A PHASE II STUDY OF DOSE-DENSE GEMCITABINE PLUS CISPLATIN (DDGC) IN PATIENTS WITH MUSCLE-INVASIVE BLADDER CANCER WITH BLADDER PRESERVATION FOR THOSE PATIENTS WHOSE TUMORS HARBOR DELETERIOUS DNA DAMAGE RESPONSE (DDR) GENE ALTERATIONS

Eligibility Criteria (see Section 3.0)

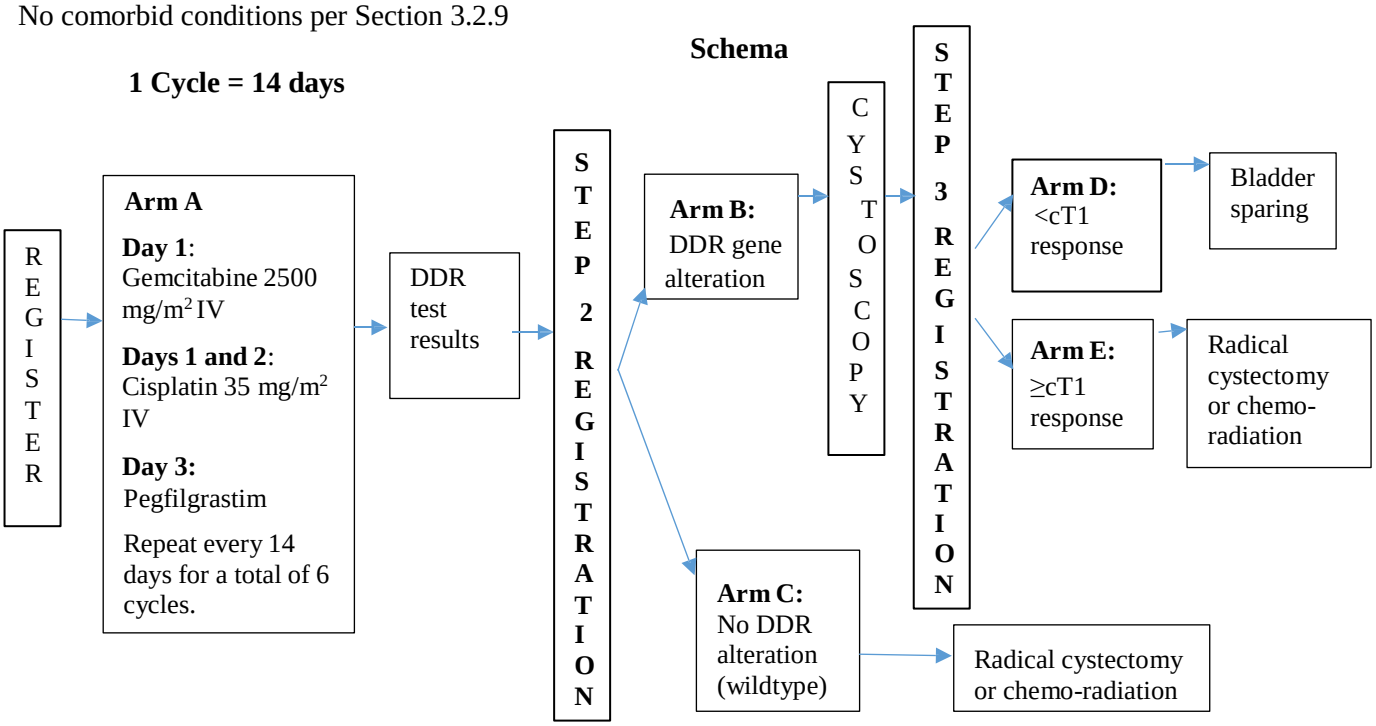
Histologically confirmed urothelial carcinoma of the bladder
10-20 unstained slides or 1 FFPE block from pre-treatment TUR available
Clinical stage T2-T4aN0/xM0
Candidate for radical cystectomy
No prior systemic chemotherapy or radiation therapy for the bladder
No major surgery or RT ≤ 4 weeks
Non-pregnant and non-nursing
Age >= 18 years
ECOG PS = 0-1
No comorbid conditions per Section 3.2.9

Required Initial Laboratory Values

Absolute neutrophil count (ANC): ≥ 1000/mm^3
Platelet count: ≥ 100,000/mm^3
Calc. creatinine clearance: ≥ 55 mL/min
Total bilirubin: ≤ 1.5 x ULN
AST/ALT: ≤ 2.5 x ULN
Alkaline phosphatase: ≤ 2.5 x ULN

Schema

1 Cycle = 14 days



Chemotherapy is to continue for 6 cycles or unacceptable adverse events (at least 4 cycles must be given for patients to proceed to Step 2 registration). Patients will be followed for five years after completion of chemotherapy or radical cystectomy, or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness that would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day that a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

Step 1 Patient Registration Eligibility Criteria

___ 3.2.1 Documentation of Disease

- Histologically confirmed muscle-invasive urothelial carcinoma of the bladder. Urothelial carcinoma invading into the prostatic stroma with no histologic muscle invasion is allowed, provided the extent of disease is confirmed via imaging and/or EUA. The diagnostic TURBT sample must have been obtained within 60 days prior to registration.
- 10-20 unstained slides (10 micron thickness) of formalin-fixed paraffin-embedded (FFPE) pre-treatment diagnostic transurethral resection (TUR) specimen available (for sequencing), with 2 (5 micron) slides at the start and end of the 10-20 slides, for a total of 12-22 unstained slides. An FFPE block is also acceptable.
- Clinical stage T2-T4aN0/xM0 disease
- Medically appropriate candidate for radical cystectomy as assessed by surgeon
- No concomitant multifocal carcinoma in situ; a single focus is allowed
- One focus of muscle-invasive bladder cancer and/or a tumor <5 cm in size
- No clinical or radiographic evidence for locally advanced or metastatic disease

___ 3.2.2 Prior Treatment

- No prior anti-PD-1, anti PD-L1 therapies, or systemic chemotherapy (prior intravesical induction immunotherapy for non-muscle invasive disease is allowed,

defined as BCG x6 treatments; BCG refractory disease, defined as disease recurrence within 3 months of BCG therapy, is not allowed)

- No prior radiation therapy to the bladder
- No major surgery or radiation therapy ≤4 weeks of registration

___ **3.2.3 Not pregnant and not nursing**

This study involves an agent that has known genotoxic, mutagenic and teratogenic effects. For women of childbearing potential only, a negative pregnancy test done ≤ 14 days prior to registration is required.

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status 0-1**

___ **3.2.6 Required Initial Laboratory Values:**

- Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3
- Platelet Count ≥ 100,000/mm^3
- Calculated creatinine clearance ≥ 55 mL/min
- Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)
- (For patients with documented Gilbert's syndrome Bilirubin ≤ 3 x ULN)
- AST / ALT ≤ 2.5 x ULN
- Alkaline Phosphatase ≤ 2.5 x ULN

___ **3.2.7 Comorbid conditions**

- No hydronephrosis refractory to urinary diversion
- No evidence of NYHA functional class III or IV heart disease
- No ongoing cardiac dysrhythmias of NCI CTCAE Version 5.0 grade ≥2
- No pre-existing sensory grade ≥2 neuropathy
- No pre-existing grade ≥2 hearing loss
- No serious intercurrent medical or psychiatric illness, including serious active infection
- None of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, or transient ischemic attack
- No known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness or other active infection. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with the drugs used in this trial. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy, when indicated.

- No history of allergic reaction attributed to compounds of similar chemical or biologic composition to the agents used in this study.
- No concurrent treatment on another clinical trial; supportive care trials or non-therapeutic trials (e.g., quality of life) are allowed.
- No prior malignancy except for: adequately treated basal or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years. Patients with localized prostate cancer who are being followed by an active surveillance program are also eligible.

Step 2 Patient Registration Eligibility Criteria

- Patients must have completed 4 or more cycles of protocol-directed chemotherapy.

Step 3 Patient Registration Eligibility Criteria (only patients with a DDR gene alteration)

- Deleterious alteration within 1 or more of 9 pre-defined DDR genes within the pre-treatment TURBT DNA (see Appendix I for further information)
- Cystoscopy and imaging performed to determine stage/treatment assignment.