CLINICAL STUDY PROTOCOL: NUCOG II – VINTREX

An exploratory phase I study of pemetrexed in addition to vinflunine as second-line treatment in patients with metastatic urothelial cell carcinoma after prior treatment with platinum.

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1 SYNOPSIS OF PROTOCOL NUCOG II - VINTREX

Title	An Exploratory phase I study of Pemetrexed in Addition to Vinflunine as second-line treatment in patients with metastatic urothelial carcinoma after prior treatment with platinum		
Sponsor	Investigator initiated study	**Clinical Phase**	I
Indication	Metastatic urothelial carcinoma prior treated with platinum		
Objectives:	Primary - To explore the safety of pemetrexed in combination with vinflunine in patients with transitional cell carcinoma of the urothelial tract		
	Secondary - Overall response rate, ORR(= CR+PR), - Clinical benefit rate (= CR + PR + SD) - Progression free survival, PFS		
Trial Design	An exploratory, multicenter, clinical phase I study of the combination of vinflunine and pemetrexed This is an exploratory phase I study evaluating the combined treatment with pemetrexed and vinflunine in advanced urothelial tract cancer. A fixed dose of vinflunine per square meter will be administered to all patients on day one every third week. Pemetrexed will be administered once every third week and escalated in dose steps. A minimum of 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 none of three patients has experienced a DLT (see definition of DLT) until the end of week 6, pemetrexed will be escalated to the next dose level for the following patients. If one of three patients has a DLT, three additional patients will be enrolled at that dose level. If none of the additional patients has a DLT until the end of week 6, then the pemetrexed dose will be increased to the next dose step for the following patients. If one of the additional patients (i.e. two out of six patients) experiences a DLT, dose escalation is stopped and this dose is declared the maximally tolerated dose (MDT). An additional three patients will be accrued to the prior dose level if only three patients had been enrolled at this dose. If at this dose level none or one patient out of six experience DLT the recommended phase II dose has been reached. If at any dose level three or more of six patients have a DLT, this dose level will be deemed too toxic and the process will be repeated at the previous dose level as described above. If, at the initial dose step of pemetrexed (400 mg/m^2 iv. every third week), two or more patients experience a DLT, no further patients will be recruited. If at the highest planned dose level for pemetrexed (500 mg/m^2), no DLT is observed, then this level will be declared the MTD for the purpose of selecting a Phase II dose. In this case MTD is equal to RPTD.		

Number of Patients	3 to 18 evaluable patients
Number of Centers	4 or more centers from the Nordic countries
Target Population	Patients with metastatic urothelial carcinoma as per inclusion/ exclusion criteria defined below
Selection criteria	**Inclusion Criteria** • Histologically or cytologically documented diagnosis of unresectable (T3-4), locally advanced (lymph node positive (N+)) or metastatic (M1) urothelial carcinoma (including renal pelvic tumors, uretheral tumors, urinary bladder tumors and urethral primary tumors). • Progressive disease not suited for re-induction with platinum based chemotherapy, defined as progression during or less than 6 months after initial chemotherapy for locally advanced or metastatic disease OR relapsed/progressing less than 6 months after neo-adjuvant/adjuvant chemotherapy. • Prior treatment with only one chemotherapy regimen. • Exposure to platinum as part of initial chemotherapy. • Measurable disease according to the RECIST 1.1 criteria. Verification by a CT-scan performed no later than 2 weeks prior to inclusion. • Progressing tumors occurring in tissue previously exposed to radiotherapy are only considered evaluable if radiotherapy was terminated min. 3 months before entry. • ECOG performance status of 0 – 1 • Sufficient renal function defined as GFR>45 ml/min. GFR (glomerular filtration rate) must be calculated directly from CrEDTA / iohexol-clearance or creatinine clearance • ≥ 4 weeks since prior surgery or radiation therapy • Fertile men and women of childbearing potential must use sufficient contraception from before entering the study until 6 months after end of chemotherapy. • Between 18 and 80 years of age. • Before randomization the patient must give written (signed) informed consent to participate in the study according to ICH/GCP and the ethical comity **Exclusion Criteria** • Not fulfilling inclusion criteria as described above. • Prior treatment with vinflunine and/or pemetrexed. • Any other systemic disease or co-morbid condition which according to the investigator contraindicates the use of the study drug by rendering the subject at increased risk of treatment complications (including, but not restricted to, active infection or server infection within the last 2 weeks, unstable angina, myocardial infarction within the previous month, inflammatory bowel disease or hepatic disease)

	• Impaired liver function defined as serum bilirubin ≥ 1.5 upper limit of normal (ULN) or AST and/or ALT ≥ 3 x ULN (or ≥ 5 x ULN if clearly attributable to liver metastasis • Impaired bone-marrow function defined as platelets<100,000/mm3 and ANC<1,500/mm3 • Presence of brain metastasis or other central nervous system disease involvement. • Any other malignancy within 5 years (except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer). • Nursing mothers or pregnant women. • Hypersensitivity to pemetrexed, vinflunine, other vincaalcaloids, mannitol, hydrochloric acid, sodium hydroxide • Concomitant yellow fever vaccination
Length Of Study	2 years inclusion period.
Investigational Products Dose/Route/ Regimen	Vinflunine (Javlor®, Pierre Fabre Pharma): 280 mg/m^2 I.V., day 1, repeated every 21 days Pemetrexed (Alimta^R, Eli Lilly) day 1, repeated every 21 days: Step 1: 400 mg/m^2 Step 2: 450mg/m^2 Step 3: 500mg/m^2 Treatment continues until disease progression, unacceptable toxicity or patients wish to stop treatment.
Key dates	Anticipated start of study: Q3, 2014 Estimated recruitment period: Q3, 2014 – Q3, 2016
Study duration	The study will be terminated after every living patient has had a follow up of at least 3 months after stopping chemotherapy, or when all patients have died.
Statistical consideration	The minimal total accrual of patients to define RPTD for starting dose of vinflunine is 9, and the maximal 18, since a minimum of 3 patients must be accrued at each dose level of pemetrexed. Efficacy parameters will be evaluated and presented by descriptive methods and statistics.

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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 (Lægemiddelstyrelsen)
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
UCC	Urothelial cell carcinoma

3 GENERAL INFORMATION: STUDY ADMINISTRATIVE STRUCTURE

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5 BACKGROUND

5.1 Urothelial Cell Carcinoma (UCC)

UCC is the most frequent histological type of cancer developing in the urinary organs (>90%). Bladder cancer is the most frequent presentation of UCC (>90%), but the disease can also originate in the renal pelvis, the ureter and the urethra. UCC ranks seventh among the malignant diseases regarding lives lost. In the Nordic countries alone, 6476 persons each year are diagnosed with this disease (2004-2008 average incidence) and more than 2000 succumb to it (1)– the vast majority after a shorter or longer period of symptomatic metastatic or locally advanced disease. Even UCC diagnosed at an early stage – before invasive growth develops – carries a 10% risk of progression to frank invasion and an up to 5% risk of a fatal outcome in spite of close surveillance(2). When reaching a muscle invasive stage approximately 15% of patients already harbour clinically detectable, regional or distant metastasis at diagnosis and a further 35-50% develop disease dissemination even after aggressive surgical intervention with cystectomy and careful pelvic lymph node dissection(3;4).

The development of bladder cancer is associated with tobacco smoking and probably half of male bladder cancer is attributable to cigarette smoking. UCC is 2-3-fold more frequent in males than in females. The disease incidence increases with age and UCC is most frequent in the 6th and 7th decade(5).

The standard treatment for patients with locally advanced or metastatic UCC is combination chemotherapy containing cisplatin (CPPD). At the moment 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 (CPPD, vinblastine, adriamycin and methotrexate)(6). Metastatic UCC is a chemo-sensitive disease with response rates above 50% in phase III studies of the above mentioned CDDP-containing combination regimes. The survival gain obtained with these treatments have never been quantified in a phase III setting comparing with best supportive care but is estimated to be in the order of 6-9 month of the median 14-15 months of overall survival seen after first line CPPD based chemotherapy.

For the majority of patients metastatic UCC is a disease with an ultimately fatal outcome. Selected patients with uncompromised performance status and without involvement of parenchymal organs – typically patients with only lymph nodal involvement – can expect an up to 20-25% chance of 5 year relapse-free survival (which for practical purposes equals cure) with first line chemotherapy(6). The remaining patients, constituting the bulk of the clinical challenge with this disease, will progress and potentially be candidates for second line therapy.

5.2 Second line treatment of UCC

A number of non-comparative phase II studies have been performed, testing the activity of single-agent chemotherapy of metastatic and/or locally advanced UCC. However, these studies often have included a mixture of first-line and second-line patients and tested different response endpoints. These studies show response rates ranging from 0 to 29% and median overall survival in the range of 2 to 13 months(7). Recently, a large, randomized phase III trial comparing vinflunine + “best supportive care” (BSC) with BSC alone in patients with UCC in good performance status (PS 0/1)

progressing after prior treatment with platinum-based chemotherapy, demonstrated a survival benefit and a significant reduction in risk of death in the active arm(8). The study demonstrated a significant improvement in overall survival in the vinflunine group, 6.9 versus 4.6 months, but also secondary endpoints of ORR, disease control and PFS were all statistically significant favouring patients treated with Vinflunine + BSC. For PFS the difference was 3.0 versus1.5 months (p=0.0293).

The phase III study, has led to the registration of vinflunine (Javlor) in many countries for second-line, mono-therapy in locally advanced or metastatic UCC progressing after platinum-based 1st line combination chemotherapy. Even though a modest increase in survival has been introduced by this treatment, there is still plenty of room for improvement and urgent need for second-line treatments with better outcome in metastatic UCC

5.3 Research hypothesis

It is possible, without unacceptable toxicity, to administer combined treatment with the two products with known activity in UCC (Vinflunine (Javlor^{R}) and Pemetrexed (Alimta^{R})) in second line setting after cisplatin-based first line treatment in a population of patients with metastatic or locally advanced UCC.
A tolerated dose of the two drugs in combination can be found and this dose can be further tested in phase II, provided this phase I indicates activity of the combination.

5.4 Investigational products

5.4.1 Vinflunine (Javlor^{R})

Javlor^{R} (Vinflunine) has in 2010 been approved by the authorities (EMEA) as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

Vinflunine is a new bi-fluorinated microtubule inhibitor. The activity of vinflunine is directly linked to the disturbance of micro-tubular dynamics resulting from tubulin-binding affinity with inhibition of free tubulin molecules and microtubule tread milling. Compared to previous generation vinca-alkaloids vinflunine causes a high level of antitumor activity even though it has a relatively low tubulin-binding affinity. Vinflunine has, in preclinical studies, demonstrated a marked anti-tumor activity both in vitro and in vivo, and additionally shown anti-angiogenic and vascular-disrupting activities in experimental tumor models.

An overview of selected clinical trials is presented below; for a complete and detailed overview the Javlor^{R} Investigator Brochure is recommended.

5.4.2 Pemetrexed (Alimta^{R})

Alimta^{R} (pemetrexed, a multi-targeted anti-cancer antifolate) is approved by the EMEA as second-line therapy in advanced or metastatic non-small cell lung cancer patients and first-line therapy in mesotheliomas in combination with cisplatin. The effect of pemetrexed as single agent in second-line TCC of the urothelium has been investigated in small non-randomized clinical trials (n=12-47),

reporting the response rate to be 9-28% and the median time to progression to be 2.9 months(9;10).

Pemetrexed exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed behaves as a multi-targeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides.

For a complete and detailed overview the Alimta^{R} Investigator Brochure is recommended(11).

5.5 Clinical Studies with investigational products in urothelial cell and other cancers

5.5.1 Vinflunine as 2nd line treatment in UCC

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 failure of a prior platinum-containing regimen. It was approved in Europe in September 2009 and is still (April 2012) the only approved drug in this setting, where there was no previous established standard of care. Based on the recommended dose schedule of one intravenous infusion every 3 weeks of either 320 mg/m2 or 280 mg/m2 – the latter dose level 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(8;12;13). Vinflunine as a single agent showed consistent results through these randomized 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 (an increase of 2.6 months in the eligible population as compared to best supportive care arm, HR 95% CI 0.78 [0.61-0.99])(8).
Vinflunine exhibited neither renal toxicity, nor deterioration of a 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) without occurrence of problematic toxicity.
The safety profile within the entire population of 450 patients with urothelial tract cancer treated by vinflunine demonstrated that grade 3-4 neutropenia was observed in 54.6% of patients but was both reversible and non-cumulative. Severe anemia and thrombocytopenia (grades 3 or 4) were less common (17.3% and 4.9 % respectively). Febrile neutropenia was observed in 6.7% of patients (all grades). Infection with grade 3/4 neutropenia was observed in 3.8% of patients(11;14).
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).
Conclusively, vinflunine-related constipation does not seem to lead to significant increase in abdominal pain in TCCU disease. Other symptoms occurring 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 in a total of six patients 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.
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

5.5.2 Vinflunine and pemetrexed in refractory solid tumors

The combination of vinflunine and pemetrexed has been investigated in treatment refractory solid tumours(15). A phase I study was performed in 19 patients with refractory solid tumors to investigate the safety of vinflunine and pemetrexed. This study was preceded by investigations in xenograft models showing an additive activity, when combining pemetrexed with vinorelbine, another vinca-alcaloid, suggesting that the combination of such drugs may provide substantial clinical activity. The patients enrolled in this phase I study had various solid tumours and had previously been exposed to between 1 and 6 other treatment regimens. The patients were treated with pemetrexed 500 mg/m2 in combination with 280, 300 and 320 mg/m2 of vinflunine, respectively, in 3 different cohorts. Most common grade 3 and 4 adverse events were neutropenia and leucopoenia. No objective partial- or complete responses were seen, but 2 patients experienced prolonged stable disease for 25 and 20 cycles respectively. Based on the experience from this phase I study the research group recommended vinflunine 300 mg/m2 and pemetrexed 500 mg/m2 in combination every 3 weeks for future studies.

6 STUDY RATIONALE

A significant subset of the patients experiencing progression of transitional cell carcinoma after first line, cisplatin based combination chemotherapy maintain a performance status that warrants further systemic anti-neoplastic treatment. A benefit, both in terms of survival and tumor response, has been documented with single agent Vinflunine in this patient population. Treatment of advanced transitional cell carcinoma with single agent pemetrexed has demonstrated significant activity of

this agent in this setting with very manageable side effects. Weather the combination of pemetrexed and vinflunine is superior to single agent vinflunine as a second line therapy after failure of cisplatin based combination chemotherapy can only be explored through randomised, controlled clinical studies. The rationale for the present study is to investigate the toxicity of a combination of these two drugs in a classical phase I trial in the relevant patient population. Provided that a combination with manageable toxicity and signs of activity can be demonstrated, this schedule can form the basis for further testing and quantification of anti-neoplastic activity in this specific disease setting in phase II and III studies.

6.1 Rationale for schedule

The clinical development of vinflunine was started with three mono-therapy, dose escalating and pharmacokinetic phase I studies employing three different administration schedules: once every 3 weeks, weekly administration, and Dl -D8 every 3 weeks. Based on these results administration once at 3 week intervals (q3w) was chosen. At the start of the Phase II program, 350 mg/m²was initially the recommended dose for further evaluation. This schedule was chosen because it was the most extensively tested and the one in which the majority of objective responses were observed. In early Phase II studies, an interim analysis was performed after approximately 61 patients were enrolled and approximately 25 were evaluated at 350 mg/m². An unexpectedly high rate of myelosuppression (64% Grade 3 and 4 with 15% febrile neutropenia) prompted a reduction of the recommended dose to 320 mg/m² every 3 weeks. Following phase III testing vs. best supportive care, Vinflunine is now approved for second line chemotherapy q3w(8).

6.2 Rationale for clinical dose

Using Vinflunine at 320 mg/m², myelotoxicity and constipation are the primary toxicities requiring dose reductions and/or delays. Standard dose levels for single agent vinflunine, based on the phase III and previous studies, propose initial dosing of vinflunine of 320 mg/m² for the first cycle in patients with ECOG performance status 0 and no preceding radiotherapy to the pelvis. However in patients with PS1, age above 75 years at the date of inclusion and/or preceding radiotherapy to the pelvis an initial dose of 280 mg/m² in cycle 1 is recommended and only dose escalation to 320 mg/m² from cycle 2 in such patients in the absence of significant hematologic toxicity. Since patients belonging to the latter group is expected to constitute a significant number of the patients eligible to treatment in this disease setting and the fact that we are adding another myelotoxic agent to the treatment the fixed dose for vinflunine will be 280 mg/m².

Pemetrexed at a dose of 500 mg/m² has been combined with vinflunine in phase I studies of a mixed population of pre-treated patients with various solid tumors(15). As the relevant patient population for this study, as mentioned above, are typically older than the 58 years that constituted the median age of the study population of that study, a starting dose of 400 mg/m² has been chosen. From this dose pemetrexed will be increased in steps of 50 mg/m² until a maximum tolerated dose (MTD) is reached as described in section 11.1

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7 STUDY OBJECTIVES

7.1 Primary objective

- To explore the toxicity and safety of chemotherapy with the combination of vinflunine and pemetrexed as second line treatment after cisplatin based first line treatment in patients with metastatic and/or locally advanced urothelial cell carcinoma. The purpose is to establish a recommended dose for further study – a recommended phase two dose (RPTD)

7.2 Secondary objective

- To get an impression of the overall response rate, ORR(CR+PR), clinical benefit rate (NC+PR+CR) and the progression free survival time (PFS) in patients with UCC treated with 2^{nd} line chemotherapy as outlined above to explore the relevance of further testing in phase two.

8 STUDY ENDPOINTS

8.1 Primary endpoints

- Toxicity and safety parameters from cycle 1 and 2 to determine the maximal tolerated dose (MTD) and the RPTD

8.2 Secondary endpoints

- Toxicity and safety parameters from all treatment cycles.
- Objective overall response rate, ORR(CR+PR), and clinical benefit rate (NC+PR+CR) measured according to RECIST 1.1, every second cycle
- Progression free survival time

9 STUDY DESIGN

9.1 Study outline

This is a multicenter, phase I study of the combination of vinflunine and pemetrexed in second line treatment of locally advanced and/or metastatic UCC in patients who progress after first line cisplatin-based combination chemotherapy. The primary endpoint in this study is toxicity.

This is an exploratory phase I study evaluating the combined treatment of pemetrexed and vinflunine in advanced urothelial tract cancer. This study applies a conventional phase I study design (3+3).
A fixed dose of **vinflunine** per square meter will be administered to all patients on day one every third week.
Pemetrexed will be administered on day one every third week and escalated in dose steps. A minimum of 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 none of three patients has experienced a DLT (see definition of DLT) until the end of week 6, pemetrexed will be escalated to the next dose level for the following patients.
If one of three patients has a DLT, three additional patients will be enrolled at that dose level. If none of the additional patients has a DLT until the end of week 6, then the pemetrexed dose will be increased to the next dose step for the following patients.
If one of the additional patients (i.e. two out of six patients) experiences a DLT, dose escalation is stopped and this dose is declared the maximally tolerated dose (MDT).
An additional three patients will be accrued to the prior dose level if only three patients had been enrolled at this dose. If at this dose level none or one patient out of six experience DLT the recommended phase II dose has been reached.
If at any dose level three or more of six patients have a DLT, this dose level will be deemed too toxic and the process will be repeated at the previous dose level as described above.
If, at the initial dose step of pemetrexed (400 mg/m^2 i.v. every third week), two or more patients experience a DLT, no further patients will be recruited.
If at the highest planned dose level for pemetrexed (500 mg/m^2), no DLT is observed, then this level will be declared the MTD for the purpose of selecting a Phase II dose. In this case MTD is equal to RPTD.
A maximum of 6 patients can be accrued at each dose level. Therefore, the maximum total accrual is 18 patients.

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

A patient will enter the study after informed consent 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.

Drugs will be administered according to guidelines with the modifications described in section 12.1.2.

Patients who discontinue chemotherapy without evidence of Progressive Disease (PD) will continue to be monitored for progression until PD, death or end of study.

Tumor response according to RECIST 1.1 will be assessed every 3rd treatment cycle.

9.2 Study assesments and procedures

9.2.1 Assessments per visit

Screening visit (doctor visit, within 2 weeks before study drug administration)

Collection of written Informed consent
Medical/surgical history
Physical examination
Inclusion and exclusion criteria
Height
Weight
Blood pressure, heart rate
ECG (including QTc)
ECOG/WHO
Blood/plasma analysis:

- Hematology
- Electrolytes (including creatinine)
- Hepatic function
- Renal function (measured due to local standards)
- Concomitant medication
- Pregnancy test, if applicable

Tumor assessment–radiology (baseline CT of thorax and abdomen)

Day -1 (≤72 h before **first** cycle)

Doctor visit with evaluation of eligibility.

Day 1 (= day 22) (nurse visit, day of drug administration)

Vinflunine and Pemetrexed administration

Day 8 + 15 (first cycle)

Doctor visit
Physical examination
Adverse events
Blood/plasma analysis:

- Hematology

Day 8+15 (remaining cycles)

Blood/plasma analysis:

- Hematology

Day 21/Follow-up (FU) (≤72 h before **drug administration)**

Doctor visit
Physical examination
Weight
Blood pressure, heart rate
ECOG/WHO
Blood/plasma analysis:

- Hematology
- Electrolytes (including creatinine)
- Hepatic function

Concomitant medication
Adverse events
Tumor assessment – radiology (CT) (every 9 weeks/3rd cycle)

Extra visit Only relevant assessments should be performed:

The schedule of events will be repeated each treatment cycle until any discontinuation criteria is met.

10 SELECTION AND WITHDRAWAL OF SUBJECTS

This phase 1 study will include a maximum of 18 patients with verified metastatic UCC. The patients will be recruited at participating centers in Denmark, Sweden, Finland and Norway.

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10.1 General eligibility criteria

Only patients that fulfill the inclusion criteria (11.2.1) and none of the exclusion criteria (11.2.2) are eligible for enrolment.

10.2 Screening and enrolment of subjects

Potentially suitable patients will be screened by physicians or research nurses at the centers in order to find eligible participants. The screening procedure aims at confirming that the inclusion and exclusion criteria are met. Every eligible participant will be reported to the staff at the clinical research unit at Rigshospitalet. The clinical research unit will coordinate the continuously inclusion of patients in the protocol and give information on the actual dose-level to be administered. The communication will be per official hospital e-mail. Decision on number of patients at each dose level, observation time before next inclusion or proceeding to next dose level is based on the criteria for the study design as described in 9.1 Study outline.
Only the chief investigator can take decision on dose escalation.

10.2.1 Subject inclusion criteria

Histologically or cytologically documented diagnosis of unresectable (T3-4), locally advanced (lymph node positive (N+)) or metastatic (M1) urothelial carcinoma (including renal pelvic tumors, uretheral tumors, urinary bladder tumors and urethral primary tumors).

- Progressive disease not suited for re-induction with platinum based chemotherapy, defined as progression during or less than 6 months after initial chemotherapy for locally advanced or metastatic disease OR relapsed/progressing less than 6 months after neo-adjuvant/adjuvant chemotherapy.
- Prior treatment with only one chemotherapy regimen.
- Exposure to platinum as part of initial chemotherapy.
- Measurable disease according to the RECIST 1.1 criteria. Verification by a CT-scan performed no later than 2 weeks prior to inclusion.
- Progressing tumors occurring in tissue previously exposed to radiotherapy are only considered evaluable if radiotherapy was terminated min. 3 months before entry.
- ECOG performance status of 0 – 1
- Sufficient renal function defined as GFR>45 ml/min. GFR (glomerular filtration rate) must be calculated directly from CrEDTA / iohexol-clearance or creatinine clearance
- ≥ 4 weeks since prior surgery or radiation therapy
- Fertile men and women of childbearing potential must use sufficient contraception from before entering the study until 6 months after end of chemotherapy.
- Between 18 and 80 years of age.

Before randomization the patient must give written (signed) informed consent to participate in the study according to ICH/GCP and the independent ethical committee (IEC)

10.2.2 Subject exclusion criteria

- Not fulfilling inclusion criteria as described above.
- Prior treatment with vinflunine and/or pemetrexed.
- Any other systemic disease or co-morbid condition which according to the investigator contraindicates the use of the study drug by rendering the subject at increased risk of treatment complications (including, but not restricted to active infection or server infection within the last 2 weeks, unstable angina, myocardial infarction within the previous month, inflammatory bowel disease or hepatic disease)
- Impaired liver function defined as serum bilirubin ≥ 1.5 upper limit of normal (ULN) or AST and/or ALT ≥ 3 x ULN (or ≥ 5 x ULN if clearly attributable to liver metastasis
- Impaired bone-marrow function defined as platelets<100,000/mm3 and ANC<1,500/mm3
- Presence of brain metastasis or other central nervous system disease involvement.
- Any other malignancy within 5 years (except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer).
- Nursing mothers or pregnant women.
- Hypersensitivity to pemetrexed, vinflunine, other vincaalcaloids, mannitol, hydrochloric acid, sodium hydroxide

- Concomitant yellow fever vaccination

10.3 Continuation criteria

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

10.3.1 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 AE is diagnosed and *has not* decreased to grade ≤2 within 14 days of planned retreatment (see definition of DLT 13.6)
- The patient does not comply with the instructions given by the study personnel
- Disease 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).

10.3.2 Considerations after withdrawal

A participant that has been withdrawn (for any reason), cannot be re-included in the study. Their subject number cannot be reused.

11 Treatment of subjects

The investigational products are:

Vinflunine (Javlor®, Pierre Fabre Pharma)
Pemetrexed (Alimta®, Eli Lily)

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

11.1 Treatment administration and dosage schedule

11.1.1 Pre-defined dosage schedule

In the investigational, combination treatment:

Vinflunine (Javlor®, Pierre Fabre Pharma) at a dose of 280 mg/m2 i.v. on 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, patients exposed to radiation of the lower pelvis region or with impaired renal function (creatinine clearance 45-60 ml/min) but adequate hepatic function (as described in the inclusion criteria), the dose of vinflunine is **250** mg/m2 I.V. day 1, repeated every 21 days.

in combination with

Pemetrexed (Alimta®, Eli Lily) at a dose of 400 mg/m^2 i.v. on day 1 at the first dose level escalated with 50 mg/m^2 per dose level over 3 levels as described in the trial design, thus 450 mg/m^2 at level 2 and 500 mg/m^2 at level 3 if reached. According to the summary of product characteristics for pemetrexed profylactic steroids will be administrered the day before treatment, on the treatment-day and rhe day after treatment. Further vitamin B12 and folic acid will be given as supply according to the summary of product characteristics. This supplu treatment must be initiated one week before the startr of pemetrexed treatment.

11.1.2 Individual dose adjustment

If an AE grade > 2 occurs, the treatment should be interrupted until the AE is decreased to grade 2 or less. No treatment can be re-administered before the haematological threshold values and security parameters described in the summary of product characteristics for pemetrexed and vinflunine, respectively, are reached. If the AE *has not* decreased to grade ≤2 within 14 days after planned treatment administration, the patient will be withdrawn from the study.

No dose reductions are allowed.

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

11.2.1 List of common and expected treatment related toxicity:

- Constipation
- Myelotoxicity
- Diarrhea
- Nausea
- Vomiting

- Stomatitis
- Myalgia including arthralgia
- Skin reaction at site of injection

11.3 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 and medications.

11.3.1 Prohibited and restricted therapies during the study

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

Patients with mild to moderate renal insufficiency (GFR 45-79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAID's) from 2 days prior to and until 2 days after each pemetrexed administration. Cardiovascular prophylactic low dose acetylsalicylic acid is allowed.

11.4 Compliance with 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/her 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).

The drug administration will be performed according to treatment schedules describing concomitant fluid administration, prophylactic dosing of anti-emetics and observation time. Any interruption must be stated in the CRF. If any extra anti-emetics or fluid was administered this must also be recorded.

When the drugs are administered to the patient for the first time in the first treatment cycle a doctor must be present in the hospital ward to allow fast handling of acute side-effects and the patient must be under observation in the ward for 1 hour.. If no acute side-effects occurs in the first treatment cycle the following cycles can be administered by the nurse solely and no additional observation will be necessary.

11.5 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 both study drugs in the CRF.

11.6 Packaging and labeling of investigational products

Commercially available vinflunine and pemetrexed vials will be administered in this study.
Date of administration and dose will be recorded in the CRF. Batch and lot number will be available at the pharmacy, but are not routinely recorded in the CRF.
The content of the labeling is in accordance with requirements set by the regulatory authorities.

11.7 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°C 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.
Permetrexed (Alimta®, Eli Lilly) diluted solution can be stored up to 24 hours in refrigerator (2°C to 8°C).
The diluted solutions will be prepared by the hospital pharmacy, which is under the inspection of regulatory authorities. All drugs will be handled due to the manufacturer's description

12 ASSESMENT OF EFFICACY

12.1 Tumor Response

Tumor response will be evaluated at baseline and during treatment every 9 weeks/3rd treatment cycle. The same method of assessments and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up.

Tumor lesions will be categorized as measurable and/or non-measurable lesions using RECIST 1.1 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 tumor 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 Overall response criteria

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

Laboratory tests include:

- Hematology: 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 clearance (if creatinine increases ≥20%)

13.2 ECG

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

13.3 Blood pressure and heart rate

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

13.4 Definitions 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.

13.5 Definition of Dose Limiting Toxicity (DLT)

A DLT is defined as any of the following:

13.5.1 Hematological toxicity

- Grade ≥4 neutropenia (absolute neutrophil count $<0.5 \times 10^9$ for ≥7 days or $<0.1 \times 10^9$ for ≥3 days),
- Febrile neutropenia of grade ≥3 (absolute neutrophil count $<1.0 \times 10^9$ and temperature ≥38.5˚C)
- Platelet count $<25 \times 10^9$/L or thrombocytopenia with bleeding or requiring platelet transfusion.

13.5.2 Non-hematological 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 12.2

13.6 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.

13.7 Definition of Serious Adverse Events

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

- Results in death
- Is considered life threatening
- Results in persistent or significant disability
- Requires acute or unplanned hospitalization or prolongation of existing hospitalization
- 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.

13.8 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. To judge if a side-effect should be considered a SUSAR the information in paragraph 4.8 in the respective summary of product characteristics must be used.

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 XX.x.

SUSARs will be reported to the authorities within 7 days if life-threatening or death all others will be reported within 15 days.

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.

13.9 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 stabilization.

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 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.

Secondary endpoints are to evaluate progression free survival, overall response rate and clinical benefit rate. Patients who have received two cycles or more will be included in the efficacy analyses.

The 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 1.1) or death

14.2.2 Analyses

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

15 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.

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 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 authorized personnel of the sponsor (or thereof affiliated).

16.2 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 GCP Unit at the University Hospital of Copenhagen will be appointed for monitoring in Copenhagen, local GCP units will be appointed to monitor other sites in collaboration with the Danish GCP-units.

This GCP Unit at the University Hospital of Copenhagen 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 GCP-unit direct access to all study related documents.

17 ETHICS

17.1 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.

17.2 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).

All patients in this study have progressive advanced urothelial cell carcinoma. Recently, vinflunine was approved as a second line treatment, with an improvement of the median overall survival of 2.6 months. Pemetrexed in combination with vinflunine has recently demonstrated some activity in solid tumors, and pemetrexed is known to have significant effect as a second line drug in non-small cell lung cancer and is also known to have effect against urothelial cell carcinomas. 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 best 2nd line therapy known presently, vinflunine, combined with the known active drug pemetrexed. The combination of vinflunine and pemetrexed has not previously been tested in bladder cancer, but studies in other solid tumors have shown manageable and acceptable toxicity of the combination and there is thus a reasonable chance of significant benefit for the participating patients from this treatment regime during the study period.
The patients in the study 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 for this patient population in great need of more efficacious treatment options.

17.3 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 has the right to ask questions about the study and should be given adequate time to make the decision whether 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.

18 DATA HANDLING AND RECORD KEEPING

18.1 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 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. 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, initialed 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.

18.2 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.

19 INSURANCE

Patients included and treated in Denmark will be covered by Patientforsikringen. Patients treated in other Scandinavian countries will be covered by their national public insurance system.

20 PUBLICATION POLICY

The results will be presented in a scientific article.

21 FINANCIAL SUPPORT

This study has been initiated and the protocol written by the Chief Investigators on behalf of NUCOG – a cooperative group of physicians in the nordic countries working clinically with urothelial cancer. The study is supported financially by Pierre Fabre Pharma with an amount of 10.000 d.kr. per patient to cover expences related to medical procedures. The amount is transferred directly to the clinical trial units of the participating departments. The Investigators have no financial involvment with the financial supporter Pierre Fabre Pharma

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 MPA 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 authorization 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.
- Unacceptably 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 considered unacceptably low.

22.5 Study time schedule

Anticipated start of study: Q3, 2014

Estimated recruitment period: Q3, 2014 – Q1, 2016