Alliance A031704: PD-Inhibitor (Nivolumab) and Ipilimumab Followed by Nivolumab Vs. VEGF TKI Cabozantinib with Nivolumab: A Phase III Trial in Metastatic Untreated REnal Cell CancEr [PDIGREE]

Tian Zhang, MD, MHS and Toni Choueiri, MD

Duke University Medical Center and Dana-Farber Cancer Institute

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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Rationale

First line management of metastatic renal cell cancer (mRCC) is in flux: ipilimumab and nivolumab (ipi/nivo) is a pure immunotherapy combination standard of care for patients with mRCC. Some patients may achieve a complete response (or near complete response) to the ipi/nivo regimen, but based on data from the CheckMate 214 study, the majority of patients will achieve a partial response, stable disease or mixed response. [1] In these patients, the ipi/nivo induction regimen is followed by nivolumab monotherapy until progression, followed by a switch to a VEGFR TKI. Phase I studies have demonstrated that nivolumab 3mg/kg and cabozantinib 40mg daily is well tolerated [2]. Cabozantinib may also be immunomodulatory and enhance the immune activation effects of nivolumab. To what extent the addition of cabozantinib could improve the CR or near CR rate and/or improve the overall survival for this population is unknown. Therefore, we propose an open-label phase III clinical trial of ipilimumab-nivolumab induction followed by randomization of non-CR non-PD patients to either nivolumab or nivolumab and cabozantinib. The primary endpoint is an improvement in 3-year cumulative OS rate with key secondary endpoints of 1-year CR rate and PFS. The successful completion of this study would likely contribute to the development of an improved post-induction combination treatment for patients with mRCC treated with ipi/nivo.

References

1. Motzer RJ et al. N Engl J Med. 2018, Epub ahead of print. PMID: 29562145
2. Nadal et al, ASCO 2018 abstract 4528

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Objective

Primary

- To compare the overall survival (OS) in patients with metastatic renal cell cancer (RCC) treated with ipilimumab-nivolumab followed by either nivolumab versus cabozantinib-nivolumab.

Secondary

- To determine progression free survival (PFS) of patients treated with nivolumab versus nivolumab-cabozantinib.
- To evaluate the 12-month complete response rate in patients treated with ipilimumab-nivolumab followed by cabozantinib-nivolumab versus ipilimumab-nivolumab followed by nivolumab (patients who have complete response [CR] and relapse before 12 months will not be counted as a CR at 12-months).
- To evaluate the rates of discontinuing therapy at 1 year.
- To compare objective response rates (ORR, assessed by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and Immune-Related Response Evaluation Criteria in Solid Tumors [irRECIST] criteria) for patients treated with ipilimumab-nivolumab followed by cabozantinib-nivolumab versus ipilimumab-nivolumab followed by nivolumab.
- To document the adverse event profile of ipilimumab-nivolumab followed by cabozantinib-nivolumab.

Biomarker

- To evaluate biomarkers associated with exceptional responses in both arms (exceptional responses defined as CRs with treatment discontinuation at 12 months or 24 months).

Quality of Life

- To compare health-related quality of life at 18 months post-registration as assessed by the Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index 19 (FKSI-19) between patients randomized to nivolumab (nivo) versus (vs) cabozantinib (cabo)/nivo.
- To compare health-related quality of life as assessed by the FKSI-19 between patients randomized to nivo vs cabo/nivo at other time points.
- To compare patient-reported fatigue using Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue between patients randomized to nivo vs cabo/nivo.
- To compare quality-adjusted survival (overall survival x utility score assessed by EuroQol five-dimensional questionnaire [EQ5D-5L]) between patients randomized to nivo vs cabo/nivo.

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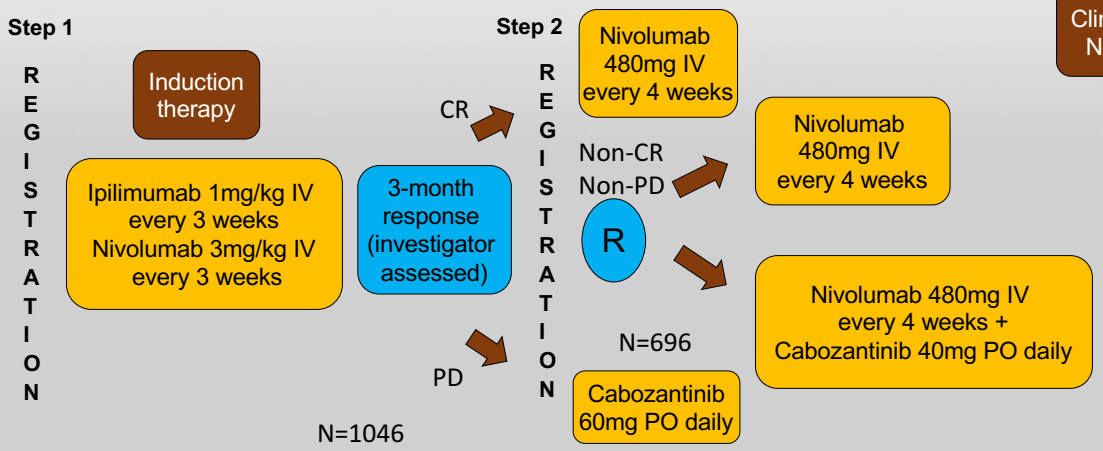
Study Schema



Clinicaltrials.gov: NCT03793166

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Discontinue treatment for progression of disease or unacceptable toxicity.
Patients with a complete response at 1 year following registration will discontinue treatment.
Patients will be followed for 5 years or until death, whichever comes first.

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Treatment Plan

Patients will be treated with induction ipilimumab and nivolumab (see schema) and 3-month response assessments dictate next treatments outlined below.

Patients with progression of disease (PD) receive cabozantinib orally (PO) daily on days 1-28. Treatment repeats every 28 days until further disease progression or unacceptable toxicity.

Patients with complete response (CR) receive nivolumab IV on day 1 of every 28 days. Treatment repeats every 28 days in the absence of disease progression or unacceptable toxicity.

Patients with non-CR/non-PD are randomized to 1 of 2 arms.

ARM A

- Patients receive nivolumab IV over 30 or 60 minutes on day 1. Treatment repeats every 28 days.

ARM B

- Patients receive nivolumab IV over 30 or 60 minutes on day 1 and cabozantinib PO daily on days 1-28. Treatment repeats every 28 days.

Treatment is discontinued for disease progression, unacceptable toxicity, or CR at 1 year.

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

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Key Eligibility Criteria

Step 1 Registration Criteria

- Histologic documentation of renal cell carcinoma with clear cell component
- Metastatic disease
- Measurable disease
- Intermediate or poor risk per IMDC criteria
  - At least one of the following: Karnofsky performance status <80, <1 year from diagnosis to systemic therapy, hypercalcemia, neutrophilia, anemia, and thrombocytopenia
- CNS disease is allowed, if stable
- Karnofsky PS ≥70%
- Prior systemic therapy for metastiatc disease per protocol
  - high dose IL-2 and adjuvant sunitinib allowed
- Non-pregnant and non-nursing
- Age ≥18 years
- Ineligible conditions per protocol

Step 2 Registration Criteria

- Must have completed at least 1 cycle of ipi/nivo
- All AEs have resolved to ≤grade 1
- ≤ 56 days from last dose of ipi/nivo

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https://acknowledgments.alliancefound.org.

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