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A randomised phase II pilot study of 3 weekly Cabazitaxel versus weekly Paclitaxel chemotherapy in the first line treatment of HER2 negative metastatic breast cancer

CONCEPT Trial

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Sponsor University Hospitals Bristol NHS Foundation Trust

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Coordinating Unit Bristol Haematology and Oncology Centre
Clinical Trials Unit

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This protocol describes the CONCEPT Trial and provides information about procedures for entering and treating 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 University Hospitals Bristol NHS Foundation Trust to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

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 1998 and other regulatory requirements as appropriate.

Protocol Authorised By:

…….

Dr Amit Bahl (Chief Investigator)

Date.....

Principal Investigator

Site:……

Name:……

Date:……

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TRIAL SCHEMA

Patients with Her 2 negative metastatic breast cancer (MBC)

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Taxane based chemotherapy selected as first line systemic treatment

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Disease defined as:

- Histologically-proven adenocarcinoma of the breast with measurable metastatic disease (according to RECIST criteria version 1.1)
- Her-2 receptor status negative (assessed by IHC and/or FISH at diagnosis)
- Stage IV disease
- May have received prior cytotoxic chemotherapy as adjuvant or neo-adjuvant treatment (but this is not a requirement)

Stratification according to:

- ER+ve or ER-ve
- Prior Docetaxel in neo/adjuvant setting- Yes or No

↓

RANDOMISATION 1:1

N = 160 patients

Metastatic Breast Cancer

(TNBC or ER+/HER2 negative)

Screening investigation:

Including CT/MRI Chest/ Abdomen/Pelvis

1:1

R

Cabazitaxel 25 mg/m^2 q3w

Paclitaxel 80 mg/m^2 q1w

TRIAL SUMMARY

Title

A randomised phase II pilot study of 3 weekly cabazitaxel versus weekly paclitaxel in the first line therapy of Her2 negative metastatic breast cancer

Objectives

Primary:

To compare the progression free survival (PFS) between the two groups, (defined as the time from randomisation to the first of one of the following: development of disease progression (RECIST 1.1) or death from any cause).

Secondary:

- To assess Clinical Benefit Rate (CBR) defined as stable disease rate + partial response rate + complete response rate according to RECIST 1.1 criteria
- To assess Objective Response Rate (ORR) in each group; defined as CR and PR
    - *In the Bristol sub-pilot study, blood samples for CTC count will be correlated to radiological response*
- To assess the time to response in each group – time from randomisation to the CT scan showing response as per RECIST1.1
- To assess the overall survival (time from randomisation to the date of death due to any cause) in each treatment group
- To evaluate safety and tolerability
- To assess quality of life using EQ-5D and FACT-B assessment tools (measured at baseline, prior to cycles 3 and 5 and at the end of treatment visit)
- To assess the time to next cytotoxic chemotherapy treatment from the date of completion of trial chemotherapy (for both ER+ve and ER-ve patients - it is assumed that some ER+ve patients will be commenced on endocrine treatment after finishing trial chemotherapy even in the absence of disease progression)

Trial Design

Two arm randomised open-label Phase II trial with 1:1 randomisation

Type and number of patients

Patients with Her2 negative metastatic breast cancer will be eligible if they are fit to receive chemotherapy in first line setting.

In this trial up to 160 patients will be recruited.

Main inclusion Criteria:

- Metastatic breast cancer, fit to receive cytotoxic chemotherapy as palliative treatment
- Her2 negative breast cancer confirmed by prior histology (HER-2 negative defined as IHC 0+, 1+ or IHC 2+ and FISH/SISH/CISH (ratio <2.0) negative in case of IHC 2+)

- Measurable disease as per RECIST 1.1
- ECOG performance status 0 or 1
- Adequate liver, renal and bone marrow function
- Informed consent
- No prior cytotoxic chemotherapy for metastatic disease (neoadjuvant and adjuvant chemotherapy permitted)
- Patients may be taxane-naive or have received docetaxel chemotherapy in the adjuvant or neoadjuvant setting

Main exclusion criteria:

- Previous paclitaxel chemotherapy
- Prior cytotoxic chemotherapy for metastatic disease
- Concurrent palliative radiotherapy to target lesions.
- Palliative radiotherapy to non-target lesions given on the same day as chemotherapy
- Brain metastases that are symptomatic (must be shown on CT/MRI brain scan)
- History of malignancy within 5 years of randomisation with the exception of those malignancies with a negligible risk of metastasis or death and treated with curative intent. Please confirm patient eligibility with the CI.
- Pregnancy or lactation
- Grade ≥2 peripheral motor and/or sensory neuropathy
- Grade ≥2 oral mucositis
- History of severe hypersensitivity reaction (≥grade 3) to taxanes
- History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80-containing drugs
- Other concurrent serious illness or medical conditions which make it undesirable for the patient to enter the trial (including uncontrolled diabetes mellitus)
- Inadequate organ and bone marrow function as evidenced by:
    - Haemoglobin <10.0 g/dL
    - Absolute neutrophil count <1.5 x 10^9/L,
    - Platelet count <100 x 10^9/L,
    - ALT/SGPT >2.0 x ULN,
    - Total bilirubin >1.5 x ULN,
    - Serum creatinine >1.5 x ULN.
- Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments) (see section 11.4)
- Participation in another clinical trial with any investigational drug within 30 days prior to randomisation (wash-out period of 30 days from last dose of trial drug).

Treatment	**ARM A:** 6 cycles of chemotherapy using paclitaxel 80mg/m^2 on days 1, 8 and 15 of each 21 day cycle. (overall treatment time 18 weeks accounting for 18 *i.v.* infusions in total) OR **ARM B:** 6 cycles of chemotherapy using cabazitaxel 25mg/m^2 day 1 of each 21 day cycle. (overall treatment time 18 weeks accounting for 6 *i.v.* infusions in total)
Endpoints	**Primary**: Assessment of the difference in progression free survival between the two groups, (defined as the time from randomisation until one of the following: development of disease progression (RECIST 1.1) or death from any cause, whichever comes first). **Secondary:** • Clinical Benefit Rate (CBR) defined as stable disease rate + partial response rate + complete response rate according to RECIST 1.1 criteria recorded from the start of treatment to completion of 6 cycles of treatment • Objective Response Rate (ORR) in each group; defined as CR and PR recorded from the start of the treatment to completion of 6 cycles of treatment • Overall Survival defined as the time from randomisation to death from any cause. • Time to next cytotoxic chemotherapy treatment from the date of completion of the study chemotherapy treatment (for both ER+ve and ER-ve patients - it is assumed that ER+ve patients may be commenced on endocrine treatment after finishing trial chemotherapy even in the absence of disease progression) • Time to response determined by time from randomisation to the CT scan showing partial response as per RECIST 1.1 criteria. • Quality of Life using EQ-5D and FACT-B assessment tools (measured at baseline, prior to cycles 3 and 5 and at the end of treatment visit) • Safety: frequency, severity, seriousness, and relatedness of study treatment-emergent adverse events will be assessed according to NCI CTCAE v.4.03. Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.03.

1 BACKGROUND

Breast cancer is the most common cancer in the UK with almost 50,000 new diagnoses annually. (1) Although the majority present with early breast cancer without metastases, around 30% of these patients will go on to develop recurrent metastatic breast cancer (MBC). MBC is incurable, but the availability of a number of effective agents has led to substantial improvements in the prognosis for this group in recent decades.

The biology of individual tumours is complex and highly variable; our understanding and ability to predict the behaviour of individual tumours continues to improve through molecular genetic research. However, in current clinical practice, treatment decisions are largely based on patient factors and the level of expression of the oestrogen receptor (ER) and HER2 receptor by tumour cells.

The outlook for patients with ER-positive disease with bone-only metastases is favourable – maintained responses and disease stabilisation can often be achieved using endocrine therapies in a sequential fashion and survival is frequently measured in years, whereas the presence of visceral metastases (typically seen in the liver, lungs and brain) may confer a worse prognosis. First line treatment in this group is usually with cytotoxic chemotherapy, with or without additional targeted agents – the rationale for this more intensive approach being to induce a more rapid tumour response, preventing progression to organ failure. It is therefore this group who likely have most to gain from developments in novel cytotoxic chemotherapy drugs.

Her2 positive MBC commonly involves the viscera, and first line cytotoxic chemotherapy is usually combined with trastuzumab, a monoclonal antibody directed at the Her2 receptor. There is strong evidence that trastuzumab offers additional survival benefits over chemotherapy alone in this group, and treatment is well tolerated. (2, 3) In trials of novel agents, although activity may be seen in Her2 positive patients, it can be difficult to establish the relative contribution of cytotoxics in the context of concomitant trastuzumab or other anti-Her2 agents. For patients with Her2 negative tumours, however, the preferred approach to the first line management of MBC is to treat sequentially with combination or single agent cytotoxic chemotherapy alone.

A proportion of patients presenting with MBC with visceral metastases will have received prior cytotoxic chemotherapy in the adjuvant setting. Adjuvant chemotherapy in early breast cancer improves relapse rates and overall survival, and is frequently offered, where appropriate, to all but the lowest risk patients. (4) Anthracycline based chemotherapy has long been the mainstay of adjuvant therapy – however in recent years additional taxane chemotherapy has been used with increasing frequency, particularly for patients with pathological lymph node positive disease (whose risk of later progression to MBC is highest) – large trials show an additional benefit with adjuvant taxanes in this group, and docetaxel is the most commonly administered agent. (5)

The treatment landscape in MBC is thus already highly complex, with many patients having been pre-treated with a variety of different agents by the time of presentation. Typically, however, patients with Her2 negative MBC following prior chemotherapy in the adjuvant setting have received doses of anthracyclines approaching lifetime tolerances (rechallenging with anthracycline based treatment may carry an unacceptable risk of cardiac toxicity), and are therefore offered taxane based chemotherapy with docetaxel or paclitaxel.

Several studies have assessed the efficacy and tolerability of paclitaxel in MBC patients – it has been used in routine clinical practice for over a decade. (6-10) Overall response rates range from 23 to 56%. Previous studies have also demonstrated a better efficacy for the weekly schedule of Paclitaxel compared to the 3 weekly schedule. The dose of Paclitaxel 80mg/m^2 given weekly on days 1, 8 and 15 of a 21 day cycle based on the randomised phase III trial (CALGB 9480) is chosen as the standard arm of the CONCEPT study. This dosing schedule is used in several oncology centres in the UK. (11)

In a landmark phase 3 trial in early breast cancer, assessing patients receiving neoadjuvant therapy prior to surgery, patients were randomised to receive paclitaxel chemotherapy every 3

weeks, or using a dose dense weekly schedule, prior to anthracycline based chemotherapy and surgery.(12) In these treatment-naive groups, overall response rates were similar, but pathological complete responses (pCR) were observed in 28.2% of patients receiving weekly paclitaxel, versus 15.7% of patients given the 3 weekly regimen (p=0.02). The doses used in the neoadjuvant study were greater than those typically given in MBC; however phase 2 trials had also suggested favourable efficacy with a weekly schedule in MBC. (13, 14)

A subsequent phase 3 trial in MBC patients, using paclitaxel 80mg/m2 weekly , versus 175mg/m2 3 weekly, in almost 600 patients, demonstrated superiority with the weekly schedule (response rate 42% vs. 29%; unadjusted odds ratio = 1.75, p=0.0004). (15) This regimen is now a standard of care and is well tolerated, although notably some toxicity, including the incidence of grade 3 peripheral neuropathy, was higher (24% vs. 12%) in the weekly paclitaxel cohort.

It remains to be seen whether the use of adjuvant taxane chemotherapy leads to an increase in taxane resistance at the onset of MBC, although for patients with a relatively short disease free interval this may be the case. Patterns of care studies suggest that if docetaxel was used in the adjuvant setting then the preferred taxane in first line metastatic setting is paclitaxel. Although other classes of cytotoxic agents have shown promise following the development of taxane resistance, capecitabine (16) and vinorelbine (17) can induce prolonged responses in a proportion of patients and recently eribulin (18) has been approved as well, the prognosis at this stage is significantly worse than for taxane sensitive tumours.

There is thus an unmet need for more effective first line systemic therapy in patients with MBC, particularly those who have received taxane chemotherapy in the adjuvant setting and where only a short disease free interval has elapsed.

Cabazitaxel is a novel taxoid which was specifically selected for development due to preclinical evidence of activity in cell lines resistant to docetaxel and paclitaxel. (19) Of interest, it was found to be active in a Her2 positive breast cancer tumour xenograft, with innate resistance to docetaxel. (20)

In the clinical setting cabazitaxel is licensed for use in the treatment of metastatic castration-resistant prostate cancer (mCRPC) following progression during or after docetaxel chemotherapy. A large phase 3 randomised trial in this patient group (the TROPIC study, 2010 (21)) demonstrated an overall survival benefit of 2.4 months for patients receiving cabazitaxel and prednisolone chemotherapy, compared with those receiving the previous standard mitoxantrone and prednisolone. Treatment was well tolerated; diarrhoea and neutropenia were the most common toxicities but severe toxicity was infrequent. An early access programme in mCRPC was subsequently established to gain further safety and quality-of-life data; and the results show trend to improving QOL and a better safety profile than that reported in the TROPIC study. (22)

A phase II trial of cabazitaxel in 71 patients with MBC (23) demonstrated an objective response rate of 14% in the treated population, with disease stabilisation in a further 38% of patients (median duration of response of 7.6 months). Specifically, patients were eligible for this study if their disease demonstrated evidence of taxane resistance – at least 3 months of prior taxane therapy following development of MBC, or a disease free interval of 12 months or less if adjuvant taxane therapy had been given, were required for eligibility. 65% of patients had received docetaxel previously, 35% paclitaxel and 10% had received more than one taxane. 52% were ER positive and 27% Her-2 positive. Notably eight patients with stable disease for more than 3 months with cabazitaxel had not responded to previous taxane chemotherapy.

In this phase II trial patients were treated with cabazitaxel 20mg/m^2 at cycle 1, increasing to 25mg/m2 at cycle 2 if treatment was well tolerated – this was feasible in 28% of patients. However, increased efficacy with dose escalation is not evident to date. Treatment was well tolerated – neutropenia was the most common grade 3/4 toxicity (73%); however febrile neutropenia and neutropenic infections were observed in fewer than 1% of cycles.

Further potential advantages of cabazitaxel as an alternative to other taxanes in MBC include a low observed incidence of alopecia and a possible reduction in the incidence of peripheral neuropathy (22, 23) (although it is recognised that patient selection in large studies may be a confounding factor) - it is becoming increasingly apparent that such quality of life factors play a major role in

selection of systemic therapy agents in MBC patients. Cabazitaxel may penetrate the blood-brain barrier (24) – this has obvious potential benefits for a patient group where brain metastases are not infrequent. From a practical viewpoint, the 3 weekly schedule may be preferable for patients, involving fewer hospital visits and intravenous infusions than the weekly paclitaxel regimen.

A further phase I/2 trial in heavily pretreated MBC patients (n=30) evaluated the combination of cabazitaxel with capecitabine chemotherapy. (25) The ORR in this small study was 23%, with median response duration of 3.1months. Treatment was consistent with a taxane-capecitabine combination. This study lends further support to the efficacy of cabazitaxel in a pre-treated MBC population. However, the potential increased toxicity from this combination may preclude its use in routine clinical practice. In addition there is often reluctance from clinicians and patients alike to combine agents due to no definite evidence of improving survival in comparison to sequencing single agent treatment and the potential for increased toxicity and resultant effect on QOL.

This proposed randomised phase 2 trial is a pragmatic study to include those patients with Her-2 negative MBC where weekly paclitaxel chemotherapy would be the standard treatment of choice. This may include patients who have received prior docetaxel in the adjuvant setting, and also taxane-naive patients. In addition to establishing efficacy, this trial will serve to evaluate safety in the MBC population, and to assess quality of life factors

2 AIMS OF THE STUDY

2.1 Primary

- Progression free survival

2.2 Secondary

- Objective response rate defined as partial response rate + complete response rate according to RECIST 1.1 criteria recorded from the start of treatment to completion of 6 cycles of treatment
    - In the Bristol sub-pilot study, blood samples for CTC count will be assessed for response and correlated to radiological response
- Clinical Benefit Rate in each group; defined as stable disease rate + partial response rate + complete response rate according to RECIST 1.1 criteria recorded from the start of treatment to completion of 6 cycles of treatment
- Time to response determined by time from randomisation to the CT scan showing response as per RECIST 1.1 criteria.
- Overall survival as defined as the time from randomisation to death from any cause
- Evaluate safety and tolerability
- To assess quality of life using EQ-5D and FACT-B assessment tools (measured at baseline, prior to cycles 3 and 5 and at the end of treatment visit)
- Time to next cytotoxic chemotherapy treatment from the date of completion of the study chemotherapy treatment (for both ER+ve and ER-ve patients - it is assumed that some ER+ve patients will be commenced on endocrine treatment after finishing trial chemotherapy even in the absence of disease progression)

3 TRIAL DESIGN

This is a prospective multicentre, randomised, open label, study comparing the efficacy and the safety of six 3-weekly cycles of cabazitaxel versus 18 weekly doses of paclitaxel given as first line chemotherapy treatment in patients with HER2-negative metastatic breast cancer. Randomisation will be conducted by a 1:1 ratio.

The first patient was recruited in January 2015 and the planned recruitment duration is until December 2020.

The scheduled duration of the study for a patient should be considered completed for a patient at the time she completes all the scheduled study procedures, including the relevant follow-up.

The trial would be overseen by the Trial Management Group in accordance with the charter which will be written before study conduct (i.e. before first patient in).

4 PATIENT SELECTION AND ELIGIBILITY

4.1 Number of patients planned

Total number planned is 160 patients (80 in each arm) with 1:1 randomisation.

Competitive recruitment will be allowed at each participating site.

4.2 Inclusion Criteria

- Written informed consent for all study according to regulatory requirements prior to beginning specific protocol procedures.
- Metastatic breast cancer, fit to receive cytotoxic chemotherapy as palliative treatment
- Measurable disease as per RECIST 1.1 by CT scan or MRI within 6 weeks of the first dose of chemotherapy (cycle 1 day 1)
- ECOG performance status 0 or 1
- Able to provide informed consent
- No prior cytotoxic chemotherapy for metastatic disease (neoadjuvant and adjuvant chemotherapy permitted if given more than 3 months prior to randomisation)
- Patients may be taxane-naive or have received docetaxel chemotherapy in the adjuvant setting
- Prior histology to confirm that it is HER-2 negative defined as IHC 0+, 1+ or IHC 2+ and FISH/SISH/CISH (ratio <2.0) negative in case of IHC 2+. NB all pending biopsy results must be received before the patient can be randomised.
- ER+ and ER- are both eligible.
- Female age ≥ 18 years.
- Anticipated life expectancy > 6 months.
- Adequate liver, renal and bone marrow function
- Laboratory requirements:
    - Haemoglobin ≥ 10.0 g/dL
    - Absolute neutrophil count ≥ 1.5 x 10^9/L,
    - Platelet count ≥ 100 x 10^9/L,
    - ALT/SGPT ≤ 2.0 x ULN,
    - Total bilirubin ≤ 1.5 x ULN,
    - Serum creatinine ≤ 1.5 x ULN
- Negative pregnancy test (urine or serum) within 7 days prior to randomisation for all women of childbearing potential.
- Patients must be available and compliant for diagnostics, treatment and follow-up.

4.3 Exclusion Criteria

- Her2 positive breast cancer (IHC 3+ or FISH/SISH/CISH ratio>2.0
- Previous paclitaxel chemotherapy
- Prior cytotoxic chemotherapy for metastatic disease
- Concurrent palliative radiotherapy to identified target lesions
- Concurrent palliative radiotherapy given on the same day as chemotherapy
- Brain metastases which are symptomatic (must be shown on CT/MRI brain scan)
- History of malignancy within 5 years of randomisation with the exception of those malignancies with a negligible risk of metastasis or death and treated with curative intent. Please confirm patient eligibility with the CI.

- Grade ≥2 peripheral motor and/or sensory neuropathy (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.4.03) except if neuropathy is localised to one limb and due to causes other than taxane exposure.
- Grade ≥2 oral mucositis (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.4.03).
- History of severe hypersensitivity reaction (≥grade 3) to taxanes
- History of severe hypersensitivity reaction (≥grade 3) to polysorbate 80-containing drugs
- Clinically significant (i.e. active) cardiovascular disease, including cerebrovascular accident (=6 months before randomisation), myocardial infarction, arterial thrombotic events (=6 months before randomisation) unstable angina pectoris, New York Heart Association (NYHA) = grade 2 congestive heart failure and/or hypertension, serious cardiac arrhythmia requiring medication during the study and that might interfere with regularity of the study treatment, or not controlled by medication
- Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or to comply with the study procedures or interfere with interpretation of study results (such as significant neurological or psychiatric disorders including psychotic disorders, dementia or seizures).
- Active infection requiring systemic antibiotics or antifungal medication
- Sex hormones. Prior treatment must be stopped before study entry.
- Administration of any live virus vaccine, including yellow fever vaccine within 6 weeks preceding consent and for the duration of the chemotherapy treatment.
- Inability and unwillingness to comply with study visits, treatment, testing, and to comply with the protocol.
- Other concurrent serious illness or medical conditions which make it undesirable for the patient to enter the trial (including uncontrolled diabetes mellitus)
- Inadequate organ and bone marrow function as evidenced by:
    - Haemoglobin < 10.0 g/L
    - Absolute neutrophil count < 1.5 x 10^9/L,
    - Platelet count <100 x 10^9/L,
    - ALT/SGPT >2.0 x ULN,
    - total bilirubin >1.5 x ULN,
- Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments) (see section 11.4)
- Participation in another clinical trial with any investigational drug within 30 days prior to randomisation (wash-out period of 30 days from last dose of trial drug).
- Pregnant or breastfeeding women
- Patients with childbearing potential who do not agree to use accepted and effective method of contraception (barrier methods, intrauterine contraceptive devices, sterilisation) during the study treatment period and following a period of 12 months after the last study drug administration.
- Contraindications to the use of corticosteroid treatment

5 RANDOMISATION

Central randomisation will be performed by clinical and coordinating staff at the Clinical Trials Unit, Bristol Haematology and Oncology Centre, on behalf of the sponsor (UH Bristol).

All registered patients must be fit to receive chemotherapy. An eligibility checklist must be completed by the clinician/research nurse prior to randomisation. The following information will be required:

- Site ID, oncology consultant and person randomising patient;
- Confirmation that patient is eligible for the trial by completion of the checklist;
- Confirmation that the disease being followed in the trial has beenassessed by CT imaging within 6 weeks of first dose of chemotherapy (cycle 1 day 1);
- Confirmation that patient has given written informed consent for randomisation;

Sites should email a scanned copy of the eligibility checklist to:

CONCEPT@UHBristol.nhs.uk **OR** fax to: 0117 342 4198

Method of assigning patients to treatment group

After central confirmation of eligibility criteria, all eligible patients will be randomly assigned to one of the two arms (either cabazitaxel 25 mg/m² or paclitaxel 80 mg/m²) in a 1:1 ratio by BHOC CTU staff using a computerised system. Patient assignment to a treatment group will be performed according to a stratified randomisation list (randomisation by permuted bloc) according to the previous chemotherapy in adjuvant setting (docetaxel vs no docetaxel) and subtype tumour (ER positive or negative).

The patient will be assigned a unique trial identification number (Trial ID) and randomisation arm. This trial ID is recorded on all documentation and will be used for identification purposes in the CONCEPT Trial.

Randomisation confirmation will be emailed to site staff confirming Trial ID and randomisation arm.

Patients should commence chemotherapy within 3 weeks of randomisation.

6 TRIAL EVALUATIONS

6.1 Baseline

Patients will undergo general assessment and assessment of their disease to include:

- Physical examination (including height, weight and body surface area) to assess fitness and ECOG performance status; vital signs (blood pressure, heart rate, respiratory rate);
  NB. This must be conducted by a medically qualified doctor.
- Recording of concomitant medication use, with relevant dates;
- ECG;
- MRI/CT scan of chest, abdomen and pelvis to be performed within 6 weeks of the first dose of chemotherapy (cycle 1 day 1)
- Peripheral blood test for CTC measurement, if participating in the CTC substudy (Bristol site only) and randomised to receive Cabazitaxel
- Full blood count, Urea and Electrolytes (U+Es, including Na, K, Ca and Creatinine) liver function tests (to include ALP, ALT, Alb and Bil) and LDH;
- GFR to be assessed according to local practice (recommended technique of eGFR using the CKD-EPI formula (see Appendix 2));
- Baseline assessment of symptoms using common toxicity scoring (CTCAE v4.03).
- Completion of Quality of life questionnaires EQ-5D and FACT-B.

6.2 On-treatment assessments

Patients will be seen and assessed within 3 days prior to each cycle of chemotherapy. Assessment should include:

- Physical examination (including height, weight and body surface area) and vital signs to include blood pressure, heart rate, respiratory rate;
  NB. This may be conducted by a nurse who holds the required qualifications and has demonstrated competency for performing physical examinations. Evidence of this must be provided to the sponsor, and delegation of the task must be authorised by the PI on the trial delegation log. A note to file documenting this arrangement must also be provided.
- BSA (should be calculated as per local practice);
- Full blood count, U+Es (including Na, K, Ca, and Creatinine), liver function tests (to include ALP, ALT, Alb and Bil) and LDH;
- GFR to be assessed according to local practice (recommended technique of eGFR using the CKD-EPI formula (see Appendix 2));
- Safety assessment (CTCAE v4.03);
- Updated recording of concomitant medication use, with relevant dates
- Quality of life questionnaires EQ-5D and FACT-B prior to cycles 3 and 5
- MRI/CT scan of the chest, abdomen and pelvis to be carried out every 6 weeks, based on the start date of chemotherapy (+/- 7 days), until the end of treatment visit.
- Blood test for circulating tumour cell (CTC) measurement prior to cycles 1, 3 and 5 of Cabazitaxel chemotherapy and at the end of treatment if participating in the CTC substudy (Bristol site only)

6.3 End of chemotherapy treatment

Patients should be seen no later than 6 weeks after the first day of the final cycle of chemotherapy. Assessments should include:

- Physical examination to assess fitness and ECOG performance status;
  NB. This may be conducted by a nurse who holds the required qualifications and has demonstrated competency for their performing physical examinations. Evidence of this must be provided to the sponsor, and delegation of the task must be authorised

by the PI on the trial delegation log. A note to file documenting this arrangement must also be provided.

- Full blood count, U+Es (including Na, K, Ca, Alb and Creatinine), liver function tests (to include ALP, ALT, Alb and Bil) and LDH;
- GFR to be assessed according to local practice (recommended technique of eGFR using the CKD-EPI formula (see Appendix 2));
- Safety assessment (CTCAE v4.03).
- Updated recording of concomitant medication use, with relevant dates
- Quality of life questionnaires EQ-5D and FACT-B.
- MRI/CT of chest, abdomen and pelvis.
- Blood test for circulating tumour cell (CTC) measurement if participating in the CTC substudy (Bristol site only) and have been treated with Cabazitaxel
- Recording of any subsequent treatment the patient has received for their MBC.

6.4 Follow-up

Short Term

Patients will be followed up in the short term **in clinic** at 3 months and 6 months post the End of Treatment visit (+/- 7 days).

Long Term

Subsequent long term follow up can be performed via telephone with the patient and/or the patient's GP at 2 year and 5 year time points post End of Treatment visit to capture survival data and dates of subsequent treatment and progression events. This data should be recorded in the individual patient's CRF.

- MRI/CT of chest, abdomen and pelvis should be undertaken at each follow up time point until progression.

6.5 Qualitative data

Data collection forms for each visit will allow clinicians and/or participants to enter free text, to record data considered to be important but not addressed by this protocol. This may aid future design of larger studies.

Schema of Trial Evaluations

Visit Schedule

Procedure & visit window:	**Baseline**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**End of treatment**	**3 month Follow up**	**6 month Follow up**	**2 year Follow up**	**5 Year Follow up**	
	Within 7 days of randomisation		Within 3 days pre treatment	Within 3 days pre treatment	Within 3 days pre treatment	Within 3 days pre treatment	Within 3 days pre treatment	Within 6 weeks post 1st day last cycle	Within 3 months of EOT visit ±7 days	Within 6 months of EOT visit ± 7 days	Via telephone within 2 years of EOT visit ±7 days	Via telephone within 5 years of EOT visit ±7 days	
Physical Examination (inc. height, weight and BSA + assessment of peripheral neuropathy)	X[8]	X[4,8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]					
ECOG performance status	X	X[4]	X	X	X	X	X	X					
Vital signs	X	X[4]	X	X	X	X	X	X					
12 Lead ECG	X												
Urine/Serum pregnancy test (if applicable)	X												
Haematology+ biochemistry	X	X[4]	X	X	X	X	X	X					
Medical + cancer history	X												
Collection of Conmeds /AEs	X	X[4]	X	X	X	X	X	X					
CT/MRI chest/abdomen & pelvis for target lesion measurement	X[1]			X[7]		X[3,7]		X[3,7]	X[3]	X[3]	X[3]	X[3]	
Bone scan	X[2]												
Administration of GCSF (cabazitaxel arm only)		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]						
Quality of Life Assessment	X			X		X		X					
Administration of intravenous premedication		X	X	X	X	X	X						

Procedure & visit window:	**Baseline**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**End of treatment**	**3 month Follow up.**	**6 month Follow up**	**2 year Follow up**	**5 Year Follow up**	
	Within 7 days of randomisation		Within 3 days pre treatment	Within 3 days pre treatment	Within 3 days pre treatment	Within 3 days pre treatment	Within 3 days pre treatment	Within 6 weeks post 1st day last cycle	Within 3 months of EOT visit ± 7 days	Within 6 months of EOT visit ± 7 days	Via telephone within 2 years of EOT visit ±7 days	Via telephone within 5years of EOT visit ± 7 days	
Cabazitaxel administration 25mg/m^2 on day 1 +/- 3 days OR		X[5]	X	X	X	X	X						
Paclitaxel Administration (80mg/m^2) on day 1,8 and 15 of each cycle +/- 1 day		X[5]	X	X	X	X	X						
Survival status inc. dates of progression + subsequent treatment data.									X	X	X	X	
Procedure & visit window	**After randomisat-ion + before treatment**			**Cycle 3 within 3 days pre-treatment**		**Cycle 5 within 3 days pre-treatment**		**End of treatment**					
Blood collection for translational purposes (plasma/serum) CTC samples (Bristol site and Cabazitaxel patients only.	X			X		X		X					

1 Within 6 weeks of first dose of chemotherapy (cycle 1 day 1)

2 Only if clinically indicated, repeated as necessary

3 Only if not previously progressed

4 To be repeated if baseline sample is not within 7 days of treatment (Biochemistry to include Cr, Na, K, Ca, Urea, Alb, Bili, ALP, ALT, LDH)

5 Within 3 weeks of randomisation

6 Non-pegylated G-CSF to be given on Days 2-8 post cabazitaxel administration or Pegylated G-CSF on day 2 only

7 CT scan to be performed every 6 weeks (+/- 7 days), based on the start date of chemotherapy (cycle 1 day 1). This is irrespective of any delay in treatment.

8 Baseline physical exam must be performed by a medically qualified doctor. Subsequent exams may be done by a nurse. **Refer to sections 6.1, 6.2 and 6.3 for details.**

7 SCREENING, BASELINE AND TREATMENT

Screening and Baseline assessments will be completed as detailed in section 6.1

7.1 Cycle 1 Day 1 visit

Note the cycle 1 day 1 visit must take place within 21 days of randomisation. Authorisation for any delays to the cycle 1 day 1 visit may be granted at the CI's discretion.

7.2 Within 3 days of each cycle the following assessments are required:

- Physical exam + assessment of peripheral neuropathy
- Vital signs including ECOG performance status, height ,weight, BSA, toxicity assessment (CTCAE v4.03)
- Assessment of target lesions at pre assessment visits for cycles 3 and 5
- Quality of life questionnaires at pre assessment visits for cycles 3 and 5
- Haematology and biochemistry to include Cr, Na, K, Ca, Urea, Alb, Bili, ALP, ALT, LDH
- If creatinine levels are > 1.5 x ULN, microscopic dipstick analysis should be completed
- eGFR to be calculated (see Appendix 2)
- Collection of 10ml blood for translational research (CTC sample) – Bristol only, for those patients receiving Cabazitaxel chemotherapy

7.3 Day 1 of each cycle:

Cabazitaxel treatment administration:

- Premedication of Ranitidine 50mg, Piriton 10mg (chlorphenamine) and dexamethasone 8mg administered by IV infusion, at least 30 minutes prior to Cabazitaxel administration
- 25mg/m2 (Cap at BSA 2.25m^2) Cabazitaxel treatment administered by IV infusion (approximately 1 hour). Cabazitaxel to be given at full dose at cycle 1.

When calculating BSA for dosing, it is encouraged to follow the exact BSA. However as per standard practice in several centres in the UK, a dose banding of up to a 10% change in weight without modifying the actual dose administered is permitted. If the patient's weight change from the previous cycle is greater than 10%, then modify the dose accordingly.

The use of metoclopramide is recommended as antiemetic prophylaxis.

Paclitaxel premedication and treatment administration as per standard practice.

The following parameters must be met prior to each cycle of treatment at the standard dose level (25mg/m^2 for Cabazitaxel and 80mg/m^2 for Paclitaxel). Please see table 2: dose modifications on page 29 for more information.

Cabazitaxel arm on day 1:	Paclitaxel arm on days 1, 8 + 15:
Neutrophils ≥ 1.5 x10^9/L	As per standard local practice
Platelets ≥ 75 x10^9/L	As per standard local practice
Hb ≥ 80 g/L	As per standard local practice

7.4 Every 6 weeks from start of chemotherapy

- CT/MRI* scan of chest, abdomen and pelvis 6-weekly based on the date of start of chemotherapy (+/- 7 days) - regardless of any treatment delays, until the end of treatment. If the patient stops treatment early for any reason apart from disease progression the CT scan schedule should be adhered to as if they were still on treatment. Patients who have not progressed will therefore have three 6-weekly (+/- 7days) CT scans before they move onto the follow-up visit schedule.

*The same imaging modality used to identify target lesions at screening baseline must be used throughout the study

7.5 End of treatment visit

Patients should be seen no later than 6 weeks after the first day of their final cycle of treatment

The following procedures must be completed:

- Haematology and biochemistry to include Cr, Na, K, Ca, Urea, Alb, Bili, ALP, ALT, LDH
- Physical exam + assessment of peripheral neuropathy
- ECOG
- Toxicity assessment (CTCAE v4.03)
- Final Collection of 10ml blood for translational research (CTC) – Bristol site only for those patients who have received Cabazitaxel
- Complete End of Treatment form
- Quality of life questionnaires EQ-5D and FACT-B.
- CT/MRI of chest, abdomen and pelvis

7.6 Follow up visits

Clinic visits subsequently will be 3 months and 6 months, (+/- 7 days) from the date of the end of treatment visit. Progression free survival data and Overall survival data can be collected via telephone at 2 and 5 years following the end of treatment visit. CT scan of chest/abdomen/pelvis needed at every follow up time point until disease progression.

8 PROCEDURES FOR ASSESSING EFFICACY – Medical Imaging

8.1 CT/MRI scan of chest, abdomen and pelvis

A contrast CT/MRI scan of the chest, abdomen and pelvis must be completed at baseline (within 6 weeks of first dose of chemotherapy (cycle 1 day1)) in order to identify the target lesions, according to RECIST 1.1 guidelines using oral and IV contrast.

Assessment of the target lesions must take place at baseline, before cycles 3 and 5 and at the end of treatment. Further CT scans will be taken at each follow up visit until disease progression.

8.2 Selection of target lesions

The objective tumour response of target lesions will be assessed during the trial using the RECIST version 1.1 (refer to Appendix 1).

Therefore, for the patient to fulfil the inclusion criteria for this clinical trial, the patient must have measurable disease by CT scan (irrespective of scanner type). This is defined as disease measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10mm or if the target lesion is a lymph node it must be at least

15mm (shortest diameter in the plane of measurement is to be recorded). The only exception is for skin lesions that can be measured with a ruler and followed using colour photography. These must be ≥10mm in size to qualify as a target lesion and photographs must be available for monitoring purposes.

All measurable lesions, up to a maximum of 5 lesions (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. Target lesions should be selected on the basis of their size (lesions with longest diameter) and their suitability for accurate and repeated measurement (by imaging techniques). The largest lesion may not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD in the patient CRF. The baseline sum LD will be used as the reference by which to characterise the objective tumour response throughout the trial.

A scan completed prior to patient screening for this clinical trial may be used as the baseline scan, provided it was completed within 6 weeks of the first dose of chemotherapy (cycle1 day1).

8.3 Determination of response to treatment

All patients will be evaluated with contrast CT/MRI as completed at baseline for objective tumour response using RECIST version 1.1 (refer to Appendix 1) up until disease progression.

Procedures for Assessing Safety

Each patient (regardless of their study treatment allocation) will attend clinics 3-weekly (-/3days) from day 1 (start of treatment) where the PI will record any AEs. AEs will be described using the National Cancer Institute (NCI) Common Terminology Criteria (CTC) for Adverse Events (CTCAE) Version 4.03

All patients should attend clinic no later than 6 weeks after commencement of the first day of their last cycle of chemotherapy in order to capture any AEs which may have occurred. The patient should be followed up by the Investigator until the AEs have been resolved.

9 OTHER ASSESSMENTS

9.1 Quality of Life

The EQ-5D & FACT-B questionnaires are being used in this trial to assess quality of life. These should be completed by the patient whilst at the clinic at baseline, prior to cycles 3 and 5 and at the end of treatment visit.

10 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

10.1 Primary criteria

Efficacy: Progression free survival between the two groups, defined as the time from randomisation to the date of disease progression as assessed on CT scans based on RECIST 1.1 or death from any cause, whichever comes first. CT scans will be done as per the protocol (at baseline, then every 6 weeks (+/- 7 days) from start of chemotherapy until completion of trial related chemotherapy or equivalent time points if patient stops treatment early for any reason other than disease progression, and then at each follow up time point thereafter until disease progression is documented).

10.2 Secondary criteria

10.2.1 Safety & Tolerability

Descriptive statistics for the two treatments will be given on the number of patients whose treatment had to be reduced, delayed or permanently stopped. The reason for termination includes aspects of efficacy (e.g. termination due to tumour progression), safety (e.g. termination due to adverse events (AEs), including SAEs, AEs leading to death, AEs leading to permanent treatment discontinuation, laboratory data) and compliance (e.g. termination due to patient's withdrawal of consent). Reasons for premature termination will be categorised according to the main reason and will be presented in frequency tables. Safety by toxicity grades is defined by the NCI-CTCAE version 4.03.

10.2.2 Other secondary endpoints

- To assess Clinical Benefit Rate (CBR) defined as stable disease rate + partial response rate + complete response rate according to RECIST 1.1 criteria
- To assess objective response rate in each group; defined as CR and PR
    - *In the Bristol sub-pilot study, blood samples for CTC count will be correlated to radiological response*
- To assess the time to response in each group – time from randomisation to the CT scan showing response as per RECIST1.1
- To assess the overall survival (time from randomisation to the date of death from any cause) in each treatment group
- To assess quality of life using EQ-5D and FACT-B assessment tools (measured at baseline, prior to cycles 3 and 5 and at the end of treatment visit)
- To assess the time to next cytotoxic chemotherapy treatment from the date of completion of trial chemotherapy (for both ER+ve and ER-ve patients - it is assumed that some ER+ve patients will be commenced on endocrine treatment after finishing trial chemotherapy even in the absence of disease progression)

11 TREATMENTS

11.1 Investigational Medicinal Products

11.1.1 Cabazitaxel

Cabazitaxel 25 mg/m² IV (cap at BSA 2.25/m^2) Day 1 of each 21 day cycle as 1-hour infusion for a total of up to 6 cycles. See Appendix 3 for handling and preparation.

Throughout the treatment with Cabazitaxel patients should receive adequate hydration (3 litres of fluid daily) for 3 days after each treatment to prevent complications like renal failure.

The recommended premedication regimen should be performed at least 30 minutes prior to each administration of Cabazitaxel with the following intravenous medicinal products to mitigate the risk and severity of hypersensitivity:

- Antihistamine (chlorphenamine 10mg)
- Corticosteroid (dexamethasone 8 mg or equivalent)
- H_2 antagonist (ranitidine 50mg)

Storage conditions:

Vials should be stored according to their labelling and kept in their kit until use.

Further details of the vial contents are listed in the Pharmacy Manual and the current SmPC.

11.1.2 Paclitaxel

Paclitaxel is an IMP (Comparator).

Paclitaxel 80 mg/m² as 1-hour i.v. infusion. Patients will receive weekly (Days 1, 8, 15 of each 21 day cycle) paclitaxel administrations up to 18 infusions in this study.

Paclitaxel is used according to the recommendations of the manufacturers via normal procedures at each site.

11.2 Non Investigational Medicinal Products

11.2.1 Granulocyte colony stimulating factor (G-CSF)

Non-pegylated GCSF such as Zarzio (0.5 million units per kg) or the equivalent G-CSF is to be administered subcutaneously on days 2-8 of each cycle for those patients randomised to receive Cabazitaxel. Alternatively long lasting Pegylated G-CSF 6 mgs may be given instead on day 2 only

11.3 Risk-benefit Analysis for the Participants

Study participants in the control arm will receive a standard chemotherapy with a taxane (this would be considered a standard of care option in the participating centres) at a dose and duration in concordance to current treatment guidelines. Therefore under-treatment can be excluded. Patients randomised to cabazitaxel will receive this agent instead of paclitaxel. Cabazitaxel has shown high efficacy in docetaxel-resistant prostate cancer with a better toxicity profile. It is therefore considered that patients in the experimental arm will not be under-treated. Participating patients will have marginal additional burden due to investigations required for study participation. However, the option to receive a better tolerable drug with a potentially higher efficacy is considered to balance this additional burden.

11.4 Concomitant treatment

11.4.1 Permitted Medications

All patients will be asked to provide a complete list of prescription and over-the-counter medications that have been taken from the date of consent. The investigator must be informed as soon as possible about any new medication(s) taken from the time of consent until the completion of the End of Treatment visit.

Concomitant medications taken during the study will be recorded in the case report form (CRF) with indication, dose information, and dates of administration.

Patients should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates when appropriate.

Antiemetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) should be administered prophylactically in the event of nausea.

Permitted concomitant treatments are:

- Antiemetics
- Antiallergic measures
- Erythropoietin stimulating factors (only if Hb drops below 10g/dL)
- Non-pegylated G-CSF to be given on days 2-8 after cabazitaxel chemotherapy or Peglyated G-CSF to be given on day 2 only.
- *i.v.* antibiotics in case of febrile neutropenia or documented infection
- Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) are recommended
- Use of erythropoietin for chemotherapy-related anaemia.
- Denosumab or Bisphosphonates
- Supportive treatment as medically indicated for the patient's well-being (including hyperalimentation and blood transfusion) may be prescribed at the investigator's discretion.
-
- Palliative radiotherapy is permitted to non-target lesions at the investigators discretion but not on the same day as chemotherapy.

Maintenance dexamethasone (or equivalent corticosteroid treatment) is permitted at ≤ 2mg per day at initiation of trial chemotherapy. Subsequently up to 4mg per day may be prescribed whilst the patient is receiving trial chemotherapy.Higher doses should be discussed with the Chief Investigator.

Every medication or treatment taken by the patient during the trial from time of consent to the end of treatment and the reason for its administration must be recorded on the CRF.

11.4.2 Prohibited Medications

Not permitted concomitant treatments are:

- Patients must not receive any other non-licensed, investigational drug or anticancer treatment including immunotherapy, targeted therapy or biological therapies until end of study treatment.
- Concurrent radiotherapy on the day of chemotherapy.
- Concurrent treatment with strong inhibitors of cytochrome P450 3A4, such as ketoconazole, itraconazole, clarythromycin. Or concurrent treatment with potent strong inducers of

cytochrome P450 3A4 such as the antielileptic drugs carbamazepine, phenytoin, phenobarbital and St John's Wort (millepertuis) (a non-definitive list of CYP3A4 inducers and inhibitors may be found at https://liferaftgroup.org/long-list-of-inhibitors-and-inducers-of-cyp3a4-and-cyp2d6/). For patients who were receiving treatment with such agents, a one-week washout period is required prior to treatment.

- Dexamethasone is allowed only when given as a pre-medication immediately before the chemotherapy or as an anti-emetic in the first few days following each treatment (see above as well).
- Hormone therapy is not allowed. Prior treatment should be stopped once consented.
- Concomitant treatment with amifostine (Ethyol) or cardioprotectors (e.g. Savene) will not be allowed during the course of study treatment.

11.5 Post-Study treatment

On completion of the study treatment or on stopping study treatment, subsequent treatment is at the discretion of the individual investigator. The investigator records the subsequent treatments in the appropriate page(s) of the CRF, including initiation of subsequent chemotherapy.

11.6 Treatment accountability and compliance

Investigational Product accountability:

- The investigator records the dosing information on the appropriate page(s) of the CRF;
- The Monitor in charge of the study then checks the CRF data by comparing them with the Investigational Product Log which he/she has retrieved and treatment log forms.

11.7 Guidelines for the Management of Toxicity

General Rules

Every effort will be made to administer the full dose regimen to maximise dose-intensity.

If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to improve signs and symptoms including antiemetics for nausea and vomiting, antidiarrhoeals for diarrhoea, and antipyretics, and/or antihistamines for drug fever.

Dose modifications:

11.8 Dose reduction

Dose can be reduced for cabazitaxel and for paclitaxel when necessary. Only 1 dose reduction will be allowed per patient. If a second dose reduction is required, the patient should discontinue study treatment. Dose levels for each arm in case of dose reduction are described in Table 1 below.

Table 1: Dose Reduction Levels

	Initial dose (mg/m²)	One dose reduction (mg/m²)
Cabazitaxel	25	20
Paclitaxel (suggested)	80	60

Chemotherapy Delay

All treatment delays will be reported in the CRF. A treatment delay ≥ 4 days for cabazitaxel and ≥ 2 days for paclitaxel should be justified. Treatment may be delayed no more than 3 weeks from the planned date of infusion to allow recovery from acute toxicity. In case of treatment delay of greater than 3 weeks, the patient should discontinue the study treatment, unless there is strong evidence for tumour response justifying continuation of study treatment. The investigator must discuss the rationale with the Chief Investigator before a decision is taken.

11.9 Dose modification and dose delay

The dose of cabazitaxel or paclitaxel, depending on the treatment arm, will be modified in case of toxicity. See section 7.3 for minimum FBC levels required to proceed with treatment. Dose modifications for cabazitaxel are summarised in Table 2.

Table 2: Dose modifications for cabazitaxel.

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia	If not recovered on D21, delay** next infusion until recovery to grade ≤1 (ANC ≥1.5 x 10^9/L)	No dose reduction if isolated and duration ≤7 days. If duration more than 7 days or not recovered on D21 delay** next infusion until ANC ≥1.5 x 10^9/L - 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level. - 2nd episode despite prophylactic G-CSF: Discuss with CI Potential to withdraw from study	
Febrile neutropenia or neutropenic infection	Not applicable	Delay** next infusion until recovery and ANC ≥1.5 x 10^9/L - 1st episode: reduce the dose and administer prophylactic G-CSF treatment in subsequent cycles. - 2nd episode: Discuss with CI. Potential to withdraw from study	
Thrombocytopenia	Delay** next infusion until recovery to grade ≤ 1 (platelets ≥75 x 10^9/L). No dose reduction required.	Delay** infusion until platelets ≥75 x 10^9/L. If grade 3 without delay, no dose reduction required. If grade 4 with or without delay, or grade 3 with delay - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Withdraw from study treatment in case of recurrence.	
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Diarrhoea	Delay** next infusion until recovery (grade ≤1). Start prophylaxis with loperamide for subsequent cycle No dose reduction required.	Delay** next infusion until recovery (grade ≤1): - 1st episode: Reduce dose by 1 dose level and start prophylaxis with loperamide for subsequent cycle - 2nd episode: Discuss with CI	

Stomatitis	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	Delay** next infusion until recovery (grade ≤1): - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Discuss with CI.	
Cutaneous Reactions	Delay** next infusion until recovery (grade ≤1) Consider slowing down the infusion rate from 1 hour to 3 hours No dose reduction required.	Delay** next infusion until recovery (grade ≤1): - 1st episode: Reduce dose by 1 dose level and consider slowing down the infusion rate from 1 hour to 3 hours. - 2nd episode: Withdraw from study treatment.	Withdraw from study treatment.
Creatinine increase		In case of creatinine >1 x ULN, do not delay treatment, calculate creatinine clearance according to CKD-EPI formula on D21: - if ≥60 ml/min, no dose modification - if clearance ≥40 ml/min and < 60ml/min, reduce dose by one dose level - if clearance <40 ml/min, Withdraw from study treatment.	
Neurological toxicity* **	No delay and no dose reduction	1st Episode : Reduce by 1 dose level 2nd episode: If worsening grade or persistent grade 4 discuss with CI.	
Bilirubin Elevation	Delay** until recovery to bilirubin ≤1.5 x ULN and reduce dose by 1 dose level		
Transaminases Elevation	Delay** until recovery to ALT ≤ 2.5 x ULN and reduce dose by 1 dose level		
Hypersensitivity	No dose reduction. Ensure full treatment and administration of chlorpheniramine, ranitidine and dexamethasone or as per local guidelines Consider slowing down the infusion rate from 1 hour to 2 hours	1st episode: Discuss with CI 2nd episode: Withdraw from study	Withdraw from study treatment
** maximum of 3 weeks delay, otherwise the patient will be withdrawn from study treatment		*** Including hearing disorders	

Cabazitaxel dose modifications and dose delay:

Haematological toxicity

Blood counts will be performed in case of fever or infection. Blood count should be monitored weekly to determine if G-CSF or dosage modification is needed. Study treatment should not be given to patients with neutrophil counts <1.5 x10^9/L (cabazitaxel). For patients receiving Paclitaxel, neutrophil, haemoglobin and platelet levels should be commensurate with standard local practice for treatment to continue on days 1, 8 + 15. If symptomatic, patients to be transfused to enable chemotherapy to continue

Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel and paclitaxel. Neutropenic complications should be managed promptly with antibiotic support and use of G-CSF should be considered according to ASCO or ESMO guidelines. Infections concomitant with grade 3-4 neutropenia should be reported in the CRF with the term febrile neutropeania or “neutropenic infection” if no fever but infection is present.

No dose modification will be made for anaemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO or ESMO guidelines).

The cabazitaxel dose will be modified in case of haematological toxicity. Dose modifications are summarised in Table 2.

Allergy (Anaphylactic and Hypersensitivity reactions)

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of the start of the first or second infusion of cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well-being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention can occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation along with the medications (i.e. antihistamine, corticosteroids, aminophylline, and adrenaline) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g. adrenaline in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below:

Mild: localised cutaneous reaction, such as: pruritus, flushing, rash.	o Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside o Complete cabazitaxel infusion at the initial planned rate.
Moderate: Generalised pruritus, more severe flushing or rash, mild dyspnoea, hypotension with systolic B.P. >80 mmHg	o Stop cabazitaxel infusion o Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg o Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. o Re-administer premedication regimen as described in Section 11.1 when cabazitaxel is reinfused more than 3 hours after the interruption o Administer cabazitaxel over 2 hours for all subsequent infusions
Severe: bronchospasm, generalised urticaria, hypotension with systolic B.P.	o Stop cabazitaxel infusion

≤80 mmHg, angioedema.	○ Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg ○ Add adrenaline or bronchodilators and/or IV plasma expanders if indicated ○ Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible ○ Re-administer premedication regimen as described in Section 11.1 when cabazitaxel is reinfused more than 3 hours after the interruption ○ Administer cabazitaxel over 2 hours for all subsequent infusions ○ If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (Grade 4 reaction)	Withdraw treatment

Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to patients in all cycles. The use of metoclopramide is recommended. More aggressive anti-emetic prophylaxis (i.e. ondansetron, etc.) should be given to the patient who has experienced grade ≥3 nausea/vomiting in a preceding cycle. If despite the appropriate medication, grade ≥3 nausea/vomiting still occurs, reduce the dose of cabazitaxel. If despite dose reduction and prophylaxis, nausea/vomiting still occur at grade ≥3, the patient should be withdrawn from treatment with cabazitaxel.

Stomatitis

If grade 3 stomatitis occurs, cabazitaxel should be withheld until resolution to grade ≤1. Treatment may then be resumed, but the dose of cabazitaxel should be reduced for all subsequent doses. In case of grade 4 stomatitis, the patient will be withdrawn from treatment with cabazitaxel.

Diarrhoea

No prophylactic treatment for diarrhoea is recommended in Cycle 1. However, following the first episode of diarrhoea, the patient should be treated with rehydration or antidiarrheal medications as needed. In case of grade ≥ 3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolytes replacement, delay treatment until improvement or resolution, then reduce the dose. If despite dose reduction, diarrhoea still occurs at grade ≥3, the patient will be withdrawn from treatment with cabazitaxel.

Renal function

1) To plan microscopic urinalysis/ dipstick:

- at baseline (reference value)
- and during study treatment if creatinine increases to >1.5 x ULN

2) To consider nephrologist advice in case of creatinine increase by at least 2 x ULN or eGFR (according to CKD-EPI formula) decrease by 50% from baseline value.

3) To recommend i.v. hydration for CT scan with contrast in case of eGFR <60 ml/min (see Appendix 2)

4) In case of renal function impairment, to make every effort to identify the cause and to report the cause as the adverse event. The existing renal failure should be considered in the grading of the event. If no cause is identified (no diagnostic), report eGFR decrease as the adverse event.

Creatinine and eGFR should be assessed until recovery or stabilisation.

Haematuria

An imbalance in the incidence of haematuria was observed in the Phase III study in second line mCRPC (EFC6193). More haematuria was reported in cabazitaxel arm versus mitoxantrone arm (62 patients/16.7% versus 14 patients/3.8%). In cabazitaxel arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In addition, in prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy).

Therefore, in case of haematuria with no clear possible explanation every effort should be undertaken to document the cause (e.g. urine cultures, urinary tract ultrasound, and if no cause identified cystoscopy with or without biopsy).

Peripheral neuropathy

Dose modification should be performed as follows:

- Grade ≤1: No change
- Grade 2: No delay and no dose reduction
- Grade 3: 1st episode: Reduce by 1 dose level. 2nd episode: If worsening grade or persistent grade 4 discuss with CI.

Liver toxicity

In case of increase of SGPT(ALT) to >2.5 x ULN or bilirubin to >1.5 x ULN, delay cabazitaxel treatment for up to 3 weeks until SGPT(ALT) returns to ≤2.5 x ULN and bilirubin to ≤1.5 x ULN. Then retreat patient at reduced dose for rest of the treatment.

Other Toxic Effects

For ≥grade 3 toxicities except fatigue, local reaction, fluid retention, anaemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, chemotherapy should be held for a maximum of 3 weeks from the planned date of reinfusion until resolution to ≤grade 1, then reinstituted, if medically appropriate. A dose reduction of subsequent doses will be left to the investigator's judgment. These patients will be withdrawn from study treatment if 2 dose reductions are needed. Any measures such as frozen gloves or socks or scalp cooling cap to prevent nail toxicity or alopecia are left to the investigator's judgment.

Recovery of chemotherapy related toxicities

Following recovery of toxicity which has required dose reduction, it is permissible, but not mandatory, for patients to receive chemotherapy at the 100% dose for subsequent cycles provided all assessments are within the limits set out above.

12 SAFETY & PHARMACOVIGILANCE

12.1. Definitions

12.1.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence in a patient administered a drug; the event does not necessarily have a causal relationship with the treatment or usage.

The following should not be recorded as AEs if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Pre-existing conditions found as a result of screening procedures unless the condition worsens from the first trial related activity after the subject has signed the informed consent.

Procedure for collecting Adverse Events

- For the purpose of this trial, any detrimental change in the patient's condition that occurs after the subject has started trial treatment, until the end of treatment visit, which is not due to progression of disease (advanced breast cancer), should be considered an AE.
- All AEs regardless of their seriousness or relationship to the product should be reported. Investigator's assessment of the seriousness and causal relationship between the AE and the study medication should be provided on the CRF. Additional relevant follow-up information should be provided to the marketing authorization holder (MAH) within the specified timelines.
- In addition, any Serious Adverse Event (SAE) that appears to be related to the Investigational Medicinal Product (IMP) or Non-Investigational Medicinal Product (NIMP) must be reported by the Investigator to the Sponsor or delegate at any time, even after the subject has completed the study.
- Whenever one or more signs and/or symptoms correspond to a disease or a well-defined syndrome only the main disease/syndrome should be reported. The severity of adverse events will be graded according to the NCI-CTC criteria (CTCAE v4.03).
- All adverse events (AE) must be reported on the Case Report Forms (CRF).

12.1.2 Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence or reaction that occurs after the commencement of randomised treatment and within 30 days of the last administration of the trial regimen, that at any dose:

- Results in death;
- Is life threatening,

Note: the term “life-threatening refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe

- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Is a congenital anomaly/birth defect; or
- Is a medically important event or reaction.

Note: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Procedure for recording Serious Adverse Events/Reactions

SAEs in this study that are fatal or life threatening or result in persistent or significant disability/incapacity or are related to the trial drug (including prolongation of existing hospitalisation) should be reported using a Serious Adverse Event (SAE) form.

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in persistent or significant disability/incapacity.

The following list of medically important events is intended to serve as a guideline for determining which conditions should be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
- Allergic bronchospasm
- Blood dyscrasias (i.e., agranulocytosis, aplastic anaemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
- Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse
- Alanine aminotransferase (ALT) >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicide
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).
- Suspected transmission of an infectious agent: if any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination)
- Required intervention to prevent permanent impairment or damage related to device use.

Related Adverse Event, i.e. Adverse Drug Reaction (ADR): there is a reasonable possibility according to the investigator and/or the sponsor that the Product may have caused the event.

Unexpected ADR: An adverse drug reaction (ADR) is considered unexpected if the nature or severity, specificity, or outcome is not consistent with the applicable product reference safety information (RSI) which can be found in the Cabazitaxel (Jevtana) SmPC dated 20th April 2017 section 4.8 or for the IMP comparator Paclitaxel in the Teva SmPC dated 10th February 2017 section 4.8. The expectedness of an ADR will be determined by whether or not it is listed in the applicable RSI. An expected ADR with a fatal outcome should be considered unexpected unless the RSI specifically states that the ADR might be associated with a fatal outcome.

If the unexpected adverse event meets the criteria of being serious then it is classed as a Serious Unexpected Adverse Reaction (SUSAR) and expedited reporting by the sponsor to the regulatory authorities will occur.

The following events should be immediately reported to the Marketing Authorisation holder by the chief investigator.

- Pregnancy
- Symptomatic overdose both serious and non serious with the IMP/NIMP

12.1.3 Causality (relatedness)

The assignment of causality for serious adverse events should be made by the investigator responsible for the care of the patient using the definitions in Table 12.1.4. If any doubt about the causality, the investigator should inform the sponsor who will notify the Chief Investigator. Pharmaceutical companies and/or other clinicians may be asked to advise.

Relationship to Investigational Medicinal (IMP) Product Assessment Definitions:

Investigators must assess whether there is a reasonable causal relationship with the IMP administered, or with the study procedure(s), for each reported AE. “Reasonable causal relationship” means that there are facts/evidences or arguments to suggest a causal relationship [based on ICH E2A Guideline].

- Associated to investigational product
- Not associated to investigational product

Outcome Categories and Definitions:

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

12.1.4 Definitions for causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
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

12.1.5 Serious Adverse Reactions (SAR)

A SAR is an SAE that has a definite, probable or possible causal relationship to the trial drug.

12.1.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any adverse reactions that have a suspected relationship to the trial drug that are both serious and unexpected, as judged by the CI.

12.1.7 Reporting of Serious Adverse Events/Reactions to the Sponsor

Serious adverse events require **immediate reporting** to the **sponsor** within 24 hours of the Principal Investigator or designated representative becoming aware of the event.

Please email the SAE/SUSAR form for the attention of the sponsor at Research and Innovation to research@UHBristol.nhs.uk **AND** to CTU either via fax: 0117 3424198 or email: BHOC-CTU-Safety@UHBristol.nhs.uk, indicating it is an SAE

Forms must be completed, signed and dated by the site Principal Investigator or designated representative.

12.1.8 Review of Serious Adverse Events/Reactions

Events reported using an SAE/SUSAR form will be forwarded to the Chief Investigator immediately (or designated representative) for assessment of causality and expectedness.

Centres should respond as soon as possible to requests from the CI or designated representative (via the sponsor) for further information that may be required for final assessment.

12.1.9 Expedited Reporting of SUSARs

If an SAE/SAR is defined as a SUSAR (both related and unexpected and is fatal or life threatening, the sponsor will report this to the MHRA and the Main REC within 7 days from the date of being notified of the event.

If an SAE/SAR is defined as a SUSAR and is not fatal or life threatening, the sponsor will report this to the MHRA and Main REC within 15 days.

The Principal Investigator at all actively recruiting centres will be informed of any SUSARs occurring within the trial.

12.2 Follow-up of Serious Adverse Events/Reactions

The patient must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of the SAE which may not be available at the time the SAE was initially reported should be completed on the follow-up SAE form within 15 days of resolution of the event and faxed or emailed to the sponsor as in section 12.1.7.

12.2.1 Annual Reporting of Serious Adverse Events/Reactions

An annual report will be provided to the MHRA and the Main REC by the sponsor at the end of the reporting year. This will be defined as the anniversary of the date when the Clinical Trials Authorisation (CTA) and REC favourable opinion were obtained. This will include all SARs and SUSARs.

13 END OF TREATMENT (EOT)

The regular end of treatment for a patient is defined as no later than 6 weeks after the first day of the last treatment cycle.

13.1 Treatment discontinuation of Individual Patient

If a patient shows one of the following reasons, the study treatment has to be discontinued:

- Progression of metastatic breast cancer as per RECIST1.1,
- Unacceptable toxicity
- Patients request or non-compliance.

The reason and date of discontinuation for all patients will be documented on the CRF (e.g. progressive disease, death, adverse event, withdrawal of consent, lost to follow-up, etc.).

The investigator will attempt to complete all discharge procedures at the time of discontinuation of systemic treatment. The procedures have to be documented in the CRF.

14 END OF STUDY (EOS)

14.1 Regular End of Study

The planned recruitment end date is December 2020. The end of this study is defined as 4 weeks after the last patient has completed her last follow up visit.

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 5 years after the last patient has attended their end of treatment visit.

14.2 Premature Termination of Study

The study may be terminated prematurely for safety reasons, slow accrual, or upcoming new data impairing the relevance of the study objective, by the University Hospitals Bristol NHS Trust (UHBristol) as the sponsor, or the data monitoring committee. The Independent Data Monitoring Committee will provide advice. The sponsor is allowed to close the trial for any reason at any time. A decision to prematurely terminate the study is binding to all investigators of all study sites. Responsible ethics committees and regulatory authorities will be informed about the reason(s) and time of termination according to the applicable laws and regulations.

Premature Termination of Study at a Particular Study Site

The UHBristol as the sponsor reserves the right to discontinue the study at a particular study site at any time. The reasons will be discussed with the investigator.

The UHBristol may terminate this study in one particular study site for one of the following reasons:

- Non-compliance with GCP and/or regulatory requirements.
- Insufficient number of recruited patients.
- Failure to comply with trial protocol and guidelines
- Inadequate co-operation with UHBristol or its representatives.
- The Investigator requests to close his/her study site.

If the study is prematurely terminated in a study site, the responsible investigators have to inform their patients and take care of appropriate follow-up and further treatment of the patients.

14.3 Temporary treatment discontinuation with Investigational Medicinal Product

Re-initiation of treatment with the Investigational Medicinal Product (IMP) should be done under close and appropriate clinical and/or laboratory monitoring once the investigator has considered according to his/her best medical judgment that the responsibility of the Investigational Medicinal Product(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (ref to Section 4).

All temporary treatment discontinuation and date of treatment re-initiation should be recorded by the investigator in the appropriate pages when considered to be confirmed.

14.4 Permanent treatment discontinuation with Investigational Medicinal Product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the investigator or the patient not to re-expose the patient to the IMP at any time.

List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with IMP, at any time and irrespective of the reason, or this may be the investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should also be documented in the CRF.

Handling of patients after permanent treatment discontinuation

Patients should be followed up according to the study procedures as specified in this protocol in case of premature permanent treatment discontinuation, or up to recovery or stabilisation of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients should be assessed using the procedure normally planned for the end of treatment visit.

Procedure for withdrawal of patients from study

The patients may withdraw from the study, before study completion if they decide to do so, at any time and irrespective of the reason, or at the investigator's decision.

All study withdrawals should be recorded by the investigator in the appropriate pages when considered as confirmed.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

The investigator should make every effort to establish the reason via the patient's GP to determine the patient's overall health status. Patients who did not complete the study and for whom no endpoint data are available should be considered as lost to follow-up.

Consequence

Patients who have been withdrawn from the study cannot be re-included in the study. Their inclusion and treatment number must not be reused. In specific situations to be discussed between the

investigator and the sponsor, patients who have not yet been randomised can be re-included in the study.

15 STATISTICAL CONSIDERATIONS

The statistical analysis of the present study is performed in accordance with the principles stated in the Consensus Guideline E9 (Statistical Principles for Clinical Trials) of the International Conference on Harmonisation (ICH).

15.1 Disposition of patient

Screened patients are defined as metastatic breast cancer patients who were considered for inclusion into the trial, as detailed on the screening log.

Randomised patients consist of all patients, who have been allocated a trial number based on the randomisation process. It will consist of all patients with a trial number allocated and recorded in the computerised system database, and regardless of whether the treatment was administered or not.

Patients treated without being randomised will not be considered as randomised and will not be included in any population.

For patient study status, the total number of patients for each one of the following categories will be presented:

- Screened patients
- Randomised patients
- Randomised and treated patients
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation.

15.2 Analysis populations

Randomised patients consist of all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomisation number through the web-based data collection interface.

Intent to treat (ITT) efficacy population:

All randomised patients (including those not starting treatment).

This population is for some supportive efficacy analyses only. Patients will be analysed according to the treatment group they were randomised to.

All treated population:

All randomised patients who received at least one (even incomplete) part of the study treatments.

This is the primary population for all efficacy analyses and the only population for all Safety analyses. Patients will be analysed according to the treatment they actually received.

15.3 Sample Size Determination

The primary endpoint for the study is progression free survival (PFS).The assumption is an improvement in median PFS from 5.5 months in the control arm to 8.5 months in the experimental group (corresponding to a hazard ratio/HR (test/control) of 0.647).

A total of 127 PFS events are required to detect a 35.3% hazard rate reduction in PFS (HR=0.647) with 85% power using the log-rank test at a one-sided 10% significance level. A total of approximately 160 patients (80 in each arm) are required to achieve the target number of PFS events.

All calculations were done using East Software, version 5.4.2.0.

The IDMC will examine futility at their regular data reviews, by using 'conditional power' (CP); this is the chance of obtaining the target hazard ratio of 0.647 given the accumulated data so far (and assuming that the remaining data are consistent with this effect), if the trial continued to the end. If the CP is low (e.g. <15%) on two consecutive occasions the IDMC might recommend early stopping, after considering other endpoints including the safety profile.

15.4 Statistical Methods

Unless otherwise specified, efficacy analyses will be performed on the All treated population, in the overall cohort and will be repeated by previous chemotherapy in adjuvant setting (docetaxel vs No docetaxel) and subtype tumour (ER positive or negative) as specified at the time of randomisation. Safety analyses will be performed on the All treated population.

15.4.1 Analyses of primary endpoint

Primary efficacy endpoint is the PFS, defined as the time interval between the date of randomisation and the date of tumour progression (defined according to RECIST version 1.1) or death from any cause, whichever comes first. In the absence of confirmation of disease progression or death, PFS time will be censored at the earlier between the date of last valid tumour assessment without evidence of tumour progression and the cut-off date. PFS for patients who have no tumour assessments after baseline and do not die will be censored on the day of randomisation (Day 1).

PFS will be compared between the two treatments by the log-rank test procedure stratified by previous chemotherapy in adjuvant setting (docetaxel vs No docetaxel) and subtype tumour (ER positive or negative) as specified at the time of randomisation.

The estimates of the hazard ratio and corresponding 80% and 95% confidence intervals will be provided using a Cox proportional hazard model stratified by the same baseline stratification factors as those used for the log-rank test, with treatment effect as single covariate.

The PFS curves will be estimated using Kaplan-Meier estimates as well as PFS rates and associated 80% CI at 1, 3, 6, 9 and 12 months. The median PFS and associated 80% and 95% CI will also be provided.

Imaging response will be assessed at 6, 12 and 18 weeks after first trial treatment (cycle 1 day 1) based on RECIST1.1 criteria and in those patients who have not progressed the imaging will be repeated at 3 months, 6 months, 2 years and 5 years post-completion of treatment until disease progression is noted.

15.4.2 Secondary endpoints analysis

Response rates will be estimated as the number of patients with clinical benefit rate (CR + PR + SD) and objective response (CR+PR) recorded from the start of treatment to the completion of 6 cycles of treatment divided by the number of patients in the population of interest (All treated population). The 80% and 95% confidence intervals will be calculated in each treatment group.

Overall Survival will be defined as the time period between randomisation and death and will be analysed after the end of the study by referring to data from the hospital statistics. Curves will be estimated using the Kaplan-Meier method, based on the all randomised and treated patients' efficacy population. The median survival times (and 95% CIs) will be estimated. Univariate and multivariate Cox-proportional hazards model will be used to adjust hazard ratios for stratification factor.

Tolerability and Safety: Descriptive statistics for the 2 treatments will be given on the number of patients whose treatment had to be reduced, delayed or permanently stopped. Analysis of AEs and laboratory values will be presented for safety analysis.

Quality of Life: FACT-B and EQ-5D scores will be presented by treatment group at baseline, prior to cycles 3 and 5 and at the end of treatment visit.

For EQ-5D, descriptive summary statistics (size, mean, standard deviation, median, range) will be provided for the single index utility score and the VAS by treatment group as well as for the difference in means at baseline, prior to cycles 3 and 5 and at the end of treatment visit. Change from baseline will be also described. For each EQ-5D item, information on the frequency and proportion with its 95% CI of the population reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) per item will be reported by treatment group.

For FACT-B, descriptive summary statistics will be provided for the overall score and subscales of the FACT-B by treatment group, at baseline, prior to cycles 3 and 5 and at the end of treatment visit.

15.4.3 Interpretation of Potential Study Results

Four scenarios of results can be envisaged which will lead to the following conclusions:

1. The substitution of weekly paclitaxel by cabazitaxel leads to a significant increase in PFS with a similar or better toxicity profile. This will lead to the conclusion that it is worthwhile that cabazitaxel should be further investigated in subsequent phase III studies as a potential standard treatment in metastatic breast cancer.
2. The substitution of weekly paclitaxel by cabazitaxel leads to a significant increase in PFS without an intolerable excess of toxicity. This will lead to the conclusion that dose and schedule of cabazitaxel have to be optimised before further development in subsequent phase III studies should be conducted.
3. The substitution of weekly paclitaxel by cabazitaxel shows a trend (but not statistically significant) for a longer PFS with a better toxicity profile. This will lead to the conclusion that dose and schedule of cabazitaxel has to be optimised before further development in subsequent phase III studies.

4. The substitution of weekly paclitaxel by cabazitaxel shows no difference or even a reduced PFS. This will lead to the conclusion that cabazitaxel should not be further developed in metastatic breast cancer.

16 RESEARCH GOVERNANCE

16.1 Trial Administration

The sponsor for this trial is **University Hospitals Bristol NHS Foundation Trust** (referred to in this protocol as UHBristol)

Sponsorship activities and delegated responsibilities are 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 Good Clinical Practice.

All parties agree to allow inspection of their premises by the competent authorities.

16.2 Responsibilities

UHBristol has sponsorship responsibility for obtaining authorisation and appropriate research ethics committee (REC) opinion (Part 3 of the Regulations) and for pharmacovigilance (Part 5 of the Regulations).

The sponsor warrants that the Study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

The sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.

The sponsor shall be responsible for all required periodic updates to the health authorities and expedited reporting of all Serious Adverse Events occurring during the performance of the study, in accordance with local and regional regulations.

The sponsor shall also be responsible to provide to the investigators and the Ethics Committee all relevant study related information (including information submitted to the Health Authorities and any “Dear Investigator Letter” received from Sanofi.

The sponsor must report the following information in English to the Sanofi Pharmacovigilance contact:

- Copy of all individual **S**uspected (drug related) and **U**nexpected **S**erious **A**dverse **R**eactions (SUSARs) at time of submission to Health Authorities (format sent to Authorities) or, if submission of SUSAR is not required in the participating country, such individual reports shall be sent to Sanofi on an ongoing basis.
- In addition to SUSARs, any other events that have been submitted to the Health Authorities according to local regulatory requirements in the participating country shall be sent to Sanofi at time of submission to these Authorities.
- Any significant safety issues, events or results, e.g. Data Safety Monitoring Board recommendations, occurring or found during the course of the Study which might affect performance thereof shall be sent to Sanofi on an ongoing basis.

The reference safety text to be used for evaluation of expectedness of adverse events will be the current approved product label in the country of the sponsor.

Responsibilities may be delegated to the Chief Investigator (or named Deputy in his absence) and to the Clinical Trials Unit, Bristol Haematology and Oncology Centre, as deemed appropriate by the sponsor.

The delegation of 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 the Clinical Trials Unit, Bristol Haematology and Oncology Centre, UHBristol and the Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

This is an NHS-sponsored research study. For NHS sponsored research HSG (96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial.

NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

Ex-gratia payments may be considered in the case of a claim.

16.3 Protocol Compliance & Initiation

The CONCEPT Trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Directive.

16.4 Data Acquisition & On-Site Monitoring

The CONCEPT Trial will be monitored and audited in accordance with UHBristol's policy. All trial related documents will be made available on request for monitoring and audit by UHBristol, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies.

16.5 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the trial data collected. Essential documents will be maintained by the Clinical Trials Unit, Bristol Haematology and Oncology Centre and at participating centres in a way that will facilitate the management of the trial and inspection. Documents will be securely stored and access restricted to authorised personnel. Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 15 years following the end of the study. Where trial related information is documented in the medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where date is 15 years after the last patient last visit.

16.6 Data Protection Act

UHBristol will comply with all aspects of the Data Protection Act 1998. Any requests from patients for access to data held about them should be directed to the Trial Coordinator in the first instance, who will refer the request to the Data Protection Officer.

17 TRIAL MANAGEMENT

17.1 Trial Management Group

A Trial Management Group (TMG) will be set up and will include the Chief Investigator and identified collaborators, the trial statistician and trial co-ordinator. Principal Investigator(s) and key study personnel will be invited to join the TMG as appropriate to ensure representation from relevant professionals.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial.

17.2 Trial Steering Committee

A Trial Steering Committee will be set up and will include an independent chairman, two other independent members, the trial coordinator, trial statistician, the Chief Investigator and site Principal Investigator. Observers from Sanofi and the sponsoring organisation will be invited to meetings as appropriate.

17.3 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to oversee the safety and efficacy of the trial. This committee will be constituted according to Good Clinical Practice. The IDMC will meet on a regular basis as they see fit, but no less than annually. Following each meeting, the IDMC will report their findings and recommendations to the TSC and to the TMG.

18 PUBLISHING POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trial Management Group. All participating centres and clinicians will be acknowledged in this publication. All presentations and publications relating to the trial must be reviewed and approved by the Trial Management Group on whose behalf publications should usually be made. Authorship of any secondary publications will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to the trial without prior permission from the Trial Management Group.

The Sponsor, Sanofi and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Sanofi and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Sanofi for review and approval 30 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable subject matter which, at Sanofi's discretion, warrants intellectual property protection, Sanofi may delay any publication or presentation for up to 60 days for review and approval i.e. 90 days in total.

19 CONFIDENTIALITY AND LIABILITY

19.1 Risk assessment

Generic risk assessment hazards to patients, study and organisation have been performed for the trial.

19.2 Liability/Indemnity/Insurance

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

19.3 Patient Confidentiality

The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain. However, a log of patients' trial ID numbers, names, addresses and hospital numbers kept by the Principal Investigator will be collected to allow tracing through GP and national records to assist with the collection of long term follow-up information. The investigators must maintain trial documents, which are to be held at the participating centre (e.g. patients' written consent forms), in strict confidence.

The Principal Investigator must ensure the patients' confidentiality is maintained.

The sponsors will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Representatives of the sponsor and the regulatory authorities are required to have access to patient notes for quality assurance purposes. Patient 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.

20 ETHICAL CONSIDERATIONS

The CONCEPT trial will be performed subject to Research Ethics Committee (REC) approval, including any provisions of Site Specific Assessment and local Research and Development (R&D) approval.

Patients should be asked to sign the main consent form after having received both verbal and written information. The consent form must be countersigned by the Principal Investigator or a designated individual. A record of who the designated individuals are and the circumstances under which they may countersign consent forms must be clearly documented at the research site as part of the Delegation Responsibilities Log. This log, together with original copies of all signed patient consent forms, must be available for inspection.

The patient information sheet should be provided in addition to any standard patient information sheets that are provided by the centre and which are used in routine practice.

21 WITHDRAWAL OF PATIENTS

21.1 Withdrawal of patients from trial treatment

Patients who do not receive their full trial chemotherapy for any reason (see below) should be treated if appropriate, according to local practice, at the discretion of their clinician. Specific regimens are beyond the scope of this protocol. All CRFs, including long term follow-up, should be completed, regardless of how much treatment is actually received, as an analysis of outcome efficacy data will be performed on the basis of intention to treat (i.e. all randomised patients). Any subsequent treatment for metastatic breast cancer should be recorded on the Additional Treatment CRF.

The following are possible reasons as to why a patient may not receive the trial related chemotherapy:

- Unacceptable toxicity
- Adverse event requiring discontinuation of treatment;
- Unforeseen events: any event, which in the judgement of the Investigator makes further treatment inadvisable;
- Evidence of disease progression;
- Withdrawal of consent;
- Serious violation of the study protocol (including persistent patient attendance failure and persistent non-compliance).

Every attempt should be made to obtain disease assessments for all patients.

21.2 Withdrawal of patients from trial follow-up

Patients are asked prior to randomisation to consent to follow-up should they withdraw from their allocated treatment (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.

A trial deviation form should be completed in the unlikely event that the patient withdraws consent for further follow-up data to be collected. If this situation is suspected, clarification should be sought to ensure that the patient is not simply withdrawing from allocated treatment. In the extremely unlikely event that the patient wishes to have their data removed from the trial completely (the implications of this should be discussed with the patient to ensure that this is their intent) this should be indicated as such on the trial deviation form.

22 FINANCIAL MATTERS

This trial is investigator designed and led.

This trial is supported by a grant from Sanofi.

Patients will not be remunerated for participation in this trial.

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GLOSSARY

AE	Adverse Event
ALT	Alanine Aminotransferase
AR	Adverse Reaction
BSA	Body Surface Area
BHOC	Bristol Haematology & Oncology Centre
CI	Chief Investigator
CISH	Cytokine-inducible SH2-containing protein
CNS	Central Nervous System
CR	Complete Response – refer to RECIST 1.1
CRF	Case Report Form
CSS	Cell Search System
CTA	Clinical Trial Authorisation
CTC	Circulating tumour cells
CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Event Reporting
CTU	Clinical Trials Unit
CV	Curriculum Vitae
ECG	Electrocardiograph
FACT-B	Functional Assessment of Cancer Therapy for Breast Tumours
FISH	Fluorescent in situ hybridisation
G-CSF	Granulocyte colony-stimulating factor
GP	General Practitioner
HER2	Human Epidermal Growth Factor Receptor 2
IB	Investigator's Brochure
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISDMC	Independent Safety and Data Monitoring Committee

IMP	Investigational Medicinal Product
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NIMP	Non-Investigational Medicinal Product
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PI	Principal Investigator
PD	Progressive Disease – refer to RECIST 1.1
PR	Partial Response – refer to RECIST 1.1
QOL	Quality of Life
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease – refer to RECIST 1.1
SISH	Silver in situ hybridisation
SMPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Co-ordinator
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal

APPENDIX 1: RECIST CRITERIA version 1.1

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

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/lymph node. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions: lesions that can be accurately measured in at least one dimension with longest diameter a minimum of size of 10mm by CT scan (CT scan slice no greater than 5mm), 10mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers are considered non-measurable) or 20mm by chest X-ray.

Bone lesions:

- Bone scan, PET scan or plain films are not adequate imaging techniques to measure lesions but can be used to confirm presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic/blastic lesions, with identifiable soft tissue components, which can be evaluated using e.g. CT or MRI scan are considered measurable if the *soft tissue component* meets the criteria for measurable lesions described previously.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts are not considered as malignant lesions.
- 'Cystic lesions' that are thought to represent cystic metastases are considered measurable if they meet the criteria for measurable lesions described previously.
- If non-cystic lesions are present in the same patient then these are preferred for selection as target lesions.

Malignant Lymph nodes: to be considered pathologically measurable a lymph node must be ≥15mm in *short* axis when assessed by CT scan (CT scan slice thickness no greater than 5mm). At baseline and in follow-up, only short axis will be measured and followed.

Non-measurable lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis), i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques. Lymph nodes to be measured by CT scan >10-<15mm.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy are not considered measurable unless progression in the lesion is demonstrated.

Methods of Measurement:

- All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. For this study baseline CT scan will be no more than 6 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. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.
- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Measurability by CT scan is based on the assumption that CT slice thickness is 5mm or less. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. If new lesions are identified by US then confirmation by CT or MRI is desired.
- Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

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

- All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- The short axis of Lymph nodes should be noted since they are normal anatomical structures which may be visible by imaging.
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterise the objective tumour.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Documentation of New Lesions

- The presence of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something

other than tumour (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions).

- A lesion identified at a follow-up visit in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Response Criteria	**Evaluation of target lesions**
* Complete Response (CR):	Disappearance of all target lesions. Pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition the smallest sum LD must also demonstrate an absolute increase of at least 5mm.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level
*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):	Unequivocal progression of existing non-target lesions (1). The appearance of one or more new lesions is also considered progression.

(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).

Lesions that become ‘too small to measure’

- All lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation – even if very small (e.g. 2mm).
- If lesion is reported as ‘too small to measure’ and the radiologist feels the lesion has disappeared then the measurement should be recorded as 0mm on the CRF.
- If the lesion is reported as ‘too small to measure’ and is believed to be present but only faintly seen then a default value of 5mm should be assigned.

- *However,* if the radiologist is able to provide an exact measurement, even if below 5mm, then this value should be recorded.

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). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The table below provides a summary of the overall response calculation at each time point.

Target lesions	**Non-Target lesions**	**New Lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
CR	Not-evaluated*	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	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

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

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than four weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than six-eight weeks) that is defined in the study protocol

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 start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) Unevaluable for response: specify reasons (early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify))
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-5 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-5 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g. early death due to other

reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.

APPENDIX 2: MEASUREMENT OF GFR

Estimated GFR is required. The recommended technique is eGFR using the CKD-EPI formula according to the table below:

Race and Sex	Serum Creatinine Level, µmol/L (mg/dl)	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.7)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$

- An acceptable alternative is direct measurement using local standard methodologies. Where the CKD-EPI formula produces a result that is lower than 60ml/min, a result of ≥60ml/min from this method should be regarded as the more accurate estimate.

Reference

Levey AS, Stevens LA, Schmid CH et al. for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) A New Equation to Estimate Glomerular Filtration Rate *Ann Intern Med.* 2009;150:604-612.

APPENDIX 3: CABAZITAXEL PRODUCT INFORMATION AND HANDLING

Cabazitaxel:

Cabazitaxel is supplied for parenteral administration as a sterile, non-pyrogenic non-aqueous solution contained in a 15 mL clear glass vial closed with a rubber closure. The closure is crimped to the vial with an aluminium cap covered with a light green plastic flip-off cap.

The solution is clear and yellowish to brownish-yellow.

Each vial contains 60 mg of cabazitaxel, expressed on anhydrous and solvent-free basis, per 1.5 mL of solution.

The fill volume has been established to include an overfill [i.e., 1.5 mL (nominal volume) + 0.33 mL]. This overfill was determined to ensure that a 10 mg/mL (corresponding to 60 mg/mL) concentration is obtained in the premix and that 60 mg dose can be extracted.

This must be done with the entire contents [i.e., 4.5 mL (nominal volume) + 1.17 mL) of the solvent for dilution for cabazitaxel.

Solvent vial:

The solvent used for the preparation of the premix is a sterile, non-pyrogenic solution containing a 13% w/w ratio of ethanol 95% in water for injection. This solution is contained in a 15 mL clear type I glass vial closed with a rubber closure. The closure is crimped to the vial with either an aluminium cap covered with a light grey plastic flip-off cap or a gold-colour aluminium cap covered with a colourless plastic flip off cap.

The solution is a clear colorless liquid.

Each vial is overfilled to ensure that a 10 mg/mL concentration is obtained in the Premix and that 60 mg dose can be extracted [i.e., 4.5 mL (nominal volume) + 1.17 mL].

Excipients:

Polysorbate 80 from vegetable origin, for the drug product vial.

Water for injection and ethanol for the solvent vial.

Storage conditions:

Vials should be stored according to their labelling and kept in their kit until use.

Preparation

Cabazitaxel drug products should be administered only by intravenous route.

It is supplied as a kit containing one single-use vial of cabazitaxel concentrate for solution for infusion and one single vial of solvent for dilution. The administration of the product requires two dilutions prior to administration.

This pharmaceutical dosage form is a concentrate for solution for infusion and must be diluted before administration. First the dosage form is diluted with the solvent supplied (preparation of the "cabazitaxel premix solution"). Then this premix solution must be diluted in an infusion vehicle (preparation of the "cabazitaxel infusion solution"). Each cabazitaxel vial and each corresponding solvent vial are overfilled to ensure that a 60 mg dose can be withdrawn after the preparation of the premix.

- **Preparation of cabazitaxel premix solution under aseptic conditions:**

Use one solvent vial per each vial of cabazitaxel concentrate.

Withdraw, under aseptic conditions, the **entire** contents of the solvent vial and inject it into the corresponding vial of cabazitaxel concentrate. **Gently** mix the reconstituted solution by repeated inversions for at least 45 seconds until obtaining clear and homogenous solution. **Do not shake**. Let the premix solution stand for a few minutes at room temperature to allow foam to dissipate. The solution is homogeneous and contains no visible particulate matter. It is normal for foam to persist after this time period.

In order to compensate for liquid loss during preparation and to ensure that the JEVTANA initial diluted solution (premix) can be prepared at the concentration of 10 mg/mL and that a nominal volume of at least 6 mL can be withdrawn from the premix vial, the JEVTANA 60 mg/1.5 mL concentrate vials are filled with a 22% overfill (total fill volume 1.83 mL) and the diluent vials with a 26% overfill (total fill volume 5.67 mL).

The concentration of 10 mg/mL in the premix [60mg/1.5 mL (concentrate) + 4.5 mL (diluent)] can be calculated as follows taking into account the overfilling: 73.2mg/ 1.83 ml (22% overfill concentrate) + 5.49 mL (overfill diluent *) = 10 mg/mL

Thus, the preparation obtained ensures a minimal extractable volume of the premix solution of 6 mL corresponding to a concentration of 10 mg/mL of cabazitaxel corresponding to 60mg/6 ml.

Preparation of cabazitaxel infusion solution under aseptic conditions:

WARNING: Since foam is normally present, the required dose must be accurately adjusted using a graduated syringe.

Withdraw, under aseptic conditions, the volume of the premix solution containing 10 mg/mL of cabazitaxel that corresponds to the required dose (mg) and inject the required premix volume

into a 125 to 500 mL infusion container (either 5% glucose solution for injection or 0.9% sodium chloride solution for injection). Mix the content of the infusion container manually by gently inverting the bag or bottle. The concentration of the infusion should be between 0.10 mg/mL and 0.26 mg/mL (based on Maximum Tolerated Dose of 30 mg/m² and a Body Surface Area of 2.1 m²).

- **Infusion conditions:**

The recommended infusion duration is one hour. The infusion solution should be used within 8 hours at ambient temperature (including the one hour infusion time) or within a total of 48 hours if refrigerated (including the one hour infusion time).

The infusion solution should be administered at room temperature under normal lighting conditions.

- **Do not use PVC infusion containers for cabazitaxel preparation and administration.**
- **Do not use polyurethane infusion sets for cabazitaxel preparation and administration**

Glass bottles could also be used.

Use an in-line filter of 0.22 µm nominal pore size (also referred to as 0.2 µm) during cabazitaxel administration.

- **Shelf life:**

Cabazitaxel premix solution

Premix solution should be used immediately after preparation and within 1 hour at ambient temperature.

Cabazitaxel infusion solution

The infusion solution is stable for 8 hours at ambient conditions (including the 1 hour infusion time) or a total of 48 hours if refrigerated, from preparation to end of infusion.

- **Recommendation for the safe handling:**

Cabazitaxel is an antineoplasic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing cabazitaxel solutions. The use of gloves is recommended.

If cabazitaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If cabazitaxel concentrate, premix solution, or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

FACT B

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐