

# Genitourinary (Non-Prostate) Cancers: ASCO20 Virtual Scientific Program Highlights for the Advanced Practitioner



Following coverage from *The ASCO Post*, **Jeannette Hammond, PA-C**, of Seattle Cancer Care Alliance, comments on the results of practice-changing studies on novel therapies in urothelial cancer and renal cell carcinoma.

## Abstract LBA1

### Advanced Bladder Cancer Survival Improved With Maintenance Avelumab

By *The ASCO Post Staff*

Visit <https://meetinglibrary.asco.org/record/186872/abstract> to read the full abstract and view author disclosures.

According to an interim analysis of the phase III JAVELIN Bladder 100 trial, rates of survival among patients with advanced urothelial carcinoma who did not progress on first-line platinum-based chemotherapy were significantly prolonged by maintenance therapy with avelumab and best supportive care vs best supportive care alone. The data, presented during the Plenary Program of the ASCO20 Virtual Scientific Program, indicated the survival benefit among all patients enrolled in the trial, in patients who were PD-L1 positive, and in all prespecified subgroups.

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“This study met its primary objective, demonstrating significantly prolonged overall survival with first-line maintenance avelumab and best supportive care vs best supportive care alone in the overall population and in PD-L1-positive patients whose disease did not progress on platinum-based chemotherapy. Avelumab as first-line maintenance therapy represents a new first-line standard of care for advanced urothelial cancer that has not progressed on first-line platinum-based chemotherapy,” said lead author Thomas Powles, MD, PhD, of Barts Cancer Institute, London.

“The maintenance setting is an attractive time for using a checkpoint inhibitor. Patients have gone through chemotherapy, and the disease is under control. But instead of waiting for disease to progress after chemotherapy—which it will quickly do in patients with advanced urothelial cancer—adding avelumab significantly improved survival,” he said.

Patients with advanced urothelial cancer who respond to first-line platinum-based chemotherapy typically relapse eventually, and theoretically, maintenance therapy can prolong progression-free survival. JAVELIN Bladder 100 is the first maintenance trial to show a survival advantage in patients with advanced urothelial cancer with stable disease or better after first-line chemotherapy. Avelumab is a PD-L1 inhibitor approved for the treatment of advanced urothelial cancer that has progressed on platinum-based chemotherapy. The immune checkpoint inhibitor is also approved for renal cell carcinoma and Merkel cell carcinoma.

### Study Details

JAVELIN Bladder 100 is a randomized phase III trial that enrolled patients with unresectable locally advanced or metastatic urothelial cancer without disease progression who had a response or stable disease after being treated in the first line with four to six cycles of gemcitabine/cisplatin or gemcitabine/carboplatin. Patients were randomly assigned 1:1 to receive maintenance avelumab at 10 mg/kg intravenously every 2 weeks plus best supportive care vs best supportive care alone. Treatment was continued until disease progression, toxicity, or death.

The primary endpoint was overall survival in all 700 randomly assigned patients and in 358 patients (51%) with PD-L1-positive tumors according to the Ventana SP263 assay. Results were stratified according to best response to first-line chemotherapy (complete response, partial response, or stable disease) and by visceral vs nonvisceral disease at the time of initiating first-line chemotherapy.

Patients were followed for 19.6 months in the avelumab group and 19.2 months in the best supportive care-alone group. The combination of avelumab plus best supportive care significantly prolonged overall survival by 31% ( $P = .001$ ) vs best

supportive care alone. The median overall survival was 21.4 months vs 14.3 months, respectively—a 7-month gain.

Among patients with PD-L1-positive tumors, survival was significantly prolonged by 44% ( $P = .001$ ). In this group, the median overall survival was not reached for avelumab-treated patients vs 17.1 months for the best supportive care-alone group. All prespecified subgroups had an overall survival benefit from avelumab, including age, Eastern Cooperative Oncology Group performance status, first-line chemotherapy regimen, best response to chemotherapy, site of baseline metastasis, creatinine clearance, and PD-L1 status.

Adverse events of any grade occurred in 98% of avelumab recipients vs 77% in the best supportive care-alone group. Grade 3 or higher events—most frequently urinary tract infection, anemia, hematuria, fatigue, and back pain—were reported in 47.4% vs 25.2%, respectively. ●

### Reference

1. Powles T, et al: Maintenance avelumab + best supportive care (BSC) vs BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma. ASCO20 Virtual Scientific Program. Abstract LBA1.

### The Advanced Practitioner Perspective

Jeannette Hammond, PA-C  
Seattle Cancer Care Alliance

Interim analysis of the JAVELIN Bladder 100 phase III clinical trial led to FDA approval for a new, practice-changing indication for avelumab for patients with urothelial cancer. Avelumab is an anti-PD-L1 antibody that originally gained FDA approval in 2017 for patients with urothelial cancer whose disease had progressed on a platinum-containing chemotherapy regimen.

In the current study, patients with unresectable locally advanced or metastatic urothelial cancer whose disease responded or stabilized after 4 to 6 cycles of gemcitabine in combination with either cisplatin or carboplatin were eligible for study. 700 patients were enrolled and randomized to receive avelumab at 10 mg/kg every 2 weeks plus best supportive care vs. best supportive care alone. All patients in the avelumab arm had significantly prolonged overall survival, with median overall survival of 21.4 months compared to 14.3 months.

Notably, in patients with PD-L1-positive tumors, overall survival had not been reached at the time of interim analysis (compared to 17.1 months in the best supportive care arm). Treatment with avelumab continues until disease progression or unacceptable toxicity.

29% of patients receiving avelumab experienced immune-related adverse events of any type and grade. The most common immune-related toxicities were hypothyroidism (10%), rash (5%), and pneumonitis (1.5%). Treatment-emergent adverse events led to discontinuation of avelumab in 11.9% of patients.

Advanced practitioners should be aware of this practice-changing study, as maintenance avelumab after platinum chemotherapy offers a meaningful overall survival benefit and is the new standard of care in the first-line setting for patients with locally advanced or metastatic urothelial cancer.

**Disclosure:** Ms. Hammond has no conflicts of interest to disclose.

**Abstract 5003****HIF2A Inhibitor for von Hippel-Lindau Disease-Associated Renal Cell Carcinoma**

By The ASCO Post Staff

Visit <https://meetinglibrary.asco.org/record/185945/abstract> to read the full abstract and view author disclosures.

**I**n an international trial, treatment with MK-6482, a small-molecule inhibitor of hypoxia-inducible factor (HIF)-2 $\alpha$ , was well tolerated and resulted in clinical responses for patients with von Hippel-Lindau disease-associated renal cell carcinoma (RCC).

The results of the phase II trial were shared in the Genitourinary Cancer Oral Abstract Session during the ASCO20 Virtual Scientific Program by principal investigator Eric Jonasch, MD, Professor of Genitourinary Medical Oncology at The University of Texas MD Anderson Cancer Center (Abstract 5003).

**von Hippel-Lindau Disease-Associated RCC**

von Hippel-Lindau disease is a rare inherited mutation of the *VHL* gene. Renal cell carcinoma affects approximately 40% of people with von Hippel-Lindau disease and is one of the most common causes of disease-related death.

The *VHL* mutation causes cells to lose their ability to respond to oxygen levels properly and leads to a buildup of HIF proteins inside the tumor cell. This process incorrectly signals that the cells are starved of oxygen, causing the formation of blood vessels and driving tumor growth. The inactivation of the *VHL* tumor-suppressor protein is also observed in more than 90% of sporadic RCC tumors. MK-6482 directly targets HIF-2 $\alpha$ , hindering cancer cell growth, spread, and abnormal blood vessel development.

Treatment of von Hippel-Lindau disease-associated renal tumors consists of active surveillance until surgery is required for tumors larger than 3 cm to prevent metastatic disease. Repeated surgical procedures can carry significant complications as many patients develop renal insufficiency.

“Therapy options that can delay or avoid the need for surgery by decreasing tumor size are

needed,” said Dr. Jonasch. “This agent could profoundly change the way we manage lesions in patients with von Hippel-Lindau disease.”

**Methods**

As of data cut-off, the single-arm clinical trial had enrolled 61 adult patients with a germline mutation diagnosis of von Hippel-Lindau disease, no prior systemic cancer therapy, measurable non-metastatic RCC tumors, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients received MK-6482 orally once daily until disease progression, unacceptable toxicity, or investigator’s or patient’s decision to withdraw. Tumor size was evaluated at screening and every 12 weeks thereafter. No patients had progressive disease on treatment and 58 patients (95.1%) remain on treatment.

**Results**

The trial met its primary endpoint and showed an objective response rate in RCC tumors per RECIST by independent review. The confirmed response rate was 27.9%. When also considering the eight patients with unconfirmed response, the objective response rate was 41.0%. Additionally, 86.9% of patients had a decrease in the size of their target lesions. The median time to response was 5.5 months.

Most treatment-related adverse events were grade 1 or 2. Grade 3 adverse events occurred in 9.8% of patients. There were no grade 4 or 5 treatment-related adverse events reported. The most common adverse events were anemia (86.9%), fatigue (57.4%), headache (36.1%), dizziness (31.1%), and nausea (24.6%). Anemia was safely managed with long-acting erythropoietin injections.

“Patients with von Hippel-Lindau disease are at risk of developing several types of cancer and other tumors, and there are currently no approved therapies,” said Dr. Jonasch in a statement. “We are encouraged by the results of this clinical trial and look forward to seeing further study of MK-6482 as we work to make this treatment option available for patients with von Hippel-Lindau disease.”

“MK-6482 was well tolerated and had few side effects,” Dr. Jonasch continued. “This is the

first therapeutic agent that has shown the efficacy and safety required to make it a real option for the management of patients with von Hippel-Lindau disease.”

Future studies to be considered include testing whether MK-6482 can prevent the development of new lesions in patients with von Hippel-Lindau disease. ●

### The Advanced Practitioner Perspective

Jeannette Hammond, PA-C  
Seattle Cancer Care Alliance

The exciting new first-in-class small molecule hypoxia-inducible factor (HIF)-2 $\alpha$  inhibitor, MK-6482, is being explored in von Hippel-Lindau-associated and sporadic clear cell renal cell carcinoma (ccRCC). *VHL* is an inherited autosomal dominant disorder characterized by benign and malignant tumors, including ccRCC. Screening for RCC is recommended in the teen years. The typical treatment is partial nephrectomy. In this population, RCC is often multicentric and bilateral; therefore, alternatives to surgery are appealing.

The *VHL* gene is a tumor suppressor gene, and when it is not fully functioning, there is a buildup of HIF proteins that signal a low oxygen state, causing increased expression of VEGF, PDGF, and erythropoietin, and ultimately leads to angiogenesis and cell proliferation. The *VHL* gene is not functional in the majority of sporadic ccRCC as well.

In this phase II trial, 61 adults with germline *VHL* variations with measurable, non-metastatic RCC received MK-6482 at 120 mg daily. The majority of patients had lesions outside of the kidney as well, including CNS hemangioblastomas and pancreatic lesions. 53 of the 61 patients had some reduction in the size of the target lesions, and 17 had confirmed partial responses. Median time to response was 5.5 months. Responses were also observed in nontarget lesions in the retina, CNS, and pancreas. Treatment-related adverse events were mostly grade 1 or 2 and included anemia, fatigue and dizziness. One patient discontinued study secondary to intolerable dizziness.

Advanced practitioners should look for ongoing research into this class of molecules, as it represents a new targeted option in the treatment of ccRCC and is attractive for its impact further upstream in this tumorigenic pathway.

**Disclosure:** Ms. Hammond has no conflicts of interest to disclose.

### Abstract 5077

#### Immune Checkpoint Inhibitor Rechallenge in Metastatic Renal Cell Carcinoma

By Matthew Stenger

Visit <https://meetinglibrary.asco.org/record/191149/abstract> to read the full abstracts and view author disclosures.

In a study presented at the ASCO20 Virtual Scientific Program (Abstract 5077) and published as a brief report in *JAMA Oncology*, Ravi et al found that rechallenge with immune checkpoint inhibitor therapy was capable of producing responses in patients with metastatic renal cell carcinoma, including patients whose

disease did not respond to initial immune checkpoint inhibitor therapy.

#### Study Details

The retrospective cohort study included 69 consecutive patients with metastatic renal cell carcinoma from nine U.S. institutions who received at least two separate lines of immune checkpoint inhibitor therapy alone or in combination with other therapies between January 2012 and December 2019. Immune checkpoint inhibitors included anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-programmed cell death protein 1 (PD-1), and anti-programmed cell death ligand 1 (PD-L1) therapies.

Median age at diagnosis of metastatic renal cell carcinoma was 61 years (range = 36–86 years);

50 (75%) of patients were male; and 60 (87%) had clear cell histology. Response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1.

### Treatment and Responses

At first-line treatment, treatments were immune checkpoint inhibition plus targeted therapy in 29 patients (42%), single-agent immune checkpoint inhibitors in 27 (39%), dual immune checkpoint inhibitors in 9 (13%), immune checkpoint inhibition plus chemotherapy in 2 (3%), and immune checkpoint inhibition plus an investigational agent in 2 (3%). Among 68 patients evaluable for response, 25 (37%) had partial response (no complete responses), 29 (43%) had stable disease, and 14 (21%) had progressive disease. Reasons for discontinuation of immune checkpoint inhibitor treatment were disease progression in 50 (72%), toxicity in 16 (23%), and other in 3 (4%).

At second-line treatment, treatments were single-agent immune checkpoint inhibitors in 26 (38%), dual immune checkpoint inhibitors in 22 (32%), immune checkpoint inhibition plus targeted therapy in 13 (19%), immune checkpoint inhibition plus chemotherapy in 1 (1%), and immune checkpoint inhibition plus an investigational agent in 7 (10%). Among 64 patients evaluable for response, partial response (no complete responses) was observed in 15 (23%), stable disease in 26 (41%), and progressive disease in 23 (36%).

Median time to progression was 8.2 months with first-line therapy vs 5.7 months with second-line therapy ( $P = .045$ ).

Response with second-line therapy was observed in 7 (29%) of 24 patients with response to first-line therapy and in 3 (21%) of 14 pa-

tients with best response of progressive disease with first-line therapy. Response was observed in 7 (30%) of 23 patients receiving single-agent immune checkpoint inhibition at second-line therapy and in 3 (23%) of 13 receiving an immune checkpoint inhibitor plus targeted therapy. Among six evaluable patients receiving combined PD-1 and CTLA-4 inhibition as second-line therapy, response was observed in one patient (17%) who had received single-agent PD-L1 inhibition as first-line therapy.

### Immune-Related Adverse Events

Immune-related adverse events of any grade occurred in 71% of patients with first-line therapy and 45% with second-line therapy. Grade  $\geq 3$  immune-related adverse events were observed in 18 patients (26%) undergoing first-line therapy, with the most common being elevated liver enzymes (9%), elevated amylase/lipase (6%), and pneumonitis (4%). Grade  $\geq 3$  events were observed in 11 patients (16%) undergoing second-line therapy, with the most common being elevated amylase/lipase (4%) and arthritis (3%). The risk of immune-related events with second-line therapy was higher in patients with such an event with first-line therapy ( $n = 20$ , 41%) vs those without such an event ( $n = 4$ , 20%). No treatment-related deaths were reported.

The investigators concluded, “The findings of this multicenter cohort study suggest that immune checkpoint inhibitor rechallenge in patients with metastatic renal cell carcinoma may be safe and reasonably efficacious, with an overall response rate of 23%. Data from prospective studies are needed to validate these findings and determine the role of sequential immune checkpoint inhibitor regimens in treatment of metastatic renal cell carcinoma.” ●

### The Advanced Practitioner Perspective

Jeannette Hammond, PA-C  
Seattle Cancer Care Alliance

In a retrospective, multicenter observational study, Ravi and colleagues gathered data from 69 patients with metastatic clear cell renal cell carcinoma who received 2 separate lines of immune checkpoint inhibitor (ICI)

therapy. ICI in either setting could be single agent or in combination with other ICIs or targeted agents. The majority of patients discontinued the original ICI secondary to progression (72%). 23% discontinued secondary to toxicity.

Overall response rate to the second ICI was 23%, compared with 36% for the original ICI. Patients were more likely to respond

a second time if they did originally (7 out of 24 patients). It is important to note that they did see responses to rechallenge in 3 out of the 14 patients who had progressive disease as their best response to the original ICI. They did not observe an increase in immune-related adverse events with rechallenge.

Oncology advanced practitioners should be on the lookout for prospective studies fur-

ther investigating the role of multiple lines of ICI therapy. Rechallenging with ICIs is an interesting idea, as the tumor-related immune environment will fluctuate over time. It will be interesting to see in the future what impact the choice of intervening therapy has on subsequent responsiveness to a second ICI.

**Disclosure:** Ms. Hammond has no conflicts of interest to disclose.