ATTAIN: 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

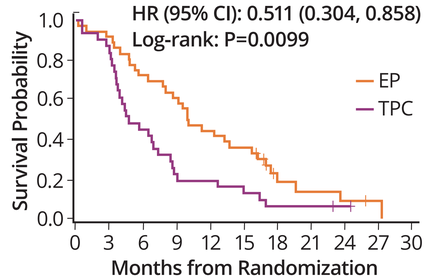
- Treatment of patients with breast cancer brain metastases (BCBM) remains a challenging consequence of advanced breast cancer (ABC)
  - The incidence of brain metastases in unselected patients with metastatic breast cancer is estimated to be as high as 30%[1]
- Treatment options following prior local 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]
- Currently no cytotoxic or molecularly targeted agent is approved for the treatment or prevention of BCBM[3,7,8]

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[9]
  - Grade 3 adverse events were significantly less common with EP (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 with TPC
- Although OS did not reach statistical significance, there was a clinically meaningful improvement in OS for a predefined subgroup of patients with BCBM (**Figure 1**)

Figure 1. Overall Survival for Patients With BCBM in the BEACON Phase 3 Trial

- 67 patients with a history of baseline brain metastases randomized
- Reduction in risk of death with EP relative to TPC with HR=0.511
- 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)



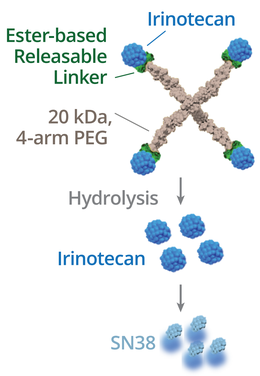
Number at Risk:

EP	36	33	26	22	16	13	4	3	2	1	0
TPC	31	27	14	7	6	4	2	2	1	0	

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

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[10,11]
- EP avoids P-glycoprotein and BCRP/ABCG2-mediated efflux, which could provide an added benefit for retention of SN38 in brain lesions



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[12] for peripheral lesions; RANO-BM[13] 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

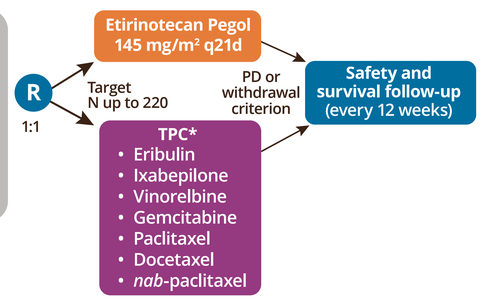
RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; ESMO, European Society for Medical Oncology

Design

- In ATTAIN (**Figure 2**), up to 220 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 physician's 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 2. Study Design

- Patients with BCBM
- Previously treated (SRS/WBRT or surgery) and stable brain metastases
- Previously treated with an anthracycline, a taxane, and capecitabine
- ECOG PS 0-1



Stratification by:

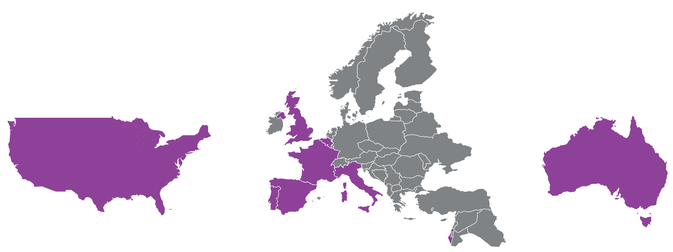
- Geographic region
- Hormone and HER2 Receptor Status (TNBC, HER2+, or HR+/HER2-)
- ECOG PS

BCBM, breast cancer brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; q21d, every 21 days; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy

*The agent must be available at the treating institution

Status

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



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 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

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

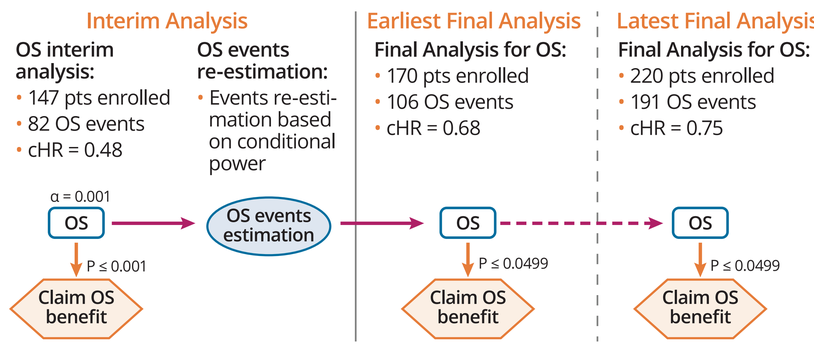
- All patients will complete the EORTC QLQ-C30, version 3.0 with the BN-20 subscale, the EQ-5D-5L™, and the BFI on Day 1 prior to infusion for each cycle and at the End of Treatment visit

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 Design – Promising Zone Adaptive Design[14]



OS, overall survival; cHR, critical value for HR to be significant

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