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ATTAIN: Phase III study of etirinotecan pegol versus treatment of physician's choice in patients with metastatic breast cancer and brain metastases

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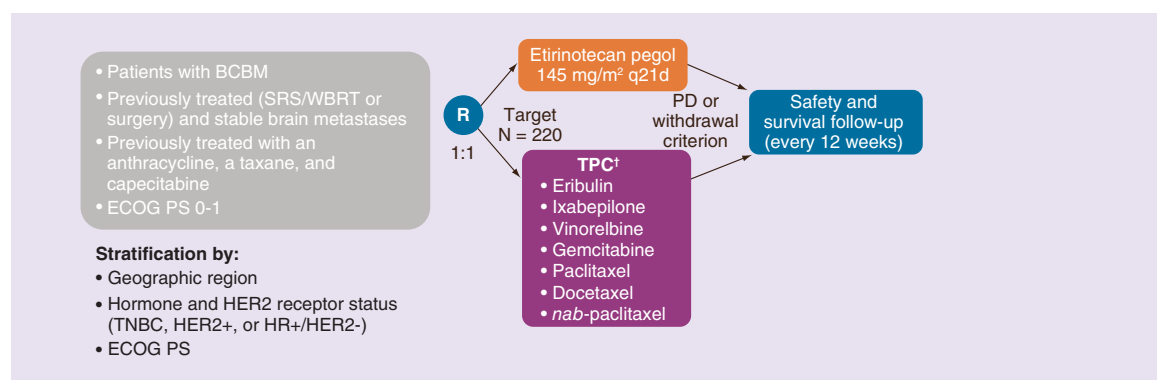
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The increasing incidence of breast cancer brain metastases is a major clinical problem with its associated poor prognosis and limited treatment options. The long-acting topoisomerase-1 inhibitor, etirinotecan pegol, was designed to preferentially accumulate in tumor tissue including brain metastases, providing sustained cytotoxic SN38 levels. Motivated by improved survival findings from subgroup analyses from the Phase III BEACON trial, this ongoing randomized, Phase III trial compares etirinotecan pegol to drugs commonly used for advanced breast cancer in patients with stable, treated breast cancer brain metastases who have been previously treated with an anthracycline, taxane and capecitabine. The primary end point is overall survival. Secondary end points include objective response rate, progression-free survival and time to CNS disease progression or recurrence in patients with/without CNS lesions present at study entry. Trial registration number: NCT02915744.



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Keywords: brain metastases • chemotherapy • etirinotecan pegol • metastatic breast cancer • NKTR-102

The incidence of brain metastases (BM) among women with metastatic breast cancer (MBC) has been significantly underestimated, likely due to patients succumbing to systemic progression prior to symptomatic CNS disease [1–4]. In recent years, the incidence of BM has been estimated to be as high as 30% in unselected patients and approaching or exceeding 35–50% in subpopulations with HER2-positive or ‘triple-negative’ (TNBC; estrogen and progesterone receptor negative, HER2 normal) disease [2,3,5–15]. This high incidence of BM is thought to be associated with prolonged survival secondary to improvements in the management of systemic disease and better imaging studies, but also in large part due to the lack of efficacy and CNS penetration of existing therapies [3–5,16,17]. Despite advances in the management of MBC, breast cancer brain metastases (BCBM) remains a significant clinical problem, portending a poor prognosis and leading to neurocognitive deterioration as well as interruptions in systemic disease management.

Treatment of BCBM is driven primarily by critical prognostic factors (age, tumor subtype, performance status, number of BM and presence of extracranial metastases) and comprises varying combinations of surgery (+/- adjuvant radiotherapy to whole brain or tumor-bed alone), whole-brain radiation therapy (WBRT; +/- a focal boost), stereotactic radiosurgery (SRS; alone or +/- WBRT) and systemic therapies (chemotherapy or targeted therapy, either separately or in conjunction with other localized therapeutic approaches) [2–7,10–12,16,18–26]. The most widely used treatment for patients with multifocal BCBM is WBRT, most notably in patients with BM that are not amenable to surgical resection or in select populations, such as those with poor performance status or rapidly progressing systemic disease [3,6,18]. The evolution of SRS (alone or in combination) into a safe and focal high-dose treatment for BCBM has been demonstrated by consistent rates of local control in most series [23,27–31]. While improved intracranial control has been demonstrated, survival evidence is lacking and patients are at risk of serious quality-of-life altering adverse effects, including significant neurocognitive impairment and decline [3–6,11,16,18–21,23,26,30]. Careful patient selection is key as timing and appropriate use of these modalities remains debated.

Chemotherapy has traditionally played a limited role in the management of BCBM due to formidable obstacles, including the blood–brain barrier (BBB), with its tight junctions that limit the blood-to-brain passage of many agents [10,16,32]. Additionally, despite the apparent structural and functional breakdown of the BBB secondary to BM as well as RT, and the subsequent development of new permeable vasculature (blood–tumor barrier or BTB), data indicate that the BBB and BTB remain sufficiently intact to significantly impair drug delivery (although trastuzumab emtansine, a large monoclonal antibody drug conjugate, has been shown in case reports to result in intracranial responses in selected patients) [33–36]. Furthermore, the BBB and BTB harbor various efflux transporters, including P-glycoprotein and breast cancer resistance protein (BCRP), which bind many of the chemotherapeutics approved for MBC and render them ineffective [32].

It is typically desired that BCBM be treated with systemic chemotherapy before or after RT or surgery, and more recently as an appealing option to avoid or delay WBRT and its associated complications. However, there are no approved chemotherapy regimens indicated for the management of BCBM, nor are there consensus-based recommendations for the general chemotherapeutic management with reasonable level of evidence, except for a guideline on the disease management of patients with HER2-positive breast cancer and BM published in 2014 [3,5,6,10,12,22,37,38]. Although SRS may be repeatedly administered for untreated and, in some instances, for radiated lesions, treatment options are limited for patients with BCBM that relapse or progress after initial surgery/RT/SRS therapeutic approaches, supported by small prospective trials reporting only modest response rates and short durations of benefit [3,7,10,11,22,38,39]. Targeted agents alone or with chemotherapy are being explored; however, the results have been conflicting in this heavily pretreated population [40–44]. Cross-resistance, the primary impediment to the successful treatment of patients in the advanced disease setting, as well as overlapping and/or cumulative toxicities, most commonly neurotoxicity and myelosuppression, also frequently preclude the use of commonly used agents in the BCBM setting [11,45–47]. Thus, novel systemic treatment approaches are critically needed.

Etirinotecan pegol (NKTR-102)

Etirinotecan pegol (EP; also known as NKTR-102) is a novel long-acting topoisomerase I inhibitor-polymer conjugate engineered by attaching irinotecan molecules via a biodegradable cleavable ester-based linker to a polyethylene glycol (PEG) polymer core. Through *in vivo* hydrolysis of the cleavable linker, EP was specifically

designed to provide a slow and extended release of irinotecan and subsequently slower transformation to its main active metabolite, SN38 (7-ethyl-10-hydroxycamptothecin), resulting in reduced maximum plasma concentrations (C-max) yet sustained SN38 concentrations [48]. Preclinical and early clinical trials demonstrated an approximate tenfold reduction in the C-max of SN38 after EP administration compared with administration of irinotecan and a prolongation of the SN38 half-life to approximately 50 days, which is in contrast to the half-life of SN38 following conventional administration of irinotecan of ≤ 2 days [48–51]. By not overwhelming the capacity of the carboxyl-esterase enzymes that deacetylate irinotecan to SN38, the slow release of irinotecan from EP allows for a more efficient drug activation and resultant greater SN38 area under the concentration time-curve (AUC). This continuous exposure to SN38 is intended to improve antitumor activity while providing a more favorable toxicity profile.

In addition to the pharmacokinetic (PK) advantages, the EP polymer conjugate achieves selective drug targeting by exploiting abnormalities of the tumor vasculature, a phenomenon called the enhanced permeability and retention effect or EPR [48,52,53]. This unique phenomenon of solid tumors is based on their anatomical and pathophysiological differences from normal tissues, namely hypervascularization, aberrant architecture, hyperpermeability and lack of lymphatic drainage. Because EP is a large macromolecule, it penetrates the leaky vasculature within the tumor environment more readily than normal vasculature, concentrating and trapping the drug in the tumor tissue providing prolonged exposure of the tumor.

The ATTAIN study

Here we describe the design and rationale for ATTAIN (NCT02915744), an ongoing open-label, randomized, multicenter, international Phase III study of EP versus treatment of physician's choice (TPC) in patients with MBC and stable BM. The study is funded by Nektar Therapeutics, San Francisco, CA, USA.

Background & rationale for EP in the treatment of BCBM

Preclinical & early clinical investigations

Currently, available chemotherapeutic agents distribute poorly to lesions in the brain due to difficulties penetrating the BBB and BTB, and, because many of these chemotherapeutics are substrates of the efflux transporters expressed at these sites [32,33]. EP is not a substrate of such efflux transporters, and as demonstrated in early clinical investigations, tumor localization via EPR is pronounced and sustained, likely from the prolonged circulation in plasma, resulting in high concentrations of SN38 in brain tumors [48,54,55]. In a mouse xenograft BM model, EP exhibited preferential accumulation and generated higher SN38 concentrations in brain tissue over corresponding plasma concentrations (170- and 30-fold, respectively) [54,55]. Analyses of brain sections assessing for drug uptake demonstrated that the SN38 concentration in brain tissue was 100-fold greater and more prolonged subsequent to EP administration compared with non-conjugated irinotecan administration. This prolonged SN38 brain exposure was associated with a significant regression of established BM (size and number) and a doubling of the animals' median survival (74 days vs 37 days, for EP and irinotecan, respectively). The efficacy observed in this preclinical model demonstrates the ability of EP to cross the BTB, leading to preferential accumulation and retention in brain tumor, followed by sustained and efficacious concentrations of SN38.

Additional evidence for activity in the CNS was reported from a Phase II study in patients with bevacizumab-refractory, high-grade glioma [56]. In this open-label study, 18 patients (with a median of three prior therapies) were diagnosed with glioblastoma multiforme; three of the 18 (17%) had a partial response to single-agent EP, with two responses lasting for ≥ 18 months. Additionally, a Phase II trial for patients with BCBM testing iniparib and irinotecan yielded a response rate of 12%, primarily attributed to irinotecan [57]. These data further support the preclinical evidence for the activity of irinotecan-based drugs within the brain.

Phase III BEACON trial results

The BrEAsT Cancer Outcomes with NKTR-102 (BEACON; NCT01492101) trial was a Phase III, open-label, randomized, multicenter study of EP versus TPC in patients with heavily pretreated, locally recurrent or MBC previously treated with an anthracycline, a taxane and capecitabine [58]. Eligible patients had received a minimum of two prior cytotoxic regimens for advanced disease and no more than five for breast cancer in any setting. The study was designed to compare the overall survival (OS) of patients treated with EP given every 3 weeks (n = 429) or a single-agent TPC (n = 423), a control arm that allowed investigators to choose one of seven commonly used cytotoxic drugs (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or *nab*-paclitaxel) administered

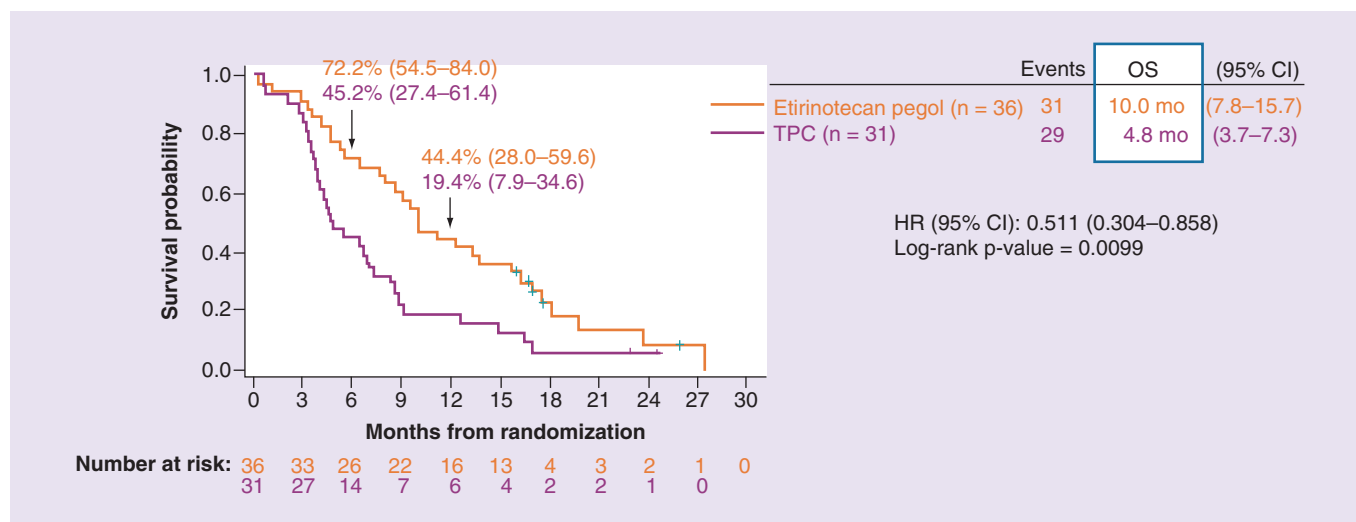


Figure 1. Kaplan-Meier plot of overall survival for patients with stable, treated brain metastases in the BEACON Phase III trial.

EP: Etirinotecan pegol; HR: Hazard ratio; OS: Overall survival; TPC: Treatment of physician's choice.

Created using data from Shah *et al.* [54].

according to local practice. Based on the preclinical data suggesting benefit, patients with a history of stable treated BM were eligible for inclusion and were specified as a subgroup of interest in the analysis plan prior to the final analysis of the trial. Ninety percent of the patients enrolled in the BEACON study had HER2-negative disease. Patients in both treatment groups received a median of three treatment cycles. In the overall study population, EP was associated with a 2.1-month median OS benefit over TPC (12.4 vs 10.3 months; $p = 0.084$); the hazard ratio (HR) of 0.87 (95% CI: 0.747–1.019) missed statistical significance. However, EP was associated with statistically significant survival improvements ($p < 0.05$) relative to TPC in important, prospectively defined subgroups with poor prognoses, including patients with liver metastases at baseline (median OS: 10.9 vs 8.3 months, respectively; HR: 0.73) and those with stable, pretreated BM at study entry as described below.

BM subgroup analysis

A total of 67 patients with a history of BM were randomized in the BEACON study. Eligibility criteria required previous treatment with surgical resection, WBRT and/or stereotactic radiation, use of corticosteroids for BM discontinued for ≥ 3 weeks prior to randomization, and that signs or symptoms of BM were stable for ≥ 28 days prior to randomization. No known progression of BM (as assessed by Response Evaluation Criteria in Solid Tumors [RECIST]) was permitted, and patients with leptomeningeal disease or meningeal carcinomatosis were excluded. In the primary survival analysis, 60 deaths occurred in the BCBM subgroup (EP: 31 [86%]; TPC: 29 [94%]). The prespecified BCBM subgroup analyses demonstrated a significant improvement in survival with a doubling of OS for patients receiving EP (10 months) versus TPC (4.8 months) [59]. This reduction in death resulted in a HR of 0.51 (95% CI: 0.304–0.858; $p < 0.01$) (Figure 1). The median OS of 4.8 months for patients with BCBM treated with TPC was consistent with reported median OS from previously published clinical studies in this setting, with OS ranges of 5.0 to 6.4 months [39]. EP was also associated with improvements in 6- and 12-month survival rates; corresponding to 72.2 and 45.2% for EP and TPC, respectively, and 44.4 and 19.4%, respectively (Figure 1). Median progression-free survival (PFS) was 3.1 months for EP and 2.7 months for TPC (HR: 0.840; 95% CI: 0.492–1.433; $p = 0.52$). In patients with measurable systemic disease, partial responses were observed in five of 32 (15.6%) patients treated with EP and 1 of 27 (3.7%) patients on TPC; there were no complete responses in either treatment group.

The survival trends favoring EP over TPC were also observed (*post hoc*) in 37 patients with radiographic evidence of brain lesions at baseline. Median OS for this subgroup was 13.2 months (95% CI: 8.6–19.6) for EP ($n = 19$) and 5.8 months (95% CI: 3.5–8.6) for TPC ($n = 18$). In order to correct for potential imbalances between the groups, the BEACON investigators undertook a *post hoc* evaluation utilizing the Graded Prognostic Assessment (GPA) Index, an assessment tool that assigns scores for significant prognostic indices of Karnofsky performance

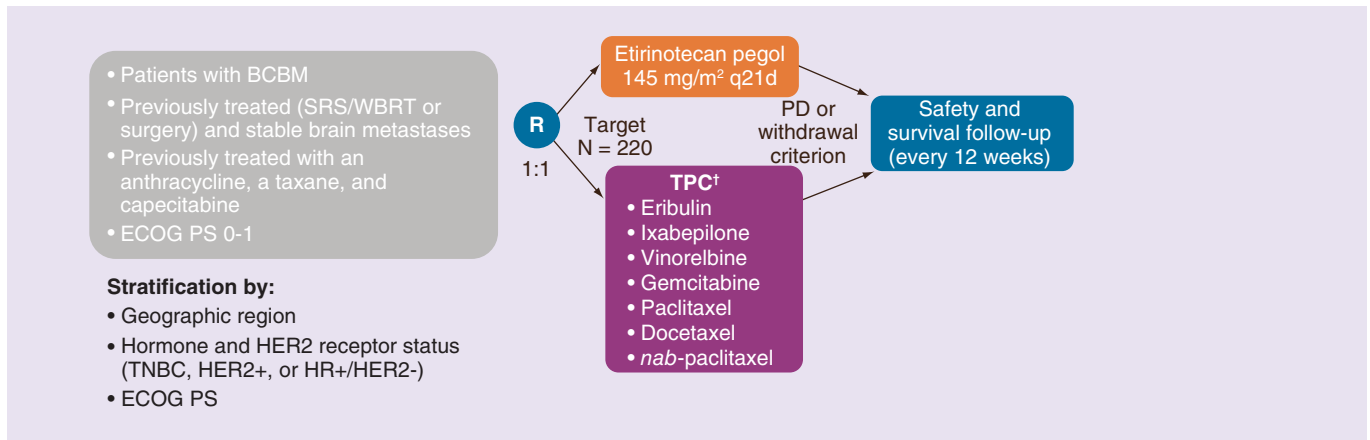


Figure 2. Study design.

†The agent must be available at the treating institution.

BCBM: Breast cancer brain metastases; ECOG: Eastern Cooperative Oncology Group; HR: Hormone receptor; PD: Progressive disease; PS: Performance status; q21d: Every 21 days; SRS: Stereotactic radiosurgery; TNBC: Triple-negative breast cancer; TPC: Treatment of physician's choice; WBRT: Whole-brain radiation therapy.

score (KPS), tumor subtype and age that was developed to predict prognosis in patients with newly diagnosed BM [24,25]. In these analyses, treatment with EP was associated with improved OS for patients in both better and worse prognosis groups; the HR for OS of the 67 patients after adjusting for the two GPA groups was 0.467 favoring EP, reinforcing the activity of EP in BCBM patients.

Safety of EP

The nature, scope and severity of the safety findings to date with EP have been clinically manageable and consistent. In the BEACON trial [58,60] and the BCBM subgroup [59], EP demonstrated a significantly lower rate of grade 3 or greater and dose-limiting/quality of life-reducing toxicities (notably neuropathy, myelosuppression and alopecia). EP was associated with more gastrointestinal toxicities, including diarrhea, with grade 3 diarrhea reported as 9.6 versus 1% in the entire BEACON population and 5.9 versus 3.7% in the BCBM subgroup for EP and TPC, respectively; no grade 4 diarrhea was reported.

In the analysis of patient-reported outcomes in the BEACON trial [61], there was evidence of benefit associated with EP compared with current standard of care agents in multiple Health-Related Quality of Life measurements, including global health status and physical functioning, despite worse gastrointestinal symptoms (e.g., diarrhea). Differences were seen favoring EP up to 32 weeks for global health status (GHS) and physical functioning scales ($p < 0.02$); numerical improvement was reported in other functional scales.

The encouraging survival findings, the favorable safety profile and quality of life findings among the BEACON study patients with BCBM together with the Phase II evidence of single-agent activity in recurrent high-grade primary brain tumors, provides strong rationale and justification for the further exploration of EP in patients with BCBM previously treated with an anthracycline, taxane and capecitabine.

ATTAIN study design

Study design & objectives

ATTAIN will randomize up to 220 patients to EP (145 mg/m² every 21 days [q21d] as a 90-min intravenous [iv.] infusion on day 1 of each treatment cycle) or to TPC consisting of single-agent iv. chemotherapy limited to one of the following seven agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel (administered [every 21 to 28 days] per standard of care) (Figure 2). Treatment will continue until disease progression per RECIST version 1.1 [62] and/or Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria [63], unacceptable toxicity, patient withdrawal, investigator decision, loss to follow-up, death, noncompliance, pregnancy or study termination by the sponsor. Crossover to EP is not allowed.

The investigator must determine at screening which TPC regimen will be offered to the patient as part of the informed consent process and provide that choice to the independent contract research organization responsible

Box 1. ATTAIN trial objectives.**Primary objective**

- To compare OS of patients who receive EP with OS of patients who receive TPC selected from the following list of seven single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or *nab*-paclitaxel

Secondary objectives

- To compare the ORR between the two treatments; assessment of tumor outside the CNS will use RECIST (version 1.1) criteria; assessment of CNS metastases will use RANO-BM criteria
- To compare PFS of the two treatments; assessment of tumor outside the CNS will use RECIST (version 1.1) criteria; assessment of CNS metastases will use RANO-BM
- To compare the CBR of the two treatments (i.e., the proportion of patients having CR, PR, or SD for at least 4 months); CBR for peripheral lesions and for CNS lesions will be separately described
- To compare DoR of the two treatments; peripheral lesions and CNS lesions will be separately described
- To compare the time to CNS disease progression in those patients with CNS lesions present at study entry
- To compare the time to CNS recurrence in those patients with without CNS lesions present at study entry
- To compare the incidence and cumulative frequency of WBRT after date of randomization
- To compare the time-to-WBRT in those patients who received WBRT after the date of randomization
- To evaluate the safety profiles of EP and TPC (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or *nab*-paclitaxel)
- To compare HRQoL between the two treatments using the EORTC QLQ C30 with the BN-20 questionnaire, EQ 5D-5L™ and the BFI
- To evaluate PK data (in patients randomized to EP only)
- To correlate presence of reduced function UGT1A1 variants with EP safety (in patients randomized to EP only)
- To evaluate the pharmacoeconomic implications of EP therapy using selected measures of health care utilization
- To evaluate the magnitude of clinical benefit using ESMO-MCBS

Exploratory objectives

- To identify biomarkers that correlate with ORR, PFS and OS

BFI: Brief Fatigue Inventory; BN-20: Brain neoplasms 20-question subscale; CBR: Clinical benefit rate; CR: Complete response; DoR: Duration of response; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; EP: Etrirotecan pegol; EQ 5D-5L™: EuroQol 5D questionnaire; ESMO-MCBS: European Society for Medical Oncology magnitude of clinical benefit scale; HRQoL: Health-related quality of life; ORR: Objective response rate; OS: Overall survival; PK: Pharmacokinetic; PR: Partial response; PFS: Progression-free survival; RANO-BM: Response Assessment in Neuro-Oncology Brain Metastases; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease; TPC: Treatment of physician's choice; WBRT: Whole-brain radiation therapy.

for creating and administering the randomization scheme. Patients will then be randomized centrally (1:1) via an interactive response system to EP or the registered TPC regimen for the individual patient. Patients will be stratified by geographic region (US vs rest of world), tumor receptor status (TNBC versus HER2-positive versus hormone receptor-positive/HER2-negative) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1).

The primary objective is to compare OS between the two treatment groups. Secondary and exploratory objectives are listed in [Box 1](#) and include objective response rate [outside the CNS (ORR) and in BM (ORR-BM)], PFS (outside the CNS, in BM [PFS-BM] and CNS plus peripheral [PFS-overall]), clinical benefit rate (CBR), duration of response (DoR), time to CNS progression in patients with CNS lesions present at study entry, time to CNS recurrence in patients without CNS lesions present at study entry, incidence and cumulative frequency of WBRT, time-to-WBRT in those patients who received WBRT after randomization, PK, correlation of reduced function UGT1A1 variants with EP safety, pharmacoeconomic implications, toxicity and health-related quality of life (HRQoL).

Eligibility criteria

Key eligibility criteria are listed in [Supplementary Table 1](#) and include patients willing and able to comply with the protocol and provide written informed consent prior to study-specific screening procedures, are female or male, age ≥ 18 years, and have histologically confirmed carcinoma of the breast (either primary or metastatic lesion) for which single-agent cytotoxic chemotherapy is indicated. Patients may have either measurable or non-measurable metastatic disease according to RECIST, version 1.1 but must have a history of BM that are non-progressing and that had been previously treated with either combination therapy (WBRT with stereotactic radiation and/or surgery)

≥ 14 days prior to randomization or single agent modality (WBRT, stereotactic radiation, or surgical resection, if combination therapy is contraindicated) ≥ 7 days prior to randomization. Patients must have sufficiently recovered from local BCBM treatment with stable signs and symptoms of BM per the investigator. For patients who have received WBRT, or stereotactic radiation and/or surgical resection ≥ 28 days prior to randomization, the signs or symptoms of BM must be stable ≥ 28 days prior to randomization. An eligible patient may therefore have received definitive local therapy within the 28-day screening period as long as clinically stable. Corticosteroids may be used as long as patients are on a stable or decreasing dose for ≥ 7 days prior to randomization. Prior systemic therapy (administered in the neoadjuvant, adjuvant and/or metastatic setting) must have included an anthracycline, a taxane and capecitabine (prior anthracycline may be omitted if not medically appropriate or contraindicated for the patient) and the last dose of chemotherapy must have been administered within 6 months of the date of randomization. Depending on receptor status, specific mandates for previous treatment with cytotoxic agents, hormonal therapy and/or HER2-targeted agents are required for eligibility (Supplementary Table 1). Of note, HER2-targeted therapy must be stopped in any patient with HER2-positive disease ≥ 14 days prior to randomization. Patients may have received an unlimited number of prior therapies for advanced breast cancer; minimum therapy is listed in Supplementary Table 1. Patients must have an ECOG performance status of 0 or 1 with demonstration of adequate organ function. All anticancer- and radiation therapy- related toxicities must be completely resolved or downgraded to grade 1 or less according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, except for diarrhea, which must be completely resolved to baseline without supportive antidiarrheal medications. Stable sensory neuropathy must be resolved to grade ≤ 2 , and alopecia can be any grade.

Planned sample size & study period

ATTAIN is expected to be conducted in 11 countries in three regions. Recruitment is ongoing with a planned accrual of up to 220 patients. The interim analysis for OS (in which the final number of projected events will be estimated) is anticipated to occur in the second half of 2019. Depending on the number of OS events required for the final analysis, the timing of the final analysis is currently expected to occur sometime between mid-2020 to early 2021.

Efficacy & safety evaluation

Clinical laboratory tests will be performed by a central laboratory and used to determine eligibility and treatment decisions; in situations where central laboratory results are not available, the Medical Monitor may approve use of a local laboratory. Demographics and baseline disease characteristics are collected at the screening visit, together with a physical examination, vital signs, bodyweight, medical history, complete blood count (CBC) with differential, serum chemistry, urinalysis, prothrombin time, tumor receptor status and a detailed history of prior cancer therapies, surgeries and radiotherapy. A serum pregnancy test is required at screening, ≤ 5 days prior to each cycle and at the end-of-treatment (EOT) visit.

Tumor assessments will be performed at screening, every 8 weeks (± 7 days) through week 24 and every 12 weeks (± 7 days) thereafter until documented disease progression (PD) or death. To ensure that both groups are assessed for progression in a similar manner, tumor assessments will be obtained at this interval, regardless of delays in chemotherapy due to toxicity. The same method of assessment and technique for acquisition of tumor assessment data must be used to characterize each identified and reported lesion at each measurement. All patients must have tumor assessments performed at the participating study center or a radiology facility associated with the site. Tumor measurements will be evaluated locally and centrally per RECIST and RANO-BM criteria for non-CNS and CNS disease, respectively. All tumor imaging (head, chest, abdomen and other as appropriate) and digital photography must be forwarded to a central imaging facility to permit blinded independent review (local assessment will be used for patient management and continue until PD).

The safety assessments include CBC with differential, serum chemistry, vital signs and symptom-directed physical exam ≤ 5 days prior to each cycle and EOT. Treatment decisions require results from the following tests: hemoglobin, absolute neutrophil count (ANC) and platelets. In addition, patients randomized to EP require testing for electrolytes (bicarbonate/ CO_2), calcium, chloride, potassium, sodium and serum creatinine. Additional requirements for TPC patients should follow institutional guidelines. Dose delays, reductions and discontinuations due to adverse events (AEs) are defined in the protocol for EP and made according to the prescribing information or local practice guidelines for TPC. Patients randomized to EP will receive loperamide for treatment of diarrhea

and/or prophylaxis (at the discretion of the investigator and/or patient preference in the absence of constipation starting with cycle 2 to mitigate the risk for late-onset diarrhea). Use of growth factor support in the setting of neutropenia is permitted and must follow American Society of Clinical Oncology (ASCO) guidelines, European Society for Medical Oncology (ESMO) guidelines, or standard of care at the local institution. Other supportive care and permitted and/or prohibited concomitant treatments are listed in [Supplementary Table 2](#).

All patients will complete HRQoL assessments, consisting of the European Organisation for Research and Treatment of Cancer (EORTC; version 3.0) Quality of Life Core 30 (QLQ-C30) with the brain neoplasms 20-question subscale (BN-20) questionnaire, the EuroQol 5D (EQ 5D 5L™) questionnaire, and the Brief Fatigue Inventory (BFI) on day 1 prior to infusion for each cycle and at EOT. If possible, patients should complete the questionnaire in the same setting each time. For those patients who consent, serial blood samples for biomarker analysis will be obtained prior to cycle 1 dosing, prior to cycle 2 dosing and at the EOT visit; analysis will consist of cell-free circulating tumor DNA using next-generation sequencing to correlate with efficacy. Additionally, patients randomized to EP will be tested for the following: presence of UGT1A1 gene alteration (cycle 1, day 1); PK analyses of EP, irinotecan and its metabolites SN38, SN38-glucuronide and 7-ethyl-10-(4-*N*-(5-aminopentanoic acid)-1-piperidine) carbonyloxycamptothecin (APC; prior to each dose); and, for those patients who consent, PEG-antibody measurements in blood (prior to cycle 1, prior to cycle 2 and EOT).

After discontinuation of therapy, all patients except those who withdraw consent will be followed (by contact via phone, clinic visit, or chart views) at least every 12 weeks (± 2 weeks) until death. If allowed by country regulatory authorities and consented to by the patient, study personnel may use public records to check for mortality for any patient considered lost to follow-up and for patients who withdraw consent for follow-up contact. Data will be collected on subsequent anticancer therapies in both treatment groups from the time patients come off the study treatment until the time of primary data analysis for OS.

Statistical considerations

The study uses an adaptive design powered for detecting superiority of EP compared with TPC for the primary efficacy end point of OS. The number of death events needed to provide 80% conditional power for the final analysis will be determined at an interim analysis when approximately 82 death events are available using the promising zone adaptive method [64]. Two-sided α of 0.001 will be used to test efficacy at the interim analysis. The minimum and maximum number of death events for the final analysis will be 106 and 191, respectively. The maximum (191) death events will be sufficient to demonstrate statistical significance for any observed hazard ratio of 0.75 or better, which corresponds to a median difference of approximately 2 months if the median OS for TPC is 6 months and the proportional hazard model assumption is approximately met. If OS does not reach statistical significance, event size needed for the final OS analysis will be determined based on conditional power per the adaptation rules described in the Data Monitoring Committee (DMC) charter.

The main efficacy analyses for the primary and secondary end points (except ORR and DoR) will be performed in the intention-to-treat (ITT) population (i.e., all randomized patients). The secondary end point analyses of ORR and DoR will utilize the Response Evaluable Population, which consists of all patients who are randomized in the study with measurable disease in the periphery by RECIST at baseline (as determined by the investigator). Safety analyses will be conducted in all patients who are randomized and receive at least one dose (or partial dose) of study drug (EP or TPC). The PK and biomarker populations will be those patients with sufficient data to permit analysis.

The primary analysis of OS will be the Cui, Hung and Wang (CHW) test with prespecified weights [65] to ensure type I error control and the conventional test with equal weights for every patient will be conducted as a sensitivity analysis. The hazard ratio (EP/TPC) and its 95% CI will be calculated using a Cox regression model adjusting for geographic region, tumor receptor status and ECOG. The two-sided significance level for superiority at final analysis of OS will be 0.0499. If more than 10% of the study population (i.e., >22 patients) received local treatment for CNS lesions (SRS, WBRT or surgery) during the study, the proportion of patients who received treatment for CNS lesions will be compared between treatment groups using Fisher's exact test. The impact of treatment for CNS lesions on OS will be evaluated using a Cox regression model comparing patients who received treatment for CNS lesions with those who did not. Additional secondary efficacy analyses will be undertaken, including (1) the difference in survival outcome depending on prior radiotherapy (SRS vs WBRT); (2) the extent of tumor burden at study entry (two or fewer vs three or more sites of disease); (3) the impact of liver metastases; and (4) the impact of removal of all patients selecting ixabepilone as the TPC agent.

Secondary end points (PFS, ORR, CBR and DoR) will be assessed by the investigator as well as by independent central review. Analysis for secondary end points will not include any adjustment for multiplicity. Statistical tests will be two-sided with a type I error rate of 0.05. Progression-free survival (PFS-outside the CNS, PFS-BM and PFS-overall) will be compared with a two-sided, log-rank test with the same stratification factors that were used for randomization. Two sensitivity analyses of PFS (outside the CNS) will be performed based on the censoring criteria with considerations of informative censoring as described in the statistical analysis plan. Kaplan–Meier median PFS times and their 95% CI, as well as PFS curves, will be summarized by treatment group. The hazard ratio (EP/TPC) and its 95% CI will be calculated using a Cox regression model adjusting for geographic region, tumor receptor status, and baseline ECOG status. The analysis of ORR will be performed using Fisher's exact test. Clinical benefit rate (defined as CR, PR or SD ≥ 4 months to reflect shorter life expectancy of the BM population) will be compared between the treatment groups using a Cochran Mantel–Haenszel test stratified by the randomization factors. Clopper Pearson exact two-sided 95% confidence limits will be calculated in determining the proportion of patients with ORR and CBR in each treatment group. Additionally, the magnitude of clinical benefit of EP will be assessed by the ESMO-magnitude of clinical benefit scale (ESMO-MCBS, version 1.0); this information will be summarized and applied to comparative outcome studies evaluating the relative benefit of treatments using outcomes of survival, quality of life, surrogate outcomes for survival, or treatment toxicity in solid cancers. Kaplan–Meier median DoR curves will be summarized by treatment group. DoR will be calculated based on the central imaging facility assessment of response and progression, as well as the investigator's assessment of response and progression. Incidence and frequency of WBRT, as well as time to WBRT, will be compared and summarized by treatment group. Summary statistics of absolute scores at each assessment point and changes from baseline will be calculated by treatment group for HRQoL measures. Changes from baseline will be compared between treatment groups using Repeated Measures Linear Mixed Effects and Generalized Linear Mixed Models Analyses. The safety analysis will be summarized by treatment group (EP and TPC) and further tabulated for each TPC drug. Additional safety analyses will be undertaken to investigate: (1) diarrhea, neutropenia, neuropathy and hypersensitivity reactions; (2) pulmonary toxicity including pneumonitis and interstitial lung disease; and, (3) the impact of prophylactic loperamide on the management of diarrhea. All additional analyses (laboratory, PK, UGT1A1 mutation, PEG-antibodies and biomarker) will be summarized with descriptive statistics; exploratory analyses will be undertaken to correlate selected biomarkers as well as the appearance of PEG-antibodies with ORR, PFS and OS.

Conclusion

There remains a critical need for therapeutic interventions that prolong patient survival and maintain or improve quality of life of patients with BCBM, in particular, using agents that are effective against both CNS and systemic disease. The lack of consensus regarding treatment and the lack of robust data supporting current clinical practices demonstrate the need for more controlled trials in this setting. Etirinotecan pegol (EP) is a next-generation, long-acting topoisomerase-1 inhibitor engineered to penetrate into the brain, provide sustained anti-tumor activity (systemically and within the CNS) and reduce systemic toxicities. The ATTAIN trial will compare the survival of patients receiving EP to that of standard of care agents in the treatment of patients with MBC and stable BM. The trial is a registration trial, which is currently actively recruiting eligible patients. If ATTAIN meets its primary end point, EP treatment will establish a new and much needed therapeutic option for patients with BCBM.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website. An infographic also accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2019-0180

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MA Tagliaferri is CMO at Nektar and has ownership interest (including stock, patents, etc.) in the same.

AL Hannah is a consultant to Nektar Therapeutics.

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Executive summary

Breast cancer brain metastases

- Breast cancer brain metastases (BCBM) remain a challenging consequence of advanced disease with cumulative incidence rates approaching or exceeding 35–50%, particularly in high-risk populations.
- The development of BCBM is associated with a poor prognosis and detrimental effects on quality of life.
- Treatment options for patients with BCBM following prior local surgery and/or radiotherapy remain limited with existing chemotherapy hindered by poor penetration and distribution into the CNS.
- As deemed a critical unmet medical need, there is increasing optimism and interest in exploring novel treatments for this challenging clinical problem.

Etirinotecan pegol (also called NKTR-102)

- Etirinotecan pegol (EP) is a next-generation, long-acting topoisomerase-1 inhibitor engineered to produce sustained exposure to irinotecan and its active metabolite SN38.
- A mouse xenograft model of BCBM demonstrated preferential accumulation of EP in brain tumors, a decrease in both tumor burden and lesion size and extended survival times compared with conventional irinotecan.
- Etirinotecan pegol avoids P-glycoprotein and BCRP/ABCG2-mediated efflux, providing a potential added benefit for uptake in brain lesions.
- In a prespecified subgroup analysis of the randomized Phase III BEACON trial, EP prolonged survival in patients with breast cancer and stable brain metastases (BM) compared with commonly used drugs for the treatment of advanced breast cancer.

The ATTAIN trial

- ATTAIN is a randomized Phase III trial of etirinotecan pegol (EP) versus treatment of physician's choice (TPC) in patients with MBC who have stable BM.
- Primary end point is overall survival.
- Key secondary end points include objective response rate, clinical benefit rate, duration of response and progression-free survival (assessed by local investigator and independent central review); additionally, review of CNS lesions will be performed using RANO-BM guidelines [63].
 - Other key secondary end points include time to CNS disease progression in patients with CNS lesions present at study entry, time to CNS recurrence in patients without CNS lesions present at study entry, toxicity, magnitude of clinical benefit assessed by the European Society for Medical Oncology magnitude of clinical benefit scale (ESMO-MCBS, v1.0), incidence and cumulative frequency of WBRT, time-to-WBRT in those patients who received WBRT and health-related quality of life.
- Eligibility includes patients with historically-confirmed breast cancer, either measurable or nonmeasurable metastatic disease, stable treated (whole-brain or stereotactic radiation and/or surgical resection) brain metastases, prior treatment with an anthracycline (unless not medically appropriate or contraindicated), a taxane and capecitabine administered in the neoadjuvant, adjuvant and/or metastatic setting (last dose of chemotherapy must have been administered within 6 months of randomization), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Depending on receptor status, 1 or 2 prior cytotoxic regimens are required prior to enrollment in this trial; hormonal and/or HER2-targeted agents may be required (minimum requirements for number of prior regimens may be found in [Supplementary Table 1](#)).
- This study will randomize patients 1:1 to either etirinotecan pegol 145 mg/m² as a 90-minute intravenous (iv.) infusion on day 1 of a 21-day cycle or to TPC (administered per standard of care) and stratified based on geographic region, tumor receptor status and ECOG status.
- Patients randomized to TPC will receive single-agent iv. chemotherapy, limited to choice of one of the following seven agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or *nab*-paclitaxel (doublet therapy, including trastuzumab-based doublets) are not permitted.
- The proposed sample size of 220 patients provides 80% power to detect a HR of 0.75 or better, corresponding to a 2-month increase in survival favoring etirinotecan pegol at a two-sided significance level of 0.05.
- This trial is expected to be conducted in 11 countries in three regions; for participating trial sites, please visit: <https://clinicaltrials.gov> and search NCT02915744.

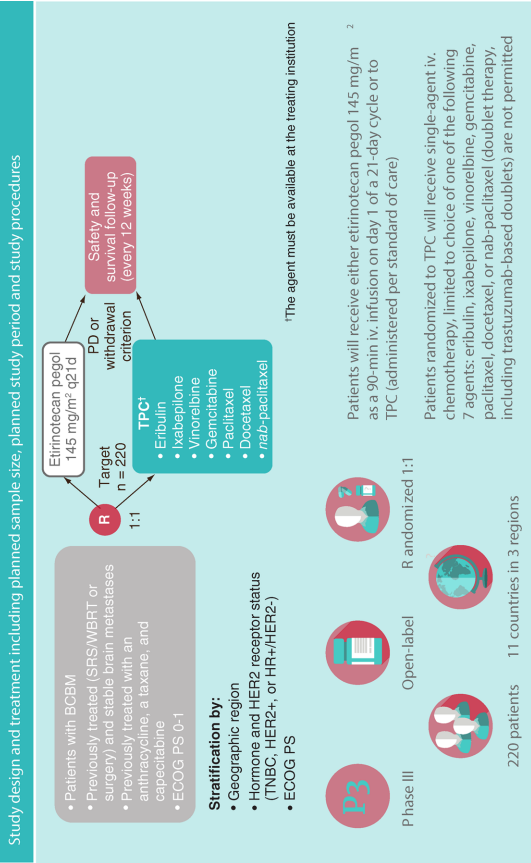
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Article details

Title of article
ATTAIN: Phase 3 study of etirinotecan pegol versus treatment of physician's choice in patients with metastatic breast cancer and brain metastases

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Trial registration number
NCT02915744

Primary objectives/rationale

Primary objective
Compare OS between the two treatment groups

Secondary and exploratory objectives
ORR (outside the CNS and in BM [ORR-BM]); PFS (outside the CNS, in BM [PFS-BM], and CNS plus peripheral [PFS-Overall]); CBR, DoR; time to CNS progression in patients with CNS lesions present at study entry, time to CNS recurrence in patients without CNS lesions present at study entry, incidence and cumulative frequency of , time-to-WBRT in those patients who received WBRT after randomization, PK, correlation of reduced function UGT1A1 variants with etirinotecan pegol safety, pharmacoeconomic implications, toxicity, and HRQoL

Key eligibility criteria

- 18+ Age ≥18 years
- Stable treated (whole-brain or stereotactic radiation and/or surgical resection) brain metastases
- ECOG 0 or 1
- Histologically-confirmed BC (either measurable or non-measurable metastatic disease)
- Prior treatment with an anthracycline (unless not medically appropriate or contraindicated), a taxane, and capecitabine administered in the neoadjuvant, adjuvant, and/or metastatic setting (last dose of chemotherapy must have been administered within 6 months of randomization)

Depending on receptor status, 1 or 2 prior cytotoxic regimen are required prior to enrollment in this trial; hormonal and/or HER2-targeted agents may be required

Glossary

BC: Breast cancer; BM: Brain metastases; CBR: Clinical benefit rate; DoR: Duration of response; ECOG: Eastern Cooperative Oncology Group; HER2: Human epidermal growth factor receptor 2; HRQoL: Health-related quality of life; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetics; TPC: Treatment of physician's choice; WBRT: Whole brain radiation therapy

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Outcome measures/end points

Primary end point:
OS

Secondary end points:
ORR, CBR, DoR, PFS