Single-arm phase II clinical trial to evaluate the initial efficacy and safety of Sintilimab injection combined with Inlyta in fumarate hydratase-deficient renal cell carcinoma

FH- fumarate hydratase

RCC- renal cell carcinoma

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Study Background

Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) is a kind of autosomal dominant diseases featured by FH gene mutation [1]. Since FH-deficient RCC not only demonstrates distinct genetic alteration patterns and also shows a very aggressive clinical pattern, WHO/ISUP has redefined it as a RCC subtype (it was once classified into papillary RCC (pRCC)) [2]. FH-deficient RCC patients are likely to develop metastasis at the early phase, and they also response poorly to common targeted drugs in RCC. In another words, there is no standard therapy for FH-deficient RCC.

Loss-of-function mutation of FH results in accumulation of fumarate, impairment of oxidative phosphorylation, alteration of metabolic state, and stabilization of hypoxia-inducible factor (HIF)-1α, ultimately leading to the activation of angiogenic and oxidative stress response pathways [3-5]. Evidence suggests that accumulated fumarate also diminishes AMPK levels and consequent activation of mTOR and downstream pathway. Although there are current results of clinical trials (NCT01130519 and NCT01399918) suggesting the use of bevacizumab plus erlotinib or everolimus as standard

treatment for FH-deficient RCC [6, 7]. However, we retrospectively analyzed eight confirmed FH-deficient RCC in our center between 2010-2018 and found that most (7/8，87.5%) of them did not respond well to targeted therapy (TKIs and/or mTOR inhibitors.

To date, effective treatments for FH-deficient RCC remain a major unmet clinical need. Unlike three other subtypes of RCC, including clear cell RCC (ccRCC), pRCC and chromophobe RCC (chRCC), the genomic landscape of HLRCC has not yet been reported. Without any genomic information, it is challenging to develop targeted therapy and clinical trials for FH-deficient RCC. We previously performed a Whole-exosome sequencing on FH-deficient RCC cases confirmed at our center and found that it harbored high rate of microsatellite instability (MSI), high PD-L1 positive rate. Consequently, we concluded that these patients might be sensitive to immunotherapy.

Currently numerous studies have shown that immunotherapy might be an important tool in RCC treatment [8-10], while first-line PD-1/PD-L1 inhibitors showed an merely 20%-30% overall response rate and a similar progression-free survival to that of targeted therapy. Considering the possible crosstalk between antiangiogenic therapy and tumor immune microenvironment, the immunogenicity of FH-deficient RCC could hinder the efficacy of TKI monotherapy, which indicates that combination of immunotherapy and TKI might be a potential way. Therefore, we intend to perform this clinical trial.

Reference:

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Protocol

Study Type: Interventional
Primary Purpose: Treatment
Study Phase: Phase 2
Interventional Study Model: Single Group Assignment
Number of Arms: 1
Masking: None (Open Label)
Allocation: N/A
Enrollment: 20 [Anticipated]

Experimental: Sintilimab injection combined with Inlyta (Sintilimab injection 10ml: 100mg, 200mg intravenously, once every three weeks. Course of treatment: discontinue medication when the disease progresses clinically or radiologically. Inlyta 5mg orally, twice a day. Course of treatment: continue treatment as long as a clinical benefit is observed, or until an unacceptable toxicity is present that cannot be controlled by combination or dose adjustment.)

In the whole research process, if the disease progresses, the attending doctor has the right to carefully choose other anti-tumor methods, including radiotherapy, chemotherapy and other targeted drugs

Outcome Measures
Primary Outcome Measure:
1. PFS: progression-free survival
[Time Frame: 3 years]
2. ORR: objective response rate
[Time Frame: 3 years]
Secondary Outcome Measure:
3. OS: overall survival
[Time Frame: 3 years]
4. life quality: evaluate life quality
[Time Frame: 3 years]
Other Pre-specified Outcome Measures:
5. drug related adverse effect
[Time Frame: 3 years]

Eligibility
Minimum Age: 18 Years
Maximum Age:
Sex: All
Gender Based:
Accepts Healthy Volunteers: No
Criteria: Inclusion Criteria:
1. age ≥ 18;
2. histology characteristics accord with FH-deficient RCC;
3. gene testing confirms germline and/or somatic FH gene mutation ;
4. ECOG (Eastern Cooperative Oncology Group)≤2;
5. expected survival >3 months;
6. blood routine indexes: neutrophils ≥1.5*109, platelets ≥100*109, hemoglobin ≥90g/L;
7. liver function: bilirubin ≤ normal upper limit 1.5 times, AST≤ normal upper limit 2.5 times;Serum creatinine ≤ 1.5 times of normal upper limit;Serum calcium concentration: ≤12.0 mg/dL;
8. coagulation function: PT≤ 1.5 times of normal upper limit;
9. the following diseases did not appear within 12 months: myocardial infarction, severe or unstable angina pectoris, asymptomatic heart failure, cardiovascular and cerebrovascular accident or transient ischemic attack, etc.
10. all patients signed informed consent.
Exclusion Criteria:
1. other malignancies previously or at the same time that are different

from the primary site or histology of the tumor assessed in this study, except cervical carcinoma in situ, basal-cell carcinoma that has been fully treated, superficial bladder tumor (Ta, Tis, T1) or other malignancies that occurred before the enrollment and have been cured for more than 3 years;
2. renal decompensation requires hemodialysis or peritoneal dialysis;
3. arrhythmia need anti-arrhythmic treatment, symptomatic coronary artery disease or myocardial ischemia (myocardial infarction), nearly six months, or congestive heart failure than NYHA # level; Hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) that has been treated with 2 or more antihypertensive treatments and still cannot be controlled;
4. severe active clinical infection;
5. patients with coagulation disorder or bleeding constitution;
6. major surgery or severe trauma was performed within 4 weeks before enrollment;
7. a history of allogeneic organ transplantation or bone marrow transplantation;
8. drug abuse and medical, psychological or social conditions that may interfere with patients' participation in research or affect the evaluation of results;
9. known or suspected allergy to the study drug;
10. those who received treatment other than this study within 4 weeks prior to and during the study period.