Bladder Cancer 3 (2017) 141–142
DOI 10.3233/BLC-179016
IOS Press

Clinical Trials Corner

Dear Readers,

The management of non-muscle invasive bladder cancer (NMIBC) has seen little innovation given the reasonable efficacy of BCG and the ability to salvage refractory cases with radical cystectomy. However, recent threats to BCG supply, the rise of BCG-unresponsive disease, patient reluctance to accept bladder removal and an increased interest in immunotherapy with checkpoint inhibitors have prompted the urologic and medical oncologic communities to develop alternate therapies. This month's issue of the Clinical Trials Corner of *Bladder Cancer* is devoted towards two new SWOG trials that hope to change treatment patterns for NMIBC. They have been described at several urology and oncology society meetings but the trials are now open and actively recruiting patients. In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at: piyush.agarwal@nih.gov or cnsternberg@corasternberg.com and/or at BLC@iospress.com.

Sincerely,

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Study Title: S1602, A Phase III Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming With Intradermal BCG Before Intravesical Therapy for BCG-Naive High-Grade Non-muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT03091660

Sponsor: Southwest Oncology Group (SWOG)

Enrollment: 969

Rationale: Pre-existing immunity as suggested by a positive purified protein derivative (PPD) test is associated with a higher recurrence-free survival rate after BCG therapy in both patients and pre-clinical murine models. Furthermore, initial reports of BCG therapy in bladder cancer by Morales et al described subcutaneous BCG vaccination of patients concurrent with intravesical BCG. However, patients today are no longer treated with intradermal BCG vaccination at the time of intravesical instillation and are often treated without regard to their PPD status. Therefore, this trial evaluates whether intradermal priming 3 weeks before intravesical BCG instillation improves outcomes at one year compared to intravesical BCG instillation without priming. In addition, given the recent shortage of TICE and Connaught BCG strains and the announcement that Sanofi will no longer manufacture the BCG TICE strain, this trial evaluates treatment response with the Tokyo BCG strain as well.

Study Design: S1602 also known as the "PRIME" study is a three-arm, phase III trial that will compare the effect of BCG strains (Tokyo vs TICE) and the effect of intradermal priming before intravesical instillation in patients with BCG-naïve high-grade non-muscle invasive bladder cancer. Eligible patients will be randomized

ISSN 2352-3727/17/€27.50/$35.00

to either standard intravesical TICE strain BCG or Tokyo-172 strain BCG or priming (intradermal Tokyo-172) followed by intravesical Tokyo-172 BCG. The accrual goal is 969 patients (323 patients per arm).

Endpoints: The primary endpoint is time to high-grade recurrence. The secondary endpoint is disease-free rates at 6 months.

Comments: The primary objectives are: (1) to demonstrate non-inferiority of Tokyo-172 BCG strain compared to TICE and (2) to test the hypothesis that intravesical Tokyo-172 BCG with priming is superior to intravesical Tokyo-172 BCG without priming. All groups will undergo BCG induction followed by maintenance therapy as per the SWOG protocol. This trial is aimed at BCG-naïve patients and therefore it will be extremely important that each academic center reach out to local community urologists and encourage trial participation and/or patient referrals in order to successfully accrue the nearly 1000 patients required for this trial as these are the urologists who routinely see BCG-naïve disease.

Study Title: S1605, Phase II Trial of Atezolizumab in BCG-Unresponsive Non-muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT02844816

Sponsor: National Cancer Institute/Southwest Oncology Group

Enrollment: 148

Rationale: There are no established 2nd line therapies other than radical cystectomy with urinary diversion for patients with high-risk non-muscle invasive bladder cancer that is unresponsive to BCG. Building on the track record of immunotherapy in this disease in the form of BCG, as well as preclinical drug testing in animal models and the clinical efficacy of checkpoint blockade in the metastatic setting, this protocol aims to test the efficacy of atezolizumab in BCG-unresponsive high risk NMIBC.

Study Design: S1605 is a single arm, phase II registration trial testing atezolizumab (PD-L1 inhibitor) in BCG-unresponsive, high-risk non-muscle invasive bladder cancer (Ta/T1/Tis). Eligible patients will receive intravenous atezolizumab every 3 weeks for one year.

Endpoints: There are two primary endpoints: 1) the complete response rate at 6 months in patients with carcinoma in situ (CIS; with or without concomitant Ta/T1 tumors) and 2) the event-free survival rate at 18 months in the overall cohort. To the first endpoint, the trial aims to accrue at least 70 patients with CIS. Secondary endpoints include the following: bladder cancer-specific survival, cystectomy-free survival, event-free survival at 18 months in the Ta/T1 subset, incidence of adverse events, toxicity assessment, overall survival, and progression-free survival. Correlative endpoints include expression of PD-L1 status on tumor and immune cells and CD8 in tumor and normal cells by immunohistochemistry (IHC) and expression of immune signatures by RNA sequencing.

Comments: This trial moves checkpoint blockade therapy into the high-risk non-muscle invasive BCG unresponsive disease setting after demonstrating success in metastatic disease. These patients do have an option for radical cystectomy, which is likely curative and so patients must be appropriately counseled. However, most patients can be carefully screened for enrollment with imaging and strict criteria for previous BCG treatment and can likely be salvaged with surgery or trimodal therapy in the event of disease recurrence or progression. A potential concern is whether a systemically delivered therapy will have activity locally within the bladder and whether it will come at the cost of systemic toxicity.