Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

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:
   - Histologic Documentation: Histologically documented renal cell carcinoma with clear cell component, including patients who have sarcomatoid or rhabdoid 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 systemic cancer therapy less than 28 days prior to registration; no radiation therapy 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 ≤ 14 days prior to registration is required.

8. Age ≥ 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
___ Active hepatitis B/C, or active tuberculosis (PPD response without active TB is allowed)
___HIV-infected patients with detectable viral load within 6 months prior to registration. Patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible.
___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 of 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 ≤ 180 days, hemoptysis, or other signs of pulmonary hemorrhage ≤ 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 (treated hypothyroidism on thyroid replacement therapy is

allowed. Abnormal TSH is acceptable with normal T3/free T4 if treatedon thyroid replacement therapy)

___ 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

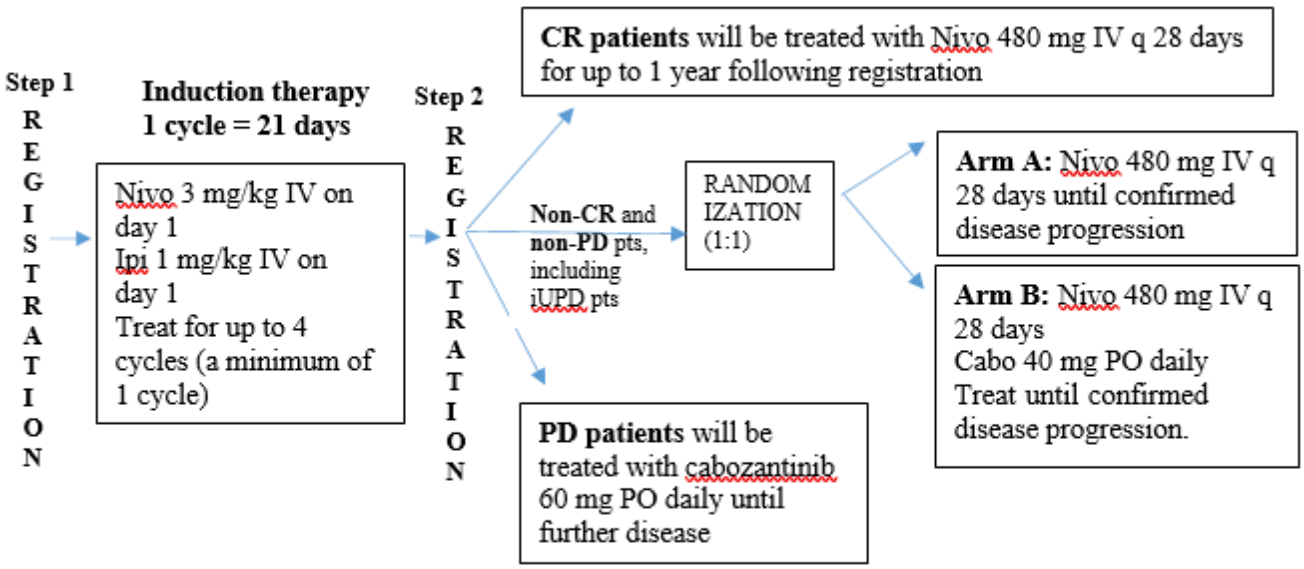
10. Required Initial Laboratory Values
    - Absolute Neutrophil Count (ANC) ≥ 1,500/mm3
    - Platelet Count ≥ 100,000/mm3
    - Hemoglobin ≥8 g/dL
    - Calc. Creatinine Clearance ≥ 30 mL/min
    - Urine protein ≤1+ or UPC Ratio <1
    - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN) [except for patients with known or likely Gilbert's syndrome, for whom total bilirubin up to 3 mg/dL is allowed with direct bilirubin ≤20% total bilirubin]
    - AST / ALT ≤ 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), with prednisone-equivlent dosing at 10 mg daily or less. 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 80 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.