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 (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

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