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Dear Readers,

In this issue, we highlight recently presented and published trials from ASCO GU 2024 and SUO 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: Phase III Randomized Adjuvant Study of Pembrolizumab in muScle invaSive and locAlly aDvanced urOthelial caRcinoma (AMBASSADOR) Versus Observation

Clinicaltrials.gov identifier: NCT03244384

Sponsor: National Cancer Institute (NCI)

Enrollment: 739

Rationale: Muscle invasive urothelial cancer (MIUC) with adverse pathologic features after surgical resection is at high risk of local recurrence and/or metastatic disease despite the use of neoadjuvant platinum-based chemotherapy (NAC). This trial in the adjuvant setting was ended early after adjuvant nivolumab (Checkmate 274) demonstrated a disease-free survival advantage after radical cystectomy in patients with high-risk features after surgery and the US FDA approval of nivolumab for MIUC. However, earlier adjuvant trials, such as the IMVIGOR-010 trial evaluated atezolizumab, a PDL-1 inhibitor in the adjuvant setting did not demonstrate a significant benefit in disease-free survival.

Study Design: This was an open-label, randomized, phase III trial of muscle-invasive urothelial cancer of the bladder, upper tract, or urethra following radical surgery (radical cystectomy, nephroureterectomy, and urethrectomy respectively) in patients who are either: Post-neoadjuvant chemotherapy (NAC) and >/ pT2 and/or N+/+margins or cisplatin ineligible or refusing NAC and >/ pT3 and/or pN+/+ margins. 739 patients were enrolled up to 16 weeks after surgery and randomized 1:1 to either pembrolizumab (200 mg IV every 3 weeks)

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or observation. Stratification of randomization was performed to account for pathologic stage, centrally tested PD-L1 status, and prior NAC. The arms were well balanced with bladder cancer in 75.4% vs 75.9% in the pembrolizumab arm vs the observation arm, urethral cancer in 1.7% vs 3.4% and upper tract (renal pelvis and ureter) in 22.9% and 20.7% in the pembrolizumab vs observation arm respectively.

Endpoints: The dual primary endpoints were disease-free survival (DFS) and overall survival (OS). The secondary endpoints included evaluation of DFS by PD-L1 status, evaluation of OS by PD-L1 status, and safety. Correlative endpoints are also planned.

Results: A total of 702 patients were randomized between September 2017 and August 2021: 354 patients to pembrolizumab (a PD-1 inhibitor) and 348 patients to observation. Ultimately, 17.4% and 27.2% of patients withdrew from the study in the pembrolizumab and observation arms, respectively, due to the changing landscape and FDA approval. In addition, up to 74 patients (27%) in the observation arm received an immune checkpoint inhibitor compared to 7% in the pembrolizumab arm.

At a median follow-up of 22.3 months, median DFS was 29 months (95% CI: 21.8 – not reached) in the pembrolizumab arm and 14 months (95% CI: 9.7-20.2) in the observation arm (HR: 0.69 [95% CI: 0.54-0.87], p=0.001]. Median OS (at interim analysis with 257 events) was 50.9 months (95% CI: 43.8-not reached) in the pembrolizumab arm and 55.8 months (95% CI: 53.3-not reached) in the observation arm (HR: 0.98 [95% CI: 0.76-1.26], p=0.88). Adverse events were higher in the pembrolizumab arm: 48.4% vs. 31.8% of patients, respectively.

Comments: Adjuvant pembrolizumab in patients with advanced pathologic features after radical surgery provides a statistically significant benefit in DFS that is more than double the benefit seen in the observation arm. However, no benefit was seen in OS. This may be due to contamination with up to 27% of patients in the observation arm receiving an immune checkpoint inhibitor. This trial included patients with upper tract urothelial cancer and urethral cancer. The trial also included patients with variant histologies. The trial was not blinded and the changing landscape and FDA approval of Nivolumab as adjuvant therapy, compromised the trial. PDL-1 positivity using the CPS score was associated with a better prognosis but was not predictive of treatment efficacy and cannot be used to select patients for therapy. Data is still pending on analyses of DFS and OS in the subgroups stratified by PD-L1 status and ctDNA analyses. These data suggest that both pembrolizumab and nivolumab can be used in the adjuvant setting to improve DFS but to date, no trial has reported final OS results.

Reference: Apolo AL et al. J Clin Oncol 42, 2024 (suppl 4; abstr LBA531). Presented at ASCO GU 2024.

Study Title: Enfortumab vedotin (EV) in combination with pembrolizumab (P) versus chemotherapy in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC): Subgroup analyses results from EV-302, a phase 3 global study.

Clinicaltrials.gov identifier: NCT04223856

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

Enrollment: 990 estimated (ESMO 2023 presentation and ASCO GU 2024 presentation on 886 patients)

Rationale: At ESMO 2023, results of the EV-302 trial were presented demonstrating a benefit in both PFS and OS with the combination of Enfortumab vedotin (EV), an antibody drug conjugate, and Pembrolizumab (EV+P) compared to chemotherapy (gemcitabine plus either carboplatin or cisplatin) in patients with locally advanced or metastatic urothelial cancer. At the ASCO GU 2024 meeting, results in pre-specified subgroups from that practice-changing trial were presented.

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). A stratified Cox proportional hazards regression model controlling for the stratification factors (cisplatin eligibility, PD-L1 status [high/low], and liver metastases [yes/no]) was performed for each predefined subgroup between the two treatment arms. Secondary endpoints included confirmed objective response rate (cORR), duration of response, and safety.

Results: Overall, 886 patients were randomized to either EV and pembrolizumab (442) or chemotherapy (444). PFS and OS were prolonged for the EV+P arm across all prespecified subgroups including race, cisplatin eligibility, PD-L1 status, site of metastasis, liver involvement, and renal function. Specifically, there was a PFS benefit favoring the EV+P arm in liver metastases (HR: 0.53 [95% CI: 0.38-0.76]), lymph node only disease (HR: 0.40 [95% CI: 0.26-0.62]), and in visceral metastases (HR: 0.45 [95% CI: 0.37-0.55]). PFS benefit was consistent with the overall population regardless of cisplatin eligibility or PDL-1 expression status. OS benefit was also seen to favor the EV+P arm in liver metastases (HR: 0.47 [95% CI: 0.32-0.71]), lymph node only disease (HR: 0.46 [95% CI: 0.27-0.78]), and in visceral metastases (HR: 0.47 [95% CI: 0.37-0.60]). OS benefit was seen for both upper tract and lower tract disease. Side effects were presented at the ESMO meeting.

Comments: mPFS and mOS were nearly doubled in the EV +P arm compared with chemotherapy. The EV+P combination provided a PFS and OS benefit across all of the prespecified subgroups. No subgroup fared better with chemotherapy reaffirming the benefit of EV+P as a first line therapy for all patients with locally advanced or metastatic urothelial carcinoma. The FDA has already granted approval for the treatment of locally advanced or metastatic urothelial cancer with this combination.

Reference: Van Der Heijden et al. J Clin Oncol 42, 2024 (suppl 4; abstr LBA530). Presented at ASCO GU 2024.

Study Title: A Phase 3 Study of CG0070 in Patients With Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus-Calmette-Guerin (BCG)

Clinicaltrials.gov identifier: NCT04452591

Sponsor: CG Oncology, Inc.

Enrollment: 116 (data presented on 66 evaluable patients)

Rationale: Cretostimogene grenadenorepvec, CG0070, is a novel intravesical viral oncolytic therapy that has demonstrated efficacy in BCG unresponsive disease as a single agent in preclinical and Phase I and Phase II clinical trials. It binds to the coxsackie adenovirus receptor that is highly expressed in bladder cancer. 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 median duration of response, median progression-free survival, time to tumor progression, incidence of adverse events, and recurrence-free survival.

Results: The results of the first 66 enrolled patients were presented. The complete response rate at any time was 75.7% (95% CI: 63-85%). The complete response rate at 6 months was 63.6% (95% CI: 51-75%). Up to 31% of patients required a second induction course. Among the complete responders, 74% maintained their response for at least 6 months. Any grade adverse events were seen in 56.3% patients but no grade 3 or greater adverse events were noted.

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 very early, and it will be important to see 12-month recurrence free survival rates to be able to compare with other agents at this important time point by which most patients fail treatment.

Reference: Tyson M et al. Presented at SUO 2023. Nov. 28 – Dec. 1, 2023. Washington, DC.

Study Title: A Phase 3, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of UGN-102 as Primary Chemoablative Therapy in Patients With Low Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence (the ENVISION trial)

Clinicaltrials.gov identifier: NCT05243550

Sponsor: UroGen Pharma Ltd.

Enrollment: 240

Rationale: Low grade Intermediate risk non-muscle invasive bladder cancer (LG IR NMIBC) does not have a standard of care therapy and can be managed with resection followed by intravesical therapy with BCG or chemotherapy. A previous randomized trial, the ATLAS trial, demonstrated comparable complete response rates at 3 months for LG IR NMIBC managed by either transurethral resection of bladder tumors (TURBTs) or by chemoablation using UGN-102, a thermally responsive gel containing mitomycin, that becomes a semi-solid gel depot upon intravesical instillation that can provide sustained release of mitomycin over several hours with each instillation. The ENVISION trial sought to evaluate the response of LG IR NMIBC in a single arm study with UGN-102.

Study Design: Single arm, multicenter, phase 3 study evaluating the efficacy of UGN-102 as a primary chemoablation approach in patients with LG IR NMIBC. Tumors were histologically confirmed with the absence of high-grade disease on voided urine cytology. Patients received six weekly intravesical instillations of UGN-102. Patients were assessed for responses in the usual fashion with office cystoscopy and voided urine cytology at 3-month intervals for up to 24 months.

Endpoints: The primary endpoint was complete response rate (CRR) measured as the proportion of patients achieving a CR at 3 months. The secondary endpoints included duration of response, disease-free survival (DFS), and treatment-emergent adverse events (TEAEs).

Results: The CR rate at 3 months following treatment was 79.2% (190/240 patients). Among the 50 patients without a CR, 35 had residual disease, 6 progressed to high grade NMIBC, 4 had indeterminate results, and data

were missing in 5. Duration of response data were not presented. The product was well-tolerated with a 52.9% rate of TEAEs with the most common being dysuria (22.1%), hematuria (8.3%), pollakiuria (6.3%), and urinary tract infection (5.8%). Most side effects were mild or moderate but 6.7% had severe TEAEs with 2 patients experiencing life threatening TEAEs (urethral stenosis and urinary retention).

Comments: Treatment with UGN-102 may provide a non-surgical, chemoablative option for the treatment of LG IR NMIBC. Unfortunately, it is unknown whether mitomycin in a standard format given weekly or another regimen (e.g. gemcitabine, gemcitabine/docetaxel, epirubicin) also given weekly would be comparable to UGN-102 or not. Furthermore, the duration of response will be essential in order to effectively compare outcomes with those achieved with standard TURBTs.

Reference: Prasad S, Mladenov B, Shishkov D, et al. Primary chemoablation with UGN-102 for recurrent low grade intermediate risk (LG IR) NMIBC: The ENVISION trial. Presented at SUO 2023. Nov. 28 – Dec. 1, 2023. Washington, DC.

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, Foundation Medicine, UroToday, Medscape

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