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Dear Readers,

In this issue, we highlight recently presented and published trials from ASCO GU 2024, EAU 2024 and AUA 2024 Annual Meetings. 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: 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

Enrollment: Estimated enrollment (200)

Rationale: Patients with high-risk non-muscle-invasive bladder cancer particularly BCG-unresponsive CIS have a high risk of recurrence and need effective therapies to reduce the risk of disease recurrence or progression. TAR-200 is a novel intravesical drug delivery device that can deliver sustained low-doses of gemcitabine in the bladder over a 21-day dosing cycle to provide prolonged treatment. Gemcitabine has demonstrated efficacy in the bladder as an intravesical agent and the thought is that the response to continued dosing might be greater. This trial evaluated this agent in BCG unresponsive NMIBC (CIS with or without papillary disease). The data on TAR-200 monotherapy was presented at the AUA 2024 meeting.

Study Design: SunRISE-1 is an ongoing Phase IIb randomized, open label study for patients with BCG-unresponsive NMIBC (CIS with or without papillary disease) treated with TAR-200 with or without cetrilimab, an investigational anti-PD-1 monoclonal antibody administered intravenously (combination (cohort 1), TAR-200

alone (cohort 2), or cetrilimab alone (cohort 3)). The data presented was only from the TAR-200 monotherapy cohort. TAR-200 was dosed every 3 weeks through week 24, and then every 12 weeks until week 96. Complete response (CR) was determined by cystoscopy, central review of cytology and bladder biopsy pathology at 24 and 48 weeks.

Endpoints: The primary endpoint is overall complete response (CR) rate. Secondary endpoints included duration of response (DOR), overall survival, safety, and tolerability.

Results: At data cutoff (Jan 2, 2024), 85 patients received TAR-200. 58 patients were evaluable for efficacy and data were reported on 48 patients. The TAR-200 device achieved a centrally assessed CR rate of 83% (95% CI: 71-91%) at any time. The CR at 12 months was 62%. The estimated 1-year duration of CR was 75% (95% CI: 50-88) with median follow-up in responders of 30 weeks. The majority of CRs (98%) were achieved at 12 weeks. At least 1 treatment related adverse event (TRAE) was seen in 61 patients (72%) with the most common being pollakiuria (35%), dysuria (29%), and micturition urgency (15%) and urinary tract infection (15%). Four (5%) had TRAEs leading to discontinuation.

Comments: With the recent approvals of nadofaragene and BCG/N803 in the BCG-unresponsive NMIBC space, the TAR-200 results exceed or are in line with these other novel agents. It remains to be seen whether this therapy is more effective than the commonly used administration of intravesical gemcitabine and docetaxel in BCG-unresponsive patients and whether similar results can be seen in patients refractory to gemcitabine and docetaxel. Further, the duration and frequency of treatments is more intense than other regimens and issues of patient tolerability and cost reimbursement may also impact clinical uptake of this product.

Reference: Abstract P2-01, Presented at the AUA 2024 Annual Meeting by Joseph Jacob, MD, see also: P van Valenberg FJ**,** Eur Urol Open Sci 2024 Feb 16:62:8-15 (Phase 1b study).

Study Title: A Phase 1/2 Study of EG-70 as an Intravesical Administration to Patients with BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC) and High-Risk NMIBC Patients Who Are BCG Naïve or Received Incomplete BCG Treatment

Clinicaltrials.gov identifier: NCT04752722

Sponsor: enGene, Inc.

Enrollment: 222 (estimated)

Rationale: EG-70 (detalimogene voraplasmid) is a non-viral, non-integrating gene therapy consisting of a nanoparticle formulation of plasmids that activates innate and adaptive immune responses. Immune stimulation of the bladder locally avoids systemic toxicities, and this therapy was evaluated in the treatment of BCG unresponsive NMIBC.

Study Design: This is a Phase I/II study with dose escalation to assess safety and tolerability of EG-70.

Endpoints: The primary endpoint of the Phase I portion was to assess safety and tolerability of EG-70 through the first 12 weeks. Complete response rate and duration of response were secondary endpoints.

Results: Twenty-four patients received at least one dose of intravesical EG-70. Overall, 13 (54.2%) patients experienced TRAEs which were mostly grade 1 and 2 with one grade 3 TRAE of renal failure in a patient with pre-existing renal failure. The most common TRAEs were urinary tract infection (12.5%), micturition urgency (12.5%), hematuria (12.5%), and dysuria (12.5%). Across all treatment doses, the anytime CR was 73%. The CR was 45% at 6 months. The CR was improved at 60% at 6 months in those patients that received the recommended phase II dose (R2PD).

Comments: This novel agent at the RP2D has good efficacy with excellent tolerability at 6 months. Given that the other agents in this space now have 12-month data, we need to wait for those results to be able to assess durability and potentially compare with other agents.

Reference: Abstract P2-08, Presented at the AUA 2024 Meeting by Gordon Brown, DO.

Study Title: A Phase 3 Study of Cretostimogene Grenadenorepvec in Patients With Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus-Calmette-Guerin (BCG) (BOND-003)

Clinicaltrials.gov identifier: NCT04452591

Sponsor: CG Oncology, Inc.

Enrollment: 190 (estimated)

Rationale: Cretostimogene grenadenorepvec, CG0070, is a novel intravesical oncolytic adenoviral therapy that has demonstrated efficacy in BCG unresponsive disease as a single agent in preclinical and Phase I and Phase II clinical trials. Its mechanism of action involves direct lysis of cancer cells and stimulation of an anti-cancer immune response.

Study Design: Single-arm Phase III study in patients with BCG unresponsive NMIBC with CIS +/- Ta/T1 who had all disease resected. The patients were treated with an intravesical induction course weekly for 6 weeks consisting of a bladder wash with 5% n-dodecyl-B-D-maltoside (DDM), a transduction-enhancing agent, followed by the active agent, CG0070, an engineered oncolytic adenovirus also known as cretostimogene grenadenorepvec. Non-responders were re-induced with a second 6-week induction. Maintenance courses were given weekly for 3 weeks every 3 months in year 1 and every 6 months in year 2.

Endpoints: The primary endpoint was complete response rate. Secondary endpoints duration of response, cystectomy-free survival rate, and overall survival.

Results: Overall, 112 patients were enrolled and 105 were analyzed for efficacy. The complete response rate at any time was 75.2% (95% CI: 65-83%). Up to 25% of patients required a second induction course. Up to 53.8% of patients who underwent repeat induction converted to a CR. Among the complete responders, 83% maintained their response at 12 months. Overall treatment was tolerable with only 1 treatment discontinuation and no patients with grade 3 or higher TRAEs.

Comments: This trial reported impressive results in BCG unresponsive CIS that are comparable or better to other agents in this space including N-803 + BCG, Nadofaragene, Pembrolizumab, and TAR-200. However, these results are still early, and similarly to TAR-200, several treatments are required and patient compliance and reimbursement issues may affect implementation.

Reference: Abstract P2-02, Presented at the AUA 2024 Annual meeting by Mark Tyson, MD.

Study Title: Extended follow-up from CheckMate 274 including the first report of overall survival outcomes

Clinicaltrials.gov identifier: NCT02632409

Sponsor: Bristol- Myers Squibb

Enrollment: 709

Rationale: Nivolumab (NIVO) became a standard of care adjuvant treatment for patients with high-risk MIUC after radical surgery based on the initial results from the phase 3 CheckMate 274 trial, which assessed adjuvant NIVO for patients with high-risk MIUC after radical surgery and met both of its primary endpoints.

Study Design: Phase 3, randomized, double-blind, multicenter study of adjuvant NIVO versus PBO for high-risk MIUC. Eligible patients had ypT2-ypT4a or ypN+ MIUC with prior neoadjuvant cisplatin chemotherapy or pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and were not eligible or refused adjuvant cisplatin chemotherapy. Patients underwent radical surgery within the past 120 days and had disease-free status within 4 weeks of randomization.

Primary endpoints: DFS in all randomized patients (ITT population) and DFS in all randomized patients with tumor PD-L1 ≥ 1%. Key secondary endpoints: time from date of randomization to first local non-urothelial tract or distant recurrence or death (from any cause; NUTRFS) and OS.

Endpoints: With initial follow-up (median follow-up, 20.9 months for NIVO and 19.5 months for PBO), adjuvant NIVO improved DFS versus PBO in the ITT population (HR 0.70 [0.55–0.90]; $P < 0.001$) and in patients with tumor PD-L1 expression ≥ 1% (HR 0.55 [0.35–0.85]; $P < 0.001$. The authors present extended follow-up results from CheckMate 274, including the first report of OS outcomes from the trial.

Results: EAU new data: Median (minimum) follow-up in the ITT population, 36.1 (31.6) months; median (minimum) follow-up in PD-L1 ≥ 1% population, 37.1 (32.1) months. DFS was defined as time from date of randomization to date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death (from any cause).

OS data from interim analyses favored adjuvant NIVO over PBO. In the ITT population, median OS reached 69.5 months with NIVO versus 50.1 months with PBO (HR 0.76 [0.61-0.96]. In the PD-L1 ≥ 1% population, median OS was not reached with either treatment (HR 0.56 [0.36-0.86]; 36-month OS rates were 71.3% with NIVO versus 56.6% with PBO. There was a trend for OS benefit with NIVO among prespecified subgroups of ITT patients.

Comments: With extended follow-up in CheckMate 274, adjuvant NIVO continued to show improved DFS, NUTRFS, and DMFS (DMFS was time from the date of randomization to first distant recurrence (non-local) or date of death (from any cause) benefits versus PBO in both the ITT and PD-L1 ≥ 1% populations. Continued follow-up of OS is ongoing. These results, along with those of the AMBASSADOR study presented at GU ASCO, provide additional support for adjuvant immunotherapy as a standard of care for high-risk MIUC after radical resection, potentially providing an opportunity for a curative outcome.

Galsky M et al. EAU 2024 and Apollo A, ASCO GU 2024 (AMBASSADOR Trial; AO31501)

DISCLOSURES:

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Advisory Board or Consultant: Pfizer, Merck Ga, MSD, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Gilead, Amgen, Bayer, Bristol Myers Squibb, Seattle Genetics, Janssen, Lilly, Foundation Medicine, UroToday, Medscape

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