Cancer Research Consortium of West Michigan
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FAST FACTS

A032201: Short TeRm Intensified Pembrolizumab (KEytruda) and Tivozanib for High-risk renal cell carcinoma – STRIKE

Registration Eligibility Criteria

1. Histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features following complete resection of the primary tumor (radicalor partial nephrectomy).
   Note: Patients with microscopically positive soft tissue or vascular margins without gross residual disease are permitted.
   Intermediate-high risk RCC:
   - pT2 Grade 4 or sarcomatoid features, N0M0 or NxM0
   - pT3 any grade N0M0 or NxM0

   OR
   High-risk RCC
   - pT4, any grade, N0M0 or NxM0
   - pT, any stage., any grade, N+, M0

   OR
   cM1 NED RCC
   - Participants who have had resection of primary tumor (radical or partial nephrectomy) and resection or definitive radiation or ablation of solid, isolated, soft tissue metastases (excluding brain and bone lesions) at the time of primary tumor removal (synchronous) or ≤1 year from primary tumor removal (metachronous).
2. Surgery (radical or partial nephrectomy or metastasectomy or ablation) >4 weeks but ≤ 16 weeks prior to study registration with no ongoing complications from surgery
3. No evidence of disease at time of randomization as assessed by investigator by either CT or MRI scan
4. No prior systemic treatment for RCC
5. Age ≥ 18 years
6. ECOG performance status ≤ 2 (or Karnofsky ≥ 60%).
7. Required Initial Laboratory Values:
   - Absolute Neutrophil Count (ANC) ≥ 1,000/mm3
   - Platelet Count ≥ 100,000/mm3a
   - Hemoglobin ≥ 8 g/dL
   - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)
   - AST (SGOT)/ALT (SGT) ≤ 3 x upper limit of normal (ULN)
   - Calc. Creatinine Clearance ≥ 30 mL/min (using Cockcroft Gault equation or the estimated glomerular filtration rate from the modification of diet in renal disease trial)
   - Urine Protein ≤ 1+ on UA or UPCR < 2mg/mg

8. 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 pregnancy test is required ≤ 14 days prior to registration.
9. HIV Status:-HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
10. Hepatitis
    - Hepatitis B: For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with resolved HBV infection, defined as positive hepatitis B core antibody (anti-HBc) and negative hepatitis B surface antigen (HbsAg), are eligible.
    - Hepatitis C: Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
11. Cardiac Disease: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class IIB or better. No history of myocarditis; pneumonitis.
12. No history of myocarditis
13. No history of clinically significant pneumonitis
14. No Uncontrolled hypertension (systolic BP > 150 mm Hg or diastolic BP > 90 mm Hg) documented on 2 consecutive measurements taken at least 2 hours apart
15. No serious non-healing wound, ulcer or bone fracture within 28 days prior to registration
16. No serious/active infection requiring parenteral antibiotics
17. No moderate or severe hepatic impairment (child-Pugh B or C)
18. No significant bleeding disorders within 1 month prior to registration, for example:
    - Hematemesis, hematochezia or other gastrointestinal bleeding Grade 3 or higher
    - Hemoptysis of pulmonary bleeding grade 3 or higher
    - Hematuria or other genitourinary bleeding grade 3 or higher
19. No history of allogeneic organ transplantation
20. No history of allergy of hypersensitivity to study drugs or components
21. No condition requiring systemic treatment with either corticosteroid (> 10 mg daily or prednisone equivalent) within 14 days of treatment initiation or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids and adrenal replacement doses ≤10 mg daily prednisone equivalent are permitted in absence of active autoimmune disease.
22. No active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis or other gastrointestinal condition associated with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 4 weeks prior to registration.
23. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

24. No patients with a history of autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids > 10 mg/day, or immunosuppressive drugs) with the following exceptions:
    - Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    - Brief (<7 days) use of systemic corticosteroids is allowed when use is considered standard of care.
    - Patients with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy will not be excluded.
    - Patients requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded.
    - Patients with hypothyroidism that is stable with hormone replacement, or Sjögren's syndrome will not be excluded.
25. Concomitant Medications
    - Chronic concomitant treatment with strong CYP3A4 inducers is not allowed.
    - Patients must discontinue the drug 14 days prior to the start of study treatment. See Section 8.1.10 for more information. Chronic concomitant treatment with CYP3A4 inhibitors are allowed.

Schema

1 Cycle = 12 weeks

RANDOMIZE

ARM 1

Pembrolizumab 400 mg every 42 days, for up to 8 doses (a total of 2 doses per 12-week cycle)
OR
Pembrolizumab 200mg every 21 days, for a total of 4 doses per 12-week cycle.

ARM 2

Tivozanib 1.34mg taken daily for 21 days, rest 7 days and repeat for a total of 3 courses during cycles 1 and 2 for a total of 63 doses per 12-week cycle. Treatment with tivozanib should not exceed 27 weeks

AND

Pembrolizumab 400 mg every 42 days, for up to 8 doses (a total of 2 doses per 12-week cycle)
OR
Pembrolizumab 200mg every 21 days, for a total of 4 doses per 12-week cycle.

Treatment is to continue for up to a total of 4 cycles or until disease progression or unacceptable adverse event. Patients will be followed for 10 years following registration or until death, whichever comes first.