CLINICAL STUDY PROTOCOL: NUCOG I - VINGEM

A multicenter, randomized phase II trial of vinflunine/gemcitabine versus carboplatin /gemcitabine as first line treatment in patients with metastatic urothelial carcinoma unfit for cisplatin based chemotherapy due to impaired renal function.

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SYNOPSIS OF PROTOCOL NUCOG I - VINGEM

Titel	A multicenter, randomized phase II trial of vinflunine/gemcitabine versus carboplatin /gemcitabine as first line treatment in patients with metastatic urothelial carcinoma unfit for cisplatin based chemotherapy due to impaired renal function.
Sponsor	Investigator initiated study, NUCOG.
Rational	The standard first line treatment for patients with metastatic urothelial carcinoma unfit for cisplatin due to renal impairment is carboplatin containing chemotherapy, with a median overall survival of approximately 8-10 month. New, more effective regimens in terms of tumor control and quality of life are urgently needed. Vinflunine has proven efficacy in urothelial carcinoma and is registered as second line treatment. The combination of gemcitabine and vinflunine has not yet been evaluated in first line treatment for patients with metastatic urothelial carcinoma.
Trial Design	Multicenter, 1:1 randomized phase II screening design.
Target Population	First line treatment in patients with locally advanced or metastatic urothelial carcinoma, unfit for cisplatinbased chemotherapy due to impaired renal function, as per inclusion/exclusion criteria defined below.
Objectives	To compare the efficacy, safety and quality of life of vinflunine/gemcitabine and carboplatin/gemcitabine.
End points	Primary 1) Progression-free survival (PFS)
	Secondary 1) Overall response rate, ORR (= CR + PR) 2) Overall survival (OS) 3) Disease control rate, DCR (=CR + PR + SD) 4) Safety (Data on safety parameters) 5) Quality of Life (QoL)
Number of patients	120 evaluable patients.
Number of Centers	>5 from different Nordic countries
Selection criteria	**Inclusion Criteria** • Signed informed consent. • Histological or cytological confirmed transitional cell carcinoma of the urothelial tract (mixed histology including transitional cell carcinoma are allowed). • Unresectable (T4b), locally advanced (lymph node positive (N+)) or metastatic (M1) urothelial carcinoma (including renal pelvic tumours, ureteral tumours, urinary bladder tumours and urethral primary tumours). • No prior chemotherapy or other anti-cancer drugs. Patients who have received neoadjuvant or adjuvant platinum containing chemotherapy and who are diagnosed with loco regional recurrent or metastatic disease after 6 months are eligible. • Creatinine clearance 30 – 60 ml/min (measured by Iohexol or Cr-EDTA technique) • ECOG/WHO Performance Status (PS) 0-1.

	• ≥ 4 weeks since prior surgery, ≥ 2 weeks since prior radiation therapy. • Measurable and/or non-measurable disease using the RECIST criteria defined as: - Measurable disease: lesions that can be measured in at least one dimension and which have not been previously irradiated. Longest diameter ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral CT scan or MRI. - Non-measurable disease: lesions which have not been previously irradiated, longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan or MRI, or truly non measurable lesions including bone lesions, ascites, pleural/pericardial effusion, and lymphangitis cutis/pulmonitis. • CNS metastases and/or leptomeningeal metastases are allowed provided these have been adequately treated with radiotherapy are stable and not generating any symptoms. • Spinal cord compression due to metastatic lesions is allowed provided adequate surgery and/or radiotherapy has been delivered, the metastases are stable and not generating any symptoms. • No known or suspected allergy to the investigational agents or any agents given in association with this trial. • 18 years of age or older. • Fertile men and women of childbearing potential must use secure contraception (women - intrauterine devices, hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release), men – condom and for a female partner as described above) from before 2 months entering the study until 6 months after end of chemotherapy. **Exclusion Criteria** • Not fulfilling inclusion criteria as described above • Pure non-transitional cell carcinoma of the urothelial. • Bleeding tumours. • Impaired bone marrow function defined as WBC < 3.0 x 10^9/L, neutrophils < 1.5 x 10^9/L, platelets < 125 x 10^9/L, haemoglobin < 100 g/L. • Impaired liver function defined as serum bilirubin > 1.5 x upper limit of normal (ULN) and/or ASAT/ALAT > 2.5 x ULN (> 5 x ULN if known liver metastasis). • Electrocardiogram (ECG) with significant modifications suggesting a high risk of occurrence of angina pectoris or high risk of arrhythmia. • Other malignancies, except adequately treated basal carcinoma or squamos cell carcinoma of the skin or in-situ cervix carcinoma or incidental prostate cancer (T1a, Gleason score ≤ 6,

	PSA < 0.5 ng/ml), or any other tumour with a disease free survival of ≥ 5 years. • History of serious or concurrent illness or uncontrolled medical disorder; any medical condition that might be aggravated by chemotherapy treatment or which could not be controlled; including, but not restricted to: - Active infection requiring antibiotics within 2 weeks before the study inclusion, - Unstable diabetes mellitus, - Hypercalcaemia >2.9 mmol/L (= grade ≥ 2 according to CTCAE v 4.0), - Concurrent congestive heart failure NYHA (class III-IV), - Unstable angina pectoris, or myocardial infarction within 6 months and/or poorly controlled hypertension, - QTc > 450 ms at baseline, - Inflammatory bowel disease, - Peripheral neuropathy grade ≥ 2 according to CTCAE v 4.0, • Patients who require treatment with ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, rifampicine (any potent CYP3A4 inhibitor or inducer) or phenytoine. • Pregnant or lactating women. • Any psychological, familial, sociological, or geographical condition which does not permit protocol compliance and medical follow-up.
Investigational Drugs Dose/Route/Regimen	50% of the patients will receive vinflunine in combination with gemcitabine. Vinflunine: **250 mg/m^2** for patients with age > 80 years and/or GFR 30-40 ml/min, given I.V. on day 1, repeated every 21 days. **280 mg/m^2** for patients with GFR 40-60 ml/min, given I.V. on day 1, repeated every 21 days. Gemcitabine: **1000 mg/m^2** given I.V. on day 1 and 8 of every 21 day cycle.

Reference Drugs Dose/Route/Regimen	50% of the patients will receive carboplatin in combination with gemcitabine. Carboplatin: **AUC 4.5** given I.V. on day 1, repeated every 21 days. Gemcitabine: **1000 mg/m^2** given I.V. on day 1 and 8 of every 21 day cycle.
Duration of treatment	In both arms treatment continues until disease progression, unacceptable toxicity or patient wish to stop treatment.
Follow up	Survival information will be collected every third month until death for both treatment arms.
Sample size	Primary endpoint is progression-free survival. The study is designed to detect a 50% increase in median PFS from 5 months to 7.5 months using a significance level of 10% and a power of 80%. To be able to detect a difference of this magnitude the study must observe 110 PFS-events. With an annual accrual rate of 60 patients per year during two years and an extra year of follow-up the study is expected to generate the necessary number of events within a three-year period.
Statistical Analysis	The study is designed as a nondefinitive randomized phase II screening trial, with the primary endpoint progression free survival (PFS). The Kaplan-Meier technique will be used to estimate PFS and differences in survival will be tested using the log-rank test. Treatment effect will be estimated using proportional hazards regression.
Key dates	Anticipated start of study: Q 3, 2013 Estimated recruitment period: Q 3, 2013 – Q 1, 2016

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BSC	Best Supportive Care
CRF	Case Report Form
CR	Complete Response
CT	Computerized Tomography
DCF	Data Clarification Form
DCR	Disease Control Rate
ECG	Electrocardiogram
EMA	European Medicines Agency
FU	Follow-Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IEC	Independent Ethics Committee
MPA	Medical Product Agency
MRI	Magnetic Resonance Imaging
NUCOG	Nordic Urothelial Cancer Oncology Group
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PD	Progressive Disease
PR	Partial Response
PS	Performance Status
SAE	Severe Adverse Event
SD	Stable Disease
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCCU	Transitional Cell Cancer of the Urothelium
VHP	Voluntary Harmonisation Procedure
QoL	Quality of Life

2 GENERAL INFORMATION/STUDY ADMINISTRATIVE STRUCTURE

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PHARMACY:	The hospital pharmacy at each site

2.1 PARTICIPATING CANCER CENTERS

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3 BACKGROUND

3.1 UROTHELIAL CARCINOMA AND SYSTEMIC TREATMENT

Urothelial tract cancer (ICD-10 C66.9-C68.9) consists of primary cancers from the urinary organs (excluding kidney). The most common urothelial tract cancer is bladder cancer which accounts for approximately 95% of the cases. Other primary sites are the renal pelvis, ureter, urethra and urachus. The annual global incidence of bladder cancer is estimated at 382 660 cases per year (Globocan 2008). Urothelial carcinoma ranks seventh among the malignant diseases regarding lives lost. In the Nordic countries alone, 6 362 persons each year are diagnosed with this disease (2004-2008 average incidences) and more than 2000 succumb to it – the vast majority after a shorter or longer period of symptomatic metastatic or locally advanced disease. The total number of new urothelial tract cancer cases in Sweden in 2010 was 2 528, consisting of 1 855 men and 673 women (Cancer Incidence in Sweden 2010, Socialstyrelsen, December 9, 2011).

Approximately one third of all bladder cancer patients develop locally invasive or metastatic disease and when the disease is generalised it remains largely incurable (1). The standard treatment for patients with locally advanced or metastatic urothelial carcinoma is cisplatin containing combination chemotherapy (2). The combination of cisplatin and gemcitabine is considered standard first-line treatment in most countries. An alternative of at least equal efficacy, but higher toxicity, is MVAC (methotrexate, vinblastine, adriamycin and cisplatin) (3). Metastatic urothelial carcinoma is a chemo sensitive disease with response rates above 50% in phase III studies of the above mentioned cisplatin-containing combination regimes (3). During the last 20 years significant attempts have been made to improve the efficacy of this treatment modality, unfortunately, with limited success. Currently, the median overall survival time is limited to 14-15 months (3), and clearly, the development of new treatment strategies, remains a major challenge.

For patients that are progressive following platinum-based polychemotherapy, vinflunine is the only approved treatment option. In the pivotal trial by Bellmunt et al (4), a significant median overall survival benefit of 2.6 months was achieved following to vinflunine plus best supportive care (BSC) as compared to BSC only. More than 50% of the patients who received vinflunine presented with stable disease or better, however responses were rare (4). Vinflunine is, based on these data, the reasonable second line option and has a grade A recommendation in the 2012 EAU guidelines (1).

3.2 FIRST LINE TREATMENT FOR METASTATIC UROTHELIAL CARCINOMA IN PATIENTS UNFIT FOR CISPLATIN

Up to 50 % of the patients with locally advanced or metastatic urothelial cancer are ineligible, “unfit”, for cisplatin-based chemotherapy, either due to impaired renal function and/or poor performance status (PS), or due to different co-morbidities (e.g. hearing impairment, peripheral neuropathy, heart-failure NYHA class III-IV preventing high volume hydration) or elderly patients (5). Unfortunately, there is no general consensus as to how to define who is considered “unfit”. Clinical trials should be designed to clearly distinguish among these different unfit-subgroups (2,5,8)

Non-nephrotoxic drug regimens have been developed, including single-agent treatment with taxanes, gemcitabine and carboplatin as well as different carboplatin combination therapies. Median survival of patients with renal impairment in these trials was 8-10 months, thus generally inferior to the median survival seen in trials with cicplatin combinations (2,3,7). The patient inclusion criteria regarding the definition of “unfit” has varied substantially in different trials, making it hard to interpret and compare the results.

The treatment combination of carboplatin and gemcitabine is well established, and is considered as one of the first-line standard options in the unfit patients (1,2). Recently the European Organization for Research and Treatment of Cancer (EORTC), De Santis et al, reported the first randomized phase II/III trial in patients unfit for cisplatin, comparing methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (Carbo/Gem) (6,7,8). The definition for ”unfit” used was PS 2 and/or a GFR < 60 ml/min. Both regimens were active but there were no significant difference between the two groups in tumor response (OS 9.3 month with Carbo/Gem vs. 8.0 month with M-CAVI and ORR 41 % vs. 30 % respectively). There was a significant difference in severe acute toxicity (SAT) in favor of Carbo/Gem (9 % for Carbo/Gem vs. 21% for M-CAI). Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provides limited benefit.

New, more effective regimens in terms of tumor control and quality of life are however urgently needed. Vinflunine is a new drug with known tumor activity in urothelial carcinoma as second line treatment in platinum-resistant patients (4). So far, vinflunine has not been evaluated in the first line setting. The treatment combination of gemcitabine and vinflunine, i.e. two drugs known to be active in urothelial carcinoma, has not either been evaluated for patients with metastatic urothelial bladder cancer. A randomized trial investigating the tumor response and safety of vinflunine/gemcitabine versus carboplatin/gemcitabine as first line treatment for cisplatin unfit patients due to renal impairment is therefore initiated by the NUCOG group.

3.3 RESEARCH HYPOTHESIS

The research hypothesis is that the progression free survival (PFS) in the study population treated with vinflunine in combination with gemcitabine is superior to that in patients treated with carboplatin in combination with gemcitabine. The study population consists of patients with locally advanced or metastatic urothelial carcinoma who are unfit for cisplatin based chemotherapy as first-line treatment due to impaired renal function.

3.4 INVESTIGATIONAL PRODUCTS

3.4.1 VINFLUNINE (JAVLOR®)

Vinflunine is a new microtubule inhibitor. Microtubules are an important chemotherapeutic target because of the crucial role they play during mitosis, particularly for rapidly dividing cancer cells (9). Microtubule inhibitors such as vinca alkaloids, taxanes, and epothilones have been evaluated against many tumor types in the clinical setting (10,11). Vinflunine binds to tubulin at or near to the vinca binding sites inhibiting its polymerization into microtubules, which results in tread milling suppression, disruption of microtubule dynamic, mitotic arrest and apoptosis.

In preclinical studies, vinflunine was identified as having a marked anti-tumor activity both *in vitro* and *in vivo* through a large panel of experimental tumor models (murine and human tumor xenographs) in terms of survival prolongation and tumor growth inhibition, including a dose-dependent decrease in tumor incidence and a significant increase in survival in an orthotopic model of mouse bladder cancer and some drug-refractory models such as murine B16 melanoma model and JJN3/VelcadeR (resistant multiple myeloma) tumor xenographs. When compared with several vinca-alkaloids (vinblastine, vincristine, vindesine, vinorelbine), vinflunine showed the highest level of activity.

Current indication for vinflunine in patients with advanced or metastatic urothelial tract cancer is second line treatment following failure to prior platinum-containing regimen (1).

3.4.2 CARBOPLATIN

Carboplatin is an alkylation chemotherapy drug. In terms of its structure, carboplatin differs from cisplatin in that it has a bidentate dicarboxylate ligand in place of the two chloride ligands, which are the leaving groups in cisplatin (12). It exhibits lower reactivity and slower DNA binding kinetics, although it forms the same reaction products in vitro at equivalent doses with cisplatin. Carboplatin is less potent than cisplatin, depending on the strain of cancer. Relative to cisplatin, the greatest benefit of carboplatin is its reduced side effects, particularly the elimination of nephrotoxic effects. Nausea and vomiting are less severe and more easily controlled. The main drawback of carboplatin is its myelosuppressive effect.

Carboplatin is widely used in many different types of cancer, e.g. breast cancer due to BRCA-1 and BRCA-2 genes, lung cancer, ovarian carcinoma, lung cancer, head and neck cancers, testicular cancer.

Current indication for carboplatin in patients with advanced or metastatic urothelial tract cancer is first-line combination treatment for patients unfit for cispaltin (1).

3.4.3 GEMCITABINE

Chemically gemcitabine is a nucleoside analog in which the hydrogen atoms on the 2' carbon of deoxycytidine are replaced by fluorine atoms. As with fluorouracil and other analogues of pyrimidines, the triphosphate analogue of gemcitabine replaces one of the building blocks of nucleic acids, in this case cytidine, during DNA replication (13). The process arrests tumor growth, as only one additional nucleoside can be attached to the "faulty" nucleoside, resulting in apoptosis. Another target of gemcitabine is the enzyme ribonucleotide reductase (RNR). The diphosphate analogue binds to RNR active site and inactivates the enzyme irreversibly. Once RNR is inhibited, the cell cannot produce the deoxyribonucleotides required for DNA replication and repair, and cell apoptosis is induced (14).

Gemcitabine is used in various carcinomas e.g. non-small cell lung cancer, pancreatic cancer, ovarian cancer, breast cancer, esophageal cancer.

Current indication for gemcitabine in patients with advanced or metastatic urothelial tract cancer is first-line treatment in combination with cisplatin or carboplatin and as single treatment for patients unfit for combination therapy (1).

3.5 CLINICAL STUDIES WITH INVESTIGATIONAL PRODUCTS IN UROTHELIAL CARCINOMA AND OTHER CANCERS

3.5.1 VINFLUNINE IN UROTHELIAL CARCINOMA

Vinflunine, as single agent, provides both survival advantage over best supportive care and clinical benefits in patients with advanced or metastatic urothelial tract cancer after prior failure of a platinum-containing regimen (4). It is the only drug approved in Europe (September 2009) in this setting, where there was no prior established standard of care. Based on the recommended dose schedule of one intravenous infusion every 3 weeks, at 320 mg/m^2 or 280 mg/m^2 in patients with PS=1 or with PS=0 plus prior pelvic irradiation, 450 patients received vinflunine treatment as single agent in two phase II and in one large randomized phase III study in second-line urothelial tract cancer (4,16,17). Vinflunine as a single agent showed consistent results through the randomised phase II-III trials with a disease control rate of 41 % and a median survival time of 6.9 months in the phase III trial (+2.6 months in the eligible population as compared to best supportive care arm, HR 95% CI 0.78 [0.61-0.99]) (4). Vinflunine exhibited neither renal toxicity, nor increase of prior renal impairment. As demonstrated in earlier clinical trials, patients with a creatinine clearance as low as 40 mL/min could safely receive the drug. The drug was also assessed in a few patients with an even lower clearance value (20-40 mL/min). Efficacy and safety of vinflunine has not been studied in patients with performance status ≥2 (15).

The safety profile among the entire population of 450 patients with urothelial tract cancer treated by vinflunine allowed to establish that grade 3-4 neutropenia was observed in 54.6% of patients but was as well reversible and non-cumulative. Severe anaemia and thrombocytopenia (grades 3 or 4) were less common (respectively 17.3% and 4.9 %). Febrile neutropenia was observed in 6.7% of patients (all grades). Infection with grade 3/4 neutropenia was observed in 3.8% of patients (15,18).

Severe fatigue (grade 3-4) was experienced by 15.8% of patients. Constipation was frequently reported (54.9% of patients during treatment) with 15.3% of grade 3-4. However, this adverse event was manageable by prophylactic laxative treatment. The number of grade 3/4 constipation per cycle decreased from 10% at cycle 1 to 2% at cycle 3 in the phase III pivotal trial (4); constipation lasted less than 8 days in 80% of the patients and resolved in all cases with laxatives and/or enema. In this phase III study, constipation (non-drug related) was also reported in 25% of the patients in the BSC control arm. Similarly, the incidence of all grades abdominal pain was 21.6% in the phase III trial (4.7% grade 3-4) but was 17.9% with BSC (6% grade 3-4). Consequently, vinflunine-related constipation doesn't seem to lead to an increase in abdominal pain in patients with urothelial carcinoma. Other symptoms occurred with the vinflunine use: grade 3-4 myalgia (3.1 % of patients); injection site reactions in 27.6% of patients (grade 3-4 of 0.4%); and peripheral sensory neuropathy (all grades: 9.8 %, grade 3: 0.9 %) in patients previously exposed to platinum derivatives.

Overall drug related events leading to death were reported during the three studies performed in patients with urothelial tract cancer (among the entire population of 450 patients): three patients died after septicemia, one of myocardial infarction, one of cardio-pulmonary arrest and one due to pancytopenia.

A summary of the safety profile of vinflunine (pooled doses of 320 mg/m² and 280 mg/m² given as single agent) in patients with urothelial tract cancer is presented in the table below (15).

Summary of safety profile of vinflunine as single agent in urothelial tract cancer studies (450 patients); most relevant grade 3/4 adverse events (AE) (below):

Related AEs Grade 3/4 (% pat.)	TCCU
Haematological Events	**445 pat.**
Neutropenia	**54.6**
Leucopenia	**45.2**
Anaemia	17.3
Thrombocytopenia	4.9
Febrile Neutropenia	6.7

Related AEs Grade 3/4 (% pat.)	TCCU
Non-haematological Events	**450 pat.**
Asthenia/Fatigue	**15.8**
Constipation	**15.3**
Abdominal pain	4.7
Neutropenic infection	3.8
Infection	2.7
Myalgia	3.1
Vomiting	2.9
Nausea	2.9
Stomatitis	2.7
Anorexia	2.7
Peripheral sensory neuropathy	0.9
Injection site reaction	0.4
Renal failure	0.2

3.5.2 VINFLUNINE AND GEMCITABINE IN UROTHELIAL CARCINOMA AND OTHER CANCERS

The combination vinflunine and gemcitabine has been explored in a Phase I dose-finding and pharmacokinetic study for treatment of advanced non-small cell lung cancer in chemotherapy-naive patients. The trial showed a good toxicity tolerance profile and no pharmacokinetic interactions were observed (19). Vinflunine was administered on day 1 every 21 days combined with gemcitabine given on days 1 and 8 every 3 weeks. The patients had a performance status of 0 - 1 and a GFR ≥ 50 ml/min. The recommended dose was established at the dose of vinflunine 320 mg/m^2 combined with gemcitabine 1000 mg/m^2. In the dose-step with vinflunine 280 mg/m^2 and gemcitabine 1000 mg/m^2 (the same doses proposed in this NUCOG-I trial), the main haematological toxicity was leucopenia and neutropenia; for leucopenia grade ≥ 1 in 3/4 patients, grade 3 in 2/4 patients and grade 4 in 1/4 patient; for neutropenia grade ≥ 1 in 3/4 patients, grade 3 in 0/4 patients and grade 4 in 3/4 patients. No febrile neutropenia was reported. For thrombocytopenia 2/4 patients experienced grade ≥ 1, but no grade 3 or 4 thrombocytopenia was observed. For anaemia 3/4 patients experienced grade ≥ 1, but no grade 3 or 4 anaemia was observed. In the dose-step with vinflunine 280 mg/m^2 and gemcitabine 1000 mg/m^2 no grade 3 or 4 non-haematological toxicity was observed. Grade ≥ 1 non-haematology toxicity was reported for constipation (2/4 patients), abdominal pain (2/4), nausea (3/4), stomatits (2/4), vomiting /2/4), fatigue (2/4), pain in jaw (1/4), peripheral sensory neuropathy (2/4) and alopecia (1/4).

Vinflunine has not yet been tested in first line in urothelial carcinoma patients, neither for the cisplatin eligible or ineligible patients. There is one ongoing international, company initiated phase II trial, comparing the combination of vinflunine (280 or 250 mg/m^2) and gemcitabine (1000 or 750 mg/m^2) to the combination of vinflunine (280 or 250 mg/m^2) and carboplatin (AUC 4.5) in urothelial carcinoma patients unfit for cisplatin (JASINT-1, Pierre-Fabre Pharma AB) . The definition used for unfit in the JASINT-1 trial is GFR < 60 mL/min or congestive heart failure NYHA Stage III-IV, (PS ≥ 2 excluded). The number of patients is 31 in each arm and the primary objective is disease control. The trial is estimated to be reported in the end of 2013.

As the combination vinflunine and gemcitabine has not yet been tested in patients with urothelial carcinoma, the first ten patients included in the study will be fully monitored regarding all safety parameters. After five and after ten patients respectively, the sponsor will decide if the combination is safe and if the study will proceed. There will also be an independent Trial Safety Committee that will meet yearly and will be eligible to stop randomization for safety reasons at any time during the trial.

3.5.3 CARBOPLATIN AND GEMCITABINE IN UROTHELIAL CARCINOMA

Carboplatin based combination therapy is, as mentioned above, well established as first line treatment for patients unfit for cisplatin containing chemotherapy. The recently published phase III EORTC trial by De Santis et al, recommended the combination of carboplatin and gemcitabine to be the first choice of treatment over methotrexate/carboplatin/vinblastine (M-CAVI), due to the more beneficial toxicity profile (8). (See chapter 4.2). Severe Acute Toxicity (SAT) was defined as death resulting from toxicity, grade 4 thrombocytopenia with bleeding, grade 3 to 4 renal toxicity, neutropenic fever, or grade 3 to 4 mucositis (7,8). SAT was observed in 9.3 % of the patients with carbo/gem and in 21.2 % in the M-CAVI arm. The most common grade 3 to 4 toxicities in the carbo/gem arm were: leucopenia (44.9%), neutropenia (52.5%), febrile neutropenia (4.2%), thrombocytopenia (48.3%) and infection (11.8%). There were more SATs in patients with impaired renal function (9.1%) compared to patients with normal renal function but a PS $\geq$ 2 (4.8%). For patients with both impaired renal function and PS $\geq$ 2 there were 12.5% SAT. The reasons for treatment discontinuation in the EORTC trial was mainly progressive disease (25.2%) and after that toxicity (21.0%).

Single-agent gemcitabine has been studied in many phase I and II trials; response rates of 23% to 45% have been reported (a mixture of studies with first/second line treatment, different PS, normal/impaired renal function, elderly patients etc.) (2,20,21). In view of these results of several single-arm phase I/II studies, it remains uncertain to what extent carboplatin adds to the effects of gemcitabine monotherapy in cisplatin unfit patients. Only a randomized phase III study will be able to answer this question (8).

4 STUDY RATIONAL

For locally advanced and metastatic urothelial carcinoma cisplatin-based polychemotherpy is well established as standard treatment, with a response rate above 50% and median overall survival time about 14 to 15 months (3). For patients ineligible to cisplatin treatment, due to renal impairment, PS>2 or concomitant co morbidity, carboplatin-based polychemotherapy is recommended; preferably with carboplatin combined with gemcitabine due to a more tolerable toxicity profile compared to M-CAVI, as recently showed in a phase III trial (8). The response rate is around 30-40 % and the median overall survival time is limited to 8-10 months (1,8); clearly, the development of new effective treatment strategies, remains a major challenge.

The treatment combination of gemcitabine and vinflunine, i.e. two drugs known to be active in urothelial carcinoma, has not been evaluated for patients with metastatic urothelial bladder cancer. The combination is well tolerated in other solid cancer (19). Whether the combination of vinflunine and gemcitabine is superior to the combination of carboplatin and gemcitabine as first line treatment for patients unfit for cisplatin due to impaired renal function, can only be explored through controlled clinical studies. The rational for the present study is thus to investigate potential gain in efficacy and safety by combining vinflunine and gemcitabine and, if positive, to form the basis for further testing in phase III.

4.1 RATIONAL FOR STUDY POPULATION

The definition of “unfit” to cisplatin is usually impaired renal function and/or poor performance status (PS), or due to different co-morbidities (e.g. hearing impairment, peripheral neuropathy, heart-failure NYHA class III-IV preventing high volume hydration) or elderly patients (5). Clinical trials should be designed to clearly distinguish among these different unfit-subgroups (2,5,8). The subgroup that has impaired renal function consists of about 55 %

of the unfit population (8). For this large subgroup special care has to be taken into account regarding the choice of cytotoxic drugs. Both vinflunine and gemcitabine is well tolerated in patients with impaired renal function, and is thereby a good treatment rational for the present study.

4.2 RATIONAL FOR SCHEDULE

For vinflunine different schedules have been explored: once every 3 weeks, weekly administration, and day 1 + day 8 every 3 weeks. The 3 week schedule was chosen as it as most extensively tested and the one in which objective responses were observed (4,16,17). In the investigational arm, vinflulnine/gemcitabine, vinflunine is given on day 1 and gemcitabine on day 1 + day 8 every 3 weeks, according to the schedule in the phase I study by Tournoux-Facon et al (19). The treatment schedule in the reference arm, carboplatin/gemcitabine, is well established with carboplatin given on day 1 and gemcitabine on day 1 and day 8 (7,8). The two treatment arms will thus have an identical time schedule.

4.3 RATIONALE FOR CLINICAL DOSE

In early studies for vinflunine the recommended dose was 320 mg/m^2 and 280 mg/m^2 for patients with PS 1 and/or previous radiotherapy of the pelvis. For patients with impaired renal function the standard dose is 280 mg/m^2 or 250 mg/m^2 for GFR 40-60 ml/min and 30-40 ml/min respectively. The recommended doses in the dose finding phase I trial for vinflunine combined with gemcitabine in lung cancer (19) was vinflunine 320 mg/m^2 and gemcitabine 1 000 mg/m^2. In the study population in the present NCOG trial all patients have impaired renal function, and thus the dose of vinflunine has been adjusted for this (280 mg/ m^2 or 250 mg/ m^2).

For treatment in the reference arm, carboplatin/gemcitabine, a feasibility study of carboplatin with fixed dose of gemctiabine (1000 mg/m^2) in unfit patients with advanced bladder cancer showed a recommended carboplatin dose of AUC 4.5. This AUC-dose appeared to be active and well tolerated regimen with acceptable toxicity (6). This feasibility study defined the doses of carboplatin and gemcitabine in the phase III study by De Santis (7,8).

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6 STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVE

- To compare the progression free survival (FPS) of vinflunine/gemcitabine versus carboplatin/gemcitabine in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract unfit for cisplatin based chemotherapy due to impaired renal function.

6.2 SECONDARY OBJECTIVES

- To evaluate the tumour response (ORR), overall survival (OS) and disease control rate (DCR) of vinflunine/gemcitabine versus carboplatin/gemcitabine in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract unfit for cisplatin based chemotherapy due to impaired renal function.
- To assess the safety and toxicity of vinflunine/gemcitabine versus carboplatin/gemcitabine.
- To investigate and compare Quality of life during treatment with vinflunine/gemcitabine and carboplatin/gemcitabine respectively.

7 STUDY ENDPOINTS

7.1 PRIMARY ENDPOINT

- Progression free survival (PFS), (CR + PR + SD)

7.2 SECONDARY ENDPOINTS

- Overall response rate (ORR) (ORR = CR + PR)
- Overall survival (OS)
- Disease control rate (DCR), (DCR = CR + PR + Stable Disease (SD)), according to RECIST, every 2nd cycle
- Data on safety (Serious Adverse Events, Adverse Events leading to premature withdrawal)
- Data on Quality of Life (Quality of Life Questionnaire C30 (QLQ-C30) Version 3.0)

8 STUDY DESIGN

8.1 STUDY OUTLINE

This is an open label, 2 arms, prospective randomized multicenter, clinical phase II screening trial. An unblinded design is not appropriate due to the two different drug-regimens different toxicity profiles with different dose modification schedules (see Chapter 10.1) and with different recommended and prohibited concomitant treatments (see Chapter 10.3).

A screening visit will be performed within 4 weeks before first study drug administration.

A patient is entering the study when all of the inclusion criteria and none of the exclusion criteria are fulfilled. Adverse events occurring during the screening period will be recorded as an updated baseline status.

The patients are randomized into two treatment arms.

Arm I: 50% of the patients will receive vinflunine in combination with gemcitabine.

Vinflunine:

250 mg/m^2 for patients with age > 80 years and/or GFR 30-40 ml/min, given I.V. on day 1, repeated every 21 days.

280 mg/m^2 for patients with GFR 40-60 ml/min, given I.V. on day 1, repeated every 21 days.

Gemcitabine:

1000 mg/m^2 given I.V. on day 1 and 8 of every 21 day cycle.

Arm II: 50% of the patients will receive carboplatin in combination with gemcitabine.

Carboplatin:

AUC 4.5 given I.V. on day 1, repeated every 21 days.

Gemcitabine:

1000 mg/m^2 given I.V. on day 1 and 8 of every 21 day cycle.

In both arms treatment continues until progression, unacceptable toxicity or patients wish to stop treatment.

Patients that are withdrawn from the study, will be followed-up at day 30 (±2 days) after last treatment. Survival parameters will be collected every third month until death.

If any symptoms need to be followed up the patient will be scheduled for an additional appointment as soon as possible.

Tumour response according to RECIST criteria will be assessed every 2nd treatment cycle.

8.2 STUDY ASSESSMENTS AND PROCEDURES

8.2.1 ASSESSMENTS PER VISIT

Screening visit (Within 28 days before first Study drug administration)	Collection of written Informed consent Medical/surgical history Physical examination Inclusion and exclusion criteria Height Weight Blood pressure, heart rate Electrocardiogram (ECG) ECOG/WHO Blood/plasma analysis: Haematology[1)] Electrolytes (including creatinine) [2)] Hepatic function[3)] Renal function (Iohexol or Cr-EDTA clearance) Concomitant medication Pregnancy test, if applicable Central line for infusion is recommended Tumour assessment–radiology (baseline CT/MR abdomen + CT thorax) - Within 28 days before first study drug administration QLQ-C30 v3.0
Day -1	Medical/surgical history (i.e. update baseline status)

(≤72 h before **first** cycle)	Concomitant medication (i.e. update baseline status) Physical examination Weight Blood pressure, heart rate ECOG/WHO Blood/plasma analysis: Haematology[1)] Electrolytes (including creatinine)[2)] Hepatic function[3)]	
Day 1 (= day 22) (Day of drug admin)	Administration of study drugs according to arm I or arm II	
Day 8 (Day of drug admin)	Blood/plasma analysis: Haematology[1)] Creatinine Administration of study drugs according to arm I or arm II	≤72 h before drug admin
Day 21 (≤72 h before **drug admin)**	Physical examination Weight Blood pressure, heart rate ECOG/WHO Blood/plasma analysis: Haematology[1)] Electrolytes (including creatinine)[2)] Hepatic function[3)] Concomitant medication Adverse event Continuation criteria Tumour assessment – radiology (CT/MR) QLQ-C30 v3.0	 (every 6 weeks/2nd cycle) (every 6 weeks/2nd cycle)
Extra visit	Only relevant assessments should be performed: Physical examination Weight Blood pressure, heart rate ECOG/WHO Blood/plasma analysis: Haematology[1)] Electrolytes (including creatinine)[2)] Hepatic function[3)] Concomitant medication Adverse event Continuation criteria	
Follow-up visit (Day 30 ± 2 after last treatment administration)	Physical exam Weight Blood pressure/heart rate ECOG/WHO PS Concomitant medication Blood/plasma analysis: Haematology[1)] Electrolytes (including creatinine)[2)] Hepatic function[3)] Adverse event QLQ-C30 v3.0	

8.2.2 SCHEDULE OF EVENTS

The schedule of events will be repeated each treatment cycle until any discontinuation criteria is met. A summary of study events to be performed each treatment cycle, presented in the tabular format below.

Study parameter	**Screening** Day ≤ -28	**Day -1** ≤72 h prior 1st dose	**Day 1** Drug admin.	**Day 8** Drug admin.	**Day 21** ≤72 h prior to drug admin. [8]	**Extra visit** [11]	**Follow-Up visit** [12]
Informed consent	X						
Medical/surgical history	X	X[6]					
Inclusion/exclusion criteria	X						
Physical exam	X	X	X[7]	X[7]	X	X	X
Height	X						
Weight	X	X			X	X	X
Blood pressure/heart rate	X	X			X	X	X
Electrocardiogram (ECG)	X						
ECOG/WHO PS	X	X			X	X	X
Concomitant medication	X	X[6]			X	X	X
Pregnancy test (if applicable)	X						
Central line for infusion (recommended)	X						
Tumour assessment – radiology (CT/MR)	X				X[9]		
Haematology[1]	X	X		X	X	X	X
Electrolytes (including creatinine[4])[2]	X	X		X	X	X	X
Hepatic function[3]	X	X			X	X	X
Renal function (Iohexol or Cr-EDTA clearance)	X						
Adverse event					X	X	X
QLQ-C30 v3.0	X				X[10]		X
Continuation criteria[5]					X	X	

1) Haematology: Hb, Platelets, WBC including neutrophils
2) Electrolytes: P-Na, P-K, P-Ca, P-Alb, P-creatinine
3) Hepatic function: P-ASAT, P-ALAT, P-bilirubin, P-LD, P-ALP
4) Cr-EDTA or Iohexol clearance clearance should be done if creatinine increases ≥20%.
5) Continuation criteria: Se chapter 9.5
6) Prior to cycle 1: Update baseline status
7) Control of general condition by oncology nurse at the treatment ward according to clinical praxis
8) A doctor-visit is mandatory before the three first cycles. Thereafter doctor visit every, or every second cycle, at the discretion of the investigator.
9) Tumour assessment – radiology (CT/MR): every 6 weeks/2nd cycle, until progress
10) Assessment of QoL – QLQ-C30 v3.0 every 6 weeks/2nd cycle
11) Assessments according to the relevance on a case to case basis
12) Follow-up visit: day 30±2 days after last treatment administration.

8.3 FOLLOW-UP PERIOD ASSESSMENT

The follow-up period is the time from 30 days after the last study treatment administration until death or decision for study closure. For patients who discontinued the study due to progressive disease, survival information will be collected approximately every 3 months until death. For patients who discontinued the study treatment before the occurrence of disease progression, clinical and radiological assessments will be performed every 6th week until disease progression. After progression, survival information will be collected as stated above, approximately every 3 months until death.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

This phase 2 study will include 120 evaluable patients with verified transitional cell carcinoma of the urinary tract. The patients will be recruited at centers in Denmark, Norway and Sweden.

9.1 GENERAL ELIGIBILITY CRITERIA

Only patients that fulfil the inclusion criteria (10.3) and none of the exclusion criteria (10.4) are eligible for enrolment.

9.2 SCREENING AND ENROLMENT OF SUBJECTS

Potentially suitable patients will be screened by physicians or research nurses at the centres in order to find eligible participants. The screening procedure aims at confirming that the inclusion and exclusion criteria are met.

9.3 SUBJECT INCLUSION CRITERIA

Patients with:

- Signed informed consent.
- Histological or cytological confirmed transitional cell carcinoma of the urothelial tract (mixed histology including transitional cell carcinoma are allowed).
- Unresectable (T4b), locally advanced (lymph node positive (N+)) or metastatic (M1) urothelial carcinoma (including renal pelvic tumours, urethral tumours, urinary bladder tumours and urethral primary tumours).
- No prior chemotherapy or other anti-cancer drugs. Patients who have received neoadjuvant or adjuvant platinum containing chemotherapy and who are diagnosed with loco regional recurrent or metastatic disease after 6 months are eligible.
- Creatinine clearance 30 – 60 ml/min (measured by Iohexol or Cr-EDTA technique)
- ECOG/WHO Performance Status (PS) 0-1.
- $\geq$ 4 weeks since prior surgery, $\geq$ 2 weeks since prior radiation therapy.
- Measurable and/or non-measurable disease using the RECIST criteria defined as:
    - Measurable disease: lesions that can be measured in at least one dimension and which have not been previously irradiated. Longest diameter $\geq$ 20 mm with conventional techniques or $\geq$ 10 mm with spiral CT scan or MRI.
    - Non-measurable disease: lesions which have not been previously irradiated, longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan or MRI, or truly non measurable lesions including bone lesions, ascites, pleural/pericardial effusion, and lymphangitis cutis/pulmonitis.
- CNS metastases and/or leptomeningeal metastases are allowed provided these have been adequately treated with radiotherapy, are stable and not generation any symptoms.
- Spinal cord compression due to metastatic lesions is allowed provided adequate surgery and/or radiotherapy has been delivered, the metastases are stable and not generating any symptoms.
- No known or suspected allergy to the investigational agents or any agents given in association with this trial.
- 18 years of age or older.

- Fertile men and women of childbearing potential must use secure contraception (women - intrauterine devices, hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release), men – condom and for a female partner as described above) from before 2 months entering the study until 6 months after end of chemotherapy.

9.4 SUBJECT EXCLUSION CRITERIA

Patients with:

- Not fulfilling inclusion criteria as described above
- Pure non-transitional cell carcinoma of the urothelial.
- Bleeding tumours.
- Impaired bone marrow function defined as WBC < 3.0 x 10^9/L, neutrophils < 1.5 x 10^9/L, platelets < 125 x 10^9/L, haemoglobin < 100 g/L.
- Impaired liver function defined as serum bilirubin > 1.5 x upper limit of normal (ULN) and/or ASAT/ALAT > 2.5 x ULN (> 5 x ULN if known liver metastasis).
- Electrocardiogram (ECG) with significant modifications suggesting a high risk of occurrence of angina pectoris or high risk arrhythmia.
- Other malignancies, except adequately treated basal carcinoma or squamos cell carcinoma of the skin or in-situ cervix carcinoma or incidental prostate cancer (T1a, Gleason score ≤ 6, PSA < 0.5 ng/ml), or any other tumour with a disease free survival of ≥ 5 years.
- History of serious or concurrent illness or uncontrolled medical disorder; any medical condition that might be aggravated by chemotherapy treatment or which could not be controlled; including, but not restricted to:
    - Active infection requiring antibiotics within 2 weeks before the study inclusion,
    - Unstable diabetes mellitus,
    - Hypercalcaemia >2.9 mmol/L or grade ≥ 2 according to CTCAE v 4.0,
    - Concurrent congestive heart failure NYHA (class III-IV),
    - Unstable angina pectoris, or myocardial infarction within 6 months and/or poorly controlled hypertension,
    - Inflammatory bowel disease,
    - Peripheral neuropathy grade ≥ 2 according to CTCAE v 4.0,
- Patients who require treatment with ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, rifampicine (any potent CYP3A4 inhibitor or inducer) or phenytoine.
- Pregnant or lactating women.
- Any psychological, familial, sociological, or geographical condition which does not permit protocol compliance and medical follow-up.

9.5 CONTINUATION CRITERIA

Treatment according to the logarithm will not be disrupted unless any of the below listed criteria are valid (9.6)

9.6 WITHDRAWAL OF SUBJECTS

A participant will be withdrawn immediately if:

- he or she withdraws his/hers informed consent at his/hers own request
- unacceptable toxicity not manageable by symptomatic therapy, dose delay or dose modification (according to chapter 11)
- he or she does not comply with the instructions given by the study personnel
- tumour progression
- pregnancy
- physician's decision, including the need of other cancer therapy

The reason and date of a withdrawal must be stated in the patient's CRF and in the medical records. Patients that have been withdrawn will continue to be tracked and assessed (unless the patient explicitly declines).

9.7 CONSIDERATIONS AFTER WITHDRAWAL

A participant that has been withdrawn (by any reason) cannot be reincluded in the study. Their subject number cannot be reused.

10 TREATMENT OF SUBJECTS

10.1 TREATMENT ADMINISTRATION AND TREATMENT MODIFICATIONS

10.1.1 PRE-DEFINED DOSAGE SCHEDULE

In the investigational arm vinflunine (Javlor®, Pierre-Fabre Pharma AB) and gemcitabine is combined as follow: For patients with age > 80 years and/or GFR 30-40 ml/min, vinflunine **250** mg/m^2 is given I.V. on day 1, repeated every 21 days. For patients with GFR 40-60 ml/min vinflunine, **280** mg/m^2 is given I.V. on day 1, repeated every 21 days. Gemcitabine 1000 mg/m^2 is given I.V. on day 1 and 8 of every 21 day cycle.

In the reference arm carboplatin and gemcitabine is combined as follow: Carboplatin AUC 4.5 is given I.V. on day 1, repeated every 21 days. Gemcitabine 1000 mg/m^2 is given I.V. on day 1 and 8 of every 21 day cycle.

10.1.2 INDIVIDUAL DOSE MODIFICATIONS

Treatment will be modified in case of significant or dose limiting haematological and/or non-haematological toxicity. Dose adjustment and/or treatment delay are to be made according to the body system showing the greatest degree of toxicity.

Any patient who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. No dose re-escalation will be performed after dose reduction (re-escalation of day 8 gemictabine is allowed). In case of 2nd event requiring dose-reduction, the treatment should be stopped.

Dose adjustments at the start of a subsequent cycle should be based on nadir haematological counts or maximum non-haematological toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in the following tables. If the study treatment cannot be administered after a 2 week delay (cycle duration > 5 weeks) because of any toxicity, it should be definitively discontinued.

- For both treatment arms, *to start a new treatment cycle*, WBC ≥ 3 x 10^9, neutrophils ≥ 1.5 x 10^9 and platelets ≥ 100 x 10^9 is required. For non-haematological toxicity, all toxicity, except alopecia, fatigue, nausea or vomiting, should have recovered to CTCAE grade ≤ 1 or baseline. The onset of a new treatment cycle should be withheld until the criteria's for starting a new cycle are met. If the criteria are not met within 14 days the treatment will be discontinued (see chapter 11.1.3)

- For both treatment arms the dose of gemcitabine *on day 8* should be adjusted according to the following table:

	Gemcitabine (% of the gemcitabine dose day 1 in the same cycle)
WBC 2.0 – 2.9 and Neutrophils 1.0 – 1.5 and Platelets > 100	100 %
WBC 1.0 – 1.9 and/or Neutrophils 0.5 – 1.0 and/or Platelets 50 – 99	50 % or dose omitted[1)]
Non-hematologic toxicity grade 3 or 4 (except alopecia, fatigue, nausea or vomiting)	50 % or dose omitted[1)]
WBC < 1 and/or Neutrophils < 0.5 and/or Platelets < 50	Dose omitted

1) At the discretion of the investigator

10.1.2.1 Dose modification for the Investigational arm: vinflunine and gemcitabine

- The doses of vinflunine and gemcitabine *in the next treatment cycle* should be adjusted according to the following table:

		Vinflunine initial dose **280 mg/m^2**	Vinflunine initial dose **250 mg/m^2**	Gemcitabine (% of previous cycle dose day 1)
Hematologic Toxicity				
- Neutropenia grade 4 for ≥ 7 days - Febrile neutropenia (Neutrophils < 1 and fever ≥ 38,5 °C)	First event	250 mg/m^2	225 mg/m^2	75 %
- Grade 4 thrombocytopenia - Thrombocytopenia with active bleeding	Second event	Stop treatment	Stop treatment	Stop treatment
Non-hematologic Toxicity [2,3)]				
Mucositis or constipation (grade 2 ≥ 5 days or grade 3 any duration)	First event	250 mg/m^2	225 mg/m^2	75 %
Any grade 3 toxicity (except alopecia, fatigue, nausea or vomiting)	Second event	Stop treatment	Stop treatment	Stop treatment
Any grade 4 toxicity (except alopecia, fatigue, nausea or vomiting)	First event	250 mg/m^2 or stop treatment [1)]	225 mg/m^2 or stop treatment [1)]	50 % or stop treatment [1)]
	Second event	Stop treatment	Stop treatment	Stop treatment

1) At the discretion of the investigator
2) If decrease in GFR to 30-40 ml/min, the dose 250 mg/m^2 of vinflunine should be given in the next treatment cycle
3) If the liver function is affected as follows:
   Bilirubin 1.5-3.0 x ULN or ASAT/ALAT ≥ x 2.5 ULN (or ≥ 5 x ULN if known liver metastases) the dose 250 mg/m^2 of vinflunine should be given in the next treatment cycle.
   Bilirubin 1.5-3.0 x ULN and ASAT/ALAT ≥ x 2.5 ULN (or ≥ 5 x ULN if known liver metastases) the dose 200 mg/m^2 of vinflunine should be given in the next treatment cycle.

10.1.2.2 Dose modification for the Reference arm: carboplatin and gemcitabine

- The doses of carboplatin and gemcitabine *in the next treatment cycle* should be adjusted according to the following table:

		Carboplatin (% of previous cycle dose day 1)	Gemcitabine (% of previous cycle dose day 1)
Hematologic Toxicity			
- Neutropenia grade 4 for ≥ 7 days - Febrile neutropenia (Neutrophils < 1 and fever ≥ 38,5 °C)	First event	75 %	75 %
- Grade 4 thrombocytopenia - Thrombocytopenia with active bleeding	Second event	Stop treatment	Stop treatment
Non-hematologic Toxicity [2)]			
Mucositis or constipation (grade 2 ≥ 5 days or grade 3 any duration)	First event	75 %	75 %
Any grade 3 toxicity (except alopecia, fatigue, nausea or vomiting)	Stop treatment	Stop treatment	Stop treatment
Any grade 4 toxicity (except alopecia, fatigue, nausea or vomiting)	First event	50 % or stop treatment [1)]	50 % or stop treatment [1)]
	Second event	Stop treatment	Stop treatment

1) At the discretion of the investigator
2) If creatinine increases > 20 %, a new Cr-EDTA or Iohexol clearance should be measured and the dose of carboplatin adjusted according to the new GRF

10.1.3 DOSE DELAY

If any toxicity has not decreased to CTCAE ≤ 1 or baseline within 14 days, or criteria to start a new treatment cycle has not been reached within 14 days, treatment will be discontinued and the patient withdrawn (see chapter 10.6) unless approved by the sponsor. Any cycle longer than 5 weeks will be a withdrawal criterion for the patient.

10.2 EXPECTED, MANAGEABLE TREATMENT RELATED TOXICITY

In the investigational arm of this study, two registered compounds will be used. The side effect profiles of these compounds given in monotherapy are well known and well characterized. In the present protocol, the below listed side effects are considered expected and should be managed according to clinical routine.

10.2.1 LIST OF COMMON AND EXPECTED TREATMENT RELATED TOXICITY

- Constipation
- Abdominal pain
- Myelotoxicity
- Fatigue
- Nausea
- Vomiting
- Stomatitis/Mucositis
- Myalgia including artralgia
- Skin reaction at site of injection

10.3 CONCOMITANT THERAPY

Concomitant therapy is defined as any drug taken by the patient up to 30 days prior to the start of the study treatment or at any time during the study and up to 30 days after ending the study treatment. All treatments that are taken accordingly are regarded as concomitant treatment and must be recorded in the CRF.

Patients are requested to inform study personnel about any changes in concomitant treatments.

10.3.1 RECOMMENDED CONCOMITANT TREATMENTS

Standard anti-emetic prophylaxis is recommended according to the institution's practice.

Laxatives and dietary measures are recommended for the patients treated in the experimental arm, starting from day 1 of each vinflunine administration to day 5. Oral hydration of at least 1.5 liters of water per day) and diet containing high fiber foods is recommended. As laxatives, a stool softener or a stimulant is recommended at the investigator discretion. For patients with an increased risk of serious constipation the use of a stool softener together with a stimulant is recommended to maximize efficacy (e.g. patients with a history of chronic or refractory constipation; concomitant treatment with opioids; peritoneal carcinomatosis or abdominal tumor masses; persistent symptoms under vinflunine despite the days 1 to 5 measures and laxatives administration)

10.3.2 PROHIBITED AND RESTRICTED THERAPIES DURING THE STUDY

Potent CYP3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole, amprenavir, indinavir, grape fruit juice) and CYP3A4 inducers (e.g. rifampicine, St John´s wort) are known to interact with vinflunine and should therefore, if possible, be avoided. Concomitant therapy of opioids and vinflunine might increase the risk of constipation.

Radiotherapy increases the effect of gemcitabine. Radiotherapy should not be given 14 days before or after treatment with gemcitabine.

Nephrotoxic drugs should not be given during or one month after the treatment with carboplatin. Phenytoin is contraindicated in patients receiving carboplatin.
Concomitant use of yellow fever vaccine is contraindicated due to the risk of fatal generalized vaccinal disease.
Concomitant use of live attenuated vaccines is not recommended due to the risk of systemic, possible fatal disease.

10.3.3 SUPPORTIVE AUTHORIZED TREATMENTS

Patients should receive full supportive treatment including steroids as antiemetic, opiates in case of pain, palliative radiotherapy, bisphosphonate therapy, antibiotics, antidiarrhoeals, and transfusion of blood products, when appropriate.

Granulocyte colony-stimulating factor (G-CSF) is allowed and shall be documented, but reserved for those patients in whom the recommended dose modifications are insufficient. Erythropoietin may be given to patients who experienced anaemia grade 3-4 according to institutional practice

10.4 COMPLIANCE WITH THE TREATMENT

The nurse responsible for drug administration to the patient will check the patient's name and identity (the patient will need to state his/hers date of birth and social security number (if applicable)). The following information must be recorded in the patient record: drug name, date and time of administration (start, end). Any interruption must be stated in the patient record. If any extra antiemetic or fluid was administered this must also be recorded.

10.5 ACCOUNTABILITY OF INVESTIGATIONAL PRODUCTS

Administration of study drugs will be managed by the investigator or co-investigators. The research nurse will be accountable for drug dispensing and will maintain records of the study drugs in the patient record.

10.6 PACKAGING AND LABELLING OF INVESTIGATIONAL PRODUCTS

Commercially available vinflunine, carboplatin and gemcitabine vials from the local pharmacy will be administered in this study. The content of the labelling is in accordance with requirements set by the regulatory authorities.

11 ASSESSMENT OF EFFICACY

11.1 TUMOUR RESPONSE

Tumour response will be evaluated at baseline and every 6 weeks/2nd treatment cycle. If the patient stops treatment due to unacceptable toxicity or any other reason other than tumor progression, radiological evaluation will continue every 6 week until radiological progress. If any objective response is documented, the response should be confirmed either at the next scheduled radiological assessment (i.e. after 2 more cycles of treatment) or with an additional assessment 28 days after the response has been observed (if the patient has discontinued the treatment due to any other reason). The same method of assessments and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up.

Tumour lesions will be categorized as measurable and/or non-measurable lesions using the RECIST criteria defined as:

- Measurable disease: lesions that can be measured in at least one dimension and which have not been previously irradiated. Longest diameter (LD) ≥20 mm with conventional techniques or ≥10 mm with spiral CT scan or MRI.
- Non-measurable disease: lesions which have not been previously irradiated. Longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan or MRI, or truly non measurable lesions including bone lesions, ascites, pleural/pericardial effusion, and lymphangitis cutis/pulmonitis;

Measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of involved organs, should be identified as **target lesions** and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repetitive measurements. A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumour response.

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 the follow-up.

11.1.1 RESPONSE CRITERIA FOR EVALUATION OF TARGET LESIONS

Complete response (CR)	The disappearance of all target lesions.
Partial response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable disease (SD)	Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started.
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.

11.1.2 RESPONSE CRITERIA FOR EVALUATION OF NON-TARGET LESIONS

Complete response (CR)	The disappearance of all non-target lesions.
Stable disease (SD)	The persistence of one or more non-target lesion(s).
Progressive disease (PD)	The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

11.1.3 RESPONSE CRITERIA FOR EVALUATION OF BEST OVERALL RESPONSE

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

12 ASSESSMENT OF SAFETY

The combination vinflunine and gemcitabine has been explored in a Phase I dose-finding and pharmacokinetic study for treatment of advanced non-small cell lung cancer. The trial showed a good toxicity tolerance profile and no pharmacokinetic interactions were observed (19). As the combination vinflunine and gemcitabine has not yet been tested in patients with urothelial carcinoma, the first ten patients entering the study will be fully monitored regarding all safety parameters. After five and after ten patients respectively, the sponsor will decide if the combination is safe and if the study will proceed.

The below listed tests (13.1-13.4) will be performed prior to and on specified days for the duration of study.

12.1 LABORATORY ASSESSMENTS

Laboratory tests include:

- Haematology: Hb, Platelets, WBC including neutrophils
- Electrolytes: P-Na, P-K, P-Ca, P-Alb, P-creatinine
- Hepatic function: P-ASAT, P-ALAT, P-bilirubin, P-ALP, P-LD
- Cr-EDTA or Iohexol clearance (at baseline and if creatinine increases ≥ 20 %)

12.2 CT THORAX AND ABDOMEN

CT scan of the thorax and abdomen is required at baseline (within 28 days before first study drug administration) to confirm or reject distant metastasis. The CT can be exchanged for an MRI if applicable. If any objective response is documented, the response should be confirmed either at the next scheduled radiological assessment (i.e. after 2 more cycles of treatment) or with an additional assessment 28 days after the response has been observed (if the patient has discontinued the treatment due to any other reason).

12.3 BLOOD PRESSURE AND HEART RATE

It is compulsory to measure and record (in the CRF) blood pressure and heart rate at each visit.

12.4 ELECTROCARDIOGRAM (ECG)

At baseline a 12-lead electrocardiogram is required to measure the QTc.

12.5 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any adverse change from baseline condition.

Adverse events on this protocol are graded according to the National Cancer Institute Common Toxicity Criteria version 4.0.

12.6 METHODS FOR ELICITING, RECORDING AND FOLLOW-UP OF ADVERSE EVENTS

If an adverse event occurs, it must be documented in the CRF. Clinical findings and symptoms should be described. Duration and outcome of the adverse event should also be stated and if any treatment was given and in that case the relation to the adverse event.

12.7 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) includes, but is not limited to an event which:

- results in death
- is life-threatening
- results in persistent or significant disability
- requires acute or unplanned hospitalisation or prolongation of existing hospitalisation
- is a congenital anomaly or birth defect
- medically important event (in which the investigators finds or suggests a significant hazard)

Exceptions: In this trial, events due to progression of the cancer shall not be reported as SAE. Hospitalisation due to study procedures or due to cancer morbidity shall not be reported as SAE.

Any serious event up to 30 days after ending study treatment must be reported.

12.8 DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

Suspected unexpected serious adverse reaction (SUSAR) is any serious event that is suspected to be connected to the study treatment and not described in the Summary of Product Characteristics (SPC). The sponsor will decide if the SADR (Serious Adverse Drug Reaction) is a SUSAR or not.

12.9 REPORTING OF SERIOUS ADVERSE EVENT (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

All serious adverse events, as listed above and suspected unexpected serious adverse reaction must be documented by the investigator immediately as he or she is notified of the event. The investigator must inform the sponsor of a SAE within 24 hours. SAEs should be faxed to the Clinical Trial Office, Department of oncology, Karolinska University Hospital. Please use the form 'Notification of Serious Adverse Event (SAE)', in Appendix 25.5.

SAE fax no:+46 8 30 69 89

The sponsor must report to the Regulatory Authorities in every country, all SUSARs that are lethal or life threatening within 7 days and any relevant complementary information within another 8 days. All other SUSARs shall be reported within 15 days. Suspect Adverse Reaction Report Form (CIOMS Form I) will be used for submitting reports to the regulatory authorities for registration in EudraVigilance. The sponsor will inform all investigators of SUSAR as they occur. A copy of all SUSARs must be sent to Pierre-Fabre Pharma AB by the sponsor.

The sponsor will perform all safety reports pursuant to applicable laws and regulations as set by the Regulatory Authorities and Ethics Committees in participating countries.

12.10 FOLLOW-UP OF SERIOUS ADVERSE EVENTS

All serious adverse events must be followed-up and recorded. Please use the follow-up part of the form 'Notification of Serious Adverse Event (SAE)', Appendix 25.5., and fax to Clinical Trial Office, Department of oncology, Karolinska University Hospital. The serious adverse events must be followed-up until resolution or stabilisation.

12.11 ANNUAL SAFETY REPORT

Once a year throughout the clinical trial, the sponsor will provide an updated safety report highlighting SAEs and SUSARs to the Regulatory Authorities and Ethics Committees in the respective countries. A copy shall be sent to the local Pierre-Fabre Pharma AB drug safety office.

12.12 TRIAL SAFETY COMMITTEE

The sponsor will designate an independent Trial Safety Committee to be eligible to stop randomisation for safety reasons. It will meet yearly for preparation of a safety report. It will also meet on a need to basis to verify patient eligibility, discuss recruitment rate, discuss methodological aspects and secure Good Clinical practice (GCP). The safety committee may stop the trial prematurely for any of the reasons above.

13 ASSESSMENT OF QUALITY OF LIFE

To assess Quality of Life the EORTC Quality of Life Questionnaire C30 (QLQ-C30) Version 3.0 will be used. The EORTC QLQ questionnaire was designed to be cancer specific, multidimensional in structure, appropriate for self-administration, and applicable across a range of cultural settings. The EORTC QLQ-C30 version 3.0 is the most recent version (http://groups.eortc.be/qol/qlq-c30-development). See Appendix 25.6.

The QLQ-C30 should be filled in and registered prior to treatment start (screening visit), after every second cycle and at the follow-up visit.

14 STATISTICS AND DATA MANAGEMENT

14.1 DATA MANAGEMENT

14.1.1 DATA ENTRY AND DATA VALIDATION

Data collected in the CRFs will be entered into a data base. Data will be extracted from the data base for statistical analysis. Random samples will be checked for consistency between the data base and the CRF and medical records.

14.1.2 CODING

Adverse events on this protocol are graded according to the National Cancer Institute Common Toxicity Criteria version 4.0.

14.2 STATISTICAL ANALYSIS

The study is designed as a phase II screening trial and therefore, for a statistically significant difference in the primary endpoint favouring the experimental arm, the superiority of the experimental combination will be interpreted as a signal of effect. A definitive phase III trial with survival endpoint will be necessary to confirm the results.

14.2.1 OBJECTIVES AND ENDPOINTS

The primary endpoint is to evaluate progression free survival (PFS), defined as the duration from inclusion until confirmed progression (by RECIST) or death. PFS is measured according to RECIST, every 2nd cycle until progression. To be able to detect a 50% increase in median progression-free survival from 5 to 7.5 months – or a hazard ratio of 0.67 - with a one-sided significance level of 10% and with a power of 80% the study needs to generate 110 PFS-events. With an annual entry rate of about 60 patients per year during two years, and with an extra year of follow-up, the required number of events is expected to be observed 3 years after the accrual starts.

The secondary endpoint overall response rate (ORR = CR + PR), is defined as best response within 5 months or until the patient dies or withdraws from the study. ORR is measured according to RECIST, every 2nd cycle until progression.

Overall survival is defined as survival from the date of inclusion until death or last follow-up.

14.2.2 ANALYSES

The primary endpoint PFS will be analysed using survival techniques. Survival curves will be estimated using the method of Kaplan-Meier, and differences in survival times will be tested using the log-rank test. Proportional hazards regression will be used to estimate the effect of treatment on PFS. Both the unadjusted effect – a model with only treatment included – as well as the adjusted effect – a model with the stratification factors as well as treatment included - will be estimated. Results of the analyses will be presented as hazard ratios (HRs) together with confidence intervals.

If the upper limit of a one-sided 10% confidence interval for the hazard ratio (experimental arm versus control arm) in the analysis of PFS is less than 1, the experimental treatment is to be considered for further investigation in a phase III trial with overall survival as primary endpoint.

Differences in the secondary endpoint overall response rate will be tested using Fishers exact test. Both unadjusted and adjusted effects of treatment on ORR will be estimated using unconditional logistic regression and will be presented as odds-ratios together confidence intervals.

Overall survival will be analysed using the same techniques as PFS.

The effect of treatment on QoL will be evaluated using linear mixed models.

Other secondary endpoints will be evaluated by using descriptive methods and statistics. All patients that have received at least one treatment cycle will be included in the safety and QoL analyses.

All analyses of primary and secondary endpoints will be based on the intention-to-treat principle.

The statistical analyses will be performed by the chief investigators, the statisticians and affiliated members.

14.3 RANDOMIZATION AND STRATIFICATION OF SUBJECTS

Patients should be randomized after written informed consent is obtained and all screening assessments have been performed. Centralized randomization will be performed by the Clinical Trial Unit/Department of Oncology, Karolinska University Hospital, Stockholm.

Randomization will based on permuted block technique and stratified on the following factors:

- PS 0 versus PS1
- No visceral metastases versus visceral metastases present

There will be no stratification according to study site.

15 TRANSLATIONAL ANALYSES (OPTIONAL)

In addition to the major objectives of the trial, outlined section 7.1 and 7.2, an optional exploratory translational part of the trial aim to identify presumptive biomarkers, biomarker profiles or therapy induced changes of these markers in blood, plasma and serum that may have predictive value and deserve further evaluation and validation in larger phase III trials.

At Karolinska Hospital (and presumably 3 or 4 more centers) translational research will be performed for patients willing to participate. Consecutive sampling of blood/plasma/serum (20 ml) will be collected at baseline and every 3rd weeks (i.e. prior every treatment cycle). A blood/plasma/serum sample will also be collected 48 hours post treatment in the first treatment cycle.

This biomaterial will be used for analyses such as:

a) Biomarker discovery
   1) Exosome profiling
   2) Proteomics
   3) Circulating Tumor Cells (CTC)

b) Analyses of apoptotic/necrotic induction (M30/M65) (M30 Apoptosense® and M65® ELISA)

16 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will permit study-related monitoring, audits, IEC review and regulatory inspection(s), providing direct access to source data/hospital records. The Investigator verifies that each subject has consented in writing to

direct access to the original source data/hospital records by the use of written patient information and signed Informed Consent.

The data recorded in the CRFs will be controlled for consistency with the source data/hospital records during the monitoring (source data verification). Any discrepancies of data will be documented and explained in the monitoring reports.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 SOURCE DATA

Source data is defined as all information in original records of clinical documentation (or ditto copies) that have been collected during the study.

The patient must have agreed to allow their medical records to be examined by authorised personnel of the sponsor (or thereof affiliated).

17.2 STUDY MONITORING

Representatives for each site will meet the chief investigator prior to including the centre for the study. Every potential centre will be carefully judged based on previous experience, equipment and staff resources in order to fully comply with the protocol requirements and Good Clinical Practice (GCP) guidelines.

The Clinical Trial Unit at the Dept of Oncology, Karolinska University Hospital, Stockholm, will be appointed for monitoring of all centres in Sweden. The Clinical Trial Unit at the Karolinska University Hospital of Stockholm will conduct pre-study site controls, instruct investigators and site personnel about the protocol, study procedures, reporting of outcome and any serious adverse events. The pre-study site controls aim at confirming that the site complies with the requirements as specified in the protocol and GCP guidelines.
National GCP units will monitor in Denmark and Norway.

On site visits may be conducted. This may be undertaken in order to verify that:

- the data are authentic, accurate, and complete;
- safety and rights of subjects are being protected;
- study is conducted in accordance with the currently approved protocol (and any amendments)
- GCP and applicable regulatory requirements are preserved

The investigator consents to allow the CTU/GCP unit direct access to all study related documents.

18 ETHICS

18.1 INDEPENDENT ETHICS COMMITTEE

Approval of the study protocol (including any protocol amendment, patient information and Informed Consent forms) must be obtained from the regional Independent Ethics Committee (IEC) before any subject enters into the study. The written approval from the IEC should be dated and have an attached list of those persons (with name and positions) present at the IEC meeting.

It is the responsibility of the Investigator to report all SUSARs to the IEC. Further the Investigator will report when the study is completed or if the study for any reason stops prematurely.

18.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the protocol, GCP and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions. The data will not identify any subject taking part in the study, in accordance with the EU Data Protection Directive (95/46/EU) and the Law on Personal Data (Personuppgiftslagen (PuL), SFS 1998:204).

All patients in this study have locally advanced or metastatic urothelial carcinoma. Further, the patients have renal impairment, making the patients ineligible, "unfit", for the standard drug of choice, cisplatin. Substitution of cisplatin to carboplatin is a well established treatment strategy, but with tumour response less efficient than with cisplatin; mOS around 8-10 month with carboplatin combinations vs. around 14 month with cisplatin combinations. Thus, there is an urgent need to further improve the overall survival and quality of life for this patient category

The treatment combination of carboplatin and gemcitabine is well established, and can be considered as standard treatment in the unfit patients. Recently, an EORTC phase III trial compared two carboplatin containing treatment combinations (M-CAVI and Carbo/Gem); the tumour response for these two treatment combinations were similar, but concluding that the preferred combination is carboplatin/gemcitabine due to a more tolerable toxicity profile.

Recently, vinflunine has shown significant antitumor activity in urothelial carcinoma and is approved as the first drug improving the median overall survival in second line treatment. Gemcitabine is a drug commonly used in urothelial carcinoma, with known tumour activity both in mono- and combination therapy. The combination of vinflunine and gemcitabine is evaluated in a phase I trial in non-small cell lung cancer, with tolerably toxicity profile and no observed pharmacokinetic interactions. The recommended dose of vinflunine 320 mg/m2 was found in the phase I trial. The dose used in this protocol is lower, 250 or 280 mg/m^2, due to renal impairment. The expected side effects are thus lower than in the phase I trial. As the combination vinflunine and gemcitabine has not yet been tested in patients with urothelial carcinoma, the first ten patients entering the study will be fully monitored regarding all safety parameters. After five and after ten patients respectively, the coordinating principal investigator will decide if the combination is safe and if the study will proceed. There will also be an independent Trial Safety Committee that will meet yearly and will be eligible to stop randomization for safety reasons at any time during the trial.

The combination of vinflunine and gemcitabine has not previously been tested in bladder cancer, but there is a reasonable chance for the patients in the investigational arm to benefit from this treatment regime during the study period.

In spite which treatment arm the patient is treated according to, the drugs in each arm is well used in clinical praxis, well tolerated and with known tumour efficacy in urothelial carcinoma. The combination in the investigational arm, vinflunine/gemcitabine, is not earlier studied in urothelial carcinoma but is promising and of great interest.

The patients will be monitored closely and any adverse events will be followed up. Whenever there is a medication available to prevent or alleviate a symptom, it will be offered to the patient.

The possible advantages the patient will gain from this study outweigh the risks and disadvantages that the patient might experience. Furthermore, the information gained from this study is an important step in developing new treatment regimes in this patient population in great need of new treatment options.

18.3 PATIENT INFORMATION AND INFORMED CONSENT

The subjects should be provided with full and adequate verbal and written information about the objectives, the study outline and possible risks and benefits of participating in the study. The subject have the right to ask questions about the study and should be given adequate time to make the decision to participate in the study or not. The subject should be clearly informed that the data collected in the study will not identify any subject taking part in the study, following the Law in Personal Data and the EU Data Protection Directive.

The subjects should be informed that it is voluntary to participate and that they can withdraw from the study at any time without giving any particular reason. The subjects should further be informed that a decision not to participate in the study or to withdraw will not be questioned or effect their future medical care or treatment at the clinic.

Written Informed Consent must be obtained from all participating subjects before enrolment in the study. The Informed Consent form should also be signed, at the same occasion, by the investigator who gave the written and verbal information. The Informed Consent form should be filed in the Investigator´s File and one copy should be given to the subject. No trial related procedures can take place unless a written informed consent is obtained.

The subjects will consent to: participate in the study; regulatory authorities to gain full access to hospital records, to control the data collected in the study; recording, collecting and processing data and storing data in a database; and storing of study samples in a biobank.

The Informed Consent form and the written patient information are provided in Appendices 25.2 and 25.3, and Appendices 25.4 and 25.5 for the optional Translational part of this study taking place at Karolinska Hospital (and presumably 3 or 4 more centres).

19 DATA HANDLING AND RECORD KEEPING

19.1 CASE REPORT FORMS

An electronic eCRF should be completed for each included subject. The subject´s identity must always be kept confidential. All information in the CRF should be in English. If anything is recorded in a Scandinavian language, the Monitor should translate it to English. The completed original CRF is the sole property of the Investigator and should not be made available to third parties (except for representatives of appropriate authorities).

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs. There will be a common database for all involved countries. It will be situated in Sweden at the Department of Oncology at Karolinska University Hospital.

19.2 RECORD KEEPING

The Investigator shall keep records of the study for 10 years to enable evaluations and inspections by regulatory authorities. This includes any original sours data related to the study, the subject identification list (with subject numbers, full names and addresses) and the original signed Informed Consent, copies of all CRFs.

The subject identification number will be a three digit number where the first digit indicates the clinical study site and the two last digits indicate the subjects number at that specific site (e.g. the first subject included at the Department of Oncology, Karolinska University Hospital will be 101).

20 INSURANCE

Patients included and treated in Sweden will be covered by Läkemedelsförsäkringen via Zurich Insurance, Ireland Limited and Patienförsäkringen via Landstingens Ömsesidiga Försäkringsbolag, LÖF.

Patients treated in other Scandinavian countries will be covered by their national public insurance systems.

21 PUBLICATION POLICY

Data and results from the study belong to the sponsor and principal investigators. Pierre-Fabre has no influence over the analysis, interpretation or publication of results. The results will be presented in a scientific report. All

participating clinicians and their departments should be mentioned in any manuscript or poster, or shown on a slide in connection with lectures. The trial will be public at the EU Clinical Trials Register.

22 SUPPLEMENTS

22.1 CHANGES OF THE STUDY PROTOCOL

All changes of the final study protocol must documented by signed protocol amendments. If substantial changes to the assessments or design of the study are made, the Voluntary Harmonisation Procedure, the Regulatory Authorities and/or the IEC in respective country should be notified for review and approval before the changes take effect.

22.2 APPLICATION TO REGULATORY AUTHORITIES AND ETHICS COMMITTEE

Prior to initiating the clinical study, the Investigator will submit an application for authorisation to conduct the study, including all required documents, to the Voluntary Harmonisation Procedure and the Regulatory Authorities in respective country.

Approval of the study protocol (including any protocol amendment, patient information and Informed Consent forms) must also be obtained from the regional Independent Ethics Committee (IEC) before any subject enters into the study. The written approval from the IEC should be dated and have an attached list of those persons (with name and positions) present at the IEC meeting.

It is the responsibility of the Investigator to report all SUSARs to the Regulatory Authorities and the IEC. Further the Investigator will report when the study is completed or if the study for any reason stops prematurely.

22.3 STAFF INFORMATION

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

The signature and delegation log should be continuously updated and signed by the Investigator.

22.4 CRITERIA FOR TERMINATION OF THE STUDY

The chief investigator has the right to discontinue the study prior to inclusion of the intended numbers of subjects.

The study will be prematurely discontinued in the following cases:

- Unexpectedly high proportion of AEs that are possibly or probably related to the study treatment.
- New findings about the investigational product(s) that changes the benefit/risk ratio.
- Unacceptable low Investigator, Sponsor or subject compliance.
- Critical change in personnel, administrative or scientific standards at the Sponsor or at the study centre.
- Recruitment of eligible subjects is far too low.

22.5 STUDY TIME SCHEDULE

Anticipated start of study: Q 3, 2013
Estimated recruitment period: Q 3, 2013 – Q 1, 2016

23 COORDINATING PRINCIPAL INVESTIGATOR'S AGREEMENT

EudraCT number: 2013-002417-35

Title of the study: A randomized multicenter study of carboplatin/ gemcitabine versus vinflunine/ gemcitabine as first line treatment in patients with metastatic urothelial carcinoma unfit for cisplatin based chemotherapy due to impaired renal function

I, the undersigned, have read and understand the protocol specified above and agree that it contains all necessary information for conducting the study. The study protocol, the Clinical Study Agreement and the additional information given will serve as a basis for co-operation in this study.

I agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable laws and regulations.

Sponsor Anders Ullén. M.D., Ph.D.	_____ Signature _____ Date

24 PRINCIPAL INVESTIGATOR'S AGREEMENT

EudraCT number: 2013-002417-35

Title of the study: A randomized multicenter study of carboplatin/ gemcitabine versus vinflunine/ gemcitabine as first line treatment in patients with metastatic urothelial carcinoma unfit for cisplatin based chemotherapy due to impaired renal function

I, the undersigned, have read and understand the protocol specified above and agree that it contains all necessary information for conducting the study. The study protocol, the Clinical Study Agreement and the additional information given will serve as a basis for co-operation in this study.

I agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable laws and regulations.

Principal Investigator Name:_____ Title:_____ Work Address:_____ _____ _____	_____ Signature _____ Date

25 APPENDICES

25.1 INFORMED CONSENT (IN SWEDISH AND ENGLISH)

25.2 PATIENT INFORMATION SHEET (IN SWEDISH AND ENGLISH)

25.3 INFORMED CONSENT, OPTIONAL TRANSLATIONAL PART (IN SWEDISH AND ENGLISH)

25.4 PATIENT INFORMATION SHEET, OPTIONAL TRANSLATIONAL PART (IN SWEDISH AND ENGLISH)

25.5 NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE)

25.6 EORTC QUALITY OF LIFE QUESTIONNAIRE C30 (QLQ-C30) VERSION 3.0

25.1 APPENDIX: INFORMED CONSENT (IN SWEDISH AND ENGLISH)

”Patientens samtycke till att delta i klinisk prövning”

”En jämförande studie mellan två olika cytostatikabehandlingar för patienter med spridd blåscancer och nedsatt njurfunktion.”

Genom att underteckna denna blankett samtycker jag till att deltaga in den här kliniska studien. Jag har erhållit en kopia av patientinformationen och har fått tillräckligt med muntlig och skriftlig information. Jag har också haft tillräckligt med tid att fundera över mitt deltagande och förstår mina rättigheter.

Jag känner till att mitt deltagande är helt frivilligt och att jag när som helst, utan närmare förklaring, kan avbryta mitt deltagande utan att det påverkar min fortsatta behandling eller mitt omhändertagande på kliniken.

Tystnadsplikt och sekretess enligt Hälso- och sjukvårdslagen gäller för samtliga uppgifter som lämnas. Insamlade uppgifter kommer att avidentifieras. Jag samtycker även till att berörd personal från myndigheter i och utanför EU samt en så kallad monitor får jämföra de i studien rapporterade uppgifterna med dem som finns i min patientjournal. Detta får ske under förbehåll av att den information som då blir tillgänglig inte förs vidare.

Jag kan när som helst meddela, muntligt eller skriftligt, att jag inte önskar fortsätta mitt deltagande i studien.

…….. ……
Patientens namnteckning Datum

…….
Patientens namnförtydligande

Informerade läkarens försäkran:

Jag har muntligen gått igenom och förklarat studiens syfte för patienten. Patienten har haft möjlighet att ställa frågor och fått dem grundligt besvarade. Patienten har även erhållit ett exemplar av patientinformationen.

…….. ……
Läkarens namnteckning Datum

…….
Läkarens namnförtydligande

Samtycket skall arkiveras av ansvarig läkare i Investigator’s File, Onkologiska kliniken, Karolinska Universitetssjukhuset Solna, SE-171 76 Stockholm, Sverige.

"The patient's consent to participate in clinical trials"

"A comparative study between two different chemotherapy treatments for patients with metastatic bladder cancer and renal impairment."

By signing this form, I agree to participate in this clinical study. I have received a copy of the patient information sheet and have received sufficient oral and written information. I've also had enough time to think about my participation and understand my rights.

I am aware that my participation is voluntary and that I, at any time, without explanation, may cancel my participation without prejudice to my future treatment or care in my clinic.

Confidentiality and privacy of healthcare law applies to all information submitted. Collected data will be made anonymous. I also agree that the relevant officials from authorities in and outside the EU, and so-called monitors can compare the data reported in this study with those found in my medical records. This may occur with the reservation that the information that becomes available not is passed on.

I can at any time communicate, orally or in writing, that I wish to stop continue my participation in the study.

…… ……
The patients signature Date

…….
The patient's name clearly

Informed doctor's declaration:

I've gone through and verbally explained the study's purpose for the patient. The patient has had an opportunity to ask questions and have them answered thoroughly. The patient also received a copy of the patient information sheet.

…… ……
The physician's signature Date

…….
The physician’s signature

The consent shall be filed by the responsible physician in Investigator's File, Department of Oncology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden.

25.2 APPENDIX: PATIENT INFORMATION SHEET (IN SWEDISH AND ENGLISH)

Information sheet to patients (in Swedish, 3 pages)

”Studie av två olika cytostatikabehandlingar för patienter med spridd blåscancer och nedsatt njurfunktion.”

Bakgrund
Cancer i urinvägarna är den sjunde vanligaste cancerformen i Sverige, med ca 2700 fall per år. Om sjukdomen sprider sig utanför urinblåsan är det vanligtvis till lymfkörtlar inne i buken, till lever, lungorna eller skelettet. Blåscancer är oftast känslig för cytostatika (cellgifter) och förstahandsval av behandling vid spridd blåscancer är en kombinationsbehandling av olika cytostatika, varav det mest verksamma heter Cisplatin.

Upp till så mycket som 50 % av patienter med blåscancer har en försämrad funktion av njurarna, ofta till följd av cancersjukdomen i sig. Vid försämrad njurfunktion kan man inte använda cellgiftet Cisplatin, då det kan vara skadligt för njurarna. Standardbehandlingen är då en annan cytostatikakombination bestående av Carboplatin och Gemzar.

Ett nytt cytostatika, Javlor, har nyligen visat sig effektivt mot spridd blåscancer och ges för närvarande som andrahandsbehandling efter standardbehandlingen med Cisplatin- eller Carboplatin-kombinationer. Javlor i kombination med Gemzar är prövat hos patienter med spridd lungcancer och tolererades väl. Javlor i kombination med Gemzar är ännu inte prövat vid spridd blåscancer

Syfte med studien
Syftet med denna studie är att jämföra kombinationen Javlor och Gemzar med standardbehandlingen Carboplatin och Gemzar som förstahandsbehandling hos patienter med spridd blåscancer och nedsatt njurfunktion. I första hand kommer behandlingseffekten av de två olika behandlingsalternativen att studeras, men även biverkningar och livskvalitet kommer att utvärderas noga.

Hur går studien till?
130 patienter från de Nordiska länderna kommer att delta i studien. Hälften av studiedeltagarna lottas till försöksarmen och hälften till kontrollarmen. Oavsett vilken arm du lottas till erhåller du alltså behandling med cytostatika som har bevisad effekt vid blåscancer. Varken Din läkare eller någon annan kan påverka vilken behandlingsarm som Du kommer att lottas till. All behandling ges som intravenös infusion (dropp). De doser som används av de olika cellgifterna är standarddoser för respektive läkemedel.

I försöksarmen ges en kombinationsbehandling med Javlor och Gemzar dag 1 (tidsåtgång ca 20 + 30 min) samt att Gemzar ges ytterligare en gång efter en vecka (tidsåtgång ca 30 min). Denna behandlingscykel upprepas var tredje vecka.

I kontrollarmen ges en kombinationsbehandling med Carboplatin och Gemzar dag 1 (tidsåtgång ca 60 + 30 min) samt att Gemzar ges ytterligare en gång efter en vecka (tidsåtgång ca 30 min). Denna behandlingscykel upprepas var tredje vecka.

Vad innebär studien för Dig?
Om Du bestämmer Dig för att delta i studien kommer Du få träffa en läkare och undersökas för att ta reda på om Du uppfyller de kriterier som behövs för att kunna gå med i studien. Du får lämna blodprover och genomgå EKG och datortomografi (CT).

Inför varje cytostatikabehandling kommer blodprover tas för att kontrollera Dina blodvärden, Din saltbalans och funktionen i Dina njurar och lever. På behandlingsdagarna kommer Du få förebyggande läkemedel mot t.ex. illamående och förstoppning enligt väl beprövade kliniska rutiner. Deltagande i studien innebär lika många

läkarbesök, blodprovstillfällen och röntgenundersökningar som om du skulle få sedvanlig standardbehandling utanför studien.

Behandlingen kan fortsätta så länge den är effektiv mot Din tumörsjukdom. Din läkare kan avbryta behandlingen på grund av biverkningar, om Ditt sjukdomstillstånd försämras eller om ny information om behandlingen skulle uppkomma där man konstaterar att behandlingen inte är effektiv eller säker. Du kan också välja att avbryta Ditt deltagande av annan orsak.

Utvärdering av behandlingen
Utvärdering av Din behandling görs vid läkarbesöken, via blodprov och med hjälp av röntgenundersökningar. En datortomografi görs innan behandlingen påbörjas och efter varannan behandlingscykel under hela behandlingstiden. Utvärdering av biverkningar sker fortlöpande vid samtliga läkarbesök och sjuksköterskekontakter. Utvärdering av Din livskvalitet görs med hjälp av ett standardiserat livskvalitetformulär som fylls i innan behandlingen påbörjas, efter varannan behandlingscykel och efter behandlingen avslutats.

Potentiella risker och obehag
De cytostatika som används i denna studie kan liksom många andra cytostatika påverka benmärgen med minskat bildande av blodkroppar som följd. Om antalet vita blodkroppar minskar kan Du bli mer känslig för infektioner. Om antalet blodplättar minskar kan en ökad blödningsbenägenhet uppträda. Får Du feber, en blödning eller blåmärken skall Du omedelbart kontakta Din läkare för bedömning och kontroll av Dina blodvärden. Antibiotika och inläggning på sjukhus kan behövas vid feber.

Andra vanliga biverkningar av behandling med kombinationen Javlor + Gemzar är exempelvis illamående, förstoppning, magsmärta, slemhinnepåverkan i munnen och trötthet. Andra vanliga biverkningar av kombinationen Carboplatin + Gemzar är exempelvis illamående, trötthet och njurpåverkan (ovanligt).

Om man blir gravid under en cellgiftsbehandling kan det finnas risker för fostret. Om Du är i fertil ålder måste Du använda ett säkert preventivmedel. Detta gäller både män och kvinnor. Som kvinna kan Du använda antingen spiral eller någon form av hormonbehandling (p-piller, p-stav, p-spruta eller plåster). Män skall använda kondom samt att en kvinnlig partner skall använda spiral eller någon form av hormonbehandling. Du bör använda en säker preventivmetod från 2 månader innan påbörjandet av cellgifter till 6 månader efter avslutandet av cellgifter.

Om Du önskar tilläggsinformation om riskerna och biverkningarna i denna studie, kontakta Din behandlande läkare.

Finns det några fördelar?
De studiedeltagare som lottats till kontrollarmen (Carboplatin + Gemzar) erhåller den vedertagna behandlingen för spridd blåscancer hos patienter som har en nedsatt njurfunktion. De studiedeltagare som lottats till försöksarmen erhåller två olika cellgifter, Javlor och Gemzar, som var för sig har en bevisad effekt mot spridd blåscancer och var för sig är väl tolererat vid försämrad njurfunktion. Behandlingseffekten för kombinationsbehandlingen med Javlor + Gemzar är okänd vid spridd blåscancer men torde kunna ge en behandlingseffekt som är lika bra eller bättre än standardbehandlingen. Behandlingseffekten i försöksarmen är dock ännu okänd och studien syftar till att utforska denna behandlingseffekt.

Hantering av data och sekretess
All insamlad information samt material kommer att avidentifieras och kodas för att inte någon obehörig personal skall kunna sammankoppla analyssvaren direkt med Dig. Uppgifterna är sekretesskyddade och ingen obehörig har tillgång till dessa. I samband med läkemedelsstudier förs vanlig patientjournal. De uppgifter som insamlas om Dig kommer att överföras till speciella dataformulär. Dessa kommer att kontrolleras gentemot din patientjournal för att säkerställa att de uppgifter som införts på patientformulären överensstämmer med uppgifterna i Din patientjournal. Denna kontroll görs av en speciellt utbildad så kallad monitor som har tystnadsplikt. Patientformulären märks med en unik kod. Det är Din behandlande läkare som har ansvar för kodningen och har tillgång till ”kodnyckeln” som förvaras på kliniken.

Medgivande för studiedeltagande omfattar att Du godkänner att Läkemedelsverket i Sverige eller annan samarbetspartner i studien (exempelvis monitor) får granska Din patientjournal för att insamla studierelevant information och verifiera det som rapporterats in av studieansvariga.

Resultaten från studien kommer att publiceras i en vetenskaplig rapport men utan att Din identitet kommer att framgå.

Dina medicinska uppgifter kommer att behandlas konfidentiellt i enlighet med sekretesslagen. Personuppgifter behandlas enligt personuppgiftslagen (PUL) 1998:204. För denna studie är Karolinska Universitetssjukhuset Personuppgiftsansvarig. I enlighet med biobankslagen har du rätt att begära att ditt samtycke för tagna prover skall återtas. I så fall slängs (destrueras) dina insamla prover för denna studie. Du har rätt att kostnadsfritt en gång per år skriftligen begära information om Dina insamlade personuppgifter samt begära rättelse av eventuella felaktiga uppgifter.

Försäkring, ersättning
Precis som inom sjukvården för övrigt omfattas du av Läkemedelsförsäkringen samt Patientförsäkringen. Ingen ersättning utgår till studiedeltagarna.

Deltagande och avbrytande av studien
Studiedeltagande är helt frivilligt. Du har också rätt, att när som helst meddela, utan särskild förklaring, muntligen eller skriftligen, om du önskar avbryta din medverkan i studien. Om du väljer att inte delta eller senare önskar avbryta din medverkan i studien kommer detta på inget sätt att påverka din fortsatta behandling eller vidare bemötande.

Ansvariga
Om du har några frågor om studien är Du alltid välkommen att fråga oss på kliniken:

Namn (läkare):_____Tel:_____

Namn (forksningssjuksköterska): _____ Tel: _____

Om Du vill deltaga, ber vi Dig signera bladet ”Patientens samtycke till att delta i klinisk prövning”

Information sheet to patients (in English, 3 pages)

"A comparative study between two different chemotherapy treatments for patients with metastatic bladder cancer and renal impairment."

Background
Cancer of the urinary tract is the seventh most common cancer in Sweden, with about 2,700 cases per year. If the disease has spread outside the bladder, it is usually to lymph nodes in the abdomen, to the liver, lungs or bones. Bladder cancer is usually sensitive to chemotherapy (chemo) and the treatment of choice for spread bladder cancer is usually a combination of different chemotherapy drugs, of which the most active is called Cisplatin.

Up to as much as 50% of patients with bladder cancer have a decreased function of the kidneys, often as a result of the cancer disease itself. If the renal function is impaired the chemotherapy Cisplatin can't be used, due to its nephrotoxic effect. The standard treatment is then another chemotherapy combination consisting of Carboplatin and Gemzar.

A new chemotherapy, Javlor, has recently proved effective against disseminated bladder cancer and is currently provided as a second-line treatment after standard therapy with Cisplatin or Carboplatin combinations. Javlor in combination with Gemzar is tested in patients with metastatic lung cancer and was well tolerated. Javlor in combination with Gemzar is not yet tested on spread bladder cancer.

Aim of the study
The purpose of this study is to compare the combination Javlor and Gemzar with standard treatment Carboplatin and Gemzar as first-line treatment in patients with metastatic bladder cancer and renal impairment. The main aim is to evaluate the treatment effect of the two different treatments studied in the trial, but also the side effects and quality of life will be carefully evaluated**.**

Study design
130 patients from the Nordic countries will participate in the study. Half of the study participants are randomly allocated to the experimental arm and half to the control arm. No matter which arm You are randomly allocated to receive, You will receive chemotherapy that has proven efficacy in bladder cancer. Neither Your physician nor anyone else can influence the treatment arm that you will be raffled for. All treatment is given as an intravenous infusion (drip). The doses used by the different chemotherapy are standard doses of each medicine.

In the experimental arm the combination of Javlor and Gemzar is given on Day 1 (time approx 20 + 30 min) and Gemzar is administered again after a week (time approx 30 min). This treatment cycle is repeated every three weeks.

In the control arm the combination of Carboplatin and Gemzar is given on Day 1 (time approx 60 + 30 min) and Gemzar is administered again after a week (time approx 30 min). This treatment cycle is repeated every three weeks.

What is required of you?
If You decide to participate in the study You will get to see a doctor and be examined to find out if You meet the criteria required to join the study. You will have blood tests taken and undergo electrocardiography and computed tomography (CT).

Prior to each chemotherapy treatment, blood samples will be taken to check Your blood counts, Your salt balance and the function of Your kidneys and liver. On treatment days, You get preventive medicine against nausea and constipation according to well proven clinical procedures.
Participation in the study involves as many doctor visits, blood tests and imaging tests that You would go through if You received the usual standard treatment outside the study.

Treatment may be continued as long as it is effective against Your tumor disease. Your doctor may stop the treatment because of side effects, if Your disease condition worsens or if new information on the treatment would arise where it is observed that the treatment is not effective or safe. You can also choose to suspend your participation for other reasons.

Evaluation of treatment
Evaluation of Your treatment is done at clinical visits, blood tests, and with x-ray examinations. A computer scan is done before the treatment starts and after every second treatment cycle. Assessment of adverse reactions is done continuous at all doctor visits and nursing contacts. Evaluation of the Quality of your life is done using a standardized quality of life questionnaire to be filled in before the treatment starts, after every second treatment cycle and after the treatment is completed.

Potential risks and discomforts
The chemotherapy used in this study, like many other chemotherapy drugs can affect the bone marrow with reduced formation of blood cells as a result. If the number of white blood cells decreases, You may be more susceptible to infections. If the platelet count decreases, increased risk of bleeding may occur. If You experience fever, bleeding or bruising You should immediately contact Your doctor for evaluation and control of Your blood. Antibiotics and hospitalization may be needed.

Other common side effects of the treatment with the combination Javlor + Gemzar include nausea, constipation, abdominal pain, ulcers in the mucous membranes of the mouth and fatigue. Other common side effects of the combination of Carboplatin + Gemzar include nausea, fatigue, and renal dysfunction (uncommon).

If You become pregnant during the treatment with chemotherapy there is a risk to harm the fetus. If You are of childbearing potential, You must use an adequate contraception method. This applies to both men and women. As a woman, You can use either intrauterine devices or some form of hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release). Men should use condoms and a female partner must use either intrauterine devices or some form of hormonal contraceptives as described above. You should use a reliable method of contraception from 2 months before the start of chemotherapy to 6 months after completion of chemotherapy.

If you would like additional information about risks and side effects in this study, contact your doctor.

Are there any advantages to participate?
The study participants who are randomly assigned to the control arm (Carboplatin + Gemzar) will receive the conventional treatment for disseminated bladder cancer in patients who have renal impairment. The study participants who are randomly assigned to the experimental arm will receive two different chemotherapy, Javlor and Gemzar, each of which on its own have a proven efficacy against disseminated bladder cancer and are each well tolerated in patients with renal impairment. The treatment effect of the combination treatment with Javlor + Gemzar is unknown at disseminated bladder cancer, but would likely be able to provide a therapeutic effect that is as good as or better than the standard treatment combination in the control arm. The treatment effect in the experimental arm, however, is still unknown and the study aims to explore the treatment effect.

Handling of data and confidentiality
All collected information and materials will be made anonymous and coded to avoid any unauthorized personnel to link the analytical results directly with You. The information is confidential and no unauthorized person has access to them. In the context of drug studies regular health records are conducted. Information collected about You will be transferred to special data forms. These will be checked against Your medical records to ensure that the information entered on the patient forms is in accordance with the information in Your health record. This verification is done by

a specially trained so-called monitor who is sworn to secrecy. Patient forms are labeled with a unique code. It is Your doctor, who is responsible for the coding and has access to the "key code" held at the clinic.

Consent for study participation includes Your acceptance that the Medical Products Agency in Sweden or another partner in the study (e.g. monitor) may review Your medical records to collect study relevant information and verify what has been reported by the study managers.

The results of this trial will be published in a scientific report but without Your identity to be evident.

Your medical information will be treated confidentially in accordance with the Official Secrets Act. Personal data are processed according to the Personal Data Act (PUL) 1998:204. For this study, Karolinska University Hospital is responsible for the personal data. In accordance with the Biobank Act, You are entitled to request that your consent for samples taken shall be withdrawn. In that case, Your collect samples for this study will be discarded (destroyed). You have the right, once a year, to free of charge request information about Your personal data collected and to request correction of any inaccuracies.

Insurance, compensation
Just as in general healthcare You are covered by the Medical Insurance and Patient insurance. No compensation is paid to the study participants.

Participation and study discontinuation
To participate in the trial is entirely voluntary. You also have the right, at any time to communicate, without specific explanation, orally or in writing, if You wish to cancel your participation in the study. If You choose not to participate or later wish to discontinue Your participation in the study, this will in no way affect Your future treatment at the clinic.

If You have any questions about the study, You are always welcome to ask us at the clinic:

Name (physician):_____Phone:_____

Name (research nurse): _____ Phone: _____

If You wish to participate, we ask You to sign the sheet, "The patient's consent to participate in clinical trials"

25.3 APPENDIX: INFORMED CONSENT, OPTIONAL TRANSLATIONAL PART (IN SWEDISH AND ENGLISH)

”Patientens samtycke till att delta i klinisk prövning”

”Patientens samtycke till att lämna extra blodprover för biomarkörstudien – en frivillig tilläggsstudie till huvudstudien”

Informationen om att lämna extra blodprov för så kallad biomarkörstudier har jag fått dels av min läkare och dels genom den skriftliga patientinformationen. Jag känner till att mitt deltagande till detta är helt frivilligt och att jag när som helst utan närmare förklaring kan avbryta mitt deltagande. Detta kommer inte att påverka mitt framtida omhändertagande negativt.

Jag har fått en kopia av detta medgivandeformulär att behålla.

Härmed samtycker jag genom att signera nedan till att lämna extra blodprov för så kallad biomarkörstudier dvs. att studier av proteiner, gener eller andra molekyler som kan visa/indikera om man som enskild patient har en sjukdom som är mer eller mindre känslig för behandlingen.

…… ……
Patientens namnteckning Datum

……
Patientens namnförtydligande

Informerade läkarens försäkran:

Jag har muntligen gått igenom och förklarat studiens syfte för patienten. Patienten har haft möjlighet att ställa frågor och fått dem grundligt besvarade. Patienten har även erhållit ett exemplar av patientinformationen.

…… ……
Läkarens namnteckning Datum

……
Läkarens namnförtydligande

Samtycket skall arkiveras av ansvarig läkare i Investigator’s File, Onkologiska kliniken, Karolinska Universitetssjukhuset Solna, SE-171 76 Stockholm, Sverige.

"The patient's consent to participate in clinical trials"

"The patient's consent to Analysis of biomarkers - a voluntary supplementary study to the main study"

I have got information about leaving extra blood test for analysis of biomarkers, both from my doctor and through the written patient information. I am aware that my participation is completely voluntary and that I at any time without explanation can cancel my participation. This will not affect my future treatment or care in my clinic.

I have received a copy of this consent form to keep.

I hereby consent by signing below to submit additional blood test for analysis of biomarkers i.e. study of proteins, genes, or other molecules that can show / indicate if you as an individual patient has a disease that is more or less sensitive to treatment.

…….. ……
The patient's signature Date

…….
The patient's name clearly

Informed doctor's declaration:

I've gone through and verbally explained the study's purpose for the patient. The patient has had an opportunity to ask questions and have them answered thoroughly. The patient also received a copy of the patient information sheet.

…….. ……
The physician's signature Date

…….
The physician’s signature

The consent shall be filed by the responsible physician in Investigator's File, Department of Oncology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden.

25.4 APPENDIX: PATIENT INFORMATION SHEET, OPTIONAL TRANSLATIONAL PART (IN SWEDISH AND ENGLISH)

Information sheet to patients (in Swedish, 1 page)

”Tilläggsstudie – analys av biomarkörer”

Syfte med studien
Till huvudstudien “Studie av två olika cytostatikabehandlingar för patienter med spridd blåscancer och nedsatt njurfunktion.” finns en frivillig tilläggsstudie med syfte att undersöka om det i blodet finns proteiner, gener eller andra molekyler som kan visa om man som enskild patient har en tumörsjukdom som är mer eller mindre känslig för cytostatikabehandlingen, en så kallad biomarkörstudie. I studien samlas blodprover regelbundet, med syfte att i efterhand studera om det finns proteiner eller andra molekyler som kan avslöja om en enskild patient kan ha nytta av de givna behandlingarna eller inte.

Hur går studien till?
Vi önskar för detta ändamål ta ett extra blodprov på 20 ml (ca 4 teskedar) inför varje ny behandling (var 3:e vecka). Ett extra blodprov (20 ml) kommer också att tas 48 timmar efter första behandlingen.

Hantering av data och sekretess
Proverna lagras i en biobank på Karolinska Universitetssjukhuset, Stockholm, men kan komma att skickas till EU-land, USA och/ eller tredje land för analys. Proverna kommer att förvaras kodade, vilket innebär att de inte direkt kan härledas till dig som person. Proverna liksom en tillhörande identifieringslista (kodnyckel) förvaras på ett säkert sätt och åtskilda. Proverna kommer att sparas efter avslutad studie, men får endast användas på det sätt som du givit ditt samtycke till och kan endast bli aktuella för ett nytt forskningsprojekt efter det att du lämnat ett nytt samtycke och/eller godkännande skett från Etikprövningsnämnden. Du har full rätt att utan närmare förklaring begära att dina prover skall förstöras eller avidentifieras (dvs. de kan inte spåras till din person). Biobankslagen (SFS 2002:297)

Deltagande och avbrytande av studien
Studiedeltagande är helt frivilligt. Du har också rätt, att när som helst meddela, utan särskild förklaring, muntligen eller skriftligen, om du önskar avbryta din medverkan i studien. Om du väljer att inte delta eller senare önskar avbryta din medverkan i studien kommer detta på inget sätt att påverka din fortsatta behandling eller vidare bemötande.

Ansvariga
Om du har några frågor om studien är Du alltid välkommen att fråga oss på kliniken:

Namn (läkare):_____Tel:_____

Namn (forksningssjuksköterska): _____ Tel: _____

Om Du vill deltaga, ber vi Dig signera bladet ”Patientens samtycke till att delta i klinisk prövning

Information sheet to patients (in English, 1 page)

"Supplementary Study - Analysis of biomarkers"

Aim of the study
In addition to the main study, "Study of two different chemotherapy treatments for patients with metastatic bladder cancer and renal impairment." there is a voluntary supplementary study with the aim to examine if there are proteins, genes or other molecules in the blood that can show if individual patients have tumors that are more or less sensitive to chemotherapy, a so called biomarker study. The blood samples will be collected with regular intervals, with the aim to retrospectively examine whether there are proteins or other molecules that can reveal whether an individual patient may benefit from the given treatment or not.

Study design
We wish for this purpose to collect an extra blood sample of 20 ml (about 4 teaspoons) before each treatment (every 3 weeks). An additional blood sample (20 ml) will also be taken 48 hours after the first treatment.

Handling of data and confidentiality
The samples will be stored in a biobank at Karolinska University Hospital, Stockholm, but may be sent to European countries, the United States and / or third countries for analysis. The samples will be stored encrypted, which means that they can't be directly traced to You as a person. The samples, as well as an associated identification list (Passkey) will be stored safely and separately. The samples will be kept after the completion of the study, but may only be used in the way You have given Your consent and may only be relevant for a new research project after You made a new consent and / or approval has been obtained from the Ethics Committee. You have the right to without explanation request Your samples will be destroyed or made anonymous (i.e. they can´t be traced to Your person). Biobank Act (SFS 2002:297)

Participation and study discontinuation
To participate in the trial is entirely voluntary. You also have the right, at any time to communicate, without specific explanation, orally or in writing, if You wish to cancel Your participation in the study. If You choose not to participate or later wish to discontinue Your participation in the study, this will in no way affect Your future treatment or care at the clinic.

If You have any questions about the study, You are always welcome to ask us at the clinic:

Name (physician):_____Phone:_____

Name (research nurse): _____ Phone: _____

If You wish to participate, we ask You to sign the sheet, "The patient's consent to participate in clinical trials"

25.5 NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE)

For the Sponsor	Received (date/signature):	SAE no:
NUCOG 1-VINGEM	**Serious Adverse Event**	
Patient number ☐☐☐	**Patient age:** **Patient sex: male** ☐ **female** ☐	**Center:**

FAX THE SAE REPORT WITHIN 24 HOURS TO: +46 8 30 69 89

Investigator name	Type of report: Initial ☐ Follow up ☐	
Treatment arm	☐ Arm I: vinflunine and gemcitabine ☐ Arm II: carboplatin and gemcitabine	Date of onset of SAE ☐☐-☐☐-☐☐☐☐
Date of last dose of vinflunine ☐☐-☐☐-☐☐☐☐	Date of last dose of gemcitabine ☐☐-☐☐-☐☐☐☐	
Date of last dose of carboplatin ☐☐-☐☐-☐☐☐☐		

Reason for considering the event serious: Fatal ☐ Life-threatening ☐
Hospitalization/prolonged hospital stay ☐ Disabling/incapacitating ☐
Associated with congenital abnormality ☐ Other event ☐ specify: _____

Diagnosis/description of event:

.....

Type of toxicity: ..... CTCAE Grade1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Relation to vinflunine (only arm I): Not related ☐ Unlikely ☐ Probable ☐ Certain ☐

Relation to carboplatin (only arm II): Not related ☐ Unlikely ☐ Probable ☐ Certain ☐

Relation to gemcitabine: Not related ☐ Unlikely ☐ Probable ☐ Certain ☐

Action taken regarding vinflunine (only arm I): None ☐ Discontinued ☐ Dose reduction ☐ Delayed ☐ Reduction of infusion rate ☐

Action taken regarding carboplatin (only arm II): None ☐ Discontinued ☐ Dose reduction ☐ Delayed ☐ Reduction of infusion rate ☐

Action taken regarding gemcitabine: None ☐ Discontinued ☐ Dose reduction ☐ Delayed ☐ Reduction of infusion rate ☐

Names and doses of drug(s) given to treat the SAE:

.....

Other actions to treat the event: No ☐ Yes ☐

Describe:

Outcome Recovered ☐ Recovered with sequelae ☐ Ongoing ☐ Unknown ☐

Dead ☐ Date of outcome/death: ☐☐-☐☐-☐☐☐☐

Signature of person completing the form Date ☐☐-☐☐-☐☐☐☐

Investigator's signature Date ☐☐-☐☐-☐☐☐☐

All dates as ddmmyyyy CTO, Oncology Clinic, Karolinska University Hospital VINGEM SAE-form, version 1.0, 28.05.2013

25.6 APPENDIX: EORTC QUALITY OF LIFE QUESTIONNAIRE C30 (QLQ-C30) VERSION 3.0

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: bbbb
Your birthdate (Day, Month, Year): cececdde
Today's date (Day, Month, Year): 31 cececdde

		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**
Have you had diarrhea?	1	2	3	4
Were you tired?	1	2	3	4
Did pain interfere with your daily activities?	1	2	3	4
Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
Did you feel tense?	1	2	3	4
Did you worry?	1	2	3	4
Did you feel irritable?	1	2	3	4
Did you feel depressed?	1	2	3	4
Have you had difficulty remembering things?	1	2	3	4
Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent