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A Phase II Trial of Combination Cabazitaxel and Cisplatin Chemotherapy in the Neoadjuvant Treatment of Transitional Cell Carcinoma of the Urinary Bladder

Bristol Bladder Trial

Protocol version 8.0

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This protocol describes the Bristol Bladder 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:

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Prof Amit Bahl (Chief Investigator)

Date.....

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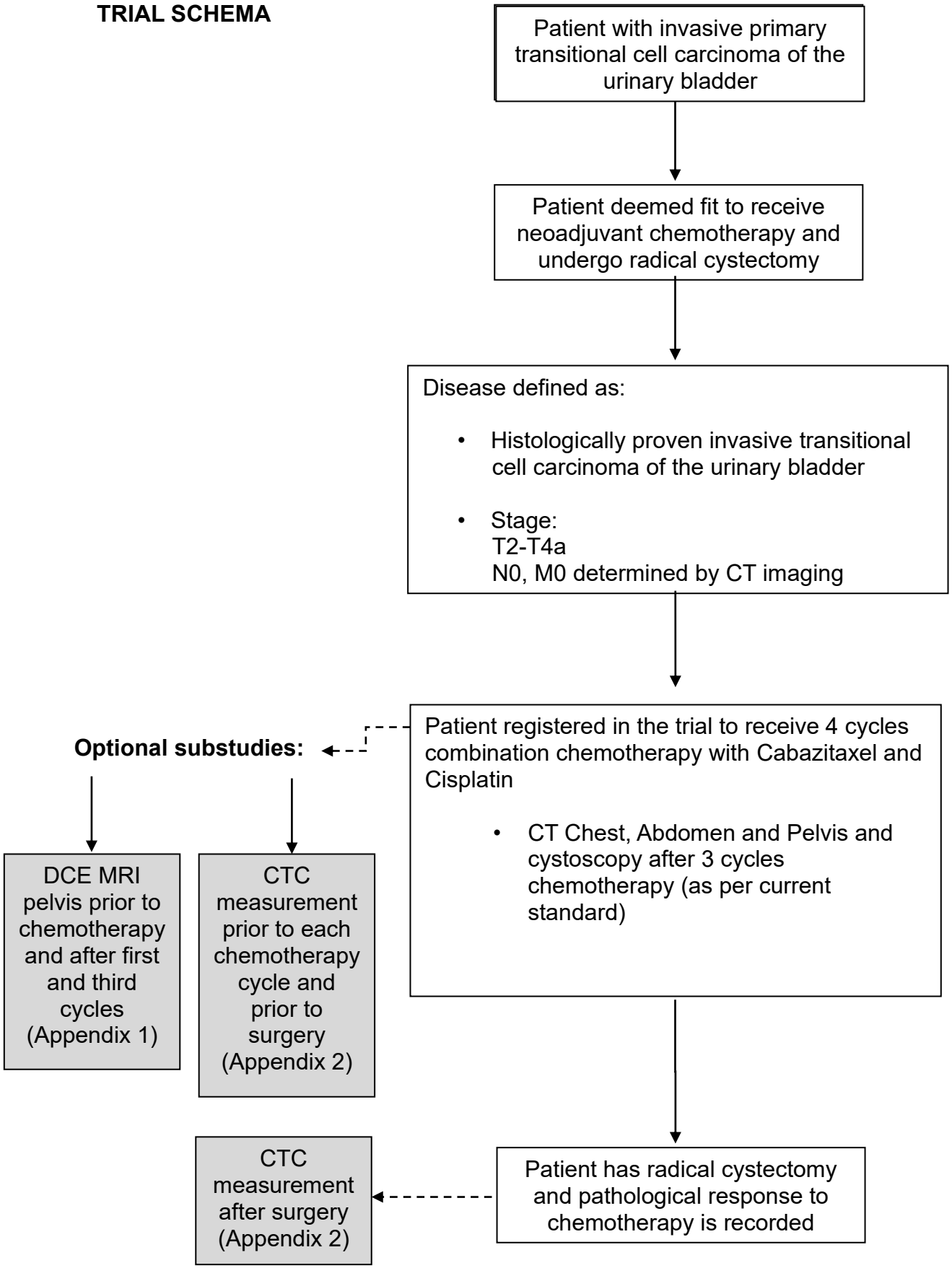
TRIAL SCHEMA



TRIAL SUMMARY

Title	A phase II trial of combination cabazitaxel and cisplatin in the neoadjuvant treatment of transitional cell carcinoma of the urinary bladder
Objectives	**Primary**: To evaluate the overall response rate with this chemotherapy regimen in the neoadjuvant treatment of transitional cell carcinoma of the bladder and thus determine whether this approach warrants further research (randomised Phase II/ III trial). **Secondary:** • To evaluate safety and tolerability; • To assess progression-free and overall survival; • To assess quality of life during treatment.
Trial Design	Non-randomised single centre trial
Type and number of patients	Patients with invasive transitional cell carcinoma of the bladder will be eligible if they are fit to receive chemotherapy as neoadjuvant treatment and to undergo a radical cystectomy. Approximately 26 patients will be recruited.
Treatment	Four cycles of chemotherapy using a combination regimen comprising: Cabazitaxel 15 mg/m^2 day 1 + cisplatin 70mg/ m^2 day 1. The combination treatment is prescribed every 21 days.
Endpoints	**Primary:** The primary endpoint is overall response rate (complete remission rate + partial remission rate) determined by histopathological staging at cystectomy. **Secondary:** • Progression-free survival; • Overall Survival; • Acute toxicity (CTCAE v4.03) after each cycle ; • Quality of life (assessed by EQ5D and EORTC QLQ-C30 and module BLM-30)
Associated Studies	Patients with no contraindications to MRI or gadolinium contrast may enter an optional substudy evaluating dynamic contrast enhanced MRI prior to therapy, and after one and three cycles of chemotherapy. Patients will be offered entry into an optional pilot substudy involving measurement of circulating tumour cell (CTC) concentration prior to each cycle of chemotherapy and prior to surgery.

1 BACKGROUND

Carcinoma of the urinary bladder is the seventh most common cancer in the United Kingdom, (1) (2) (3) (4) with around 10,000 diagnoses annually. The majority of these are transitional cell carcinoma (TCC). 30% of cases present with disease invading into the muscle wall of the bladder (tumour stage T2 or greater) and a further 50% of patients presenting with high risk non muscle invasive (superficial) bladder cancers will later develop muscle invasive disease.

5 year survival after cystectomy for patients with muscle invasive bladder cancer varies from 36% to 48%, and specifically 17% to 46% for pT3b tumours. (5) Many patients die from metastatic disease. Tumour (T) stage at diagnosis is a key prognostic factor, and so accurate staging at diagnosis is an important requirement. Other influential factors are tumour grade, presence or absence of multiple tumour foci, and tumour type.

In the absence of lymph node or distant metastases, patients with T2 to T4a disease who have adequate performance status and organ function are typically treated with first line combination chemotherapy, using a cisplatin-based regimen, followed by radical cystectomy as the current standard of care. The use of neoadjuvant chemotherapy is supported by data from two large meta-analyses, (6) (7) (8) incorporating a total of 11 individual randomised trials of over 3000 patients, demonstrating a significant overall survival advantage with this approach when compared with local treatment (cystectomy or radiotherapy) alone.

The ABC meta-analysis (6) (7) represented 98% of all published relevant randomised controlled trials. Although there were several inter-trial differences, results indicated an absolute improvement of 5% in overall survival, 14% decrease in disease specific mortality and 9% improvement in disease specific survival with chemotherapy in patients of good performance status.

Furthermore the largest BA06 trial of 970 patients, comparing no neoadjuvant therapy to 3 cycles of CMV (cisplatin, methotrexate and vinblastine) has demonstrated an improvement in 10 year overall survival from 30% to 36% with chemotherapy. The choice of neoadjuvant chemotherapy agents is guided by the larger individual trials.

The phase III SWOG 8710 (Intergroup 0080) trial, (9) comparing neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy and cystectomy with cystectomy alone, played a pivotal role. 5 year overall survival favoured chemotherapy (57% vs. 42%), and was 85% in patients who had a pathological complete response. Although the strength of the study design is debated (10) (11), particularly the statistical methods and the duration of the trial, neoadjuvant chemotherapy with MVAC has been increasingly prescribed since its publication, particularly in the USA.

However, MVAC itself is somewhat toxic. The incidence of grade 4 granulocytopenia in the above trial was 33% and GI complications 29%.

A historical control series evaluated the efficacy of neoadjuvant gemcitabine plus cisplatin (GC) compared with MVAC in muscle invasive urothelial cancer of the bladder. (12) Earlier work had shown GC to be less toxic with similar response and survival rates compared with MVAC in advanced disease. (13) (14) Notably, however, no phase III ‘head to head’ trial has compared MVAC with GC in the neoadjuvant setting, and this trial will probably never now occur.

The common factor to positive trial results in this setting is the use of platinum, specifically cisplatin, in combination with other agents. (6) (7) (8)

Interest in taxanes in the management of invasive bladder cancer has emerged from trials in the advanced setting, following failure of platinum-based chemotherapy. (15) (16) (17) (18) Encouraging response rates are seen with paclitaxel and docetaxel in metastatic disease, and taxanes have also been evaluated in neoadjuvant studies in combination with cisplatin prior to chemoradiotherapy or surgery with success. (19) (20) (21) However, as with MVAC, toxicity remains a concern, highlighting the importance of patient selection.

Cabazitaxel (Jevtana®, Sanofi-Aventis) is a novel taxoid that was selected for clinical development based on its pharmacological profile. (22) It is effective in cell lines sensitive and resistant to docetaxel, vinca alkaloids and anthracylines, and shows activity against intracranial tumours. Early pharmacokinetic work shows that cabazitaxel exhibits dose-proportional PK, a triphasic elimination profile, a long terminal half life (77.3 hrs), a high plasma clearance (mean CL 53.5 L/h), a long T ½, and a very large volume of distribution at steady state (mean Vss 2,034L/m^2). (23)

Although major trials with cabazitaxel have primarily employed single agent treatment, benefit has been seen in combination with other cytotoxic agents in the treatment of metastatic breast cancer, and it is well tolerated (24). Recent work in animal models (25) reports synergism when cabazitaxel is combined with cisplatin. Data from phase I studies using cabazitaxel combined with cisplatin are emerging. (26)

The putative mechanism for the survival advantage seen with neoadjuvant chemotherapy is the early treatment of micrometastatic disease. However, additional benefits of this approach include the potential for local downstaging with surgical bladder preservation (partial cystectomy with or without combined radiotherapy), (27) and the ability to assess pathological response to chemotherapy. The former may afford patients a better quality of life, as a result of reduced need for extensive surgery and urinary diversion with a lower risk of sexual dysfunction. The routine practice of bladder preservation is yet to become commonplace, however; radical cystectomy remains the gold standard.

Typically, response to neoadjuvant chemotherapy is assessed preoperatively, after 3 or 4 cycles of combination chemotherapy, by clinical assessment, CT imaging and cystoscopic examination with or without biopsy, to record response to chemotherapy and exclude progression to lymph node or distant metastatic disease. This, however, is not a substitute for the assessment of pathological response obtained at cystectomy, which itself holds important prognostic value. (28; 29)

Magnetic resonance imaging (MRI) has been used to evaluate T stage at diagnosis in this condition and interest in its use was first described more than 20 years ago (30). Whereas initial studies showed the value of MRI to be limited, the evolution of this modality and specifically developments in functional MR imaging, such as dynamic contrast enhanced and diffusion weighted techniques (31), have led to renewed enthusiasm for its application in bladder cancer diagnosis and assessment of response to treatment.

Several studies (32) (33) (34) have demonstrated improved accuracy, specificity and sensitivity for staging bladder cancers when dynamic contrast enhanced techniques are performed in addition to unenhanced scans at diagnosis and after irradiation of the bladder, as these techniques allow assessment of tumour vascularisation, as well as tumour size and estimated depth of invasion. (35) Results from diagnostic dynamic MRI

scans have been shown to correlate with pathological grade and microvessel density on transurethral resection (diagnostic) specimens. (32) Furthermore, a Dutch study of 36 patients with metastatic or locally advanced disease receiving palliative chemotherapy (36) demonstrated that dynamic contrast-enhanced MRI may be used to predict failure of chemotherapy early in its course, sparing some patients toxicity from ineffective treatment.

The use of a single noninvasive imaging technique for this assessment of response has clear advantages in terms of patient experience and cost to institutions. In addition, assessment or prediction of response to chemotherapy earlier in its course would potentially allow for more individualised therapy; for example early cystectomy or radical radiotherapy in patients not responding to neoadjuvant chemotherapy. There are also implications for the use of concurrent chemoradiotherapy, an emerging modality in this area, (37) and even image-adapted radiotherapy (38) for non-surgical patients.

This Phase II study will serve to establish the response rate to combination cabazitaxel and cisplatin chemotherapy in patients with muscle invasive transitional cell carcinoma of the urinary bladder, and will evaluate survival and quality of life from this novel approach.

Via a concurrent optional substudy, response to chemotherapy will be assessed using standard techniques, with the addition of dynamic contrast enhanced MRI (DCE MRI) at diagnosis and after one and three cycles of chemotherapy, to evaluate DCE MRI in the early prediction of failure of neoadjuvant chemotherapy. This study is outlined in a separate protocol.

An additional substudy in selected patients will measure circulating tumour cell (CTC) concentrations prior to each cycle of chemotherapy and prior to and after surgery, to determine whether there is any relationship between CTC concentration and response to radical treatment. This is also outlined in a separate protocol.

2 AIMS OF THE STUDY

2.1 Primary

To evaluate overall pathological response rate with a combination regimen using cabazitaxel and cisplatin in the neoadjuvant treatment of transitional cell carcinoma of the urinary bladder, thus determining whether this approach warrants further research within the context of a phase III clinical trial.

2.2 Secondary

- To evaluate safety and tolerability
- To assess progression-free and overall survival
- To assess quality of life during treatment

3 TRIAL DESIGN

This study is not randomised. This is a limited phase II study to determine the pathological response rate and tolerability of this regimen.

Patients will receive cabazitaxel 15mg/m^2 with cisplatin 70mg/m^2 day 1. Cycles last 21 days and a total of 4 cycles will be given to each patient, with standard workup for radical cystectomy including formal re-staging with CT imaging and cystoscopy after 3 cycles of chemotherapy.

Patients who have no contraindications to contrast enhanced MRI will be offered entry into the associated dynamic contrast enhanced MRI study and will undergo DCE MRI scanning prior to cycle 1 and after cycles 1 and 3.

All patients will be asked to provide blood samples for circulating tumour cell (CTC) measurement prior to each cycle of chemotherapy and prior to surgery. Participation in this CTC substudy is not mandatory.

4 PATIENT SELECTION AND ELIGIBILITY

4.1 Source of patients

Patients undergoing radical treatment for bladder cancer must be managed under the auspices of a multidisciplinary team (MDT) whose core members must include a consultant oncologist, consultant urological surgeon, consultant radiologist and consultant histopathologist.

Patients will be eligible if they have histopathologically confirmed muscle invasive primary transitional cell carcinoma of the urinary bladder, are fit to receive neoadjuvant combination cabazitaxel and cisplatin chemotherapy, and are fit to undergo radical cystectomy.

4.2 Number of patients

Based on previous studies in this disease, an overall response rate of less than 35% (partial or complete remission at cystectomy) would not be sufficient to warrant further investigation of this approach. An overall response rate of 60% or higher would warrant further investigation.

Using a one-sided confidence interval of 95% and 80% power, a total of 26 patients are required. It is anticipated that up to 30 patients will be required to allow for lost data and patient withdrawals.

4.3 Inclusion Criteria

- Age ≥18 years
- Histologically confirmed primary TCC of the urinary bladder
- T2 to T4 disease, N0 M0 determined by CT imaging and biopsy or transurethral resection
- ECOG Performance status 0 or 1
- **GFR≥60 mls/min. GFR to be assessed according to local practice. Recommended technique of eGFR using the CKD-EPI formula (Appendix 2).**
-
- **If the baseline eGFR is 50 - <60 mls/min patient should undergo formal testing with measurement of ^{51} Cr-EDTA clearance.**
-
- **If the EDTA result is ≥ 60 mls/min the patient is eligible**
- **If the EDTA result is ≥ 55 mls/min - < 60 mls/min discuss with CI**
- **If the EDTA result is < 55mls/min patient is excluded from the study.**

- Written, informed consent

4.4 Exclusion Criteria

- ECOG Performance Status ≥ 2
- Lymph node involvement or metastatic disease
- Prior surgery (except transurethral resection of bladder tumour), radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrolment
- Active Grade ≥2 peripheral neuropathy
- Active secondary cancers
- History of severe hypersensitivity reaction (≥Grade 3) to polysorbate 80 containing drugs
- Other concurrent serious illness or medical conditions
- Inadequate organ function as evidenced by the following peripheral blood counts and serum biochemistry at enrolment:
    - Neutrophils ≤1.5 x 10^9/L
    - Haemoglobin ≤10 g/dL
    - Platelets ≤100 x 10^9/L
    - Total bilirubin > 1.5 X upper limit of normal (ULN)
    - Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)≥1.5 x ULN
    - Alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT)≥1.5 x ULN
- Electrocardiogram (ECG) evidence of uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension, history of congestive heart failure, or myocardial infarction within last 6 months.
- Uncontrolled diabetes mellitus.
- Active uncontrolled gastro-oesophageal reflux disease (GORD).
- Active infection requiring systemic antibiotic or anti-fungal medication
- Participation in another clinical trial with any investigational drug within 30 days

prior to study enrolment.

- Concurrent or planned treatment with strong inhibitors of cytochrome P450 3A4/5. A 1-week washout period is necessary for patients who are already on these treatments.
- Concurrent or planned treatment with strong inducers of cytochrome P450 3A4/5. A 1-week washout period is necessary for patients who are already on these treatments.
- Contraindications to cisplatin.
- Patient with reproductive potential not implementing an accepted and effective method of contraception.
- Concurrent yellow fever vaccine

5 ENDPOINTS

5.1 Primary

The primary endpoint is the overall response rate (complete remission rate + partial remission rate).

5.2 Secondary

- Progression free survival
- Overall survival
- Acute toxicity (defined by CTCAE v4.03) after each cycle
- Quality of life during treatment using questionnaire EORTC QLQ C-30 and supporting module BLM-30
- Quality adjusted life years assessed by EQ-5D

5.3 Definition and recording of response and disease progression

Pathologic response is determined by Tumour (T) stage on histopathological examination of the radical cystectomy specimen and comparison with diagnostic pathological findings. T stage is defined using the American Joint Committee of Cancer (AJCC) 2010 staging manual (39):

- pTX Primary tumour cannot be assessed
- pT0 No evidence of primary tumour
- pTa Noninvasive papillary carcinoma
- pTis Carcinoma *in situ*
- pT1 Tumour invades subepithelial connective tissue
- pT2a Tumour invades superficial muscularis propria (inner half)
- pT2b Tumour invades deep muscularis propria (outer half)
- pT3a Tumour invades perivesical tissue microscopically
- pT3b Tumour invades perivesical tissue macroscopically (extravesical mass)
- pT4a Tumour invades periprostatic stroma, uterus or vagina
- pT4b Tumour invades pelvic wall or abdominal wall

Response assessment for the purpose of reporting the primary endpoint is determined by pathologic staging at cystectomy (partial response, complete response, no response or progression of disease) performed by the reporting pathologist at the treating centre. All pathology specimens must be reviewed by a multidisciplinary team (MDT) specialising in the treatment of urological malignancies.

Radiological progression on cross sectional imaging (CT) is defined as a significant increase in the size of pre-existing disease according to RECIST criteria version 1.1 (an increase of at least 20% in the longest diameter, see Appendix 1) or the development of new metastases. RECIST criteria are provided in this protocol for the purposes of reporting disease *progression*, where it occurs. RECIST criteria are <u>not</u> used as the primary method of assessing response to chemotherapy for the purposes of reporting the primary endpoint (where pathologic response is used).

Recurrence is defined as the development of new metastases in a patient who was previously in complete clinical remission. Recurrence may be:

Local: at the primary site
Regional: from the primary site to the local lymph node basin
Distant: beyond the locoregional lymph nodes

Details of all recurrences must be included on the case report forms (CRFs).

6 REGISTRATION

Central registration will be performed by 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 and to undergo radical cystectomy. An eligibility checklist must be completed by the clinician/research nurse prior to registration. The following information will be required:

- Name of cancer centre, treating hospital(s), 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 been assessed by cystoscopic biopsy or transurethral resection within 2 months and CT imaging within 6 weeks of scheduled start date of chemotherapy;
- Confirmation that patient has given written informed consent for registration;
- Patient's full name, date of birth, hospital number and NHS number. These will be collected to allow tracing through GP records to assist with the collection of long term follow-up information. Data will be stored in a log by the Principal Investigator and stored in accordance with the arrangements set out in this protocol.

The patient will be assigned a unique trial identification number (Trial ID). This trial ID is recorded on all documentation and will be used for identification purposes in the Bristol Bladder Trial and both its associated substudies.

Patients should commence chemotherapy within 2 weeks of registration.

7 TRIAL EVALUATIONS

7.1 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 WHO performance status; vital signs (blood pressure, heart rate, respiratory rate)
- Recording of concomitant medication use, with relevant dates;
- ECG;
- CT scan of chest, abdomen and pelvis to be performed within 6 weeks of scheduled start date of chemotherapy;
- DCE MRI of pelvis to be performed within 4 weeks of scheduled start date of chemotherapy if participating in the DCE MRI substudy;
- Peripheral blood test for CTC measurement, if participating in the CTC substudy
- Full blood count, U+E, liver function tests (to include ALP, ALT and/or AST, Bil and GGT);
- 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 EORTC QLQ C-30 (with supporting module BLM-30) and EQ-5D.

7.2 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;
- BSA (should be calculated as per local practice);
- Full blood count, U+E, liver function tests (to include ALP, ALT and/or AST, Bil and GGT);
- Full blood count only (without biochemistry) to be checked Day 8 and 15 of cycle 1
- 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 EORTC QLQ C-30 (with supporting module BLM-30) and EQ-5D.
- CT scan of chest, abdomen and pelvis to be carried out after the third cycle of chemotherapy;
- Cystoscopic examination of the bladder to be carried out after the third cycle of chemotherapy;
- DCE MRI of pelvis to be performed after the first cycle of chemotherapy, and after the third cycle, if participating in the DCE MRI substudy
- Blood test for circulating tumour cell (CTC) measurement prior to each cycle of chemotherapy if participating in the CTC substudy

7.3 End of chemotherapy treatment

Patients should be seen 3-5 weeks after commencement of their final cycle of chemotherapy. Assessments should include:

- Physical examination to assess fitness and WHO performance status;
- Full blood count, U+E, liver function tests (to include ALP, ALT and/or AST, Bil and GGT);
- 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).
- Quality of life questionnaires EORTC QLQ C-30 (with supporting module BLM-30) and EQ-5D.
- Blood test for circulating tumour cell (CTC) measurements if participating in the CTC substudy

7.4 Radical Cystectomy

Patients should undergo planned radical cystectomy within 6 weeks of commencement of the final cycle of chemotherapy. Confirmation of the plan to proceed to surgery should be discussed by the MDT once the relevant imaging and clinical information is available.

Following surgery, histopathological tumour stage, as defined above, should be recorded by the MDT and in the patient's trial documentation.

7.5 Long term follow-up

Long-term follow-up is undertaken at the patient's original treatment/referral centre and is in accordance with local guidelines. Survival data and dates of progression events may be recorded remotely via contact with the patient and/or the patient's GP. Survival data are collected by the trial coordinator and recorded in the individual patient's CRF.

7.6 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.

7.7 Schema of Trial Evaluations (optional substudy evaluations are shaded)

Trial Evaluation	Diagnosis	Baseline[2]	Cycle 1 Day 8	Cycle 1 Day 15	Pre Cycle 2	Pre Cycle 3	Pre Cycle 4	End of Chemo-therapy[7]	Months following radical cystectomy Via telephone								
									3	6	9	12	18	24	36	48	60
					Within 3 days of treatment	Within 3 days of treatment	Within 3 days of treatment										
Cystoscopy with diagnostic histology[1]	X						X										
CT chest, abdomen & pelvis (Within 6 weeks of treatment)		X					X										
Inclusion/Exclusion Criteria		X															
Vital signs, physical examination		X			X[8]	X[8]	X[8]	X									
Recording concomitant medication		X			X	X	X	X									
Body surface area		X			X[8]	X[8]	X[8]										
Haematology		X[5]	X	X	X[8]	X[8]	X[8]	X									
Biochemistry		X[5]			X[8]	X[8]	X[8]	x									
GFR[6]		X			X	X	X	X									
ECG		X															
Adverse events and safety (CTCAE v4.03)		X			X	X	X	X									
Quality of Life assessment		X			X	X	X	X									
MRI pelvis		X[3]			X[4]		X[4]										
CTC measurement		X			X	X	X	X									
Recording survival and progression									X	X	X	X	X	X	X	X	X

1. Cystoscopy + biopsy within 2 months prior to commenciing first cycle of chemotherapy
2. Within 4 weeks prior to commencing first cycle of chemotherapy (unless otherwise specified)
3. MRI (optional substudy) baseline scan within 2 weeks of commencing first cycle of chemotherapy
4. MRI (optional substudy) within one week prior to cycles 2+4
5. Bloods to be repeated if baseline sample is not within 7 days of first cycle of treatment
6. GFR to be assessed according to local practice (recommended use of eGFR using the CKD-EPI formula (Appendix 2)
7. 3-5 weeks after commencement of the last cycle of chemotherapy
8. Within 3 days prior to treatment

8 TRIAL TREATMENT

The regimen will consist of cabazitaxel 15mg/m^2 followed by cisplatin 70mg/m^2 day 1 with cycle duration of 21 days, 4 cycles to be given in total with formal restaging after 3 cycles.

Day	Drug	Dose	Regimen
1	**Cabazitaxel**	**15mg/m^2**	Intravenous infusion over 1 hour. Premedication is required to prevent allergic reaction (see section 8.2)
1	**Cisplatin**	**70mg/m^2**	Intravenous infusion over 1-2 hours preceded by 1 litre sodium chloride 0.9% (with or without potassium and magnesium supplementation, in accordance with local policy and practice) over 2 hours and followed by sodium chloride 0.9% 1 litre (with or without potassium and magnesium supplementation, in accordance with local policy and practice) over 2 hours.

Premedication and anti-emetic regimens may be given in accordance with local policy and practice. Suggested recommended premedication and antiemetics are outlined in sections 8.2 and 8.3.

For further information and information on disallowed concomitant medication please refer to the SmPC. Unless otherwise specified, all diluents/volumes used to give this chemotherapy regimen should be according to local practice and the SmPC.

Primary prophylaxis with Granulocyte Colony Stimulating Factor (G-CSF) is mandatory for all patients. See section 8.4 below. If contraindication(s) to G-CSF administration exist, study treatment may only proceed with the approval of the Chief Investigator.

8.1 Drug supplies and labelling

Cisplatin and Cabazitaxel

- For supplies of cisplatin normal hospital stock should be used.
- Supplies of cabazitaxel will be provided by sanofi-aventis.
- For cisplatin and cabazitaxel, drug accountability, storage requirements, destruction and labelling guidelines are contained within the Clinical Trial Agreement and Trial Guidance Notes.
- All drugs should be labelled ‘for clinical trial use only’.
- For all information on drug stability please refer to each SmPC.

8.2 Pre-Medication

Cabazitaxel

The following recommended premedication regimen should be performed at least 30 minutes prior to each administration of cabazitaxel to mitigate the risk and severity of hypersensitivity.

- Chlorphenamine 10mg IV
- Dexamethasone 8mg IV *(included in antiemetic prophylaxis, see section 8.3. A duplicate dose is not required.)*
- Ranitidine 50mg IV

Antiemetic prophylaxis is recommended and is detailed in section 8.3.

Cisplatin

Apart from hydration (section 8.1) and antiemetic prophylaxis (section 8.3) no additional premedication is required prior to administration of Cisplatin.

8.3 Anti-Emetics

Suggested additional 'as required' antiemetics are detailed in the table below for each cycle of chemotherapy but may vary according to local practice. Where doubt exists the approval of the Chief Investigator should be sought.

Day	Timing	Regimen
1	60 minutes before chemotherapy.	Ondansetron 8mg IV/PO Aprepitant 125mg PO *Dexamethasone 8mg IV- duplicate dose not required, see above*
1	12 hours after chemotherapy	Ondansetron 8mg PO
2 and 3	-	Aprepitant 80mg PO Dexamethasone 4mg BD PO Domperidone 10-20mg prn QDS PO
4	-	Dexamethasone 4mg BD PO Domperidone 10-20mg prn QDS PO
5-21	-	Domperidone 10-20mg prn QDS PO

8.4 Guidelines for the Management of Toxicity

Reasonable efforts should be taken to minimise dose reduction and treatment delays in order to maintain dose-intensity and cumulative dose-delivery. Patients whose treatment is delayed because of toxicity should be evaluated on a weekly basis until adequate recovery has been made. If there is more than 2 weeks' delay then patient should be withdrawn from the study.

Primary prophylaxis using G-CSF must be used unless contraindications exist. The recommended regimen is Pegylated G-CSF 6mg subcutaneously 24 hours after administration of chemotherapy. Patients with contraindications to G-CSF administration may only proceed with trial treatment with the approval of the Chief Investigator.

Safety assessments are recorded according to NCI Common Terminology Criteria for Adverse Events v4.03 (NCI CTC AE v4.03,). For further information on expected toxicities refer to SmPCs for individual drugs.

Cisplatin

- Full Blood Count and urea, creatinine, sodium, potassium and magnesium must be measured ideally during the 48 hours prior to each cycle (where this is not possible this may be extended to 72 hours, but if the results do not meet treatment criteria at this point they MUST be repeated within 24 hours prior to each cycle).

- Adequate electrolyte replacement should be incorporated into the pre- and post-hydration schedule. A sample hydration protocol is detailed in the regimen above but this may be modified according to local practice and with the agreement of the Chief Investigator.

- GFR (recommended technique of eGFR using the CKD-EPI formula (see Appendix 2)) should be used to assess continuing adequate renal function prior to each cycle. Treatment should only proceed in accordance with GFR guidance given in section 8.5 (below).

Cabazitaxel

- **Hypersensitivity reactions:** All patients should be pre-medicated prior to the initiation of the infusion of cabazitaxel (see section 8.2).
    - Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of cabazitaxel. Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of wellbeing and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.
    - Facilities and equipment for resuscitation along with the medications (i.e. antihistamine, corticosteroids, aminophylline and epinephrine) must immediately be available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g. epinephrine in case of anaphylactic

shock, aminophylline in case of bronchospasm etc.) will be instituted. In addition, it is recommended to take the following measures:

Mild: localised cutaneous reaction such as pruritus, flushing, rash	• Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside • Complete cabazitaxel at the initial planned rate
Moderate: generalised pruritus, more severe flushing or rash, mild dyspnoea, hypotension with systolic B.P. >80mmHg	• Stop cabazitaxel infusion • Give IV chlorphenamine 10mg and/or hydrocortisone 200mg • Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate • Re-administer premedication regimen as described in section 8.2 when cabazitaxel is infused more than 3 hours after the interruption • Administer cabazitaxel over 2 hours for all subsequent infusions
Severe: bronchospasm, generalised urticaria, hypotension with systolic B.P. ≤80mmHg, angioedema	• Stop cabazitaxel infusion • Give IV chlorphenamine 10mg and/or hydrocortisone 200mg • Add epinephrine 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 • Re-administer premedication as described in section 8.2 when cabazitaxel is infused more than 3 hours after the interruption • Administer cabazitaxel over 2 hours for all subsequent infusions

- Patients experiencing a hypersensitivity reaction ≥ Grade 3 (CTCAE v.4.03) must stop treatment with cabazitaxel and will be withdrawn from the study.

8.5 Dose Modifications and Delays

This section outlines recommended dose modifications for common potential toxicities. It is not exhaustive. Where doubt exists regarding dose modifications and delays, individual patients should be discussed with the Chief Investigator.
In general, any patient requiring greater than 2 weeks' delay for recovery of toxicity should be withdrawn from the study. Any further chemotherapy is then given at the discretion of the treating clinician and is beyond the scope of this protocol.

Haematologic Toxicity

- No new cycle of chemotherapy should commence unless WBC≥ 3.0 x 10^9/L, ANC≥ 1.5 x 10^9/L and Platelet count ≥ 75 x 10^9/L. The use of G-CSF is mandatory as primary prophylaxis (see section 8.4).

- A 20% dose reduction in both drugs is recommended for subsequent cycles if one or more of the following occurs:

    - Grade IV neutropenia (ANC <0.5 x10^9/L) with fever ≥ 38.5ºC;
    - Infection with ANC <1.0 x 10^9/L;
    - Thrombocytopenia with platelets <10 x10^9/L for more than 3 days; or
    - Thrombocytopenia with active bleeding.

- If afebrile grade IV neutropenia (ANC <0.5 x10^9/L) is seen on day 8 or 15, prophylactic oral ciprofloxacin 500 mg b.d. x 7days should be used in subsequent cycles.

- Patients with anaemia should be considered for blood transfusion if clinically indicated. Chemotherapy should be delayed until recovery or correction if haemoglobin is <9.0 g/dl.

Neurotoxicity

- Patients with grade ≥2 peripheral neuropathy should discontinue chemotherapy until recovery of symptoms to ≤grade 1. Subsequent doses of both cisplatin and cabazitaxel should then be reduced by 20%. If further grade ≥2 peripheral neuropathy occurs, the patient should be withdrawn from the study. Any further chemotherapy is then given at the discretion of the treating clinician.

- Chemotherapy should be stopped and the patient withdrawn from the study if grade 3 or 4 neurotoxicity occurs. Any further chemotherapy is then given at the discretion of the treating clinician.

Nephrotoxicity

Grade 3 or 4 hypomagnesaemia should be treated accordingly and reported as an SAE

- In the event of renal toxicity ***during study treatment***, dose reductions for cisplatin and cabazitaxel should be according to the table and notes below. Patients with

eGFR < 50ml/min should undergo formal GFR testing with ^{51}Cr- EDTA before proceeding with the next cycle of chemotherapy. For other patients, GFR may be assessed according to local practice. Recommended technique using the CKD-EPI formula (Appendix 2).

- Patients developing acute renal impairment with eGFR <50ml/min after commencing study chemotherapy should be appropriately treated and monitored carefully. Study chemotherapy may be recommenced once eGFR has recovered to ≥50m/min. Cabazitaxel is minimally excreted through the kidney. Limited data are available for patients with moderate or severe renal impairment.

eGFR	Cisplatin dose	Cabazitaxel dose
≥60 mls/min	100%	100%
50- <60mls/min	75%	100%
<50 mls/min	Check formal GFR, Delay until recovery	Check formal GFR, Delay until recovery

Gastrointestinal Toxicity

- Patients with grade ≥3 diarrhoea, persisting despite appropriate treatment, including loperamide and fluid and electrolyte replacement, should discontinue chemotherapy until symptoms have resolved to ≤grade 1. Subsequent doses of cabazitaxel should then be reduced by 20% and a cisplatin dose reduction should be considered.
- If further grade ≥3 diarrhoea occurs, the patient should be withdrawn from the study. Any further chemotherapy is then given at the discretion of the treating clinician.

Hepatic Impairment

Cabazitaxel is contraindicated in patients with Hepatic impairment (bilirubin >1.5 x ULN, or AST and/or ALT ≥ 1.5 × ULN). If this occurs chemotherapy should be withheld and liver function tests checked weekly until recovery to bilirubun ≤1xULN AND AST and/or ALT <1.5 x ULN. Where this persists, resulting in greater than 2 weeks' delay, study chemotherapy treatment should be discontinued and the patient withdrawn from the study.

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.

Concomitant Medications

During the study, the Investigators may prescribe any concomitant medications as deemed necessary. Supportive treatment as medically indicated for the patient's well-being (including hyperalimentation, blood transfusion, treatment for pain relief) may be prescribed at the investigator's discretion.

During treatment with cabazitaxel, the use of potent inhibitors or potent inducers of cytochrome P450 3A4/5 should be avoided. See appendix 5.

8.7 Contraception

Patients with reproductive potential should be advised to adhere to accepted and effective method(s) of birth control during treatment with chemotherapy and for at least 1 year after last administration.

9 SAFETY & PHARMACOVIGILANCE

9.1 Definitions

9.1.1 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.

9.1.2 Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence or reaction that occurs after the commencement of 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. 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 hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.
- **Grade 3 or 4 hypomagnesaemia should be treated accordingly and reported as an SAE**
-
- Related SAE: there is a reasonable possibility according to the investigator and/or the sponsor that the Product may have caused the event.
- Unexpected: An adverse drug reaction (ADR) whose nature, severity, specificity, or outcome is not consistent with the term or description used in the reference document (e.g., Package Insert) should be considered unexpected. An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

9.1.3 Serious Adverse Reactions (SAR)

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

9.1.4 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.

An unexpected serious adverse reaction is one that is not listed as a known toxicity of the investigational drug in the current Summary of Product Characteristics (SmPC) dated 20/04/2017 section 4.8.

9.1.5 Pregnancy

Pregnancy occurring in a patient or a partner of a patient included in this trial will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils the SAE criteria. In the event of pregnancy, the Clinical Trials Unit should be informed immediately (within 1 working day) via email to bristolbladder@uhbristol.nhs.uk, even if the event does not fulfil a seriousness criterion, using the AE form. Follow-up of the pregnancy is mandatory until the outcome has been determined.

9.1.6 Overdose

Overdose of IMP occurring in a patient defined as 'the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.' will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils the SAE criteria. In the event of overdose, the Clinical Trials Unit should be informed immediately (within 1 working day) via email to bristolbladder@uhbristol.nhs.uk, even if the event does not fulfil a seriousness criterion, using the AE form.

9.2 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 1 (below). 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.

Table 1 – 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

9.3 Procedure for collecting Adverse Events

For the purpose of this trial, any detrimental change in the patient's condition that occurs after registration and within 30 days of the last administration of chemotherapy treatment, which is not due to progression of disease (transitional cell carcinoma of the urinary bladder), should be considered an AE.

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 Version 4.03.For each sign/symptoms, the highest grade observed since the last visit should be reported.

All adverse events (AE) must be reported on the Case Report Forms (CRF).

9.4 Procedure for recording Serious Adverse Events

SAEs in this study that are fatal or life threatening or result in persistent or significant disability/incapacity 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.

9.5 Reporting of Serious Adverse Events to the Sponsor

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

Please fax SAE forms for the attention of the sponsor at Research and Innovation, University Hospitals Bristol NHS Foundation Trust, Level 3 Education Centre, Upper Maudlin Street, Bristol BS2 8AE; **Fax: 0117 342 0239.or via e-mail to** research@UHBristol.nhs.uk

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

9.6 Review of Serious Adverse Events

Events reported using an SAE/SAR 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.

9.7 Expedited Reporting of SUSARs

If an SAE 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 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.

9.8 Follow-up of Serious Adverse Events

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 SAE which may not be available at the time the SAE was initially reported should be completed on the follow-up SAE form and faxed or emailed to the sponsor within 24 hours of site becoming aware of this information.

9.9 Annual Reporting of Serious Adverse Events

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) was obtained. This will include all SARs and SUSARs.

10 FURTHER MANAGEMENT AT THE END OF STUDY TREATMENT

Further medical or surgical treatment following radical cystectomy is at the discretion of the treating clinician in consultation with the patient. Details of such management are beyond the scope of this protocol.

If further treatment for transitional cell carcinoma of the urinary bladder is required during the study period, then details of such treatment should be recorded in the CRF.

11 STATISTICAL CONSIDERATIONS

11.1 Choice of principal endpoints

To determine the activity of cabazitaxel and cisplatin in invasive bladder cancer (transitional cell carcinoma) patients, the principal endpoint for the study will be the overall response rate (complete remission + partial remission) determined by pathologic staging at radical cystectomy (see above).

11.2 Sample size calculations

- It is assumed that a response rate of less than 35% is not sufficiently large enough to warrant further investigation in an expanded phase II or phase III setting, but that a rate of 60% or higher would warrant further investigation.

- Using an exact test for a single proportion, p0=0.35 and p1=0.60, setting alpha=0.05 (onesided) and power = 80%, 26 patients are required.

- In order to recruit 26 patients evaluable for the primary endpoint, recruitment will be extended to replace patients deemed not evaluable. It is anticipated that a total of approximately 30 patients will need to be recruited (see section 18.1).

- Recruitment is until end of December 2017.

11.3 Stopping rules

The study will be stopped at the point at which there is a 99% chance that the response rate is less than 60%. If no patients are seen to respond to treatment, the study will stop at the point at which 9 patients results are known. A formal assessment of the 99% one sided lower confidence limit will be calculated using the exact binomial method when requested by the trial management group in response to lower than expected levels of response and the stopping rule initiated accordingly. Thus in the event that no responses are seen in the first 9 patients, an Independent Data Monitoring Committee (IDMC) would be convened.

11.4 Analysis methods

11.4.1 Primary endpoint

Response will be evaluated according to pathologic T staging at radical cystectomy using the AJCC TNM system (39). The objective response rate for this study is defined as the proportion of patients having achieved partial or complete remission according to their pathologic stage at cystectomy compared with pathologic T stage at diagnosis. For the purposes of the trial, pathology must be viewed by a multidisciplinary team (MDT) specialising in the management of urological malignancies.

Analysis will include tabulation of baseline characteristics of recruited patients. Intention to treat analysis will be used. Baseline characteristics for those patients not completing trial treatment will be tabulated for comparison with treated patients, to ensure generalisability of results. Baseline characteristics will include (but are not limited to) demographic data, tumour stage and grade.

11.4.2 Secondary endpoints

- **Progression-free survival**
  - Progression free survival will be calculated from the date of study entry until a progression occurs. Progression events are defined as clinical, pathologic or radiologically documented disease progression, or death from any cause, Patients free from a progression event will be censored on the date of last follow up.
  - A progression-free survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. Median PFS rate will be reported with 95% CIs.
  - Duration of response as measured by Kaplan-Meier at each follow-up, or until progression, will be reported.

- **Overall survival**
  - An overall survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. The median overall survival will be reported with 95% CI.

- **Toxicity**
  - The proportion of patients experiencing grade 3 or 4 toxicity as measured by NCI-CTCAE v4.03 at trial visits or until progression and the number of SAEs will be reported.

- **Quality of Life**
  - Quality of Life is assessed using questionnaires EORTC QLQ C-30 (with supporting module BLM-30) and EQ-5D at each trial visit. Quality of life data will be reported for each time point and in terms of quality-adjusted life years (QALYs) using EQ-5D.
  - A repeated measure analysis of variance will be used to assess quality of life changes during the course of the study.

- **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.

11.4.3 Missing Data

In the event that data for an individual patient has not been collected, after the response assessment has taken place but in the absence of an event, a Last-Observation-Carried-Forward analysis will be performed.

11.5 Frequency of analyses

The Trial Management Group will meet regularly to examine safety and efficacy. An interim analysis will be required after the first 9 patients have undergone radical cystectomy. An Independent Data Monitoring Committee will be asked to advise on continuing recruitment should the response rate be lower than anticipated (see section 11.3).

12 RESEARCH GOVERNANCE

12.1 Trial Administration

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

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.

12.1.1 Responsibilities

UH Bristol 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 serious adverse events (SAEs) received from site.
- 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 Summary of Product Characteristics (SmPC) dated 20/04/2017 section 4.8..

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, UH Bristol 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.

12.2 Protocol Compliance & Initiation

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

12.3 Data Acquisition & On-Site Monitoring

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

12.4 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.

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12.5 Data Protection Act

UH Bristol 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.

13 TRIAL MANAGEMENT

13.1 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.

13.2 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to oversee the final safety data and end point analysis of the trial. This committee will be constituted according to Good Clinical Practice. The IDMC will meet after recruitment has concluded and all patients have got to the primary end point. Following this meeting, the IDMC will report their findings and recommendations to the TMG.

14 END OF STUDY

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 undergone radical cystectomy.

As described above, if no chemotherapy responses are observed in the first 9 evaluable patients, stopping rules will apply and an Independent Data Monitoring Committee (IDMC) would be convened to advise on continued recruitment.

15 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 cen-

tres 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, e.g. relating to the DCE MRI and CTC substudies, 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.

It is anticipated that the results of this trial and those of the MRI and CTC substudies will contribute to an MD thesis for Dr Susan Masson, Consultant Clinical Oncologist, University Hospitals Bristol NHS Foundation Trust.

16 CONFIDENTIALITY AND LIABILITY

16.1 Risk assessment

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

16.2 Liability/Indemnity/Insurance

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

16.3 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.

17 ETHICAL CONSIDERATIONS

The Bristol Bladder 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.

18 WITHDRAWAL OF PATIENTS

18.1 Withdrawal of patients from trial treatment

Patients who do not receive their full 4 cycles of cisplatin and cabazitaxel chemotherapy for any reason (see below) should be treated with further chemotherapy if appropriate, according to local practice, at the discretion of their clinician. Specific regimens are beyond the scope of this protocol. Unless the patient requests otherwise, 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 registered patients). A trial deviation form should be completed to record details of deviation from trial treatment.

The following are possible reasons as to why a patient may not receive 4 cycles of cisplatin and cabazitaxel 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).

In the principal analysis, where a patient is not evaluable, additional patients will be recruited to replace them. A patient is considered not evaluable if:

- The patient has not completed any cycles of study cisplatin and cabazitaxel chemotherapy for one of the following reasons:
  - Death from any cause
  -
  - Withdrawal from trial for a reason unrelated to drug or disease (e.g. patient preference, administrative reasons), regardless of the number of cycles of chemotherapy.

Or

- Disease cannot be measured at the end of study treatment for one of the following reasons:
  - Death from causes other than bladder cancer
  - Withdrawal from trial for a reason unrelated to drug or disease (e.g. patient preference, administrative reasons), regardless of the number of cycles of chemotherapy

Every attempt should be made to obtain disease assessments for all patients. The TMG will centrally review all patients to determine if any are non-evaluable and need to be replaced.

18.2 Withdrawal of patients from trial follow-up

Patients are asked prior to registration 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 registered. Patients are however free to reverse that decision at any time without giving a reason (see below).

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 (as above). 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.

19 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. However due to the requirement for additional appointments above those which comprise routine care, patients participating in the DCE-MRI substudy may have reasonable travel expenses reimbursed for DCE-MRI appointments.

20 ASSOCIATED STUDIES

20.1 DCE MRI Substudy

This is a concomitant optional substudy evaluating the use of dynamic contrast enhanced magnetic resonance imaging during neoadjuvant chemotherapy for muscle invasive transitional cell carcinoma of the urinary bladder, as a method of early response assessment.

The details of this study are outlined in the protocol. Patients participating in this trial who are eligible and willing may enter the study, which will involve additional imaging with gadolinium enhanced MRI scanning of the pelvis prior to chemotherapy and after one and three cycles of chemotherapy (a total of 3 DCE MRI scans).

20.2 CTC Substudy

This is a pilot study recording circulating tumour cell (CTC) concentrations prior to each cycle of chemotherapy and prior to radical cystectomy.

The details of this study are outlined in the protocol.. Eligible patients participating in this trial may enter the study, which will involve taking additional peripheral blood samples at the time of collection of 'routine' blood samples, with one additional sample taken at the end of treatment appointment.

Queries regarding these two substudies should be directed in the first instance to:

Dr Amit Bahl
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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 caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers 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.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize 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. **Methods of Measurement**
- 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.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- 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.
- The utilization of endoscopy and laparoscopy for objective tumour evaluation is not advised. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilization of such techniques for objective tumour response should be restricted to validation purposes in specialized centres. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- 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.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

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 characterize 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) Inevaluable 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 4-9 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 4-9 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 x $(SCr/0.7)^{-0.329}$ x $(0.993)^{Age}$
	>62 (>0.7)	GFR = 166 x $(SCr/0.7)^{-1.209}$ x $(0.993)^{Age}$
Male	≤80 (≤0.9)	GFR = 163 x $(SCr/0.9)^{-0.411}$ x $(0.993)^{Age}$
	>80 (>0.9)	GFR = 163 x $(SCr/0.9)^{-1.209}$ x $(0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	GFR = 144 x $(SCr/0.7)^{-0.329}$ x $(0.993)^{Age}$
	>62 (>0.7)	GFR = 144 x $(SCr/0.7)^{-1.209}$ x $(0.993)^{Age}$
Male	≤80 (≤0.9)	GFR = 141 x $(SCr/0.7)^{-0.411}$ x $(0.993)^{Age}$
	>80 (>0.9)	GFR = 141 x $(SCr/0.7)^{-1.209}$ x $(0.993)^{Age}$

:

- An acceptable alternative is direct measurement using ^{51}Cr-labelled EDTA clearance which is recommended for patients with borderline renal function (see main text). 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: STUDY DRUG (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 aluminum cap covered with a light grey plastic flip-off cap or a gold-color aluminum cap covered with a colorless 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 labeling 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.

APPENDIX 4: Quality of Life Questionnaires:

EORTC QLQ C30 and supporting module BLM 30

EQ-5D 5L

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - BLM30

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

PLEASE ANSWER QUESTIONS 31 - 37 ONLY IF YOU DO NOT HAVE A UROSTOMY

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had to urinate frequently **during the day**?	1	2	3	4
32.	Have you had to urinate frequently **at night**?	1	2	3	4
33.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34.	Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35.	Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36.	Have you had any unintentional release (leakage) of urine?	1	2	3	4
37.	Have you had pain or a burning feeling when urinating?	1	2	3	4

PLEASE ANSWER QUESTIONS 38 - 43 ONLY IF YOU HAVE A UROSTOMY

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
38.	Has urine leaked from your urostomy bag?	1	2	3	4
39.	Did you have problems with caring for your urostomy?	1	2	3	4
40.	Was your skin around the urostomy irritated?	1	2	3	4
41.	Have you felt embarrassed because of your urostomy?	1	2	3	4
42.	Have you been dependent on others for caring for your urostomy?	1	2	3	4
43.	Did you frequently have to change the urostomy bag?	1	2	3	4

PLEASE ANSWER QUESTION 44 ONLY IF YOU HAVE USED A CATHETER DURING THE PAST WEEK

44.	Have you had problems with self-catheterization? (inserting a tube in the bladder to pass urine)	1	2	3	4

Please go on to the next page

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
45.	Were you worried about your health in the future?	1	2	3	4
46.	Did you worry about the results of examinations and tests?	1	2	3	4
47.	Did you worry about possible future treatments?	1	2	3	4
48.	Have you had a bloated feeling in your abdomen?	1	2	3	4
49.	Have you had flatulence or gas?	1	2	3	4
50.	Have you felt physically less attractive as a result of your illness or treatment?	1	2	3	4
51.	Have you been dissatisfied with your body?	1	2	3	4
52.	Have you felt less feminine/masculine as a result of your illness or treatment?	1	2	3	4

During the past 4 weeks:		**Not at all**	**A little**	**Quite a bit**	**Very much**
53.	To what extent were you interested in sex?	1	2	3	4
54.	To what extent were you sexually active (with or without sexual intercourse)?	1	2	3	4
55.	**For men only:** Did you have difficulty gaining or maintaining an erection?	1	2	3	4
56.	**For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4

Please answer the following 4 questions only if you have been sexually active during the past 4 weeks:		**Not at all**	**A little**	**Quite a bit**	**Very much**
57.	Have you felt uncomfortable about being sexually intimate?	1	2	3	4
58.	Have you worried that you may contaminate your partner during sexual contact with the bladder treatment you have been receiving?	1	2	3	4
59.	To what extent was sex enjoyable for you?	1	2	3	4
60.	**For Women only:** did you have a dry vagina or other problems during intercourse?	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 ❑

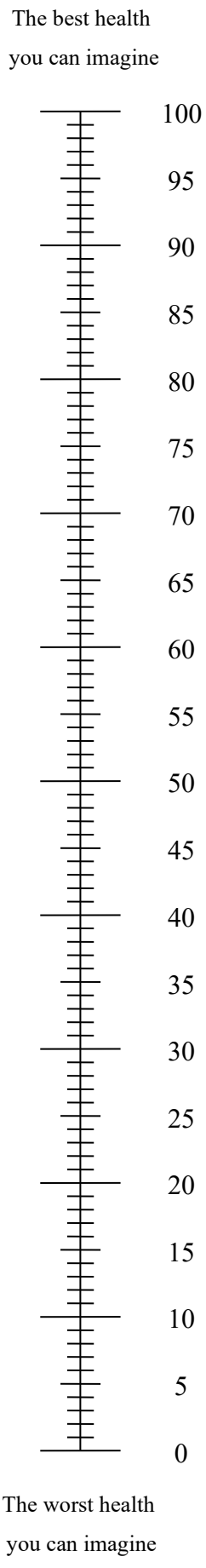
ANXIETY / DEPRESSION

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 = ☐



APPENDIX: 5

List of CYP3A Inhibitors

Precipitant	Therapeutic Class	Object (oral)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUC_r > 5)					
ritonavir	Protease Inhibitors	triazolam	**40.70**	16513448	2006 Mar
indinavir	Protease Inhibitors	vardenafil	**16.25**	NDA # 021400	2003 Aug
ketoconazole	Antifungals	midazolam[1]	**15.90**	8181191	1994 May
troleandomycin	Antibiotics	midazolam	**14.80**	15536460	2004 Dec
itraconazole	Antifungals	midazolam	**10.80**	8181191	1994 May
voriconazole	Antifungals	midazolam	**9.40**	16580904	2006 Apr
saquinavir / RIT	Protease Inhibitors	maraviroc	**9.23**	18333863	2008 Apr
mibefradil	Calcium Channel Blockers	midazolam	**8.86**	14517191	2003 Oct
clarithromycin	Antibiotics	midazolam	**8.39**	16432272	2006 Feb
lopinavir / RIT	Protease Inhibitors	aplaviroc	**7.71**	16934050	2006 Sep
nelfinavir	Protease Inhibitors	simvastatin	**6.07**	11709322	2001 Dec
telithromycin	Antibiotics	midazolam	**6.0**	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	midazolam	**5.95**	12953340	2003 Aug
conivaptan	Diuretics	midazolam	**5.76**	NDA # 021697	2005
nefazodone	Antidepressants	midazolam	**5.44**	14551182	2003 Nov
saquinavir	Protease Inhibitors	midazolam	**5.18**	10430107	1999 Jul

LIST OF INDUCERS BY CYP3A ISOENZYMES

Amobarbital
Carbamazepine
Dexamethasone
Efavirenz
Modafinil
Nevirapine
Norethindrone
Oxcarbazepine
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin
Rifampicin
Rifapentin
Ritonavir
Secobarbital
St John's Wort
Troglitazone

Referenced using University of Washington database (May 2007)