Alliance A031701: 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

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Rationale

A standard of care treatment for muscle-invasive bladder cancer (MIBC) is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy with pelvic lymph node dissection (RC-PLND), leaving most patients with an external drainage bag to collect their urine (urostomy). This surgery is associated with a risk for significant postoperative complications and substantially impacts quality of life.

Retrospective studies have found that select patients who have clinical down-staging of their MIBC following chemotherapy, as assessed by post-chemotherapy cystoscopy, can be managed with close surveillance without a cystectomy. These patients can achieve long-term bladder-intact disease-free survival rates, but there is a risk for both muscle-invasive and metastatic recurrences.

Alterations within certain DNA damage response (DDR) genes are associated with significant sensitivity to cisplatin-based chemotherapy in bladder cancer and are emerging as a predictive biomarker of chemotherapy response.

This study will attempt to identify a subset of patients with DDR mutant MIBC who can be managed with cisplatin-based chemotherapy alone and avoid RC-PLND (an organ-sparing approach). If this study meets its primary endpoint, it would lead to a paradigm shift in the management of MIBC patients with DDR gene alterations.

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Objective

Primary

- To determine the 3-year event free survival, defined as the proportion of patients without invasive or metastatic recurrence following definitive dose dense gemcitabine and cisplatin chemotherapy in those patients whose pre-treatment TURBT tumors harbor deleterious DDR gene alterations and who achieve <cT1 response to chemotherapy.

Secondary

- To determine the clinical response rate (<cT1) for patients harboring deleterious DDR gene alterations following dose dense gemcitabine and cisplatin.
- To determine the bladder-intact and overall survival for DDR-altered patients with <cT1.
- For DDR gene altered patients who elect radical cystectomy despite <cT1, to determine the pT0 rate in this patient population.

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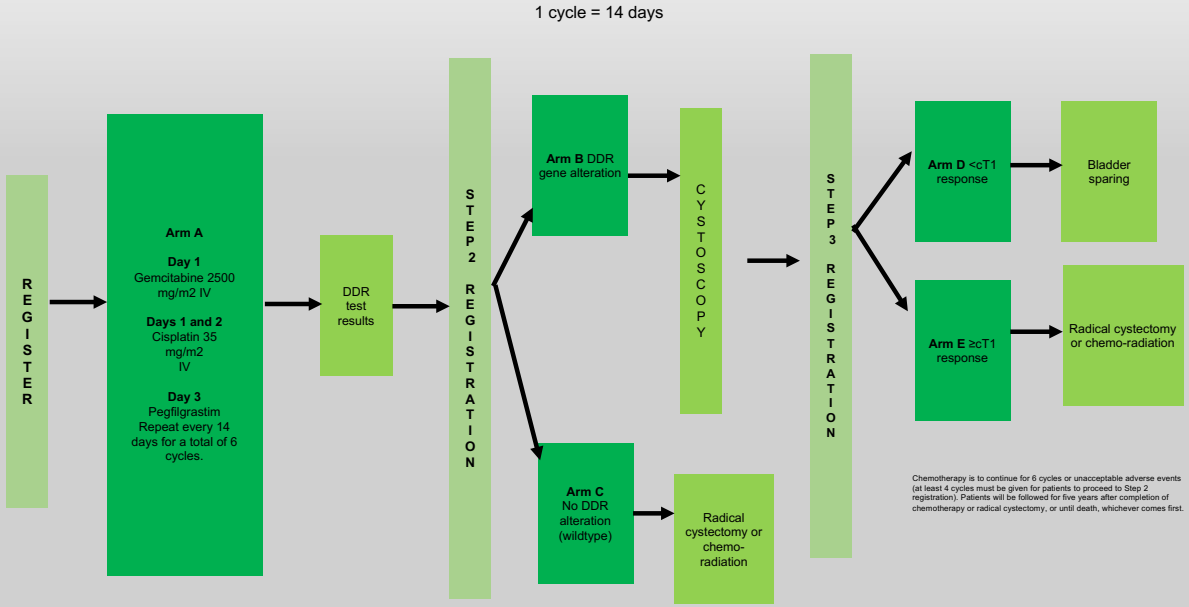
Study Schema



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Treatment Plan

- Protocol treatment is to begin ≤ 7 days from registration.
- There are three registration steps in this trial:
  - **Step 1 Registration:** Eligible patients are registered and will begin chemotherapy within 7 days of registration. Patients will receive a total of 6 cycles of chemotherapy. Those patients receiving at least 4 cycles of chemotherapy will proceed to Step 2 Registration. Patients receiving <4 cycles of chemotherapy will proceed to radical cystectomy.
  - **Step 2 Registration:** At Step 2 registration, sites will use the DDR test results they have received to determine future therapy. Patients without a DDR gene alteration will undergo a radical cystectomy or proceed to chemo-radiotherapy. Patients with a DDR gene alteration will undergo a cystoscopy and then proceed to Step 3 registration.
  - **Step 3 Registration:** Patients with a DDR gene alteration will proceed to Step 3 registration. Based on the results of the cystoscopy, patients will proceed to either bladder sparing or definitive local therapy with either a radical cystectomy or chemo-radiotherapy.

Chemotherapy

Chemotherapy will be given on an outpatient basis, with a total of 6 cycles administered every 14 days. Administration ≤ +/- 1 day of schedule will not be considered a protocol violation. Treatment will continue until disease progression or unacceptable adverse event for a maximum period of 12 weeks. Patients need to complete at least 4 cycles of chemotherapy to proceed to Step 2 registration.

Agent	Dose	Route	Day
Gemcitabine* * Gemcitabine should be administered prior to cisplatin.	2500 mg/m^2	IV	Day 1
Cisplatin	35 mg/m^2	IV	Days 1 and 2
Pegfilgrastim	6 mg	sc	Day 3
OR			
Pegfilgrastim Onpro	6 mg	sc	Applied Day 2

Surgery

Patients receiving at least 4 cycles of chemotherapy will be registered again (Step 2). (Patients receiving <4 cycles of chemotherapy will proceed to a radical cystectomy.) Patients will fit into 1 of 2 categories, based on their DDR gene sequencing results:

- **Radical cystectomy or chemo-radiotherapy:** Those patients whose tumors do not harbor deleterious DDR gene alterations, or patients whose pre-treatment TURBT specimens do harbor a deleterious DDR gene alteration but have any degree of residual invasive disease on post-chemotherapy cystoscopic evaluation or radiographic suspicion for invasive disease (≥cT1) will undergo definitive local therapy, either radical cystectomy or chemoradiotherapy, as per the local investigator's discretion.
- **Bladder Sparing:** If pre-treatment TURBT tissue contains a deleterious DDR gene alteration, patients will be offered the possibility of foregoing definitive local therapy if they achieve a clinical complete response or non-invasive residual disease (CIS/cTa) on a post-chemotherapy cystoscopic evaluation. This evaluation MUST include an aggressive TURBT of the prior site of MIBC.

Chemoradiotherapy (alternative to radical cystectomy) for patients electing for an organ-sparing approach despite not meeting genomic and/or clinical criteria for Arm D

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Key Eligibility Criteria

- Histologically confirmed urothelial carcinoma of the bladder
- Twenty unstained slides or 1 FFPE block from pretreatment TUR available
- Clinical stage T2-T4aN0/xM0
- Candidate for radical cystectomy
- No prior systemic chemotherapy or radiation therapy for the bladder (prior BCG therapy is allowed)
- No major surgery or RT 4 weeks prior to enrollment
- Non-pregnant and non-nursing
- Age > 18 years
- ECOG PS = 0-1
- Cr Clearance >55 mL/min

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