Triple Negative breast cancer Trial

A randomised phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced ER-, PR- and HER2- breast cancer.

Incorporating the BRCA Trial

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Co-Sponsors: King's College London
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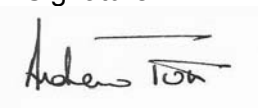
Breakthrough Breast Cancer

Coordinating Trials Unit: Clinical Trials and Statistics Unit (ICR-CTSU)
The Institute of Cancer Research

A National Cancer Research Institute Portfolio Clinical Trial (approved by CTAAC)

Protocol Authorised by:

Name & Role:	Date:	Signature:
Dr Andrew Tutt (Chief Investigator)	18/09/2013	

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The above members make up the Trial Management Group (TMG) as at April 2013. A copy of the current membership of the TMG can be obtained from the TNT Trial Manager within ICR-CTSU. Updates to the TMG membership will not be submitted as a protocol amendment.

This protocol describes the Triple Negative Trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients; every care was taken in its preparation, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact the Trials Unit to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the ICR-CTSU, The Institute of Cancer Research, Sutton.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031). It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

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TRIAL SUMMARY

TITLE:

Triple Negative breast cancer Trial (TNT): A randomised, phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced ER-, PR- and HER2- breast cancer.

OBJECTIVES:

Primary:

To compare the objective tumour response rate (CR [complete response] + PR [partial response]) of patients treated with carboplatin versus docetaxel (taxane standard of care).

Secondary:

To assess time to disease progression, progression free survival, objective tumour response to second line protocol therapy after progression on randomised trial treatment, time to treatment failure, overall survival and treatment toxicity in patients treated with carboplatin compared with those treated with docetaxel.

To compare the frequency of development of symptomatic new cerebral metastases in patients randomised to carboplatin to those randomised to docetaxel.

TRIAL DESIGN:

Phase III, multi centre, randomised trial of carboplatin versus docetaxel in women with ER-, PR- and HER2- metastatic or recurrent locally advanced breast cancer. Patients will be randomised (1:1) to carboplatin or docetaxel and will cross over to the alternative treatment (docetaxel (if randomised to carboplatin) or carboplatin (if randomised to docetaxel)) on progression.

PATIENT TYPE/NUMBER:

Women with metastatic or recurrent locally advanced breast cancer that is ER-, PR- (or unknown) and HER2- or who are known BRCA1/BRCA 2 carriers.

The required sample size is calculated as being between 370 and 450 patients, and the target is to randomise at least 370 patients and aim to accrue 400 patients with triple negative breast cancer.

TRIAL TREATMENT:

Group A Carboplatin AUC 6, q 3 weeks for 6 cycles (18 wks)

Group B Docetaxel 100mg/m^2, q 3 weeks for 6 cycles (18 wks)

On evidence of disease progression, patients will cross over to the alternative treatment.

TREATMENT DURATION:

Until evidence of disease progression (on second line protocol therapy) or treatment withdrawal due to any drug-related serious adverse event or patient choice.

ENDPOINTS:

Primary:

- Objective tumour response rate (CR + PR)

Secondary:

- Time to progression
- Progression Free Survival (PFS)
- Objective tumour response rate to second line protocol therapy after progression on randomised trial treatment
- Time to treatment failure
- Overall survival
- Toxicity
- Frequency of development of symptomatic new cerebral metastases

1. BACKGROUND

Approximately 10-15 % of breast cancers have an ER, PR and HER2 negative ("Triple Negative") phenotype (1). An analysis of the Guy's and St Thomas' Breast Tissue and Data Bank Tissue Microarray (TMA) reveals 223/1256 (17.5%) tumours with these characteristics and this figure is consistent with the published reports of other UK (2) and US groups (3). In an American study of 657 incident breast cancers, including 260 African American (AA) and 397 non African American women, 26.2% of all breast cancers were "Triple Negative". This phenotype was significantly more frequent in AA (33.9% vs. 21.2%, p=0.0003), premenopausal women (30.3% vs. 21.9%, p=0.02), those patients with mitotic index > 10 (45.8% vs. 11.3%, p<0.0001), and those with nuclear or histologic grade 3 tumours (p=0.0001). The highest incidence of "Triple Negative" breast cancers occurred among premenopausal AA women (44.3%) compared with postmenopausal AA women (24.6%, p=0.0008). In multivariate models combining all factors, the significant predictors of the "Triple Negative" phenotype were high mitotic index (p<0.0001), high nuclear or histologic grade (p<0.0001 for both), and race (p=0.03) (3). A more detailed phenotypic characterisation of this study has now been published confirming the association between these features and the prevalence of the "basal-like" form of breast cancer (4).

These estimates of incidence would equate to approximately 6 to 7,000 new "Triple Negative" cases per year in the UK. Carey's data suggest there may be particular enrichment in premenopausal women and women from ethnic minorities in urban areas of the UK.

Transcriptional profiling of breast cancers has identified a distinct cluster of basal-like breast cancers that express low levels of both ER/PR related genes and HER2 related genes (5, 6, 7). Basal-like cancers contribute to a high proportion (~80%) of the overall "Triple Negative" sub-group, and the group taken overall have a poor survival (2, 6, 7, 8). A number of putative markers of the basal-like phenotype have been described (9) but there is considerable heterogeneity of outcome between different "basal" markers within the "Triple Negative" subgroup that requires further analysis in prospective clinical trials (10). There is currently no approved means of identifying basal-like cancers and further research is required to clarify whether basal-like cancers are distinct from other "Triple Negative" cancers, and whether distinct subgroups with clinical implications exist within basal-like cancers.

Whereas greater understanding of the biology of the ER+ and HER2+ breast cancers has led to targeted therapeutics for these groups, no such development has yet been made for this recently identified poor prognosis "Triple Negative" group. As a result of therapeutic advances in ER+ and HER2+ breast cancers, patients' tumours are now routinely tested for expression of the ER and HER2 receptors to national QA standards in order to determine treatment at relapse. The addition of PR testing would allow "Triple Negative" patients to be identified for clinical studies of mechanism-based novel therapeutic strategies. However data from De Maeyer et al and Bardou et al (11,12) suggest that >95% of patients with double negative disease (ER- and HER2-) are also

PR-, therefore in the absence of routine PR testing in the UK, patients with “Double Negative” disease may be regarded as “Triple negative” for the purposes of testing treatment which is targeted at patients with triple negative tumours.

1.1 Rationale for Trial

There is a need for a proof of principle/translational research study to both test current and define new biology driven therapy hypotheses within the “Triple Negative” sub-type

Evidence for a targetable dysregulation of the BRCA1 pathway in sub-types of “Triple Negative” breast cancer

Significant evidence now points to defects in the regulation of the BRCA1 pathway within “Triple Negative” breast cancers and to functional DNA repair defects which could form a target for treatment.

1. Breast cancers developing in BRCA1 mutation carriers have “Triple Negative” characteristics and share an RNA expression profile and basal cytokeratin expression phenotype with sporadic basal-like cancers (6, 13, 14). It has been noted that abnormalities exist in the expression of BRCA1 in sporadic breast cancers with a “Triple Negative” or basal-like phenotype (2, 15). This suggests a functional deficiency of BRCA1 as a shared characteristic between BRCA1 familial breast cancers and a substantial but as yet incompletely defined subgroup of “Triple Negative” breast cancers.

2. BRCA1 functional deficiency leads to a specific DNA repair defect that sensitises cells to the DNA cross links induced by cisplatin, carboplatin and mitomycin C (16, 17, 18). BRCA1 and its binding partners are now known to be crucial components in the Fanconi anaemia protein network (19). The hallmark of functional deficiency in this network is sensitivity to DNA cross-linking agents such as carboplatin (20). There is also early preclinical data suggesting that a functional deficiency in BRCA1 may lead to taxane resistance (21). These, and similar data for BRCA2 have formed the rationale for the CTAAC funded NCRI BRCA trial in BRCA1 and BRCA2 mutation carriers with metastatic breast cancer. This phase II study examines the response to, and toxicity of, single agent carboplatin compared with docetaxel in metastatic breast cancer in BRCA1 and BRCA2 mutation carriers. The evidence of abnormality in the BRCA1 pathway in basal-like breast cancers (15) allows the scientific rationale for this translational clinical trial to be extended to and tested in “Triple Negative” breast cancer as well as familial BRCA1 and BRCA2 germline mutation-associated breast cancer with the strongest evidence of tumour inactivation of the homologous recombination pathway. The recent incorporation of the NCRN BRCA Trial eligible population, as a defined sub-group within the TNT trial protocol, allows the trial hypothesis to be tested and results compared within the same protocol strengthening both trials.

3. Other therapeutic methods have been developed for targeting the DNA repair defect in BRCA1 and BRCA2 deficient cells (22); inhibitors of the enzyme polymerase, PARP, have shown a signal of efficacy in BRCA1 and BRCA2 associated cancers (23) and in some basal-like breast cancer models (24). There are currently proof of concept Phase II clinical trials due to report (25). Patients identified and treated on this TNT protocol may subsequently be eligible for current (26) and future phase II trials, including a PARP inhibitor.

Evidence for co-expression of ΔNp63 / TAp73 in triple negative breast cancers tumours and its relationship with pre-clinical sensitivity to platinum salts

Work by Leong et al (27) has demonstrated that the p53 family member p63 controls a pathway for p73-dependent cisplatin sensitivity specific to these “triple-negative” tumours. In vivo, ΔNp63 and TAp73 isoforms were coexpressed exclusively within a subset of triple negative primary breast cancers that commonly exhibited mutational inactivation of p53. The ΔNp63α isoform promoted survival of breast cancer cells by binding TAp73 and thereby inhibiting its proapoptotic activity. Consequently, inhibition of p63 by RNA interference led to TAp73-dependent induction of proapoptotic Bcl-2 family members and apoptosis. Breast cancer cells expressing ΔNp63α and TAp73 exhibited cisplatin sensitivity that was uniquely dependent on TAp73. Thus, in response to treatment with cisplatin, but not to doxorubicin or paclitaxel, TAp73 underwent c-Abl–dependent phosphorylation, which promoted dissociation of the ΔNp63α/TAp73 protein complex, TAp73-dependent transcription of proapoptotic Bcl-2 family members and apoptosis. Their findings define p63 as a survival factor in a subset of breast cancers. Furthermore, they also suggest a novel mechanism for platinum salt sensitivity in these triple negative cancers and they suggest that such cancers may share the putative platinum salt sensitivity of BRCA1-associated tumours.

1.2 Proof of Principle

A DNA repair defect in Triple Negative breast cancers leads to greater sensitivity to DNA cross-linking agent therapy than to a "standard of care" taxane spindle poison in this tumour sub-group.

This is a proof of principle study to determine whether there is evidence that carboplatin is particularly active agent in women with "Triple Negative" or BRCA1 or BRCA2 mutation associated breast cancer. It is believed that these breast cancers may show unusual sensitivity to carboplatin that is significantly greater than to that shown for the current standard of care docetaxel. Even if the activity of carboplatin is equivalent to docetaxel in this subtype, this drug's acceptable toxicity profile may warrant its further investigation as a standard of care in "Triple Negative" breast cancer and BRCA1 or BRCA2 mutation-associated breast cancer. A docetaxel comparator group will allow us to document whether these tumours have higher or lower sensitivity to the current taxane standard of care. Parallel prospective laboratory analyses will be performed on acquired primary tumour blocks and biopsied metastatic tumour tissues (where safe and available and by optional consent) to characterise subgroups within the "Triple Negative" phenotypic group that may exhibit dysfunction of tyrosine kinase receptor family signalling pathways, p63 family pro-apopotic pathways and the BRCA1/Fanconi/BRCA2 pathway that may be targeted by novel therapeutics.

2. AIMS OF THE TRIAL

1. To test mechanistically driven therapeutic approaches in a group of breast cancers with no current mechanism-based therapeutic approach.

2. To develop a “Triple Negative” and BRCA1 or BRCA2 mutation associated breast cancer Tissue Bank and DNA collection linked to the trial data in order to:

    a. study and refine understanding of the biology and identification of sub-groups of “Triple Negative” breast cancer (e.g. basal-like) BRCA1 or BRCA2 mutation-associated breast cancer in a large, prospectively acquired population of patients within a randomised treatment intervention study.

    b. aid identification of new targets for therapy in these patients, and define clinically relevant sub-groups.

3. TRIAL OBJECTIVES

3.1 Primary Objectives

To compare the objective tumour response rate (CR [complete response] + PR [partial response]) of patients treated with carboplatin versus docetaxel (taxane standard of care) as assessed by RECIST criteria.

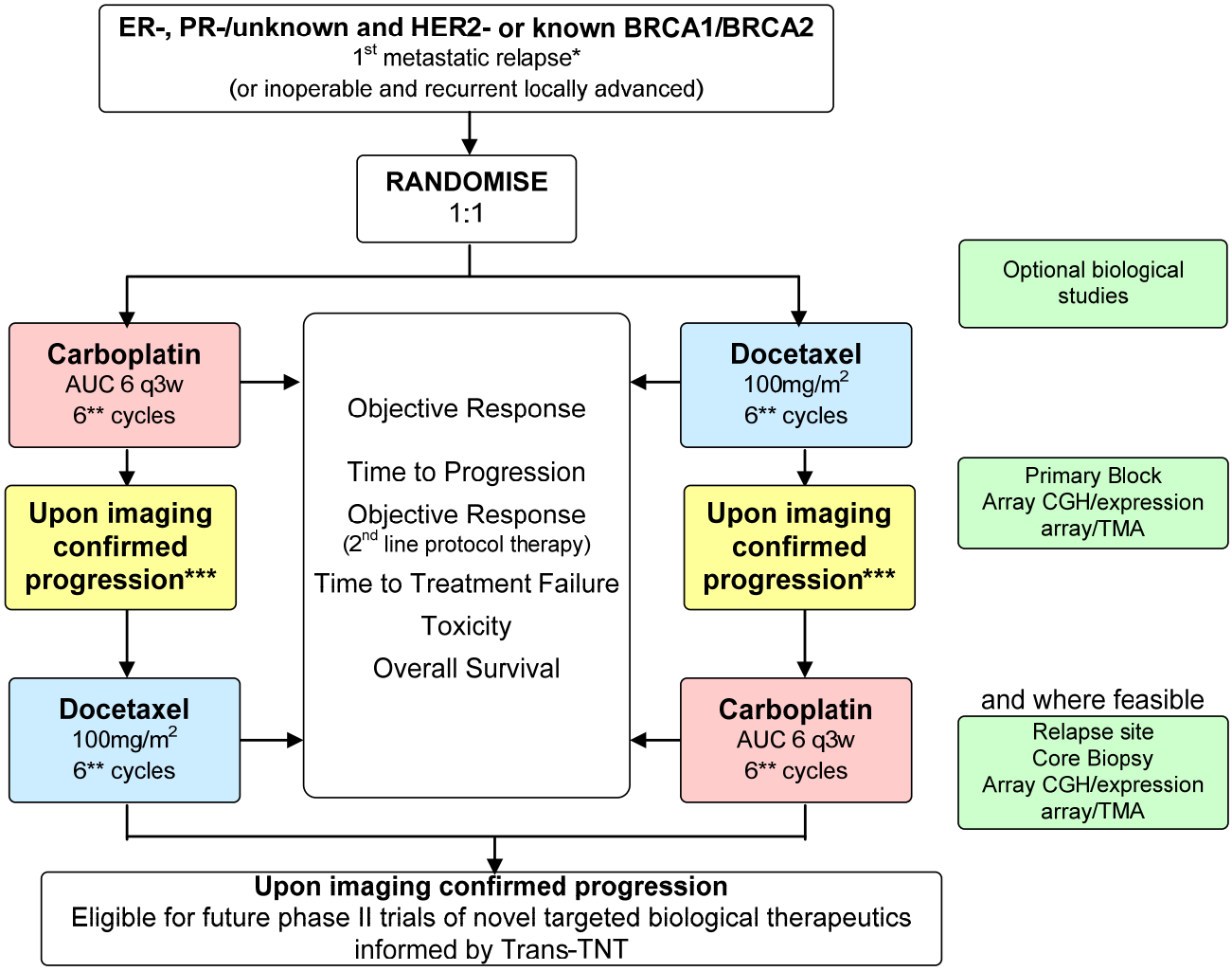
3.2 Secondary Objectives

To assess time to disease progression, progression free survival, objective tumour response to second line protocol therapy after progression on randomised trial treatment, time to treatment failure, overall survival and treatment toxicity in patients randomised with carboplatin compared with those randomised with docetaxel.

To compare the frequency of development of symptomatic new cerebral metastases in patients randomised to carboplatin to those randomised to docetaxel

4. TRIAL DESIGN

4.1 Main Trial Design



This is a randomised phase III trial in women with metastatic or recurrent locally advanced ER-, PR-/unknown and HER2- breast cancer.

* Patients who have not received anthracycline based chemotherapy in the adjuvant setting or for locally advanced disease may have received a non-taxane, anthracycline regimen as their first treatment at relapse and are eligible to enter the trial at confirmed progression after the anthracycline treatment (2nd metastatic relapse).

**For patients responding to and tolerating treatment well, a further two cycles (six weeks) may be given if this is in accordance with local centre policy, but is not encouraged.

***As defined by RECIST version 1.1 criteria. See Appendix 2.

4.2 Study Treatments

Group A Carboplatin AUC 6, q 3 weeks for 6 cycles (18 wks)

Group B Docetaxel 100mg/m^2, q 3 weeks for 6 cycles (18 wks)

If progression occurs at any time, switching to the alternative treatment (docetaxel if randomised to carboplatin or carboplatin if randomised to docetaxel) will be offered. If initial allocated treatment is withdrawn because of toxicity, cross over to the alternative treatment group should be considered by the local investigator if anticipated toxicities are thought appropriate.

4.3 Biological Studies

For consenting patients one blood sample and tissue samples will be taken (existing diagnostic samples from the original primary tumour, lymph nodes and recurrent tumour if available – please refer to Section 9).

White blood cell DNA and plasma DNA where available will be subjected to genetic profiling, including next generation sequencing techniques in order to attempt to determine underlying germline genetic factors that may contribute to the aetiology of ER-, PR- and HER2- breast cancer. This will include analysis of the BRCA1 and BRCA2 gene or confirmation of the BRCA1 or BRCA2 genotype in known BRCA1 or BRCA2 carriers. The results from research genetic profiling will not be made available to patients. Results of the research tests for relevant genes will be made available on request to a patient's clinical geneticist, the geneticist having first received agreement from the patient, to assist NHS genetic analyses in the context of NHS approved local counselling. Validation of the research results must be performed in a NHS approved laboratory.

NB: Research genetic analysis performed within the TNT trial is not a substitute for referral to an NHS genetic service.

Tissue samples will be analysed using a variety of techniques for markers of basal-like breast cancer and function of the BRCA1 and BRCA2 and p53 gene family. We will also analyse samples for a variety of other biomarkers for known, and as yet unknown, gene function. These analyses of the cancer genome, gene expression that may include next generation sequencing techniques and protein expression profile may reveal new biomarkers of response and prognosis and new targets for therapy.

5. PATIENT SELECTION AND ELIGIBILITY

5.1 Source of Patients

Women with ER, PR and HER2 negative (or ER-, HER2- and PR unknown), metastatic or recurrent locally advanced breast cancer.

Women with known BRCA1 or BRCA2 germline mutation and metastatic or recurrent locally advanced breast cancer with any ER, PR or HER2 status

These women will be recruited from clinics within UK (and possibly European) centres. Patients previously entered into trials of adjuvant therapy are eligible for inclusion in this trial.

5.2 Number of Patients

The required sample size is calculated as being between 370 and 450 patients, and the target is to randomise at least 370 and attempt to accrue 400 patients with triple negative breast cancer. BRCA1/2 patients recruited as part of the BRCA trial will be in addition to these figures.

5.3 Inclusion Criteria

Either:

- Histologically confirmed ER-, PR-, HER2- primary invasive breast cancer

Allred/quick score <3 or H score <10 or ER and PR negative, if other cut-offs used (e.g., 1%, 5% or 10%), see Appendix 3. HER2 negative defined as immunohistochemistry scoring 0 or 1+ for HER2, or 2+ and non-amplified for HER2 gene by FISH or CISH; see Appendix 3.

or:

- PR unknown but ER- and HER2-, and otherwise eligible. Please arrange urgent PR testing. If PR unknown and PR testing is not possible within a reasonable timeframe, the patient is eligible for the trial provided that ER and HER2 status are negative and all other eligibility criteria are met.

or:

- Confirmed BRCA1 or 2 mutation carrier, with any ER, PR and HER2 status

plus:

- Measurable confirmed metastatic or recurrent locally advanced disease unsuitable for local therapy but suitable for taxane chemotherapy.

NB: Patients who have not received anthracycline based chemotherapy in the adjuvant setting or for locally advanced disease may have received a non-taxane, anthracycline regimen as their first treatment at relapse and are eligible to enter the trial at confirmed progression after the anthracycline treatment

- Patients with stable, treated brain metastases will be eligible providing informed consent can be given and that other sites of measurable disease are present
- Patients with bone metastases currently receiving bisphosphonates for palliation will be eligible providing other sites of measurable disease are present
- ECOG Performance Status 0, 1 or 2 (see Appendix 4)
- Adequate haematology, biochemical indices (FBC, U & Es)
- LFTs = Normal bilirubin, AST and/or ALT ≤3 x ULN if Alk Phos >5 x ULN (or an isolated elevation AST/ALT of ≤5 x ULN)
- Adequate renal function – Glomerular Filtration Rate (GFR) of >25mls per minute (see Appendix 5)
- Written informed consent, able to comply with treatment and follow-up

5.4 Exclusion Criteria

- Original primary tumour or subsequent relapse known to be positive for any of ER, PR, or HER2 receptors (defined above and in Appendix 3)* unless patient is a known BRCA1 or BRCA 2 mutation carrier
- Patients unfit for chemotherapy or those with neuropathy >grade 1 (sensory or motor)
- Known allergy to platinum compounds or to mannitol
- Known sensitivity to taxanes
- Patients with inoperable locally advanced disease suitable for local radiotherapy or an anthracycline containing regimen.
- Previous chemotherapy for metastatic disease other than an anthracycline as in inclusion criteria above.
- Previous exposure to a taxane in adjuvant chemotherapy within 12 months of trial entry
- Previous treatment with a taxane for recurrent locally advanced disease which was not completely excised.
- Previous treatment with a platinum chemotherapy drug
- LFTs = Abnormal bilirubin (> ULN) and/or AST and/or ALT >3 x ULN with Alk Phos >5 x ULN, or an isolated elevation AST/ALT of >5 x ULN.
- Patients with a life expectancy of less than 3 months

- Previous malignancies other than adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin, unless there has been a disease-free interval of at least 10 years
- Previous or synchronous second breast cancer (unless also confirmed ER-, PR-/unknown and HER2-)*
- Patients with bone limited disease
- Other serious uncontrolled medical conditions or concurrent medical illness likely to compromise life expectancy and/or the completion of trial therapy
- Pregnant, lactating or potentially childbearing women not using adequate contraception
  (documentation of a negative serum HCG pregnancy test should be available for pre-menopausal women with intact reproductive organs, or women less than two years after the menopause. Fertile women and their partners must use a medically acceptable contraceptive throughout the treatment period and for six months following cessation of treatment. Subjects must be made aware before entering the trial of the risk in becoming pregnant).

*Patients that have had a previous ER+, PR+ or HER2+ primary tumour, but a subsequent ER-, PR-/unknown and HER2- primary tumour with a histologically confirmed ER-, PR-/unknown and HER2- recurrence may be eligible on approval of the Chief Investigator or Clinical Coordinator. Details of the patient's medical history and tumour pathology will be requested by the TNT Trial Manager in order to ascertain eligibility. Please note that patients that meet these criteria must not be entered into the trial without approval of the Chief Investigator or Clinical Coordinator.

N.B. Prior exposure to taxanes in adjuvant setting does not exclude patients providing that there is ≥12 months between previous exposure and trial entry.

6. ENDPOINTS

6.1 Primary

- **Objective tumour response rate (CR + PR):** Response will be evaluated after three and six cycles of chemotherapy using modified RECIST criteria, in line with v1.1 of the guidance (see Appendix 2), with appropriate clinical assessment and radiological investigations. There will be a 'response evaluation committee' to independently assess all claimed responses (see section 14.2).

6.2 Secondary

- **Time to progression (TTP):** This will be defined according to RECIST v1.1 criteria and will be measured from randomisation until the confirmation of progression.
- **Progression Free Survival (PFS):** This will be defined according to RECIST v1.1 criteria and will be measured from randomisation until the confirmation of progression or death.
- **Response to second line protocol therapy on progression** will be assessed using RECIST v1.1 criteria as described for the primary endpoint.
- **Time to Treatment Failure (TTF):** This will be defined as time from randomisation to discontinuation of protocol treatment for any reason, or progression of disease as defined by RECIST v1.1.
- **Overall Survival (OS):** This will be defined as time from randomisation until death from any cause in the intention to treat population.
- **Toxicity:** This will be assessed throughout the treatment period using the NCI CTC AE v3.0 (see Appendix 6).
- **Frequency of development of symptomatic new cerebral metastases**

7. RANDOMISATION

7.1 Randomisation Procedures

Sufficient time, as long as they require, but a minimum of 24 hours, should be allowed for the patient to decide on trial entry, but the time which elapses between randomisation and start of chemotherapy should be minimised. An eligibility checklist and randomisation checklist should be completed prior to randomisation. To randomise a patient, telephone ICR-CTSU. The person randomising the patient will then be asked to confirm that an eligibility checklist has been completed and to verify that the patient has signed the TNT consent form (this will be the subject of a later audit). They will also be asked for all the information on the randomisation checklist. A trial number and treatment allocation will be given over the telephone and later confirmed in writing.

Randomisation telephone:	+44 (0)20 8643 7150
Fax:	+44 (0)20 8770 7876
Office Hours:	09:00 – 17:00 Monday-Friday

7.2 Minimisation Balancing Factors

Minimisation will be the technique used to allocate patients to either carboplatin or docetaxel. There are five balancing factors:

- centre
- previous adjuvant taxane chemotherapy vs. none;
- liver or lung metastasis affecting the parenchyma vs. none;
- performance status 0/1 vs. 2;
- recurrent inoperable locally advanced vs. metastatic carcinoma.

7.3 Following Randomisation

The relevant pharmacy department and research nurse will be sent a fax confirming patient details and trial ID together with the randomised treatment allocation (carboplatin or docetaxel).

8. TRIAL EVALUATIONS

8.1 Pre-Randomisation Clinical Evaluations

The following pre-treatment evaluations should be carried out:

- Confirmation of ER-, PR-/unknown and HER2- status (primary tumour and any areas of recurrence subjected to biopsy) by report from local histopathology laboratory please see Appendix 3
- **Or** Confirmation of germline BRCA1 or BRCA2 mutation
  N.B A copy of the genetic report confirming BRCA1/2 mutation will be requested after randomisation.
- Confirmation of measurable metastatic or recurrent locally advanced breast cancer (by surgery, histology, cytology, X-ray, or MRI) or confirmation of measurable disease by CT scan (excepting superficial metastases, measured & photographed with ruler) as defined by modified RECIST v1.1 (see Appendix 2). The maximum time between the baseline CT scan and start of treatment is 28 days.
- Full blood count
- Urea & electrolytes
- Liver function tests (including AST and/or ALT, Alk Phos and Bilirubin)
- Calculated GFR (see Appendix 5) or measured GFR if this is stated local policy.
- Audiogram if clinically indicated

8.2 Family History Questionnaire

Patients who give consent will be asked to complete a brief, optional family history questionnaire during their baseline visit. This information will be used to supplement blood sample tests from those that provide consent for this procedure, but also to identify those patients most at risk. The member of staff at the centre should check the questionnaire and use NICE Guidance on

appropriate referral to the NHS genetics service. Questionnaires should then be sent to the ICR-CTSU along with the other completed baseline CRFs.

8.3 Ethnicity

Ethnicity data will be collected on all patients (please refer to the TNT Trial Guidance Notes for further details).

8.4 Post-Randomisation Clinical Evaluations

Once patients have been randomised and the start date of treatment is known, the first CT scan (to be carried out at week 8 – see section 10 and Appendix 7) should be booked.

During Treatment

All toxicity and adverse reactions will be assessed and recorded at the end of each cycle of chemotherapy using the NCI CTC AE v3.0 (Appendix 6).

Patients will be assessed by CT scan after three and six cycles of allocated treatment. Patients with no progression after three cycles will receive a further three cycles of allocated treatment. Patients with proven progression will be offered six cycles of the alternative treatment, with a repeat response assessment after three and six cycles. The most appropriate "Target lesions" for response assessment may be re-allocated prior to commencement of cross-over treatment. Copies of CT scans should be requested and made available to the Response Evaluation Committee (see section 14.2).

Confirmation of final response by repeated CT scan four weeks after the post 6 cycle response assessment scan, as defined by RECIST v1.1, is recommended but will not be mandatory due to the constraints of booking CT scans.

Long-Term Follow-Up

Following treatment, patients will be reviewed at least three monthly (this may be more frequent according to the hospital's routine follow up procedures). Follow up data will be collected on all patients until death. CT scans should be carried out every three months during follow up and progression of disease must be confirmed by CT scan before the patient receives any further treatment.

Treatment On Progression

If the CT scan shows progression after three cycles of allocated treatment, they will be offered six cycles of the alternative treatment, with a CT scan being performed after three and six cycles of the alternative treatment. If there is clear progression at this stage treatment will be stopped and further management will be at the discretion of the local treating clinician.

If a patient completes six cycles of allocated treatment and progresses (imaging confirmed as defined by RECIST v1.1) at this stage or at a later date, six cycles of the alternative treatment

should be offered. A CT scan should be performed after three cycles (as above) and treatment stopped if there is no response to the alternative treatment.
If patients have a further progression after completing both allocated and alternative treatment groups, further management will be at the discretion of the local clinician.

9.0 BIOLOGICAL SPECIMEN COLLECTION

9.1 Collection of blood samples

For all patients who provide written informed consent, one 20ml research blood sample (EDTA) will be collected. Samples will be stored by The Institute of Cancer Research, Sutton in a CPA accredited laboratory, under appropriate Human Tissue Authority licence, where DNA will be extracted from samples according to good clinical practice.

DNA will be subjected to genetic profiling, including next generation whole genome sequencing, to attempt to determine underlying germline genetic factors that may contribute to the aetiology of triple negative and BRCA1 and BRCA2 associated breast cancer. The results from research genetic profiling will not be made available to patients. Results of the research tests for relevant genes will be made available on request to a patient's clinical geneticist, the geneticist having first received agreement from the patient, to assist NHS genetic analyses in the context of local counselling. The patient's clinical geneticist will identify the patient using the patient name, date of birth and trial number. Validation of the research results must be performed in a NHS approved laboratory.

An aliquot of extracted white blood cells gDNA, and plasma where available, will be transferred from The Institute of Cancer Research to the Guy's and St Thomas' Breast Tissue and Data Bank to facilitate analyses of the tumour genome being conducted on that site. Additional aliquots may be sent to other research laboratories with the agreement of the Trial Management Group.

9.2 Collection of tissue samples from primary and recurrent tumour

For all patients who provide written informed consent, representative paraffin-embedded tissue samples from the original primary tumour, lymph nodes and recurrent tumour if available will be collected, along with a copy of the original histology report(s). These blocks will be requested directly from the pathology department where the tissue sample is stored.

All patients will, at the discretion of the local principal investigator, be considered for a radiological guided core biopsy of recurrent tumour for allied translational research studies. These patients will be separately consented for this procedure, which will take place prior to start of first treatment if considered safe and acceptable by the investigator. The costs of the radiological guided biopsy and associated processing (up to £416) will be reimbursed by the Trials Unit on receipt of a satisfactory invoice.

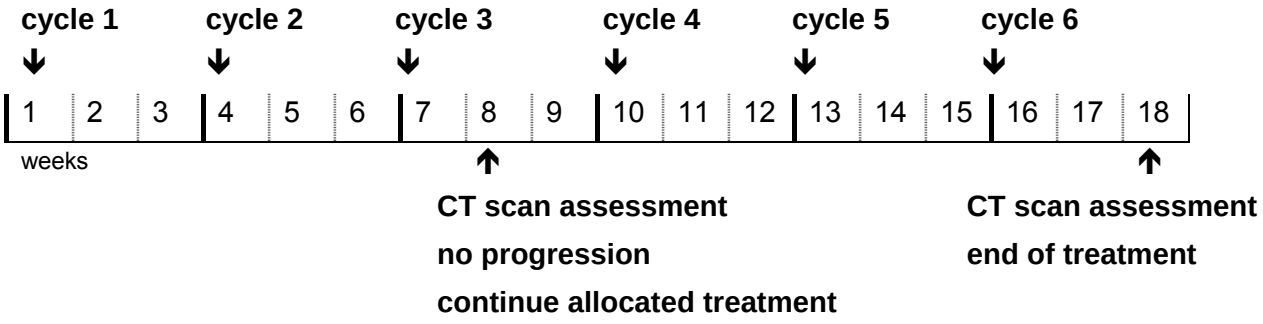
All tissue samples (from the primary and recurrent tumour) will be sent to the Guy's and St Thomas' Breast Tissue and Data Bank where they will be stored under the appropriate Human Tissue Authority licence. Tissue microarrays will be produced from cores of these paraffin blocks. Thick sections (approximately 15-20 in number) will be taken for DNA/RNA extraction. Analysis of other biomarkers on tissue sections will be undertaken, as described below.
Tissue samples will be analysed using a variety of techniques for markers of basal-like breast cancer, and function of the BRCA1 and BRCA2 and p53 gene family. Analyses of samples for a variety of other biomarkers for known and as yet unknown gene function will also be conducted. These analyses of the cancer genome, gene expression and protein expression profile may reveal new biomarkers of response and prognosis and new targets for therapy. These assays may include next generation whole genome sequencing techniques.

All participants will be asked to consent for storage of the samples to be used for future research. Coded data and coded samples will be used so that in almost all circumstances researchers will not have access to any details that identify the patient and will see all data in anonymised form. Key TNT trial individuals within the ICR−CTSU, Institute of Cancer Research Blood DNA Collection and Guy's and St Thomas' Breast Tissue and Data Bank will be able to link the unique identifier code with the patient identifiers (blood = patient name and date of birth; tissue = patient initials and date of birth) to ensure that on receipt the samples have been associated with the correct trial patient before code assignment and to ensure that no erroneous or duplicate samples are received.

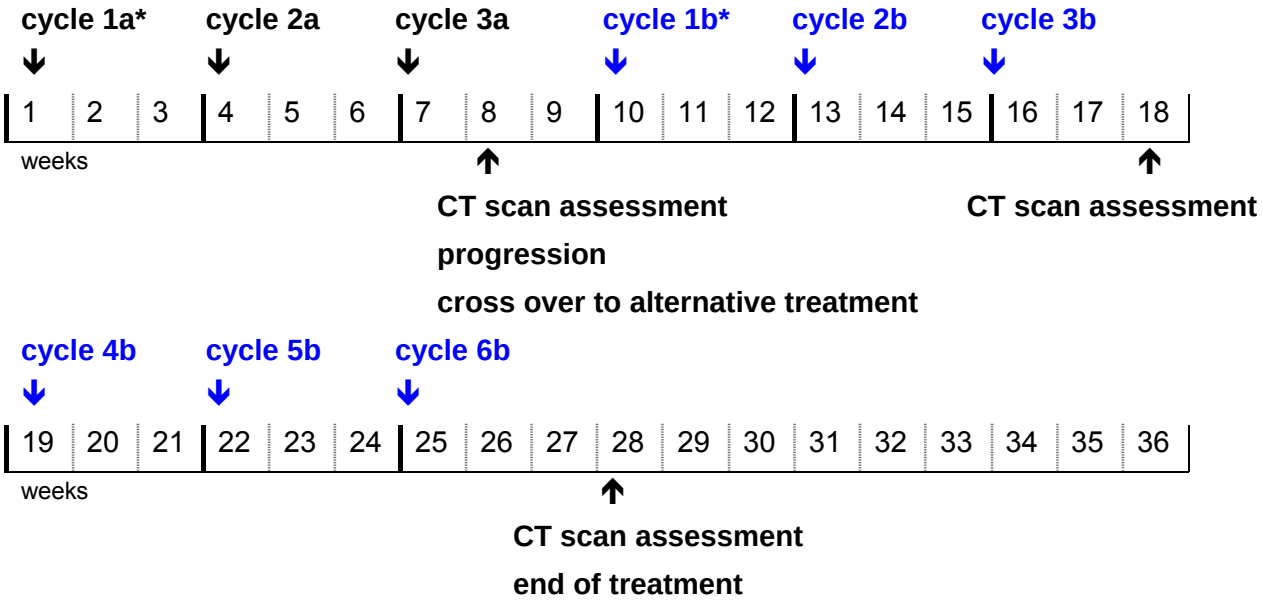
10. TREATMENT DETAILS

10.1 Treatment Summaries

No progression



Progression After 3 Cycles



***a = allocated treatment; b = cross over treatment**

Chemotherapy is given on day one every three weeks. Assessment of response by CT scan is carried out after three cycles (during week eight). Those who have clearly progressed after the initial three cycles will be offered six cycles of the alternative treatment group. A CT scan will be performed after three cycles of this alternative treatment. If progression is still present, treatment will be stopped and further management will be at the discretion of the local clinician.

For patients who have not progressed after three cycles of allocated treatment, a further three cycles will be given. Following disease progression after completion of these six cycles, treatment with the alternative group will be offered with a CT scan being performed after the first three cycles (as above) and at the end of treatment.

10.2 Trial Treatment

Patients should receive chemotherapy intravenously at the following doses. It is intended that patients will receive six cycles in three-weekly intervals, but response will be assessed by CT after three cycles in addition to the CT scan at the end of cycle six.

Carboplatin AUC 6
Patients with serum urea or serum creatinine outside the local normal range, or GFR calculated as being greater than 100ml/minute or less than 60ml/minute should have GFR measured (using the 51CrEDTA method) rather than calculated (see Appendix 5).
NB: If GFR is measured (as opposed to calculated) AUC 6 should still be maintained.

Docetaxel 100mg/m^2 (BSA calculated according to local policy and capped at 2.0m^2)

N.B: Docetaxel should be given at a dose of 75 mg/m^2 if ALT and/or AST is greater than 1.5 x ULN and the alkaline phosphatase is abnormal. Investigators please note exclusion criteria for more severe derangements of LFTs noted in protocol and the docetaxel SmPC.

Additional information on the safety and administration of these drugs can be found in Appendix 8.

10.3 Pre-Medication

Docetaxel
When giving docetaxel chemotherapy it is recommended that a pre-medication regimen be employed to reduce the risk of hypersensitivity reactions.

24 hours prior to docetaxel infusion: Dexamethasone 8mg po bd and continued for at least two days.

G-CSF or PEG G-CSF should be given as primary prophylaxis for all patients according to the SmPC for the selected agent and local protocols for use.

Carboplatin
Prophylactic antibiotics and G-CSF may be given with carboplatin according to local protocol or for the persistence of neutropenic fever according to NCCN 2005 and ASCO 2006 guidance (28) (see Appendix 9). Antibiotic prophylaxis may be given according to local practice.

10.4 Anti-Emetics

Patients should be given anti-emetic therapy according to local practice.

Carboplatin

Carboplatin has a high emetogenic potential and it is recommended that pre-treatment with a 5-HT_3 antagonist (e.g. granisetron, ondansetron) is given, together with a corticosteroid (e.g. dexamethasone). This should be continued for 3-5 days following chemotherapy according to local anti-emetic policy.

Docetaxel

Docetaxel is much less emetogenic and the recommended pre/post dexamethasone treatment may be sufficient (see Appendix 8).

10.5 Guidelines For The Management Of Toxicity

In order to maintain dose-intensity and cumulative dose-delivery reasonable efforts should be taken to minimise dose reduction and treatment delays. Patients whose treatment is delayed because of toxicity should be evaluated on a weekly basis until adequate recovery has been made.

Primary prophylactic G-CSF should be used for all patients on the Docetaxel arm. G-CSF may be used according to local policy for patients on the Carboplatin arm (see Appendix 9). Institution policy on G-CSF usage must be declared before starting the trial. Use of G-CSF for each patient at each cycle of chemotherapy will be recorded on the CRFs.

Toxicity is graded according to NCI Common Terminology Criteria for Adverse Events v3.0 (NCI CTC AE V3.0) (Appendix 6).

Docetaxel

Full Blood Count and LFTs must be measured immediately prior to each cycle (i.e. no more than 1 week prior to the first cycle or 4 days before the start of subsequent cycles). Docetaxel should be administered when neutrophil count is greater than or equal to 1.5 x 10^9/L and platelet count greater than or equal to 100 x 10^9/L.

N.B. If initial allocated treatment is withdrawn because of toxicity, cross over to the alternative treatment group should be considered by the local investigator if anticipated toxicities are thought appropriate.

Type of Toxicity	Grade	Previous dose level		
		Docetaxel 100mg/m^2	**Docetaxel 75mg/m^2**	**Docetaxel 60mg/m^2**
	CTC AE V3.0	**Dose modification**		
HAEMATOLOGICAL				
Neutrophil	1 (≥1.5 x 10^9/L)	100mg/m^2	75mg/m^2	60mg/m^2
	2 (1.0 – 1.4 x 10^9/L)	Delay until grade 0/1*, then 100mg/m^2	Delay until grade 0/1*, then 75mg/m^2	Delay until grade 0/1*, then 60mg/m^2
	3 (<1.0 x 10^9/L)	Delay until grade 0/1*, then 100mg/m^2	Delay until grade 0/1*, then 75mg/m^2	Delay until grade 0/1*, then 60mg/m^2
	4 >1 week (<0.5 x 10^9/L)	Delay until grade 0/1*, then 75mg/m^2	Delay until grade 0/1*, then 60mg/m^2	**Stop**
Febrile Neutropenia	3 (present)	Delay until grade 0/1*, then 75mg/m^2	Delay until grade 0/1*, then 60mg/m^2	**Stop**
	4 (life-threatening)	Delay until grade 0/1*, then 75mg/m^2	Delay until grade 0/1*, then 60mg/m^2	**Stop**
Platelets ≥100		100mg/m^2	75mg/m^2	60mg/m^2
Platelets <100		Delay until >100, then 75mg/m^2	Delay until >100, then 60mg/m^2	**Stop**
NON-HAEMATOLOGICAL				
Cutaneous	1	100mg/m^2	75mg/m^2	60mg/m^2
	2	100mg/m^2	75mg/m^2	60mg/m^2
	3	75mg/m^2	60mg/m^2	**Stop**
Peripheral Neuropathy	1	100mg/m^2	75mg/m^2	60mg/m^2
	2	75mg/m^2	60mg/m^2	**Stop**
	3	75mg/m^2	**Stop**	**Stop**
	4	**Stop**	**Stop**	**Stop**

*delay for a maximum of three consecutive weeks, then stop treatment if blood counts have not recovered. Further treatment is at the discretion of the treating clinician.

The dose should be reduced following dose delays for haematological toxicity on two separate occasions.

Carboplatin

Full Blood Count and renal function must be measured immediately prior to each cycle (i.e. no more than 1 week prior to the first cycle or 4 days before the start of subsequent cycles). Carboplatin should be administered when neutrophil count is greater than or equal to 1.5 x 10^9/L and platelet count greater than or equal to 75 x 10^9/L. ASCO/NCCN guidance on use of G-CSF is provided in Appendix 9.

If serum creatinine changes by more than 25% then GFR must be recalculated and the dose of carboplatin adjusted to maintain the target AUC.

If carboplatin is delayed for three consecutive weeks and blood counts have not recovered, then treatment should be stopped and further treatment conducted at the discretion of the treating clinician.

N.B. If initial allocated treatment is withdrawn because of toxicity, cross over to the alternative treatment group should be considered by the local investigator if anticipated toxicities are thought appropriate.

Dose Reduction Table

			Neutrophils			
			Grade 1	Grade 2	Grade 3	Grade 4
			≥1.5 x 10^9/L – LLN	1.0 – 1.5 x 10^9/L	0.5 – 1.0 x 10^9/L	<0.5 x 10^9/L
Platelets	Grade 1	LLN - ≥75 x 10^9/L	AUC 6	Delay until grade 0/1*, then repeat AUC 6	Delay until grade 0/1*, then repeat AUC 6	Delay until grade 0/1*, then reduce to AUC 5
	Grade 2	<75 – 50 x 10^9/L	Delay until grade 0/1*, then repeat AUC 6	Delay until grade 0/1*, then repeat AUC 6	Delay until grade 0/1*, then reduce to AUC 5	Delay until grade 0/1*, then reduce to AUC 5
	Grade 3	<50 – 25 x 10^9/L	Delay until grade 0/1*, then reduce to AUC 5	Delay until grade 0/1*, then reduce to AUC 5	Delay until grade 0/1*, then reduce to AUC 5	Delay until grade 0/1*, then reduce to AUC 5
	Grade 4	<25 x 10^9/L	Delay until grade 0/1*, then reduce to AUC 5	Delay until grade 0/1*, then reduce to AUC 5	Delay until grade 0/1*, then reduce to AUC 5	**Stop**

*delay for a maximum of three consecutive weeks, then stop treatment if blood counts have not recovered. Further treatment is at the discretion of the treating clinician.

Type of Toxicity	Grade	Carboplatin AUC 6	Carboplatin AUC 5
	CTC AE V3.0	**Dose modification**	
HAEMATOLOGICAL			
Febrile Neutropenia	3 (present)	AUC 5 or G-CSF prophylaxis	**Stop**
	4 (life-threatening)	**Stop or AUC 5 +/- G-CSF at PI discretion**	**Stop**
NON-HAEMATOLOGICAL			
Peripheral Neuropathy	1	AUC 6	AUC 5
	2	AUC 5	**Stop**
	3	AUC 5	**Stop**
	4	AUC 5	**Stop**
Increased creatinine	≥2	**Stop**	**Stop**

A dose reduction to AUC5 for subsequent cycles should be given for the following reasons:

- febrile neutropenia (where G-CSF is not being initiated);
- neutrophil count <0.5 x 10^9/L (where G-CSF is not being initiated);
- a dose delay for haematological toxicity on two separate occasions;
- platelet count of <50 x 10^9/L;
- day 21 neutrophil count of <1 x 10^9/L with platelet count of <75 x 10^9/L; or
- ≥ grade 2 peripheral neuropathy

If the patient continues to have these reactions at AUC 5 the protocol defined treatment should be discontinued and further treatment be conducted at the discretion of the treating clinician. The nature of this "post-protocol" treatment must be recorded in the CRF.

In patients who have grade 4 thrombocytopenia **and** grade 4 neutropenia, or grade 4 neutropenic sepsis, treatment should be stopped and further treatment conducted at the discretion of the treating clinician. If initial allocated treatment is withdrawn because of toxicity, cross over to the alternative treatment group should be considered by the local investigator if anticipated toxicities are thought appropriate.

10.6 Guidelines For Management After Treatment Withdrawal

Patients who do not receive their allocated treatment for any reason should be treated at the discretion of their clinician. However, analyses of all outcome data will be on the basis of intention to treat. Unless the patient requests otherwise, all CRFs, including long term follow up, should be completed, regardless of treatment actually received. A trial deviation form should be completed to record details of deviation from treatment allocation, and also for any patient who withdraws consent for further follow up. Patients are asked prior to randomisation to consent to follow up

should they withdraw from the treatment allocation (see patient information sheet and consent form), and any patient unwilling to give that assurance prior to trial entry should not be randomised. Patients are, however, free to reverse that decision at any time without giving a reason.

11. PHARMACOVIGILANCE

11.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial 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 an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the Investigational Medicinal Product (IMP). Signs and symptoms of metastatic disease, as determined by the local clinical investigator, are not adverse events.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the IMP. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature and severity of which is not consistent with the applicable product information (i.e. summary of product characteristics (SmPC) for carboplatin and docetaxel, which are licensed products*). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event or **Serious Adverse Reaction**: Any untoward medical occurrence or effect that occurs after the commencement of randomised treatment and within 30 days of the last administration of the trial drug (i.e. carboplatin or docetaxel) that at any dose:

- results in death: *the patient's death is suspected as being a direct outcome of the AE.*
- is life-threatening: *refers to an event in which the subject was at risk of death at the time of the event. It also refers to an event that would result in death with the continued use of the product; it does not refer to an event which hypothetically might have caused death if it were more severe*
- requires hospitalisation, or prolongation of existing inpatient hospitalisation: *admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE. Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it*

may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study.

- results in persistent or significant disability or incapacity: *the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.*
- is a congenital anomaly or birth defect

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms (i.e. progression form for relapse and death form for death).

Medical judgement should be exercised in deciding whether other AE/ARs are serious. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR): any adverse event with a suspected relationship to an IMP that is both unexpected and serious.

11.2 Causality

Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities due to either of the drugs used in this trial (see table 2). The local clinical investigator is responsible for the assessment of causality of serious adverse events using the definitions in table 1.

If any doubt about the causality the investigator should inform ICR-CTSU who will notify the Chief Investigator. Pharmaceutical companies and/or other clinicians may be asked to advise.

Table 1 – Definitions for causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

11.3 Reporting Procedures

All adverse reactions should be reported on the chemotherapy assessment form. Depending on the nature of the event the additional reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the TNT Trial Manager at ICR-CTSU in the first instance.

Expedited Reporting of Serious Adverse Events/Reactions & SUSARs

SARs shown in Table 2 do not require immediate reporting using an SAE form. Hospitalisation or prolongation of existing inpatient hospitalisation as a result of the SARs shown in Table 2 should be reported using the TNT Known SAR form and sent with any other CRFs (or when requested by the ICR-CTSU). All other SAEs should be reported within 24 hours of the investigator becoming aware of the event, by completing the TNT SAE form and faxing it to:

Please fax SAE forms for the attention of TNT Trial Manager:
Fax: +44 (0)20 8722 4368 (Monday – Friday 09:00 – 17:00)
The Safety Desk
Clinical Trials & Statistical Unit (ICR-CTSU)
Section of Clinical Trials
Institute of Cancer Research
Sir Richard Doll Building
Cotswold Road, Sutton. SM2 5NG

Table 2 – Hospitalisation or prolongation of existing inpatient hospitalisation as a result of the following SARs do not require immediate reporting on the TNT SAE form, but should be reported using the TNT Known SAR form. Please note that the NCI CTC AE v3.0 criteria define a Grade 4 event as a life-threatening or disabling AE. Any life-threatening event must be reported as an SAE. As such if the event is listed below but meets the NCI CTC AE v3.0 criteria for a Grade 4 event, it must be reported immediately on the TNT SAE form.

Toxicity	Carboplatin	Docetaxel
Haempoeitic:		
Anaemia	✓	✓
Bleeding episodes		✓
Leucopenia	✓	✓
Neutropenia	✓	✓
Sepsis	✓	✓
Thrombocytopenia	✓	✓
Febrile neutropenia	✓	✓
Gastrointestinal:		
Abdominal pain		✓
Anorexia	✓	✓
Constipation	✓	✓
Diarrhoea	✓	✓
GI bleeding		✓
Oesophagitis		✓
Nausea	✓	✓
Stomatitis		✓
Taste perversion	✓	✓
Vomiting	✓	✓
Neurotoxicity:		
Ocular toxicity	✓	
Neuropathy – Peripheral	✓	
Neuropathy – motor/sensory		✓
Biochemistry:		
Decreased serum calcium/magnesium/potassium	✓	
Renal:		
Decreased creatinine clearance (GFR)	✓	
Increased blood urea nitrogen	✓	
Increased serum creatinine	✓	
Increased uric acid	✓	
Hepatic:		
Increased alkaline phosphatase	✓	✓
Increased ALT	✓	✓
Increased AST	✓	✓
Increased bilirubin	✓	✓
Cardiac:		
Dysrhythmia/hypertension/hypotension		✓

Musculoskeletal:		
Arthralgia/myalgia		✓
Respiratory:		
Dyspnoea		✓
Skin:		
Alopecia	✓	✓
Cutaneous reactions		✓
Nail changes		✓
Fluid retention:		
Peripheral oedema		✓
Others:		
Asthenia		✓
Chest pain		✓
Generalised pain		✓
Hypersensitivity	✓	✓
Infusion site reaction		✓
Injection site reaction	✓	
Ototoxicity	✓	

The causality of the event should be assessed by the responsible investigator or designated representative. The outcome of the SAE must be reported within 15 days of the initial report.

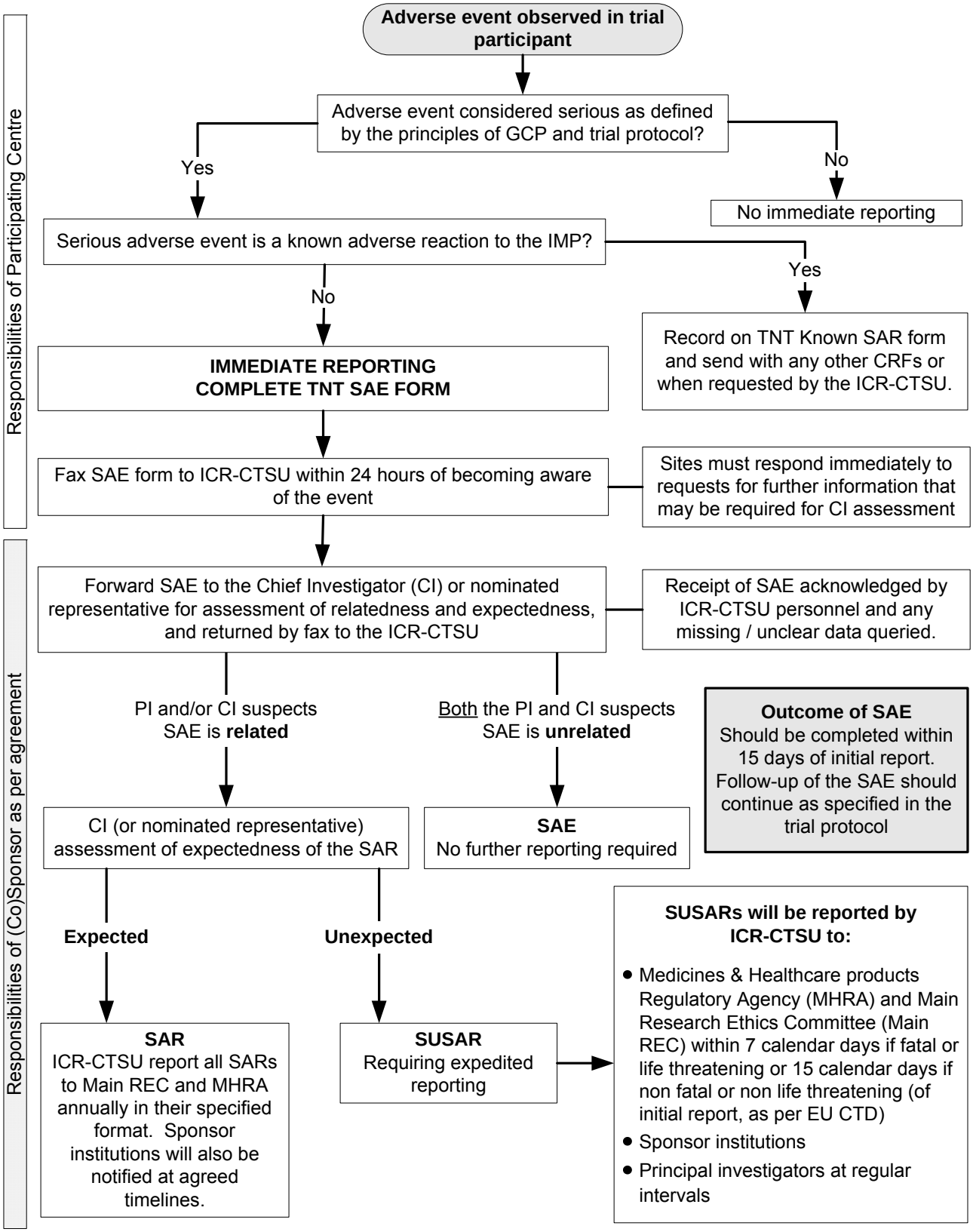
Follow-up of the SAE should continue until the subject recovers (or recovers with sequelae).

Safety reporting of SARs and SUSARs, including expedited reporting, will be carried out by ICR-CTSU on behalf of the CI in accordance with NRES and MHRA guidelines.

Please refer to the flow diagram for a summary of SAE reporting.

Summary of SAE Reporting

Flow diagram for SAE reporting, and action following report



Non-serious adverse reactions

Non-serious adverse reactions whether expected or not should be reported on the chemotherapy assessment forms and sent to ICR-CTSU within one month of the form being due.

12. STATISTICAL CONSIDERATIONS

12.1 Randomisation

A 1:1 treatment randomisation will be performed. Treatment will not be blinded, as it would be impracticable due to the different side effect profiles of the two trial treatments. Allocation will be by the minimisation technique, balancing for centre, and known prognostic factors (previous adjuvant (or primary medical) taxane chemotherapy vs. not, liver or lung metastasis affecting the parenchyma vs. not, performance status 0/1 vs. 2, recurrent inoperable locally advanced vs. metastatic carcinoma). Minimisation is a widely recognised method of ensuring balance between treatment groups for several prognostic factors in clinical trials with smaller sample sizes. Treatment allocation to the next participant enrolled depends on the characteristics of the patients already involved, thus minimising the imbalance across the prognostic factors.

12.2 Sample Size

This trial is a comparative phase III trial primarily in patients with triple negative breast cancer with response rate as the primary endpoint. Thus the overall sample size is determined for the triple negative population.

Docetaxel is the standard of care in this patient group, and a response rate of 30% can be expected in unselected anthracycline treated patients who receive docetaxel as first line chemotherapy for metastatic disease (29, 30). No specific information is available however concerning response rates to docetaxel in the ER-, PR- and HER2- patient group we intend to study. Preclinical data relating to BRCA1 function (21) and the recently presented results of the ECOG 2100 study (31), heavily enriched for HER2- cancers, suggest that single agent taxane response may be lower in this histological group and thus the response rate after docetaxel might be expected to be 20-30%. The trial aims to show the superiority of single agent carboplatin in this patient group and an improvement in response rates of 15% would be sufficient to prove this concept. Equivalence of response rates however, accompanied by reduced toxicity with carboplatin, would also influence future clinical practice.

The sample sizes required (assuming 90% power and α=0.05 (2 sided)) for likely response rates are given in the following table:

Number of patients required:

Docetaxel response rate	Number of patients (Carboplatin response rate)
20%	370 (35%)
25%	406 (40%)
30%	434 (45%)

It is planned therefore to recruit between 370 and 450 patients, with a target of at least 370 patients, aiming to accrue 400 patients as agreed by the IDMC.

Due to the lack of response rate data it is imperative that stopping rules are defined to terminate the trial in the case of a lack of therapeutic efficacy. The IDMC will evaluate the trial after the first 28 randomised patients have completed the first three cycles of treatment. If 0 out of the first 14 patients treated achieve a response to therapy, one can be reasonable certain that the true response rate is <20% in that patient group treated with a specific therapeutic regimen. Early response rates on each group of the trial will be monitored and reported to the IDMC. If 0/14 carboplatin treated patients respond (and responses are seen in docetaxel treated patients) then it is expected that the IDMC will recommend closure of the trial. If 0/14 patients on the docetaxel group of the trial respond, this will be discussed by the IDMC but may not necessarily terminate the trial given that this is the standard of care for this patient group outside the trial and thus secure evidence of lack of efficacy will be required to change established practice.

BRCA1 and BRCA2 mutation carrier subgroups

It is recognised that this trial is unlikely to have sufficient power to detect clinically meaningful differences in the BRCA1 and BRCA2 mutation carrier subgroups and therefore, there are no formal sample size calculations; any results will be seen as hypothesis-generating.

It is expected that there will be only a small number of known BRCA1 mutation carriers randomised into the trial. However, in combination with the 31 known BRCA1 patients already randomised into the BRCA trial (20 carboplatin, 11 docetaxel), the additional known BRCA1 patients gained in the BRCA International trial and the centrally determined BRCA1 subgroup of triple negative patients (expected to be approximately 10% of the total), it is hoped that there will be approximately 60 BRCA1 patients in total.

The BRCA2 mutation is not usually found in patients with triple negative breast cancer, therefore, the BRCA2 mutation carrier subgroup will predominately consist of patients where BRCA2 status is already known prior to randomisation. These data will be combined with the 10 BRCA2 patients already recruited into the BRCA trial and any additional BRCA2 patients participating in the BRCA International trial. It is expected that there will be a total of approximately 30 known BRCA2 mutation carriers for the analysis.

12.3 Analyses

Primary endpoint

Analysis will review both overall and differential response rates (as measured by a point estimate and confidence interval for the difference in proportions responding in the two treatment groups) in patients with triple negative breast cancer randomised via ICR-CTSU with regular review by the IDMC.

A sensitivity analysis will include any triple negative patients not randomised by ICR-CTSU, e.g. any patients with triple negative breast cancer randomised into the BRCA trial or BRCA International trial.

Secondary endpoints

TTP, PFS, TTF and OS for patients with triple negative breast cancer will be presented using Kaplan-Meier survival plots and analysed using the Log-rank test and Cox proportional hazards models. Cox proportional hazards models will also be used to investigate confounding of treatment effect with clinically prognostic factors. Other survival models e.g. exponential, Weibull, will be explored too to determine if any of these models is a more suitable fit for the data.

A sensitivity analysis will include any triple negative patients not randomised by ICR-CTSU, e.g. any patients with triple negative breast cancer randomised into the BRCA trial or BRCA International trial.

Non-biological subgroup analyses

Subgroup analyses are exploratory in nature and will include, but are not limited to, exploring the consistency of the effect of whether patient have received adjuvant taxane therapy. In addition to a univariate analysis, adjustment will be made for known prognostic factors to determine if any taxane effect is independent.

12.4 Interim Analyses

The IDMC will be asked to provide guidance as to the suitability of continuation of the trial after response is evaluable in the first 14 patients with triple negative breast cancer in each of the treatment groups. Response rates will be monitored frequently by the IDMC.

In addition to the early stopping rules defined above should, at a later point in the trial, the upper confidence limit (95%) indicate a true response rate of less than 20% to either drug or the observed recruitment rate render the accrual target unachievable then the IDMC will recommend a review of the appropriateness of continuing the trial.

12.5 Planned Retrospective Biological Subgroup Analyses

The subgroups below are planned analyses. These analyses will check for consistency of effect with the overall, intention to treat analysis, on all randomised patients and will also look at interactions between the treatment and the subgroup, although it is recognised that the power to detect any significant interactions in this number of patients will be low. Any findings from these subgroup analyses will be exploratory and seen as hypothesis generating.

1. "Basal-like" sub-group: The phenotypic overlap with familial BRCA1 cancers is greatest for a large "basal-like"(85%) sub-group of "Triple-Negative" breast cancers (6). These cases cannot be characterised prior to study entry as the markers are not part of the reported NHS breast pathology minimum dataset. An analysis of study endpoints will be performed within this sub-group after central histopathological analysis using expanded immunopanel criteria (ER, PgR, HER2 negative, CK5/6+ve or EGFR+ve) to define core basal(32) and using analysis of the "Basal-like" subgroup using the PAM-50 classifier from the FFPE material (33).

2. BRCA1 mutation carrier group: A small proportion 10-20% (34) of patients in this trial may carry mutations in BRCA1. It is expected that the response rate to carboplatin in this sub-population may be higher than in the group overall. This group of cases will be detected by BRCA1 mutation testing. Data from this subgroup of patients with both triple negative breast cancer and BRCA1 mutation will be analysed in combination with the known BRCA1 mutation carriers already randomised to the original BRCA trial and additional patients participating in TNT, due to their known BRCA1 status or through the BRCA International trial.

3. BRCA2 mutation carrier group: Patients with known BRCA2 mutation participating in TNT or the BRCA International trial will be analysed with data from patients already participating in the original BRCA trial. It is not expected that patients with triple negative breast cancer will also be BRCA2 mutation carriers. Similar to the BRCA1 subgroup, the response rate to carboplatin is expected to be higher in this subgroup than in patients with triple negative breast cancer.

4. Combined BRCA1 and BRCA2 mutation carrier group.

5. Analysis of the other putative markers of platinum salt sensitivity: Functional inactivation of the homologous recombination (HR) DNA repair pathway may confer platinum salt sensitivity. Epigenetic down regulation of BRCA1 mRNA is frequent in TNBC, appears highest in an gene expression profile classified basal sub population (35) and may be important in defining sensitivity to platinum (36) . BRCA1 mRNA expression will be characterised by Q-RT PCR using FFPE optimised Q R-PCR and levels will be correlated with response (summarised as an ordinal variable, 1=CR, 2=PR, 3= SD, 4=PD) Changes in the genome landscape which may arise as a consequence of defective HR may also

provide an indicator of platinum salt sensitivity (36). Allelic imbalance (AI) has also been shown to correlate with platinum salt sensitivity in TNBC (37) and will be assessed using technologies such as Affymetrix MIP arrays. The number of AI regions will be examined as a continuous variable and correlated with response as an ordinal factor, as previously. Translational analysis will also include other recognised markers that reflect regulation of HR including scoring of RAD51, geminin, histone gamma-H2AX (38), and 53BP1 foci (39) as well as platinum salt sensitivity such as low ERCC1 (40) expression or p63 (27).

6. Analysis of multiple exploratory biomarkers will include characterising p63 expression and DNp63 and Tap73 ratio, and PTEN loss of expression. examined as a continuous variables with response as an ordinal factor (1=CR, 2=PR, 3= SD, 4=PD). Exploratory analysis will determine proof of principle and suggested "cut off" requiring validation in future trials. Additional exploratory analyses based on subgroups defined by associated translational studies will be performed subject to successful outcome of grant applications to support these translational analyses.

In addition, a confirmed ER-, PR- and HER2- subgroup analysis may be performed to examine response rates to the study drugs following exclusion of cases positive for any of these proteins and in situ hybridisation assays (FISH and/or CISH) for the HER2 gene (See ER/PR/HER2 inclusion criteria in Appendix 3). This subgroup analysis will be performed if central review of initial samples reveals a high proportion of discrepant case. The size of the initial sample and proportion of discrepancies will be pre-defined in the Statistical Analysis Plan.

13. PATIENT PROTECTION & ETHICAL CONSIDERATIONS

13.1 Ethics Approval

The study has been approved by East London and The City Main Research Ethics Committee (Main REC) dated 11/06/2007. Before entering patients, the principal investigator at each site is responsible for gaining Site Specific Assessment (SSA) and advising the Main REC. Patients should be asked to sign the main consent form and the appropriate sections for the donation of biological samples after having both verbal and written information. Patients who do not wish to take part in one or any of the biological studies may take part in the main trial. The consent form must be countersigned by the Principal Investigator or a designated individual, and a record of who designated individuals are, and the circumstances under which they countersign consent forms must be clearly documented at the research site and be available for inspection together with original copies of all signed patient consent forms. The TNT patient information sheet should be provided in addition to the standard chemotherapy patient information sheets that are provided by the centre and used in routine practice.

The trial will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

The TNT patient information sheet, consent form and GP letter are provided as separate documents.

13.2 Treatment Compliance

After the patient has entered the trial the clinician remains free to give treatments alternative to that specified in the protocol at any stage if he/she feels it is in the patient's best interest, but the reasons for doing so should be recorded. In these cases the patients remain within the study for the purposes of follow-up and data analysis. All patients are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

13.3 Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number (CHI number in Scotland) will be collected at randomisation to allow tracing through national records and to assist with long term follow-up. The personal data recorded on all documents will be regarded as confidential, and to preserve each subject's anonymity, only their initials and date of birth will be recorded on subsequent Case Report Forms.

The investigator must keep a separate log of patients' trial numbers, names, addresses and hospital numbers. The investigator must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The investigator must ensure the patient's confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the Trials Unit will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. (In the case of special problems and/or government queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected).

ICR-CTSU is registered under the Data Protection Act.

14. TRIAL MANAGEMENT

14.1 Trial Steering Committee & Trial Management Group

The role of the Trial Steering Committee (TSC) is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

The Trial Management Group (TMG) will include principal investigators, oncologists, surgeons, scientists and trials staff from ICR-CTSU. This group will report to regular meetings of the investigators, the NCRI Breast Clinical Studies Group, the TSC and the IDMC.

14.2 Response Evaluation Committee

A Response Evaluation Committee will be appointed to independently and blindly assess all claimed responses on CT scans. This group will consist of two radiologists.

14.3 Drug Supply & Dispensing

Both carboplatin and docetaxel are used in the routine management of breast cancer and are available in the oncology pharmacy of all participating centres. The trial treatments will therefore be supplied via hospital stock. On dispensing, study drug/s will be labelled in accordance with local policy, which must satisfy the requirements of the EU Clinical Trials Directive 2004, GCP Directive 2006 and Draft guidance on 'specific modalities' for non-commercial clinical trials. Further details regarding the pharmacy requirements for TNT are provided in the Trial Guidance Notes and Pharmacy Information Document stored in the Pharmacy Site File.

15. RESEARCH GOVERNANCE

15.1 Trial Administration & Logistics

The co-sponsors are The Institute of Cancer Research (ICR) and King's College London (KCL), the Chief Investigator's host institution. Sponsorship activities and delegated responsibilities are shared between KCL and ICR, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Both parties agree to allow inspection of their premises by the competent authorities. Responsibilities of the co-sponsors are set out in an agreement letter between ICR and KCL.

KCL has sponsorship responsibility for obtaining authorisation and appropriate ethics committee opinion (Part 3 of the Regulations) and for pharmacovigilance (Part 5 of the Regulations). The following responsibilities have been delegated:

A to Chief Investigator:

1. Selection of investigators

B to ICR:

1. Ensure an appropriate ethics opinion has been sought, and any amendments have been approved;

2. Give notice of amendments to protocol, make representations about amendments to the main REC;

3. Give notice a trial has ended;

4. Keep records of all serious adverse events reported by investigators;

5. Ensure recording and prompt reporting of serious adverse reactions to the Chief Investigator;

6. Report to the MHRA any serious adverse events which the chief investigator considers to be SUSARs;

7. Ensure principal investigators are informed of SUSARs;

8. Ensure all SUSARs including those in third countries entered into European database;

9. Provide annual list of SUSARs and a safety report.

The following responsibilities are retained by the Chief Investigator, or delegated in his absence, a named deputy:

10. Making an initial assessment as to which serious events are SUSARs;

11. Prompt decision as to which serious adverse events are SUSARs, and prompt reporting of that decision to the Director, Section of Clinical Trials, ICR-CTSU, The Institute of Cancer Research for onward reporting to the licensing authority;

12. Reporting to the licensing authority and sponsorship institutions.

C to participating centres:

1. Ensure recording and prompt reporting of suspected unexpected serious adverse reactions (SUSARs) – delegated to participating centres;

ICR has responsibility for ensuring the research is conducted in accordance with Good Clinical Practice (Part 4 of the Regulations). The following responsibilities have been delegated:

A to KCL:

1. Take appropriate urgent safety measures – delegated to the Chief Investigator.

B to participating centres:

1. Put and keep in place arrangements to adhere to GCP;
2. Keep a copy of all 'essential documents' (as defined under ICH GCP) and ensure appropriate archiving and destruction of documentation once the study has ended;
3. Ensure IMPs (investigational medicinal products) are made available to subjects free of charge;
4. Take appropriate urgent safety measures

Responsibilities are defined in an agreement between an individual participating centre and the co-sponsors.

ICR is responsible for administering funding and co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between ICR and KCL/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

15.2 Protocol Compliance & Monitoring

TNT is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Directive. Before activating the trial, participating centres are required to sign an agreement accepting sponsorship responsibility for all trial activity which takes place within their centre.

Staff from centres that have attended the Investigator Launch meeting will not require start-up visits unless they are requested by the Trials Unit or the Principal Investigator.

15.3 Data Acquisition & On-Site Monitoring/Auditing

On-site monitoring/auditing will be based on a risk-based strategy. Trials Unit staff may visit centres to confirm that agreements are being adhered to, specifically to carry out source data verification and confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996. By participating in TNT, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs
- source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- all staff at their centre who are involved with the trial will meet the requirements of the EU Directive
- original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent
- copies of CRFs are retained for 20 years to comply with the co-sponsor requirements.
- staff will comply with the Trial Guidance Notes for TNT

ICR-CTSU will monitor receipt of CRFs and evaluate incoming CRFs for compliance with the protocol, inconsistent or missing data.

Participating centres may be monitored by ICR-CTSU and possibly by Health Authorities. Monitoring by ICR-CTSU aims to verify compliance with the protocol and to conduct source data verification (SDV).

Site auditing/monitoring will be conducted at a proportion of participating centres at least once during the course of the trial. If a monitoring visit is required ICR-CTSU will contact the centre to discuss dates of proposed visit. Once a date has been confirmed a list of patients whose notes will be monitored/audited during the visit will be sent to the centre. This list will be sent out in advance to give sufficient time for the notes to be made available. (The Trial Statistician will decide what percentage of patients are to be monitored/audited).

If any problems are detected in the course of the monitoring/auditing visits then the Principal Investigator and ICR-CTSU will work together to resolve queries to determine the centre's future participation in the study.

15.4 Archiving

Source data (including data on any patients who die) must be retained for the duration of the recruitment, treatment and follow up phases of the trial for inspection by representatives of ICR-CTSU and regulatory authorities.

15.5 Financial Matters

The trial is investigator designed and led, and has been approved by CTAAC. It is endorsed by Cancer Research UK and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

Research costs (for the clinical trial management) are being funded by Cancer Research UK and Breakthrough Breast Cancer. If additional financial support is received from any other source, this will be made apparent to the approving Main REC and CTAAC, but will not require a protocol amendment.

No individual per patient payment will be made to Trusts or investigators, but NCRN (or regional equivalent) network resources should be made available as the trial is a part of the NCRI portfolio by virtue of its approval by CTAAC.

15.6 Clinical Risk Assessment

Generic Risk Assessment Hazards to patients, study and organisation have been evaluated and will be considered throughout the duration of the trial.

16. OTHER REGULATORY ISSUES

16.1 Regulatory Status

The trial has Clinical Trials Authorisation from the MHRA (dated 05/07/2007).

16.2 Good Clinical Practice

The trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

16.3 Liability/Indemnity/Insurance

This study is an investigator-led trial endorsed by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

16.4 Completion of the study & definition of study end date

According to the applicable regulations, the study is deemed to have ended on the date of last data capture.

The duration of time for which patient follow up data will be collected is dependent on future funding arrangements. Current funding is secured for this to continue for 5 years after the start of the trial, and further funding will be sought for this to continue indefinitely.

17. PROTOCOL AMENDMENTS

The Trial Management Group will agree protocol amendments on behalf of the investigators prior to acceptance and submission to the Main REC.

18. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results will be in the name of the TMG. Members of the TMG will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Contributing healthcare professionals in this study will also be acknowledged. Authorship of parallel studies initiated outside of the TMG will be according to the individuals involved in the project but must acknowledge the contribution of the TMG.

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APPENDIX 1: ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CPA	Clinical Pathology Accreditation
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Awards and Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DPA	Data Protection Act
EGFR	Epidermal Growth Factor Receptor
ER	Oestrogen receptor
EU	European Union
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
gDNA	Genomic deoxyribonucleic acid
GFR	Glomerular Filtration Rate
HER2	Human Epidermal growth factor Receptor 2
ICR-CTSU	Institute of Cancer Research Clinical Trials and Statistics Unit
IDMC	Independent Data Monitoring Committee
IHC	Immunohistocompatibility Complex
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
MHRA	Medicines & Healthcare products Regulatory Agency
Main REC	Main Research Ethics Committee
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NICE	National Institute for Clinical Excellence
OS	Overall Survival
PFS	Progression Free Survival
PO	Per Oral
PR	Progesterone receptor
RECIST	Response Evaluation Criteria In Solid Tumours
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics

SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitors
TMG	Trial Management Group
TSC	Trial Steering Committee
TTF	Time to Treatment Failure
TTP	Time To Progression
ULN	Upper Limit of Normal

APPENDIX 2: RECIST V1.1 CRITERIA

Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 Quick Reference Eligibility

Please note that this appendix contains a summary of the RECIST v1.1 criteria only. Please refer to the full RECIST v1.1 guidelines when reporting tumour assessments.

- Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

Measurable disease

The presence of at least one measurable lesion. This lesion must not have received or be due to receive radiotherapy or surgery.

Measurable lesions

Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: 10mm by CT scan (CT scan slice thickness no greater than 5 mm); 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); 20mm by chest X-ray. To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. Any target lesions subsequently irradiated or resected should not continue to be used to indicate treatment response.

Non-measurable lesions

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions i.e. leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Methods of Measurement

- CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
- Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- The utilisation of endoscopy and laparoscopy for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained.
- Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.
- Cytology and histology can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Baseline documentation of "Target" and "Non-Target" lesions

- When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as **target lesions** and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.
- All other lesions (or sites of disease) including pathological nodes with short axis ≥10mm but <15 mm should be identified as **non-target lesions** and should also be recorded at baseline. (Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed). Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response Criteria

	Evaluation of target lesions
* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
* Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
*Incomplete Response / Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair). Please refer to the full RECIST v1.1 criteria for further guidance.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. This means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).
- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- Confirmation of final response by repeated CT scan four weeks after the post cycle 6 response assessment scan is recommended but will not be mandatory due to the constraints of booking CT scans.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the date of randomisation until the criteria for disease progression are met, taking as reference the smallest sum recorded on study.
- The clinical relevance of the duration of SD varies for different tumour types and grades.

Response review

- All responses will be reviewed by experts independent of the study at the study's completion.

APPENDIX 3: ER, PR and HER2 inclusion criteria

The following cut-offs will be used to define “Triple Negative”. The breast tumour must have been recorded to be negative for Oestrogen Receptor α (ER), and HER2 in a previous sample usually of the primary tumour.* These phenotypes may have been recorded on different pathology reports, and do not have to be recorded on every previous biopsy.

*Patients that have had a previous ER+, PR+ or HER2+ primary tumour, but a subsequent ER-, PR-/unknown and HER2- primary tumour with a histologically confirmed ER-, PR-/unknown and HER2- recurrence may be eligible on approval of the Chief Investigator or Clinical Coordinator. Details of the patient’s medical history and tumour pathology should be provided to the TNT Trial Manager in order to ascertain eligibility. Please note that patients that meet these criteria must not be entered into the trial without approval of the Chief Investigator or Clinical Coordinator.

It is anticipated that many Breast Units will also have performed progesterone receptor (PR) assay and confirmed PR negativity on the primary tumour. However, if the cancer is PR unknown but ER- and HER2-, and otherwise eligible, please arrange urgent PR testing. If PR unknown and PR testing is not possible within a reasonable timeframe, the patient is eligible provided that ER and HER2 status are negative and all other eligibility criteria are met.

As per the national guidelines, all laboratories undertaking ER and HER2 assessment should take part in quality assurance of testing, such as NEQAS.

The following definitions will be used:

Oestrogen receptor negative when scored as

i) <3 using Allred/quick score scoring system

OR

ii) <10 using the H score system

OR

iii) ER negative, when other cut-offs were used (e.g., 1%, 5% or 10%).

Progesterone receptor negative when scored as

i) <3 using Allred/quick score scoring system

OR

ii) <10 using the H score system

OR

iii) PR negative, when other cut-offs were used (e.g., 1%, 5% or 10%).

HER2 negative when scored as

0 or 1+ for HER2 by immunohistochemistry (e.g. Dako HercepTest or equivalent)

OR

2+ for HER2 by immunohistochemistry (e.g. Dako HercepTest or equivalent) AND non-amplified for HER2 by fluorescent in situ hybridisation (FISH or CISH).

APPENDIX 4: ECOG PERFORMANCE STATUS

0. Fully active, able to carry on all pre-disease performance without restriction.

1. Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2. Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

3. Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.

4. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

APPENDIX 5: ASSESSMENT OF GFR

The recommended formulae for the calculation of GFR is that of Wright (1). These have been shown to be more accurate in the estimation of GFR than the Cockcroft and Gault formula.

Patients with serum urea or serum creatinine outside the local normal range, or GFR calculated as being greater than 100ml/minute or less than 60ml/minute should have GFR measured (using the 51CrEDTA method) rather than calculated.

NB: If GFR is measured (as opposed to calculated) AUC 6 should still be maintained.

The creatinine kinase (CK) versions of these formulae are reported to be slightly more accurate than the non-creatinine kinase versions. However, if the measurement of CK presents logistical problems the non-CK version of the formulae may be used. Centres will be asked to specify which formula is to be used before the first patient is entered and should use this for all patients. The formulae are given below:

Enzymatic creatinine analysis

Without CK: $$GFR = \frac{(6230 - 32.8 \times Age) \times BSA \times (1 - 0.23 \times 1^*)}{SCr}$$

With CK: $$GFR = \frac{(4350 - 34 \times Age + 522 \times Ln(CK)) \times BSA \times (1 - 0.217 \times 1^*)}{SCr}$$

Jaffe serum creatinine analysis

Without CK: $$GFR = \frac{(6580 - 38.8 \times Age) \times BSA \times (1 - 0.168 \times 1^*)}{SCr}$$

With CK: $$GFR = \frac{(4520 - 40 \times Age + 570 \times Ln(CK)) \times BSA \times (1 - 0.15 \times 1^*)}{SCr}$$

* denotes female; in males this is 0.

Where: Age = Age in years

Ln(CK) = natural logarithm of creatinine kinase in units l^{-1}

BSA = Dubois body surface area ($0.007184 \times weight(kg)^{0.425} \times height(cm)^{0.725}$)

SCr = Serum Creatinine in μmol l^{-1}

Centres unable to use the Wright Formula or 51CrEDTA clearance rate should contact the Trials Unit.

1. Wright JG, Boddy AV, Highley M, Fenwick J, McGill A and Calvert AH. Estimation of glomerular filtration rate in cancer patients. *Br J Cancer* 2001; 84: 452-459.

APPENDIX 6: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

(NCI CTC v3.0 12.12.03)

Listed below are selected categories for toxicities likely to be experienced by some patients in this trial.

ADVERSE EVENT	0	1	2	3	4
Blood/Bone Marrow (p4)					
Haemoglobin	WNL	<LLN - 10.0 g/dL	<10.0 – 8.0 g/dL	<8.0 – 6.5 g/dL	<6.5 g/dL
Leucocytes	WNL	<LLN – 3.0 x10^9/L	<3.0 – 2.0 x10^9/L	<2.0 – 1.0 x10^9/L	<1.0 x10^9/L
Neutrophils	WNL	<LLN - 1.5 x10^9/L	<1.5 – 1.0 x10^9/L	<1.0 – 0.5 x10^9/L	<0.5 x10^9/L
Platelets	WNL	<LLN - 75.0 x10^9/L	<75.0 – 50.0 x10^9/L	<50 – 25.0 x10^9/L	<25.0 x10^9/L
Infection (p35)					
Febrile Neutropenia (no documented infection)	None	-	-	Present	Life-threatening consequences (e.g. septic shock, hypotension, acidosis, necrosis)
Infection (documented infection with grade 3/4 neutrophils)	None	-	Localised, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g. septic shock, hypotension, acidosis, necrosis)
Gastrointestinal (p19)					
Anorexia	None	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g. inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences
Constipation	None	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g. obstruction, toxic megacolon)

ADVERSE EVENT	0	1	2	3	4
Gastrointestinal (p19)					
Diarrhoea	None	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools/day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools/day over baseline; IV fluids ≥ 24hrs; hospitalisation; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g. haemodynamic collapse)
Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24hrs	Life-threatening consequences
Mucositis/Stomatitis (clinical exam)	None	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Mucositis/Stomatitis (functional/ symptomatic)	None	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences Symptoms associated with life-threatening consequences
Taste alteration	None	Altered taste but no change in diet	Altered taste with change in diet (e.g. oral supplements); noxious or unpleasant taste; loss of taste	-	-
Vomiting	None	1 episode in 24 hrs	2-5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs or need for IV fluids or TPN indicated ≥24hrs	Life-threatening consequences
Haemorrhage/Bleeding (p31)					
Haemorrhage, GI	None	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterisation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (e.g. haemostatis of bleeding site)	Life-threatening consequences; major urgent intervention indicated

ADVERSE EVENT	0	1	2	3	4
Neurology (p47)					
Neuropathy: motor	Normal	Asymptomatic, weakness on exam/testing only	Symptomatic weakness, interfering with function, but not with ADL	Weakness, interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Life-threatening; disabling (e.g. paralysis)
Neuropathy: sensory	Normal	Asymptomatic; loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	Sensory alteration or paraesthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paraesthesia interfering with ADL	Disabling

Metabolic/Laboratory (p40)					
Alkaline Phosphatase/ ALT/AST	Normal	>ULN – 2.5 ULN	>2.5 – 5 x ULN	>5 – 20.0 x ULN	>20.0 x ULN
Bilirubin	Normal	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Calcium, serum - low	Normal	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 mg/dL – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 mg/dL – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Creatinine	Normal	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN
Glomerular Filtration Rate	Normal	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated
Magnesium, serum - low	Normal	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 - 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L
Potassium, serum - low	Normal	<LLN – 3.0 mmol/L	-	<3.0 – 2.5 mmol/L	<2.5 mmol/L
Uric acid, serum - high	Normal	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	-	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L

ADVERSE EVENT	0	1	2	3	4
Cardiac General (p7)					
Hypertension	None	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100v if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g. hypertensive crisis)
Hypotension	None	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g. academia; impairment of vital organ function)
Musculoskeletal/Soft Tissue (p43)					
Muscle weakness, generalised	Normal	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling
Pulmonary/Upper Respiratory (p56)					
Dyspnoea	None	Dyspnoea on exertion but can walk 1 fight of stairs without stopping	Dyspnoea on exertion, but unable to walk 1 fight of stairs without stopping	Dyspnoea with ADL	Dyspnoea at rest; intubation/ventilator indicated
Dermatology/Skin (p14)					
Alopecia	None	Thinning or patchy	Complete	-	-
Injection site reaction	None	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	-
Nail changes	None	Discolouration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	-
Pruritus/Itching	None	Mild or localised	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/desquamation	None	Macular or popular eruption without associated symptoms	Macular or popular eruption or erythema with pruritis or other associated symptoms; localised desquamation or other lesions covering <50% of BSA	Severe, generalised erythroderma or macular, popular or vesicular eruption; desquamation covering ≥50% BSA	Generalised exfoliative, ulcerative, or bullous dermatitis

ADVERSE EVENT	0	1	2	3	4
Lymphatics (p38)					
Oedema: Limb (peripheral)	None	5-10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting oedema	>10-30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e. lymphangiosarcoma); amputation indicated; disabling
Constitutional Symptoms (p11)					
Fatigue (lethargy, malaise, asthenia)	None	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling
Pain (p55)					
Pain (Select)	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling
Allergy/Immunology (p1)					
Allergic reaction/ hypersensitivity (including drug fever)	None	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dypnoea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related oedema/angioedema; hypotension	Anaphylaxis
Auditory/Ear (p2)					
Tinnitus	None	-	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling

For full list of the common terminology criteria go to: http://ctep.cancer.gov/reporting/ctc.html

APPENDIX 7: SCHEDULE OF EVENTS AND EVALUATIONS

Schedule of Events – Treatment

			Weeks of Treatment																	
	Prior to Randomisation	In between randomisation and Week 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Chemotherapy Cycle Number			**1**			**2**			**3**			**4**			**5**			**6**		
Informed consent	X																			
History, physical examination, vital signs	X																			
Physical examination and adverse events					X			X			X			X			X			X
Haematology	X				X			X			X			X			X			X
Biochemistry	X				X			X			X			X			X			X
CT Scan	X**									X										X
Chest X-ray	If indicated																			
ECG	If indicated																			
Performance status	X				X			X			X			X			X			X
BSA		X			X			X			X			X			X			
Calculated GFR*	X																			
Pregnancy Test (women of child-bearing potential)	X																			
Chemotherapy			X			X			X			X			X			X		

* GFR should be recalculated if creatinine changes by >25% (see Appendix 5)

**The maximum time between the baseline CT scan and start of treatment is 28 days

Schedule of Events – Follow Up

	Follow Up Month											
	3	6	9	12	15	18	21	24	27	30	33	36
Physical examination, vital signs and adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	If clinically indicated											
Biochemistry	If clinically indicated											
CT Scan	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	If clinically indicated											
ECG	If clinically indicated											
Performance status	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (women of child-bearing potential)												

APPENDIX 8: DRUG SAFETY INFORMATION ON TRIAL DRUGS

Carboplatin and docetaxel should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications including acute hypersensitivity reactions.

Peripheral blood counts and renal function tests should be monitored closely. Blood counts should be performed prior to commencement of therapy, and immediately prior to each cycle thereafter. This will monitor toxicity and help determine the nadir and recovery of haematological parameters, and assist in subsequent dosage adjustments.

Warnings

Infrequent allergic reactions to carboplatin have been reported, e.g. erythematous rash, fever with no apparent cause or pruritus. Rarely anaphylaxis, angio-oedema and anaphylactoid reactions including bronchospasm, urticaria and facial oedema have occurred. These reactions are similar to those observed after administration of other platinum containing compounds and may occur within minutes. The incidence of allergic reactions may increase with previous exposure to platinum therapy; however allergic reactions have been observed upon initial exposure to carboplatin. Patients should be observed carefully for possible allergic reactions and managed with appropriate supportive therapy.

Carboplatin desensitisation protocols have been explored in patients with gynaecological cancers who develop carboplatin sensitivity (1). If attempts at desensitization are thought appropriate by the local investigator then the chief investigator may be contacted via the ICR-CTSU to indicate where further expert guidance on desensitization protocols may be obtained.

Guidelines on the management of toxicity and dose modification in the trial are given in section 10.5. Full prescribing information, found in the SmPC for the individual products, should be consulted. Copies of the latest versions of the SmPCs are available in the Site Investigator File, however, investigators should confirm that the copy of the SmPC referred to is the most up-to-date.

1. Lee CW, Matulonis UA and Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecologic Oncology 2004; 95: 370–376

APPENDIX 9: RECOMMENDATIONS ON THE USE OF G-CSF

G-CSF prophylaxis

NCCN and ASCO Guidance on use of G-CSF for prophylaxis were published in 2005 and 2006 (1). These indicate an expected rate of neutropenic sepsis of 10-20% with the use of single agent docetaxel and <10% with single agent carboplatin. Guidance indicates that primary and secondary prophylaxis may be considered with docetaxel, depending on other patient risk factors. G-CSF prophylaxis is not recommended with single agent carboplatin.

Docetaxel: G-CSF prophylaxis on single agent docetaxel: G-CSF should be given as primary prophylaxis for all patients on the Docetaxel arm of the trial (either as randomised or crossover treatment) in order to prevent neutropenic sepsis

Carboplatin: Primary prophylaxis – As the expected frequency of neutropenic sepsis is <10% G-CSF should not be used. This is in accordance with current NCCN and ASCO guidance (1). Secondary prophylaxis – Dose delay or dose reduction is preferred as described in Section 10.5. This is in accordance with current NCCN and ASCO guidance (1). The TMG will allow the use of G-CSF for secondary prophylaxis if this is in accordance with local policy. Local policy for use of G-CSF with carboplatin must be registered with the Trials Unit.

Guidelines for CSF Administration in patients with neutropenia

A. Afebrile Patients

ASCO 2006 recommendation: CSFs should not be routinely used for patients with neutropenia who are afebrile.

B. Febrile Patients

ASCO 2006 recommendation: CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 x 109/L) neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalised at the time of the development of fever. This was the consensus opinion of the update committee, as there are no new data. Prior Infectious Disease Society of America guidelines have supported the use of CSFs in similar circumstances, referring to the ASCO guidelines (1).

1. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; 24 (19): 3187-3205.