A Study of Toripalimab in Adjuvant Therapy After Resection of High-risk Renal Cancer (TUORA)

Protocol

Protocol Number：TUOAD-RCC

Study Registration：NCT06584435

Protocol Version Number：V1

Protocol Version Number Date:： October 01, 2022

Principal Investigator：

Sponsor： Tianjin Medical University Second Hospital

Principal Investigator Signature Page

Principal Investigator Signature

I confirm that this clinical study is an Investigator-Initiated Trial (IIT). The principal investigator of this clinical study will simultaneously assume the relevant responsibilities of both the investigator and the sponsor as stipulated in GCP.

I will diligently fulfill the responsibilities of both the sponsor and the investigator in accordance with GCP, personally participate in, and directly guide this clinical study. I confirm this study protocol. I agree to perform the relevant duties in accordance with Chinese laws, the Declaration of Helsinki, GCP, and this clinical study protocol. I confirm that this study protocol and any subsequent protocol amendments must be approved by the Ethics Committee before implementation. I will keep this study protocol and documents and information related to this study confidential.

Research Unit: Tianjin Medical University Second Hospital

		October 01, 2022
Principal Investigator (Printed Name)	Principal Investigator (Signature)	Signature Date (Year/Month/Day)

Protocol Summary

Study Title	A Study of Toripalimab in Adjuvant Therapy After Resection of High-risk Renal Cancer (TUORA)
Protocol Number	NCT06584435
Protocol Version Number	V1
Protocol Version Date	2022-10-01
Clinical Study Type	Registrational Clinical Trial
Clinical Study Registration	Investigator-Initiated Trial，IIT
Clinical Trial Approval Document	
Clinical Research Unit	Tianjin Medical University Second Hospital
Sponsor	
Study Population	Treatment-naive subjects confirmed by pathology and imaging: Patients with advanced renal cell carcinoma who have no radiologically evident residual tumor after surgical treatment, with an ECOG score of 0-1, and meeting at least one of the following criteria: 1) pT2, with Grade 4 or sarcomatoid differentiation, N0, M0; 2) pT3/4, N0, M0 (any grade); 3) Any T classification with N1, M0; 4) Post nephrectomy (radical/partial) plus complete resection of metastasis, M1 No Evidence of Disease (NED).
Study Objectives	1) To investigate the impact of Toripalimab on tumor control and survival in high-risk renal cell carcinoma (RCC) patients following nephrectomy. 2) To evaluate the feasibility and application value of Toripalimab as adjuvant therapy in high-risk RCC patients after nephreectomy.

Study Design	Single-center, prospective, single-arm, Phase II clinical study
Sample Size	40~100 Cases
Study Endpoints	**Primary Endpoints:** Disease-free survival (DFS) **Secondary Endpoints:** Overall survival (OS), Safety, and Quality of Life
Investigational Product for Experimental Group	Toripalimab intravenous injection, fixed dose of 240mg, administered once every 3 weeks as one treatment cycle, until tumor recurrence, intolerance to toxic side effects, or completion of 17 treatment cycles.
Study Procedures	This clinical study includes three main phases: Screening, Treatment, and Follow-up. **Screening Period:** 1) From the date the subject signs the ICF until before the first dose of investigational product. 2) The screening period should not exceed 14 days. **Treatment and Efficacy Evaluation:** 1) DFS evaluation by imaging (CT/MRI) at 12 weeks after the first dose of Toripalimab and then every 12 weeks during the treatment period for the experimental group. 2) Safety monitoring (complete blood count, liver/kidney function, electrolytes, thyroid function) at 3 weeks after the first dose of Toripalimab and then every 3 weeks during the treatment period for the experimental group. **Follow-up Period:** 1) Safety follow-up: Defined as safety follow-up at the end of each treatment cycle, tracking adverse events until resolution, stabilization, or return to baseline. 2) Survival follow-up: Every 3 months, recording survival status. 3) Tumor progression follow-up: Re-examination every 3 months within 3 years to assess DFS and safety.
Inclusion Criteria	Subjects must meet ALL of the following criteria: 1) Signed written Informed Consent Form (ICF) before enrollment. 2) Age > 18 years at the time of signing ICF, either gender. 3) Pathologically and radiologically confirmed renal cell carcinoma subjects: Advanced RCC patients with no radiologically evident residual tumor after

	surgical treatment, meeting at least one of the following conditions: pT2 with G4 or sarcomatoid, N0, M0; pT3/4, N0, M0 (any grade); Any T classification with N1, M0; Post nephrectomy (total/partial) plus complete resection of metastasis, M1 NED. 4) No suspected brain metastases. 5) ECOG performance status score: 0 ~ 1. 6) Adequate function of major organs meeting the following requirements (excluding use of any blood components or growth factors within 14 days): Normal bone marrow reserve: neutrophils ⩾ 1,500/mm ^{3} , platelets ⩾ 100,000/mm ^{3} , hemoglobin ⩾5.6 mmol/L (9 g/dL); Normal renal function: serum creatinine ⩽ 1.5 mg/dL and/or creatinine clearance ⩾ 60 ml/min; Normal liver function: bilirubin ⩽1.5xULN, AST & ALT ⩽1.5xULN. 7) For non-sterilized or women of childbearing potential: Use of a medically approved contraceptive method (e.g., IUD, oral contraceptives, or condoms) during the study treatment period and for 3 months after treatment ends; negative serum or urine HCG test within 7 days prior to study enrollment; must be non-lactating. For non-sterilized men of childbearing potential: Agreement to use a medically approved contraceptive method with their partner during the study treatment period and for 3 months after treatment ends. 8) The subject voluntarily joins the study, has good compliance, and cooperates with safety and survival follow-up.
Exclusion Criteria	Subjects meeting ANY of the following criteria cannot be enrolled: 1) Previous receipt of radiotherapy, chemotherapy, long-term or high-dose hormone therapy, or immune checkpoint inhibitors. 2) Subject has a history of or concurrent other malignancies. 3) Previous treatment with other PD-1/PD-L1 inhibitors; known allergy to macromolecular protein preparations or any component of PD-1 inhibitors. 4) Presence of any active autoimmune disease or history of autoimmune disease (including, but not limited to to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism; subjects with vitiligo or childhood asthma that has completely resolved and requires no intervention in adulthood may be included; subjects with asthma requiring bronchodilator intervention cannot be included). 5) Subject is using immunosuppressants for immunosuppressive purposes and continues use within 2 weeks prior to enrollment.

6) Poorly controlled cardiac clinical symptoms or diseases, such as: (1) NYHA Class II or above heart failure; (2) Unstable angina; (3) Myocardial infarction within 1 year; (4) Clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention.

7) Coagulation abnormalities (PT>16s, APTT>43s, TT>21s, Fibrinogen<2g/L), bleeding tendency, or receiving thrombolytic or anticoagulant therapy.

8) Presence of esophageal varices, active gastroduodenal ulcer, ulcerative colitis, portal hypertension, or other gastrointestinal diseases, or active bleeding from unresected tumor, or other conditions deemed by the investigator likely to cause gastrointestinal bleeding or perforation, within 3 months.

9) History or current presence of severe hemorrhage (>30ml within 3 months), hemoptysis (>5ml of fresh blood within 4 weeks) or thromboembolic events (including stroke and/or transient ischemic attack) within 12 months.

10) Subject has active infection or unexplained fever >38.5 ° C occurs during screening or before the first dose.

11) Abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to study drug administration.

12) Objective evidence of history or current presence of pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonia, severely impaired pulmonary function, etc.

13) Congenital or acquired immunodeficiency, such as HIV infection, or active hepatitis (liver enzymes not meeting inclusion criteria; for hepatitis B: HBV DNA ≥ 10^4 copies/ml; for hepatitis C: HCV RNA ≥ 10^3 copies/ml); chronic HBV carriers with HBV DNA ≥2000 IU/ml (≥10^4 copies/ml) can only be enrolled if they receive concurrent antiviral therapy during the trial.

14) Subject is participating in another clinical study or less than 1 month has passed since the end of the previous clinical study; subject may receive other systemic anti-tumor therapy during the study period.

15) Vaccination with live vaccines within 4 weeks prior to study drug administration or possible during the study period.

16) Known history of psychotropic drug abuse, alcoholism, or drug use.

17) Subject is unable or unwilling to bear the self-paid portion of examination and treatment costs.

18) The investigator deems it necessary to exclude the subject from the study, for example, due to other factors that may lead to premature termination of the study, such as other severe diseases (including mental illness) requiring combined treatment, severe laboratory abnormalities, or family or social

	factors that may affect subject safety, or the collection of data and samples.
Withdrawal Criteria	1) The subject or their legal representative requests early withdrawal. 2) Occurrence of unexpected rapid progression or radiologically confirmed progression. 3) Continued participation in the study would be harmful to the subject's health. 4) Occurrence of Grade 4 hematological toxicity, or Grade 3 neutropenia with fever (>38.5 ℃), or Grade 3 thrombocytopenia with bleeding tendency, esophageal perforation, combined severe pulmonary/mediastinal infection, hemorrhage, myocardial infarction, heart failure, severe arrhythmia, etc., during treatment. 5) Occurrence of intolerable toxicity. 6) Treatment delay of 2 weeks for any reason. 7) Subject becomes pregnant or is lost to follow-up. 8) The investigator deems it necessary to withdraw the subject from the study. 9) All withdrawn subjects should be followed up according to the study protocol, and follow-up results recorded, unless the patient withdraws the informed consent form and refuses follow-up.
Concomitant Medications/Therapies	**Permitted Concomitant Medications/Therapies:** Supportive care; topical analgesics; all adverse reactions should be actively treated, especially those related to the immune system. **Not Permitted Concomitant Medications/Therapies:** Discontinue various anti-tumor drugs and tumor treatment-related auxiliary drugs during the treatment period, including anti-tumor Chinese herbal medicine, immune agents (interferon, interleukin, thymosin), etc. **Concomitant Medications/Therapies to be Used with Caution:** Drugs that interfere with hepatic P450 enzymes; drugs that prolong the QT interval.
Safety Evaluation	Safety evaluation will be based on NCI CTCAE v5.0 terminology criteria to judge the severity of symptoms, signs, laboratory tests, and adverse events, including the time of occurrence, severity, duration, measures taken, and outcome of AEs.
Efficacy Evaluation	In the Intention-to-Treat population, tumor recurrence and metastasis will be assessed based on imaging techniques (CT, MRI, and/or ECT).
Tumor Imaging	Tumor imaging evaluation will be performed according to the following standards: 1) Baseline tumor imaging evaluation of the renal area, lungs, and bones to be completed within 2 weeks before the first treatment during the screening period.

	2) Clinical tumor imaging evaluation at 12 weeks after treatment initiation. 3) Subsequent clinical tumor imaging evaluations every 12 weeks thereafter. 4) Upon first disease recurrence, a confirmatory clinical tumor imaging evaluation is required 3 weeks later. 5) The investigator may add unscheduled tumor imaging examinations as clinically needed, such as PET/CT.
Statistical Methods	1) The primary analysis of this study will be descriptive statistical summaries, not involving formal hypothesis testing. Any hypothesis testing or model-based statistical exploration will be supplementary only. 2) In this study, unless otherwise specified, data will be summarized using descriptive statistics according to the following general principles. Measurement data will be summarized using mean, standard deviation, median, maximum, and minimum; count data will be summarized using frequency and percentage. 3) Safety Analysis: Adverse events will be summarized using frequency and percentage; laboratory tests (blood routine, blood biochemistry, etc.), ECOG, vital signs, and ECG will be summarized using descriptive statistics. 4) Efficacy Evaluation: Point estimates with 95% confidence intervals will be provided for efficacy endpoints such as DFS and OS. Additionally,DFS and OS will be estimated using the Kaplan-Meier method for survival rates and m -edian survival time along with their 95% confidence intervals.
Interim Analysis	An interim analysis will be performed when the median follow-up reaches 12 months.
Treatment Discontinuation	Defined as termination of treatment for any reason, e.g., disease recurrence, intolerance, or early withdrawal. Safety follow-up must still be completed after treatment discontinuation to assess AE resolution.
Study Completion	Defined as the last subject completing follow-up, or early withdrawal from follow-up.
Study Termination	1) The investigator identifies unexpected, significant, or unacceptable risks to subjects. 2) A major design flaw is discovered during the study execution. 3) The investigational product/treatment is ineffective, or the investigator judges that continuing the trial is meaningless. 4) The research institution or ethics committee decides to terminate the clinical study early.

Study Timeline	Estimated date of first subject enrollment: October 2022 Estimated date of last subject enrollment: October 2025 Estimated study completion date: November 2027