Neoadjuvant Zanzalintinib Plus Nivolumab in Patients With Locally Advanced and/or Inoperable Clear Cell Renal Cell Carcinoma With or Without Non-measurable Metastasis

Status: RECRUITING

Eligibility Criteria

Age: 18 years and over

This study is NOT accepting healthy

Healthy Volunteers: volunteers

Inclusion Criteria:

1. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization for release of personal health information prior to registration. NOTE: HIPAA authorization may be included in the informed consent or obtained separately. 2. Age ≥ 18 years at the time of consent. 3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 within 30 days prior to registration. 4. Histologically confirmed (i.e., tissue from primary kidney tumor of interest) diagnosis of clear cell renal cell carcinoma with or without sarcomatoid features. NOTE: biopsy should be performed at least 5 days before the first dose of study treatment and must be completely healed before dosing. 5. Locally advanced (cT3/T4, N0-1) OR deemed surgically challenging/inoperable per surgeon discretion. Satisfying either of the criteria allows for enrollment. NOTE: Surgically challenging/inoperable per surgeon discretion is based on one or more of the following, which will be documented on the Surgical Operability and Outcomes Form and evaluated per central surgery review: * cT4 disease * N1 disease * Surgery may be significantly complex and/or significantly affect residual renal function, where neoadjuvant therapy may downsize/downstage primary tumor for maximum renal preservation, including: * IVC tumor thrombus involvement * cT1-3 tumor with pre-surgery calculated creatinine clearance \<60 mL/min per Cockcroft-Gault formula OR solitary kidney (any calculated creatinine clearance), with potential to convert from radical to partial nephrectomy * High complexity on RENAL Nephrometry Score (score ≥ 10) * Other reversible comorbidity(ies) that in the opinion of the surgeon renders the patient surgically challenging/inoperable at baseline, where neoadjuvant therapy and medical optimization may allow subsequent surgery 6. Non-measurable soft tissue metastasis with longest diameter \< 10mm or pathological lymph nodes \< 15 mm in short axis are allowed. 7. Recovery to baseline or Grade ≤ 1 severity (CTCAE v5) from adverse events (AEs) related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy (eg, physiological replacement of corticosteroid). Low-grade or controlled toxicities such as alopecia, Grade ≤ 2 hypomagnesemia, Grade ≤ 2 neuropathy are permitted). 8. Adequate organ and marrow function, based upon meeting all the following laboratory criteria within 30 days before first dose of study treatment: * Platelets (Plt): ≥ 100,000 /mm3; without transfusion within 2 weeks of screening laboratory sample collection * Absolute Neutrophil Count (ANC): ≥ 1500 K/mm3; without granulocyte colony-stimulating factor support within 2 weeks of screening laboratory sample collection * Hemoglobin (Hgb): ≥ 9 g/dL; without transfusion within 2 weeks of screening laboratory sample collection * Creatinine OR Calculated creatinine clearance: ≤ 1.5 x ULN OR ≥ 40 mL/min * Urine protein-to-creatinine ratio (UPCR): ≤ 1.5 mg/mg (≤ 169.8 mg/mmol) creatinine * Total bilirubin: ≤ 1.5 × upper limit of normal (ULN); for subjects with Gilbert's disease ≤ 3 x ULN * Aspartate aminotransferase (AST): ≤ 3× ULN * Alanine aminotransferase (ALT): ≤ 3 × ULN * Alkaline Phosphatase (ALP): ≤ 3 × ULN 9. Females of childbearing potential must have a negative urine or serum pregnancy test within 48 hours of Cycle 1 Day 1. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects are considered to be of childbearing potential unless one of the following criteria is met: permanent sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or documented postmenopausal status (defined as 12 months of amenorrhea in a woman \> 45 years-of-age in the absence of other biological or physiological causes. For females \< 55 years old, confirmation of menopausal status is per institutional standards. NOTE: documentation may include review of medical records, medical examination, or medical history interview by study site staff. 10. Females of childbearing potential who are sexually active with a male able to father a child must be willing to abstain from penile-vaginal intercourse or must use an effective method(s) of contraception. Males able to father a child who are sexually active with a female of childbearing potential must be willing to abstain from penile-vaginal intercourse or use an effective method(s) of contraception. 11. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

Exclusion Criteria:

1. Non-clear cell histology. 2. Measurable metastatic disease per RECIST 1.1 criteria and other non-measurable lesions including bone metastasis, leptomeningeal disease, lymphangitic involvement of lung or skin, pathologically confirmed-malignant ascites/pleural/pericardial effusion. 3. Prior systemic therapy, including zanzalintinib, nivolumab and other vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs)/immune checkpoint inhibitors(IOs), for the treatment of renal cell carcinoma. 4. Prior surgery and/or radiation to the primary renal cell carcinoma tumor of interest. NOTE: prior surgery and/or radiation to other areas of the kidney (i.e., prior small kidney tumor resection or radiation) is allowed if \> 4 weeks before first dose of study treatment. 5. Concomitant anticoagulation with oral anticoagulants (eg, warfarin, direct thrombin inhibitors) and platelet inhibitors (eg, clopidogrel). NOTE: For prohibited anticoagulants, subjects must have discontinued the anticoagulant within 3 days or 5 half-lives prior to first dose of study treatment, whichever is longer. Allowed anticoagulants are the following: * 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, or apixaban in subjects without known brain metastases who are on a stable dose of the anticoagulant for at least 1 week before first dose of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen. 6. Use of any complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks before first dose of study treatment. 7. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions: * Unstable or deteriorating cardiovascular disorders: * Congestive heart failure New York Heart Association Class 3 or 4, class 2 or higher, unstable angina pectoris, new-onset angina, serious cardiac arrhythmias (eg, ventricular flutter, ventricular fibrillation, Torsades de pointes) * Uncontrolled hypertension defined as sustained blood pressure (BP) \> 140 mm Hg systolic or \> 90 mm Hg diastolic despite optimal antihypertensive treatment * Stroke (including transient ischemic attack \[TIA\]), myocardial infarction, or other clinically significant arterial thrombotic and/or ischemic event within 6 months before first dose of study treatment * Pulmonary embolism (PE) or deep vein thrombosis (DVT) or prior clinically significant venous or non-CVA/TIA arterial thromboembolic events within 3 months before to first dose of study treatment NOTE: Subjects with a diagnosis of DVT within 6 months are allowed if asymptomatic and stable at screening and are on stable dose of the anticoagulant for at least 1 week before first dose of study treatment without clinically significant hemorrhagic complications from the anticoagulation regimen. NOTE: Subjects who don't require prior anticoagulation therapy may be eligible but must be discussed and approved by the Sponsor-Investigator. * Prior history of myocarditis * Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation: * Tumors invading the GI-tract from external viscera * Active peptic ulcer disease, inflammatory bowel disease, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, or acute pancreatitis * Acute obstruction of the bowel, gastric outlet, or pancreatic or biliary duct within 6 months before first dose unless cause of obstruction is definitively managed and subject is asymptomatic * Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose. Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose of study treatment. * Known gastric or esophageal varices * Ascites, pleural effusion, or pericardial fluid requiring drainage in last 4 weeks 8. Clinically significant hematuria, hematemesis, or hemoptysis of \> 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (eg, pulmonary hemorrhage) within 12 weeks before first dose of study treatment. 9. Symptomatic cavitating pulmonary lesion(s) or endobronchial disease (asymptomatic or radiated lesions allowed). 10. Lesions invading a major blood vessel. NOTE: Subjects with intravascular tumor extension (eg, tumor thrombus in renal vein or inferior vena cava) are eligible. 11. Active infection requiring systemic treatment. NOTE: Prophylactic antimicrobial treatments (antibiotics, antimycotic, antiviral) are allowed. 12. Known infection with acute or chronic hepatitis B or

C. 13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. NOTE: Subjects meeting all the following criteria: (1) on stable anti-retroviral therapy (ART); (2) CD4+ T cell count ≥ 200/µL; and (3) an undetectable viral load may be eligible. Subjects taking CYP inhibitors (eg, zidovudine, ritonavir, cobicistat, didanosine) or CYP3 inducers (efavirenz) must change to a different regimen not including these drugs at least 7 days prior to initiation of study treatment. ART must have been received for at least 4 weeks prior to the first dose. NOTE: CD4+ T cell counts, and viral load are monitored per standard of care by the local health care provider. 14. Serious non-healing wound/ulcer/bone fracture. 15. Malabsorption syndrome. 16. Pharmacologically uncompensated, symptomatic hypothyroidism. 17. Moderate to severe hepatic impairment (Child-Pugh B or C). 18. Requirement for hemodialysis or peritoneal dialysis. 19. History of solid organ or allogeneic stem cell transplant. 20. Major surgery (as defined in Appendix A) within 8 weeks prior to first dose of study treatment. Prior laparoscopic surgeries (ie nephrectomy) within 4 weeks prior to first dose of study treatment. Minor surgery (eg, simple excision, tooth extraction) within 5 days before first dose of study treatment. Complete wound healing from major or minor surgery must have occurred at least prior to first dose of study treatment. NOTE: Tumor biopsies should be performed at least 5 days before the first dose of study treatment. Subjects with clinically relevant ongoing complications from prior surgical procedures, including biopsies, are not eligible. 21. QTc calculated by the Fridericia formula \> 480 ms within 14 days per electrocardiogram (ECG) before first dose of study treatment. NOTE: Triplicate ECG evaluations will be performed at screening and the average of these 3 consecutive results for QTc will be used to determine eligibility. 22. History of psychiatric illness likely to interfere with ability to comply with protocol requirements or give informed consent. 23. Pregnant or lactating females. 24. Inability to swallow tablets or ingest a suspension either orally or by a nasogastric (NG) or gastrostomy (PEG) tube. 25. Previously identified allergy or hypersensitivity to components of the study treatment formulations. 26. Another malignancy that requires active therapy and in the opinion of the Investigator would interfere with monitoring of radiologic assessments of response to study treatment within 2 years before first dose of study treatment. Superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy are allowed. Incidentally diagnosed prostate cancer is allowed if assessed as stage ≤ T2N0M0 and Gleason score ≤ 6. 27. Other conditions, which in the opinion of the Investigator, would compromise the safety of the subject or the subject's ability to complete the study. 28. Any active, known or suspected autoimmune disease. NOTE: Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 29. Known positive test for tuberculosis infection if supported by clinical or radiographic evidence of disease. 30. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 31. Known free thyroxine (FT4) outside the laboratory normal reference range. Asymptomatic subjects with FT4 abnormalities can be eligible after sponsor-investigator approval. 32. Diagnosis of immunodeficiency or is receiving systemic steroid therapy (\> 10 mg daily prednisone equivalent) or any other form of immunosuppressive therapy within 2 weeks prior to first dose of study treatment. Inhaled, intranasal, intraarticular, and topical corticosteroids and mineralocorticoids are allowed. NOTE: Adrenal replacement steroid doses \> 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. Transient short-term use of higher doses of systemic corticosteroids for allergic conditions (eg, contrast allergy) is also allowed. 33. Administration of a live, attenuated vaccine within 30 days before first dose of study treatment.

Conditions & Interventions

Interventions:
DRUG: Zanzalintinib, DRUG: Nivolumab
Conditions:
Locally Advanced Renal Cell Carcinoma
Keywords:
XL092, Zanzalintinib

More Information

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