

2019 ASCO Annual Meeting Highlights for the Advanced Practitioner: Genitourinary (Non-Prostate) Cancers

Jeannette Hammond, PA-C, of the Seattle Cancer Care Alliance comments on major research presented at the ASCO Annual Meeting: a study addressing an unmet need in the metastatic urothelial cancer setting, a study showing no benefit from an adjuvant therapy, and the results of a study to institute a specialized pain management program. Coverage is provided by *The ASCO Post*.

Abstract LBA4505

Enfortumab Vedotin After Checkpoint Inhibition in Metastatic Urothelial Cancer

By Alice Goodman

Visit <https://meetinglibrary.asco.org/record/171836/abstract> to read the full abstract and view disclosures.

A phase II study found that treatment with the antibody-drug conjugate enfortumab vedotin achieved responses in 44% of patients with locally advanced or metastatic urothelial cancer previously treated with platinum chemotherapy and a checkpoint inhibitor. This is a noteworthy study because it addresses the new question of what to do after patients with metastatic urothelial cancer experience disease progression on second-line treatment with a checkpoint inhibitor.

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“The fact that we have a therapy to help people who don’t benefit from a checkpoint inhibitor is gratifying,” said lead author Daniel P. Petrylak, MD, Professor of Medicine and Urology at Yale Cancer Center, New Haven, Connecticut, who presented these findings at the 2019 ASCO Annual Meeting (Petrylak et al., 2019). “This study addresses an unmet need. Enfortumab vedotin is the first novel therapy to demonstrate substantial clinical activity in patients whose disease progressed after platinum chemotherapy and a programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitor. The response rate was 44%, the complete response rate was 12%, and the median duration of response was 7.6 months. Enfortumab vedotin may have the potential to become a new standard of care for patients who experience disease progression on platinum and a checkpoint inhibitor.”

Ongoing phase III trials are comparing enfortumab vedotin with “dealer’s choice” of chemotherapy, and phase I trials are beginning to explore this agent in combination with others. The results of the phase III trials are expected to support phase II findings.

Study Rationale

After a diagnosis of locally advanced or metastatic urothelial cancer, patients usually receive first-line platinum-based chemotherapy; at disease progression, they often receive second-line checkpoint inhibitor therapy. Five different checkpoint inhibitors are currently approved for the treatment of urothelial cancer, but response rates are low, and

about 75% to 80% of patients will experience disease progression on these agents. There is no approved standard of care for patients whose disease progresses on checkpoint inhibitor therapy.

Enfortumab vedotin is an antibody-drug conjugate that targets Nectin-4, a cellular adhesion molecule with low expression in normal cells but upregulation in urothelial cancer cells and other types of solid tumors. Enfortumab vedotin binds to Nectin-4 and delivers chemotherapy to microtubules, leading to apoptosis of cancer cells. Based on phase I data, enfortumab vedotin was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration. The antibody-drug conjugate is being investigated in the treatment of other cancers that express Nectin-4, including lung and breast.

EV-201 Details

EV-201 is a global trial conducted at 51 sites. Dr. Petrylak presented the results of cohort 1–128 platinum-eligible patients with locally advanced or metastatic urothelial cancer previously treated with platinum-based therapy and a checkpoint inhibitor. Cohort 2 comprises platinum-naïve, cisplatin-ineligible patients, and accrual is ongoing and results are not available at this time. Patients in cohort 1 had metastatic or unresectable urothelial cancer. Exclusion criteria were sensory neuropathy, active central nervous system metastases, and uncontrolled diabetes.

Patients received enfortumab vedotin at 1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle. Seventy percent were male; the median patient age was 69 years (27% were older than age 75); 34% had upper urinary tract cancers; 42% had two or more poor prognostic factors; and patients had a median of two previous systemic therapies. A total of 90% had visceral disease; 40% had liver metastases; 35% had PD-L1–positive disease; and all patients had Nectin-4–positive disease.

Of the 128 patients enrolled in the trial, 125 were treated and comprised the intent-to-treat analysis. The maximum time on treatment was 15.6 months. A total of 16% of patients were continuing on treatment at the time of the presentation.

Treatment Outcomes

The objective response rate was 44%, the complete response rate was 12%, and the partial re-

Key Points

- In the EV-201 trial, the antibody-drug conjugate enfortumab vedotin achieved a 44% response rate and a 12% complete response rate in patients with metastatic urothelial cancer whose disease progressed on platinum-based chemotherapy and immune checkpoint inhibition.
- Treatment of this patient population is considered an unmet need, and enfortumab vedotin holds promise as third-line therapy if phase III studies replicate these results.

sponse rate was 32%. A waterfall plot showed that 84% of patients had some tumor shrinkage as measured by computed tomography scans. All of the prespecified subgroups demonstrated responses, including 38% with liver metastases.

“Prior treatment with PD-L1 or PD-L1 staining was not correlated with response,” Dr. Petrylak noted.

The median time to response was 1.8 months, and most responses were observed at the first assessment. The median duration of response was 7.6 months. Most responders are still being followed, he said. Median progression-free survival was 5.8 months, and median overall survival was 11.7 months.

Tolerability

Treatment with enfortumab vedotin was generally well tolerated. Most adverse events were grades 1 and 2. The most common adverse events were fatigue, alopecia, decreased appetite, dysgeusia, and peripheral sensory neuropathy. A total of 12% of patients discontinued treatment due to treatment-related adverse events (5% due to neuropathy).

A total of 50% of patients had neuropathy of any grade; 3% had grade 3 or higher peripheral neuropathy. Peripheral neuropathy present at baseline worsened in 52% of patients. However, 76% had resolution of events ongoing at grade 1 at last follow-up. Rash of any grade was reported in 48%; 12% had grade 3 or higher rash; there was no case of grade 4 rash. One patient had grade 3 Stevens-Johnson syndrome.

Additional Commentary

“Metastatic urothelial cancer is common, yet we have limited therapeutic options,” said ASCO expert Robert Dreicer, MD, of the University of Virginia Cancer Center, Charlottesville, speak-

ing at a press conference where these data were discussed. “For decades, all we had was chemotherapy. Now, we have second-line checkpoint inhibitor therapy, but basically one in four patients responds. New therapies are badly needed, and I find these data on enfortumab vedotin compelling. The drug has activity in patients treated with prior chemotherapy and immunotherapy, as well as activity in disease sites considered difficult to treat such as the liver. Survival approaches 1 year.”

Dr. Dreicer continued: “We are seeing durable responses in heavily treated patients. The response rate in patients with liver metastases is

compelling, as this is a resistant disease site. These patients today have limited therapeutic options, and there is no question that this drug will benefit some of these patients. I am hopeful the phase III studies will confirm these results.” ●

Reference

Petrylak, D. P., Balar, A. V., O'Donnell, P. H., McGregor, B. A., Heath, E. I., Yu, E. Y.,...Rosenberg, J. E. (2019). EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors [Abstract 4505]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 37(18-suppl). <https://doi.org/10.1200/JCO.2019.37.18-suppl.LBA4505>.

The Advanced Practitioner Perspective

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Platinum-based chemotherapy has been the backbone of treatment for patients with urothelial cancer. Checkpoint inhibitors then entered the treatment space in 2016, with atezolizumab earning the first FDA approval in 30 years for the treatment of urothelial cancer. Recurrence rates remain high, and there is an unmet need for effective therapies for patients refractory to or ineligible for these two options.

Enfortumab Vedotin

Enfortumab vedotin (EV) is a drug with a distinct mechanism that shows promise in treating patients with locally advanced or metastatic urothelial cancer who have previously received platinum-based therapy and immune checkpoint inhibitors. The preliminary data in this phase II study shows a response rate of 44% and a complete response rate of 12%.

Most adverse events were grade 1 or 2 and included fatigue, decreased appetite, alope-

cia, rash, and peripheral neuropathy. Peripheral neuropathy in all grades affected 50% of patients. The most common grade 3 adverse event was neutropenia.

While in phase I studies, EV received Breakthrough Therapy designation from the FDA. Breakthrough Therapy designation requires evidence that the study drug is being developed to treat a serious illness and shows improvement over current therapies in clinically meaningful ways. This program gives the company access to increased communication with and advice from the FDA around development of the drug, eligibility for accelerated approval, and rolling review.

Advanced practitioners should keep an eye out for this exciting agent as it is considered for accelerated approval, tested against chemotherapy in phase III studies, and evaluated in combination with chemotherapy and checkpoint inhibitors.

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

Abstract 4502**No Benefit From Pazopanib in Advanced Renal Cell Carcinoma After Metastasectomy***By The ASCO Post*

Visit <https://meetinglibrary.asco.org/record/171840/abstract> to read the full abstract and view disclosures.

The E2810 trial was conducted to determine whether treatment with the oral drug pazopanib following surgery to remove further metastases in patients with advanced renal cell carcinoma would improve their disease-free survival. Results from the study—which showed that primary endpoint of disease-free survival was not met—were presented by Appleman et al. at the 2019 ASCO Annual Meeting (Abstract 4502).

“E2810 found that pazopanib treatment for 1 year did not improve the chance of survival without disease recurrence,” said lead trial investigator Leonard J. Appleman, MD, PhD, a medical oncologist at the University of Pittsburgh and the University of Pittsburgh Medical Center Hillman Cancer Center. “This finding is important because these patients are at particularly high risk of recurrence, and treatments shown to benefit patients with metastatic disease in place have been attractive to study after surgery to completely remove all visible sites of cancer.” These findings are consistent with earlier studies with other VEGF tyrosine kinase inhibitors.

Study Background

Following initial surgery, select patients with stage IV renal cell carcinoma may undergo metastasectomy to remove one or a very limited number of metastases that develop. This approach can remove all evidence of disease and can sometimes lead to durable control of disease—however, most patients ultimately recur. No systemic therapy has been shown to benefit this population, thus, the current standard of care outside of a clinical trial remains surveillance following the surgery to remove the metastases.

Pazopanib is an inhibitor of VEGFR and other kinases that is approved by the U.S. Food and Drug Administration for the treatment of metastatic renal cell carcinoma.

E2810 was a randomized, double-blind, placebo-controlled trial to test the hypothesis that pazopanib would improve disease-free survival in stage IV patients with no evidence of disease following metastasectomy.

From August 2012 to July 2017, 129 eligible patients were enrolled into the trial by physicians at 58 clinical sites across the United States. Patients were randomly assigned 1:1 to receive pazopanib starting at 800 mg daily vs placebo for 52 weeks. Patients were stratified by 1 vs > 1 site of resected disease, and by disease-free interval ≤ vs > 1 year. Clinical assessments for toxicity and patient-reported outcomes were performed every 4 weeks and restaging scans were performed every 12 weeks.

Results

“The trial did not show a benefit and in fact, there was a suggestion that the patients who received pazopanib had a shorter lifespan,” said Dr. Appleman. “This observation was not statistically conclusive and longer follow-up of the patients who participated in this study may clarify this observation.”

The median follow-up from randomization was 30 months (range 0.4–66.5 months). More than half the patients have had a recurrence of their cancer either during the treatment period or in later follow-up. Most (83%) of the patients are still alive and some have begun further treatment.

“Given the results of E2810, the role of adjuvant VEGF tyrosine kinase inhibitor therapy appears to be limited for both primary resected kidney cancer at high risk for recurrence and for resected metastases,” said co-investigator Naomi B. Haas, MD, a medical oncologist at the University of Pennsylvania and Co-Chair of the ECOG-ACRIN Genitourinary Cancer Research Committee. “This may be due to the absence of tumor blood vessels to target, compounded with an intolerable side effect profile in many patients. The focus has now turned to the role of immune checkpoint inhibition in both settings.” ●

Reference

Appleman, L. J., Puligandla, M., Pal, S. K., Harris, W., Agarwal, N., Costello, B. A.,...Carducci, M. A. (2019). Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy.

tomy: A trial of the ECOG-ACRIN cancer research group (E2810) [Abstract 4502]. *Journal of Clinical Oncology*

(*ASCO Annual Meeting Abstracts*), 37(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.4502

The Advanced Practitioner Perspective

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Pazopanib is a multikinase inhibitor (including VEGFR) that is FDA approved for the treatment of advanced/metastatic renal cell carcinoma.

Pazopanib Details

It is common to evaluate drugs approved in the metastatic setting earlier in the disease process, particularly when the risk of relapse or recurrence is high. This study asked the question of whether pazopanib could improve disease-free survival in patients with oligometastatic disease who were without evidence of disease, status post metastectomy. Current standard practice for these patients is surveillance. Patients in the study received full-dose daily pazopanib or placebo. Patients were monitored clinically at least every 4 weeks and radiographically every 12 weeks. One year of

pazopanib did not improve disease-free survival in this setting.

In this setting, the patient population is without evidence of disease and presumably without symptoms related to their disease, so one of the challenges is tolerability of the treatment. Side effects of pazopanib are well characterized and most commonly include diarrhea, hypertension, nausea, poor appetite, vomiting and hair color changes. Less commonly there have been reports of hepatotoxicity that has been severe and/or fatal, requiring regular LFT monitoring.

Advanced practitioners should look for data on immune checkpoint inhibitors being tested in this space in the future. These agents may offer a mechanistic advantage in this setting.

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

Abstract 6502

Pain Management Program for Patients Undergoing Robotic Urologic Surgery

By *The ASCO Post*

Visit <https://meetinglibrary.asco.org/record/172023/abstract> to read the full abstract and view disclosures.

A specialized pain management program for patients who underwent robotic surgery for urologic cancers resulted in 8% of patients going home with narcotics after discharge, compared to 100% who would have received them without this enhanced recovery protocol. The group of patients who *did* receive narcotics went home with fewer pills than they would have under regular guidelines. These findings were presented by Talwar et al. at the 2019 ASCO Annual Meeting (Abstract 6502).

“The key to our program was to start patients with over-the-counter medications, then escalate them as needed. This means patients whose pain can be managed without opioids never end

up getting them in the first place, while patients whose pain warrants these prescriptions receive them when needed,” said lead author Ruchika Talwar, MD, resident in urology at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

Program Details

This study specifically looked at robotic urologic procedures, including radical prostatectomy, radical nephrectomy, and partial nephrectomy. In all of these cases, guidelines indicate sending patients home with varying amounts of oxycodone—between 15 and 45 pills.

In September 2018, Penn researchers began a new program that started patients without narcotics and escalated only if needed. Patients received gabapentin and acetaminophen before surgery, then received the drugs again every 8 hours after surgery, along with an intravenous dose of ketorolac.

If they were still in pain, patients received tramadol. If complaining of persistent pain despite the standing regimen, patients were given 50 mg or 100 mg of tramadol every 6 hours as needed for

a pain level of 5 to 7 or 8 to 10 on the visual analog scale, respectively. If they required further escalation, patients were given 5 or 10 mg of oxycodone every 6 hours as needed on the aforementioned scale. Regardless of escalation status, all patients were discharged on the standing nonnarcotic protocol. If the regimen was escalated, 10 pills of tramadol at 50 mg or oxycodone at 5 mg were prescribed accordingly.

Results

Out of 170 patients in the program between September 2018 and January 2019, 115 (68%) were discharged without prescriptions for opioids. Another 41 (24%) went home with 10 pills of the nonnarcotic tramadol. Only 14 (8%) were prescribed 10 pills of oxycodone.

The study also compared pain scores among patients, and there was no difference among the three groups despite patients receiving different medications. Dr. Talwar said this shows the pain management technique was effective while still recognizing what each patient requires.

“There have been calls to go opioid-free, but some patients do need them, and our data indi-

cate that among our patients, everyone’s pain was controlled after surgery,” Dr. Talwar explained. “We managed to achieve that while still seeing an overwhelming reduction in the amount of opioids we prescribed.”

Dr. Talwar commented in a press release that this reduction helps more than just the patients, since there are fewer pills in the home and thus fewer pills moving through the community. Researchers also point out that while this model is specific to patients at Penn, the principle is generalizable.

“Every practice is different, and so our next goal is to test this approach in a multi-institutional study, but we felt it was important to share our success to start the conversation about how other centers may want to implement something like this,” said senior study author Thomas J. Guzzo, MD, MPH. ●

Reference

Talwar, R., Xia, L., Serna, J., Lee, D., Ziemba, J., & Guzzo, T. J. (2019). Preventing excess narcotic prescriptions in MIS urologic oncology discharges (PENN): A prospective cohort quality improvement initiative [Abstract 6502]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 37(15_suppl). https://doi.org/10.1200/JCO.2019.37.15_suppl.6502

The Advanced Practitioner Perspective

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The urology team at University of Pennsylvania developed a pain management algorithm for patients who were status post-robotic urologic surgeries, including radical prostatectomy, radical nephrectomy, and partial nephrectomy. Their previous practice guideline was to provide between 15 and 45 oxycodone tablets to each patient at discharge.

They built a process where they initiated nonopioid medication, including gabapentin and acetaminophen preoperatively, and then provided the same medications on a schedule postoperatively with the addition of IV ketorolac. They built in responsiveness and escalation of management based on pain ratings, adding tramadol first and subsequently oxycodone as needed. Two thirds of the patients were discharged without opioids, a quarter received

10 tablets of tramadol, and the remainder received 10 tablets of oxycodone. They did not see any difference in postoperation telephone encounters between the groups. Individual patients’ pain was well managed with the added benefit of decreasing the number of opioids in circulation more broadly.

Advanced Practitioner Creativity

Advanced practitioners can bring that same creativity to pain management—utilizing multiple modalities and medications with varying mechanisms to achieve great results.

These are the kind of initiatives that could easily be advanced practitioner-driven as well. This was one department at a single institution bringing extra discernment to their standard processes that resulted in responsive and ongoing patient-centered care while mitigating the impact of opioids in the community.

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