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Dear Readers,

In this issue, we highlight three trials that were recently presented at the ASCO meeting in various stages of urothelial cancer. One evaluates the efficacy of atezolizumab immunotherapy in BCG unresponsive non-muscle invasive bladder cancer. One evaluates the efficacy of atezolizumab in the treatment of high-risk muscle invasive urothelial cancer. The third evaluates the concept of Switch Maintenance with avelumab immunotherapy in patients with advanced urothelial 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: Phase II Trial of Atezolizumab in BCG-Unresponsive Non-Muscle Invasive Bladder Cancer (SWOG 1605)

Clinicaltrials.gov identifier: 02844816

Sponsor: National Cancer Institute/Canadian Cancer Trials Group and Southwest Oncology Group

Enrollment: 202 (total enrollment was 178)

Rationale: Immunotherapy and in particular anti PD-1 and anti PD-L1 therapies have demonstrated efficacy in metastatic urothelial cancer and in muscle-invasive bladder cancer. Therefore, these drugs are now being evaluated alone or in combination with other agents in BCG-unresponsive non-muscle invasive bladder cancer. The PD1 inhibitor pembrolizumab was approved in January 2020 and this trial is the first reporting results of a PD-L1 inhibitor (atezolizumab) in this high risk patient population.

Study Design: This is a single-arm Phase II trial in which patients with BCG-unresponsive high-grade non-muscle muscle invasive bladder cancer (CIS ± Ta/T1 OR Ta/T1) received one year of atezolizumab anti PDL-1

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therapy intravenously every 3 weeks x 17 cycles. Patients were evaluated every 3 months with cystoscopy and cytology with a mandatory biopsy done at 6 months.

Endpoints: The primary endpoint of the trial was the pathological CR rate at 6 months in patients with BCG-unresponsive CIS determined by a mandatory biopsy. The secondary endpoints included: 18-month event-free survival in the Ta/T1 cohort, progression-free survival in all patients, cystectomy-free survival in all patients, bladder-cancer specific survival in all patients, and overall survival in all patients.

Results: The trial launched in 2017 but had a required futility analysis after 25 eligible CIS patients reached the 6 month-endpoint. In order to proceed, at least 7 patients had to have a CR and only 5 patients actually achieved a CR, so the trial was closed to accrual. Ultimately, 172 patients at 68 centers were enrolled of which 128 were eligible: 74 CIS ± Ta/T1 and 54 Ta/T1 without CIS. The CR rate at 6 months in CIS patients was 27% which fell below the null hypothesis of 30%. Of note, the CR rate at 3 months was 42% but this was an unplanned secondary endpoint. Toxicity data is yet unavailable but at least 9 patients in the CIS ± Ta/T1 cohort encountered grade 3-5 AEs during the course of the trial.

Comments: The trial is a herculean effort to treat non-muscle invasive bladder cancer with systemic immunotherapy. Unfortunately, the strict statistical criteria for closure of this trial led to its falling short of its primary endpoint as the expectation of novel therapies in this disease space should provide a higher 6-month CR rate in patients with CIS. However, the 42% 3-month CR noted was similar to that seen with pembrolizumab which has been FDA-approved although the duration of response for atezolizumab is still pending at this time.

Study Title: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Versus Observation as Adjuvant Therapy in Patients With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection

Clinicaltrials.gov identifier: NCT02450331

Sponsor: Hoffman-La Roche/Genentech

Enrollment: 809

Rationale: There is no standard adjuvant treatment regimen after surgery for high-risk muscle invasive urothelial carcinoma (MIUC) based in great part on difficulties with accrual in previous trials. Therefore, the standard of care for adjuvant therapy is observation. This trial evaluates the impact of adjuvant atezolizumab on patients randomized after surgery on disease recurrence and survival.

Study Design: Patients with high-risk MIUC (bladder, renal pelvis, ureter) post radical cystectomy or nephroureterectomy with LN dissection within ≤ 14 weeks that were ypT2-T4a or ypN+ if treated with neoadjuvant chemotherapy (NAC) or pT3-T4a or pN+ if not treated with NAC were eligible. No postsurgical radiation or prior adjuvant therapy was permitted and if no prior NAC was given, patients had to be ineligible for, or declined, cisplatin-based adjuvant therapy. Patients were randomized between Atezolizumab 1200 mg q3w (16 cycles or 1 year) or observation. Crossover was not permitted as part of the protocol.

Endpoints: The primary outcome of the trial was disease-free survival (DFS) and the main oncologic secondary endpoints were overall survival, disease-specific survival (DSS), distant metastasis-free-survival, and non-urinary tract recurrence-free survival.

Results: Unfortunately, the trial did not meet its main primary endpoint of DFS. The median DFS was 19.4 vs. 16.6 months in the atezolizumab versus observation groups, respectively (DFS HR (95% CI) =0.89 (0.74 to 1.08), p=0.2446). Furthermore, no pre-specified groups, including PD-L1 status, demonstrated treatment benefit. The median overall survival was not reached in this interim analysis but no difference between the groups was noted. The toxicities were in line with previous checkpoint inhibitor trials and mostly were grade 1 and 2.

Comments: This is the first Phase III study reported that evaluates the benefit of an adjuvant checkpoint inhibitor in MIUC. It is also the first adjuvant trial to complete accrual, as all others have failed in the past. The safety profile for atezolizumab monotherapy was consistent with that in prior studies in the advanced setting, with no new safety concerns. However, patients and their physicians may have had less tolerance to maintain patients on therapy in the adjuvant setting than in the metastatic setting. In addition, there is always an underlying question of whether immunotherapy is less effective after the majority of disease has been removed. Overall survival is still immature and additional exploratory biomarker and subgroup analyses warrant further study.

Study Title: Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma: JAVELIN Bladder 100 phase III results

Clinicaltrials.gov identifier: NCT02603432

Sponsor: Merck and Pfizer Inc

Enrollment: 700

Rationale: Platinum-based combination chemotherapy has remained the standard-of-care as first-line treatment for advanced urothelial carcinoma (UC). However, durations of progression-free survival (PFS) and overall survival (OS) are limited by chemotherapy resistance

Study Design: Patients with unresectable locally advanced or metastatic UC treated with Cisplatin + gemcitabine or Carboplatin + gemcitabine chemotherapy (4-6 cycles) and obtained a CR, PR, or SD that was maintained for 4-10 weeks were entered into the study. They were randomized (1:1) between IV Avelumab (anti PDL-1) given every 2 weeks or best supportive care.

Endpoints: The primary endpoint was overall survival. Primary analysis populations included all randomized patients and separately the PD-L1+ population. Secondary endpoints included PFS and objective response per RECIST 1.1, Safety and tolerability and patient reported outcomes.

Results: Maintenance avelumab significantly prolonged overall survival compared to best supportive care alone. The overall survival at 1 year was 71.3% vs 58.4%, and median overall survival was 21.4 vs 14.3 months (HR 0.69; 95% CI, 0.56, 0.86; 1-sided P<0.001). Avelumab also significantly prolonged overall survival in the PD-L1+ population as the overall survival at 1 year was 79.1% vs 60.4% (HR 0.56; 95% CI, 0.40, 0.79; 1-sided P<0.001). Adverse events occurred in 98.0% of patients in the avelumab arm and 77.7% of patients in the best supportive care alone arm, including grade ≥3 events in 47.4% and 25.2%, respectively.

Comments: This Late Breaking Abstract was presented at the ASCO plenary session. Switch maintenance avelumab significantly prolonged overall survival vs best supportive care alone in selected patients with UC whose disease had not progressed on first line platin based chemotherapy. These results are practice changing. Based on these results, this concept has already been approved by the FDA on June 30, 2020.

CONFLICT OF INTEREST

Cora N. Sternberg
Consultant: Pfizer, Merck, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Incyte, Medscape, Clovis Oncology, UroToday, MSD

Piyush K. Agarwal
Advisory Board (unpaid): AstraZeneca

Editor-in-Chief **Seth P. Lerner** is a coinvestigator and as committee chair responsible for trial S1605