

CLINICAL STUDY PROTOCOL: VINSOR (NUCOG III)

An Exploratory Phase I Study with Sorafenib in Addition to Vinflunine in Progressive Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract

EudraCT Number: 2011-004289-14

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All information in this protocol is confidential.

SYNOPSIS

Study title:	An Exploratory Phase I Study with Sorafenib in Addition to Vinflunine in Progressive Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract
Objectives:	- To explore the safety of sorafenib in combination with vinflunine in patients with transitional cell carcinoma of the urothelial tract - To correlate early dual tracer ¹⁸F-FDG-PET/CT functional imaging readouts with standard RECIST evaluations with the intention to explore new endpoints for targeted therapy - To find predictive tumour tissue biomarkers for sorafenib/vinflunine treatment - To evaluate serum and urine markers of apoptosis as potential markers of sorafenib/vinflunine treatment
Methodology:	An explorative translational phase I study
Number of patients:	18 to 36 evaluable patients
Rationale/Goal:	To evaluate the tolerability and activity of sorafenib combined with vinflunine in patients with advanced or metastatic urothelial cancer. Tumour biopsies will be collected before and after one cycle of therapy. The translational part of this study aims to explore the predictive value of a number of biomarkers related to the targeted properties of sorafenib and presumptive markers for vinflunine treatment. In addition, the predictive value of an early functional imaging dual tracer ¹⁸F-FDG-PET/CT will be evaluated.

Selection criteria:	<i>Inclusion criteria:</i> <u>Patients with:</u> - signed informed consent; - histologically confirmed transitional cell (pure or mixed histology including transitional cell carcinoma are allowed) carcinoma of the urothelial tract; - patients who have received neoadjuvant or adjuvant platinum-containing chemotherapy and who have a maximal interval of 6 months between the completion of systemic therapies and the diagnosis of locoregional recurrent or metastatic disease, are eligible <u>or</u> - patients who have received palliative platinum-containing chemotherapy and have a documented progression within 6 months since completion of systemic therapy, are eligible <u>or</u> - patients who have contraindication to platinum-containing chemotherapy; - previous systemic chemotherapy must have been stopped 14 days before the inclusion with full recovery from any related toxicity; - measurable and/or non-measurable disease using RECIST and defined as: . <u>Measurable disease</u>: 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. . <u>Non-measurable disease</u>: lesions which have not been previously irradiated, or 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; - age 18 up to 80 years; - ECOG / WHO Performance Status (PS) ≤ 1; - haematological function: - haemoglobin ≥ 100 g/L - absolute neutrophil count $\geq 1.0 \times LL$ (lower limit of normal value) - platelets $\geq 100 \times 10^9$ /L; - hepatic function: - bilirubin $< 1.5 \times N^*$, - transaminases $< 2.5 \times N^*$ *N = upper limit of normal value - renal function: - creatinine clearance ≥ 40 ml/min (measured by either iohexol clearance or Cr-EDTA technique);
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	- ECG (12 lead) with corrected QT interval (QTc) <480 ms; - Clinically normal cardiac function based on ejection fraction (LVEF assessed by MUGA or ECHO, LVEF ≥ 40%); - able to swallow and retain oral medication; - no presence of asthenia, hand-foot skin reaction or rash greater than grade 1 (NCI CTCAE version 3.0) at enrolment; - no known or suspected allergy to the investigational agent or any agents given in association with this trial; Exclusion criteria: <u>Patients with:</u> - non-transitional cell carcinoma of the urothelial tract (e.g. pure adenocarcinoma or squamous cell carcinoma); - prior treatment with vinflunine; - diagnosed brain metastases or leptomeningeal involvement. Brain CT-scans or MRI are not required unless there is clinical suspicion of central nervous system involvement. - peripheral neuropathy ≥G3 (grade 3) according to NCI CTCAE version 3.0; - history of serious or concurrent illness or uncontrolled medical disorder; any medical condition that might be aggravated by treatment or which could not be controlled: . active infection requiring antibiotics within 2 weeks before the study inclusion, . unstable diabetes mellitus, . uncontrolled hypercalcaemia >2.9 mmol/L (or >G2 NCI CTCAE v3.0), . concurrent congestive heart failure NYHA (class III-IV) or patients with unstable angina pectoris, patients with myocardial infarction within 6 months and/or poorly controlled hypertension will be excluded, . cardiac arrhythmias requiring anti-arrhythmics (excluding beta-blockers or digoxin for chronic atrial fibrillation); - patients having received more than one previous systemic chemotherapy for advanced or metastatic disease; - patients who have received any other investigational or anti-cancer therapy 14 days before the inclusion; - other malignancies, except adequately treated basal carcinoma of the skin or <i>in-situ</i> 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; - pregnant or lactating women; - men or women of childbearing potential not employing adequate contraception; - any psychological, familial, sociological, or geographical condition which does not permit protocol compliance and medical follow-up. - poorly controlled hypertension. At baseline, blood pressure >150/90 is defined as poorly controlled. - renal dysfunction: creatinine clearance <40 ml/min measured by
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	either iohexol clearance or Cr-EDTA technique. - ECOG / WHO Performance Status ≥ 2 - presence of hand-foot skin reaction or rash > grade 1 at enrolment; - known or suspected allergy to the investigational agent or any agents given in association with this trial;
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Design:	This is an exploratory phase I study evaluating the combined treatment of sorafenib and vinflunine in advanced urothelial tract cancer. A fixed dose of vinflunine per square meter is administered to all patients according to the clinical guidelines for vinflunine treatment. Sorafenib will be administered twice daily and escalated in dose steps. Three patients are to be treated at each dose level sequentially. Patients will be evaluated for toxicity weekly during cycle 1 and thereafter every third week. If no patient has experienced a DLT (see definition of DLT) until the end of week 9, sorafenib will be escalated to the next dose level. If 1 patient has a DLT, 3 additional patients will be enrolled at that dose level. If no or one of the additional patients have a DLT until the end of week 9, then the sorafenib dose will be increased to the next dose step for the following patients. If two or more of the additional patients have a DLT (i.e. 3 or more of 6 patients), then this dose level will be deemed too toxic and an additional 3 patients will be accrued to the prior dose level if only 3 patients had been enrolled at this dose. If none or one patient has a DLT at that level, MTD will have been determined. If 2 of 3 patients have a DLT, this dose level will be deemed too toxic and the process will be repeated at the next lower dose level. However, if this is the initial dose step of sorafenib (i.e. sorafenib 200 mg P.O. b.i.d.), no further patients will be recruited in this vinflunine dose group. The study may however continue in the other vinflunine dose group until MTD has been determined. The two vinflunine dose groups are evaluated and dose escalated independently of each other. If at the highest planned dose level for sorafenib, no DLTs are seen, then this level will be declared the MTD for the purpose of selecting a Phase II dose (RPTD). A maximum of 6 patients can be accrued at each dose level. Therefore, the maximum total accrual is 36 patients (18 per vinflunine dose group).
Dose Limiting Toxicity (DLT)	Adverse events on this protocol are graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. A DLT is defined as any of the following: <u>Haematological toxicity</u> - i/ grade ≥ 4 neutropenia (absolute neutrophil count $<0.5 \times 10^9$ for ≥ 7 days or $<0.1 \times 10^9$ for ≥ 3 days), - ii/ febrile neutropenia of grade ≥ 3 (absolute neutrophil count $<1.0 \times 10^9$ and temperature $\geq 38.5^\circ\text{C}$) - iii/ platelet count $<25 \times 10^9/\text{L}$ or thrombocytopenia with bleeding or requiring platelet transfusion. <u>Non-haematological toxicity</u> - Liver toxicity (ALAT/ASAT) of grade ≥ 3 for >7 days - Any other grade ≥ 3 major organ toxicity according to the NCI CTCAE v3.0. - Alopecia will not be recorded as a DLT.

	For expected and manageable side effects, please see chapter 11.4
Treatment: Test product, dose and mode of administration	Vinflunine (Javlor[®], Pierre Fabre Pharma): 320 mg/m² I.V., day 1, repeated every 21 days for patients with PS 0, adequate renal (creatinine clearance >60 ml/min) and hepatic function (as described in the inclusion criteria). For patients with PS 1, or age 75 to 80 years, or exposed to radiation of the lower pelvis region, or with impaired renal function (creatinine clearance 40-60 ml/min) but adequate hepatic function (as described in the inclusion criteria), the dose of vinflunine is 280 mg/m² I.V. day 1, repeated every 21 days. Sorafenib (Nexavar[®], Bayer HealthCare) daily per oral dosage from day 2 through day 21 (repeated every 21 days): Step 1: 200 mg: one (1) tablet 200 mg morning and evening (1+0+1) Step 2: 300 mg: one (1) tablet 200 mg morning and two (2) tablets 200 mg evening (1+0+2) Step 3: 400 mg: two (2) tablets 200 mg morning and evening (2+0+2) Doses of sorafenib higher than 400 mg P.O. twice daily are not allowed.
Duration of treatment:	The treatment will be discontinued in the case of: - clinical or radiological verified disease progression according to RECIST; - unacceptable toxicity; - concomitant illness or other reactions which would, in the judgement of the investigator, affect clinical status of the patient to a significant degree, and require discontinuation of the drug; - the patient is withdrawn; Survival information will be collected approximately every 4 weeks during the first 6 months and then every 6th week until death.
Criteria for evaluation:	Safety: Patients that have received any amount of study medication will be included in the safety analyses. Efficacy: Patients that have received at least 2 cycles of study treatment will be included in the efficacy evaluation (PFS, disease control rate, tumour response rate) and in the explorative biomarker and functional imaging evaluations using dual tracer PET/CT. The first evaluating CT will be performed after 2 cycles of therapy. Thereafter, tumour assessment will be performed every 2 cycles using conventional CT. Treatment decisions are based on the standard CT evaluation according to RECIST and not on the PET readouts.
Safety Assessment:	- examination by physician (including PS (WHO-ECOG scale) and body weight) weekly during cycle one and thereafter prior to every treatment cycle (i.e. every third week); - complete blood counts, electrolytes, renal and hepatic function prior

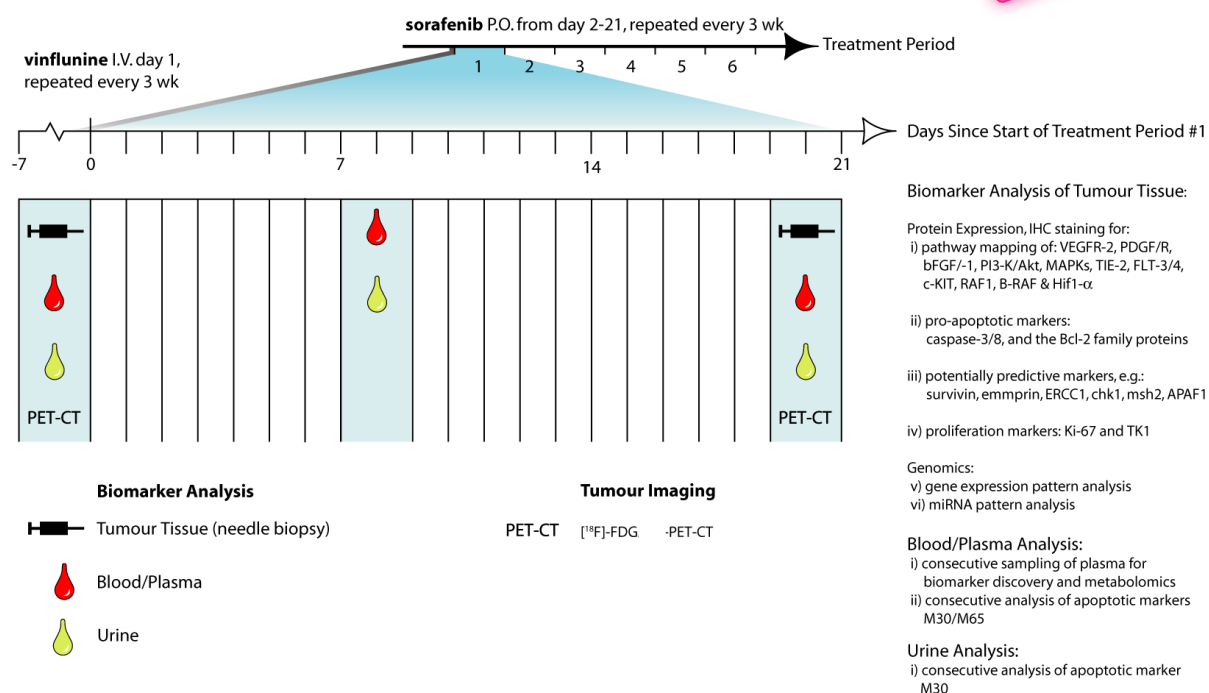
	to and at day 8 in every treatment cycle; - all patients will be followed-up by a oncology nurse at day 8 and 15 during treatment cycles 2 and 3. Blood pressure will be monitored weekly during the first two cycles and thereafter every third week as long as active treatment remains. - all adverse events or toxicity will be graded according to the NCI CTCAE v3.0.
Endpoints:	Primary endpoints: - safety parameters from cycle 1-3 to define RPTD Secondary endpoints: - duration of progression free survival - response rate (disease control rate and tumour response) measured according to RECIST, every second cycle - overall survival - readouts of the early ¹⁸F-FDG-PET/CT in relation to conventional RECIST evaluations - baseline tumour biomarker expression patterns and therapy induced biomarker dynamics including changes in apoptotic serum/urine markers in relation to RECIST and functional imaging readouts - data on safety parameters from all treatment cycles
Statistical Considerations:	The minimal total accrual of patients to define RPTD for the two fixed starting doses of vinflunine is 18, and the maximal 36, since a minimum of 3 patients must be accrued at each dose level of sorafenib. Efficacy parameters will be evaluated and presented by descriptive methods and statistics. Each patient will serve as his/her own control. Baseline genomic and protein profiles will be compared with samples taken prior to the start of the second treatment cycle. The samples (blood and urine) collected during the first treatment cycle will serve for consecutive marker analysis.
Translational research: (please see Study Outline (next page) for an overview)	I/ Biomarker analyses of: Tumour tissue: <i>Protein expression; immunohistochemistry staining for</i> i) pathway mapping of VEGFR-2, PDGF/PDGFR, bFGF/FGF-1, PI3-K/Akt, MAPKs (pERK/tERK; p38/pP38), FLT-3, FLT-4, c-KIT, RAF1, B-RAF, and Hif1-α. ii) pro-apoptotic marker analysis; caspase-3, caspase-8, Bcl-2 (e.g. Bak/Bax and phosphorylated Bad) iii) potentially predictive markers; survivin, emmprin, ERCC1, chk1, msh2, Apaf-1 iv) proliferation markers: Ki-67, TK1 <i>Genomics</i> v) gene expression pattern analysis vi) miRNA pattern analysis Blood / Plasma: Consecutive analyses of i) consecutive sampling of plasma for biomarker discovery and metabolomics ii) apoptotic markers (M30/M65)

	Urine: Consecutive analyses of i) apoptotic markers (M30) II/ Functional Tumour Imaging (not mandatory) ¹⁸ F-FDG-PET-CT will be performed at baseline and at three weeks (early evaluation)
Key dates:	Anticipated start of study: Q3, 2011 Estimated recruitment period: Q3, 2011 – Q2, 2013
Request of drug and/or finances:	Study drug sorafenib and financial support according to present contracts dated 2011-04-28 (Bayer Healthcare AB) and 2011-03-09 (Pierre-Fabre Pharma AB)

Study Outline: VINSOR

An Exploratory Phase I Study with Sorafenib in Addition to Vinflunine in Progressive Metastatic Transitional Cell Carcinoma of the Urothelial Tract

Dept of Oncology, Karolinska University Hospital and Karolinska Institute, Stockholm
(Anders Ullén, MD PhD; C-H Shah, MD; 2010)



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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
b.i.d	Twice Daily
CRF	Case Report Form
CR	Complete Response
CT	Computerized Tomography
DCF	Data Clarification Form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
EMA	European Medicines Agency
FU	Follow-Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
IEC	Independent Ethics Committee
MTD	Maximum Tolerated Dose
MPA	Medical Products Agency (Läkemedelsverket)
MRI	Magnetic Resonance Imaging
NUCOG	Nordic Urothelial Cancer Oncology Group
PD	Progressive Disease
PO	Per Oral
RPTD	Recommended Phase Two Dose
SAE	Severe Adverse Event
SD	Stable Disease
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
WHO	World Health Organisation

3. GENERAL INFORMATION/STUDY ADMINISTRATIVE STRUCTURE

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PHARMACY:

The hospital pharmacy at each site

DRUG DEPOT:

TBA

3.1 PARTICIPATING CANCER CENTERS

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4. BACKGROUND

4.1 UROTHELIAL TRACT CANCER 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). The total number of new urothelial tract cancer cases in Sweden in 2009 was 2 363, consisting of 1 743 men and 620 women (Cancer Incidence in Sweden 2009, Socialstyrelsen, December 17, 2010). Thus, the total annual incidence rate for Sweden was 25 new cases per 100 000 in 2009. The estimated figures for the US in 2008, are 68 810 new cases and 14 100 fatalities of bladder cancer (National Cancer Institute).

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). Systemic cisplatin-based combination chemotherapy is the only modality shown to improve survival (2). The widely employed clinical regimes are gemcitabine and cisplatin (GC), the combination gemcitabine, cisplatin and paclitaxel (GCP), and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) (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 survival time is limited to 14-15 months (2), 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, a significant overall survival benefit of 2.6 months was achieved following to vinflunine plus best supportive care (BSC) as compared to BSC only and more than 50% of the patients in receiving 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 2010 EAU guidelines.

In order to further improve the outcome and quality of life for this group of patients, novel treatment regimens or treatment combinations that can further improve the effects of vinflunine are needed.

Sorafenib has recently been reported in a small, phase II, second line trial in patients with advanced urothelial carcinoma. The trial was reported negative since there were no responses and few patients with stable disease. However the trial included only 27 patients of which only 22 were evaluable and in fact, the OS (6.8 months) was comparable with the OS in the drug registration trial of vinflunine (6.9 months), which recently has been approved for second line treatment of transitional cell carcinoma in the EU (5, 6). It can be discussed if clinically meaningful treatment effects on survival parameters can be achieved following sorafenib therapy that may not necessarily include tumour shrinkage. Lately, it has become evident that disease control rate or PFS, and not objective response rates, may be the relevant surrogate endpoints for targeted drugs with a predominant effect on the VEGF pathway, such as sorafenib (7, 8). For example, in the pivotal placebo controlled trials of sorafenib in metastatic renal cancer and hepatocellular cancer, the objective response rates were comparable between sorafenib and placebo, but survival evaluations favoured sorafenib treatment.

The combination of vinflunine and sorafenib has never previously been evaluated. The side effect profiles of these compounds in monotherapy are well documented and indicate that the treatment combination may be well tolerated.

4.2 INVESTIGATIONAL PRODUCTS

4.2.1 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 (MTIs) such as vinca alkaloids, taxanes, and epothilones have been evaluated against many tumour types in the

clinical setting (10, 11). Vinflunine binds to tubulin at or near to the vinca binding sites inhibiting its polymerisation into microtubules, which results in treadmilling suppression, disruption of microtubule dynamic, mitotic arrest and apoptosis.

In preclinical studies, vinflunine was identified as having a marked anti-tumour activity both *in vitro* and *in vivo* through a large panel of experimental tumour models (murine and human tumour xenografts) in terms of survival prolongation and tumour growth inhibition, including a dose-dependent decrease in tumour 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) tumour xenografts. 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.

For further information on vinflunine, please see the attached SPC for Javlor® (Appendix 24.1).

4.2.2 Sorafenib (Nexavar®)

The anti-neoplastic agent sorafenib is an orally administered compound with inhibiting properties on RAF kinases including Raf-1 and BRAF; members of the RAF/MEK/ERK signalling pathway. In addition, sorafenib has significant activity against a number of RTKs involved in neo-angiogenesis and tumour progression including vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3, platelet derived growth factor receptor β (PDGFR β), Flt-3 and c-KIT (12). Current indications, approved in Sweden, are confined to the treatment of patients with advanced renal cell carcinoma (RCC) and patients with hepatocellular carcinoma (HCC) (FASS 2011).

For further information on sorafenib, please see the attached SPC for Nexavar® (Appendix 24.2).

4.3 POSITRON EMISSION TOMOGRAPHY (PET) AND PET-CT

PET imaging studies have gained increased acceptance and popularity for diagnosis and staging of a long list of tumours, e.g. lung cancer, lymphoma, colon cancer and malignant melanoma (13). In the future, however, probably the greatest potential of PET will be in exploiting the technique visualizing early responses and at demonstrating a tumour specific uptake of anticancer drugs with specific targets (13, 14). PET can also be utilized for the selection of the most optimal drugs, in relation to a certain tumour type and target, and consequently early therapy evaluation (14-21). More recently the PET instrument has been integrated with the CT equipment, offering both examinations simultaneously, allowing a better anatomical localization for metabolic activities (22).

4.4 CLINICAL STUDIES WITH INVESTIGATIONAL PRODUCTS IN UROTHELIAL CANCER

4.4.1 Clinical studies with vinflunine

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. It is the only drug approved in Europe (September 2009) in this setting where there was no prior established standard of care. Efficacy and safety of vinflunine has not been studied in patients with performance status ≥ 2 (23). Based on the recommended dose schedule of one intravenous infusion every 3 weeks at 320 mg/m² or 280 mg/m² 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 a large randomized phase III study in second-line urothelial tract cancer (4, 24, 25). 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).

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 (23, 26).

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 (median of treatment) in the phase III trial; 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 TCCU disease. 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 (23).

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

4.4.2 Clinical studies with sorafenib

Sorafenib has been evaluated in a clinical setting for urothelial carcinoma in two small phase II trials. In the trial by Dreicer et al. sorafenib treatment was given in 2nd line (ref). The trial had a 2-stage design, with 4-month PFS rate as the primary endpoint but with a first-stage stopping rule based on response rates. It included 27 patients of which only 22 were eligible for response evaluation. No response was observed among eligible patients. Three (14%) patients had stable disease, and 9 (41%) had progression as their best overall response. Ten other patients were deemed unevaluable for response, and 6 patients had at least 1 follow-up assessment not performed within the mandated time frame. The remainder did not have follow-up imaging before death or removal from study either from clinical deterioration or therapy-related toxicity. The 4-month PFS rate based on the Kaplan-Meier method was 11.0%, Median PFS was 2.2 months (range 1.8– 3.7 months, 90% confidence interval (CI)). Median survival was 6.8 months (5.7– 8.5 months, 90% CI)

In the trial by Sridhar et al, which was a first line trial, objective tumour response rate as measured by RECIST was the chosen primary endpoint (27). Secondary endpoints included rate of prolonged stable disease (>3 months), time to progression, median and 1 year survival and safety and tolerability. The trial was very small as it included only seventeen patients. Fourteen patients were evaluable for response. Four patients had stable disease, eight patients had objective progressive disease and 2 patients had symptomatic PD as their best response. Median time to progression was 1.9 months (population range 0.7–8.7 months, 1.7–4.3 months 95% CI) and 3-month progression-free survival rate was 27% (12–61%, 95% CI). The six-month survival rate was 47% (28–78%, 95% CI) and median survival was 5.9 months (population range 0.9–16 months, 2.9–10.6 months 95% CI).

4.5 PREDICTIVE FACTORS

True tailored therapeutic concepts, based on functional biological tumour characteristics and understanding of malignant processes will be important for medical oncology in the future (28). So far, there are no available predictive biomarkers for sorafenib on bladder cancer. The well defined targeted properties of this drug provide a unique basis for studies on predictive factors, which is a major objective of this study (12). The known sorafenib-target molecules including RAF-kinases and RTKs as described in section 4.2.2 are of particular interest, including their downstream signalling proteins. The signalling within RTK pathways has a complex regulation and recently a signalling network model was suggested. In this model, inter-pathway interactions and intrinsic feedback loops are assumed rather than a strict vertical cascade for each RTK signal (29, 30). This indicates that not only target molecules but also secondary downstream signalling proteins may have predictive value.

In this study, we aim to perform pathway analyses by use of several genomic and proteomic techniques, which will provide possibilities to look at pathway molecules on both gene and protein levels. This will provide a unique possibility to not only to identify possible predictive patterns or signatures, but also to reveal the underlying cause of an aberrant expression of a presumptive particular predictive protein, for instance a mutation. Since each biomarker will be assessed at two stages, at baseline and prior to the second cycle, the patients will serve as their own controls.

Possible changes in blood/plasma and urine concentration of angiogenic and apoptotic markers, offers a platform to study dynamic effects of the ongoing treatment. Consequently, presumptive markers of angiogenesis and apoptosis, respectively, will be measured consecutively.

Finally, baseline- and therapy-induced changes in biomarker expression patterns will be compared and correlated to the FDG-PET evaluations and clinical efficacy parameters.

5. STUDY RATIONAL

Recently, vinflunine was approved in EU as a second line treatment for patients with metastatic urothelial carcinoma with progressive disease on first line platinum-containing polychemotherapy. In the pivotal phase III trial, the progression free survival was improved by 1.5 months from 1.5 to 3 months and the median overall

survival was improved by 2.6 months after adjustment for prespecified prognostic factors (4). Even though the data from the Bellmunt trial and the approval of this drug by EMA were important steps for the treatment of these patients in daily practice, there is still an urgent need to further improve the overall survival and quality of life for this patient category.

Sorafenib is an interesting small molecule, multi- tyrosine kinase inhibitor, with expected predominant effects on the VEGFR, PDGFR and C-KIT pathways. This compound has been evaluated in the 2nd line setting in urothelial carcinoma in one small phase II trial (6). The trial had a 2-stage design, with 4-month PFS rate as the primary endpoint but with a first-stage stopping rule based on response rate. No responses were observed among eligible patients and the trial was reported negative. The median overall survival was however 6.8 months, which is comparable to the data from the registration trial of vinflunine in the same clinical context. This indicates signs of sorafenib activity that may affect survival parameters but do necessarily not involve tumour shrinkage that can be measured by CT. Similar effects of sorafenib have been seen in other diagnoses. For example, in the pivotal, placebo-controlled trials in hepatocellular- and renal carcinoma, the response rates were rather similar but PFS in favor of sorafenib (7, 8). Furthermore, a dual-case report (Shah et al *manuscript*) of sorafenib in urothelial carcinoma supports a possible benefit for a fraction of patients with this disease.

Combining several compounds is an established method in clinical oncology in order to improve the antitumoral effects of the treatment as compared to monotherapy. With combined treatment however, there is always a risk of increased and intolerable toxicity. The toxicity profiles of both sorafenib and vinflunine are well characterized and since they are not overlapping but differ significantly, it is reasonable to anticipate the combination to be well tolerated. Other phase I trials combining sorafenib and established cytotoxic agents have demonstrated that the addition of sorafenib at clinically relevant doses is very well tolerated (31-33). The safety of the treatment combination of vinflunine and sorafenib has not been evaluated yet and is one of the major endpoints of this study. Two cohorts with different starting dose of vinflunine (280 mg/m² and 320 mg/m², depending on the patients renal function and performance status according to clinical routine) will be evaluated. Sorafenib will be administered in three dose steps in order to identify the RPTD for the treatment combination.

Moreover, tumour biopsies will be performed prior to the first treatment cycle and prior to the second treatment cycle. In addition, blood samples will be collected for translational analyses at same time-points as well as at day 8 in the first treatment cycle. These biological tissues will serve the basis for the explorative translational part of the trial which aim to analyse and detect possible predictive biomarkers for the treatment combination. Objective efficacy parameters will be analysed and related to several tumour biological features, i.e. expression profiles of target receptors for sorafenib, downstream signaling pathway proteins of these receptors and a battery of proteins that may have a predictive potential for the targeted-chemotherapy combined treatment (please see chapter 4 above and the Study Outline figure for details) with the overall intention of identifying biomarkers or expression profiles that may have predictive values and deserve further evaluation and validation in larger phase II/III trials. Also the value of dual tracer FDG-PET/CT, as a method for early treatment evaluation, i.e. already after three weeks, will be evaluated. FDG-PET/CT PERCIST data will be correlated to standard CT RECIST evaluation data following to two treatment cycles and furthermore to biomarker data.

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7. STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVE

To explore the safety of sorafenib in combination with vinflunine in patients with transitional cell carcinoma of the urothelial tract

7.2 SECONDARY OBJECTIVES

To correlate early dual tracer ^{18}F -FDG-PET/CT functional imaging readouts with standard RECIST evaluations with the intention to explore new endpoints for targeted therapy

To find predictive tumour tissue biomarkers for sorafenib/vinflunine treatment

To evaluate serum and urine markers of apoptosis as potential markers of sorafenib/vinflunine treatment

8. STUDY ENDPOINTS

8.1 PRIMARY ENDPOINTS

- safety parameters from cycle 1-3 to define/confirm RPTD

8.2 SECONDARY ENDPOINTS

- data on safety parameters from all treatment cycles
- duration of progression free survival
- response rate (disease control rate and tumour response) measured according to RECIST, every second cycle
- overall survival
- readouts of the early ^{18}F -FDG-PET/CT in relation to conventional RECIST evaluations
- baseline tumour biomarker expression patterns and therapy induced biomarker dynamics including changes in apoptotic serum/urine markers in relation to RECIST and functional imaging readouts

9. STUDY DESIGN

9.1 STUDY OUTLINE

This is a prospective, single armed, explorative, dose finding phase I study.

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.

A fixed dose of vinflunine per square meter is administered for all patients. The dose will be adjusted to any renal and/or hepatic malfunction according to guidelines for vinflunine treatment. Sorafenib will be administered twice daily and escalated in dose steps. Three patients are to be treated at each dose level sequentially. This procedure is set up to define the MTD and RPTD, described in details in chapter 11.3.

All patients will receive vinflunine 320 or 280 mg/m² on day 1 during each treatment cycle, see chapter 11.2.1 with 21 days between treatments. Sorafenib will be taken orally twice daily from day 2 through day 21 in either one of the three predefined dose escalated steps: Step 1: 200 mg P.O. twice daily; Step 2: 200 + 400 mg P.O. daily.; Step 3: 400 mg P.O. twice daily.

For patients that experience a DLT, the following strategy is used in the present protocol: If a DLT occurs, the treatment should be stopped. If the DLT *has not* decreased to grade ≤ 2 within 14 days the patient will be withdrawn from the study. If the DLT *has* decreased to grade ≤ 2 within 14 days, the patient could upon recovery

be re-challenged with both study drugs at the same dose, or at the previous lower dose-step for sorafenib and/or reduction of vinflunine according to clinical praxis, at the investigators discretion (the patient has objective signs of a possible favourable risk-benefit balance of the study treatment). Such patients will also be included in the efficacy and translational analyses.

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 6th week until death.

Biomarker analysis (tumour tissue (needle biopsy), blood/plasma, urine) and tumour imaging - PET-CT will be performed according to a special schedule in cycle one (chapter 15).

The patients will return to the clinic for safety checks weekly during cycle 1 and thereafter every third week. 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 will be assessed every 2nd treatment cycle.

9.2 STUDY ASSESSMENTS AND PROCEDURES

9.2.1 Assessments per visit

Screening visit (within 4 weeks before study drug administration) Doctor visit	Collection of written Informed consent Medical/surgical history Physical examination Inclusion and exclusion criteria Height Weight Blood pressure, heart rate ECG (including QTc) Echocardiography ECOG/WHO <u>Blood/plasma analysis:</u> Haematology Electrolytes (including creatinine) Hepatic function Renal function (Iohexol clearance) Concomitant medication Pregnancy test, if applicable Central line for infusion is recommended Tumour assessment–radiology (baseline CT abdomen + CT thorax/chest X-ray) Tumour imaging - PET-CT (not mandatory) Biomarker analysis - tumour tissue needle biopsy (not mandatory) - blood/plasma + urine (not mandatory)
Day -1 (≤ 72 h before first cycle) Doctor visit	Medical/surgical history (i.e. update baseline status) Concomitant medication (i.e. update baseline status) Physical examination Weight Blood pressure, heart rate ECOG/WHO <u>Blood/plasma analysis:</u> Haematology Electrolytes (including creatinine) Hepatic function
Day 1 (= day 22) (Day of Vinflunine admin)	Vinflunine administration

Nurse

Day 8 + 15 Doctor visit cycle 1 Nurse telephone call cycle 2 and 3	Safety check: - Physical examination - Weight - ECOG/WHO - Concomitant medication - Adverse event Blood pressure, heart rate (first 2 cycles) <u>Blood/plasma analysis:</u> - Haematology (d 8 only, all cycles) - Electrolytes (including creatinine) (d 8 only, all cycles) - Hepatic function (d 8 only, all cycles) - Biomarker analysis (blood/plasma + urine) (not mandatory) (d 8 cycle 1 only)
Day 21/Follow-up (FU) (≤72 h before vinflunine admin) Doctor visit	- Physical examination - Weight - Blood pressure, heart rate - ECG (QTc) (cycle 1 only) - ECOG/WHO <u>Blood/plasma analysis:</u> - Haematology - Electrolytes (including creatinine) - Hepatic function - Concomitant medication - Adverse event - Continuation criteria - Tumour assessment – radiology (CT) (every 6 weeks/2nd cycle) - Tumour imaging - PET-CT (not mandatory) (cycle 1 only) - Biomarker analysis - tumour tissue needle biopsy (not mandatory) (cycle 1 only) - blood/plasma + urine (not mandatory) (cycle 1 only)
Extra visit	Only relevant assessments should be performed: - Physical examination - Weight - Blood pressure, heart rate - ECOG/WHO <u>Blood/plasma analysis:</u> - Haematology - Electrolytes (including creatinine) - Hepatic function - Concomitant medication - Adverse event - Continuation criteria

9.2.2 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 1 st dose	Day 1 Vinflunine	Day 8	Day 15 d 2-21 Sorafenib	Day 21	Extra visit ¹²⁾	Follow- up ¹³⁾
Informed consent	X							
Medical/surgical history	X	X ⁵⁾						
Incl/excl criteria	X							
Physical exam	X	X	X ⁶⁾	X ⁷⁾	X ⁷⁾	X	X	X
Height	X							
Weight	X	X		X ⁷⁾	X ⁷⁾	X	X	X
Blood pressure/heart rate	X	X		X ⁸⁾	X ⁸⁾	X	X	X
ECG (including QTc)	X					X ⁷⁾		
Echocardiography	X							
ECOG/WHO PS	X	X		X ⁷⁾	X ⁷⁾	X	X	X
Concomitant medication	X	X ⁵⁾		X ⁷⁾	X ⁷⁾	X	X	X
Pregnancy test (if applicable)	(X)							
Central line for infusion (recommended)	(X)							
Tumour assessment – radiology (CT)	X					X ¹⁰⁾		
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	X
Renal function – iohexol clearance	X							
Adverse event				X ⁷⁾	X ⁷⁾	X	X	X
Telephone check-up (oncology nurse)				X ⁹⁾	X ⁹⁾			
Continuation criteria						X ¹¹⁾	X	
PET-CT (not mandatory)	X					X ⁷⁾		
Tumour tissue, needle biopsy (not mandatory)	X					X ⁷⁾		
Biomarker analysis – Blood/plasma + urine (not mandatory)	X			X ⁷⁾		X ⁷⁾		

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) Iohexol clearance should be done if creatinine increases ≥20%.

5) Prior to cycle 1: Update baseline status

6) Control of general condition by oncology nurse at the treatment ward according to clinical praxis

7) Cycle 1 only

8) First 2 cycles only

9) Safety check by nurse, telephone All cycles but cycle 1.

10) Tumour assessment – radiology (CT): every 6 weeks/2nd cycle

11) Continuation criteria: See chapter 10.6

12) Assessments according to the relevance on a case to case basis

13) Follow-up: day 30±2 days after last treatment administration. Survival parameters will be collected every 6th week until death.

10. SELECTION AND WITHDRAWAL OF SUBJECTS

This phase 1 study will include 18 to 36 evaluable patients with verified transitional cell carcinoma of the urinary tract. The patients will be recruited at three centers in Denmark and Sweden.

10.1 GENERAL ELIGIBILITY CRITERIA

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

10.2 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:

10.3 SUBJECT INCLUSION CRITERIA

Patients with:

- signed informed consent;
- histologically confirmed transitional cell (pure or mixed histology including transitional cell carcinoma are allowed) carcinoma of the urothelial tract;
- patients who have received neoadjuvant or adjuvant platinum-containing chemotherapy and who are diagnosed with locoregional recurrent or metastatic disease prior to or at the 6-months' visit, are eligible or
- patients who have received palliative platinum-containing chemotherapy and who are diagnosed with progression prior to or at the 6-months' visit, are eligible or
- patients who have contraindication to platinum-containing chemotherapy;
- previous systemic chemotherapy must have been stopped 14 days before the randomisation with full recovery from any related toxicity;
- measurable and/or non-measurable disease using RECIST and 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, or 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;
- age 18 up to 80 years;
- ECOG / WHO Performance Status (PS) ≤ 1 ;
- haematological function:
 - haemoglobin ≥ 100 g/L
 - absolute neutrophil count $\geq 1.0 \times LL$ (lower limit of normal value)
 - platelets $\geq 100 \times 10^9 / L$;
- hepatic function:
 - bilirubin $< 1.5 \times N^*$,
 - transaminases $< 2.5 \times N^*$
 - *N = upper limit of normal value
- renal function:
 - creatinine clearance ≥ 40 ml/min (measured by either iohexol clearance or Cr-EDTA technique);

- ECG (12 lead) with corrected QT interval (QTc) <480 ms;
- Clinically normal cardiac function based on ejection fraction (LVEF assessed by MUGA or ECHO, LVEF $\geq 40\%$);
- able to swallow and retain oral medication;
- no presence of asthenia, hand-foot skin reaction or rash greater than grade 1 (NCI CTCAE version 3.0) at enrolment;
- no known or suspected allergy to the investigational agent or any agents given in association with this trial;

10.4 SUBJECT EXCLUSION CRITERIA

Patients with:

- non-transitional cell carcinoma of the urothelial tract (e.g. pure adenocarcinoma or squamous cell carcinoma);
- prior treatment with vinflunine;
- diagnosed brain metastases or leptomeningeal involvement. Brain CT-scans or MRI are not required unless there is clinical suspicion of central nervous system involvement.
- peripheral neuropathy $\geq G3$ (grade 3) according to NCI CTCAE version 3.0;
- history of serious or concurrent illness or uncontrolled medical disorder; any medical condition that might be aggravated by treatment or which could not be controlled:
 - . active infection requiring antibiotics within 2 weeks before the study inclusion,
 - . unstable diabetes mellitus,
 - . uncontrolled hypercalcaemia >2.9 mmol/L (or $>G2$ NCI CTCAE v3.0),
 - . concurrent congestive heart failure NYHA (class III-IV) or patients with unstable angina pectoris, patients with myocardial infarction within 6 months and/or poorly controlled hypertension will be excluded,
 - . cardiac arrhythmias requiring anti-arrhythmics (excluding beta-blockers or digoxin for chronic atrial fibrillation);
- patients having received more than one previous systemic chemotherapy for advanced or metastatic disease;
- patients who have received any other investigational or anti-cancer therapy (chemotherapy/biological agent) 14 days before the inclusion;
- other malignancies, except adequately treated basal 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;
- pregnant or lactating women;
- men or women of childbearing potential not employing adequate contraception;
- any psychological, familial, sociological, or geographical condition which does not permit protocol compliance and medical follow-up.
- poorly controlled hypertension. At baseline, blood pressure $>150/90$ is defined as poorly controlled.
- renal dysfunction:
 - creatinine clearance <40 ml/min measured by either iothexolclearance or Cr-EDTA technique.
- ECOG / WHO Performance Status ≥ 2
- presence of hand-foot skin reaction or rash $>$ grade 1 at enrolment;
- known or suspected allergy to the investigational agent or any agents given in association with this trial;

10.5 CONTINUATION CRITERIA

Treatment according to the logarithm will not be disrupted unless any of the below listed criteria are valid (10.6)

10.6 WITHDRAWAL OF SUBJECTS

A participant will be withdrawn immediately if:

- he or she withdraws his/hers informed consent at his/hers own request
- one or more DLT is diagnosed and *has not* decreased to grade ≤ 2 within 14 days (see definition of DLT 13.6)
- 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).

10.7 CONSIDERATIONS AFTER WITHDRAWAL

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

11. TREATMENT OF SUBJECTS

The investigational products are:

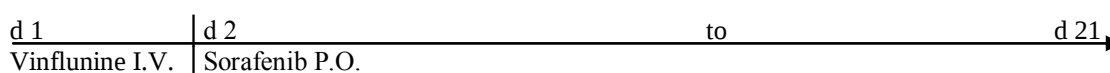
Vinflunine (Javlor[®], Pierre Fabre Pharma)

Sorafenib (Nexavar[®], Bayer HealthCare)

For complete information, please consult the attached manufacturer's SPC.

11.1 TREATMENT ADMINISTRATION

The treatment will be administered as follows:



11.2 DOSAGE SCHEDULE

11.2.1 Pre-defined dosage schedule

Vinflunine (Javlor[®], Pierre Fabre Pharma): **320 mg/m²** I.V., day 1, repeated every 21 days for patients with PS 0, adequate renal (creatinine clearance >60 ml/min) and hepatic function (as described in the inclusion criteria).

For patients with PS 1, or age 75 to 80 years, or exposed to radiation of the lower pelvis region, or with impaired renal function (creatinine clearance 40-60 ml/min) but adequate hepatic function (as described in the inclusion criteria), the dose of vinflunine is **280 mg/m²** I.V. day 1, repeated every 21 days.

Sorafenib (Nexavar[®], Bayer HealthCare) daily dosage from day 2 through day 21 (repeated every 21 days):

Step 1: 200 mg P.O. b.i.d. (i.e. one (1) tablet 200 mg morning and evening, 1+0+1)

Step 2: 200+400 mg P.O. (i.e. one (1) tablet 200 mg morning and two tablets evening, 1+0+2)

Step 3: 400 mg P.O. b.i.d. (i.e. two (2) tablets 200 mg morning and evening, 2+0+2)

Doses of sorafenib higher than 400 mg P.O. b.i.d. are not allowed.

11.2.2 Individual dose adjustments

If a DLT occurs, the treatment should be stopped. If the DLT *has not* decreased to grade ≤ 2 within 14 days the patient will be withdrawn from the study. If the DLT *has* decreased to grade ≤ 2 within 14 days, the patient could upon recovery be re-challenged with both study drugs at the same dose, or at the previous lower dose-step for sorafenib and/or reduction of vinflunine according to clinical praxis, at the investigators discretion (the patient has objective signs of a possible favourable risk-benefit balance of the study treatment).

11.3 DEFINITION OF MTD AND RPTD

A fixed dose of vinflunine per square meter is administered to all patients according to the clinical guidelines for vinflunine treatment.

Sorafenib will be administered twice daily and escalated in dose steps. Three patients are to be treated at each dose level sequentially. Patients will be evaluated for toxicity weekly during cycle 1 and thereafter every third week. If no patient has experienced a DLT (see definition of DLT) until the end of week 9, sorafenib will be escalated to the next dose level.

If 1 patient has a DLT, 3 additional patients will be enrolled at that dose level. If no or one of the additional patients have a DLT until the end of week 9, then the sorafenib dose will be increased to the next dose step for the following patients.

If two or more of the additional patients have a DLT (i.e. 3 or more of 6 patients), then this dose level will be deemed too toxic and an additional 3 patients will be accrued to the prior dose level if only 3 patients had been enrolled at this dose.

If none or one patient has a DLT at that level, MTD will have been determined.

If 2 of 3 patients have a DLT, this dose level will be deemed too toxic and the process will be repeated at the next lower dose level. However, if this is the initial dose step of sorafenib (i.e. sorafenib 200 mg P.O. b.i.d.), no more patients will be recruited in this vinflunine dose group. The study may however continue in the other vinflunine dose group until MTD has been determined. The two vinflunine arms are evaluated and dose escalated independently of each other.

If at the highest planned dose level for sorafenib, no DLTs are seen, then this level will be declared the MTD for the purpose of selecting a Phase II dose.

A maximum of 6 patients can be accrued at each dose level. Therefore, the maximum total accrual is 36 patients (18 per vinflunine dosage dose group).

11.4 EXPECTED MANAGEABLE TREATMENT RELATED TOXICITY

In 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. The side effects will only be recorded as DLT's if present as grade ≥ 3 for more than 14 days, despite routine prophylactic medication or after adequate medical treatment has been offered.

List of common and expected treatment related toxicity (below):

Vinflunine

- Constipation
- Diarrhoea
- Nausea
- Vomiting
- Stomatitis
- Myalgia including arthralgia
- Skin reaction at site of injection

Sorafenib

- Hypertension
- Hypothyroidism

- Constipation
- Diarrhoea
- Hand-foot syndrome
- Skin rash / erythema / alopecia

11.5 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.

Administration of any granulocyte colony-stimulating factor (G-CSF) is prohibited.

11.6 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 CRF: drug name, date and time of administration (start, end). Any interruption must be stated in the CRF. If any extra antiemetics or fluid was administered this must also be recorded.

11.7 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 both study drugs in the CRF. The batch and/or lot number of vinflunine and sorafenib must be recorded in the CRF.

11.8 PACKAGING AND LABELLING OF INVESTIGATIONAL PRODUCTS

Commercially available vinflunine vials and sorafenib tablets will be administered in this study.

Batch or lot number, date of administration and dose will be recorded in the CRF.

The content of the labelling is in accordance with requirements set by the regulatory authorities.

11.9 STORAGE AND HANDLING

Vinflunine (Javlor[®], Pierre Fabre Pharma) diluted solution stored in light protecting infusion bags (made of polyethylene or polyvinyl chloride) can be stored up to 6 days in refrigerator (at +2 to +8 °C), or up to 24 hours at +25°C. If the solution is exposed to light it must not be stored more than 1 hour at +25°C.

Sorafenib (Nexavar[®], Bayer HealthCare) tablets shall not be stored at a room temperature above +25°C.

12. ASSESSMENT OF EFFICACY

12.1 TUMOUR RESPONSE

Tumour response will be evaluated at baseline and every 6 weeks/2nd treatment cycle. 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 RECIST and 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;

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.

12.1.1 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.

12.1.2 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.

12.1.3 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

13. ASSESSMENT OF SAFETY

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

13.1 LABORATORY ASSESSMENTS AND TUMOUR MARKERS (IF APPLICABLE)

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
- Iohexol clearance (if creatinine increases $\geq 20\%$)

13.2 CHEST X-RAY OR CT THORAX SCAN

Chest X-ray or CT scan of the thorax is required at baseline to confirm or reject distant metastasis.

13.3 ECG

At baseline and after the 1st cycle, 12-lead electrocardiogram is required to measure the QTc .

13.4 ECHOCARDIOGRAPHY.

At baseline a echocardiography is required accessing cardiac function based on ejection fraction.

13.4 BLOOD PRESSURE AND HEART RATE

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

13.5 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 3.0.

13.6 DEFINITION OF DLT

A DLT is defined as any of the following:

Haematological toxicity

i/ grade ≥ 4 neutropenia (absolute neutrophile count $< 0.5 \times 10^9$ for ≥ 7 days or $< 0.1 \times 10^9$ for ≥ 3 days),

ii/ febrile neutropenia of grade ≥ 3 (absolute neutrophile count $< 1.0 \times 10^9$ and temperature $\geq 38.5^\circ\text{C}$)

iii/ platelet count $< 25 \times 10^9/\text{L}$ or thrombocytopenia with bleeding or requiring platelet transfusion.

Non-haematological toxicity

Liver toxicity (ALAT/ASAT) of grade ≥ 3 for > 7 days

Any other grade ≥ 3 major organ toxicity according to the NCI CTCAE v3.0.

Alopecia will not be recorded as a DLT.

For expected and manageable side effects, please see chapter 11.4

13.7 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.

13.8 DEFINITION OF SERIOUS ADVERSE EVENTS

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)

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

13.9 REPORTING OF DOSE LIMITING TOXICITY (DLT), SERIOUS ADVERSE EVENT (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

All dose limiting toxicities or serious adverse events, as listed above, must be documented by the investigator immediately as he or she is notified of the event.

Suspected unexpected serious adverse reactions (SUSAR) are serious adverse events judged to be related to study treatment.

The investigator must inform the sponsor of a dose limiting toxicity or serious adverse event by writing within 24 hours. Please use the form Notification of Dose Limiting Toxicity (DLT) or Serious Adverse Event (SAE) in Appendix 24.6.

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

13.10 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All serious events must be followed-up and recorded. Please use the follow-up part of the form 'Notification of Dose Limiting Toxicity (DLT) or Serious Adverse Event (SAE)'. The serious events must be followed-up until resolution or stabilisation.

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 3.0. DLT is defined in this protocol.

14.2 STATISTICAL ANALYSIS

14.2.1 Objectives and endpoints

The primary endpoint of defining RPTD is based on the safety analyses and reported DLT's. The minimal total accrual of patients to define RPTD for the two fixed starting doses of vinflunine is 18, and the maximal 36, since a minimum of 3 patients must be accrued at each dose level of sorafenib.

Secondary endpoints including efficacy and translational parameters will be evaluated and presented by descriptive methods and statistics.

All patients that have received at least one treatment cycle will be included in the safety analyses. Patients that have received two cycles or more will be included in the efficacy analyses.

The secondary endpoints relating to survival are defined as follows:

- survival from the date of inclusion until death or last follow-up (if censored)
- progression-free survival, is the duration from inclusion until confirmed progression (by RECIST) or death

14.2.2 Analyses

The statistical analyses will be performed by the chief investigator, the statistician and affiliated members.

14.3 DETERMINATION OF SAMPLE SIZE

Serving as an exploratory phase 1 study, the number of patients to include (n=18 to 36) is solely based on the numbers required to meet the MTD and RPTD.

15. TRANSLATIONAL ANALYSES

Apart from mapping side effects and identifying the optimal dose of sorafenib for combined treatment with standard dose vinflunine, one major aim of this study is to identify presumptive biomarkers, biomarker profiles or therapy induced changes of these markers in tumour material, blood/serum or urine, which can predict outcome of the combined treatment

As seen in in the Study Outline figure, tumour samples will be collected prior to treatment and after one treatment cycle by fine or core needle biopsies. In addition, blood/serum and urine will be collected at indicated and specified time points in a repetitive manner in the first treatment cycle. These biological tissues will serve the basis for the explorative translational part of the trial which aim to analyse and detect possible predictive biomarkers for the treatment combination. Objective efficacy parameters will be analysed and related to several tumourbiological features, i.e. expression profiles of target receptors for sorafenib, downstream signaling pathway proteins of these receptors and a battery of proteins that may have a predictive potential for the targeted-chemotherapy combined treatment (please see chapter 4.5 and the Study Outline figure for details) with the overall intention of identifying biomarkers or expression profiles that may have predictive values and deserve further evaluation and validation in larger phase II/III trials.

Also the value of dual tracer FDG-PET/CT, as a method for early treatment evaluation, i.e. already after three weeks, will be evaluated. FDG-PET/CT PERCIST data will be correlated to standard CT RECIST evaluation data following to two treatment cycles and furthermore to biomarker data.

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 and contacting the recruited sites.

This Clinical Trial Unit will conduct pre-study site controls, instruct investigators and site personnel about the protocol, study procedures, reporting of outcome and any serious adverse events (including DLT). The pre-study site controls aim at confirming that the site complies with the requirements as specified in the protocol and GCP guidelines.

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 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 all have progressive advanced urothelial carcinoma. Recently, vinflunine was approved as a second line treatment, with an improvement of the median overall survival of 2.6 months. Sorafenib as a single drug has been evaluated in urothelial carcinoma in two small phase II trials and a dual-case report, giving indications of potential effect for this type of cancer. Even though the approval of vinflunine is an important step for the treatment options of urothelial carcinoma patients in daily practice, there is still an urgent need to further improve the overall survival and quality of life for this patient category. The patients in the study will receive the today best known 2nd line therapy, vinflunine, and to that the potentially improving drug sorafenib. The combination of vinflunine and sorafenib has not previously been tested in man, but there is a reasonable chance for the patients to benefit from this treatment regime during the study period.

Combining several compounds is an established method in clinical oncology in order to improve the antitumoral effects of the treatment as compared to monotherapy. With combined treatment however, there is always a risk of increased and intolerable toxicity. The safety of the treatment combination of vinflunine and sorafenib has not yet been evaluated and is one of the major endpoints of this study. However, other combination regimens with sorafenib and a cytotoxic drug have shown good tolerability for sorafenib (31-33). The toxicity profiles of both sorafenib and vinflunine are well characterized and since they differ significantly it is reasonable to anticipate the combination to be well tolerated. Vinflunine will be tested at two different dosages and sorafenib in three escalating dose steps, according to a strict pre-defined schedule, to early detect any safety issues. 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.

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 written patient information and the Informed Consent form are provided in Appendices 24.3 and 24.4.

19. DATA HANDLING AND RECORD KEEPING

19.1 CASE REPORT FORMS

A CRF 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 Swedish, 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. The CRFs should be completed by using a black or blue ballpoint pen. Any corrections of data can only be made by drawing one single line through the incorrect data, leaving the incorrect data clearly visible. Erasure by any method is not allowed. Corrections must be made in original CRFs and should be visible on the Investigator's copies. Corrections to the CRFs must be dated, initialled and explained (if necessary) by the Investigator or a designated representative.

The CRFs should be monitored and collected on a regular basis. Any corrections of data after CRF pages have been collected will be done by using Data Clarification Forms (DCFs). The DCF should state the question or data to be changed together with the correct data. Each DCF should be dated and signed by the Investigator. The original DCF should be filed together with the copy of the CRF in the Investigator's File.

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 source 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 Patientförsäkringen via Landstingens Ömsesidiga Försäkringsbolag, LÖF.

Patients included and treated in Denmark will be covered by the Danish Patient Insurance Association.

21. PUBLICATION POLICY

The results will be presented in a scientific report.

22. SUPPLEMENTS

22.1 CHANGES OF THE STUDY PROTOCOL

All changes of the final study protocol must be documented by signed protocol amendments. If substantial changes to the assessments or design of the study are made, the MPA (Läkemedelsverket) and the IEC should be notified for review and approval before the changes take effect.

22.2 APPLICATION TO REGULATORY AUTHORITIES

Prior to initiating the clinical study, the Investigator will submit an application for authorisation to conduct the study, including all required documents, to the MPA.

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 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: Q3, 2011

Estimated recruitment period: Q3, 2011 – Q2, 2013

23. CHIEF INVESTIGATOR'S AGREEMENT

EudraCT number: 2011-004289-14

Title of the study: An Exploratory Phase I Study with Sorafenib in Addition to Vinflunine in Progressive Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract

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.

Chief Investigator	_____ Signature
Anders Ullén, M.D., Ph.D.	_____ Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

EudraCT number: 2011-004289-14

Title of the study: An Exploratory Phase I Study with Sorafenib in Addition to Vinflunine in Progressive Locally Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract

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: _____	_____ Signature
Title: _____	_____ Date
Work Address: _____	

24. APPENDICES

- 24.1 SUMMARY OF PRODUCT CHARACTERISTICS VINFLUNINE (JAVLOR®)
- 24.2 SUMMARY OF PRODUCT CHARACTERISTICS SORAFENIB (NEXAVAR®)
- 24.3 INFORMED CONSENT (IN SWEDISH, 1 PAGE)
- 24.4 PATIENT INFORMATION SHEET (IN SWEDISH, 2 PAGES)
- 24.5 COPY OF THE ETHICS APPROVAL (IN SWEDISH)
- 24.6 NOTIFICATION OF DOSE LIMITING TOXICITY (DLT) OR SERIOUS ADVERSE EVENT (SAE)

Medgivande

”Tidig klinisk prövning av tolerabilitet samt analys av biomarkörer vid behandling av avancerad cancer utgången från urinvägarna med standardcytostatika vinflunin (Javlor®) med tillägg av cancerläkemedlet sorafenib (Nexavar®)”

Genom att underteckna denna blankett samtycker jag till att delta i den här kliniska studien. Jag har erhållit en kopia av patientinformationen och har fått tillräckligt med 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 kan när som helst meddela, muntligt eller skriftligt, att jag inte önskar fortsätta mitt deltagande i studien.

Jag ger mitt godkännande till att de prover (blod, urin och tumörmaterial) jag lämnar, lagras för användning i denna studie:

Ja ☐

Nej ☐

Jag ger mitt godkännande till att de prover (blod, urin och tumörmaterial) jag lämnar, lagras för användning i framtida forskning (som i förekommande fall måste godkännas av en etikprövningsnämnd):

Ja ☐

Nej ☐

.....
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.

Information sheet to patients (in Swedish, 2 pages)

Tidig klinisk prövning av tolerabilitet samt analys av biomarkörer vid behandling av avancerad cancer utgången från urinvägarna med standardcytostatika vinflunin (Javlor®) med tillägg av cancerläkemedlet sorafenib (Nexavar®)

Bakgrund

Cancer i urinvägarna är en relativt vanlig cancerform och antalet nya fall per år i världen är 360 000; av dessa härrör 2 300 från Sverige.

Syftet med studien

Studien syftar till att analysera tolerabilitet (biverkningar, säkerhet) vid standardbehandling (Javlor®) med tillägg av ett andra tumörhämmande läkemedel i tablettform (Nexavar®). Vi vill också med analyser av blod, urin och tumörvävnad försöka hitta sk biomarkörer som i framtiden kan hjälpa oss att förutse om en patient har nytta, eller ej av behandlingen. Studien syftar även till att undersöka om en ny röntgenmetod, sk PET-CT tidigare än vanlig skiktröntgen (datortomografi, CT) kan identifiera de patienter, som har nytta av den givna behandlingen.

Vad innebär det att delta i studien?

Deltagande i tilläggsstudien förutsätter ditt skriftliga godkännande. Därefter kommer du, innan behandlingsstart kallas för ett vävnadsprov av tumören samt en röntgenundersökning med PET-CT. Detta upprepas ytterligare en gång före behandlingsomgång nr 2 (tre veckor senare). I samband med blodprovstagning inför samt under första behandlingsomgången i huvudstudien, tas tre extra rör med blod och urin för de analyser som skall göras i studien.

Observera att studiedeltagande innebär att samma cellgiftsbehandling som ges rutinmässigt kommer att ges men med tillägg av ytterligare ett tumörhämmande läkemedel.

Mer om behandlingen

Med cellgift menas cytostatika, det vill säga läkemedel mot cancer. I denna studie kommer du att få ett cytostatika som heter Javlor® som är godkänt för behandling av patienter med avancerad cancer från urinvägarna. Nexavar® är ett så kallat målriktat läkemedel mot cancer och hämmar direkt inne i cancercellerna. Nexavar® har visat effekt vid behandling av vissa andra svårbehandlade cancerformer som ex lever- och njurcancer. Kombinationsbehandling med Javlor® och Nexavar® har inte tidigare studerats men kombinationer mellan Nexavar® och andra cytostatika har tolererats väl.

Mer om PET-CT

Behandlingseffekterna kommer som nämnt ovan att studeras med modern röntgen och nuklearmedicinsk undersökning; datortomografi i kombination med positron emissions tomografi, så kallad PET-CT. Denna undersökning möjliggör, förutom mätning av tumörens storlek, som vid vanlig skiktröntgen (CT), att även ämnesomsättningen i cancercellerna kan studeras. Detta kan vara ett sätt att tidigt mäta om en behandling är effektiv eller ej. Analysen av PET resultatet genomförs först efter att samtliga patienter i studien behandlats.

Mer om blod-, urin- samt vävnadsprovtagning

För att kunna utvärdera effekten av behandling kommer analys av blod-, urin- samt vävnadsprov från cancertumören att utföras. Analysen kommer att inriktas på gener samt proteiner som eventuellt kan förklara om man har nytta eller ej av behandlingen i studien.

Vävnadsprovet från cancertumören kommer att tas på Röntgenavdelningen, Karolinska Universitetssjukhuset Solna. Provet tas med en mellan- eller fin nål (upp till 0.6 mm i diameter). Ett mellannålsprov medför att du måste kvarstanna för observation fyra timmar på en vårdavdelning (utifall blödningar eller andra komplikationer uppkommer). Val av nålstorlek görs utifrån cancertumörens placering (avstånd till större blodkärl), eventuell annan mediciner (t.ex. blodförtunnande behandling) samt tillgängliga resurser.

Sammantaget medför tilläggsstudien följande 2 extra besök:

- Vävnadsprov och PET-CT-undersökning veckan före start av första cellgiftsbehandlingen
- Vävnadsprov och PET-CT-undersökning före start av andra cellgiftsbehandlingen

Potentiella risker och obehag

Cytostatika

Vanliga biverkningar vid behandling med Javlor[®] samt Nexavar[®] är exempelvis trötthet, mag-tarm påverkan, benmärgspåverkan, hudbiverkan, illamående samt förhöjt blodtryck. Observera att studien syftar till att utvärdera behandlingskombinationen, varför det kan finnas risk för andra biverkningar samt kraftigare biverkningar än tidigare kända. Av denna anledning anpassas behandlingsdoserna i studien.

PET-CT

Vid varje PET-CT-undersökning kommer du att få ett radioaktivt spårämne genom en injektion via ett blodkärl i armen. Stråldosen som ges vid PET-CT är ca 17 mSi, vilket är en högre dos än för vanliga radiologiska undersökningar, men spårämnet har en kort halveringstid och försvinner på några timmar. Du bör dock inte vistas nära gravida och barn timmarna efter undersökningen. En vanlig CT ger en stråldos på ca 10mSi vilket kan jämföras med den normala strålning på 5 mSi/år som en människa i Sverige utsätts för från omgivningen.

Provtagning från tumör

Vävnadsprov taget med nål kan orsaka smärta och blåmärke på platsen för sticket. Det finns även en liten risk för blödning i samband med själva provtagningen från tumören. Karolinska Universitetssjukhuset har mångårig erfarenhet av denna provtagning och risken för komplikationer bedöms som mycket liten avseende denna metod.

Möjliga fördelar

Alla patienter som deltar i studien erhåller standardbehandling med Javlor[®]. Om studien är framgångsrik tolereras Javlor[®] och Nexavar[®] väl tillsammans och kan ge en behandlingseffekt som är bättre än vad som erhålls med enbart Javlor[®]. När det gäller vävnadsprovsanalyserna finns idag ingen möjlighet att du får någon personlig nytta, däremot finns möjligheten att i framtiden, med hjälp av studiens resultat, bättre kunna individanpassa behandlingen.

Försäkring

Precis som inom sjukvården för övrigt omfattas du av Läkemedelsförsäkringen samt Patientförsäkringen.

Datainsamling och sekretess

All insamlad information samt material kommer att avidentifieras och kodas, för att inte någon obehörig personal skall kunna sammankoppla analys svaren direkt med er. Uppgifterna är sekretesskyddade och ingen obehörig har tillgång till dessa.

Dina medicinska uppgifter kommer att behandlas konfidentiellt i enlighet med sekretesslagen. Personuppgifter behandlas enligt personuppgiftslagen (PUL) 1998:204.

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

Deltagande och avbrytande av studien

Studiedeltagande är helt frivilligt. Du har också rätt, att när som helst meddela, 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.

Vid eventuella frågor kring studien är ni välkomna att kontakta:

Dr Anders Ullén, Överläkare, Docent, Huvudprövare
Tel: 08-517 75 046 (U-mottagningen, Radiumhemmet)

Dr Carl-Henrik Shah, Leg Läkare, medprövare
Tel: 08-517 75 046 (U-mottagningen, Radiumhemmet)

Dr Karin Holmsten, Leg Läkare, medprövare
Tel: 08-517 75 046 (U-mottagningen, Radiumhemmet)

Karolinska Universitetssjukhuset Solna, Onkologiska kliniken 171 76 Stockholm

Karolinska Clinical Trial Unit		Study: Vinsor		Drugs: Vinflunine + Sorafenib	
Patient No		Name of Investigator:		Date:	

NOTIFICATION OF DOSE LIMITING TOXICITY (DLT) OR SERIOUS ADVERSE EVENT (SAE)

To be completed and sent to Dr Anders Ullén by fax or e-mail (scanned original) within 24 hours.

Fax No: +46 8 517 306989

E-mail address: anders.ullen@karolinska.se

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