Clinical Trial Protocol

Title : Immediate versus Deferred Cytoreductive Nephrectomy with Ipilimumab/Nivolumab in Metastatic Clear Cell Renal Cell Carcinoma: A Multicenter, Randomized, Open-Label Phase III Trial

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Study Objectives

The primary objective of this trial is to establish the optimal treatment strategy for patients with synchronous metastatic clear cell renal cell carcinoma (mRCC) in the era of immune checkpoint inhibitors by comparing upfront versus deferred cytoreductive nephrectomy (CN) combined with ipilimumab and nivolumab.

Study Design

This is a multicenter, randomized, open-label, phase III clinical trial conducted at 12 sites in Korea. A total of 172 participants with IMDC intermediate- or poor-risk mRCC will be randomized 1:1 to either upfront CN followed by ipilimumab/nivolumab induction and nivolumab maintenance, or ipilimumab/nivolumab induction followed by deferred CN and nivolumab maintenance. Participants will be followed for 15 months.

Arms and Interventions

Arm A (Experimental): Upfront CN → 4 cycles ipilimumab/nivolumab → nivolumab maintenance
Arm B (Experimental): 4 cycles ipilimumab/nivolumab → Deferred CN → nivolumab maintenance

Primary Outcome Measure

Progression-Free Survival (PFS): Time from randomization to first documented disease progression or death from any cause, assessed up to 15 months.

Secondary Outcome Measures

- Overall Survival (OS)
- Surgical morbidity (Clavien-Dindo classification, CTCAE v4.0)
- Radiologic tumor response (RECIST v1.1)
- Rate of unresectable tumors in deferred CN arm
- Effect of CN on early progression (within 4 weeks post-surgery)
- Comparison of surgical approach and extent
- Quality of life (QoL) assessments

Eligibility Criteria

Inclusion: Adults ≥19 years, histologically confirmed synchronous clear cell mRCC, IMDC intermediate- or poor-risk, ECOG 0–1, measurable metastatic lesion, resectable primary tumor, life expectancy >3 months, informed consent.

Exclusion: Prior systemic therapy for mRCC, other malignancy within 2 years, significant uncontrolled comorbidities, autoimmune disease, chronic immunosuppressive therapy, or deemed unsuitable by investigator.

Sample Size

A total of 172 participants (86 per arm) are required to detect a difference in PFS between arms, assuming 15-month PFS of 72% in upfront CN vs 87% in deferred CN, with 80% power and a two-sided alpha of 0.05.

Safety Assessments

Safety will be monitored through perioperative complication rates and immune-related adverse events (irAEs) associated with ipilimumab/nivolumab. Monitoring will follow CTCAE v5.0 and Clavien-Dindo classification.

Study Methods

1. Institutional Review Board (IRB) approval will be obtained from all participating institutions. The coordinating institution (Seoul National University Hospital) will establish a Data Management Plan and Data Quality Control plan, and will implement a randomization system and electronic case report form (eCRF) system. Randomization schedules will be generated by the Medical Research Collaborating Center (MRCC) using a web-based permuted block randomization approach. The coordinating institution will conduct data monitoring and external audits through its Clinical Trials Center.
2. **Enrollment**: Eligible patients with metastatic renal cell carcinoma (intermediate or poor risk) will be identified during outpatient visits. The investigator or sub-investigator will provide sufficient explanation and obtain written informed consent.
3. A biopsy of the renal mass will be performed to confirm clear cell RCC.

4. **Pre-treatment evaluations and procedures**: Baseline tests and perioperative care will be performed identically in both Arm A (Deferred CN) and Arm B (Upfront CN).

5. **Randomization**: Randomization will be performed immediately after screening using permuted block randomization, stratified by IMDC intermediate vs poor risk group. This study is conducted in an open-label design.

6. **Interventions**: Participants will follow the treatment schedule according to their randomized group.

- **Upfront CN Arm**: Patients will undergo upfront cytoreductive nephrectomy. Peripheral blood mononuclear cells (PBMCs) will be collected preoperatively, postoperatively, and after completion of 4 cycles of ipilimumab/nivolumab. Four weeks after surgery, perioperative complications and progression status will be evaluated. Based on these findings, patients will receive 4 cycles of ipilimumab/nivolumab induction within 6 weeks after surgery, followed by assessment of progression status, safety, and quality of life (QoL). Thereafter, maintenance nivolumab will be administered with assessments every 3 months. At 15 months after treatment initiation, progression and survival status will be determined.

- **Deferred CN Arm**: Patients will receive 4 cycles of ipilimumab/nivolumab induction therapy. PBMCs will be collected before and after induction. Following induction, progression status, safety, and QoL will be assessed, after which deferred cytoreductive nephrectomy will be performed. Additional PBMCs will be collected after surgery. Four weeks postoperatively, perioperative complications and progression status will be evaluated. Thereafter, nivolumab maintenance will be given with assessments every 3 months. At 15 months after treatment initiation, progression and survival status will be determined.

Additional Considerations:

- If progressive disease (PD) is observed during induction therapy, this will be defined as the progression event for the primary endpoint. At the investigator's discretion, patients may switch to second-line systemic therapy or undergo CN.

- For patients with response or stable disease (complete response, partial response, or stable disease), CN will be planned after induction therapy (approximately 3 months). However, considering potential clinical or logistical delays, a window period of up to 3.5 months after completion of induction will be allowed for surgery. During this window, additional nivolumab maintenance therapy may be administered.

9. **Perioperative management and documentation**: Pre- and post-surgical management and documentation will be standardized across both study arms.

10. **Follow-up**: Participants will be followed for 15 months from treatment initiation. Data will be collected at each immunotherapy cycle and during follow-up visits, with additional perioperative outcomes collected for 3 months post-surgery.

Data and Safety Monitoring

The study will be monitored by a centralized Data and Safety Monitoring Committee. Data will be collected via electronic CRFs and managed under secure conditions with quality control oversight.

Expected Impact

This trial will provide high-level evidence on the role and optimal timing of CN in the era of immunotherapy for mRCC, inform treatment guidelines, and improve patient survival and quality of life.

Informed Consent Form

Title of Study: Immediate versus Deferred Cytoreductive Nephrectomy with Ipilimumab/Nivolumab in Metastatic Clear Cell Renal Cell Carcinoma: A Multicenter, Randomized, Open-Label Phase III Trial

Introduction

You are invited to participate in a research study. Before you decide, please read this document carefully. The purpose of this form is to explain why the study is being done, what will happen to you, and what the risks and benefits are.

Unlike many other cancers, cytoreductive nephrectomy (surgical removal of the kidney even in the metastatic setting) has been shown to contribute to improved survival outcomes in metastatic kidney cancer. However, in the era of immune checkpoint inhibitors, some patients with metastatic kidney cancer have experienced remarkable treatment responses and significantly prolonged survival. Still, there is insufficient clinical evidence regarding which patients should undergo cytoreductive nephrectomy and at what timing. Therefore, this study has been designed to evaluate the effect of treatment sequencing by comparing two approaches in metastatic kidney cancer: combining cytoreductive nephrectomy with immunotherapy (ipilimumab plus nivolumab), but assigning patients to different treatment orders. This clinical trial aims to compare and assess how the sequence of surgery and immunotherapy impacts overall survival.

Purpose of the Study

The purpose of this study is to determine the best timing of surgery (cytoreductive nephrectomy) when combined with immunotherapy (ipilimumab plus nivolumab) in patients with metastatic kidney cancer.

Procedures

If you join this study, you will be randomly assigned to one of two groups: upfront surgery followed by immunotherapy, or immunotherapy first followed by delayed surgery. All participants will receive standard-of-care ipilimumab and nivolumab.

1) Control Group (Upfront Surgery followed by Immunotherapy)

1. **Cytoreductive nephrectomy (surgery)** will be performed.

- Three blood samples (10 cc each) will be collected: before surgery, after surgery, and after completing 4 cycles of immunotherapy, for storage of peripheral blood mononuclear cells (PBMCs).

2. **At 4 weeks after surgery**
    - Cancer progression status and perioperative complications will be evaluated.
3. **Within 6 weeks after surgery**
    - Immunotherapy with ipilimumab/nivolumab will be administered for 4 cycles (4 doses).
    - After treatment, cancer progression, safety, and quality of life will be evaluated.
4. **Maintenance therapy**
    - Following induction, nivolumab maintenance therapy will be given. Every 3 months, cancer progression, safety, and quality of life will be assessed.
5. **End of study**
    - At 15 months after treatment initiation, cancer progression and survival status will be finally evaluated.

2) Experimental Group (Immunotherapy first, followed by Surgery)

1. **Immunotherapy with ipilimumab/nivolumab** will be administered for 4 cycles.
    - Blood samples (10 cc each) will be collected before and after induction for PBMC storage.
2. **After completion of 4 cycles**
    - Cancer progression, safety, and quality of life will be evaluated.
3. **Cytoreductive nephrectomy (surgery)** will be performed.
    - An additional blood sample (10 cc) will be collected after surgery for PBMC storage.
    - In total, three blood samples (10 cc each) will be collected for analysis.
4. **At 4 weeks after surgery**

- Cancer progression status and perioperative complications will be evaluated.

5. **Maintenance therapy**
    - Nivolumab maintenance therapy will follow. Every 3 months, cancer progression, safety, and quality of life will be assessed.
6. **End of study**
    - At 15 months after treatment initiation, cancer progression and survival status will be finally evaluated.

Additional Considerations

1. **If disease progression occurs during treatment**
    - If progression is observed during immunotherapy, that time point will be defined as the "date of progression."
    - Depending on the physician's judgment, second-line systemic therapy or earlier surgery may be initiated.
2. **If the cancer responds to treatment (tumor shrinkage or stable disease)**
    - Cytoreductive nephrectomy will be planned within approximately 3 months after completion of 4 cycles of immunotherapy.
    - However, if surgery scheduling is delayed, an additional window of up to 3.5 months will be allowed.
    - During this window, nivolumab maintenance therapy may be administered depending on the patient's condition.

Patient Responsibilities in the Study

- Attend hospital visits and undergo examinations according to the study schedule.
- Adhere to immunotherapy and surgical procedures as required by the protocol.
- Follow the schedule for blood tests, imaging studies, and evaluations.
- Immediately report any unusual or adverse symptoms to the study team.
- If you wish to change or withdraw from the study treatment, you must consult the study team in advance.

Risks and Discomforts

Immunotherapy can cause immune-related side effects (skin rash, diarrhea, liver function changes, thyroid problems, etc.). Surgery may involve risks such as bleeding, infection, kidney failure, or blood clots.

Benefits

There are no direct medical benefits for participants in this study. Participation will not provide immediate therapeutic advantage. However, the results of this research may contribute to important social and scientific benefits, such as:

- Helping to clarify the optimal treatment sequence of immunotherapy and cytoreductive nephrectomy in patients with metastatic renal cell carcinoma.
- Contributing to the development of future clinical practice guidelines for the treatment of metastatic renal cell carcinoma.

Voluntary Participation

Your participation is voluntary. You may withdraw at any time without penalty or loss of medical benefits.

Confidentiality

Your personal and medical information will be kept confidential to the extent permitted by law.

Compensation and Costs

Study-related procedures and medications will be provided without additional cost. If you are injured as a result of the study, you will receive appropriate medical treatment and compensation in accordance with study insurance policies.

Contact Information

If you have questions about the study, please contact the study team at Seoul National University Hospital. If you have questions about your rights as a participant, please contact the Institutional Review Board (IRB) (+82-2-2072-0368)

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Participant Signature Date

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Investigator Signature Date