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Dear Readers,

In this issue, we highlight immunotherapy and antibody drug conjugate trials presented at the ESMO 2020 Virtual Conference on the management of patients with metastatic urothelial cancer. The results inform us of the combination of immunotherapy and chemotherapy, upfront immunotherapy followed by chemotherapy and combinations of immunotherapy. One trial updates the results with an ADC in patients previously treated with chemotherapy and immunotherapy. 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: Pembrolizumab alone or combined with chemotherapy versus chemotherapy alone as first line therapy for advanced urothelial carcinoma (UC): Keynote 361

Clinicaltrials.gov identifier: NCT02853305

Sponsor: Merck Sharpe and Dohme

Enrollment: 1010

Rationale: The current standard for first line treatment in advanced UC is cisplatin-based chemotherapy. Pembrolizumab is recommended for patients as second line therapy or as first line therapy in patients that are PDL-1 positive and ineligible for platinum. Avelumab is recommended as maintenance treatment for patients who do not progress on first line chemotherapy.

Study Design: This was a global, randomized open label phase 3 trial comparing pembrolizumab alone or combined with platinum-based chemotherapy versus chemotherapy as first line treatment for patients with locally advanced or metastatic UC. Patients were randomized 1:1:1 to pembrolizumab and chemotherapy (n=351) or pembrolizumab alone (n= 307) or chemotherapy alone (n=352).

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Endpoints: There were dual primary endpoints, progression free survival (PFS) per RECIST by blinded independent review and overall survival (OS).

Results: The combination of immunotherapy and chemotherapy did not reach statistical significance for PFS or OS in patients with untreated locally advanced or metastatic UC.

Comments: The results of this trial were unexpected as pembrolizumab is approved for metastatic disease as well as BCG unresponsive non-muscle invasive bladder cancer. The results seem to close the door for combination chemotherapy and immunotherapy in the front-line setting. In a somewhat similar study with atezolizumab, the combination led to improvement in PFS, but OS has yet to be reported.

Study Title: A phase 3 randomized open label study of durvalumab with or without tremilumimab versus standard of care (SoC) chemotherapy in patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE)

Clinicaltrials.gov identifier: NCT02516241

Sponsor: AstraZeneca

Enrollment: 1032

Rationale: Platinum-based chemotherapy is the standard of care (SoC) for first-line treatment of metastatic UC. While chemotherapy regimens yield high response rates, survival outcomes are poor. Durvalumab (anti-PD-L1) is FDA approved for the treatment of platinum-refractory, metastatic UC. Tremelimumab (anti-CTLA-4) and the combination of durvalumab plus tremelimumab have shown activity in platinum-refractory, metastatic UC regardless of PD-L1 expression.

Study Design: DANUBE is a randomized, phase 3 trial to evaluate durvalumab, with or without tremelimumab, vs platinum-based chemotherapy as a first-line treatment for metastatic UC. Patients were randomized 1:1:1 to Durvalumab 1500 mg q4w alone until progression (n=346) or Durvalumab plus Tremelimumab 75 mg q4w for up to 4 doses (n=342) or SoC chemotherapy (gemcitabine + cisplatin or carboplatin, up to 6 cycles) (n=344.)

Endpoints: The co-primary endpoints were OS comparing durvalumab monotherapy vs. chemotherapy groups among patients whose tumors had high PD-L1 expression and overall survival comparing durvalumab + tremelimumab vs. chemotherapy groups in the intention-to-treat (ITT) population.

Results: The DANUBE trial did not meet either of the co-primary endpoints of overall survival. However, secondary analyses suggested that the combination of durvalumab + tremelimumab has activity, which is enhanced in patients with tumours that have high PD-L1 expression. This trial was a negative trial but it does suggest that a biomarker-based strategy should be tested in patients whose tumors are PD-L1 positive and may benefit from the combination of durvalumab + tremelimumab.

Comments: The primary endpoints in his study were not met. With a median follow-up for survival of 41.2 months, this study has the longest follow-up to date for a randomized trial of an immunotherapy in previously untreated, metastatic UC. Further investigation of the combination in the context of checkpoint inhibitors may be warranted.

Study Title: Phase II multicenter, randomized study to evaluate efficacy and safety of avelumab with carboplatin/ gemcitabine (CG) vs CG alone in patients with unresectable or metastatic urothelial carcinoma (mUC) who are ineligible to receive cisplatin-based therapy ("INDOCUMAIN").

Clinicaltrials.gov identifier: NCT03390595

Sponsor: Associació per a la Recerca Oncologica, Spain

Enrollment: 85

Rationale: Up to 50% of patients with metastatic urothelial carcinoma (mUC) are not eligible for cisplatin. Carboplatin has activity but not comparable and so this trial evaluates whether Avelumab given as an induction therapy and in combination with carboplatin/ gemcitabine results in superior anti-tumor activity compared to standard chemotherapy in cisplatin-ineligible patients with metastatic UC. Biologically, chemotherapies can induce immunogenic cell death which may enhance the ability of checkpoint inhibitors such as avelumab.

Study Design: This is a phase II multicenter, randomized trial evaluating the safety and efficacy of the combination of avelumab plus carboplatin/ gemcitabine versus carboplatin/ gemcitabine alone in patients with metastatic UC who have not received prior systemic therapy and are cisplatin ineligible. Patients had to have an ECOG status of 0-2 and patients received 6 cycles of carboplatin/gemcitabine with or without avelumab which was given as induction (2 cycles avelumab), concurrent with chemotherapy (6 cycles), and as maintenance in the group that received it with the chemotherapy. Avelumab maintenance was continued until progression, unacceptable toxicity, or treatment discontinuation.

Endpoints: The primary endpoint was overall response rate (ORR) by RECIST criteria. The secondary endpoints included PFS, OS, duration of response (DoR), and safety and tolerability.

Results: The trial enrolled 42 patients in the chemoimmunotherapy arm and 42 patients in the chemotherapy alone arm. In an intention to treat analysis, the overall response rate was 57.1% versus 53.5% respectively, with no significant difference between the arms. Partial and complete responses were 45.2% and 11.9% in the chemoimmunotherapy arm compared with 44.2% and 9.3% in the chemotherapy arm. Median PFS was similar at 6.9 months versus 7.4 months (p=0.1356) in the chemoimmunotherapy versus chemotherapy arms respectively. Median OS was similar at 10.5 months versus 13.2 months (p=0.2642) in the chemoimmunotherapy versus chemotherapy arms respectively. Overall, the drugs were safe and tolerable with their usual expected toxicities.

Comments: Induction immunotherapy followed by chemoimmunotherapy did not significantly improve outcomes in this trial. The trial is different than the findings seen in the Javelin 100 study which demonstrated superior OS in the maintenance arm with avelumab. However, this initial analysis is still immature and further follow-up is needed for definitive conclusions.

Study Title: Phase II Open Label, Study of IMMU-132 in Metastatic Urothelial Cancer After Failure of Platinum-Based Regimen or Anti-PD-1/ PD-L1 Based Immunotherapy (TROPHY-U-01 Cohort 1)

Clinicaltrials.gov identifier: NCT03547973

Sponsor: Immunomedics, Inc.

Enrollment: 201

Rationale: Although patients with metastatic UC have multiple options for therapy, patients who do not respond to platinum-based chemotherapy and/or anti-PD-1/PD-L1 based immunotherapy have had few treatment options until recently (enfortumab vedoin and erdafitinib). Antibody-drug conjugates (ADCs) are monoclonal antibodies (mABs) conjugated to cytotoxic drugs that can deliver a toxic payload to tumor cells expressing a specific tumor target. Enfortumab vedotin is a well-known ADC targeting Nectin 4 that is now FDA-approved. In this specific trial, a different ADC, Sacituzumab govitecan (SG), also known as IMMU-132, is evaluated containing an antibody against the epithelial cell surface molecule Trop-2 conjugated SN-38 (a potent derivative of the cytotoxic drug irinotecan). Trop-2 is overexpressed in bladder cancer and SN-38 inhibits DNA topoisomerase 1 thereby preventing DNA unwinding which results in irreversible double strand DNA breaks and eventually cytotoxic cell death. SG is distinct from other ADCs, with a high drug-to-antibody ratio.

Study Design: This was a phase II, multicenter single-arm trial and updated data for the cohort of 113 patients with metastatic UC that progressed on prior platinum and immune checkpoint therapy were presented at ESMO 2020. Patients received IMMU-132 10mg/kg days 1 and 8 of a 21-day cycle that was continued until toxicity or disease progression. The null hypothesis was an overall response rate ≤ 12%.

Endpoints: The primary objective was overall response rate (ORR) and the secondary outcomes are duration of response (DOR), PFS and OS.

Results: The group was heavily pre-treated with a median number of 3 prior anti-cancer therapies and the median age of the cohort was 66. There was a 27% overall response rate. The median duration of response was 5.9 months and 76% of patients had a reduction in tumor size. As of data cut-off, 16 of the 113 patients were continuing on treatment. Overall two-thirds of patients discontinued therapy due to progressive disease. Median PFS was 5.4 months and median OS was 10.5 months. Of note, 28% of patients had liver metastases. The most common treatment-related adverse event was diarrhea with 9% of patients having a grade 3 event.

Comments: The results are encouraging given the fact that the patients were heavily pre-treated. In fact, 10 patients in the cohort were previously treated with enfortumab vedotin and despite that 3 of these patients had a partial response to SG. ADCs may represent a new salvage therapy option for patients with metastatic UC with progression after checkpoint inhibition therapy and chemotherapy.

CONFLICT OF INTEREST

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