

# Clinical Trials Corner

Dear Readers,

In this issue, we highlight interesting trials that reported results at the 2019 European Society of Medical Oncology (ESMO) Annual Meeting which were presented in Barcelona, Spain. There are novel agents and strategies with encouraging data. In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at: [pkagarwal@uchicago.edu](mailto:pkagarwal@uchicago.edu) or [cns9009@med.cornell.edu](mailto:cns9009@med.cornell.edu) and/or at [BLC@iospress.com](mailto:BLC@iospress.com).

Sincerely,

Piyush K. Agarwal, MD  
Associate Editor, Bladder Cancer  
Director, Bladder Cancer Program  
University of Chicago  
Chicago, IL

Cora N. Sternberg, MD, FACP  
Associate Editor, Bladder Cancer  
Clinical Director, Englander Institute of Precision Medicine  
Weill Cornell Medicine  
New York, New York

**Study Title:** IMvigor130: a phase III study of atezolizumab with or without platinum-based chemotherapy in previously untreated metastatic urothelial carcinoma (mUC)

**Clinicaltrials.gov identifier:** NCT02807636

**Sponsor:** Hoffmann-La Roche

**Enrollment:** 1213

**Rationale:** Cisplatin-based chemotherapy has been standard first (1st) line treatment in mUC for > 30 years. Approximately 50% of patients (pts) with mUC are ineligible for cisplatin, and they generally receive inferior carboplatin-based regimens. PD-L1 and PD-1 inhibitors are the 1st new systemic therapies for mUC, both for 1st line treatment of cisplatin-ineligible pts and for pts experiencing disease progression despite platinum-based chemotherapy. The final PFS and interim OS results for IMvigor130, assessing atezolizumab (atezo) alone or in combination with gemcitabine and carboplatin or gemcitabine and cisplatin in 1st line mUC were presented.

**Study Design:** IMvigor130 is an international phase III trial for pts with locally advanced or mUC who had not received prior systemic therapy. Pts had an ECOG PS  $\leq 2$  and were eligible for platinum-based therapy in the 1st line setting. Pts were stratified by PD-L1 IC status (IC0 vs IC1 vs IC2/3), Bajorin risk factor score including KPS <80% versus  $\geq 80\%$ , the presence of visceral metastases and investigator's choice of chemotherapy. Pts were randomized 1:1:1 to receive atezo and platinum-based therapy (cisplatin or carboplatin) plus gemcitabine (arm A; n = 451), atezo monotherapy (arm B; n = 362), or placebo plus platinum-based therapy and gemcitabine (arm C; n = 400).

**Endpoints:** The co-primary endpoints were investigator-assessed PFS and OS in arm A vs. arm C, and OS in arm B vs. arm C using a hierarchical approach. Key secondary endpoints included investigator-assessed overall response rate (ORR), duration of response, PFS and OS in arm B vs. arm C in the PD-L1 IC2/3 subgroup, and safety.

**Results:** In the intent-to-treat population, the median OS with atezo and platinum plus gemcitabine was 16 months versus and 13.4 months for chemotherapy and placebo (HR, 0.83 (95% CI, 0.69, 1.00). When stratified by PD-L1 expression, pts with PD-L1–positive tumors (IC2/3) had an improvement in OS when treated with

single-agent atezo compared with chemotherapy and placebo (HR, 0.68; 95% CI, 0.43-1.08). Median OS with the PD-L1 inhibitor was not estimated and was 17.8 mos. with chemotherapy. Follow-up of OS will be continued.

**Comments:** Whether the addition of immunotherapy to chemotherapy can improve outcomes in pts with mUC is an important question. IMvigor130 is the first trial to evaluate the combination of immunotherapy and chemotherapy in pts with mUC who are eligible and ineligible for chemotherapy. This trial represents the first positive signal in terms of PFS and a trend in OS. The results from IMvigor130 support atezo + platinum plus gemcitabine as an important new treatment option for patients with untreated mUC. Other similar trials are ongoing with other immunotherapeutic check point inhibitors.

**Study Title:** EV-103: Initial results of Enfortumab Vedotin plus Pembrolizumab for locally advanced or metastatic urothelial carcinoma (mUC)

**Clinicaltrials.gov identifier:** NCT03288545

**Sponsor:** Astellas Pharma Inc, in collaboration with Seattle Genetics

**Enrollment:** 45 of 257 planned

**Rationale:** There is a major unmet medical need for patients with mUC for whom available therapies have failed the patients. Antibody-drug conjugates (ADCs) are monoclonal Abs conjugated to cytotoxic drugs or a radionucleotide. This improves the potency and effectiveness of mAbs, allows for targeted delivery of a toxic payload to tumor cells, thereby minimizing non-specific, systemic toxicity. Enfortumab Vedotin (EV) is an ADC (anti-nectin 4 monoclonal Ab) linked to monomethyl auristatin E (MMAE) with evidence of induction of immunogenic cell death (ICD) in pre-clinical and in vitro data. MMAE disrupts microtubules resulting in ICD. EV showed an ORR of 45% in pts with prior PD-1/L1 inhibitors in a phase 1 study. In a single arm phase II trial (EV-201), single agent EV in pts previously treated with platinum and immune checkpoint inhibitors (NCT03219333) produced a 44% RR (12% CR; 32% PR) in 125 pts. The rationale for combining EV and an immune check point inhibitor such as pembrolizumab (pembro) stems from the fact that ICD releases innate immune activating molecules resulting in APC activation and presentation of tumor antigens to T cells. T cells mount antigen – specific response potentially augmented by PD-1/L1 inhibitors.

**Study Design:** This study examined the safety and anticancer activity of EV IV as monotherapy and in combination with other anticancer therapies in UC. The study will be conducted in multiple parts: dose escalation (enfortumab vedotin + pembrolizumab) and dose expansion (cohorts of enfortumab vedotin + pembrolizumab and/or chemotherapy) for locally advanced and metastatic UC and EV alone and in combination with pembrolizumab in patients with earlier stage of the disease (muscle invasive UC).

**Endpoints:** The primary goal of the study is to determine the safety, tolerability, and efficacy of EV alone and in combination with pembro and/or chemotherapy

**Results:** EV and pembro in cisplatin ineligible 1st line or second line therapy results were reported in 45 pts. The ORR was 71% with 13% CR and 58% PR with rapid responses in 91% at first assessment.

**Comments:** EV alone had a high RR, but this study demonstrated that the combination of EV and immunotherapy with pembro has an even higher RR and is likely to become an important option in the first line setting for cisplatin ineligible pts in the treatment of mUC.

**Study Title:** Initial Results From TROPHY-U-01: A Phase 2 Open-Label Study of Sacituzumab Govitecan in Patients with Metastatic Urothelial Cancer (mUC) After Failure of Platinum-Based Regimens or Immunotherapy

**Clinicaltrials.gov identifier:** NCT03547973

**Sponsor:** Immunomedics, Inc

**Enrollment:** 100 expected in Cohort A

**Rationale:** Pts who progress after platinum-based therapy or who don't respond or don't tolerate immunotherapy have limited treatment options and poor outcomes. Unfortunately, checkpoint inhibitors are ineffective for a majority of pts. Additional treatment options are needed. Sacituzumab Govitecan (SG) is a Trop-2-Directed Antibody-Drug Conjugate (ADC). Trop-2 is an epithelial cell surface antigen highly expressed in UC and a wide range of epithelial cancers. SG is distinct from other ADCs, with a high drug-to-antibody ratio. Linker hydrolysis releases the cytotoxic SN-38 in tumor tissue (intracellularly and in the tumor microenvironment. The payload for SG is SN-38, a Topo1 inhibitor and more potent active metabolite of irinotecan.

**Study Design:** TROPHY-U-01. SG 10 mg/kg was given on days 1 and 8 every 21 days. Data on Cohort A in 35 of 100 pts with mUC who progressed after prior platinum-based and checkpoint inhibition was presented.

**Endpoints:** The primary objective was overall response rate (ORR). Secondary objectives included. safety/tolerability, duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

**Results:** 35 pts included in the interim analysis received  $\geq 1$  cycle of study treatment and had  $\geq 1$  on-treatment response assessment. The ORR was 29% (2 CR, 6 PR, 2 additional PRs pending confirmation). ORR was 25.0% in pts with liver metastases. 74% of pts demonstrated a reduction in tumor size at a median follow-up of 4.1 mos. 57% of pts are continuing treatment. SG was well tolerated, with a manageable, predictable, and consistent safety profile, with neutropenia and leukopenia as the main toxicities. Diarrhea and fatigue were observed.

**Comments:** Antibody-Drug Conjugates are increasing of interest in the treatment of mUC. These data demonstrate that SG has the potential to change the treatment landscape of mUC.

## CONFLICT OF INTEREST

### **Cora N. Sternberg**

Renal

*Honoraria:* Pfizer, IPSEN

*Consultant:* Eisai, Pfizer, IPSEN, BMS, Roche, Bayer, MSD, Novartis

Bladder

*Consultant:* Merck, Clovis, BMS, Incyte, AstraZeneca

*Honoraria:* Lilly

*Institutional Funding:* Janssen

Prostate

*Consultant:* Sanofi, Bayer, Pfizer

*Honoraria:* Clovis, Janssen, AstraZeneca, Sanofi, Astellas

*Institutional Funding:* Roche-Genentech, Bayer, Sanofi, Janssen, Medivation, Exelixis, Sanofi Genzyme

### **Piyush K. Agarwal**

*Advisory Board (unpaid):* AstraZeneca