The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Patients with Advanced Urothelial Cancer "Unfit" for Cisplatin Based Chemotherapy: Phase III-Results of EORTC Study 30986

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Randomized phase II/III study assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in previously untreated patients with advanced urothelial cancer ineligible for Cisplatin based chemotherapy.

EORTC Genito-Urinary Tract Cancer Group

protocol ID: EORTC-30986
ClinicalTrials.gov Identifier NCT00014274

1. Selection of patients

1.1. Inclusion criteria

- Histologically proven transitional cell cancer of the urinary tract (including renal pelvis, ureters, urinary bladder, urethra)
- Unresected lymph node (N+), distant metastases (M1, stage IV) or unresectable primary bladder cancer (T3-4), with measurable disease as defined in the RECIST criteria (13)
- Lesions occuring in tissues which have been irradiated previously may only be assessed if irradiation treatment has been completed at least 3 months earlier, and if the lesions have since progressed or are new
- No previous systemic treatment, neither cytotoxic nor biologic
- "Unfit" patients who are ineligible for cisplatin-based chemotherapy: performance status 2 (WHO) and/ or impaired renal function (glomerular filtration rate (GFR) > 30 ml/min but < 60ml/min). GFR will be assessed by direct measurement (EDTA clearance or creatinine clearance) or, if not available, by calculation from serum/plasma creatinine (Cockcroft and Gault formula)
- Corrected calcium within the normal limit
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient randomization, written informed consent must be given according to ICH GCP, and national/local regulations.
- Fertile men and potentially chilbearing women should use an appropriate contraceptive method during and for 6 months after completion of chemotherapy. Patients should be counselled about the long term effects on fertility of chemotherapy if appropriate.

1.2. Exclusion criteria

- Any of the above criteria not met
- Previous systemic chemotherapy (including adjuvant and neoadjuvant chemotherapy)
- Inadequate bone marrow function i.e. WBC < 4000/mm3 or platelets < 125.000/mm3
- Liver function impairment (bilirubin > 1.25 x N and/ or ASAT/ALAT > 3 x N; in case of known liver metastases ASAT/ALAT > 5 x N)
- Presence of brain metastases or other CNS lesions
- A concomitant, second or previous malignancy except for cured basal cell skin cancer and carcinoma in situ of the cervix
- Women who are pregnant or lactating

2. Schema and treatment plan

This is a randomized phase II trial assessing Gemcitabine/Carboplatin and Carboplatin/Methotrexate/Vinblastine extended into a randomized phase III study.

Treatment should be continued until disease progression or intolerable toxicity occurs. In case of a complete response, two more cycles should be given.

Treatment I: Carboplatin/Methotrexate/Vinblastine

Methotrexate	30 mg/m^2	i.v. days 1, 15, 22	q 4 weeks
Carboplatin	dose in mg=4.5x(GFR+25)	i.v. day 1	q 4 weeks
Vinblastine	3 mg/m^2	i.v. days 1, 15, 22	q 4 weeks

Treatment II: Gemcitabine/Carboplatin

Gemcitabine	1000 mg/m^2	i.v. days 1 and 8	q 3 weeks
followed by			
Carboplatin	dose in mg=4.5x(GFR+25)	i.v. day 1	q 3 weeks

2.1. Methotrexate

The drug is supplied in 2-ml vials containing 50 mg of sterile cryodesiccated sodium MTX powder without preservatives. The drug may be diluted with 30 ml or less of a suitable diluent (e.g., sodium chloride for injection USP).
Methotrexate 30mg/m^2 will be given on days 1, 15 and 22 of treatment arm I by the intravenous route by bolus injection.

2.2. Carboplatin

The drug is supplied in 5ml/15ml/45ml vials containing 50mg/150mg/450mg carboplatin and water for injection.
The total dose of carboplatin is based on renal function (dose in mg= 4.5x(GFR+25)) and will be given on day 1 of treatment arm I or day 1 of treatment arm II intravenously over one hour in 500 ml of 5% dextrose after administration of Gemcitabine.

2.3. Vinblastine

The drug is supplied as a lyophilized powder in ampoules of 10 mg. The drug is reconstituted by adding 10 ml of sodium-chloride injection to the 10 mg vial.
Vinblastine 3mg/m^2 will be given on days 1, 15, 22 of treatment arm I intravenously via a newly placed freely flowing catheter, by bolus injection. Care must be taken to avoid extravasation.

2.4. Gemcitabine

Gemcitabine is supplied as a lyophilised powder in sterile vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt, mannitol, and sodium acetate. The lyophilised product should be stored below 30°C. Drug will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/ml. The concentration for 200 mg and 1 g vials should be no greater than 40 mg/ml. An appropriate amount of drug will be prepared with normal saline and administered as a continuous infusion over approximately 30 to 60 minutes, with a 30-minute infusion considered ideal. Once the drug has been reconstituted it should be stored at room temperature and used within 24 hours.

Gemcitabine 1000mg/m^2 will be given on days 1 and 8 of treatment arm II as a 30-minute intravenous infusion in 500 ml sodium chloride. Prolonged infusion time increases the toxicity.

3. Rules for dose modification

3.1. Hematological Toxicity

Treatment arm I (Carboplatin/Methotrexate/Vinblastine)

Complete white blood cell (WBC) and platelet count weekly in every cycle. Absolute neutrophils count (ANC) is recommended and is mandatory whenever WBC < 3.0 x 10^9/l.

Dose modifications day 1:

WBC x 10^9/l		**ANC x 10^9/l**		**Platelets x 10^9/l**	**% dose of Methotrexate**	**% dose of Carboplatin**	**% dose of Vinblastine**
≥ 3.0	and	≥ 1.5	and	≥ 100	100	100	100
< 3.0	or	< 1.5	or	< 100	Delay 1 week	Delay 1 week	Delay 1 week

Dose modifications days 15, 22:

WBC x 10^9/l		**ANC x 10^9/l**		**Platelets x 10^9/l**	**% dose of Methotrexate**	**% dose of Vinblastine**
≥ 3.0	and	≥ 1.5	and	≥ 100	100	100
< 3.0	or	< 1.5	or	<100	Withhold	Withhold

Dose modifications for subsequent cycles:
At day 1, 25% dose reduction of all drugs if during the nadir one or more of the following occurs:

- grade IV neutropenia (ANC < 0.5 x 10^9/l) with fever > 38.5 C or
- grade IV thrombocytopenia (<10.0 x 10^9/l) for more than 3 days or
- thrombocytopenia with active bleeding during the nadir.

If a patient requires more than 2 weeks for hematologic recovery (defined as at least WBC is ≥ 2.0 x 10^9/l, ANC ≥ 1.0 x 10^9/l and platelets ≥ 75 x 10^9/l), treatment should be continued with 75% of all three drugs.

Treatment arm II (Gemcitabine/Carboplatin)

Complete white blood cell (WBC) and platelet count weekly in every cycle. Absolute neutrophils count (ANC) is recommended and is mandatory whenever WBC < 3.0 x 10^9/l.

Dose modifications day 1:

WBC x 10^9/l		**ANC x 10^9/l**		**Platelets x 10^9/l**	**% dose of Gemcitabine**	**% dose of Carboplatin**
≥ 3.0	and	≥ 1.5	and	≥ 100	100	100
< 3.0	or	< 1.5	or	< 100	Delay 1 week	Delay 1 week

Dose modifications day 8:

WBC x 10^9/l		**ANC x 10^9/l**		**Platelets x 10^9/l**	**% dose of Gemcitabine**
≥ 3.0	and	> 1.5	and	≥ 100	100
≥ 2.0 – 3.0	and	≥ 1.0	and	>100	100
1.0 – 1.9	or	> 0.5 - <1.0	or	50-99	50
< 1.0	or	<0.5	or	< 50	Withhold

Dose modifications for subsequent cycles:
At day 1, 25% dose reduction of all drugs if during the nadir one or more of the following occurs:

- grade IV neutropenia (ANC < 0.5 x 10^9/l) with fever > 38.5 C or
- grade IV thrombocytopenia (<10.0 x 10^9/l) for more than 3 days or
- thrombocytopenia with active bleeding during the nadir.

If a patient requires more than 2 weeks for hematologic recovery (defined as at least WBC is ≥ 2.0 x 10^9/l, ANC ≥ 1.0 x 10^9/l and platelets ≥ 75 x 10^9/l), treatment should be continued with 75% of all three drugs.

3.2. Renal Toxicity

Carboplatin will be adjusted every cycle using Calvert's formula. Methotrexate in treatment arm I should be omitted when the glomerular filtration rate (GFR) is less than 30 ml/min or the serum creatinine level is greater than 2 mg/dl. The dose of Methotrexate will be reduced by 50% if serum creatinine level is between >1.5 and 2.0 mg/dl. For gemcitabine no dose modification is necessary if the GFR is ≥ 30 ml/min. Gemcitabine is withheld if the GFR is less than 30 ml/min.

3.3. Mucosal toxicity

In several studies mucositis grade 3 developed in 3%-8% of patients treated according to treatment arm I. Methotrexate will be delayed one week if any mucositis is present. Patients with severe grade 3 or 4 mucositis will have the methotrexate dose decreased to 20 mg/m^2 in all subsequent courses. Folinic acid 15 mg (oral or iv) every 6 hours x 4 may be started 24 hours after methotrexate although only in cases who have had severe grade 3 or 4 mucositis.

3.4. Neurotoxicity

The dose of vinblastine will be decreased to 2mg/m^2 in case of grade 2 neurotoxicity. In case of grade 3 or 4 neurotoxicity, vinblastine should be stopped and patients may be taken off study and treated at the investigator's discretion.

3.5. Extravasation

Vinblastine is a potent vesicant that may cause significant tissue damage if extravasation occurs. If extravasation occurs or is suspected, treatment should be discontinued and aspiration of any residual drug remaining in the tissues should be attempted. The application of local heat and injection of hyaluronidase, 150 mg, subcutaneously in a circumferential manner around the needle site are thought to minimize discomfort and the possibility of latent cellulitis.

3.6. Other toxicities

Grade 1-2: no dose reductions.
Grade 3 (alopecia excluded): 25% dose reduction in all drugs
Grade 4 (alopecia excluded): the patient may be withdrawn from the study at the investigators discretion. If the patient continues under treatment, a 50% dose reduction should be considered.

In case of nausea and vomiting, adequate parenteral fluid, electrolyte substitution and application of modern antiemetics and dexamethason if necessary should be done.
In case of pleural effusion or ascites occurrence and no clear evidence of progression, patients in arm I will withdraw Methotrexate administration until complete resolution.

4. Measurement of treatment effect (including response criteria, definitions of response and survival, and methods of measurement)

4.1. Objective tumor response

Objective tumor response, measured according to the RECIST criteria [13], will be used as the principal end-point in the phase II part of this trial. These criteria have been developed to determine whether the agent or combination under study demonstrates sufficiently encouraging activity to warrant further testing. The response rate will be used as a screen to warrant further testing. Its use does not assume a therapeutic benefit of such responses but rather implies some degree of biologic anti-tumor activity of the combination.
The response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions and followed until disease progression. Unresectable primary bladder cancer (T3-4) can only be used as a target lesion if the tumor is measurable (MRI or CT scan) as defined in the RECIST criteria.
The following paragraphs are a quick reference to the RECIST criteria. The complete criteria are in the published RECIST document [13] which is also available at http:/ww3.oup.co.uk/jnci/extra/920205.pdf.
Protocol specific options and definitions that were left open in the RECIST criteria are indicated in bold italic characters.

4.2. Measurability of tumor lesions at baseline

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm. With spiral CT scan, lesion must be ≥ 10 mm in at least one dimension.
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and other non-measurable lesions. These include: bone lesions; leptomeningeal disease; ascites; pleural / pericardial effusion; inflammatory breast disease; lymphangitis cutis / pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

4.3. Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- **Clinically detected lesions** will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography -including a ruler to estimate the size of the lesion- is recommended.
- Lesions on **chest X-ray** are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **CT and MRI** are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and pelvis while head & neck tumors and those of the extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, **ultrasound** (US) should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of **endoscopy** and **laparoscopy** for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained. ***This will apply to the present study.***
- **Tumor markers** alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared. ***In the present study, no markers will be measured at baseline or at each disease evaluation and none will be used as described above in the definition of complete response.***
- **Cytology and histology** can be used to differentiate between PR and CR in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). ***This will apply to the present study.***

4.4. Tumor response evaluation

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

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all 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 diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).
A sum of the longest diameter (LD) for **all target lesions** will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.
All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required but the presence or absence of each should be noted throughout follow-up.

4.4.2. Response Criteria

4.4.2.1. Evaluation of target lesions

* Complete Response (CR): Disappearance of all target lesions.
* Partial Response (PR): At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
* Progression (PD): At least a 20% increase in the sum of 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.
* Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

4.4.2.2. Evaluation of non target lesions

* Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.
* Incomplete Response / Stable Disease: Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
* Progression (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [(1)].

Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

4.4.2.3. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / 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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

4.4.3. Confirmation

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed. ***In the present study, responses always need to be confirmed.***
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. ***In the present study, any interval greater than or equal to 4 weeks is appropriate, but it is recommended to use a 6 week or 8 week interval depending on the treatment group.***
In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval defined in the protocol. ***In the present study, this interval is 6 weeks or 8 weeks depending on the treatment group.***

4.4.4. Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

4.5. Progression-free survival

Progression-free survival is calculated as the time from randomization to either the first progression of the disease or the date to death, whichever occurs first. Patients still alive with no evidence of disease at the time of their last visit are censored at the time of the most recent information.

4.6. Overall Survival

Overall survival is computed as the time between randomization of a patient and the date of death, death due to any cause. Patients still alive at the time of the analysis are censored at the date of the most recent follow-up.

4.7. Assessment of toxicity

In this protocol the toxicity (both acute and intermediate) will be measured using the CTC, version 2.0 available on the web site http:// ctep.info.nih.gov/CTC3/default.htm. In grading the toxicity, the worst grade observed per cycle for each side effect is to be reported.

5. Reasons for early cessation of trial therapy

6. Objectives and entire statistical section

6.1. Objectives

The primary endpoint was to compare overall survival of the 2 treatment arms.

The secondary endpoints were to compare the CR rates and progression free survival of the 2 treatment arms and to document symptoms and aspects of quality of life at baseline and after treatment, and the acute and intermediate (1-2 years) side effects of treatment.

6.2. Statistical design for the Phase III

The median duration of survival on the MTX/Carb/VBL arm is estimated to be 9 months. In order to detect an increase of 50% in median survival on the gemcitabine/carboplatin arm to 13.5 months based on a two sided logrank test at error rates alpha = 0.05 and beta = 0.20, a total of 192 deaths are required. Assuming 85 % of the patients will be followed to death, then a total of 225 patients are required. With an expected entry rate of 45 patients per year, then the required number of patients will be entered in 5 years.