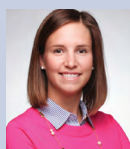


# Genitourinary Cancer: 2022 ASCO Annual Meeting Highlights for the Advanced Practitioner



**Emily Lemke, DNP, AGPCNP-BC, AOCNP®**, of the Medical College of Wisconsin Cancer Center, comments on MET and CTLA-4 inhibitors for clear cell renal cell carcinoma, maintenance targeted therapy for patients with metastatic urothelial carcinoma, the landscape of metastatic hormone-sensitive prostate cancer, a consensus definition for platinum ineligibility, and PSMA-positive metastatic castration-resistant prostate cancer.

## Abstract LBA4503

### **MET and CTLA-4 Inhibitors Do Not Add to Efficacy of Durvalumab in Advanced ccRCC**

By JADPRO Staff

Visit [https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17\\_suppl.LBA4503](https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17_suppl.LBA4503) to read the full abstract and view author disclosures.

Adding the MET inhibitor savolitinib or the CTLA-4 inhibitor tremelimumab to the PD-L1 inhibitor durvalumab did not demonstrate efficacy in patients with previously treated advanced clear cell renal cell carcinoma (ccRCC), according to data from CALYPSO presented at the 2022 ASCO Annual Meeting.

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## Study Details

CALYPSO was a phase II study examining durvalumab alone, savolitinib alone, durvalumab with savolitinib, and durvalumab with tremelimumab in patients with ccRCC who previously received VEGF-targeted therapy but not immune checkpoint inhibitors or MET inhibitors. The primary endpoint was confirmed response rate (cRR). The savolitinib arm was closed early due to lack of efficacy. DNA alterations were measured using Foundation One. PD-L1 analysis was performed with SP263.

## Study Results

Investigators reported the data from 139 patients after 12 months of treatment. 39 patients were assigned to the durvalumab alone arm, 22 to savolitinib, 39 to durvalumab and tremelimumab, and 39 to durvalumab and savolitinib. Confirmed response rates for the four arms were 10% for durvalumab, 5% for savolitinib, 28% for durvalumab and tremelimumab, and 13% for durvalumab and savolitinib. 12-month progression-free survival rates were 26% for durvalumab, 21% for savolitinib, 33% for durvalumab and tremelimumab, and 17% for durvalumab and savolitinib.

There was one treatment-related death in the durvalumab and tremelimumab arm. Of the 136 patients who received treatment, grade 3 or greater treatment-related adverse events occurred in 10% of patients in the durvalumab arm, 26% in the savolitinib arm, 23% in the durvalumab and tremelimumab arm, and 23% in the durvalumab and savolitinib arm.

### The Advanced Practitioner Perspective Emily Lemke, DNP, AGPCNP-BC, AOCNP®

Medical College of Wisconsin Cancer Center

Investigators continue to search for a superior immunotherapy-based combination therapy as compared to the current standard-of-care options for metastatic renal cell carcinoma (mRCC) with varying success. CALYPSO adds to this body of work, with researchers reporting on the results of this randomized control trial evaluating the efficacy of durvalumab (PD-L1 inhibitor) alone or with savolitinib (MET inhibitor) or tremelimumab (CTLA-4 inhibitor) in previously treated advanced clear cell RCC (ccRCC).

Patients (n = 139) included in this trial had previously received VEGF-targeted therapy but no prior immunotherapy or MET inhibitors. The four arms were durvalumab, savolitinib, durvalumab + tremelimumab, and durvalumab + savolitinib. The most common treatment response in all four arms was progres-

sive disease. Median overall survival for the durvalumab arm was 26.1 months, savolitinib 23.1 months, durvalumab + tremelimumab 21.9 months, and durvalumab + savolitinib 16.1 months. It was unexpected that in *MET*-driven ccRCC the response rate (RR) was just as low as in the other arms.

While *MET* inhibition has not showed success in ccRCC, future directions for *MET*-driven therapy, including savolitinib in combination with durvalumab, are warranted for papillary RCC (pRCC). Despite there being no clinical efficacy of savolitinib + durvalumab in ccRCC, investigators of CALYPSO reported an objective RR of 27% in the pRCC arm of this trial as presented at the 2020 ASCO Genitourinary Cancer Symposium. Continued trials are needed in this space to better understand and identify biomarkers for mRCC.

**Disclosure:** Dr. Lemke has no conflicts of interest to disclose.

### Abstract LBA4505

#### Rucaparib Following Chemotherapy for Urothelial Carcinoma: Update From the ATLANTIS Trial

By JADPRO Staff

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**R**esults from the ATLANTIS trial show that although tolerable, cabozantinib did not show a significant benefit compared with placebo when used in the switch maintenance setting following platinum-based chemotherapy in patients with metastatic urothelial carcinoma (mUC). Simon J. Crabb, PhD, MBBS, of the Southampton Experimental Cancer Medicine Centre, discussed the findings at the 2022 ASCO Annual Meeting.

#### Study Details

Platinum-based chemotherapy is a first-line therapy in mUC, but duration of response is usually short. ATLANTIS is an adaptive, multi-comparison, phase II trial platform that tests multiple maintenance

therapies for mUC patients who complete 4 to 8 cycles of platinum-based chemotherapy without disease progression. Patients in ATLANTIS who were not selected for the biomarker-driven arms of the study were randomized 1:1 to commence either cabozantinib 40 mg once-daily or matching placebo within 10 weeks of completing platinum-based chemotherapy until progression.

The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, response rate, maximum percentage decrease in measurable disease, safety, and tolerability.

#### Study Results

30 patients were randomized to cabozantinib and 31 to placebo from 25 sites. Patients had a median age of 69, 75.4% were male, 67.2% had an Eastern Cooperative Oncology Group Performance Status of 0, 70.5% had prior cisplatin, and 36.1% had visceral metastases.

25 (83.3%) and 26 (83.9%) PFS events occurred in the cabozantinib and placebo arms, respectively. Median PFS was 13.7 weeks with cabozantinib and 15.8 weeks with placebo (adjusted hazard ratio 0.89 favouring cabozantinib;  $p = .35$ ). There was no difference in overall survival.

Treatment-related adverse events were mostly low grade. The most frequent were more common with cabozantinib: fatigue (56.7% vs. 32.2%), hypertension (43.3% vs. 12.9%), nausea (30% vs. 19.4%), and diarrhea (40.0% vs. 6.5%).

### The Advanced Practitioner Perspective

Emily Lemke, DNP, AGPCNP-BC, AOCNP®

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The role of platinum-based therapy for patients with metastatic urothelial carcinoma (mUC) is well understood and adopted among clinicians. Exploring whether there is a role for tyrosine kinase inhibitors (TKIs) in mUC treatment has remained under investigation. Pre-clinical data suggest activity of TKIs in mUC, although there remains a paucity of tangible success in phase II trials warranting practice changes or phase III investigations. Cabozantinib (Cabometyx) is a TKI that inhibits MET, AXL, and VEGFR, and is approved at varying doses in other solid tumor malignancies.

The ATLANTIS trial is a randomized, multi-arm, phase II biomarker-directed umbrella screening trial of maintenance targeted therapy following chemotherapy for patients with mUC. This abstract reports on the cabozantinib comparison arm of the study. Patients (n = 60) previously treated with 4 to 8 cycles of platinum-

Overall, cabozantinib was tolerable with a median duration of treatment of 13 28-day cycles of cabozantinib or 10 of placebo. 13 (43%) vs. 3 (9.7%) patients required dose reduction in the cabozantinib and placebo arms, respectively.

based chemotherapy who were not selected for the biomarker-driven arms of this trial were randomized to receive either cabozantinib or placebo. A total of 30 patients received cabozantinib 40 mg daily. The primary endpoint was progression-free survival (PFS), which is fitting given the propensity of mUC to progress quickly. Median PFS was 13.7 weeks in the cabozantinib arm and 15.8 weeks in the placebo arm ( $p = .35$ ) with no differences in overall survival.

This abstract reports no clinical benefit of cabozantinib for maintenance therapy in mUC. It is important to call attention to trials such as this one to better shape future clinical trials and add to clinicians' disease expertise. Furthermore, having a working knowledge of both trials that demonstrate efficacy and trials that do not show a significant benefit can help advanced practitioners better address patient treatment questions and improve patient education.

**Disclosure:** Dr. Lemke has no conflicts of interest to disclose.

## Abstract LBA5004

### ENZAMET: Updated Overall Survival Outcomes of Enzalutamide in Metastatic Hormone-Sensitive Prostate Cancer

By JADPRO Staff

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At the 2022 ASCO Annual Meeting, researchers presented updated overall survival (OS) findings of ENZAMET, which supported earlier findings that adding enzalutamide to testosterone suppression provides statistically and clinically meaningful survival improvements in metastatic hormone-sensitive prostate cancer (mHSPC).

### Study Details

Patients with mHSPC were randomized to treatment with testosterone suppression plus either a conventional nonsteroidal antiandrogen (NSAA) or enzalutamide. Stratification factors included age, volume of disease (high vs. low according to the CHARTED definition), and planned use of concurrent docetaxel assigned by the treating physician (docetaxel yes vs. no).

### Study Findings

The study included 1,125 patients with a median age of 69 years, including 503 in the docetaxel stratum, and 602 with high volume metastatic disease. Overall survival results were based on 476 deaths and a median follow-up of 68 months. The 5-year OS rates were 67% for enzalutamide and 57% for NSAA. Median OS was not reached in the enzalutamide arm and was 73.2 months in

the control arm. The hazard rate for death was 30% lower among all those assigned enzalutamide vs. control.

The benefits were more pronounced in patients with low-volume disease, and were also seen in the subgroup with M1 high-volume mH-

SPC despite the relatively high survival with testosterone suppression, docetaxel, and NSAA.

The researchers concluded that enzalutamide added to testosterone suppression compared with NSAA provided clinically meaningful improvements in OS for the combined overall cohort.

### The Advanced Practitioner Perspective

Emily Lemke, DNP, AGPCNP-BC, AOCNP®

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If one had to summarize the landscape for metastatic hormone-sensitive prostate cancer (mHSPC) in 2022, it would be “more is more.” ENZAMET builds on this concept with this abstract reporting updated overall survival (OS) data.

This international, phase III, randomized, open label trial investigated the benefit of adding enzalutamide to standard of care (testosterone suppression with bicalutamide, nilutamide, or flutamide with or without docetaxel) in men with mHSPC. The trial design allowed for the addition of docetaxel in either arm as assigned by the treating physician. Notably, the hazard ratio (HR) for death was 30% lower in the group treated with enzalutamide. Furthermore, the 5-year OS in the enzalutamide arm was 67% as compared with 57% in the standard-of-care arm.

It is difficult to interpret this data in the current 2022 mHSPC landscape without biases based on the now widely adopted data from ARASENS and PEACE-1 trials, which both report a survival advantage for triplet therapy

in mHSPC. One key question in this space that lacks any data is who needs docetaxel? The addition of docetaxel was not randomized, nor was ENZAMET powered to answer the question of OS benefit of triplet therapy; however, it did stratify based on volume of disease and addition of docetaxel, therefore helping clinicians continue to tease out the role of triplet therapy. One clear theme is that docetaxel was predominantly given to patients with high-volume mHSPC (71%).

Androgen deprivation monotherapy is now considered substandard care for patients with mHSPC. With therapy intensification now indicated for many patients with mHSPC, it is important that advanced practitioners (APs) understand the benefits of additional therapy and help patients navigate this sometimes overwhelming treatment path. Educating patients on anticipated side effects while also helping them understand potential benefits of intensified therapy is a key role for APs caring for patients with mHSPC.

**Disclosure:** Dr. Lemke has no conflicts of interest to disclose.

## Abstract 4577

### Urothelial Cancer: Defining Who Is ‘Platinum Ineligible’

By JADPRO Staff

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**S**hilpa Gupta, MD, of the Cleveland Clinic, presented on an updated consensus definition for standard therapy and clinical trial eligibility for patients with metastatic urothelial carcinoma (mUC) who are platinum ineligible at the 2022 ASCO Annual

Meeting in Chicago. These criteria are proposed to guide treatment recommendations for this population. This may be especially important now that the US Food and Drug Administration (FDA) has restricted the use of first-line pembrolizumab to those who are considered platinum-ineligible.

### Background

Front-line therapy for patients with mUC who are cisplatin ineligible has evolved significantly. The current standard of care is carboplatin and gemcitabine followed by avelumab maintenance. Although pembrolizumab and atezolizumab were approved as first-line therapy for these patients in 2017, the FDA has now restricted the use

of first-line pembrolizumab to platinum ineligible patients.

In 2019, Gupta and colleagues suggested a consensus definition for platinum-ineligible patients with metastatic urothelial cancer. At the 2022 ASCO Annual Meeting, they presented an updated consensus definition for standard therapy and clinical trial eligibility in the current treatment era.

### Study Details

60 genitourinary medical oncologists in the US (similar to the 2019 cohort) were surveyed using an online tool consisting of several clinical parameters used in the initial survey with additional questions related to current available treatment options. Different age and creatinine thresholds along with other clinically relevant established criteria were analyzed.

#### The Advanced Practitioner Perspective

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After decades of little progress, the past 5 years have ushered in a host of welcome changes to the management of metastatic urothelial carcinoma (mUC). Key among these changes was the addition of immunotherapy, which established treatment options for platinum-ineligible patients who previously had few.

Specifically, atezolizumab (Tecentriq) and pembrolizumab (Keytruda) gained approval for front-line treatment of mUC in platinum-ineligible patients. Given the FDA restriction to only those deemed platinum ineligible by their treating physician, it is important to have a consensus among genitourinary (GU) medical oncologists as to its definition.

Gupta and colleagues conducted a nationwide survey of 60 GU medical oncologists practicing in the United States that assessed the value of different parameters used to define platinum eligibility. Based on the responses, meeting one of the following criteria has been proposed to establish a standardized definition for platinum ineligibility: Eastern Co-

### Results

All 60 respondents provided 100% responses. Respondents (94%) reported using a carboplatin-based regimen followed by avelumab, and 6% reported using carboplatin-based regimen followed by pembrolizumab for cisplatin-ineligible mUC patients. 17/60 (28.3%) and 29/60 (48.3%) checked PD-L1 status prior to using pembrolizumab or atezolizumab, respectively.

### Consensus Definition

Based on the survey, any mUC patient meeting one of the following five parameters should be considered “platinum-ineligible”: Eastern Cooperative Oncology Group Performance Score (ECOG PS)  $\geq 3$ ; creatinine clearance  $< 30$  mL/min; peripheral neuropathy  $\geq$  grade 2; New York Heart Association Heart Failure Class  $> 3$ ; and ECOG PS 2 and creatinine clearance  $< 30$  mL/min.

operative Oncology Group Performance Score (ECOG PS)  $\geq 3$ ; creatinine clearance (CrCl)  $< 30$  mL/min; peripheral neuropathy  $\geq$  grade 2; New York Heart Association (NYHA) Heart Failure Class  $> 3$ ; ECOG 2 and CrCl  $< 30$  mL/min.

To note, this differs from the definition of cisplatin eligibility as established by Glasky and colleagues (2011), which defines unfit patients as having to meet at least one of the following criteria: ECOG PS  $\geq 2$ ; CrCl  $< 60$  mL/min; hearing loss  $\geq$  grade 2; neuropathy  $\geq$  grade 2; and/or NYHA  $\geq$  class 3.

Platinum eligibility has become synonymous with chemotherapy eligibility for patients with mUC. Advanced practitioners (APs) often care for patients with mUC treated with chemotherapy and therefore need to have a working knowledge of platinum and cisplatin eligibility definitions. Patients treated with platinum-based therapy should be assessed at frequent intervals to ensure continued treatment is acceptable; APs are well poised to assume this role.

**Disclosure:** Dr. Lemke has no conflicts of interest to disclose.



## Abstract 5000

**LuPSMA Improves Progression-Free Survival vs. Cabazitaxel in PSMA-Positive Metastatic Castration-Resistant Prostate Cancer**

By Alice Goodman

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**L**utetium-177-labeled PSMA-617 (LuPSMA; lutetium Lu 177 vipivotide tetraxetan) achieved longer progression-free survival with fewer toxicities compared with cabazitaxel in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer whose disease progressed after treatment with docetaxel and an androgen receptor pathway inhibitor.

These findings of the randomized, open-label phase II TheraP trial, presented at the 2022 ASCO Annual Meeting, suggest that LuPSMA represents an improved third-line option over cabazitaxel for patients with PSMA-positive disease progression on docetaxel and an androgen receptor pathway inhibitor, mainly because of its effect on progression-free survival, low toxicity profile, and improvements in patient-reported outcomes.

At a median of 36 months of follow-up, there was no statistically significant or clinically meaningful difference in overall survival between the LuPSMA arm and the cabazitaxel arm. Treatment with LuPSMA significantly improved progression-free survival compared with cabazitaxel. Updated median progression-free survival was 7.1 months with LuPSMA vs 5 months with cabazitaxel, representing a 38% reduction in the risk of disease progression or death ( $P = .0028$ ).

“TheraP supports the choice of [LuPSMA] over cabazitaxel for patients with PSMA PET-positive progressive metastatic castration-resistant prostate cancer after treatment with docetaxel and an androgen receptor pathway inhibitor, on the basis of its higher prostate-specific antigen response rate, greater progression-free survival benefit, quality-of-life benefits, favorable safety profile and dosing schedule, and similar survival

outcomes,” stated lead author Michael S. Hofman, MBBS, of the Peter MacCallum Cancer Centre, Melbourne. “Survival was considerably shorter for patients excluded on PSMA/FDG-PET [fluorodeoxyglucose (F-18) positron-emission tomography] with either low PSMA expression or PSMA-discordant disease.”

LuPSMA is a radioligand that targets PSMA, which is expressed almost exclusively by metastatic prostate cancer cells but is not present in all metastatic prostate cancer cells. Previously, the VISION trial showed that LuPSMA plus the standard of care significantly improved radiographic progression-free survival and overall survival in 831 men with PSMA-positive metastatic castration-resistant prostate cancer compared with the standard of care. All men received previous treatment with a taxane and androgen receptor pathway inhibitor.

TheraP is the first randomized controlled trial comparing LuPSMA with the standard third-line option for metastatic castration-resistant prostate cancer, cabazitaxel, but it is a smaller trial than VISION.

**Study Details**

TheraP enrolled a total of 291 men with metastatic castration-resistant prostate cancer following docetaxel treatment who had a rising prostate-specific antigen (PSA) and a PSA level  $\geq 20$  ng/mL. All men underwent PET imaging with gallium-68-PSMA-11 and were required to have high PSMA expression. Patients with FDG-positive/PSMA-negative disease sites (discordant disease) were excluded.

Of the 291 patients screened, 200 were eligible for inclusion and were randomly assigned at a 1:1 ratio to receive treatment with either LuPSMA at 8.5 GBq every 6 weeks for a maximum of 6 cycles ( $n = 99$ ), or cabazitaxel at 20 mg/m<sup>2</sup> every 3 weeks for a maximum of 10 cycles ( $n = 101$ ). A total of 15 men withdrew from the trial postrandomization.

In the previously published analysis of TheraP, responses and secondary endpoints were all improved with LuPSMA. By 12 months, progression-free survival was 19% in the LuPSMA arm, compared with 3% in the cabazitaxel arm. A PSA reduction of 50% or more from baseline occurred more frequently in the LuPSMA arm at 66% vs. the cabazitaxel arm at 37%, reflecting a 29%

improvement for LuPSMA that was statistically significant. The objective response rate was 49% vs 24%, respectively. Grade 3 and 4 toxicities were 33% in the LuPSMA arm vs 53% in the cabazitaxel arm.

At a median follow-up of 36 months, deaths were reported in 70 of 101 patients receiving cabazitaxel, 77 of 99 patients receiving LuPSMA, and 55 of 61 patients excluded after PSMA/FDG-PET screening.

Post protocol, patients had access to cabazitaxel, LuPSMA, abiraterone acetate, and enzalutamide. Of the patients randomly assigned to

LuPSMA, 32% went on to receive cabazitaxel, and 5% received additional LuPSMA. In the cabazitaxel arm, 21% of patients received additional cabazitaxel, and 20% received LuPSMA.

Overall survival was also evaluated in the patients who were excluded due to screening failure; 61 of 80 patients consented to follow-up. The next line of treatment for these patients was cabazitaxel (48%), enzalutamide (7%), LuPSMA (5%), carboplatin (5%), other (5%), and mitoxantrone (2%). Overall survival was 18.8 months in the randomly assigned patients vs 11.0 months in the patients with PSMA/FDG-PET screening failure.

### The Advanced Practitioner Perspective

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The recent FDA approval of lutetium-177-PSMA-617 (LuPSMA) has led to a practice change for patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel chemotherapy who have prostate-specific membrane antigen (PSMA) expression as evaluated by Ga 68 PSMA-11 (PSMA PET). LuPSMA is a small molecule radioligand therapy that targets surface protein PSMA, which is present in roughly 80% of patients with mCRPC.

TheraP is a phase III, randomized controlled trial comparing LuPSMA to cabazitaxel (Jevtana) in patients with mCRPC who progressed on docetaxel therapy. Primary endpoint data were initially reported in 2021 where men treated with LuPSMA had an improved prostate-specific antigen response as compared with cabazitaxel. This abstract provides an update reporting the secondary endpoint of overall survival (OS) after a median follow-up of 3 years.

TheraP included 200 eligible patients, where 99 patients were randomized to LuPSMA and 101 to cabazitaxel. LuPSMA dosing was 8.5 GBq every 6 weeks for a maximum of 6 cycles. Overall survival was similar in both groups (19.1 months vs. 19.6 months). Despite the similar OS in the cabazitaxel and LuPSMA arms, two notable outcomes are the improved rate of adverse events and improved patient-reported outcomes in the LuPSMA treatment arm. This is important given that in late-line therapy where treatment is palliative, tolerability is a key driver of treatment decisions. Furthermore, every-6-week scheduling as compared with every-3-weeks for cabazitaxel is likely more attractive to patients.

The most commonly reported side effects for LuPSMA included anemia, thrombocytopenia, dry mouth, dry eyes, fatigue, and nausea. Understanding the side effects and clinical trial data behind LuPSMA will help advanced practitioners guide treatment decisions and patient counseling.

**Disclosure:** Dr. Lemke has no conflicts of interest to disclose.