MD Anderson Protocol Cover Sheet

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Protocol Title	Phase II Trial of 5-FU, Leucovorin, Gemcitabine, and Cisplatin for Adenocarcinomas of the Urothelial Tract and Urachal Remnant
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1.0 OBJECTIVE

1.1 To estimate the response rate and overall survival of patients with metastatic or unresectable adenocarcinomas of the urothelial tract or urachal remnant who are treated with combination chemotherapy consisting of 5-FU, leucovorin, gemcitabine and cisplatin.

2.0 BACKGROUND

2.1 Adenocarcinoma is an uncommonly encountered histology in the urinary tract, and in fact, such cancers are not a homogeneous group. The differential diagnosis includes metastatic cancers from other sites (usually GI), clear cell carcinomas of the urethra;[1] truly urothelial cancers with glandular differentiation;[2] and finally, enteric-type adenocarcinomas arising in the urachus/bladder dome that have a histology and natural history very much like colon cancer.[3]

2.2 Because urothelial adenocarcinomas are uncommon, there are literally no reports of any prospective, systematic approach to their classification and therapy. Currently, we see about 10 to 15 cases per year, and thus, it seems that we have an opportunity to conduct such a study. Moreover, we have now accumulated several anecdotal cases of patients treated with a 4-drug combination regimen developed by the GI group at Emory University[4] that seems active enough to merit a formal evaluation. Finally, in the context of our position of having the only funded SPORE in bladder cancer, we believe that we will have an opportunity to bring some of the other larger centers into a collaboration to consistently evaluate and treat some of the less common cancers, and by such a mechanism increase accrual.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion *Criteria*

3.1.1 Histologic proof of cancer originating from the urinary tract with adenocarcinoma as the predominant (≥ 50%) histology. Dr. Czerniak and/or Dr. Tamboli will be consulted in equivocal cases of mixed histology. The Study Chairman is the final arbiter in questions of mixed histology.

3.1.2 Bi-dimensionally measurable disease. All patients must have measurable or evaluable disease. In general, liver and lung lesions should be at least 1 cm, and patients with node-only disease should have lesions of ≥ 1.5 cm in greatest dimension. Patients with disease confined to bone may be eligible if a measurable lytic

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defect, or soft-tissue component is present. Those without measurable disease may be eligible if a serum marker is elevated (≥ 4 x ULN) (ie: CEA, CA-125, CA19-9, βhCG, etc). The Study Chairman is the final arbiter in questions related to measurability. Patients with a three-dimensional mass or pelvic sidewall fixation on bladder examination under anesthesia are considered to have measurable disease.

3.1.3 Patients are eligible if they have evidence of metastatic disease, or if their tumor is surgically unresectable. In the absence of grossly metastatic disease, all patients should be seen and evaluated by a member of the Urology staff to assess their potential for resection.

3.1.4 Patients must have adequate physiologic reserves as evidenced by:

- Life expectancy of at least 9 months (based on co-morbidity) & at least 9 weeks based on the natural history of their cancer.
- Zubrod Performance Status (PS) of ≤ 2; or 3 if of recent onset and due entirely to the cancer and not to comorbidity, and especially if the compromised performance status is due to uncontrolled pain which is expected to be rapidly reversible when therapy starts.
- Adequate bone marrow function as defined by absolute neutrophil count ≥ 1,800 and platelet count ≥ 150,000. Supranormal values judged to be of benign or inconsequential etiology are acceptable.
- Transaminase (either SGPT or SGOT) ≤ 2x the upper limit of normal.
- Conjugated bilirubin ≤ 2x the upper limit of normal.
- Creatinine clearance (either measured or estimated using the formula of Cockcroft and Gault) of ≥ 35 mL/min:

  CL_{cr} = [(140-age) • wt(kg)]/[72 •Creat (mg/dL)] (For females, x 0.85)

3.1.5 Patients must sign an informed consent indicating that they are aware of the investigational nature of this study, in keeping with the policies of this hospital.

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3.1.6 Patients must be at least 6 weeks out from pelvic irradiation, and must not have had more than 10% of the bone marrow irradiated.

3.1.7 Patients with a history of cardiac disease, or evidence of ischemic heart disease on EKG must have adequate cardiac function with an EF ≥ 40% to participate.

3.1.8 Patient must be at least 18 years of age to participate in this study.

3.2 Exclusion Criteria

3.1.1 Patients with metastases to the bladder from a primary adenocarcinoma arising outside the urinary tract are ineligible.

3.1.2 Overt psychosis or mental disability or otherwise incompetent to give informed consent.

3.1.3 A life threatening illness (unrelated to tumor) that would prevent completion of protocol therapy.

3.1.4 Pregnant or nursing women, as the drug therapy regimen, and support medications pose significant potential risks to the fetus and newborn.

3.1.5 Patients with second malignancies are eligible provided that the expected outcome from the second cancer is such that this will not interfere in the delivery of this therapy, or the assessment of response.

3.1.6 Patients with uncontrolled CNS metastases are not eligible.

4.0 TREATMENT PLAN

4.1 Patients will treated on a 21 day cycle according to the following schedule:

Agent	Day	Dose
5-Fluorouracil	1 - 5	200 mg/m^2 IVCI daily x 5 days
Leucovorin	1 - 5	10 mg/m^2 daily x 5 days
Cisplatin	1 - 5	20 mg/m^2 daily x 5 days
Gemcitabine	1 & 5	200 mg/m^2 (Two doses only)

4.2 G-CSF and other supportive measures can be given freely as seen fit by the attending physician. It is suggested that the first cycle be administered in the hospital, especially if the estimated creatinine clearance is less than

60 mL/min.

4.3 Standard orders for this regimen are included as appendix E.

4.4 Patients will receive full dose chemotherapy unless they experience unacceptable toxicity, as outlined in Section 8, have evidence of progressive disease, or the patient or physician wishes to discontinue treatment. While there is no limit on the total number of cycles of chemotherapy, it is expected that most patients will receive between 2-6 cycles of therapy.

4.5 In general, hematopoietic growth factor support will be used according to ASCO guidelines.[5] Patients may receive anti-emetics, corticosteroids, anxiolytics and other supportive measures freely.

4.6 Most patients will have a long-term central venous access device; this will be mandatory for out-patient chemotherapy administration. Patients may receive this treatment as an inpatient, or as an outpatient at the discretion of their treating physician.

4.7 Low-dose warfarin (i. e., 1 or 2 mg daily, such that the prothrombin time is minimally prolonged, i. e. INR < 1.5) is strongly recommended for thrombosis prophylaxis in patients with a central line.[6] In addition, all patients with a significant pelvic mass or pelvic adenopathy should have prophylactic anticoagulation with both low dose warfarin and aspirin. Warfarin should be held during periods where the platelet count is less than 50,000 or if the patient experience bleeding. Though routine monitoring of INR is not required with this dose of warfarin, a PT or INR will be monitored every 2 cycles.

4.8 Patients experiencing gemcitabine related skin rash will be treated prophylactically with dexamethasone 2 mg p.o. bid and benadryl 25 to 50 mg p.o. q 6 h ATC x 5 days starting on day 1.

5.0 PRE-TREATMENT EVALUATION

5.1 All patients must have an appropriate history and physical examination. The medical record should include the following details: the date of original diagnosis, the date of the first documentation of metastatic disease, dates and details related to systemic chemotherapy, extent of disease when systemic chemotherapy was started, patient height and weight, and the extent of disease at the time of registration on this protocol. The physical examination must include the presence or absence of pathologic adenopathy; the results of cardiovascular examination, including, and the presence or absence of peripheral edema; examination of the oral cavity;

chest examination, and abdominal examination. All patients without grossly metastatic disease must be seen by a member of the Urology department at M. D. Anderson and have a cystoscopy and examination under anesthesia (EUA) prior to registration.

5.2 Laboratory studies: CBC with platelets and automated differential; electrolytes, magnesium, calcium, albumin, LDH, AST (or ALT), alkaline phosphatase, total bilirubin, creatinine, BUN and prothrombin time. These studies should be obtained within 3 weeks of study entry. Tumor markers to be drawn prior to initiation of therapy (but are not part of the assessment of eligibility) are: CA125, CA19.9 and CEA.

5.3 Other baseline studies required at study entry: chest x-ray (within 6 weeks) & EKG (within 6 months), CT (or MRI) of the abdomen and pelvis within 6 weeks of study entry. In addition, patients with a history of cardiac disease, or ischemic heart disease on EKG must have a baseline measurement of ejection fraction.

6.0 ON-STUDY EVALUATION

6.1 All patients will have a clinical assessment every 2 cycles (6weeks). In addition to tumor response, data on symptom status, pain medication use, and acute and cumulative toxicity will be recorded. Particular note will be made of any transfusion requirements. Patients must be seen at M.D. Anderson Cancer every 6 weeks for these assessments.

6.2 Patients may receive chemotherapy either at M.D. Anderson, or locally under the supervision of their outside oncologist. The following documents will be provided to their physician:

- A letter to the home physician (Appendix G)
- A copy of the informed consent
- The protocol abstract
- The protocol “evaluation during treatment” section
- A sample set of chemotherapy orders outlining treatment (Appendix E)

6.3 The attending physician and/or oncology research nurse, or the outside physician and/or their designated nurse must see every patient prior to each cycle of chemotherapy. All patient will have a CBC with differential and platelet count and creatinine, electrolytes, magnesium, and glucose prior to each cycle of chemotherapy.

6.4 For one cycle, all patients will have a CBC with differential and platelet count every day staring on day 9 or 10, and continuing until the ANC is ≥ 1,000 and the platelets count is ≥ 50,000 . In addition, electrolytes and creatinine will be measured on cycle days 10 and 16. The treating physician may decrease the intensity of blood count monitoring in subsequent cycles as appropriate.

6.5 Patients with elevated tumor markers at study entry should have these repeated at the six-week evaluation, even if they normalize.

6.6 Long-term follow-up will be done at the Center for GU Oncology, usually around every 3-6 months. Standard follow-up will consist of periodic CT of the abdomen and pelvis, chest x-ray, CBC, and biochemical profile.

7.0 CRITERIA FOR RESPONSE, PROGRESSION AND CENSORING

7.1 Response will be assessed every 2 cycles with application of the following assessment definitions:

7.2 Assessment Definitions:

7.2.1 **Evidence of Benefit**: This applies to patients having completed one six-week block of therapy, and corresponds to the threshold of response necessary for continuing with that particular regimen for another 6 weeks. This designation requires a 50% decrease in disease volume (estimated by the product of the two greatest dimensions of a representative measurable lesion) with no evidence of progression in any site. For patients with cancer related pain (or other symptoms) at study entry, these must be improving. In addition, patients with elevated tumor marker(s) at entry must demonstrate ≥ 50% marker reduction.

7.2.2 **Complete Response**: Patients will be counted as a complete response if they have no radiological evidence of tumor, have no signs or symptoms of disease, and have normalized their tumor markers (in those with initially elevated markers). In addition, those with an intact, tumor-containing bladder, must have a cystoscopy and exam under anesthesia to confirm a complete response.

7.2.3 **Partial response**: Any response (as noted in section 7.2.1) less than a complete response.

7.2.4 **Progressive disease**: Progressive disease is at least 25% increase in tumor volume, or any new site of involvement, including the CNS. Increasing severity of symptoms, if judged by

the treating physician to be due to progressive disease, will also be counted as progression, even if these are not accompanied by an "objective" indicator. In general, any unequivocal increase (i.e. to greater than 5 mi.u./mL in beta-hCG) in a male patient will be taken to represent progressive disease, as will two consecutive rises amounting to a total of at least 125% of baseline for any other tumor marker.

8.0 CRITERIA FOR TOXICITY & DISCONTINUING/ALTERING THERAPY

8.1 NCI Common Toxicity Criteria (CTC) v 2.0 will be used for evaluating toxicity and adverse events. These criteria are available at http://ctep.info.nih.gov, and are incorporated into the GU database toxicity module.

8.2 Non-Hematologic Toxicities

8.2.1 **Angina**: Although uncommon, fluorouracil has been associated with chest pain, anginal attacks, ischemic electrocardiographic changes, myocardial infarction, cardiomyopathy, and very rarely, sudden death. Any patient experiencing cardiac symptoms while on the study will be removed from the study and counted as toxicity to therapy.

8.2.2 Patients with **transaminases** greater than 4 times the upper limit of normal (ULN) should discontinue all therapy until the transaminases are < 2x ULN. At the discretion of the treating physician, treatment can restart with WEEKLY liver enzyme monitoring.

8.2.3 Grade 3 or 4 **mucositis** should be treated prophylactically with carafate (and possibly with antifungals and antivirals) in subsequent cycles.

8.3 Hematologic Toxicity

8.3.1 Grade 3 & 4 **hematologic** toxicity by CTC v2.0 is anticipated to be universal. Hematologic toxicity requiring dose reduction in subsequent cycles will be defined as: 1) Any episode of **neutropenic fever**; 2) ANC < 500 for ≥ 5 days; 3) Platelet count < 10,000 at any time; 4) Platelet count < 30,000 ≥ 4 days.

8.3.2 Growth factors will be used in accordance with ASCO guidelines.[5] Erythropoeitin and Neumega may be used as the treating physician deems appropriate.

8.4 Dose reduction schedule:

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8.4.1 For **5-Fluorouracil**

In the event of **hand-foot syndrome** ≥ Grade (G)3, **diarrhea** ≥ G3, or **mucositis/stomatitis** ≥ G3, the dose of 5-fluorouracil will be reduced according to the following schedule:

Dose Level	5-Fluorouracil	Leucovorin	Gemcitabine	Cisplatin
0	200 mg/m^2	10 mg/m^2	200 mg/m^2	20 mg/m^2
-1	150 mg/m^2	7.5 mg/m^2	200 mg/m^2	20 mg/m^2

Patients will continue receiving gemcitabine and cisplatin at the initial dose level. Patients with persistent toxicity at dose level –1 will be removed from the study.

8.4.2 For **Gemcitabine**:

In the event of **thrombocytopenia** as outlined in section 8.3.1, the dose of gemcitabine will be reduced according to the following schedule:

Dose Level	5-Fluorouracil	Leucovorin	Gemcitabine	Cisplatin
0	200 mg/m^2	10 mg/m^2	200 mg/m^2	20 mg/m^2
-1	200 mg/m^2	10 mg/m^2	150 mg/m^2	20 mg/m^2

Patients will continue receiving 5-fluorouracil, leucovorin, and cisplatin at the initial dose level. Patients with persistent toxicity at dose level –1 will be removed from the study.

8.4.3 All other toxicities:

In the event of generalized myelosuppression, and for all other toxicities, agents will be dose reduced according to the following schedule:

Dose Level	5-Fluorouracil	Leucovorin	Gemcitabine	Cisplatin
0	200 mg/m^2	10 mg/m^2	200 mg/m^2	20 mg/m^2
-1	150 mg/m^2	7.5 mg/m^2	150 mg/m^2	15 mg/m^2

Patients with persistent toxicity at dose level –1 will be removed from the study.

8.5 Patients will continue on therapy until:

- Completion of therapy as outlined above
- Unacceptable toxicity
- Patient or treating physician wishes to stop

8.6 Dose escalations are not allowed.

9.0 STATISTICAL CONSIDERATIONS

9.1 Simon's optimal two-stage design will be used for the two patient cohorts separately. For the urachal cohort, it is estimated that 5 patients may be recruited per year. The null hypothesis is that the response from the conventional chemotherapy is less than or equal to 10% versus the alternative hypothesis that will lead to a response rate of 30% or greater. At the first stage, 7 patients will be enrolled. If none of the first 7 patients respond, the trial will be terminated; otherwise another 11 patients will be treated for a total of 18. If fewer than 4 patients respond among 18 patients, the combination chemotherapy will be concluded ineffective.

9.2 For the adenocarcinoma cohort, it is estimated that a maximum of 28 patients can be recruited in total with the accrual rate of 15 patients in a year. The null hypothesis is that the response from conventional chemotherapy is less than or equal to 40% versus the alternative hypothesis that the response rate is greater than or equal to 60% for the combination therapy. At the first stage, 16 patients will be enrolled. If 6 or less of the first 16 patients respond, the trial will be terminated; otherwise another 12 patients will be treated for a total of 28. If fewer than 15 patients respond among 28 patients, the combination chemotherapy will be concluded ineffective. The design for each cohort has type I and II errors of 0.1 and 0.2, respectively.

9.3 For each single arm trial, a stopping boundary is also imposed to monitor the dose-limiting toxicity of the new combination chemotherapy. The trial should be stopped for the 90% probability that the dose-limiting toxicity is greater than 40%. We will monitor patients in groups of 3 sequentially. The stopping boundary can be obtained using Bayesian monitoring rule. The results are summarized in the following table. For example, if dose-limiting toxicity is observed in 4 out of the first 6 patients, we should stop

the trial.

# of patients	*3*	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*27*
# of patients with dose-limiting toxicity	3	4	6	7	9	10	12	13	14

10.0 DATA AND PROTOCOL MANAGEMENT

10.1 All patients will be registered at M.D. Anderson Cancer Center. All patients will be registered on the MDACC OPR approved database prior to the initiation of therapy. All patients data will be entered into GURU, the research database for the GU Center. GURU will be the primary repository of all data related to this trial.

10.2 Dr. Siefker-Radtke is the Study Chairman for this study and is the final arbiter in all questions of response or toxicity grading.

10.3 Toxicity and adverse event reporting will be according to institutional policy as outlined in Appendix B. The policy and procedures related to IRB oversight of data monitoring are included as Appendix A.

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11.0 REFERENCES

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