ATTAIN: Phase 3 Study of Etiromotecan Pegol versus 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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ABSTRACT

- Treatment of patients with breast cancer brain metastases (BCBM) remains a challenging consequence of advanced breast cancer (ABC).
- The incidence of brain metastases in untreated patients with metastatic breast cancer is estimated to be as high as 30%.
- Treatment options following prior local surgery and/or radiation therapy 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 organ site-related differences in the rates and short duration of palliative benefit.

- Currently, no cytotoxic or molecularly targeted agent is approved for the treatment or prevention of BCBM.

BEACON PHASE 3 TRIAL

- The randomized Phase 3 BEACON trial compared etirinotecan pegol (EP) 145 mg/m² every 3 weeks to treatment of physician’s choice (TPC).
- TPC included eribulin, vinorelbine, gemcitabine, cabazitaxel, docetaxel, paclitaxel, and combination chemotherapy.

- EP was administered as a 90-minute intravenous (IV) infusion on Day 1 of each 21-day treatment cycle.
- Patients with BCBM who had previously received anthracyclines and taxanes were eligible for inclusion.

- Patients received EP or TPC until disease progression, unacceptable toxicity, withdrawal of consent, or withdrawal by investigator.

- Key Inclusion Criteria:
  - Patients with BCBM
  - ECOG PS 0 or 1
  - Prior systemic treatment:
    - At least one prior anthracycline and taxane
    - Must have previously received anthracyclines and taxanes
  - High-dose chemotherapy followed by autologous stem cell transplantation (palliative or alternative) or prior systemic therapy with a total dose of 800 mg/m² or more of docetaxel

- Key Exclusion Criteria:
  - Prior treatment for a metastatic breast cancer brain metastasis that is or was suspected to be responsive to radiation therapy
  - Disease consistent with leptomeningeal disease or meningeal carcinomatosis
  - Chronic or acute GI disorders resulting in diarrhea of any grade

- Assessments and Follow-up:
  - Serial imaging including brain imaging will be performed at baseline, every 4 weeks for the first 24 weeks, and every 12 weeks thereafter until PD.
  - Response to EP will be based on RECIST v.1.1 and RANO-BM criteria.
  - Follow-up for survival information may be conducted via phone, clinic visit, or patient chart review approximately every 12 weeks.
  - Follow-up contacts will continue until death, withdrawal from the study by patient, or study termination.

- Quality of Life:
  - All patients will complete the EORTC QLQ-C30, version 3.0 with the EORTC QLQ-BM22 subscale, and the EORTC QLQ-SD14 at the first treatment cycle and at the end of Treatment Visit.

- Biomarkers, Pharmacokinetics, and Pharmacogenetics:
  - Blood samples will be collected at baseline and every 12 weeks.
  - Pharmacogenetics will be determined for the CYP2B6 gene.

- Statistical Design – Promising Zone Adaptive Design®

- ORR analysis will be based on standard endpoints (CBO, ECOG PS 0-1). Final analysis will be based on a similar endpoint.

- The statistical design is based on Simon’s 2-stage design.

Background

ETIRINOTECAN PEGOL (EP)

- A phase 1/2, open-label, single-arm trial evaluated brain metastases in breast cancer patients.
- Epetogol was administered q21d during 6 cycles of 21 days.
- The primary endpoint was time to progression (TTP).

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 v. 1.1] for peripheral lesions and RANO-BM for CNS lesions using central imaging
  - Compare progression-free survival (PFS) [RECIST v. 1.1, RANO-BM, and/or CNS]
  - Compare duration of response
  - Compare health-related quality of life (HRQoL), including neurological function via the BN-20 subscale
  - Compare clinical benefit rate (CBR)
  - Compare disease burden (DBC)

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

Study Design

- In the ATTN trial (Figure 2), up to 220 patients will be randomly assigned in a 1:1 ratio to receive either:
  - Single-agent etirinotecan pegol 145 mg/m² IV as a 90-minute intravenous (IV) infusion on Day 1 of each treatment cycle
  - Treatment of physician’s choice (TPC) including single-agent or combination chemotherapy (whole-brain radiation with or without radiosurgery)

- Patients will continue until disease progression, unacceptable toxicity, withdrawal of consent, or withdrawal by investigator.

- Treatments will be confirmed disease progression per RECIST version 1.1, intolerable toxicity, patient withdrawal of consent, or physician’s decision.

- All patients will complete the EORTC QLQ-C30, version 3.0 with the EORTC QLQ-BM22 subscale, and the EORTC QLQ-SD14 at the first treatment cycle and at the end of Treatment Visit.

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References

- American Society for Clinical Oncology. 2015;16:e270–e278.