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Trial Protocol - Kidney Cancer

The ITALIC-RCC: A Randomized Trial on Clinical and Humoral Impact of Primary Tumor Ablation by Surgery or Radiotherapy in Metastatic Renal Cell Carcinoma Treated with Checkpoint Inhibitors

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Abstract

Background: Immunotherapy-based combinations have improved overall survival (OS) in metastatic renal cell carcinoma (mRCC), but recent evidence suggests a therapeutic plateau, underscoring the need for more personalized strategies. Many patients start systemic therapy with the primary kidney tumor still in situ, and the role of cytoreductive nephrectomy (CN) in the immunotherapy era remains uncertain after CARMENA and SURTIME trials. In parallel, stereotactic body radiotherapy (SBRT) has emerged as a noninvasive option that achieves local control of primary RCC with limited toxicity. The ITALIC-RCC study evaluates whether local ablation of the primary tumor—by deferred CN or SBRT—improves outcomes in patients with mRCC who derive early benefit from anti-PD-1–based standard-of-care (SOC) therapy.

Study design: ITALIC-RCC is a phase 4, randomized, multicenter trial. Patients with tumors ≤ 4 cm are randomized 1:1:1 to CN + SOC, radiotherapy (RT) + SOC, or SOC alone; those with tumors >4 cm are randomized 1:1 to CN + SOC or SOC alone.

End points: The primary end point is OS comparing CN + SOC versus SOC alone from the time of randomization. Secondary end points include OS from systemic therapy

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TKI Proteomic biomarkers

initiation and progression-free survival (PFS) in the CN+SOC cohort versus the SOC-alone cohort, OS and PFS in the SBRT cohort, safety and complications of local treatments, and changes in quality of life. Exploratory end points include proteomic and tissue-based biomarkers associated with OS and PFS.

Patients and methods: The study plans to enroll 409 adults with predominantly clear-cell mRCC, Eastern Cooperative Oncology Group performance status 0–1, a primary tumor in situ, and no progression after 24–52 wk of first-line anti-PD-1-based SOC (axitinib + pembrolizumab, cabozantinib + nivolumab, lenvatinib + pembrolizumab, or nivolumab after ipilimumab + nivolumab). Systemic therapy continues until progression by RECIST v1.1 or unacceptable toxicity. Imaging is performed every 12 ± 2 wk. Safety is assessed by CTCAE v5.0 and Clavien–Dindo; quality of life by EQ-5D-5L and FKSI-19. Blood samples at randomization and 8 ± 2 wk after intervention undergo proteomic profiling.

Trial registration

ClinicalTrials.gov identifier: NCT06903312.

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1. Introduction and hypotheses

The current treatment landscape of metastatic renal cell carcinoma (mRCC) has been transformed by the introduction of immunotherapy-based combination regimens, which have substantially improved overall survival (OS) compared with prior vascular endothelial growth factor receptor (VEGFR)–tyrosine kinase inhibitor (TKI)–based therapies [1]. Despite these advances, recent data suggest that systemic therapies have reached a plateau, underscoring the need for more personalized strategies, including better integration of local and systemic approaches.

Approximately one-third of patients with mRCC present with the primary renal tumor still in situ [2]. In these cases, the potential role of cytoreductive nephrectomy (CN) remains clinically relevant but uncertain. CN historically provided symptomatic relief—reducing bleeding and pain, with a potential impact also on the risk of subsequent metastatic spread by eliminating a source of immunosuppressive or tumor-promoting growth factors [3,4]—and was shown to improve OS in the era of interferon-based therapy within randomized trials [5]. However, with the advent of VEGFR-TKIs, the role of CN was investigated by the CARMENA and SURTIME trials [6,7]. CARMENA was a non-inferiority study comparing upfront CN followed by sunitinib with sunitinib alone. The trial showed that patients with intermediate- and poor-risk mRCC receiving sunitinib monotherapy achieved OS outcomes comparable to those of patients undergoing immediate CN and subsequent sunitinib [6]. Nonetheless, a subgroup analysis stratified by baseline International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)–risk suggested that selected patients with only one IMDC risk factor might still benefit from CN [8]. The SURTIME trial evaluated deferred CN after sunitinib versus immediate CN followed by sunitinib in patients with mRCC. Owing to slow accrual, the study was downsized and ultimately included 99 patients. Those assigned to deferred CN reported longer OS than those treated with upfront surgery (hazard ratio [HR], 0.57; 95% CI, 0.34–0.95; $p = 0.03$)

[7]. Importantly, the study demonstrated that initial systemic therapy and the response to it may serve as a biomarker for selecting patients suitable for deferred CN. Patients who responded to systemic therapy and subsequently underwent CN experienced prolonged survival.

Based on this evidence, contemporary guidelines recommend initiating systemic therapy for most patients with intermediate- or poor-risk disease, reserving CN for those who demonstrate clinical benefit or require local symptom control [9]. To date, no completed randomized trial has evaluated deferred CN specifically in the context of modern immunotherapy-based combinations, leaving its role in the current therapeutic era undefined.

Radiotherapy directed to the primary tumor has emerged as an additional local strategy. Safety data show a very low incidence of high-grade toxicity (3.8%) [10], supporting its feasibility even in frail patients or patients who are not surgical candidates. More recently, prospective and retrospective studies have shown that stereotactic body radiotherapy (SBRT) can offer durable local control with favorable toxicity in both metastatic and primary RCC lesions, particularly in the oligometastatic and oligoprogressive settings, suggesting that radiotherapy may represent a viable local treatment option in selected patients and potentially complement systemic therapy in modern clinical practice [10–13].

The ITALIC-RCC study is designed to address these knowledge gaps in a contemporary setting in which most patients achieve early systemic disease control with an anti-programmed death (PD)–1–based combinations. The trial evaluates whether ablative treatment of the primary tumor—either through cytoreductive surgery or stereotactic radiotherapy—offers clinical benefit in addition to systemic therapy and integrates translational proteomic analyses to identify biological predictors of benefit and guide future personalization of care.

The primary hypothesis is that delayed CN combined with anti-PD-1–based systemic therapy improves OS compared with systemic therapy alone. Secondary hypotheses

include the possibility that SBRT may improve outcomes for patients with primary tumors smaller than 4 cm, that both CN and SBRT induce measurable systemic proteomic changes consistent with immune modulation, that specific proteomic signatures correlate with OS, progression-free survival (PFS), and response to local treatment, and that local treatment of the primary tumor is safe, feasible, and compatible with ongoing immunotherapy.

2. Design

The ITALIC-RCC study is a phase 4, randomized, controlled, multicenter, low-interventional clinical trial designed to evaluate whether treatment of the primary renal tumor—either through deferred CN or SBRT—improves outcomes in patients with mRCC who have achieved initial disease control with anti-PD-1–based systemic therapy. The design reflects real-world clinical practice in the immunotherapy era: enrolled patients have already completed 24–52 wk of systemic anti-PD-1–based therapy, such as nivolumab, pembrolizumab-based combinations, or nivolumab maintenance, and have demonstrated overall disease control (stable disease, partial response, or complete response) at metastatic and primary sites at the time of enrollment. This ensures that the study population includes individuals likely to benefit from continued immunotherapy, thus allowing the trial to assess the incremental effect of local treatment of the primary tumor.

Eligible patients must fulfill all of the following criteria:

1. Age ≥ 18 yr and able to provide written informed consent.
2. Histologically confirmed clear-cell RCC with an identifiable primary renal mass.
3. Documented metastatic disease, measurable or non-measurable, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [14].
4. Completed 24–52 wk of anti-PD-1–based systemic therapy without progression (nivolumab maintenance after ipilimumab–nivolumab, pembrolizumab + axitinib, pembrolizumab + lenvatinib, nivolumab + cabozantinib)
5. Eastern Cooperative Oncology Group performance status 0–1 at screening.
6. Life expectancy ≥ 9 mo.
7. Adequate organ function.
8. Ability to comply with study requirements, including blood sampling for proteomic analysis.
9. Women of childbearing potential must have a negative pregnancy test.

Participants will be excluded for any of the following:

1. More than one prior systemic therapy for mRCC.
2. Solitary kidney (incompatible with CN or high-risk SBRT).
3. Contraindications to either CN or SBRT (cardiopulmonary, anatomical, or anesthetic risks).
4. Progression during systemic therapy prior to randomization.

5. Major surgery within 6 wk before randomization.
6. Uncontrolled comorbidities such as severe cardiovascular disease (New York Heart Association class 3/4), uncontrolled hypertension, active infections ($\geq$ Grade 2), recent myocardial infarction, or stroke.
7. Autoimmune disease requiring systemic immunosuppression.
8. Concurrent malignancy requiring active treatment, except certain skin cancers or low-risk prostate cancer.
9. Uncontrolled central nervous system metastases.
10. Patients who are pregnant or breastfeeding.

The study requires a minimum follow-up of 30 mo for all randomized patients to adequately capture survival events.

Patients with a primary tumor measuring 4 cm or less in maximum diameter are randomized 1:1:1 into three arms: (Fig. 1):

1. Deferred CN + standard-of-care (SOC) therapy
2. SBRT to the primary tumor + SOC therapy
3. SOC therapy alone (control arm)

Patients with a primary tumor larger than 4 cm are randomized 1:1 into two arms:

1. CN + SOC therapy
2. SOC therapy alone

The study was designed for a formal comparison between CN + SOC and SOC alone. The inclusion of SBRT for patients with a primary tumor measuring 4 cm or less in maximum diameter will be descriptive only.

SBRT is not included for patients with tumors larger than 4 cm because ablative radiotherapy for larger renal tumors remains less well established and is associated with a higher risk of toxicity or inadequate renal preservation. Conversely, CN remains a feasible and standard option for larger lesions.

Allocation concealment will be ensured through a centralized, independent, web-based system.

The study focuses on patients with metastatic clear-cell RCC who have received continuous anti-PD-1–based systemic therapy for 24 to 52 wk before randomization, without evidence of disease progression and with a life expectancy of at least 9 months. This population represents the group most likely to benefit from adjunctive local therapy, while reducing the risk that the primary tumor harbors rapidly progressive disease.

The study is coordinated by Fondazione Policlinico Universitario A. Gemelli IRCCS and includes participation from multiple Italian oncology and urology centers with expertise in CN, SBRT, and immunotherapy for RCC.

3. Protocol overview

Possible interventions include deferred CN (radical nephrectomy, partial nephrectomy when feasible, or lumpectomy/tumor excision), within 6–8 wk after randomization unless medically contraindicated. Surgical objec-

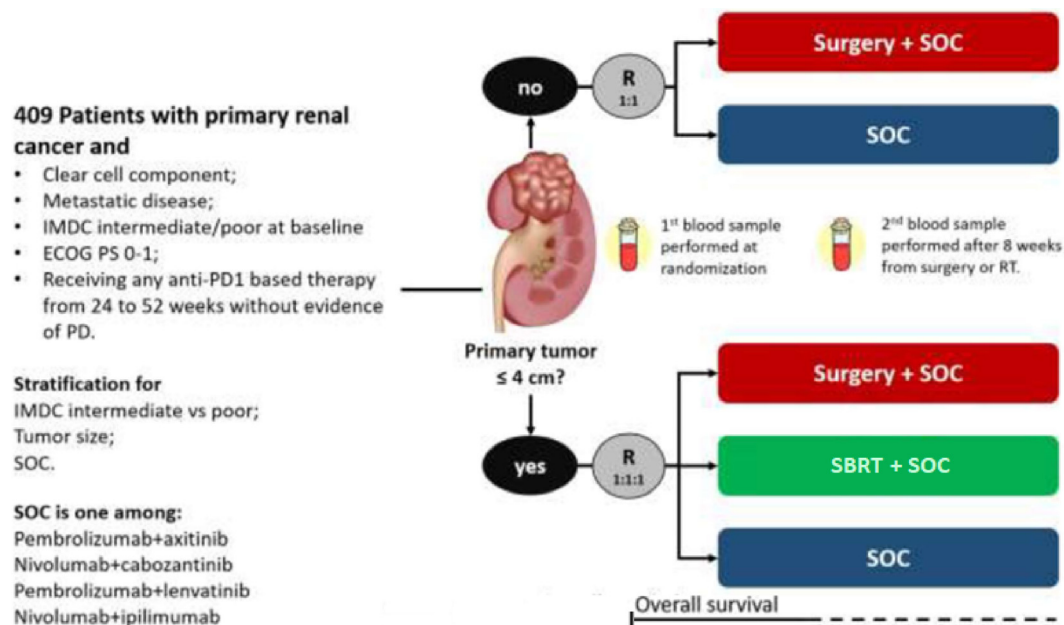


Fig. 1 – Schematic study design.

tives are to remove the primary tumor mass and associated immunosuppressive microenvironment, minimize perioperative morbidity, and allow resumption of systemic therapy in a timely fashion. Another possible intervention is stereotactic radiotherapy with a recommended dose of 25 Gy in a single fraction or a biologically equivalent multi-fraction regimen. SBRT offers a noninvasive local treatment option and is particularly suitable for patients with primary tumors ≤ 4 cm. It must be delivered by centers equipped with dedicated stereotactic technology (eg, CyberKnife, VMAT-based LINAC systems) and experienced in renal SBRT. Systemic therapy will be resumed postoperatively once adequate wound healing is confirmed; SOC therapy consists of the anti-PD-1-based regimen the patient is already receiving, continued uninterrupted except during postsurgical recovery: (1) axitinib + pembrolizumab, (2) cabozantinib + nivolumab, (3) lenvatinib + pembrolizumab, and (4) nivolumab monotherapy.

The timing and frequency of clinical assessments are aligned with oncologic standards for mRCC and with the needs of a randomized interventional protocol. Assessments occur at screening, baseline, post-intervention, during systemic therapy, at the end of treatment, and during long-term follow-up. Safety assessment is consistent with Good Clinical Practice and CTCAE v5.0 [15].

All adverse events (AEs) will be recorded, with special attention to surgical complications (graded by Clavien-Dindo [16,17]), renal function decline after CN or SBRT, immune-related AEs (colitis, hepatitis, endocrinopathies), and TKI-associated toxicity (hypertension, diarrhea, and hand-foot syndrome).

4. Statistical analysis

The statistical analysis plan for the ITALIC-RCC trial includes predefined primary, secondary, and exploratory end points,

detailed population definitions, methodologies for time-to-event analyses, handling of missing data, and the rationale for sample size determination.

Three major populations are defined for this study:

1. The intent-to-treat population includes all randomized patients, regardless of treatment received or protocol deviations. This is the primary population for analysis of efficacy end points, including the primary end point of OS.
2. The per-protocol population includes patients who received their allocated treatment (CN, SBRT, or SOC), had no major protocol deviations, and completed baseline and at least one post-baseline disease assessment.
3. The safety population includes all patients who received any study intervention (CN, SBRT, or SOC) after randomization for safety analyses (AEs, serious AEs, surgical complications, renal toxicity, and immune-related events).

The proteomic/exploratory biomarker population includes patients with valid baseline proteomic samples and valid samples at 8 ± 2 wk after nephrectomy/radiotherapy and is used exclusively for exploratory end points.

The primary end point is OS, defined as the time from randomization to death from any cause. OS will be compared between patients undergoing CN + SOC therapy and those receiving SOC alone across the pooled population. This comparison addresses the fundamental biological question of whether cytoreductive removal of the primary tumor enhances survival in patients benefiting from anti-PD-1-based therapy.

The primary analysis method includes Kaplan-Meier estimation, a stratified log-rank test, and hazard ratio estimation using a Cox proportional hazards model; analyses will be stratified by the factors used for randomization. As the primary hypothesis corresponds to a reduction in haz-

ard ($HR < 1$), the primary analysis is based on a one-sided test at the 2.5% significance level, and the upper bound of the one-sided 97.5% confidence interval for the hazard ratio will be reported. Statistical significance will be concluded if this upper bound is below 1.

Secondary end points include OS from initiation of first-line anti-PD-1-based therapy and PFS, defined as the time from randomization to radiologic disease progression according to RECIST version 1.1 or death from any cause, whichever occurs first, comparing patients undergoing CN + SOC and SOC alone. Additional secondary end points include OS and PFS in patients with tumors ≤ 4 cm at randomization, comparing those receiving radiotherapy to the primary tumor in addition to SOC versus SOC alone, as well as safety of CN and radiotherapy, quality of life, and surgical complications. The date of progression is defined as the date of the radiological assessment documenting disease progression. Patients without disease progression or death will be censored at the date of the last adequate tumor assessment. For OS from randomization, patients alive at the time of analysis will be censored at the date they were last known to be alive.

For the secondary end point “OS from initiation of first-line anti-PD-1-based therapy,” treatment allocation will be modeled as a time-varying exposure in a Cox proportional hazards model to account for potential immortal time and time-dependent selection bias. Patients will contribute person-time to the SOC group until randomization and to their assigned treatment group thereafter. In addition, a landmark sensitivity analysis will be performed. The study is powered to detect a clinically meaningful improvement in OS associated with CN when added to SOC systemic therapy. The primary comparison focuses on CN plus SOC versus SOC alone in the pooled study population.

Quality of life will be assessed using the EQ-5D-5L and FKS-19 questionnaires at baseline (prior to randomization) and at 8 ± 2 wk after nephrectomy or radiotherapy, with additional assessments during follow-up. Changes from baseline over time will be analyzed using mixed-effects models for repeated measures, accounting for within-patient correlation.

Proteomic analyses will be conducted on blood samples collected at randomization and 8 ± 2 wk after nephrectomy or radiotherapy. These analyses will follow an exploratory approach aimed at identifying associations between proteomic profiles and clinical outcomes, including OS and PFS.

The sample size calculation is based on the assumption that the 30-month OS rate in the SOC group is approximately 60%, while an absolute improvement to 72% is expected in patients receiving CN. This corresponds to a hazard ratio of 0.643. The analysis is planned using a one-sided significance level of 0.025 and a statistical power of 80%.

Under these assumptions, a total of 162 death events is required to adequately power the primary survival analysis. Based on the anticipated event rate and assuming 24 mo for accrual and 30 mo of follow-up, 372 randomized patients (186 per arm in the pooled comparison) are necessary to observe the required number of events.

To ensure sufficient representation across all randomization strata and to account for the three-arm randomization among patients with primary tumors ≤ 4 cm (approximately a 30% rate), as well as for a limited degree of loss to follow-up or post-randomization ineligibility, the total target sample size has been increased to 409 patients.

The sample size was calculated using standard time-to-event power formulas under exponential survival assumptions and was further validated through simulation analyses to confirm the robustness of the design.

5. Summary

mRCC remains a challenging malignancy despite major advances in systemic therapy over the past decade. The introduction of immune checkpoint inhibitors, particularly in combination with TKIs or cytotoxic T-lymphocyte-associated protein 4 blockade, has substantially improved long-term survival. Nevertheless, the role of the primary renal tumor in modulating systemic disease biology—especially in patients receiving anti-PD-1-based immunotherapy—remains incompletely understood. Historically, CN improved survival in the cytokine era, but its benefit in the targeted therapy era became controversial following the CARMENA and SURTIME trials. At the same time, SBRT has emerged as a powerful ablative tool capable of achieving excellent local control with minimal toxicity. These evolving paradigms have generated renewed interest in understanding whether local treatment of the primary tumor could enhance the therapeutic efficacy of immunotherapy.

The ITALIC-RCC trial is the first randomized study specifically designed to answer this question in the immunotherapy era. This phase 4, multicenter, low-interventional study evaluates whether deferred CN or SBRT of the primary tumor provides a survival benefit to patients with mRCC who have already demonstrated clinical benefit from systemic anti-PD-1-based therapy. The study targets a carefully selected population of responders or patients with stable disease after 24–52 wk of immunotherapy, ensuring that local treatment is delivered only to patients who are biologically poised to benefit.

The trial employs a stratified randomization framework based on primary tumor size. Patients with primary tumors ≤ 4 cm are randomized among CN + SOC, SBRT + SOC, or SOC alone, allowing evaluation of both surgical and radiotherapeutic local therapies. Patients with tumors > 4 cm are randomized to CN + SOC or SOC alone, reflecting the different clinical feasibility of ablative radiotherapy in larger lesions. This design ensures clinical appropriateness while enabling robust comparison of treatment arms.

The primary end point is OS, comparing CN + SOC with SOC alone in the pooled population. Secondary end points include PFS, OS from the start of systemic therapy, outcomes specific to the SBRT-eligible subgroup, safety profiles, quality of life, and surgical complication rates. Importantly, ITALIC-RCC incorporates a comprehensive translational research component using SomaScan proteomic profiling,

enabling detailed evaluation of systemic immune and inflammatory signatures before and after local tumor treatment. Biomarker analyses will explore correlations between proteomic shifts and clinical outcomes, potentially identifying predictive signatures that could guide personalized therapy in the future.

The study's sample size—409 patients, with 372 evaluable for the primary analysis—ensures adequate statistical power to detect a meaningful OS improvement. The trial is powered to detect a hazard ratio of 0.643, corresponding to a 12% absolute improvement in 30-mo OS. Safety monitoring includes detailed evaluation of AEs, surgical morbidity, immune-related toxicities, and renal function. Quality-of-life assessments complement clinical end points to ensure that any survival benefit is not achieved at the cost of unacceptable patient burden.

If successful, the ITALIC-RCC trial may fundamentally reshape the management of mRCC in the immunotherapy era. By prospectively exploring the role of surgery in a population stabilized by immunotherapy, the trial will clarify whether reducing or eliminating the primary tumor improves long-term outcomes and augments systemic immune activity. The translational component will provide mechanistic insights into how local interventions influence systemic immunity and tumor-host interactions.

In summary, ITALIC-RCC aims to:

1. Determine whether CN or SBRT enhances survival in patients responding to anti-PD-1 therapy.
2. Assess safety, feasibility, and quality-of-life outcomes associated with these local treatments.
3. Identify systemic proteomic biomarkers linked to treatment response and resistance.
4. Provide robust prospective evidence to guide multidisciplinary treatment strategies.

The findings of this study have the potential to redefine the therapeutic algorithm for mRCC and to contribute significantly to precision oncology approaches integrating local treatment, systemic therapy, and biomarker-driven patient selection.

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Acquisition of data: NA.

Drafting the manuscript: Iacovelli, Ciccarese, Arduini, Troisi.

Critical revision: All.

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