

FAST FACTS

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]

Step 1 Registration Eligibility Criteria

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

1. **Documentation of Disease: (e.g., adenocarcinoma) (if applicable)**
 - **Histologic Documentation: Histologically documented renal cell carcinoma with clear cell component, including patients who have sarcomatoid features.**
 - **Stage: Any metastatic disease, including visceral, lymph node, other soft tissue and bone, measurable per RECIST 1.1.**
2. **Measurable disease as defined in Section 11.0.**
3. **Must be intermediate or poor risk patient per IMDC criteria (1 or more of the following: KPS<80, <1 year from diagnosis (including initial nephrectomy) to systemic treatment for metastatic disease, hemoglobin less than LLN, corrected calcium concentration greater than ULN, absolute neutrophil count greater than ULN, platelet count>ULN)**
4. **CNS disease permitted, if stable and not otherwise causing symptoms or needing active treatment**
5. **Karnofsky performance status >70%**
6. **Prior Treatment**
 - **No prior treatment with PD-1, PD-L1, or CTLA-4 targeting agents (including but not limited to nivolumab, pembrolizumab, pidilizumab, durvalumab, atezolizumab, tremelimumab, and ipilimumab), or any other drug or antibody specifically targeting T-cell co-stimulation or checkpoint pathways. The only exception is for prior treatment with nivolumab or other PD-1/PD-L1/CTLA-4 targeting therapy on pre- or post-operative trials, as long as >1 year since completion of systemic therapy.**

- **No prior previous systemic therapy for renal cell carcinoma (prior HD IL-2 (>28 days) prior adjuvant sunitinib >180 days since completion and prior immunotherapy as above are allowed).**
No cancer therapy less than 28 days prior to registration; this includes radiation therapy, except for bone lesions less than 14 days prior to registration. There must be a complete recovery and no ongoing complications from radiotherapy.
7. **Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.**
Therefore, for women of childbearing potential only, a negative serum or urine pregnancy test done \leq 14 days prior to registration is required.
 8. **Age \geq 18 years**
 9. **None of the following:**
 - Active autoimmune disease requiring ongoing therapy**
 - Ongoing acute toxicity > Grade 2 from previous treatment**
 - History of severe allergic, anaphylactic or other hypersensitivity reactions to chimeric or humanized antibodies**
 - History of HIV or active hepatitis B/C, or active tuberculosis (PPD response without active TB is allowed)**
 - Concurrent use of immunosuppressive medication including prednisone above 10 mg daily.**
 - Uncontrolled adrenal insufficiency**
 - Uncontrolled hypertension (systolic BP >150mmHg or diastolic BP >90mmHg)**
 - Major surgery less than 28 days prior to registration.**
 - Any serious non-healing wound, ulcer, or bone fracture within 28 days prior to registration**
 - Any arterial thrombotic events within 180 days prior to registration**
 - Clinically significant hematuria, hematemesis, or hemoptysis within 12 weeks prior to registration**
 - Cavitating pulmonary lesions or known endotracheal or endobronchial disease manifestations**
 - Lesions encasing or invading any major blood vessels (this does not include tumor thrombus extending into/through renal vein/IVC). Patients with tumor thrombus extending into/through renal vein are considered eligible.**
 - Moderate or severe hepatic impairment (child-Pugh B or C)**
 - Any history of untreated pulmonary embolism or deep venous thrombosis (DVT) in the 180 days prior to registration. (Any asymptomatic, treated pulmonary embolism or asymptomatic, treated deep venous thrombosis >30 days prior to registration allowed).**
 - Corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms (use <https://qxmd.com/calculate/ecg-corrected-qt>)**
 - Unstable cardiac arrhythmia within 6 months prior to registration**
 - Any GI bleeding \leq 180 days, hemoptysis, or other signs of pulmonary hemorrhage \leq 90 days prior to registration**

___ **History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, bowel obstruction, or gastric outlet obstruction within 180 days prior to registration**

___ **Active peptic ulcer disease, inflammatory bowel disease, or malabsorption syndrome within 28 days prior to registration**

___ **Untreated hypothyroidism, evidence of pancreatitis, history of organ transplant, or history of congenital QT syndrome**

___ **Active treatment with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct Xa inhibitor betrixaban or platelet inhibitors (e.g., clopidogrel) within 5 days of registration.**

Allowed anticoagulants include: prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH), therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, apixaban. Allowed also in patients with known brain metastases who are on a stable dose of the anticoagulant for at least 1 week prior to registration without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor.

___ **Significant cardiac ischemia events (STEMI or NSTEMI) within 6 months or active NY Heart Association Class 3-4 heart failure symptoms**

10. Required Initial Laboratory Values

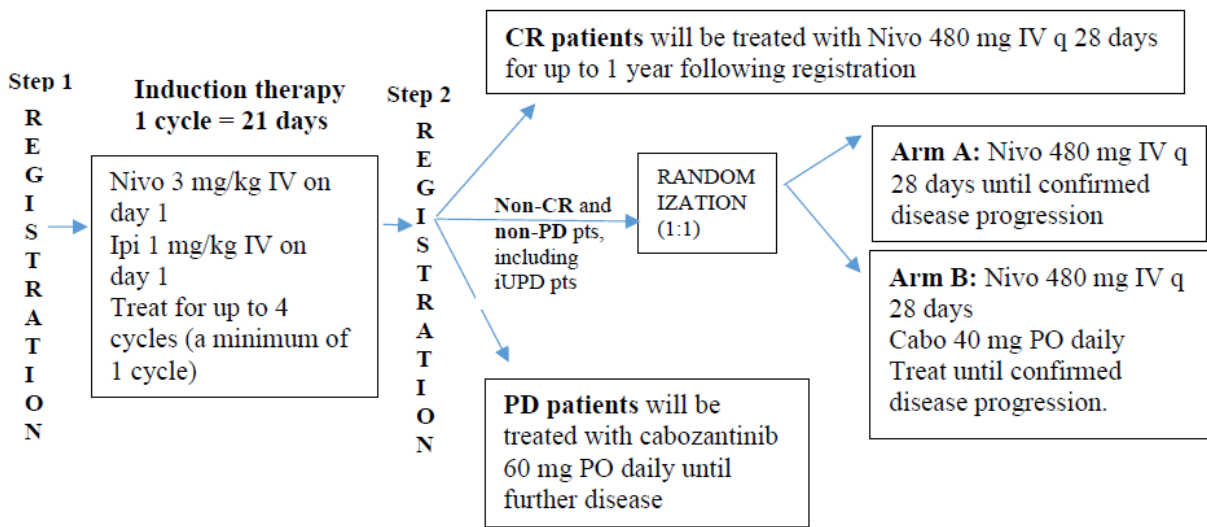
- **Absolute Neutrophil Count (ANC) \geq 1,500/mm³**
- **Platelet Count \geq 100,000/mm³**
- **Hemoglobin \geq 8 g/dL**
- **Calc. Creatinine Clearance \geq 30 mL/min**
- **Urine protein \leq 1+ or UPC Ratio $<$ 1**
- **Total Bilirubin \leq 1.5 x upper limit of normal (ULN)**
- **AST / ALT \leq 2.5 x upper limit of normal (ULN) or $<$ 5 x ULN if hepatic metastases present**

Step 2 Registration Eligibility Criteria

1. **Successful completion of at least 1 cycle of ipilimumab/nivolumab**
 2. **Resolution of any treatment-related adverse events to grade 1 or less per dose modification section (this criteria does not include any AEs not attributable to treatment which are present due to disease). Exceptions for this criteria include patients receiving replacement hormone treatments (such as levothyroxine for treatment-related hypothyroidism or glucocorticoid replacement for adrenal insufficiency). Please contact study chair if further discussion is needed.**
3. **No more than 70 days from last dose of ipilimumab/nivolumab.**

Schema

1 cycle = 28 days



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.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.