Bladder Cancer 9 (2023) 187–190
DOI 10.3233/BLC-239007
IOS Press

Clinical Trials Corner Issue 9(2)

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

Received 25 May 2023
Accepted 31 May 2023
Pre-press 16 June 2023
Published 27 June 2023

Dear Readers,

In this issue, we highlight recently presented trials at the 2023 AUA meeting. 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
Associate Editor, Bladder Cancer
Director, Bladder Cancer Program
The University of Chicago
Chicago, Illinois

Cora N. Sternberg, MD, FACP
Associate Editor, Bladder Cancer
Clinical Director, Englander Institute for Precision Medicine
Weill Cornell Medicine
New York, New York

Study Title: Extended Follow-up in Patients with Muscle-Invasive Bladder Cancer in the Checkmate 274 trial (An Investigational Immuno-therapy Study of Nivolumab, Compared to Placebo, in Patients With Bladder or Upper Urinary Tract Cancer, Following Surgery to Remove the Cancer)

Clinicaltrials.gov identifier: NCT02632409

Sponsor: Bristol-Myers Squibb

Enrollment: 709

Rationale: Based on the previous Checkmate 274 trial, adjuvant nivolumab for 1 year has become the standard of therapy after radical surgery for patients with muscle invasive urothelial cancer (MIUC) due to improvement in disease-free survival. This presentation at the AUA 2023 was on the extended follow-up of the muscle invasive bladder cancer cohort (MIBC) with a median follow-up of 3 years.

Study Design: This was an international, randomized, double-blind phase III trial. The original study randomized patients between IV nivolumab (NIVO) Q 2 weeks and IV placebo (PBO) Q 2 weeks after surgery. Patients were high-risk MIUC; if ypT2-ypT4a or ypN+, received neoadjuvant cisplatin CT; if pT3-pT4a or pN+, or did not receive neoadjuvant cisplatin CT and were ineligible for or refused adjuvant cisplatin CT. Patients underwent radical surgery within 120 days and were disease free within 4 weeks of study dosing.

Endpoints: The primary endpoint was disease-free survival (DFS) in the ITT population and DFS in all randomized patients with PD-L1 ≥ 1%.The secondary endpoints were distant metastasis-free survival and non-urothelial tract recurrence-free survival (RFS).

Results: Of 709 randomized pts, 560 had MIBC (NIVO, n=279; PBO, n=281). DFS was improved with NIVO vs PBO in all pts with MIBC (HR 0.63), and in the PD-L1 ≥1% (HR 0.44) and PD-L1 <1% (HR 0.74) subgroups. HR favored NIVO vs PBO for non-urothelial tract recurrence-free survival (HR 0.64) and distant metastasis-free survival (HR 0.70). Grade 3–4 treatment-related adverse events occurred in 17.3% and 5.8% of NIVO and PBO pts, respectively. In this study, there was a continued benefit in DFS, distant-metastasis-free survival, and RFS in both the ITT and muscle-invasive bladder cancer populations. Of note, all patients with PD-L1 greater than or equal to 1%, experienced a benefit in DFS. However, even MIBC with PD-L1 less than 1% still saw a benefit in DFS with nivolumab.

Comments: Only approximately 40% of patients in this study received prior neoadjuvant chemotherapy. From the original presentation, it appeared that the HRs overlapped 1 for patients with upper tract tumors and more benefit was seen in the cohort with MIBC. With extended 3-year median follow-up, continued improvement in DFS was maintained. Although, overall survival data have still not been presented, this study is practice changing.

Reference: AUA 2023, LBA02-08, Milowsky M et al.

Study Title: Intravesical Photodynamic Therapy (“PDT”) in BCG-Unresponsive/Intolerant Non-Muscle Invasive Bladder Cancer (“NMIBC”) Patients

Clinicaltrials.gov identifier: NCT03945162

Sponsor: Theralase Technologies Inc.

Enrollment: 57 of planned 125

Rationale: This study evaluates a novel targeted form of photodynamic therapy in patients with BCG unresponsive CIS with or without papillary disease. The photosensitizer is instilled in the bladder and then activated by an intravesical laser.

Study Design: This is a phase II, open-label, single-arm, multi-center study conducted in Canada, the United States and internationally. Patients with NMIBC CIS with or without resected papillary disease (Ta, T1) that are considered bacillus Calmette-Guerin (BCG)-Unresponsive or who are intolerant to BCG therapy are included. The patients are treated with two photodynamic therapy treatments with TLD-1433 (a photosensitizer that specifically targets transferrin) at 0 and 180 days upon enrollment. The photosensitizer is instilled in the bladder and then activated with an intravesical laser. The interim results of the trial are reported at this meeting.

Endpoints: The primary endpoint is complete response (CR) rate and the main secondary endpoint is duration of CR.

Results: The primary outcome was a 54% CR rate at any time. However, of the 12 patients who were evaluated at 450 days, 67% had a CR. There were 9 serious adverse events (SAEs) but none were deemed to be due to the photodynamic therapy

Comments: Photodynamic therapy has been proven to be effective in the past but was often plagued by side effects. The SAEs seen on this trial were not deemed to be due to the therapy and the historical concerns of bladder damage and sunlight sensitivity seen with older photodynamic therapy agents were not seen in this interim trial.

Reference: AUA 2023, MP 63-01, Kulkarni G et al.

Study Title: A Study of TAR-200 in Combination With Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants With Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guérin Who Are Ineligible for or Elected Not to Undergo Radical Cystectomy (SunRISe-1)

Clinicaltrials.gov identifier: NCT04640623

Sponsor: Janssen Research & Development, LLC

Rationale: Patients with BCG unresponsive disease have limited treatment options. They may respond to the sustained release of gemcitabine through the use of a novel intravesical delivery system, TAR-200, either alone or in combination with a PD-1 antibody, cetrelimab. In addition, the trial evaluates the effect of cetrelimab alone as well.

Study Design: Phase 2b, multi-center study randomizing BCG-unresponsive high risk non-muscle invasive bladder cancer with CIS with or without papillary disease randomized 2:1:1 (by presence or absence of papillary disease) to TAR-200 + cetrelimab, TAR-200 alone, or cetrelimab alone.

Endpoints: The primary endpoint was complete response (CR) rate. The secondary endpoints were duration of response, overall survival, pharmacokinetics, and safety/tolerability.

Results: The data from the two monotherapy arms was presented from a planned interim analysis. Seventy-three (73%) of patients in the TAR-200 arm achieved a CR while the CR rate was 38% in the cetrelimab arm. Grade greater than or equal to 3 adverse events (AEs) in TAR-200 group was 30% compared to 8% in the cetrelimab group. Of note, 15 of the 16 CRs in the TAR-200 group were still ongoing at the median follow-up of 11 months.

Comments: The cetrelimab alone response rates are in line with what has been seen with pembrolizumab alone. However, TAR-200 responses were impressive and higher than seen with gemcitabine dosed in a usual intravesical fashion. However, toxicity was worse but consisted of local symptoms that are grade 1-2 in nature.

Reference: AUA 2023, LBA02-03, Daneshmand et al.

Study Title: Abstract #23-5631 - CORE-001: Phase 2 Single Arm Study of CG0070 Combined with Pembrolizumab in Patients with Non-Muscle Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guerin (BCG)

Clinicaltrials.gov identifier: NCT04387461

Sponsor: CG Oncology, Inc in collaboration with Merck

Rationale: Patients with BCG unresponsive disease have limited treatment options. Cretostimogene grenadenorepvec (CG0070) is a novel intravesical viral oncolytic therapy that has demonstrated efficacy in BCG unresponsive disease as a single agent. The addition of pembrolizumab may augment the immune response triggered by CG0070 and thereby, enhance efficacy. This trial evaluates the combination of CG0070 and pembrolizumab.

Study Design: Core-1 is a single arm phase II study. CG0070 was administered intravesically (IVE) weekly x 6. If the patient demonstrates persistent high-grade disease at Week 12, the patient will receive another cycle of 6 weekly treatments. If there is no disease present at Week 12 (e.g., CR) then the patient will receive 3 weekly treatments. Beginning at Week 24, patients will receive 3 weekly treatments every 3 months through Week 48 and then every 24 weeks thereafter. Pembrolizumab was administered intravenously every 3 weeks for up to 2 years and was started on day 1.

Endpoints: Complete response rate.

Results: Using a data cut-off of March 3, 2023, 34 patients were evaluable for efficacy with a minimum of 3-months of follow up. At the initial 3-month timepoint, 29 of 34 (85%) patients achieved a CR. Of those patients evaluable for CR at additional timepoints, 82% (n=27/33) have also maintained a CR through 6 months, 81% (n=25/31) through 9 months and 68% (n=17/25) at the 12-month assessment. The combination of CG0070 and pembrolizumab has been well tolerated. The most common treatment-related AEs reported include transient grade 1-2 local genitourinary symptoms.

Comments: This small phase II study is encouraging and demonstrates higher CR rates than are seen with CG0070 or pembrolizumab alone. The current landscape of approved agents for BCG-unresponsive NMIBC may quickly expand beyond single agents to effective combination regimens. It is important to note that although the side effect profile was not any worse with combination therapy in this study, there are still rare, but potentially significant side effects that are possible with systemic therapies such as pembrolizumab.

Reference: AUA 2023, PD13-08, Li R et al.

DISCLOSURES:

Cora N. Sternberg
Consultant: Pfizer, Merck Ga, MSD, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Immunomedics now Gilead, Amgen, Clovis Oncology, Bayer, Bristol Myers Squibb, Seattle Genetics, Impact Therapeutics, Janssen, Foundation Medicine, UroToday, Medscape.

Piyush K. Agarwal
Advisory Board (paid): AURA, Verity, UROGEN, Janssen, AstraZeneca, PeerView, Nonagen Therapeutics.

Collaborator and participant in the Theralase trial presented above.