

ANGLO CELTIC COOPERATIVE ONCOLOGY GROUP
CLINICAL TRIAL PROTOCOL

ANGLO CELTIC IV
“Will Weekly Win” www.taxol-uk.com

Will Weekly Win for Taxol in the UK: Comparison of Outcomes in Metastatic and locally advanced breast cancer with weekly vs. 3 weekly administration of paclitaxel

Trial Administration by:
SCOTTISH CANCER THERAPY NETWORK

Study No: BR 0201

Study Title: A randomised 2-arm, prospective, multi-centre, open-label Phase III trial comparing the activity and safety of a weekly versus a 3 weekly Paclitaxel treatment schedule in patients with advanced or metastatic breast cancer

Approved	
_____	Date
Dr Mark Verrill Principal Investigator	

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1. OVERVIEW

Rationale:

Paclitaxel (Taxol™) has significant antitumour activity in patients with metastatic breast cancer who either relapse after or are resistant to an anthracycline based treatment. In the UK, this indication has been endorsed by guidance from the National Institute of Clinical Excellence (NICE). In this setting, paclitaxel is usually given as a 3-hour IV infusion at a dose of 175 mg/m² every 3 weeks. Weekly paclitaxel schedules have been developed with the aim of optimising dose density, activity and toxicity. An initial report by Seidman et al. suggested weekly paclitaxel treatment to be more active and better tolerated than 3-weekly treatment.

In this study time to progression, response rate and toxicity using a weekly regimen will be compared to that using the standard 3-weekly schedule. In the experimental arm, Paclitaxel will be given as a 1-hour infusion at a dose of 90 mg/m² every week, (planned dose intensity 90 mg/m²/week). In the reference arm, Paclitaxel will be given as a 3-hour infusion at a dose of 175 mg/m² every 3 weeks, (planned dose intensity 58.3 mg/m²/week) for a maximum of 6 cycles. Inter-patient variations in the expression of genes involved in paclitaxel metabolism and distribution will also be studied.

The total dose of Paclitaxel in the reference and experimental arms will be balanced by restricting the maximum duration of treatment in the weekly arm to 12 weeks. In this way, the trial will be drug-cost neutral and will explore whether dose intensity and schedule of paclitaxel are important when maximum total drug dose is balanced in the two trial arms.

The administration time of Paclitaxel in the weekly arm will be reduced to 1 hour. Dexamethasone premedication will be reduced, compared to that recommended in the drug data sheet, in both arms of the study.

Co-administration of trastuzumab (Herceptin™) is strongly recommended for those patients whose tumours over express HER-2. Use of trastuzumab will be a stratification factor.

Objectives:

Primary Objectives:

- To compare the antitumour efficacy of weekly versus 3-weekly Paclitaxel as determined by the time to disease progression
- To study polymorphisms in the genes responsible for paclitaxel metabolism and link these to response rates and toxicity

Secondary Objectives:

- To compare the toxicity of weekly versus 3-weekly Paclitaxel
- To compare the response rate of weekly vs 3-weekly Paclitaxel
- To compare overall survival in patients receiving weekly versus 3-weekly Paclitaxel
- To compare quality of life in patients receiving weekly versus 3-weekly Paclitaxel

Duration of Treatment:

Patients will be treated for a maximum of 6 cycles of paclitaxel (18 weeks) in the 3 weekly arm or a maximum of 12 (weekly) cycles of paclitaxel in the weekly arm. Treatment will cease if there is evidence of either disease progression or unacceptable toxicity.

Study Design and Methodology:

This is a randomized two arm, prospective, multi-centre, open-label phase III trial comparing the activity and safety of a weekly versus a 3-weekly Paclitaxel treatment schedule in patients with advanced or metastatic breast cancer.

The following treatment will be given:

ARM 1 (experimental arm or weekly arm)

Paclitaxel: 90 mg/m² IV over 1 hour on day 1 every week.

ARM 2 (reference arm or 3-weekly arm)

Paclitaxel: 175 mg/m² IV over 3 hours on day 1 every 3 weeks.

600 patients will be recruited into this study. Patients will be randomized between arm 1 and arm 2 in a 1:1 ratio.

Diagnosis/Target Population and Key Inclusion Criteria

(for detailed description of inclusion/exclusion criteria please see main body of protocol):

- Histologically proven breast cancer
- Locally advanced or metastatic disease
- Presence of measurable or evaluable lesions
- Prior treatment with anthracyclines (either in the adjuvant setting or for metastatic disease) or contra-indication to anthracyclines
- Age 18 years or greater
- WHO/ECOG performance status ≤ 2
- Adequate haematological, renal and hepatic function
- Written informed consent

Key Exclusion Criteria:

- Prior taxane treatment
- Previous malignancies
- Significant history of cardiac disease
- Serious active infection or serious underlying medical conditions
- Symptomatic brain metastases
- No measurable or evaluable disease
- Pregnant or breast-feeding females, or not using adequate methods of birth-control

Primary Efficacy Outcome Measure:

- Time to progression

Secondary Efficacy Outcome Measures:

- Objective response rate (CR and PR)
- Survival time

Pharmacokinetic/Pharmacodynamic Measures:

- Frequency of genetic polymorphisms likely to affect paclitaxel metabolism

Primary Safety Outcome Measure:

- Incidence and severity of overall toxicity, symptoms and adverse events using the NCI Common Toxicity Criteria (CTC) version 2.0.

Secondary Safety Outcome Measures:

- Incidence and severity of hypersensitivity reactions using a simplified dexamethasone premedication schedule.

Quality of Life Outcome Measure:

- EORTC QLQ-30 questionnaire
- Supplementary, trial specific QoL questions

Sample Size Determination:

Statistical analysis of the trial will be on an intention to treat basis. Assuming that the accrual period will be 18 Months, the follow up period will be 18 Months and the median progression free survival is 6 Months, 560 patients evaluable patients are required to detect a hazard ratio for time to progression of 1.33 (increase in TTP from 6 to 8 months) with a p-value of 0.05 (2-sided) and 90% power. A total of 600 patients will be recruited to allow for any ineligible patients and for those lost to follow up.

Statistical Methods:

Time to progression and survival in the two treatment arms will be plotted as a function of time using Kaplan-Meier product limit method. The log rank test will be used to compare the treatment arms.

Descriptive summary tables will be presented on safety parameters by treatment arm. Incidence and severity of peripheral neuropathy as well as overall toxicity will be compared between treatment arms using the Chi squared test.

Stratification:

- Study centre
- Measurable vs. Evaluable disease
- Intention to co-administer Trastuzumab (Herceptin™)

Interim Analysis:

Will be performed after the first 200 evaluable patients have been enrolled

1.1 Flow Chart/Time and Events Schedule

Assessment	Pre-treatment	Weekly	Every 3 weeks	Every 6 weeks	Every 9 weeks	OFF study	Follow up ³
Medical History	X						
Consent Form	X						
Physical Examination	X		X			X	X
Haematology	X	X ¹	X			X	
Chemistry	X		X			X	
Pregnancy test if applicable	X						
Tumour Evaluation	X			X ²		X	X ⁴
Assessment of Symptoms & Toxicity	X		X			X	X
Quality of life evaluation	X				X ⁵		X ⁵

¹ Haematology (haemoglobin, leukocytes, differentials, thrombocytes) will be done weekly for patients randomized to the weekly arm

² No requirement for response confirmation if PR or CR.

³ Every 3 months

⁴ Until disease progression.

⁵ After the baseline QOL questionnaire completed at the time of randomisation, QOL forms will be sent by post to each participating patient directly from SCTN at 9, 18, 27 and 52 weeks after randomisation

2 BACKGROUND AND RATIONALE

2.1 Product and disease background

2.1.1 *Breast cancer*

Breast cancer is by far the most common malignancy in women, comprising 18% of all female cancers. The incidence approaches two per 1000 females per year, giving an annual total of 860,000 new cases worldwide (of which 162,000 occur in the United States and 190,000 in the European Union). The disease is the single most common cause of death among women aged 40-50 accounting for about one fifth of all deaths in this age group. An estimated 46,000 women in the USA and some 58,000 women in the European Union will die of the disease every year (1,2,3). At initial presentation, the majority of patients with breast cancer have disease that is clinically limited to the breast. However, more detailed assessment of the disease extent, including surgical/pathological evaluation of regional lymph nodes, suggests that 20-65% of women with clinically limited disease have invasive disease in regional nodes (4).

Metastatic breast carcinoma, whether primary or at recurrence, is usually considered to be an incurable disease. At this stage, obtaining a remission of the current disease with the hope of impacting on symptom palliation, time to progression of disease and on survival becomes an important therapeutic goal. While many combination chemotherapy regimens are associated with high response rates in metastatic disease, complete remissions occur in fewer than 20% of the patients and median survival time is generally around 2 years.

Results of second-line chemotherapy are disappointing, complete remissions are rare and overall response rates for most regimens range from 10% to 35%. There is a need for new therapeutic strategies, as well as new drugs to incorporate into such strategies (5).

2.1.2. *Paclitaxel every 3 weeks in metastatic breast cancer*

Three phase II studies with Paclitaxel monotherapy by 24-hour infusion have established its activity in patients with metastatic breast carcinoma. The first two studies accrued patients with favourable baseline characteristics including good performance status and infrequent visceral involvement when compared to the third study (Table 1, ref. 6-8). More importantly, the first two studies enrolled patients with limited prior exposure to chemotherapy (maximum of only one prior regimen, often in the adjuvant setting) whereas patients accrued in the third study had received a higher number of prior chemotherapy programs (the vast majority for metastatic disease). These differences in patients may account for the variation in response rates comparing the first two with the third studies.

Table 1 Phase II studies: Paclitaxel 24-hour Metastatic Breast Cancer				
<u>Study</u>	<u>Dose (mg/m²)</u>	<u>No. of Patients (evaluable)</u>	<u>Prior Therapy</u>	<u>RR(%)</u>
F.A. Holmes (6)	250	25	14 adj 11 meta 23 anthr	56 44 PR 12 CR
L. Norton (7)	250 (G-CSF)	26	16 adj	62 50 PR 12 CR
A.D. Seidman (8)	200	30	30 meta 20 adj 29 anthr	30 30 PR 0 CR

Once preliminary data had confirmed that 3-hour infusion of Paclitaxel was safe and associated with less hematologic toxicity, two randomized trials were conducted using Paclitaxel given by 3-hour infusion for the second-line treatment of MBC.

In the first trial patients were randomized between 135 versus 175 mg/m² of Paclitaxel as a 3-hour intravenous infusion administered every three weeks (9). Patients with advanced breast carcinoma could have had one or two prior chemotherapy regimens with a maximum of one for metastatic disease. Four hundred and seventy-one patients were accrued; 60% were symptomatic at study entry, and 73% had visceral involvement. Patients were heavily pre-treated with surgery (99%), radiotherapy (76%), hormone therapy (73%), and chemotherapy, either adjuvant (30%), metastatic (39%), or both (31%). This study showed a dose effect relationship. In the higher dose (175 mg/m²) arm, the overall response rate was 29% (65/223) and in the lower dose (135 mg/m²) arm, the overall response rate was 22% (51/227). This difference was not statistically significant (p=0.09), however, progression free survival was longer in the higher dose arm, median 4.2 months versus 3.0 months (p=0.03). Median survival times in the high-dose and low-dose treatment arms did not differ; 11.7 and 10.5 months respectively (p=0.32).

The second was a randomized phase II trial of Paclitaxel (175 mg/m², 3-hour, every three weeks) versus mitomycin-C (12 mg/m² bolus every six weeks) for second-line therapy of MBC (10). Patients had received prior chemotherapy for metastatic disease, and had also received chemotherapy in the adjuvant setting. All patients enrolled in this trial had advanced MBC; 58% had an impaired performance status, and 88% had visceral sites of disease. All patients had previously undergone surgery, 93% radiotherapy, and 74% hormonal therapy. All had prior chemotherapy for metastatic disease, and half had prior chemotherapy in the adjuvant setting as well. The mitomycin-C arm was closed at the second interim analysis after

only one patient had a partial response among 25 evaluable patients treated with mitomycin-C. After completion of the trial, response rates were 17% (6/36) in the Paclitaxel arm and 6% (2/36) in the mitomycin-C arm ($p=0.14$). Treatment with Paclitaxel significantly delayed tumour progression when compared with treatment with mitomycin-C: 3.5 months versus 1.6 months ($p=0.03$). The median survival in the Paclitaxel arm was longer than that in the mitomycin-C arm (12.7 versus 8.4 months), but the comparison of survival was confounded by allowing crossover in this trial.

A third large randomized study demonstrated that the efficacy of the 3- and the 24-hour infusion was comparable (11). The objective of this multicentre study was to compare the therapeutic index of the two different schedules of Paclitaxel (3 hr and 24 hr) administered at the starting dose of 175 mg/m² in patients with MBC. 521 patients were entered in the study. Two-thirds of the patients had prior exposure to anthracyclines, of whom 24% were classified as resistant. The overall response rate (CR+PR) was comparable in the two treatment arms: 29% in the 3-hour versus 32% in the 24-hour infusion ($p=0.629$). Patients treated over 24 hours had a significantly prolonged time to progression (median 3.8 months in the 3-hour versus 4.6 months in the 24-hour infusion arm; $p=0.021$) and a prolonged survival time (median 9.8 months versus 13.4 months; $p=0.021$). However, this treatment advantage did not retain statistical significance after adjustment for prognostic factors, neither in the time to progression analysis ($p=0.081$) nor in terms of survival ($p=0.099$). The overall response rate to Paclitaxel was 28%, in anthracycline-pretreated patients, as compared to 34% in those without such prior exposure. In the anthracycline-resistant patient population an overall response rate of 30% was noteworthy. The two treatment schedules were not equitoxic, even after individual dose adjustments. The 24-hour infusion resulted in significantly more severe haematological toxicity and gastrointestinal side effects. The 3-hour infusion resulted in a significantly higher incidence of peripheral neuropathy when all grades were considered. However, there was no significant difference in severe neurotoxicity.

A summary of these 3 randomized trials is given in table 2.

2.1.3. *Weekly paclitaxel in metastatic breast cancer*

The optimal dose and schedule of Paclitaxel is not yet defined and is the subject of a number of clinical trials in various tumour types. Preclinical data have suggested that duration of exposure is an important factor in the cytotoxic activity of this drug. Depending on the duration of exposure, cellular cytotoxicity can be achieved at relatively low concentrations of paclitaxel, in the order of 0.01 $\mu\text{mol/L}$ (12,13). Plasma concentrations of this magnitude are easily achievable clinically (14). That duration of exposure can be an important element in the clinical activity of Paclitaxel has been demonstrated by the activity of prolonged, 96 hour infusions of Paclitaxel in some patients with metastatic breast cancer whose disease had recently progressed during shorter infusions of the drug (15,16). However, the administration of 96-hour continuous infusions of Paclitaxel may impose a certain inconvenience on both the clinic and the patient.

Another method to produce extended cumulative exposures is frequent, repetitive drug administrations, such as in a weekly schedule. Weekly dosing of Paclitaxel has been demonstrated to be a well-tolerated and feasible administration schedule (17,18). Weekly administration of Paclitaxel is dose-intense but has a favourable toxicity profile. In addition to exposure duration issues, cellular cytokinetic considerations imply that frequent exposure to

cytotoxic agents with brief intervals between exposures affords less opportunity for the emergence and regrowth of drug-resistant cell clones (19), a premise upon which dose-dense therapy is based. Weekly administration of Paclitaxel can be considered dose-dense therapy. Thus, weekly Paclitaxel therapy may have advantages with respect to both sustained cumulative exposure and dose-dense drug delivery.

Seidman et al have evaluated the efficacy and toxicity of Paclitaxel administered as a 1-hour infusion on a weekly basis, without interruption. Thirty patients with metastatic breast cancer, who have received prior chemotherapy, received sustained weekly Paclitaxel at an initial dose of 100 mg/m² until disease progression. Prior therapy included adjuvant only (n = 17), metastatic only (n = 7), or both (n = 6). Eighteen patients had received prior anthracycline therapy, 12 of whom had demonstrated progression of disease within 12 months. A median dose-intensity of 91 mg/m²/wk was given. The median number of cycles was 14 (treatment given without interruption). The overall response rate was 53 % (10 % complete responders). Median response duration was 7.5 months. Responses were observed in 9 of 18 patients with prior anthracycline therapy, including 6 of 12 with disease progression on anthracycline within 1 year. The therapy was well tolerated and remarkable for a lack of overall and cumulative myelosuppression. Grade 3-4 neutropenia occurred in four patients; febrile neutropenia was not observed. Peripheral neuropathy prohibited dose escalation above 100 mg/m², and grade 3 neuropathy was observed in two out of 21 patients at \leq 100 mg/m² (20).

Several other studies with weekly Paclitaxel in metastatic breast cancer have been published. An overview is given in table 3 (20-24). Response rates in these studies vary from 21-68 %. In some trials, weekly Paclitaxel was given as salvage treatment, including taxane pretreated patients. The incidence of grade 3-4 neutropenia is low and no cases of febrile neutropenia have been reported.

2.1.4 *Paclitaxel plus trastuzumab in metastatic breast cancer*

The use of paclitaxel in combinations has also been studied. In a randomised trial in patients with HER-2 over expressing tumours, the combination of paclitaxel with trastuzumab (HerceptinTM) led to improvements in response rate, time to progression and overall survival compared to paclitaxel alone. Weekly paclitaxel with trastuzumab has also been shown to produce a high response rate in patients with HER-2 positive tumours.

Table 2
Randomised trials: Paclitaxel 175 mg/m² 3-hours in Metastatic breast cancer

<u>Author</u>	<u>Regimen</u>	<u># patients</u>	<u>OR (CR+PR)</u>	<u>Time to progression</u>	<u>Median survival time</u>
K. Gelmon (9)	Paclitaxel 175 mg/m ² - 3h. q3w vs Paclitaxel 135 mg/m ² - 3h. q3w	471	29 % p = 0.09 22 %	4.2 mo p = 0.03 3.0 mo	11.7 mo p = 0.32 10.5 mo
V. Dieras (10)	Paclitaxel 175 mg/m ² - 3h. q3w vs Mitomycin C 12 mg/m ² q6w	36 36	17 % p = 0.14 6 %	3.5 mo p = 0.03 1.6 mo	12.4 mo p = not av. 8.4 mo
T. Peretz (11)	Paclitaxel 175 mg/m ² - 3h. q3w vs Paclitaxel 175 mg/m ² - 24h. q3w	521	29 % p = 0.63 32 %	3.8 mo p = 0.02 4.6 mo	9.8 mo p = 0.02 13.4 mo

Table 3
Phase II studies of weekly paclitaxel in Metastatic breast cancer

Author	Setting	Regimen	Patients	OR%	CR%	G3/4 Neutropenia
AD Seidman (20)	Met. Breast cancer 1 st /2 nd line	Paclitaxel 100 mg/m ² 1h weekly	30	53 %	10 %	14 %
SE Waintraub (21)	Met. Breast cancer Salvage	Paclitaxel 90 mg/m ² 1h weekly	10	40 %	0 %	No significant myelosuppression
E. Mickiewicz (22)	Met. Breast cancer salvage	Paclitaxel 80 mg/m ² 1h d1 + 8 + 15 q4w, Or 100 mg/m ² 1h weekly	49	61 %	16 %	
E.A. Perez (23)	Met. Breast cancer 1 st -2 nd -3 rd line	Paclitaxel 80 mg/m ² 1h weekly	130	21 %	5 %	11 %
C. Sola (24)	Met. Breast cancer after high dose chemotherapy	Paclitaxel 80 mg/m ² 1h weekly	28	68 %	21 %	5 %

2.2 Summary of Rationale

Paclitaxel has significant antitumour activity in patients with metastatic breast cancer who either relapse after or are resistant to an anthracycline based treatment.

In this setting, Paclitaxel is usually given as a 3-hour IV infusion at a dose of 175 mg/m² every 3 weeks.

With the aim to optimise dose and schedule of Paclitaxel for patients with metastatic breast cancer, a weekly, dose-dense regimen has been developed. The phase II data, reported by Seidman et al. indicate weekly Paclitaxel treatment to be a more active and better tolerated regimen as compared to a 3-weekly treatment.

In the present study, a weekly regimen will be compared to the standard 3-weekly regimen, aiming at a superior antitumour activity with no increase in toxicity for the weekly arm while balancing the total paclitaxel dose given.

In the reference arm, Paclitaxel will be given as a 3-hour infusion at a dose of 175 mg/m² every 3 weeks, which corresponds with a planned dose intensity of 58.3 mg/m²/week. This is the current standard dose and schedule.

In the experimental arm, Paclitaxel will be given as a 1-hour infusion at a dose of 90 mg/m²/week, resulting in a planned dose intensity of 90 mg/m²/week. The administration time of Paclitaxel in the weekly arm will be reduced to 1 hour and the premedication dose of dexamethasone will be reduced in both arms compared to that recommended in the summary of product

3 STUDY OBJECTIVES

3.1 Primary Objectives:

- To compare the antitumour efficacy of weekly versus 3-weekly Paclitaxel as determined by the time to disease progression
- To study polymorphisms in the genes responsible for paclitaxel metabolism and link these to response rates and toxicity

3.2 Secondary Objectives:

- To compare the toxicity of weekly versus 3-weekly Paclitaxel
- To compare the response rate of weekly vs 3-weekly Paclitaxel
- To compare overall survival in patients receiving weekly versus 3-weekly Paclitaxel
- To compare quality of life in patients receiving weekly versus 3-weekly Paclitaxel

4 ETHICS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and will be consistent with Good Clinical Practice (GCP) and applicable national and European regulatory requirements.

- The study will be conducted in compliance with the protocol. The protocol and any Amendments and the subject informed consent will receive Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favourable opinion prior to initiation.
- Freely given written informed consent must be obtained from every subject prior to clinical trial participation.
- The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).
- This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licence, debarment).
- Systems with procedures will be implemented to assure the quality of every aspect of the study.

5 INVESTIGATIONAL PLAN

5.1 Study Design

This is a randomized two arm, prospective, multi-centre, open-label phase III trial comparing the activity and safety of weekly versus 3-weekly treatment with Paclitaxel in patients with advanced or metastatic breast cancer.

5.2 Selection of Study Population

5.2.1 *Inclusion Criteria*

1. Histologically proven breast carcinoma (cytological documentation by thin needle biopsy is insufficient).
2. Locally advanced or metastatic disease.
3. Presence of at least one measurable or evaluable lesion
4. Prior treatment with anthracyclines (either given as adjuvant treatment or for metastatic disease) or contra-indication to anthracycline use.
5. No radiotherapy to indicator lesions within 3 months of randomisation
6. Immunotherapy and/or hormone therapy must be discontinued prior to study start.
7. Age 18-80 years, inclusive. Both males and females are eligible.
8. ECOG/WHO performance status ≤ 2

9. Adequate haematological, renal and hepatic functions as defined by:
 - Absolute neutrophil count (ANC)* $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 100 \times 10^9/L$
 - Total bilirubin $\leq 1.5 \times$ upper normal limit
 - SGOT (AST) and/or SGPT (ALT) $\leq 2.5 \times$ upper normal limit
 - Creatinine $\leq 1.5 \times$ upper normal limit

* ANC = Neutrophil segments + neutrophil bands
10. Written informed consent
11. Patient must be accessible for treatment and follow-up
12. Women of Child Bearing Potential (WOCBP) and in whom there is any possibility of pregnancy must have a negative serum or urine pregnancy test within 72 hours prior to start of study medication.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhoea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level >35 mIU/ml]. Even women who are using oral, implanted or, injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practising abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

5.2.2 Exclusion Criteria

1. Prior taxane treatment
2. Previous malignancies, excluding curatively treated basal or squamous cell carcinoma of the skin, *in-situ* cervical cancer or any other cancer treated more than five years prior to study entry and presumed cured.
3. Uncontrolled arterial hypertension, unstable angina, cardiomyopathy or ventricular arrhythmias requiring treatment. Patients with adequately controlled atrial fibrillation ARE allowed to participate in the trial
4. Active infection or other serious underlying medical condition which would impair the ability of the patient to receive protocol treatment, including history of hypersensitivity to any components of the TaxolTM formulation (Cremophor EL)
5. Symptomatic brain metastases.
6. Patients with no measurable or evaluable disease.
7. Pre-existing motor or sensory neurotoxicity $>$ grade 1 according to CTC criteria version 2.0 (see appendix 2).
8. Dementia or significantly altered mental status that would prohibit the understanding and giving of informed consent.
9. Pregnant or breast-feeding females, or not using adequate methods of birth control.
10. Any other condition or therapy that, in the investigator's opinion, or as indicated in the product(s) label may pose a risk to the patient or interfere with the study objectives.
11. Any investigational drug given within 30 days of initiation of therapy, or participation in other systemic anticancer therapy or bisphosphonate studies while enrolled in this protocol.

5.3 Randomisation

Patients will be randomized only if:

- **The investigator in charge is satisfied that the patient is eligible for the study**
- **The patient has measurable or evaluable disease**
- **A decision has been made on the intention to co-administer trastuzumab**

When written informed consent has been obtained from a woman who is eligible for the study the Scottish Cancer Therapy Network (SCTN) Randomisation Line should be contacted by:

1. telephone on **0131 - 551 - 8950** or **0131 - 551 - 4950**
(Monday to Friday 9.00am to 5.00pm)

OR

2. fax on **0131 - 552 - 4085**
(24-hour secure line)

The Randomisation Checklist should be completed and sent to SCTN as soon as convenient. Eligibility will be confirmed verbally and the patient will be stratified according to:

- Treatment Centre
- Measurable or evaluable disease
- Intention to co-administer trastuzumab

The SCTN will inform the investigator of the patient trial number and treatment assignment by phone and/or fax and this will be confirmed by mail.

The patient trial number should be used on all further documentation (including Case Report Forms) and correspondence with reference to this patient.

Patients should receive their first dose of study medication within 7 days after randomization.

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5.4 Blinding/Unblinding

Not applicable

5.5 Study Therapy

5.5.1 *Treatment Administration*

The method of Dubois and Dubois should be used to calculate surface area. Use actual (current) unadjusted weight when calculating dose. Doses need only be recalculated for each cycle if there has been a clinically relevant change in weight. Surface area should be calculated to 1 decimal place. Surface area should be “capped” at the discretion of the investigator - it is recommended that this should only occur for surface areas > 2.0 m².

The following treatments will be given:

ARM 1 (experimental arm or weekly arm)

Paclitaxel: 90 mg/m² IV over 1 hour on day 1 every week.

ARM 2 (reference arm or 3-weekly arm)

Paclitaxel: 175 mg/m² IV over 3 hours on day 1 every 3 weeks.

600 patients will be recruited to this study. Patients will be randomised between arm 1 and arm 2 in a 1:1 ratio. There will be 300 patients in each arm.

Guidelines for Paclitaxel Administration

Commercial Paclitaxel (TaxolTM) supplies for use in this study must be obtained from:

Bristol-Myers Squibb
141-149 Staines Road
Hounslow
Middlesex
TW3 3JA

Telephone 0208 572 7422

Fax 0208 754 3789

Paclitaxel should be diluted in 5% dextrose (or normal saline) to a final concentration of 0.3 to 1.2 mg/ml and given by intravenous administration. IV tubing should not consist of polyvinyl chloride (PVC). The calculated dose of Paclitaxel should be administered via a free flowing intravenous line as a 3-hour infusion (reference arm) or as a 1-hour infusion (experimental arm).

In-line filtration is mandatory, since a small number of fibres within acceptable limits of USP Particulate Matter Test for LVP have been observed. Cellulose acetate filters with 0.22 micron pore size (such as IVEX II) should be used. Solutions exhibiting excessive particulate formation should be discarded.

Concentrations of up to 1.2 mg/ml in 5% dextrose or normal saline solution have demonstrated chemical and physical stability for at least 27 hours at room temperature.

Premedication - Paclitaxel

Due to known toxicity of paclitaxel and/or of the Cremophor EL® vehicle, the following premedication must be given 30 minutes prior to paclitaxel administration to minimize the chances of a hypersensitivity reaction.

Agent	Dose in weekly arm	Dose in 3 weekly arm
Dexamethasone	First week: 8 mg iv Subsequent weeks 4mg iv	First cycle: 20 mg iv Subsequent cycles 12 mg iv
Chlorpheniramine (or equivalent)	10 mg iv	10 mg iv
Cimetidine or Ranitidine	300 mg iv 50 mg iv	300 mg iv 50 mg iv

Resuscitation equipment should be readily available during the infusion for emergency treatment of hypersensitivity reactions.

5.5.2 Dose Modifications

The following dosing levels will be used:

Treatment arm	Paclitaxel dose levels (mg/m ²)		
	0	-1	-2
Weekly	90	72	58
Three weekly	175	140	112

Following a dose reduction all subsequent courses will be administered at the reduced dosage and no subsequent dose escalation will be allowed. If more than 2 dose reductions are needed, the patient should go off study. Toxic effects will be graded using NCI Common Toxicity Criteria, version 2.0 (Appendix 2). If, for a given symptom, no NCI-CTC grade is described, toxicity should then be graded as 1 = mild, 2 = moderate, 3 = severe, and 4 = life threatening.

Any patient who does not tolerate dose level - 2 will go off study.

Hematologic toxicities

Patients will not begin a new cycle of therapy (i.e., not receive day 1 therapy of a cycle) until ANC $\geq 1.0 \times 10^9/l$ and platelets $\geq 75 \times 10^9/l$. If recovery is not achieved after 2 weeks of delay, the patient will be off treatment.

Patients developing grade 4 neutropenia (ANC $< 0.5 \times 10^9/l$) lasting ≥ 7 days will have further therapy given at one dose level lower when recovered from neutropenia.

Patients developing thrombocytopenia with platelets $< 25 \times 10^9/l$ will have further therapy given at one dose level lower when recovered from thrombocytopenia.

Patients developing febrile neutropenia (ANC $< 1.0 \times 10^9/l$ AND fever > 38.0 C) or sepsis with grade 3 or 4 neutropenia will have further therapy given at one dose level lower when recovered from the episode.

Non-hematologic toxicities

Patients will not begin a new cycle of therapy (i.e., receive day 1 therapy) until non-hematologic toxicities, deemed by the investigator to be definitely or possibly related to the study drug (except alopecia), resolve to baseline or \leq Grade 2. If recovery is not achieved after 2 weeks, the patient will be off treatment.

Dose modifications and delays within a cycle and for subsequent cycles, due to non-hematologic toxicity will be made according to the following:

- SGOT and/or SGPT $>$ grade 2 ($>$ grade 3 in case of liver metastases): stop therapy; patient goes off protocol.
- Bilirubin $>$ grade 2: Stop therapy; patients go of protocol.
- Peripheral neurotoxicity $>$ grade 1 : start next cycle with a dose-reduction of one level.
- Peripheral neurotoxicity $>$ grade 2 : stop therapy, patient goes off protocol.
- Other non-hematologic toxicity (excluding nausea, vomiting, asthenia): If grade 3, patients should have a dose-reduction of one level. Patients who experience grade 4 should discontinue therapy

5.5.3. Hypersensitivity reactions

Discontinue Paclitaxel infusion, for significant hypersensitivity reactions defined as:

- hypotension requiring pressor therapy
- angioedema
- respiratory distress requiring bronchodilator therapy
- generalised urticaria.

For other hypersensitivity reactions, the Paclitaxel infusion may be discontinued at the investigator's discretion.

Any significant hypersensitivity reaction and any hypersensitivity reaction requiring treatment discontinuation should be reported as an adverse event.

The following management of hypersensitivity reactions is recommended:

- Administer chlorpheniramine 10mg IV, or equivalent.
- Administer adrenaline (or its equivalent) SC every 15-20 minutes until the reaction subsides or a total of six doses are given.
- If hypotension is present that does not respond to adrenaline, administer IV fluids.
- If wheezing is present that is not responsive to adrenaline, administration of nebulized salbutamol (Ventolin®) solution (or equivalent) is recommended.

Although corticosteroids have no effect on the initial reaction, they have been shown to block "late" allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg IV (or its equivalent) may be administered to prevent recurrent or ongoing allergy manifestations.

Patients should not be re-challenged with paclitaxel in case of a severe hypersensitivity reaction. These patients should go off protocol.

5.6 Prior and Concomitant Therapy

Patients may NOT receive any other investigational anticancer drugs (including bisphosphonates) or other antineoplastic therapy while participating in the study with the exception of trastuzumab (Herceptin™). **The co-administration of trastuzumab with paclitaxel is strongly recommended in patients whose tumours over-express HER-2.** Concurrent trastuzumab use is a stratification factor and so the decision to co-administer the drug must have been made prior to randomisation, and trastuzumab treatment must start at the same time as paclitaxel. The current summary of product characteristics for trastuzumab recommends a loading dose of 4mg/kg followed by 2 mg/kg/week. Trastuzumab use in this trial should be compatible with the product licence and/or any guidance issued by the National Institute of Clinical Excellence. Once paclitaxel therapy in the trial has ended, the decision to continue trastuzumab are at the discretion of individual investigators.

Patients may receive palliative and supportive care for disease-related symptoms. Bisphosphonates are allowed for bone pain, but must be commenced a minimum of one week before commencing study therapy. The need to initiate bisphosphonate treatment for hypercalcaemia is an indicator of disease progression - the patient will go off study. Patients who require palliative radiation therapy, other than single fractions to painful bony sites within 6 weeks of starting study treatment, will similarly be considered to have progressive disease.

The choice of antiemetic therapy, analgesics, etc., if needed, is at the investigator's discretion. Since nausea and vomiting have generally been infrequent after administration of Paclitaxel, antiemetic therapy may be unnecessary. Prophylactic use of antiemetics is allowed. Corticosteroids, other than the premedication doses outlined in the protocol, should not be used prophylactically but may be instituted at the discretion of the investigator for severe emesis not responsive to other anti-emetics.

Colony stimulating factors (i.e., G-CSF, GM-CSF, etc.) should not be administered during the study period unless severe, prolonged myelosuppression or neutropenic fever occurs. In case of myelotoxicity, dose reduction of study therapy will be performed (see Section 5.5.2.2.).

Prophylactic use of growth factors is not allowed.

5.7 Withdrawal of Subjects from Therapy or Assessment

Protocol treatment will be discontinued when one of the following occurs:

- Progressive disease at any time during treatment
- Unacceptable toxicity (including severe hypersensitivity reactions, or any side effect reported as intolerable by patients)
- Patient request or withdrawal of consent
- Physician decision in light of other medical reasons/clinical data
- Patient non-compliance with the protocol requirements
- Pregnancy

5.8 Study Procedures and Observations

See also flow chart in section 1.1

5.8.1 *Subject Evaluation*

5.8.1.1 Pretreatment

Baseline evaluation must be performed within 4 weeks prior to first administration of study medication. Physical examination, haematology and chemistry must be performed within 7 days prior to first administration of study medication.

Medical History

General and disease specific medical history including:

Disease status

Date of initial and metastatic diagnosis

Details and outcome of prior therapy

Consent Form

Physical Examination

Height, weight, body surface area (BSA)

Performance status (ECOG or WHO)

Haematology

Haemoglobin

White blood cell count

Absolute Neutrophil count

Platelet count

Chemistry

Serum creatinine

Total bilirubin

AST

ALT

Pregnancy Test (if applicable) within 72 hours prior to start of study medication.

Tumour Evaluation

Documentation of measurable and non-measurable disease sites by:

Physical examination

Chest X-ray or CT-scan

Bone scan if clinically indicated

Assessment of symptoms at baseline

Record of signs and symptoms at baseline.

Quality of life questionnaire

5.8.1.2. Every 3 weeks

Repeat following examinations as described in 5.8.1.1. :

Physical examination

Haematology (weekly for patients randomised to the weekly arm)

Blood Chemistry

Assessment of symptoms and toxicity

5.8.1.3 Every 6 weeks

Tumour evaluation

Tumour evaluation will be done every 6 weeks. There is no requirement for patients with a documented objective response (CR or PR) to have a confirmatory evaluation procedure

5.8.1.4 Off-study and Follow-up

When a patient goes off study for other reasons than disease progression (i.e. for completion of treatment, toxicity, etc), tumour measurement and follow-up of disease status should be performed clinically and with imaging technique(s) similar to the one(s) used throughout the study. Patients should be seen a minimum of once every 3 months until disease progression or two years has elapsed. Follow-up of study medication related toxicity will be performed.

After progression, follow-up for survival will be performed every 3 months for the first two years and then every 6 months.

5.8.1.5 Quality of life questionnaires

Apart from the initial QoL questionnaire which will be administered at the time of randomisation, QoL forms will be sent directly to the patients from the SCTN. This will be 9, 18, 27 weeks and 1 year after randomisation. SCTN will ensure by telephone contact with relevant health professionals that it is still appropriate to send out QoL forms at the various time points.

5.8.2 *Measurability of tumour lesions and tumour response evaluation*

Measurability of tumour lesions at baseline

1. Definitions

Measurable tumour lesions : Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.

Non-measurable tumour lesions : All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT-scan) and including:

- bone lesions
- leptomeningeal disease
- ascites
- pleural/pericardial effusion
- inflammatory breast disease
- lymphangitis cutis/pulmonis
- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- previously irradiated lesions
- lesions measured by ultrasound scan

These lesions may, however, be evaluable

2. Specifications by methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of treatment.

2.1. Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by Collor photography including a ruler to estimate the size of the lesion is recommended.

2.2. Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

2.3. CT, MRI

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

2.4. Ultrasound

Ultrasound scanned lesions are evaluable but not measurable

Tumour response evaluation

1. Assessment of overall tumour burden and measurable disease

To assess objective response, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Patients with measurable disease at baseline will be stratified in this protocol.

Representative measurable lesions up to a maximum of 10 from all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

Measurements are not required for lesions or sites of disease identified as non-target lesions. They should be recorded at baseline “present” or “absent”.

2. Response criteria

2.1. Evaluation of target lesions

Evaluation will follow RECIST (unidimensional) criteria

Complete response (CR): Disappearance of all target lesions.

Partial response (PR): at least a 30 % decrease in the sum of the LD of target lesions taking as a reference the baseline sum of LD.

Progression (PD): at least 20 % increase in the sum of LD of target lesions taking as references the smallest sum of LD recorded since the treatment started or the appearance of one or more new lesions.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

2.2. Evaluation of non-target lesions

Complete response (CR): Disappearance of all non-target lesions and normalization of tumour marker level (if used for evaluation of response).

Non-Complete response (non-CR)/ Non-progression (non-PD): persistence of one or more non-target lesions or/and maintenance of tumour marker level above the normal limits.

Progression (PD): appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Increase in tumour marker level >25% (unless still within normal limits).

Evaluable for response:

All eligible patients who have received at least 4 weeks of treatment in the weekly arm and at least 2 cycles of treatment in the 3-weekly arm will be considered evaluable for response. In addition, those patients who develop rapid tumour progression after at least one course of therapy (3 weeks of weekly treatment) will be considered evaluable for response.

Best overall response:

The best overall response is the response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-target lesions	New lesions	Overall Response
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CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Time to progression

will be calculated for all patients from the day of enrollment until the date PD or death is first reported. Patients should not receive any subsequent therapy after study treatment until disease progression or relapse. Any patient receiving alternative systemic chemotherapy should be considered as a treatment failure and will be considered to have progressed on the first day of the secondary treatment. Maintenance hormone therapies and bisphosphonates started electively at the end of the study treatment period are allowed and do not constitute evidence of disease progression. Patients receiving local palliative treatment (i.e. radiotherapy for previously present bone disease) can still be followed for progression and survival and should not be censored. However, if this treatment is performed on the only evaluable site of disease, the patient will be considered to have progressed on the first day of the secondary treatment. Patients who did not progress will be censored at the last date they were known to be alive. Patients who died from disease and for whom a date of progression is not available, will be considered to have progressed on the day of their death.

Survival.

For all patients, survival will be calculated from the day of enrollment to death. Patients who did not die will be censored at the date they were last known to be alive.

5.8.3 *Precautions/Restrictions*

Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or other components of the formulations, especially polyoxyethylated castor oil.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

Patients must be pretreated with corticosteroids, antihistamines and H₂ antagonists (section 5.5.1.1.).

Drug interactions

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel to 6- α -hydroxypaclitaxel is the major metabolic pathway in humans. Based on current knowledge, clinically relevant interactions between paclitaxel and other CYP2C8 substrates are not anticipated. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the administration together without dose adjustment. Further data on the potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited.

Hypersensitivity reactions

Significant hypersensitivity reactions characterized by dyspnoea and hypotension requiring treatment, angioedema and generalized urticaria have occurred in < 1 % of patients, receiving Paclitaxel after adequate premedications. These reactions are probably histamine mediated. In the case of severe hypersensitivity reactions, the Paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patients should not be re-challenged with the drug.

Bone marrow suppression

Bone marrow suppression (primarily neutropenia) is dose-limiting. Care should be taken to monitor blood counts (see 5.8.1) and to obtain the WBC differential and, in particular, the absolute neutrophil count.

Cardiac toxicity

Severe cardiac conduction abnormalities have been reported rarely. If patients develop significant conduction abnormalities during Paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Paclitaxel. Hypotension, hypertension, and bradycardia have been observed during Paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of Paclitaxel infusion, is recommended.

Peripheral neuropathy

The occurrence of peripheral neuropathy is frequent and the dose of paclitaxel may need to be reduced (see 5.5.2).

5.9 Laboratory Tests (See Flow Chart section 1.1)

Safety laboratory testing (blood haematology, chemistries and pregnancy testing) will be performed at each participating site. Required laboratory tests are described in section 5.8.1.

5.10 Pharmacogenomics

5.10.1 *Pharmacogenetics of paclitaxel*

The response of a given patient to chemotherapy can be associated with the concentrations of the drug attained in plasma and in the tumour. The processes of distribution, activation and removal of various drugs are governed by proteins such as enzymes and membrane pumps, which are themselves governed by the expression of different genes. For instance, genetic variations in the MDR1 gene, which encodes the p-glycoprotein membrane pump, have been described. This pump acts to exclude paclitaxel from cells and may influence the systemic and tumour pharmacology of the drug. Similarly, genetic variation in the gene encoding the cytochrome P450 enzyme CYP2C8, involved in the systemic metabolism of paclitaxel has also been described²⁷⁻³⁰.

5.10.2 *Plan of investigation*

Blood samples will be obtained from the study group of 600 patients receiving either weekly or 3-weekly paclitaxel. The frequency of the known polymorphisms in the MDR1 gene (expected allelic frequency 50%) will be determined using denaturing HPLC. Functionally-significant polymorphisms in the genes coding for CYP2C8 (allelic frequency 13% in Caucasians) and CYP3A (total frequency 6%) will be detected by either PCR-RFLP or denaturing HPLC. Relationships between P450 and MDR1 genotypes and clinical outcome will be studied.

5.10.3 *Specimen Collection and Transport*

Blood samples for pharmacogenomic analysis will be obtained from all patients participating in the study, provided that they agree to this procedure and give the relevant written consent. A single 10 ml blood sample should be collected into an EDTA vacutainer tube and labelled using the labels supplied. These labels will contain no information which will allow the patient to be directly identified by the scientists undertaking the pharmacogenomic analysis, but will include the trial number (assigned at randomisation) and the patients date of birth which will be used for verification purposes only. In this way, samples will be link anonymised.

Samples should be stored at -20 C and shipped in batches by prior arrangement to:

Julieann Sludden
Cancer Research Unit
University of Newcastle
Medical School
Framlington Place
Newcastle NE2 4HH
United Kingdom
tel. (+44) 0191 222-8215
fax. (+44) 0191 222-7556

Appropriate address labels and packaging will be supplied

6 STATISTICAL METHODS

6.1 Introduction

This is a randomized two arm, prospective, multi-centre, open-label phase III trial comparing the activity and safety of a weekly versus 3-weekly treatment with Paclitaxel in patients with advanced or metastatic breast cancer. Patients will be randomized to the weekly or 3-weekly regimen in a 1:1 ratio.

6.2 Sample Size and Power

Statistical analysis of the trial will be on an intention to treat basis. Assuming that the accrual period will be 18 Months, the follow up period will be 18 Months and the time to progression (TTP) is 6 Months, 560 patients evaluable patients are required to detect a hazard ratio for time to progression of 1.33 (increase in TTP from 6 to 8 months) with a p-value of 0.05 (2-sided) and 90% power²⁶. A total of 600 patients will be recruited to allow for any ineligible patients and for those lost to follow up.

Time to progression and survival in the two treatment arms will be plotted as a function of time using Kaplan-Meier product limit method. The log rank test will be used to compare the treatment arms.

6.3 Data Set Descriptions

Evaluable for response: patients having received at least 4 weeks of treatment when randomized to the weekly arm and at least 2 cycles of treatment when randomized to the 3-weekly arm will be considered evaluable for efficacy as well as patients developing disease progression after at least 1 cycle of treatment.

Evaluable for time to progression and survival: all randomized patients will be included in the survival analysis (intention to treat).

Evaluable for safety: patients having received any study drug will be considered evaluable for safety.

6.4 Analyses

6.4.1 *Baseline Comparability*

Prior to randomization, the patient will be stratified according to the following stratification parameters:

- Treatment centre
- Intention to co-administer Trastuzumab
- Measurable vs. evaluable disease

Descriptive summary tables on pretreatment characteristics will be presented.

6.4.2 *Efficacy Analyses*

Time to progression and survival in the two treatment arms will be plotted as a function of time using Kaplan-Meier product limit method. The log rank test will be used to compare the treatment arms.

6.4.3 *Safety*

Descriptive summary tables will be presented on safety parameters by treatment arm. Incidence and severity of peripheral neuropathy as well as overall toxicity will be compared between treatment arms using the Chi Squared test.

6.4.4 *Quality of life*

QOL in the two arms of the study will be compared using the Chi squared test

6.4.5 *Pharmacogenomic Analyses*

Descriptive statistics of the frequency of genetic polymorphisms in the trial population will be prepared. These will be correlated with outcome.

6.4.6 *Interim Analyses*

This will be performed once 200 patients have been randomised.

7 PACLITAXEL PRODUCT INFORMATION

Paclitaxel is licenced in the UK and is commercially available. The use of paclitaxel in the clinical context described in this trial has been recommended by the National Institute for Clinical Excellence. No particular dose or schedule of Paclitaxel have been mandated by the NICE guidance.

7.1 Name and Chemical Information

Paclitaxel for Injection Concentrate is a clear colourless to slightly yellow viscous solution. It is supplied as a solution in a non aqueous medium. It is intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5 ml) and 100 mg (17 ml) vials.

Each ml of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Paclitaxel is a natural product. It is off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is extremely lipophilic and melts at around 216-217 °C. Paclitaxel is highly insoluble in water.

7.2 Mechanism of Action

The antitumour activity of paclitaxel has been attributed primarily to effects on microtubule assembly. *In vitro* studies have shown that paclitaxel induces tubulin assembly in the absence of GTP and microtubule-associated proteins. In the cell, paclitaxel promotes microtubule bundling in all Phases of the cell cycle and inhibits cell replication in the late G2 and/or M phases of the cell cycle. Extracellular concentrations as low as 0.1 μ M (85 ng/ml) have been shown to be pharmacologically active *in vitro* against tumour cells taken from patients before treatment.

7.3 Pharmacokinetic Information

Following intravenous administration of paclitaxel, the disposition of paclitaxel has been described as a biphasic process with some studies noting a multiphasic decline at the end of infusions. The initial rapid decline in post-infusion plasma concentrations represents significant elimination of the drug from the central compartment and distribution to the peripheral compartment; the terminal elimination phase is due, in part, to slow efflux of paclitaxel from the peripheral compartment. Non-linear pharmacokinetics have been observed. Mean terminal half-life was estimated to range from 6.4 to 12.7 hours. Mean values for total body clearance ranged from 6.9 to 15.6 L/h/m². The mean apparent steady state volume of distribution ranged from 68-162 L/m², indicating extensive extra vascular distribution and/or tissue binding of paclitaxel.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μ g/ml, indicate that on average 89% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

The disposition of paclitaxel has not been fully elucidated in humans. After intravenous administration of paclitaxel, mean values for cumulative urinary recovery of unchanged drug ranged from 1.9 to 12.7% of the dose, indicating extensive non-renal clearance. High paclitaxel concentrations have been reported in the bile of patients.

7.4 Supply of Paclitaxel

Commercial Paclitaxel (TaxolTM) supplies for use in this study must be obtained from:

Bristol-Myers Squibb
141-149 Staines Road
Hounslow
Middlesex
TW3 3JA

Telephone 0208 572 7422
Fax 0208 754 3789

Paclitaxel is available as a single dose vial of 30 mg contained in 5 ml (6 mg/mL) or a vial of 100 mg contained in 16.6 ml (6 mg/ml) Unopened vials of TAXOL for Injection Concentrate are stable until the date indicated on the package when stored at room temperature (15-30 °C). Refrigeration is not required for shipping. Freezing does not adversely affect the concentrate.

Solutions for infusion which are prepared as recommended are stable at ambient temperature and lighting for up to 27 hours.

8 ADVERSE EVENT REPORTING

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product. AE's include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the drug(s) under study. The collection of non-serious AE information should begin at initiation of investigational product. Serious AE's should be collected following the subjects written consent to participate in the study.

Timely and complete reporting of all AE's assists the SCTN in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study subjects; (2) a greater understanding of the overall safety profile of the investigational product; (3) recognition of dose-related investigational product toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

Investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded.

AE's may be either spontaneously reported or elicited during questioning and examination of a subject. All identified AE's must be recorded and described on the appropriate Non-serious or Serious AE page of the CRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

Subjects experiencing AE's that cause interruption or discontinuation of investigational product, or those experiencing AE's that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE was considered by the investigator to be certainly, probably, or possibly related to investigational product.

8.1 Non-serious Adverse Events (AE's)

Any AE that is not designated as serious, as defined in Section 8.2 below, must be recorded on the NON-SERIOUS AE page of the CRF. Those AE's should be followed to resolution or stabilization, and reported as SAE's if they become serious.

8.2 Serious Adverse Events (SAE's)

An event that is serious must be recorded on the SERIOUS AE (SAE) page of the CRF and requires expeditious handling to comply with regulatory requirements.

A Serious Adverse Event or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening-
(Defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a cancer;
- Is a congenital anomaly/birth defect;
- Results in an overdose-
(Defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.);
- Results in the development of drug dependency or drug abuse;
- Is an important medical event-
(Defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Adverse events classified as "serious" require expeditious handling and reporting to SCTN to comply with regulatory requirements. Any serious AE that, in the opinion of the Investigator, is certainly, probably, possibly, not likely related or unrelated to the investigational product must be immediately reported by telephone, if feasible. Regardless, all serious AE's whether related or unrelated to investigational product, must be immediately reported by confirmed facsimile transmission and mailing of the completed SAE page (top, white original). A facsimile transmission does not preclude mailing of the SAE page. Overnight express mail may be used in lieu of facsimile. If only limited information is initially available, follow-up reports are required.

Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the investigational product, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to SCTN.

- SAE telephone contact:- Dr Liz Foster 0131 551 8940
- SAE fax transmission: - 0131 552 4085 FAO Dr Liz Foster
- SAE Mailing address:-
Dr Liz Foster
Scottish Cancer Therapy Network
Trinity Park House
South Trinity Road
Edinburgh EH3 5SQ

As required, SCTN will notify Investigators of all AE's that are serious, unexpected, and certainly, probably, possibly, or of undetermined relationship to the investigational product. An AE, whether serious or not, is designated unexpected (unlabeled) if it is not reported in the summary of product characteristics or if the event is of greater frequency, specificity or severity.

Upon receiving such notices, the Investigator must review and retain the notice with the study file and immediately submit a copy of this information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to local regulations. The Investigator and IRB/IEC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures for reporting any other safety information. Where required, submission of Safety Updates by the Investigator to Health Authorities, should be handled according to local regulations.

8.3 Laboratory Test Abnormalities

In addition to being recorded on the appropriate laboratory test results pages of the CRF, any laboratory test result that meets the criteria for a Serious Adverse Event (see section 8.2) must also be recorded on the SAE page of the CRF in order for SCTN to collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and resolution.

8.4 Other Safety Considerations

Any clinically significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate AE page of the CRF (i.e., NON-SERIOUS or SERIOUS) in order for SCTN to collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and resolution.

8.5 Pregnancy

Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. (See Section 5.2.1 for definition of WOCBP.)

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. During the study, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

If a subject or Investigator suspects that the subject may be pregnant prior to investigational product administration, the investigational product must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive investigational product and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the investigational product must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety) and the subject withdrawn from the trial. Exceptions to study discontinuation may be considered for life-threatening conditions only after consultation with the trial co-ordinators.

The Investigator must immediately notify the SCTN of any pregnancy associated with investigational product exposure, including at least 30 days after product administration.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Investigator must report to SCTN follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome.

9 ADMINISTRATIVE SECTION

9.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, SCTN. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favourable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favourable opinion
 - Regulatory Authority(ies), if required by local regulations
- Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to SCTN.

If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favourable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

9.2 Informed Consent

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that the SCTN and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other information to be provided to the subjects. All patients must sign to consent form.

If the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject understands and has freely given consent.

The informed consent and any other information provided to subjects or the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favourable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject.

9.3 Monitoring for Protocol Compliance

Representatives of SCTN must be allowed to visit all study site locations if deemed necessary to assess the data, quality and study integrity. On site they will review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by government inspectors, for example the Medicines Control Agency, who must be allowed access to CRF's, source documents and other study files.

The investigator must notify SCTN promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to SCTN.

9.4 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported on the CRF, that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained.

The CRF must be completed legibly in ink. Subjects are to be identified by initials, birth date and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a Signature Sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRF's. A correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialled and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF must be promptly reviewed, signed, and dated by a qualified physician who is an Investigator or Sub-investigator. The Investigator must retain copies of the CRF's including records of the changes and corrections.

9.5 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before study initiation, the Investigator must have written and dated approval/favourable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process, and any other written information to be provided to subjects. The Investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labelling, information to be provided to subjects and any updates.

The Investigator should provide the IRB/IEC with reports, updates, and other information (e.g., Safety Updates, Amendments, Administrative Letters) according to regulatory requirements or Institution procedures.

9.6 Insurance

Drugs and treatment schedules used in this protocol are currently in common usage. Normal NHS (or equivalent for Non-UK centres) indemnity arrangements will apply to enrolled patients.

9.7 Publication rules

This study will be presented at appropriate scientific meetings and will be submitted for publication in a peer reviewed medical journal. Authors for any presentation will include the trial co-ordinators, statistician, representative from SCTN and at least the highest 5 recruiting investigators. Other individuals who have made a substantial contribution to the design, conduct or analysis of the trial will be acknowledged. Where the pharmacogenomic endpoints of the study are presented, scientists performing these analyses will be included in the authorship.

The data generated in this trial remain the property of the Anglo-Celtic Co-operative Oncology Group and no presentation or manuscript may be made without agreement of the group.

9.8 Records Retention

The Investigator must retain investigational product disposition records, copies of CRF's (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact The SCTN prior to destroying any records associated with the study.

SCTN will notify the Investigator when the trial records are no longer needed.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator, IRB). Notice of such transfer will be given in writing to the SCTN.

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APPENDIX 1 INFORMED CONSENT ELEMENTS

The informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following mandatory topics:

- 1 That the study involves research.
- 2 The purpose of the study.
- 3 The expected duration of the subject's participation in the study.
- 4 The study treatment(s) and the probability for random assignment to each treatment.
- 5 The study procedures to be followed, including all invasive procedures.
- 6 Those aspects of the study that are experimental.
- 7 The reasonably foreseeable risks or inconveniences to the subject, and when applicable, to an embryo, fetus, or nursing infant.
- 8 The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- 9 The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- 10 That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- 11 That the SCTN, IRB/IEC, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing and dating a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- 12 The subject's responsibilities.
- 13 The compensation and/or treatment available to the subject in the event of study-related injury.
- 14 The anticipated prorated payment, if any, to the subject for participating in the study.
- 15 The person(s) to contact for further information regarding the study and the rights of study subject's, and whom to contact in the event of study-related injury.
- 16 That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- 17 The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- 18 The anticipated expenses, if any, to the subject for participating in the study.
- 19 The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- 20 That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- 21 The approximate number of subjects involved in the study.
- 22 Any element(s) required by local regulations (eg, MREC, LREC).