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Dear Readers,

In this issue, we highlight recently presented and published trials from ASCO 2023 and ESMO 2023 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 Phase III Surgical Trial to Evaluate the Benefit of a Standard Versus an Extended Pelvic Lymphadenectomy Performed at Time of Radical Cystectomy for Muscle Invasive Urothelial Cancer

Clinicaltrials.gov identifier: NCI-2011-02604

Sponsor: SWOG Cancer Research Network

Enrollment: 658

Rationale: The benefit of an extended lymphadenectomy over a standard lymphadenectomy at the time of radical cystectomy for bladder cancer is unknown. This trial evaluates the two different types of lymph node dissections in a randomized fashion with the primary outcome of disease-free survival (DFS).

Study Design: Phase III, multi-center, trial of stage T2-T4aN0-2 urothelial bladder cancer requiring radical cystectomy and pelvic lymphadenectomy. Patients were randomized between two arms: standard lymphadenectomy up to the common iliac bifurcation or extended lymphadenectomy which included the common iliac and pre-sacral lymph nodes at least up to the aortic bifurcation. Patients were allowed to receive neoadjuvant chemotherapy provided that therapy was completed prior to surgery.

Endpoints: The primary endpoint was disease-free survival (DFS) from muscle-invasive bladder cancer between patients undergoing extended pelvic lymph node dissection (PLND) versus standard PLND. The secondary endpoints included overall survival (OS), operative time, length of hospital stay, peri-operative complications, lymph node counts/densities, and patterns of recurrence between the two groups.

Results: No significant difference in DFS (HR = 1.10, 95% CI: 0.87-1.42, p=0.40) or in OS (HR = 1.15, 95% CI: 0.89-1.48, p=0.29) between the extended PLND arm compared to the standard PLND arm was found. Although the median number of nodes removed in the extended PLND arm was greater (39 nodes vs. 24 nodes), there was a similar percentage of nodes found to have metastatic disease in both arms (26% vs. 24% respectively). Furthermore, more grade 3 and 4 adverse events were seen in the extended PLND arm including more deaths within 90 days of surgery.

Comments: This trial conducted by high-volume open surgeons convincingly disproves traditional Halstedian dogma that "more is better" when it comes to a lymph node dissection for bladder cancer. However, it is important to realize that a lymph node dissection is not obsolete, and the standard lymph node dissection still evaluates the main lymph nodes that drain the bladder and provides optimal local control.

Reference: Lerner SP et al, Presented at ASCO 2023, Abstract 4508.

Study Title: An Open-label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination With Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer (EV-302)

Clinicaltrials.gov identifier: NCT04223856

Sponsor: Seagen Inc., Astellas Pharma, Merck & Co., Inc.

Enrollment: 990 estimated (ESMO presentation on 886 patients)

Rationale: Previous studies (EV-103, Cohort K) have demonstrated a high objective response rate of 64.5% for the combination of Enfortumab vedotin (EV) and Pembrolizumab (EV+P) in untreated cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. Given these encouraging results, the next step was to test this combination against chemotherapy in the first line setting for locally advanced or metastatic urothelial cancer.

Study Design: This was a Phase III trial of patients with locally advanced or metastatic urothelial cancer randomized to either EV and Pembrolizumab (EV+P) or chemotherapy (gemcitabine plus either carboplatin or cisplatin). Patients with a GFR ≥30 mL/min could be entered. Pembrolizumab was given up to 35 cycles, while EV was given with no maximum number of cycles. Chemotherapy was administered for 6 cycles. Patients were treated until maximum number of cycles or until disease progression or unacceptable toxicity.

Endpoints: The dual primary endpoints were progression-free survival (PFS) by RECIST v1.1 by blinded independent central review (BICR) and overall survival (OS). Secondary endpoints included objective response rate (ORR) and safety.

Results: Overall, 886 patients were randomized to either EV and pembrolizumab (442) or chemotherapy (444). Median PFS was better in the EV+P arm vs. the chemotherapy arm (12.5 months vs. 6.3 months, HR 0.45 [95% CI: 0.38-0.54], p<0.00001). OS was also significantly better in the EV+P arm compared to the chemotherapy arm at 31.5 months vs. 16.1 months, HR 0.47 [95% CI: 0.38-0.58], p<0.00001. The median survival follow-up

was 17.2 months and 33% of patients in the EV+P arm remain on treatment at the time of analysis. The benefit was maintained regardless of cisplatin eligibility or PD-L1 expression. Grade 3 or greater treatment related adverse events (TRAEs) were 55.9% in the EV+P group vs. 69.5% in the chemotherapy group. The OR rate for EV was 67.7% vs 44.4% for chemo and the CR rates were 29.1% vs 12.5%, respectively. The main toxicities were maculopapular rash and neuropathy in the EV+P group and anemia in the chemotherapy group.

Comments: The risk of death was reduced by 53% in patients who received EV+P. This landmark trial demonstrates safety and improved PFS and OS with the combination of EV and pembrolizumab over the current standard of care regimen of platinum-based combination chemotherapy with gemcitabine and cisplatin or carboplatin for first line locally advanced or metastatic urothelial cancer. Of note, in the SOC, avelumab switch maintenance therapy was only given to approximately 30% of patients. Nonetheless, this establishes a new standard of care. Subgroup analysis will be interesting to generate hypotheses as to which patients are most benefited by the combination of EV+P. Reducing toxicity by perhaps lowering the number of cycles of EV will also be of interest to evaluate.

Reference: Powles TB, et al. EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). Presented at ESMO Congress 2023. Oct. 20-24, 2023. Madrid, Spain. Abstract LBA6.

Study Title: A Phase 3, Open-label, Randomized Study of Nivolumab Combined With Ipilimumab, or With Standard of Care Chemotherapy, Versus Standard of Care Chemotherapy in Participants With Previously Untreated Unresectable or Metastatic Urothelial Cancer

Clinicaltrials.gov identifier: NCT03036098

Sponsor: Bristol-Myers Squibb

Enrollment: 1290 (estimated)

Rationale: In Phase III first line trials of urothelial cancer, there have been no immunotherapeutic agents in combination with platinum chemotherapy that have improved upon overall survival in unresectable or metastatic urothelial cancer. This randomized trial evaluates the addition of immunotherapy to chemotherapy,

Study Design: Phase III trial of patients with unresectable or metastatic urothelial carcinoma randomized to Gemcitabine and cisplatin (304 patients) for 6 cycles vs. Gemcitabine and cisplatin for 6 cycles and nivolumab for up to 24 months (304 patients). Of note, all patients in this trial were cisplatin eligible.

Endpoints: The primary endpoints were overall survival and progression-free survival by blinded independent review.

Results: Overall survival was longer in the nivolumab and chemotherapy group with a HR of 0.78 [95% CI: 0.63 to 0.64], p=0.02. Median survival was 21.7 months vs. 18.9 months favoring the combination arm. Progression-free survival also favored the combination arm with a HR of 0.72 [95% CI: 0.59 to 0.66], p=0.001. The overall objective response was 57.6% with nivolumab and chemotherapy and 43.1% with chemotherapy alone. The median duration of complete response was 37.1 months in the combination therapy group and 13.2 months in the chemotherapy alone group.

Comments: For the first time, a checkpoint inhibitor added to standard chemotherapy improved both survival and progression-free survival in unresectable or metastatic urothelial carcinoma. Of note, all patients in this

study were cisplatin eligible, perhaps selecting for a better population of patients. In addition, only 20% of patients in the standard of care chemotherapy alone arm received maintenance avelumab. The CR rate was nonetheless nearly doubled, and the duration of CR was almost 3 times longer with the combination. The combination with nivolumab resulted in no new toxicity signals, and the safety profile was consistent with the established safety of these agents in prior trials. It is always difficult to compare results between trials, especially with different entry criteria. Given the exceptional results with EV and pembrolizumab, it is likely but unclear if this immunotherapy plus chemotherapy combination will become another standard of care for advanced and surgically unresectable disease. Other considerations such as availability and cost will also play a role.

Reference: Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: Results from the phase III CheckMate 901 trial. MS Van der Heijden, MS. ESMO Congress 2023. Oct. 20-24, 2023. Madrid, Spain. Abstract LBA7. MS Van der Heijden, M et al, N Engl J Med. 2023 Nov 9;389(19):1778-1789.

Study Title: Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination With Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants With High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guérin (BCG) Who Are Ineligible for or Elected Not to Undergo Radical Cystectomy

Clinicaltrials.gov identifier: NCT04640623

Sponsor: Janssen Research & Development, LLC

Enrollment: 200

Rationale: Limited treatment options are available to treat BCG-unresponsive high risk non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS). 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).

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) to TAR-200 monotherapy, TAR-200 with cetrelimab (an anti PD-1 antibody), or cetrilimab. The data presented was only from the TAR-200 monotherapy (cohort 2) group. Complete response (CR) was determined by cystoscopy, central review of cytology and bladder biopsy pathology at 24 and 48 weeks.

Endpoints: The primary endpoint was overall CR rate.

Results: The TAR-200 device achieved a centrally assessed CR rate of 76.7% and 21 of 23 (91%) responses are ongoing with a median follow-up in responders of 48 weeks. None of the patients who achieved CR required a radical cystectomy to date. TAR-200 was well tolerated, with mainly low grade 1 or 2 manageable urinary symptoms. Only 7.4% of patients experienced at least 1 grade 3 or greater treatment related adverse event.

Comments: The caveat to successful intravesical therapy is patient compliance with weekly instillations and the patient's ability to hold the medication. The novel TAR-200 intravesical delivery device can maintain sustained release of gemcitabine in the bladder that cannot be achieved with standard intravesical therapy. The findings indicate that sustained administration of intravesical agents could lead to complete responses, raising the question of their potential as first-line treatments for NMIBC.

Reference: Results from SunRISe-1 in patients (Pts) with bacillus Calmette–Guérin (BCG)-unresponsive high-risk non–muscle-invasive bladder cancer (HR NMIBC) receiving TAR-200 monotherapy. Necchi, A et al. ESMO Congress 2023. Oct. 20-24, 2023. Madrid, Spain. Abstract LBA105.

CONFLICTS OF INTEREST

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

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