Informed Consent Form

Subject Information Sheet

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

Principal Investigator:

Study Registration: NCT06584435

Sponsor: Tianjin Medical University Second Hospital

Protocol Version Number Date: October 01, 2022

Dear Subject:

You are invited to participate in the research study titled "A Study of Toripalimab in Adjuvant Therapy After Resection of High-Risk Renal Cancer." This study is supported by Tianjin Medical University Second Hospital. Please read this informed consent form carefully and deliberate on your decision to participate. Participation in this research is entirely your voluntary choice. As a subject, you must provide your written consent before joining the clinical study. When your study doctor or research staff discusses this informed consent form with you, you can ask them to explain anything you do not understand. We encourage you to discuss fully with your family and friends before deciding to participate in this study. You have the right to refuse to participate in this study and may withdraw at any time without penalty or loss of any benefits to which you are otherwise entitled. If you are currently participating in another study, please inform your study doctor or research staff. The background, purpose, procedures, and other important information about this study are as follows:

1. Study Background

Renal cell carcinoma (RCC) accounts for 2%-3% of all adult malignant tumors and is the urological cancer with the highest mortality rate. The incidence of kidney cancer varies by country or region, being higher in developed countries, where it constitutes about 3% of adult malignancies. In most countries and regions, the incidence of kidney cancer has shown a continuous increasing trend, with an annual increase of 0.7%-2% over the past decade. The peak incidence occurs at 60-70 years of age, with a median age at diagnosis of 64 years, and a male-to-female incidence ratio of approximately 2:1. Data from China's cancer registry annual reports indicate that the incidence of kidney cancer in China has been increasing from 1988 to 2014. Data from the National Cancer Center shows that in 2014, the incidence of kidney cancer in China was 4.99 per 100,000, with rates of 6.09 per 100,000 for men and 3.84 per 100,000 for women. In 2015, there were

approximately 668,000 new cases ofkidney cancer in China, resulting in 234,000 deaths, with the peak age of onset shifting earlier to 50-60 years.

Partial nephrectomy and radical nephrectomy are standard treatments for localized clear cell renal cell carcinoma. However, nearly half of the patients experience recurrence and metastasis after surgery. Targeted therapy has been used for advanced clear cell RCC for many years and can delay disease-free survival (DFS) in high-risk T3 stage tumors, but it does not improve overall survival (OS). Subsequently, the KEYNOTE-564 study confirmed that pembrolizumab monotherapy is more effective in high-risk patients with no residual disease after resection, showing benefits not only in DFS but also in OS.

Toripalimab is a novel, self-developed, recombinant humanized (97% human) anti-PD-1 monoclonal antibody (Chinese Patent Authorization No. CN104250302B, PCT Patent Publication No. WO2014/206107A1). It belongs to the human IgG4/Kappa subtype and incorporates a point mutation (Serine to Proline, S228P) at position 228 in the IgG4 heavy chain hinge region to increase antibody stability and reduce potential IgG4 Fab chain exchange. Compared to foreign drugs of the same target, Nivolumab and Pembrolizumab, JS001 injection has different complementarity-determining regions (CDRs) and higher affinity. It specifically binds to PD-1 and effectively blocks the interaction between PD-1 and its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), thereby activating cytotoxic T lymphocytes, enhancing lymphocyte proliferation, and the secretion of cytokines, especially IFN-γ, aiming to utilize the body's own immune system to kill tumor cells. Toripalimab is currently undergoing multiple Phase II and III studies in China. Results from Phase I/II studies have shown that Toripalimab has demonstrated definite efficacy and a good safety profile in various solid tumors, including gastric cancer, esophageal cancer, nasopharyngeal carcinoma, and head and neck cancer. It has been approved by the NMPA for the treatment of melanoma, urothelial carcinoma, nasopharyngeal carcinoma, esophageal cancer, and lung cancer.

To demonstrate the efficacy of Toripalimab in preventing recurrence in high-risk renal cancer patients with no radiologically evident residual tumor after radical surgery, our center plans to conduct a single-center, prospective, single-arm, Phase II clinical study of Toripalimab as adjuvant therapy. The sample size was calculated based on the objective response rate reported in previous literature. The target assumption is a 2-year recurrence rate of 30%. Toripalimab adjuvant therapy is expected to prevent 50% of recurrences. To observe recurrence in more than 10 patients, we plan to enroll 40 to 100 patients. After surgery, patients will receive Toripalimab intravenous injection at a fixed dose of 240 mg every 3 weeks (one cycle) until tumor recurrence or intolerance to toxic

side effects. Imaging will be repeated every 12 weeks during adjuvant therapy. The primary endpoints are DFS and OS, and the secondary endpoint is drug safety.

2. Study Objectives

The purposes of this study are:

To investigate the impact of Toripalimab on tumor control and survival in high-risk renal cell carcinoma patients after radical nephrectomy.

To evaluate the feasibility and application value of Toripalimab for high-risk renal cell carcinoma patients after radical nephroureterectomy.

3. Study Process

3.1 How many people will participate in this study?

Approximately 40 to 100 people will participate in this study at our center.

3.2 Study Procedures

3.2.1. If you agree to participate in this study, please sign this informed consent form. During the entire study period, blood draws are planned for (17) times, (15) ml each time.

3.2.2. Before you can enter the study, the doctor will inquire about and record your medical history and perform screening tests, including complete blood count, alkaline phosphatase, lactate dehydrogenase, bone scan, CT/MRI of the entire abdomen, chest CT, and tissue biopsy.

3.2.3. After confirming your eligibility for the study, you will receive Toripalimab intravenous injection at a fixed dose of 240 mg every 3 weeks (one treatment cycle) until tumor recurrence, intolerance to toxic side effects, or completion of 17 treatment cycles.

3.2.4. After joining the study, you will undergo blood tests every three weeks and imaging examinations every 12 weeks, including bone scan, CT/MRI of the entire abdomen, and chest CT.

3.3 How long will this study last?

The investigational drug treatment period will last for one year, or until disease recurrence, or discontinuation due to side effects. Follow-up will continue for life.

You may choose to withdraw from the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, we encourage you to discuss it with your doctor first. If you experience a serious adverse event, or if your study doctor believes that continued participation is not in your best interest, he/she will decide to withdraw you from the study. The sponsor or regulatory authorities may also terminate the study during its course. Your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation. If the doctor deems it necessary, you may also be required to undergo laboratory tests and physical examinations.

3.4 Information and Biological Specimens Collected in the Study

With your consent, your doctor will send a portion of the tumor tissue obtained from your biopsy to the study laboratory for related biomarker research. The collection of tumor tissue samples in this study is to better understand the tumor and its treatment. The purpose of researching molecular markers is to understand why the drug is effective for some patients but not for others; why some patients have adverse reactions; or what factors cause or alter kidney cancer.

Your tumor tissue will be used directly to detect PD-L1 expression and may also be used for further research related to kidney cancer and other related diseases. These studies may include additional tests and information analysis related to this study on your tumor tissue. The aforementioned research on molecular markers may take several years, but if fruitful, it may contribute to early diagnosis or more effective treatment of tumors.

Your decision regarding biomarker testing will not affect your participation in this study.

4. Risks and Benefits

4.1 What are the risks of participating in this study?

Anti-tumor treatments all carry risks. Due to the disease itself, other existing comorbidities, or drug combinations, previously unknown or unpredictable adverse reactions may occur during the study. Based on safety data from multiple clinical studies of Toripalimab conducted domestically and internationally, common adverse reactions are summarized in the table on the following page.

Table for Immune-Related Adverse Reactions would be translated here:

Immune-Related Adverse Reactions (Total Patients N=598) Incidence n (%)				
Sequence Number	Adverse Reaction	n（%）	CTCAE Grade	
			CTCAE 1-2 Grade (%)	CTCAE ⩾3 Grade (%)
1	Hypothyroidism	77（12.9%）	77（12.9%）	0
2	Hyperthyroidism	29（4.8%）	29（4.8%）	0

3	Hepatitis	21（3.5%）	2（0.3%）	19（3.2%）
4	Skin Adverse Reactions	19（3.2%）	19（3.2%）	0
5	Hyperglycemia And Diabetes Mellitus	17 (2.8%)	14（2.4%）	3（0.4%）
6	Pancreatitis	16（2.7%）	1（0.2%）	15（2.5%）
7	Infusion Reactions	15（2.5%）	14（2.3%）	1（0.2%）
8	Interstitial Lung Disease	11（1.8%）	5(0.8%)	6(1.0%)
9	Thrombocytopenia	6（1.0%）	0	6（1.0%）
10	Nephritis	5（0.8%）	1(0.2%)	4（0.7%）
11	Adrenal Insufficiency	2（0.3%）	2（0.3%）	0
12	Diarrhea and Colitis	1（0.2%）	0	1（0.2%）
13	Hypophysitis	1（0.2%）	0	1（0.2%）
14	Ocular Toxicity	1（0.2%）	0	1（0.2%）

Note: CTCAE = Common Terminology Criteria for Adverse Events.

4.2 What are the benefits of participating in the study?

Definite Benefit: If no special circumstances occur, enrolled patients will receive 17 doses of Toripalimab treatment. The last 3 doses will be provided free of charge, equivalent to a market value of RMB 830 * 3 doses * 3 times = RMB 7,470.

Potential Benefit: During this study, you will receive good medical care. Your disease may be alleviated by participating in this clinical research, but it might also not achieve the expected effect, or even recurrence may occur.

Contribution to Social Value: Undergoing biomarker testing of tumor tissue may not directly benefit you, but your participation will help further medical research and understanding of this type of disease, potentially improving future diagnosis and

treatment levels. Here, we thank you for your participation in scientific research and your contribution to the development of medicine!

5. Alternative Treatment Options

Besides participating in this study, you can receive other conventional treatments provided by your doctor:

- Other similar PD-1 antibodies (such as Pembrolizumab, Camrelizumab) and/or tyrosine kinase receptor inhibitors (such as Axitinib)
- PD-1 antibody monotherapy or tyrosine kinase receptor inhibitor monotherapy

Please discuss these and other possible options with your doctor.

6. Use of Research Results and Confidentiality of Personal Information

With your understanding and assistance, the results of this research project may be published in medical journals, but we will keep your study records confidential as required by law. The personal information of study subjects will be kept strictly confidential and will not be disclosed unless required by relevant laws. When necessary, government management departments, the hospital ethics committee, and other relevant researchers can access your information according to regulations.

7. Study Costs and Related Compensation

7.1 Costs of investigational drugs/ devices and related tests

This study covers the costs of PD-L1, MSH2, and MSH6 testing for patients. Not all participants will successfully undergo testing, as sufficient specimens are required. Not every genetic test will meet quality control requirements. Please be aware of this situation.

7.2 Compensation for participation

There are no additional tests or travel outside of normal diagnosis and treatment in this study, so there is no extra compensation.

7.3 Compensation for injuries

If you experience serious adverse reactions during the study, your doctor will examine you and provide symptomatic treatment. If you cannot tolerate the drug's adverse reactions or do not follow the doctor's requirements, the doctor may suggest you withdraw from the study. The research team has purchased insurance for all subjects participating in this study. If you suffer harm during the trial due to the use of the investigational product or due to following the procedures specified in the protocol, the

medical expenses incurred in diagnosing and treating this harm will be borne by the research team.

8. Subject Rights and Relevant Precautions

8.1 Your Rights

Your participation in this study is voluntary throughout. If you decide not to participate, it will not affect other treatments you should receive. If you decide to participate, you will be asked to sign this written informed consent form. You have the right to withdraw from the trial at any stage at any time without discrimination or unfair treatment, and your corresponding medical treatment and rights will not be affected.

8.2 Precautions

As a subject, you need to provide truthful information about your medical history and current physical condition; inform the research doctor of any discomfort you discover during the study; not take restricted drugs or foods as informed by the doctor; and tell the research doctor if you have recently participated or are currently participating in other studies.

9. Contact Information for Obtaining Information

If any important new information arises during the study that may affect your willingness to continue participation, your doctor will notify you promptly. If you have questions about your research data, or if you wish to know the findings ofthis study after its completion, you can raise any questions about this study at any time and receive corresponding answers. Please contact Yajun Li at 18812715434.

The study has been reviewed and approved by the Ethics Committee. If you have any questions related to your rights/benefits, or if you wish to report difficulties, dissatisfaction, or concerns encountered during your participation, or provide comments and suggestions related to the study, please contact the Ethics Committee of Tianjin Medical University Second Hospital at 022-88328108.

Subject Signature Page

Informed Consent Statement:

I have been informed about the purpose, background, procedures, risks, and benefits ofthis research. I have had sufficient time and opportunity to ask questions, and the answers provided have satisfied me.

I have also been informed whom to contact if I have questions, wish to report difficulties, concerns, or suggestions regarding the study, or want to obtain further

information or provide help for the research.

I have read this informed consent form and agree to participate in this study.

I understand that I can choose not to participate in this study or withdraw at any time during the study without giving any reason.

I understand that if my condition worsens, or ifI experience a serious adverse event, or if my study doctor believes that continued participation is not in my best interest, he/she will decide to withdraw me from the study. The funding party or regulatory authorities may also terminate the study during its course without requiring my consent. If this occurs, the doctor will notify me promptly, and the study doctor will discuss my other options with me.

I will receive a copy of this informed consent form, containing the signatures of both myself and the investigator.

Subject Signature:_____ Date:_____

（Note: If the subject lacks capacity/has limited capacity, the legal representative must sign and date）

Subject Contact Information:_____

Legal Representative Signature:_____ Date:_____

（Note: If the subject cannot read this informed consent form, an independent witness is required to attest that the investigator has explained all contents of the informed consent form to the subject. The independent witness must sign and date）

Legal Representative Contact Information:_____

Independent Witness Signature:_____ Date:_____

Independent Witness Contact Information:_____

Investigator Signature_____ Date:_____

Investigator Contact Information:_____