Bladder Cancer 7 (2021) 103–106
DOI 10.3233/BLC-200016
IOS Press

Clinical Trials Corner Issue 7(1)

Piyush K. Agarwal[a,1] and Cora N. Sternberg[b,1]
[a]*The University of Chicago, Chicago, IL, USA*
[b]*Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY, USA*

Received 1 February 2021
Accepted 9 February 2021
Pre-press 11 March 2021
Published 19 March 2021

Dear Readers,

In this issue, we highlight several clinical trials for various stages of localized bladder cancer. These trials are currently actively recruiting and we hope to draw your attention to these trials in an effort to encourage accrual as they answer interesting clinical questions and hopefully can advanced our understanding of bladder cancer and improve upon current treatments for patients. In the future, please reach out to us directly in order to highlight any specific clinical trials at pkagarwal@uchicago.edu or cns9006@med.cornell.edu and/or at BLC@iospress.com.

Sincerely,

Piyush K. Agarwal, MD	Cora N. Sternberg, MD, FACP
Associate Editor, Bladder Cancer	Associate Editor, Bladder Cancer
Director, Bladder Cancer Program	Clinical Director, Englander Institute for Precision Medicine
The University of Chicago	Weill Cornell Medicine
Chicago, Illinois	New York, New York

Study Title: Phase II Trial of Intravesical Gemcitabine and MK-3475 (Pembrolizumab) in the Treatment of Patients With BCG-Unresponsive Non-Muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT04164082

Sponsor: National Cancer Institute/Alliance

Enrollment: 161

Rationale: The current gold standard treatment for BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) is radical cystectomy. However, many patients refuse radical cystectomy and some are unfit for surgery and therefore are treated with various regimens of intravesical chemotherapy or clinical trials. Until recently, many patients in this group were treated with single-agent gemcitabine based on prospective series demonstrating less disease recurrence in patients treated with gemcitabine compared with BCG again in BCG-refractory high grade NMIBC. The recent approval of pembrolizumab as a single-agent for BCG-unresponsive CIS has also widened the therapeutic options for these group of patients. This trial evaluates the combination of both gemcitabine and pembrolizumab in BCG-unresponsive high grade NMIBC (Ta, T1, and/or CIS).

[1]Contributed equally.

Study Design: This is a multicenter Alliance cooperative group trial in which BCG unresponsive NMIBC patients who refuse or are unfit for radical cystectomy undergo weekly gemcitabine intravesical instillation for 6 weeks during the first 2 cycles of concurrent IV pembrolizumab every three weeks until week 10. Patients are then evaluated with cystoscopy and cytology in Week 13 and if no evidence of disease, they then continue to receive both intravesical gemcitabine and systemic pembrolizumab concurrently every 3 weeks with cystoscopy and cytology every 3 months. Mandatory biopsies are performed in the CIS containing cohort at 6 months and all patients undergo an end of study cystoscopy and cytology at 18 months.

Endpoints: There are dual primary endpoints: 6-month complete response rate for patients with a CIS tumor component and 18-month event-free survival rate for all patients. An interim analysis will be performed after 37 patients and at least 12 complete responses are required in order to proceed with the trial. The null hypothesis is a 30% 6-month complete response rate and a 25% 18-month event-free survival rate.

Results: The trial has only accrued 10 of the planned 161 patients and a safety run-in was performed on the first 6 patients and no adverse events were noted. Unfortunatley, the trial was temporarily suspended during the COVID-19 pandemic but is now open for accrual at many centers.

Comments: With efficacy of both agents as single therapies, there is optimism that some synergy will be noted with the combination approach. Unfortunately with the disease space of BCG unresponsive NMIBC crowded with several clinical trials, this trial may not be getting the much needed attention it deserves.There is great interest in immunotherapy in all stages of bladder cancer and it is hoped that prolonged responses can occur and patients will be able to maintain their bladders . Chemotherapy promotes tumor immunity by inducing immunogenic cell death as part of its intended therapeutic effect, and by disrupting strategies that tumors use to evade immune recognition. Chemotherapy may be able to stimulate neoantigens that would make immunotherapy more effective. Given the popularity of the combination off label approach of gemcitabine and docetaxel for BCG-unresponsive NMIBC, supporting this potentially practice changing trial is important in order to understand the role of combination therapy.

Study Title: Phase III Randomized Trial of Concurrent Chemoradiotherapy With or Without Atezolizumab in Localized Muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT03775265

Sponsor: National Cancer Institute/SWOG/Alliance/ECOG-ACRIN

Enrollment: 475

Rationale: Chemoradiation has an established therapeutic role in localized muscle-invasive bladder cancer. This trial is designed to understand the potential of immunotherapy, specifically atezolizumab, to enhance the bladder intact even-free survival rate with chemoradiation.

Study Design: This is a randomized trial for patients with localized muscle-invasive bladder cancer who have refused or are unfit for radical cystectomy whereby patients are randomized to radiation therapy (three-dimensional conformal or intensity-modulated) with chemotherapy as per the treating physician with or without atezolizumab. The chemotherapy can consist of either gemcitabine, cisplatin, or fluorouracil and mitomycin. Patients treated in the atezolizumab arm are treated every 3 weeks for up to 6 months.

Endpoints: The primary outcome is bladder intact event-free survival (BI-EFS) rate for up to 5 years. This composite endpoint includes the absence of muscle invasive bladder recurrence, regional pelvic soft tissue or nodal recurrence, distant metastases, bladder cancer or toxicity related death or cystectomy). Secondary

endpoints include: overall survival at 5 years, disease-specific survival, NMIBC recurrence rate, cystectomy rate, and several immunologic and biologic endpoints.

Results: This trial is actively accruing patients and has accrued 119 of the 475 planned enrollment.

Comments: This trial is ambitious and the criteria for tradiational chemoradiation or trimodal therapy has been expanded in this trial to allow patients with unilateral hydronephrosis and non-diffuse CIS to be enrolled. These clinical features are typically associated with poor response to bladder-sparing therapy so it will be interesting to see how the addition of atezolizumab impacts patients with these features on the trial. The correlatives are extensive and may provide clues towards prediction of responses.

Study Title: 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

Clinicaltrials.gov identifier: NCT03609216

Sponsor: National Cancer Institute/Alliance

Enrollment: 271

Rationale: Bladder preservation is an important topic to address in patients witn muscle invasive bladder cancer (MIBC). Some prospective series have demonstrated a subset of patients with MIBC who have experienced a complete response to neoadjuvant chemotherapy and who have remained free of disease. Patients whose tumors harbor deleterious DNA Damage Response (DDR) Gene Alterations have a greater chance of responding to cisplatin based chemotherapy and obtaining a complete response, perhaps avoiding cystectomy. This trial prospectively tests this hypothesis in patients with MIBC.

Study Design: This trials enrolls patients with histologically confirmed MIBC (cT2-T4aN0/xM0) disease on TURBT and sequences their tumors with MSK-IMPACT. All patients are treated with dose-dense gemcitabine and cisplatin (undergoing current amendment to be given at investigator's discretion with six cycles over 12 weeks or 4 cycles over 12 weeks). Patients with deleterious alterations in at least one or more DDR genes can undergo repeat TURBT and if residual disease is cT0 or CIS, patients can undergo bladder-sparing (observed without additional therapy). Patients with cT1 disease or greater will go on to receive chemoradiation or radical cystectomy. Patients without deleterious alterations in DDR genes will have an option to either undergo chemoradiation or radical cystectomy.

Endpoints: The primary endpoint is 3-year event-free survival in the bladder-sparing group which is 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 harbored DDR gene alterations and who achieved <cT1 response to chemotherapy. The secondary endpoint is the pT0 and <pT2 rate in all patients who ultimately undergo a radical cystecdtomy.

Results: This trial is still accruing and has enrolled at least 91 patients to date.

Comments: This trial is very similar to a trial being conducted at Fox Chase Cancer Center and both test the premise that DDR alterations (genes such as ERCC2, ERCC5, BRCA1, BRCA2, RAD51C, ATR, ATM, FANCC, and RECQL4) in MIBC can predict for patients that might be exceptional responders to chemotherapy. We eagerly await this intelligent strategy for selection of patients for bladder-sparing. Questions still linger regarding the development of MIBC and the potential aggressiveness of any resulting NMIBC in the patients that undergo bladder sparing and have a NMIBC recurrence.

CONFLICT OF INTEREST

Cora N. Sternberg

Consultant: Pfizer, Merck, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Incyte, Medscape, Immunomedics, Clovis Oncology, UroToday, MSD

Piyush K. Agarwal

Advisory Board (unpaid): AstraZeneca; *Advisory Board (paid):* AURA, Verity