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Dear Readers,

In this issue, we highlight two recently published phase II clinical trials evaluating combination immunotherapies in bladder cancer. 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,

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

Clinicaltrials.gov identifier: NCT03022825

Sponsor: ImmunityBio, Inc.

Enrollment: 171 (200 planned)

Rationale: Some 80% of new bladder cancer diagnoses are non–muscle-invasive bladder cancer (NMIBC). BCG-unresponsive NMIBC is an increasingly interesting disease state for drug development in bladder cancer. Impaired T-cells and natural killer (NK) cells may contribute to BCG-unresponsiveness. The immune cell–activating interleukin-15 (IL-15) superagonist Nogapendekin alfa inbakicept (NAI), also known as N-803, can activate and proliferate NK cells and T-cells. Therefore, the hypothesis that the addition of N-803 to BCG could potentially enhance BCG efficacy was preliminarily tested in a small Phase I trial with limited toxicity and an impressive response rate. The current trial was a Phase II/III multicenter study to look at efficacy.

Study Design: Phase II/III single arm, multi-center study of patients with BCG-unresponsive CIS with or without papillary (Ta/T1) NMIBC treated with intravesical NAI/N-803 (400 lg/instillation) plus BCG intravesical BCG (50 mg/ instillation) (cohort A) or without BCG (cohort C). Patients with BCG-unresponsive high-grade papillary (Ta/T1) NMIBC without CIS were also treated with intravesical NAI/N-803 plus BCG (cohort B).

Patients had to be absent of resectable disease after TURBT procedures, and those with high-grade Ta and/or T1 disease had a complete resection before study treatment. Biopsy was required at week 12 (approximately 3 months).

Endpoints: The primary endpoint was the incidence of a complete response (CR) at the 3- or 6-month assessment for cohorts A and C and the disease-free survival of cohort B at 12 months. Secondary endpoints include disease-specific survival, progression-free survival, overall survival, and avoidance of cystectomy.

Results: A total of 171 patients were enrolled with 84 patients in cohort A, 77 patients in cohort B, and 10 patients in cohort C. In cohort A, 82 patients were evaluable with at least 3-month follow-up. Overall, a CR at any time was seen in 71% of patients (45 patients with response to initial treatment and 13 patients with response to re-induction). The CR rate was 45% at 12 months and 33% at 18 months for patients in cohort A. Furthermore, progression-free survival at 24 months was 84.7%. In the 71% of patients with a CR, only 7% underwent a subsequent cystectomy. In cohort B, the 12-month DFS for 72 evaluable patients was 55.4% and the cystectomy rate among responders was also 7%. In Cohort C, a CR at 3 months was only achieved in 2 (20%) patients. Despite reinduction at 6 months, only one patient (10%) maintained a CR at 6 months. Treatment-related adverse events in cohorts A and B were grade I to 2 in 86%.

Comments: There is considerable activity with the combination of N-803 and BCG in BCG-unresponsive NMIBC that leads to good response rates at 12 months and beyond and avoidance of cystectomy. The data are in line with expectations for novel therapies in this disease space. From this study, it emerges that the treatment is tolerable with a side effect profile that can be expected with intravesical therapy. However, the activity of N-803 as a single agent appears to be minimal. A subgroup that requires further careful observation is high-grade T1 tumors associated with CIS (HGT1/CIS), as these patients have the highest risk of progression. Only 9 patients were included in this trial. However, comparisons with other single-arm trials are always difficult in that there is substantial heterogeneity among BCG-unresponsive patient cohorts, and variation in the patient population and the quality of the TURBT among surgeons. For instance, development of UC of the prostatic urethra was not counted as treatment failure in this trial. In addition, a lower CR rate in female patients is an interesting observation, that has been seen in other trials. It will be interesting to see whether the combination is equally effective in the BCG-naïve high-risk NMIBC disease state.

Reference: NEJM Evid. 2022; 2(1). https://doi.org/10.1056/EVIDoa2200167

Study Title: Abraxane With Anti-PD1/PDL1 in Patients With Advanced Urothelial Cancer (ABLE)

Clinicaltrials.gov identifier: NCT03240016

Sponsor: University of Michigan Rogel Cancer Center

Enrollment: 36

Rationale: The current first-line standard of care for locally advanced or metastatic urothelial carcinoma is cisplatin-based combination chemotherapy. Despite responses in 50%-70% of patients in the first line setting, most eventually progress and median overall survival is about 14 months. For cisplatin ineligible patients OS is even worse, around 9 months.

Cisplatin-ineligibility or unresponsiveness to cisplatin presents a treatment challenge for patients. Pembrolizumab is an anti-PD-1 monoclonal antibody approved in the treatment of urothelial cancer after chemotherapy or in platinum ineligible patients who express PDL-1. Nanoparticle albumin-bound paclitaxel (Nab-paclitaxel; abraxane) does not require pre-medication and is also effective in platinum-refractory advanced urothelial carcinomas. This study evaluates the combination of pembrolizumab and nab-paclitaxel in patients with advanced urothelial carcinoma who are platinum-refractory or cisplatin-ineligible.

Study Design: This is a single arm, single center, phase II study of nab-paclitaxel and pembrolizumab in patients with platinum-refractory or cisplatin-ineligible advanced urothelial carcinoma. Eligible patients had RECIST 1.1 measurable disease. Patients were treated with nab-paclitaxel 125 mg/m2 IV on days 1 and 8 and pembrolizumab IV 200 mg in 21-day cycles Nab-paclitaxel could be discontinued after 6 cycles.

Endpoints: The primary endpoint was overall response rate (ORR). Secondary endpoints include: duration of response, safety/toxicity, progression-free survival, and overall survival.

Results: Overall 36 patients were enrolled onto the study. There was an equal number of platinum-refractory and cisplatin-ineligible patients. The ORR was 50% (18/36) and tumor shrinkage was confirmed in 31 of 36 patients. Confirmed overall response rate was 50.0% (18/36) including 3 complete and 15 partial responses; 31/36 patients experienced some tumor shrinkage. At a median follow-up of 19.7 months, the median duration of response was 4.4 months. Median PFS and OS were 6.8 months and 18.2 months, respectively. Of note, grade 3 or greater adverse events were noted in 21 of 36 patients. The combination was effective in patients refractory to or ineligible for cisplatin based chemotherapy albeit with some toxicity.

Comments. In the Keynote 045 trial, after which pembrolizumab was registered as second line therapy, the median OS was 10.1 months in the pembrolizumab arm and superior to OS with chemotherapy. In the Keynote 052 trial of patients who were platinum ineligible, median OS with pembrolizumab was 11.3 months. In a phase II trial of Nab-paclitaxel median overall survival was 9.8 months. As it is always difficult to compare among trials, a median OS of 18.2 months in platinum refractory or cisplatin-ineligible patients with this combination is certainly promising and hypothesis generating. A phase III randomized trial of the combinaton versus Pembrolizumab is warranted.

Reference: J Urol 2023. 209 (1): 121-130.

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. Also Dr. Agarwal was a collaborator and co-author on the N-803 study reported.