Cancer Research Consortium of West Michigan
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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. Intermediate or poor risk patients per IMDC criteria will be eligible (1 or more of the following: KPS<80, <1 year from diagnosis to systemic treatment, 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 Tcell co-stimulation or checkpoint pathways
   - No prior previous systemic therapy for renal cell carcinoma (prior HD IL-2 (>28 days) and prior adjuvant sunitinib >180 days since completion 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 ≤ 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
   ___History of HIV or active hepatitis B/C, or tuberculosis
   ___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
   ___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
   ___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, evidence of pancreatitis, history of organ transplant, or history of congenital QT syndrome
   ___Active treatment with warfarin or any oral factor Xa inhibitors (treatment with LMWH is allowed)
   ___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)
- 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
3. No more than 56 days from last dose of ipilimumab/nivolumab.

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