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TWO SCHEDULES OF ETIRINOTECAN PEGOL (NKTR-102) IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC BREAST CANCER: A RANDOMISED PHASE 2 STUDY

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ABSTRACT

Background New therapeutic options are needed for patients with heavily pretreated breast cancer. Etirinotecan pegol is a long-acting topoisomerase-I inhibitor designed to provide prolonged tumour-cell exposure to SN38, the active metabolite. We aimed to assess the efficacy and safety of two etirinotecan pegol dosing schedules in patients with previously treated metastatic breast cancer to determine an optimum dosing schedule for phase 3 trials.

Methods In this randomised, two-stage, open-label phase 2 trial, we recruited patients aged 18 years or older who had received taxane therapy and undergone two or fewer previous chemotherapy regimens for metastatic breast cancer, with an Eastern Cooperative Oncology Group performance status of 0 or 1, from 18 sites in three countries. Eligible patients were randomly assigned (1:1) to etirinotecan pegol 145 mg/m^2 every 14 days or every 21 days. The primary endpoint was the proportion of patients with a confirmed objective response as defined by Response Evaluation Criteria in Solid Tumors version 1.0, analysed by intention to treat. Safety was assessed in all patients who received at least one dose of study drug. This trial is registered at ClinicalTrials.gov, number NCT00802945.

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Findings 70 patients (35 in each group) were randomly assigned to treatment between Feb 17, 2009 and April 13, 2010. Of the 70 patients, 20 (29%; 95% CI 18.4-40.6) achieved an objective response (two [3%] had a complete response and 18 [26%] had a partial response). Ten patients on the 14-day schedule achieved an objective response (29%; 95% CI 14.6-46.3; eight partial responses, two complete responses) as did ten on the 21-day schedule (29%; 95% CI 14.6-46.3; all partial responses). The most common grade 3 or worse adverse events were delayed diarrhoea (seven [20%] of 35 patients on the 14-day schedule vs eight [23%] of 35 patients on the 21-day schedule), fatigue (five [14%] vs three [9%]), neutropenia (four [11%] vs four [11%]), and dehydration (three [9%] vs four [11%]); 14 [20%] patients discontinued treatment because of drug-related toxicity. There were two possible drug-related deaths (acute renal failure and septic shock) in the 14-day group; other drug-related serious adverse events reported by more than one patient included ten [14%] patients with diarrhoea (six [17%] patients on the 14-day schedule vs four [11%] on the 21-day schedule), six [9%] with dehydration (two [6%] vs four [11%]), two [3%] with nausea (two [6%] vs none), and two [3%] with vomiting (two [6%] vs none).

Interpretation On the basis of the overall clinical data, pharmacokinetics, and tolerability profile, etirinotecan pegol 145 mg/ m^2 every 21 days has been selected for a phase 3 trial against treatment of physician's choice in patients with advanced breast cancer.

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Introduction

With less than 25% of patients diagnosed with metastatic breast cancer surviving for 5 years, new treatments are urgently needed—especially for those patients who have disease progression after receiving anthracyclines, taxanes, and capecitabine.[1] The activity of newer drugs is unsatisfactory in these heavily pretreated patients—eg, only 9-12% of patients who receive eribulin and ixabepilone in this setting achieve an objective response, with median progression-free survival (PFS) between 2.6 months to 3.1 months.[2,3]

Etirinotecan pegol (NKTR-102) is a long-acting topoisomerase-I inhibitor derived from camptothecin. It consists of the topoisomerase-I inhibitor irinotecan bound to a proprietary polyethylene glycol core by a biodegradable linker. The linker slowly hydrolyses in vivo to form SN38, the active moiety of etirinotecan pegol. The drug is designed to provide continuous exposure to SN38 while reducing the toxicities associated with excessively high irinotecan and SN38 plasma concentrations reported in patients who receive irinotecan directly. In the initial phase 1 clinical trial,[4,5] etirinotecan pegol resulted in sustained and controlled exposure to SN38, which had a mean half-life of about 50 days. Preclinical and clinical studies of etirinotecan pegol have provided encouraging evidence of enhanced antitumour activity and less haematopoietic toxicity than with irinotecan.[6-12] In the phase 1 study,[4,5] three schedules of etirinotecan pegol were investigated, two of which (one dose every 2 or 3 weeks) established a recommended dose for future study of 145 mg/m^2. Although no dose-limiting toxicity was reported at this dose on either schedule, a dose of 145 mg/ m^2 was regarded as optimum for future investigation because of the long terminal elimination half-life of SN38 and the observation that four of 12 patients had grade 3 diarrhoea after the first cycle (the dose-limiting toxicity observation period). Etirinotecan pegol showed promising activity with confirmed partial responses reported in eight patients with various cancers, including a patient with triple-negative breast cancer, accompanied by limited myelotoxicity.[4,5]

Previously reported activity of irinotecan in patients with metastatic breast cancer supported the idea that exposure to a drug with a different mechanism of action from that of tubulin-targeted agents or antimetabolites might result in enhanced clinical benefit. In a phase 2 trial, an irinotecan dose of 100 mg/ m^2 per week had more favourable activity (objective response 23%; median PFS 2.8 months) than did a dose of 240 mg/m^2 every 3 weeks (objective response 14%; median PFS 1.9 months), suggesting that more continuous exposure to SN38 might be beneficial.[13]

In this phase 2 study, we aimed to assess the efficacy and safety of two different schedules of etirinotecan pegol in patients with metastatic breast cancer to provide further evidence for the best possible dosing schedule for future phase 3 investigations.

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Methods

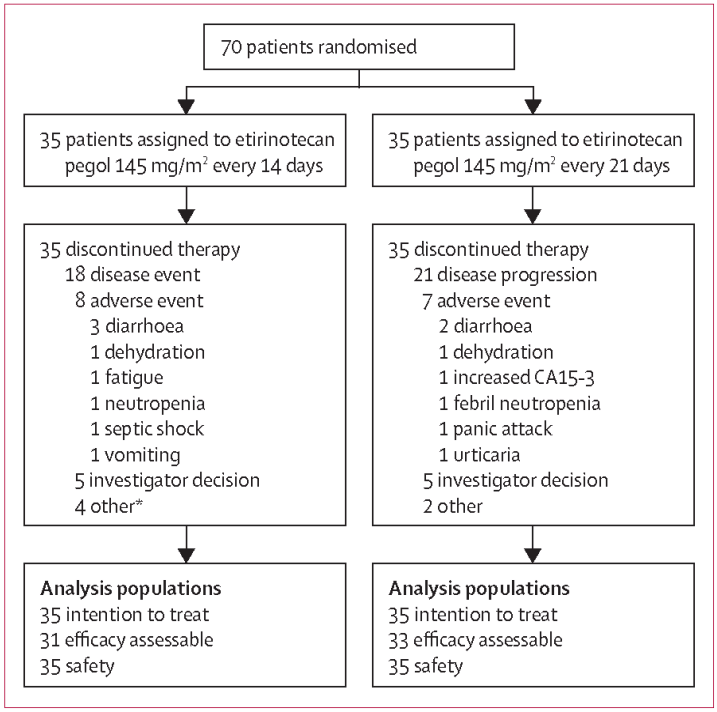
STUDY DESIGN AND PATIENTS

This study was a randomised, two-stage, open-label phase 2 trial that recruited patients from 18 sites in three countries (five sites in Belgium, seven sites in the USA, and six sites in the UK; appendix).

Eligible patients were those aged 18 years or older with inoperable metastatic breast cancer who had undergone two or fewer previous chemotherapy regimens in a metastatic setting, had received taxane therapy (adjuvant or metastatic setting), and had measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ and bone marrow function. Exclusion criteria consisted of chemotherapy, radiotherapy or major surgery within 4 weeks of enrolment, no recovery from grade 2 or worse toxicity from previous chemotherapy, concomitant use of biological agents (including bevacizumab or trastuzumab) or investigational agents, previous treatment with a camptothecin derivative, administration of cytochrome P450 inducers or inhibitors, pregnancy or lactation, a history of intolerance to pegylated drugs, CNS metastases, or inflammatory or unresolved bowel disease.

The protocol and patient materials (informed consent documentation and patient information forms) were approved by the independent ethics committee for each site. The study was done in accordance with the International Conference on Harmonisation guidelines concerning Good Clinical Practice and the Declaration of Helsinki. All participants provided informed consent.

Figure 1: *Trial profile*



*One patient was transferred to a continuation protocol.

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RANDOMISATION AND MASKING

Patients were randomly assigned (1:1) to two treatment groups: 145 mg/ m^2 etirinotecan pegol given every 14 or 21 days. Randomisation was done with an interactive voice or web response system by a contract research organisation (PPD, Wilmington, NC, USA). PPD also provided medical, clinical, pharmacovigilance, and database support, did regulatory filings, and offered interactive voice response system and drug supply support from study start throughout the trial. PPD (until Jan 1, 2010) and Nektar Therapeutics (Jan 1, 2010, onwards) reviewed patient eligibility data and provided approval for patients to proceed to randomisation. Stratification was not done. The system restricted the number of randomly assigned patients per site to ten. A permuted block size of two was used; the investigators and the sponsor were masked to the block size. Because of the nature of the two different dosing regimens, masking of the patients, investigators, and those analysing the data was not feasible.

PROCEDURES

Patients received etirinotecan pegol hydrochloride triflutate in lactate buffer (drug substance was made by Carbogen AMCIS, Bubendorf, Switzerland; drug product was manufactured by Baxter Oncology, Halle/Westfalen, Germany) at 145 mg/ m^2 every 14 days or 145 mg/ m^2 every 21 days as an intravenous infusion for 90 min. Patients continued to receive treatment every 14 or 21 days until disease progression, or unacceptable toxicity. Etirinotecan pegol was dose-reduced by 25 mg/m^2 for grade 3-4 haematological toxicity, grade 3-4 diarrhoea, or other grade 2-4 non-haematological toxicities (other than alopecia, anorexia, asthenia, untreated nausea, or vomiting). The re-treatment protocol required that a new cycle of therapy should not begin until the following were reached: neutrophils count of 1500 per µL or more; platelets count of 100000 per µL or more; haemoglobin count of 90 g/L or more, resolution of all treatment-related diarrhoea to grade 0, and recovery of any other treatment-related non- haematological grade 1 toxicity. The protocol recommended that diarrhoea be managed with loperamide, with a dose of 4 mg at the first instance of loose stool or diarrhoea, and thereafter 2 mg every 2 h (4 mg every 4 h at night) until diarrhoea cessation.

Myeloid growth factors were administered at the discretion of the investigator. Prophylactic premedications (including antihistamines, steroids, and atropine) were not needed.

Patients had a physical examination, serum CA27-29 test, complete blood count with a blood differential test, and serum chemistry analysis at screening, on the first dose of each cycle, and at end of treatment. Radiological examination occurred at screening (within 28 days of first day of treatment) and every 6 weeks thereafter until progressive disease, start of new anticancer therapy, or end of study. Patients were contacted every 3 months after the end of treatment to assess progression (in the absence of progression on study), survival, receipt of subsequent anticancer therapy, and resolution of toxicity.

Safety laboratory assessments were analysed at a central laboratory (Quest Diagnostics Clinical Trials, Valencia, CA, USA); local laboratories could be used for clinical management. We measured response by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0[14] and graded toxicities according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

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The primary endpoint was the proportion of patients who achieved an objective response (their best response to treatment at any time during the study), with confirmation of all responses by a second imaging procedure at least 28 days from the initial observation of response. Secondary endpoints were PFS (defined as time from randomisation to progression or death), overall survival, 6-month survival, 1-year survival, and safety. Exploratory analyses included assessment of change from baseline in CA27-29 concentration, and *UGT1A1* and *ABCC2* polymorphism status, and their associations with selected toxicities.

Table 1: *Baseline characteristics*

	Etirinotecan pegol 145 mg/m² every 14 days (n=35)	**Etirinotecan pegol 145 mg/m² every 21 days (n=35)**
Age, years	53.0 (33-83)	56.0 (37-77)
Women	34(97%)	35 (100%)
Ethnic origin		
White	31 (89%)	33 (94%)
Black	2 (6%)	2 (6%)
Asian	1 (3%)	0
Other	1 (3%)	0
ECOG performance status		
0	15 (43%)	13 (37.1%)
1	20 (57%)	22 (63%)
Postmenopausal	24 (71%)*	29 (83%)
Time from initial diagnosis to first dose of study drug, years	4.0 (0-15)	5.4 (1-19)
Time from initial diagnosis to metastatic disease, years	1.5 (0-7)	2.0 (0-12)
Receptor status		
Oestrogen-receptor positive	21 (60%)	20 (57%)
Progesterone-receptor positive	11 (31%)	13 (37%)
HER2 positive	3 (9%)	2 (6%)
Triple negative†	11 (31%)	10 (29%)
Visceral disease	28 (80%)	32(91%)
Number of previous cytotoxic regimens in metastatic setting	1.0 (0-3)	2.0 (0-2)
Any previous cytotoxic regimen in metastatic setting	34(97%)	34(97%)
1 previous cytotoxic regimen	17 (49%)	9 (26%)
2-3 previous cytotoxic regimens	17 (49%)	25 (71%)
Previous systemic treatments‡		
Taxane	35 (100%)	35 (100%)
Anthracycline	31 (89%)	31 (89%)
Capecitabine	9 (26%)	10 (29%)
Anthracyline/taxane	23 (66%)	21 (60%)
Anthracycline/taxane/capecitabine	8 (23%)	10 (29%)
Previous cytotoxic neoadjuvant or adjuvant therapy	27 (77%)	24 (69%)
Previous adjuvant anthracycline	15 (43%)	17 (49%)
Previous adjuvant taxane	9 (26%)	5 (14%)
Previous adjuvant anthracycline and/or taxane	19 (54%)	18 (51%)

Data are median (range) and number (%). ECOG=Eastern Cooperative Oncology Group. *Out of women only (n=34). †Oestrogen-receptor negative, progesterone-receptor negative, and HER2 negative. ‡In adjuvant or metastatic setting.

STATISTICAL ANALYSIS

The trial was not prospectively designed to compare the individual groups with each other, because a sample size of 35 patients per group would be insufficiently powered to show any

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significant result, nor was the trial intended to be compared with a historical control in breast cancer. We planned to assess the efficacy and safety in each group independently with Simon's two-stage design. For each group, patient enrolment occurred in two successive stages: during stage 1, 20 patients were to be enrolled and treated. If one or more responses were noted in 20 assessable patients per group, 15 additional patients would be enrolled in stage 2. If five or more of the 35 patients responded, the drug would meet the efficacy threshold. The sample sizes for each stage were chosen on the basis of the null hypothesis (ie, that 5% or fewer of patients assigned to the study drug would have an objective response according to RECIST criteria) and the alternative hypothesis (ie, that 20% or more of patients assigned to the study drug would have an objective response according to RECIST criteria). In previous studies, an objective response of 20% or greater was selected as showing promising antitumour activity that justified further clinical development, and an objective response of 5% or less was regarded as evidence of insufficient antitumour activity to justify further development; a null hypothesis using a 5% objective response has been used in similar phase 2 trials.[2,3,15,16] The type 1 error was 0.029 (target 0.050) and the type 2 error was 0445 (target 0.20).

We defined three populations for analysis: intention-to- treat, efficacy assessable, and safety. The intention-to- treat population was the primary population for all efficacy analyses and included all randomly assigned patients. The efficacy assessable population included all randomly assigned patients with measurable disease that had at least one tumour assessment after study drug administration or had disease progression or died within 6 weeks of the first study drug administration. The safety population consisted of all patients who received at least one dose of study drug.

Summary statistics were used for continuous variables, and frequency counts and percentages were used for categorical variables. 95% CIs were calculated for objective response using the exact method. Time-to-event variables were estimated using the Kaplan-Meier method. All analyses were done with SAS software version 9.1.3.

This study is registered at ClinicalTrials.gov, number NCT00802945.

ROLE OF THE FUNDING SOURCE

The sponsor of the study was involved in study design, data collection, data analysis, and interpretation of the results. During the study, the primary data were obtained and managed by the sponsor (including ALH and CZ); at study conclusion, data were analysed by statisticians employed by the sponsor (including CZ), and the detailed clinical study report was first drafted by the sponsor (including ALH) and made available to the corresponding author (AA). The Article was written by the corresponding author (AA), and was amended after review by all authors. The sponsor and corresponding author had full access to all raw data in the study; all authors had final responsibility for the decision to submit for publication.

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Results

Between Feb 17, 2009, and April 13, 2010, 70 patients were randomly assigned; 35 patients to each group (figure 1). At time of database lock, 69 patients were off study-drug treatment; one patient (with stable disease after 18 months of therapy) was transferred to a continuation protocol. The median age was 544 years (range 33-83), 28 (40%) patients had an ECOG performance status of 0, and 42 (60%) had an ECOG performance status of 1. The median number of cytotoxic regimens for metastatic breast cancer was two (range none to three; table 1); one patient, on the 14-day schedule, had been inappropriately enrolled because she had received three previous regimens for metastatic disease. All 70 patients had received a taxane (53 [76%] patients had received docetaxel; 28 [40%] patients had received paclitaxel); 62 (89%) patients had received a previous anthracycline (44 [63%] epirubicin; 17 [24%] doxorubicin; one [1%] mitoxantrone); 19 (27%) patients had received capecitabine. 15 (21%) patients had received previous bevacizumab (seven [20%] on the 14-day schedule and eight [23%] on the 21-day schedule). Baseline characteristics were generally balanced between groups with a small number of exceptions (table 1). Of the five patients with HER2-positive disease, all had received previous trastuzumab; none had received previous lapatinib.

Table 2. *Objective response in the intention-to-treat population*

	Etirinotecan pegol 145 mg/m² every 14 days (n=35)	**Etirinotecan pegol 145 mg/m² every 21 days (n=35)**
Objective tumour response*	10 (29%)	10 (29%)
95% exact CI	14.6-46.3	14.6-46.3
Complete response	2 (6%)	0
Partial response	8 (23%)	10 (29%)
Stable disease	16 (46%)	15 (43%)
>6 months	3 (9%)	7 (20%)
<6 months	13 (37%)	8 (23%)
Progressive disease	9 (26%)	10 (29%)
Clinical benefit†	13 (37%)	17 (49%)
95% exact CI	21.5-55.1	31.4-66.0
Median duration of response, months	8.3	4.2
95% CI of median	2.3-14.0	2.3-5.9

Data are number (%) or 95% CI. *Complete response or partial response. †Complete reponse, partial response, or stable disease for ≥6 months.

For both schedules, more than the minimum number of objective responses needed to move into the second stage of the study were recorded (four of the first 20 patients for the 14-day schedule; five of the first 20 patients for the 21-day schedule). A confirmed objective response was recorded in 20 (29%, 95% CI 18.4-40.6) of 70 patients in the intention-to-treat population (two with a complete response and 18 with a partial response); ten patients achieved an objective response in each dosing schedule (table 2). 13 (37%, 95% CI 214-55 4) patients on the 14-day schedule and 17 (49%, 31.4-66.0) patients on the 21-day schedule had some form of clinical benefit (either a confirmed partial or whole RECIST response, or maintenance of stable

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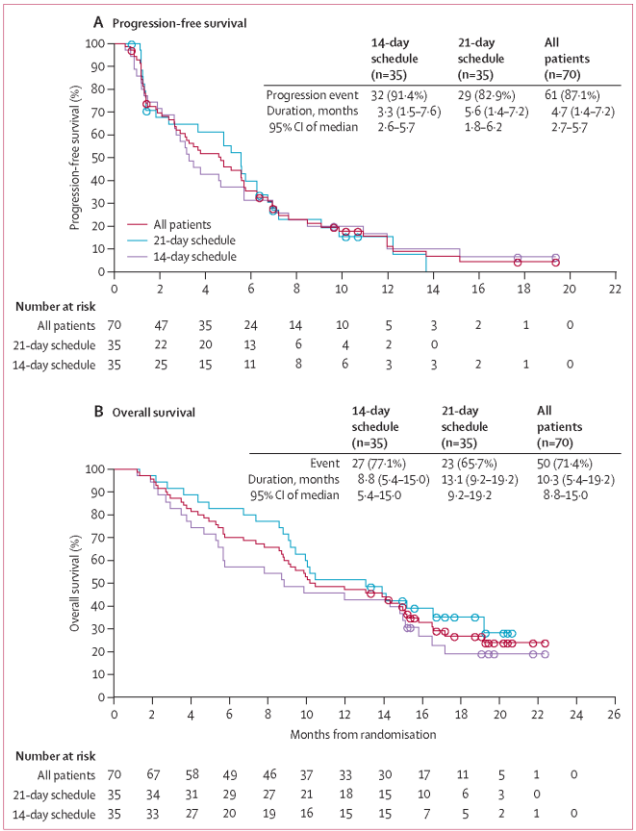
disease for ≥6 months; table 2). Of the 18 patients with a partial response, four (two [6%] in each group) had complete resolution of target lesions with unresolved non-target lesions (such as bone lesions).

Figure 2. **Secondary outcomes**



Progression-free survival (A) and overall survival (B) in the intention-to-treat population. Circles show censored patients. In the tables, data are number (%), median (IQR), and 95% CI. An event in (A) is either progression or death; and event in (B) is death.

The efficacy assessable population consisted of 64 patients: four patients on the 14-day schedule who did not have post-baseline tumour assessments were excluded because of patient withdrawal (n=2), an adverse event (n=1), and an investigator decision to remove the patient because of symptom deterioration (n=1); two patients on the 21-day schedule were excluded because of an adverse event (n=1) and an investigator decision because of symptom deterioration (n=1). For the efficacy assessable population, 20 (31%, 95% CI 20.2-44.1) patients achieved an objective response (ten in each group).

In the intention-to-treat population, median PFS was 4.7 months (95% CI 23-5 3). Overall, median PFS was 3 3 months (2.6-5.7) for patients on the 14-day schedule, and 5.6 months (1.8-6.2) for patients on the 21-day schedule (figure 2A). Median overall survival for the whole population was 10.3 months (95% CI 8.8-15.0); it was 8.8 months (5.4-15.0) for patients in the 14-day group and 13.1 months (9.2-19.2) for patients in the 21-day group (figure 2B). 6-month overall survival was 57.1% (95% CI 39.3-71.5) for patients on the 14-day schedule compared

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with 82.9% (65 3.8-91.9) patients on the 21-day schedule. 12-month overall survival was 423.9% (95% CI 26.4-58.3) and 51.4% (34.0-66.4), respectively.

In exploratory analyses, efficacy variables were further examined in subsets of patients who have the poorest outcomes—specifically, patients with triple-negative breast cancer and patients who had received previous anthracycline and taxane or anthracycline, taxane, and capecitabine. Measures of efficacy were generally more favourable for all patients on the 21-day schedule, particularly in patients who had previously received anthracycline, taxane, and capecitabine (table 3). Objective response outcomes were also calculated for patients who had received zero, one, or two to three cytotoxic regimens for metastatic disease (appendix).

The safety population consisted of all 70 patients. Patients in each group received a median of six cycles (range 1-40 in 14-day group; 1-21 in 21-day group), with a longer median duration of treatment for patients on the 21-day schedule than for those on the 14-day schedule (130 days [range 21-440] *vs* 98 days [14-560]); 15 patients (seven [20%] on the 14-day schedule and eight [23%] on the 21-day schedule) had more than 6 months of therapy. Patients on the 14-day schedule had a greater median dose intensity than did those on the 21-day schedule (70.9 mg/m^2 per week [range 42-76] *vs* 45.6 mg/m^2 per week [33-55]). In view of the long elimination half-life of SN38, dose delays were needed for ten (14%) patients overall with any-grade diarrhoea (six [17%] on the 14-day schedule *vs* four [11%] on the 21-day schedule; appendix). Dose delays and reductions were also required for ten (14%) patients with grade 2 or worse neutropenia (four [11%] *vs* six [17%]). Dose delay or reduction for grade 3 or worse toxicity occurred in 21 (30%) of the 70 patients (12 [34%] patients on the 14-day schedule *vs* nine [26%] patients on the 21-day schedule), including grade 3 diarrhoea, fatigue, and neutropenia. An additional 14 (20%) patients underwent dose delay or reduction for grade 1-2 toxicities (four [11%] *vs* ten [29%]; mainly dose delay for diarrhoea).

Both grade 3 and worse and serious adverse events occurred more frequently in patients on the 14-day schedule than in those on the 21-day schedule (table 4). The most common grade 3 or worse treatment-emergent adverse events across schedules were diarrhoea, fatigue, dehydration, neutropenia, and vomiting (table 4). There were two possible drug-related deaths (acute renal failure and septic shock) in the 14-day group; other drug- related serious adverse events reported by more than one patient included ten [14%] patients with diarrhoea (six [17%] patients on the 14-day schedule *vs* four [11%] on the 21-day schedule), six [9%] with dehydration (two [6%] *vs* four [11%]), two [3%] with nausea (two [6%] *vs* none), and two [3%] with vomiting (two [6%] *vs* none).

Of the 15 patients who developed grade 3 or worse diarrhoea, one event was of grade 4 severity, occurring in a patient on the 14-day schedule. Grade 3 or worse diarrhoea occurred with a median onset of 88 days (range 1-121) in the 14-day group and 90 days (8-107) in the 21-day group. The median duration of grade 3 or worse diarrhoea was 8.5 days (1-16) in patients on the 14-day schedule and 16 days (2-39) in those on the 21-day schedule. Review of the 51 patients who developed diarrhoea of any grade revealed that the protocol- stipulated antidiarrhoeal supportive care and retreatment guidelines were not followed for 30 patients (59%). This number included ten patients who did not receive any antidiarrhoeal supportive care, 15 patients who were administered etirinotecan pegol in a setting of unresolved diarrhoea, and failure to dose reduce for grade 3 or worse diarrhoea in one patient. Additional patients were

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not compliant with loperamide administration guidelines (not initiating treatment with grade 1-2 diarrhoea, as required by the protocol). One patient might have had toxicity that was consistent with an anticholinergic syndrome consisting of mild diarrhoea, watery eyes, blurred vision, and salivary hypersecretion that occurred once on study day 85; this patient was given atropine and the symptoms resolved in 1 day without recurrence on re-treatment.

Myelosuppression was infrequent. Grade 3 or worse neutropenia occurred in four patients, anaemia in one patient, and thrombocytopenia in one patient on the 14-day schedule and in four patients, one patient, and no patients, respectively, on the 21-day schedule. Neutropenia of any grade occurred in 13 (19%) of 70 patients (six [17%] patients on the 14-day schedule *vs* seven [20%] patients on the 21-day schedule), with febrile neutropenia occurring in one patient. Alopecia was rare (ten patients with grade 1; one patient with grade 2). No cardiotoxicity of any grade was reported.

The proportion of patients who discontinued study drug because of drug-related adverse events was similar between groups (eight [23%] patients on the 14-day schedule and six [17%] patients on the 21-day schedule). Diarrhoea led to discontinuation in three (9%) patients on the 14-day schedule and two (6%) on the 21-day schedule.

Overall, four people died within the 30-day period after the last dose of study drug. Of these, two were considered possibly related to etirinotecan pegol and occurred in patients on the 14-day schedule (one patient with acute renal failure and one with septic shock). The other two deaths that occurred within 30 days of last dose were thought to be related to disease progression (one patient on each schedule). Six additional patients were listed as having a fatal adverse event more than 30 days after last dose of study drug, none of which was thought to be related to study drug. These adverse events included disease progression (four patients), pneumonia (one patient), and pneumonitis (one patient).

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Table3. *Subgroup analysis of efficacy variables*

	Etirinotecan pegol 145 mg/m² every 14 day (n=35)	**Etirinotecan pegol 145 mg/m² every 21 days (n=35)**
Triple-negative breast cancer	n=11	n=10
Objective response*	2 (18%, 2.3-51.8)	5 (50%, 18.7-81.3)
Clinical benefit†	3 (27%, 6.0-61.0)	5 (50%, 18.7-81.3)
Progression-free survival		
Progressed and/or died	11 (100%)	10 (100%)
Duration, months	2.9 (0.9-5.7)	4.8 (1.2-5.6)
Overall survival		
Died	11 (100%)	8 (80%)
Duration, months	5.7 (2.1-15.1)	9.1 (2.2-10.4)
Anthracycline and taxane	n=23	n=21
Objective response*	7 (30%, 13.2-52.9)	5 (24%, 8.2-47.2)
Clinical benefit†	9 (39%, 19.7-61.5)	8 (38%, 18.1-61.6)
Progression-free survival		
Progressed and/or died	21 (91%)	17(81%)
Duration, months	3.2 (1.5-6.9)	5.1 (1.4-7.2)
Overall survival		
Died	17 (74%)	13 (62%)
Duration, months	12.0 (5.4-15.8)	13.9 (8.6-NE)
Anthracycline, taxane, and capecitabine	n=8	n=10
Objective response*	2 (25%, 3.2-65.1)	4 (40%, 12.2-73.8)
Clinical benefit†	2 (25%, 3.2-65.1)	7 (70%, 34.8-93.3)
Progression-free survival		
Progressed and/or died	7 (88%)	9 (90%)
Duration, months	3.8 (1.3-10.9)	6.2 (1.1-9.1)
Overall survival		
Died	6 (75%)	6 (60%)
Duration, months	8.2 (2.1-NE)	12.7 (3.6-NE)

Data are number (%, 95% CI), number (%), or median (95% CI). NE=not estimable. *Complete response or partial response. †Complete reponse, partial response, or stable disease for ≥6 months.

We used data from the 43 patients who had pretreatment and post-treatment measurements of CA27-29 in our exploratory analyses to assess the correlation between a change in CA27-29 concentration and tumour size (figure 3). Of the 15 patients within this subset with a complete or partial response, 14 (93%) had at least a 10% decline in CA27-29; five (83%) of six patients who had stable disease for 6 months or longer also had a 10% or greater reduction in CA27-29. Of the 11 patients with progressive disease, nine (82%) patients had increases in CA27-29 from baseline.

Further exploratory analyses included assessment of *UGT1A1* and *ABCC2* polymorphisms and their association with the incidence of selected toxicities. *UGT1A1* status was available for 66 patients; however, only five patients were poor metabolisers (ie, they had TA 7/7, 7/8, or 8/8 genotypes). No association between *UGT1A1* status and either neutropenia or diarrhoea could be made. *ABCC2* status was also available for 66 patients. Only two patients were homozygous

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for the *ABCC2* 24C→T mutation, and three patients were homozygous for the ABCC2 3972G→A mutation; no obvious pattern for neutropenia or diarrhoea was seen. A separate population-based analysis of combined phase 1 and 2 data for these polymorphisms is underway.

Table 4. *Adverse events*

	Etirinotecan pegol 145 mg/m² every				Etirinotecan pegol 145 mg/m²				All patients (n=70)			
	All grades	Grade 3	Grade 4	Grade	All grades	Grade 3	Grade	Grade 5	All grades	Grade 3	Grade	Grade 5
Treatment-emergent AEs occurring in >10% of patients and all grade 5 AEs												
Diarrhoea	24 (69%)	6 (17%)	1 (3%)	0	27 (77%)	8 (23%)	0	0	51 (73%)	14	1 (1%)	0
Nausea	25 (71%)	2 (6%)	0	0	26 (74%)	1 (3%)	0	0	51 (73%)	3 (4%)	0	0
Fatigue	15 (43%)	5 (14%)	0	0	18 (51%)	3 (9%)	0	0	33(47%)	8 (11%)	0	0
Vomiting	19 (54%)	3 (9%)	0	0	14 (40%)	2 (6%)	0	0	33(47%)	5 (7%)	0	0
Decreased appetite	14 (40%)	1 (3%)	0	0	12 (34%)	0	0	0	26 (37%)	1 (1%)	0	0
Constipation	14 (40%)	0	0	0	9 (26%)	0	0	0	23 (33%)	0	0	0
Abdominal pain	7 (20%)	1 (3%)	0	0	8 (23%)	0	0	0	15 (21%)	1 (1%)	0	0
Blurred vision	9 (26%)	0	0	0	6 (17%)	0	0	0	15 (21%)	0	0	0
Dehydration	7 (20%)	3 (9%)	0	0	6 (17%)	4 (11%)	0	0	13 (19%)	7 (10%)	0	0
Neutropenia	6 (17%)	2 (6%)	2 (6%)	0	7 (20%)	3 (9%)	1 (3%)	0	13 (19%)	5 (7%)	3 (4%)	0
Alopecia	7 (20%)	0	0	0	4 (11%)	0	0	0	11 (16%)	0	0	0
Anaemia	6 (17%)	1 (3%)	0	0	4 (11%)	0	1 (3%)	0	10 (14%)	1 (1%)	1 (1%)	0
Decreased weight	3 (9%)	0	0	0	7 (20%)	0	0	0	10 (14%)	0	0	0
Dyspnea	6 (17%)	1 (3%)	0	0	3 (9%)	0	0	0	9 (13%)	1 (1%)	0	0
Headache	4 (11%)	0	0	0	4 (11%)	0	0	0	8 (11%)	0	0	0
Lethargy	3 (9%)	1 (3%)	0	0	5 (14%)	0	0	0	8 (11%)	1 (1%)	0	0
Pyrexia	5 (14%)	0	0	0	3 (9%)	0	0	0	8 (11%)	0	0	0
Upper-abdominal pain	3 (9%)	0	0	0	4 (11%)	0	0	0	7 (10%)	0	0	0
Dizziness	4 (11%)	1 (3%)	0	0	3 (9%)	1 (3%)	0	0	7 (10%)	2 (3%)	0	0
Dry mouth	3 (9%)	0	0	0	4 (11%)	0	0	0	7 (10%)	0	0	0
Dysgeusia	3 (9%)	0	0	0	4 (11%)	0	0	0	7 (10%)	0	0	0
Acute renal failure*	1 (3%)	0	0	1 (3%)	0	0	0	0	1 (1%)	0	0	1 (1%)
Septic shock*	1 (3%)	0	0	1 (3%)	0	0	0	0	1 (1%)	0	0	1 (1%)
Any treatment-emergent AEs occurring in all patients												
Any treatment-	35 (100%)	13	3 (9%)	3 (9%)	35	14	3 (9%)	1 (3%)	70	27	6 (9%)	4 (6%)
≥1 serious AE	18 (51%)	••	••	••	15 (43%)	••	••	••	33(47%)	••	••	••

Data are number of patients who had an event (% of patients). AE=adverse event. *These toxicities were thought to be possibly drug-related fatalities and are listed despite not meeting the threshold of at least 10% incidence

Discussion

In this randomised phase 2 trial, single-agent etirinotecan pegol showed clinical activity in pretreated patients with aggressive advanced breast cancer, thus validating previous phase 2 data that showed anticancer activity for topoisomerase inhibition in advanced disease.[13]

For patients with incurable, advanced breast cancer, chemotherapy is directed at extending life while maintaining a reasonable quality of life. As such, standard of care is typically sequential single-agent therapy at maximally tolerated doses. Etirinotecan pegol exceeded the efficacy

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threshold of five or more responses per group, with ten of 35 patients in each treatment schedule responding to treatment, including patients with visceral disease. Toxicity was mainly gastrointestinal; myelosuppression was rare, cardiotoxicity and neurotoxicity were absent, and alopecia was minimal. Placing these results in context (panel), studies assessing single-agent intravenous compounds ixabepilone,[2,17] eribulin,[3,16,18] and albuminbound paclitaxel[19] (comparing two doses) reported objective responses of 12%, 9-12%, and 14-16%, respectively, for patients with advanced breast cancer who had received a previous anthracycline or taxane (toxicities typically included severe myelosuppression, neuropathy, and alopecia). The oral compounds sunitinib,[20,21] capecitabine,[21] sorafenib,[22] and everolimus[23] produced objective responses of 11%, 16%, 0%, and 12%, respectively; common toxicities included fatigue, gastrointestinal toxicity (nausea, diarrhoea, and anorexia), skin rash, and mucositis. Median PFS for the intravenous compounds was 2.2-3.1 months (ixabepilone), 2.6-3.7 months (eribulin), and 3.0-3.5 months (albumin-bound paclitaxel); for the oral compounds, PFS was 2.8 months (sunitinib), 4.2 months (capecitabine), and 2.0 months (sorafenib), and was not reported for everolimus.

Although the proportion of patients who achieved an objective response was identical between the two schedules, etirinotecan pegol on the 21-day schedule had a generally more favourable toxicity profile despite the extended time on study. Patients on the 21-day schedule had less drug-related grade 3 or worse toxicity and fewer discontinued because of drug-related toxicity than did those on the 14-day schedule, and no grade 4 diarrhoea or drug-related deaths was reported in this group. A comparison of baseline demographics between the two groups did not show any substantial difference to account for this difference in tolerability. Some characteristics might favour the 21-day schedule group (slightly younger age, longer median time from primary diagnosis to study entry, and longer median time from diagnosis of metastatic disease to study entry); however, other characteristics might favour the 14-day schedule group (fewer patients with an ECOG performance status of 1, fewer patients with visceral disease, and a lower average number of previous cytotoxic regimens for advanced disease).

Phase 2 trials investigating several doses, schedules, or infusion lengths are common in breast cancer, providing crucial information about the best possible administration of a cytotoxic drug for future phase 3 investigations. Recent examples include trials of ixabepilone,[17] eribulin,[16] albumin-bound paclitaxel,[19] and everolimus.[23] The results of our randomised phase 2 study led to selection of the 21-day schedule for a subsequent phase 3 trial comparing etirinotecan pegol in patients with advanced breast cancer with a treatment of physician's choice (NCT01492101).

Etirinotecan pegol showed efficacy in subsets of patients with triple-negative breast cancer and those who had previously received anthracycline, taxane, and capecitabine. Although numbers of patients in each of these subgroups was small, efficacy was generally more favourable with the 21-day schedule and compared favourably with responses seen with other single agents.[2,3,24-28] Although our results seem promising they are based on small subsets of patients and intertrial comparisons should always be viewed with caution.

Delayed diarrhoea was the most common serious toxicity associated with etirinotecan pegol. Compliance with protocol-stipulated antidiarrhoeal supportive care, re-treatment guidelines, and dose reduction for grade 3 or worse diarrhoea was regarded as unacceptable in 30 (59%) of

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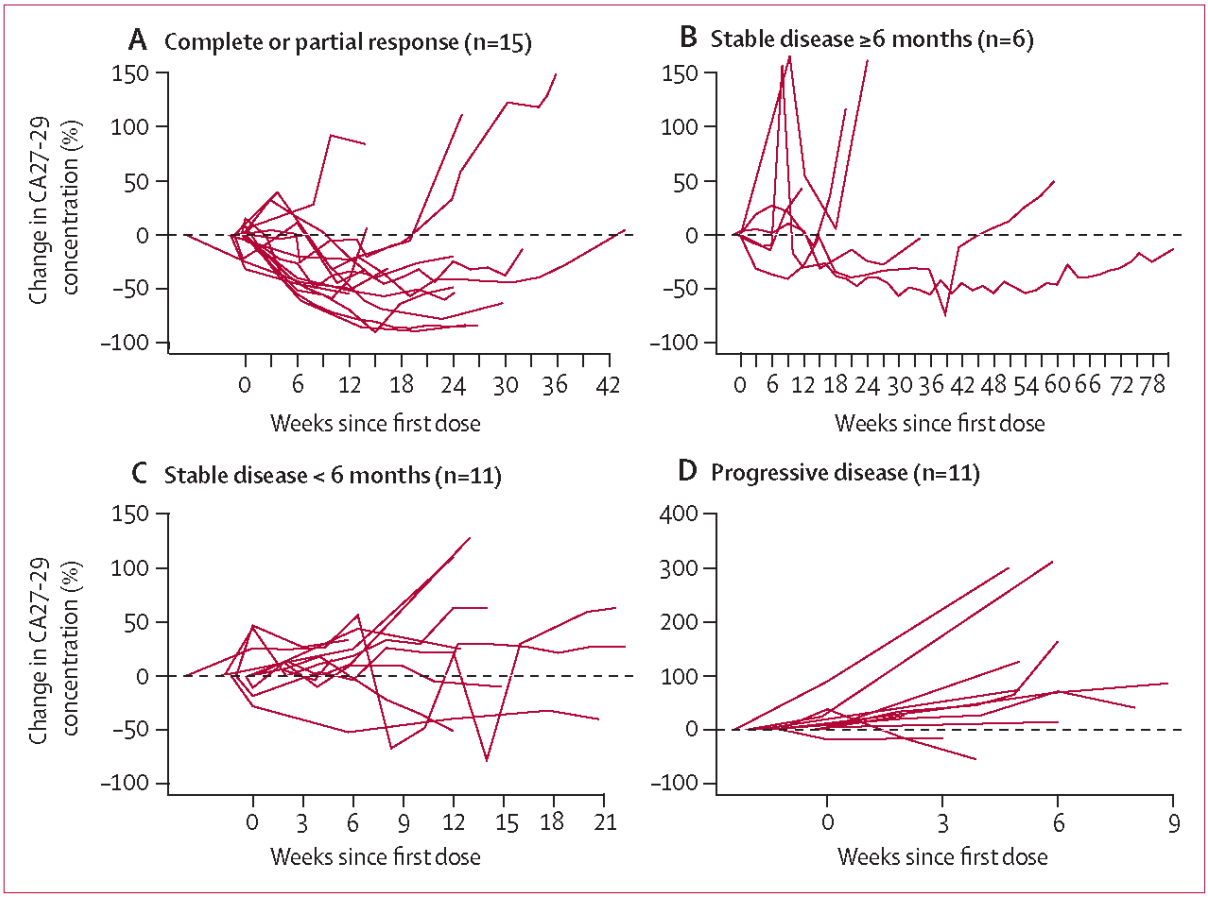
the 51 patients who reported at least one episode of diarrhoea. Increased monitoring of antidiarrhoeal supportive care and re-treatment practices in continuing etirinotecan pegol trials is in place to assure that patients receive appropriate care at first occurrence, lowering the risk of escalation to more severe toxicity. Treatment delays to allow resolution of diarrhoea can be implemented without interruption of continuous exposure to SN38.

Figure 3. *Change in serum CA27-29 over time, by response*



Percentage change in CA27-29 over time in patients with a complete or partial response (A), stable disease for 6 months or longer (B), stable disease for less than 6 months (C), and progressive disease (D) as defined by Response Evaluation Criteria in Solid Tumors (version 1.0). Solid lines represent individual patients. Datapoints above the dotted horizontal line show an increase in CA27-19 from baseline; datapoints below the dotted horizontal line show a decrease in CA27-19 from baseline. The first CA27-29 measurement was obtained during the 28-day screening period, not immediately before dosing at week 0. CA27-29=cancer antigen 27-29.

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***Panel*: Research in context**

Systematic review

We searched PubMed and the American Society of Clinical Oncology database for reports published in English between Jan 1, 2007, and Aug 1, 2013, with the terms "breast cancer", "phase 2", or "phase II", and "taxane and anthracycline resistant". Clinical trials for the following single-agent chemotherapeutics were discovered: ixabepilone,[24547] eribulin,[348] albumin-bound paclitaxel,[19] sunitinib,[20-21] sorafenib,[22] capecitabine,[21] and everolimus.[23] The anticancer mechanism of action varies for these drugs: ixabepilone, eribulin, and albumin-bound paclitaxel (all intravenous) target tubulin; sunitinib and sorafenib (oral) each target multiple receptor tyrosine kinases; capecitabine is regarded as an antimetabolite; and everolimus targets mTOR. We searched the published clinical trials for signs of anticancer activity, including the proportions of patients who achieved an objective response and progression-free survival. Overall survival was not uniformly reported.

Interpretation

The results of our randomised phase 2 study, when combined with those of previous phase 2 trials and other related studies, led to the selection of the 21-day schedule for a subsequent phase 3 trial comparing etirinotecan pegol to treatment of physician's choice in patients with breast cancer whose disease had progressed after receiving anthracycline, taxane, and capecitabine.

As shown in the phase 1 clinical trial,[5] the plasma concentrations of both irinotecan and SN38 after etirinotecan pegol administration showed that there was sustained and controlled systemic exposure, which probably contributed to the absence of cholinergic toxicities and low rate of neutropenia, while maintaining evidence of antitumour response. Maximal irinotecan plasma concentrations—the moiety responsible for cholinergic toxicities temporarily associated with an irinotecan infusion (eg, rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis)—are about 35 times lower with etirinotecan pegol than with typical irinotecan administration.[29] These lower plasma concentrations are probably contributing to the absence of cholinergic toxicities with etirinotecan pegol, precluding the necessity of atropine premedication before etirinotecan pegol infusions. Similarly, maximal SN38 concentrations are at least 6-10 times lower with etirinotecan pegol than with standard irinotecan administration, possibly decreasing the incidence of severe neutropenia, which was infrequent after administration of etirinotecan pegol, occurring in just four patients in each group without any neutropenia-related deaths. Several other toxicities associated with common chemotherapies used in breast cancer were absent or occurred at a low frequency in this trial, including neuropathy, alopecia, and cardiotoxicity. This tolerability profile suggests that etirinotecan pegol offers a treatment option with a different toxicity profile compared with other frequently used chemotherapy agents for breast cancer.

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Contributors

All authors were involved in the writing of the report and approved the final draft. AA, AAG, SC, GHMJ, REC, MTH, AM, SMO'R, JTH, PJB-L, VC, KS, DEY, and EAP were involved in data collection. AA, AAG, and EAP were involved in study design, data analysis, and interpretation. ALH, CZ, YLC, and UH were also involved in data analysis and interpretation.

Conflicts of interest

REC has received honoraria from Amgen and has provided expert testimony to Novartis. AM has received research funding from Stockton Hematology Oncology Medical Group. DEY has received research funding from Nektar Therapeutics. ALH is a consultant to Nektar Therapeutics. CZ, YLC, and UH are employed by Nektar Therapeutics, and CZ and YLC own stocks in Nektar Therapeutics. All other authors declare that they have no conflicts of interest.

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