



Alliance A031702: A Phase II Study of Ipilimumab, Cabozantinib, and Nivolumab in Rare Genitourinary Cancers (ICONIC)

Andrea Apolo, MD and Amir Mortazavi, MD

National Cancer Institute, National Institutes of Health and The Ohio State University Comprehensive Cancer Center

TAP TO
RETURN TO
KIOSK MENU



Rationale

Rationale

Objective

Study Schema

Treatment Plan

Key Eligibility Criteria

Follow Up

Rare genitourinary (GU) tumors are tumors of aberrant histology occurring in the GU tract, including kidney, bladder, ureters, and penis. These tumors occur so infrequently that they are not systematically captured by currently available registries, treatment protocols or tissue banks. Large randomized clinical trials to develop optimal effective therapies are logistically difficult in very small patient populations. Therefore, treatment information is obtained from case reports, retrospective studies and small-size (often incomplete) clinical trials.

This trial aims to investigate the role of combination nivolumab, ipilimumab, and cabozantinib in the rare histological variants of the GU tract, specifically: bladder/urachal adenocarcinoma, squamous cell carcinoma, and small cell carcinoma; variants of urothelial carcinoma including plasmacytoid, sarcomatoid, and others; renal tumors including sarcomatoid renal cell carcinoma and renal medullary carcinoma; and penile cancers. This triple combination of cabozantinib, nivolumab and ipilimumab and the doublet cabozantinib and nivolumab are being studied in a phase III trial for renal cell carcinoma and in development for urothelial carcinoma. Based on the preliminary efficacy seen in the phase I study, we are initiating this trial for rare GU tumors.

Please use the headings above to navigate through the different sections of the poster



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TAP TO
RETURN TO
KIOSK MENU



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Primary

- To evaluate the efficacy of cabozantinib s-malate (cabozantinib) combined with nivolumab and ipilimumab in the first or second-line (and beyond) setting for patients within each of the rare genitourinary (GU) variant histology group of interest, as measured by objective response rate (ORR).

Secondary

- To estimate the progression-free survival (PFS) for patients treated with cabozantinib combined with nivolumab and ipilimumab within each rare variant histology.
- To estimate the overall survival (OS) for patients treated with cabozantinib combined with nivolumab and ipilimumab within each rare variant histology.
- To estimate the clinical benefit rate (defined as complete response [CR] or partial response [PR] or stable disease [SD]) for patients treated with cabozantinib combined with nivolumab and ipilimumab within each rare variant histology.
- To assess the safety of treating patients with rare variant histologies with cabozantinib combined with nivolumab and ipilimumab.
- To support tissue banking and collection of clinical follow-up data for GU tract rare histological variants.

Exploratory

- To assess effects of treatment in patients with bone-only disease by bone scan.



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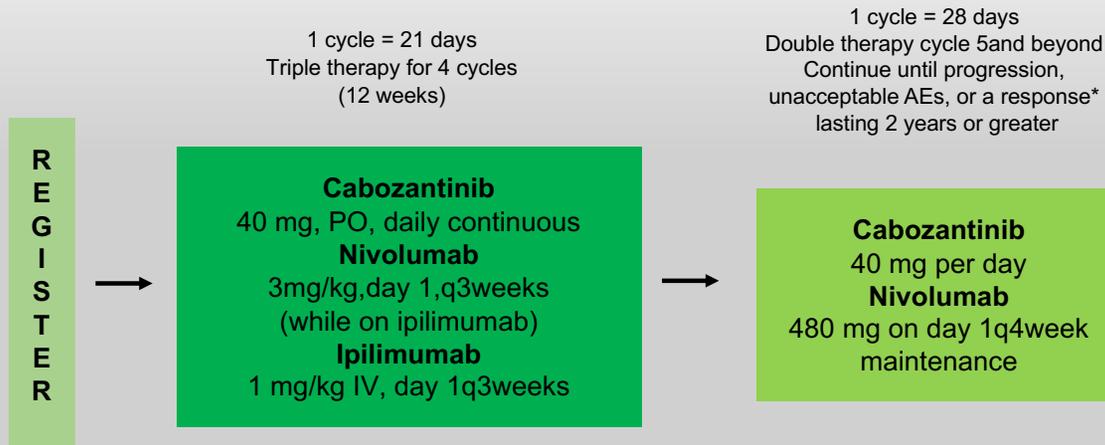
TAP TO RETURN TO KIOSK MENU



Study Schema

- Rationale
- Objective
- Study Schema**
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- Key Eligibility Criteria
- Follow Up

Please use the headings above to navigate through the different sections of the poster



*Response is defined as a complete or partial response or stable disease >9 months. Patients will be followed for a total of 5 years from the date of registration or until death, whichever comes first.



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TAP TO
RETURN TO
KIOSK MENU



Rationale

Objective

Study Schema

Treatment Plan

Key Eligibility Criteria

Follow Up

Treatment Plan

- Patients receive cabozantinib orally (PO) once daily (QD) on days 1-21 of cycles 1-4 and on days 1-28 of subsequent cycles.
- Patients also receive nivolumab intravenously (IV) over 30 minutes on day 1 and ipilimumab IV over 90 minutes on day 1 of cycles 1-4.
- Patients then receive nivolumab IV over 30 minutes on day 1 of subsequent cycles.
- Treatment repeats every 21 days for cycles 1-4 and every 28 days for subsequent cycles for 2 years in the absence of disease progression or unacceptable toxicity.

After completion of study treatment, patients are followed up every 2 months for 5 years.

Please use the headings above to navigate through the different sections of the poster



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TAP TO
RETURN TO
KIOSK MENU



- Rationale
- Objective
- Study Schema
- Treatment Plan
- Key Eligibility Criteria**
- Follow Up

Key Eligibility Criteria

- Metastatic disease defined as new or progressive lesions on cross-sectional imaging or bone scan.
- Patients may have received any number of prior anti-cancer treatments or be treatment naïve
- Patients must be able to swallow oral formulation of the tablets
- Karnofsky performance status $\geq 70\%$
- Absolute neutrophil count (ANC) $\geq 1,200/\text{mcl}$
- Platelet count $\geq 75,000/\text{mcl}$
- Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN).
- Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq 3.0 \times$ institutional upper limit of normal (ULN) (or $\leq 5 \times$ ULN for patients with liver metastases or Gilbert's disease)
- Creatinine $\leq 1.5 \times$ upper limit of normal (ULN) OR creatinine clearance $\geq 40 \text{ mL/min/1.73 m}^2$ for patients with creatinine levels above institutional normal
- Hemoglobin $\geq 9 \text{ g/dL}$
- Serum albumin $\geq 2.8 \text{ g/dL}$ Lipase and amylase $\leq 2.0 \times$ ULN and no radiologic or clinical evidence of pancreatitis
- Prior treatment with MET or VEGFR inhibitors is allowed.

Please use the headings above to navigate through the different sections of the poster



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TAP TO
RETURN TO
KIOSK MENU



Rationale
Objective
Study Schema
Treatment Plan
Key Eligibility Criteria

Follow Up

Funding Support

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Please use the headings above to navigate through the different sections of the poster

Study Chair: Andrea Apolo, MD
National Cancer Institute
National Institutes of Health
E-mail: andrea.apolo@nih.gov
Phone: 301-480-0536

Study Co-Chair: Amir Mortazavi, MD
The Ohio State University
Comprehensive Cancer Center
E-mail: amir.mortazavi@osumc.edu
Phone: 614-293-2886

Statistician: Karla Ballman, PhD
E-mail: Kab2053@med.cornell.edu
Phone: 646-962-8023

Protocol Coordinator: Colleen Watt
E-mail: cboyle@uchicago.edu
Phone: 773-702-4670

Data Manager: Nolan Grimm
E-mail: Grimm.nolan@mayo.edu
Phone: 507-266-9322