Phase I Study of Cabozantinib and Nivolumab Alone or With Ipilimumab for Advanced or Metastatic Urothelial Carcinoma and Other Genitourinary Tumors

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PURPOSE We assessed the safety and efficacy of cabozantinib and nivolumab (CaboNivo) and CaboNivo plus ipilimumab (CaboNivoIpi) in patients with metastatic urothelial carcinoma (mUC) and other genitourinary (GU) malignancies.

PATIENTS AND METHODS Patients received escalating doses of CaboNivo or CaboNivoIpi. The primary objective was to establish a recommended phase II dose (RP2D). Secondary objectives included objective response rate (ORR), progression-free survival (PFS), duration of response (DoR), and overall survival (OS).

RESULTS Fifty-four patients were enrolled at eight dose levels with a median follow-up time of 44.6 months; data cutoff was January 20, 2020. Grade 3 or 4 treatment-related adverse events (AEs) occurred in 75% and 87% of patients treated with CaboNivo and CaboNivoIpi, respectively, and included fatigue (17% and 10%, respectively), diarrhea (4% and 7%, respectively), and hypertension (21% and 10%, respectively); grade 3 or 4 immune-related AEs included hepatitis (0% and 13%, respectively) and colitis (0% and 7%, respectively). The RP2D was cabozantinib 40 mg/d plus nivolumab 3 mg/kg for CaboNivo and cabozantinib 40 mg/d, nivolumab 3 mg/kg, and ipilimumab 1 mg/kg for CaboNivoIpi. ORR was 30.6% (95% CI, 20.0% to 47.5%) for all patients and 38.5% (95% CI, 13.9% to 68.4%) for patients with mUC. Median DoR was 21.0 months (95% CI, 5.4 to 24.1 months) for all patients and not reached for patients with mUC. Median PFS was 5.1 months (95% CI, 3.5 to 6.9 months) for all patients and 12.8 months (95% CI, 1.8 to 24.1 months) for patients with mUC. Median OS was 12.6 months (95% CI, 6.9 to 18.8 months) for all patients and 25.4 months (95% CI, 5.7 to 41.6 months) for patients with mUC.

CONCLUSION CaboNivo and CaboNivoIpi demonstrated manageable toxicities with durable responses and encouraging survival in patients with mUC and other GU tumors. Multiple phase II and III trials are ongoing for these combinations.

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INTRODUCTION An estimated 362,860 new genitourinary (GU) tumors are expected to be diagnosed in the United States in 2020.1 Treatment options for these tumors have changed in recent years. The US Food and Drug Administration recently approved seven new agents for metastatic urothelial carcinoma (mUC), including five immune checkpoint inhibitors (ICIs).2-6 In addition, the development of antiangiogenic agents and ICIs for metastatic renal cell carcinoma (mRCC) has led to survival benefits;7 and new androgen receptor and poly(ADP-ribose) polymerase inhibitors have demonstrated clinical benefit in castration-resistant prostate cancer (CRPC).8,9 Yet, in the metastatic setting, these diseases are incurable,7,10 and effective treatment options are still needed, especially for less common GU histologies. Cabozantinib inhibits multiple receptor tyrosine kinases (TKs) involved in tumor growth, angiogenesis, and immune cell regulation, including MET, VEGFR, RET, KIT, TIE-2, ROS1, and the TAM family of kinases (TYRO3, AXL, and MER).11 VEGFR2 contributes to...
tumor angiogenesis, carcinogenesis, and progression of GU malignancies such as urothelial carcinoma, renal cell carcinoma (RCC), and prostate cancer. The MET pathway also has an important role in the tumorigenesis of these tumors and seems to cooperate with the VEGF pathway in tumor angiogenesis. Preclinical models have suggested that the MET pathway mediates resistance to VEGF-targeted therapy in several cancers, including RCC, and multiple clinical trials investigating cabozantinib in GU tumors have shown clinical activity. 

ICIs are now part of the standard of care for mUC and mRCC and have been investigated in CRPC and metastatic germ cell tumors (mGCTs). Nivolumab is a monoclonal antibody against the programmed cell death protein 1 (PD-1) cell surface membrane receptor. The clinical activity of nivolumab has been reported in clinical trials for patients with mRCC and mUC. Ipilimumab is a monoclonal antibody specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4). The PD-1 and CTLA-4 signaling cascades use nonredundant mechanisms to block T-cell activation, and clinically, the combination of ipilimumab and nivolumab has shown meaningful activity in patients with mRCC and mUC.

TK inhibitors (TKIs) against VEGFR and other receptor tyrosine kinases may have antitumor immune-mediated mechanisms. Preclinical studies have shown that antiangiogenic TKIs, such as cabozantinib, can modify the tumor microenvironment by reducing the percentage of immunosuppressive T regulatory cells and myeloid-derived suppressor cells and can increase T-cell infiltration. In addition, the combination of anti-VEGF–targeted therapies with ICIs has shown improvements in clinical outcomes for patients with mRCC and CRPC.

The objectives of this phase I trial were to determine dose-limiting toxicities (DLTs) and the recommended phase II dose (RP2D) for the combinations of cabozantinib and nivolumab (CaboNivo) and cabozantinib, nivolumab, and ipilimumab (CaboNivoIpi) in patients with GU tumors and to assess the clinical efficacy of these combinations.

**PATIENTS AND METHODS**

**Patient Selection**

Eligible patients had a histologically confirmed diagnosis of metastatic GU tumors with new or progressive lesions on cross-sectional imaging, measurable by RECIST v1.1. Patients must have received one or more lines of standard therapy unless no standard treatment existed that had been shown to prolong survival. For complete inclusion and exclusion criteria, see the Data Supplement.

The study protocol (ClinicalTrials.gov identifier: NCT02496208) was approved by institutional review boards at all participating institutions. Patients were enrolled per international standards of good clinical practice and institutional safety monitoring. All patients provided written informed consent before study entry.

**Study Design**

This phase I dose-escalation study initially had seven dose levels divided into two parts (Table 1). The study used a rolling six, phase I trial design. Two to six patients could be concurrently enrolled onto a dose level. The DLT period refers to the first 4 weeks for CaboNivo and the first 6 weeks for CaboNivoIpi during the dose-escalation phase for all seven dose levels. A DLT was defined as an adverse event (AE) potentially attributable to any of the study drugs or the combination that required permanent discontinuation of protocol therapy or was grade ≥ 3 according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 5.0. If dose reduction or interruption of cabozantinib led to a patient taking ≤ 75% of the planned dose within the DLT observation period, the event was considered a DLT.
| Dose Level | Cabozantinib Dose | Nivolumab Dose | Ipilimumab for 4 Doses | No. of Patients | Tumor Types |
|------------|-------------------|----------------|------------------------|----------------|-------------|
| Part 1: cycle length, 28 days |                  |                |                        |                |             |
| 1          | 40 mg PO daily     | 1 mg/kg every 2 weeks | 0                      | 6              | GCT (n = 3), urothelial carcinoma (n = 1), bladder squamous cell carcinoma (n = 1), urachal adenocarcinoma (n = 1) |
| 2          | 40 mg PO daily     | 3 mg/kg every 2 weeks | 0                      | 6              | Urothelial carcinoma (n = 2), bladder squamous cell carcinoma (n = 1), GCT (n = 1), urachal adenocarcinoma (n = 1), RCC (n = 1) |
| 3          | 60 mg PO daily     | 1 mg/kg every 2 weeks | 0                      | 6              | Prostate cancer (n = 4), urethral squamous cell carcinoma (n = 1), trophoblastic tumor (n = 1) |
| 4          | 60 mg PO daily     | 3 mg/kg every 2 weeks | 0                      | 6              | Urothelial carcinoma (n = 4), urachal adenocarcinoma (n = 2) |
| Part 2: cycle length, 21 days for first 4 cycles, then 28 days |                  |                |                        |                |             |
| 5          | 40 mg PO daily     | 1 mg/kg every 3 weeks | 1 mg/kg every 3 weeks | 6              | Urothelial carcinoma (n = 6) |
| 6          | 40 mg PO daily     | 3 mg/kg every 3 weeks | 1 mg/kg every 3 weeks | 6              | Prostate cancer (n = 3), penile cancer (n = 2), Sertoli tumor (n = 1) |
| 7          | 60 mg PO daily     | 3 mg/kg every 3 weeks | 1 mg/kg every 3 weeks | 6              | Urothelial carcinoma (n = 2), prostate cancer (n = 1), penile cancer (n = 1), RCC (n = 1), prostate small-cell carcinoma (n = 1) |
| Dose level 8: cycle length, 21 days for first 4 cycles, then 28 days |                  |                |                        |                |             |
| 8          | 40 mg PO daily     | 1 mg/kg every 3 weeks | 3 mg/kg every 3 weeks | 12             | Renal medullary carcinoma (n = 3), PNET (n = 2), prostate cancer (n = 2), GCT (n = 2), bladder small-cell carcinoma (n = 1), RCC (n = 1), small-cell renal pelvis carcinoma (n = 1) |

Abbreviations: GCT, germ cell tumor; PNET, primitive neuroectodermal tumor; PO, oral; RCC, renal cell carcinoma.

*After cycle 21, nivolumab was given at a maintenance dose of 480 mg every 4 weeks.
Dose level 8 was added after completion of the dose-escalation portion of the study as an exploratory cohort of 12 patients to assess the safety and efficacy of Cabo-Nivolpi with a higher dose of ipilimumab (3 mg/kg; Table 1). This cohort was added after the results of the phase I/II CheckMate 032 study were first presented suggesting that ipilimumab 3 mg/kg plus nivolumab 1 mg/kg was more active in mUC than ipilimumab 1 mg/kg plus nivolumab 3 mg/kg.

**Treatment**

Part 1 had four escalating dose levels of continuous daily oral cabozantinib and intravenous (IV) nivolumab administered every 2 weeks for a 28-day cycle (Table 1). Restaging was performed every 8 weeks.

| TABLE 2. Patient Characteristics | No. of Patients (%) | N = 54 |
|----------------------------------|---------------------|-------|
| Median age, years (range)        | 56 (20-82)          |       |
| Male                             | 48 (89)             |       |
| Type of tumor                    |                     |       |
| Urothelial carcinoma             | 15 (28)             |       |
| Prostate cancer                  | 10 (19)             |       |
| Germ cell tumor                  | 6 (11)              |       |
| Urachal adenocarcinoma           | 4 (7)               |       |
| Clear cell renal cell carcinoma* | 3 (5)               |       |
| Bladder squamous cell carcinoma  | 3 (5)               |       |
| Penile cancer                    | 3 (5)               |       |
| Renal medullary carcinoma        | 3 (5)               |       |
| Bladder or renal pelvis small-cell carcinoma | 3 (5) | |
| Testicular primitive neuroectodermal tumor | 2 (4) | |
| Trophoblastic tumor              | 1 (2)               |       |
| Sertoli cell tumor               | 1 (2)               |       |
| No. of prior systemic regimens   |                     |       |
| 0                                | 5 (9)               |       |
| 1                                | 19 (35)             |       |
| ≥ 2                              | 30 (56)             |       |
| Karnofsky performance status     |                     |       |
| 70%                              | 4 (7)               |       |
| 80%                              | 17 (31)             |       |
| 90%                              | 33 (62)             |       |
| Baseline metastatic sites        |                     |       |
| Lymph node only                  | 12 (22)             |       |
| Bone metastasis                  | 17 (31)             |       |
| Visceral (and bone disease)      | 42 (78)             |       |
| Visceral disease                 | 35 (65)             |       |
| Liver metastasis                 | 19 (35)             |       |
| Lung metastasis                  | 24 (44)             |       |

**NOTE.** Values are numbers and percentages, unless otherwise indicated.

*Two patients with RCC had > 50% sarcomatoid features.
TABLE 3. Adverse Events

| Adverse Event | Cabozantinib and Nivolumab (n = 24) | Cabozantinib, Nivolumab, and Ipilimumab (n = 30) |
|---------------|-----------------------------------|-----------------------------------------------|
|               | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Clinical events |                     |                          |                       |                     |                      |
| Fatigue       | 10 (83)   | 1 (8)     | 10 (83)   | 3 (25)    | 18 (75)   | 2 (8)     |
| Diarrhea      | 8 (67)    | 0         | 10 (83)   | 1 (8)     | 14 (58)   | 2 (8)     |
| Anorexia      | 7 (58)    | 0         | 9 (75)    | 0         | 10 (42)   | 0         |
| Skin toxicity | 9 (75)    | 0         | 5 (42)    | 0         | 16 (67)   | 0         |
| Dysphonia     | 5 (42)    | 0         | 6 (50)    | 0         | 4 (17)    | 0         |
| Nausea        | 4 (33)    | 0         | 7 (58)    | 1 (8)     | 10 (42)   | 0         |
| Myalgia       | 5 (42)    | 0         | 5 (42)    | 0         | 4 (17)    | 0         |
| Mucositis     | 2 (17)    | 0         | 8 (67)    | 0         | 9 (38)    | 1 (4)     |
| Dry skin      | 3 (25)    | 0         | 3 (25)    | 0         | 7 (29)    | 0         |
| Dry mouth     | 3 (25)    | 0         | 6 (50)    | 0         | 6 (25)    | 0         |
| Dysgeusia     | 4 (33)    | 0         | 5 (42)    | 0         | 8 (33)    | 0         |
| Weight loss   | 2 (17)    | 0         | 6 (50)    | 0         | 10 (42)   | 0         |
| Vomiting      | 3 (25)    | 0         | 6 (50)    | 2 (17)    | 7 (29)    | 0         |
| Palmar-plantar erythrodysesthesia | 3 (25) | 0 | 5 (42) | 0 | 5 (21) | 0 |
| Abdominal pain | 4 (33) | 0 | 4 (33) | 1 (8) | 3 (13) | 0 |
| Sore throat | 1 (8) | 0 | 5 (42) | 0 | 1 (3) | 0 |
| Hypertension | 4 (33) | 3 (25) | 4 (33) | 2 (17) | 5 (21) | 2 (8) |
| Headache      | 2 (17)    | 0         | 4 (33)    | 0         | 2 (8)     | 1 (4)     |
| Cough         | 3 (25)    | 0         | 2 (17)    | 0         | 5 (21)    | 0         |
| Blurred vision | 2 (17) | 0 | 2 (17) | 0 | 4 (17) | 0 |
| Arthralgia    | 1 (8)     | 0         | 3 (25)    | 0         | 5 (21)    | 0         |
| Edema limb    | 3 (25)    | 0         | 1 (8)     | 0         | 2 (8)     | 0         |
| Constipation  | 2 (17)    | 0         | 2 (17)    | 0         | 4 (17)    | 0         |
| Dehydration   | 1 (8)     | 0         | 2 (17)    | 2 (17)    | 3 (13)    | 0         |
| Infection     | 1 (8)     | 0         | 1 (8)     | 1 (8)     | 3 (13)    | 0         |
| Thromboembolic event | 1 (8) | 1 (8) | 0 | 0 | 2 (8) | 2 (8) |
| Fever         | 1 (8)     | 0         | 1 (8)     | 0         | 4 (17)    | 0         |
| Laboratory events |                      |                          |                       |                     |                      |
| Neutrophil count decrease | 4 (33) | 3 (25) | 7 (58) | 2 (17) | 2 (8) | 0 |

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Immune-related events requiring high-dose corticosteroids

| Adverse Event | Cabozantinib and Nivolumab (n = 24) | Cabozantinib, Nivolumab, and Ipilimumab (n = 30) |
|---------------|-----------------------------------|-----------------------------------------------|
|               | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any           | 2 (17)    | 1 (8)     | 7 (29)    | 2 (33)    |                      |
| Aseptic meningitis | 1 (8) | 1 (8) | 0 | 0 | 0 | 0 |
| Hypogonadism | 1 (8) | 0 | 0 | 0 | 0 | 0 |
| Pneumonitis | 0 | 0 | 1 (8) | 1 (8) | 1 (4) | 0 |
| Hepatitis | 0 | 0 | 0 | 0 | 3 (13) | 3 (13) |
| Bullous pemphigoid | 0 | 0 | 0 | 0 | 1 (4) | 1 (4) |
| Colitis | 0 | 0 | 0 | 0 | 2 (8) | 2 (8) |

Hematology

| Adverse Event | Cabozantinib and Nivolumab (n = 24) | Cabozantinib, Nivolumab, and Ipilimumab (n = 30) |
|---------------|-----------------------------------|-----------------------------------------------|
|               | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Neutrophil count decrease | 4 (33) | 3 (25) | 7 (58) | 2 (17) | 2 (8) | 0 |

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patients. The ORR was estimated, along with an exact 95% CI. The 95% CIs were determined using the exact Clopper-Pearson method. DoR was defined as the date the response was noted until date of radiologic PD, clinical PD, or death. PFS and OS were estimated using the Kaplan-Meier method, starting from the on-study date until PD, death, or last follow-up, as appropriate, with PFS being defined as progression or death without prior progression. For responding patients, PFS and OS were determined starting from the date of response until the date of death, PD, or last follow-up. The Kaplan-Meier plots and all analysis were done using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients with GU tumors (N = 54) were enrolled in this study from July 2015 through August 2017 (CaboNivo, n = 24; CaboNivoIpi, n = 30). Baseline demographics and clinical characteristics are listed in Table 2.

Six patients in seven dose levels completed the dose-escalation phase, and 12 patients were treated at dose level 8. All 54 patients were evaluable for safety and time-event outcomes. Five patients (CaboNivo, n = 1; CaboNivoIpi, n = 4) had early PD or withdrew before completing cycle 1 and were not evaluable for ORR.

Median follow-up time was 44.6 months for all patients, the median duration of treatment was 4.8 months (interquartile range [IQR], 2.1-16.3 months), and time to best response was 1.9 months (IQR, 1.7-2.8 months). For patients who received CaboNivo, the median duration of treatment was 6.36 months (IQR, 2.66-19.51 months), and the median time to best response was 1.94 months (IQR, 1.71-2.79 months). Patients who received CaboNivoIpi had a median duration of treatment of 3.7 months (IQR, 2.07-7.62 months), and the median time to best response was 1.94 months (IQR, 1.71-2.79 months).

The most common treatment-related AEs (TRAEs) of any grade and grade 3 or 4 per cabozantinib dose and the most common reasons for treatment discontinuation, dose hold, and dose reduction are reported in Tables 3 and 4. No DLTs were noted during the defined observation period. Grade 3 or 4 TRAEs occurred in 87% of

*High-dose corticosteroid refers to ≥ 40 mg of prednisone daily or equivalent. One patient also received infliximab for colitis.

### TABLE 3. Adverse Events (continued)

| Adverse Event                      | No. of Patients (%) | Cabozantinib and Nivolumab (n = 24) | Cabozantinib, Nivolumab, and Ipilimumab (n = 30) |
|-----------------------------------|---------------------|-------------------------------------|-----------------------------------------------|
|                                  | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Lymphocyte count decrease         | 5 (42)    | 1 (8)     | 6 (50)    | 0         | 5 (21)    | 3 (13)    | 2 (33)    | 0         |
| Anemia                            | 1 (8)     | 0         | 7 (58)    | 2 (17)    | 8 (33)    | 0         | 2 (33)    | 0         |
| Platelet count decrease           | 6 (50)    | 0         | 5 (42)    | 2 (17)    | 5 (21)    | 0         | 2 (33)    | 0         |
| Electrolytes                      |           |           |           |           |           |           |           |           |
| Hypocalcemia                      | 6 (50)    | 0         | 6 (50)    | 0         | 8 (33)    | 1 (4)     | 1 (17)    | 0         |
| Hyponatremia                      | 6 (50)    | 1 (8)     | 5 (42)    | 2 (17)    | 5 (21)    | 2 (8)     | 2 (33)    | 0         |
| Hypophosphatemia                  | 5 (42)    | 2 (17)    | 6 (50)    | 3 (25)    | 13 (54)   | 4 (17)    | 1 (17)    | 1 (17)    |
| Hypomagnesemia                    | 4 (33)    | 0         | 5 (42)    | 1 (8)     | 4 (17)    | 0         | 2 (33)    | 0         |
| Hypokalemia                       | 4 (33)    | 0         | 1 (8)     | 0         | 4 (17)    | 0         | 2 (33)    | 0         |
| Renal                             |           |           |           |           |           |           |           |           |
| Proteinuria                       | 5 (42)    | 1 (8)     | 3 (25)    | 1 (8)     | 5 (21)    | 0         | 2 (33)    | 0         |
| Hepatic                           |           |           |           |           |           |           |           |           |
| ALT elevation                     | 8 (67)    | 0         | 8 (67)    | 0         | 6 (25)    | 1 (4)     | 5 (83)    | 1 (17)    |
| AST elevation                     | 8 (67)    | 1 (8)     | 8 (67)    | 1 (8)     | 7 (29)    | 0         | 4 (67)    | 0         |
| Hypoalbuminemia                   | 5 (42)    | 0         | 5 (42)    | 0         | 6 (25)    | 0         | 0         | 0         |
| Pancreatic                        |           |           |           |           |           |           |           |           |
| Amylase elevation                 | 3 (25)    | 2 (17)    | 3 (25)    | 0         | 5 (21)    | 2 (8)     | 2 (33)    | 0         |
| Lipase elevation                  | 2 (17)    | 1 (8)     | 6 (50)    | 3 (25)    | 13 (54)   | 6 (25)    | 1 (17)    | 0         |
| Endocrine                         |           |           |           |           |           |           |           |           |
| Hyperthyroidism                   | 1 (8)     | 0         | 3 (25)    | 1 (8)     | 2 (8)     | 0         | 0         | 0         |
| Hypothyroidism                    | 6 (50)    | 0         | 3 (25)    | 1 (8)     | 6 (25)    | 0         | 2 (33)    | 0         |
patients receiving CaboNivoIpi and 75% of patients receiving CaboNivo. Although there were no DLTs at the highest dose levels using cabozantinib 60 mg daily during the observation period, there were many grade 1 and 2 toxicities attributable to cabozantinib requiring dose holding or dose reduction to cabozantinib 40 mg. There were no grade 5 TRAEs, and immune-related AEs (irAEs) were similar among nivolumab dose levels.

In the 49 patients evaluable for tumor response, the confirmed ORR was 30.6% (15 of 49 patients; 95% CI, 18.3% to 45.4%), and four patients (8.2%) had a CR (Fig 1A and Data Supplement). One patient (included as a responder) had pseudoprogression in the liver (Data Supplement). The DCR was 77.6% (38 of 49 patients; 95% CI, 63.4% to 88.2%), and the median DoR was 21.0 months (95% CI, 5.4 to 24.1 months; Fig 1B). For all patients (N = 54), the median PFS was 5.1 months (95% CI, 3.5 to 6.9 months), and the median OS was 12.6 months (95% CI, 6.9 to 18.8 months; Figs 2A and 2B). Among responders (n = 15), the median OS and PFS are shown in Figures 2C and 2D. Efficacy and follow-up for the CaboNivo and CaboNivoIpi groups are reported in Table 5 and the Data Supplement.

Among patients with mUC (15 [28%] of 54 patients; seven treated with CaboNivo and eight treated with CaboNivoIpi), the ORR for evaluable patients was 38.5% (five of 13 patients; 95% CI, 13.9% to 68.4%), and three patients (23.1%) had a CR (Table 5 and Data Supplement). Among responders with mUC (n = 5), the 24-month DoR probability was 80.0% (95% CI, 20.4% to 96.9%). Median DoR was not reached at the time of analysis. For patients with mUC (n = 15), median PFS was 12.8 months (95% CI, 1.8 to 24.1 months); median OS was 25.4 months (95% CI, 5.7 to 41.6 months). One (11.1%; 95% CI, 0.3% to 48.3%) of nine patients with CRPC achieved a PR, and seven patients (77.8%; 95% CI, 40.0% to 97.2%) had SD (Table 5 and Data Supplement). No objective responses were observed in patients with mGCT (Table 5 and Data Supplement). Clinical activity was also observed in patients with urachal adenocarcinoma; one had a PR lasting 16.2 months, and three patients had SD lasting 18.3, 16.2, and 5.2 months.
including one patient with reduced ascites. Patients with penile squamous cell carcinoma also demonstrated clinical benefit (Table 5).

Five CaboNivo patients were challenged with ipilimumab at PD, and four CaboNivoli patients were rechallenged with ipilimumab at PD. There were no objective responses in this exploratory cohort. Additional data on outcomes for all patients in this exploratory cohort, including patients in the expansion cohorts, will be reported separately. A baseline CTC count of < 5, compared with a CTC count of ≥ 5, was associated with longer median OS in patients with EpCAM-positive cells, EpCAM- and MET-positive cells, and EpCAM- and CXCR4-positive cells (Data Supplement).

**DISCUSSION**

This phase I study demonstrated that CaboNivo and CaboNivoli toxicities can be managed in patients with advanced GU tumors. The safety profiles were largely

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**FIG 1.** Clinical activity of cabozantinib and nivolumab (CaboNivo) and cabozantinib, nivolumab, and ipilimumab (CaboNivoli). (A) Plot of confirmed tumor regression from baseline as measured by RECIST in all evaluable patients (n = 49). Upper dotted line represents progression at 20%; lower dotted line represents the RECIST boundary for complete response or partial response at 30%. (*) Patient with 40% increase in longest diameter of targeted lung lesion with cavitation. The protocol prespecified that patients with lung cavitory lesions who are experiencing clinical benefit may be allowed to stay on therapy until they experience disease progression based on non-cavitary lung lesions. (B) Time to response, duration of treatment, and duration of response to CaboNivo and CaboNivoli (16 confirmed responses as of data cutoff). Numbers represent duration of response in months. IQR, interquartile range; PFS, progression-free survival.
similar between CaboNivo and CaboNivoIpi, with a slightly higher incidence of some grade 3 or 4 clinical and laboratory TRAEs with CaboNivoIpi. The longer duration of treatment for CaboNivo than for CaboNivoIpi (6.36 vs 3.7 months, respectively) may have led to the higher TRAEs observed in some cases. The grade 3 or 4 TRAE rates for CaboNivo (75%) and CaboNivoIpi (87%) were higher than those previously reported in other studies of nivolumab plus ipilimumab,27,39 in part as a result of the longer follow-up in our study and the addition of cabozantinib. Although cabozantinib led to more grade 3 or 4 TRAEs, including hypertension, neutropenia, lymphopenia, amylase elevation, and hypophosphatemia, than previously reported in trials with ICIs,27,39 these were manageable. irAEs, including hepatitis and colitis, were similar to those previously reported with nivolumab monotherapy and nivolumab plus ipilimumab,27,39 and were higher with CaboNivoIpi (30%) than with CaboNivo (13%).

| Tumor Type and Treatment | All Evaluable Patients (n = 49) | CR | PR | SD | PD | ORR (CR+PR) | DCR (CR+PR+SD) |
|--------------------------|---------------------------------|----|----|----|----|-------------|----------------|
| Tumor type, No. of patients |                                |    |    |    |    |             |                |
| Urothelial carcinoma | 13 | 3 | 2 | 7 | 1 | 5 | 12 |
| Prostate cancer | 9 | 0 | 1 | 7 | 1 | 1 | 8 |
| GCT | 6 | 0 | 0 | 1 | 5 | 0 | 1 |
| RCC | 3 | 0 | 3 | 0 | 0 | 3 | 3 |
| Urachal | 4 | 0 | 1 | 3 | 0 | 1 | 4 |
| Penile adenocarcinoma | 3 | 0 | 1 | 2 | 0 | 1 | 3 |
| Renal medullary carcinoma | 2 | 0 | 1 | 0 | 1 | 1 | 1 |
| Bladder squamous cell carcinoma | 2 | 1 | 1 | 0 | 0 | 2 | 2 |
| PNET | 2 | 0 | 0 | 1 | 1 | 0 | 1 |
| Small-cell prostate cancer | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Sertoli cell tumor | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| Trophoblast tumor | 1 | 0 | 0 | 1 | 0 | 0 | 1 |
| Urethral SCC | 1 | 0 | 1 | 0 | 0 | 1 | 1 |
| Bladder/renal pelvis small-cell carcinoma | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Treatment |                                |    |    |    |    |             |                |
| CaboNivo |                                |    |    |    |    |             |                |
| No. of patients | 23 | 3 | 6 | 10 | 4 | 9 | 19 |
| % (95% CI) | 13.0 (2.8 to 33.6) | 26.1 (10.2 to 48.4) | 43.5 (23.2 to 65.5) | 17.4 (5.0 to 38.8) | 39.1 (19.7 to 61.5) | 82.6 (61.2 to 95.1) |
| CaboNivolpi |                                |    |    |    |    |             |                |
| No. of patients | 26 | 1 | 5 | 13 | 7 | 6 | 19 |
| % (95% CI) | 3.8 (0.1 to 19.6) | 19.2 (6.6 to 39.4) | 50.0 (30.0 to 70.0) | 26.9 (11.6 to 47.8%) | 23.1 (9.0 to 43.7) | 73.1 (52.2 to 88.4) |
| All |                                |    |    |    |    |             |                |
| No. of patients | 49 | 4 | 11 | 23 | 11 | 15 | 38 |
| % (95% CI) | 8.2 (2.3 to 19.6) | 22.5 (11.8 to 36.6) | 46.9 (32.5 to 61.7) | 22.5 (11.8 to 36.6) | 30.6 (18.3 to 45.4) | 77.6 (63.4 to 88.2) |

Abbreviations: CaboNivo, cabozantinib and nivolumab; CaboNivolpi, cabozantinib, nivolumab, and ipilimumab; CR, complete response; DCR, disease control rate; GCT, germ cell tumor; ORR, objective response rate; PNET, primitive neuroectodermal tumor; PR, partial response; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SD, stable disease.
Overlapping toxicities with the use of TKIs and ICIs included thyroid dysfunction, diarrhea, and elevated liver enzymes. The TRAEs of hypothyroidism (32% of patients) and hyperthyroidism (11% of patients) were commonly attributed to all study agents because it was difficult to distinguish between a TKI-caused TRAE and an irAE. Diarrhea was easier to attribute to either a TKI or ICI. Cabozantinib-induced diarrhea occurred as small, frequent stools associated with meals and was generally controlled by holding doses for 5-7 days, dose reduction if recurrent, and anti-diarrheal agents. Immune-related diarrhea or colitis tended to be more liquid, was associated with cramping and larger volumes, persisted despite dose holding of all agents or treatment with immunosuppressants, and required high-dose corticosteroids. Elevated liver enzymes (ALT and AST) were a common TRAE, and often, both AST and ALT were concurrently elevated. Grade 3 or 4 liver enzyme elevation occurred in two patients treated with CaboNivo and two patients treated with CaboNivoli. Immune-related hepatitis requiring high-dose corticosteroids occurred in four patients treated with CaboNivolpi and in no patients treated with CaboNivo. Overall, hepatic toxicities were manageable with judicious dose holds, reductions, and/or conservative therapy.

Cabozantinib 60 mg/d led to higher rates of clinical TRAEs of all grades, including fatigue, diarrhea, anorexia, weight loss, nausea, vomiting, mucositis, and dehydration. Although the study did not have any DLTs, the RP2Ds were cabozantinib 40 mg/d plus nivolumab 3 mg/kg for the doublet and cabozantinib 40 mg/d, nivolumab 3 mg/kg, and ipilimumab 1 mg/kg for the triplet, based on better clinical tolerability and similar efficacy of cabozantinib at 40 mg/d compared with 60 mg/d.

The study had a long median follow-up time of nearly 45 months, a promising ORR of 30.6%, and a median OS of 12.6 months in a heterogeneous group of patients with metastatic GU tumors, including tumor types with poor prognosis such as renal medullary carcinoma, small-cell...
bladder cancer, and primitive neuroectodermal tumor. Among the 15 responders, the median OS was 32.2 months. In patients with mUC, the efficacy was higher than previously reported for single-agent ICIs (15%-20%) or monotherapy with cabozantinib (19%), with an ORR of 38.5%, DCR of 92.3%, median PFS of 12.8 months, and median OS of 25.4 months. Other smaller tumor cohorts that showed promising responses included clear cell and sarcomatoid RCC, pure squamous cell carcinoma of the bladder, and urethral squamous cell carcinoma. Given these promising findings, expansion cohorts were added to the study.

Although ORR was numerically higher in the CaboNivo group than in the CaboNivoIpi group (39.1% vs 26.9%, respectively), patients treated in the triplet group had more aggressive tumors and rarer histologies, such as renal medullary carcinoma, primitive neuroectodermal tumor, Sertoli cell tumor, small-cell bladder/upper tract tumors. No responses were seen in patients who were challenged or rechallenged with ipilimumab at PD. Three recent studies evaluating similar challenge or rechallenge strategies reported modest efficacy in RCC.40-42 Our exploratory analysis demonstrated that baseline CTC levels of less than five cells were associated with prolonged OS (Data Supplement). However, changes in CTCs during treatment were not associated with treatment response or outcome. To explore the role of the cabozantinib target MET in the current trial, we looked at both total EpCAM-positive CTCs and the subset of CTCs expressing MET and found that a baseline CTC count of less than five, compared with a CTC count of ≥ 5, was associated with longer median OS for patients with EpCAM-positive, EpCAM- and MET-positive, and EpCAM- and CXCR4-positive cells, demonstrating that MET and CXCR4 expression in CTCs at baseline is associated with poorer survival.

Our study is limited by the tumor heterogeneity and small sample size in each group. Correlative analysis should be interpreted cautiously.

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**DISCLAIMER**
Patients have granted consent to the authors for use of photographic and radiologic images used in this publication.

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CLINICAL TRIAL INFORMATION
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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