Bladder Cancer 5 (2019) 185–187
DOI 10.3233/BLC-199005
IOS Press

Clinical Trials Corner

Dear Readers,

In this issue, we highlight two exciting trials that reported early results at the 2019 American Urological Association (AUA) Annual Meeting which just concluded in Chicago. These are novel agents with encouraging preliminary data. 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 cns9009@med.cornell.edu and/or at BLC@iospress.com.

Sincerely,

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Received 13 May 2019
Accepted 15 May 2019

Study Title: QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guerin (BCG) in Combination With ALT-803 in Patients With BCG Unresponsive High Grade Non-Muscle Invasive Bladder Cancer (NMIBC)

Clinicaltrials.gov identifier: NCT03022825

Sponsor: Altor BioScience

Enrollment: 160

Rationale: N-803 (also known as ALT-803) is an IL-15 immunostimulatory protein complex (IL-15RαFc) that can promote activation and proliferation of NK (natural killer) cells and CD8+ T cells without recruiting regulatory T cells. It was initially evaluated in a phase Ib trial as an intravesical agent in combination with BCG (NCT02138734) for BCG-naïve patients. Remarkably, all patients on the trial remained disease-free at 24 months; however, as a single arm study, the responses could have been due to the BCG. Therefore, a randomized trial is underway in BCG-naïve patients. In preclinical experiments, the combination of N-803 and BCG reduced tumor burden and recruited cytotoxic T lymphocytes. This led to the combination of intravesical N-803 and BCG being evaluated in BCG unresponsive, high grade NMIBC. Initial findings of this study were just reported at the AUA annual meeting.

Study Design: The Phase II single-arm multicenter trial targeted BCG unresponsive high grade NMIBC patients who refused radical cystectomy. Two cohorts were enrolled: cohort A included patients with CIS with or without Ta or T1 tumors while cohort B only had Ta and/or T1 disease. Patients were then treated with intravesical N-803 + BCG in an induction schedule of weekly treatments for 6 weeks. At 3 months, patients were re-evaluated by cystoscopy and biopsy and either treated with a second induction course or a 3-week maintenance course consisting of weekly treatments for 3 weeks. Maintenance courses continued at 6, 9, 12, and 18 months for eligible patients.

ISSN 2352-3727/19/$35.00

Endpoints: The primary endpoint was complete response (CR) rate of CIS at any time point in cohort A and the disease-free rate at 12 months in cohort B.

Results: 62 patients have been enrolled to date on this trial with 35 patients with CIS (cohort A) and 27 patients with papillary tumor only (cohort B). In cohort A, of 18 evaluable patients, 16 (89%) have achieved CR. In cohort B, of 13 evaluable patients, 10 (77%) demonstrated no disease at their 3-month and 6-month assessment. Of the 8 patients evaluated beyond this time point, no recurrences have been noted. Three treatment-related adverse events (AEs) were reported (infection, anemia, and bacteremia) ranging grades 2-3. None of the patients experienced immune-related AEs.

Comments: This trial is limited for many reasons mainly because this is an early analysis with accrual still ongoing and analysis being limited to few patients. Nevertheless, important takeaways from this interim analysis are that 1) CIS patients had a high CR rate (with some CRs as long as 12-18 months) and 2) patients with papillary only disease had a 77% 6-month disease-free survival rate. CIS is historically difficult to treat when unresponsive to BCG and so the high CR rate in cohort A is extremely encouraging. Furthermore, the use of intravesical N-803 in combination with BCG may emerge to be a less toxic, less cumbersome, and less costly approach to BCG unresponsive disease than systemic immunotherapies that are now under evaluation.

Study Title: A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of UGN-101 on Ablation of Upper Urinary Tract Urothelial Carcinoma (OLYMPUS Study)

Clinicaltrials.gov identifier: NCT02793128

Sponsor: UroGen Pharma Ltd.

Enrollment: 71

Rationale: Upper tract urothelial cancer is difficult to treat given its relative scarcity compared to bladder urothelial cancer and the difficulties in delivering effective instillation of treatment within the upper urinary tract. UGN-101 is a novel investigational formulation of mitomycin C (MMC) admixed with a reverse thermal hydrogel that can be instilled as a liquid but that solidifies into a gel at body temperature. This allows for longer exposure of the urinary tract to MMC. Therefore, UGN-101 is an attractive agent for upper tract urothelial cancer that is unresectable and at high risk of recurrence.

Study Design: This was a Phase III multicenter, single-arm study evaluating the efficacy, safety, and tolerability of UGN-101 in the treatment of low-grade, non-invasive upper tract urothelial cancer. Patients had to have at least one lesion measuring between 5 and 15 mm left in place prior to treatment on this trial. Patients were treated by six weekly instillations of UGN-101 via a retrograde injection through a ureteral catheter and then evaluated 4-6 weeks after the last instillation.

Endpoints: The primary endpoint was a complete response (CR) rate defined as the percent of patients who achieved CR at the primary disease evaluation (PDE) visit which occurred on average at 11 weeks following initiation of treatment. The PDE consisted of ureteroscopy with biopsy of any remaining tumor and urine cytology. Patients who achieved CR at PDE were then treated once monthly with a maintenance regimen of UGN-101 for up to an additional 11 months or first recurrence.

Results: The trial successfully enrolled 71 patients. Forty-two (59%) of the patients achieved a CR at the PDE visit. Of the 71 patients, 34 (48%) were deemed to have unresectable disease by their treating urologist and 19 (56%) of these "unresectable" patients achieved CR at the PDE visit. At 6 months of follow-up, 85% of evaluable patients with unresectable disease and 89% overall remained disease-free. The most common treated-related adverse events (AEs) were urinary tract infections, ureteral narrowing, and ureteral stricture formation. However, most of these were characterized as mild and resolved on follow-up.

Comments: This trial is trailblazing as it represents the first phase III trial in upper tract urothelial cancer. Furthermore, it demonstrates the tumor-ablative capacity of UGN-101 especially in patients deemed to be

unresectable endoscopically at the start of the trial. Although serious side effects were seen, the mean age of patients was approximately 71 years and the fatal events were not deemed to be related to UGN-101. Furthermore, the side effects of ureteral narrowing and stricture could also have been due to the natural history of the disease and so without a comparator control group, it is hard to know if an observation cohort would have had the same side effects or not.

CONFLICTS OF INTEREST

PKA: *Advisory Board (unpaid):* AstraZeneca
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